Optical palpation for tumor margin assessment in breast-conserving surgery

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Abstract: Intraoperative margin assessment is needed to reduce the re-excision rate of breast-conserving surgery. One possibility is optical palpation, a tactile imaging technique that maps stress (force applied across the tissue surface) as an indicator of tissue stiffness. Images (optical palpograms) are generated by compressing a transparent silicone layer on the tissue and measuring the layer deformation using optical coherence tomography (OCT). This paper reports, for the first time, the diagnostic accuracy of optical palpation in identifying tumor within 1 mm of the excised specimen boundary using an automated classifier. Optical palpograms from 154 regions of interest (ROIs) from 71 excised tumor specimens were obtained. An automated classifier was constructed to predict the ROI margin status by first choosing a circle diameter, then searching for a location within the ROI where the circle was ≥ 75% filled with high stress (indicating a positive margin). A range of circle diameters and stress thresholds, as well as the impact of filtering out non-dense tissue regions, were tested. Sensitivity and specificity were calculated by comparing the automated classifier results with the true margin status, determined from co-registered histology. 83.3% sensitivity and 86.2% specificity were achieved, compared to 69.0% sensitivity and 79.0% specificity obtained with OCT alone on the same dataset using human readers. Representative optical palpograms show that positive margins containing a range of cancer types tend to exhibit higher stress compared to negative margins. These results demonstrate the potential of optical palpation for margin assessment.

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1. Introduction

Breast-conserving surgery (BCS) is one of the main treatments for early-stage breast cancer [1], however, 20–30% of patients must undergo more than one procedure due to positive margins on the excised specimen [2–7], which increases the risk to patient health [7–11], worsens cosmetic outcomes [7–12], and causes adverse socioeconomic effects [7,8,10,11]. Although histopathological intraoperative margin assessment techniques such as frozen section histology and imprint cytology can reduce re-excision rates by 9–36% [9,13,14], these techniques have not been widely adopted [15] due to the additional time (10–30 minutes) [16,17] and resources (e.g.,...
a specialized pathologist) [13] required and the broad range of reported sensitivities (59–100%), and specificities (71–100%) [9,16,17]. Another technique, specimen radiography, has had minimal impact on re-excision rates [14,17], in part due to the suboptimal diagnostic accuracy (33–66% sensitivity, 60–95% specificity) [9,16] and difficulties in detecting and interpreting calcifications [9,16,18]. More recently, a tool using radiofrequency spectroscopy (MarginProbe) has been approved for use in the USA, however, the reported sensitivity (70%) and specificity (70%) are relatively low [14,19]. Therefore, an effective intraoperative margin assessment tool is yet to be widely adopted.

Several optical imaging techniques, such as Raman spectroscopy, fluorescence imaging, and optical coherence tomography (OCT), are currently being investigated to improve intraoperative margin assessment [19]. In particular, OCT generates images based on differences in the optical backscattering of tissues in real-time, without the use of contrast agents and with relatively high spatial resolution (5–10 µm) [19,20], however, benign fibroglandular tissue and tumor tissue can sometimes appear similar in OCT images [20–24]. Another family of techniques, tactile imaging, visualizes the force applied across a sample surface (stress) as an indicator of tissue stiffness [25,26]. This relies on the same principle as manual palpation, in which the surgeon locates embedded lesions by applying a force to the tissue and feeling the resistance using their fingertip. Previous implementations of tactile imaging have utilized electronic sensors with the spatial resolution determined by the sensor spacing (typically ~1 mm) [27–33]. Our group has pioneered a novel form of tactile imaging, termed optical palpation [34], in which a uniform, transparent, silicone layer is compressed on the tissue surface and the resulting strain (i.e., the relative deformation of the layer) is measured with OCT. Using the pre-characterized layer stress-strain curve, a two-dimensional (2-D) stress map (termed an optical palpogram) can be generated, with greater stress indicating stiff tissue (e.g., tumor) [24]. Surgeons may then be trained to identify cancer from these images, which may be facilitated by an appropriate choice of colormap (e.g., a divergent colormap that provides contrast between stiff and soft regions) and applying the optical palpogram as a semi-transparent overlay over the OCT image to provide additional structural information. The spatial resolution of optical palpation has previously been shown to be 160–390 µm [24,34,35], which outperforms many previously developed tactile imaging techniques (0.8–2 mm) [27–33].

Optical palpation is expected to be particularly useful for breast cancer margin assessment because cancer alters the mechanical properties of tissue [36]. Surgeons currently utilize this to locate the tumor during surgery through manual palpation [16,37], however, this is subjective, and many breast lesions are clinically impalpable (i.e., too small or soft to be felt) [38]. Although the fingertip reportedly has a spatial resolution of 1.5–2.5 mm [39] in ideal conditions, lesions up to 15 mm in size may be impalpable [38], due to surgical gloves degrading both spatial resolution and the ability to detect mechanical contrast in the tissue [40]. With the enhanced resolution and decreased subjectivity afforded by optical palpation, however, such impalpable lesions may potentially be identified. Optical palpation is related to quantitative micro-elastography (an OCT-based imaging technique that generates a three-dimensional (3-D) tissue stiffness map) [41], however, a significant advantage of optical palpation is the potential for alternative implementations using more cost-effective imaging systems, which would facilitate uptake by medical institutions, particularly in lower resource settings. For example, our group has recently demonstrated camera-based optical palpation, which uses a simple digital camera to measure the silicone layer deformation [42]. Additionally, as optical palpation does not rely on the detection of optical signals directly from the tissue, it may be more robust and practical for surgical deployment, as it is not affected by factors such as blood at the tissue surface that can inhibit other optical imaging techniques, such as OCT. Whilst we have previously shown that optical palpation can provide contrast between benign fibroglandular tissues and tumor tissues [24], the sensitivity and specificity has not yet been reported.
In this paper, the diagnostic accuracy of optical palpation is assessed. Seventy-one BCS specimens were imaged and 154 optical palpation regions of interest (ROIs) (130 benign, 24 containing tumor within 1 mm of the margin) from 142 margins were generated. We additionally propose a classification algorithm to differentiate benign and malignant ROIs. An ROI is classified as malignant if, at any location within the ROI, a circle centered on that location contains high stress over \( \geq 75\% \) of its area. Sensitivity and specificity are calculated by comparing the predicted margin status from the automated classifier with the true margin status, as determined from co-registered histology. The performance of this automated classifier is assessed and optimized, and the results indicate optical palpation shows promise for intraoperative margin assessment.

2. Materials and methods

2.1. Patient recruitment and dataset construction

Seventy-one female patients undergoing breast-conserving surgery at Fiona Stanley Hospital (Project No: FSH-2015-032) in Western Australia were included in this study. Ethics approval was granted by the Sir Charles Gairdner and Osborne Park Health Care Group Human Research Ethics Committee (Lead HREC No: 2007–152) with all participants providing informed consent. One fresh tissue specimen was scanned per patient, with on average two margins scanned per specimen. Of these 71 specimens, final pathology showed 32 (45\%) had tumor within 1 mm of any margin, 36 (51\%) had tumor \( \geq 1 \) mm from any margin, and 3 (4\%) did not have any tumor.

A dataset containing 154 \( 10 \times 10 \, \text{mm}^2 \) ROIs was selected from 139 imaged margins. 174 ROIs were initially selected from the imaged margins (prior to reviewing the post-operative histology), with preference for regions with good contact between the specimen, layer and imaging window; no extensive thermal damage from cauterization during resection; and reliable histology available. After imaging, post-operative histology was obtained following the standard protocol at the institution, which involved fixing the specimen in formalin, inking to preserve orientation and slicing in a ‘bread-loaf’ manner to obtain histology slides in a plane orthogonal to the en face plane. These were co-registered with ROIs by consulting the specimen photographs and blocking diagrams (which indicated the corresponding tissue slice for each histology slide) and cross-checking features in histology with those in the OCT images, using the OCT depth cross section where needed. Following review of the histology with a pathologist, 20 ROIs were excluded for reasons including extensive thermal damage visible in the histology slides (3 ROIs), inconclusive histology slide co-registration (4 ROIs), imaging artifacts (4 ROIs), insufficient contact (3 ROIs), insufficient stress data in solid tissue regions (2 ROIs), tumor < 1 mm in size (2 ROIs), and presence of mucinous ductal carcinoma in situ (DCIS) (a rare form of cancer, for which insufficient samples were present) (2 ROIs). ROIs were assigned a true class of positive if any region with positive margins existed within the ROI, and a true class of negative otherwise. Positive margins are defined here as cancer < 1 mm from the surface as determined by pathologists from postoperative histology, which is the currently accepted surgical excision margin required at the clinical practice that we obtained specimens from and consistent with similar BCS diagnostic accuracy studies [43,44]. The pathologists were blinded to any optical palpation information. The final dataset of 154 ROIs (24 positives, 130 negatives) was also used in a recent reader study assessing the diagnostic accuracies of OCT and quantitative micro-elastography [22], thus enabling direct comparison between these modalities and optical palpation.

2.2. Imaging protocol and system

A Thorlabs Telesto II spectral-domain OCT system in common-path configuration with a superluminescent diode source (1300 nm center wavelength, 220 nm full width at half maximum bandwidth) was used for tissue imaging. 3-D volumes (C-scans) were constructed by combining...
2-D images (B-scans), which in turn consisted of a sequence of one-dimensional (1-D) scans in depth (A-scans). A Thorlabs LSM04 objective lens was used, providing measured axial and lateral resolutions (in air) of 5.5 µm and 13 µm respectively, and a field-of-view (in air) of 16 × 16 × 3.5 mm³. Wide-field benchtop scanning was implemented by placing the sample on a pair of orthogonal translation stages, enabling up to a 3 × 3 grid of subvolumes to be acquired per sample for a total field-of-view of ~45 × 45 mm². Each subvolume comprised 808 × 808 × 1024 pixels (xyz) after averaging. To apply compression, the sample was placed on a motorized laboratory jack and an imaging window (65 mm diameter) was fixed above the sample, such that raising the laboratory jack would press the sample against the imaging window. The imaging window was fixed parallel to the laboratory jack baseplate to minimize uneven compression from a tilted imaging window, since this could otherwise result in image misclassification. Further details on the imaging setup are provided in [23].

Prior to tissue imaging, a transparent, compliant silicone layer (~5 cm diameter) with uniform thickness (~500 µm) was manufactured from Wacker Elastosil P7676 (cross-linker catalyst mixing ratio 1:1). The mechanical characteristics (stress-strain curve) of the silicone were characterized using a uniaxial compression testing apparatus [34], and the undeformed layer thickness was measured with an OCT system. A new layer was used for each imaged margin. As the field-of-view was smaller than both the imaging window and the layer, conditions at the boundary of the imaging window and layer could be ignored, since only the central region was imaged.

Fresh BCS specimens (~1–4 cm thick) acquired immediately after surgery and kept hydrated with saline were imaged. The specimens were not trimmed to reduce geometric irregularity prior to imaging. During imaging, the silicone layer was placed on the tissue and lubricated with silicone oil (Wacker AK50) on the surface facing the imaging window, and the specimen was placed on the laboratory jack. The laboratory jack was then raised to apply bulk compression (~10–30% strain per specimen, 6.5% standard deviation) against the imaging window, which was fixed to an actuator to enable both quantitative micro-elastography images and optical palpograms to be generated from the same data. No mechanism was used to constrain the specimen laterally, such that it was free to expand during compression. As the compression force was distributed over the relatively large area of the imaging window, the specimen did not slip substantially during compression, even after applying saline and silicone oil. Each margin was imaged within nine minutes, and specimens were returned for standard histopathological processing within an hour of collection from surgery.

To ensure optical palpograms obtained from different specimens can be meaningfully compared, we controlled the bulk compression to be largely consistent between specimens. In particular, this allows comparable optical palpograms to be obtained from specimens with different thicknesses. The applied range of bulk compression was chosen to maximize contact with the imaging window and generate good contrast in quantitative micro-elastography images, while accommodating for variations in specimen surface topology.

To generate optical palpograms, a map of layer strain (defined as the change in layer thickness divided by the undeformed thickness) across the compressed tissue surface is measured by identifying the layer/tissue interface in each averaged B-scan using an automatic algorithm based on the Canny edge detector in post-processing [34]. Using the stress-strain curve, the layer stress due to bulk compression is determined to generate optical palpograms. Converting layer strain to stress enables an intuitive physical interpretation for optical palpograms as the force applied at each location on the surface of the specimen; additionally, non-linearity in the stress-strain curve results in additional contrast between stiff and soft features when converted to stress. If negative stress occurs in a region (for example, because the local layer thickness increases after compression, or the edge detector fails), a stress of 0 kPa is recorded. This procedure is illustrated in Fig. 1.
Fig. 1. Optical palpation working principle. Before imaging, a silicone layer with initial (relaxed) thickness $L_I(x,y)$ is placed on the tissue and bulk compression is applied. For each OCT B-scan (a), the layer/tissue interface is detected, allowing the final (compressed) layer thickness $L_F(x,y)$ to be measured and the en face map of layer strain (b) to be computed. This is then mapped to stress, presented in the optical palogram (c), using the pre-characterized layer stress-strain curve. Scale bars = 1 mm.

2.3. Data processing and analysis

To assess the sensitivity and specificity of optical palpation, a classifier algorithm was constructed to predict whether an ROI contained cancer in the margin based on the stress map, and the prediction was compared to the true margin status as determined by co-registered post-operative histology. Essentially, the classifier predicts an ROI is positive if a circle $\geq 75\%$ filled with high stress can be found anywhere in the ROI, for a given circle diameter and stress threshold. More concretely, the optical palpograms are first binarized by setting all pixels greater than or equal to the stress threshold to one, and all other values to zero. These images are then convolved with a circular kernel such that the output of the convolution indicates the fraction of the circle filled with “ones” at the corresponding location, and if any output is $\geq 75\%$, the ROI is predicted to be positive. A 75% threshold was chosen to match the criteria used for both manual and automated classification in a previous study assessing the accuracy of quantitative micro-elastography [22].

Two variants of this classifier were tested: the first is exactly the algorithm described above, whereas the second includes a prefiltering step in which stress outside regions of dense tissue (identified from an en face OCT image at a single plane $\sim 100 \mu m$ below the surface using an intensity-based segmentation algorithm detailed previously) [45] is filtered out (i.e., set to 0 kPa). The main steps performed by the segmentation algorithm to generate a dense tissue mask from the OCT image were noise removal, intensity thresholding, removal of connected components in the binary image with $< 200$ pixels, and clean-up by applying morphological closing to fill in small holes. The removal of non-dense tissue regions from optical palpograms was motivated by the observation that false positives tend to occur due to high surface stress in regions with adipose tissue at the surface (possibly due to tumor just outside the margin, as illustrated in Fig. 2), as well as artifactual high stress due to layer edge misdetection in regions of poor contact between the layer and tissue surface. Additionally, the layer edge detection algorithm was less reliable in adipose tissue compared to dense tissue, since the layer interface with adipose tissue often
exhibited lower intensity in OCT than that with dense tissue; furthermore, the honeycomb texture of adipose tissue sometimes confused the edge detection algorithm. The classifier is illustrated by the flowchart in Fig. 3(a).

Fig. 2. Optical palpation in adipose tissue. All optical palpograms are shown overlaid over the en face OCT image ∼100 µm below the tissue surface. (a) Example of an ROI that is classified as a true negative whether or not non-dense tissue is removed. Histology for this ROI (d) shows mostly adipose tissue and no tumor below this ROI. (b) Example of an ROI that is classified as a false positive when non-dense tissue is not removed but becomes a true negative when non-dense tissue is removed (c). Histology for this ROI (e) shows a large tumor is present ∼7.3 mm from the tissue surface, with mostly adipose tissue close to the surface. Histology was taken in a plane orthogonal to the en face view at the location and orientation indicated by the dashed red lines. A, adipose tissue; S, stroma tissue; T, tumor tissue; D, ducts; V, vessels. Scale bars = 1 mm.

To optimize the classifier performance, a range of input parameters (circle diameter and stress threshold) were tested. The circle diameters ranged from 0.1 mm to 2 mm in increments of 0.1 mm. For each circle diameter, a receiver operating characteristic (ROC) curve was constructed by varying the stress threshold and plotting sensitivity against (1 − specificity). To determine the stress thresholds, for each circle diameter and each ROI, the maximum stress threshold below which the ROI would be classified positive was calculated. Choosing the stress thresholds in this way removes sampling error from the ROC curves, which would likely be present if a linearly spaced sequence of stress thresholds were used instead. The optimum circle diameter is obtained by maximizing the area under the ROC curve (AUC), and the optimum stress threshold is obtained from the point on the optimum ROC curve that is closest to the top-left corner (which represents perfect classification). The classifier optimization procedure is summarized in the flowchart in Fig. 3(b).

To indicate the potential classifier performance on an independent dataset, leave-one-patient-out cross-validation was performed. Specifically, in a single iteration of cross-validation, all ROIs from a single patient are assigned to the validation set, and all remaining ROIs are assigned to
Fig. 3. (a) Flowchart illustrating the classifier algorithm. The classifier was tested both with and without a prefiltering step to remove non-dense tissue regions (indicated by the gray dashed box). The progress of an example positive ROI through the classifier pipeline is shown below the flowchart. The stress threshold used in this example was 7.04 kPa (indicated by the red triangle on the color scale), and the circle shown on the binary image has a diameter of 1.1 mm. (b) Flowchart illustrating the classifier parameter optimization procedure used to determine the optimum circle diameter and stress threshold (and, hence, optimum sensitivity and specificity). OP, optical palpation. Scale bars = 3 mm.

the training set. The optimum classifier parameters are calculated by applying the previously described method to the training set, and the optimum classifier is then applied to the validation set. This is repeated 71 times, with the ROIs from each patient comprising the validation set exactly once. As each ROI is tested once, randomization of the training and validation sets is not applicable. The final reported optimum circle diameter, stress threshold, sensitivity and specificity are the average of the results over all ROIs. All data processing and analysis was done using MATLAB R2016A.

3. Results

Figure 4 shows four representative optical palpograms for several tissue types. Each optical palpogram is presented as a semi-transparent overlay in dense tissue regions of the corresponding en face OCT image at \( \sim 100 \) \( \mu \)m depth. Figure 4(a) shows an example of a negative margin in a region of dense stroma (validated by histology in Fig. 4(c)), in which the stress appears relatively homogeneous and low. This is distinct to the stress above positive margins (Figs. 4(b), 4(e), and 4f), each of which exhibits regions of elevated stress of varying degree and distribution, depending on the cancer type. For example, Fig. 4(b) shows a positive margin containing invasive ductal carcinoma (IDC) (validated by histology in Fig. 4(d)), which exhibits a large region of very high stress corresponding to the location of the tumor. By comparison, DCIS embedded in benign dense tissue (Fig. 4(e), with histology in Fig. 4(g)) corresponds to a much smaller region of moderately elevated stress. Although the contrast in DCIS appears lower than in
IDC, with an appropriate choice of stress threshold and circle size, DCIS may nonetheless be identified in optical palpograms, demonstrating how this technique may be sensitive to even small tumors. The additional contrast gained by optical palpation over OCT in Fig. 4(e) has been quantified by measuring the OCT signal and stress in the tumor and benign regions, indicated by the regions along the red line between the black bars and white bars, respectively. Only dense tissue regions were included in this calculation, and values are reported as mean ± standard deviation. In OCT, the signal in benign regions and tumor regions was 22.15 ± 4.95 dB and 20.62 ± 5.37 dB, respectively, indicating tumor and benign tissue are indistinguishable in OCT in this case. However, in the optical palpogram, the stress in benign regions and tumor regions was 4.15 ± 1.13 kPa and 8.99 ± 1.19 kPa, respectively, illustrating that optical palpation can provide contrast between tumor tissue and benign dense tissue regions. Finally, Fig. 4(f) shows an example of mucinous carcinoma. Here, high stress is visible in the region corresponding to the pools of mucin, which may be a result of fluid pressure caused by the mucin.

To demonstrate the relationship between tumor depth and stress, Fig. 5 shows boxplots describing the stress distribution above regions with tumor < 1 mm from the surface compared to stress above regions with tumor either ≥ 1 mm from the surface or absent. The stress above regions with tumor < 1 mm from the surface was obtained from positive ROIs. Since a typical positive ROI could contain regions where tumor was ≥ 1 mm from the surface, the stress corresponding to only regions with tumor < 1 mm from the surface was obtained by averaging the stress in a sliding 0.6 mm diameter circular window throughout the ROI, then taking the maximum of this average for each ROI. The window size was chosen to match the optimum circle diameter for the unfiltered optical palpograms (see Table 1). To ensure fair comparison with regions where tumor was ≥ 1 mm from the surface or absent, this procedure was also used to obtain the negative ROI stresses. From these boxplots, the median and interquartile range of the stress in regions with negative margins appears lower than that in regions with positive margins, although there is a large overlap over the extent of the boxplot whiskers (representing the range). The statistical significance between the two populations was assessed using the Wilcoxon rank-sum test (also known as the Mann-Whitney U test or Mann-Whitney-Wilcoxon test), which test the null hypothesis that two populations have equal medians. This was chosen instead of other common tests (e.g., Student’s t-test) because it does not assume the populations are normally distributed. The population medians were thus found to be different to a statistical significance of P < 3.4 × 10⁻⁷. Therefore, in this dataset, regions above tumor < 1 mm from the surface exhibited a statistically significantly higher stress than regions with tumor ≥ 1 mm from the surface or absent.

| Table 1. Optimum diagnostic accuracies and classifier parameters. |
|-------------|-------------|-------------|-------------|
|             | Sensitivity | Specificity | AUC     | Circle diameter [mm] | Stress threshold [kPa] |
| Optical palpation | 83.3%      | 73.8%       | 0.847 | 0.6       | 12.55          |
| Optical palpation (dense tissue only) | 83.3%      | 86.2%       | 0.908 | 1.1       | 7.04           |
| Quantitative micro-elastography | 100.0% | 97.7%       | 1.0   | 26.3       |
| OCT (human reader study) | 69.0% | 79.0%       |       |           |

*Leave-one-patient-out cross-validation

|             | Sensitivity | Specificity | AUC     | Circle diameter [mm] | Stress threshold [kPa] |
| Optical palpation | 75.0%      | 74.6%       | 0.61 ± 0.05 | 12.60 ± 0.53 |
| Optical palpation (dense tissue only) | 75.0%      | 86.2%       | 1.12 ± 0.13 | 7.04 ± 0.21 |

*From [22].

*For quantitative micro-elastography, stress refers to the local tissue elasticity [41].

*Mean ± standard deviation.
Fig. 4. Examples of optical palpation images overlaid on dense tissue regions of *en face* OCT ~100 µm below the tissue surface for ROIs containing only benign stroma (a), IDC (b), DCIS (e), and mucinous carcinoma (f). Corresponding histology is shown in (c), (d), (g) and (h). Histology was taken in a plane orthogonal to the *en face* view at the location and orientation indicated by the dashed red lines. For (e), regions along the red line between the white bars indicate the regions used to measure the OCT signal and stress in benign dense tissue, and regions along the red line between the black bars indicate the regions used to measure the OCT signal and stress in tumor tissue. S, stroma; IDC, invasive ductal carcinoma; DCIS, ductal carcinoma *in situ*; MC, mucinous carcinoma. Scale bars = 1 mm.
The results of both classifier variants on the 154 ROIs using a range of circle diameters and stress thresholds are summarized by the AUC plots in Fig. 6(a) and the optimum ROC curves in Fig. 6(b). In each of the AUC plots, a global peak can be identified corresponding to the optimal diameter (indicated by the triangles). When only dense tissue regions are included in the optical palpograms, the AUC plateaus after \(\sim 0.7\) mm, indicating circle size has little effect on the classifier performance after this point. In particular, although the optimum circle diameter increases from 0.6 mm to 1.1 mm after excluding non-dense tissue, similar performance (as indicated by the AUC) can be achieved with a circle size as small as 0.7 mm. The ROC plots show that excluding non-dense tissue regions enables the plot to more closely approach 100% sensitivity and specificity, indicating improved classifier performance. The optimum stress threshold, sensitivity, and specificity for each classifier variant is indicated by a cross marking the point closest to the top-left corner.

The optimum sensitivities and specificities (and corresponding AUC, circle diameter and stress threshold) are summarized in Table 1. The optimum sensitivity and specificity of the basic optical palpation classifier are 83.3% and 73.8%, respectively, obtained using a circle diameter of 0.6 mm and stress threshold of 12.55 kPa. Pre-filtering non-dense tissue increases specificity to 86.2% by reducing false positives due to high stress in adipose tissue and artifactual high stress in non-contact regions. Filtering out these regions also increases the optimum circle diameter (1.1 mm compared to 0.6 mm) and reduces the optimum stress threshold (7.04 kPa compared to 12.55 kPa). However, since pre-filtering non-dense tissue regions causes classifier performance to plateau after \(\sim 0.7\) mm (Fig. 6(a)), this variation in optimum classifier parameters may be a result of the classifier optimization procedure, rather than a change in the optical palpograms. To provide some context for these results, the sensitivity and specificity of optical palpation with dense tissue regions filtered out are lower than those of quantitative micro-elastography (100.0% and 97.7%, respectively), but higher than those of OCT (69.0% and 79.0%, respectively), when tested on the same dataset. The diagnostic accuracy of OCT shown here is also similar to that reported by others in previous studies [44]. The method used to obtain the quantitative micro-elastography and OCT results has been described in detail previously [22]; briefly, quantitative
micro-elastography images were classified by searching for regions where a 1 mm diameter circle was \( \geq 75\% \) filled with elasticity above 26.3 kPa, whereas OCT images were classified by seven human readers based on criteria including the presence and organization of solid tissue, the continuity of solid tissue with depth, and the presence of mucin. The lower accuracy of optical palpation compared to quantitative micro-elastography is expected, since quantitative micro-elastography generates more information than optical palpation (a 3-D map of tissue stiffness in quantitative micro-elastography images, compared to the 2-D map of layer stress in optical palpograms), albeit with more demanding costs (financial, hardware, software, and time), both during acquisition and processing. However, the benefit of the additional contrast provided by optical palpation compared to OCT is also reflected in the superior performance.

Leave-one-patient-out cross-validation decreased sensitivity by 8.3\% from 83.3\% to 75.0\% for both the basic and non-dense tissue excluded classifiers, which corresponds to an additional two of the 24 positive ROIs becoming false negatives. This occurs because the dataset contains only two examples of tumor exhibiting a small, concentrated region of high stress. When either of these ROIs are used for testing (i.e., they are excluded from the training set), the circle diameter increases and stress threshold decreases, causing them to be misclassified (since the small region of high stress is not large enough to fill 75\% of the increased circle diameter). Therefore, including more positive ROIs would likely improve the cross-validated sensitivity. However, cross-validation had practically no effect on the specificity, and the classifier parameter standard deviation is small, suggesting that application of this classifier, with the optimum parameters found here, to an independent dataset may yield a similar specificity to that achieved in this study. It should be noted that while the cross-validated results provide an indication of the classifier performance on an independent dataset, they do not indicate the diagnostic accuracy of applying the classifier with the stated parameters to the dataset in this study; this is indicated by the non-cross-validated results.

4. Discussion

In this study, the diagnostic accuracy of optical palpation for detecting tumor < 1 mm from the tissue surface in 154 ROIs taken from BCS specimens was measured for the first time. A classifier based on simple thresholding and convolution was proposed and optimized for this...
ROI dataset, with leave-one-patient-out cross-validation performed to assess generalizability to an independent dataset. Two variants of this classifier were tested to evaluate whether the diagnostic accuracy could be improved by filtering non-dense tissue regions. 83.3% sensitivity and 86.2% specificity were achieved using a circle diameter of 1.1 mm and stress threshold of 7.04 kPa with non-dense tissue regions filtered. To support these findings, representative images of optical palpograms in regions containing benign stroma, IDC, DCIS, and mucinous carcinoma were presented. Additionally, an analysis of the stress distribution showed that the stress above positive margins was higher than that above negative margins to a statistical significance of $P < 3.4 \times 10^{-7}$.

For the optimum classifier parameters (1.1 mm circle diameter, 7.04 kPa stress threshold, and non-dense tissue filtered out), there were four false negatives and 18 false positives. Of the false negatives, three contained DCIS and one contained mucinous carcinoma. One of the DCIS cases contained multiple small regions with high stress (> 7.04 kPa), however these were too small (~0.7 mm diameter) to be classified positive using a 1.1 mm circle diameter. This suggests DCIS and mucinous carcinoma may be more challenging to identify in optical palpograms compared to IDC (since all IDC ROIs were correctly classified), perhaps because regions of DCIS or mucinous carcinoma may often be smaller or softer than IDC. Of the false positives, 15 were classified positive due to regions > 1.1 mm in diameter with stress only slightly above the threshold (<3 kPa above 7.04 kPa). This suggests specificity could be increased substantially by a small increase in stress threshold, although at the expense of sensitivity.

In this study, a fixed threshold of 75% was chosen for the minimum percentage of the circle required to be filled with high stress to result in a positive classification. This threshold was based on the criteria used in a previous study on the diagnostic accuracy of quantitative micro-elastography [22]. It is possible that changing this threshold criterion could affect the sensitivity and specificity. For example, requiring the circle to be 100% filled could bias the algorithm to classify ROIs as negative, since then a single pixel below the high stress threshold within the circle would cause a negative classification. This could potentially significantly degrade sensitivity, especially for cases using a large circle diameter, high stress threshold, or excluding non-dense tissue. Assessment of the impact of the circle percentage threshold on sensitivity and specificity could be a possible direction for future study.

The optical palpation technique presented in this manuscript is still at an early stage, and as such the results presented here demonstrate proof-of-principle rather than a clinical study. While this paper has presented an assessment of optical palpation on excised BCS specimens, one future research avenue of great interest towards clinical application would be implementing and assessing optical palpation in vivo directly in the surgical cavity. Current margin assessment techniques have so far only been applied to excised specimens (indeed, histopathological techniques would be impossible to perform on in vivo tissue). However, direct assessment of the cavity would enable surgeons to directly locate residual tumor, thus avoiding the problem of co-registering the excised specimen to the cavity. Therefore, future research may involve developing and assessing optical palpation for in vivo applications.

The straightforward and practical nature of optical palpation provides several notable benefits. Unlike some elastography techniques, optical palpation does not require an actuator [41,46], decreasing the cost of the system. The removal of a moving mechanical part and associated electronics may also increase system robustness and, in the case of in vivo surgical cavity imaging, simplify probe design. Additionally, optical palpation requires less data compared to other elastography techniques, as optical palpation requires only a single measurement at each location, while alternative elastography techniques (such as quantitative micro-elastography) require multiple measurements to calculate displacement [46]. This may enable faster acquisition and processing times, which may be particularly desirable due to intraoperative time constraints; alternatively, the sampling density or field-of-view may be increased while maintaining the same
acquisition and processing times. Recently, our group have demonstrated optical palpation can be achieved without an OCT system using camera-based optical palpation [42], which uses a simple digital camera to measure the compression-dependent change in optical attenuation in a specially designed stress layer. This can generate optical palpograms with similar contrast and resolution to OCT-based optical palpation, while drastically reducing the cost of the system by a factor of $\sim 100$ compared to an OCT system (the camera and lens in total cost $\sim$ $800$ USD), and also significantly reducing data size and acquisition and processing times (since only 2-D images are captured, rather than 3-D OCT data) [42]. Developing camera-based optical palpation handheld probes could allow surgeons to image suspicious locations in the cavity in seconds; furthermore, the conceptual similarity between optical palpation and the routine practice of manual palpation may help reduce the training needed to operate such probes and interpret optical palpograms.

It should be noted that optical palpation does not enable direct measurement of the distance between tumor and the tissue surface; rather, the deeper a stiff tumor is embedded, the less visible it will be in the optical palpogram. This effect helps explain why regions above positive margins exhibit higher stress than regions above negative margins (Fig. 5), as well as how the reasonably high diagnostic accuracy of optical palpation was achieved. Additionally, the diagnostic accuracy reported here will vary with the definition of a positive margin (defined here as tumor within 1 mm of the excised tissue surface); furthermore, the optimal circle diameter and stress threshold would likely change, since the size and intensity of an embedded inclusion in an optical palpogram depends on the inclusion depth. Since OCT was used as the underlying imaging modality, the OCT image may also be used to ascertain the distance of tumor from the surface, and thus, through combination with optical palpation, potentially increase diagnostic accuracy, however, this was not done in this paper (although OCT images from a single plane $\sim 100$ µm below the surface were used for the non-dense tissue filter). Previous work in tactile imaging has also demonstrated “mechanical imaging”, in which a 3-D map localizing stiff lesions in breast tissue is generated from a 2-D force sensor array output and an initial model of the tissue structure [26,47]. In future work, this technique may also be applied to optical palpation to enable the margin distance to be estimated without needing an OCT system.

Our results show that, for our dataset, including only dense tissue regions generally increased specificity whilst having little effect on sensitivity. One potential explanation for this may be that benign adipose tissue can be distinguished from dense tissue with high confidence in OCT images [48–50]; therefore, excluding regions with adipose tissue at the surface results in the exclusion of some regions with no tumor at the surface. If these regions correspond to negative margins, excluding these regions removes the chance of false positives occurring (thus increasing specificity); however, if they correspond to positive margins (for example, due to cancer $< 1$ mm from, but not touching, the tissue surface), the likelihood of false negatives increases (thus decreasing sensitivity). It should be noted that as there has been an increasing trend towards only classifying “tumor on ink” (i.e., tumor touching the surface) as a positive margin for IDC [8], the reduced ability to detect tumor below the surface may not be too detrimental clinically (although a 2 mm margin is still recommended for DCIS) [51]. The improved performance for our classifier when only dense tissue is included indicates that, for our dataset, regions with adipose tissue at the surface are more likely to correspond to negative margins than positive margins. The improved performance after excluding non-dense tissue may also be partially attributed to the removal of artifacts in optical palpograms in which high stress was displayed in regions of non-contact (most often due to errors in the edge detection algorithm), further reducing the number of false positives detected. However, more data is needed to determine if the potential reduction in false positives achieved by excluding non-dense tissue outweighs the potential increase in false negatives across a larger dataset.

It should also be considered that optical palpation generates a map of layer stress, which increases with applied compression. By comparison, for ideal, linear elastic samples, techniques
that measure tissue stiffness are independent of bulk compression, however, for hyperelastic samples (e.g., breast tissue) [52] stiffness also increases with applied compression. Therefore, it is important to keep the applied bulk compression relatively constant between tissue samples. In this paper, bulk strain was maintained between \( \sim 10\% - 30\% \), which was sufficiently uniform to enable comparison between different scans. Alternatively, a larger bulk strain may be used to increase the visibility of tumors embedded in deeper regions. Additionally, in this paper, stress was estimated from layer strain using a simple 1-D model that is described by the stress-strain curve, but does not account for the effects of friction or lateral effects (i.e., changes in the stress-strain curve at a given lateral location due to compression at an adjacent location). The use of this simple model therefore likely results in some error in the stress estimate, however, this was minimized experimentally by applying lubricant between the stress layer and the imaging window to reduce friction. In future work, an improved model utilizing finite element analysis (termed “computational optical palpation”) may also be used to account for lateral effects, which has been shown to improve resolution [53].

One potential challenge facing optical palpation is the impact of surface topology variations on the resulting stress map. Highly variable surface topology may generate variations in the stress map, which may suggest the presence of a stiff inclusion that does not exist. To reduce this effect, we have designed the stress layer stiffness to match that of breast tumors. As a result, surface topology variations due to soft benign tissue do not cause significant deformation in the layer (thus not appearing in the optical palpogram), whereas stiff tumors still cause deformation in the stress layer and are thus visible. An experimental analysis of the effect of surface topology on the stress map in silicone phantoms has also showed that topology variations have little impact on stress compared to stiff features [35]. As a result, in this paper, surface topology variations did not seem to greatly affect the ability of optical palpation to detect stiff tumors, as demonstrated by the reasonably high diagnostic accuracy.

In conclusion, the diagnostic accuracy of optical palpation for identifying positive margins was found to be 83.3\% sensitivity and 86.2\% specificity using a dataset containing 154 ROIs taken from BCS specimens. This result was achieved using a classifier that searched for 0.6 mm diameter circular regions in optical palpograms with non-dense tissue filtered that were \( \geq 75\% \) filled with stress above 7.04 kPa. These results demonstrate the potential of optical palpation as a tumor margin assessment tool for BCS.

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