Live Laser Microscopic Evaluation (OCT) of Radiation Induced Preclinical Alterations of the Skin in Head and Neck Cancer Patients

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Study protocol

Early detection of radiation-induced skin damage using Optical Coherence Tomography

1. Background

One of the unresolved issues in radiation oncology is the prediction of individual radiosensitivity of normal, tumor-free tissue. To avoid severe tissue reactions during and after radiotherapy, the concept of so-called "tolerance doses" has been established. Tolerance doses consider individual dose distributions in organs at risk and comorbid conditions but not individual radiosensitivity. Before radiation damage becomes clinically visible, molecular, cellular, and microscopic damage already occurs [1, 2]. Optical Coherence Tomography (OCT) is a promising technique to visualize such microscopic changes in the skin without biopsy and without additional ionizing radiation. Early detection and monitoring of such subclinical changes could contribute to understanding the pathophysiological effects of ionizing radiation. Correlations of observed changes with clinical side effects could enable early intervention and individualized dose prescription as part of personalized medicine in oncology.

2. Objectives

The aim of this project is to characterize skin damage that often occurs as a consequence of radiotherapy in the head and neck area and, in the long term, to develop a method to detect it early. OCT is to be established as a non-invasive examination method for this purpose. OCT allows early detection of structural defects in the skin (and capillary structures) caused by ionizing radiation during radiotherapy. The examinations are non-invasive; the technical basis is an optical (interferometric) procedure using a broadband, short-coherence laser in the near-infrared, allowing superficial penetration of radiation into the skin. No ionizing radiation is used. OCT imaging methods enable documentation of skin changes over the entire therapy period, including before and after care. These data should be used in the future for in vivo investigation of individual radiosensitivity of each patient. This individual radiosensitivity could serve as a biomarker for tolerance dose-oriented individual dose prescription.

Such image-based biomarkers, derived from non-invasive examinations and without biopsy, are of great interest in medicine and biology. In the future, such concepts could make a major contribution to personalized medicine.

3. Methods

Optical Coherence Tomography enables visualization of structures (interfaces, tissue changes, etc.) at approximately 1–2 mm depth [3]. Depending on the wavelength used by the OCT system, the skin layers can be differentiated into epidermis, the dermo-epidermal junction, dermis, and subcutis. A significant advantage of OCT is that lateral and axial resolution are independent of each other. Axial and lateral resolution for established OCT systems ranges approximately from 1 to 15 µm depending on the wavelength. Structural OCT can be functionally extended by additional units, e.g., angiographic or polarization-sensitive OCT, which utilize phase or birefringence properties.

This method has been standard in ophthalmology for many years, but it is also advancing in dermatology [4]. Among other things, it is already used for imaging skin layers and skin changes [5],

melanoma and non-melanoma skin cancer [6, 7], fibrosis and sclerosis of the skin [8], skin damage due to thermal [9, 10] and ultraviolet [11] radiation, etc. It has also been used to obtain quantitative biomarkers for scleroderma [12]. This broad application area alone in dermatology shows that it is a promising technique that could be routinely used in the future. This study aims to introduce OCT as a method for early detection of skin damage as a side effect of radiotherapy.

4. Technical aspects for device selection:

In dermatology, OCT is already used for non-invasive diagnosis of actinic keratoses, basal cell carcinomas, and squamous cell carcinomas of the skin to avoid biopsies [13, 14, 15]. Additionally, qualitative and functional information of the upper skin layers is obtained, and micromorphological details of the layers are visualized.

Thorlabs (Newport, NJ, USA) has played an important role in establishing OCT systems for clinical use. Both spectral domain and swept source OCT systems have been adapted for dermatological imaging. A recent development is small, handy (handheld) OCT systems that can be used flexibly and are our preferred choice.

For clinical dermatological applications, several handheld OCT systems are commercially available:

The Thorlabs Telesto OCT system with handheld scanner has a declaration of conformity extending beyond the laboratory (listed in the operating manual) but does not consider medical use.

Lumedica Labscope offers an interesting device variant with similar technical capabilities at a price point up to €10,000.

Depending on funding approval from the Cancer Aid Upper Austria, either the Thorlabs Telesto system will be rented from the project partner RECENCT, or the Lumedica Labscope system will be purchased. The latter option is preferred.

Regarding laser safety, the following points apply:

The Thorlabs Telesto OCT system with handheld scanner corresponds to laser safety class 1M according to manufacturer information. This means it is safe for the eye but can be dangerous when using optical aids (magnifier, glasses, etc.). Laser radiation is emitted as soon as the system is turned on.

The Lumedica Labscope is declared "eye safe, with a power on the sample of <750 microWatts" by the manufacturer.

Thus, no additional laser safety measures are necessary.

In general, study participants and personnel are informed to follow these guidelines:

- Warning: invisible laser radiation!
- Do not look into the optics of the scanner!
- Do not wear reflective jewelry/clothing! (Remove before examination!)
- Do not point the scanner at reflective objects!
- Always return the scanner to the designated holder!

5. Timeline:

To recruit at least 50 patients, a recruitment period of about 2 years is planned. Annual follow-ups up to 5 years post-radiotherapy are planned.

During radiotherapy, data collection using OCT for patients will occur at the following time points:

- Before the start of radiotherapy
- An early (predictive) time point in the first week of radiotherapy
- Weekly evaluations during radiotherapy
- 6 weeks after radiotherapy
- One year after radiotherapy

This schedule results in approximately 12 measurement time points per patient, depending on the prescribed dose fractionation.

6. Measurement sites:

- At the height of the irradiation isocenter (right and left neck side)
- 5 cm below the isocenter marking (right and left neck side)
- Inner side of the left forearm (unirradiated skin), 10 cm above the wrist

The positions of the measurement points will be measured relative to suitable anatomical landmarks (nose, lips, earlobe, etc.) during the first OCT measurement and recorded on a sketch attached to the data collection form.

These positions will be located again at every OCT data collection, so permanent skin marking is not necessary.

7. Additional data collection:

- Individual and total dose of therapy
- Concomitant chemo- or antibody therapy
- Tumor resection yes/no
- Neck dissection left, right, bilateral, or none
- Age
- Gender
- Body Mass Index
- Weight loss before radiotherapy
- Alcohol and tobacco consumption (pack-years, current smoker, ex-smoker)
- Type and extent of comorbidities and medications
- Concomitant enteral or parenteral nutrition
- HPV status (p16 positive/negative)

- TNM stage
- Toxicity according to CTC AE (version 5.0)

These data are collected before radiotherapy at the first OCT measurement session.

8. Inclusion criteria:

In general, all patients scheduled for radiotherapy in the head and neck area, regardless of sex and age, are eligible for the study.

Specifically, the following inclusion criteria apply:

- Squamous cell carcinoma of the pharynx, oral cavity, or larynx
- Unilateral or bilateral neck irradiation (+/- chemo or cetuximab)
- Definitive or postoperative radiotherapy (R(Ch)T)

9. Exclusion criteria:

- Manifest skin disease
- Previous radiotherapy in the head and neck area
- Lack of compliance

10. References:

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