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SURGICAL ASPECTS OF NONPALPABLE BREAST CANCER

J.G.M. Tinnemans
Saint Agatha (Catania, Italy, 3rd century A.D.) was treated cruelly by the Roman governor of the island of Sicily because she would not accept his lustful designs and, on the pretext of the persecution of Christians, he ordered that she should be bound to a stake and her breasts removed. In the Western Church Saint Agatha is regarded as the patron saint of diseases of the breast.

On this picture Saint Agatha holds her attribute, a severed breast, with iron pincers. She stands against a dark crimson textile on which is represented a repeated motif in gold of a phoenix rising in flames toward a burning sun. This motif is appropriate to Agatha, also known as the fire maiden, through her association with volcanos and lava and her patronage of forging and casting. Reference to this patronage is to be found in the border: in her monograms wrought of gold, in the gold and enamel jewelry, and in gift-wrapped boxes of jewels. Also in the border are careful imitations of various kinds of weaving.

SURGICAL ASPECTS OF NONPALPABLE BREAST CANCER

PROEFSCHRIFT

ter verkrijging van de graad van doctor in de geneeskunde aan de Katholieke Universiteit te Nijmegen op gezag van de Rector Magnificus Prof. Dr. J.H.G.I. Giesbers volgens besluit van het college van decanen in het openbaar te verdedigen op donderdag 27 november 1986 des namiddags te 3.30 uur

door

Johannes Gerardus Maria Tinnemans

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Dr. R. Holland
Dr. J.H.C.L. Hendriks

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Aan Wil,
Brechje, Kirsten en Mascha
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Cancer of the female breast is a major public health problem in The Netherlands (total female population in 1982: 7.221.000), affecting one out of twelve women in the course of their lives. Annually about 6800 cases are newly detected and at the same time 2893 patients died of the disease in 1982 (1,2). Thus the mortality rate is approximately 40% and this figure has remained almost constant over the past thirty years (3,4). A slight increase in survival may be attributed to the earlier clinical stage in which patients nowadays present themselves for treatment. Different treatment modalities all aimed at locoregional tumour control have little or no influence on long-term survival given a certain stage of the tumour (T1-T4). Therefore, all hope to improve prognosis of mammary carcinoma is focused on earlier detection, i.e. in its pre-clinical or nonpalpable stage (T0).

Various diagnostic methods have their inherent limitations or disadvantages:
- Transillumination is now largely of historical interest (5).
- Infrared thermography, although cheap and noninvasive, has a relatively low sensitivity and specificity for the detection of occult carcinomas (6,7).
- Ultrasound examination is usually not appropriate for solid lesions with a diameter of 10 mm or less and for microcalcifications (8).
- Computerized tomography of the breast using body CT machines requires a high dose of intravenous iodinated contrast material, is a lengthy procedure and extraordinarily expensive (9,10).
- Arteriography with iodinated contrast material requires selective cannulation of the subclavian or internal mammary artery and is time-consuming; the radiation dose is high and only large lesions over 1.5 cm in diameter were examined (11).
- Digital subtraction angiography (DSA) of the breast has the same disadvantage: venous catheterization into the superior
vena cava, a total radiation exposure of approximately 2 cGy for each DSA study and relatively expensive, mainly because of the duration of the examination of approximately one hour (12).

- Galactography is only to be used in case of nipple discharge (13).

- Breast scintigraphy with 99m Tc-diethylene triamine penta-acetic acid is able to differentiate between benign and malignant tumours, but in view of the low sensitivity its diagnostic value is limited (14).

- Nuclear magnetic resonance imaging as a tool in the diagnosis of breast disease is still in its experimental stage and its merit has to be confirmed through large-scale clinical studies (15,16).

Mammography has proven to be most apt to visualize mammary carcinoma even in its nonpalpable stage with nowadays a sensitivity of up to 95% (17,18). The fear of cancer induction through repeat mammographies (19) might have been true in the early days of conventional mammography or xeroradiography in the sixties, but is totally unwarranted since the development of the dedicated mammography unit with a molybdenum target tube and filter, the introduction of screen-film combinations, compression devices and small focal spots (20). These technical improvements have caused that the average mid-breast radiation dose does not exceed 1 mGy per image (21). As a result of this it has been extrapolated that the average excess risk of breast cancer induction by mammographic screening is 0.042% per mGy (22), which is negligible in view of the anticipated possible benefits.

Despite some persistent pessimism (23), there is now increasing evidence that mammography is able to reduce mortality from breast cancer by earlier detection:

- First of all the much quoted randomized study of the Health Insurance Plan of Greater New York (HIP), which started already in 1963, using physical examination (palpation) and conventional mammography as screening tests, has shown after
14 years a 30% reduction in mortality rate in women offered screening, initially only in the age group over 50, but later also in women aged 40-49 years (24).

- The second controlled trial, randomized on community level, started in 1977 and was carried out in Kopparberg and Östergötland, Sweden. Here the only screening modality was single mediolateral oblique view mammography (25). After seven years of follow-up a 31% reduction in mortality from breast cancer was observed (26).

- The last two population-based studies, which have been evaluated so far, are non-randomized, but have a case referent design. In the Utrecht study, started in 1974, xeromammography plus physical examination were used as screening modality involving women between 40-64 years. After four screening rounds or six years of follow-up mortality from breast cancer was reduced 70% in screened versus unscreened women (27).

- The Nijmegen study, using modern mammography only with a single oblique view, started in 1975 and was aimed at all women over 35 years of age. The results after four rounds of screening showed a 52% reduction in mortality amongst screened subjects (28). In this study no benefit of screening in respect of relative risk of dying from breast cancer could be demonstrated in the youngest age group (35-49 at entry) (29).

- More breast cancer screening projects are under way in the United States (30,31), Canada (32), United Kingdom (33,34) and Sweden (35,36).

Although the above vital statistics are of utmost importance for the population in general, the practising clinician in particular might wish to know more details regarding the individual patient with clinically occult or nonpalpable breast carcinoma. This thesis tries to elucidate some of these aspects from a surgeon's point of view.

- Chapter I deals with the problem how to remove a nonpalpable, yet mammographically suspicious breast lesion. Three methods
of localization and excision are evaluated. The efficacy is assessed in respect of number and size of the biopsies. It is not only important for malignancies that the correct piece is removed for pathological examination, but also for benign biopsies that this is carried out with the least possible loss of volume. The failure rate is investigated and the results of repeated biopsies are presented.

- In Chapter II the clinical significance of pure microcalcifications without palpable mass in a large series of patients is examined: the reasons for mammography, the age distribution, the yield of malignancies, the histological types and the axillary status. The appearance of the microcalcifications is discussed and an overview of the literature is given.

- Various mammographic-histopathologic correlations of nonpalpable breast lesions are studied in Chapter III and the respective yields of invasive and noninvasive carcinomas are presented. The feasibility of the frozen section examination is investigated and its consequences for treatment policy are discussed.

- In Chapter IV the results of oestrogen and progesterone receptor studies in nonpalpable breast cancers are documented. The receptor phenotypes are compared between nonpalpable primary breast cancer, palpable primary breast cancer, locoregionally advanced primary breast cancer and first metastatic breast cancer. Its significance for tumour biology is considered.

- Chapter V deals with multicentricity (invasive or noninvasive carcinoma outside the quadrant of the reference tumour) and residual tumour (invasive or noninvasive carcinoma outside the excisional biopsy cavity) in nonpalpable breast carcinoma. This is especially important in view of the modern trend of breast conserving surgery for small carcinomas.

- The role of mammography in the detection of contralateral primary breast cancer is evaluated in Chapter VI. Nonpalpable breast cancers are studied in synchronous and
metachronous bilateral breast disease in respect of multi-centricity and axillary status. Failure to discover meta-chronous second primary breast cancer in its nonpalpable stage is analysed. The 5- and 10-year survival rates of bilateral primary breast cancer are presented.

In Chapter VII treatment and long-term survival results of nonpalpable breast cancers are demonstrated and analysed according to invasive tumour size (upper limit at 5 or 10 mm) or axillary status (positive versus negative nodes). The concept of minimal breast cancer is reconsidered in light of the present figures.

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Chapter I

LOCALIZATION AND EXCISION OF NONPALPABLE BREAST LESIONS; A SURGICAL EVALUATION OF THREE METHODS


Arch Surg, accepted for publication
1.1 INTRODUCTION

With the increased use of mammography, especially in breast screening programs, more and more suspect but nonpalpable breast lesions are being detected which require excisional biopsy for histological diagnosis. The management of these clinically occult lesions poses a challenge to the surgeon who is requested to remove the correct piece of breast tissue with the least possible harm. The latter is particularly important in case the radiographic lesion turns out to be benign.

Several preoperative localization techniques have been described to guide the surgeon during biopsy. Most authors claim improved accuracy of the biopsy with their method of localization, but little or no proof of this has been given. Only a few evaluations have been published so far, but data comparing different methods of localization are even more scarce (1-4).

1.2 PATIENTS AND METHODS

Between January 1, 1975, and December 31, 1983, 300 consecutive women underwent breast biopsies because of non-palpable, radiographically suspicious findings. All patients were treated in the St. Radboud University Hospital, Nijmegen, The Netherlands. Out of 335 biopsies, 101 clinically occult breast cancers (invasive and non-invasive ductal carcinoma) have been encountered in 96 patients.

From 1975 until mid 1977, we performed 'blind' biopsies by measuring the distances in two projections (craniocaudal and lateral) using the nipple as a reference point. Since mid 1977 we started using a preoperative needle localization technique with a flexible self-retaining barbed guide wire (5). The insertion of the wire was aided by a multiperforated compression plate, as described below, since January 1982 (6,7). Localization: Before the scheduled operation, the patient is
taken to the mammography unit of the radiology department, which is equipped with a Senographe 500 T (CGR). The usual compression plate is replaced by a home-made multiperforated plexiglas compression plate, which is placed over the breast. A craniocaudal view is taken and the film is developed while the breast remains compressed. After identifying the hole overlying the radiographically suspicious lesion, a commercially available localization needle containing a flexible hooked guide wire (Cook) is introduced into the breast through the appropriate hole. The needle is inserted perpendicular to the compression plate and advanced to the desired depth as determined earlier on the lateral view of the compressed breast. Thereafter, the needle is withdrawn, leaving the barbed wire anchored in the breast parenchyma in close proximity to the radiographical lesion. Postlocalization mammograms in the two projections are obtained to document the position of the wire tip relative to the lesion. Because of its self-retaining nature, the guide wire does not need to be taped to the skin. The skin area and the exposed guide are covered with a sterile dressing while transfer to surgery is being awaited.

Operation: Biopsy is performed under general anaesthesia using a transverse skin incision, but for subareolar lesions, a semi-circumareolar incision may be preferred. The surgeon searches for the wire subcutaneously. After exposure of the guide in the wound, the wire is followed to the calculated depth and a piece of mammary tissue, including the wire tip, is excised en bloc. Radiography of the excised specimen is mandatory in order to confirm that the mammographic lesion has actually been removed and also to direct histological examination.

During this 9-year period, one of us (JHCLH) performed or supervised all localization procedures, but the biopsies were performed by various surgical residents, usually supervised by members of the surgical staff.

All case-sheets and operation reports were studied.
Table 1: Comparison of two methods of preoperative needle localization of nonpalpable mammographic lesions

<table>
<thead>
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<th>Total Distance</th>
<th>Distance of the wire tip relative to the lesion</th>
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<tr>
<td></td>
<td>known</td>
<td>0</td>
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<td>Needle localization</td>
<td>N 163</td>
<td>131</td>
</tr>
<tr>
<td>%</td>
<td>100</td>
<td>21.4</td>
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<tr>
<td>Needle localization</td>
<td>with multiperforated N 62</td>
<td>55</td>
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<tr>
<td>compression plate</td>
<td>%</td>
<td>100</td>
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retrospectively in regard to the following items: the distance between the tip of the wire and the mammographic lesion, the adequacy of removal of the nonpalpable lesion by x-ray confirmation (specimen radiography or postoperative repeated mammography) and the number and size of the biopsies. Failures and complications were noted.

I.3 RESULTS

Preoperative needle localization was highly successful right into or transfixing the mammographic abnormality in 21.4% of the patients without the perforated compression plate, increasing to 49.1% in the group with the perforated compression plate (Table 1). The localization procedure was considered to be unsatisfactory if the distance of the wire tip relative to

<table>
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<th>X-ray confirmation</th>
<th>Histological confirmation only</th>
<th>Failure</th>
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<td>Mastectomy</td>
<td>N 3</td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>% 100</td>
<td></td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>Blind biopsy</td>
<td>N 107</td>
<td>100</td>
<td>5</td>
<td>2</td>
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<tr>
<td></td>
<td>% 100</td>
<td>93.4</td>
<td>4.7</td>
<td>1.9</td>
</tr>
<tr>
<td>Biopsy after needle localization</td>
<td>N 163</td>
<td>146</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>% 100</td>
<td>89.6</td>
<td>8.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Biopsy after needle localization with multi-perforated compression-plate</td>
<td>N 62</td>
<td>56</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>% 100</td>
<td>90.3</td>
<td>8.1</td>
<td>1.6</td>
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Table 3: Analysis of failures of excision of nonpalpable mammographic lesions

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<th>Patient</th>
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<th>Mammographic abnormality</th>
<th>Method of localization</th>
<th>Specimen x-ray</th>
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<tr>
<td>A</td>
<td>50</td>
<td>spiculated opacity</td>
<td>blind</td>
<td>3x neg.</td>
</tr>
<tr>
<td>B</td>
<td>55</td>
<td>circular opacity</td>
<td>blind</td>
<td>4x neg.</td>
</tr>
<tr>
<td>C</td>
<td>19</td>
<td>microcalc.</td>
<td>needle (tip at 1 cm)</td>
<td>2x neg.</td>
</tr>
<tr>
<td>D</td>
<td>52</td>
<td>microcalc.</td>
<td>needle (tip at 1 cm)</td>
<td>3x neg.</td>
</tr>
<tr>
<td>E</td>
<td>58</td>
<td>microcalc.</td>
<td>needle (tip at 1 cm)</td>
<td>2x neg.</td>
</tr>
<tr>
<td>F</td>
<td>47</td>
<td>microcalc.</td>
<td>needle (tip at 2½ cm)</td>
<td>4x: 1x pos.? 3x neg.</td>
</tr>
<tr>
<td>G</td>
<td>68</td>
<td>microcalc.</td>
<td>needle through perforated compression plate (tip at 2 cm)</td>
<td>3x neg.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient</th>
<th>Repeat mammography</th>
<th>Follow-up</th>
<th>Final histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>+</td>
<td>after 5 months repeated biopsy (quadrant excision)</td>
<td>small invasive ductal carcinoma with negative axillary nodes</td>
</tr>
<tr>
<td>B</td>
<td>+</td>
<td>after ½ month repeated biopsy</td>
<td>invasive ductal carcinoma Ø 10 cm with negative axillary nodes</td>
</tr>
<tr>
<td>C</td>
<td>+</td>
<td>because of young age no further action taken; probably of traumatic origin</td>
<td>normal mammary tissue with fibrosis</td>
</tr>
<tr>
<td>D</td>
<td>+</td>
<td>after 3 months repeated biopsy</td>
<td>proliferative fibro-cystic disease with atypia</td>
</tr>
<tr>
<td>E</td>
<td>+</td>
<td>after 25 months repeated biopsy</td>
<td>multifocal in situ ductal carcinoma with negative axillary nodes</td>
</tr>
<tr>
<td>F</td>
<td>+</td>
<td>after 7 months repeated biopsy</td>
<td>simple fibrocystic disease</td>
</tr>
<tr>
<td>G</td>
<td>+</td>
<td>after ½ month repeated biopsy</td>
<td>simple fibrocystic disease</td>
</tr>
</tbody>
</table>
the breast lesion was greater than 2 cm, which was the case in 14.5% without the perforated compression plate and in 7.3% with the aid of the perforated compression plate. In the latter group the distance never exceeded 3 cm, while in the former group poor localization occurred in 6.1%.

As can be seen in Table 2, the great majority in each of the three groups had x-ray confirmation, mainly by specimen radiography, but in 8 patients proof that the suspicious lesion had been removed was given by repeated mammography.

Primary subcutaneous mastectomy with immediate prosthetic implant was performed in three patients and consequently x-ray confirmation of the removed breast was considered to be superfluous. All three had in situ ductal carcinoma.

Of 23 others, no x-ray confirmation was carried out or could be retrieved from the records, but it was most likely, on histological grounds, that the mammographic abnormality had been removed: 13 cases of malignancy, 6 cysts, and 4 cases of microcalcifications.

True failures were encountered in 7/332 = 2.1%. A detailed analysis is presented in Table 3. Repeated biopsies in six patients revealed three malignancies: 2 infiltrating ductal carcinomas and 1 in situ ductal carcinoma.

Table 4 shows the efficacy with which the impalpable mammographic lesions have been removed. Four out of five biopsies were successful at first attempt with any method, but there is a tendency that fourth and fifth attempts occurred a bit more often if no needle localization was used.

The average size of the biopsies decreased from 93.4 cm$^3$ without needle localization to 68.1 cm$^3$ when localized with a wire through the perforated compression plate. The difference, however, did not reach statistical significance (Table 5).

Difficulties with specimen radiography were encountered twice: both patients had blind biopsies because of microcalcifications. After the fourth attempt, the operations were terminated, but the radiologist reported afterwards that the suspicious lesions had been removed yet on the first attempt!
Table 4: Comparison of three methods of excision of nonpalpable breast lesions: number of biopsies

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Number of biopsies</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blind biopsy</td>
<td>N 107</td>
<td>84</td>
<td>10</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>% 100</td>
<td>78.5</td>
<td>9.3</td>
<td>5.6</td>
<td>4.7</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>Biopsy after needle</td>
<td>N 163</td>
<td>131</td>
<td>22</td>
<td>9</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>needle localization</td>
<td>% 100</td>
<td>80.4</td>
<td>13.5</td>
<td>5.5</td>
<td>0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy after needle</td>
<td>N 62</td>
<td>49</td>
<td>8</td>
<td>4</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>localization with</td>
<td>% 100</td>
<td>79.0</td>
<td>12.9</td>
<td>6.5</td>
<td>1.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>multiperforated</td>
<td></td>
<td>compression plate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 5: Comparison of three methods of excision of nonpalpable breast lesions: size of biopsies

<table>
<thead>
<tr>
<th>Method</th>
<th>Total number</th>
<th>Number size known</th>
<th>Median size (cm³)</th>
<th>Mean size (cm³)</th>
<th>Range (cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blind biopsy</td>
<td>107</td>
<td>63</td>
<td>62</td>
<td>93.4</td>
<td>2 - 420</td>
</tr>
<tr>
<td>Biopsy after needle localization</td>
<td>163</td>
<td>118</td>
<td>61</td>
<td>82.6</td>
<td>3 - 476</td>
</tr>
<tr>
<td>Biopsy after needle localization with multiperforated compression plate</td>
<td>62</td>
<td>30</td>
<td>71.5</td>
<td>68.1</td>
<td>4 - 180</td>
</tr>
</tbody>
</table>

* p > 0.30 (Kruskal-Wallis test)
Complications of wire placement were seen in four instances. Two guide wires broke off, but the mammographic lesions, including the broken wires, have been removed on the first and second attempt respectively. Intra-operative wire dislodgement occurred once, yet the first biopsy was successful. In one case the guide was inadvertently introduced below the fascia of the underlying pectoralis musculature, but this was recognized in time with successful removal on the initial biopsy attempt.

1.4 DISCUSSION

A variety of methods to aid in localizing mammographic nonpalpable lesions prior to surgery has been developed and they may be grouped into non-invasive and invasive techniques.

Non-invasive techniques employ geometrical coordinates, using the nipple as reference point either plotted on a diagram (4,8,9) or visibly marked on the skin (10). Others used stereomammograms (11) or visual and radiopaque external skin markers (12,13). Although this method may be suitable for lesions located superficially or adjacent to the nipple, in general, the technique lacks precision when dealing with deep lesions, especially in voluminous and pendulous breasts. This is caused by the difference in shape and position between the sitting posture during compression mammography and the surgical supine position. As a result of this, usually generous biopsies are obtained or segmentectomies (4,10,14) performed. In order to minimize the size of the excised specimen, several invasive techniques using internal markers have been advocated.

The percutaneous placement of single or multiple hypodermic or spinal needles have been described (1,15,16,17,18). The point of insertion of the needle(s) may be calculated according to the linear or the arc method (19,20). Needle placement may be facilitated by the use of a perforated grid compression device (6) or a stereotaxic instrument (21). Needles inserted perpendicular to the skin have the chance of accidentally
perforating the pleural cavity and one case of transgression into the chest has been reported (22). By placing the needle parallel to the chest wall this risk is reduced (23). The indwelling straight needles are usually introduced to its hub and taped to the skin. However, tape may come off if wet, during transport or surgical preparation, and a modified needle has been described which can be sutured to the skin to prevent dislodgement (24). The drawback of the fixation to the skin of any straight needle is that with compression the needle may be driven farther into the breast.

A way of overcoming the problem of needle motion and subsequent displacement is the spot method which consists of injecting a mixture of radiopaque and visible dye (25,26,27,28). A water-soluble contrast medium is preferable, because oily contrast agents may obscure the visualization of the tiny microcalcifications on specimen radiograms and, if not removed, may cause foreign body granulomas (25,26). The visible dye, methylene blue or Evans blue, serves as an internal surgical landmark (25,27,28,29). Because of gradual diffusion into the surrounding breast parenchyma, biopsy should follow within four hours of injecting the localizing visible dye (27). When blue dye enters mammary ducts, it may result in rapid dispersion, blurring the original spot.

Spherical marking is a different method, which is independent from the localization/operation interval. Through a wide bore needle, radiopaque internal markers are introduced like platinum coated gold grains (30) or small stainless steel balls (31). The disadvantage of this method is that proof of an appropriate biopsy and retrieval of the internal markers will not be seen by the surgeon until specimen radiography has been performed.

The needle localization technique has essentially been improved by the introduction of the Frank needle, a flexible guide wire which can firmly be anchored in the breast tissue by its barbed end (5). This method has gained widespread popularity (2,32-37) and some minor modifications have been
Accuracy in positioning of the marking wire may be increased by the perforated plexiglass compression plate and a combination of the Frank needle and the Mühlow localization technique (18) has been reported from Scandinavia (3,7,43,44). In order to ensure the introduction of the needle in the correct perpendicular direction, a special aiming device has been constructed, which can be placed on the compression plate over the appropriate hole (43).

Correct excision of the occult breast lesion on the first attempt has been reported between 78% and 100% in small series (2,3,31,34). Using the Frank needle for localization, Chetty et al (36) performed accurate excision at first attempt in 62 of 80 mammographic abnormalities (=78%). Rosen and Snyder (45) reported successful initial biopsies in 90 out of 98 non-palpable breast lesions (=92%), but the biopsies guided by preoperative mammography only were usually 'generous'. Powell et al (4) demonstrated that more than one biopsy was required in 33 out of 200 segmentectomies (=17%), decreasing to 4 out of 82 (=5%) when dye contrast injection was done prior to segmentectomy. However, the size of the segments removed was not indicated, but was said to be large.

Only a few authors mention the size of the biopsies. Taking generous blind biopsies in 52 patients because of clustered microcalcifications Roses et al (14) found an average maximal diameter of the specimens removed of 6.4 cm. Hoehn and co-workers (33,35), using the Frank needle, reported a mean volume of the excised tissue of 82.4 cm³, diminishing with increasing experience to 67.9 cm³, approximately a cube of 4.1 cm on each side.

In our series, about 80% of the occult mammary lesions were removed at first attempt with any method of localization. However, the size of the biopsies seemingly decreased, but did not differ significantly between the three groups studied. The lack of significance is caused by the wide range of the biopsy specimen volumes and this rather reflects the large biopsy specimens.
for deep-sited lesions in large-breasted women.

Failure to remove the mammographically suspicious area during the initial operation, despite multiple biopsies, has been reported to be from 1.6% to 8.8% (1,2,35,36,43-46).

Lack of communication between surgeon, radiologist, and pathologist has been considered a major potential cause of failure (1).

Our failure rate of 2.1% in a large series of 332 biopsies for occult breast lesions compares favourably with the above-mentioned figures. Furthermore, since three of the six repeated biopsies in our material yielded malignancy, the persistent presence of a radiographically suspect lesion on the post-operative mammogram is an urgent indication for re-operation.

1.5 SUMMARY

Three methods of excising nonpalpable breast lesions have been evaluated: 1. 'Blind' method using mammographic coordinates. 2. Preoperative localization with the Frank needle. 3. Frank needle localization aided by a multiperforated compression plate. Successful removal at first attempt occurred in about 80% with any method. The size of the biopsies did not differ significantly between the three groups and is most probably a function of the breast volume. The failure rate was seven out of 332 biopsies (2.1%). Since three of the six repeated biopsies yielded malignancy, the persistence of a radiographically suspicious lesion on follow-up mammogram of the operated breast is an urgent indication for re-operation.

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THE SIGNIFICANCE OF MICROCALCIFICATIONS WITHOUT PALPABLE MASS IN THE DIAGNOSIS OF BREAST CANCER

J.G.M. Tinnemans, Th. Wobbes, E.J.C. Lubbers
R.F. van der Sluis, H.H.M. de Boer

Surgery 1986; 99: 652-657

The radiologic and pathologic data used in this chapter are based on the studies of Dr. J.H.C.L. Hendriks and Dr. R. Holland from the Departments of Radiology and Pathology of the St. Radboud University Hospital in Nijmegen.
11.1 INTRODUCTION

During the past two decades, mammography has been established as an indispensable addition to complete evaluation of symptomatic women and as a valuable screening method to detect early breast cancer in asymptomatic adults. The surgeon is increasingly asked to remove clinically occult breast lesions to obtain a histologic diagnosis. The smallest among these nonpalpable mammographic lesions are the microcalcifications without an associated mass. This article presents our experiences as viewed by the clinician in excising these clinically occult microcalcifications and discusses its significance in relation to breast carcinoma.

11.2 PATIENTS AND METHODS

The data of 150 consecutive female patients with nonpalpable clusters of microcalcifications without an associated mass treated between January 1, 1975, and December 31, 1983, at the St. Radboud University Hospital in Nijmegen, The Netherlands, formed the basis of our study. Eighty-five women were completely asymptomatic and detected by a single-view, mammographic, population-screening program conducted within the city of Nijmegen aimed at the entire female population older than 35 years of age (1). The remaining 65 patients attended because of breast complaints, but had no palpable mass associated with the radiographic calcifications.

Table 1 shows the reasons for mammography. The vast majority are women without symptoms found by population screening (52.5%). In 34 patients (21%) breast complaints, mainly mastodynia, were an indication for mammography. The others were patients with an increased risk of developing a breast malignancy and were under periodic mammographic checkup because of a known premalignant lesion such as
Table 1: Reasons for mammography in 162 operations

<table>
<thead>
<tr>
<th>Reason</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population screening</td>
<td>85</td>
<td>52.5</td>
</tr>
<tr>
<td>Mastodynia</td>
<td>34</td>
<td>21.0</td>
</tr>
<tr>
<td>Control 'premalignant lesion'</td>
<td>18</td>
<td>11.1</td>
</tr>
<tr>
<td>Mastectomy of contralateral breast</td>
<td>10</td>
<td>6.2</td>
</tr>
<tr>
<td>Other reasons</td>
<td>9</td>
<td>5.6</td>
</tr>
<tr>
<td>Carcinophobia</td>
<td>5</td>
<td>3.1</td>
</tr>
<tr>
<td>Positive family history</td>
<td>1</td>
<td>0.6</td>
</tr>
</tbody>
</table>

atypia (11.1%) or had a mastectomy of the contralateral breast in the past (6.2%).

Each woman received routine mammographic examination that consisted of craniocaudal and lateromedial views. Mammography was carried out with a molybdenum anode and a 0.3 mm focus. If necessary, small details could be visualized more accurately by microfocal spot magnification with a 0.1 mm focus.

The sole indication for biopsy was an isolated group of five or more microcalcifications per square centimeter. Thus a total of 173 groups of microcalcifications were excised and studied.

In 1977 a preoperative needle localization technique was introduced that used a flexible, self-retaining, hooked guide wire (2). Before then we performed 'blind' biopsies by calculating the three-dimensional distances on the mammogram. In the past few years, insertion of the wire was aided by a multiperforated plexiglass compression plate that was placed over the breast for the mammogram (3). The needle containing the wire could be inserted through the appropriate hole to the desired depth. The exact position of the wire tip was checked radiographically.

All operations have been performed under general
anesthetic. The surgeon then excised the area around the wire hook, and the specimen was always radiographed. After confirmation that the excised tissue contained the mammographic microcalcifications concerned, the specimen was sent to the pathologist who cut the tissue in slices, and these slices, arranged in proper order, were again radiographed. Sometimes, frozen section was possible, but often the definitive diagnosis had to be deferred until the paraffin sections were ready (4).

II.3 RESULTS

The 173 biopsies in 150 patients for multiple calcifications only were 13% of the total of 1329 breast biopsies performed on inpatients during this 9-year period.

Table 2: Histologic diagnosis of nonpalpable radiographic microcalcifications

<table>
<thead>
<tr>
<th>Lesion</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple fibrocystic disease</td>
<td>63</td>
<td>51.6</td>
</tr>
<tr>
<td>Mastopathy with atypia</td>
<td>31</td>
<td>25.4</td>
</tr>
<tr>
<td>Papillomatosis</td>
<td>18</td>
<td>14.8</td>
</tr>
<tr>
<td>Fibroadenoma</td>
<td>8</td>
<td>6.6</td>
</tr>
<tr>
<td>Hyperestrogenic effects</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Normal mammary tissue</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Malignant lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive ductal carcinoma</td>
<td>19*</td>
<td>37.3</td>
</tr>
<tr>
<td>Invasive lobular carcinoma</td>
<td>2</td>
<td>3.9</td>
</tr>
<tr>
<td>DCIS</td>
<td>22</td>
<td>43.1</td>
</tr>
<tr>
<td>LCIS</td>
<td>7</td>
<td>13.7</td>
</tr>
<tr>
<td>Basal cell epithelioma</td>
<td>1</td>
<td>2.0</td>
</tr>
</tbody>
</table>

* Including one patient with Paget's disease
In 20 patients, more than one group of microcalcifications had been excised: 17 patients had two clusters, and 3 patients had three clusters of microcalcifications removed.

In 11 patients two clusters of x-ray film calcifications had been removed within one operation: five times from the same breast and six times from both breasts. Thus 162 operations were required to have the 173 mammographic lesions removed.

The left to right ratio was 1.40 : 1.00. Most x-ray film calcifications were located in the upper outer quadrants of the breasts (41.6%) or centrally behind the nipple (22%). The lower inner quadrants were a less frequent site (8.7%).

As shown in Table 2 benign breast lesions were noted in 122 biopsies, or 70.5% of the total group.

In 63 cases it comprised simple fibrocystic disease without epithelial proliferation. Papillomatosis and the presence of atypical ductal or lobular hyperplasia were encountered 49 times (40.2% of all benign biopsies).

Table 2 also shows the distribution of the malignancies. Fifty-one malignant lesions (29.5% of all biopsies) were found in 47 patients (31.3% of all patients). Four patients had two malignancies: one patient was found to have a ductal carcinoma with early invasion at two different places of the same breast. Another patient with lobular carcinoma in situ (LCIS) was kept under regular physical and radiographic control; three years later she had microcalcifications in another quadrant of the same breast that again proved to be LCIS.

Two patients had bilateral nonpalpable malignancies: one patient with ductal carcinoma in situ (DCIS) in both breasts and one patient with an invasive ductal carcinoma on one side and a LCIS on the other side.

DCIS was seen most frequently (22 cases, or 43.1% of all malignancies). If LCIS is included, all 29 noninvasive cancers account for 56.8 of the malignant biopsies.

Invasive ductal carcinoma was encountered 19 times
(37.3% of the malignancies); invasive lobular carcinoma was the least frequent cancer and was seen in only two cases (3.9%).

In Figure 1 the age distribution of the patients at the time of the 162 operations is given. The mean age was 50.2 years (range 19 to 73 years).

Breast cancer has not been found in any of the 17 patients under the age of 40 years who had a biopsy for nonpalpable microcalcifications.

From 1975 to 1977, the treatment policy at the St. Radboud University Hospital for invasive carcinoma and DCIS consisted of radical mastectomy for lateral tumors and simple mastectomy followed by irradiation of the regional lymph nodes for medial and central tumors. Since 1977 the primary surgical treatment has shifted toward modified radical mastectomy, including an infraclavicular apical biopsy.

Thus only 14 patients with nonpalpable invasive breast cancer and 13 patients with nonpalpable DCIS had a fully evaluable axillary status. In three cases (11.1%) there were regional or distant metastases (Table 3).

One patient with an invasive ductal carcinoma with a
Table 3: Axillary status of nonpalpable radiographic microcalcifications

<table>
<thead>
<tr>
<th></th>
<th>Evaluable axillary lymph nodes</th>
<th>Positive lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive carcinoma</td>
<td>20 14</td>
<td>3</td>
</tr>
<tr>
<td>Noninvasive carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCIS</td>
<td>22 13</td>
<td>0</td>
</tr>
<tr>
<td>LCIS</td>
<td>7 0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Including one patient with distant metastases

pathologic diameter of 30 mm had three positive lymph nodes of 25 axillary nodes found: one minimal localization at level 3 and two with extranodal localizations at level 2.

The second patient had an invasive lobular carcinoma with a pathologic size of 80 mm, and four of 34 nodes contained secondary tumors: two at level 3 and two at the interpectoral level.

The third patient was first discovered because of a pathologic fracture of the sternum. There were no palpable findings in the breasts or the axillae. Mammography disclosed a group of microcalcifications in a typical triangular configuration, and at biopsy an invasive ductal carcinoma was found. Results of both sternal and crista biopsies showed the same type of cancer cells.

II.4 DISCUSSION

Although Albert Salomon (5), a surgeon in Berlin, discovered in 1913 that x-ray film calcifications are associated with breast cancer, it was not until the 1930s that the first reports appeared on the clinical use of mammography (6,7). After Raúl Leborgne (8), a radiologist
in Montevideo, described in 1951 a radiologic technique that made it possible to visualize tiny microcalcifications, modern mammography has developed further in the past decades by the introduction of the molybdenum anode, the so-called low-dose screen-film combination, and recently by the use of 0.1 mm microfocus, which allows focal spot magnification of 1.5 to 2 times.

Microcalcifications contain calcium hydroxyapatite or tricalcium phosphate (9,10) and are considered a secretion product of increased cellular activity in the lobuloductal complex (11) rather than the result of mineralization of necrotic cellular debris.

The appearance of the microcalcifications varies in size, shape, density, number, and distribution, and accordingly the level of suspicion of malignancy may increase or decrease. For example, very fine calcifications that vary greatly in form (polymorphism) are considered a clue to the presence of carcinomas (12). On the other hand, coarse-plaqued calcifications that appear on the lateral film as sickle- or linear-shaped configurations are regarded as typical 'tea-cups' corresponding with benign microcysts filled with calcium milk (13). A marked increase in the number of microcalcifications compared with previous examinations favors the diagnosis of malignancy (14). On the basis of the anatomy of the lactiferous ducts, a triangular configuration of grouped microcalcifications has diagnostic significance in respect of DCIS (15).

Even though several attempts have been made to differentiate radiologically between benign and malignant calcifications (16-18), most investigators found no conclusive difference between mammograms of patients with benign or malignant biopsies when films were analyzed for size, shape, and radiographic density of individual or clustered calcifications (12,19-21). The only exception is that none of the malignant clusters contained less than five calcifications (12,21,22), although in extremely rare cases even carcinomas with less than five microcalcifications have been
Table 4: Review of literature of microcalcifications without palpable mass

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of nonpalpable microcalc.</th>
<th>No. of carcinoma</th>
<th>% of carcinoma</th>
<th>No. of invasive carcinoma</th>
<th>No. of noninvasive carcinoma</th>
<th>No. of lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rogers &amp; Powell, 1972 (22)</td>
<td>46</td>
<td>19</td>
<td>41.3</td>
<td>5</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Murphy &amp; DeSchryver-Kecskemeti, 1978 (19)</td>
<td>15</td>
<td>7</td>
<td>46.7</td>
<td>3</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Roses et al, 1980 (29)</td>
<td>52</td>
<td>17</td>
<td>32.7</td>
<td>10</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Lányi &amp; Citoler, 1981 (18)</td>
<td>135</td>
<td>36</td>
<td>26.7</td>
<td>0</td>
<td>33</td>
<td>3</td>
</tr>
<tr>
<td>Colbassani et al, 1982 (20)</td>
<td>55</td>
<td>15</td>
<td>27.3</td>
<td>8</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Hoehn et al, 1982 (36)</td>
<td>26</td>
<td>4</td>
<td>15.4</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Powell et al, 1983 (21)</td>
<td>282</td>
<td>47</td>
<td>16.7</td>
<td>11</td>
<td>26</td>
<td>10</td>
</tr>
<tr>
<td>Chetty et al, 1983 (24)</td>
<td>103</td>
<td>25</td>
<td>24.3</td>
<td>10</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Meyer et al, 1984 (25)</td>
<td>203</td>
<td>45</td>
<td>22.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present series</td>
<td>173</td>
<td>51</td>
<td>29.5</td>
<td>21</td>
<td>22</td>
<td>7</td>
</tr>
</tbody>
</table>
reported (23). Thus microcalcifications on the mammogram are not pathognomonic of carcinoma, but represent a high-risk area of the breast that requires a biopsy for histologic examination.

For the entire procedure, including preoperative localization, close cooperation is required between the surgeon, radiologist, and pathologist. A postoperative mammogram should be performed if there is doubt concerning the actual removal of the grouped microcalcifications in question.

A search of the literature revealed that only a few large series of nonpalpable calcifications have been published so far (Table 4). The malignancy rate in those reports varies between 15% and 46% in mostly small series and from 16% to 26% in the larger series (18,21,24,25). Our malignancy rate of 29.5% compares favorably with these figures.

Breast cancers detected by mammography alone and that are nonpalpable are more often noninvasive, smaller in size, and more often associated with negative axillary nodes than those that presented with a palpable mass (24,26,27). The same seems to apply to nonpalpable malignant calcifications. Powell et al (21) showed in their large series that 36 (77%) of the total number of 47 cancers were noninvasive: 26 were DCIS and 10 were LCIS. In our series of 51 cancers, 29, or more than half (56.8%), were also noninvasive: 22 DCIS and seven LCIS.

Many of those breast tumors that are invasive have no nodal extension. Positive axillary nodes vary in the literature between 2% and 25% (20-22,26,28,29). We found axillary involvement or distant metastases in 11% of the fully evaluable axillae, which warrants the expectation that this group of occult breast cancers might have a better prognosis.

It should be noted that no nonpalpable microcalcifications proved to be malignant on histopathologic examination in patients younger than 40 years of age. Moreover, in the Breast Cancer Detection Demonstration Project, sponsored by the American Cancer Society, the rate of breast cancer in the
35- to 39-year-old age-group was extremely low (30). However, in Egan's (12) series 12% of all biopsy-proved malignant calcifications were detected in the 30- to 39-year-old age-group. Apparently, the age of the woman is not helpful in differentiating benign from malignant lesions.

After biopsy of the suspicious occult calcifications and subsequent histologic examination of the radiographed and fixed specimens, no malignancy could be found in 70.5% of our biopsies. In half of the cases (51.6%), the microcalcifications were associated with simple fibrocystic disease. However, in one quarter of the benign biopsies (25.4%), mastopathy with cell atypia was found, while papillomatosis was the final diagnosis in 18 biopsies (14.8%). This means that 40.2% of the benign biopsies showed some degree of proliferative unrest. The risk of subsequent development of breast cancer among women whose benign biopsies showed some degree of hyperplastic lesions or atypical changes ranges from two to five times that of the general population (31-33). Since 'epithelial proliferative disease of the breast' (33) is predictive of increased subsequent risk, we see these patients every six months for a physical and annually for radiographic follow-up.

Calcifications are more commonly found in DCIS and less frequently within the LCIS (34), since in LCIS the calcifications, if present, are localized in adjacent benign fibrocystic tissue (35).

Clustered punctate calcifications without an associated mass on the mammogram in the absence of any clinical findings is the earliest possible sign of breast cancer. To a physician it is almost axiomatic that detection at this 'early' stage would result in a better prognosis for the patient. However, caution is required in drawing this conclusion because of the effect of lead time and length time bias inherent in screening. The low rate of positive axillary nodes is promising and may indicate an early stage of disease, but the results of additional long-term survival studies have to be awaited.
II.5 SUMMARY

Microcalcifications constitute an important part of nonpalpable breast lesions and may be the first sign of a breast carcinoma. Between 1975 and 1984, 150 consecutive patients with clusters of at least five microcalcifications without palpable findings as the only indication for biopsy were treated. One hundred seventy-three groups of microcalcifications were excised and 51 malignancies were detected (29.5%). Most of the malignant lesions were noninfiltrating (56%). Axillary or distant metastases occurred in 11% of the fully evaluable cases. This warrants the expectation that these patients have a very favorable prognosis. Breast biopsy for nonpalpable-clustered microcalcifications is a feasible and valuable procedure. Close cooperation is required between the surgeon, radiologist, and pathologist.

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Chapter III

MAMMOGRAPHIC-HISTOPATHOLOGIC CORRELATION OF NONPALPABLE BREAST LESIONS AND THE RELIABILITY OF THE FROZEN SECTION DIAGNOSIS


Surg Gynecol Obstet, accepted for publication
III.1 INTRODUCTION

The surgeon who is going to perform a breast biopsy is faced with a decision-making problem. Although other risk factors have also to be taken into account he will heavily depend upon the report of the pathologist. In the past frozen section examination has proved to be a highly reliable method in breast biopsies because of palpable lesions (1,2). Thus in case of malignancy the biopsy could be followed by mastectomy or breast conserving surgery in the same session (one-stage procedure) instead of awaiting the routine paraffin section report and performing further surgery at a later date (two-stage procedure).

We have undertaken to review our 10-years experience with nonpalpable breast lesions and the place of the frozen section diagnosis.

III.2 MATERIALS AND METHODS

The data of 359 biopsies performed because of clinically occult mammographic lesions form the basis of this study. All patients were treated at the St. Radboud University Hospital, Nijmegen, The Netherlands, in the period between 1.1.1975 and 1.1.1985. Almost half of them were detected as a result of an ongoing population screening programme and the greater half were referred to the surgical out-patients' department as a result of individual screening.

The 359 mammographic abnormalities occurred in 321 patients: 287 patients had one biopsy, there were 30 patients with two biopsies and 4 patients with three biopsies. These 321 patients underwent 346 operations since in 13 cases two mammographic lesions were excised during the same operation. All patients were female. All case-sheets were checked for the following items: age of the patient, year of the diagnosis, character and site of the mammographic lesion(s), reason of mammography, whether or not frozen section was performed, in
which cases the initial frozen section diagnosis was deferred to the permanent sections and the final paraffin section report.

In all but one confirmation was obtained, almost exclusively by specimen radiography and in a few cases by post-surgical repeat mammography that the correct mammographic abnormality had been excised. In principle frozen section was performed guided by the radiogram of the in toto or sliced specimen (3). When any doubt existed a provisionary report was given but the definitive diagnosis was deferred to the paraffin sections. In recent years frozen section was not performed anymore in all cases with microcalcifications only or with very small solid tumours of less than 5 mm (4). The data presented here do not refer to the number of patients, but to the number of specimens examined.

III.3 RESULTS

The 359 biopsies in 321 patients for nonpalpable breast lesions constituted 24.3% of the total of 1475 breast biopsies performed on in-patients during this 10-year period.

Clinically occult cancer was proved in 118 biopsies representing a malignancy rate of 32.9%. Since 1982 the predictive value positive of the mammographic breast cancer test (= number of screen-detected cancers/number of biopsies) has increased considerably up to 68% in 1984 (Figure 1).

Table 1 shows the reasons for mammography. The malignancy rate of the biopsies amongst the population-screened women is 35.6% and similar to the 30.3% of the biopsies in women discovered by individual screening.

The age distribution is shown in Figure 2. The patients with benign biopsies had an average age of 49.8 years (range 19 to 75), while patients with malignant biopsies had an average age of 57.2 years (range 37 to 76). Below the age of 40 years no malignancy was encountered except for one patient with lobular carcinoma in situ (LCIS). As can be seen from the
Figure 1: Predictive value of the mammographic breast cancer test (predictive value positive) = number of screen detected breast cancer cases/number of biopsies

![Graph showing predictive value over time from 1976 to 1984.]

Figure 2: Age distribution of benign and malignant biopsies because of nonpalpable mammographic lesions

![Bar chart showing age distribution of biopsies by type of lesion.]

*Note: The bar chart shows the total number of biopsies performed and the distribution by type of lesion: invasive carcinoma, ductal carcinoma in situ, lobular carcinoma in situ, and others. The age distribution is indicated on the x-axis with the number of cases per 10-year age group.
Table 1: Reasons for mammography in 359 biopsies because of clinically occult breast lesions

<table>
<thead>
<tr>
<th>Reason</th>
<th>Total Number</th>
<th>Number Malignant</th>
<th>Percentage Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population screening</td>
<td>174</td>
<td>62</td>
<td>35.6</td>
</tr>
<tr>
<td>Individual screening</td>
<td>185</td>
<td>56</td>
<td>30.3</td>
</tr>
<tr>
<td>Breast complaints</td>
<td>99</td>
<td>28</td>
<td>28.3</td>
</tr>
<tr>
<td>Control 'premalignant lesions'</td>
<td>33</td>
<td>16</td>
<td>48.5</td>
</tr>
<tr>
<td>Contralateral mastectomy</td>
<td>27</td>
<td>8</td>
<td>29.6</td>
</tr>
<tr>
<td>Carcinophobia</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Positive family history</td>
<td>3</td>
<td>2</td>
<td>66.7</td>
</tr>
<tr>
<td>Other reasons</td>
<td>14</td>
<td>2</td>
<td>14.3</td>
</tr>
</tbody>
</table>

same histogram the malignancy rate increases with the higher age groups. Below 55 years of age there were 50 malignancies in 221 biopsies representing 22.6%, while in patients of 55 years and over 68 malignancies or 49.3% were found out of 138 biopsies. The average age of the patients with invasive breast cancer is 59.8 years (range 42 to 76) and in patients with non-invasive breast cancer (ductal carcinoma in situ = DCIS, and LCIS) the average age is 52.1 years (range 37 to 68).

The location of the nonpalpable breast lesions is presented in Table 2. The upper outer quadrant was by far the commonest site containing 46.2% of the biopsies and 50.8% of the malignancies. The lower inner quadrant was the least frequent location. The left/right ratio was 1.22 for the biopsied mammographic abnormalities and 1.19 for the occult cancers.

Table 3 shows that the majority of the mammographic lesions consists of clustered microcalcifications only: 188 or 52.4% of all lesions. The malignancy rate of different mammographic lesions varies greatly. When a stellate-shaped
Table 2: Location of 359 nonpalpable breast lesions

<table>
<thead>
<tr>
<th>Quadrant</th>
<th>Number of biopsies</th>
<th>Number of malignancies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>Central</td>
<td>28</td>
<td>35</td>
</tr>
<tr>
<td>Upper outer</td>
<td>80</td>
<td>86</td>
</tr>
<tr>
<td>Upper inner</td>
<td>28</td>
<td>41</td>
</tr>
<tr>
<td>Lower outer</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>Lower inner</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>162</td>
<td>197</td>
</tr>
</tbody>
</table>

mass is detected, two out of every three biopsies proves to be malignant. In case of microcalcifications with or without a non-spiculated density the malignancy rate is 28.6% and 32.4%. A circumscribed or nodular density yields a malignancy in 12.7% only.

The histology of the benign biopsies is given in Table 4. Of 241 benign biopsies 120 or 49.8% show simple fibrocystic disease. In 86 cases or 35.7% there was some form of proliferative unrest: 56 biopsies or 23.2% showed fibrocystic disease with atypia and 30 times or 12.5% the diagnosis was papillomatosis. Fibroadenoma occurred in 27 or 11.2% of the biopsies. Noteworthy is the fact that benign scar tissue may manifest itself as a stellate-shaped mass.

In Table 5 the histology of the malignant biopsies is presented in correlation with the mammographic findings. Of the whole group of 118 malignant biopsies 59 (50.0%) were infiltrating carcinomas, either ductal or lobular, including one patient with Paget's disease with infiltrating ductal cancer. Well-differentiated tubular carcinoma was a frequent finding (17 cases or 14.4%) of which 14 cases were detected as a stellate-shaped mass. There were 40 non-invasive breast cancers (33.9%): 32 DCIS and 8 LCIS. Of these 40 non-invasive carcinomas 33 occurred in the group with microcalcifications.
Table 3: Mammographic-histopathologic correlation in 359 non-palpable breast lesions

<table>
<thead>
<tr>
<th>Mammography</th>
<th>Total number</th>
<th>Number malignant</th>
<th>% malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circumscribed or nodular mass</td>
<td>71</td>
<td>9</td>
<td>12.7</td>
</tr>
<tr>
<td>Clustered microcalcifications</td>
<td>188</td>
<td>61</td>
<td>32.4</td>
</tr>
<tr>
<td>Mass with microcalcifications</td>
<td>49</td>
<td>14</td>
<td>28.6</td>
</tr>
<tr>
<td>Stellate-shaped mass</td>
<td>51</td>
<td>34</td>
<td>66.7</td>
</tr>
<tr>
<td>Total</td>
<td>359</td>
<td>118</td>
<td>32.9</td>
</tr>
</tbody>
</table>

only: 26 DCIS and 7 LCIS. Of note is also the fact that no in situ cancers were found in the group with the stellate-shaped mass. Others (1.7%) included one case of basal cell carcinoma of the skin and one patient with a non-Hodgkin's lymphoma.

Table 6 gives the correlation between the peroperative frozen sections and the final paraffin sections. No frozen sections were performed in 62 cases (17.3%), mostly when microcalcifications alone were present (47 biopsies) or when the circumscribed density was too tiny (10 biopsies). In only a few cases no frozen section was done on patient's request. On the basis of the 62 paraffin sections 7 invasive and 17 non-invasive cancers were diagnosed, most of them belonging to the group with microcalcifications only: 4 x invasive carcinoma and all 17 non-invasive carcinomas (14 x DCIS and 3 x LCIS).

In 44 occasions (12.2%) frozen section was performed but the definitive diagnosis deferred until the paraffin sections were ready. In 22 cases (50% of the deferrals) there was some degree of proliferative unrest: 18 times a proliferative lesion with atypia and 4 times papillomatosis. In 11 cases (25% of the deferrals) malignancy was the final diagnosis: 3 x invasive cancer, 4 x DCIS, 3 x LCIS and 1 x malignant lymphoma.
Table 4: Histology of benign biopsies

<table>
<thead>
<tr>
<th>Histology</th>
<th>Circumscribed or clustered mass</th>
<th>Mass with microcalc.</th>
<th>Stellate-shaped mass</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Simple fibrocystic disease</td>
<td>30</td>
<td>48.4</td>
<td>65</td>
<td>51.2</td>
</tr>
<tr>
<td>Fibrocystic disease with atypia</td>
<td>13</td>
<td>21.0</td>
<td>33</td>
<td>26.0</td>
</tr>
<tr>
<td>Papillomatosis</td>
<td>7</td>
<td>11.3</td>
<td>18</td>
<td>14.1</td>
</tr>
<tr>
<td>Fibroadenoma</td>
<td>10</td>
<td>16.1</td>
<td>9</td>
<td>7.1</td>
</tr>
<tr>
<td>Inflammation</td>
<td>1</td>
<td>1.6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Post-biopsy scar tissue</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Others</td>
<td>1</td>
<td>1.6</td>
<td>2</td>
<td>1.6</td>
</tr>
<tr>
<td>Total</td>
<td>62</td>
<td>100.0</td>
<td>127</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Table 5: Histology of malignant biopsies

<table>
<thead>
<tr>
<th>Histology</th>
<th>Circumscribed or nodular mass</th>
<th>Clustered microcalc.</th>
<th>Mass with microcalc.</th>
<th>Stellate-shaped mass</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Infiltrating carcinoma</td>
<td>5</td>
<td>55.6</td>
<td>24</td>
<td>39.4</td>
<td>9</td>
</tr>
<tr>
<td>(ductal or lobular)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubular carcinoma</td>
<td>1</td>
<td>11.1</td>
<td>2</td>
<td>3.3</td>
<td>-</td>
</tr>
<tr>
<td>M. Paget with infiltrating ductal carcinoma</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1.6</td>
<td>-</td>
</tr>
<tr>
<td>DCIS</td>
<td>2</td>
<td>22.2</td>
<td>26</td>
<td>42.6</td>
<td>4</td>
</tr>
<tr>
<td>LCIS</td>
<td>-</td>
<td>-</td>
<td>7</td>
<td>11.5</td>
<td>1</td>
</tr>
<tr>
<td>Others</td>
<td>1</td>
<td>11.1</td>
<td>1</td>
<td>1.6</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>100.0</td>
<td>61</td>
<td>100.0</td>
<td>14</td>
</tr>
</tbody>
</table>

DCIS = ductal carcinoma in situ
LCIS = lobular carcinoma in situ
Table 6: Concordance between frozen and paraffin sections in biopsies performed because of nonpalpable mammographic lesions

<table>
<thead>
<tr>
<th>Histology</th>
<th>Mammography</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Circumscribed or</td>
<td>Clustered</td>
<td>Mass with</td>
<td>Stellate-</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>nodular mass</td>
<td>microcalc.</td>
<td>microcalc.</td>
<td>shaped mass</td>
<td>No.</td>
</tr>
<tr>
<td></td>
<td>No.   %</td>
<td>No.   %</td>
<td>No.   %</td>
<td>No.   %</td>
<td>No.   %</td>
</tr>
<tr>
<td>Correct diagnosis:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>benign</td>
<td>44 62.0</td>
<td>84 44.7</td>
<td>28 57.1</td>
<td>12 23.5</td>
<td>168 46.8</td>
</tr>
<tr>
<td>malignant</td>
<td>5 7.0</td>
<td>29 15.4</td>
<td>10 20.4</td>
<td>32 62.7</td>
<td>76 21.2</td>
</tr>
<tr>
<td>False positive</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>2 3.9</td>
<td>2 0.6</td>
</tr>
<tr>
<td>False negative</td>
<td>0 0</td>
<td>4 2.1</td>
<td>2 4.1</td>
<td>1 2.0</td>
<td>7 1.9</td>
</tr>
<tr>
<td>Deferred</td>
<td>12 16.9</td>
<td>24 12.8</td>
<td>5 10.2</td>
<td>3 5.9</td>
<td>44 12.2</td>
</tr>
<tr>
<td>No frozen section</td>
<td>10 14.1</td>
<td>47 25.0</td>
<td>4 8.2</td>
<td>1 2.0</td>
<td>62 17.3</td>
</tr>
<tr>
<td>Total</td>
<td>71 100.0</td>
<td>188 100.0</td>
<td>49 100.0</td>
<td>51 100.0</td>
<td>359 100.0</td>
</tr>
</tbody>
</table>

- Sensitivity: 100.0
- Specificity: 100.0
- Accuracy: 100.0
A correct diagnosis, whether benign or malignant, was achieved with frozen section technique in 244 biopsies or 68.0%.

False negative reports constituted 1.9% (7 cases) of the total number of biopsies: 2 x invasive carcinoma of which one tubular carcinoma, 2 x DCIS, 2 x LCIS and 1 x basal cell carcinoma.

In 2 cases a false positive report had been given. Both were radiographically characterized by a spiculated mass. One patient was reported to have a LCIS and underwent no further surgery. Paraffin section diagnosis revealed a 4 mm focus of sclerosing adenosis and no further abnormalities.

The second report had more serious consequences. Frozen section diagnosis was an extensive intraductal cancer without clear signs of invasive growth (DCIS). After an infraclavicular apical biopsy had revealed no signs of secondaries a radical mastectomy was performed in the same session because of violation of the underlying pectoralis fascia during excision of the deep lying radiographical density. On permanent paraffin sections five locations of a so-called 'radial scar lesion' were found in several quadrants and foci of intraductal epithelial proliferations with severe atypia. There was no invasive growth and all lymph nodes were free of disease.

III.4 DISCUSSION

In recent years evidence is emerging that mammographic screening may reduce the risk of dying from breast cancer (5-9). As a result of this there is a justifiable growing demand for more radiographical services for early detection of breast cancer both from the public and the medical profession. Consequently, clinicians will increasingly be confronted with nonpalpable mammographic lesions. Leaving apart the surgical problem of correctly removing the tiny abnormalities the attending doctor will like to know the 'yield' of these biopsies.
In our series the malignancy rate is 32.9% and compares favourably with the frequencies in other large series: 18.2-28.9% (10-14). The malignancy rate rises with increasing age and also depends upon the type of mammographic abnormality. The lowest figures of malignancy were found in the group with a nodular or circumscribed mass and the highest in the group with the stellate-shaped masses. Calcifications yielded intermediate results which is in accordance with the tendency in other smaller series (11,14).

A peculiar finding was the sudden increase of the predictive value positive since 1982. Since all mammograms had been reported by the same radiologist this may partly be due to increasing experience. Another influencing factor may be the advent in January 1982 of technical improvements like a mammographic grid and a microfocus of 0.09 mm allowing a magnification of 1.5 to 2 times and visualizing more details. Echography has only seldom been used by us in nonpalpable breast lesions because its resolution of ½ to 1 cm is often unable to differentiate between small solid masses and cysts, especially in fatty breast tissue.

Suspicious mammograms detected by population or individual screening have a similar predictive value positive. This means that suspicious mammograms should be considered on its own merits and should not be influenced by the fact that they belong to women in certain high-risk groups. Fear seems to be a bad adviser as no woman with carcinophobia in this small series had cancer.

The left/right ratio of the occult cancers is 1.19 which is in agreement with the left predominance of breast carcinoma reported by others (15). An explanation of the phenomenon is that the occurrence of breast cancer is tissue volume dependent. Measuring the relative breast volume from the mammogram in asymptomatic women the left breast was larger in 55% (15). The same explanation applies to the predominance of carcinoma in the upper outer quadrant, which is largest.

The non-invasive cancer patients in our study are on
average 7.7 years younger than the patients with invasive cancer. This age discrepancy supports the view that in situ cancer is a pre-invasive lesion in a transitory stage of malignant transformation into invasive cancer. Other support for this view is found in retrospective studies of pre-invasive ductal carcinoma treated by biopsy only and revealing a subsequent development into invasive carcinoma in 28-67% (16-17).

Of interest is the fact that 35.7% of the benign biopsies showed some degree of proliferative unrest. The risk of subsequent development of breast carcinoma amongst patients with atypical proliferative lesions is two to five times higher than that of the general population (18-20). That is why we are following these women with physical examination every six months and an annual mammogram.

Cheek and Sears found surprisingly only three DCIS in 57 carcinomas as a result of 314 biopsies because of non-palpable mammographic lesions (10). Others reported a much higher frequency of 40.3-72.7% pre-invasive or in situ lesions amongst occult breast cancers (11-13). Considering our 118 malignant biopsies, 40 or 33.9% of these were non-invasive and 38 of them had calcifications with or without an associated mass. So clustered microcalcifications represent an earlier stage of disease than the other types of mammographic abnormalities like circumscribed densities and spiculated masses do (21).

Through the greater use of x-ray mammography the relatively infrequent occurrence of the slow growing tubular carcinoma with a favourable prognosis has risen from 2% to 9% in a screening setting including both palpable and non-palpable tumours (22,23). In the latter series there were 9 tubular carcinomas in 62 occult cancers representing 14.5%. Also in our experience of the 118 non-palpable cancers 17 or 14.4% were tubular carcinomas and 14 of them became visible as a stellate mass on x-ray which can be explained by its nature of a strong desmoplastic stroma and infiltrating margins. The high rates of non-invasive and low grade tubular carcinomas
both contribute to the length bias inherent in screening. In contrast, fast growing tumours are relatively more often diagnosed clinically between two screening examinations as so-called interval cancers and different growth rates have been calculated for screen-detected interval cancers (24).

The reliability of frozen section diagnosis of breast biopsies because of palpable findings is well established (2,25). In biopsies for non-palpable breast lesions, however, frozen section interpretation is considered to be difficult and is therefore not advocated by some authors (11,14). Only Cheek and Sears reported in their series of 314 biopsies that 47 of the 57 occult cancers were diagnosed at the time of surgery by frozen section examination after specimen radiography had confirmed the lesion (10). Indeed specimen x-ray and comparison with the original mammogram are essential prerequisites in order to ascertain proper removal of the suspicious lesion. Moreover, its position in the sliced tissue can be determined radiographically when grossly no obvious suspicious lesion appears (3). In our hands the rate of false negative reports is 1.9%. Rosen who reviewed 556 consecutive breast biopsies had 1.4% false negatives (25). However, the two series are not fully comparable since in our series for clinically occult lesions alone diagnosis was delayed or no frozen section performed in 29.5% of the cases while Rosen had only 5.4% of his (mostly palpable) biopsies deferred to permanent sections.

False negative frozen section examination will do no harm provided a definite diagnosis will be given on the basis of the paraffin sections. Patients have to be cautioned by their attending surgeon that a frozen section diagnosis of benignancy is always provisional and that the final paraffin sections have to be awaited.

Great care must be taken against false positive reports and in case of the faintest doubt expressed by the pathologist the option of deferment should prevail. In this respect the so-called radial scar lesion, which is a form of florid
sclerosing ductal adenosis, may pose diagnostic problems.

As breast conserving surgery is gaining more and more acceptance the criteria for selection of patients for this treatment method are becoming more important. Accordingly, it is nowadays not sufficient anymore to know whether the biopsy shows malignancy or not, but more data are required like histological size and type, the extent of the intraductal component of the tumour, the differentiation of the tumour and adequacy of surgical excision (26). That is why in recent years a shift has begun towards a two-stage procedure, i.e. a diagnostic breast biopsy specimen is first studied with permanent sections before definitive therapeutic alternatives are discussed with the patient (27).

III.5 SUMMARY

Of 359 biopsies in 321 patients because of nonpalpable mammographic lesions 118 or 32.9% proved to be malignant. Approximately half of the lesions were located in the upper outer quadrant. The left/right ratio was 1.22 for biopsies and 1.19 for occult cancers. The malignancy rate was 12.7% in case of a circumscribed or nodular mass, 32.4% for clustered microcalcifications only, 28.6% when a mass with microcalcifications was found and 66.7% when a stellate-shaped mass was present. Seventy-six were invasive breast cancers of which 17 tubular carcinomas. There were 40 non-invasive breast cancers: 32 DCIS and 8 LCIS, the great majority of them belonging to the group with clustered microcalcifications only. Others included one case of non-Hodgkin's lymphoma and one case of basal cell carcinoma of the skin. The average age of patients with invasive breast cancer was 59.8 years (range 42-76) and in patients with non-invasive breast cancer 52.1 years (range 37-68).

Frozen section examination was correlated with the final paraffin section report and a correct diagnosis was achieved in 68.0%. No frozen section examination was performed in 17.3%.,
and in 12.2% the diagnosis was deferred to the paraffin sections. False negative reports were encountered in 7 cases (1.9%) and false positives in 2 (0.6%), both of them cases of florid sclerosing adenosis. Provided the pathologist is not reluctant to defer a diagnosis to the permanent paraffin sections the frozen section method is a feasible and reliable procedure, even in nonpalpable breast lesions. Specimen radiography of the in toto or sliced biopsy is, however, mandatory. It is probably prudent not to use this method for pure microcalcifications and very tiny solid masses of 5 mm and less.

It is discussed that modern breast conserving surgery requires more histopathological details (type of tumour, other foci around the reference tumour and whether or not the surgical margins of the excisional biopsy or segmentectomy are free). Frozen section examination often cannot meet these new requirements and one has to rely upon the definitive paraffin sections in a two-stage procedure.

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Chapter IV

STEROID-HORMONE RECEPTORS IN NONPALPABLE BREAST CANCER; A CONTRIBUTION TO THE BIOLOGY AND NATURAL HISTORY OF CARCINOMA OF THE FEMALE BREAST

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L.V.A.M. Beex, H.H.M. de Boer

Submitted
IV.1 INTRODUCTION

The determination of oestrogen (ER) and progesterone receptor (PgR) activity in primary and metastatic breast cancer is nowadays standard medical practice since steroid-hormone receptors represent valuable prognostic indicators along with nodal status and tumour size (1-3). Hypothetically, it is assumed that all breast cancers are hormone-dependent from the beginning. In the course of their tumour life they dedifferentiate losing endocrine responsiveness and becoming increasingly receptor-negative. To our knowledge no studies have ever reported the receptor activities in subclinical or nonpalpable breast cancer. From a tumour biological point of view it would be interesting to know whether the above stated hypothesis is valid in light of the fact that nonpalpable breast tumours differ from the palpable ones by their lead time which has been calculated at three years (4,5).

IV.2 PATIENTS AND METHODS

All patients were diagnosed and treated at the St. Radboud University Hospital, Nijmegen, in the period between 1974 and July, 1986.

Four groups of patients were studied for steroid receptor content in their tumour tissues. Firstly, patients with non-palpable primary breast cancer, i.e. clinically occult and detected by mammographical means only (n=62). Secondly, patients with palpable operable primary breast cancer, including those patients with tumour stages T_1-3 N_0-2 M_0 according to the TNM-classification (n=259). Thirdly, patients with locoregionally advanced primary breast cancer, i.e. any T_4 or N_3 with M_0 (n=73). The fourth group consisted of patients with metastatic breast cancer, whose receptor status was assessed at the time of their first relapse (n=58). The median disease-free interval of the latter group was 33 months. None of these patients had systemic adjuvant therapy in the past.
The breast cancer tissue specimens have all been processed at one laboratory for steroid receptor assays. ER and PgR concentrations were measured by the dextran-coated charcoal method with multiple-point Scatchard plot analysis as previously described from here (6). Only those assays with cytosol protein contents of >2 mg/ml were included. We considered the tissue specimen to be receptor-negative at a cut-off level of 10 fmol/mg protein, for both ER and PgR.

Statistical analysis was performed using Fisher's Chi Square test (P denoted by p) and Wilcoxon's two-sample test (P denoted by p*). The four groups of patients did not differ in mean age (p* >0.1) or menopausal status (p>0.1).

IV.3 RESULTS

Of 62 nonpalpable breast cancers ER-positivity was seen in 37 of 46 invasive ductal cancers (80.4%), in eight of 10 invasive lobular carcinomas (80%), and in three of six patients with ductal carcinoma in situ (50%). The PgR status was known in 57 of those 62 cancers and was positive in 33 of 43 patients with invasive ductal carcinoma (76.7%), eight of nine invasive lobular carcinomas (88.9%), and in none of the five in situ ductal carcinomas (0%).

With regard to the invasive cancers, ER activity was positive in 31 of 39 tumours with a diameter over 10 mm (79.5%), and in 14 of 17 tumours smaller than or equal to 10 mm (82.5%). PgR-positive tumours occurred in 30 of 36 available assays of invasive carcinomas >10 mm (83.3%), and in 11 of 16 invasive carcinomas ≤10 mm (68.8%).

The quantitative ER and PgR values of the 56 nonpalpable invasive breast cancers are given in Figure 1. The median ER level of 75 fmol/mg protein in postmenopausal women was significantly higher (p*<0.02) than the median ER level of 21 fmol/mg protein in premenopausal women. Conversely, the median PgR level of 62 fmol/mg protein in postmenopausal patients is lower than the median PgR value of 105 fmol/mg.
protein in premenopausal patients, but reached no statistical significance (\(p > 0.1\)).

Table 1 demonstrates the ER and PgR status of the tumours in groups of patients with a different stage of the disease. Both receptors were analysed in 52 of the 56 invasive nonpalpable breast cancers. In this group of patients with nonpalpable primary breast cancer 84.6% had an ER-positive tumour whereas in the group of metastatic breast cancer 68.9% of the tumours were classified as ER-positive (\(p < 0.05\)). For PgR, an even more striking loss of receptor activity was
TABLE 1: Steroid receptor assays in patients with primary (nonpalpable, palpable operable and locoregionally advanced) and (first) metastatic breast cancer

<table>
<thead>
<tr>
<th>Group</th>
<th>ER Positive</th>
<th>ER Negative</th>
<th>PgR Positive</th>
<th>PgR Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Nonpalpable primary breast cancer (n=52)</td>
<td>44</td>
<td>84.6</td>
<td>8</td>
<td>15.4</td>
</tr>
<tr>
<td>Palpable operable primary breast cancer (n=259)</td>
<td>180</td>
<td>69.5</td>
<td>79</td>
<td>30.5</td>
</tr>
<tr>
<td>Locoregionally advanced primary breast cancer (n=73)</td>
<td>49</td>
<td>67.1</td>
<td>24</td>
<td>32.9</td>
</tr>
<tr>
<td>First metastatic breast cancer (n=58)</td>
<td>40</td>
<td>68.9</td>
<td>18</td>
<td>31.1</td>
</tr>
</tbody>
</table>

observed: 78.8% PgR-positive tumours in the nonpalpable group via 64.5% in the palpable operable group and 58.9% in the locoregionally advanced group to only 46.6% in the metastatic group (p<0.005).

The observed shift in receptor phenotype was also seen when both receptors were considered simultaneously, as shown in Table 2: ER+ PgR+ tumours were observed in 71.1% of the patients in the nonpalpable breast cancer group, gradually decreasing to only 41.3% in the metastatic group (p<0.005). Er- PgR- tumours increased from 7.7% in the nonpalpable group to 25.8% in the metastatic group (p<0.02). The remaining phenotypes ER+ PgR- and ER- PgR+ did not show any significant difference between the four groups studied (p>0.1).
TABLE 2: Receptor phenotypes in patients with primary (non-palpable, palpable operable and locoregionally advanced) and (first) metastatic breast cancer

<table>
<thead>
<tr>
<th>Group</th>
<th>ER+</th>
<th>PgR+</th>
<th>ER+</th>
<th>PgR-</th>
<th>ER-</th>
<th>PgR+</th>
<th>ER-</th>
<th>PgR-</th>
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</thead>
<tbody>
<tr>
<td>Nonpalpable primary breast cancer (n=52)</td>
<td>37</td>
<td>71.1</td>
<td>7</td>
<td>13.5</td>
<td>4</td>
<td>7.7</td>
<td>4</td>
<td>7.7</td>
</tr>
<tr>
<td>Palpable operable primary breast cancer (n=259)</td>
<td>149</td>
<td>57.5</td>
<td>31</td>
<td>12.0</td>
<td>18</td>
<td>6.9</td>
<td>61</td>
<td>23.5</td>
</tr>
<tr>
<td>Locoregionally advanced primary breast cancer (n=73)</td>
<td>35</td>
<td>47.9</td>
<td>14</td>
<td>20.0</td>
<td>8</td>
<td>10.9</td>
<td>16</td>
<td>21.9</td>
</tr>
<tr>
<td>First metastatic breast cancer (n=58)</td>
<td>24</td>
<td>41.3</td>
<td>16</td>
<td>27.6</td>
<td>3</td>
<td>5.2</td>
<td>15</td>
<td>25.8</td>
</tr>
</tbody>
</table>

IV.4 DISCUSSION

By the time a breast cancer has reached a mammographically discernable size of 5 mm, already 22 doublings or between half and two-third of its tumour life-span have passed. Another 14 doublings further is uniformly lethal (7,8). This means that nonpalpable breast cancer is still detected relatively late in the course of its tumour life.

The above proven shift of receptor phenotype from a high frequency of ER+ PgR+ tumours in nonpalpable breast cancer towards less frequent ER+ PgR+ and more ER- PgR- tumours in palpable and advanced breast cancer, suggests that the earlier stages, after less doubling times and not yet detectable by mammographic means, may contain steroid receptors in even higher frequency, reaching 100% at its inception.

It should be noted that the loss of PgR in the course of time is more marked than the loss of ER, which is in keeping with previous data on sequential biopsies in advanced breast cancer, clearly showing that the inconsistency in PgR is
significantly higher than in ER (3,9).

Two sources of bias, however, should be recognized. It is well known that nonpalpable breast cancers found by mammographic screening predominantly are relatively slow-growing tumours. Tumours with a low proliferation activity tend to be ER-positive (10). So the way of detection of nonpalpable breast cancer could have influenced the present analysis. However, for patients with advanced disease, the location of accessible skin and lymph node metastases could have increased the actual number of ER-positive tumours, because non-accessible visceral metastases are more often ER-negative (11).

For an adequate Scatchard plot analysis on a micro scale at least 100 mg of tumour is required, which means approximately a cube of tissue 0.5 cm on each side. Of our 17 invasive carcinomas ≤10 mm all had diameters between six to 10 mm, except for one which was smaller than five mm, but had a large in situ ductal component.

Although the long-term prognosis of nonpalpable breast cancer is extremely good (12-14), some will develop to advanced disease. It may be concluded from the above results that the hormone-responsiveness of metastases after nonpalpable breast cancer is not automatically predicted by its primary tumour receptor status.

The development of assays based on monoclonal antibodies against ER (not yet for PgR) has opened new perspectives for measuring steroid-hormone receptors in small tissue specimens (15). It is expected that in the near future more data will become available on the smallest and earliest possible stages of breast cancer.

IV.5 SUMMARY

Four groups of patients, comparable in mean age and menopausal status, with i) nonpalpable primary breast cancer, ii) palpable operable primary breast cancer, iii) loco-regionally advanced primary breast cancer, and iv) first
metastatic breast cancer, were studied in respect of their steroid receptor phenotype. A significant shift in receptor phenotype (ER+ PgR+) was observed from nonpalpable primary breast cancer (71%) via palpable operable (58%) and loco-regionally advanced primary breast cancer (48%) to first metastatic breast cancer (41%). A reversed extrapolation of these figures supports the hypothesis that every breast cancer contains steroid receptors and is hormone-dependent from its inception.

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Chapter V

MULTICENTRICITY IN NONPALPABLE BREAST CARCINOMA
AND ITS IMPLICATIONS FOR TREATMENT

J.G.M. Tinnemans, Th. Wobbes, R.F. van der Sluis,
E.J.C. Lubbers, H.H.M. de Boer


The pathologic and radiologic data used in this chapter are based on the studies of Dr. R. Holland and Dr. J.H.C.L. Hendriks from the Departments of Pathology and Radiology of the St. Radboud University Hospital in Nijmegen
In the past decade, breast conserving surgery in the management of operable breast carcinoma has gained and is still gaining more and more acceptance both among women and physicians. Many surgeons were encouraged by the preliminary results of Veronesi and co-workers (1) who, in a prospective, randomized study, reported comparable recurrence and five year survival rates in patients with $T_1N_0$ lesions who underwent either radical mastectomy or quadrantectomy, axillary dissection, and radiation therapy to the breast. Opponents, however, claim that as time passes, more and more therapeutic failures will come forward due to further disease in the treated breast. Such disease may be regarded as a true local recurrence or as a second primary tumor in the ipsilateral breast.

A basic problem in a discussion of breast conserving surgery is the rate of residual tumor in the remaining breast and the question of how this can be dealt with adequately by radiotherapeutic means (2). Residual tumor may either be due to incomplete excision of the primary malignancy or to other foci of carcinoma elsewhere in the breast. Although much is known regarding the multifocality of palpable breast cancer with reported incidences between 30 and 60 percent (3-8), much less data are available on non-palpable breast carcinomas (9). Theoretically, one might expect figures of the same magnitude. This study was undertaken to test this hypothesis.

V.2 MATERIAL AND METHODS

Between January 1, 1975 and December 31, 1983, 300 consecutive women were biopsied at the department of general surgery of the St. Radboud University Hospital because of nonpalpable, radiographically suspicious abnormalities judged to be indicative of carcinoma of the breast. Patients were in
part drawn from a population screening program within the city of Nijmegen aimed at the whole female population over 35 years of age (10) and in part from our surgical outpatient department where patients were seen for breast complaints or for follow-up of previous breast cancer.

The following radiographic findings mandated a recommendation for biopsy: clustered fine microcalcifications of five or more per square centimeter, a nodular or well-circumscribed mass (not suggestive of a cyst) with or without microcalcifications, and a stellate-shaped mass. All mammographic abnormalities were clinically occult. Since 1977, biopsy of the nonpalpable masses was aided by a needle localization technique using a self-retaining hooked wire (11).

In general, invasive and minimally invasive carcinomas, whether ductal or lobular, were treated by radical or modified radical mastectomy. Until 1977, however, central and medial invasive cancers were treated by simple total mastectomy combined with irradiation of regional lymph nodes. Ductal carcinoma in situ was treated by the same methods. Patients with lobular carcinoma in situ did not undergo mastectomy but had frequent follow-up examinations.

Since 1978, all mastectomy specimens were studied systematically according to the method of Egan (12), correlating radiographic and microscopic findings. With this method, the chilled breast specimen was sliced at a thickness of 5 mm and subsequently each slice was radiographed. Tissue blocks were taken from all grossly and radiographically suspicious areas, in addition to some randomly chosen ones from each quadrant and the nipple. On average, 20 blocks of each mastectomy specimen were obtained and examined (8). The data before 1978 were studied retrospectively from the routine pathology reports.

Multicentricity or multifocality was defined as the presence of any ductal or lobular carcinoma, whether invasive, noninvasive, or both, in a quadrant other than the quadrant harboring the primary tumor. In the case of a retromamillary
or central tumor, multicentricity was considered only if additional cancer foci were demonstrable at a distance of at least 5 cm beyond the nipple and vice versa. Residual carcinoma was considered to be any cancerous breast tissue left behind after biopsy of the mammographically suspicious lesion. Since all lesions were impalpable an excisional biopsy was undertaken in all cases and confirmed by radiography.

V.3 RESULTS

The 335 biopsies undertaken in 300 patients because of nonpalpable mammary lesions represented 25.2 percent of the total of 1,329 breast biopsies performed on in-patients during the nine year period of study. A malignancy was encountered in 102 cases (30.4 percent of the total number of biopsies) or 96 patients (32 percent of the total number of patients).
When dividing the occult cancers into subgroups based on histologic type and degree of invasion, there were 65 invasive cancers, including 6 minimally invasive ductal carcinomas (≤5 mm), and 35 noninvasive carcinomas (Table 1). Twenty-seven of the biopsies showed ductal carcinoma in situ, and lobular carcinoma in situ was detected eight times. In one case, a localized malignant non-Hodgkin's lymphoma was found.

Of the entire group of 100 primary breast cancers, 85 were of ductal origin and 15 were of the lobular small cell type. Of the 65 patients with invasive carcinoma, a modified radical or simple total mastectomy was undertaken in 56 and consequently, the mastectomy status became known. One patient had two generous biopsies performed in different quadrants of the same breast, both of which revealed malignancy. Because of malignant secondary disease in the infraclavicular apical biopsy specimen, this patient did not undergo a mastectomy but was treated with radiotherapy. Therefore, the mastectomy status was known in 57 patients (88 percent) with invasive carcinoma. Of the 35 patients with noninvasive carcinomas, 23 had a modified radical or simple total mastectomy and three patients had a subcutaneous mastectomy. Thus in 26 patients (74 percent) with noninvasive carcinoma mastectomy specimens were evaluable.

Using the definition of multicentricity outlined herein, of the entire group of 83 breasts studied, 39 or 47 percent had multifocal disease (Table 2). When primary invasive carcinomas are considered, the overall rate of multifocality was 27 of 57 breasts or 47.4 percent, whereas the multifocality rate of the primary noninvasive cancers was 12 of 26 breasts or 46.2 percent.

Invasive foci of cancer within a quadrant other than the one containing the primary tumor were demonstrable in 15 mastectomy specimens, representing 15 of 57 (26.3 percent) of the invasive cancers or 15 of 83 (18.1 percent) of the whole group. The remaining multicentric foci of noninvasive
Table 2: Multifocality of Nonpalpable Breast Cancer

<table>
<thead>
<tr>
<th>Primary diagnosis</th>
<th>Mastectomy performed</th>
<th>Unifocal</th>
<th>Other foci of cancer*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive ductal carcinoma</td>
<td>44</td>
<td>25</td>
<td>IDC, 9, MIDC, 3, DCIS, 3, LCIS, 4</td>
</tr>
<tr>
<td>Invasive lobular carcinoma</td>
<td>6</td>
<td>2</td>
<td>ILC, 3, DCIS, 1</td>
</tr>
<tr>
<td>Invasive Paget's disease</td>
<td>1</td>
<td>..</td>
<td>DCIS, 1</td>
</tr>
<tr>
<td>Minimally invasive ductal carcinoma (&lt;5 mm)</td>
<td>6</td>
<td>3</td>
<td>DCIS, 3</td>
</tr>
<tr>
<td>Total invasive cancer</td>
<td>57</td>
<td>30</td>
<td>27</td>
</tr>
<tr>
<td>Ductal carcinoma in situ</td>
<td>25</td>
<td>14</td>
<td>DCIS, 10, LCIS, 1</td>
</tr>
<tr>
<td>Lobular carcinoma in situ</td>
<td>1</td>
<td>..</td>
<td>LCIS, 1</td>
</tr>
<tr>
<td>Total noninvasive cancer</td>
<td>26</td>
<td>14</td>
<td>12</td>
</tr>
</tbody>
</table>

* Values refer to the number of patients.
DCIS = ductal carcinoma in situ; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; LCIS = lobular carcinoma in situ; MIDC = minimally invasive ductal carcinoma (<5 mm).

cancer were encountered in 24 cases (28.9 percent of the whole group): 18 had other foci of ductal carcinoma in situ and multifocal lobular carcinoma in situ was seen in six.

When tumors were divided according to histologic type, multicentricity was present in 34 (44.7 percent) of the 76 primary ductal carcinomas and in five (71.4 percent) of the seven primary lobular carcinomas. When any cancerous tissue outside the biopsy cavity and not limited to another quadrant of the breast was included, residual carcinoma was present in 50 of 83 cases (60.2 percent) (Table 3). In cases of primary invasive carcinoma, residual carcinoma was found in 33 of
Table 3: Residual Carcinoma after Excisional Biopsy for Nonpalpable Breast Cancer

<table>
<thead>
<tr>
<th>Primary diagnosis</th>
<th>Mastectomy performed</th>
<th>No residual carcinoma</th>
<th>Residual carcinoma*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive ductal carcinoma</td>
<td>44</td>
<td>21</td>
<td>IDC, 13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MIDC, 3</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>DCIS, 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LCIS, 4</td>
</tr>
<tr>
<td>Invasive lobular carcinoma</td>
<td>6</td>
<td>1</td>
<td>IDC, 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ILC, 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DCIS, 1</td>
</tr>
<tr>
<td>Invasive Paget's disease</td>
<td>1</td>
<td>..</td>
<td>DCIS, 1</td>
</tr>
<tr>
<td>Minimally invasive ductal carcinoma (&lt;5 mm)</td>
<td>6</td>
<td>2</td>
<td>DCIS, 4</td>
</tr>
<tr>
<td>Total invasive cancer</td>
<td>57</td>
<td>24</td>
<td>33</td>
</tr>
<tr>
<td>Ductal carcinoma in situ</td>
<td>25</td>
<td>9</td>
<td>DCIS, 15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LCIS, 1</td>
</tr>
<tr>
<td>Lobular carcinoma in situ</td>
<td>1</td>
<td>..</td>
<td>LCIS, 1</td>
</tr>
<tr>
<td>Total noninvasive cancer</td>
<td>26</td>
<td>9</td>
<td>17</td>
</tr>
</tbody>
</table>

* Values refer to the number of patients.

DCIS = ductal carcinoma in situ; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; LCIS = lobular carcinoma in situ; MIDC = minimally invasive ductal carcinoma (<5 mm).

57 instances (57.9%), whereas in cases of primary non-invasive carcinoma, residual disease was seen in 17 of 26 instances (65.4%).

Residual invasive carcinoma would have been left in situ in 20 mastectomy specimens, accounting for 20 of 57
(35.1%) of the invasive cancers or 20 of 83 (24.1%) of the whole group. Residual noninvasive cancer was demonstrable in 30 cases (36.1% of the whole group). In patients with primary ductal carcinoma, residual breast tumor was present in 44 cases, representing 44 of 76 (57.9%) of these carcinomas, but in primary lobular carcinoma, residual tumor was seen in 6 of the 7 breasts (85.7%). Of 25 cases of primary ductal carcinoma in situ, residual ductal carcinoma in situ was found in 15 (60%).

In the total group of 96 patients bilateral breast cancer was present in 19 (Table 4). Six patients were treated previously because of invasive carcinoma. Since they bias the rate of bilaterality, they were excluded. The true incidence is still 13 of 90 (14.4%) of these patients. Simultaneous bilateral cancer occurred in 10 of 90 (11.1%) patients.

Table 4: Status of the Contralateral Breast in 96 Patients with Ipsilateral Nonpalpable Breast Carcinoma

<table>
<thead>
<tr>
<th></th>
<th>Palpable</th>
<th>Nonpalpable</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous carcinoma</td>
<td>5, IDC</td>
<td>1, DCIS</td>
<td>6</td>
</tr>
<tr>
<td>Synchronous carcinoma</td>
<td>5, IDC</td>
<td>1, DCIS</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>3, ILC</td>
<td>1, LCIS</td>
<td></td>
</tr>
<tr>
<td>Metachronous carcinoma</td>
<td>1, IDC</td>
<td>1, ILC</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1, LCIS</td>
<td></td>
</tr>
</tbody>
</table>

DCIS = ductal carcinoma in situ; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; LCIS = lobular carcinoma in situ.
Studies on the multicentricity of breast tumors show a wide variation in frequency based on differences in case material, criteria for diagnosis of multicentricity and extent of sampling (3-8, 13-17). Overestimation of multicentricity occurs if the study population includes patients with locally advanced breast cancer or if any focus of cancer separate from, but in close proximity to the primary tumor is counted.

The low incidence of multicentric cancer of 13.4 percent reported by Fisher et al in 1975 (17) is explained by the limited number of tissue blocks examined from each mastectomy specimen. Most investigators who have performed whole organ sectioning and correlated mammographic findings have demonstrated a much higher incidence (30 to 74 percent) (6,8,14). This applies to palpable breast carcinomas, but at first glance, one might expect similar figures for non-palpable breast carcinoma since palpable and nonpalpable tumors differ only in epidemiologic lead time. As time passes, an impalpable tumor becomes palpable. This is true for invasive carcinoma because of continued growth. For non-invasive carcinoma, the situation is more complicated, although there is now some evidence that in patients with ductal carcinoma in situ treated by biopsy only, ipsilateral invasive ductal carcinoma eventually develops in 28 to 67 percent within 10 years (18,19). Among biopsy-treated patients with lobular carcinoma in situ, the frequency of subsequent invasive lobular carcinoma is 9 to 12 times the expected rate, occurring with equal frequency in the ipsilateral and contralateral breast after 15 to 20 years (19,20).

In 1980, in a series of 53 mastectomies performed because of clinically occult breast carcinoma, Schwartz et al (9) demonstrated multicentricity in 21 mastectomy specimens (39.6 percent), and multicentric invasive foci were present in 4 (11.1 percent) of 36 specimens of occult invasive disease. Using the same criteria, we found an overall multi-
centricity rate of 47 percent and distant multicentric invasive foci in 15 (26.3 percent) of the 57 evaluable occult invasive carcinomas.

Nonpalpable breast carcinoma is clinically considered to be the earliest among the $T_1$ tumors and consequently a patient with such a tumor is an eligible candidate for breast conserving surgery and postoperative local radiotherapy. Thus, remaining invasive cancer foci may be responsible for short-term recurrences, and remaining noninvasive cancer foci may eventually develop into invasive cancer and cause long-term recurrences.

In our series, invasive tumor foci outside the quadrant of the primary tumor would have been left behind in about 1 of 4 patients (15 of 57 patients, 26.3 percent) and residual invasive tumor outside the excisional biopsy cavity in about 1 of 3 patients (20 of 57 patients, 35.1 percent) with impalpable primary invasive cancer. Local irradiation should eradicate these invasive cancer cells and is apparently able to do so because, in the Milan trial, no difference in local recurrences within 5 years (including so-called second primary tumors) were shown between $T_1 N_0$ patients treated with Halsted mastectomy or with quadrantectomy, axillary dissection, and radiotherapy (1).

Local recurrences after breast conserving surgery followed by radiotherapy for $T_1$ breast cancer have been reported between 2.3 and 8.2 percent (21-24). Salvage mastectomy for recurrence in the breast still shows a 5 year survival rate of 67 percent (23).

With regard to the occult noninvasive breast carcinomas, we found that multicentric noninvasive foci outside the primary quadrant were present in 46.2 percent of the primary noninvasive carcinomas and in 21.1 percent of the primary invasive carcinomas. If residual noninvasive carcinoma outside the excisional biopsy cavity is considered, then the multifocality rates increase to 65.4 percent and 22.8 percent, respectively.
Treatment of noninvasive breast carcinoma is still somewhat controversial. Because of its multifocal nature, total mastectomy would be the treatment of choice as it can cure these patients with almost 100 percent certainty. Moreover, a sampling error, that is, invasive foci in a quadrant remote from the in situ biopsy, has been demonstrated in 6 to 11 percent of patients (25,26). But in our series of 26 evaluable breast specimens with occult noninvasive cancers, we did not encounter a sampling error.

Analogous to small invasive carcinoma, conservation surgery and postoperative irradiation of the remaining breast is being performed for these usually occult noninvasive tumors. However, the unjustifiable assumption has been made that in situ carcinoma has the same radiosensitivity as invasive carcinoma, which is probably not true because of the low mitotic activity of in situ carcinoma. A disadvantage is that the irradiated breast is less easily watched both clinically and mammographically and the diagnosis of local recurrence might be delayed. Radiotherapy might also contribute to carcinogenesis de novo.

Because of the natural history of in situ carcinoma, when left alone after biopsy, it may take up to 10 years for ductal carcinoma in situ or 20 years and more for lobular carcinoma in situ, before invasive carcinoma becomes manifest (19,20). More study is required in regard to long-term local recurrences after radiotherapy of in situ cancer of the breast. That is why we think there is still a place for total mastectomy in ductal carcinoma in situ, especially in the younger patient with a long life expectancy. Such a patient is also the best candidate for subsequent breast reconstruction. In lobular carcinoma in situ, the development of a new occurrence of invasive lobular carcinoma after excisional biopsy takes many years and the risk is bilateral (19,20). Therefore, these patients are kept under close supervision and regular follow-up examinations for the remainder of their lives (27).
The rate of bilaterality in the literature varies considerably depending on the characteristics of the study population (age, a personal or family history of breast cancer, and histologic type), extent of sampling, and duration of observation (28). The advent of mammography has contributed to the differentiation between primary and metastatic tumors and to earlier recognition, which has caused more tumors to be detected simultaneously (29). Liberal routine contralateral biopsy procedures also increase the detection rate of simultaneous bilaterality. Random sampling (a fifth of the mammary tissue in the upper outer quadrant), as well as mirror image biopsies, revealed simultaneous bilateral tumors in 9.5 percent of these patients (30). However, not performing contralateral biopsies as a routine, and instead, only for mammographic indications, we found synchronous bilateral cancer in 11.1 percent of the patients. Considering this high yield, mammography of the contralateral side is, therefore, mandatory in the preoperative workup of patients scheduled for biopsy due to palpable lesions on the ipsilateral side.

V.5 SUMMARY

During a 9 year period, 300 consecutive women underwent breast biopsies solely because of nonpalpable, mammographically suspicious findings. One hundred clinically occult breast carcinomas were found, 65 of which were invasive and 35 noninvasive. Eighty-three mastectomy specimens were evaluable for evidence of multifocal carcinoma in another quadrant of the breast or at a distance of 5 cm and residual cancer outside the excisional biopsy cavity. Multicentricity was present in 47 percent and residual tumor in 60 percent of the whole group. When only clinically occult invasive carcinomas were considered, other foci of invasive carcinoma were demonstrated in 26 percent of the patients and residual invasive cancer in 35 percent. The rate of bilaterality was 14 percent, occurring synchronously in 11 percent of the
patients.

Any therapeutic procedure for nonpalpable breast carcinoma, whether invasive or noninvasive ductal carcinoma, should be directed to the whole breast. Mammography of the contralateral side should be an integral part of the preoperative workup of patients with palpable lesions ipsilaterally.

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Chapter VI

THE ROLE OF MAMMOGRAPHY IN THE DETECTION OF
BILATERAL PRIMARY BREAST CANCER

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R. Holland, R.F. van der Sluis, H.H.M. de Boer

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VI.1 INTRODUCTION

The concept of bilateralism in carcinoma of the breast is not new (1). Since the breast is a paired organ and, as cancer of this organ is frequently of multicentric origin, the development of simultaneous or subsequent independent malignancies on both sides is a well-established characteristic of breast carcinoma (2).

In the past the discovery of the second primary was restricted to palpation and excision of abnormal masses (3-5). Alternative methods included routine 'random' biopsies of the upper outer quadrant or 'mirror-image' sampling of the opposite breast (6,7) and prophylactic contralateral mastectomy for patients at high risk (8-10). The advent of modern mammography has made it possible to detect contralateral breast cancer selectively in its clinically occult or nonpalpable stage (11).

The present study reviews our experience with bilateral breast cancer when routine mammography was used as a diagnostic adjunct in order to detect synchronous or metachronous (occult) breast carcinoma.

VI.2 PATIENTS AND METHODS

From 1970 through October, 1985 a total of 824 patients with breast cancer have been treated at the Department of General Surgery, St. Radboud University Hospital, Nijmegen, The Netherlands.

In 1970 modern mammographic equipment consisting of a molybdenum anode was installed and since then mammography has been used as an integral part of the preoperative work-up of (sub)clinical patients with primary breast cancer and of the regular follow-up of postmastectomy patients.

Histological criteria for diagnosis of a second primary tumour included difference in histological types, demonstration of in situ change and different grade of differentiation. In
the absence of these criteria a second cancer was considered to be an independent primary when there was no evidence of local, regional or distant metastatic disease from the first primary.

Synchronous carcinomas are defined as bilateral malignancies occurring within three months apart and metachronous tumours as those occurring more than three months of each other.

A breast was considered to harbour multicentric carcinoma if invasive and/or in situ carcinoma was found in a quadrant other than the one containing the primary tumour. In case of doubt or in retro-areolar locations, multicentricity was considered only if other cancer foci were at a distance of at least 5 cm (12). Thus, residual cancer after excisional biopsy or non-contiguous foci of cancer in the same quadrant, regardless of histology, are unicentric for the purpose of this paper.

This report concerns 55 patients with biopsy-proven bilateral breast cancer, discovered clinically and/or radiographically. Routine contralateral biopsy was not practised, while prophylactic mastectomy was carried out only occasionally, resulting in two bilateral malignancies, which are included in this series. Complete follow-up data were available at the closure of this study in October, 1985.

VI.3 RESULTS

The 55 patients with bilateral breast cancer represent 6.7% of the total number of 824 patients with breast carcinoma treated during this 15-year period (Table 1). Twenty-three (=2.8%) had simultaneous primaries and 32 patients (=3.9%) subsequently developed a second primary carcinoma in the opposite breast.

The mean age of the patients with synchronous tumours was 60.3 years (range 43-76). In metachronous disease the mean age at the diagnosis of the first carcinoma was 52.5 years
Table 1: Some characteristics of 55 patients with bilateral primary breast cancer

<table>
<thead>
<tr>
<th>Feature</th>
<th>Bilateral primary cancer</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Synchronous Metachronous</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1st 2nd</td>
<td></td>
</tr>
<tr>
<td>Number of patients*</td>
<td>23 32</td>
<td>55</td>
</tr>
<tr>
<td>Percentage*</td>
<td>2.8 3.9</td>
<td>6.7</td>
</tr>
<tr>
<td>Mean age in years (range)</td>
<td>60.3 52.5 57.8</td>
<td>(43-76) (34-79) (37-83)</td>
</tr>
<tr>
<td>Mean interval in months (range)</td>
<td>0.2 64.8</td>
<td>(0-3) (8-289)</td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- pre</td>
<td>6 15 8</td>
<td></td>
</tr>
<tr>
<td>- post</td>
<td>17 17 24</td>
<td></td>
</tr>
<tr>
<td>Fertility</td>
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<tr>
<td>- nulliparous</td>
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<tr>
<td>- parous</td>
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<tr>
<td>Nursed</td>
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<td>Personal history of other malignancies</td>
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<td>Family history of breast cancer</td>
<td>6 10</td>
<td>16</td>
</tr>
<tr>
<td>Family history of other malignancies</td>
<td>3 13</td>
<td>16</td>
</tr>
</tbody>
</table>

* Total number of breast cancers (unilateral + bilateral) is 879; total number of breast cancer patients is 824 (=100%)

(range 34-79), and at the second was 57.8 years (range 37-83).

The younger age of the metachronous patients is reflected in the menopausal status: 15 or 46.9% were premenopausal during presentation of the first tumour, while only eight or 25% had still their menses when the second tumour was detected,
similar to the synchronous group of whom six or 26.1% were still premenopausal.

The mean interval between the two primaries was 64.8 months (range 8-289). Twenty-four (=75%) of the second primary carcinomas occurred within five years following the first primary.

A positive family history of breast cancer was found in six (=26.1%) of the patients with synchronous disease and in 10 (=31.3%) of the patients in the metachronous group.

If in simultaneous bilateral carcinoma the breast with the larger invasive lesion is considered to be the dominant side (11 x left, 10 x right and 2 x equivocal) and in subsequent disease the breast in which the tumour first occurred (18 x left and 14 x right), then the left/right ratio is 1.21.

Of 49 patients in whom the intra-breast location was known only 5 of the 21 patients with synchronous tumours (=23.8%) and 13 of the 28 patients with metachronous tumours (=46.4%) had 'mirror-image' tumours, 11 of them sited in the upper outer quadrant.

Table 2 shows the relation between physical examination and mammography in the detection of bilateral breast cancer. Of the 100 breasts examined radiographically 89 had an abnormal mammogram: 50 with a palpable and 39 with a non-

Table 2: Correlation between clinical and radiographical findings in bilateral primary breast cancer

<table>
<thead>
<tr>
<th>Physical examination</th>
<th>Mammogram</th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Abnormal</td>
<td>None/Unknown</td>
<td></td>
</tr>
<tr>
<td>Nonpalpable</td>
<td>2</td>
<td>39</td>
<td>0</td>
<td>41</td>
</tr>
<tr>
<td>Palpable</td>
<td>9</td>
<td>50</td>
<td>10</td>
<td>69</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>89</td>
<td>10</td>
<td>110</td>
</tr>
</tbody>
</table>
palpable tumour. In 11 cases the malignant lesion was mammographically occult: 9 with a palpable and 2 with a non-palpable tumour. The latter underwent a prophylactic mastectomy and both had lobular carcinoma in situ (= LCIS) on histopathological examination.

The nine palpable tumours with normal mammograms showed dense mastopathy in 7 cases (histopathology: 3 x invasive lobular carcinoma, 2 x tubular carcinoma, 1 x comedo carcinoma and 1 x invasive ductal carcinoma, not otherwise specified, and were radiographically completely normal in the remaining 2 cases, both advanced invasive lobular carcinomas with pathological diameters of 60 and 90 mm, respectively. The mean age of the patients with mammographically occult tumours due to dense mastopathy was only 42.9 years (range 38-50).

The stage of the tumour in the two groups of patients was analysed (Table 3). In the synchronous series, 5 or 22% had a nonpalpable tumour on the first side, but 15 or 65% on

<table>
<thead>
<tr>
<th></th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synchronous</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1*</td>
<td>5</td>
<td>2</td>
<td>9</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>S2</td>
<td>15</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metachronous</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1*</td>
<td>5</td>
<td>6</td>
<td>13</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>M2**</td>
<td>16</td>
<td>3</td>
<td>5</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

* S1 and M1 indicate the first primary breast carcinoma found
** S2 and M2 indicate the second or contralateral primary breast carcinoma found
Table 4: Analysis of failures to detect metachronous second primary breast cancer in its nonpalpable stage

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Total number palpatable</th>
<th>Detected by physician/patient Pathology (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammographically visible</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-interval carcinoma</td>
<td>6</td>
<td>2 comedo ca. (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>invasive ductal ca., NOS* (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>medullary ca. (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mucinous ca. (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DCIS (1)</td>
</tr>
<tr>
<td>-observer's error</td>
<td>1</td>
<td>- Paget's disease with invasive ductal ca. (1)</td>
</tr>
<tr>
<td>Mammographically occult</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-masking effect of dense mastopathy</td>
<td>2</td>
<td>1 invasive lobular ca. (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tubular ca. (1)</td>
</tr>
<tr>
<td>-truly occult</td>
<td>-</td>
<td>1 invasive lobular ca. (1)</td>
</tr>
<tr>
<td>Bad patient compliance</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 invasive lobular ca. (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>papillary ca. (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>invasive ductal ca., NOS* (1)</td>
</tr>
</tbody>
</table>

* NOS = not otherwise specified
Table 5: Histological types of 110 breast cancers in patients with bilateral disease

<table>
<thead>
<tr>
<th>Histology</th>
<th>Clinically overt</th>
<th>Clinically occult</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Ductal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- invasive, NOS*</td>
<td>36</td>
<td>52.2</td>
<td>16</td>
</tr>
<tr>
<td>- scirrhous</td>
<td>9</td>
<td>13.0</td>
<td>2</td>
</tr>
<tr>
<td>- tubular</td>
<td>2</td>
<td>2.9</td>
<td>7</td>
</tr>
<tr>
<td>- DCIS</td>
<td>3</td>
<td>4.3</td>
<td>7</td>
</tr>
<tr>
<td>Lobular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- invasive</td>
<td>15</td>
<td>21.7</td>
<td>4</td>
</tr>
<tr>
<td>- LCIS</td>
<td>-</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Others/Cancer, NOS*</td>
<td>4</td>
<td>5.8</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>69</td>
<td>99.9</td>
<td>41</td>
</tr>
</tbody>
</table>

* NOS = not otherwise specified

the contralateral side. Also in the metachronous cases the number of nonpalpable tumours increased from 5 or 16% on the first side to 16 or 50% on the second side.

Thus 16 patients subsequently developed a palpable second breast cancer (Table 4): nine physician-discovered in the course of a regular follow-up and seven patient-discovered, of whom three had defaulted from follow-up. Of the 13 patients with palpable second primaries despite periodical check-ups nine had an abnormal mammogram (one radiographical density of 5 mm had been missed 18 months earlier), while the remaining four showed no abnormalities on the mammogram, apart from mastopathy thrice. Pathologically, three were invasive lobular carcinomas and one was a tubular carcinoma.
Table 6: Axillary status in synchronous and metachronous bilateral primary breast cancer

<table>
<thead>
<tr>
<th></th>
<th>No. of axillae</th>
<th>No. evaluable</th>
<th>No. with pos. nodes</th>
<th>Pos. nodes %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Synchronous</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1*</td>
<td>23</td>
<td>13</td>
<td>6</td>
<td>46.2</td>
</tr>
<tr>
<td>S2**</td>
<td>23</td>
<td>11</td>
<td>3</td>
<td>27.3</td>
</tr>
<tr>
<td><strong>Metachronous</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1*</td>
<td>32</td>
<td>20</td>
<td>7</td>
<td>35.0</td>
</tr>
<tr>
<td>M2**</td>
<td>32</td>
<td>19</td>
<td>7</td>
<td>36.8</td>
</tr>
<tr>
<td>Total</td>
<td>110</td>
<td>63</td>
<td>23</td>
<td>36.5</td>
</tr>
</tbody>
</table>

* S1 and M1 indicate the first primary breast carcinoma found
** S2 and M2 indicate the second or contralateral primary breast carcinoma found

Two of the three defaulters had evaluable axillary nodes and both had multiple lymph node involvement. They were diagnosed at intervals of 4, 5 and 24 years after treatment of the first primary carcinoma.

The main histological types of the carcinomas in the 55 bilateral breast cancer patients are recorded in Table 5. Invasive lobular carcinoma and scirrhous carcinoma are well represented in the clinically overt group. Tubular carcinoma, ductal carcinoma in situ (= DCIS) and LCIS are more prominent in the clinically occult group.

A study was made of the incidence of metastasis to the axilla in synchronous and metachronous breast cancers (Table 6). In the synchronous group axillary involvement was noted in 46.2% on the first or dominant side and in 27.3% on the opposite side. In the metachronous cases 35% had positive
Table 7: Correlation between clinical stage of the tumour and axillary involvement in bilateral primary breast cancer

<table>
<thead>
<tr>
<th>No. of axillae evaluable</th>
<th>No. pos. nodes</th>
<th>No. with pos. nodes</th>
<th>Pos. nodes %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonpalpable</td>
<td>41</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Palpable</td>
<td>69</td>
<td>37</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>110</td>
<td>63</td>
<td>23</td>
</tr>
</tbody>
</table>

Axillary lymph nodes on the first side and so had 36.8% also on the second side.

Comparing clinically overt and clinically occult tumours 54.1% of the evaluable palpable tumours showed axillary involvement, but only 11.5% of the evaluable nonpalpable tumours (Table 7).

Table 8 demonstrates the rate of multicentricity, which is higher in the synchronous than in the metachronous group: 70.6% and 44.2%, respectively. The size of the primary tumour, whether palpable or nonpalpable, has little influence on multicentricity: 50.0% versus 61.1%. When looking at the main histological types invasive ductal carcinoma is multicentric in 44.6%, while invasive lobular carcinoma shows multicentricity in 73.3%. The rate of multicentricity is even higher (87.5%) in DCIS. The numbers of LCIS and others are too small to draw meaningful conclusions.

The estimated survival according to the life-table method (13) of the bilateral breast cancer patients (all stages) is shown in Figure 1. Of the 23 patients with synchronous tumours four died from cancer and 19 were alive (of whom seven with disease) after a mean observation period of 69 months. Of the 32 patients with metachronous tumours nine died (seven from breast carcinoma and two from unrelated causes) and 23
Table 8: Multicentricity in bilateral primary breast cancer

<table>
<thead>
<tr>
<th></th>
<th>No. of breasts</th>
<th>No. evaluable</th>
<th>No.* uni-centric</th>
<th>No. multicentric inv./noninv.</th>
<th>Multi-centricity rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>According to onset:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Synchronous</td>
<td>46</td>
<td>34</td>
<td>10 (R=3)</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>- Metachronous</td>
<td>64</td>
<td>52</td>
<td>29 (R=6)</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>According to physical findings:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Palpable</td>
<td>69</td>
<td>50</td>
<td>25 (R=6)</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>- Nonpalpable</td>
<td>41</td>
<td>36</td>
<td>14 (R=3)</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>According to histology:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Invasive ductal carcinoma</td>
<td>72</td>
<td>56</td>
<td>31 (R=7)</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>- Invasive lobular carcinoma</td>
<td>19</td>
<td>15</td>
<td>4 (R=2)</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>- Ductal carcinoma in situ</td>
<td>10</td>
<td>8</td>
<td>1</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>- Lobular carcinoma in situ</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>- Others</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>TOTAL</td>
<td>110</td>
<td>86</td>
<td>39</td>
<td>24</td>
<td>23</td>
</tr>
</tbody>
</table>

* In parentheses: R = Residual tumour in the same quadrant
stayed alive (of whom three with disease) after a mean follow-up of 115 months. The survival of synchronous patients is 91% at 5 years and 74% at 10 years. In the metachronous group survival after the first diagnosis at 5 and 10 years is 90% and 85%, respectively, and when measured from the second primary 84% and 59%, respectively.
Papers on bilateral breast cancer are difficult to compare because of differences in definition (primary or metastatic, synchronous or metachronous, pathological criteria of noninvasive carcinoma), composition of the various series (age, prognostic status, high-risk patients), diagnostic modality (clinical or mammographic signs, routine random biopsies and extent of sampling), duration and intensity of follow-up and analysis techniques (3,9,14,15). Bearing this in mind the reported incidence of bilateral metachronous disease is 4.3 - 8.2 second breast cancers per 1000 patient years (3,16-19). Bilateral synchronous mammary cancers are diagnosed in from 0.1 to 1.9 per cent of cases (3-5, 11, 19-25).

Chaudary et al (18) have shown an almost fivefold increase of simultaneous bilateral disease till 2.4% after introduction of routine mammography in screening the opposite breast of women with ipsilateral breast carcinoma. By identifying subclinical lesions, more second cancers are placed into the synchronous category. Through the use of mammography the relative rate of synchronous cancers among bilateral breast carcinomas has risen to 26.9-50% (11,19,26), which is comparable with the high proportion of synchronous carcinomas (41.8%) that we found. In the course of time this percentage will fall to about 30% due to the steady development of metachronous tumours at a rate of approximately 1% per year per woman at risk (3,18).

In series employing contralateral biopsies the occurrence rate of simultaneous tumours varies between 2 and 12.7%, depending on how extensively has been sampled by the surgeon and how thoroughly the sections have been studied by the pathologist (7-9,27-31). However, many of these were non-invasive carcinomas, especially LCIS, and its fate and management remain a source of discussion (32,33). Urban et al (7) reported on 301 random opposite breast biopsies, truly occult in the absence of any physical or mammographical signs,
and diagnosed 23 carcinomas (7.6%): 5 x infiltrating and 18 x noninfiltrating. Recently, Wanebo et al (34) described their results with elective contralateral biopsies: 13 of 62 patients (21%) had simultaneous cancer in the second breast. Six, however, were either palpable (two) or had a suspicious mammogram (four), so the true incidence of clinically and radiographically occult contralateral breast carcinoma is 11.3% (7 out of 62 patients). Ten out of 13 were noninvasive: 6 x LCIS and 4 x DCIS.

In autopsy series the reported incidence is 10-21% (35-37). Those percentages of bilateral breast cancer, exceeding 8 to 10% observed clinically, suggest that some second primaries either regress or do not develop into invasive cancers during the patient's life-time.

If a woman has had breast cancer on one side, she has a 5-8 times greater risk of developing a second primary on the other side than women in the general population have to develop cancer in their first breast (3,4,18,36). Or in the words of Foote and Stewart's (38) much cited quotation: 'The one most common "precancerous" lesion of the left breast is a cancer of the right breast and vice versa'. This risk of the remaining breast is not augmented by previous radiotherapy (39,40).

We believe that follow-up of unilateral breast cancer patients, who belong to the population at the highest risk, is valuable because in our patients 29 out of 55 synchronous or metachronous malignancies (=52.7%) of the opposite breast were detected by mammographic means alone, excluding the two patients (=3.6%) who underwent a prophylactic mastectomy. The following reasons may explain why mammography failed to discover the malignancy in its nonpalpable or subclinical stage: first, because of fast growing interval cancers; second, because of the masking effect of dense mastopathy; third, because of lobular carcinoma, both infiltrating and in situ, which are difficult to visualize radiographically; fourth, because of technical or observer's errors (41,42). These
reasons, leaving apart bad patient compliance in 3 cases, have probably biased the rate of positive axillary nodes of the second primary tumours in our metachronous group, despite the low rate of positive nodes (11.5%) in the nonpalpable tumours. Moreover, any radiographical miss in the patients with synchronous bilateral breast carcinoma will contribute to the bias of the figures in the metachronous group. Survival of patients with synchronous bilateral primary breast cancer has been reported to be poor (5,19,24,39,43,44), while others (31,40) found no unfavourable difference in prognosis when compared with unilateral breast cancer patients or with patients in the metachronous group.

In metachronous breast cancer patients the survival measured from the time of presentation of the first tumour is usually better than the survival of patients with unilateral disease because of selection bias: only those surviving the first tumour, do live long enough to stand a chance to develop another primary in the opposite breast (19,34,44,45).

Although a contralateral prophylactic mastectomy, routinely (46) or for patients at high risk (8,9), has been advocated in the past, it is obvious that this would result in many unnecessary mastectomies and the anticipated benefits would be minimal.

Slack et al (16) calculated a maximum gain of 0.8% in the relative survival of all women developing a second breast cancer in the first five years at the expense of 98% futile mastectomies.

We believe that a watchful waiting policy is the strategy of choice now mammography has provided us with a useful tool for screening the remaining breast. Breast x-ray (low-dose mammography) should be performed annually (47). However, any palpable lump, regardless of mammogram, must be examined histologically, except for cysts.

In case of a dense parenchymal pattern rendering mammography less efficient in detecting carcinomas, an elective contralateral biopsy could be considered. The technique
involves removal of a wedge-shaped piece of tissue from the upper outer quadrant including a wedge from the retro-mamillary tissue via a circumareolar incision (31). This is particularly advisable in case of LCIS or LCIS coexisting with invasive ductal carcinoma or invasive lobular carcinoma (2), and DCIS (48), because of their tendency of multicentricity and bilaterality.

VI.5 SUMMARY

The significance of mammography in the detection of contralateral primary breast cancer was evaluated in 55 patients with bilateral breast disease. Fifteen of 23 patients (=65%) in the synchronous group and 16 of 32 patients (=50%) in the metachronous group had clinically occult carcinoma in the opposite breast. Excluding the two malignancies discovered by prophylactic mastectomy, mammography alone was responsible for the detection of 29 nonpalpable, contralateral breast carcinomas (=52.7%). The whole series of 110 malignant breasts comprised 41 nonpalpable carcinomas, of which 12 were noninvasive (7 x DCIS and 5 x LCIS) and the remaining 29 were invasive carcinomas, either ductal of various types (25 x) or lobular (4 x). With regard to the evaluable axillary nodes, 20 of 37 palpable breast cancers (=54.1%) and only 3 of 26 nonpalpable breast carcinomas (=11.5%) had positive lymph nodes. The multicentricity rate was particularly high in synchronous tumours (=70.6%), and in invasive lobular (=73.3%) and noninvasive (=75%) carcinomas. The favourable 5- and 10-year survival of patients, both in synchronous and metachronous bilateral primary breast cancer, justify that they be treated with aggressive optimism.

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Chapter VII

TREATMENT AND SURVIVAL OF FEMALE PATIENTS WITH NONPALPABLE BREAST CARCINOMA


Submitted
VII.1 INTRODUCTION

When the concept of minimal breast cancer (MBC) was first proposed in 1971 (1), it was intended, entirely on hypothetical grounds, to delineate a certain subgroup of breast carcinoma patients with an extremely favourable prognosis. According to the original definition MBC included lobular carcinoma in situ (LCIS), ductal carcinoma in situ (DCIS) and minimally invasive carcinoma (MIC), either lobular or ductal, not exceeding 5 mm in diameter. Based on this it was assumed that axillary lymph node involvement would occur in less than 10% and it was predicted that the long-term survival rate would be approximately 95% (2).

Only a few authors have so far published their results with regard to axillary status and long-term follow-up (3-6). Their results, summarized recently (7), do support the validity of the original concept showing a 5.5% rate of positive axillary nodes and a disease-free survival of well over 96%. The vast majority of the lesions in the above mentioned reports was self-discovered as a palpable mass. The favourable outcome of MBC, however, has been challenged by the large inter-institutional survey of the American College of Surgeons (8). Also controversy exists with regard to the upper limit of MIC of either lobular or ductal type whose greatest diameter has been extended and may be equal to, but does not exceed 1 cm as defined by the American College of Surgeons (8) or may be less than 1 cm in greatest diameter as recommended by the American Cancer Society and in use by the Breast Cancer Detection Demonstration Projects of the National Cancer Institute (9).

Because of the various definitions of MBC used, the present study from one single institution has the following objectives:
- to present our experience with a large series of clinically occult breast cancers in relation to residual tumour after excisional biopsy.
- to compare the nodal status of nonpalpable, noninvasive
tumours, MIC of 5 mm or less, 6 to 10 mm and invasive carcinomas larger than 10 mm.

to analyse the long-term survival of nonpalpable breast carcinomas when divided according to nodal status and size of the tumour: noninvasive and MIC with the upper limit at 5 or at 10 mm.

VII.2 PATIENTS AND METHODS

In 1970 modern mammographic equipment has been installed at the St. Radboud University Hospital, Nijmegen, The Netherlands, and since then clinically occult, only radiographically visible breast carcinomas have been diagnosed with increasing frequency.

With effect from 1st January, 1975 a population screening programme has been going on in the city of Nijmegen aimed at the whole female population over 35 years of age and patients with suspicious findings were referred to the surgical department of one of the two hospitals serving the city. Thus our patient material includes a part of the population screenees.

When it was indicated that a biopsy was needed, the nonpalpable, mammographic abnormality was localized and excised by one of the methods described by us previously (10). Because of the supposedly small sizes of the nonpalpable mammographic abnormalities, an excisional biopsy had always been aimed at. Specimen radiography was considered to be mandatory. Frozen-section examination was left to the discretion of the pathologist who used to judge it feasible in nonpalpable masses of 5 mm or more, but was inclined to defer his final diagnosis until the paraffin sections were ready in case of clustered microcalcifications only and of nonpalpable masses of less than 5 mm (11).

Since 1978 all mastectomy specimens were examined using Egan's technique of correlating radiographical and histopathological findings (12-14). Our data before 1978 are based
on the routine pathology reports. In case of invasive breast carcinoma the pathological diameter was used primarily. Where this was not available in 12 cases (7.8%) we had to resort to the radiograpnical measurements. Residual tumour was defined by us as any ductal or lobular carcinomatous tissue, either invasive or noninvasive, left behind outside the biopsy cavity within the mastectomy specimen.

The treatment modality has changed in the course of time. Before 1977 radical mastectomy was the usual treatment for lateral carcinomas, while centrally and medially seated tumours were treated by simple total mastectomy combined with postoperative irradiation of the regional lymph nodes. Since 1977 modified radical mastectomy has been the treatment of choice for both lateral and central/medial tumours. This applied to invasive carcinomas, whether ductal or lobular, and noninvasive DCIS. Patients with LCIS were kept under close observation for the remainder of their lives.

At the closure of this study in March, 1986, a 100% follow-up has been attained. However, for the sake of the survival of the nonpalpable breast cancers all patients with prior, synchronous or metachronous, contralateral breast malignancies, which were palpable, have been excluded. But patients with bilateral synchronous or metachronous non-palpable tumours are included.

The estimated survival was calculated according to the life-table method (15). For comparison of the survival rates Gehan-Mantel's modification of the Wilcoxon test was used (16,17).

VII.3 RESULTS

From 1st January, 1971, through February, 1986, 153 non-palpable breast carcinomas have been treated at the department of general surgery of the St. Radboud University Hospital. This represents 17.2% of the total of 889 breast cancers operated upon during this 15-year period.
Sixty-eight cancers were found as a result of population screening while the remaining 85 cancers were detected at the surgical out-patients' department through individual screening: annual mammogram after prior contralateral mastectomy 19 x, mastodynia 16 x, mammographic control because of histologically proven 'premalignant' lesion 16 x, synchronous cancer of the opposite breast 8 x, nipple discharge 7 x, unsuspicous palpable mass elsewhere in the same breast 5 x, palpable axillary mass 4 x, positive family history 3 x, follow-up of an irradiated breast 1 x, pathological fracture of the sternum 1 x and no apparent reason 5 x.

Clusters of microcalcifications were the most frequent mammographic lesion (74=48.4%), followed by stellate shaped masses (44=28.7%), masses with microcalcifications (17=11.1%), circumscribed or nodular masses (13=8.5%), disturbed architecture (2=1.3%) and, at last, no abnormalities (3=2.0%).

The mean age of the patients was 56.4 years (range 37-78). Only three patients were younger than 40 years: one patient of 37 years had LCIS, another of 38 years had DCIS and the third patient was also 38 years of age and she had a tubular carcinoma with a diameter of 7 mm.

The several surgical treatment modalities are summarized in Table 1. Please note that excisional biopsy for invasive breast cancer (5 x) was practised only in very special circumstances: distant metastases (1 x), local recurrence in a post-irradiated breast because of a N3 tumour in the past (1 x), synchronously an inoperable T4 tumour in the opposite breast (1 x) and contralateral invasive T2 tumours in elderly people (2 x).

They all had additive radiotherapeutical and/or hormonal/chemotherapeutical treatment. Excisional biopsy for noninvasive DCIS (5 x) was also limited to exceptional cases: diagnosis made later on after revision of the pathology slide (1 x), age over 70 years (2 x), patient's refusal of further treatment (1 x) and one patient who had breast conserving treatment for a contralateral invasive T2 tumour in the past (1 x).
Table 1: Treatment modalities of nonpalpable breast cancer

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Invasive carcinoma</th>
<th>Noninvasive carcinoma</th>
<th>Others**</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;10 mm</td>
<td>6-10 mm</td>
<td>&lt;5 mm</td>
<td>DCIS</td>
</tr>
<tr>
<td>Radical mastectomy</td>
<td>7</td>
<td>2</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Modified radical mastectomy</td>
<td>30</td>
<td>21</td>
<td>8</td>
<td>23</td>
</tr>
<tr>
<td>Simple total mastectomy</td>
<td>7</td>
<td>4</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Subcutaneous mastectomy</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Lumpectomy and axillary dissection</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Excisional biopsy</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

*Irrespective of adjuvant/palliative radiotherapy and/or chemotherapy
**One case of non-Hodgkin's lymphoma and one basal cell carcinoma

DCIS = ductal carcinoma in situ
LCIS = lobular carcinoma in situ

Table 2 notes the incidence of residual tumour outside the biopsy cavity in the 118 mastectomy specimens fully evaluable histologically after prior 'excisional' biopsy. The overall incidence of residual tumour, including LCIS, was 76/118, or 64.4%. The rate of residual carcinoma is the same in the nonpalpable invasive as well in the nonpalpable noninvasive group: 64.0% versus 65.6%. When looking at the clinically occult invasive breast cancers alone, then invasive cancerous tissue would have been left behind in 34 of 86 evaluable mastectomy specimens, or 39.5%.
Table 2: Residual tumours outside the biopsy cavity after 'excisional' biopsy because of clinically occult breast cancer

<table>
<thead>
<tr>
<th>Invasive ductal or lobular carcinoma</th>
<th>Total No.</th>
<th>No. of mastectomy specimens evaluable</th>
<th>No. with residual tumour</th>
<th>% with residual tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10 mm</td>
<td>53</td>
<td>43</td>
<td>23 4 2</td>
<td>67.4</td>
</tr>
<tr>
<td>6-10 mm</td>
<td>29</td>
<td>27</td>
<td>9 3 2</td>
<td>51.9</td>
</tr>
<tr>
<td>≤5 mm</td>
<td>18</td>
<td>16</td>
<td>2 8 2</td>
<td>75</td>
</tr>
</tbody>
</table>

| Total invasive carcinoma            | 100       | 86                                   | 34 15 6                  | 64.0                   |
| DCIS                                | 39        | 30                                   | 0 19 0                  | 63.3                   |
| LCIS                                | 12        | 2                                    | 0 0 2                   | 100                    |

| Total noninvasive carcinoma         | 51        | 32                                   | 0 19 2                  | 65.6                   |
| Others                              | 2         | 0                                    | 0 0 0                   | 0                      |
| Grand total                         | 153       | 118                                  | 34 34 8                 | 64.4                   |

The axillary lymph node involvement of the different subgroups of nonpalpable breast cancers is presented in Table 3. One patient had primarily evidence of distant metastases (pathological fracture of the sternum and bone marrow involvement as proven by a needle aspiration biopsy of the
Table 3: Axillary status of patients with clinically occult breast cancer

<table>
<thead>
<tr>
<th>Invasive ductal or lobular carcinoma</th>
<th>Total No.</th>
<th>No. of axillas evaluable</th>
<th>No. with positive nodes</th>
<th>% with positive nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10 mm</td>
<td>53</td>
<td>44</td>
<td>13*</td>
<td>29.5</td>
</tr>
<tr>
<td>6-10 mm</td>
<td>29</td>
<td>24</td>
<td>3</td>
<td>12.5</td>
</tr>
<tr>
<td>&lt;5 mm</td>
<td>18</td>
<td>13</td>
<td>1</td>
<td>7.7</td>
</tr>
<tr>
<td>DCIS</td>
<td>39</td>
<td>25</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LCIS</td>
<td>12</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Others</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>153</td>
<td>108</td>
<td>17</td>
<td>15.7</td>
</tr>
</tbody>
</table>

* includes one patient with distant metastases

iliac crest). The other 16 patients had secondaries in the axilla: one patient had a positive infraclavicular apical biopsy (pN3), there was one patient with a pN2 axillary tumour and one patient with a pN1b axillary tumour. In the remaining 13 patients a detailed axillary picture was known: 4 x 1 positive lymph node, 3 x 2 positive nodes, 4 x 3 and 2 x 4 positive nodes (range of nodes examined 12-42). The non-invasive breast cancers did not show any secondary spread into the axillary lymph nodes, but the invasive breast cancers
Table 4: Clinical T-stage of tumours of the contralateral breast in ipsilateral nonpalpable breast cancer

<table>
<thead>
<tr>
<th></th>
<th>( T_0 )</th>
<th>( T_1 )</th>
<th>( T_2 )</th>
<th>( T_3 )</th>
<th>( T_4 )</th>
<th>( T_x )</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior carcinoma</td>
<td>0</td>
<td>4</td>
<td>9</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>Synchronous carcinoma</td>
<td>5</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Metachronous carcinoma</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>6</td>
<td>14</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>39</td>
</tr>
</tbody>
</table>

showed with increasing diameter more regional lymph node involvement: 7.7% in the invasive cancers equal to or smaller than 5 mm, 12.5% in the invasive cancers of between 6 and 10 mm and 29.5% in the invasive cancers of over 10 mm.

Table 4 shows the number of bilateral tumours in this series of 153 nonpalpable breast cancers. In order to avoid bias all 30 patients with a prior, synchronous and metachronous contralateral breast carcinoma, which was palpable, have been excluded for actuarial calculation of the disease-free survival. Also the patient with the basal cell carcinoma which is not a breast carcinoma strictly speaking and the patient with the local recurrence in the irradiated breast have been excluded. This leaves 121 evaluable, nonpalpable breast cancers, nine of which are bilateral.

The current status of the patients as per 1st March, 1986, is demonstrated in Table 5, which is self-explanatory.

As depicted in Figure 1 the patients with negative axillary nodes exhibit a significant better \((p < 0.001)\) disease-free survival than patients with positive nodes: 95.7% and 76.0%, respectively. The disease-free survival also differs significantly \((p < 0.01)\) in patients with noninvasive carcinoma and \(\text{MIC} < 10 \text{ mm}\) (97.7%), when compared with invasive tumours.
Table 5: Current status* of patients with 153 nonpalpable breast cancers

<table>
<thead>
<tr>
<th>Feature</th>
<th>Total no.</th>
<th>NED</th>
<th>AWD</th>
<th>DOC</th>
<th>DWD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusions</td>
<td>121</td>
<td>109</td>
<td>2</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Exclusions</td>
<td>32</td>
<td>23</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

* Closure of the study: 1st March, 1986
100% follow-up
Mean observation period 68.9 months (range 1-174)

Abbreviations: NED = No Evidence of Disease
AWD = Alive With Disease
DOC = Dead of Other Cause
DWD = Dead With Disease

>10 mm (77.3%), as shown in Figure 2. However, there is no significant difference (p = 0.06) in disease-free survival, when noninvasive carcinoma and MIC £ 5 mm are compared with invasive tumours > 5 mm.

The overall survival was significantly higher (p < 0.0001) in patients with negative axillary nodes than in the group of patients with positive nodes: 96.7% versus 72.2%, respectively (see Figure 3). At last, the overall survival achieved statistical significance (p < 0.03) and is better in noninvasive carcinoma and MIC £ 10 mm (96.9%) than in invasive tumours measuring over 10 mm (83.6%), as demonstrated in Figure 4. When the upper limit for invasive cancer is drawn at 5 mm, however, then there is no statistical difference (p = 0.14) in overall survival between noninvasive carcinoma and MIC £ 5 mm in comparison with invasive carcinoma > 5 mm.

No statistically significant differences have been found in disease-free survival (p = 0.26) and overall survival (p = 0.42) between pre- and postmenopausal women. Furthermore,
Figure 1:
Disease-free survival in non-palpable breast cancer according to axillary nodal status

Figure 2:
Disease-free survival in non-palpable breast cancer according to tumour size

I = noninvasive carcinoma + minimally invasive carcinoma ≤ 10 mm
II = invasive carcinoma > 10 mm
Figure 3:
Survival in nonpalpable breast cancer according to axillary nodal status

Figure 4:
Survival in nonpalpable breast cancer according to tumour size
I = noninvasive carcinoma
   + minimally invasive
carcinoma ≤ 10 mm
II = invasive carcinoma > 10 mm
patients with nonpalpable breast cancer originating from the population screening programme had no better disease-free survival \( p = 0.31 \) or overall survival \( p = 0.10 \) than patients who were detected as a result of individual screening.

Noninvasive DCIS and LCIS were not associated with positive axillary nodes and the disease-free survival was 100\%, after a mean observation period of 66.1 months (range 4-174).

VII.4 DISCUSSION

First of all we should reconsider some definitions in respect of favourable phases of breast cancer.

With 'early' is commonly meant any carcinoma not associated with axillary lymph node metastasis, i.e. mainly stage I \((T_1N_0M_0)\) disease, but also a few in stages II \((T_2N_0M_0)\) and III A \((T_3N_0M_0)\) according to the American Joint Committee on Cancer Classification (18).

'Minimal' breast cancer was originally designated to include DCIS, LCIS and MIC ≤ 5 mm \((1,4,5)\). Others limited themselves to DCIS and MIC of the ductal type only up to and including 5 mm \((6)\) or extended the definition to all invasive cancers 1 cm or less in diameter presenting in the outer half of the breast only and with clinically no evidence of axillary lymph node metastases and also including some low-grade infiltrating cancers like adenoid cystic carcinoma, colloid carcinoma, intracystic papillary carcinoma, tubular carcinoma and malignant cystosarcoma phyllodes \((3)\). In recent years the American College of Surgeons in their breast cancer surveys redefined MBC as any DCIS, LCIS or any invasive carcinoma of either pathological type measuring 1 cm or less \((8)\), while the Breast Cancer Detection Demonstration Projects included the same category only when the invasive lesion was less than 1 cm in its greatest diameter \((9)\).

The term 'occult' or 'subclinical' breast cancer is reserved for nonpalpable cancers which are usually demonstrable
only by mammographic means. In the absence of any roentgenologic abnormality in the breast occult breast cancer may also be a serendipitous finding when performing excision of breast tissues on other grounds.

So occult cancer may not be minimal, if over 0.5 or 1 cm, when buried deeply within large or nodular breasts, although the majority of the occult cancers will be minimal. Depending on which definition of MBC is used, 69/151 or 45.7% of our series was in situ carcinoma or MIC ≤ 5 mm, and 98/151 or 64.9% was in the category of in situ carcinoma or MIC ≤ 10 mm.

Most occult cancers will also be early, but positive axillary lymph nodes do occur. Again, depending on the definition, the rate of positive axillary lymph nodes is 1/40 or 2.5%, if we consider the in situ carcinomas and MIC ≤ 5 mm, and 4/64 or 6.3%, if in situ carcinomas and MIC ≤ 10 mm are counted. Conversely, many early cancers are too large to fit in the diagnosis clinically occult or subclinical.

Through the use of mammography in population and individual screening an ever increasing number of nonpalpable breast cancers is emerging, representing a special subgroup of clinically occult cancers amongst the T1 tumours. The occult tumours differ from those, that surfaced clinically as a palpable mass, through their lead time, which is estimated at approximately three years (19,20). Also length bias plays a role because fast growing interval cancers, which become palpable between two roentgenologic screening examinations, are missed mammographically (21,22). Schwartz et al (23) have proposed that for staging of nonpalpable breast cancer the mammographic size of the mass be considered with the addition of the notation that it was discovered by mammography, for instance T1(m), T2(m) etc. The nonpalpable breast cancers detected by clustered microcalcifications and areas of distorted architecture without a roentgenologic mass should then be staged T0(m). Similarly, T1S could be modified into T1S(m), if it refers to an occult DCIS or LCIS detected mammographically.
The prognosis of clinically occult breast cancers has recently been reported to be extremely good with long-term survival rates of 95% (24) and 96.8% (25).

Our actuarial estimates of 10-year survival of non-invasive and small invasive carcinomas < 10 mm reaches 96.9% and is well comparable with the aforementioned results. The indicator of this good prognosis is the low rate of positive axillary lymph nodes (6.3%) amongst these tumours. This is illustrated by the fact that node-negative patients with occult tumours do have a 96.7% long-term actuarial survival rate.

On the other hand, occult invasive carcinomas > 10 mm show a 29.5% rate of positive axillary lymph nodes and are associated with a less favourable long-term actuarial survival rate of 83.6%. This is reflected in the finding that node-positive patients, whose tumours have been detected by mammography alone, have a long-term survival of only 72.2%.

This means that nodal status (negative vs. positive) and size of the invasive tumour (equal to or less than 10 mm vs. over 10 mm) are both strong determinants of prognosis in clinically occult breast cancer. As a result of this we concur with the American College of Surgeons' definition (8) that the upper limit of MIC is at 10 mm and that MBC includes, apart from non-invasive DCIS and LCIS, all invasive lesions of 10 mm or less.

The prognosis was not influenced by the fact whether the patient was detected by population or individual screening which means that the mammogram itself has a certain predictive value per se.

Contrary to others (25), who found better survival in women over 50 years of age with clinically occult breast cancer, we did not find any difference in relation to menopausal status.

The high rate (64%) of residual tumour in nonpalpable breast cancer implies that the whole breast must be subject of treatment, whether surgically or radiotherapeutically. This
has been discussed by us already in detail elsewhere (14). The only exceptions are patients with noninvasive LCIS who are kept under periodical follow-up examinations for the rest of their lives (26).

Then remains the question whether or not an axillary dissection should be done. Though positive axillary nodes have been described in association with DCIS (27,28), we did not encounter any axillary lymph node involvement in 27 fully evaluable specimens of axillas in patients with noninvasive carcinoma. That is why we think that axillary dissection in noninvasive carcinoma is unwarranted, provided the whole breast is thoroughly examined histopathologically in order to rule out hidden foci of invasive cancer. In invasive cancer, however, the rate of positive axillary lymph nodes in patients with invasive carcinoma ≤ 10 mm is low (4/37 or 10.8%), albeit not insignificant. Of the four patients with axillary involvement in this category one patient had one positive lymph node at level I, two patients had three positive nodes at level II and another one had one positive node at level III. All are disease-free alive after 157, 44, 7 and 2 months, respectively. We, therefore, believe that the removal of only the basal, level I nodes in invasive cancer ≤ 10 mm is insufficient locoregional treatment and a complete axillary dissection should be performed. Similarly, invasive breast cancer > 10 mm, with axillary metastases at a rate of 29.5%, must be treated by full axillary dissection.

Although possible lead time and length bias (21) should be taken into account, the above reported long-term recurrence and survival results of nonpalpable breast cancer from one single institution show an excellent prognosis and support the view derived from various population screening programmes (29-31) that secondary prevention of breast cancer can save more lives.
One hundred and fifty-three nonpalpable breast cancers have been diagnosed and treated since 1971, including 100 invasive carcinomas, 39 in situ ductal carcinomas and 12 lobular carcinomas in situ. Of the 100 clinically occult invasive carcinomas, 53 had pathologic diameters of more than 10 mm, 29 had a size of between 6 and 10 mm, and 18 were tumours of 5 mm or less.

Residual tumour outside the 'excisional' biopsy cavity was encountered in 64.4% of the 118 fully evaluable mastectomy specimens. Invasive residual tumour would have been left behind in 34 of 86 (39.5%) mastectomy specimens.

No patient with in situ carcinoma had evidence of axillary lymph node metastases in 27 specimens studied. Invasive carcinoma, however, showed axillary lymph node involvement in 7.7% when the size of the primary tumour was not more than 5 mm, in 12.5% when the size was between 6 and 10 mm, and in 29.5% when the primary tumour was over 10 mm in diameter.

There was a significantly better disease-free (p<0.001) and overall survival (p<0.0001) in patients with clinically occult breast cancer with negative axillary nodes (95.7% and 96.7%, respectively) than in patients with positive axillary nodes (76.0% and 72.2%, respectively). If the upper limit of occult invasive carcinoma was drawn at 10 mm, then statistically significant differences in disease-free (p<0.01) and overall survival rates (p<0.03) were achieved for occult minimal breast cancer (noninvasive carcinoma + invasive carcinoma ≤10 mm) (97.7% and 96.9%, respectively) versus occult invasive carcinoma >10 mm (77.3% and 83.6%, respectively). However, if the upper limit of occult invasive carcinoma was chosen at 5 mm, then no statistically significant differences (p>0.05) could be obtained in disease-free and overall survival rates between occult minimal breast cancer (noninvasive carcinoma + invasive carcinoma ≤5 mm) and occult invasive carcinoma >5 mm. Also there was no significant difference (p>0.05) in disease-free
and overall survival between pre- and postmenopausal women with clinically occult breast cancer.

In conclusion, the validity of the concept of minimal breast cancer has been re-enforced. However, the results of this study suggest that the upper limit of the original definition of minimal breast cancer is too narrow and should be extended, so that, apart from the noninvasive tumours regardless of their size, all invasive tumours up to and including 10 mm in greatest diameter should be regarded as minimal breast cancers.

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Borstkanker bij de vrouw is een maatschappelijk belangrijk gezondheidsprobleem in Nederland, dat één op de twaalf vrouwen in de loop van hun leven zal treffen. Aangezien de lange-termijn overleving na therapie al vele jaren vastligt op ongeveer 60% en afhangt van het klinische stadium waarin de patiënt zich voor het eerst met een palpabele tumor presenteert, is alle hoop op verbetering van de prognose gevestigd op vroege opsporing, dat wil zeggen ontdekking in een stadium wanneer de tumor nog niet palpabel is. De beste techniek om borstkanker in zo een vroeg, nog niet-palpabel stadium op te sporen, is het mammografisch onderzoek. Recente gegevens uit enkele bevolkingsonderzoeken, met behulp van mammografie, wijzen er onderdaad op dat de prognose door vroege opsporing kan verbeteren. De clinicus-practicus wordt in toenemende mate geconfronteerd met niet-palpabele, slechts röntgenologisch zichtbare mamma-afwijkingen. Dit proefschrift tracht enkele aspecten hiervan te verhelderen, gezien vanuit het standpunt van de chirurg.

Het localiseren en excideren van niet-palpabele borstafwijkingen wordt geëvalueerd in hoofdstuk I.

Er worden drie methoden om niet-palpabele, maar mammografisch verdachte borstafwijkingen te excideren met elkaar vergeleken: (1) 'blinde' methode, gebruik makend van mammografische coördinaten, (2) preoperatieve localisatie met behulp van de naald van Frank, en (3) localisatie met de naald van Frank via een compressieplaat met multipele gaatjes. In ongeveer 80% gelukte het, met welke methode dan ook, om de bewuste röntgenologische afwijking bij de eerste biopsiepoging te verwijderen. De grootte van de biopsie verschilde ook niet significant in de drie groepen en is waarschijnlijk afhankelijk van het borstvolume. In zeven van de 332 (2.1%) biopsieën werd het verdachte röntgenologische plekje niet verwijderd tijdens de eerste operatie.

Aangezien drie van de zes biopsieën in tweede instantie
na een heroperatie toch nog een maligniteit opleverden, is de conclusie gewettigd dat een persisterende, röntgenologisch verdachte afwijking op een postoperatief controle-mammogram een indicatie is om opnieuw te opereren.

Hoofdstuk II gaat over de betekenis van microcalcificaties zonder palpabele massa voor de diagnostiek van het mammarcinoom.

Zuivere microcalcificaties vormen een belangrijk gedeelte van de niet-palpabele borstafwijkingen en kunnen het eerste, zichtbare teken van een mammarcinoom zijn. Tussen 1975 en 1984 werden 150 patiënten behandeld met groepjes van tenminste vijf microcalcificaties als enige indicatie voor mammabiopsie. In totaal werden 173 groepjes microcalcificaties verwijderd en er werden 51 maligniteiten ontdekt (29.5%). De meeste maligne laesies waren niet-invasief (56%). Axillaire metastasen of metastasen op afstand werden in 11% van de volledige evalueerbare gevallen gevonden. Dit wettigt de verwachting dat deze patiënten een zeer gunstige prognose hebben.

Het biopteren van niet-palpabele, gegroepeerde zuivere microcalcificaties is een uitvoerbare en waardevolle procedure, waarvoor een nauwe samenwerking is vereist tussen chirurg, röntgendiagnost en patholoog-anatoom.

In hoofdstuk III wordt de correlatie nagegaan tussen het mammografische beeld en de patholoog-anatomische diagnose van niet-palpabele mamma-afwijkingen met in het bijzonder de betrouwbaarheid van het peroperatieve vriescoupe-onderzoek.

Van de 359 biopsieën bij 321 patiënten wegens niet-palpabele, mammografische laesies bleken er 118 of 32.9% maligne te zijn. Ongeveer de helft van de laesies was gelocaliseerd in het laterale bovenkwadrant. De links/rechts verhouding was 1.22 voor de biopsieën en 1.19 voor de occulte carcinomen. De 'malignancy rate' was 12.7% in geval van een circumscription of nodulaire schaduw, 32.4% voor de zuivere, gegroepeerde microcalcificaties, 28.6% als een schaduw met microcalcificaties werd gezien en 66.7%, wanneer een stervormige schaduw aanwezig was. Er waren 76 invasieve carcinomen, waarvan 17 tubulaire
carcinomen. Veertig waren niet-invasieve carcinomen: 32 DCIS en 8 LCIS, voornamelijk behorend tot de groep van de zuivere, gegroepeerde microcalcificaties. Overige: twee. De gemiddelde leeftijd van de patiënten met invasief mammacarcinoom was 59.8 jaar (spreiding 42-76) en bij de patiënten met niet-invasief carcinoom 52.1 jaar (spreiding 37-68).

De uitslagen van het vriescoupe-onderzoek werden vergeleken met die van de uiteindelijke paraffine-coupes en een correcte diagnose werd in 68.0% van de gevallen gesteld. In 17.3% werd geen vriescoupe-onderzoek verricht en in 12.2% werd de diagnose als een voorlopige afgegeven en geadviseerd de definitieve paraffine-coupes af te wachten. Er waren zeven fout-negatieve (1.9%) en twee fout-positieve (0.6%) uitslagen, beide gevallen van floride scleroserende adenose. Het vriescoupe-onderzoek is zelfs bij de niet-palpabele borstlaesies een technisch uitvoerbare en betrouwbare methode van onderzoek gebleken op voorwaarde dat de patholoog-anatoom bij twijfel niet moet aarzelen om te adviseren de definitieve paraffine-coupes af te wachten. Röntgenologische controle van het biopt, hetzij in toto of nadat het in plakjes gesneden is, is echter in alle gevallen noodzakelijk. Het is waarschijnlijk verstandig het vriescoupe-onderzoek niet te gebruiken voor zuivere microcalcificaties en zeer kleine schaduwtjes van 5 mm of kleiner.


Het voorkomen van steroidhormoonreceptoren (oestradiol-receptor=ER en progesteronreceptor=PgR) bij het niet-palpabele mammacarcinoom werd nagegaan in hoofdstuk IV. Vier groepen patiënten, vergelijkbaar in gemiddelde leeftijd en menopauze-status, werden bestudeerd met betrekking tot hun steroidreceptorphenotype. De eerste groep bestond uit
patiënten met niet-palpabel primair mammacarcinoom, de tweede groep uit palpabele en operabele primaire mammacarcinoom-patiënten, de derde groep had een locaal of regionaal reeds voortgeschreden primair mammacarcinoom en de vierde groep bestond uit patiënten ten tijde van hun eerste metastase. Er was een statistisch significante verschuiving in receptor-phenotype (ER+ PgR+) van het niet-palpabel mammacarcinoom (71%) via het palpable en operable primaire mammacarcinoom (58%) en het locaal of regionaal reeds voortgeschreden primaire mammacarcinoom (48%) naar het uitgezaaide mammacarcinoom ten tijde van de eerste metastase (41%).

Extrapolatie van deze gegevens geeft steun aan de theorie dat elk mammacarcinoom vanaf het begin van zijn ontstaan steroidreceptoren bevat en hormoonafhankelijk is.

Hoofdstuk V handelt over de multicentriciteit van het niet-palpabel mammacarcinoom en de consequentie die dit heeft voor het therapeutisch handelen.

Tussen 1975 en 1984 werden 100 klinisch occulte borstkankers ontdekt, 65 hiervan waren invasief en 35 niet-invasief (27 x DCIS en 8 x LCIS). Drieëntachtig mastectomiepreparaten waren evalueerbaar met betrekking tot het voorkomen van multifocaal carcinoom in een ander kwadrant van de borst of op 5 cm afstand van de referentie-tumor, en wat betreft resttumor buiten de biopsieholte. Multicentriciteit was aanwezig bij 47% en resttumor bij 60% van de hele groep. Als alleen de klinisch occulte, invasieve carcinomen werden beschouwd, dan werden andere haarden van invasief carcinoom aangetoond bij 26% van de patiënten, en achtergelaten invasief carcinoom buiten de biopsieholte bij 35%. Het bilateraal voorkomen van mammacarcinoom in deze serie was 14%, waarvan 11% synchroon voorkwamen.

Ieder therapeutisch beleid bij het niet-palpabel mammacarcinoom, hetzij invasief carcinoom of niet-invasief ductaal carcinoom, moet gericht zijn op de hele borst. Mammografie van de contralaterale zijde behoort een integraal onderdeel te zijn van de preoperatieve voorbereiding van patiënten met
een palpabele laesie ipsilateraal.

In hoofdstuk VI wordt de betekenis van het mammografisch onderzoek voor het ontdekken van contralateraal primair mammacarcinoom nagegaan aan de hand van 55 patiënten met een dubbelzijdig mammacarcinoom.

Vijftien van de 23 patiënten (=65%) in de synchrone groep en 16 van de 32 patiënten (=50%) in de metachrone groep hadden een klinisch occult carcinoom in de andere borst. Wanneer afgezien wordt van de twee maligniteiten die ontdekt werden door een prophylactische mastectomie, dan was mammografie louter verantwoordelijk voor het ontdekken van 29 niet-palpabele, contralaterale mammacarcinomen (=52.7%). De hele serie van 110 borsten met maligniteit bevatte 41 niet-palpabele carcinomen, waarvan 12 niet-invasieve (7 x DCIS en 5 x LCIS) en de overige 29 invasieve carcinomen, hetzij ductaal van welk type dan ook (25 x) of lobulair (4 x). Voor zover de okselklieren evalueerbaar waren, hadden 20 van de 37 palpabele borstcarcinomen (=54.1%) en slechts drie van de 26 niet-palpabele borstkakers (=11.5%) positieve klieren. De 'multicentricity rate' was bijzonder hoog bij synchrone tumoren (70.6%), en bij invasief lobulair (=73.3%) en niet-invasieve (=75%) carcinomen.

De gunstige 5- en 10-jaars overleving van de patiënten, zowel met synchroon als met metachroon dubbelzijdig primair borstkanker, pleit ervoor deze patiënten op dezelfde manier te behandelen als patiënten met enkelzijdig mammacarcinoom en niet met pessimisme tegemoet te treden.

En hoofdstuk VII beschrijft de behandelingsresultaten van niet-palpabel mammacarcinoom.

Van de 151 niet-palpabele mammacarcinomen, die sedert 1971 werden gediagnostiseerd en behandeld, waren 100 invasieve carcinomen, 39 DCIS en 12 LCIS. Van de 100 klinisch occulte, invasieve carcinomen waren er 53 met een diameter groter dan 10 mm, 29 met een grootte van 6-10 mm, en 18 waren tumoren kleiner dan 5 mm.

Bij 64.4% van de 118 volledig evalueerbare mastectomie-preparaten werd nog resttumor buiten de excisiëriopsieholte
aangetroffen. Invasieve resttumor zou achtergelaten zijn bij 34 van de 86 (39.5%) mastectomiepreparaten.

Van 27 patiënten met in situ carcinoom was de okselstatus bekend en bij geen van hen werden okselkliermetastasen gevonden. Bij de invasieve carcinomen echter waren okselkliermetastasen aanwezig in 7.7% als de primaire tumor kleiner was dan 5 mm, in 12.5% bij een grootte van 6-10 mm, en in 29.5% als de primaire tumor groter dan 10 mm was.

Er was een significant betere ziekte-vrije (p<0.001) resp. algehele overleving (p<0.0001) bij patiënten met klinisch occult mammacarcinoom en negatieve okselklieren (95.7% resp. 96.7%) dan bij patiënten met positieve okselklieren (76.0% resp. 72.2%). Indien de bovengrens van occult invasief carcinoom werd gelegd bij 10 mm, dan werden er statistisch significante verschillen in ziekte-vrije (p<0.01) resp. algehele overleving (p<0.03) gevonden tussen occult 'minimal breast cancer' (= niet-invasief carcinoom + invasief carcinoom <10 mm) (97.7% resp. 96.9%) en occult invasief carcinoom >10 mm (77.3% resp. 83.6%). Echter, indien de bovengrens van occult invasief carcinoom werd gesteld op 5 mm, dan waren er geen statistisch significante verschillen (p>0.05) in ziekte-vrije en algehele overleving tussen occult 'minimal breast cancer' (= niet-invasief carcinoom + invasief carcinoom <5 mm) en occult invasief carcinoom >5 mm. Ook werd er geen significant verschil (p>0.05) gevonden in ziekte-vrije en algehele overleving tussen pre- en postmenopauzale vrouwen met occult mammacarcinoom.

Concluderend kan gesteld worden dat het begrip 'minimal breast cancer' een zinvol begrip is, echter met dien verstande dat de grenzen van de oorspronkelijke definitie te nauw zijn en moeten worden uitgebreid, zodat naast de niet-invasieve tumoren, ongeacht hun grootte, ook alle invasieve tumoren tot en met 10 mm in grootste diameter moeten worden beschouwd als 'minimal breast cancers'.

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Thereafter he studied medicine at the Catholic University of Nijmegen. In 1969 he stayed for four months at Sumve District Hospital, Tanzania. After graduation on March 20th, 1970, he worked for half a year as a surgical registrar in the Canisius Hospital, Nijmegen (W.M. Fokke, surgeon) and for half a year as a registrar in gynecology/obstetrics at the St. Lambertus Hospital, Helmond (Dr. G.A.J. Dunselman, gynecologist). Meanwhile he had followed the National course in tropical medicine and hygiene at the Royal Tropical Institute in Amsterdam (1970/1971). From August, 1971 till September, 1976 he was employed by the Ministry of Health in Malawi, where he served as a Government Medical Officer at Zomba General Hospital (1971-1972), District Medical Officer of Mzimba District Hospital (1972-1974) and Medical Superintendent of Lilongwe General Hospital (1975-1976).

In November, 1976 he commenced his training in general surgery at the St. Radboud University Hospital, Nijmegen, in the Department of General Surgery (head: Prof.Dr. W.J.H. Schmidt, and since February 1977: Prof.Dr. H.H.M. de Boer). In 1981 he spent half a year as a senior registrar in the Department of General Surgery of the Municipal Hospital, Arnhem (head: Dr. M.N. van der Heyde). He was registered as a general surgeon on November 1st, 1982. In March 1983 he did a locum in the Zuiderzee Hospital, Lelystad. On November 1st, 1984, he moved from Nijmegen to the Municipal Hospital, Arnhem. With effect from August 1st, 1986 he was appointed chef de clinique at the Department of General Surgery, Academic Medical Centre, University of Amsterdam (head: Prof.Dr. M.N. van der Heyde).
STELLINGEN

behorende bij het proefschrift

SURGICAL ASPECTS OF NONPALPABLE BREAST CANCER

J.G.M. Tinnemans
I
Gezien de multicentriciteit van het mammacarcinoom moet ook de locale behandeling van het niet-palpabele mamma-carcinoom, hetzij chirurgisch hetzij radiotherapeutisch, gericht zijn op de gehele borst (dit proefschrift).

II
Onder het begrip 'minimal breast cancer' dienen te vallen zowel alle in situ carcinomen als ook de invasieve carcinomen met een diameter van 10 mm of kleiner (dit proefschrift).

III
Mammografie van de contralaterale zijde is aangewezen bij de preoperatieve voorbereiding van palpabele afwijkingen ipsilateraal en bij de periodieke controle van postmastectomie-patienten (dit proefschrift).

IV
Er zijn aanwijzingen dat alle mammacarcinomen bij het begin van hun ontstaan steroidhormoon-receptoren bevatten (dit proefschrift).

V

VI
Indien bij een adolescent met een enkeltrauma op de voor-achterwaartse röntgenfoto een fractuur Salter-Harris type III en op de zijdelingse röntgenfoto een fractuur Salter-Harris type II wordt gezien, is er sprake van een triplane (drievlaks) fractuur van de distale tibia epiphyse en moet er een CT-scan van de enkel worden gemaakt (Tinnemans en Severijnen. Injury 1981; 12: 393-396).
VII
Bij ernstige comminutieve fracturen van het olecranon, waarbij een oefenstabiele, anatomische reconstructie niet mogelijk is, is excisie van de losse olecranonfragmenten en re-insertie van de tricepspees aan de ulna de therapie der keuze, mits de processus coronoides behouden blijft (Estourgie en Tinnemans. Neth J Surg 1982; 34: 127-129).

VIII
Het laat zich aanzien dat de terescardiopexie een goede chirurgische techniek is ter behandeling van de symptomatische refluxoesophagitis. Wegens de betrekkelijke eenvoud van de operatie en het gebruik van lichaamseigen materiaal is een prospectief vergelijkend onderzoek met andere operatiemethoden gewenst (B. Narbona. Hernia hiatal reflujo gastroesofagico <terescardiopexia>. Valencia 1981).

IX
Voor de kleine letteren faculteiten valt te vrezen dat bij de huidige bezuinigingsdrift wordt vergeten dat de universiteit niet alleen onderwijs- en onderzoeksinstituut is, maar ook cultuurdrager.

X
De toekenning van de Nobelprijs voor literatuur aan de Nigeriaanse schrijver Wole Soyinka is niet alleen een teken van emancipatie van de zwarte neo-Afrikaanse cultuur, maar evenzeer van de bekronende Nobelprijscommissie die de laureaat heeft gezocht in een niet-westerse beschaving.

XI
De mens wordt verraden als hem niets meer dan de mens wordt geboden (Gabriel Marcel).