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Tissue reactions to ionizing radiation—Oral mucosa

Sylvia Gruber[a,b,*], Wolfgang Dörr[a]

[a] Applied and Translational Radiobiology (ATRAB), Department of Radiation Oncology, Medical University of Vienna, Austria
[b] Christian Doppler Laboratory for Medical Radiation Research for Radiation Oncology, Medical University of Vienna, Austria

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ABSTRACT

Radiotherapy is one of the most effective treatment strategies for solid malignancies, including head-and-neck tumors (HNT). Oral mucositis is the most frequent, often dose-limiting early adverse event of radio(chemo)therapy for HNT. The oral mucosal response is – like that of typical turnover tissues – based on radiation-induced impairment of epithelial proliferation and cell production, in face of ongoing physiological cell differentiation and cell loss, consequently resulting in hypoplasia and eventually mucosal ulceration. The regenerative epithelial response, i.e. repopulation, and hence the impact of overall treatment time, besides intrinsic radiosensitivity, is the dominant parameter of the radiation tolerance of oral mucosa in fractionated radiotherapy protocols.

The epithelial changes are accompanied, at the molecular and cellular level, by various changes in non-epithelial cell populations, i.e. vascular endothelial cells, macrophages, and fibroblasts. An inflammatory response precedes and parallels the epithelial changes; this includes vasodilation associated with rheological consequences and the manifestation of local hypoxia, activation of macrophages and endothelial cells. During these processes, a variety of intra- and intercellular communication pathways are modulated; NF-κB associated signaling is one prominent example. The interactions of these extra-epithelial changes with epithelial hypoplasia, ulceration and regeneration currently remain largely unclear. Research on the molecular mechanisms underlying the clinical manifestation of oral mucositis will allow for identification of potential early biomarkers of oral mucosal morbidity and thus for individualization of patient follow-up and treatment, and also for the development of targeted strategies for prophylaxis and/or mitigation of oral mucositis.

This review summarizes the features of the clinical manifestation of oral mucositis and its consequences, the "classical" radiobiological parameters of mucosal radiation sensitivity. It moreover focuses on the underlying "molecular" mechanisms, and on biology-based approaches for the amelioration of radiation-induced oral mucositis.

1. Introduction

Radiotherapy, often combined with surgery and/or chemotherapy, is one of the most efficient modalities for the treatment of solid malignancies. Over the last decades, progress in medical radiation physics and radiotherapy technology resulted in a progressive increase in the conformation of the high-dose volume to the target. However, effective curative radiotherapy is unavoidably associated with the exposure of normal tissue components to significant radiation doses. This refers to normal structures within the tumor (e.g. vasculature, connective tissue, immune cells), in the close proximity of the gross target volume, where microscopic tumor spread must be expected (clinical target volume), in normal tissue volumes which need to be included in the high-dose volume for practical reasons (planning target volume), and also in the entrance and exit channels of the radiation beams [1,2]. Therefore, a certain risk for adverse events inevitably needs to be accepted in order to guarantee for the projected treatment outcome [3].

Abbreviations: G-CSF, granulocyte colony stimulating factor; GI, gastro-intestineal; HIF-1α, hypoxia-nducable factor 1 alpha; HNT, head-and-neck-tumours; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; KGF-1, keratinocyte growth factor-1; NF-κB, nuclear factor kappa B; PBM, photobiomodulation; RChT, radiochemotherapy; ROS, reactive oxygen species; SDF-1, stromal cell derived factor 1; TLR, toll-like receptors; TNF-α, tumour necrosis factor alpha.

* Corresponding author at: ATRAB—Applied and Translational Radiobiology, Dept. of Radiation Oncology & Christian Doppler Laboratory for Medical Radiation Research for Radiooncology, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria.
E-mail address: sylvia.gruber@meduniwien.ac.at (S. Gruber).

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Adverse events of cancer radiotherapy comprise early effects, occurring within the first 90 days after the onset of treatment, late effects, with a first diagnosis at later time points, usually months to even many years after the treatment [3,4]. Consequential late effects (CLE) represent late effects for which the risk is significantly promoted by the severity and duration of the early effect in the same organ or tissue, based on a breakdown of the protective barrier function associated with the early radiation response [3,4].

Radiation-induced oral mucositis is a typical early complication of radio(chemo)therapy (RChT) for head-and-neck tumors (HNT). These early reactions occur in tissues with a high proliferative activity, such as the epidermis or the mucosae of the upper and lower gastro-intestinal tract, but also e.g. the bone marrow [2,3].

2. Clinical manifestation and consequences

Radiation-induced oral mucositis is the most frequent and often dose-limiting early side effect of radio(chemo)therapy (RChT) for head-and-neck tumors. Virtually all HNT patients receiving RChT develop oral mucositis—most of them in a severe, confluent, ulcerative manifestation. Regarding the typical time course, initially erythema occurs in the second week after the onset of conventional radiotherapy with 5×2 Gy/week, corresponding to grade 1 according to common classification criteria. Already this initial reaction is accompanied by pain and functional impairment, such as dysphagia. Subsequently, in weeks 2 and 3 of the treatment, the mucosal lining gradually erodes and focal epithelial lesions develop (grade 2). This is followed by confluent ulcerations (grade 3), usually in the fourth week of therapy. A detailed photographic documentation of radiation-induced oral mucosal lesion of various grades is found in Riesenbeck et al. [5]. An example of a typical grade 3 confluent reaction is shown in Fig. 1. In general, confluent lesions in the oral cavity develop after a period of 9 days after a cumulative dose, representing the mucosal tolerance dose to fractionated radiotherapy, of ca. 20 Gy [6]. The time course, however, is dependent on the localization within the upper GI tract [7]. A pseudomembrane, composed mainly of cell debris, keratin and fibrin, covers the ulcerative erosions. Grade 4 oral mucositis, i.e. necrosis and hemorrhage, are rarely seen with radiotherapy alone, but may develop in patients receiving additional mucotoxic chemotherapy.

The early epithelial radiation-induced changes usually resolve completely, within several weeks after the end of the treatment. However, late manifestations of vascular and soft tissue damage can result in secondary, late atrophy, with increased epithelial vulnerability [1,8]. Moreover, the severity and duration of the early mucosal lesions affect the risk for (consequential) late effects in the oral cavity [3,4], such as chronic ulcers and, in an extreme form, osteoradionecrosis, mainly of the mandible [9].

The ulcerative epithelial lesions and the inflammatory response are associated with severe pain, and consequently difficulties with nutrition and speaking, and thus significantly impact on the quality of life of the patients [10,11]. Mucositis-related treatment interruptions and prolongations of the overall treatment time markedly impact on the outcome of the therapy [12,13]. Moreover, the breakdown of the protective mucosal barrier bears a risk for local and systemic infections [10,11,14]. Furthermore, radiation-induced oral mucositis is a considerable socio-economic factor. Severe epithelial reactions require hospitalization and feeding via tubes or parenteral gastrostoma, with additional costs up to 6000 $ per patient [15].

So far, no biology-based treatment strategy was implemented into clinical practice; prophylactic and interventional strategies are limited to symptomatic measures, increased oral hygiene, including frequent mouth washes, pain management, and anti-infective treatment, without, however, a clear consensus. This is also reflected in the recommendations in the various guidelines, as well as in recent reviews (e.g. [14,16,17]). With regard to treatment planning, dose peaks at the mucosa related to metallic dental implants, which can reach up to 190% of the target dose, need to be avoided by mechanically moving the mucosa from the teeth, e.g. via individual spacer tooth racks [18].

3. Anatomy and histology of oral mucosa

The lining of the oral mucosa represents a stratified squamous epithelium. Structurally and functionally, specialized, masticatory and lining mucosa can be differentiated [19]. The specialized mucosa is mainly found on the dorsum of the tongue and contains mechanical papillae, taste buds and tactile and temperature sensory structures. Masticatory mucosa is found in sites with marked mechanical stress, like the hard palate and the gingiva; the epithelium is keratinizing. The lining mucosa covers the remainder of the oral cavity; the epithelium is non-keratinizing in humans, in contrast to rodents.

A typical representation of human lining mucosa is shown in Fig. 2. The basal epithelial cell layer, comprising cylindrical cells, is separated from the submucosa – containing the vasculature and

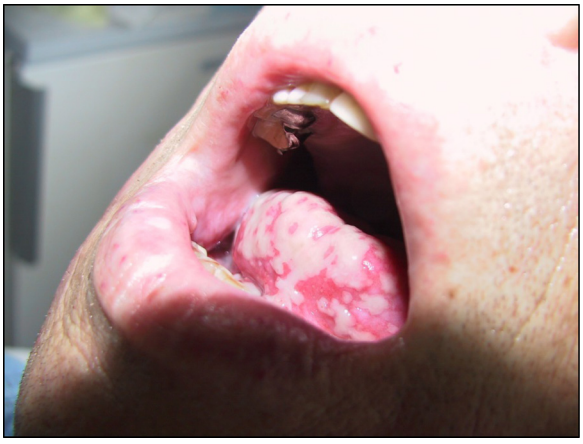

Fig. 1. Confluent radiation-induced oral mucositis.
Confluent oral mucositis (grade 3 according to RTOG/EORTC classification) observed in a HNT patient in the 4th week of conventional radiotherapy with 5×2 Gy/week. The ulcerative lesions are covered by a whitish pseudomembrane and accompanied by typical signs of inflammation (erythema).

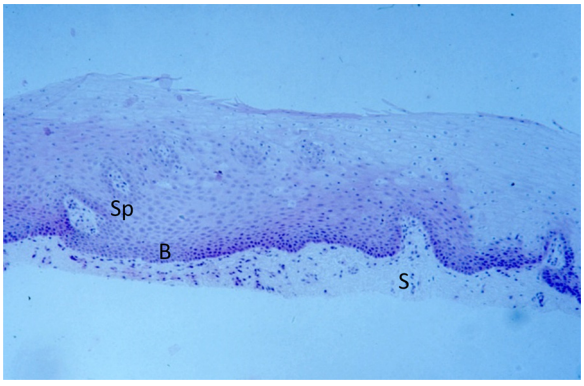

Fig. 2. Histology of human oral mucosa.
The epithelium is separated from the submucosal structures (S) by a basement membrane. Cell proliferation is confined to the basal (B) and lower spinous layer (Sp). The superficial layers contain postmitotic, differentiating cells that are eventually lost at the surface due to mechanical and chemical stress.