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Original Research

Raman spectroscopy for assessment of bone resection margins in mandibulectomy for oral cavity squamous cell carcinoma

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Abstract ***Objectives:*** The aim of this study was to investigate the potential of Raman spectroscopy for detection of oral cavity squamous cell carcinoma (OCSCC) in bone resection surfaces during mandibulectomy.
Materials & methods: Raman mapping experiments were performed on fresh mandible resection specimens from patients treated with mandibulectomy for OCSCC. A tumour detection algorithm was created based on water concentration and the high-wavenumber range (2800 cm^{-1}–3050 cm^{-1}) of the Raman spectra.
Results: Twenty-six ex vivo Raman mapping experiments were performed on 26 fresh mandible resection specimens obtained from 22 patients.

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The algorithm was applied on an independent test set and showed an accuracy of 95%, a sensitivity of 95%, and a specificity of 87%.
Conclusion: These results form the basis for further development of a Raman spectroscopy tool as an objective method for intraoperative assessment of bone resection margins.

1. Introduction

Oral cavity squamous cell carcinoma (OCSCC) is the most frequent type of cancer in the head and neck region. The 5-year survival is around 50% [1,2]. Every year, 145.000 deaths are registered worldwide [3,4].

The primary treatment for OCSCC is surgery aiming at complete removal of tumour with an adequate resection margin [5,6]. During the operation, the surgeon decides where to cut based on preoperative imaging (CT, MRI), visual inspection and palpation of the tumour and surrounding tissues.

For OCSCC surgery, results obtained from two Dutch centres (Erasmus MC, University Medical Center Rotterdam and Leiden University Medical Center) showed inadequate soft tissue resection margins in about 85% of the cases [7]. Similar results were reported by the Harborview Medical Center and the University of Washington Medical Center in Seattle (USA) [8]. With respect to bone resection margins, studies have reported tumour-positive bone resections in 2–20% of the cases [9–12]. In addition, a retrospective study performed by our group showed that tumour-positive bone resection margins were found in 21% of the patients [13].

Adequate resection margins are paramount for disease control and survival: a number of studies have shown that 5-year disease-free survival decreases significantly when the margins are inadequate [7,9,14–19]. Ideally, all resection margins (soft- and bone tissue) should be controlled by intraoperative assessment. This would enable additional resection during the same surgical setting to ensure adequate tumour resection and a tumour-free wound bed for tissue transplants.

For soft tissue resection margins, the so-called frozen section procedure is available for intraoperative assessment [20–24]. The surgeon samples a piece of suspicious tissue from the wound bed and submits it for microscopic evaluation by the pathologist.

In contrast to soft tissue, for bone resection margins the assessment by frozen sections is virtually impossible [25–29], whereas histopathological information on the presence of tumour or free of tumour in the bone margins is available only after a few weeks [7].

The resection of advanced OCSCC with mandible involvement requires immediate reconstruction with microvascular-free flaps. By that time the wound is healed, which makes a second surgery undesirable [25–29]. Therefore, current histopathology does not contribute to more radical resections. During surgery, other than visual inspection, there is no routine intraoperative technique to evaluate the bone resection margins.

Recently, Nieberler *et al.* (2014, 2016) showed that intraoperative cytological assessment of bone resection margins can be used. This intraoperative approach was established and validated to assess bone specimens, including the inferior alveolar nerve. The technique revealed a sensitivity of 94.4%, a specificity of 97.4%, a positive predictive value of 85% and a negative predictive value of 99.1%. Although these results are very promising, this approach is not widely used. The authors mention a number of limitations of the technique. Desiccation of the bone margin caused altered cell morphologies, which led not only to false-positive results but also to false-negative results. In addition, the authors mention that insufficient cellular material or excessive trabecular bone material and the interference by blood cells resulted in low quality cytological preparations [28,29].

The use of Raman spectroscopy for intraoperative assessment of tumour resection margins is currently being investigated [30–32]. This optical technique is based on inelastic scattering of light by the molecules in the tissue and provides detailed quantitative and qualitative information about its molecular composition [30–34]. The technique can be used directly on tissue because it is non-destructive, and there is no need for reagents or labelling [30–41].

In earlier work, we showed that Raman spectroscopy can be used to discriminate OCSCC from surrounding healthy soft tissue with a sensitivity of 99% and a specificity of 92%, based on clear differences in tissue water concentration. The water concentration was found to be significantly higher in the tumour than in the surrounding healthy soft tissue [35]. Furthermore, we demonstrated that the tumour border could be determined based on water concentration. The water concentration decreases from 76% (±8%) inside the tumour to 54% (±24%) at a distance of 5 mm from the tumour border, corresponding to the targeted tumour-free margin in OCSCC resections [36].

The goal of the current study was to investigate whether Raman spectroscopy can also be used to detect OCSCC in bone resection surfaces enabling surgeons