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Potential for Improved Thyroid Cancer Screening Aided by Multi-modal Clinical Ultrasound and Hybrid Diffuse Optics (LUCA Platform)

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Abstract: LUCA platform combines clinical ultrasound with near-infrared time-domain and correlation spectroscopies to improve thyroid cancer screening. We characterized its precision and classified thyroid nodules in a clinical campaign on 45 subjects.

1. Introduction

Thyroid cancer is the most common cancer type of the endocrine system, with more than 500 thousand new cases diagnosed annually worldwide. The detection is normally done through the ultrasound screening of thyroid nodules, which may suggest a follow-up or a fine-needle aspiration biopsy (FNAB) making up more than 2 million screenings per year in Europe. [1] However, both of these methods have limited sensitivity and specificity (10-87% and 58-96% respectively, depending on the type of nodule) resulting in a high number of ~150 thousand unnecessary surgeries per year in Europe and calling for new techniques to improve on these deficiencies. [1] Hemodynamic parameters are studied as candidates to improve the diagnosis. [2]

We have developed the LUCA device [3], a combination of clinical ultrasound (US) and two different near-infrared diffuse optical techniques: time-domain near-infrared spectroscopy (TD-NIRS) and diffuse correlation spectroscopy (DCS), to address this clinical problem. It is a collaboration of an international consortium of public photonic and biomedical research institutions, private high-technology companies and stake-holder end users (hospitals and patient groups).

We present preliminary results of a clinical campaign on n=45 subjects (12 healthy subjects and 33 patients with thyroid nodules), on which the LUCA device is able to measure local tissue hemodynamic parameters, such as blood oxygen saturation (StO2), blood flow (BFi) and total haemoglobin concentration (tHb), as well as water concentration and structural tissue information in terms of the reduced scattering coefficient (μ'_s). The results are analysed with the aim of improving sensitivity and specificity of thyroid cancer diagnosis with the use of a new set of biomarkers that can be gathered routinely in the US screening workflow.

2. Methods

LUCA operation and protocol. The optical sources and detectors of the LUCA device are arranged on an US probe allowing simultaneous US-guided acquisition of TD-NIRS (eight different wavelengths, two detection channels) [4] and DCS (one wavelength, sixteen detection channels). Furthermore, the platform includes a computational module based on NIRFAST [5], a finite-elements based forward/inverse solver for diffuse optics, for

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real time parameter recovery. The probe is utilized on at least four different positions on the neck with the use of a mechanical arm to prevent motion artifacts. Furthermore, all measurements are repeated twice. The positions include every distinct nodule visible in the US in addition to the left and right thyroid lobes (if any volume is nodule-free) and left and right sternocleidomastoid muscle, taking around 90 s per repetition.

Analysis. TD-NIRS data, i.e., the distribution of times of flight of photons inside the tissue are fitted with the analytical solution of the diffusion equation in the case of semi-infinite homogenous medium convoluted with the measured instrument response function. This allows to obtain values of absorption coefficient (μ_a), μ'_s as well as tHb and StO_2 for the probed tissue. DCS data are fitted using the analogue correlation diffusion equation and the μ_a and μ'_s values of TD-NIRS to find the tissue blood flow index (BFi).

Group results analysis is performed with linear mixed effect models and malignant-nodule detection is evaluated through receiver operating characteristic (ROC) curve analysis and logistic regression models.

3. Results and discussion

Data quality estimation. The precision and stability of the measurements were evaluated initially through measurements on phantoms and control subjects, i.e., volunteers with healthy thyroids. Coefficients of variation (CV) in a single placement of the probe in phantoms were found to be <1% for fitted TD-NIRS parameters (μ_a and μ'_s) and <6% for BFi. On clinical measurements, median CV values on thyroid (first quartile, third quartile) were found to be of 0.9% (0.5%, 1.5%) for μ_a, 0.5% (0.3%, 0.9%) for μ'_s and 3.9% (2.3%, 6%) for BFi. The values obtained are in line with or better compared to other state-of-the-art devices [6]. Minimum measurable differences for each parameter (95% confidence interval of the mean) on subject's thyroids are thus of $4x10^{-3}$ cm^{-1} for μ_a, $1x10^{-3}$ cm^{-1} for μ'_s and $5x10^{-10}$ cm^2/s for BFi.

Nodule classification. Logistic regression models have been used to find biomarkers for the classification of the nodules as benign or malignant. The subset of single-nodule patients (n=13), of clinical interest, shows a very good classification outcome. For these subjects a model including three variables correctly classifies all of the nodules (8 benign, 5 malignant). The model considers:

$$Malignancy \sim \mu'_s + BFi + StO_{2\ \mathrm{thy-mus}}, \quad (1)$$

where $StO_{2\ \mathrm{thy-mus}}$ is the difference in Oxygen saturation between nodule tissue and muscle tissue on the same side of the neck, which serves as reference value for each patient. The regression found a positive relationship between malignancy and μ'_s or BFi and a negative relationship between malignancy and StO_2 contrast. Figure 1 shows the values of these variables for nodules of single-nodule patients as well as their benign/malignant condition.

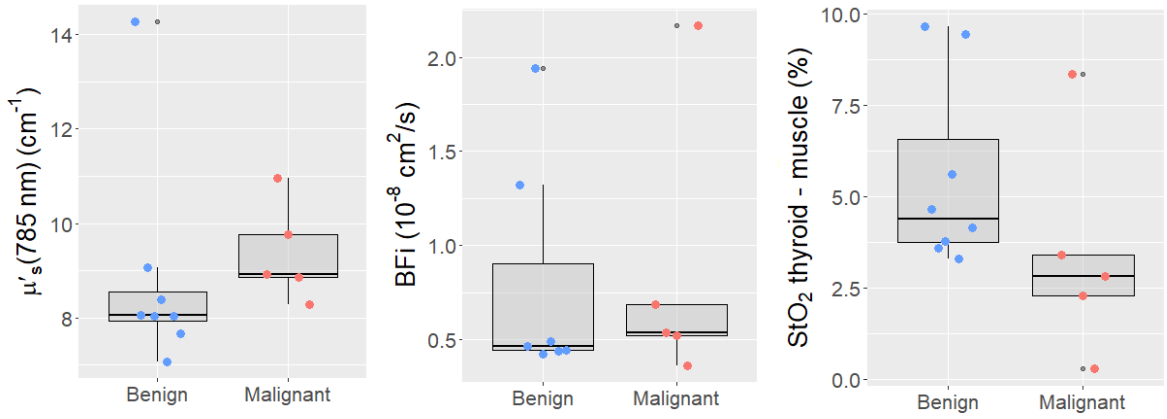

Figure 1. Boxplots for classification variables in logistic regression, measured in nodules of single-nodule patients: mean μ'_s, StO_2 thyroid-to-muscle contrast and BFi.

4. Conclusion

The preliminary measurements on the cohort of subjects presented has allowed us to determine the coefficients of variation and the measurable differences of the hemodynamic variables measured by the LUCA device, placing it in a good position with respect to other devices. In addition, a logistic regression model has been able to classify the nodules of single-nodule patients with 100% sensitivity and specificity, showing a promising start for further exploration towards complementing thyroid cancer screening. Additional biomarkers, such as lipid, water, collagen and thyroid-specific chromophore concentrations are being evaluated for further analysis on the increasing number of patients being recruited, in order to increase the power of the study for the general case of multi-nodular subjects.

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6. References

[1] Lindner et al., "Diffuse Optical Characterization of the Healthy Human Thyroid Tissue and Two Pathological Case Studies". PlosOne (2016)
[2] Sancak et al., "Comparison of Color Flow Doppler Sonography (CFDS) and Immunohistologic Detection of Microvessels for the Assessment of the Malignancy of Thyroid Nodules". Hormone and metabolic research. (2010)
[3] Cortese et al., "The LUCA device: a multi-modal platform combining diffuse optics and ultrasound imaging for thyroid cancer screening." Paper submitted to Biomed. Opt. Express. (2020)
[4] Renna et al., "Eight-Wavelength, Dual Detection Channel Instrument for Near-Infrared Time-Resolved Diffuse Optical Spectroscopy," in IEEE Journal of Selected Topics in Quantum Electronics. (2019)
[5] Dehghani et al., "Near Infrared optical tomography using NIRFAST: Algorithm for numerical model and image reconstruction" Communications in numerical methods in engineering. (2009)
[6] Giovannella et al., "Accuracy and precision of tissue optical properties and hemodynamic parameters estimated by the Baby Lux device: a hybrid time-resolved near-infrared and diffuse correlation spectroscopy neuro-monitor". Biomed. Opt. Express (2019)