Efficacy and safety of direct and frontal macrobiopsies in breast cancer


Recent innovations in tissue acquisition for the human breast have led to the development of unique direct frontal systems. We intend to evaluate efficacy and safety in a multicenter clinical study. Efficacy was considered optimal if the diagnosis by transcutaneous biopsy was identical to the surgical specimen in case of malignancy or in line with clinical follow-up when benign. One hundred and seventy-three women (age 22–95 years) with a suspect lesion in the breast were eligible for transdermal biopsy. One hundred and seventeen biopsies were performed with the Spirotome and 56 with the Coramate under radiological or ultrasound guidance. Sample quality was evaluated by comparing the pathology results of the samples with definitive pathology at subsequent surgery or follow-up in case of benign lesions. An average of 1.66 biopsies per procedure was obtained. All patients had sufficient sample size (up to 5 mm diameter/20 mm length) to make a reliable diagnosis. The average length was 1.39 cm and the average diameter 3.72 mm. There were three false-negative diagnoses implicating a correct diagnosis in 170 patients. None of the patients suffered from a serious complication, and the procedure was generally well tolerated. The new direct frontal transdermal tissue acquisition approach gives adequate diagnostic results through high-quality tissue samples. No major patient discomfort was noted. European Journal of Cancer Prevention 00:000–000 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Keywords: breast cancer, Coramate, early detection, large core biopsy, macrobiopsy, Spirotome

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Introduction

The best hope for long-term survival for cancer patients is an accurate diagnosis in the earliest detectable stage of the disease. This well-established fact makes it imperative that all physicians who diagnose and treat patients with a suspect lesion in the breast act in a multidisciplinary manner. Any technological advance that improves the ability to more rapidly and accurately diagnose soft tissue lesions is important. Transdermal macrobiopsies with dimensions between 8 and 14 gauge have been increasingly accepted over microbiopsies (14–20 gauge) for diagnosis and therapeutic guidance of breast cancer Kertriz et al. (2004). Breast Imaging Reporting and Data System Levy et al. (2007) reports that four breast lesions are a standard indication, but also that fibroadenomas, lesions close to delicate structures, very small lesions, etc are generally accepted Bussieres et al. (2003).

Tissue acquisition is also a prerequisite for a correct and complete diagnosis, in particular, for molecular biology and gene profiling. There is a need for tissue samples of over 150 mg that are representative of the area of interest. In general, macrobiopsies should be able to replace surgery for diagnostic purposes. Widespread use of macrobiopsies, however, has been tempered by the costs of the procedure, tolerance and safety, and tissue quality Verkooijen et al. (2000). Classical vacuum-assisted macrobiopsy expenses are between $250 and 1000 per procedure, and are far beyond the reach of regional hospitals, even in well-developed countries. A second major problem is the lateral uptake of tissue, forcing the operator to go off target for tissue uptake. This leads to increased complication rates and pain Hoorntje et al. (2003).

Both tru-cut microbiopsies and vacuum-assisted macrobiopsies need multiple sampling. The samples for the tru-cut systems are often too small for complete histological and molecular diagnosis. For macrobiopsies, the lateral uptake needs multiple (360°) takes for optimal representativity. Although mixing ‘normal’ tissues with malignant tissues is not very important for histology, molecular biology requires tissue samples devoid of contaminating ‘normal’ or non-target tissues. To improve sampling quality without implications for safety, technological ameliorations are welcome.
The Spirotome (MedInvents, Hasselt, Limburg, Belgium) and the Coramate (MedInvents) use another biopsy concept. Both products have a new design that reduces the costs substantially. They access the target lesion in a direct and frontal way, and realize an almost pain-free procedure Rotenberg et al. (2004). The systems compare well with the traditional vacuum-assisted types Polkowski (2007) with regard to sample size.

New technologies bring new possibilities, but should not compromise tissue quality and safety. This paper evaluates the safety aspects and tissue quality of the Coramate and Spirotome single-use large-core biopsy systems.

Materials and methods
The study was carried out in the period 2006–2008 in three different breast clinics. Samples were sent to three different routine pathological labs of the investigating hospitals. All patients gave informed consent according to the guidelines of the ethics committee of the participating hospital. The biopsy procedure was standardized in different steps: localization technique (ultrasound), skin disinfection, skin anesthesia, deep anesthesia, skin incision, biopsy (either manual and computerized), fixation of sample, and immediate transport of sample to the laboratory.

The patient population was 173 women (age between 22 and 95 years) with a suspect lesion in the breast that was clinically apparent or visible during ultrasound. They were included without any further selection. The recorded efficacy data were identification of patient, target site, number of samples, length and diameter of largest cylinder, length and diameter of shortest cylinder, data on hematoxylin and eosin staining, grading, immunohistochemistry of estrogen receptor, progesterone receptor, human epidermal growth factor receptor type 2, fluorescence immunostaining histochemistry data on human epidermal growth factor receptor type 2 amplification, and agreement between diagnosis on the sample and subsequent surgery (if surgery has taken place).

The manual technique was performed with the Spirotome (MedInvents) or with the computerized version (Coramate, MedInvents). Both systems are based on a rotational cutting on a tissue receiving helix www.medinvents.com. There are two maximal needle diameters: 4 mm (10 gauge) and 5 mm (8 gauge). As in earlier clinical experiments, there was no significant difference between the 8-gauge and the 10-gauge needle, the indications for use of either of these was upon the discretion of the operator, but overall the use of the 8-gauge was advocated for maximal standardization. Eventually, the 8-gauge needle was used in 143 of the 173 patients.

The quality of the samples was evaluated by studying the information obtained from the biopsy sample compared with the surgical specimen or clinical follow-up of the patient. The scientific question was whether the information from the transdermal biopsy was complete based on contemporary standards. The data were collected through a clinical research file and depicted in tabular format for statistical analysis. Patients were observed at the day of the biopsy and 1 week later to communicate the diagnosis and to evaluate possible late side effects.

A subanalysis was done for the Coramate and the Spirotome samples separately, but did not reveal any differences (data not shown). In case the result of the biopsy shows no malignancy, a clinical follow-up of at least 6 months is offered or the lesion is removed when requested by the patient. The pathologists were asked to document the quality of pathology by using pictures of the samples. Safety data were gathered at the time of biopsy and at a subsequent visit 1 week after the procedure. Bleeding was scored as none, minimal (only skin), or important (local hemostasis by pressing for 5 min). Infection or scar larger than 5 mm was scored 1 week later. Pain was scored as no pain at all, minimal pain reporting without necessity of additional local anesthesia, moderate pain necessitating additional local anesthesia, or pain that needed interruption of the procedure. In addition, overall pain was scored in relation to the discomfort of mammography. A complication was reported when the patient needed additional support, prolonged stay in the hospital, or an intervention. Statistical evaluation between Coramate and Spirotome samples was carried out with the Mann–Whitney U test when appropriate (no statistical differences were noted throughout the study – see Results).

Results
The samples of the Spirotome (n=117)/Coramate (n=56) have a tissue weight between 120 (minimal sample) and 300 mg (maximal sample) each. For the Spirotome 8 gauge, the average sample weight was 210 [±35 SD (n=153)] and for the Coramate 8 gauge 194 [±43 SD (n=87)]. The 8-gauge needle gave consistently more tissue compared with the 10-gauge needle. However, in this study, the 8-gauge needle was used in 143 of the 173 procedures. Therefore, the data represent mostly the 8-gauge needle. An average of 1.66 samples were taken from each patient (one to eight samples). The average length was 1.39 cm (between 0.5 and 3.5 cm) with a thickness of 3.72 mm (between 2 and 5 mm) each.

A comparison between macrobiopsy and surgery is possible when malignancy is highly probable. This was the case in 83 patients. In 90 patients, general anesthesia was thus avoided. One hundred and seventeen procedures were carried out manually with the Spirotome and 56 with the computerized version, the Coramate. There
seemed to be no differences between the two procedures with regard to sample size, number of samples, sample quality, and safety aspects.

Although one representative sample was considered the goal, in some cases more than one sample was taken at the discretion of the operator. In one case, up to eight samples were taken because of the complexity of the case (Table 1). The length of the largest or single sample was on average 1.39 cm (± 0.63 cm SD) with an average diameter of 3.72 mm (± 0.89 mm SD). When more than one sample was taken, we measured also the smallest that did not differ significantly compared with the largest sample [average length (cm) of 1.29 ± 0.50 SD and average diameter (mm) of 3.57 ± 0.53 SD]. In some cases, with maximal 360° vacuum the maximal diameter went up to 5 mm in some fatty samples, while the length approached up to 3.5 cm. Again, subanalysis between the Spirotome and Coramate samples showed no significant differences (data not shown).

In 173 procedures of the breast in the same number of patients, three false-negative diagnoses were observed. The accuracy of the diagnosis was not influenced by the number of samples because in one patient with a negative diagnosis two samples were taken. In the true positive diagnoses, most are single samples. Further analysis of the false negative cases showed that these samples were obtained under clinical guidance and in the absence of imaging techniques.

There seemed to be no significant differences between the sample and the surgical specimen with regard to diagnostic possibilities. The pathological examination was considered completely possible in all patients, as the specimen were large enough to perform the typical pathological diagnosis (Fig. 1) and immunohistochemistry analysis (Fig. 2). In 68 of 73 patients with malignancy, the malignant disease was present in more than 50% of the sample.

In 173 procedures, there was no single complication necessitating hospitalization or prolonged stay. All patients could return immediately after the procedure. No procedure was interrupted. Pain needing additional local anesthesia was noted in four patients. Approximately 169 patients reported no pain during and after the procedure. In only seven patients, discomfort was rated

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**Table 1** Characteristics of study results

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(a) Macroview example of breast tissue samples. Two typical samples are sliced and placed on a glass carrier after fixation and hematoxylin and eosin coloration. (b) Low power view of a sample of breast tissue. On lower magnification the absence of artifacts is appreciated. Fatty, cancerous and stromal tissues are equally well biopsied. (c) High power view of a sample of breast tissue. Details of cells can be equally appreciated and compared with the surgical specimen.
higher than mammography. The scar formation was always under 5 mm in diameter and did not affect the patients emotionally. A coloring of the skin as a visible sign of hematoma was usually visible 1 week after the procedure. No hematoma masses were felt or seen during ultrasound. One hundred and seventy of the patients stated that they would not mind another procedure if needed.

Discussion
Recent innovations in large core biopsy for the human breast led to the development of unique direct frontal and 360° vacuum-aspiration systems Rotenberg et al. (2004). The systems complete the range of more classical devices such as the tru-cut microbiopsies and vacuum-aspiration biopsy (VAB) macrobiopsies. As a result of their new design, they address the well-known traditional technical inconveniences of older systems. Preclinical and single-center clinical trials proved the usefulness of these methods, but detailed data on sample quality (efficacy data) and safety have not been shown. This multicenter clinical experience describes in detail the obtained samples, and compares the diagnosis with the data at surgery or prolonged follow-up. In addition, the safety of the patient is evaluated in more detail.

In this study, 173 women with a suspect lesion were eligible. In general, we harvested only one representative sample when possible. This sample is considered the best in comparison to subsequent samples because neither bleeding nor ultrasound image artifact is anticipated at this time. Subsequent samples are considered to have less quality (i.e. more contamination with non-target cells) and to cause more patient discomfort. Nevertheless, when the operator felt that more biopsies were needed, the procedure was continued without removal of the cutting cannula. The maximum number of samples in one procedure was eight. To our surprise, more samples did not significantly affect the size of the sample, suggesting that the quality of the sample was not related to repetition of the procedure.

In this evaluation, the number of samples did not influence the accuracy of the diagnosis. This is in contrast to the literature of the classical VABs Plantade et al. (2004), and can be explained by the direct and frontal approach of the targeted lesion. The VABs take up the sample from the site, and lesions can be missed when present at the other side of the needle aperture. Therefore, it is recommended to take at least five to 30 samples with the classical VAB system (Heywang Kobrunner et al., 2003; Zagouri et al., 2008). This recommendation is not endorsed for direct frontal tissue acquisition, although a larger subset of patients is needed to confirm this finding.

The samples from both the Spirotome and Coramate are large and in the range of those published for VABs. There is no appreciable difference between the Spirotome and Coramate samples. This can be explained by the patient/instrument interface, which is exactly the same. Hence, no further difference is noted between the indications for tissue sampling between the manual and automated devices; it is upon the discretion of the operator who decides to use the Spirotome or Coramate in the routine clinical situation. The manual approach can have advantages in specific occasions where the access to the skin is limited and there is no room available for the automated device.

The accuracy of diagnosis is evaluated by comparing the pathology results of the samples and definitive pathology at subsequent surgery or follow-up of the patient in the case of benign lesions. Correct diagnosis was made in 170 patients. One patient had a minimal invasive cancer on definitive pathology after resection, whereas the sample contained only ductal carcinoma in situ. In two other patients, invasive cancer was not detected. These figures are also quite acceptable and comparable to what is published in the literature. In at least 2 patients in whom the correct diagnosis was not detected, the sample was taken under clinical guidance. Most clinical researchers would agree that biopsy without imaging guidance leads to an increase of false negative samples. This is confirmed in this study, and it is the policy of the institutes now to proceed with breast biopsies under ultrasound or stereotaxis whenever possible.

In these 113 patients, no single complication was observed despite the fact that no premedication is given. Furthermore, anticoagulant medication was accepted.
Bleeding was minimal and mostly originated from the skin incision. Of note is the apparent tolerance of the patient during the procedure. The almost pain-free biopsy, despite the 5 mm needle diameter, can be well explained on clinical and medical grounds. The breast is composed mainly of fat. Local anesthesia is generally a hydrophilic solution of Xylocaine or Lidocaine. One should expect that the anesthesia solution does not diffuse readily in this fatty tissue. Within 10 min, the usual time interval between injection of the anesthetic and the biopsy procedure, the diffusion is about 1-cm diameter, creating in this way a pain-free cylinder of 1-cm diameter, as long as the anesthesia is injected in the depth. The low pain sensation is in contrast with the tru-cut systems that are inserted and withdrawn repeatedly and up to even 20 times. When the first tissue is taken, the needle can be inserted in the anesthesia tract, but afterwards other directions are taken. Pain occurs when the point of the needle penetrates outside the anesthesia tract. The vacuum-assisted biopsy systems with a lateral uptake of the tissue can be positioned into the anesthesia cylinder. However, when the tissue is taken up from aside the anesthesia tract, pain will start to occur. The Spirotome and the Coramate have a direct and frontal action in a coaxial way. This means that the biopsy is taken exactly within the biopsy tract, thereby avoiding any pain. Where histology does not require homogenous cancerous tissue for maximal interpretation, molecular biology does. The more cancerous, or better targeted, tissue in the sample, the better the diagnosis. The quality of the data decreases when contaminating non-cancerous tissues or body fluids (blood) are present in the sample. This is reflected in (semi-quantization) quantization of overexpression and under-expression of genes, for example in PCR microarrays. Fine needle aspirations have no control on the amount and representativity of the biological material. Although tru-cuts and macrobiopsies harvest more material, multiple sampling suffers again from dilution of the targeted material. Direct and frontal biopsies that concentrate on one single but representative sample seem to set a new standard in the preparation of molecular diagnostics.

**Conclusion**

The tissue samples of the Coramate and Spirotome are comparable to each other in view of the same interface with the patient. The quality of the tissue samples is better than those of the microbiopsies because the samples are larger than the classical vacuum-assisted biopsies owing to the direct and frontal approach, and are identical to open surgery. The direct and frontal biopsy systems are safe for the patient, and the procedure can even be considered relatively painless. The quality of the sample is sufficient for research on molecular biology. The direct frontal tissue-acquisition systems can be added to the list of safe and efficient macrobiopsy methods to be used in the early detection of breast cancer.

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**References**


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