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Original article

Optical segmentation of unprocessed breast tissue for margin assessment

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ABSTRACT

Visual and tactual examination of unprocessed breast specimens is the standard for intraoperative surgical margin assessment in the United States. However, this procedure does not provide surgeons or pathologists with microscopic views of the tissue, which makes it difficult to accurately assess margin status or the extent of the disease, especially in non-palpable cases. We use a combination of spectral and polarization macroscopic imaging to optically segment the adipose and collagen tissues thus highlighting regions suspected of containing epithelium in order to facilitate optical microscopy techniques. A small study on five lumpectomy and mastectomy samples showed a sensitivity of 70% ± 20% and specificity of 50% ± 10% for adipose segmentation and a sensitivity of 50% ± 20% and specificity of 50% ± 20% for collagen segmentation. This sensitivity and specificity are sufficient for providing morphological information to the pathologist in order to guide microscopic examination of regions likely to be of clinical significance.

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Introduction

In the United States, breast conserving surgery (BCS) is a common course of treatment for women with non-palpable cancerous breast lesions. While BCS is less invasive, has a shorter recovery time, and has less of an emotional impact on the patient, there is a higher possibility of local recurrence if all the cancer is not removed or if the margins are close or positive [1]. Silverstein reports that for initial diagnosis of ductal carcinoma in-situ fifty percent of local recurrences are invasive carcinoma, which require aggressive treatment, lymph node sampling, and often mastectomies [2]. This highlights the importance of intraoperative margin assessment, which can determine close or positive margins and prevent the need for re-excisions. Current intraoperative pathology procedures rely on visual and tactual examination of breadloafed breast specimens and do not offer pathologists a microscopic view of the tissue structures. At University of Rochester Medical Center (Rochester, NY) the standard protocol is for the tissue to arrive fresh (not fixed or frozen) to pathology, the margins are painted using tattoo inks or India ink, then the specimen is breadloafed into 5 mm thick slices and examined visually and tactually for intraoperative margin assessment. Evaluation of margins in this way without microscopic examination can be extremely difficult. In some studies, the gross pathological examination of breast specimens during surgery has been shown to be accurate only 50% of the time [3]. In addition, using current methods of pathological examination, re-excision rates of around 38% have been reported, though they vary from institution to institution [4].

Some institutions perform intraoperative frozen sections to allow for microscopic examination, but this method presents problems such as tissue artifacts and high additional cost. The high adipose content of breast tissue makes frozen sectioning difficult, and freezing also introduces nuclear and other tissue artifacts, thus resulting in slides that are considered inferior to traditionally fixed paraffin embedded “permanent” histologic slides [3].

An ideal situation for both patient and surgeon is one in which the pathologist could accurately assess the margins and the extent of the disease during the initial surgery instead of having to wait for the “permanent” slides to be created. With such a method, the surgeon could be directed to remove more tissue at the time of the initial surgery if margins were positive or close or, in the case of a

Abbreviations: BCS, breast conserving surgery; RCM, reflectance confocal microscopy; OCM, optical coherence microscopy; ASCO, American Society of Clinical Oncologists; CAP, College of American Pathologists; DCIS, ductal carcinoma *in situ*.

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larger or more extensive carcinoma than expected, perform a mastectomy with prior consent of the patient. Optical techniques such as diffuse reflectance spectroscopy [5,6] offer rapid methods of determining whether or not cancer is present within a couple millimeters of the surface margins of an intact specimen. However, such systems are low resolution (~1 mm) and only determine whether or not cancer is present grossly, they do not provide pathologist with an exact location of the cancer or a microscopic view of the cancer. Other optical methods such as reflectance confocal microscopy (RCM) and optical coherence microscopy (OCM) produce sub-cellular resolution images of unprocessed breast tissue but take 45 min to scan the surfaces of a breadloafed 30 mm specimen [7–11]. Since recent ASCO/CAP recommendations are that excised breast tissue be fixed in formalin within one hour [12], intraoperative use of RCM or OCM is impractical.

We present a method of optically segmenting the tissue into its main components (adipose, collagen, and epithelium) using intrinsic optical properties of the tissue. Nearly all breast cancers are derived from epithelial cells; therefore, detailed examination of adipose tissue or collagen is not necessary for clinical evaluation of specimens. In addition, adipose tissue and collagen can comprise as much as 60% and 30% of breast tissue, respectively [13]. Therefore, by identifying and eliminating regions of adipose tissue and collagen, rather than scanning the entire specimen the pathologist can guide microscopic examination to the areas likely to be of clinical interest. Adipose tissue and collagen both have intrinsic optical properties that make it possible to detect them without the use of exogenous contrast agents. By contrast, there currently is no imaging mode that is specific to epithelium without the use of exogenous contrast agents. We take advantage of the intrinsic optical properties of adipose tissue and collagen to optically segment the tissue. This information is used to generate a mask that, when overlaid on the macroscopic image of the tissue, can be used to provide morphological information to the pathologist that can be used on its own or for guiding intraoperative optical microscopy techniques. We identify regions of adipose tissue using color signatures that are unique to adipose in a white light image. Collagen structures have a unique birefringence signature that can be identified using polarization illumination and detection. Optical segmentation can be achieved from wide field of view images taken with a standard camera in conjunction with image processing algorithms. This technique requires less than 2–3 min of imaging and processing, making it a rapid tool viable for intraoperative use. In addition, these imaging modalities do not alter the tissue through the use of any exogenous contrast agents, meaning the tissue is still available for standard histological processing.

Adipose tissue in the human breast appears yellow, due to high levels of vitamin A, while fibroglandular tissue (which contains collagen and epithelium) appears white or gray-white. When imaged under white light illumination with a color sensitive (red, green, blue) detector, adipose has different green (G), blue (B), hue (H) and saturation (S) signals when compared to non-adipose regions. We exploit the differences in *B vs. G* as well as *S vs. H* to create metrics that determine areas of fat from surrounding tissue.

Collagen segmentation is achieved through polarization imaging. Collagen is constructed of proteins that arrange themselves into a structure made up of three polypeptide chains. These strands of collagen then organize themselves into fibrils, which are then organized into fiber bundles [14]. This banded structure of collagen, combined with the proteins that create it, give collagen form birefringence and intrinsic birefringence [15]. This unique property of collagen means that the polarized components of light will scatter differently from collagen tissue than from adipose tissue or epithelium.

Polarized light has been used to highlight collagen in tissue sections including use in the heart and in skin [16–18]. The ability to use polarized light to image skin pathology and to discern birefringent structures in tissue has been shown by Jacques et al. [19,20] and Yaroslavsky [21,22]. The tissue surface is illuminated with linearly-polarized white light and the diffusely scattered light is detected using an analyzer oriented parallel to the incident polarization and perpendicular. As with the white light imaging for adipose segmentation, the incident light is oblique to the surface normal, and detection is normal to the tissue surface to eliminate specular reflection. Fig. 1 shows the basic layout. During polarization imaging, the analyzing polarizer is rotated so that light parallel (I_{par}) and perpendicular (I_{per}) to the incident polarization are detected in two different images. Once the images associated with reflected parallel and perpendicular light from the tissue are detected, the pixel by pixel polarization ratio was calculated using the standard polarization contrast equation [23]:

$$POL = \frac{I_{par} - I_{per}}{I_{par} + I_{per}}. \quad (1)$$

The value of *POL* will range from −1 (light converted entirely to the perpendicular state) to +1 (all light maintains original polarization).

Since collagen is birefringent, it will exhibit a different *POL* signature than the depolarizing epithelium or adipose tissue. Purely depolarizing tissue will convert approximately equal amounts of light into the parallel and perpendicular states, giving a *POL* value of ~0, while birefringent structures will be closer to ±1. Pure epithelium is depolarizing; however, depending on the imaging resolution, the image may show cancer is a mixture of epithelial cells and an extracellular collagen network. Therefore, cancerous tissue may not present as depolarizing; it may present with a unique birefringent signature that can be used for segmentation. Furthermore, the reactionary or desmoplastic stroma that often surrounds cancer is strongly birefringent and can highlight cancerous regions in the tissue.

Color and polarization sensitive imaging can be combined to optically segment the tissue into regions of adipose tissue, fibrous tissue containing collagen, and regions suspected to be epithelium. In this study, our aim was to validate these methods of optically segmenting unprocessed breast tissue into its major components (adipose tissue and collagen). This information was presented to the pathologist in the form of masks overlaid on the image of the tissue, which were used to guide pathologists to regions of interest. We used a modified camera to take white light and polarization sensitive images of lumpectomy and mastectomy tissue samples and compared the resulting optical segmentation masks to the composition of the tissue based on reflectance confocal microscopy (RCM) mosaics and the resulting histology slides. The

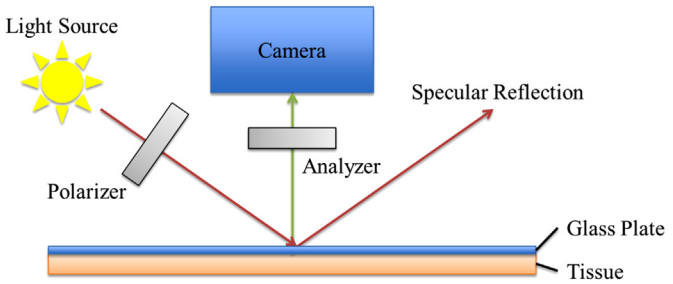

Fig. 1. Basic layout of birefringent imaging system for tissue. Polarized illumination is oriented oblique to the tissue surface. A polarizing analyzer is used for detection normal to the tissue surface.

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