An Intraoperative MRI System for Margin Assessment in Breast Conserving Surgery: Initial Results From a Novel Technique

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Background and Objectives: One of the major unmet needs in Breast Conserving Surgery (BCS) is a rapid and accurate margin assessment of the lumpectomy specimen. This study evaluates the ability of a novel MRI system (prototype of the ClearSight^{TM} system; Clear-Cut Medical Ltd., Rehovot, Israel) to distinguish malignant and non-malignant tissues in freshly excised breast specimen by comparing MR measurements to histopathology results.

Methods: Seventy-seven samples were obtained from 22 patients undergoing BCS enrolled in the study. A T2* (T2 Star) value in milliseconds (ms) was calculated for each sample and correlated with histopathology results.

Results: Of the 77 samples, 35 samples were classified by histopathology as malignant and 42 as non-malignant. T2* values were significantly higher in malignant samples compared to non-malignant samples (15.3 ± 2.72 ms and 10.6 ± 1.47 ms, respectively [$P < 0.00001$]). Analysis for a determined cutoff of 11.7 ms revealed 91% sensitivity, 93% specificity, and 92% accuracy. ROC curve analysis yielded AUC of 0.97.

Conclusions: This study demonstrates that the system is sensitive and specific in differentiating malignant and non-malignant tissues in freshly excised breast specimen. The system has the potential to be used for breast specimen margin assessment during BCS, with the goal of decreasing the need for re-operation.

J. Surg. Oncol.

KEY WORDS: breast cancer; breast conserving surgery; intraoperative margin assessment; surgical margins; lumpectomy; intraoperative MRI

INTRODUCTION

Breast cancer is the most common malignancy among women (excluding skin cancer), accounting for nearly one in three cancers diagnosed in women in the United States [1]. About 15% of cancer deaths in women are caused by breast cancer, being the second leading cause of cancer death in women [2].

BCS is currently the most common surgical treatment procedure [3], usually followed by breast irradiation either with post-operative external beam radiation [4] or more recently with intraoperative radiotherapy (IORT, IOERT) [5,6].

In order to verify that all cancerous tissue has been removed, the margins of the lumpectomy specimen are assessed histopathologically. Complete histopathology evaluation is time consuming and may require at least 48 hr. Therefore results are not available until after surgery.

If residual disease is present at the margins, re-excision is necessary to optimally treat the patient and decrease the incidence of local recurrence [4]. Studies demonstrate that 20–25% of patients undergoing lumpectomy will require additional surgery for residual disease found at the margins in histopathological assessment [7,8]. Surgical re-excision is associated with discomfort to the patient, substantial anxiety and emotional consequences, inferior cosmetic outcomes, risks of additional anesthesia, additional costs, and delay in initiation of adjuvant therapy [9].

Hence one of the major unmet needs in BCS is a rapid and accurate margin assessment of the lumpectomy specimen during surgery. With the recent implementation of intraoperative radiotherapy, this need is even greater. Currently, several methods are being used by surgeons for intraoperative margin assessment [10–13]. However, the accuracy of these modalities vary and only complete histopathology evaluation can reliably determine margin status.

Magnetic Resonance Imaging (MRI) may be a suitable modality for margin assessment. MRI is already being used for breast cancer diagnosis and has a high sensitivity for breast cancer detection with reported sensitivities ranging from 71% to 100% versus 16% to 40% for mammography and ultrasound in high risk populations [14–17].

Grant sponsor: Clear-Cut Medical Ltd.

Conflicts of interest: Prof. Papa, Dr. Sandbank, and Dr. Brem are Clear-Cut's consultants and have financial interest in the company.

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Received 26 January 2016; Accepted 22 March 2016

DOI 10.1002/jso.24246

Published online in Wiley Online Library (wileyonlinelibrary.com).

Diffusion weighted MRI, an advanced MR methodology based on the diffusion characteristics of water molecules in tissues, has been shown by in vivo [18] and ex vivo studies [19] to be sensitive to tissue cellularity and malignancy, and specifically, to breast cancer [20–26]. However, intraoperative MRI is expensive, needs specifically designed operating rooms, is not widely available and therefore, not useful in clinical practice for real-time margin assessment.

The potential benefits of this modality have led to the development of a novel device (prototype of the ClearSight^{TM} system; Clear-Cut Medical Ltd., Rehovot, Israel, referred here as "the system"), aiming to overcome both the cost and the availability issues associated with intraoperative MRI. This is achieved by miniaturization of the technology for scanning excised tissue rather than whole bodies or limbs. The system utilizes conventional water diffusion weighted magnetic resonance (MR) to distinguish malignant and non-malignant tissues in freshly excised breast specimen.

One of the unique characteristics of the system is that the diffusion weighted MRI measurements can be performed on freshly excised breast tissue, without the need of using contrast media.

This study evaluates the ability of the system to distinguish malignant and non-malignant tissues in freshly excised breast specimen.

MATERIALS AND METHODS

System Description

The system used in this study is a novel, transportable, compact MRI device designed specifically for real-time, ex vivo margin assessment in the operating room during the time of surgery. The system is composed of permanent static magnets, designed to produce a static magnetic field, and a single RF coil. As opposed to standard clinical MRI, the system does not require special shielding and therefore is compatible for use in a standard operating room.

Diffusion weighted MRI, an advanced MR methodology is based on water mobility within the tissue and its restriction by barriers such as membranes. The rate of water diffusion is quantified by the Apparent Diffusion Coefficient (ADC). T2* is a measurement which is inversely proportional to ADC [27], hence, it can be useful in distinguishing malignant and non-malignant, freshly excised breast tissue.

The system measures a volume of 4 mm diameter and 1 mm thickness of the tissue specimen. The signals are analyzed in real-time and a T2* value is calculated. Each measurement requires approximately 1–2 sec to complete and is classified as malignant or non-malignant based on criteria described below.

Study Design

This study is HIPPA compliant and was approved by the Institutional Review Board (IRB) of each participating center. All subjects have signed informed consent prior to the procedures performed in the study. Twenty-two patients undergoing lumpectomy for breast cancer were enrolled in the study (mean age 55 ± 12.7 years). From each of the 22 lumpectomy specimens between two and five samples were obtained, leading to a total of 77 freshly excised breast tissue samples.

Each sample was taken from different areas of the lumpectomy specimen by the pathologist, following an on-site, real-time, macro-pathology assessment, in order to obtain a variety of tissue types. The individual tissue samples were then analyzed by the system, which determined the T2* value utilizing a fat suppression technique [28]. The calculated T2* values were correlated with final histopathology results.

Specimens' Preparations and MR Measurement

The pathologist bread-loafed each freshly excised breast specimen, and using a punch biopsy technique, obtaining samples of approximately 6 mm in diameter and 2–5 mm in depth. The pathologist was instructed to extract punches from a variety of tissue types, according to the macro-histology assessment. The samples were inserted into the MR system and the MR signal magnitude as well as the T2* value of each sample were calculated by applying an algorithm for fat suppression., as otherwise the fat MR signal may mask the MR diffusion signal. All measurements were performed immediately after tissue removal by the surgeon.

Histopathology Evaluation Procedure

Following determination of the T2* value, the tissue samples were sent for standard histopathology evaluation using routine H&E staining.

Data Analysis

Classification of a sample by the MR system as malignant or non-malignant was performed based on the measured MR signal magnitude following fat suppression and the calculated T2* value. If the MR signal magnitude measured following fat suppression was lower than a specific threshold (reflecting a very fatty tissue where most MR signal was eliminated by fat suppression), the tissue was classified as non-malignant. Otherwise, if the MR signal magnitude following fat suppression was higher than the threshold, T2* was calculated.

Receiver Operating Characteristic (ROC) curve analysis was performed based on the comparison to histopathology classification, by choosing different T2* cutoff values. Samples with a T2* value higher or lower than the T2* cutoff value were classified as malignant or non-malignant, respectively.

The range of T2* cutoff values used for the ROC curve analysis was the entire range of T2* values measured in the study, which was 8–21 ms. The sensitivity and specificity was calculated for each cutoff value within that range.

T2* averages and standard deviations were calculated for malignant and non-malignant samples, as confirmed by the histopathology, and displayed in Figure 1. Student's *t*-test was used for statistical analysis.

RESULTS

Of the 77 samples, 35 samples were malignant (out of which 31, 3, and 1 were IDC, IDC + DCIS, and DCIS, respectively), and 42 were

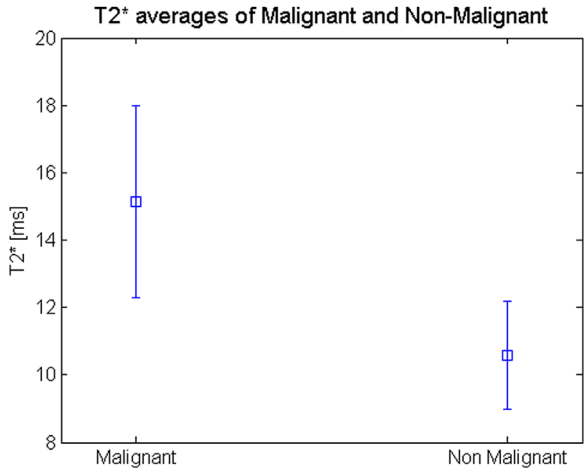

Fig. 1. T2* of malignant and non-malignant tissue. The average and standard deviation of T2* for malignant tissue was 15.3 ± 2.72 ms and for non-malignant was 10.6 ± 1.47 ms.

non-malignant according to the final histopathology report. The average pathologic size of the malignant tissue within the samples was 2.6 mm.

The average T2*, that was calculated for each sample and presented as a numerical output, was 15.3 ± 2.72 ms for malignant tissue and 10.6 ± 1.47 ms for non-malignant tissue. T2* was significantly different between the two groups ($P < 0.00001$), as demonstrated in Figure 1.

Examples of a malignant and non-malignant histopathology tissue samples are shown in Figure 2. In this example, the T2* value for the malignant specimen was 14.8 ms and for the non-malignant specimen was 9.7 ms. In the non-malignant sample, the slide contains adipose cells as well as normal ductal epithelium. The normal cells are sparse, with an area of extracellular matrix (Fig. 2a,b white arrows). In the malignant sample the cells are dense, and more cells are stained using H&E staining compared to the non-malignant sample (Fig. 2c,d).

ROC curve analysis describing the sensitivity versus the false positive rate (100% minus specificity) for different T2* cutoff values was performed, and is shown in Figure 3. The ROC curve visually presents the accuracy of the system with an Area Under Curve (AUC) of 0.97. Different T2* cutoff values were examined in order to specify the cutoff value providing the optimal performance.

A cutoff value of 11.7 ms provided an optimal sensitivity, specificity, and accuracy of 91%, 93%, and 92%, respectively.

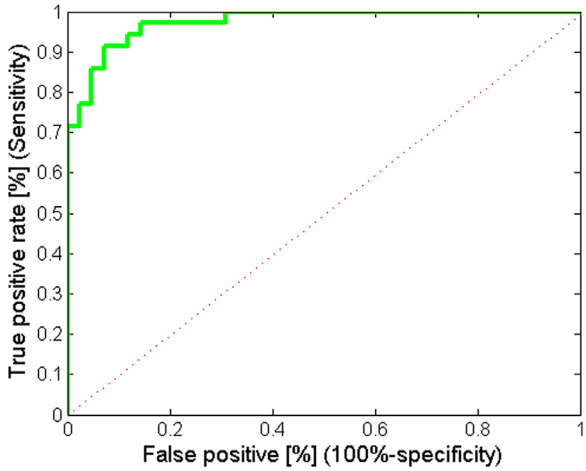

Fig. 3. ROC curve for the dataset describing the false positive rate (%) versus the true positive rate (%) using different cutoff values (green solid line) plotted against the line of no discrimination as reference (dotted line).

DISCUSSION

One of the major unmet needs in BCS is rapid and accurate margin assessment of the lumpectomy specimen during surgery. Surgical re-excision for positive margins is associated with discomfort to the patient, substantial anxiety and emotional consequences, inferior cosmetic outcomes, risks of additional anesthesia, additional costs, and delay in adjuvant therapy [9]. Therefore it is critical to ensure that margins of the removed breast portion are non-malignant. For that reason, currently, several methods are being used by surgeons for intraoperative margin assessment including: Gross clinical evaluation of the lumpectomy specimen, histopathological evaluation with touch preparation cytology, frozen section analysis, Intraoperative Ultrasound (IOUS) Guided Resection, Near-Field RF Spectroscopy, Specimen Radiography (X-ray), Positron Emission Tomography (PET), and Near-Infrared Fluorescence (NIRF) optical imaging. Additional approaches which relate to localization include: Radioguided Occult Lesion Localization (ROLL) and Cryoprobe-Assisted Localization (CAL) [10–13].

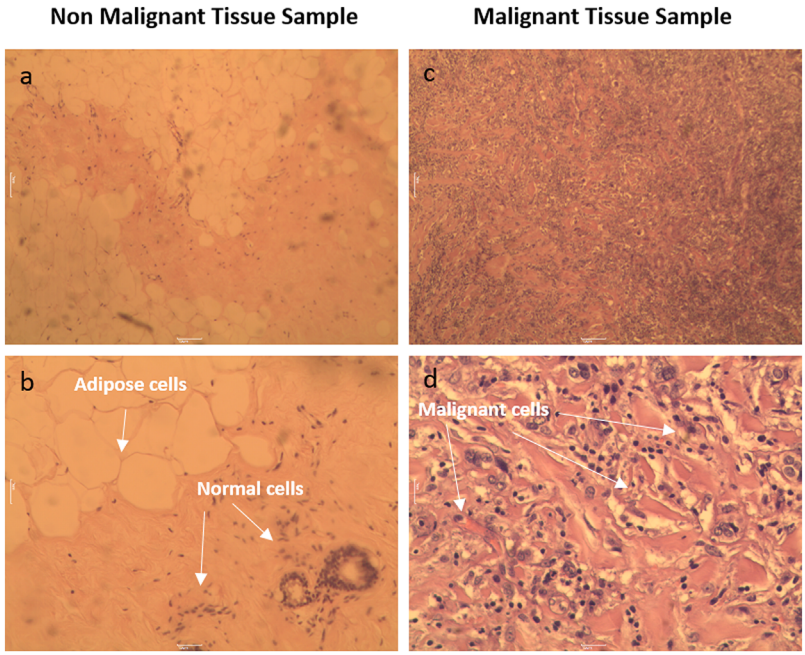

Fig. 2. Histopathology slides (H&E staining) of a non-malignant tissue sample (**a**, magnified ×4; **b**, magnified ×20) and a malignant tissue sample (**c**, magnified ×4; **d**, magnified ×200). Images **b** and **d** are magnification images of **a** and **c**, respectively. In the non-malignant sample, the slide contains adipose cells as well as normal ductal epithelium. The normal cells are sparse, with an area of extracellular matrix. In the malignant sample, the cells are dense and more cells are stained using H&E staining compared to the non-malignant sample. T2* value for the malignant specimen is 14.8 ms and is for the non-malignant specimen is 9.7 ms.

While MRI is an important tool in the diagnosis of breast cancer, usually with the use of contrast media [14–17], until now it is not used ex vivo in the evaluation of the excised breast tissue following BCS, for reasons related to cost and availability of intraoperative MRI.

The system presented in this study, a real-time, intraoperative MR system, uses diffusion weighted MRI, a technique to track the displacement of water molecules in a given tissue. The result of such measurements can be quantified by the ADC value, which relates directly to the water diffusion characteristics in the tissue being imaged.

The use of ADC to identify malignancy has been shown previously in many studies in oncology in general [29,30] and breast cancer in particular [20–26]. These studies demonstrate a decrease in the ADC value in malignant tissue, since water diffusion is influenced by tissue cellularity and density. Diffusion does not require a contrast media, therefore, it is suitable for ex vivo measurement performed by the system. MRI systems can measure, using dedicated sequences, the $T2^*$ value of the tissue, which is inversely proportional to ADC [26], therefore being higher in malignant tissue than in non-malignant tissue. Therefore, without determining the exact mathematical relationship between ADC and $T2^*$, which depends on system-specific as well as environmental parameters, one can extract clinically meaningful data by measuring $T2^*$ rather than determining the ADC value itself.

Indeed, the present study provides evidence for the ability of the system to differentiate malignant and non-malignant tissues in freshly excised breast specimen, using $T2^*$ values.

Analysis for a determined cutoff of 11.7 ms shows high sensitivity, specificity, and accuracy for discriminating between malignancy and non-malignancy based on $T2^*$ values (91%, 93%, and 92%, respectively). Additional prospective trials are underway to further establish the role of $T2^*$ in assessing the whole surgical margin of the lumpectomy specimen in clinical practice.

The innovation of the system presented in this study is its ability to evaluate ex vivo breast specimen's margins for malignancy immediately after breast tissue removal.

The system does not require a special magnetic field shielding suite (but rather shields itself) and its compact size and transportable nature enables placement in a standard operating room. The measurements are performed ex vivo immediately after the operation, and each sample measurement takes approximately 1–2 sec to complete, which allows for rapid, real-time assessment during surgery. These advantages indicate that the system could be used for clinical assessment of breast specimen margin status ex vivo following BCS.

The present study has some limitations. The cutoff $T2^*$ value for classifying a tissue as malignant or non-malignant was empirically calculated based on the samples tested in the present study, and this cutoff value should be examined on a new set of samples. A larger cohort can also add additional information regarding the relation between tumor size and detectability. Since breast malignancy is not homogenous, future studies may focus also on the ability to distinguish between malignancy types (e.g., IDC, DCIS) and other tissue characteristics (e.g., tissue density).

Future studies will be required to address the performance of the system when scanning entire margins rather than specific samples like the ones taken in this study. In addition, the effect of the time elapsed since tissue excision on the MR signal should be further investigated.

The purpose of this study was to demonstrate the applicability of the system for breast conserving surgery, and explore the cutoff values for differentiating malignant from non-malignant tissues in freshly excised breast specimen. While it was shown that diffusion MRI may be capable of distinguishing between malignant and non-malignant tissues in many clinical applications [31], the applicability of the system for applications other than breast tissue should be explored in further studies.

A new clinical study currently underway is addressing some of the limitations mentioned above. Instrumental improvements will be introduced and reviewed in further studies in the future.

CONCLUSIONS

This study demonstrates that the ClearSight^{TM} system is sensitive and specific in differentiating malignant and non-malignant tissues in freshly excised breast specimen. The system has the potential to be used for breast specimen margin assessment during BCS, with the goal of decreasing the need for re-operation.

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SYNOPSIS

This study demonstrates the ability of a novel MRI system (prototype of the ClearSight^{TM} system; Clear-Cut Medical Ltd.) to distinguish between malignant and non-malignant tissues in freshly excised breast specimen. Possible application may be intraoperative margin assessment during Breast Conserving Surgery (BCS), with the goal of decreasing the need for re-operation.