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Core Biopsy of Breast and Axillary Lesions:
Technical and Clinical Aspects

by

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Uppsala 2006

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Printed at Eklundshofs Grafiska, Uppsala, 2006.

Dissertation for the Degree of Doctor of Philosophy, Faculty of Medicine, Uppsala University, to be examined in Grönwallsalen at Akademiska sjukhuset, Uppsala, on March 31st 2006, at 13:15.

Abstract

Abdsaleh, S 2006. Core Biopsy of Breast and Axillary Lesions: Technical and Clinical Aspects. 42 pp. Uppsala ISBN 91-506-1858-X

The aims of this work were to image and analyze the needle behavior at automated core biopsy, to investigate the clinical utility of an alternative core biopsy technique using a semiautomated gun in breast and axillary lesions, and also to compare core biopsy with surgical specimens in malignant breast lesions regarding histologic features and hormone receptor expression.

In two experimental studies, using butter and silicon phantoms, respectively, the needle pass was imaged and its dynamic behavior studied. It was shown that the needle took a curved course in phantoms. It deviated to the same side as where the tip lay, and the degree of the curvature increased with increasing hardness of the phantoms. Our experimental methods can be applied for imaging of needle behavior and thereby improvement of needle configuration.

In two clinical studies, a semiautomated gun was used for large needle core biopsy of breast and axillary lesions in two series of 145 and 21 patients, respectively. The sensitivity of the method for diagnosis of malignancy was 87% (108/124), and in 37% (31/83) of cases the full length of the needle notch was filled with specimen. No injury to the neurovascular structures of the axillary area was observed. It was concluded that the semiautomated gun can be used as an alternative to the automated gun when the size and location of the lesion render use of the automatic device uncertain or dangerous, e.g., in small breast lesions or lesions located in the axilla.

In a series of 129 cases of breast cancer, comparison of core biopsy and surgical specimens showed that core biopsy provided enough information on the histologic type and grade of the lesions. Also, there was moderate to high concordance between the two methods for assessment of progesterone receptors and estrogen receptors (Spearman`s kappa 0.67 and 0.89, respectively).

Key words: Automatic core needle biopsy, Semiautomatic core needle biopsy, surgical specimen, Dynamic needle behavior, Hormone receptors.

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DEDICATION

To my wife, Zohre, for her endless love, and my children Sofie and Sam

LIST OF PAPERS

The thesis is based on the following papers, referred to in the text by their Roman numerals I - V:

I. Abdsaleh S, Azavedo E, Lindgren PG.
Behaviour of the 2.1-mm (14 G) Automated Biopsy Needle in Phantoms.
Acta Radiol. 2002 Mar;43(2):225-9

II. Abdsaleh S, Azavedo E, Lindgren PG.
Semiautomatic Core Biopsy. A Modified Biopsy Technique in Breast Diseases.
Acta Radiol. 2003 Jan;44(1):47-51

III. Abdsaleh S, Azavedo E, Lindgren PG.
Ultrasound-guided Large Needle Core Biopsy of The Axilla.
Acta Radiol. 2004 Apr;45(2):193-6

IV. Abdsaleh S, Carlsson T, Fateh-Alavi K, Azavedo E, Lindgren PG.
Dynamic Behavior of Core Biopsy Needle: High-speed Video Imaging of the Needle Course in Silicon Phantoms.
In manuscript

V. Abdsaleh S, Wärnberg F, Azavedo E, Lindgren PG, Amini RM.
Comparison of Core Needle Biopsy and Surgical Specimens in Malignant Breast Lesions Regarding Histologic Features and Hormone Receptor Expression.
In manuscript

CONTENTS

ABBREVIATIONS

US	Ultrasound
MRI	Magnetic resonance imaging
FNAB	Fine needle aspiration biopsy
ABBI	Advanced breast biopsy instrumentation
DCIS	Ductal carcinoma in situ
ER	Estrogen
PR	Progesterone

INTRODUCTION

Breast cancer is the leading form of cancer in women worldwide. In Sweden, more than 6,000 new cases are detected every year and 1 out of 9 women is expected to get breast cancer during the lifetime (1,2). Since survival from breast cancer depends on removal of the cancer before it spreads, early diagnosis and initiation of treatment are likely to be the key elements for success. The current approach to early breast cancer detection is a combination of public education and mammography. In Sweden, regular screening mammography has been shown to significantly decrease the mortality from breast cancer by detecting malignant lesions at an early stage when treatment has the greatest chance of success (3,4,5).

However, despite its value as a cancer detection tool, mammography is still an imprecise diagnostic technique, and lesions detected at mammography have to be evaluated by additional tests to establish a definitive diagnosis.

Imaging Modalities

The most promising imaging modalities that are currently employed as adjuncts to mammography are **ultrasound (US)** and **magnetic resonance imaging (MRI)**.

Ultrasound

Real-time, B-mode, gray-scale equipment using a high resolution probe (at least 7.5 mHz) is the standard US modality in breast imaging. Color Doppler may be used as an adjunct to real-time imaging for visualization of abnormal tumor vessels. Breast US is commonly performed as a target examination, directed only to the area of a palpable lump or of a mammographically detected mass.

According to Skaane (6), indications for breast US are:

- differentiation between a cyst and solid mass
- guidance for interventional procedures
- evaluation of a palpable mass
- further evaluation of a mammographically visible mass
- inflammation
- use as the initial imaging modality in assessment of a palpable lump in pregnant women and women under the age of 35 years
- evaluation of mammographic asymmetry
- differentiation of benign from malignant solid masses
- examination after augmentation mammoplasty and breast conservation surgery.

US has also been tested as a screening tool in patients with dense breasts and normal mammographic findings (7,8,9). However, the value of US for this purpose remains controversial because of its inconsistent depiction of microcalcifications.

Magnetic Resonance Imaging (MRI)

MRI is useful as a complement to mammography and ultrasound because of the advantage of its high sensitivity in detecting occult breast lesions. Its specificity, however, has been a matter of concern (10). Contrast enhanced MRI is commonly used. The breast is imaged with a T1-weighted pulse sequence before and after intravenous administration of a contrast agent containing gadolinium. Owing to the paramagnetic properties of gadolinium, enhanced tissues are visualized as areas of increased signal intensity. In spite of a lack of widely accepted image acquisition protocols and standardized diagnostic guidelines, interpretation of the area of concern is based on the speed, pattern, and intensity of enhancement. Cancers more often show early strong enhancement with rapid washout (11,12,107,108).

Nevertheless, neither US nor MRI is sufficient in terms of specificity, and the need for more accurate discrimination between benign and malignant breast lesions has made needle biopsy the mainstay of the work-up procedure before surgery.

Several percutaneous imaging-guided biopsy techniques have been developed for presurgical assessment of breast lesions. The current procedures include fine needle aspiration biopsy (FNAB), core needle biopsy, directional vacuum assisted biopsy and Advanced Breast Biopsy Instrumentation (ABBI), each most often performed with mammographic or ultrasound guidance. There is also an increasing number of reports on MRI guided percutaneous biopsies (13,14,15,16,17).

Fine Needle Aspiration Biopsy (FNAB)

Needle puncture of the breast lesions has been practiced for more than a century. In 1899, Bull (18) presented his experience regarding the utility of this method for diagnosis and treatment of cystic disease of the breast. Referring to different types of mammary cysts, e.g., retention cysts and general cystic disease of the breast known as maladie de Reclus, he was convinced that puncture would become commonly used for diagnosis of cysts of the breast.

FNAB provides specimens for cytologic evaluation and has been practiced as the first-line biopsy procedure for diagnosis of solid palpable breast lesions for several decades (18,19,20,21,22). Screening mammography has resulted in detection of occult, non-palpable breast lesions, and several methods have been developed for FNAB of mammographically detected non-palpable lesions. Muhlow (23) and Löfgren et al (24) designed various types of fenestrated compression paddles. Svane (25) presented a stereotactic technique for preoperative marking of non-palpable breast lesions and Azavedo et al (26,27) studied the diagnostic yield of stereotactic fine needle biopsy in non-palpable lesions of breast. Ultrasound-guided FNAB is also a well-established method (28,29,30)

FNAB is inexpensive, quick to perform and well tolerated by the patients. There are, however, several obvious limitations to the use of cytologic examinations of breast lesions. There are substantial rates of insufficient specimens and false negative results, and it may be difficult to obtain definitive benign diagnoses. This is basically due to the very small size of the specimens (31). In addition, histologic examination is necessary in many instances for differentiating invasive from in situ ductal carcinoma.

Vacuum-assisted Biopsy (Mammotome)

The Mammotome was introduced in the mid 1990s (32). This device uses vacuum to pull tissue into the probe, and permits directional, contiguous tissue acquisition. Several specimens can be retrieved in clockwise rotation, and the captured tissues can be removed without withdrawing the probe each time. Initially 14- or 11-gauge probes were used (33, 34, 35), but in recent years probes as large as 9-gauge have been tried in conjunction with MRI-guided biopsies (36, 37). Directional vacuum-assisted biopsy diminishes but does not eliminate the problem of histologic understimates (38). The instrument is particularly helpful for biopsy of calcified lesions. Rates of calcification retrieval of 99-100% have been reported for 14- or 11-gauge directional vaccum-assissted breast biopsy, which are significantly higher than the 86-94% rates observed with 14-gauge automated large-core biopsy (39,40,41,42).

Advanced Breast Biopsy Instrumentation (ABBI)

The ABBI system is a tissue acquisition device by which a large volume of specimen extending from the subcutaneous tissue to beyond the lesion can be obtained. Hence, the entire lesion can potentially be removed in a single specimen (38). It is available with a variety of cannula sizes ranging up to 2 cm. Initially, there was much enthusiasm regarding this device, but it has many disadvantages. In women with benign diseases, the large volume of the sampled tissue (reportedly up to 13 cm^3) is likely to cause considerable scarring and deformity with little benefit (43). The 1.1% complication rate of ABBI biopsy is significantly higher than the 0.1% complication rate for automated core and vacuum-assisted biopsy (44,45). In cases of cancer diagnosed at ABBI biopsy, tumor has been present at the margins in 64-100%. Moreover, the ABBI is substantially more expensive than other existing percutaneous biopsy technologies. It has not yet been established that the ABBI system has benefits that outweigh its disadvantages (38).

Core Biopsy

PG Lindgren invented core biopsy technique with an automatic gun and presented it in the early 1980s (46). Working with the engineers at Radi Medical Systems, a medical product company in Uppsala, Sweden, Lindgren improved both needles and guns and subsequently developed gun-specific needles and a powerful double spring automatic gun known as the Biopty (47). Parker, who recognized the advantages of core histology, used the Biopty gun in the diagnosis of breast tumors (48). Since then, the importance of the device for diagnosis of breast carcinoma has been evaluated in a large number of studies (49,50,51,52,53).

There are basically two types of core biopsy guns available on the market: **automatic** and **semiautomatic**.

The **automatic** guns consist of a spring-trigger system for firing of a specially designed needle consisting of two separately moving parts: an inner needle and an outer cannula (46). The inner needle has a solid tip followed by a beveled notch that functions as a sampling chamber. When the gun is fired, the inner needle strikes first, and as it is advanced as far as permitted, it automatically triggers a system for immediate advancement of the outer cannula to cut the sampled tissue in the notch, Fig 1. The entire needle assembly is then withdrawn, and the sampled tissue is removed from the needle for examination by the pathologist.

Guns produced by several companies are commercially available, and in a study by Mladinich et al no significant difference in specimen quality was found on comparison of the various guns (54). The length of strike of the needle can be adjusted on some guns (BARD™), as 15 or 22 mm. It has been shown that the short-throw guns (length of strike less than 2 cm) perform worse, acquiring lesser amount of tissue with poorer quality than the long-throw guns (55,56).

There are commercially available needles varying in length (10 and 16 cm), caliber (14-, 16- and 18-gauge) and length of notch (15 to 19 mm). There is currently no general agreement as to the most appropriate needle, and the choice today depends on the experience of the radiologist and on the expertise of the pathologist at each hospital. Smaller needles have been thought to be safer, but the morbidity does not seem to be adversely affected by an increase in needle calibre (57). Furthermore, studies have shown that the quality and quantity of specimens improve with larger-gauge needles (58,59) because of their ability to provide larger specimens for more definitive histologic diagnosis (60). Parker (61) has had preferred the 14-gauge needle as the standard.

In our institute, we use an automated long-throw (22 mm) biopsy gun fitted with a 14-G needle that has a 17 mm long notch.

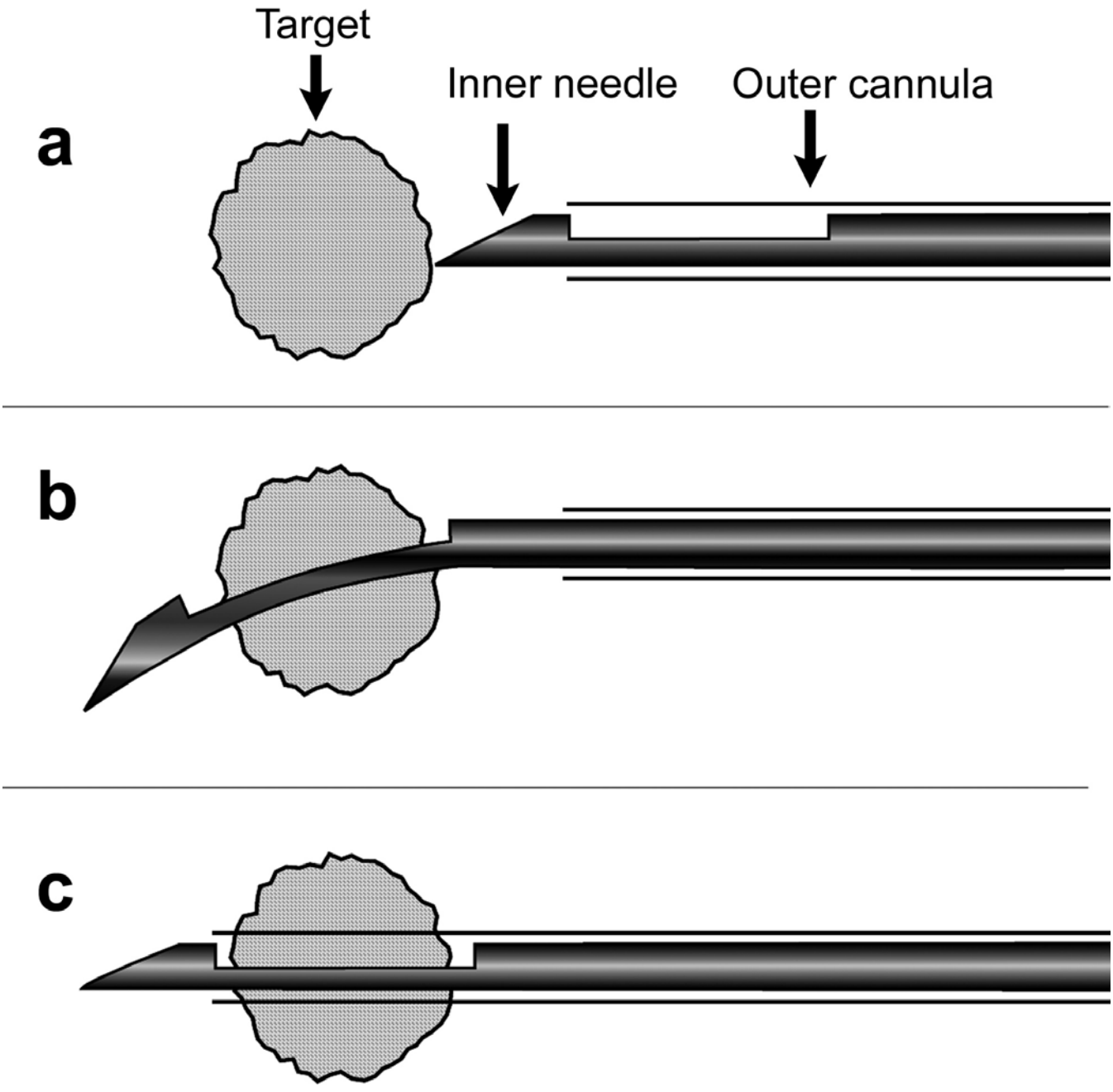

Fig 1.
Schematic presentation of the needle course at automatic biopsy.
a) Before fire,
b) Through the target where the inner needle bends and
c) After firing when the needle bending restores by the outer cannula.

The **semiautomatic** guns are commercially available as disposable biopsy devices. The spring-trigger system in these types of guns consists of one series of springs to shoot the outer cannula. To perform a biopsy, the notch of the inner needle has to be placed manually in the center of the target. The outer cannula is then fired, Fig 2. To our knowledge the clinical impact of these types of guns on breast lesions has not been studied as extensively as that of automatic guns (62). The semiautomatic gun used in our institute is available as a prototype (63).

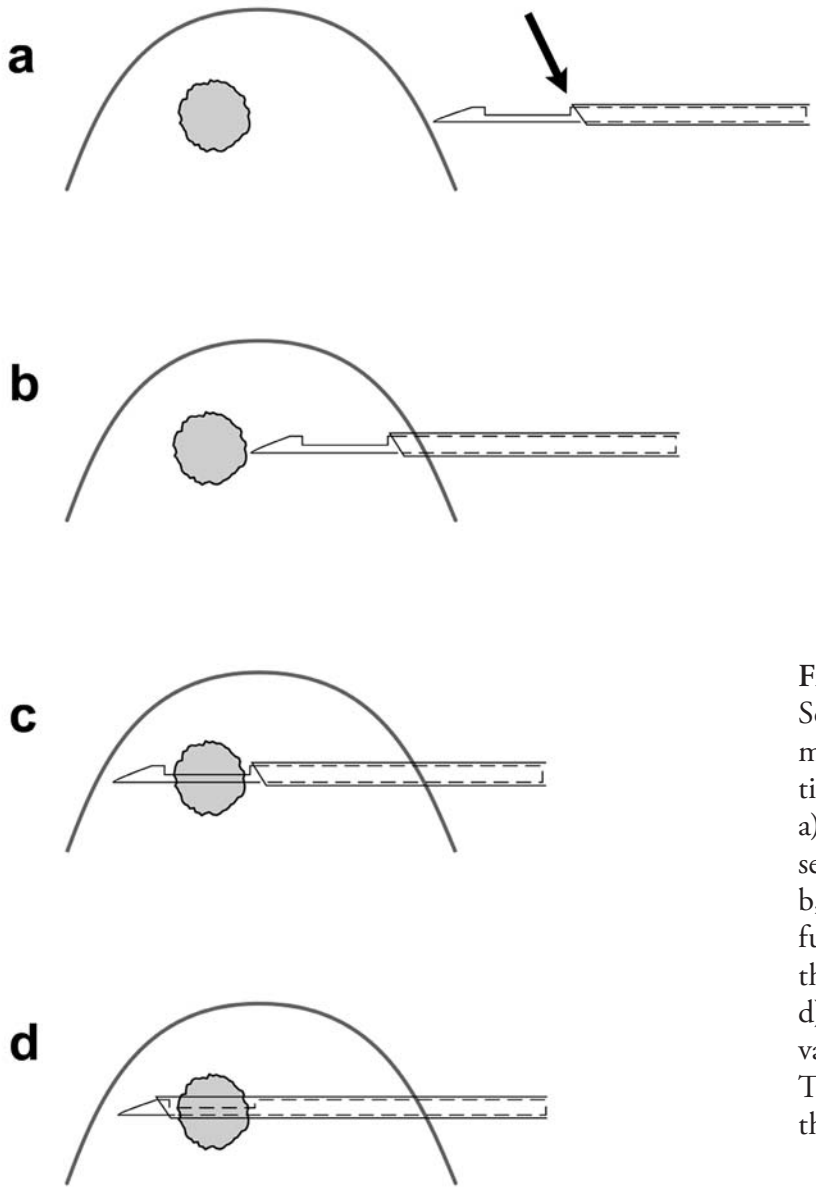

Fig 2.
Schematic illustration of the semiautomatic core biopsy procedure as is practiced by the author.
a) The needle notch is exposed before insertion of the needle in the breast.
b, c) Needle insertion in the breast and further manual insertion of the notch in the target.
d) After being triggered, the cannula advances over the notch.
The arrow shows the right angle shape of the end of the needle notch.

Advantages

Large core needle biopsy has several advantages: it has a very high tissue recovery rate, which allows for diagnosis of primary or metastatic malignancy, grading of malignant tumors, and definitive diagnosis of benign lesions. It is less expensive and invasive than surgery, does not deform the breast, causes minimal injury, and can be performed quickly.

With an accuracy that is least equal to that of open surgical breast biopsy, core biopsy can replace diagnostic surgical procedures (64).

Benign lesions account for 70-85% of all breast lesions in patients in whom biopsies are performed (65,66), and if histologic examination of core biopsy specimens reveal a benign lesion concordant with imaging characteristics, surgery can be rendered (67).

If core biopsy yields a malignant diagnosis, the diagnostic surgery can be avoided and the patient can go directly to definitive therapeutic surgery. (68). Smith et al (69) found that the number of surgical procedures was lower in women with cancer diagnosed by core biopsy than in those with surgically diagnosed cancer.

Core biopsy can also allow a minimally invasive approach for sentinel lymph node resection in conjunction with breast conserving surgery in patients with infiltrating breast carcinomas (70).

It can also allow recognition of more than one focus of carcinoma in the same breast, altering the surgical approach (71,72).

Moreover, Liberman et al found that the likelihood of obtaining clear histologic margins of resection at the first operation was higher in women with core biopsy-diagnosed cancer than in women with surgically diagnosed cancer (73).

Core biopsy is a cost effective alternative to surgical biopsy and can significantly decrease the cost of diagnosis of breast lesions (74). Stereotactic core biopsy has been reported to reduce the marginal cost per year of life by 23% (75, 76) and ultrasound-guided core biopsy has been shown to yield a 56% decrease in the cost of diagnosis (77).

At our institute, The University Hospital, Uppsala, Sweden the cost of stereotatctic and ultrasound-guided core biopsy is about 40% of diagnostic surgical wedge resection.

Calcifications

Core biopsy of calcifications is primarily carried out under stereotactic guidance. There have been reports, however, on ultrasound-guided biopsy of microcalcifications (78).

A major drawback of core biopsy is its limited ability to retrieve diagnostic samples from areas of microcalcifications (79,80). To increase the accuracy of the method several cores have to be obtained, and a minimum of ten passes has been suggested (81,82).

Specimen radiography of the cores can help to identify microcalcifications and to reinforce the need for more specimens (83).

Larger needles than 14-gauge have also been tried in core biopsy of mammographic calcifications. Evans et al (84) compared 12-G and 14-G needles for core biopsy of calcifications, and found that 12-G needles did not appear to be superior to 14-G needles.

Mammographic calcifications usually indicate ductal carcinoma in situ (DCIS). Nevertheless, an infiltrative component may be present, and presurgical identification of the infiltration allows planning for appropriate surgical treatment. Core biopsy can help to confirm infiltration, but cannot reliably indicate the absence of tumor infiltration when only DCIS is found. Liberman et al (85) reported a negative predictive value of 80%. Won et al (86) compared the 14-gauge automated needle with the 11-gauge vacuum-assisted device regarding rates of underestimation of tumor infiltration, and concluded that the accuracy was improved with the lat-

ter device, but that underestimation still occurred. Predictors of invasive breast cancer in patients with an initial diagnosis of DCIS were studied by Yen et al (87), and four independent predictors were found: 55 years of age or younger, diagnosis by core needle biopsy, mammographic size of DCIS of at least 4 cm, and high-grade DCIS.

Complications

There is a potential risk of injury to the thoracic wall and of bleeding and infection at the site of core biopsy of breast lesions. These complications are rare, however, with a frequency of pneumothorax, hematoma and infection of less than one in 1000 each (49,88).

In patients with anticoagulation therapy, an increased risk of bleeding might be anticipated. But in a study by Mellotti (89) the rates of bleeding after core breast biopsy in patients with and without concurrent anticoagulation therapy were found to be similar. Discontinuation of anticoagulation medication prior to core biopsy is advised, but may not be necessary.

Seeding

Displacement of epithelium may occur during needle biopsy. However, reports on the risk of dissemination of malignant cells into the needle track or tissues away from the target lesion are contradictory (90,91,92,93,94).

Diaz et al (95) observed that the incidence and amount of tumor dissemination were inversely related to the interval between core biopsy and surgical excision, and Willy et al (96) found that tumor cells did not survive displacement, but were destroyed by reparative processes induced by tissue injury.

To reduce the risk of seeding and subsequent tumor recurrence, it is recommended that the core biopsy tract be excised at the time of surgical resection of the primary tumor. This can easily be accomplished in virtually all cases if the radiologist chooses the shortest distance between the skin and the target, and inserts the biopsy needle in the breast in the same direction as that in which the surgeon will perform wedge resection (97).

Learning Curve

The outcome of breast biopsy depends upon the degree of experience of the radiologist carrying out the procedure. An optimum outcome will be achieved if the radiologist is skilled in mammography and ultrasound and has extensive experience in performing image-guided interventional procedures (98). Brenner et al (99) observed trends toward increased accuracy with more experience for all types of breast lesions, especially for calcifications.

Liberman et al (100) showed that there is a learning curve for stereotactic breast biopsy. They noted significantly higher technical success rates and lower false-negative rates after the first five to 20 cases of 14-G automated core biopsy.

AIMS OF THE THESIS

Automatic large-needle core biopsy has been employed in diagnosis of breast lesions for almost two decades, and its clinical impact on the diagnosis of breast cancer has been studied extensively. Nevertheless, to our knowledge, the technical aspects of the procedure have not been thoroughly investigated. There is no doubt, however, that performance of a successful core needle biopsy requires good knowledge of the needle behavior during the biopsy procedure. Therefore, in two experimental studies technical aspects of needle behavior at automatic biopsy were addressed (papers I and IV).

A further aim was to study the clinical impact of an alternative biopsy gun that is a semiautomatic device in order to analyze its potential clinical indications, diagnostic yield, and safety aspects in the breast and axillary regions (papers II and III).

Finally, in a clinical study of malignant breast lesions the status of hormone receptors and histologic tumor grades obtained at core biopsy specimens were compared with those obtained from surgical specimens (paper V).

MATERIAL AND METHODS

Study I:

Commercially available packages of butter blocks were used as phantoms, and 14-gauge (2.1-mm) core biopsy needles were fired into them with an automated double-spring device (Manan PRO-MAG 2.2). To mimic the hardness of breast tissues and tumors, butter blocks were prepared at different temperatures ranging from -5 to +19°C. A specimen radiography technique was used to document positions and courses of the needles on pre- and post-fire images in each pass. Moreover, after each pass the lengths of retrieved samples were measured. In addition to passes with a standard outer cannula, one series of passes was performed with a hand-made shortened cannula.

Study II:

A semiautomated gun (63), which is a modified version of the automated gun, was used in a consecutive series of 180 patients. The gun functioned successfully in 145 women for biopsy of lesions in the breast (n=142) and axilla (n=3). Needles of 14-gauge were used. Biopsies were performed either stereotactically (CGR Senographe 500T) (n=18) or with ultrasound guidance (Acuson 128, 7.5- or 10-MHz transducer) (n=127). The three axillary biopsies were ultrasound-guided. Indications for biopsy were mammographically evident lesions presenting as microcalcifications (n=15) or opacities (n= 130). The size of the lesions ranged between 6 and 80 mm.

In 34 patients the semiautomated gun could not function appropriately. In these cases the tumors were so hard that either manual advancement of the inner needle through the tumor was impossible (n=24), or the outer cannula was unable to move as intended (n=10). Moreover, one patient was excluded because of technical errors.

Study III:

The same type of semiautomated gun and core biopsy needles as described in paper II were used in study III for biopsy of axillary lesions in a consecutive series of 21 patients. This was a prospective study and patients enrolled in it were selected after consensus with surgeons, oncologists or pathologists in order to meet the need for specimens larger than those obtainable with a fine needle. All biopsies were ultrasound-guided (Acuson 128 and 10 MHz linear transducer).

Study IV:

High-speed video imaging was used to document the behavior of needles in silicon phantoms in the automated core biopsy procedure. The needles used in this study included commercially available 14-gauge needles, and also three types of hand-made needles with modified projectile heads: lengthened tip, reversed tip, and screwdriver tip, Fig 3. The gun was the same as was used in study I. The phantoms were made of polydimethylsiloxane resins, specially prepared for this study, and had two important properties:

- they were as transparent as glass, allowing video imaging
- they were prepared in three different consistencies (average crosslink densities of 700 g/mol, 11,000 g/mol and, 38,000 g/mol) to mimic breast lesions of different hardness, i.e., hard, intermediate, and soft. Each needle pass was imaged at 2000 frames per second for 10 milliseconds, yielding a total number of 20 images.

Using a commercially available computer program (Optimas™) the following variables were measured:

- velocity (m/s)
- length of stroke (mm)
- deviation of the needle tip from the base line when it took a curved course and its direction toward or away the side of the tip.

Study V:

The amounts of estrogen and progesterone receptors (ER and PR) on core biopsy specimens were assessed and compared to that obtained from surgical specimens in a retrospective review of 129 cases of breast carcinoma. ER and PR were classified into three quantitative groups as less than 10%, 10-50% and more than 50%. In addition the grading of malignancy according to Elston-Ellis (101,102,103) was assessed and compared in the two groups of specimens.

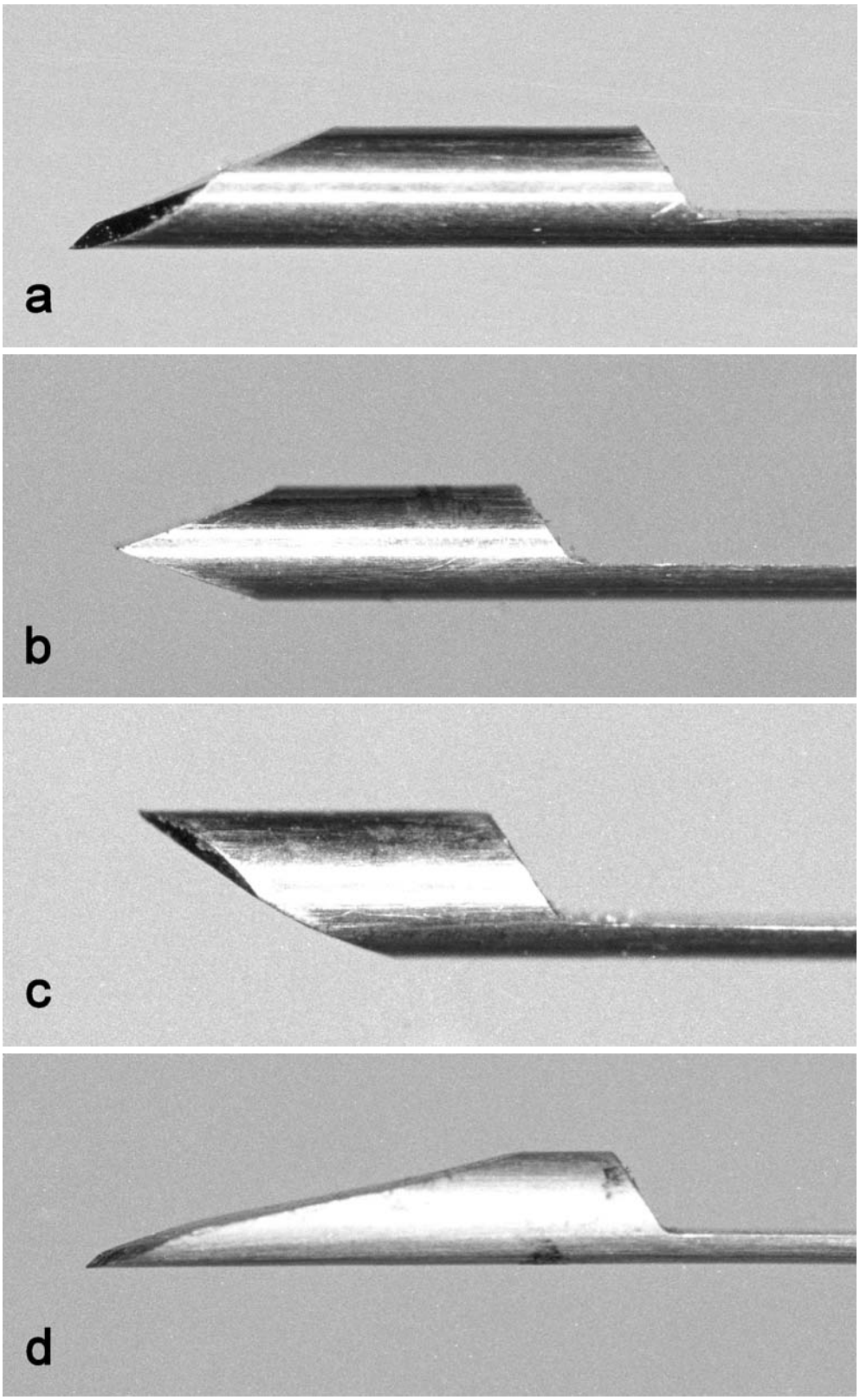

Fig 3.
A commercially available standard needle (a) and handmade needles with modified projectile heads as b) Screwdriver, c) Reversed tip and d) Lengthened tip are shown.

RESULTS

Study I:
In hard butter (temperatures -5°, -2° and +1°C) the outer cannula did not work and no sample was obtained. The inner needle, however, had moved with a curved course deviated toward its tip, Fig 4. At +4°C, both the outer cannula and the inner needle functioned and samples were obtained. The longest sample was obtained at this temperature (12 mm). On the post-fire images, there was an angle between the cannula and the needle tip, Fig 5a, indicating needle deviation. At temperatures of +7, +10, and +13°C the cannula worked and samples were obtained; however, samples gradually decreased in size. At higher temperatures, +16 and +19°C, the needle was straight, and the samples obtained were the smallest. In the second series, using the inner needle in conjunction with a shortened non-operating cannula, a curved course was apparent at all passes, Fig 5b. However, the grade of deviation decreased along with increasing temperature.

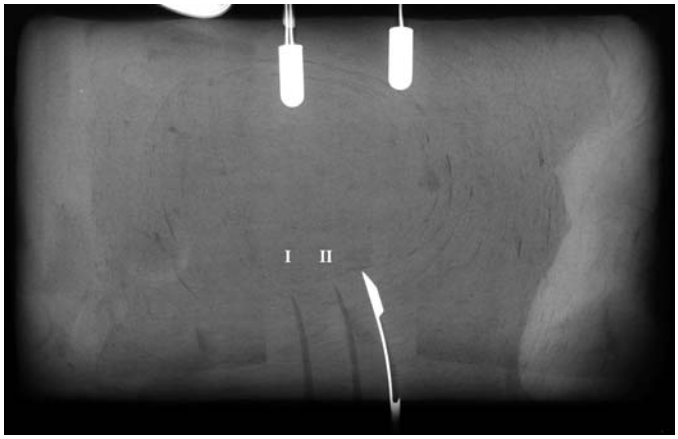

Fig 4.
Post-fire image of the third pass at -5°C.
The needle was bent and the cannula did not function. No sample was obtained.
I and II: Tracks of the first and the second passes.

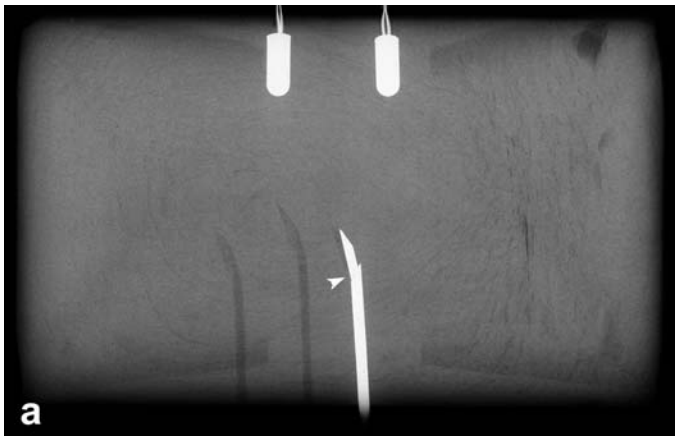

Fig 5a.
Post-fire image of the third pass at+4°C.
The arrowhead shows that the needle is angulated.

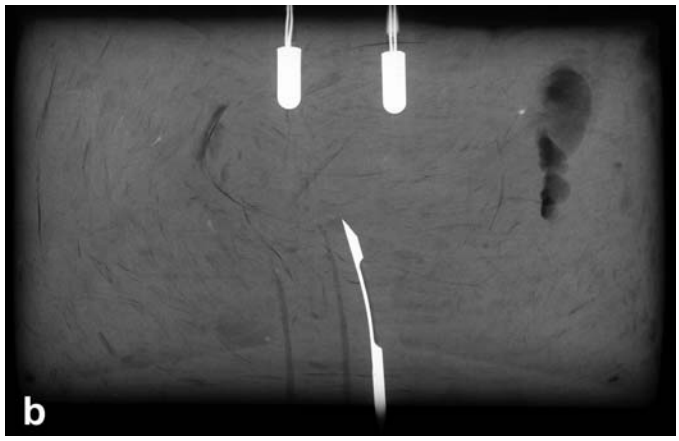

Fig 5b.
Post-fire image at +4°C using a hand-made shortened non-functioning cannula. The needle is curved.

Study II:

Histopathologic examination of core biopsy specimens obtained with a semiautomatic device in 145 patients showed malignant lesions in 108 patients and non-malignant conditions in 37 patients. Among the patients with a malignant lesion, 101 later underwent surgery and malignancy was confirmed in all of them. Of those with non-malignant core biopsy findings, 31 underwent surgery, and in 16 of them malignant lesions were revealed. Thus, semiautomatic core biopsy provided a correct diagnosis in 89% of the cases, (129/145) cases with a sensitivity of 87% (108/108 +16) for detection of cancer.

In 107 patients, only one specimen was obtained at core biopsy, and this showed malignancy in 83 patients and non-malignant conditions in 24 patients. Among the latter, there were 12 false-negative diagnoses. Thus, with one needle pass, the diagnostic sensitivity was 87%.

The length of the specimens retrieved with the semiautomatic gun ranged from 3 mm (n=2) to 17 mm (n=31). Among the patients with a 17 mm long specimen, there was only one false-negative diagnosis. The smallest lesions in the study were 6 mm in diameter, and were seen in 2 patients. The core biopsy diagnoses in these two patients were ductal carcinoma and fibroadenoma, respectively, and both of them were confirmed at surgical histopathology.

No clinically significant bleeding was noted at the time of the biopsy or later. No sign of injury to neural or vascular structures was noted in the axillary biopsies.

Study III:

A summary of the results of this study is presented in Table 1. In 12 patients, metastasis from breast cancer was revealed. In one patient, core biopsy resulted in a false negative diagnosis: core biopsy did not show malignant cells, whereas surgical biopsy revealed metastasis from breast cancer. In 2 patients the specimens were not diagnostic because of technical problems. In 3 patients malignant lesions other than breast cancer metastasis were seen. In another 3 patients benign lesions were diagnosed, of which one was tuberculosis. No injuries to neural or vascular structures were noted in any of the patients.

Table 1:
Summary of the results of large needle core biopsies of axillary lesions.
(*): In one patient, the diagnosis was made through repeated biopsy.

	Number of patients
- Metastasis from breast cancer	12*
- Metastasis from other malignancies than breast cancer	2
- Malignant tumor with mesenchymal phenotype	1
- No sign of malignancy (false negative)	1
- Hematoma	1
- Tuberculosis	1
- Reactive lymphadenitis	1
- No specimen retrieved	1
- Uncooperative patient	1
	21

Study IV:

The commercially available needle when shot into the air followed a straight course. But in all silicon phantoms it followed a curved course, which deviated toward the side of the tip. The degree of deviation increased with increasing hardness of the phantoms. Needles with a modified projectile head also took a curved course deviated toward the side of their tips. Both the velocity and the length of the strokes of the needles decreased with increasing silicon hardness. The needle with a reversed tip had the lowest velocity and the smallest stroke length.

Study V:

Expression of estrogen receptors on surgical specimens was assessed as negative (less than 10%) in 23 patients. In one of these patients the ER was more than 50% at core biopsy. ER at core biopsy was more than 50% in 96 patients. In only one of them it was negative (less than 10%) on the surgical specimen.

Expression of progesterone receptors on the surgical specimen was negative in 51 patients. In 14 (28%) of these it was positive at core biopsy. PR was more than 50% on the surgical specimens in 47 patients, in 4 (8%) of whom it was negative at core biopsy.

To assess the coefficient of agreement between the two methods, a cross table comparison was made (Table 2) and the degree of agreement was evaluated by means of Cohen's kappa. Using the three groups

Table 2.
Cross tables of Core biopsy and Surgical specimen findings concerning estrogen and progesterone receptors.

		Estrogen receptor Surgical specimen			
		<10 %	10-50 %	>50 %	Total
Estrogen receptor Core biopsy	<10 %	21	1	1	**23**
	10-50 %	1	5	4	**10**
	>50 %	1	7	88	**96**
	Total	**23**	**13**	**93**	**129**

		Progesterone receptor Surgical specimen			
		<10 %	10-50 %	>50 %	Total
Progesterone receptor Core biopsy	<10 %	37	2	4	**43**
	10-50 %	8	20	10	**38**
	>50 %	6	9	33	**48**
	Total	**51**	**31**	**47**	**129**

<10%, 10-50% and <50%, the kappa values were 0.87 for ER and 0.64 for PR. To assess the agreement of either a positive or negative receptor status using the clinical "cut off" of 10%, the Spearman's kappa value was determined and was found to be 0.89 for ER and 0.67 for PR.

In 112 cases (86%) at core biopsy, tubular formation and mitosis could not be assessed because of the sparse amount of retrieved tissue. In these cases, only grades of nuclear atypia were assessed and these were compared to nuclear atypia found on the surgical specimens. Comparison showed corresponding results in 101 (90%) of these 112 cases with a kappa value of 0.78 according to a Spearman correlation test at a significant level of $p<0.05$.

DISCUSSION

In two experimental studies (papers I and IV) we demonstrated how a core biopsy needle behaves when fitted with an automatic gun.

In automatic biopsy, an interaction of forces in a gun-needle-target complex is used to obtain tissue samples. Thus, using the same type of gun we studied the impact of the hardness of the target and the configuration of the needle on the needle behavior. In very hard targets the needle bent and did not work properly. This finding might explain why biopsy fails in hard tumors, particularly if the needle is targeted to the center of the tumor. In very soft targets, the needle moved in a straight line and retrieved small and fragmented samples. This observation may explain the failure of core biopsy to obtain diagnostic samples from areas of microcalcifications in a soft fatty breast tissue. In targets of intermediate hardness (butter at 4°C or silicon with an average crosslink density of 11,000 g/mol) the needle took a curved course, and the samples were largest. This finding may indicate that sufficiently large samples could only be obtained from tumors of intermediate hardness in which the needle is able to take a curved course, Fig 6.

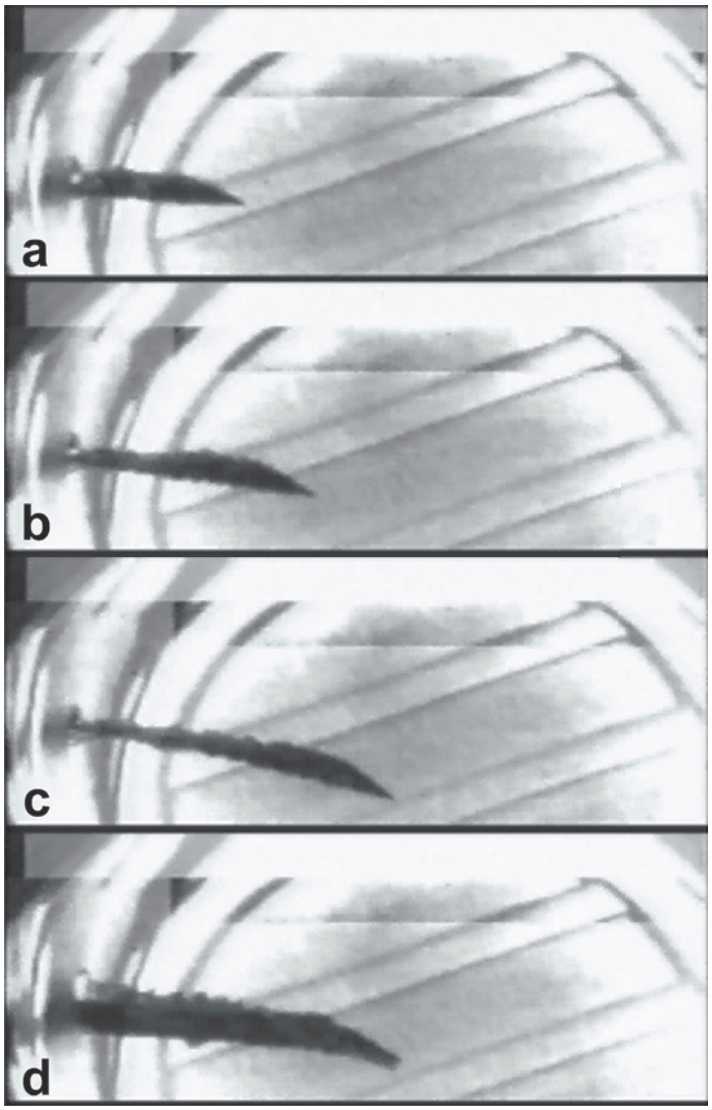

Fig 6 a-d.
Course of a standard needle in an intermediate hard silicon phantom. The needle does not take a straight course, but bends.

Our observations might be applied to human breast tumors, as both types of phantoms were prepared in series of different hardness to resemble breast tissue. Both normal breast tissues and malignant breast lesions have varying degrees of hardness. Moreover, in the same lesion the degree of hardness varies in different parts, depending on the size and shape of the lesion. Thus, there is no given amount of hardness that applies to all tumors or to all parts of the same tumor. Hence, it is not possible to prepare phantoms that will exactly simulate breast tumors. Our phantoms, however, could be used to study needle function.

To examine the impact of the configuration of the needle on its behavior, courses of a commercially available needle and of three hand-made needles differing at the projectile head were imaged and analyzed. It was shown that the needles took curved courses, which deviated toward the side of their tips. The clinical implication of this finding is that knowledge of the curved course of the needle will help to avoid injury to neighboring structures at biopsy. When targeting a lesion, the tip of the needle has to be turned toward the lesion, away from the adjacent structures, Fig 7.

In two clinical studies (papers II and III), we investigated the use of a semiautomatic biopsy gun in breast and axillary lesions. Semiautomatic devices have a one-stage mechanism of function, and are commercially available in different models. The possible advantage of this type of gun over the two-stage automatic guns is their potential for higher targeting precision. Thus, semiautomatic guns might be employed when a biopsy method with higher precision than is provided by automatic guns is desired, for example when targeting small lesions or lymph nodes adjacent to an artery. In our study of a series of 145 breast and axillary lesions (paper II), 129 (89%) of the lesions could be correctly diagnosed, and the sensitivity for malignancy was 87% (108/124).

In a previous study, by using a nonautomatic "Surecut" device Vega Bolivar et al (104) showed a diagnostic yield of 87% with multiple passes. In our material, in patients who underwent biopsy with only one pass, the sensitivity of the method for detection of malignancy was also as high as 87% (83/95). It might be concluded that it is not only the number of passes but also other factors, e.g., the size of the samples, experience of the operator, and so on, that are important for retrieving diagnostic specimens. In study II, we reviewed the sizes of the samples in our material. We found that in 37% (31/83) of the cases the samples were 17 mm long: the full length of the needle notch was filled with specimen; and in these 31 cases there was only one false-negative result.

A drawback of the semiautomatic gun was noted at biopsy of very hard tumors. Patients experienced much pain when the needle was pushed through the tumors. Moreover, the cannula did not strike completely forward. The former is a real limitation of the semiautomatic gun, while the strike of the cannula could probably be improved using stronger spirals.

Study III was an extension of study II. Since the semiautomatic gun could be successfully used at biopsy of lesions as small as 6 mm in diameter in and no clinically significant bleeding or signs of injury to neurovascular structures were seen at biopsy of three axillary lesions (paper II), we used ultrasound-guided large needle semiautomatic core biopsy in 18 further cases of axillary lesions (paper III). These were patients in whom larger specimens than those obtainable with a fine needle were desired.

We found a variety of etiologies (Table 1), and were able to differentiate breast cancer metastases (n=12) from other malignancies (n=3) and benign lesions (n=3). One patient had tuberculosis presenting as an enlarged lymph node in the left axilla, and the diagnosis was made through culture of the core biopsy specimen. She had a normal chest X-ray.

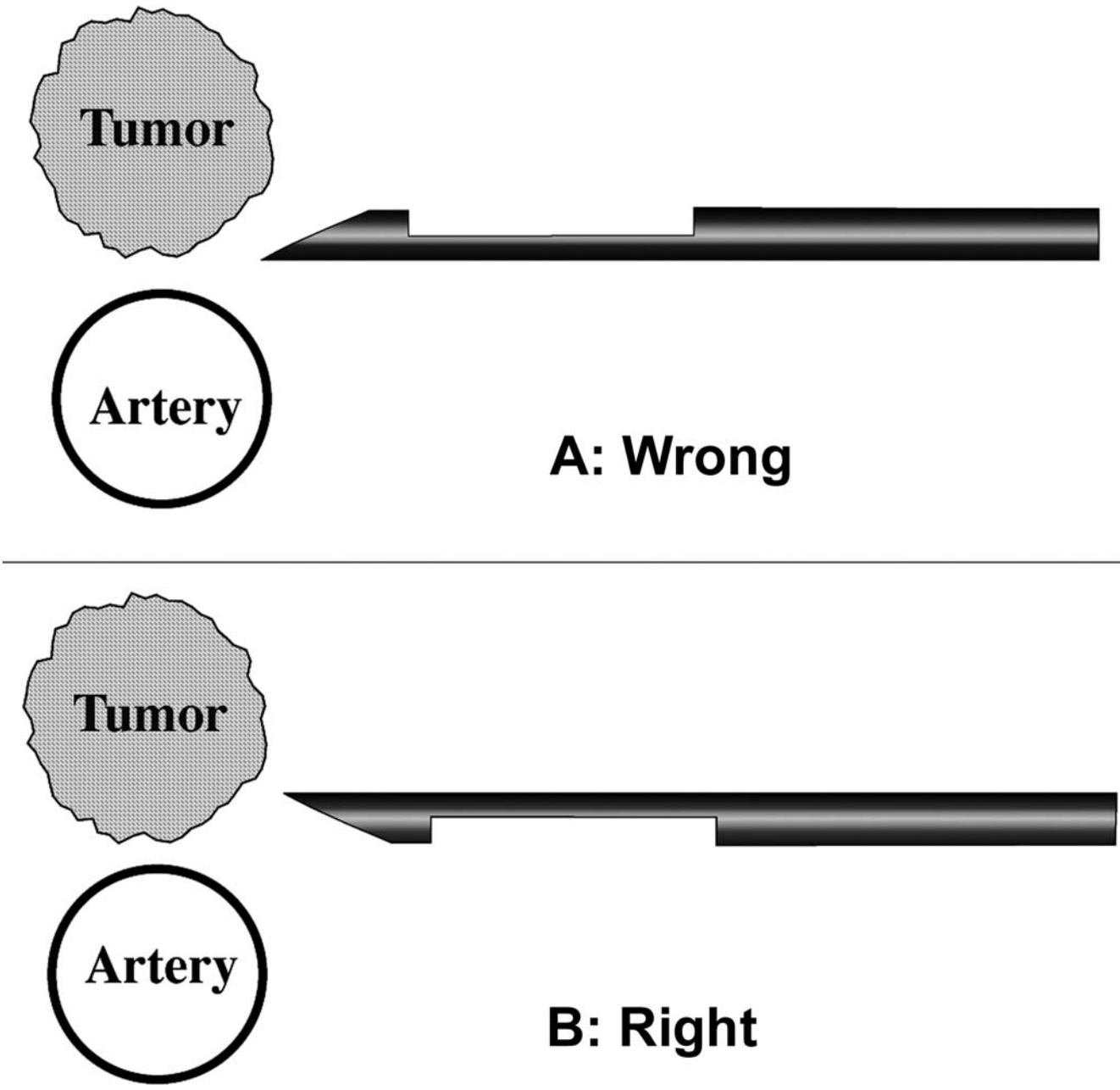

Fig 7.
The tip of the needle has to be turned toward the target to avoid injury to neighboring structures.

The presence of vessels and nerves in the axilla makes invasive procedures of the area rather hazardous and special skills are therefore required. Nerves are not visible on ultrasound, while the axillary vein and artery can easily be recognized. As the larger nerves lie between the vein and artery, their path can be assumed through imaging of the vessels. Lymph nodes, on the other hand, lie more superficially than the neurovascular structures. Thus, knowledge of the anatomy of the area and proper positioning of the needle are highly important if traumatic injuries are to be avoided. We used a semiautomatic gun because of its higher precision in targeting compared to the conventional automatic guns. We also limited the numbers of passes to one or two. No injury to axillary nerves or vessels was noted on clinical follow-up of the patients.

The surgical and chemotherapeutic options for breast cancer treatment have increased and become more complex over time. As the options increase, the importance of core biopsy as a pre-surgical source of information also increases. The accuracy of the information obtained from core biopsy specimens is particularly important in prognostic assessment and in identifying those patients who are most likely to respond to chemotherapy.

Several prognostic predicators are used in breast cancer: tumor size, tumor type, lymph node involvement, hormone receptor status, and histologic grading (105).

Estrogen and progesterone receptors are heat–labile proteins that bind circulating hormones, and their reactivity is degraded in specimens that are not properly prepared (106). In study V, levels of ER and PR on core biopsy specimens were compared with those on the excised specimens in 129 patients. We did not observe a general reduction of hormone receptors on surgical specimens. Moreover, the numbers of patients with low or high levels of hormone receptor expression were comparable. We also compared the histologic grading of the tumors according to the Nottingham modification of the Bloom and Richardson grading scheme (101,102,103). We found that the amount of tissue retrieved at core biopsy was insufficient to assess mitotic activity and tubule formation in 112 cases (86%). In these cases, only grades of nuclear atypia could be assessed, which, however, were in acceptable agreement with combined grading performed on surgical specimens. Such an agreement has also been observed by other authors (105).

Remarks

It's suggested that different biopsy devices should be available in a mammography department and that radiologists dealing with breast imaging should be well trained not only in one but in all biopsy techniques. There is no biopsy method of choice that can be generally applied to all types of breast lesions, but in each lesion the appropriate method of biopsy has to be chosen with regard to the purpose of the biopsy as well as to the mammographic appearance, size, and location of the lesion. Moreover, the least invasive method is always to be preferred.

Fine needle aspiration biopsy is still in the first line among biopsy procedures, and is used in the majority of cases as an adjunct to mammography and ultrasound examination. Core biopsy should be employed in cases where fine needle biopsy cannot provide a diagnostic specimen.

The automatic core biopsy gun is considered the standard core biopsy device for breast lesions, and good knowledge of the behavior of the needle at automatic core biopsy is essential for a successful biopsy. Although there is no general agreement on the appropriate size of core needles for use in breast lesions, we suggest 14-G needles with a 17 mm notch fitted to a gun with a 22 mm stroke length.

The semiautomatic gun has to be used as an alternative to the automatic gun when the size and location of the lesion make the use of the automatic device uncertain or dangerous, e.g., small breast

lesions or lesions located in the axilla.

Biopsy guided by ultrasound is easier than stereotactically guided biopsy and is thus preferable in biopsy of ultrasonographically visible tumors.

To confirm the presence of malignancy in a mammographically malignant lesion, fine needle aspiration biopsy would suffice. On the other hand, exclusion of malignancy in a mammographically benign lesion such as fibroadenoma requires larger specimens; thus large needle core biopsy is the preferred method. Also, in malignant lesions core biopsy has to be employed if presurgical evaluation of tumor markers, e.g., grading, and hormone receptors is desired.

For biopsy of mammographically depicted areas of microcalcifications, particularly scattered microcalcifications vacuum-assisted biopsy (mammotome) is the preferred method.

Whether there is any indication for using Advanced Breast Biopsy Instrument is doubtful.

ACKNOWLEDGMENTS

I wish to express my sincere gratitude to all my colleagues and friends who have contributed to this work and helped me to complete it, and in particular to:

PG Lindgren, my tutor, who taught me the mysteries of the core biopsy technique, which resulted in two experimental and three clinical research projects.

Edward Azavedo, my co-tutor, for all help and good advice over the years.

Per Liss, Director of the Centre of Medical Imaging and Physiology at Uppsala University Hospital for his sincere support.

Ture Åkerfeldt, Torgny Carlsson and Kamyar Fateh-Alavi for preparing needles and phantoms, for performing the tests and for analysis of the findings in study IV.

Rose-Marie Amini, Fredrik Wärnberg and Hans Garmo for their contribution to paper V.

Catrin von Below and Per Eckerbom for their help at the Section of Mammography.

The staff of the Section of Mammography at Uppsala University Hospital for their patience and kind support over the years.

Nora Velastegui Pettersson and Håkan Pettersson for all help with the images and for accomplishing the final layout of this thesis.

But most of all, my beloved wife Zohre and my children Sofie and Sam.

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