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Marking of tumor resection borders for improved radiation planning facilitates reduction of radiation dose to free flap reconstruction in head and neck cancer surgery

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A B S T R A C T

Accurate localization of tumor resection borders is crucial for adjuvant radiotherapy. An improvement to adjuvant radiotherapy with the reduction of radiation doses to free flap reconstruction by virtual navigation procedures and titanium clips was evaluated.

Thirty-three patients with oral cancer were prospectively included in the study. Following complete local excision of the primary tumor, resection borders were marked virtually using a navigation pointer and with titanium ligature clips. Postoperative delineation of tumor resection borders was examined. In five patients with microvascular free flap reconstruction a reduction of the radiation dose to the free flap reconstruction was achieved. The tumor resection borders in 30 patients were marked with titanium ligature clips. Surgical clip insertion was successful in 91%. We demonstrate a significant relationship between the reconstruction volume and the part of the target volume which will receive a reduced radiation dose. A cumulative dose of 60 Gy was administered to the target volume and a significant reduction of the administered radiation dose to the center of the flap could be demonstrated. We demonstrate an accurate delineation of the tumor resection margins. These improvements in tumor resection margin delineation allow for increased accuracy in adjuvant treatment and a reduction of radiation dose to the vascular free flap reconstruction.

1. Introduction

Modern head and neck cancer therapy seeks for complete resection of the tumor. In this relation, analyses of tumor and resection margins are fundamental and require a multidisciplinary approach. Oral squamous cell carcinoma (SCC) is commonly treated by a combination of surgical resection, local reconstruction and additional radiotherapy.

Surgical resection of these malignancies frequently leads to complex bone and soft tissue defects. Whenever there is a lack of sufficient adjacent tissue for primary closure, immediate microvascular free tissue reconstruction is an established method (Choi et al., 2004).

When there is lymph node involvement in the neck, R1 or Rx tumor resection, or there are close tumor margins, the comprehensive treatment of advanced head and neck cancers frequently mandates the use of adjuvant radiotherapy, but it is challenging for the oncologist to plan radiotherapy focused on the tumor resection margins (Choi et al., 2004; Chen et al., 2012).

Radiotherapy might cause a loss of flexibility for the vascular system and has the potential to adversely affect microvascular anastomosis by diminished smooth muscle density, endothelial cell dehiscence and vessel wall fibrosis. Scarring of connective tissue and vessels might influence and reduce blood flow, but clinical studies suggest that radiotherapy does not have any obvious effect on the viability of microvascular flap reconstruction (Chao et al., 2012; Hohlweg-Majert et al., 2012; le Nobel et al., 2012; Benatar et al., 2013). Controversy remains as to the effect of radiotherapy on the rate and severity of local surgical bed complications after free tissue transfer (Choi et al., 2004; Geretschlager et al., 2012; le Nobel

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et al., 2012). An essential prerequisite of external beam irradiation is the accurate localization of tumor resection margins. For detecting these margins CT scans are used by the radiation oncologists, however the detection is still challenging (Kirby et al., 2013).

Uncertainty still exists regarding the optimal radiotherapy target volume definition (Kirby et al., 2010). Therefore, precise orientation of the boundaries between resection borders and graft reconstruction becomes important. Delineation of reconstructed tissue from resection margins on postoperative CT scans is often difficult (Coles et al., 2009; Yang et al., 2013). Various refinements in the field of computer-aided surgery (CAS) have been implemented in order to improve marking of resection margins but CAS alone is insufficient in delineating tumor margins apart from hard tissue in soft tissue due to the effects of gravity and swelling on the tissue whether native or reconstructed (Essig et al., 2011; Bittermann et al., 2013). In this situation marking of margins by titanium ligature clips could be useful (Bittermann et al., 2013). Markers implanted in surgical cavity walls provide additional localization information compared with CT-imaging alone. Marker-based tumor resection margin delineation has been recommended as the current gold standard in breast cancer surgery (Coles et al., 2009; Kirby et al., 2013).

The aim of this study is to show the feasibility of using titanium ligature clips and a navigation-assisted technique to mark the tumor resection margin physically and virtually leading to an improvement in the planning and performing of radiotherapy for head and neck cancer.

There are no trials to test the hypothesis that by limiting the radiotherapy to the region containing the microvascular free flap, there will be a significant reduction in late graft tissue toxicity whilst maintaining adequate local control. This is particularly important in the context of planned secondary bony reconstruction after completion of radiotherapy. This pilot study demonstrates the potential benefit of marking the tumor resection margin by reducing the radiation boost volume over the majority of the graft reconstruction whilst maintaining the boost dose at the former tumor resection margin.

2. Methods and materials

A prospective study was initiated from November 2012 to October 2013 at the University Medical Center Freiburg, Department of Oral and Maxillofacial Surgery and Department of Radiation Oncology, Germany. Ethical approval for the study was obtained before undertaking this study. Written informed consent was obtained from all study patients.

During the study period, 33 consecutive patients were recruited and prospectively included. Inclusion criteria were: excision of an oral SCC and microsurgical defect coverage or full-thickness primary closure. Exclusion criteria were: preoperative radiation, previous tumor therapy in the local area and secondary wound healing of the tumor excision cavity due to possible loss of exposed surgical clips.

All patients underwent tumor resection, neck dissection, defect reconstruction and tumor resection margin marking in one stage by the same oral and maxillofacial surgical team. Recorded parameters included: age, sex, stage of cancer, tumor localization, type of microvascular free flap, preoperative tumor volume, number of acquired clips or navigation points for tumor resection margin marking, tumor resection margin surface of full thickness closure, reconstruction volume if a microvascular free flap was required, time between operation and postoperative CT imaging.

2.1. Marking of resection margins

Intraoperative frozen section examination of the resection margins was performed to ensure microscopic clearance of disease. When collecting frozen sections the site of the biopsy was marked and mapped by the navigation probe. The precise localization data was saved so that the labeled frozen sections could then be incorporated into the 3D treatment software (iPlan 3.0.3 BrainLab, Feldkirchen, Germany). Following complete local excision of the primary tumor, the tumor resection margin was marked with the navigation pointer and titanium clips if the margin lay on the maxilla or close to it. Otherwise marking was done with radio-opaque titanium ligature clips alone (Ethicon Endo-Surgery, Ligaclip Extra Titanium Medium).

All patients had titanium clips placed at the time of tumor ablation and before tissue reconstruction in which each excision cavity boundary was defined by clips positioned at the deep, superficial, medial, lateral, inferior and superior boundaries. Additional markers were placed at 15–20 mm intervals on the soft tissue margins if the tumor resection margin was irregularly configured. The number of inserted clips and additional time required were recorded for each patient. Successful clip insertion was defined as at least six clips inserted in the correct position around the tumor resection margin.

Depending on tumor size and adjacent tissue, full thickness closure or a microvascular free flap was used to reconstruct the defect. The graft was chosen preoperatively, based on clinical and radiological examination. A CT scan was used for preoperative radiological assessment. The graft selection was based on evaluation of 3D-extension, infiltration of neighboring structures and tumor localization.

2.2. Postoperative processing

All patients had CT scans with slice thickness $\leq$3 mm postoperatively as per standard practice. Preoperative and postoperative images were fused and all landmarks and ligature clips were detected in an axial view by using the planning software iPlan 3.0.3 (BrainLab, Feldkirchen, Germany).

Tumor resection margins were then outlined manually using the brushing tool on the software. Contouring was carried out by outlining virtual landmarks and the outer part of the titanium clips and architectural distortion relating to the surgical excision visible on each CT slice. Delineation of the tumor resection margin was performed with a fixed window level (0 Hounsfield units) and width (500 Hounsfield units) by a single experienced observer. The second contouring was performed three weeks later, and the mean value was calculated to reduce and to compare intraobserver variability.

In patients who had received microvascular free flap reconstruction, the volume was determined. In patients with full thickness closure of the excision cavity, the surface area of the tumor resection margin was calculated.

Subsequently the radiation oncologist created a treatment plan using his knowledge of the tissue markings focused on the resection margins in native tissue while sparing the tumor-free vascularized graft.

2.3. Adjuvant radiochemotherapy

The treatment of all patients was in accordance with local protocols and based on an interdisciplinary tumor board decision. If clinically indicated, adjuvant radiation therapy was delivered as radiochemotherapy, consisting of two cycles of cisplatin (100 mg/kg/d) administered during treatment weeks 1 and 4 (3/5 patients). Radiation treatment was planned and delivered as intensity-modulated radiation therapy (IMRT) in combination with image-guided radiation therapy (IGRT) using either the step-and-shoot technique with Oncentra Masterplan software version 4.3