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A phantom study**

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Electrosurgical knife equipped with diffused reflectance spectroscopy sensing for tumor margin detection during breast conserving surgery - A phantom study

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ABSTRACT

Distinguishing the diseased breast tissue from the healthy tissue is a sorely challenging task for the surgeons during breast conserving surgery (BCS) as both tissues own relatively similar visual and haptic characteristics. It has been shown that diffused reflectance spectroscopy (DRS) has the potential to be used as a real-time tumor margin detection technique during BCS. In this research, an electrosurgical knife is equipped with fiber-based DRS sensing to provide the surgeon with real-time oncological guidance during BCS. To prevent overheating of the fibers, they were placed inside quartz tubes which were mounted on the electrosurgical knife. The effect of using quartz tubes and debris formation during electrosurgery on the DRS measurements on porcine tissue was investigated. Furthermore to investigate the performance of the new device, a heterogeneous breast phantom representing optical properties and anatomical shape of the real breast was developed. The new device was then used to cut through the phantom's layers to assess the performance of the new knife while cutting. Finally, a BCS was performed on the phantom using the new knife without receiving visual and haptic feedback from the tissue. The results show that both using the quartz tubes and the formed debris do not have a significant effect on the DRS output. Moreover, the DRS outputs obtained during cutting the layered phantom showed the transition between the layers clearly, demonstrating that the cutting effect on the phantom tissue does not significantly affect the measurements. The X-ray images from the phantom before and after BCS using the new device confirmed the complete resection of the tumors from the breast phantom. The results indicate that the electrosurgical knife equipped with DRS is a promising technique for simultaneously distinguishing and cutting the tissue, and assessing real-time tumor margins during BCS.

Keywords: Tumor margin assessment, diffused reflectance spectroscopy, breast conserving surgery, tumor detection, breast phantom.

1 INTRODUCTION

Breast conserving surgery (BCS) is the preferred surgical treatment for women diagnosed with early stage breast cancer. At this stage, the cancerous tissue only forms a small portion of the breast and during BCS the surgeon removes this portion of the breast along with some surrounded healthy tissue to assure the complete resection of the tumor and meanwhile satisfactory cosmetic outcomes [1]. On the surgical side, the diseased and normal breast tissue cannot always be clearly distinguished, making it difficult for the surgeon to determine where to dissect the tissue. Difficulty in detecting the border of the tumor in BCS can result in positive margins and therefore in an unsuccessful surgery [2, 3]. Using an intraoperative margin assessment technique during cancer surgery could help the surgeon with detecting the border of the tumor and distinguish it from the breast's healthy tissue. Considering the high occurrence rate of positive margin, the demand for developing a more reliable and convenient real-time tumor margin detection technique is still standing [4, 5]. Among different type of techniques, diffused reflectance spectroscopy (DRS) has recently become known as a promising tumor detection technique and has been widely studied for its application in this field [6-8].

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In principle, each component in tissue such as fat, water and collagen has its own specific absorption and scattering for each wavelength. Based on the theory and by applying analytical models on the diffused reflectance spectrum measured from a tissue, it has been shown feasible to determine the constituent elements of the tissue as well as the concentration of each element [9-11]. Recently, researchers demonstrated the possibility of distinguishing healthy breast tissue from malignant tissue by using the diffused reflectance spectrum. In these studies, the outputs were classified based on either the Fat/Water ratio and collagen content of the tissue (extracted from the DRS outputs using an analytical model) or measurements in specific wavelengths, which eventually resulted in accurate tissue identification [8, 12]. The results show that, translation of the DRS, as a robust margin assessment technique, to the BCS surgical setup seems advantageous and inevitable. In our previous studies, we investigated the feasibility of equipping an electrosurgical knife, which is vastly used by surgeons in BCS, with a DRS system to enable real-time tumor detection during cutting/coagulating tissue in operation side [13, 14].

During electrosurgery, the produced heat burns the tissue which might affect its optical characteristics. Moreover, utilizing the optical fibers of the DRS system close to the tip of the electrosurgical knife where it is exposed to the heat and in connection with the tissue, leads to fiber burning and production of debris on it, which disturb the function of the optical fibers and DRS [13, 14]. In our new design, we included quartz tubes to protect the optical fibers from the produced heat during electrosurgery.

Though we showed the effectiveness of combining DRS and an electrosurgical knife lately [13, 14], further investigation is required to confirm the final successful transition of DRS equipped electrosurgical knife to the clinical setup. In this work, we investigated the effect of using the quartz tubes and the produced debris during the electrosurgery on the DRS output while cutting porcine muscle and adipose tissue. Moreover, a breast phantom representing the optical properties of the breast was produced to study the performance of the new device in a more realistic setup. As recent studies introduced the Fat/Water ratio as a robust discriminative factor between malignant breast and normal tissue, we produced the phantom layers according to the Fat/Water ratio of breast's different layers. The Fat/Water ratio of each layer (adipose layer, fibroglandular layer and tumor layer) matches the Fat/Water ratio of the target tissue in breast, as shown in [15]. By first using a layered phantom followed by a more realistic breast phantom, we investigated the performance of the DRS equipped electrosurgical knife as a real-time tumor margin assessment technique during cutting the phantom or performing a BCS on it.

2 MATERIALS AND METHODS

2.1 DRS equipped electrosurgical knife

To integrate an electrosurgical knife with DRS system, first two metallic tubes were soldered on an electrode of a normal electrosurgical knife, and the quartz tubes were placed inside these metallic tubes. Then, the optical fibers, which were connected to a Philips custom-designed diffused reflectance spectroscopy setup (Philips Research, Eindhoven), were placed inside these quartz tubes. From the measured spectra, information regarding the composition of the tissue, as well as their concentration, were extracted using a Philips custom-developed software (Philips Research, Eindhoven). More information and details about the design of the DRS setup, signal calibration and the software can be found in previous work [8, 13].

2.2 Effect of debris on DRS

To investigate the effect of debris formation (on the surface of the quartz tube during the electrosurgery) on the DRS output, a *needle* with DRS optical fibers as control group (without quartz tube) and the electrosurgical *knife* with DRS optical fibers was used to first obtain spectra from fresh porcine muscle and adipose tissue, separately. Then DRS equipped electrosurgical knives were used to cut (blend mode, 60W, 1 minute) the porcine muscle and adipose tissue (a slice of layered meat). Afterwards, these contaminated knives were used to obtain spectra from the fresh muscle and adipose tissue. These spectra were used to calculate the Fat/(Fat+Water) and Fat/Water.

In total three sets of knives (Knife 1, Knife 2, and Knife 3) were used to cut the tissue. Moreover, the DRS measurement for each tissue was taken from three separated locations (3 location for muscle, 3 location for adipose) and for each location three spectra were acquired which resulted in nine spectra per knife per tissue.

2.3 Phantom preparation

Gelatin, lard and water were used to prepare the phantom. For the adipose layer, fibroglandular layer and tumors, the compositions of lard, water and gelatin are summarized in Table 1. Briefly, to produce the phantom the gelatin was added to in 60°C water placed on hitter/stirrer. After the gelatin was solved completely, the lard on room temperature was poured into the gelatin-water mixture.

Next, the final composition was poured inside the mold and placed in the freezer for 1 hour and then in the refrigerator overnight. To make the tumors visible on X-ray imaging and create contrast between the tumors and other layers, Barium sulfate was added to the mixture of the tumors during stirring.

Table 1. The composition of each layer of the breast phantom

	Adipose mimicking layer	Fibroglandular mimicking layer	Tumor mimicking layer
Lard	50%	40%	20%
Water	50%	60%	80%
Gelatin	15% (of water volume)	15% (of water volume)	15% (of water volume)

2.4 Cutting and DRS measuring on the layered phantom

To determine the performance of the DRS equipped electrosurgical knife during cutting, the device was used to cut through a phantom with layers mimicking fibroglandular, tumor and adipose, respectively. A linear stage was used to control the movement of the knife with steps of 2 mm during cutting. At each location (after cutting for 2mm) the knife was kept still and three DRS measurement were acquired. Finally, the Fat/(Fat+Water) and Fat/Water were extracted from each spectrum.

2.5 Breast conserving surgery on the breast mimicking phantom

A heterogeneous breast phantom consisting of an adipose and a fibroglandular layer with two tumors was produced with the composition mentioned in Table 1. Using the DRS equipped electrosurgical knife a breast conserving surgery was performed (by a person with no clinical experience) on the breast phantom to remove the tumors. The Fat/(Fat+Water) of each spectrum was displayed on a monitor and these were used as discriminating factors between the healthy layers (adipose and fibroglandular layer) and the tumors. An X-ray imaging system was used to scan the breast phantoms before and after surgery.

2.6 Statistics

All the experiments (except the breast conserving surgery on the final breast phantom) were replicated three times. The One-way ANOVA (significant with P-values <0.05) was used to compare the data in the GraphPad Prism (version 8.0.0 for Windows, GraphPad Software, San Diego, California USA (www.graphpad.com)).

3 RESULTS

The schematic representation of the DRS equipped electro-surgical knife, designed by mounting optical fibers of the DRS system to the blade of the electro-surgical knife, is shown in Figure 1A. The blade of the electro-surgical knife with the equipped quartz tubes and optical fibers is shown in Figure 1B. This design was used for further experiments, including cutting and measuring DRS from porcine tissue and the phantom.

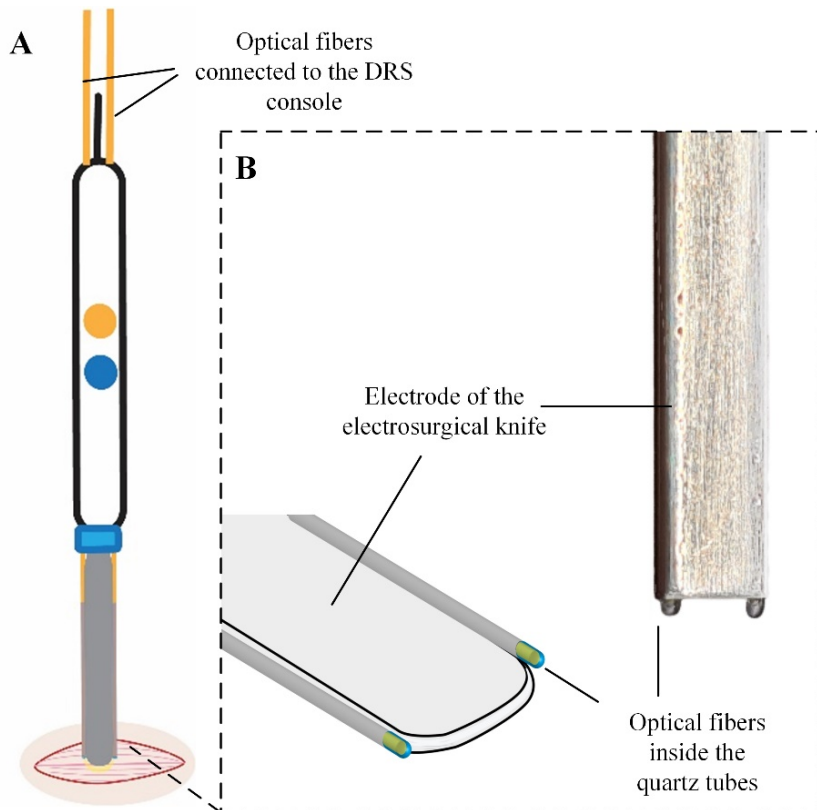


Figure 1. (A) The electro-surgical knife equipped with DRS optical fibers. (B) the blade of the electro-surgical knife with the attached metallic and quartz tubes covering the optical fibers.

3.1 Effect of debris on DRS

Nine spectra from three locations of porcine adipose and muscle tissue were acquired using (1) a DRS needle probe (without quartz tubs), (2) a clean DRS equipped electro-surgical knife and (3) three contaminated DRS equipped electro-surgical knives (Knife 1, Knife 2, and Knife 3, contaminated by cutting mixed porcine tissue). The Fat/(Fat+Water) and Fat/Water of each spectrum is shown in Figure 2. Comparison of the results between the needle probe and the unused knife shows a slight increase of Fat/(Fat+Water) and Fat/Water for both tissue when using the unused knife.

This difference is also visible between the Fat/(Fat+Water) and Fat/Water of spectra obtained with a needle probe and the contaminated knives. However, the deviation of the results between the unused and contaminate knife is negligible. The Fat/(Fat+Water) and Fat/Water values obtained from all the spectra, either the probe or the used and unused knife, show that it is possible to distinguish the muscle tissue from adipose tissue, even when the quartz tubes are used or the knives are contaminated due to the electro-surgery.

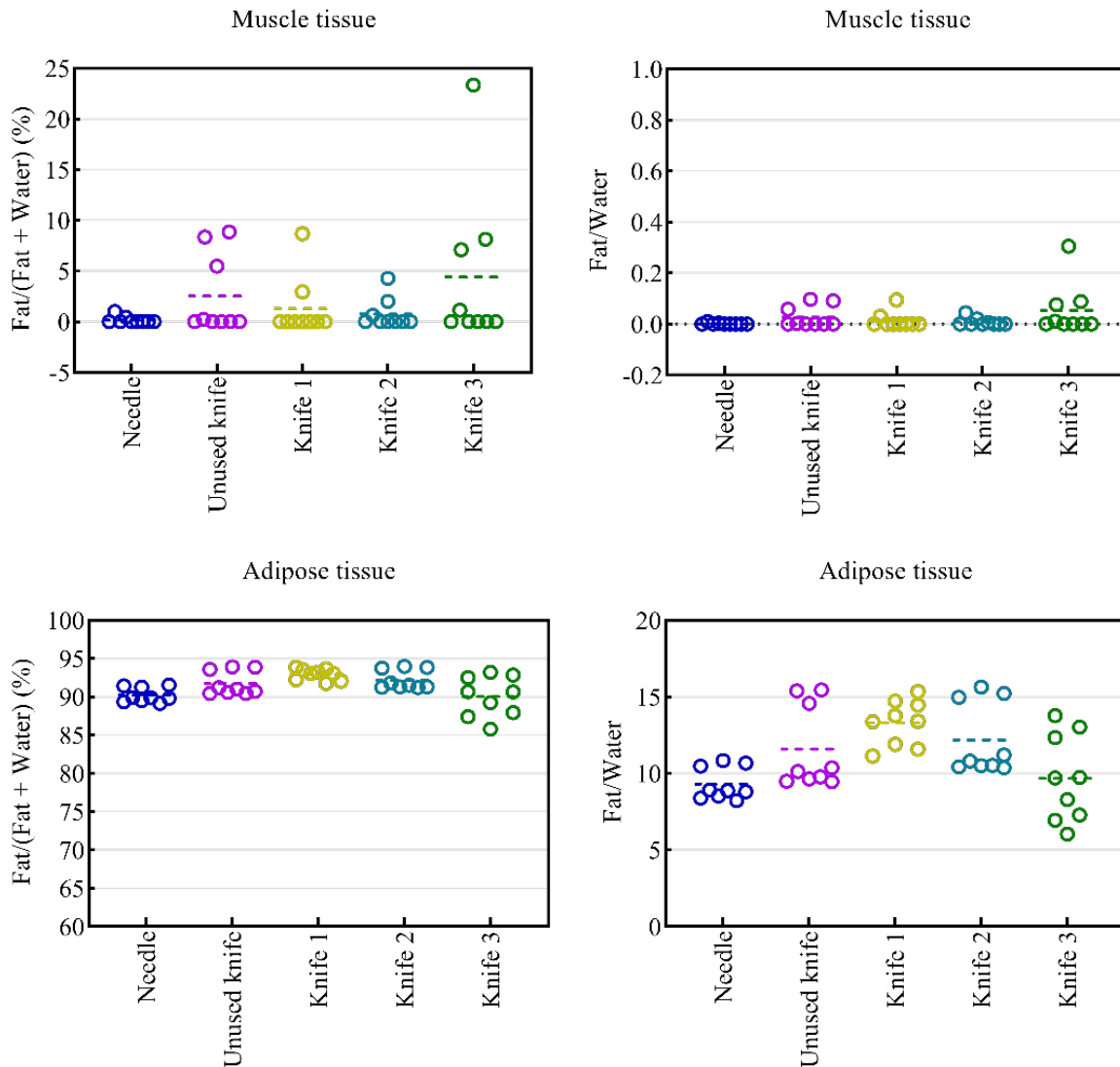


Figure 2. Showing Fat/(Fat+Water)% and Fat/Water ratio of the porcine muscle and adipose tissue using the DRS needle, unused knife, and contaminated knives. The dashed line shows the median of the measurements.

3.2 Cutting and DRS measuring on layered phantom

The layered phantom, used to cut through with a clean DRS equipped electro-surgical knife and perform DRS measurement using steps of 2 mm, is shown in Figure 3A. The Fat/(Fat+Water) and Fat/Water of each measurement (three measurements per location) per point of measurement are shown in Figure 3B. The clear transition from starting inside the fibroglandular layer with 40% fat to the tumor with the 20% fat is visible from the Fat/(Fat+Water) and Fat/Water. This transition is also visible while cutting from tumor layer with 20% fat into the adipose layer with 50% fat. Moreover, these numbers indicate that it is possible to determine when the knife is close to the border of the layers. Depending on the type of the tissue, the Fat/(Fat+Water) and Fat/Water values are gradually increasing or decreasing until it reaches the boarder of the two layers.

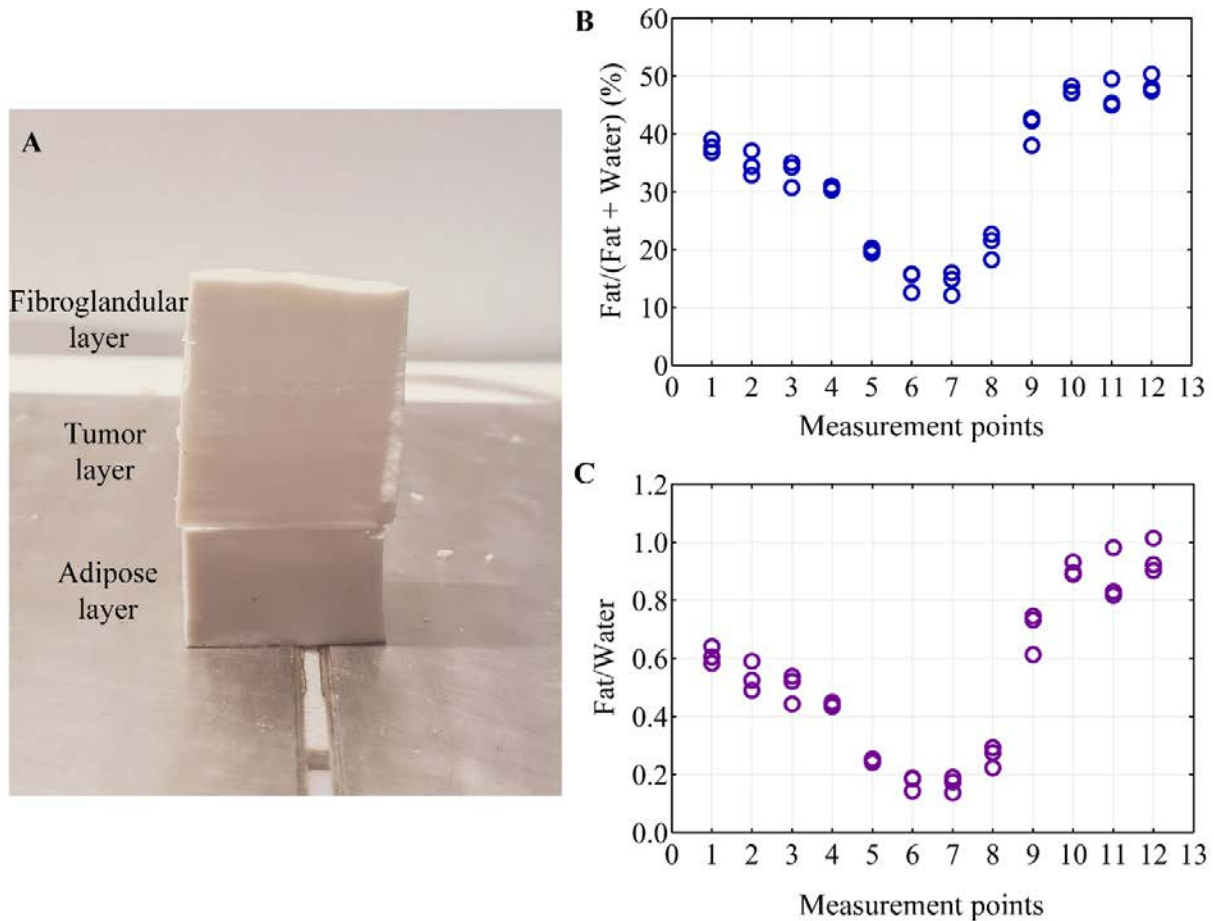


Figure 3. (A) The layered phantom material consisting of fibroglandular (top), tumor (middle) and adipose (bottom) mimicking layer. (B) and (C) show the Fat/(Fat+Water)% and Fat/Water of the phantom extracted from the DRS equipped knife when cutting through this phantom and measuring after every step of 2 mm.

3.3 Breast conserving surgery on the breast mimicking phantom

Figure 4A shows the produced heterogeneous breast mimicking phantom laying on a return electrode pad of the electrosurgery unit. An X-ray image from the breast phantom, showing the tumors inside the phantom before surgery, is shown in Figure 4B. During surgery, the DRS setup was running constantly and the Fat/(Fat+Water) of each measurement was displayed on the monitor. Knowing that the Fat/(Fat+Water) of tumor tissue is around 20%, it was possible to distinguish the tumor tissue from other layers. As shown in Figure 4C, the X-ray image from the breast after the surgery confirms the complete tumor resection from the phantom. Figure 4C also shows the excised specimens, visible in bright white color (due to the Barium Sulfate) above the breast phantom.

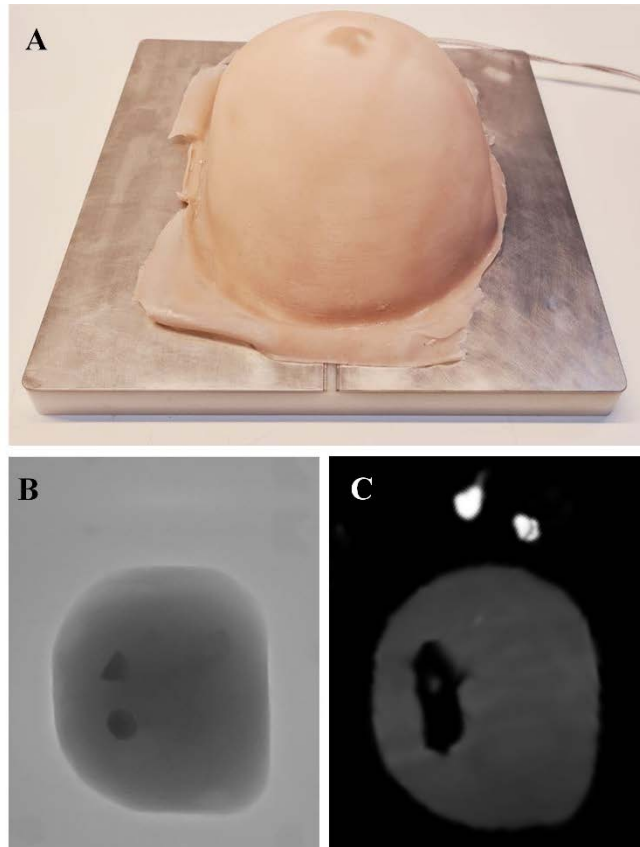


Figure 4. (A) The produced heterogeneous breast mimicking phantom. (B) X-ray scan of the breast phantom before performing the surgery showing the tumors and their location. (C) X-ray scan from the phantom after the surgery. The two excised tumors from the phantom are shown in white above the phantom and the black area inside the breast phantom shows the hole formed after removing the tumors.

4 DISCUSSION AND CONCLUSION

With the increasing number of women diagnosed with breast cancer in its early stage, it is more likely that breast conserving surgery becomes more and more common in the therapeutic process of breast cancer. In BCS more adaptable and meanwhile effective newfound margin detection techniques are demanded to ease not only the workflow of the surgery for the operation room personnel but also increase the satisfaction and comfort of the patient. Using a reliable margin detection technique would help the surgeon to find the tumor border clearly which can lead to complete tumor resection and decreased rate of the re-excision surgery [4, 5]. Recently it has been shown that DRS is a promising margin assessment technique which enables real-time tumor detection based on optical properties of the tissue [8]. The Electrosurgical knife is widely used by surgeons during this type of surgery to cut/coagulate the tissue and remove the tumor from the breast. So combining an electrosurgical knife with DRS seems to be an effective way to include the DRS in the workflow of cancer surgery [13, 14]. In this research, the effectiveness of a DRS equipped electrosurgical knife in real-time tumor margin detection during breast conserving surgery was investigated. First, the effect of using quartz tube, as a protective shield against the high-temperature heat produced during the electrosurgery, on the DRS measurements from the porcine muscle and adipose tissue was studied. Moreover, three sets of used (to cut the porcine tissue) DRS equipped knives (Knife 1, Knife 2 and Knife 3 in Figure 2.) which had debris attached to the quartz tube, were used for the DRS measurements from the fresh porcine tissue. The results (Figure 2) demonstrate that the quartz tube itself did not change (increase) the mean of the measured Fat/(Fat+Water) and Fat/Water of the muscle and adipose tissue significantly (p -value >0.9). This also applies to the Fat/(Fat+Water) and Fat/Water of the spectrum which were taken from the muscle and adipose tissue using the used knives (Knife 1, 2 and 3). In their work, Lisanne de Boer et al. showed that by considering a threshold for

the Fat/Water, it is possible to discriminate the tumor tissue (Fat/Water less than the threshold) from healthy tissue (Fat/Water more than the threshold) in breast. This threshold is different for each patient and can be determined at the beginning of the surgery by taking some spectra from the healthy tissue of the patient [15]. From Figure 2, it can be seen that although presence of quartz tube or contamination might change the Fat/Water slightly, the differences between Fat/Water of the adipose (Fat/Water <1) and muscle (Fat/Water >5) tissue is still large and we can clearly consider a Fat/Water threshold for discriminating the muscle tissue from adipose tissue. Hence, none of these effects is expected to affect the tissue discriminating power of the DRS equipped knife significantly. This is also verifiable in the outcome of the experiment in which the DRS measurements were taken during cutting the layers of the breast phantom. In Figure 3, the clear transition from the fibroglandular to the tumor tissue mimicking layer and from tumor tissue to adipose mimicking layer is noticeable. From the Fat/Water measurements of the tissue layer, it is even possible to determine during cutting whether the knife is coming close to the border of the tumor tissue or not.

Performing breast conserving surgery on the breast mimicking phantom also confirmed the effectiveness of the DRS integrate knife in detecting the tissue while cutting it. In this semi-realistic setup the spectrum was acquired constantly from the tissue and the Fat/(Fat+Water) of each spectrum was calculated and shown on the monitor. Knowing that Fat/(Fat+Water) of $\approx 20\%$ is associated with tumor tissue, it was possible to detect the border of the tumor and resulting in a complete tumor resection. The X-ray image from the breast phantom confirms the complete tumor resection. Although this setup is not simulating the realistic breast conserving surgery, the outcome shows that the technique has the potential to be used as an intra-operational margin assessment device during this kind of surgery. For final confirmation of the effectiveness of the DRS equipped electrosurgical knife, further experiments are necessary to take place, such as investigation of the device performance on replicated surgeries in collaboration with surgeons who can simulate the surgery more closely to the reality. Also, the excised specimens should be investigated more accurately to investigate whether we have a negative margin (or 2mm of healthy tissue around the tumor in all direction) or not. Therefore, more elaboration in this part of the research is still needed to make the device ready for the clinical application. In conclusion, the results of this research demonstrate that the DRS equipped electrosurgical knife is a promising device for simultaneously distinguishing and cutting the tissue, thus it has the potential for being used as a real-time tumor margin assessment device during BCS.

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