MA Stokman
FR Burlage
FKL Spijkervet

Authors' affiliations:
MA Stokman, FKL Spijkervet, Department of Oral and Maxillofacial Surgery, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
FR Burlage, Department of Radiotherapy, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
FR Burlage, Department of Radiotherapy, Radiation Institute Friesland, Leeuwarden, The Netherlands

Correspondence to:
M.A. Stokman
Department of Oral and Maxillofacial Surgery
University Medical Center Groningen
PO Box 30.001
9700 RB Groningen
The Netherlands
Tel.: +31 50 3613840
Fax: +31 50 3611136
E-mail: m.a.stokman@umcg.nl

The effect of a calcium phosphate mouth rinse on (chemo) radiation induced oral mucositis in head and neck cancer patients: a prospective study

Abstract: *Objectives:* Promising results of a calcium phosphate (CP) mouth rinse on reduced severity of oral mucositis have been reported. The aim of this study was to determine the effect of a CP mouth rinse on the frequency, duration and severity of (chemo) radiation induced oral mucositis in patients with head–neck cancer. *Material and method:* patients with oral malignancies, treated with (chemo) radiotherapy, were included. Patients rinsed four times a day with a CP mouth rinse. Patients not willing to rinse with the CP mouth rinse served as control. Mucositis was scored according to the WHO score at baseline and twice a week during the full course of (chemo) radiotherapy. Patient's self-reported mouth-throat soreness (MTS) was evaluated at the same time interval using a diary in the CP mouth rinse group. The outcomes on MTS were compared with a historical control group. *Results:* Fifty-two patients were analysed: 25 CP mouth rinse group, 11 control group and 16 historical group. There was no significant difference between the CP group and control group on development and severity of oral mucositis. No significant difference was found for subjective outcomes on MTS between the CP group and the historical group. *Conclusions:* The CP mouth rinse seems to have no influence on the frequency, duration and severity of oral mucositis during (chemo) radiation in patients with head and neck cancer. A trend to develop less MTS for drinking and eating was found when applying the CP mouth rinse.

Key words: calcium phosphate rinse; chemoradiation; head and neck cancer; mucositis; oral care; radiotherapy

Dates:
Accepted 18 June 2012

To cite this article:
Int J Dent Hygiene **10**, 2012; 175–180
DOI: 10.1111/j.1601-5037.2012.00574.x
Stokman MA, Burlage FR, Spijkervet FKL. The effect of a calcium phosphate mouth rinse on (chemo) radiation induced oral mucositis in head and neck cancer patients: a prospective study.

Introduction

Oral mucositis induced by radiotherapy, chemotherapy or chemoradiation is frequently occurring in patients with cancer. It is painful and restricts oral function such as speech, swallowing and chewing. Clinical signs of mucositis are erythema, pseudo-membranes and ulceration of the oral mucosa (1). Secondary infection of mucosal ulcers is seen in severe mucositis and could provide a port of entry for micro-organisms into the circulation, which can lead to life-threatening septicaemia, especially in myelosuppressed patients (2). Oral mucositis is associated with an

increase in the number of systemic infections, days in hospital stay and overall costs (3, 4). These aspects can limit the cancer therapy and have a negative impact on the patients' health-related quality of life (HRQOL) (5). Mucositis was reported to be the most troubling side effect of cancer therapy by 38% of patients treated with head and neck radiation and 42% of the patients treated with high-dose chemotherapy (6, 7).

The incidence of mucositis is dependent on the cancer treatment regimen. The current head and neck radiotherapy protocols have a mucositis incidence of 85–100% (8).

Many studies have been published on interventions for the prevention of mucositis but the outcomes are mainly symptomatic or palliative until now.

Calcium phosphate (CP) mouth rinse is a neutral supersaturated calcium, and phosphate mouth rinse designed to recover the normal ionic and pH balance in the oral cavity. It is intended to moisten, lubricate and clean the oral mucosa, tongue and throat. CP is indicated for dryness of the mouth and also indicated as an adjunct to standard oral care in the prevention and treatment of the mucositis that may be caused by radiation or high-dose chemotherapy. The mechanism about the possible beneficial effect of the CP mouth rinse is unknown, and there is no further pharmacologic scientific information available in the literature. Papas *et al.* (9) showed a significant reduction in the frequency, duration and severity of oral mucositis in patients undergoing hematopoietic stem cell transplants rinsing with CP mouth rinse. Positive effects of CP mouth rinse in a study with patients who underwent head and neck (chemo) radiation were found on the occurrence and severity of mucositis (10). However, this was an open-label observational study.

The aim of this prospective study was to evaluate the effect of CP mouth rinse on the frequency, duration and severity of oral mucositis during (chemo) radiation in head and neck cancer patients.

Patients and method

Patient selection

Patients with an oral or oropharyngeal malignancy to be treated with primary curative or postoperative (chemo) radiotherapy were eligible for this study and were included when at least 50% of the oral mucosa was in the field of radiation. Radiation protocol: radiotherapy was delivered using megavoltage equipment (six MV linear accelerator). The dose was calculated using computerized planning. Patients received a conventional fractionation schedule of 2 Gy daily, five times per week up to 70 Gy or an accelerated scheme with six fractions per week, up to a total dose of 70 Gy in 6 weeks. Patients treated with postoperative radiotherapy received a dose varying from 56 to 66 Gy, 2 Gy per fraction, five fractions per week. Until the end of 2007, the majority of patients were treated with three-dimensional conformal radiation therapy (3D-CRT). Since 2008, patients were increasingly treated with an Intensity Modulated Radiotherapy (IMRT) plan to spare one or both parotid glands. Therefore, most patients in this study were treated with IMRT. The elective dose in the IMRT plans varied from 1.55 to 1.8 Gy per fraction, depending on the total dose and the number of fractions. Most patients in the historical control group were treated with 3D-CRT. The dose specification was in line with ICRU 50 recommendations, for all radiation protocols. Patients treated with concomitant chemotherapy with cisplatin or cetuximab received the chemotherapy once a week during the total radiation period. Patients who were treated with a combination of carboplatin and 5-fluorouracil (5-FU) received carboplatin on day 1 and 5-fluorouracil (5-FU) from day 1 to 4 by continuous infusion consisting of three courses given with an interval of 3 weeks.

Criteria for exclusion were as follows: concurrent participation in a clinical trial in which the subject is taking or receiving any investigational agent that may affect the frequency, severity or duration of mucositis and/or receiving investigational treatment for the prevention or treatment of mucositis.

All consecutive patients with a tumour in the oral cavity or oropharyngeal region were asked whether they were willing to rinse their mouth with the CP mouth rinse (Caphosol®; EUSA Pharma, Cuijk, The Netherlands). Patients rinsed four times a day with the CP mouth rinse according to manufacturers' instructions, rinse the mouth twice with 15 ml solution for 1 min. Patients who were not willing to rinse with the CP mouth rinse served as control and followed the standard oral care programme. The standard oral care programme for these patients consisted of mouth rinsing by the patients themselves with a 10 ml salt/baking soda solution (1 tsp. of salt and 1 tsp. of baking soda in a litre of tap water) at least eight times a day to remove sticky saliva and debris.

As a standard procedure, all patients were evaluated before radiation treatment for dental foci of infection by means of a thorough oral and dental evaluation, including a radiographic examination (11). All potential risk factors were eliminated appropriately before the start of radiotherapy amongst others impacted teeth, peri-apical pathology, etc. All patients received an oral care regimen consisted of a daily cleansing of the oral cavity with a saline (0.9% sodium chloride) spray administered with a Ritterspray by a dental hygienist until no visible mucosal debris left. This Ritterspray is a spray cylinder filled with 0.9% sodium chloride and connected with the pressured air system at the dental unit. The pressure is that high that the liquid will come out like a fine haze. All dentate patients applied a neutral fluoride gel every second day using custom-made trays.

The study was performed in accordance with Dutch law on ethical rules and principles for human research and in accordance with the Declaration of Helsinki.

Treatment evaluation

The study period included only the first 6 weeks of radiation because most patients were radiated for 6 weeks.

Primary outcome parameter with regard to the frequency, duration and severity of mucositis was the WHO score (12). The WHO mucositis score is as follows: grade 0 – normal, no mucositis; grade 1 – soreness and erythema; grade 2 – erythema, ulcers/pseudo-membranes, can eat solids; grade 3 – ulcers/pseudo-membranes, requires liquid diet only; grade 4 – alimentation not possible. This is a standard procedure for all patients treated with (chemo) radiotherapy. Thus, the CP rinsing patients and standard oral care patients followed this institutional scoring protocol. Mucositis was scored by independent observers (JB, HG, WR, CZ) at baseline and twice a week, on Tuesday and Friday. All observers were qualified by training to establish adequate inter-evaluator reliability (13).

Secondary parameters were change in bodyweight, frequency of nasogastric tube feeding and the subjective outcome on mucositis scored by the Oral Mucositis Daily Questionnaire (OMDQ).

Patients' body weight was scored in kg at baseline and at the end of the radiotherapy treatment. The use of a gastric tube for additional feeding during the cancer treatment was scored.

The subjective outcome on mucositis was evaluated with a daily questionnaire, the OMDQ (14). Patients treated with CP mouth rinse completed this daily questionnaire. The OMDQ evaluates self-reported mouth and throat soreness (MTS) and oral pain. The OMDQ contains MTS activity-limitation questions. Five response categories to define mouth and throat pain (from '0' indicating no soreness to '4' indicating extreme soreness). The five categories are swallowing, drinking, eating, talking and sleeping. Oral pain was scored with a VAS pain score. As this is not a standard institute procedure, these data were not evaluated in the standard oral care patients. The outcomes of the OMDQ of the CP group was compared with a cohort of patient data on file in the UMC Groningen, the Netherlands, site served as historical control group (2006–2007) for analysis of the MTS outcome in the CP mouth rinse group. In this historical cohort, patients self-report their mouth and throat soreness (MTS) in a daily questionnaire (OMDQ) together with the oral pain VAS score in the same way as in the CP group. The patients in this historical control group received standard oral care according the same protocol as the standard oral care programme.

Statistical analysis

Differences between the groups were analysed with chi-square for categorical data and *t*-test for numerical data. The Mann–Whitney *U*-test was used to analyse the differences in WHO mucositis score, the use of a gastric-tube feeding and the MTS activity-limitation questions for swallowing, drinking, eating, talking and sleeping. Student's *t*-test for independent samples was used to analyse the loss of weight and oral pain. Two-sided *P*-values <0.05 were considered statistically significant.

Results

During 8 months, 39 patients were included, 27 patients received the CP mouth rinse and 12 the standard oral care programme. Of the 39 included patients, 36 patients were evaluable for the total evaluation period. Three patients (8%) dropped out earlier from the study, two of the CP mouth rinse group (7%) and one of the placebo group (8%). The two patients in the CP mouth rinse group stopped the rinse because of nausea. This nausea was not related to the CP mouth rinse. In the control group, one patient died during his radiotherapy treatment. Figure 1 shows a flowchart of the participants who were enrolled in the study. The historical control group consisted of 16 patients. Patients' characteristics are shown in Table 1.

Mucositis

No significant difference was seen between the CP mouth rinse group and the control group (Fig. 2). During the period of 6-week observation, all patients in both groups experienced a mucositis score $\geq$ grade 2, so all patients experienced pseudo-membranes. In the CP mouth rinse group, 64% of the patients developed grade 3 or 4 mucositis, and in the control group, 55% of the patients did (not significant) (Figs 3 and 4). These are the patients with pseudo-membranes and were not able to eat a solid diet. There was no difference between both groups in the onset of pseudo-membranes.

Body weight and feeding

The mean weight loss after 6 weeks of radiation was 4.0 kg (SD 3.7) in the CP mouth rinse group and in the control group 3.5 kg (SD 3.1) ($P = 0.7$).

Use of gastric tubes was necessary in 12 of the 25 patients in the CP mouth rinse group (55%) and in six of the 11 patients in the control group (48%) ($P = 0.8$).

Self-reported mouth and throat soreness (MTS) and oral pain

For the MTS scores and oral pain, the study group was compared with the historical control group. Only for the activity, drinking, a significant difference between both groups was

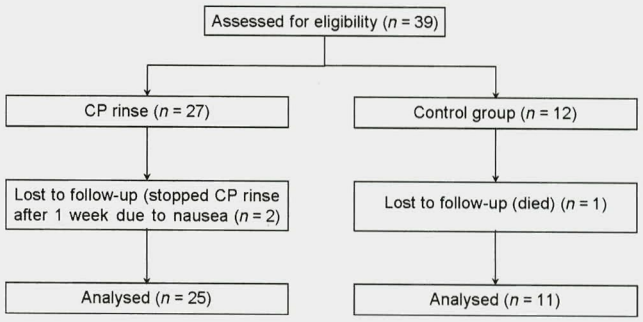

Fig. 1. Flowchart of patient recruitment for the study.

Table 1. **Patients' characteristics compared with the control group and the historical control group**

Patients characteristics	CP mouth rinse	Control	Historical control	*P*-value†	*P*-value‡
Age mean ± SD (years)*	57.6 (12.9)	62.1 (6.7)	60.4 (9.5)	0.28	0.43
Gender: male/female (*n*)	14/11	9/2	13/3	0.14	0.09
Tumour site					
Oral cavity (*n*)	17	5	6	0.20	0.20
Oropharynx (*n*)	8	6	10		
Histology					
Squamous (*n*)	25	9	16	0.09	1.0
Other (*n*)	0	2	0		
T-stage					
T1 (*n*)	4	2	3	0.35	0.52
T2 (*n*)	9	2	5		
T3 (*n*)	3	0	5		
T4 (*n*)	8	7	3		
Tx (*n*)	1	0	0		
N-stage					
N0	9	5	4	0.13	0.30
N1	8	0	3		
N2	7	4	9		
N3	1	2	0		
Total dosis mean ± SD (Gy)*	64.4 (6.1)	65.6 (7.2)	66 (5.7)	0.63	0.41
IMRT					
Yes	16	9	2	0.29	0.01
No	9	2	14		
Fractionation					
Conventional	20	8	8	0.63	0.04
Accelerated	5	3	8		
Chemotherapy					
Yes	10	4	3	0.84	0.15
No	15	7	13		
Type chemotherapy					
Cisplatin	6	1	0	0.36	0.1
Carboplatin/5FU	4	2	3		
Cetuximab	0	1	0		
Dentures					
Yes (*n*)	15	4	8	0.19	0.53
No (*n*)	10	7	8		
Smoking					
No, never	4	1	2	0.59	0.05
No, former	4	3	9		
Yes, <1 pack per day	8	5	3		
Yes, >1 pack per day	9	2	2		
Alcohol consumption					
No, never	6	5	0	0.23	0.16
No, former	1	0	2		
Yes, <2 drinks per day	10	1	7		
Yes, >2 drinks per day	8	5	7		

*All differences between the groups were analysed using chi-squred test except in which *t*-test was used.
†The difference between the CP group and control group.
‡The difference between the CP group and historical control group.

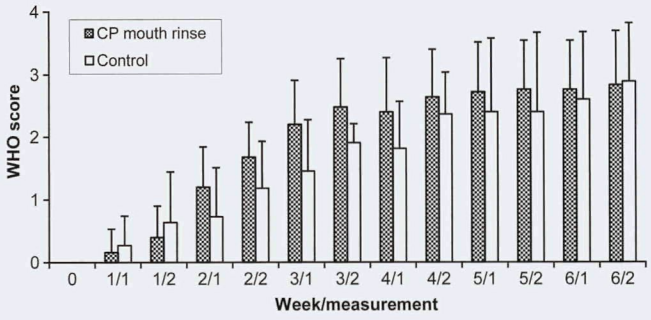

Fig. 2. The WHO mucositis score (±SD) for the CP mouth rinse (lines) and the control group (white) during the 6-week radiation period.

found during the first assessment in week 3. For the other four MTS activity-limitation questions, no significant difference was found. A trend to develop less MTS was found for drinking and eating when applying the CP mouth rinse.

No significant difference was found for oral pain between both groups. Patients in the CP mouth rinse group experienced less oral pain than the historical control group from week 4, but this was not a significant difference.

Discussion

In this limited prospective study, no significant effect was found of the CP mouth rinse on the frequency, duration and severity of oral mucositis during (chemo) radiation in patients with head and neck cancer compared with a control group.

In a different study population, the hematopoietic stem cell transplantation, two studies published a positive effect of the CP mouth rinse. Papas *et al.* (9) found a significant difference between a group of patients rinsing with the CP mouth rinse and a group of patients rinsing with fluoride. From this study, it is not clear whether the applied fluoride rinse was a pH neutral rinse. It might be possible that if the rinse was not pH neutral it could harm the oral mucosa and play a role in the development of mucositis and could make the difference between both study groups. Wasko-Grabowska *et al.* (15) published a positive significant effect of the CP mouth rinse on development and severity of mucositis in a study in patients treated with high-dose chemotherapy (BEAM) prior to autologous blood stem cell transplantation. No significant difference was found in the group that was treated with high-dose melphalan. They compared their data only with a historical study group but no simultaneous control group.

The only publication in a head and neck population is an abstract published by Haas (10). This study is an open-label observational study in patients with head and neck cancer. From this study, it was concluded that these data support the use of the CP mouth rinse in patients undergoing radiation or combined chemoradiation based on the low occurrence and severity of mucositis. This is an observational study without a control group. Moreover, no clear description of the type of

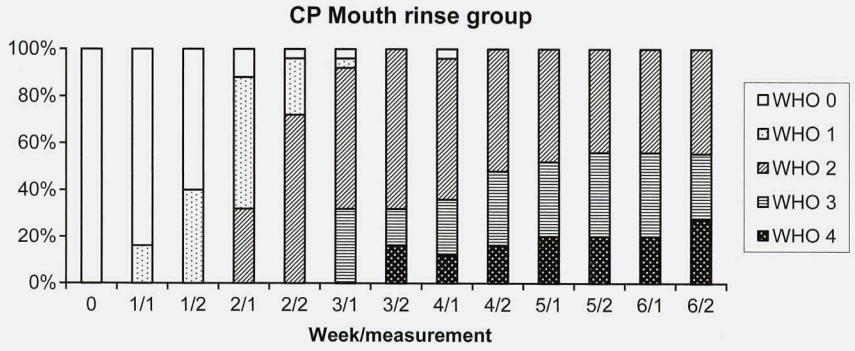

Fig. 3. Percentage of the different WHO mucositis grades in the CP mouth rinse group during the 6-week radiation period.

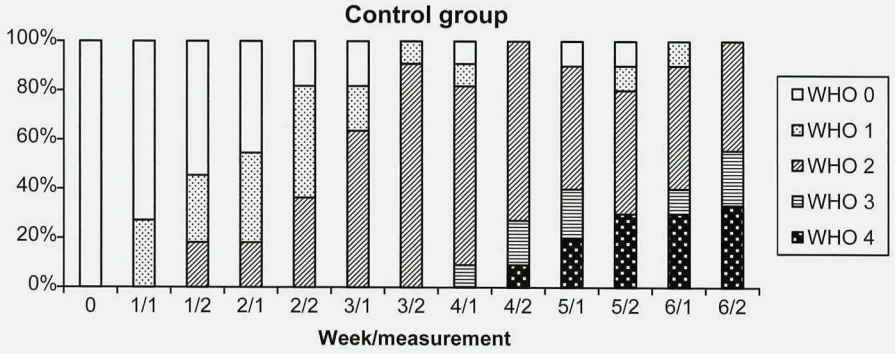

Fig. 4. Percentage of the different WHO mucositis grades in the control group during the 6-week radiation period.

included head and neck tumours is available, as well as no description of the field-size of radiation, and no information is available on radiation dose and the chemotherapy schedules. Oral mucositis was only scored in weeks 3 and 8. Moreover, it is not clear whether the published data about mucositis are the data from week 3 or week 8 or whether these data are an overall score about the total radiation period.

There might be a difference between the development of mucositis from head and neck radiation and high-dose chemotherapy. Mucositis is recognized as an epithelial and subepithelial injury and is thought to develop in a five-stage model (16). Until now, no clear information is available on the working mechanism of the CP mouth rinse and how it can prevent or influence the severity and duration of oral mucositis based on the current concept of mucositis development. It might be important to obtain more information from an *in-vitro* study about the working mechanism of the CP mouth rinse and have more understanding about the working of the CP mouth rinse in the development of oral mucositis.

A trend to develop less MTS was found for drinking and eating when applying the CP mouth rinse compared with the historical group. Both groups are not totally comparable for the radiation protocols (Table 1). In the CP group, more patients received IMRT. Vergeer *et al.* (17) published that the incidence of grade 3 mucositis or higher was significant lower in patients treated with IMRT. The change in radiation protocol is a potential reason for the trend to develop less MTS for drinking and eating than the CP mouth rinse.

So far, non-conclusive results are published on the effects on oral mucositis with the application of a CP mouth rinse in patients with head and neck (chemo) radiation. However, this study has some limitations (no randomization, no blinding, no placebo and small groups), in regard to our study results with a minimal effect on mucositis with the use of the CP mouth rinse, it is doubtful whether a large RCT will be able to show positive results of a CP mouth rinse in this study population.

Conclusion

In conclusion, the CP mouth rinse seems to have no influence on the frequency, duration and severity of oral mucositis during (chemo) radiation in patients with head and neck cancer.

Conflict of interest

The authors declare that they have no conflict of interests.

Financial support

This research was supported by an unrestricted grant of EUSA Pharma, the Netherlands.

References

1 Spijkervet FKL, van Saene HKF, Panders AK, Vermey A, Mehta DM. Scoring irradiation mucositis in head and neck cancer patients. *J Oral Pathol Med* 1989; **18**: 167–171.

2 Ruescher TJ, Sodeifi A, Scrivani SJ, Kaban LB, Sonis ST. The impact of mucositis on alpha-hemolytic streptococcal infection in patients undergoing autologous bone marrow transplantation for hematologic malignancies. *Cancer* 1998; **82**: 2275–2281.

3 Elting LS, Cooksley C, Chambers M, Cantor SB. The burdens of cancer therapy – clinical and economic outcomes of chemotherapy-induced mucositis. *Cancer* 2003; **98**: 1531–1539.
4 Sonis ST, Oster G, Fuchs H *et al.* Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. *J Clin Oncol* 2001; **19**: 2201–2205.
5 Ohrn KE, Sjoden PO, Wahlin YB, Elf M. Oral health and quality of life among patients with head and neck cancer or haematological malignancies. *Support Care Cancer* 2001; **9**: 528–538.
6 Bellm LA, Epstein JB, Rose-Ped A, Martin P, Fuchs HJ. Patient reports of complications of bone marrow transplantation. *Support Care Cancer* 2000; **8**: 33–39.
7 Rose-Ped AM, Bellm LA, Epstein JB, Trotti A, Gwede C, Fuchs HJ. Complications of radiation therapy for head and neck cancers – the patient's perspective. *Cancer Nurs* 2002; **25**: 461–467.
8 Trotti A, Bellm LA, Epstein JB *et al.* Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. *Radiother Oncol* 2003; **66**: 253–262.
9 Papas AS, Clark RE, Martuscelli G, O'Loughlin KT, Johansen E, Miller KB. A prospective, randomized trial for the prevention of mucositis in patients undergoing hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2003; **31**: 705–712.
10 Haas M. Supersaturated electrolyte oral rinse aids quality of life for head and neck chemoradiation patients. *Oncol Nurs Forum* 2008; **35**: 505–506.
11 Jansma J. Protocol for the prevention and treatment of oral sequelae resulting from head and neck radiation therapy. *Cancer* 1992; **70**: 2171–2180.
12 Anonymous. Handbook for reporting results of cancer treatment. *WHO Offset Publ* 1979; **48**: 15–22.
13 Stokman MA, Sonis ST, Dijkstra PU, Burgerhof JG, Spijkervet FK. Assessment of oral mucositis in clinical trials: impact of training on evaluators in a multi-centre trial. *Eur J Cancer* 2005; **41**: 1735–1738.
14 Elting LS, Keefe DM, Sonis ST *et al.* Patient-reported measurements of oral mucositis in head and neck cancer patients treated with radiotherapy with or without chemotherapy: demonstration of increased frequency, severity, resistance to palliation, and impact on quality of life. *Cancer* 2008; **113**: 2704–2713.
15 Wasko-Grabowska A, Rzepecki P, Oborska S *et al.* Efficiency of supersaturated calcium phosphate mouth rinse treatment in patients receiving high-dose melphalan or BEAM prior to autologous blood stem cell transplantation: a single-center experience. *Transplant Proc* 2011; **43**: 3111–3113.
16 Sonis ST. The pathobiology of mucositis. *Nat Rev Cancer* 2004; **4**: 277–284.
17 Vergeer MR, Doornaert PA, Rietveld DH, Leemans CR, Slotman BJ, Langendijk JA. Intensity-modulated radiotherapy reduces radiation-induced morbidity and improves health-related quality of life: results of a nonrandomized prospective study using a standardized follow-up program. *Int J Radiat Oncol Biol Phys* 2009; **74**: 1–8.