Oral Oncology 58 (2016) 32–40

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Head and neck intensity modulated radiation therapy leads to an increase of opportunistic oral pathogens

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ARTICLE INFO

Article history:
Received 4 February 2016
Received in revised form 28 April 2016
Accepted 10 May 2016
Available online 27 May 2016

Keywords:
Head and neck neoplasms
Intensity modulated radiotherapy
Chemoradiotherapy
Microbiota
Periodontitis

SUMMARY

Objectives: The introduction of intensity modulated radiation therapy (IMRT) has led to new possibilities in the treatment of head and neck cancer (HNC). Limited information is available on how this more advanced radiation technique affects the oral microflora. In a prospective study we assessed the effects of various advanced treatments for HNC on the oral microflora, as well as the effects of elimination of oral foci of infection.

Materials and methods: All consecutive dentate patients >18 years, diagnosed with a primary oral or oropharynx carcinoma and seen for a pre-treatment dental screening (May 2011–May 2013) were included. Patients were grouped by oncologic treatment: surgery (SURG), IMRT (IMRT) or IMRT +chemotherapy (CHIMRT). Dental screening data, demographic data, subgingival biofilm samples, oral lavages and whole saliva samples were obtained to microbiologically analyze the effects of cancer treatments (1-year follow-up).

Results: This study included 82 patients (29 SURG, 26 IMRT and 27 CHIMRT). The trends in changes in prevalence and proportions of microorganisms were comparable in the IMRT and CHIMRT group. However, relative to the SURG group, increased prevalence of enteric rods, staphylococci and Candida species was observed in the IMRT and CHIMRT groups. In these groups, elimination of oral foci decreased the frequency of detection of pathogens such as *Porphyromonas gingivalis*, *Tannerella forsythia* and *Streptococcus mutans*.

Conclusion: Different treatments in HNC patients result in different changes in the oral microflora. Opportunistic pathogens such as staphylococci, enteric rods and *Candida* sp. tend to increase in prevalence after IMRT with or without chemotherapy, but not after surgical intervention.

Introduction

Head and neck cancer (HNC) patients treated with radiotherapy (RT) have a lifelong risk of developing severe oral problems. These patients may suffer from loss of salivary gland function, which predisposes them to secondary problems such as rapidly progressing dental caries and fungal and bacterial infections [1–3]. Radiation-induced hyposalivation and subsequent dental caries are associated with an increased risk for dental extractions and development of osteoradionecrosis (ORN) [4]. To prevent ORN and other oral sequelae after radiotherapy, pre-radiation dental screening is commonly performed to locate and eliminate oral foci of infection, although the efficacy of these interventions is unclear [5].

During the last decade, treatment techniques in HNC have changed substantially, due to the introduction of intensity modulated radiation therapy (IMRT) and concomitant chemoradiation [6]. The differences between 3D conformal radiotherapy (3D-CRT) and IMRT, with or without chemotherapy, have not been studied regarding their effects on oral microflora. For example, the reduced salivary secretion observed after IMRT relative to 3D-CRT may result in a less acidic oral environment and a lower incidence of hyposalivation-induced dental caries [7]. Teeth might be preserved longer after IMRT, since a less acidic environment may be less prone to induce and promote dental caries. As a consequence,

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http://dx.doi.org/10.1016/j.oraloncology.2016.05.005
1368-8375/

longer survival of teeth provides more time for periodontal pathogens to cause periodontal problems. This might explain why recently periodontal pocket progression in irradiated patients was seen [8].

Although IMRT reduces the risk of xerostomia, it is not known whether the effects on the oral microflora are similar or different compared to changes induced by 3D-CRT. Changes related to 3D-CRT have been described for both the short term (<1 year) [9–12] and long term (⩾1 year) [13–15]. In general, microorganisms associated with oral disease increased in time after RT. This was related to salivary secretion rate and buffering capacity [14]. Only short-term effects (during 6 weeks of RT) of IMRT have been reported for a small sample of patients [16]. The latter study showed that IMRT is more conducive to maintaining the relative stability of the oral ecosystem than 3D-CRT. To the best of our knowledge long term (>1 year) effects of IMRT on oral microflora have not been described so far. Since loss of salivary secretion is less after IMRT than after 3D-CRT, it is worth studying whether this results in less pronounced alterations to the oral flora. Due to ethical considerations, it is not possible to compare 3D-CRT with IMRT prospectively. Therefore, we conducted a prospective study to assess the effects of three advanced HNC treatments—surgery, IMRT and IMRT with chemoradiation—on the oral microbial composition with a follow-up of 1 year. Also, the effects of elimination of oral foci of infection on the oral microbial composition in patients subjected to IMRT or IMRT and chemoradiation were assessed.

Materials and methods

Patients

All consecutive dentate or partially dentate patients >18 years, diagnosed with a primary oral cavity or oropharynx carcinoma, who were referred to the Department of Oral & Maxillofacial Surgery of the University Medical Center Groningen (UMCG) in the Netherlands for a pre-treatment dental screening between May 2011 and May 2013, were included in this study. To be eligible for this study, post-oncologic treatment microbial follow-up had to be available for at least 6 months. Treatment plans of all patients were discussed in the multidisciplinary tumor board of the UMCG. Patients were placed into one of three groups according to their oncologic treatment: (1) intensity modulated radiation therapy (IMRT), (2) IMRT concurrent with chemotherapy (CHIMRT) or (3) surgery (SURG). Patients who had undergone previous surgical removal of a tumor and/or RT and/or chemoradiation to the head and neck region were excluded, as were patients with an unknown primary or parotid gland tumor. The medical ethical committee of the University Medical Center of Groningen approved the study protocol (METC 2012/091).

Surgery group

The surgery group consisted of patients who received oral oncologic surgery (SURG), not followed by IMRT or CHIMRT. Patients eligible for oncologic surgery were operated according to the guidelines of the Dutch Head & Neck Society (NWHTT) [17].

Radiotherapy and chemoradiation groups

The radiotherapy group (IMRT) consisted of patients who were subjected to definitive primary or post-operative IMRT. The chemoradiation group (CHIMRT) consisted of patients who were subjected to definitive primary or post-operative CHIMRT.

IMRT was delivered using megavoltage equipment (6 MV linear accelerator). For all patients, a contrast-enhanced planning CT scan was made in supine treatment position. Patients received a conventional fractionation schedule of 2 Gy daily, five times per week up to 70 Gy on the primary tumor and pathological lymph nodes in 7 weeks or an accelerated schedule with 6 fractions per week. Elective lymph node areas in the neck (both sites) were irradiated with a dose of 54.25 Gy, in fractions of 1.55 Gy. IMRT treatments attempted to spare the parotid glands without compromising the dose to the target volumes. In general, 7-field equidistant, non-opposing beams were applied. The radiation dose was delivered using a simultaneously integrated boost IMRT technique.

Chemotherapy was given concurrently with fractionated IMRT and consisted of Carboplatin on day 1 (300–350 mg/m^2 in 30 min intravenously) and 5-fluorouracil (5-FU) from day 1 to 4 by continuous infusion (600 mg/m^2/24 h), consisting of 3 courses given with an interval of 3 weeks. Postoperative chemotherapy consisted of 6 × 50 mg Cisplatin weekly. When chemotherapy was considered to be infeasible, patients were treated with cetuximab using a loading dose of 400 mg/m^2 one week prior to radiotherapy and a weekly dose of 250 mg/m^2 during radiotherapy.

Dental screening

All patients were evaluated before their oncologic treatment as part of routine clinical practice by means of an oral and dental screening, including radiographic examination. This screening is based on the protocol published by Jansma et al. [18]. Oral foci of infection were defined as follows [5]:

- deep caries in which excavation may lead to pulpal exposure;
- active periodontal disease with pockets ⩾6 mm, furcation >grade 1, mobility >grade 1, gingival recession ⩾6 mm and especially a combination of these periodontal problems;
- non-restorable teeth with large restorations, especially those extending beyond the gum line or with root caries, or those with severe erosion or abrasion;
- periapical granuloma and avital teeth;
- impacted, partially impacted or partially erupted teeth not fully covered by bone or showing radiolucency;
- cysts and other radiographic abnormalities.

To quantify periodontal disease, the periodontal inflamed surface area (PISA) was used [19]. Patients were asked about their smoking and drinking habits. Self-reported smoking options were ‘current smoker’, ‘past smoker’, or ‘never smoked’ and self-reported alcohol consumption options were ‘never drink alcohol’ or ‘drink alcohol’.

Additionally, baseline oral lavage, subgingival biofilm samples and unstimulated and stimulated whole saliva samples were taken at the dental screening. All data obtained at baseline and follow-up visits were collected in a predetermined order and recorded using a standardized study form designed for this study.

Sampling methods

At various time points, an oral lavage [20] and subgingival biofilm samples [21] were obtained for microbiological evaluation. The total anaerobic bacterial count as well as detection frequencies and bacterial load of the periodontal pathogens *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Tannerella forsythia*, *Parvimonas micra*, *Fusobacterium nucleatum*, and *Campylobacter rectus* were determined in subgingival biofilm samples. Total aerobic bacterial count and detection frequencies and bacterial load of *Streptococcus mutans*, lactobacilli, *Actinomyces species*, Gram negative enteric rods and *Candida albicans* were determined in the oral lavage samples. Microbiological analysis of the samples was performed by the Oral Microbiology Laboratory of the UMCG, according to standard laboratory