Nonpalpable breast lesions:

challenges in diagnosis and treatment

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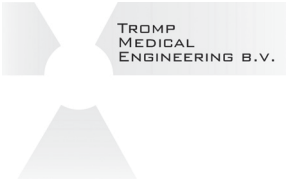

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Nonpalpable breast lesions:

challenges in diagnosis and treatment

(with a summary in Dutch)

Niet palpabele borstafwijkingen:

uitdagingen in diagnose en behandeling

(met een samenvatting in het Nederlands)

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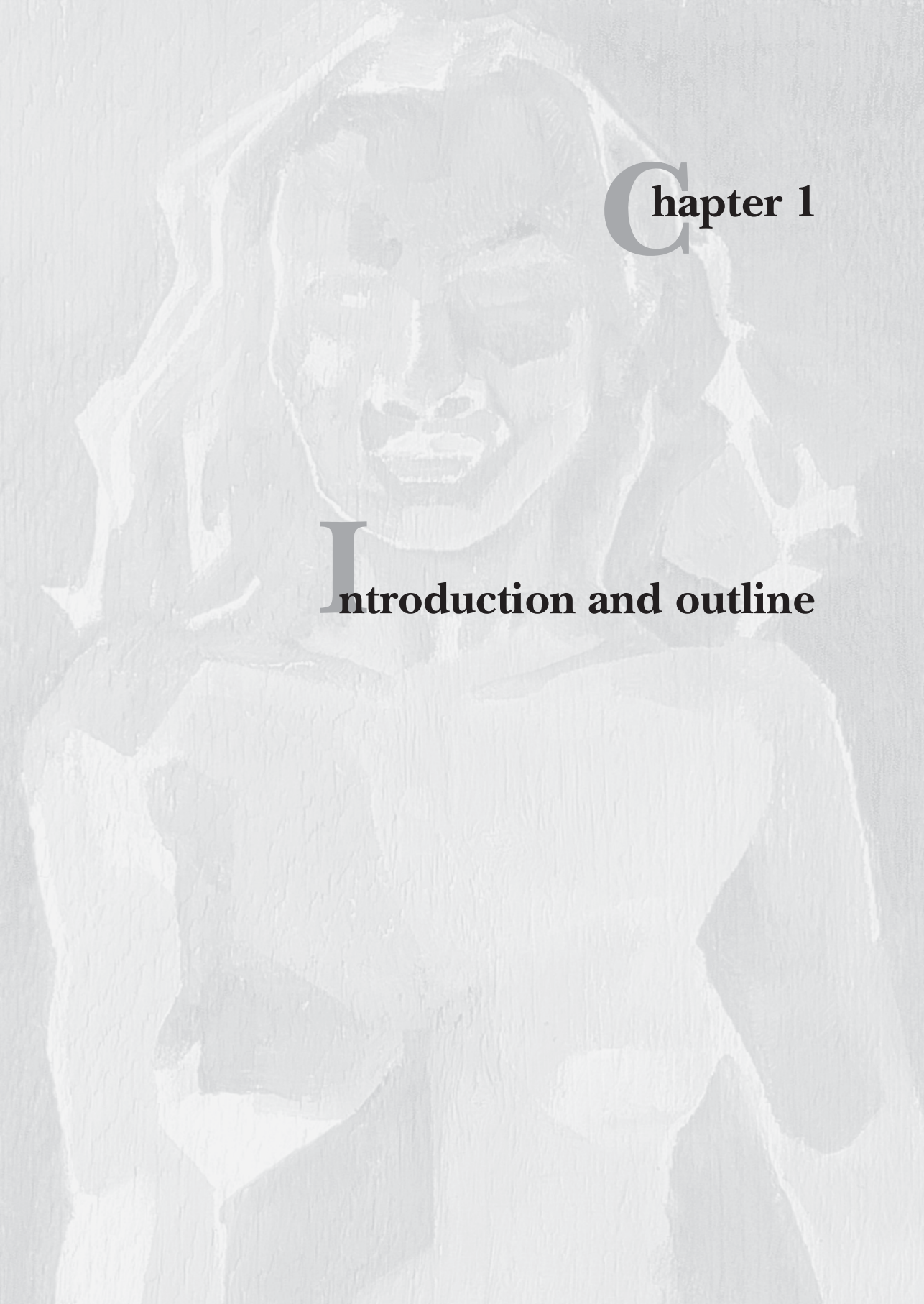

Chapter 1

Introduction and outline

Introduction

Breast cancer is the most common malignancy in women and the leading cause of death for women aged 25-64 years in western countries. Approximately one out of every nine women is diagnosed with breast cancer at some point during her life. The number of breast cancer cases has been increasing worldwide in the past decades.[1;2] This increase is influenced by a growing and ageing population, a later age at the birth of a first child, earlier menarche, as well as by the introduction of national mammographic screening programs.[1;2]

The aim of screening asymptomatic women mammographically is to detect breast cancer at an earlier stage, so that less aggressive treatment can be offered and mortality be reduced.[2-5] In the Netherlands, all women aged 50-70 (and since 1998, 50-75) years are invited to participate.[6;7] The participation rate is 80%.

Since most of the discovered mammographic abnormalities are nonpalpable, confirmation of the diagnosis is a challenge for the surgeon. Diagnostic wire-localised surgical breast biopsy has long been the gold standard for diagnosing nonpalpable breast disease. To localise the lesion, a radio-opaque wire is inserted into the breast using image guidance. The surgeon then excises breast tissue surrounding the tip of the wire, careful to minimise the sample volume. A specimen radiograph is obtained to ensure that the excised specimen contains the lesion. A histological tissue diagnosis can then be obtained at the pathology department. A review article describing 49 articles published between 1976 and 1997 on the diagnostic wire localised surgical excision, reported that on average 2.6% of the nonpalpable lesions was not removed by the surgery, resulting in a missed cancer rate of 2%.[8] However, the studies described in this review had a short follow-up. Verkooijen et al. reported that the sensitivity for diagnostic surgical excision decreased to 96% after 5 years follow-up, i.e. that 4% of cancers was originally missed.[9] Since, in the Netherlands, approximately 50% and in the USA about 80-90% of women referred for histological confirmation of a nonpalpable breast lesion, turn out to have benign disease,[6] using surgical excision to get a diagnosis is clearly undesirable. To overcome the disadvantages of the diagnostic surgical excision biopsy, various minimally invasive, percutaneous, diagnostic breast biopsy techniques have been developed in the last decade.[10]

Image guidance

Image guidance is essential for percutaneous biopsy of nonpalpable breast lesions, since they cannot be located by tactile perception. This can be performed with the aid of ultrasound, conventional (stereotactic) X-ray, or more recently, magnetic resonance imaging (MRI). Ultrasound guidance is particularly suitable for mammographically detected densities and stellate lesions or cysts; approximately 80% of the lesions can be visualised with this technique.[11] An advantage of ultrasound guided breast biopsy is the real-time visualisation during the biopsy procedure and the fact that essentially every hospital has ultrasound equipment. A disadvantage is, that the diagnostic accuracy of this technique is rather operator-dependant. Lesions consisting of mammographic calcifications are better approached by conventional x-rays than ultrasound.[12] Overall, the diagnostic accuracy of ultrasound guided needle biopsy for nonpalpable breast lesions has not been thoroughly investigated; no prospective randomised trials exist to date that compare ultrasound guided needle biopsy to stereotactic guided biopsy or diagnostic surgical excision.

When conventional x-rays are projected in two different angles, a three-dimensional (stereotactic) projection of the suspicious lesion can be visualised. Stereotactic mammographic evaluation can be applied for all lesions, including those consisting of microcalcifications only. Stereotactic imaging can be performed with add-on equipment, mounted on an existing mammography unit, or with a dedicated prone biopsy table.[13;14] Large randomised studies comparing the diagnostic performance of the add-on equipment to the prone table are not available. Studies using the dedicated prone table have shown very good results in very large series,[15] but results of the add-on equipment are only scarcely available in current literature.[13;16] The prone position is much more comfortable for the patient, since vasovagal reactions are reduced and the biopsy equipment and biopsy procedure cannot be seen by the patient. Prone biopsy tables obtain localisation images in digital format and these are available almost instantaneously.

MR imaging can reveal breast cancer that is not detected on mammography, ultrasound or physical examination.[17;18] MR imaging has a high sensitivity in detecting breast cancer, approaching 100%, but the reported specificity ranges from 37-97%.[17;18] Although MR imaging is most sensitive for the detection of small tumours, routine preoperative MR imaging appears to be unnecessary for most patients if a combination of mammography and breast sonography is used.[19] For the evaluation of the extent of breast cancer, e.g. to evaluate multicentricity or multifocality of disease, MR imaging seems promising.

Enthusiasm exists for the potential for breast MR imaging to address the problem of screening high-risk women.[20] Published experience with MR-guided large-core needle biopsy is limited.[17;21-23]

Percutaneous breast biopsy techniques

Fine needle aspiration (FNA; 20-24-gauge) of nonpalpable breast lesions is used to obtain cytologic material. Reported sensitivity rates of FNA vary between 43.8% and 91.7%.[24;25;25] Malignant cells can be diagnosed, but a distinction between ductal carcinoma in situ (DCIS) and invasive carcinoma cannot be made, while nondiagnostic results are rather common: up to 38.8% in an overview of 10 studies on ultrasound guided FNA-cytology.[26] In addition, approximately 15% of malignancies were missed with ultrasound guided FNA.[26] FNA is unsuitable for lesions consisting of microcalcifications only.[24;27] The use of FNA in the diagnosis of nonpalpable breast lesions is questionable, if not obsolete.[28]

In contrast, large-core needles (14-gauge) may be used to obtain histologic tissue samples of a nonpalpable suspicious breast lesion. This results in almost no misdiagnoses while a distinction between DCIS and invasive cancer can be made preoperatively.[15] Biopsy specimens are taken by using an automated gun firing multiple passes. The diagnostic accuracy of the stereotactic large-core needle biopsy and that of diagnostic surgical excision were compared in the COBRA study (below).[29]

Vacuum-assisted breast biopsy was developed to obtain larger samples, without the need to withdraw the needle before all biopsy specimens are retrieved. Mostly 11-gauge needles are used, but the use of 14- and 8-gauge has been reported as well.[30;31] Large prospective, randomised trials comparing its accuracy with the diagnostic surgical excision have not been reported. An advantage seems to be the more thorough sampling of lesions consisting of calcifications only in comparison to stereotactic 14G automated needle biopsy. Disadvantages are the higher costs associated with the disposable material of this technique, and the need to leave a radio-opaque marker in place to permit future identification of the biopsy site, e.g. when surgical excision is indicated.

The COBRA study

The diagnostic accuracy of stereotactic large-core (14-gauge) needle biopsy (SLCNB) for the evaluation of nonpalpable breast lesions was explored in the Dutch COBRA (*CO*re *B*iopsy after *RA*diological localisation) study.[29] This was a multicenter study starting

in June 1997 and funded by the Dutch National Health Insurance Council (Fund for Investigative Medicine OG97-032). The COBRA study was co-ordinated by the University Medical Center Utrecht, with co-operation of five centers: University Medical Center Utrecht, Antoni van Leeuwenhoek Hospital Amsterdam, Bosch Medicentrum Den Bosch, Dr Daniel den Hoed Clinic Rotterdam and Martini Hospital Groningen.
The conclusion of the study was that SLCNB can reliably replace needle localised surgical excision for the diagnosis of nonpalpable breast lesions. Accordance to the proposed recommendations for the management of SLCNB diagnoses (Table 1) will result in a sensitivity rate of 97% and a specificity of 99%.[29]

Table 1: Recommendations for management of different large-core needle diagnoses

Large-core needle diagnosis	Strategy
Normal breast tissue	Repeat LCNB or surgical excision
Benign but discordant with mammography	Repeat LCNB or surgical excision
Benign* and concordant with mammography	Mammographic follow-up
High-risk lesion**	Surgical excision
DCIS	Surgical excision
Invasive breast cancer	Surgical excision + axillary assessment

LCNB = large-core needle biopsy; DCIS = ductal carcinoma in situ
** including complex sclerosing adenosis (radial scar)*
*** atypical (ductal or lobular) hyperplasia and lobular carcinoma in situ*

The COBRA study achieved these good results in a controlled study setting. However, after the COBRA study several questions remained regarding the introduction into daily practice. We therefore set out to study SLCNB in daily practice and we tried to further improve guidelines by addressing several shortcomings. SLCNB procedures were performed in four centers and patients were referred from 40 hospitals (listed below).

Surgical therapy

The introduction of percutaneous breast biopsy techniques has led to a reduction of the time to diagnosis as well as the time for complete surgical treatment in patients with nonpalpable breast cancer.[32-35] With a preoperative diagnosis of cancer, the frequency of

positive resection margins decreases, and thus fewer operations are needed to complete surgical therapy.[32-35] Guidelines in the Netherlands state that at least 70% of nonpalpable suspicious breast lesions that are excised should have a preoperative diagnosis.[36]

In the past two decades, the surgical approach of breast cancer has changed. The traditional way to excise breast cancer was the radical or modified radical mastectomy. In the 1970's large randomised trials were started,[37] showing less radical surgery to achieve comparable local recurrence, disease-free survival and overall survival rates.[38,39] As a result, surgical approach for stage I and II breast cancer has shifted from mastectomy to breast conserving therapy. As a consequence, breast conserving procedures also seem the logical alternative for nonpalpable DCIS. Although large randomised studies comparing breast conserving therapy to mastectomy for the surgical treatment of DCIS do not exist, randomised studies reporting on breast conserving therapy with or without radiotherapy have been published.[40-43] These have shown reduced recurrence rates following radiotherapy.

With breast conserving therapy, the challenge is to obtain adequate resection of the tumour necessary for local control; (a margin of 1 to 2 cm of normal surrounding tissue is aimed for in most cases) while achieving an acceptable cosmetic result. Obviously, optimal local control and a desirable cosmetic outcome are competing challenges. The surgeon should therefore aim to excise no more tissue than necessary for optimal local control. This is especially difficult as tumour extension into the surrounding healthy tissue can often not be palpated during the operation. To aid the surgeon in adequately localising the malignant lesion, a guidewire is often inserted into the lesion before the operation (above).

Finally, another challenge in surgery of nonpalpable breast lesions is the axillary assessment of patients with invasive breast cancer. Where in most of the twentieth century, axillary lymph node dissection was performed in all cases, sentinel node biopsy is now widely advocated. The sentinel node (SN) is defined as the first node that receives afferent lymph flow from the tumour. When a tumour has metastasised, the SN is expected to be the first gland to contain metastatic cells. Excising the SN is a minimal invasive procedure with virtually no morbidity. Only patients with a positive SN will now need to undergo axillary lymph node dissection. With a preoperative diagnosis of invasive cancer, SN biopsy can be planned as part of the first surgical procedure.

Outline of this thesis

The aim of this thesis is to address pitfalls and concerns of the diagnostic evaluation of nonpalpable breast lesions, in an attempt to further improve preoperative diagnostic assessment (chapters 2-7), as well as surgical strategies of nonpalpable breast lesions (chapters 8 and 9).

The results of SLCNB in current practice (2000-2002) are described and compared to results of the controlled study setting during COBRA (1997-2000) in **chapter 2**. The feasibility of the COBRA guidelines is evaluated. Through follow-up of women with benign diagnoses at SLCNB who no longer need to undergo surgical excision, we try to identify potentially missed cancers.

In **chapter 3**, we assess differences in cancer prevalence between women with nonpalpable breast lesions referred through the national screening program and a non-screening group, and assess whether the validity of SLCNB differed between these groups.
SLCNB is recommended for all nonpalpable breast lesions. However, for lesions that are highly suspicious for malignancy, one might consider to start with a diagnostic surgical excision biopsy, since SLCNB might be a no more than an extension of the diagnostic process. Surgical excision will always be necessary, even when SLCNB shows a benign lesion, to exclude a false negative result. In **chapter 4**, we set out to find a subgroup of mammographically malignant lesions for which SLCNB might be omitted.

Seeding of biopsy needle tracks with viable malignant cells was an initial concern with all diagnostic breast needle procedures, including SLCNB. In an attempt to further evaluate this phenomenon we address this issue in **chapter 5**: 1) Are the tracks left by the needle biopsy procedure detectable in the surgical excision specimen? 2) Are displaced tumourcells visible along the needle tracks? and 3) Is it possible to identify and excise the entire needle track for thorough histopathologic evaluation?

Another concern of SLCNB is that it is a sampling method: since not the entire lesion is available for diagnostic evaluation, severity of disease may be underestimated. When invasive carcinoma is found at surgical excision, after a preoperative diagnosis of DCIS made at SLCNB, this is called a DCIS-underestimate. Since surgical therapy for invasive cancer includes axillary assessment, but surgical therapy for DCIS does not, initially

underestimating the invasive component results in delay of diagnosis and hence, appropriate treatment. In **chapter 6** we describe DCIS-underestimates in detail to assess reasons for missing the invasive component at core biopsy. This evaluation also includes a histological comparison with 'true DCIS' (DCIS at core and excision).

Vacuum-assisted biopsy is an image-guided technique introduced in 1995 and claimed to be superior to SLCNB for the evaluation of nonpalpable breast lesions beacuse larger biopsy specimens are obtained and the needle is inserted into the breast only once, and then rotated in place to take samples. It is expected to decrease the number of underestimated diagnoses. Its use, especially in the United States, is growing rapidly. However, well-designed clinical studies evaluating its diagnostic performance are unavailable. We reviewed the currently available literature on the accuracy of vacuum-assisted biopsy in **chapter 7**.

DCIS comprises a growing percentage of mammographically detected breast cancer. Therapy consists of mastectomy or local excision followed by radiotherapy in most cases. With a preoperative diagnosis of DCIS obtained at SLCNB, optimal surgical therapy can be planned. **Chapter 8** describes the surgical treatment results for patients diagnosed with DCIS at SLCNB. We sought preoperative determinants predicting which patients would eventually undergo mastectomy. With this information available before the first operative procedure, a better informed choice for mastectomy or breast conserving surgery may be made.

Breast conserving therapy is the procedure of choice for patients with nonpalpable breast cancer. However, it is difficult to perform when the extension of the tumor into the surrounding healthy breast tissue cannot be palpated during the operation. This has led, in some clinics, to a situation where surgical residents in training are only sparsely allowed to perform this procedure as the operating surgeon. In **chapter 9** we compared the outcomes of surgical treatment of preoperatively diagnosed nonpalpable breast cancer in two surgical training hospitals (a university hospital and a large regional clinic). Special attention was focused on the percentage of surgical residents performing the operation as the primary surgeon.

In summary, this thesis was guided by the following research questions:

1) Are results of the SLCNB in daily practice comparable to those obtained in the COBRA study?

2) Is SLCNB as accurate for patients referred by the national screening program as for patients attending a special breast clinic?

3) Is there a subgroup of mammographic lesions that may just as well be evaluated by diagnostic surgical excision?

4) Are viable tumour cells displaced by SLCNB?

5) What are causes of DCIS underestimates and could they be prevented?

6) How does the diagnostic accuracy of vacuum breast biopsy compare to SLCNB?

7) Can preoperative factors predict which patients with DCIS at SLCNB will eventually undergo mastectomy?

8) How does surgical treatment of nonpalpable breast cancer compare between two surgical training hospitals?

Participants of the COBRA and the follow-up study

Centers where stereotactic 14-gauge breast biopsy procedures were performed:

Antoni van Leeuwenhoek Hospital, Amsterdam; Bosch MediCentrum (currently Jeroen Bosch Hospital) Den Bosch; Dr Daniel den Hoed Clinic, Rotterdam; Martini Hospital Groningen; University Medical Center, Utrecht.

Radiologists performing the stereotactic 14-gauge breast biopsy:

APE Besnard, M van den Bosch, K van Everdingen, A Fernandez, E Hanlo-Ploeger, F Houwert, R Lo, DB Piers, RM Pijnappel, P Schipper, RK Storm, E Tetteroo, PFGM van Waes, PJW Wensing, A Zwemmer.

Participating centers:

Academic Medical Center, Amsterdam; Academic Hospital Groningen; Albert Schweitzer Hospital, Dordrecht; Antoni van Leeuwenhoek Hospital, Amsterdam; Bosch MediCentrum (currently Jeroen Bosch Hospital) Den Bosch; Bovenij Hospital, Amsterdam; Bronovo Hospital, Den Haag; Diakonessenhuis Utrecht; Flevo Hospital, Almere; Gemini Hospital, Den Helder; Groene Hart Hospital, Gouda; IJselland Hospital, Capelle aan de IJssel; Isala Clinics, Zwolle; Laurentius Hospital, Roermond; Leids University Medical Center Centrum, Leiden; Lorentz Hospital, Zeist (currently: Diakonessenhuis location Zeist); Martini Hospital Groningen; Reinier de Graaf Gasthuis, Delft; Rijnstate Hospital, Arnhem; Rode Kruis Hospital, Beverwijk; Spaarne Hospital, Heemstede; St. Anna Hospital, Geldrop; St. Antonius Hospital, Nieuwegein; St. Catharina Hospital, Eindhoven; St. Elisabeth Hospital, Tilburg; St. Geertruiden Hospital, Deventer; St. Jansdal Hospital, Harderwijk; St. Lucas Andreas Hospital, Amsterdam; University Medical Center St. Radboud, Nijmegen; University Medical Center, Utrecht; Waterland Hospital, Purmerend; Westfries Gasthuis, Hoorn; Hospital de Heel, Zaandaam; Hospital Eemland, Amersfoort; Hospital Elkerliek, Helmond; Hospital Gooi Noord, Blaricum; Hospital Molendael, Baarn; Hospital Overvecht, Utrecht; Hospital Rivierenland Culemborg; Hospital Rivierenland, Tiel.

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Chapter 2

Stereotactic large-core needle biopsy for the diagnosis of nonpalpable lesions of the breast: reliable without surgical excision biopsy

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Abstract

Background: The COBRA (*CO*re *B*iopsy after *RA*diological localisation) study showed that in a controlled study setting, stereotactic large-core needle biopsy (SLCNB) is as reliable for diagnosing nonpalpable breast lesions as the wire localised surgical excision. In the present study, we evaluated results of SLCNB in daily practice. Use and usefulness of COBRA guidelines were studied.

Patients and methods: Between February 2000 and June 2002 data on all (n=955) patients who were scheduled to undergo a SLCNB was assembled. SLCNB procedures were performed in four centres and patients were referred from 40 hospitals. Histological diagnosis at SLCNB and subsequent therapy were registered. High risk- and DCIS underestimate rates as well as sensitivity and specificity rates were calculated and compared to results of the COBRA study. The use of COBRA guidelines was evaluated and reasons for not following guidelines were further analysed.

Results: 905 biopsy procedures were completed in 874 patients (mean age: 59 years; range:23-86). Of the high-risk lesions, 27% were found to be carcinomas upon excision biopsy, which is comparable to the results of the COBRA study (23%). The DCIS underestimate rate (28%) was higher than found in the COBRA study (17%). No malignancies were missed but follow-up was limited (mean, 20.0 months; 5.8-34.0). 96% of the patients was treated according to the COBRA guidelines.

Conclusions: The follow-up of lesions non malignant at biopsy was limited, but so far, no malignancies were missed, and therefore the sensitivity rate seems to be comparable to the one estimated in the COBRA study. Working according to protocols and COBRA guidelines as well as multidisciplinary meeting between the radiologist, pathologist and the surgeon is and remains essential for successful use of the SLCNB.

Introduction

The multicenter COBRA (*CO*re *B*iopsy after *RA*diological localisation) study showed that for the evaluation of nonpalpable breast lesions, the diagnostic accuracy of the stereotactic large-core (14-gauge) needle biopsy is comparable to that of the diagnostic surgical excision.[1] However, this result was attained in a controlled study setting. The specialists participating in this study had experience in breast pathology and were highly dedicated. In addition, a panel of expert breast pathologists and radiologists reviewed all results of both stereotactic large-core needle biopsy (SLCNB) and surgical excision specimens. Whether these good results can be obtained in daily practice in Dutch clinics is unknown.

Based on the results of the COBRA study, guidelines were formulated for the management of different categories of SLCNB diagnosis. Whenever ductal carcinoma in situ or invasive cancer is diagnosed at SLCNB, definitive surgery can be planned. Whenever SLCNB shows benign disease and when this finding is concordant with the mammographic image, then mammographic follow-up (e.g. through the national screening program) is advised. In case of discordance between the histopathologic and radiologic findings (as is always the case with the SLCNB diagnosis 'normal breast tissue'), a repeat biopsy or diagnostic surgical excision is recommended. A high-risk lesion (e.g. lobular carcinoma in situ, atypical ductal or lobular hyperplasia) diagnosed by SLCNB is always an indication for surgical excision, given the high risk (23%) of missing a carcinoma present in the sampled breast.[2] The most important difference between the COBRA study and current daily practice is that during the study, all patients were scheduled to undergo surgical excision of their mammographic lesions, no matter what the diagnosis at SLCNB was. In daily practice, surgical excision can be omitted for benign, concordant findings. The referring doctor will need to feel confident about the diagnosis of the SLCNB, reported by the radiologist who performed the biopsy procedure, in order to feel comfortable enough to not excise the benign lesion. When there is not enough confidence in the SLCNB diagnosis, a diagnostic surgical excision will be planned. To assess the benefit of the introduction of SLCNB into current daily practice, it is important to evaluate if the COBRA guidelines are being followed correctly.

The aim of this study was to assess the diagnostic accuracy of the SLCNB outside a controlled study setting and to evaluate how many patients were treated according to COBRA guidelines. Reasons for deviation of the guidelines were analysed.

Patients and methods

All women who presented for SLCNB of a suspicious nonpalpable mammographic lesion between February 2000 and June 2002 were included in the analysis. Patients were referred from 40 regional hospitals. Exclusion criteria were 1) coagulopathies or use of anti-coagulants that could not be discontinued and 2) inability to maintain prone position for one hour.

SLCNB procedures were carried out in four centers (University Medical Centre Utrecht, Bosch MediCentre den Bosch, Martini Hospital Groningen and Antoni van Leeuwenhoek Hospital Amsterdam). SLCNB procedures were performed according to a standard protocol as described earlier.[1] Radiologists performing the biopsies underwent special training: firstly, they attended ten biopsy procedures and subsequently they performed another ten biopsy procedures under the supervision of a radiologist with considerable experience in SLCNB.

Biopsies were taken with a 14-gauge core needle, long throw (2.2cm excursion) automated biopsy device with multiple passes (Bioptygun, C.R. Bard Inc., Covington, GA) with the patient on a prone table (Fisher Imaging, Denver, CO, of Lorad Stereoguide, Danbury, CT). Lesions were localised with digital mammography. The advice was to take a minimum of five biopsy specimens. In case of mammographic microcalcifications, at least eight specimens should be obtained, and specimen radiography was carried out to identify the calcifications in the biopsy specimens. After the SLCNB procedure, patients returned to the hospital they were referred from. There, all further diagnostic and therapeutic procedures took place in a routine setting. Advice on the management of various SLCNB categories was based on guidelines formulated after the COBRA study.

Histological evaluation of the SLCNB and surgical excision specimens were carried out as a routine by pathologists working in the 40 referring hospitals. To come to an adequate histological diagnosis, the pathologists had access to clinical information and the mammographic images obtained during SLCNB. Collection of data regarding the type of mammographic lesion, the biopsy procedure, the histological diagnosis and the management following SLCNB was carried out in the University Medical Centre Utrecht.

Data analysis

To evaluate the diagnostic accuracy we used the same methods as applied in the COBRA study. We computed the following parameters: high-risk underestimate rate, DCIS underestimate rate, the sensitivity and the specificity rate.[1]

The high-risk underestimate rate is defined as the proportion of lesions diagnosed as high-risk by large-core biopsy that was upgraded to DCIS or invasive cancer in the excision specimen. The DCIS underestimate rate as the proportion of lesions diagnosed as DCIS by large core biopsy that was upgraded to invasive cancer in the surgical excision specimen. Lesions with a non-malignant histological diagnosis that was discordant with the mammographic image were classified as 'non-representative'. This category included the diagnosis 'normal breast tissue', which was the only category of non-representative lesions during the COBRA study.

We linked patients who did not undergo surgical excision (n=316) to the Dutch National Pathology Database (PALGA) in November 2002 to verify if they had subsequently developed breast cancer. The mean follow-up was 20.0 months, median 19.8 months (5.8-34.0). For 176 women (176/316=56% of the women who did not have surgical excision) follow-up was less than 12 months.

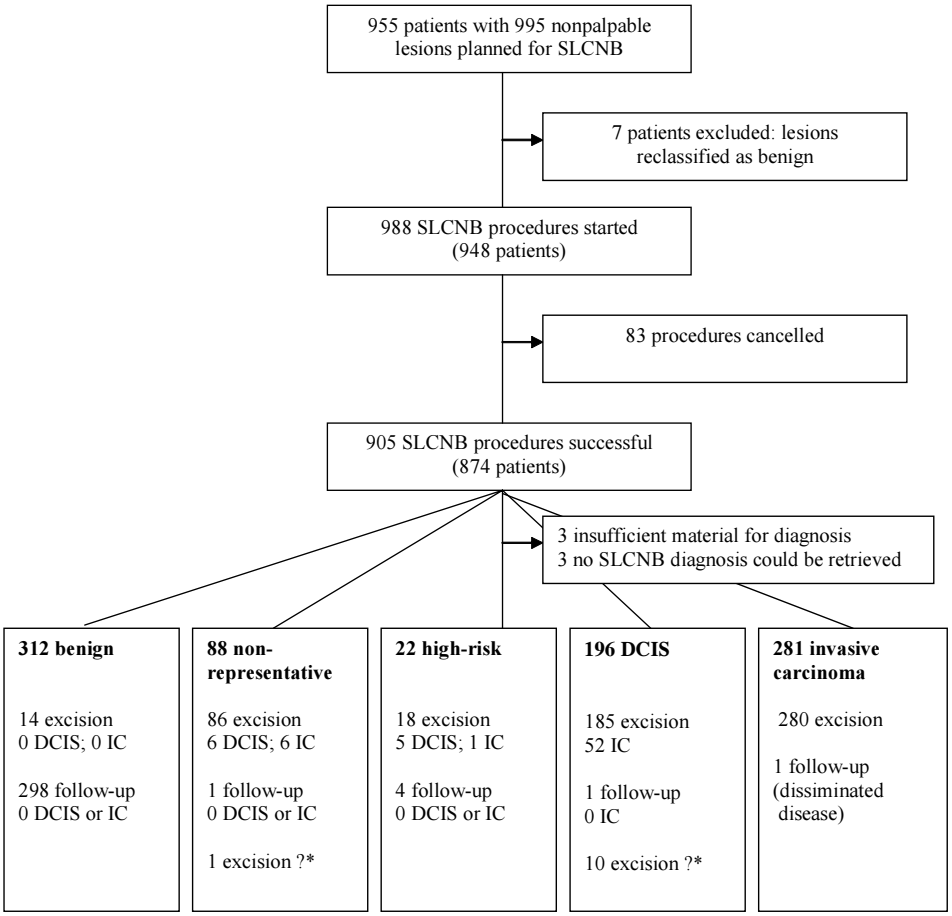
We evaluated how many patients were treated according to COBRA guidelines. In case of deviations, information about the mammographic image, the SLCNB procedure, the histological diagnosis and the rationale for the chosen management were further analysed.

Results

Between February 2000 and June 2002, 955 patients with 995 nonpalpable suspicious mammographic lesions were referred for SLCNB (Figure 1). In seven cases, the lesions were re-classified as benign before the SLCNB procedure was initiated. In 83 (8%) cases, the SLCNB procedure was terminated prematurely. Reasons for cancellations did not differ when compared to reasons found during the COBRA study, e.g. breasts too small for adequate compression or localisation of the lesion close to the thorax. Finally, 905 biopsy procedures were performed in 874 patients. Mean age of these patients was 59 years (range 23-86). Radiologic characteristics of the lesions are presented in Table 1 and comparable to those found in the COBRA study.

In three (0.3%) cases the pathologist was unable to make a histological diagnosis due to insufficient quality of the SLCNB specimens. The histological diagnosis of SLCNB could not be retrieved for three patients. We could not retrieve the followed strategy after core biopsy in another eleven patients for whom SLCNB showed DCIS in ten cases and a discordant finding in one.

Figure 1: flow chart patients and lesions



SLCNB = stereotactic large core needle biopsy; DCIS = ductal carcinoma in situ
** of 1 and 10 patients, respectively, the excision result could not be retrieved*

Table 1: Radiologic characteristics of 905 suspicious nonpalpable breast lesions

	N = 905	%
Mammographic image		
Density	336	*(37)*
Calcifications without density	464	*(51)*
Calcifications with density	85	*(9)*
Distorted architecture	6	*(1)*
Calcifications with distorted architecture	6	*(1)*
Unknown	8	*(1)*
Radiologic classification		
Benign (NHG class 2; BI-RADS 2)	13	*(1)*
Probably benign (NHG class 3; BI-RADS 3)	207	*(23)*
Suspicious for malignancy (NHG class 4; BI-RADS 4)	480	*(53)*
Radiologically malignant (NHG class 5; BI-RADS 5)	110	*(12)*
Unknown	95	*(10)*

NHG = Nederlands Huisartsen Genootschap (Dutch Society of General Practitioners)
BI-RADS = Breast Imaging Reporting and Data System (BI-RADS) developed by the American College of Radiology[6]

The comparison of the SLCNB results in daily practice and the COBRA study is presented in Table 2. The percentage non-representative lesions was 3.5% during COBRA, and 9.8% (88/899) in daily practice. This can be explained by the fact that during the COBRA study all patients with a benign diagnosis at SLCNB were subjected to a surgical excision, therefore 'confidence' in that benign result was not an integrated part of the management of that lesion. In daily practice doubts about the representativeness of the SLNCB lead to diagnostic surgical excision more often.

Reasons why SLCNB diagnosis was considered non-representative for the mammographic abnormality (n=88) are presented in Table 3. Just as in the COBRA study, the finding of normal breast tissue remains the most important reason for a diagnostic surgical excision (33/88=38%). In 17 of 88 (19%) cases no correlation was found between the mammographic lesion and histological findings. In 14 cases (16%), a surgical excision was performed after a benign diagnosis at SLCNB; reasons were not documented. Once, excision was omitted despite the fact that no calcifications were present in the specimen radiograph, because the mammographic lesion was after the SLCNB procedure re-assessed as benign. At excision

Table 2: Comparison of COBRA study results with those from daily practice

		'daily practice' (n=899)		COBRA (n=858)	
SLCNB result:		n	*(%)*	n	*(%)*
Non-representative		88	*(9.8)*	30	*(3.5)*
Normal breast tissue		33	*(3.7)*	30	*(3.5)*
Non-representative		55	*(6.1)*		
Benign		312	*(34.7)*	322*	*(37.5)*
High-risk		22	*(2.4)*	26	*(3)*
DCIS		196	*(21.8)*	190	*(22.1)*
Invasive carcinoma		281	*(31.3)*	290	*(33.8)*
			(95% CI)		*(95% CI)*
'High-risk' underestimate rate	6/22	27%	*(11-50)*	23%	*(9-44)*
DCIS underestimate rate	52/185	28%	*(22-35)*	17%	*(12-22)*
Sensitivity rate	489/489	'100%'	*(99-100)*	97%	*(95-98)*
Specificity rate	**	**		99%	*(97-100)*

95%CI = 95% confidence interval

** In the COBRA study all patients underwent surgical excision, including those with a benign diagnosis at SLCNB; in 13 patients with a benign diagnosis at SLCNB a carcinoma was found at subsequent surgical excision (11 DCIS and 2 invasive carcinomas).*

*** Cannot be determined*

a malignancy was found in 12 of the 88 non-representative cases (13.6%; 6 DCIS and 6 invasive carcinomas).

For 888 cases the management was known (e.g. excision or follow-up) and COBRA guidelines were followed in 851 (96%). Reasons for deviation of the guidelines are presented in Table 4. In 23 cases, guidelines demanded that an excision should be performed, but this was not done. In none of these patients carcinoma was found during follow-up. In none of the 14 patients who underwent surgical excision despite a concordant benign result at SLCNB, a malignancy was found. Whenever a carcinoma was found at SLCNB, the lesion was classified as 'malignant', regardless of the findings of surgical excision. Therefore, without an expert panel revising all specimens (such as in COBRA), there are no false-positives in daily practice. When after an initial SLCNB diagnosis of carcinoma, only benign disease or normal breast tissue was found in the excision specimen, we considered the carcinoma to

Table 3: Reasons why SLCNB diagnosis was considered non-representative for the mammographic abnormality (69/88 of these women underwent surgical excision)

	N
Non-representative biopsy procedure due to arterial bleeding, only 1 biopsy specimen obtained	1
No calcifications in biopsy material	7
Histopathological findings do not exclude carcinoma	9
Intraductal papilloma	2
Normal breast tissue	33[2]
Mammographic and histopathologic discordance	17
2 lesions in the same breast, 1 needed surgery[1]	2
Excision at patient's request because of familial breast cancer	2
Excision despite a benign diagnosis at SLCNB – reason unclear	14
Follow-up instead of excision because of low suspicion for cancer	1
Total	88

[1] *excision was needed because the 2nd lesion was either very suspicious for a malignancy or an intraductal papilloma*
[2] *in 18 of 33 cases no excision was performed although the guideline recommended it*

Table 4: Deviations from COBRA guidelines

SLCNB diagnosis	Guideline	Strategy	n	# of carcinomas at follow-up (Oct 2002)
non-representative	SLCNB/ excision	No excision performed/ follow-up	19	none
high-risk lesion	Excision	No excision performed/ follow-up	4	none
benign*	Follow-up	Excision	14	none

**Falsely classified as 'non-representative' e.g. reason for excision was missing*

have been completely removed by the biopsy procedure. Therefore, we are unable to present the specificity rate.

If after a non-malignant diagnosis at SLCNB carcinoma is found at excision (or during follow-up), then this lesion is classified as 'malignant'. The total number of malignancies was 489 (489/888= 55%). All 489 carcinomas were recognised by SLCNB as 'non-benign' and thus according to the guidelines a reason for surgical excision. Until now, no missed carcinomas were diagnosed during a mean follow-up of 20 months.

Discussion

The results of the SLCNB in daily practice are quite comparable to those obtained during the COBRA study. No carcinomas were missed, but follow-up of non-malignant, non-excised lesions was limited: for 56% of women follow-up was less than one year. Currently, the sensitivity rate does not seem to be different than found during the controlled study setting. The high-risk underestimate rate was comparable to findings during COBRA. The DCIS underestimate rate was higher (28% vs. 17%). This is due to the fact that patients with DCIS often need more than one operation to complete treatment. In the COBRA study only the findings of the first surgical excision were registered. In the current study we evaluated the findings of all excisions needed for complete removal of the lesion. At re-excision, invasive cancer was found in some patients originally diagnosed with DCIS both at SLCNB and in the first excision specimen. When we evaluated findings of re-excisions performed on COBRA patients, we found the DCIS underestimate rate to be higher as well.

Eight percent of the biopsy procedures were terminated prematurely. This is somewhat less often (non-significant) than in the COBRA study (11%),[1] probably because in daily practice, the mammogram of referred patient is re-evaluated prior to biopsy by a radiologist experienced in SLCNB procedures. Suspicion for malignancy as well as technical possibilities of the SLCNB are reconsidered.

Guidelines that were formulated based on COBRA results appear to be useful. They were followed in 96% of cases. Reasons for deviation of the guidelines were diverse. Intriguing is the number of times a surgical excision biopsy was performed despite a concordant benign diagnosis at SLCNB. Confidence in the result of the needle biopsy, confirmed during a multidisciplinary meeting is essential. During the controlled study setting, this confidence in the SLCNB result did not influence the choice of subsequent management, since all lesions, benign lesions as well, were scheduled to be excised. Discordance between the mammographic and histologic findings, obviously remains an indication for a diagnostic surgical excision.

In 55% (95% CI: 52-58) of women referred for SLCNB in daily practice, a malignancy was found, compared to 58% (95% CI: 55-62) during the COBRA study. The prevalence of carcinoma in the referred group does not seem to be different; apparently, criteria for referral of nonpalpable suspicious lesions are not less stringent. This will have to be re-evaluated in the future. A minimally invasive highly accurate diagnostic test like the SLCNB may result in referral of more lesions with lower suspicion for malignancy.[3;4] In

the Netherlands, approximately 50-60% of women referred for histologic evaluation of a nonpalpable suspicious lesion turn out to have breast cancer.[5] In the USA, this percentage varies between 10 and 20%. In a situation where a highly accurate diagnostic test is less invasive when compared to diagnostic surgical excision, more biopsies might be performed for non-malignant lesions and this may have an impact on the outcome of SLCNB. On the other hand, when criteria for referral are too stringent, more carcinomas will be missed and as such, diminish the success of the national breast cancer screening program.
In this study of SLCNB in daily practice, most specialists participating also participated in the COBRA study. However, there is no 100% overlap. Twice as many referring hospitals were included (19 hospitals for 5 biopsy centers during COBRA vs. 40 for 4 biopsy centers now). Four of the five biopsy centers participating in the COBRA study participated in the current study. All radiologists who performed the biopsies have been adequately trained and completed a learning curve. If more biopsy centers are being built in the future, careful monitoring of the quality of the SLCNB will be necessary to ensure the high diagnostic accuracy.

We conclude that at this moment, sensitivity rates do not seem to be different from the controlled study setting. However, since follow-up for patients who did not undergo surgical excision was limited, these results have to be interpreted with caution. There was however a higher percentage of DCIS underestimates and a higher percentage of non-representative lesions, reflecting feelings of insecurity about a non-malignant result. Working according to protocols and using guidelines as well as regulated (weekly) multidisciplinary discussions on the SLCNB results between radiologists, pathologists and surgeons are essential for proper diagnosis and treatment. Conscientious registration and feedback on the obtained results remain necessary to keep the number of incorrect diagnoses as low as possible.

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Chapter 3

Stereotactic large-core needle biopsy for all nonpalpable breast lesions?

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Abstract

Background: Stereotactic large-core needle biopsy (SLCNB) is a minimally invasive method for histological diagnosis of nonpalpable breast disease. We studied differences in cancer prevalence between a group of women referred through the national screening program and a non-screening group, and assessed whether the validity of SLCNB differed between these groups.

Methods: A group of non-selective, consecutive patients presenting with a nonpalpable mammographic lesion, who participated in a recently conducted multicenter study regarding the accuracy of SLCNB in the Netherlands, were the basis for this study. Prevalence of carcinoma, predictive value of a benign diagnosis, sensitivity and specificity rate of SLCNB were compared between the two groups.

Results: Of the 1029 lesions in 972 patients included, 858 were evaluable. In 850/858 lesions (99.1%) the reason for referral was clear. The prevalence of cancer in the screening group (n=511 lesions) was 64.0% (95%CI 59.8-68.2), versus 49.6% in the non-screening group (n=339) (95% CI 44.2-54.9). Respective predictive values of a benign diagnosis on SLCNB were 97.0 vs. 94.8% (non-significant). The sensitivity rates of SLCNB were 98.5% (screening; 95%CI 96.5-99.5) vs. 95.2% (non-screening; 95%CI 90.8-97.9). Specificity rates were 97.8 (95%CI 94.5-99.4) and 99.4% (95%CI 96.8-100), respectively.

Conclusion: Despite a significant difference in the prevalence of carcinoma, the accuracy of SLCNB did not show a statistically significant difference between both patient groups. Therefore, SLCNB appears accurate in diagnosing nonpalpable breast lesions both in screening and non-screening patient groups.

Introduction

The national breast cancer screening program is designed to screen asymptomatic women to detect malignancies at an earlier, nonpalpable stage, in order to reduce breast cancer associated morbidity and mortality.[1-5] In the Netherlands, all women aged 50-70 (and since 1998, 50-75) years are invited to participate.[6;7] Essential in the concept of screening is that all women participating are by definition asymptomatic.

Since most of the discovered mammographic abnormalities are nonpalpable, confirmation of the diagnosis is a challenge for the surgeon these women are referred to. Diagnostic wire-localised open breast biopsy has long been the reference test for nonpalpable breast disease. However, in the last decade, various minimally invasive diagnostic procedures have been developed.[8-10] Recently we have tested the stereotactic large-core needle biopsy (SLCNB) in a Dutch prospective multicenter trial, the COBRA study (*CO*re *B*iopsy after *RA*diological localisation).[11] In a group of 972 consecutive women with 1029 nonpalpable mammographic abnormalities SLCNB was performed to determine the histological diagnosis. In each patient, SLCNB was followed by surgical excision (wire localised excision biopsy for non-malignant lesions, breast conserving treatment or mastectomy for malignant lesions) to compare the initial diagnosis with that of the gold standard. The sensitivity and specificity of the new technique were 97 and 99 percent, respectively, and thus are comparable to surgical biopsy.[11-13]

Sixty percent of women included in the COBRA cohort were referred by the national screening program. Consequently, 40 percent were women with some motive other than an age-induced screening invitation to have their mammogram taken, including a personal or family history of breast cancer, perceived changes in their breast or anxiety. The purpose of this study was to compare these two groups, different in background of referral, with regard to prevalence of cancer and possible consequences for the accuracy of SLCNB. Our hypothesis was that the prevalence of carcinoma would be higher in the screening group.

As has been described before, diagnostic test parameters vary across subpopulations within a certain population.[14] We compared the two groups (screening vs. non-screening) to evaluate if the results with SLCNB obtained in the COBRA study may be applied with equal validity to different subpopulations within the cohort of patients with nonpalpable breast lesions.

Patients and methods

Study population

Data was used from the COBRA study (*CO*re *B*iopsy after *RA*diological localisation). The methods and results of this study are described elsewhere.[11] For the purpose of the present study we categorised the patients in two groups: one group referred by the national screening program ('screening', n=511 lesions) and one consisting of patients with a specific motive for mammographic surveillance ('non-screening', n=339 lesions). Demographic information, relevant medical history, breast cancer risk factors, mammographic findings and histological factors were prospectively collected and compared between the two groups.

Accuracy of large-core needle biopsy

We evaluated the diagnostic accuracy of large-core needle biopsy using a methodology adapted from Burbank and Parker.[15]

Histological diagnoses of the core biopsy specimens were divided into five categories: normal breast tissue (i.e. not explanatory for the mammographic lesion), benign breast disease, high-risk lesions, ductal carcinoma in situ (DCIS) and invasive breast cancer. Histological diagnoses of the surgical specimens were divided into the same categories.

High-risk lesions were those known to have a high prevalence of carcinoma on excision biopsy (atypical ductal hyperplasia (ductal or lobular) and lobular carcinoma in situ).[16-18] In cases of such a high-risk diagnosis on large-core needle biopsy an open breast biopsy is generally recommended.[19;20]

Subsequently, the predictive value of a 'normal breast tissue' diagnosis, the predictive value of a 'benign' diagnosis, the high-risk underestimate rate and ductal carcinoma in situ (DCIS) underestimate rate as well as the sensitivity and specificity rates were calculated and compared between the subgroups.

The predictive value of a 'normal breast tissue' diagnosis was defined as the proportion of lesions diagnosed as 'normal' on large-core needle biopsy that did not reveal carcinoma (DCIS or invasive) at excision biopsy. Similarly, the predictive value of a 'benign' diagnosis was defined as the proportion of lesions with a benign diagnosis on large-core needle biopsy that proved to be benign after excision biopsy. The high-risk underestimate rate was defined as the proportion of lesions diagnosed as high-risk by large-core needle biopsy that was upgraded to DCIS or invasive cancer in the surgical specimen. The DCIS underestimate rate was defined as the proportion of lesions diagnosed as DCIS by large-core needle biopsy that was upgraded to invasive cancer in the surgical specimen.

The sensitivity rate was defined as the proportion of malignancies that was identified as abnormal (hence, warranting surgical excision) by SLCNB and the specificity rate was defined as the proportion of benign lesions that was not categorised as carcinoma (DCIS or invasive carcinoma) by SLCNB.

Statistical analysis

Statistical analysis was performed with use of the Statistical Package for the Social Sciences 7.5 (SPSS Inc. Chicago, IL). Continuous data were tested using the Student's t-test. Nominal data were tested by means of the Chi-square test.

Results

Study population

Between April 1997 and February 2000, 972 consecutive patients with 1029 nonpalpable mammographic lesions were included in the COBRA study. For 850 of the evaluable 858 lesions (99%) the background of referral for mammographic examination was retrieved. Five hundred eleven lesions were included in the 'screening' group, and 339 in the 'non-screening' group. The characteristics of these patients and lesions are presented in Table 1. Reasons for women outside the national screening program to seek mammographic examination are presented in Table 2.

Breast cancer prevalence

The histological diagnosis found at SLCNB is presented in Table 3. The prevalence of carcinoma varied significantly between the screening group (64.0%) and the non-screening group (49.6%) ($p < 0.05$). Since the threshold of participation in the national screening program in the Netherlands is 50 years of age we studied cancer prevalence for women 50 years and older separately. In the screening group, all but ten woman were 50 years or older; these ten woman would turn 50 in the calendar year of their first screening visit. Within the non-screening group, the prevalence of carcinoma was 57.2% (115/201) for women aged 50 years and older, compared to 38.4% (53/138) for the group aged < 50 years ($p < 0.01$). Comparing only women aged 50 years or older between screening and the non-screening group, there was no significant difference in breast cancer prevalence (64 vs. 57%, respectively).

Table 1: Patient- and lesion characteristics

	Screening	Non-screening	Total
Risk factors			
Age ≥ 50 yrs (%)	98.0*	59.3	82.6
Mean age at menarche (yrs)	13.4*	13.2	13.3
Mean age at first fullterm pregnancy (yrs)	25.5	26.1	25.7
Hormone replacement therapy use (%)	45.6	54.5	49.1
History of breast cancer (%)	2.2	29.8*	13.2
History of benign breast disease (%)	16.8	28.9*	21.6
Familial history of breast cancer (%)	26.5	37.9*	30.9
Nullipara (%)	14.7	23.1	18.0
BMI (kg/m^2) (mean)	26.0*	24.9	25.6
Mammography			
Density (%)	41.1*	28.0	35.7
Microcalcifications (%)	39.9	57.2*	46.7
Density with microcalcifications (%)	15.7	11.8	14.3
Distorded architecture (%)	3.1	2.7	3.0
Focal asymmetry (%)	0.2	0.3	0.2
Radiological classification**			
Probably benign (%)	26.7	38.0	31.3
Suspicious for malignancy (%)	51.4	49.0	50.2
Malignant (%)	21.9*	13.0	18.4

** Significantly different between screening and non-screening with a p-value < 0.05*
*** radiological classification registered by radiologist performing the SLCNB*

Table 2: Reasons for women outside the national screening program to come to the clinic for mammographic evaluation:

	n	*(%)*
Family history of breast cancer	121	*(36)*
Personal history of breast cancer	101	*(30)*
Personal history of benign breast disease	98	*(29)*
Complaints of painful breast(s)	40	*(12)*
Skin retraction	24	*(7)*
Nipple discharge	19	*(6)*
Follow-up for previous malignancy other than breast cancer (e.g. ovarian cancer)	6	*(2)*

Table 3: Histological classification on SLCNB

	Screening n=511		Non-screening n=339	
	n	*(%)*	n	*(%)*
Histological classification on SLCNB:				
Normal breast tissue	14	*(2.7)*	16	*(4.7)*
Benign disease	164	*(32.1)*	154	*(45.4)*
High-risk lesion	15	*(2.9)*	11	*(3.2)*
DCIS	116	*(22.7)*	73	*(21.5)*
Invasive cancer	202	*(39.5)*	85	*(25.1)*
Prevalence of carcinoma**	327	*(64.0*)*	168	*(49.6)*

** Significantly different between screening and non-screening with a p-value < 0.05*
*** Final histological diagnosis after correlation with the excision biopsy*

Predictive values, sensitivity and specificity

The predictive value of a 'normal breast tissue' diagnosis, the predictive value of a 'benign' diagnosis, the high-risk underestimate rate and the DCIS underestimate rate are presented in Table 4. There were no significant differences in these parameters between the two groups.

On a total of 327 malignancies in the 'screening' group, five lesions would have been diagnosed as benign, and these patients would not have received adequate therapy.

Table 4: Diagnostic accuracy of stereotactic large core needle biopsy

	COBRA study[1] n=858		Screening n=511		Non-screening n=339	
	%	(95%CI)	%	(95%CI)	%	(95%CI)
Predictive value 'normal breast tissue'	83	(65-94)	71.4	(42-92)	93.8	(70-100)
Predictive value 'benign' diagnosis	96	(93-98)	97.0	(93-99)	94.8	(90-98)
'High-risk' underestimate	23	(9-44)	26.7	(8-55)	18.2	(2-52)
'DCIS' underestimate	17	(12-22)	14.7	(8-21)	20.5	(12-32)
Sensitivity large-core needle biopsy	97	(95-98)	98.5	(97-100)	95.2	(91-98)
Specificity large-core needle biopsy	99	(97-100)	97.8	(95-99)	99.4	(97-100)

[1] *data described in reference 11*

This resulted in a sensitivity rate of 98.5% (95%CI 96.5-99.5). In the 'non-screening' group this was 95.2% (95% CI 90.8-97.9) (160/168).
In the screening group, four times malignant disease (DCIS or invasive cancer, IC) was found at core biopsy, while only benign disease was found at surgical excision (4/184). For the non-screening group, one of 171 lesions was incorrectly diagnosed as malignant. After revision by an expert panel (consisting of three specialised breast pathologists and two specialised breast radiologists) it was concluded that the pathologist had incorrectly diagnosed these needle biopsies as malignant. These five patients would have been over-treated and hence the findings were called 'false positives'. This resulted in specificity rates of 97.8% (95%CI 94.5-99.4) for the 'screening' group vs. 99.4% (95%CI 96.8-100) for the 'non-screening' group ($p > 0.05$).

Discussion

Our current study shows that in a group of consecutive patients referred for histological examination of a mammographically detected nonpalpable lesion, as many as 40% (339/850) is referred from outside the national screening program. This is the first study comparing lesions of patients referred outside the national screening program to screen-detected lesions. Women seeking mammographic examination outside the national screening program have an increased prevalence of risk factors for, or symptoms suggestive of breast cancer. However, prevalence of carcinoma was lower in this subgroup. A possible explanation could be that both the patient (seeking help) and her doctor (referring her for histological examination) perceive an increased risk, and do not want to miss breast cancer; hence referral is made at a lower degree of suspicion in comparison with asymptomatic women from the screening program. This is especially true for women < 50 years, since the prevalence of breast cancer in older women is comparable to the results of the breast cancer screening program.
With the increasing knowledge about breast cancer, and the known positive effects of screening on morbidity and mortality, the awareness of women towards breast examination is growing, thereby inducing an increase in the number of nonpalpable lesions detected. Also, because of the detection of breast cancer susceptibility genes such as *BRCA1* and *2*, there may be an increase in the number of young women referred for risk assessment and counselling. At the same time, as more women survive breast cancer, they demand close surveillance, which leads to an increase of women seeking mammographic surveillance

outside the national screening program.
The diagnostic accuracy of any test used is influenced by the prevalence of disease. Specifically, the risk of finding cancer despite a benign diagnosis on SLCNB increases when the prevalence of carcinoma is higher in the population under study, resulting in a higher false negative rate.[12] Before applying test results to a new (sub)population, the prevalence of breast cancer should be assessed. In doing so, no differences were found for any of the main outcome parameters describing the accuracy of SLCNB.

In conclusion, stereotactic large core needle biopsy is an accurate diagnostic test for evaluating nonpalpable mammographic abnormalities both in women referred from the national screening program and in women referred outside screening. Careful monitoring of the implementation of this new diagnostic technique in the Netherlands is mandatory to ensure patients' safety.

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Chapter 4

Radiologically malignant (BI-RADS 5) lesions: is large-core needle biopsy necessary before surgical treatment?

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Abstract

Introduction: Due to screening mammography, more nonpalpable mammographic lesions warrant histological evaluation. Stereotactic large-core needle biopsy (SLCNB) has been shown to be as effective in diagnosing these lesions as diagnostic surgical excision. Advantages of SLCNB made it the preferred diagnostic procedure for most mammographic lesions. Since radiologically malignant BI-RADS 5 lesions are almost always carcinoma, some centers advocate diagnostic surgical excision for these lesions instead of SLCNB. For some patients this diagnostic surgical intervention may serve as definitive treatment. We set out to find a subgroup of mammographic BI-RADS 5 lesions for which surgical biopsy might be preferable.

Methods: Of 1644 consecutive nonpalpable lesions referred for SLCNB between April 1997 and May 2002, 238 were classified as BI-RADS 5. We assessed the number of carcinomas and the surgical interventions performed. Outcomes were compared between various types of mammographic lesions: density with calcifications, density without calcifications, and calcifications only. We propose different strategies for diagnostic work-up of BI-RADS 5 lesions and discuss potential consequences.

Results: Carcinoma was found in 229/238 lesions (96%). Most mammographic densities were invasive cancer (97%), while calcifications only showed the highest risk for ductal carcinoma in situ (DCIS) (51%). Compared to current practice where all lesions get SLCNB, a scenario where all lesions with only a density would be scheduled directly for sentinel node biopsy (SNB) and tumour excision (n=154; 65%), while other lesions are still scheduled for SLCNB, revealed that in our study four out of 238 patients (<2%) who would be 'overtreated' with SNB.

Conclusions: Our findings confirm a high predictive value of malignancy for BI-RADS 5 lesions (96%). Surgical excision is therefore imperative for all BI-RADS 5 lesions, irrespective of SLCNB results. For BI-RADS 5 lesions presenting as mammographic densities, we propose to consider surgical excision with SNB to be the first diagnostic and therapeutic procedure. SLCNB is preferred in all other cases.

Introduction

Due to screening mammography, an increasing number of nonpalpable mammographic lesions is referred for histological evaluation. The minimally invasive stereotactic large-core needle biopsy (SLCNB) has been shown to be equally effective in diagnosing these lesions as the diagnostic surgical excision biopsy.[1] The advantages of the minimally invasive needle technique (i.e. less morbidity, lower costs) have led to a situation where it is the diagnostic procedure of first choice for all nonpalpable breast lesions.[2,3]

A proportion of all nonpalpable breast lesions is classified as mammographically malignant, or BI-RADS 5. The Breast Imaging Reporting and Data System (BI-RADS) lexicon was developed by the American College of Radiology to standardise mammographic findings and assign a level of cancer suspicion to each finding, ranging from 1 (normal) to 5 (highly suggestive of malignancy).[4] The risk of malignancy for each category has been well established.[5] BI-RADS 5 lesions have a very high risk of malignancy, with positive predictive values between 82 and 97%.[5-7] In these cases, one might argue that SLCNB is a waste of time, since surgical excision will be necessary in all cases. Even when SLCNB shows a benign lesion, because the discrepancy with the mammographic classification the lesion will need to be removed.[5;6;8] Some centres therefore advocate diagnostic surgical excision for BI-RADS 5 lesions instead of SLCNB.[9-12] The advantage would be that for some patients the diagnostic surgical intervention may serve as definitive treatment, i.e. for those with radical excision of the lesion.

On the other hand, even though almost all BI-RADS 5 lesions are malignant, a distinction between in situ or invasive carcinoma is important in planning surgical treatment. For ductal carcinoma in situ (DCIS), wide local excision of the tumour is the standard treatment; axillary assessment is not necessary. With a preoperative diagnosis of invasive cancer, axillary sampling (i.e. sentinel node biopsy) at the time of the first surgical intervention should be planned in addition to tumourectomy. Based on SLCNB results, a distinction between in situ and invasive cancer can be made before planning the first operative procedure.

We hypothesised that for some BI-RADS 5 lesions, SLCNB does indeed not render additional value, and a (therapeutic) strategy can be planned based solely on the radiological characteristics. We assessed the number of carcinomas as well as the total number and type of surgical interventions performed on patients with BI-RADS 5 lesions. In addition, we set out to find a subgroup of mammographic BI-RADS 5 lesions for which surgical biopsy might be the procedure of first choice.

Materials and methods

In this study, all 1644 consecutive nonpalpable lesions referred for stereotactic 14G-needle biopsy between April 1997 and May 2002 were classified in accordance with the BI-RADS assessment categories before biopsy. All BI-RADS 5 lesions were included in the study (n=238). Our protocol is described in detail elsewhere.[1]
We assessed the number of carcinomas and specifically, the number of invasive carcinomas, as well as the total number of surgical interventions performed. Surgical interventions were mastectomy or local excision with or without sentinel node biopsy (SNB). In addition, we compared these outcomes between the various types of mammographic lesions: density with calcifications, density without calcifications, and calcifications only.
We propose two strategies for diagnostic work-up (diagnosis and / or treatment) of BI-RADS 5 lesions and discuss both advantages and disadvantages.

Results

Characteristics of the patients and lesions, as well as the performed surgical operations, are presented in Table 1. In 14% of patients with a mammographic density more than one operation was necessary (21/154). These percentages were 33% and 29%, respectively, for lesions consisting of a density with calcifications (14/43) and for calcifications only (12/41). Table 2 shows predictive values for these three types of mammographic lesions. All three types show a high risk for breast cancer (overall, 96%), but the risk for invasive cancer was highest in lesions presenting as a density, while calcifications only showed the highest risk for DCIS.

Next, we considered two theoretical scenarios. In scenario I all BI-RADS 5 lesions that present as a density (with or without calcifications) are scheduled directly for SNB and excision of the tumour. In our series, this would encompass 197 lesions, of which 181 (92%) were invasive cancer, nine were DCIS and seven were non-malignant. This would result in overtreatment for 16 of 238 patients (7%), for whom SNB turned out to be not necessary because no invasive carcinoma was present. All lesions consisting of calcifications only would be planned for SLCNB, after which surgical therapy would be initiated.
In scenario II all lesions with only a density (n=154) are scheduled directly for SNB and tumour excision. Four out of 238 patients (<2%) would turn out to have benign disease. All lesions with calcifications (n=84) would first undergo SLCNB, followed by surgical

therapy. Table 3 gives a summary of results compaed to SLCNB for all lesions (current practice = scenario 0). Scenario I will prevent SLCNB in 197 out of 238 cases (83%) but 16 of 238 patients would undergo unnecessary SNB. Scenario II will prevent 154 out of 238 SLCNB (65%) but 4 patients would undergo unnecessary SNB.

Table 1: Patient- and lesion characteristics of 238 BI-RADS 5 lesions

	N (238)	***(%) (range) (100)***
Age (median; years)	62	*(43-84)*
Malignant	229	*(96)*
· Invasive cancer	199*	*(84)*
· DCIS	30	*(13)*
First operative procedure		
· Mastectomy	77	*(32)*
· Local excision	159	*(67)*
· Sentinel node biopsy	2	*(1)*
Number of operations		
· 1	191	*(80)*
· 2	45	*(19)*
· 3	2	*(1)*
Reasons for >1 operation (n=47)		
· close / positive margins	36	*(77)*
· axillary clearance after positive SNB	8	*(17)*
· mastectomy after SNB	2	*(4)*
· excision of infected seroma	1	*(2)*

**In 8 cases SLCNB showed only DCIS; but subsequent surgical excision revealed invasive cancer*

Table 2: Preditive value of malignancy of three types of nonpalpable BI-RADS 5 mammographic lesions

Mammographic lesion	**Total**	**Malignant**			**Invasive carcinoma**			**DCIS**		
	n	**n**	***PV***	***(95%CI)***	**n**	***PV***	***(95%CI)***	**n**	***PV***	***(95%CI)***
Density or architectorial distorition, no calcifications	154	150	*97*	*(94-99)*	150	*97*	*(94-99)*	0	*(0)*	*(0-2)*
Density or architectorial distorition, with calcifications	43	40	*93*	*(81-99)*	31	*72*	*(56-85)*	9	*(21)*	*(10-36)*
Calcifications only	41	39	*95*	*(84-99)*	18	*44*	*(29-60)*	21	*(51)*	*(35-67)*
Total	238	229	*96*	*(93-98)*	199	*84*	*(79-88)*	30	*(13)*	*(8-17)*

PV=predicted value

Table 3: Three scenario's for BI-RADS 5 nonpalpable mammographic lesions

Diagnostic and first therapeutic procedure	LCNB		Local excision		SNB+ local excision		Unnecessary SNB	
	n	*(%)*	n	*(%)*	n	*(%)*	n	*(%)*
Scenario 0 (current practice in this study)*								
first SLCNB for all lesions	238		47		191**			
Total # of procedures: = 476	**238**	*(100)*	**47**	***(20)***	**191**	***(80)***	***0***	***(0)***
Scenario I								
all mammographic densities +/- calcifications:					197			
SNB+tumour excision								
all other lesions: first SLCNB	41		23		18			
Total # of procedures = 279	**41**	*(17)*	**23**	***(10)***	**215**	***(90)***	***16***	***(7)***
Scenario II								
all mammographic densities without calcifications:					154			
SNB+tumour excision								
All other lesions: first SLCNB	84		35		49			
Total # of procedures: = 322	**84**	*(35)*	**35**	***(15)***	**203**	***(85)***	***4***	***(2)***

** based on the assumption that when SLCNB shows invasive cancer , tumour excision+SNB is planned, and after any other SLCNB diagnosis (incl DCIS) local excision only*

***In 8 cases SLCNB showed only DCIS; thus no SNB was planned, however, subsequent surgical excision revealed invasive cancer*

Discussion

Our findings confirm the high predictive value of malignancy for BI-RADS 5 lesions (96%). Surgical excision is therefore imperative for all BI-RADS 5 lesions, even when SLCNB shows benign disease. In case we adopt a scenario where all lesions presenting as mammographic densities without calcifications would be initially planned for sentinel node biopsy and local excision of the breast tumour in stead of SLCNB, 65% of SLCNB would be omitted, and $<2\%$ of patients would be 'overtreated' with a SNB.

Our findings are comparable to results described by others: most BI-RADS 5 calcifications represent DCIS, whereas most BI-RADS 5 densities represent invasive cancer.[5;13] The preference for either of the scenario's we present obviously depends on the prevalence of invasive cancer and DCIS.

With regards to costs, the results of Fahy et al. do not support the preferential use of SLCNB or surgical biopsy for the evaluation of BI-RADS 5 lesions, since they may be evaluated by either method without a significant effect on total cost.[2] Lee et al.[14] did find small cost savings using SLCNB to diagnose BI-RADS 5 lesions; the percentage of malignancies in this group was 75%. Gisvold et al.[11] found carcinoma in 82% of BI-RADS 5 lesions and concluded that SLCNB is an unnecessary expenditure of time and money for such lesions.

Proposed scenarios and results are based on the BI-RADS classification for various types of mammographic lesions and the cancer risk linked to it. Therefore, in practice, the prevalence of cancer in the subgroups should be assessed. This may differ according to background of refferal of the patient, type of hospital or between countries.

A second limitation is the reproduciblility of the BI-RADS classification. Variability in the classification of lesions according to the BI-RADS lexicon has been reported.[15-18] It is clear that this influences further diagnostic and treatment decisions; thus cancer yield should assessed in one's population of BI-RADS 5 lesions before using proposed scenarios.

An argument in favour of a preoperative diagnosis is that it reduces the occurrence of close or positive surgical margins. We found that in our series where all patients first underwent SLCNB, that in $\sim 23\%$ of the local excision specimens (36/159) dubious or positive surgical margins were found. While some authors have reported lower rates of positive surgical margins at surgical excision after a core biopsy diagnosis (0-29%) compared with diagnostic surgical excision biopsy,[19-21] others have found margin positivity rates to be similar between the two diagnostic methods.[22;23] For BI-RADS 5 lesions, these rates have not been reported thusfar.

We do want to emphasize however, that taking a diagnostic surgical excision biopsy of a somewhat suspicious nonpalpable breast lesion is different compared to a surgical excision biopsy of a lesion that has 97% of being invasive cancer. In the latter example, the surgeon, aware of the potential presence of invasive disease, may excise a larger tissue volume, aiming for clear excision margins.

In conclusion, 96% of BI-RADS 5 lesions are malignant. Taking into account that as many of 97% of BI-RADS 5 lesions characterised by a mammographic density turn out to be invasive cancer, surgical excision with sentinel node biopsy man be performed as the first diagnostic (and therapeutic) procedure in these cases, while SLCNB is the preferred diagnostic approach in all other cases.

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Chapter 5

Tumour cell displacement after 14G breast biopsy

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Abstract

Introduction: Seeding of biopsy needle tracks with viable malignant cells was an initial concern with all diagnostic breast needle procedures, including 14G automated-needle biopsy. In an attempt to further evaluate this phenomenon we have addressed the following questions: 1) Are the tracks left by the needle biopsy procedure detectable in the surgical excision specimen? 2) Are displaced tumourcells visible along the needle tracks? and 3) Is it possible to identify and excise the entire needle track for thorough histopathologic evaluation?

Methods: Surgical biopsy specimens of patients previously diagnosed with cancer on stereotactic 14G-needle biopsy were studied to find needle tracks. These are characterised by hemosiderin, scar tissue, foreign body giant cell reaction, fat necrosis, or organizing hemorrhage. Occurrence of displaced tumourcells or groups of cells along the tracks was registered.

Results: Needle tracks were found in 22/64 excision specimens of patients who underwent 14G-needle biopsy and surgery on the same day. Tumour-cell displacement along the needle track was seen in 11/22 cases (50%). In a prospective study, an attempt was made to excise the entire needle track in 13 consecutive cancer cases after 14G biopsy. Needle tracks could be visualised in 11/13 cases; displaced cells were seen in seven.

In conclusion, needle tracks can be found in the excision specimens of patients who previously underwent 14G biopsy, and displaced tumourcells can be recognised. Excising and evaluating the entire needle track is not always possible, and based on our findings, should not be recommended as a routine, since radiotherapy is advised for all types of carcinoma after conservative surgery.

Introduction

For the evaluation of nonpalpable lesions of the breast, image guided 14G automated-needle biopsy is increasingly replacing wire-localised excision.
A disadvantage of this technique is that a potentially malignant lesion is punctured with a needle repeatedly. Seeding of malignant tumour cells along the needle tracks followed by recurrent cancer at the needle track sites after biopsy of prostate, lung or pancreatic cancer has been reported.[1-4] For breast cancer, anecdotal data has been published.[5-9]
Seeding of biopsy needle tracks with viable malignant cells was an initial concern with all diagnostic breast needle procedures, including fine-needle aspirations, needle localised excision biopsies, and large gauge needle core biopsy.[5;10-15] Since our hospital was the first in the Netherlands to introduce the stereotactic 14G breast biopsy, the issue of potential tumour cell displacement was an immediate concern.
Until now, the clinical relevance of displaced tumour cells has remained unclear. Most publications report either the existence of displaced cells, or the overall recurrence rate after diagnostic needle procedures. And although the clinical implications of displaced tumour cells may be limited, the biological characteristics of the phenomenon have not been addressed to their full extent. For example, no studies exist to date that include a detailed prospective registration of the position of the needle track at the moment of 14G stereotactic breast biopsy, nor have investigators attempted to excise the entire needle track to study it in its full length.
The present study was undertaken to evaluate the phenomenon of needle track seeding of tumour cells following large core needle biopsy in greater detail. For this purpose, the following questions were addressed: 1) Are the tracks left by the needle biopsy procedure detectable in the surgical excision specimen? 2) Are displaced tumour cells visible along the needle tracks? and 3) Is it possible to identify and excise the entire needle track for thorough histopathologic evaluation?

Methods

Biopsy procedure

Prospective registration of stereotactic large core needle biopsy for the diagnosis of nonpalpable breast lesions was started in our hospital in 1997. We use a prone table (Fisher Imaging Denver, CO), and a 14G-core needle, long throw (2.2cm excursion) automated biopsy device with multiple passes (C.R. Bard Inc., Covington, GA). Lesions are localised with digital mammography. Our protocol advises to take at least eight core biopsies in

cases of calcifications and five in cases of density or architectural distortion. Our diagnostic protocol has been described in detail elsewhere.[16]

Retrospective review

To assess the feasibility of finding and evaluating the needle tracks left by a stereotactic breast biopsy procedure, we first carried out a retrospective review. The histological slides of 64 consecutive patients who underwent surgical excision for a breast malignancy previously diagnosed at 14G-needle biopsy were evaluated. All patients underwent needle biopsy and surgical excision on the same day. Needle tracks were histologically identified by the presence of recent bleeding, fat necrosis, cellular debris, scar tissue, foreign body giant cell reaction, or organising hemorrhage (Figure 1A). In the cases where the needle track could be visualised, occurrence of tumour cell displacement (single cells or groups of cells) along the needle track was studied (Figure 1B). A tumour cell was considered to be displaced if not surrounded by basement membrane (stained with alpha-smooth muscle actin; Figure 1C) or specialised mammary stroma. In addition, tumour cells had to be morphologically identical to the cells of the primary carcinoma (stained with cam 5.2, an epithelial cell marker; Figure 1D).
Localisation of the displaced cells was registered as either inside the tumour (Figure 2) or outside (Figure 3).

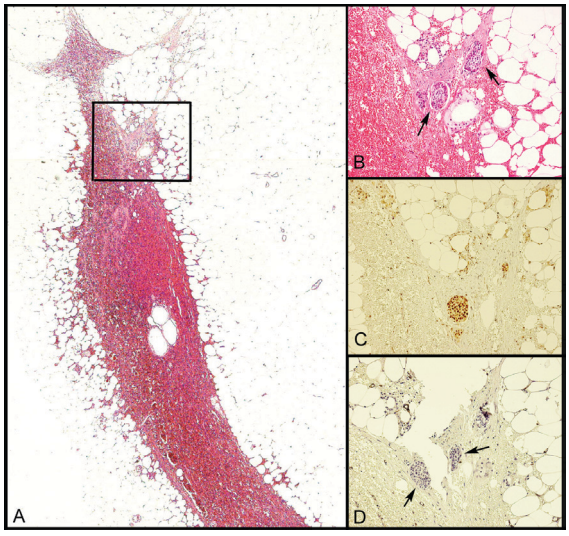
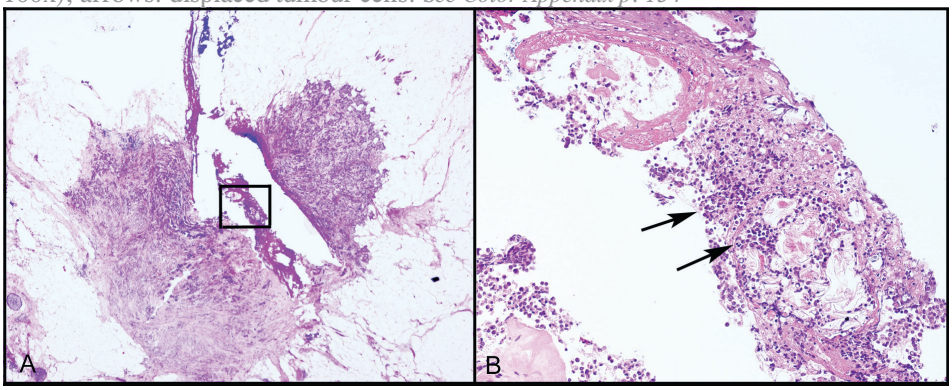


Figure 1A: Needle track surrounded by mammary and fatty tissue. (H&E, 10x)
Figure 1B: Detail with nests of vital tumour cells (arrows) growing along the needle track 18 days after stereotactic 14G core needle biopsy. Histological diagnosis of the tumour was a well differentiated invasive ductal carcinoma with lobular carcinoma in situ. (H&E, 100x)
Figure 1C: CAM-5.2 immuno-histochemistry of the same area as shown in Figure 1B.
Figure 1D: Alpha smooth muscle actin (a-sma) staining of the same section as Figure 1B demonstrating the absence of a basement membrane around the dislodged tumour cells (arrows).
See Color Appendix p. 154

Figure 2A: Displaced epithelial cells inside tumour (H&E, 2x); **Figure 2B:** Detail (H&E, 100x); arrows: displaced tumour cells. *See Color Appendix p. 154*



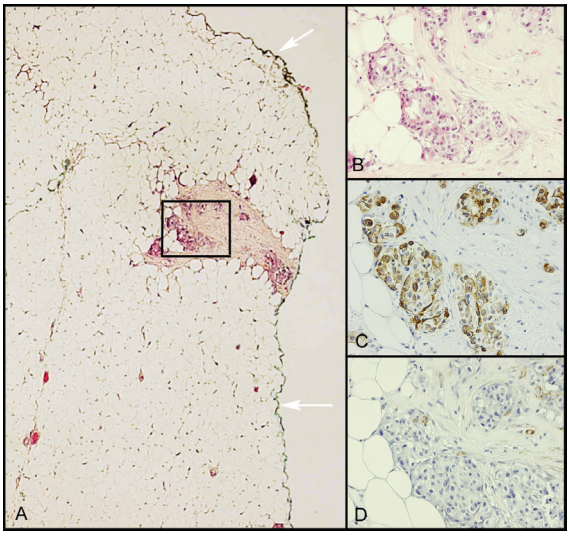


Figure 3A: Displaced groups of epithelial cells outside tumour (H&E, 2x); white arrows: inked margin of resection specimen;
Figure 3B: Detail (H&E, 100x);
Figure 3C: CAM5.2 staining of the same section as Figure 3B;
Figure 3D: Alpha-sma of the same section as Figure 3B.

See Color Appendix p. 155

Prospective study

In an attempt to examine the entire needle track for histopathological evaluation, we initiated a prospective pilot study. Our assumption was that only by evaluating the entire needle track all potentially displaced cells might be found. All patients scheduled to undergo stereotactic 14G-needle biopsy of a nonpalpable breast lesion were eligible for inclusion. During the biopsy-procedures the course of the needle track was carefully monitored and

described. After written informed consent, patients with invasive or in situ carcinoma on the large core specimen were included. The preoperative localisation wire was positioned as close as possible to and running in the same direction as the needle track. The skin puncture site of the needle track was included in the excision. The specimen was oriented on a wax plate and fixed in formaline for 24 hours. The resection margins were inked with Alcian Blue. Following a surgical and histopathological protocol, the exact direction of the needle track in the excision specimen was determined and in cross-sections the whole needle track from skin to tumour was totally embedded in paraffin blocks. The conventional serial sections were stained with hematoxylin and eosin and were examined by a breast pathologist to identify the needle track and the occurrence, localisation and amount of tumour cell displacement, as described earlier.
The amount of tumour cell displacement was divided in two groups: 'single cell' displacement, in which dislodgement of one to ten tumour cells was found, and 'cell clusters', which contained dislodgement of or ore more cell clusters, consisting of more than 10 cells per cluster. We assumed a positive relation between the amount of displaced tumour cells and clinical consequences of malignant cell seeding.

Results

Retrospective review

In 22 of 64 excision specimens the needle track could be identified. Tumour cell displacement along the needle track was seen in 11 of the 22 cases (50%) (Table 1). In 4 of these 11 cases the displacement of tumour cells was also encountered outside the tumour. Displacement of malignant cells had occurred in 7 of 16 invasive tumours and in 4 of 6 ductal carcinoma in situ (DCIS) lesions in which the needle track could be identified. In 4 cases, seeding along the needle track was seen outside the tumour (Table 1).

Prospective study

In a series of 35 consecutive biopsy procedures, malignant lesions were present in 15 patients. One patient was lost to follow-up because she underwent surgery in another hospital. Another patient was excluded because the needle track was not excised for cosmetic reasons. Median time interval between core biopsy and first surgical excision was 21 days (range; 7-35 days). The needle tracks left by core biopsy were visualised in 11 of these 13 remaining surgical specimens (Table 2). Due to technical problems, immunohistochemical staining failed in one case. Displaced tumour cells were seen in 7 cases; these were located outside

the primary tumour in 6 patients. Displacement of single cells was seen as frequent as displacement of viable cell clusters. Tumour cells were displaced approximately as often inside the tumour as outside of it.

Table 1: Retrospective assessment of excision specimens in which 14G needle tracks was identified

Histology of surgical excision specimen	Cases (n)	Occurrence of displaced tumour cells (in- or outside tumour)	Displaced tumourcells outside tumour
Invasive cancer	10	2	1
invasive+DCIS	6	5	1
DCIS	6	4	2
Total	**22**	**11 (50%)**	**4 (18%)**

DCIS=ductal carcinoma in situ

Table 2: Prospective study attempting to excise the entire needle track for evaluation

Histology	Cases	Displaced tumourcells inside tumour		Displaced tumourcells outside tumour		Interval*
	N	Single cells	Cellclusters §	Single cells	Cellclusters §	(days)
IC	4	2	2	3	2	18-35
IC+DCIS	7 #	1	2	3	3	7-25
DCIS	2¶	0	0	0	0	21-23
Total	**13**	**3 (23%)**	**4 (31%)**	**6 (46%)**	**5 (38%)**	

** Interval between core biopsy and excision;*
§ cellclusters defined as >10 cells
 # in 1 case, no needle track was identified in the excision specimen;
¶ in 1 case staining failed due to technical error;
IC=invasive carcinoma; DCIS=ductal carcinoma in situ

Discussion

This study shows that needle tracks after 14G-needle biopsy can be recognised in the subsequent excision specimen and that tumour cell displacement along these needle tracks does occur. Ours is the first study to attempt to evaluate the entire needle track. However, despite a special (radiological, surgical and histopathological) protocol the needle track could not be found in 2 cases. Also, remainders of needle tracks were found in re-excision specimens in 2 cases. Our results suggest that it is an illusion to think that all displaced tumour cells can be detected, implying that the true incidence of tumour cell displacement

after 14G automated core biopsy will never be known precisely.

The clinical implications of finding malignant tumour cells along the needle track are unclear. Diaz et al. found that the incidence and amount of tumour cell displacement was inversely related to the interval between core biopsy and excision.[7] Their conclusion was that this relation suggests that tumour cells do not survive displacement. However, Stolier et al. studied local breast cancer recurrence in relation to mammographically guided punctures and found that 1 of 2 patients with malignant needle track seeding developed a local recurrence at 34 months,[6] suggesting that displaced tumour cells may be viable.

Excising the needle track within the breast during surgical therapy might, theoretically, prevent local recurrence due to malignant cell seeding. In mastectomy, this is hardly ever a problem, although seeding might still occur occasionally in the overlying skin flaps. Nonetheless, concern about needle track seeding is greater for patients treated with breast-conserving therapy. Since the approach in stereotactic core biopsy may differ from the surgical routing, the needle track often lies outside the planned surgical excision area. In addition, excising the needle track may not always be cosmetically preferable or possible, as we found in our prospective study. On the basis of our findings, we do not recommend excising the entire needle track as a routine.

The use of radiotherapy may be adequate to kill displaced viable cancer cells. Boutin et al. studied patients with mesothelioma who underwent invasive diagnostic procedures.[17] Eight of 20 patients who did not receive radiation therapy developed metastases along the needle track vs. none of 20 patients who did receive radiation therapy. Thurfjell et al. found displaced tumour cells after fine needle aspiration and wire localised excision in 3 of 33 patients with local recurrence of breast cancer.[18] All 3 patients had not received radiotherapy. At present, the EORTC protocol advises radiotherapy after breast conserving therapy for both invasive and in situ carcinoma.[19]

In conclusion, malignant tumour cells can be displaced during 14G-needle biopsy of the breast. Excision of the entire needle track is neither feasible, nor advisable as a routine measure, since radiotherapy is advised for all types of carcinoma after conservative surgery.

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Chapter 6

The finding of invasive cancer after a preoperative diagnosis of DCIS: Causes of 'DCIS underestimates' with stereotactic 14G-needle biopsy

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Abstract

Background: For the evaluation of nonpalpable lesions of the breast, image guided 14G automated-needle biopsy is increasingly replacing wire-localized excision. When ductal carcinoma in situ (DCIS) is diagnosed at core biopsy, invasive cancer is found in ~17% of excision specimens. These so called 'DCIS underestimates' pose a problem for patients and surgeons, since they generally cause extension of treatment. We evaluated DCIS underestimates in detail to assess reasons for missing the invasive component at core biopsy. This evaluation also included a histological comparison with 'true DCIS' (DCIS at core and excision).

Methods: Between 1997 and 2000 DCIS was diagnosed at 14G-needle biopsy in 255 patients. In 41 cases invasive cancer was found at excision (16%). We performed a thorough histopathological and radiological review of all these DCIS-underestimates, including a histological comparison with core biopsy specimens of 32 true DCIS cases. We assessed the main reason for missing the invasive component at core biopsy.

Results: Causes for DCIS-underestimates were categorized into "mainly radiological"(n=20), "mainly histopathological"(n=15), and "histological disa--greements" (n=6). High-grade DCIS and periductal inflammation in core biopsies made a DCIS-underestimate 2.9 and 3.3 times more likely.

Conclusions: A variety of radiological and histopathological reasons contribute to the DCIS-underestimate rate. Approximately half of these are potentially avoidable.

Introduction

Ductal carcinoma in situ (DCIS) diagnosed at image guided core biopsy of the breast, may turn out to be underestimated at subsequent surgical excision biopsy. In roughly 17% of cases an invasive component is found at surgery.[1] These so called "DCIS underestimates" are undesirable for various reasons. Since most surgeons do not perform axillary lymph node dissection or sentinel node biopsy (SNB) for DCIS, a DCIS underestimation will result in axillary dissection or SNB at a later date. This does not only imply a delay in the definitive diagnosis and hence the appropriate treatment, but is associated with higher costs as well. Furthermore, it has been suggested by several authors that SNB, the preferred axillary approach in small size invasive breast cancer, is less accurate after prior breast surgery.[2;3] Finally, DCIS underestimates can be expected to be psychologically distressing for the patient involved. Therefore, decreasing the DCIS underestimate rate after image guided breast biopsy is most desirable.

Various studies have tried to find determinants of DCIS underestimates. Factors related to the underestimate rate are the size of the mammographic lesion (i.e. more sampling error with a larger lesion), the extent and distribution of the calcifications (i.e. a larger area of calcifications turns out to represent an invasive tumor more often), and the presence of a mass (a mammographic mass is often associated with an invasive carcinoma).[4-8] Histological factors reported to be associated with a higher likelihood of (micro)invasiveness include high grade of nuclear atypia, comedo subtype, and larger size.[6;8-12] However, these findings have not led to generally accepted recommendations for decreasing the DCIS underestimate rate.

The purpose of this study was to provide a detailed evaluation of DCIS underestimates and to assess reasons for missing the invasive component at core biopsy including a histological comparison with core biopsies of patients with "true DCIS" (i.e. DCIS at core biopsy as well as at excision).

Materials and methods

Study population

From April 1997 to January 2001, 1179 stereotactic 14-gauge (14G) needle biopsies were performed in 1113 patients. In 255 patients DCIS was diagnosed at needle biopsy and all underwent surgical excision. At excision, invasive carcinoma was diagnosed in 41 patients (41/255=16%). These cases are referred to as DCIS-underestimates. If no

invasive cancer was found at excision, these cases were labeled true DCIS (n=214). A random sample was taken from the true DCIS group (n=32) for comparative purposes.

Biopsy procedure

Since 1997 we have used stereotactic 14G core needle biopsies in five institutions (Antoni van Leeuwenhoek Hospital, Amsterdam; Bosch Medicentrum, Den Bosch; Martini Hospital, Groningen; Dr Daniel den Hoed Clinic, Rotterdam; and University Medical Center, Utrecht) to evaluate patients with nonpalpable breast lesions suspicious for carcinoma. All local Institutional Review Boards approved the study protocol.
Biopsies were performed in all centers using a 14-gauge core needle, long throw (2.2cm excursion) automated biopsy device with multiple passes (C.R. Bard Inc., Covington, GA) with the patient on a prone table (Fisher Imaging, Denver, CO). Lesions were localized with digital mammography. Our protocol advises to take at least eight core biopsies in cases of calcifications and five in cases of density or architectural distortion. In case of (micro)calcifications, a specimen radiograph was obtained and the biopsy procedure was said to be representative if some of these (micro)calcifcations were shown in the specimen. In all cases, histopathologic findings were correlated with the mammographic features at our weekly multidisciplinary meeting, attended by the radiologist performing stereotactic breast biopsies, a breast pathologist and a surgeon. Our diagnostic protocol has been described in detail elsewhere.[13] Lesions at each of the five institutions were accrued sequentially. Ultrasonographically guided percutaneous biopsy findings were not included.

Data-collection

Characteristics of participants were collected through questionnaires preceding the 14G needle biopsy and compared between the true DCIS (n=214) and DCIS underestimate group (n=41). These included patient factors (age at needle biopsy procedure; history of benign or malignant breast disease; hormone replacement therapy; parity). Furthermore, radiological characteristics were noted by the radiologist who performed the biopsy (type of mammographic lesion (mass, calcifications, or architectural distortion); radiological classification (probably benign, suspicious for malignancy, radiologically malignant); the largest diameter of the area of calcifications, accuracy of the localization of the lesions with digital imaging and of the biopsy-procedure, and the total number of biopsy specimens obtained. Histopathological characteristics included tissue diagnosis

and type and grade of the tumor. Grade of DCIS (I=well differentiated, II=moderately differentiated, III=poorly differentiated) was determined using the classification proposed by Holland and Peterse.[14]

Radiological and histopathological review

An extensive review of the radiological and histopathological material of all DCIS underestimate cases (n=41) was done to find reasons for missing the invasive cancer at core biopsy. All mammograms as well as the x-rays taken during the biopsy procedure and the specimen radiographs were re-assessed by a radiologist with experience in stereotactic breast biopsy procedures.

All core and surgical biopsy specimens were reviewed by an expert breast pathologist. In addition, we compared histopathological findings at core biopsy of an aselective sample of 32 true DCIS cases with those of the 41 DCIS underestimate cases. All tissue obtained at core biopsy was embedded in paraffin and serial sectioned in slides of 5 microns, and every tenth slide was stained with hematoxylin and eosin (H&E). Slides of the core specimens were scored on technical quality of the slide, fixation and the staining (H&E). Quality of the tissue and the damage induced by the biopsy procedure was noted. Total length of the core biopsies was registered. Presence, type (dystrophic or psammomatous) and location (in malignant or benign tissue) of calcifications were noted. Furthermore, periductal stromal reaction e.g. fibrosis and inflammatory infiltrate, was quantified as a potential predictor of invasive carcinoma.[5] All surgical excision specimens were reviewed along the same criteria, including a description of the type, size, location and multifocality of the invasive carcinoma.

Finally, for each of the 41 DCIS underestimate cases, the pathologist and the radiologist decided what the most likely reason was for missing the invasive component at core biopsy. These reasons were subsequently classified into the categories “mainly radiological” and “mainly histopathological” reasons and “histological disagreements”.

Statistical analysis

Characteristics for DCIS underestimates were compared to true DCIS. Categorical characteristics are presented as percentages and the chi-square test was used to compare proportions. Statistical analysis was performed with use of the Statistical Package for the Social Sciences 9.0 (SPSS Inc. Chicago, IL).

Results

Baseline characteristics

Patient characteristics are presented in Table 1. Apart from a lower frequency of nulliparity (10% vs. 25%; $p < 0.05$) and a higher frequency of post-menopausal women in the DCIS underestimate group (71% vs. 10%; $p < 0.05$), the results were not found to be significantly different from true DCIS patients. In the 41 DCIS underestimate cases, the mean diameter of the invasive component was 8.3 ± 6.3 mm. Eight patients had axillary metastases (range, 1-11 tumor positive lymphnodes; median 7).

Radiological characteristics

The radiological characteristics are presented in Table 2. Both in the DCIS underestimate and the true DCIS group the radiologist documented the lesion localization and biopsy procedure to be correctly executed in 95% of cases. The average extent of microcalcifications for the entire group of lesions consisting of calcifications ($n = 236$) was 16.4 mm.

Histopathological review

The average length of the sum of all core biopsy specimens per patient was 53.2 ± 19.3 mm in the DCIS underestimate group vs. 54.3 ± 29.7 mm for the true DCIS group ($p > 0.05$). Calcifications were never found in the center of the invasive tumor in the excision specimen, but in the peripheral ducts containing DCIS or in adjacent benign mammary tissue (Figure).
Results of the histopathologic review are presented in Table 3. Periductal stromal fibrosis was not related to invasiveness. A poorly differentiated DCIS in the core biopsy specimen was 2.9 times more likely to be a DCIS underestimate than a true DCIS when compared to well- or moderately differentiated DCIS, and if a periductal inflammatory infiltrate was seen this was 3.3 times more likely to be associated with invasiveness.

Correlation between histopathology and radiology

Upon combined review of the histopathological and radiological findings, the radiologist and pathologist formulated the most likely reason for missing the invasive carcinoma at core biopsy for each of the 41 DCIS underestimate cases (Table 4). The reasons were categorized into three groups.

Table 1: Patient-characteristics

	DCIS underestimates (n=41)		true DCIS (n=214)	
	n	***(%)***	**n**	***(%)***
Age – mean ±SD	59.2	±10.0	57.7	± 10.1
History of breast cancer	8	*(20)*	26	*(12)*
History of benign breast disease	10	*(24)*	58	*(27)*
Family history of breast cancer	11	*(27)*	60	*(28)*
Nullipara	4	*(10)* *	53	*(25)* *
Hormone replacement therapy use	18	*(44)*	111	*(52)*
Postmenopausal	29	*(71)* *	21	*(10)* *
Referral by National screening program	21	*(51)*	135	*(63)*

* $p < 0.05$

Table 2: Radiological characteristics of DCIS underestimates and true DCIS

Radiological characteristics	**DCIS underestimates (n=41)**		**true DCIS (n=214)**	
	n	*(%)*	n	*(%)*
Radiological classification				
Propbably benign	6	*(15)*	43	*(20)*
Suspicious for maligancy	27	*(66)*	141	*(66)*
Radiologically malignant	8	*(19)*	30	*(14)*
Lesion type				
Density only	2	*(5)*	17	*(8)*
Density with calcifications	6	*(15)*	32	*(15)*
Calcifications only	33	*(80)*	165	*(77)*
Largest diameter calcification area (mm)	23.2 *		15.0 *	
Largest diameter ≥ 10 mm	33	*(85)*	155	*(79)*
Largest diameter ≥ 25 mm	13	*(34)* *	26	*(13)* *
Largest diameter ≥ 50 mm	6	*(15)* *	4	*(2)* *
Accuracy biopsy procedure				
"Sampling of the lesion certain"	39	*(95)*	201	*(94)*
"Uncertain sampling of the lesion"	2	*(5)*	13	*(6)*
Number of core biopsies- (median; *range*)	6	*(5-13)*	7	*(1-18)*

* $p < 0.05$

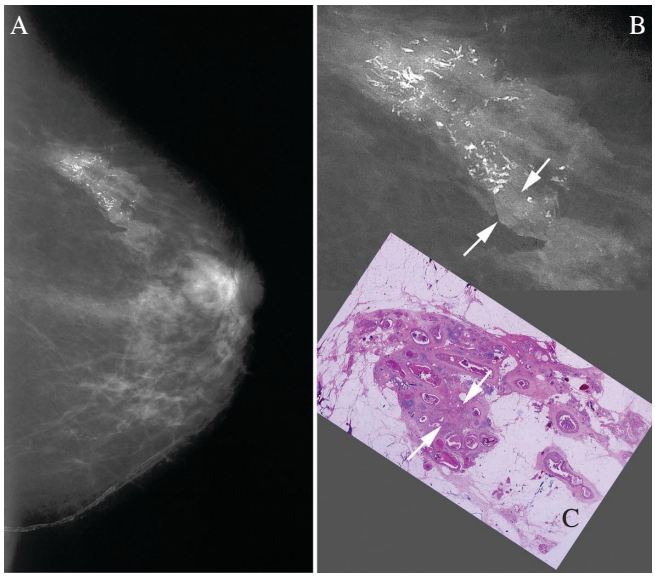

Figure
See Color Appendix p. 155

A. Representative mammogram with suspicious calcifications.
B. Detail of area with calcifications and density. Arrows indicate the density.
C. Detail of histologic slide corresponding to B. Arrows indicate the invasive component.

Table 3: Histologic features of DCIS underestimates and true DCIS

	DCIS u/e (n=41)		**true DCIS (n=32)**		**Total**
	n	*(%)*	n	*(%)*	
Histologic grade DCIS					
Poorly differentiated (gr III)	20	*(49)*	8	*(25)*	28
Well / Intermediately differentiated (gr I-II)	21	*(51)*	24	*(75)*	45
Odds Ratio 2.9 *95%CI (1.0-7.8)*					
Stromal periductal fibrosis					
Yes	25	*(61)*	20	*(63)*	45
No	16	*(39)*	12	*(38)*	28
Odds Ratio 0.9 *(0.4-2.4)*					
Periductal inflammatory infiltrate					
Yes	26	*(63)*	11	*(34)*	37
No	15	*(37)*	21	*(66)*	36
Odds Ratio 3.3 *(1.3-8.7)*					

95%CI=95% confidence interval

Table 4: Reasons for missing the invasive carcinoma on core biopsy

	n	
I. Mainly radiological problem:		**20**
A) Mammographic lesion:		
Large area of microcalcifications, no density	4	
Large area of microcalcifications plus a density; only calcifications are sampled	9 [a]	
No density can be distinguished since breast tissue is very dense	2	
Very small area of calcifications	1	
B) Biopsy procedure:		
Density cannot be visualized clearly with digital imaging (technical problem).	2	
Too few or non-representative core specimens obtained.	2[b]	
II. Mainly histopathological problem:		**15**
Poor quality of the slides / fixation / staining / too much damage induced by core biopsy to diagnose invasive cancer	3	
Suspicion of (micro)invasive carcinoma	8	
No invasive carcinoma in core biopsy but stromal response suggesting invasive cancer elsewhere in the DCIS area	1	
Coincidental finding of a small invasive cancer at excision	3	
III. Other reasons: histological disagreements:		**6**
Invasive carcinoma already present in core biopsy, but missed by routine pathologist	2	
No invasive carcinoma present in the excision specimen, only DCIS	4	

[a] *1 patient had a density on ultrasound but on the mammogram, only three clusters of calcifications were visible, which were sampled.*

[b] *Core biopsy material showed only 1 and 2 ducti in total, respectively, all three with DCIS*

The first category was “mainly radiological” problems. This included four cases where the invasive component was missed because the mammographic lesions consisted of such a large area (30, 45, 60, and 95 mm) of calcifications that only part of the lesion was sampled, which turned out not to be the invasive component (sizes of the invasive tumors were 16, 6, 9, and 2 mm, respectively). In nine cases, the mammographic lesion consisted of calcifications and an accompanying density, but only calcifications were sampled. At review, the invasive component found at excision turned out to be the mammographic density. Seven other cases were underestimated due to different sampling difficulties.

The second category was "mainly histopathological" problems – e.g. nine cases were suggestive of invasive cancer, but the diagnosis could not be made with sufficient certainty. Most of these cases involved intermediately / poorly differentiated DCIS. In three other cases the combination of a poor quality of the slide itself, the fixation, or the staining negatively affected the microscopic examination and subsequent accuracy of the histopathological diagnosis of the core biopsy specimen. In these other cases, suggestion of (micro)invasive carcinoma was seen, but due to the lack of quality of the slide, there was not enough convincing evidence for an invasive carcinoma at core biopsy. In three cases the findings of invasive tumor at excision were coincidental.
The third category consisted of "histological disagreements". Two cases appeared to have been misdiagnosed by the pathologist originally examining the core biopsy. Invasive cancer was already present in the core biopsy specimen, but missed. In an additional four cases, no invasive cancer was diagnosed in the excision specimen at revision implying that these had been incorrectly defined and treated as DCIS underestimates.

Discussion

In our consecutive series of 255 cases where DCIS was diagnosed at stereotactic 14G-needle biopsy, invasive cancer was found in 41 cases (16%). This DCIS underestimate rate is comparable to rates reported in literature.[1] Review showed that reasons for missing the invasive component at core biopsy were mainly radiological in 20 cases (49%), mainly histopathological in 15 cases (36%), and misdiagnoses (histological disagreements) in six (15%). Careful sampling, handling of biopsies and staining may prevent DCIS underestimates in up to 50% of cases. When comparing core biopsy specimens the only difference we found was that high grade DCIS and periductal inflammatory response are more often present in core specimens of DCIS underestimate cases than in true DCIS cases.
In an attempt to avoid radiological causes of DCIS underestimates one has to realize that most DCIS lesions present as calcifications on the mammogram; in our series, 236 of 255 lesions (95%). Thorough sampling of a large area of calcifications is often impossible due to technical reasons of the stereotactic breast biopsy. However, the likelihood of an invasive carcinoma is greater in the presence of extensive calcifications.[15] Interestingly, we found the invasive component of the tumor never to be present in the area of calcifications; these areas usually represented DCIS and/or benign tissue. If invasive carcinoma is present, it is most likely to be present as a mammographic density, and

hence in composed lesions, both density and calcifications should be sampled. Since 14G-needle biopsy is a sampling method, the histopathologic diagnosis can only be made on the tissue sampled, and this may be not representative of all pathologic findings in a given case.

Decreasing the DCIS-underestimate rate has been attempted by using biopsy devices that take larger biopsy specimens, such as 11G vacuum biopsy.[4;16;17] DCIS-underestimate rates for 11G vacuum-assisted biopsy are reported to be 10.3-11.4% in comparison to the 15.5% (95% confidence interval; 8-26%) reported for 14G automated core biopsy.[1] Of note, even with diagnostic excision biopsy, DCIS underestimates have been reported in up to 18% of cases.[18;19]

To decrease histopathological causes of DCIS underestimates, careful handling of the fragile material obtained at core biopsy is imperative. A sufficient number of slides should be made to gain adequate exposure of the tissue retrieved. We advocate serial sectioning of all core biopsy tissue. The histopathological assessment of 14G breast biopsies may be more complicated when compared to open breast biopsy, because a smaller amount of tissue is obtained. The context of the surrounding tissue and topographic relationships of various structures is crucial for histologic analysis in many instances. Disagreements in histopathological diagnosis between pathologists do occur, and may have a serious impact on the therapeutic decisions. In the present study, in six cases the diagnosis made at review differed from the original histopathological diagnosis. We therefore recommend, that whenever a pathologist has doubts about the histopathological diagnosis at core biopsy (considering the consequences of repeated breast surgery), (s)he should not hesitate to consult a colleague with extensive expertise in breast pathology.

The presence of stromal fibrosis or a periductal inflammatory cell infiltrate are subtle signs of early invasion.[19;20] The etiology of the periductal inflammatory response in association with carcinoma is unknown but it has been speculated to represent an immune response to (occult) basement membrane destruction and invasion, or a response to a tumor-secreted or carcinogenic agent.[19;21;22] In the present study we found that when a periductal inflammatory infiltrate is present, the risk of finding invasion at excision is more than three times higher then when no inflammation is present. Also, poorly differentiated DCIS was associated with a threefold increased risk of invasion. A lesion with poorly differentiated DCIS and a periductal inflammatory response turned out to be a DCIS underestimate in 70% (16/23) of the cases.

The diagnosis of subtle invasive carcinoma in a core biopsy specimen can be facilitated by obtaining deeper levels from the tissue block and / or by using immunohistochemical stains for basement membrane (collagen IV and laminin) and myoepithelial cells (e.g. alpha-smooth muscle actin or heavy chain myosin).[20] Cytokeratin immunostains are essential because they highlight individual invasive carcinoma cells that are beyond the bounds of the parent in situ carcinoma. These immunostains are also useful but not necessary in all cases for making the diagnosis of microinvasion.[23] Nevertheless, the alpha-SMA and cytokeratin 14 immunostains we performed on our core biopsy specimens of DCIS underestimates revealed no confirmation of invasiveness. The value of these staining-procedures is at least disputable.
The success of 14G needle biopsy procedures and the validity of pathologic diagnoses made on the core biopsy material are key determinants for the surgeon in planning the optimal management of nonpalpable breast lesions. Another option might be that when suspicion for (micro)invasion is high, treatment is directed as if invasive cancer was established at core biopsy. This may be appropriate for patients with a lesion presented by an area of microcalcifications ≥50 mm, since 60% of our cases turned out to be a DCIS underestimate. Also, when the core biopsy specimen showed poorly differentiated DCIS with a periductal inflammatory response, we found invasive cancer at excision in 16 of 23 cases (70%).

In conclusion, approximately 16% of DCIS diagnosed by stereotactic 14G-needle biopsy turn out to be invasive at excision. In our retrospective review, reasons for missing the invasive component are mostly radiological (49%) or histopathological (36%), while histopathological disagreements account for 15% of DCIS underestimates. Poorly differentiated DCIS and periductal inflammation found at core biopsy increase the chances of finding an invasive component at excision approximately threefold.

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Chapter 7

Vacuum-assisted breast biopsy: a critical review

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Abstract

Introduction: Vacuum-assisted biopsy is an image-guided technique introduced in 1995 and claimed to be superior to 14G automated-needle biopsy for the evaluation of nonpalpable breast lesions. However, prospective randomized studies evaluating its accuracy are unavailable. We conducted a critical review of the currently available literature on the accuracy of vacuum-assisted biopsy and compared it to published data on 14G automated-needle biopsy.

Methods: The diagnostic performance of vacuum-assisted biopsy was evaluated by reviewing all available English-language literature published in Medline between 1995 and November 2001. Four independent reviewers used standard forms to extract the data. Twenty-two published studies were included. *High-risk* and *DCIS underestimate rates* as well as the *miss-rate* of cancer were assessed.

Results: *High-risk* and *DCIS underestimate rates* for 11G vacuum biopsy are 16% (95%CI 12-20) and 11% (95% CI 9-12), respectively, and both lower than rates reported for 14G automated-needle biopsy (40% (95% CI 26-56) and 15% (95% CI 8-26), respectively). Due to incomplete follow-up of benign lesions it is impossible to compute *miss-rates* and thus the sensitivity rate.

Conclusion: The results of this review indicate that vacuum-assisted biopsy is able to decrease the *high-risk* and *DCIS underestimate rates*, but that it is unclear whether it will decrease *miss-rates* of cancer.

Introduction

Stereotactic 14-gauge (14G) automated-needle biopsy has been shown to be comparably accurate to wire-localized surgical excision for evaluating nonpalpable breast lesions.[1-3] This has resulted in a worldwide increase of large-core needle biopsies. Currently, it is estimated that in the USA one million needle biopsies are performed yearly, of which approximately 300,000 for nonpalpable breast lesions.[4]

Although sensitivity rates for 14G automated-needle biopsy are high (97%) some cancers are missed. Another shortcoming is that the severity of the disease is sometimes underestimated, i.e. when findings at surgical excision show a higher degree of pathology than at previous breast biopsy.[5] The finding of carcinoma after a biopsy diagnosis of atypical ductal hyperplasia (ADH), or of invasive carcinoma after a biopsy diagnosis of ductal carcinoma in situ (DCIS), define *ADH-* and *DCIS-underestimates*, respectively. Not only is it psychologically distressing for patients in whom breast cancer is underestimated, but it also implies a delay in establishing the definitive diagnosis and hence, appropriate treatment. Many of these patients will need additional surgical procedures. Finally, 16-18% of scheduled stereotactic large core-needle biopsies is cancelled, partly due to suboptimal lesion localisation or lesion size.[6;7] In an attempt to overcome some of these negative aspects of large-core needle biopsy, vacuum-assisted breast biopsy was developed at the end of 1995.[8;9] The vacuum-assisted biopsy device acquires tissue samples by using a single insertion of the probe (11- or 14-gauge) and vacuum suction to retrieve core specimens. More samples can be obtained in a shorter period of time, and the samples are larger than those obtained with 14G needle and automated gun.[8;10-12] A further advantage is that it can be used for taking biopsies from small (<5 mm) mammographic lesions, for superficial lesions and for thin breasts. Disadvantages are the higher costs associated with the disposable materials of the vacuum suction system, which are 10-20 times higher than for 14G automated-needle biopsy. Also, vacuum-assisted biopsy of a malignant lesion may lead to difficulties in estimating the true size of the tumour at excision (when most of the lesion has been sampled at vacuum biopsy), which is an important indicator for adjuvant therapy.

Vacuum-assisted biopsy is expected to decrease the *miss-rate* and the number of *ADH-* and *DCIS-underestimates*. For 14G automated-needle biopsy, these rates are 3% (95% confidence interval (95% CI): 1-5), 40% (95% CI: 26-56) and 15% (95% CI: 8-26), respectively, as published in a meta-analysis.[13] Although many studies have reported on these aspects of the vacuum-assisted breast biopsy, well-designed clinical studies comparing vacuum-assisted biopsy with surgical excision are unavailable. We reviewed the literature to assess the

diagnostic performance of vacuum-assisted breast biopsy and to evaluate its potential benefits.

Methods

Reference retrieval and in- and exclusion criteria

A Medline search of the English-language literature published between 1995 and November 2001 was performed. "Breast AND biopsy AND vacuum" or "mammotome" were used as search terms. A cross-reference search completed the exploration.
Publications were included in the review if the pre-set inclusion criteria were met: 1) all histological diagnoses of vacuum-assisted biopsy specimens had to be confirmed by either surgical biopsy or adequate follow-up; 2) the absolute number of benign and malignant diagnoses had to be derivable; 3) the method of guidance had to be stereotaxis; 4) the size of the used vacuum probe had to be described. Duplicated publications (where data were collected over the same period at the same center) were excluded. A total of 88 papers were retrieved when using the above search terms. Most of these studies reported on nonpalpable lesions, but this was not always clear, although the development of image guided breast biopsy techniques was originally intended for nonpalpable lesions. Of the 88 relevant articles, 48 were excluded, and 40 first considered. Three publications were excluded because they were review articles on various biopsy techniques and in 45 studies, the diagnostic performance of vacuum-assisted biopsy was not the object of study. Of the 40 considered articles addressing the diagnostic accuracy of large-core needle biopsy, a further 18 studies were excluded: Six studies were excluded because they partly described the same data that was published in another paper, already included in our meta-analysis. Five papers reported on sonographically guided vacuum-biopsy and were thus excluded. Four studies were excluded because the histological diagnoses from core biopsy and surgical excision or follow-up were not given. In three papers, the absolute number of (nonpalpable) lesions was not derivable. (A list of the 18 excluded publications and the reasons for exclusion is available upon request). Finally, we included 22 studies in the meta-analysis.[4;14-34]

All four authors independently extracted the data from the studies using a standard extraction form. Study period, number of patients and lesions, method of patient selection, type of lesion (calcifications or density), needle size, results of surgical excision, follow-up data, complications and the number of cancelled procedures were registered. In case of discrepancies consensus was reached.

Analysis of diagnostic performance

The diagnostic performance of vacuum-assisted biopsy was assessed using the method introduced by Burbank and Parker.[5] For this purpose, the histological outcomes from the vacuum-assisted biopsy procedures were classified according to one of the following four categories: 1) benign breast disease; 2) high-risk lesions; 3) DCIS, and 4) infiltrating breast cancer. Subsequently, the actual disease status was assessed. Lesions that were surgically removed were divided into the same four categories according to the histological diagnosis. Microinvasive carcinoma was considered as invasive cancer. Lesions with a benign histological vacuum biopsy result were most often not surgically removed and were classified as benign if no progression requiring re-biopsy was observed during adequate follow-up. We intended to include studies if at least 90% of benign lesions were either surgically removed, or mammographically followed for at least two years. If this was not the case, we describe numbers of benign lesions and numbers of missings, but without trying to combine them. If no information at all about follow-up was available studies were excluded. To assess diagnostic performance we computed for each study estimates of 1) inconclusive lesions 2) *high-risk underestimate rate* 3) *DCIS underestimate rate* and 4) *miss-rate*. Homogeneity of the estimates among the individual study results was tested using the chi-square test.[35] If the study results were homogeneous, a combined estimate was computed. Combined estimates were also computed according to 1) the size of the probe used, i.e. 11G or 14G vacuum probe; and 2) lesions consisting of calcifications only.

The proportion of inconclusive biopsy results was assessed; these are defined as lesions for which re-biopsy is indicated, because a pathohistological diagnosis concordant with mammographic findings was not drawn from the vacuum-biopsy.

High-risk lesions are benign lesions know to have a high risk of simultaneous carcinoma in the ipsilateral breast and include atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ, radial scar, papillary lesions or a possible phyllodes tumour. These high-risk lesions at biopsy are always an indication for surgical excision.[36-40]

The *high-risk underestimate rate* was defined as the percentage of high-risk lesions on vacuum-assisted biopsy that was upgraded to DCIS or invasive cancer in the surgical specimen.[5] Lesions that were not surgically excised and without follow-up of at least two years were not used for the analyses. The *DCIS underestimate rate* was defined as the percentage of DCIS lesions on vacuum-assisted biopsy upgraded to invasive cancer at subsequent excision.[5]

The *miss-rate* was defined as the proportion of all carcinomas with a benign diagnosis on

vacuum-assisted biopsy. Conventionally, sensitivity is defined as one minus the false negative rate. The false negative rate is defined as the proportion of negative diagnoses (here, benign diagnosis on vacuum-assisted biopsy) among all true positive diagnoses (here, carcinomas) based on the gold standard (surgery or adequate follow-up). Thus, sensitivity equals one minus the *miss-rate*.

Statistics were performed using Statistical Package for Social Sciences 9.0 (SPSS Inc. Chicago, IL). For studies with >20 lesions, large-approximation 95% confidence intervals (95%CI) for all estimates were calculated. For studies that included ≤20 patients, exact 95% confidence intervals (binomial distribution) were used.

Results

Twenty-two studies were included in the present review, of which seven reported on inconclusive lesions,[18;21-23;29;33;34] of which 17 contributed data to the combined *high-risk underestimate rate,*[14-24;28;30-34] of which 15 contributed to the combined *DCIS underestimate rate* [4;19-28;31-34] and finally seven studies reported on follow-up of benign lesions.[20-23;29;32;33] Four out of 22 studies reported on all these endpoints.[21-23;33] Characteristics of all studies are presented in Table 1. Three studies mentioned complications that occurred as a result of the vacuum-assisted biopsy,[20;21;30] including bleeding or hematoma (n=4), vasovagal reaction (n=1), infection (n=1), seizure (n=1) and nausea (n=1). One study reported that no complications had occurred.[32] Two studies reported that two and three planned procedures were cancelled.[24;33]

Inconclusive results

Seven studies reported on the number of inconclusive diagnoses, e.g. lesions for which re-biopsy was indicated, because a clear pathohistological diagnosis could not be drawn from the vacuum-biopsy.[18;21-23;29;33;34] The proportion of these lesions varied from 0.5% (1/216) to 9.0% (32/354), (median, 1.2%), and in three of twenty-eight cases that were followed by surgical excision, a malignancy was found (10.7%).

High-risk underestimate rate

Fifteen studies contributed data to compute the *high-risk underestimate rate* for stereotactic 11G vacuum-assisted breast biopsy.[14-24;28;32-34] Testing of homogeneity of the *high-risk underestimate rates* for each individual study was nonsignificant ($X^2=13.7$; 14 degrees of freedom (df); $p>0.25$). A total of 416 high-risk lesions were detected in these 15 studies.

Table 1: Characteristics of the studies included in meta-analysis

										Data on lesions used for analysis:			
ref	**1st author, year of publication***	**Probe used**	**consecutive patients**	**Age mean**	**(range)**	**% calcifi-cations**	**Palp**	**% DCIS and invasive cancer**	**complications**	**Inconclusive**	**HR u/e**	**DCIS u/e**	**Benign**
14	Brem, 1999	11G	Only HR	58.1	(35-74)	90	?	25	?		X		
15	Adrales, 2000	11G	Only HR	53.8	(36-82)	100	?	15	?		X		
16	Philpotts, 2000	11G	Non-cons	?		56	?	?	?		X		
17	Manganini, 2001	11G	Only HR	?		91	Np?	?	?		X		
18	Philpotts, 1999	11G	Non-cons	?		53	Np?	?	?	X	X		
19	Burak, 2000	11G	Non-cons	?		65	Np?	20	?		X	X	
20	Beck, 2000	11G	Non-cons	?		?	Np?	18	2/594		X	X	X
21	Liberman, 1998	11G	Only mc	M55	(31-85)	100	Np?	29	3/112	X	X	X	X
22	Lai, 2001	11G	Consecutive	54.7	(22-89)	?	?	22	?	X	X	X	X
23	Cangiarella, 2001	11G	Non-cons	53.5	(34-79)	100	Np	9	?	X	X	X	X
24	Lattanzio, 2001	11G	Consecutive?	54	(33-75)	76	Np?	35	3/115 cancelled		X	X	
25	Won, 1999	11G	Only DCIS	?		95	Np?	100**	?			X	
26	Brem, 2001	11G	Non-cons	58	(35-78)	75	Np	100**	?			X	
27	Jackman, 2001	11G 14G	only DCIS	57.0	(32-88)	91	np	100**	?			X	
28	Darling, 2000	11G 14G	Consecutive	54	(24-89)	98 92	?	?	?		X	X	
29	Jackman, 1999	11G 14G	non-cons*	52	(29-89)	68	Np	Benign only	?	X			X
4	Liberman, 2001	14G	Non-cons	53	(26-84)	100	Np	88	?			X	
30	Jackman, 1997	14G	Only HR	58	(38-92)	84	Np	?	3 (0,14%)		X		
31	Soo, 1999	14G	Non-mc only	?		0	Np	25	?		X	X	
32	Zannis, 1998	11+14G	Consecutive	57.7	(25-90)	83	Np	22	0		X	X	X
33	Ohsumi, 2001	11+14G	Consecutive?	51.6	(30-77)	91	Np	35	2/90 cancelled	X	X	X	X
34	Joshi, 2001	11+14G	Consecutive	55.7	(30-84)	58	Np?	15	?	X	X	X	

* *All but four studies were conducted in the United States; one study was conducted in Germany [20], one in Canada [22], one in Italy [24], and one in Japan [33].*

** *Only malignant lesions were described. Non-cons = nonconsecutive patients; M=median; np=nonpalpable; np?=probably nonpalpable; p=palpable; mc=microcalcifications; HR u/e = high-risk underestimates; X=contributed data to combined estimate.*

For 57 lesions the final diagnosis was missing: they were not removed by surgery, or disease free follow-up over two years was not reported. Therefore, these lesions were excluded from the analysis. Of the remaining 359 high-risk lesions, 57 were proven to be malignant (*high-risk underestimate rate*=57/(416-57)=15.9% (95%CI 12.1-19.7) (Table 2).

Table 2: High-risk underestimate rates (HR u/e) for stereotactic vacuum-assisted breast biopsy

Reference	High-risk at biopsy	Inadequate FU / no excision	Used for analysis	Malignant at excision	HR u/e (%)	95% CI
			11G probe			
14	20	4	**16**	4	25.0	(5.7-43.7)
15	90	28	**62**	9	14.5	(5.8-23.3)
16	26	0	**26**	6	23.1	(6.9-39.3)
17	44	11	**33**	4	12.1	(0.3-28.2)
18	21	4	**17**	4	23.5	(3.4-43.7)
19	46	0	**46**	6	13.0	(3.3-22.8)
20	13	0	**13**	0	0	(0-24.7)
21	12	1	**11**	1	9.1	(0.2-38.5)
22	12	0	**12**	2	16.7	(2.1-48.4)
23	14	4	**10**	2	20.0	(1.8-42.8)
24	10	5	**5**	1	20.0	(0.3-44.5)
28	86	0	**86**	16	18.6	(10.4-26.8)
32	4	0	**4**	0	0	(0-60.2)
33	3	0	**3**	2	66.7	(13.3-100)
34	15	0	**15**	0	0	(0-21.8)
TOTAL	**416**	**57**	**359**	**57**	**15.9**	**(12.1-19.7)**
			14G probe			
28	28	0	**28**	11	39.3	(30.1-57.4)
30	88	14	**74**	13	17.6	(13.2-26.3)
31	1	0	**1**	0	0.0	(0-97.5)
TOTAL	**117**	**14**	**103**	**24**	**23.3**	**(19.1-31.5)**

In study 28 the number of patients without surgery or adequate follow-up is not specifically reported.
Studies 32, 33, and 34: both 14G and 11G probe used, but biopsies per probe cannot be determined separately.
Study 15: 3 patients had a simultaneous breast carcinoma ipsilaterally. They are not used in the analyses.
Study 31: only lesions NOT consisting of calcifications were included.

Another three studies reported on lesions consisting of calcifications only.[15;21;23] Twelve malignancies were diagnosed in 83 patients with surgery or adequate follow-up (116-33=83). The combined *high-risk underestimate rate* was 12/83=14.5% (95%CI 7.7- 23.9%) (Table 3).

Table 3: *High-risk underestimates* after 11G vacuum-assisted breast biopsy for lesions consisting of microcalcifications only

Reference	High-risk at biopsy	Inadequate FU/ no excision	Used for analysis	Malignant at excision	HR u/e (%)	95% CI
15	90	28*	**62**	9	14.5	(5.7-23.3)
21	12	1	**11**	1	9.1	(0.2-38.5)
23	14	4	**10**	2	20.0	(1.8-42.8)
TOTAL	**116**	**33**	**83**	**12**	**14.5**	(7.7-23.9)

** Study 15: 3 patients had a simultaneous breast carcinoma ipsilaterally. They are not used in the analyses.*

DCIS underestimate rate

Thirteen studies reported on *DCIS underestimate rates* with a 11G vacuum probe.[19] Homogeneity testing of the individual study results did not show significant differences between studies ($X^2=16.6$; df=12; $p>0.1$). A total of 1157 DCIS lesions were diagnosed in these 13 studies.[20-28;32-34] Fifty-two percent of these lesions were detected in one multi-institutional study (describing the results of 16 centers).[27] Hundred twenty-two lesions showed invasive cancer at surgery: the combined *DCIS underestimate rate* was 122/(1157-4)=10.6% (95%CI 8.8-12.4%) (Table 4).

Four studies reported on DCIS lesions at 14G vacuum biopsy.[4;27;28;31] However, the test for homogeneity was significant ($X^2= 14.9$; df=3; $p<0.01$), and the calculated combined estimate (52/409=12.7% (95%CI 9.5-15.9%)) should be regarded with caution.

Two studies reported on *DCIS underestimate rates* at 11G stereotactic vacuum-biopsy for lesions appearing as calcifications only[21;23] and they were 5% (1/21) and 8% (1/12), respectively (Table 5).

Table 4: *DCIS underestimate rates* for stereotactic vacuum-assisted breast biopsy

In study 28 the number of patients without surgery or adequate follow-up is not specifically reported.
Studies 32, 33, and 34: both 14G and 11G probe used, but biopsies per probe cannot be determined separately.
Study 31: only lesions NOT consisting of calcifications were included.
The 4 patients that were excluded from the analysis did not undergo excision and follow-up was not reported.

Table 5: *DCIS underestimates* (DCIS u/e) after 11G vacuum-assisted biopsy for lesions consisting of microcalcifications only

Reference	DCIS at biopsy	Inadequate FU/ no excision	Used for analysis	Invasive CA at excision	DCIS u/e (%)	95% CI
21	21	0	**21**	1	4.8	(0.1-23.8)
23	13	1	**12**	1	8.3	(0.2-36.0)
TOTAL	**34**	**1**	**33**	**2**	**6.1**	**(0.7-20.2)**

Miss-rate

The finding of benign lesions at 11G stereotactic vacuum-biopsy with at least some follow-up was described in seven studies.[20-23;29;32;33] However, follow-up of these lesions was inadequate according to our pre-set inclusion criteria (surgery or follow up for 90% of patients for at least 2 years) (Table 6). In one study,[22] 12 of 491 patients with benign lesions had adequate follow up: 2 underwent excision which showed a malignancy, and ten had unchanged, unsuspicious mammograms two years after vacuum-assisted biopsy. In two other studies,[21;23] 1/61 and 4/120 benign lesions diagnosed at 11G vacuum biopsy lesions had been excised, but no malignancies were found. Due to incomplete follow-up of benign lesions in all studies, we were unable to calculate the *miss-rate* and thus the sensitivity rate.

Table 6: Follow-up of benign lesions diagnosed with 11G stereotactic vacuum-assisted breast biopsy

Reference	Total benign lesions at biopsy	Inadequate or missing FU	Adequate FU	Cancer	Remarks on follow-up (FU):
20	476	476	**0**	N/A	not reported for 11G vacuum biopsy separately
21	61	60	**1**	0	1 excision, rest not reported
22	491	479	**12**	2	2 excisions; 6 months FU for 254; 12 months for 43 patients
23	120	116	**4**	0	4 excisions; 6-36 months for 76 patients
29	146	146	**0**	N/A	6 months for 146 patients
32	56	56	**0**	N/A	Unsuspicious mammograms at 6 months for 33 patients
33	56	55	**1**	1	1 excision: invasive CA; FU not reported for 11G separately
TOTAL	**1406**	**1388**	**17**	**3**	

Discussion

The present review shows that stereotactic 11G vacuum-assisted breast biopsy results in a *high-risk underestimate rate* and a *DCIS underestimate rate* of 16% and 11%, respectively. When we compare these rates to published data on stereotactic 14G biopsy with an automated gun, we find a significant decrease in the *high-risk underestimate rate* (40%; difference=24%; $p<0.05$) and a nonsignificant decrease in the *DCIS underestimate rate* (15%; difference=4%; $p>0.05$).[13]

Most of the studies provided limited detail on patient selection. In many of the studies it is not clear whether patients enrolled were those with nonpalpable breast lesions, or if consecutive patients were included. The prevalence of carcinoma varies largely between the studies (Table 1), which may indeed indicate patient selection for the vacuum procedure. Given the large number of studies with missing data on various characteristics (as presented in table 1), we were unable to take into account the effect of these covariates. For example, for the DCIS underestimate rate, which is a predictive value, the prevalence of DCIS among all cancers influences this rate and is thus an important determinant of the underestimate rate. However, the proportion of patients with DCIS among all patients with carcinoma could be derived only for a small number of studies. However, we believe that among the populations described in the included studies this proportion will not vary considerably, given that generally nonpalpable lesions were included as well as comparable age groups.

An important conclusion of the present study is that the *miss-rate* could not be determined due to incomplete or non-reported follow-up of benign lesions that were not surgically removed (also referred to as a verification-problem: benign lesions are not surgically removed). The *miss-rate* for 14G automated biopsy is 3%, and it is not clear from the available data that this is lower when using vacuum biopsy.[3;13]

To estimate the benefit of vacuum biopsy over 14G automated-needle biopsy we calculated the number of preventable underestimated diagnoses in a representative, nonselective population of patients with nonpalpable breast lesions. We used the underestimate rates computed in the present study for the vacuum probe, and for 14G automated-needle biopsy those reported in a previous meta-analysis.[13] We furthermore used data from a recent multi-center trial in the Netherlands in which women were included who were referred for biopsy of a suspicious nonpalpable breast lesion,[3] to estimate the number of preventable underestimated diagnoses. In this population of 858 women a total of 20 high-risk lesions

and 158 DCIS lesions were diagnosed by surgery. 14G automated-needle biopsy would have yielded 33 high-risk lesions (underestimate rate 40.0%, thus 20 high-risk and 13 malignant at surgery) and 187 DCIS lesions (underestimate rate 15.5%, thus 158 DCIS and 29 invasive carcinomas at surgery). Vacuum biopsy would yield 24 high-risk and 176 DCIS lesions instead. This means that 9 out of 858 (1.0%) women would be spared a *high-risk underestimate* diagnosis and that 11 out of 858 (1.3%) would be spared a *DCIS underestimate* diagnosis. Hence, the total decrease in underestimated diagnoses would have been 20/858 (2.3%) when using vacuum biopsy instead of automated-needle biopsy in this well-defined population. Selective use of vacuum biopsy for lesions for which 14G automated biopsy is less accurate, such as lesions consisting of calcifications only,[41] would be another option to be further explored. In the present study we also looked at lesions consisting of calcifications only, and although the number of lesions was very low, the combined *high-risk underestimate rates* (14.5%) and *DCIS underestimate rates* (6.1%) are comparable to rates found in studies describing all lesions. It is, however, for logistic and financial reasons not always possible to use both techniques in one institution. We agree with Jackman et al.[27] that there is probably not one universally cost-effective breast biopsy method best for all lesions. The diagnostic accuracy of image-guided breast biopsy techniques is already very high, and perhaps this could be increased at best by focusing on multidisciplinary discussions on the outcomes of the biopsies and constant monitoring of the quality, and not by further improving the technical performance of biopsy devices.

In conclusion, the results of the present review indicate that vacuum-assisted biopsy, in comparison to 14G automated-needle biopsy, is able to decrease *high-risk underestimate rates* and *DCIS underestimate rates*, but that it is unclear whether it will decrease *miss-rates* of cancer. Therefore, it is presently impossible to assess whether the benefits outweigh the additional costs.

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Chapter 8

Predictive factors for mastectomy in nonpalpable ductal carcinoma in situ

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Abstract

Introduction: Due to increased mammographic screening, the incidence of nonpalpable ductal carcinoma in situ (DCIS) is increasing. Breast conserving therapy is initiated in most cases, but re-operations are frequent. For definitive surgical therapy, mastectomy is often needed. We set out to evaluate which determinants predict mastectomy.

Methods: 402 consecutive patients diagnosed with DCIS at stereotactic 14G-needle biopsy between April 1997 and June 2002 were included. Preoperative characteristics of the patient, mammographic lesion characteristics and results of core needle biopsy were included as predictive determinants for mastectomy. Multivariate logistic regression analysis was performed to evaluate prediction capacity of combined determinants. Discriminating capacity was assessed through the Area Under the Receiver Operating Characteristics (ROC) Curve (AUC). A cut-off point was taken to identify women at high risk.

Results: 102 of 402 women with DCIS underwent immediate mastectomy (25%). 300 women underwent initial breast conserving surgery, and were included in the analysis. In subsequent surgical sessions 93 of these women had mastectomy (31%). The four determinants associated with mastectomy were a history of breast cancer, mammographic calcifications (without density), measuring >2 cm and classified as radiologically malignant (BI-RADS 5). The AUC of the ROC based on the multivariate model including all these factors was 0.71 (95%CI: 0.64-0.77). Women with two or more of these four determinants, are at high risk for mastectomy (53%). This may guide the initial surgical procedure to be more aggressive for these women.

In conclusion, our study shows that 25% of patients with nonpalpable DCIS undergo mastectomy immediately after a preoperative large core needle diagnosis, while another 24% initially planned for breast conserving therapy, finally ended up with mastectomy. Four determinants were associated with risk of mastectomy, but the individual prediction was not optimal.

Introduction

Due to the introduction of national screening programs as well as an increased awareness among women, breast cancers are frequently detected in an earlier stage of development and still non-palpable. As a result of this, there has been an enormous increase in the detection of ductal carcinoma in situ (DCIS). Where 1-3% of palpable breast malignancies is DCIS, this proportion is 25-30% for mammographically detected breast malignancies.[1-3] The age-adjusted incidence of DCIS has increased five to ten-fold in the past 20 years, with the largest increase after the start of the screening programs.[3-7] In recent years, European countries report a DCIS incidence of 6.2 to 9.9 per 100,000 women per year.[4;5;7] In the United States screening is offered to women from 40 years of age, resulting in a slightly higher incidence of 13.8 to 15.8 per 100,000 women.[3;6]

With the introduction of image guided percutaneous needle biopsies for nonpalpable breast lesions, the number of diagnostic surgical procedures has decreased substantially.[8-12] In addition, guidelines now state that at least 70% of nonpalpable suspicious breast lesions should be excised after obtaining a preoperatively established diagnosis.[13;14] With a preoperative diagnosis, optimal surgical therapy can be planned, i.e. adequate local control with a minimum number of surgical procedures. Mastectomy has long been the standard of care, but when feasible, breast-conserving therapy is the treatment of choice for nonpalpable DCIS. This is considered when a DCIS lesion appears to be unifocal in localisation, smaller than 4cm, and when clear resection margins can be obtained. Finally, preferences of patient and surgeon will also guide treatment choice. Radiotherapy has been shown to reduce the local recurrence rate after breast conserving surgery for DCIS.[15-17] Although initially treated with breast conserving surgery, in some patients re-operations are needed, and in a subgroup of these patients, mastectomy will eventually be performed.

In women with preoperatively diagnosed nonpalpable DCIS we studied the proportion of patients initially treated with breast conserving surgery, but eventually treated with mastectomy. We tried to identify patients at high risk for mastectomy pre-operatively in an attempt to guide the first surgical procedure to be more aggressive in these patients.

Patients and methods

Biopsy procedure and study population

Since 1997 we have used stereotactic 14G core needle biopsies in five institutions in the Netherlands (Antoni van Leeuwenhoek Hospital, Amsterdam; Bosch Medicentrum, Den

Bosch; Martini Hospital, Groningen; Dr Daniel den Hoed Clinic, Rotterdam; and University Medical Centre, Utrecht) to evaluate patients with nonpalpable breast lesions suspicious for carcinoma. Biopsies were performed in all centres using a 14-gauge core needle, long throw (2.2cm excursion) automated biopsy device with multiple passes (C.R. Bard Inc., Covington, GA) with the patient on a prone table (Fisher Imaging, Denver, CO, or Lorad Stereoguide, Danbury, CT). In case of calcifications, a specimen radiograph was obtained and the biopsy procedure was said to be representative if calcifcations were shown in the specimen. Histopathologic findings were correlated with the mammographic features at weekly multidisciplinary meetings, attended by the radiologist performing stereotactic breast biopsies, a breast pathologist and a surgeon. Our diagnostic protocol has been described in detail elsewhere.[18] From April 1997 to June 2002, all patients in whom DCIS was diagnosed at stereotactic 14G needle biopsy were included (n= 419).

Data-collection

Characteristics of participants were collected through questionnaires preceding the 14G needle biopsy. These included patient factors i.e. age at needle biopsy; and history of malignant breast disease. Radiological characteristics were noted by the radiologist who performed the biopsy (type of mammographic lesion (mass and/or calcifications); radiological classification (probably benign (BI-RADS 3), suspicious for malignancy (BI-RADS 4), radiologically malignant (BI-RADS 5)); the largest diameter of the mammographic lesion (in lateral view), and the total number of biopsy specimens were registered. Histopathological characteristics included type and grade of the DCIS at core biopsy. Grade of DCIS (I=well differentiated, II=moderately differentiated, III=poorly differentiated) was determined using the classification proposed by Holland and Peterse.[19] Data on type of DCIS at core biopsy was available in only 50% of patients, hence this factor was not used for further analysis. The type of the first operation was registered (breast-conserving surgery or mastectomy) as well as the type and number of further operations performed. Three groups were defined: 1) patients that underwent mastectomy as initial surgical therapy, 2) patients that first underwent breast conserving surgery, but eventually were treated with mastectomy, and 3) patients that were successfully treated with breast conserving surgery.

Statistical analysis

A description of predicting factors (means or frequencies) according to the above mentioned three subgroups of lesions are presented. The first group, those patients immediately planned for mastectomy are not included in further analysis. The aim was to predict which patients,

initially planned for breast conservative surgery, finally need mastectomy (after multiple surgical procedures). For patients immediately planned for mastectomy, breast conservative treatment was not the aim and therefore we decided not to include them in the analysis.
Univariate analysis was performed to assess determinants for mastectomy in the group of patients who initially underwent breast conserving therapy. The chi-square test and student's t-test were used where appropriate; Odds ratios (OR's) were calculated. Characteristics with a p-value < 0.2 were used in a multivariate logistic regression model. The predictive power of the model was evaluated by assessing the area under the curve (AUC) of the receiver-operating-characteristics curve (ROC curve). To correct for overfitting, the regression coefficients of the independent predictors were multiplied by a heuristic shrinkage factor based on the formula: (models chi square-df)/models chi square.[20;21] The results of multivariate analysis were then used to predict for each woman her risk for mastectomy (expected value). These were compared with observed values. A cut-off level was chosen to identify women at high risk for mastectomy. Statistical analysis was performed with use of the Statistical Package for the Social Sciences 9.0 (SPSS Inc. Chicago, IL).

Results

Of the 419 patients diagnosed with DCIS at core biopsy, 17 were not included in the analysis: Two patients because they did no undergo surgical excision. Three patients presented with two lesions in one breast, one being invasive cancer. In 12 patients, the definitive type of treatment (mastectomy or breast conserving) was missing. Thus, 402 patients were included in the present study.

Mastectomy was performed as the first surgical procedure in 102 cases (25%). Breast conserving surgery was attempted in 300 cases, but 93 eventually needed mastectomy (Table 1). When compared with patients who initially underwent breast conserving surgery, patients who underwent immediate mastectomy were younger, more frequently had a history of breast cancer, had lesions with a larger mammographic diameter that consisted more often of calcifications only and were more frequently classified as radiologically malignant (BI-RADS 5).
The mean total number of operations needed for definitive surgical therapy was 1.0 for patients who underwent immediate mastectomy, 1.3 for patients who were successfully treated with breast conserving surgery, and 2.2 for patients who first underwent breast conserving surgery, but eventually had a mastectomy.

Table 1: Patient and lesions characteristics of nonpalpable DCIS lesions (n=402) diagnosed between April 1997-June 2002, according to surgical treatment

	Initial breast conserving surgery							
Determinant	**(1) Initial Mastectomy n=102**		**(2) Eventually Mastectomy n=93**		**(3) Successful breast conserving surgery n=207**		**Odds Ratio (OR) ***	**p ***
	mean		*mean*		*mean*			
Age at biopsy	*56.1*		*58.3*		*58.7*			0.75
Largest mammographic diameter	*33.7*		*18.7*		*14.6*			<0.01
# core biopsy specimens	*7.1*		*7.2*		*6.9*			0.19
Total # operations	*1.0*		*2.2*		*1.3*			<0.01
	n=102	*(100%)*	n=93	*(100%)*	n=207	*(100%)*		
Age ≤50 years	33	*(32.4)*	12	*(12.9)*	24	*(11.6)*	1.13	0.75
Previous breast cancer	25	*(24.5)*	15	*(16.1)*	16	*(7.7)*	2.30	0.03
Mammographic diameter >2 cm	44	*(46.3)*	19	*(20.4)*	26	*(12.6)*	1.79	0.08
Calcifcations only vs. other	84	*(86.1)*	73	*(78.5)*	145	*(71.1)*	1.49	0.18
BI-RADS 5 vs. other**	19	*(20.0)*	16	*(18.0)*	18	*(9.0)*	2.23	0.03
Invasive component at excision	23	*(22.5)*	34	*(36.6)*	29	*(14.0)*	3.54	<0.01

* *Statistics obtained from comparison between groups (2) and (3).*

***Radiologic classification according tot the Breast Imaging Reporting And Data System[32]; BI-RADS 5 lesions are highly suspicious for malignancy (>90% cancer).*

Table 1 shows that all factors, except for age, showed univariate relations with mastectomy. Multivariate analysis of the selected univariates with a $p < 0.2$ resulted in the following independent predictors for mastectomy: previous breast cancer, mammographic lesion diameter larger than 2 cm, mammographic calcifications only, and radiologically highly malignant classification (BI-RADS 5) (Table 2). The AUC of this model was 0.71 (95% CI 0.64-0.77). The regression coefficients of the independent predictors after correction with a shrinkage factor are presented in Table 2.

Table 2: Independent predictors of mastectomy for patients initially treated with breast conserving surgery identified by multivariate analysis

		95% CI			
Variable	**Odds ratio**	**Lower**	**Upper**	**P**	**Beta***
Intercept (constant)					-1.16
History of breast cancer	3.69	1.59	8.59	0.002	0.74
Only calcifications	1.74	0.90	3.36	0.100	0.43
Mammographic diameter > 2 cm	5.05	2.86	8.91	< 0.001	0.43
BI-RADS 5	2.28	1.01	5.15	0.047	0.60

Predicted value
= 0.74 (if history of breast cancer) + 0.43 (if mammographic calcifications only)
+ 0.43 (if mammographic diameter > 2 cm) + 0.60 (if lesion classified as BI-RADS 5)

**new beta after multiplying by the shrinkage factor (chi square-df)/chi square = (15.491-4)/15.491 = 0.741786*

Based on the results of regression analysis and subsequent adjustment for overfitting, a predicted value for mastectomy was computed for each woman, and then women were grouped into categories of predicted risks. Table 3 presents for various risk categories the total number of patients and the expected and observed risk for mastectomy. Patients with zero or one of the four determinants would have a risk of mastectomy of 19% (36/190), whereas for patients with two or more determinants this risk would be 53% (53/100).

Table 3: Performance of the prediction score in a population of 288 women initially treated with breast conserving surgery

Risk score	determinants	Total (n)	Expected n	Expected* (%)	Observed n	Observed (%)
0	none	37	6.4	*17.3*	3	*8.1*
0.43	mc or diameter >2 cm	137	37.2	*27.2*	30	*21.9*
0.60	BI-RADS 5	9	2.9	*32.0*	1	*11.1*
0.74	history	7	2.5	*36.3*	2	*28.6*
0.86	mc+diameter >2 cm	57	22.8	*40.0*	29	*50.9*
1.03	(mc or diam>2cm)+BI-RADS 5	10	4.6	*45.7*	6	*60.0*
1.17	(mc or diam>2cm)+history	16	8.1	*50.5*	7	*43.8*
1.34	BI-RADS 5+history	3	1.7	*56.1*	2	*66.7*
1.46	mc+diam>2 cm+BI-RADS 5	9	5.4	*59.9*	5	*55.6*
1.60	mc+diam>2 cm+history	2	1.3	*64.5*	2	*100.0*
1.77	(mc or diam>2cm)+history+ BI-RADS 5	2	1.4	*69.4*	1	*50.0*
2.2	mc+diam>2 cm+history + BI-RADS 5	1	0.8	*80.2*	1	*100.0*
	Total	290	95.1		89.0	*30.7*

dashed line = cut-off

** based on the formula of the multivariate logistic regression model for predicted value:*

$$=1/(1+e^{-(-1.16+\ 0.74\ (\text{if previous breast cancer})\ +\ 0.43\ (\text{if calcifications only})\ +\ 0.43\ (\text{if diameter}\ >2\ \text{cm})\ +\ 0.60\ (\text{if BI-RADS 5}))})$$

Discussion

In our study population, 25% of 402 patients with preoperatively identified nonpalpable DCIS underwent direct mastectomy. However, in a second or third setting, another 24% (n=93) of the total group had a mastectomy, resulting in a mastectomy for 49% of all patients (n=195). These 93 women underwent on average 2.2 surgical operations (77 (84%) underwent two and 15 (16%) needed three operations). We attempted to identify these women before the start of their first operation, to guide the surgical procedure. There were four important determinants, i.e. a history of breast cancer, a mammographic lesion consisting of calcifications only, a mammographic diameter over 2 cm and a BI-RADS 5 classification. A woman with two or more of these four determinants would have 53% risk of eventually undergoing mastectomy, whereas for all other women this risk would be 19%. Using the predictive determinants for selection of patients to consider more aggressive surgery may

prevent repeated surgery in some. Whether this aggressive treatment is mastectomy or wide surgical excision remains to be discussed. This can potentially improve the chance of getting adequate resection margins.

Nonetheless, it is remarkable that for non-palpable, non-invasive cancer such aggressive surgical treatment is used. The early diagnosis apparently does not prevent aggressive treatment, as has been reported before.[4;22-25] In the Netherlands, it was reported that for DCIS detected during screening the mastectomy rate is 47.1%, and 50.3% for never-screened women.[26]

There are several reasons why breast conserving surgery for women with nonpalpable DCIS is often not successful. Mammographic calcifications often under-estimate the size of nonpalpable DCIS, especially in well-differentiated DCIS, in which substantial areas of tumour may not contain calcifications.[27;28] In addition, the extension of the nonpalpable breast cancer into the surrounding healthy breast tissue cannot be palpated during surgery. This makes it difficult to excise with clear margins of at least 1 cm.[29] In the 93 patients who underwent mastectomy in a second or third operation, involved or close margins were found in 91% of cases (n=85). In addition, mastectomy for DCIS results in a nearly 100% cure rate, whereas breast conserving surgery bears the risk of local recurrence. For DCIS it is known, that approximately half of local recurrences are invasive cancer, and any invasive cancer carries the risk of metastasis and death.[17;30;31] The aim of the treatment of DCIS should therefore be to prevent an invasive local recurrence.

Finally, the choice for breast-conserving surgery is also based on preferences of the surgeon and the patient. Immediately performing a mastectomy may not be preferable in most women; the option for conservation of the breast, even when it takes more than one operation, is often desirable.

In our study, mastectomy was chosen as the first operative procedure in 102 women. Characteristics of these women as well as their mammographic lesions are quite similar compared to women who initially underwent breast conserving surgery, but eventually were treated with mastectomy. The distribution of these characteristics is however more extreme. The predictive factors may help the surgeon assess the patient's risk of eventually undergoing mastectomy, and thus, guide the surgical procedure to excise more tissue (increasing the possibility of excising the lesion with clear margins).

In conclusion, we present four independent factors that may help in identifying which patients are at high risk of eventually undergoing mastectomy for nonpalpable, preoperatively

diagnosed DCIS, but the individual prediction was not optimal. To assess the value of our predictive model, it should be tested prospectively in a validation set.

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Chapter 9

The surgical treatment of nonpalpable breast cancer in a university hospital versus a regional teaching hospital: comparable?

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Abstract

Background: With the introduction of the stereotactic large-core needle biopsy (SLCNB) for suspicious mammographic lesions, nonpalpable breast cancer is diagnosed preoperatively more often. Even though this has resulted in a lower total number of operations needed for definitive surgery, more than one operation is often required. Experience of the operating surgeon (registered surgeon vs. surgical resident in training) could play an important role. We compared results of the treatment of nonpalpable breast cancer between two surgical training hospitals: the University Medical Centre Utrecht (UMCU) and the Rijnstate Hospital Arnhem (RHA).

Methods: All patients in the UMCU and the RHA with a malignancy at SLCNB diagnosed between February 1997 and June 2002 were included (n=240). The total number of operations needed for definitive surgery was registered, as well as the type of operation and whether the first operating surgeon was still in training or already registered as a surgeon.

Results: 126 patients were operated in the UMCU and 114 in the RHA. In 74% cases one operation was sufficient for definitive surgery (69% UMCU versus 79% RHA; p=0.08). Invasive breast cancer was treated more often with breast conserving surgery in the RHA than in the UMCU (74% vs. 55%; p=0.01). The opposite was true for ductal carcinoma in situ (69% vs. 90%; p=0.02). Of all operations, 87% in the UMCU was performed by a resident in training as the first operating surgeon versus 48% in the RHA (p<0.01). This did not affect the percentage of radical resections.

Conclusion: Obvious differences in results of surgical treatment were not found between the two training hospitals, despite the fact that in the UMCU, a resident in training was more often the first operating surgeon. With adequate supervision, the experience of the first operating surgeon does not seem to affect the possibility of a radical resection.

Introduction

Since the introduction of stereotactic large core needle biopsy (SLCNB) for the diagnosis of nonpalpable breast lesions, the diagnosis of breast cancer has more frequently been made preoparatively. As a result the total number of surgical interventions needed for adequate treatment of breast cancer has declined. Nevertheless, in a large number of cases more than one operation is required to obtain tumour negative resection margins. The fact that the resection margins are often not free of tumour after the first operation could be influenced by the experience of the performing surgeon. In teaching hospitals, a large proportion of all breast surgery is performed by surgical residents. We compared the results of operative treatment of nonpalpable breast malignancies between two teaching hospitals: the University Medical Centre Utrecht (UMCU) and the Rijnstate Hospital Arnhem (RHA). We assumed that in the UMCU breast cancer surgery is more often performed by surgical residents as the first operating surgeon than in the RHA, and that this may result in a higher number of surgical interventions needed for definite treatment of breast cancer. A secondary goal of this study was to identify other possible factors influencing the number of re-operations.

Patients and methods

Biopsy procedure

Since 1997, the UMCU has used SLCNB for evaluating nonpalpable breast lesions suspicious for carcinoma. Biopsy procedures were performed according to a standard protocol as described earlier.[1] Radiologists performing the biopsies underwent special training: firstly, they attended ten biopsy procedures and subsequently they performed another ten biopsy procedures under the supervision of a radiologist with considerable experience in SLCNB. Biopsies were taken with a 14-gauge core needle, long throw (2.2cm excursion) automated biopsy device with multiple passes (Bioptygun, C.R. Bard Inc., Covington, GA) with the patient on a prone table (Fisher Imaging, Denver, CO, of Lorad Stereoguide, Danbury, CT). Lesions were localised with digital mammography. It was advised to take a minimum of five biopsy specimens. In case of mammographic microcalcifications, at least eight specimens should be obtained, and specimen radiography was carried out to identify the calcifications in the biopsy specimens. All SLCNB procedures were performed in the UMCU. The SLCNB patients originally referred by the RHA would return there for further treatment and follow-up. All other patients would remain in the UMCU.

Histological evaluation of the SLCNB and surgical excision specimens were carried out as a routine by pathologists working in the 40 referring hospitals. To arrive at an adequate histological diagnosis, the pathologists had access to clinical information and the mammographic images obtained during SLCNB. Prospective collection of data regarding the type of mammographic lesion, the biopsy procedure, the histological diagnosis and the management following SLCNB was carried out in the UMCU. In both hospitals, histopathological findings were compared to mammographic findings during the weekly multidisciplinary meeting that was attended by at least a radiologists performing SLCNB procedures, a pathologist and a surgeon.

Study population

All patients diagnosed with nonpalpable DCIS or invasive cancer at SLCNB between February 1997 and June 2002 were included (n=240). All patients underwent the SLCNB in the UMCU and surgical treatment was performed in either the UMCU or the RHA. In all patients, the aim was a primary therapeutic excision. The total number of operations needed for definitive surgical treatment was registered, as well as the type of surgery performed. In addition, we registered if the first operating surgeon was a registered surgeon or a surgical resident. In addition, data on the size of the tumour and the distance to the closest resection margins were analysed. The surgical procedure was considered to be radical when no malignancy was found at less than 1 mm of the resection margins.
Differences between the two groups were assessed using the Chi-square test or student's t-test where appropriate. A p-value <0.05 was considered to be statistically significant.

Results

Of the 240 patients diagnosed with a malignancy at SLCNB, 114 were referred from and treated in the RHA (78 IC and 36 DCIS) and 126 came from the UMCU (85 IC and 41 DCIS). Patients in the RHA were older (61.3 years vs. 58.0 years; p=0.007) (Table 1).
Table 2 presents data on the performed surgical operations. In 74% of the total patient group, clean resection margins were obtained during the first operative procedure. (RHA 79% vs. UMCU 69%; p=0.08). In the RHA the total number of operations needed to complete surgical treatment was lower than in the UMCU (1.25 vs. 1.41; p=0.02). This number includes operations performed for axillary assessment (such as sentinel node biopsy or axillary lymph node dissection). Even when only the number of operations needed for radical surgical excision of the tumour was assessed (i.e. not including an axillary assessment

Table 1: Characteristics of patients and their nonpalpable lesions

	RHA (n=114)		UMCU (n=126)	
Age (mean)	61.3*		58.0*	
	n	***(%)***	**n**	***(%)***
History of breast cancer	11	*(10)*	18	*(14)*
Ipsilateral breast cancer	1	*(1)*	5	*(4)*
Mammographic lesion				
Density	63	*(55)*	58	*(46)*
Calcifications	35	*(31)*	41	*(33)*
Density with calcifications	16	*(14)*	24	*(19)*
Distorted architecture	-		3	*(2)*
SLCNB diagnosis				
DCIS	36	*(32)*	41	*(33)*
Invasive cancer	78	*(68)*	85	*(67)*

**p=0.007*

Table 2: SLCNB diagnosis and type of surgery performed

	RHA (n=114)	UMCU (n=126)	
	n *(%)*	n *(%)*	p
Type of 1st operation for DCIS lesions			
Mastectomy	11 *(31)*	4 *(10)*	
Breast-conserving surgery (BCS)	25 *(69)*	37 *(90)*	0.02
Eventually treated with BCS	12 *(33)*	19 *(46)*	0.25
Mean tumour diameter DCIS (mm)	22.6	9.3	0.01
# of operations needed to complete treatment	1.15	1.19	0.59
Type of 1st operation for IC lesions			
Mastectomy	20 *(26)*	38 *(44)*	
Breast-conserving surgery (BCS)	58 *(74)*	47 *(55)*	0.01
Eventually treated with BCS	49 *(63)*	38 *(45)*	0.02
Mean tumour diameter IC (mm)	13.9	18.5	0.03
# of operations needed to complete treatment	1.39	1.80	0.01
1st operating surgeon			
Surgeon	59 *(52)*	17 *(13)*	
Surgical resident	55 *(48)*	109 *(87)*	<0.01
1st operation radical	90 *(79)*	87 *(69)*	0.08
# of operations needed to complete treatment	1.25	1.41	0.02

or sentinel node biopsy), this difference remained (1.22 vs. 1.38; p=0.02). A total of 70 patients underwent two operations for complete surgical treatment. In seven of them, the tumour had already been excised with clear margins. Two of these seven (1 UMCU, 1 RHA) needed ablative surgery despite radical surgery. In the other five, axillary lymph node dissection was performed. In three cases (1 UMCU, 2 RHA), a sentinel node biopsy had been performed as part of the first operation. The other two patients (UMCU) appeared not only to have DCIS (as diagnosed at SLCNB) but also invasive cancer (first diagnosed at excision), which was however radically excised during the first operative procedure. Three operations were performed in 12 patients (10 UMCU, 2 RHA). One patient first underwent local excision, followed by ablative surgery, and was finally treated with axillary lymph node dissection.

Invasive carcinomas were more often treated with breast-conserving surgery in the RHA when compared to the UMCU (74% vs. 55% ; p=0.01). However, invasive tumours found in the UMCU had a larger diameter (RHA: 13.9 mm vs. UMCU: 18.5 mm; p=0.03). Patients with DCIS were treated with breast-conserving surgery more often in the UMCU (69% vs. 90%; p=0.02). These non-invasive carcinomas were smaller in the UMCU compared to the ones in the RHA (9.3 mm vs. 22.6 mm; p=0.01).

The surgical resident was the first operating surgeon in 87% of operations performed for the total group in the UMCU versus 48% in the RHA (p<0.01). When a surgical resident was the primary surgeon, the first operative procedure was radical for 77% of patients in the UMCU, versus 78% in the RHA (p=0.87). When we looked at only breast-conserving surgery performed by a surgical resident, there were no differences in the percentage of initially radical resections between the UMCU and the RHA. (64% vs. 69%; p=0.57).

Discussion

The percentage of primary radical resections did not differ clearly between the UMCU and RHA. However, there was a difference in the total number of surgical procedures needed per patient. This could be explained partly by the surplus of patients in need of a third operation in the UMCU versus the RHA: ten versus two, respectively. Due to the relatively small sample size of both groups, a third operation has a great impact. Another explanation for these differences could be that invasive tumours, resected by the UMCU in 1.80 and by the RHA in 1.39 operations, were of larger diameter in the UMCU group. Furthermore, until 2001 it was standard procedure in the RHA to perform ablative surgery for grade I /II DCIS and for grade III DCIS a lumpectomy in combination with radiotherapy.

By contrast, the primary treatment for DCIS in the UMCU is breast conserving surgery, and radiotherapy for DCIS III since 2001.

We presumed that the level of experience of the surgeon performing the primary resection would influence the final result of the surgical treatment. Although no similar studies are available on nonpalpable breast lesions, we assumed that resection of these lesions requires specific skills. Similarly, in one study Blair et al. demonstrated that in the surgical treatment of breast carcinoma, better results are obtained by an oncologic surgeon than by a general surgeon.[2] A similar result can be expected if treatment results of experienced surgeons are compared to those of surgical residents.

However, this hypothesis could not be confirmed by this study. Although a considerable difference was found in the total number of operations performed by surgical residents (87% UMCU versus 48% RHA), this did not seem to affect the percentage of radical resections. Apparently, the level of experience of the performing surgeon only plays a minor role in producing a tumour-free resection margin. Of course it should be taken in mind that, in general, all resections performed by a surgical resident were performed under supervision of an experienced surgeon.

Another difference we found between the two training hospitals was the proportion of breast-conserving operations. In the RHA, breast conserving surgery was performed more often for invasive carcinoma whereas in the UMCU this was the case for DCIS. Partly, this can be explained by the fact that invasive cancers were larger in the UMCU. Lesions with DCIS were larger in the RHA.

This study shows that the results of surgical treatment of preoperatively diagnosed nonpalpable breast cancer are comparable between the two hospitals. In addition, we found that operations for nonpalpable breast cancer, performed by surgical residents as the primary surgeon, had good results. This is important; surgical residents need proper training in breast procedures, since these are part of the core of general surgeons' work.[3] Obviously, supervision by a senior surgeon remains an essential part of the training of surgical residents in order to guarantee high quality of (oncologic) surgery.

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Chapter 10

General discussion

In the last decade breast cancer mortality seems to be decreasing as a result of improvements in both diagnosis and treatment.[1-6] Screening programs and an increased awareness of women towards breast cancer have led to an earlier diagnosis of malignant breast tumours. Treatment outcome has improved since the introduction of adjuvant hormonal and chemotherapy, combined with modern radiotherapeutic methods.

Screening programs were introduced to diagnose breast cancer in an earlier stage of development, in an attempt to decrease associated morbidity and mortality. However, recently screening for breast cancer has been the subject of discussion.[7;8] Aside from obvious advantages, some unexpected 'adverse' effects have become clear from the evaluation of these programs. One such effect is the occurrence of false positive mammograms. These result in at unjustified anxiety and, in some cases, over-treatment. Similarly, since the introduction of screening programs more non-invasive cases of breast cancer are being detected (e.g. DCIS). Without screening some of these may never have become clinically apparent during a woman's lifetime.[9;10] Now these women are faced with a diagnosis of cancer. Ultimately, a normal or benign mammography result, and even a benign breast biopsy do not decrease the future risk of breast cancer and may give rise to a false sense of security.

The effects of breast cancer screening programs have been especially under debate since the appearance of the Olsen and Gotzsche meta-analysis in 2000[11] (updated in 2001).[7;12] Of the eight randomised trials evaluating the effectiveness of screening mammography that have been initiated, the authors used only three in their meta-analysis; five studies were excluded because of methodological concerns. The authors argued that the method of randomisation of these five studies may have resulted in potential bias of the outcomes, e.g. bias in the determination of death-causes. From the meta-analysis of the other three studies they concluded that nationwide mammography screening has not been proven to increase survival in the screened group.

In reaction to the critical reports, the Dutch Health Council also reviewed the available evidence on screening trials.[8] In an advisory report to the Dutch Government the Council concluded that, in contrast to the Olsen and Gotzsche meta-analysis, there is no evidence that the mammographic screening for women aged 50 years is not effective. However, the Council did conclude that the effect on breast cancer mortality might be smaller than anticipated. Because the Dutch breast cancer screening program is very well attended (~80%) and has shown a decrease in breast cancer mortality, it is likely to continue.[3;13]

The success of a screening program depends strongly on diagnostic and therapeutic follow-up. Hence, inadequate diagnosis and treatment can minimise the benefit of early detection of breast cancer.[14] Since the introduction of nationwide screening programs, the number of nonpalpable lesions, referred for histological evaluation, has increased. Consequently, the effect of screening programs is more and more related to effective management of these lesions.

An optimal diagnostic work-up of referred nonpalpable lesions includes an accurate diagnosis of breast cancer cases as well as a minimal number of unnecessary surgical procedures. Minimally invasive breast biopsy techniques have been developed specifically for this aim. Various techniques exist to date, but evidence-based algorithms should be established to define which types of lesions could best be approached by which biopsy technique. The choice between different strategies depends on the radiologic characteristics of the lesion, the availability of equipment and the experience of the personnel.[15] Ultrasonography is available in every hospital and costs less than biopsy under stereotactic guidance. Reported patient comfort is high and real time visualisation of the biopsy needle allows careful monitoring throughout the procedure. For lesions that are visible with ultrasound, this form of image guidance should be considered first.[16] Most mammographic densities can be identified by ultrasound, whereas small solid masses or calcifications may be best visualised by conventional röntgen-imaging. However, no well-designed studies or studies with long-term follow-up have investigated the diagnostic accuracy of ultrasound guided needle biopsy for nonpalpable breast lesions. Until such data becomes available, röntgen-guided biopsy with its well-established high diagnostic accuracy appears to be the guidance procedure of choice for nonpalpable breast lesions.

The use of MR imaging may help distinguish suspicious lesions where conventional x-ray or ultrasound cannot, especially in young women with mammographically dense breasts.[17;18] In these patients MR guided biopsies could be helpful. It should be realised however, that MR guided biopsies are cumbersome and time-consuming. Vacuum-assisted breast biopsy may be of high value in the diagnosis of lesions consisting of calcifications only, or very small mammographic masses. Adequate follow-up of benign, non-excised lesions is necessary to assess sensitivity of the vacuum biopsy technique (chapter 7). However, in addition to studies on the sensitivity and specificity of the various image guided biopsy techniques, cost-effectiveness studies incorporating quality of life assessment are needed to define optimal strategies.

In diagnosing nonpalpable lesions, a frequently applied new minimally invasive diagnostic technique is the stereotactic large-core needle biopsy (SLCNB). In a controlled study setting (COBRA study) a good diagnostic accuracy of the SLCNB was achieved. The specialists participating in this study were highly dedicated and motivated, working according to a standardised protocol. Because an expert panel of dedicated breast radiologists and pathologists reviewed all results of both SLCNB and surgical excision specimens, missed malignancies were immediately recognised and appropriate action could be initiated.

Even though SLCNB was accurate under study conditions (COBRA study), this does not guarantee that similar results will be obtained in daily practice. As described in this thesis, to ensure a high diagnostic accuracy we carefully monitored the quality of the SLCNB during implementation in daily practice (chapter 2). Although most specialists agree that quality control of medical practice is important, few are actually participating in quality control programs.[19] Moreover, financial support for quality control programs is scarce. Even though we managed to find funding for the implementation project and all centres participating in the implementation of the SLCNB in daily practice were convinced of the need for quality control, we did experience difficulties in actually obtaining complete data on all SLCNB procedures. This compliance problem is mostly one of enough personnel – someone has to actually gather the necessary data and analyse it. Compliance to quality control measures may be facilitated by the increased use of digital patient files throughout a hospital. This way, patient data are more readily available and potentially easier to access. Hopefully this will increase compliance, and thus potentially increase quality control.

We have shown that the introduction of SLCNB in daily practice is safe (chapter 2). However, biopsy centres participating in the follow-up study were the same as during the COBRA study. The radiologists performing the SLCNB were highly experienced with the technique, and so were the pathologists evaluating the biopsy specimens. When SLCNB is introduced in non-COBRA institutions in the future, radiologists performing the biopsies will need to follow special training: e.g. firstly, to attend ten biopsy procedures and subsequently to perform another ten biopsy procedures under the supervision of a radiologist with considerable experience in SLCNB. Routine pathologists seem to be able to make an accurate and reproducible histological diagnosis on SLCNB specimens, comparable to expert pathologists, but clearly more experience results in better outcomes.[20] In all centres participating in the follow-up study, weekly multidisciplinary meetings discussing the results of SLCNB were attended (at minimum) by a radiologist, a pathologist and a surgeon.

Despite this high level of experience with the technique and the regular multidisciplinary meetings, we noticed an unexpected number of so called "non-representative" diagnoses. In these cases a second diagnostic procedure i.e. a surgical excision was performed, despite a benign diagnosis at SLCNB, because the histopathological findings appeared not to correlate with the radiological image. In addition, some histologically benign lesions that did correlate with the mammographic image were excised, for unknown reasons. This category of lesions clearly reflects a lack of trust in the results of the SLCNB. During the COBRA study, all patients underwent surgical excision, also those with a benign finding at SLCNB. Confidence in the outcomes of needle biopsy was not an issue, since all cases were surgically verified. The number of excisions for benign lesions or the frequency of non-representative SLCNB diagnoses can only be minimised if confidence in the outcomes of SLCNB increases. This is expected to result from increased multidisciplinary team experience. In view of the above considerations, we continue to recommend installation of stereotactic biopsy equipment in only a limited number of hospitals to ensure a sufficient number of patients being referred. The success of 14G SLCNB procedures and the validity of pathologic diagnoses made on the core biopsy material as well as knowledge of the limitations of SLCNB are key determinants for the surgeon in planning optimal management of nonpalpable breast lesions.

Therapeutic innovations are another challenging area of further exploration. New developments in treatment must be aimed at the use of less invasive or mutilating techniques, reducing morbidity while maintaining high levels of disease-free survival. Direct reconstructive surgery for patients who underwent mastectomy is a good example of improved quality in surgical care.[21] A preoperative diagnosis of cancer, as can be obtained by SLCNB, has been shown to reduce the total number of operations required to complete surgical treatment (1.31 for SLCNB vs. 1.91 for the diagnostic surgical excision).[22] In addition, prediction rules may facilitate the choice between mastectomy and breast conserving surgery (chapter 8). The number of mastectomies performed for screen-detected malignancies in the Netherlands is still as high as 54-59% for invasive cancers and 47% for DCIS.[13] Early detection of cancer should result in less aggressive surgery, not in an increasing number of operations attempting to obtain local control.

The most important determinant of local control is obtaining tumour free margins. The most important goal for the surgical oncologist is to achieve adequate resection margins in a minimal number of operations, with an acceptable cosmetic result. For nonpalpable breast cancer, which can by definition not be palpated during surgery, this is a difficult yet

challenging task. Experience of the surgeon may facilitate this effort,[23;24] but additional methods may be valuable, such as the use of ultrasound to per-operatively to assess the completeness of tumour excision,[25] or the use of a radio-active tracer to localise the lesion.[26;27] The technique of the radio-guided occult lesion localisation (ROLL) involves intratumoral injection of 99mTc-labeled nanocolloid guided by ultrasound or stereotaxis preoperatively, which will be taken up by the tumour and one or more of the draining lymph nodes. During the operation, a gamma-probe is used to localise the tumour as well as the lymph nodes. Other methods to replace the pre-operative guide wire to aid excision of nonpalpable lesions are being studied.[28]
Non-surgical methods of tumour eradication are being explored. Radiofrequency ablation of breast tumours up to 2 cm in diameter has been reported, and those in favour of this technique consider it an attractive alternative to surgical excision. However this should first be studied in more detail.[29]

In summary, the success of population screening programs for breast cancer is largely dependent on accurate diagnosis of nonpalpable breast lesions. In a controlled study setting SLCNB has proven to be an accurate diagnostic tool for these lesions. However, the good results of SLCNB can only be maintained when specialists performing and interpreting the SLCNB are dedicated and adequately trained in the technique. The practical limitations of hospitals dealing with nonpalpable breast lesions – it is financially impossible for all hospitals to install the high-tech SLCNB equipment – should be acknowledged. The diagnostic accuracy of image-guided breast biopsy techniques is already very high, and perhaps this could be increased at best by focusing on multidisciplinary discussions on the outcomes of the biopsies and constant monitoring of the quality, and not by further improving the technical performance of biopsy devices. Early detection alone is not enough.[14]

The following conclusions may be drawn from the studies described in this thesis:

1. Results of SLCNB in daily practice are comparable to those obtained in the COBRA study. Standardised protocols as well as registration of the results and feedback remain important to minimise the number of misdiagnoses (e.g. false negative diagnoses, non-representative diagnoses or high-risk or DCIS underestimates). Surgical excision can be safely omitted after a benign diagnosis at SLCNB, but the optimal follow-up schedule for these lesions remains to be clarified.

2. SLCNB is an accurate diagnostic test for evaluating nonpalpable mammographic abnormalities both in women referred from the national screening program and in women referred outside screening.
3. Nonpalpable breast lesions presenting as mammographic densities and classified as BI-RADS 5 may be approached by diagnostic surgical excision and sentinel node biopsy, while SLCNB is the preferred diagnostic approach in all other cases.
4. Viable tumourcells are displaced during SLCNB. Excision of the entire needle track however, is neither feasible, nor advisable as a routine measure, since radiotherapy is advised for all types of carcinoma after conservative surgery.
5. In our retrospective review, reasons for missing the invasive component after a SLCNB diagnosis of DCIS were mostly radiological (49%) or histopathological (36%), while histopathological disagreements accounted for 15% of DCIS underestimates. Poorly differentiated DCIS and periductal inflammation found on core biopsy increased the risk of finding an invasive component at excision approximately threefold. Multidisciplinary meetings attended by at least a (breast)radiologist, a (breast)pathologist and a (breast)surgeon, discussing all SLCNB cases may diminish the DCIS underestimate rate.
6. In comparison to 14G SLCNB, stereotactic 11G vacuum-assisted biopsy may decrease high-risk- and DCIS underestimate rates, but it is unclear whether it will decrease miss-rates of cancer. Therefore, it is presently impossible to assess whether the benefits outweigh the additional costs.
7. The combination of several patient- and lesion- characteristics may pre-operatively identify patients at high risk for multiple surgical procedures, eventually ending in mastectomy. This may guide the initial surgery to be more aggressive.
8. Differences exist between an academic and a non-academic training hospital in the treatment of nonpalpable breast cancer diagnosed preoperatively with SLCNB. However, these do not seem to be related to the training level of the operating surgeon (i.e. resident vs. staff surgeon), provided supervision of an experienced (breast) surgeon is present.

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Chapter 11

Summary & samenvatting

Chapter 1 starts out with an overview of the current methods in preoperative diagnostic assessment of nonpalpable breast lesions. In addition, some surgical challenges in the treatment of nonpalpable breast malignancies are described. The aim of this thesis was to address pitfalls and concerns of the diagnostic evaluation of nonpalpable breast lesions, in an attempt to further improve preoperative diagnostic assessment, as well as surgical strategies of nonpalpable breast lesions. In the first chapter, the outline of the thesis is presented, summarized in eight research questions to be addressed in each of the chapters 2-9.

The results of stereotactic large-core needle biopsy (SLCNB) in current practice (2000-2002) are described and compared to results of the controlled study setting during COBRA (*CO*re *B*iopsy after *RA*diological localisation; 1997-2000) in **chapter 2**. Data on all (n=955) patients who were scheduled to undergo a SLCNB in current practice was assembled. The high-risk underestimate rate was 24%, comparable to the COBRA study. The DCIS underestimate rate (28%) was higher than found in the COBRA study (17%). By follow-up of women with benign diagnoses at SLCNB who no longer needed to undergo surgical excision, we found that no malignancies were missed. The follow-up was, however, limited (mean, 20.0 months; 5.8-34.0). 96% of patients was treated according to COBRA guidelines.

In **chapter 3**, we studied differences in cancer prevalence between women referred through the national screening program and a non-screening group, to assess whether the validity of SLCNB differed between these groups. All women included (n=850) are participants of the COBRA study with a nonpalpable mammographic lesion. The prevalence of cancer in the screening group (n=511 lesions) was 64.0% versus 49.6% in the non-screening group (n=339). The sensitivity rates of SLCNB were 98.5% (screening) vs. 95.2% (non-screening). We conclude that despite a significant difference in the prevalence of carcinoma, the accuracy of SLCNB did not show a statistically significant difference between both patient groups. Therefore, SLCNB appears accurate in diagnosing nonpalpable breast lesions both in screening and non-screening patient groups.

Since radiologically malignant BI-RADS 5 lesions are almost always carcinoma, some centres advocate diagnostic surgical excision for these lesions instead of SLCNB. For some patients this diagnostic surgical intervention may serve as definitive treatment. In **chapter 4**, we set out to find a subgroup of mammographic BI-RADS 5 lesions for which SLCNB might be omitted. 96% of 238 BI-RADS 5 lesions were carcinoma (n=229).

Hoofdstuk 1 geeft een overzicht van de op dit moment beschikbare methoden van preoperatieve diagnostiek voor niet-palpabele afwijkingen in de mamma. Tevens worden chirurgische strategieën voor de behandeling van niet-palpabel mammacarcinoom beschreven. Het doel van het in dit proefschrift beschreven promotie onderzoek was het aankaarten van tekortkomingen / mogelijkheden van verbetering en aandachtspunten van de diagnostische evaluatie van niet-palpabele mammalesies, alsmede van chirurgische strategieën hiervan. In dit eerste hoofdstuk wordt de opbouw van dit proefschrift besproken, die kan worden samengevat in 8 onderzoeksvragen welke in elk van de 8 volgende hoofdstukken zullen worden beantwoord.

De resultaten van de stereotactische histologische naaldbiopsie (SHN) in de dagelijkse praktijk (2000-2002) worden beschreven en vergeleken met resultaten uit de gecontroleerde studie-setting tijdens de COBRA (*CO*re *B*iopsy after *RA*diological localisation) studie (1997-2000) in **hoofdstuk 2**. Gegevens van alle 955 patiënten die gepland werden voor SHN in de dagelijkse praktijk werden verzameld. De hoog-risico underestimate rate was 24%, vergelijkbaar met die van de COBRA studie. De DCIS underestimate rate (28%) was hoger dan die van de COBRA studie (17%). Dit kan deels verklaard worden doordat in de COBRA studie alleen resultaten van de eerste chirurgische excisie werden meegenomen in het uiteindelijke resultaat. Opvallend was dat in 9.8% van de SHN procedures een niet representatieve diagnose werd afgegeven, tegenover 3.5% tijdens de COBRA studie. Ook werd in een aantal gevallen na een verklarende histologische diagnose een excisie verricht, waarvoor de reden onduidelijk bleef. Hoewel we tijdens follow-up van vrouwen met een benigne diagnose op de SHN zonder excisie geen gemiste carcinomen hebben gevonden, en dus de sensitiviteit hoog lijkt, is follow-up te beperkt (gemiddeld 20.0 maanden; 5.8-34.0) om sensitiviteit definitief te berekenen. 96% van de patiënten werd behandeld volgens de COBRA richtlijnen.

In **hoofdstuk 3**, onderzoeken we verschillen in borstkanker prevalentie tussen vrouwen verwezen via het nationaal bevolkingsonderzoek en een groep die niet via de screening verwezen is (non-screening). Alle vrouwen geïncludeerd in deze studie zijn deelnemers uit de COBRA studie, met niet-palpabele verdachte afwijkingen (n=850). De prevalentie van mammacarcinoom is verschillend: 64% in de screening groep (n=511); 49.6% in de non-screening groep (n=339). De respectievelijke voorspellende waardes van een benigne

Most mammographic densities were invasive cancer, while calcifications only showed the highest risk for DCIS. When all lesions with only a density would be considered directly for SNB and tumor excision (n=154; 65%), 4 out of 238 patients (<2%) would be overtreated with SNB, while SLCNB could be omitted in 65% of cases. Thus, for this subgroup surgical excision with SNB may be considered as the first diagnostic and therapeutic procedure. LCNB is preferred in all other cases.

Seeding of biopsy needle tracks with viable malignant cells was an initial concern with SLCNB. In **chapter 5** we evaluate this phenomenon. Surgical biopsy specimens of 64 patients previously diagnosed with cancer on SLCNB are studied to find needle tracks and displaced tumourcells. Needle tracks are found in approximately one third of patients who underwent 14G-needle biopsy and surgery on the same day. Tumour-cell displacement along the needle track was seen in 50% of these cases. In a prospective study, an attempt was made to excise the entire needle track in 13 consecutive cancer cases after SLCNB. Needle tracks were visualised in 11/13 cases; displaced cells were seen in seven. We conclude that needle tracks can be found, and displaced tumourcells can be recognised. Excising and evaluating the entire needle track is not always possible, and based on our findings, should not be recommended as a routine, since radiotherapy is advised for all types of carcinoma after conservative surgery.

When ductal carcinoma in situ (DCIS) is diagnosed at SLCNB, invasive cancer is found in ~17% of excision specimens. These so called 'DCIS-underestimates' pose a problem for patients and surgeons, since they generally cause extension of treatment. In **chapter 6**, we evaluated DCIS-underestimates in detail to assess reasons for missing the invasive component at SLCNB. In 41 of 255 patients diagnosed with DCIS at SLCNB from 1997-2000, invasive cancer was found at excision (16%). Causes for DCIS-underestimates were categorized into "mainly radiological"(n=20), "mainly histopathological"(n=15), and "histological disagreements" (n=6). High-grade DCIS and periductal inflammation in core biopsies made a DCIS-underestimate 2.9 and 3.3 times more likely. We concluded that a variety of radiological and histopathological reasons contribute to the DCIS-underestimate rate. Approximately half of these are potentially avoidable.

Vacuum-assisted biopsy is an image-guided technique introduced in 1995, claimed to be superior to 14G automated-needle biopsy for the evaluation of nonpalpable breast lesions. However,

diagnose op SHN waren 97.0 vs. 94.8% (niet-significant). De sensitiviteit van SHN was 98.5% (screening; 95%CI 96.5-99.5) vs. 95.2% (non-screening; 95%CI 90.8-97.9). We concluderen dat, ondanks een significant verschil in borstkanker prevalentie, de diagnostische nauwkeurigheid van de SHN niet statistisch significant verschilt tussen vrouwen verwezen vanuit het nationaal bevolkingsonderzoek naar borstkanker en vrouwen verwezen buiten de screening. Om die reden lijkt de SHN voldoende betrouwbaar voor de diagnostiek van niet-palpabele mammalesies uit beide patiëntengroepen.

Hoewel SHN wordt aangeraden voor alle verdachte niet-palpabele afwijkingen, zien sommige afwijkingen er echter op het mammogram al zo verdacht uit voor carcinoom (BI-RADS 5) dat bij excisie inderdaad bij $>90\%$ een maligniteit gevonden wordt. Excisie is toch altijd nodig, ook als SHN benigne is, om een vals negatief resultaat uit te sluiten. Sommige ziekenhuizen adviseren daarom voor dit soort afwijkingen niet eerst een SHN te doen, maar direct een chirurgische excisie. Voor sommige patiënten kan dit ook als definitieve chirurigsche therapie dienen. In **hoofdstuk 4**, onderzochten we of er BI-RADS 5 lesies zijn waarvoor SHN achterwege gelaten kan worden. In 96% van de 238 BI-RADS 5 lesies werd mammacarcinoom gevonden ($n=229$). De meeste mammografische densiteiten waren invasief carcinoom, terwijl mammografische calcificaties meestal DCIS bleken te zijn. Als alle BI-RADS 5 lesies bestaande uit alleen een mammografische densiteit direct worden gepland voor chirurigsche excisie van de afwijking met een sentinel node biopsie (SNB) dan hebben 4 van de 238 patiënten ($<2\%$) (achteraf) onnodig een SNB ondergaan. Chirurgische exicsie met SNB is dan zowel de eerste diagnostische als therapeutische ingreep. SHN is het diagnosticum van eerste keus voor alle andere afwijkingen.

Het verslepen van tumorcellen en het uitgroeien hiervan in de steekkanalen is een gevreesde complicatie van de SHN. In **hoofdstuk 5** evalueren we dit fenomeen. De chirurgische excisie preparaten van 64 patiënten met een door SHN gediagnosticeerd carcinoom zijn onderzocht op aanwezigheid van steekkanalen en het voorkomen van versleepte tumorcellen. Steekkanalen worden gevonden in ongeveer een derde van patiënten die op één dag zowel een SHN als een excisie ondergingen. Tumorcel versleping wordt gezien in de helft van deze cases. Vervolgens is getracht het gehele steekkanaal te excideren in 13 opeenvolgende patiënten met mammacarcinoom gediagnostiseerd met SHN. Het lukte steekkanalen te excideren in 11 cases en in 7 zijn versleepte tumorcellen gevonden. Onze conclusie is dat steekkanalen kunnen worden teruggevonden in het excisie preparaat, en ook versleepte

prospective randomized studies evaluating its accuracy are unavailable. In **chapter 7**, we present a critical review of the currently available literature on the accuracy of vacuum-assisted biopsy and compare it to published data on 14G automated-needle biopsy. Twenty-two published studies were included. High-risk and DCIS underestimate rates for 11G vacuum biopsy are 16% (95% CI 12-20) and 11% (95% CI 9-12), respectively, and both lower (40% (95% CI 26-56) and 15% (95% CI 8-26)) than rates reported for 14G automated-needle biopsy. Due to incomplete follow-up of benign lesions it is impossible to compute miss-rates and thus the sensitivity rate.

DCIS comprises a growing percentage of mammographically detected breast cancer. **Chapter 8** describes the surgical treatment results for patients diagnosed with DCIS at SLCNB. We sought preoperative determinants predicting which patients would eventually undergo mastectomy. 402 consecutive patients diagnosed with DCIS at stereotactic 14G-needle biopsy between April 1997 and June 2002 were included. 102 of these 402 women underwent immediate mastectomy (25%). 300 women underwent initial breast conserving surgery, and were included in the analysis. In subsequent surgical sessions 93 of these women had mastectomy. Factors associated with mastectomy were a history of breast cancer, mammographic lesions characterised by calcifications, measuring >2 cm and classified as BI-RADS 5. The combination of two of the above mentioned characteristics may identify pre-operatively patients at higher risk (53%) for multiple surgical procedures, eventually ending in mastectomy, compared to women with zero or just one of the characteristics present. This may guide the initial surgical procedure to be more aggressive.

Breast conserving therapy is the procedure of choice for patients with nonpalpable breast cancer. However, it is difficult to perform when the extension of the tumour into the surrounding healthy breast tissue cannot be palpated during the operation. This has led, in some clinics, to a situation where surgical residents in training are only sparsely allowed to perform this procedure as the operating surgeon. In **Chapter 9** we compared the outcomes of surgical treatment of preoperatively diagnosed nonpalpable breast cancer in two surgical training hospitals; the University Medical Centre Utrecht (UMCU) and the Rijnstate Hospital Arnhem (RHA; a large regional clinic). All patients with a SLCNB diagnosis of cancer between February 1997 and June 2002 were included ($n=240$; 126 UMCU and 114 RHA). In 74% cases one operation was sufficient for definitive surgery (69% UMCU versus 79% RHA; $p=0.08$). Invasive breast cancer was treated more often with breast

tumorcellen kunnen worden herkend. Het excideren en beoordelen van het gehele steekkanaal is niet altijd mogelijk en gebaseerd op onze bevindingen ook niet aan te raden als routine, aangezien radiotherapie is aanbevolen na sparende excisie van alle carcinomen.

Na de diagnose ductaal carcinoma in situ (DCIS) op de SHN wordt in ~17% van de excisie preparaten toch nog een invasief carcinoom gevonden. Deze zogenoemde 'DCIS-underestimates' zijn een probleem voor zowel de patiënte als haar chirurg, want naast een onderschatting van de ernst van de ziekte, hebben ze vaak een verlenging van behandeling tot gevolg. In **hoofdstuk 6**, bestuderen we DCIS-underestimates in detail om redenen te vinden voor het missen van de invasieve component gemist was bij SHN. Ook vergelijken we DCIS underestimates en een groep 'true DCIS' (DICS op SHN en bij excisie). Bij 41 van 255 DCIS patiënten na SHN (1997-2000), wordt bij excisie invasief carcinoom (16%). Oorzaken van deze DCIS-underestimates zijn "voornamelijk radiologische" (n=20), "voornamelijk histopathologische"(n=15), en "histopathologische discrepanties" (n=6). DCIS graad III en de aanwezigheid van periductale ontsteking in core biopten maken een DCIS underestimate beide drie keer meer waarschijnlijk dan een 'true DCIS'.

De vacuüm biopsie is een minimaal invasieve beeldgestuurde biopsietechniek voor niet-palpabele borstafwijkingen die in 1995 geïntroduceerd is en grotere weefselbiopten neemt. Prospectief gerandomiseerde studies die de diagnostische betrouwbaarheid vergelijken met de gouden standaard, bestaan echter niet. In **hoofdstuk 7**, presenteren we een samenvatting van alle beschikbare literatuur over de betrouwbaarheid van de vacuüm biopsie en vergelijken het met beschikbare gegevens over de 14G SHN. 22 gepubliceerde studies zijn geïncludeerd. Voor de gezamelijke studies worden een gepoolde hoog-risico- en DCIS 'underestimate rate' voor de vacuüm biopsie berekend van 16% (95%CI 12-20) en 11% (95%CI 9-12). Deze zijn lager voor 14G SHN (40% (95% CI 26-56) en 15% (95% CI 8-26) respectievelijk). Door incomplete follow-up van benigne lesies is het onmogelijk de miss-rate te bepalen en daarmee ook de sensitiviteit.

Van alle door screening ontdekte carcinomen neemt DCIS een steeds groter worden de plaats in. **Hoofdstuk 8** beschrijft de chirurgische behandeling van patiënten bij wie de diagnose preoperatief gesteld is door middel van de SHN. We hebben gezocht naar preoperatieve factoren, die voorspellen welke patiënten uiteindelijk een mastectomie krijgen. 402 opeenvolgende patiënten gediagnosticeerd met DCIS op de SHN tussen april 1997

conserving surgery in the RZA than in the UMCU (74% vs. 55%; p=0.01). The opposite was true for ductal carcinoma in situ (69% vs. 90%; p=0.02). Of all analysed operations, 87% in the UMCU was performed by a resident in training as the first operating surgeon versus 48% in the RZA (p<0.01). This did not affect the percentage of radical resections. With adequate supervision, the experience of the first operating surgeon does not seem to affect the possibility of a radical resection.

Chapter 10 is a general discussion on challenges of the diagnostic assessment of nonpalpable breast lesions, as well as challenges of the surgical treatment options. In addition, the research questions posed in chapter 1 are answered.

en juni 2002 worden geïncludeerd. 102 van deze 402 vrouwen krijgen direct een mastectomie (25%). 300 vrouwen krijgen eerst een borstsparende behandeling, maar in volgende operatieve ingrepen krijgen 93 vrouwen toch een mastectomie. Factoren geassocieerd met het krijgen van een mastectomie zijn: 1) een voorgeschiedenis van mammacarcinoom, 2) een lesie die mammografisch bestaat uit alleen calcificaties, 3) met een diameter groter dan 2 cm en 4) een radiologisch maligne beoordeling (BI-RADS 5). Wanneer vrouwen 2 of meer van deze kenmerken hebben, dan is hun kans 53% om een mastectomie te krijgen, en anders 19%. Deze voorkennis zou ertoe kunnen leiden dat de initiële chirurgische therapie aggressiever in opzet is, om het aantal re-operaties te beperken.

In **hoofdstuk 9** vergeleken we de resultaten van behandeling van niet-palpabele maligniteiten tussen twee opleidingsklinieken; het Universitair Medisch Centrum Utrecht (UMCU) en het Rijnstate Ziekenhuis Arnhem (RZA). Alle patiënten met een maligne uitslag op de SHN tussen februari 1997 en juni 2002 zijn geïncludeerd (n=240). 126 patiënten worden in het UMCU geopereerd en 114 in het RZA. Bij 74% van de patiënten is één operatie voldoende (69% UMCU versus 79% RZA; p=0.08). In het RZA wordt invasief carcinoom vaker sparend geopereerd (74% vs. 55%; p=0.01). Het tegenovergestelde geldt voor ductaal carcinoma in situ (69% vs. 90%; p=0.02). In het UMCU wordt 87% verricht door een chirurg in opleiding als eerste operateur versus 48% in het RZA (p<0.01). Dit had geen invloed op het percentage radicale resecties. Bij adequate supervisie lijkt de ervaring van de eerste operateur dan ook geen doorslaggevende rol te spelen.

Hoofdstuk 10 is een algemene discussie over uitdagingen op het gebied van de diagnostiek van niet-palpabele mammalesies, alsmede uitdagingen op het gebied van de chirurgische behandel mogelijkheden. Tevens wordt in dit hoofdstuk antwoord gegeven op de in hoofdstuk 1 gestelde onderzoeksvragen.

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Lidewij Hoorntje was born on August 6, 1974, in Groningen, the Netherlands. She graduated from the Gymnasium Celeanum Zwolle in 1992, after which she started her medical education at the University in Groningen. Her clinical rotations were postponed for one year to do research as an exchange student at the Dana Farber Cancer Institute and the Children's Hospital in Boston, USA (Supervisor: Dr Susan K Parsons, MD, MRP). After obtaining her doctorate degree in medicine (cum laude) in 1997 she graduated from medical school (cum laude) in 1999. She then started as a surgical resident at the University Medical Center Utrecht (Prof. Dr ThJMV van Vroonhoven). From 2000-2003 the research described in this thesis was conducted. This was made financially possible by an AGIKO stipend (Assistent Geneeskundige In Opleiding tot Klinisch Onderzoeker) from the Dutch Healthcare Research - Department of Medical Sciences (ZON-MW). Registration as an epidemiologist-B is expected in 2004. In July 2003 she continued with the residency program in general surgery, region Utrecht (Head: Prof. Dr IHM Borel Rinkes), at the St. Antonius Hospital in Nieuwegein (Dr PMNYH Go).

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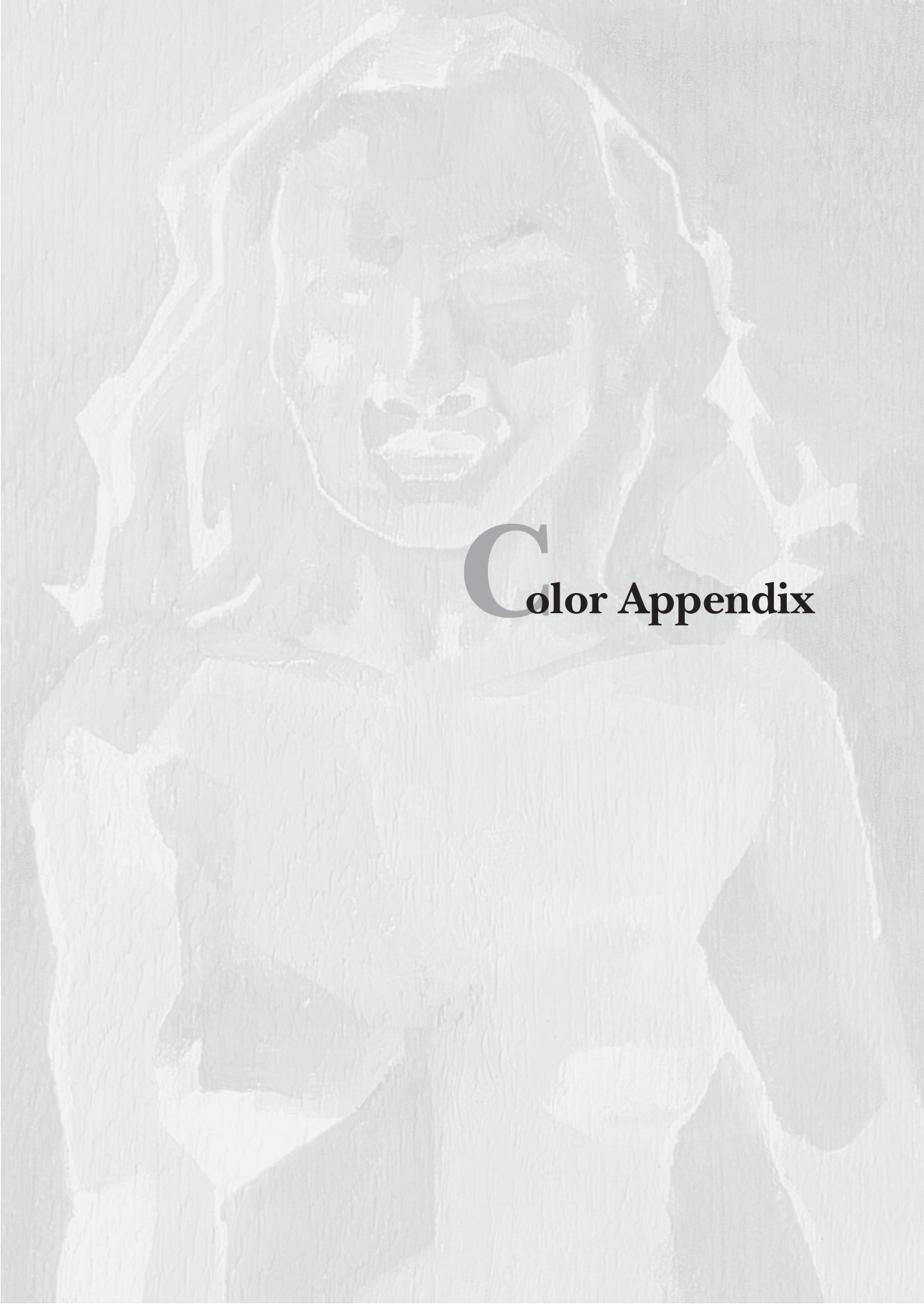
LE Hoorntje, MEI Schipper, IHM Borel Rinkes. Epithelial displacement after 14G breast biopsy. *(submitted)*

LE Hoorntje, IHM Borel Rinkes, EJA Steller, WPThM Mali, PHM Peeters. Predictive factors for mastectomy in nonpalpable ductal carcinoma in situ. *(submitted)*



Color Appendix

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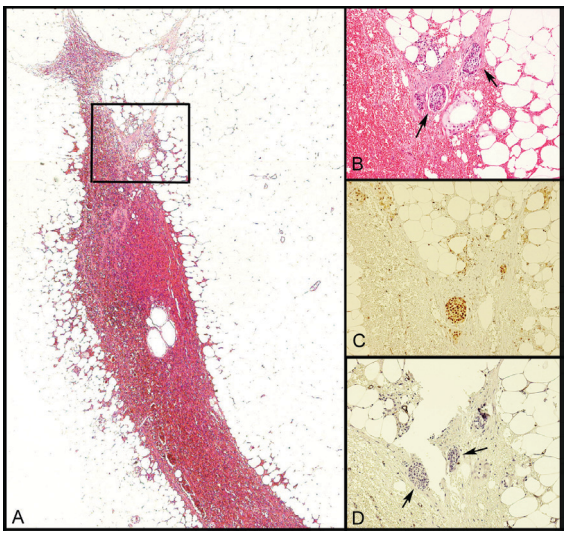

Figure 1A: Needle track surrounded by mammary and fatty tissue. (H&E, 10x)
Figure 1B: Detail with nests of vital tumour cells (arrows) growing along the needle track 18 days after stereotactic 14G core needle biopsy. Histological diagnosis of the tumour was a well differentiated invasive ductal carcinoma with lobular carcinoma in situ. (H&E, 100x)
Figure 1C: CAM-5.2 immunohistochemistry of the same area as shown in Figure 1B.
Figure 1D: Alpha smooth muscle actin (a-sma) staining of the same section as Figure 1B demonstrating the absence of a basement membrane around the dislodged tumour cells (arrows).

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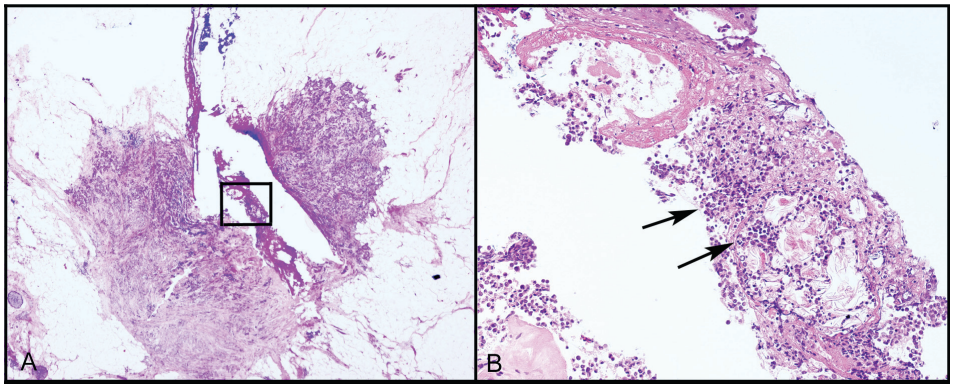
Figure 2A: Displaced epithelial cells inside tumour (H&E, 2x); **Figure 2B:** Detail (H&E, 100x); arrows: displaced tumour cells.



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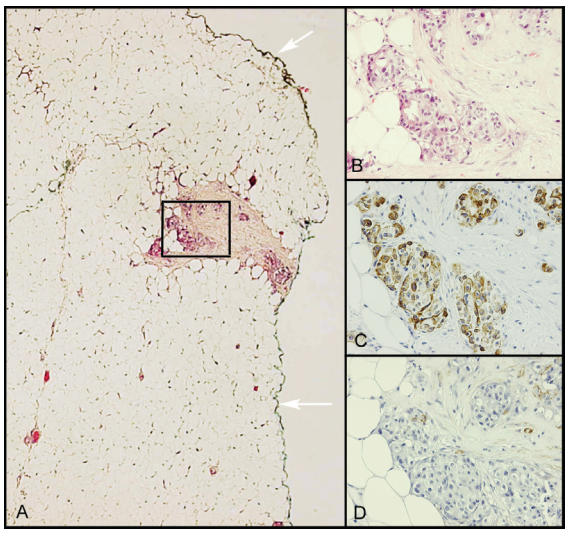

Figure 3A: Displaced groups of epithelial cells outside tumour (H&E, 2x); white arrows: inked margin of resection specimen;

Figure 3B: Detail (H&E, 100x);

Figure 3C: CAM5.2 staining of the same section as Figure 3B;

Figure 3D: Alpha-sma of the same section as Figure 3B.

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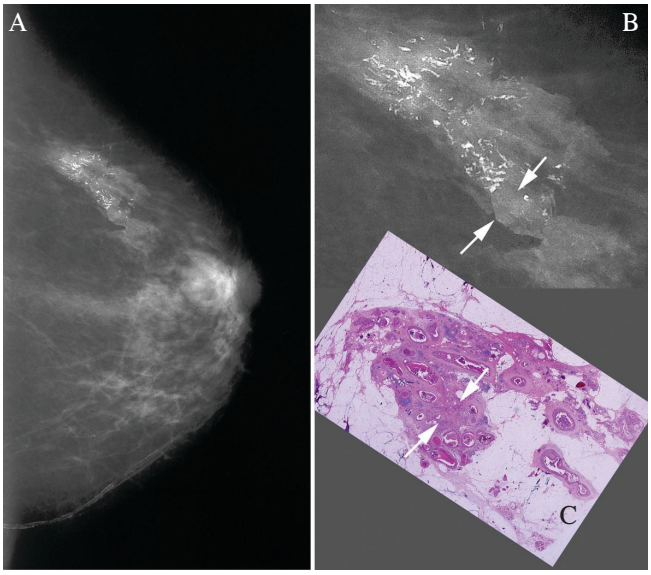

Figure

A. Representative mammogram with suspicious calcifications.
B. Detail of area with calcifications and density. Arrows indicate the density.
C. Detail of histologic slide corresponding to B. Arrows indicate the invasive component.