A randomised controlled trial of Caphosol mouthwash in management of radiation-induced mucositis in head and neck cancer

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Abstract

Purpose: This phase III, non-blinded, parallel-group, randomised controlled study evaluated the efficacy of Caphosol mouthwash in the management of radiation-induced oral mucositis (OM) in patients with head and neck cancer (HNC) undergoing radical (chemo)radiotherapy.

Patients and Methods: Eligible patients were randomised at 1:1 to Caphosol plus standard oral care (intervention) or standard oral care alone (control), stratified by radiotherapy technique and use of concomitant chemotherapy. Patients in the intervention arm used Caphosol for 7 weeks: 6 weeks during and 1-week post-radiotherapy. The primary endpoint was the incidence of severe OM (CTCAE ≥grade 3) during and up to week 8 post-radiotherapy. Secondary endpoints include pharyngeal mucositis, dysphagia, pain and quality of life.

Results: The intervention (n=108) and control (n=107) arms were well balanced in terms of patient demographics and treatment characteristics. Following exclusion of patients with missing data, 210 patients were available for primary analysis. The incidence of severe OM did not differ between the intervention and control arms (64.1% versus 65.4%, p=0.839). There was also no significant benefit observed with Caphosol for other secondary endpoints.

Conclusion: Caphosol did not reduce the incidence or duration of severe OM during and after radiotherapy in HNC.

Introduction

Radical radiotherapy with concomitant chemotherapy is the standard of care for treatment of locally advanced head and neck cancer (HNC). Despite advances in computational technology and innovations in radiotherapy planning, treatment-related acute toxicity remains considerable.

Oral mucositis (OM) is a well-recognised acute toxicity of head and neck radiotherapy. OM often causes pain and dysphagia, leading to weight loss and malnutrition [1]. More importantly, poorly managed OM may lead to treatment interruptions, which are detrimental to treatment outcome [2,3]. A systematic review of 33 studies demonstrated that 34% patients with HNC receiving radical radiotherapy will develop severe (grade 3 or more) OM and the risk increases further to 43% for those receiving concomitant chemotherapy [2]. Patients with cancers of oral cavity and oropharynx are at the highest risk, as well as those receiving altered fractionation regimens [4,5].

The process leading to the development of mucositis is complex. The sequence of biological events is initiated by the production of reactive oxygen species which cause DNA strand breaks [6]. These, in turn, not only cause clonogenic death of the basal stem cells, but also trigger the transduction pathways resulting in activation of several transcription factors that lead to expression of several pro-inflammatory cytokines [6]. Despite better understanding of these processes, the standard-of-care management in patients with radiation-induced mucositis has not changed for many years and this unpleasant condition continues to pose a therapeutic challenge.

Caphosol is an aqueous solution of concentrated calcium phosphate, which is licensed for use in conditions resulting in dryness of the mouth and throat. As its composition is similar to natural saliva, it is postulated that it could help to maintain healthy oral mucous membranes during treatment by modulating the inflammatory process and promoting tissue repair [7]. Whilst its effectiveness has been documented for patients with haematological malignancies undergoing high dose chemotherapy [7,8], the role of Caphosol in radiation-induced OM in HNC is less clear with conflicting results in the literature [9]. To date, most studies of Caphosol in HNC were retrospective and even if prospective, were single-arm.

Here, we report the result of the first prospective phase III randomised controlled trial on the efficacy of Caphosol mouthwash in the management of radiation-induced OM in HNC.

Material and methods

Study design and participants

This was a single institution, phase III, non-blinded, randomised controlled trial conducted at the Royal Marsden Hospital between December 2011 and January 2015. This study received approvals from the local clinical research and research ethical committee (CCR3571, REC no. 11/EE/0044).

Eligible participants were patients with any histologically proven carcinoma of the head and neck (except thyroid and larynx), aged 18 years or above, receiving (chemo)radiotherapy in a radical setting with Karnofsky's performance status >70%. The use of induction chemotherapy was permitted. Exclusion criteria included inability to use mouthwash, any previous radiotherapy to the head and neck region and mucosal ulceration at baseline (either post-surgery or post-induction chemotherapy).

All patients were treated with conventional fractionation (5 fractions every week). Both 3D-conformal and intensity-modulated radiotherapy (IMRT) techniques were allowed. Radiotherapy dose-fractionation were delivered as per institutional protocol: for primary treatment, macroscopic and microscopic disease were treated with 65 Gy and 54 Gy in 30 fractions, respectively, whereas for adjuvant radiotherapy, the post-operative surgical bed was treated with 60 Gy in 30 fractions, provided that there was no residual macroscopic tumour. As a general rule, tumours at or approaching midline received bilateral neck irradiation. Radiation protocol violations, such as treatment breaks greater than 1 week and failure to complete treatment, were recorded.

Concomitant platinum-based chemotherapy or cetuximab were permissible in this study. Typical systemic therapy regimens included cisplatin 100 mg/m^2 or carboplatin AUC 5 on day 1 and 29 and cetuximab 400 mg/m^2 loading dose prior to radiotherapy with weekly maintenance dose 250 mg/m^2. The choice of systemic therapy was at the discretion of the attending physician.

Study end points

The primary efficacy measure for this study was the incidence of severe (grade 3 or more) OM during and eight weeks after completion of (chemo) radiotherapy. We hypothesised that the use of Caphosol would lead to reduced incidence of severe OM compared to standard oral care alone. Other secondary efficacy measures included: a) the duration of severe OM; b) the incidence and duration of severe pharyngeal mucositis (PM); c) the incidence and duration of severe dysphagia; d) the incidence and duration of severe radiation-induced pain; and e) patients reported quality of life (QoL).

Randomisation and trial interventions

Prior to starting (chemo) radiotherapy, recruited patients were randomised (1:1) to the use of standard oral care regimen (control) or Caphosol plus standard oral care (intervention). Randomisation was performed by the Clinical Trials and Statistics Unit (CTSU) at The Institute of Cancer Research (ICR) using random permuted blocks method. Patients were stratified by radiotherapy technique (unilateral versus bilateral) and type of therapy (chemoradiotherapy versus radiotherapy only).

The patients in the intervention arm started using Caphosol from the first week of radiotherapy. Caphosol was used as a mouthwash 4 times a day but the frequency could be increased up to 10 times a day at the physician's or patient's discretion. Patients used Caphosol for a total duration of 7 weeks; 6 weeks during radiotherapy and 1 week after completion. Depending on the symptoms, patients had access to other symptom control measures available in the control arm. If patients did not tolerate Caphosol, it could be stopped immediately and the reasons for discontinuation were recorded.

Patients in the control arm received standard treatment for OM. At our institution, this included normal saline mouthwash at least 4 times a day, aspirin mouthwash 3 times a day and tooth brushing with fluoride toothpastes prescribed by a dental hygienist. All patients were prescribed analgesia according to the WHO analgesic ladder [10] and topical anaesthetics, such as lidocaine gel. Anti-fungal or anti-viral therapy were also prescribed when necessary.

Evaluation and data collection

All trial evaluation data were collected prospectively during clinic visits. Baseline assessments included head and neck examination, nutritional status, pain relief requirements, smoking status, alcohol and recreational drugs use. Patients were assessed on a weekly basis during and up to 4 weeks following completion of radiotherapy. The final assessment fell on week 8 post-radiotherapy.

The scoring of radiation-induced side effects was performed objectively by trained physicians according to the NCI Common Toxicity Criteria scoring system (CTCAE) version 4.0. QoL was assessed using the EORTC quality of life questionnaire, QLQ-C30 version 3.0 and QLQ-HN35 at the following time points: pre-radiotherapy, week 4 during radiotherapy, week 4 and 8 post-completion of radiotherapy.

Sample size

The primary objective of the study was to determine whether the difference in the rate of severe OM in the intervention and control groups was at least 20%. We assumed that the proportion of patients with severe OM would be 20% and 40% in the intervention and control groups, respectively. A two group chi-squared test with a 0.05 two-sided significance level had 90% power to detect the difference between a Group 1 proportion (intervention arm), $\pi 1$, of 0.20 and a Group 2 proportion (control arm), $\pi 2$, of 0.40 when the sample size in each group was 109. Therefore, the calculated sample size required to detect a difference of at least 20% in the proportion of severe OM between the two arms with 90% power was 218 patients.

Analytical statistics

The data were analysed using STATA statistical software (Version 13.1; StataCorp LP, Texas, USA). Descriptive statistics were used to summarise patient baseline characteristics. All quantitative data were reported as mean and standard deviation. If the data were not normally distributed, median was used together with interquartile range. Qualitative data were presented as number of observations and percentages. All missing data were recorded.

The primary analysis was performed based on treatment actually received (‘as treated’) and included all patients who received at least one week of Caphosol

mouthwash treatment. Patients with missing outcome data for more than two consecutive visits were also excluded. The proportion of patients with severe (grade 3 or more) OM at any point during radiotherapy or 8 weeks after was compared between the two treatment groups using the Chi-Squared test. The level of significance was set at $p<0.05$. The mean duration of severe OM was recorded for patients in days. The Mann-Whitney U test was used to compare the duration of severe OM between the intervention and control groups. The same analyses were repeated for other secondary endpoints: PM, dysphagia and pain.

For QoL data analysis, the global score and sub-scores associated with oral symptoms were summarised and presented graphically. Changes from baseline measurements (%) at each time point were plotted and the differences between the two arms were visually inspected with 95% confidence interval (CI). If a separation was apparent with no or minimal overlap in 95% CI, Mann-Whitney U test was used for further analysis. Comparisons for QoL were tested at a significance level of 1% to allow for multiple endpoints.

Results

Study population

This study achieved its accrual target: 220 patients were recruited and randomised. Following exclusion of 5 patients who either were ineligible or withdrew at the start, 215 patients (108 in the intervention arm and 107 in the control arm) continued with the study (figure 1). There were two allocation errors, where one patient randomised to each arm ended up receiving treatment in the opposite arm.

Baseline patient demographics and clinical characteristics were similar in both groups (table 1). The only exception was that there was a higher proportion of patients with oral cavity and oropharyngeal carcinomas in the intervention arm (75.9% versus 63.3%). The treatment characteristics were well balanced between the two groups following stratifications by type of therapy (chemoradiotherapy versus radiotherapy alone) and radiotherapy technique (unilateral versus bilateral) (table 2). However, a higher number of patients underwent induction chemotherapy prior to radiotherapy in the control arm (46.7% versus 36.1%).

Caphosol usage

The percentage of patients using Caphosol at least 4 times a day decreased with each week of radiotherapy (figure 2). In the first week of radiotherapy, 80% (84/105) of patients used Caphosol regularly but this gradually decreased to 55.2% (58/105) by week 7. The main reason for stopping Caphosol was treatment-induced nausea. Other less common reasons included oral irritation or pain, intolerable taste and perceived lack of benefit. There was no serious adverse event reported with Caphosol.

Primary endpoint

Patients had to have used Caphosol for at least one week to be included in the 'as treated' analysis. Excluding patients with inadequate or missing data, 103 patients in the intervention arm and 107 in the control arm were available for analysis. There was no difference in the incidence of severe OM between the intervention and control groups (64.1% versus 65.4% respectively, p=0.839). The incidences of maximum grade of OM for both groups are shown in appendix 1.

A subgroup analysis was also performed in the group with the highest risk of severe OM i.e. patients with oral cavity and oropharyngeal primary tumours. In this subgroup, the intervention arm had a lower occurrence of severe OM compared to the control arm but this did not reach statistical significance (61.3% [49/80] versus 72.1% [49/68] respectively, p=0.222).

Secondary endpoints

The duration of severe OM did not differ between the intervention and control arms: 16.8±17.5 vs. 17.5±21.9 days, respectively (p=0.692). Whilst the intervention arm showed a lower incidence and shorter duration of other measured radiation-induced toxicities (PM, dysphagia and pain), none of these reached statistical significance (p>0.05, table 3).

The response rate to QoL questionnaires was low, but similar between the two arms. QLQ-C30 response rate rates for the four time points, from pre-radiotherapy to week 8 post-radiotherapy, were 54.2%, 34.6%, 41.1% and 35.5% for the control arm and 59.2%, 37.9%, 39.8% and 36.9% for the intervention arm, respectively. The

corresponding response rates for QLQ-HN35 were 54.2%, 35.5%, 41.1% and 34.6% for the control arm and 57.3%, 38.8%, 40.8% and 34.0% for the intervention arm, respectively.

The pre-radiotherapy mean global health status (GHS) score and functional sub-scores measured by QLQ-C30 were identical in both arms (appendix 2). There was no difference between the two groups in the changes from pre-radiotherapy scores for GHS and functional scales at all time points (figure 3). Similarly, there was no difference between the two groups in the head and neck specific symptoms rated by patients through QLQ-HN35 (figure 4). However, it was noteworthy that more patients in the control arm were still reliant on feeding tube at week 8 post-radiotherapy compared to the intervention arm, even though it did not reach statistical significance (p=0.011).

Discussion

We conducted the largest randomised study to date, to evaluate the efficacy of Caphosol in radiation-induced mucositis in patients with HNC undergoing radical (chemo) radiotherapy. Our data did not demonstrate any benefit from Caphosol in either reducing the incidence or shortening the duration of severe OM. Caphosol also did not provide any significant improvement in other associated acute toxicities in comparison to standard oral care. Our results, therefore, confirm findings from previous smaller studies that Caphosol does not have a significant role in managing radiation-induced acute mucositis in HNC [11-13].

A previous study by Rao et al reported self-assessed improvement of pain, swallowing and eating scores with Caphosol in approximately 50% of patients [12]. However, the study did not have a control group to determine if it was truly the effect of Caphosol above other topical anaesthetics used. We also addressed this issue in this study but found no significant improvement in the QoL reported by patients in the intervention arm. Nevertheless, one observation in our study is that fewer patients in the intervention arm were dependent on a feeding tube by week 8 post-radiotherapy, albeit statistically non-significant. Whilst this may imply that Caphosol aids the speed of recovery from acute toxicity, it needs to be interpreted with caution given the fact that the data only represent a smaller subgroup of patients (~40%). Moreover, there are likely to be other contributing variables such as personal motivation, fear of eating or level of malnourishment, which were not recorded or accounted for.

It is widely acknowledged that there is a general issue with compliance with self-administered agents for prevention and treatment of mucositis. We found a similar pattern with 20% of patients not using Caphosol regularly, even in the first week of radiotherapy. This was due to a small subgroup of patients who either found it intolerable due to taste (partly precipitated by altered taste sensation secondary to treatment) or perceived lack of need for usage at an early stage during radiotherapy. The gradual decrease in its usage with each week of radiotherapy coincides with the onset of OM, at which point some patients found the mouthwash difficult to tolerate.

The contrast between our results and those in patients with haematological malignancies are likely to reflect the different treatments received by the two groups. The longer interval between administration of chemotherapy in this setting, allows more time for the oral mucosa to recover. On the contrary, with daily, fractionated radiotherapy, the insults are continuous, resulting in cumulative injury with little time for tissue repair. It is interesting to note that in the haematological studies, Caphosol was administered by trained nurses, which, invariably improved compliance but this is not a practicable solution for patients who receive radiotherapy as outpatients.

Apart from Caphosol, numerous other mucositis agents have been tested in head and neck radiotherapy. So far, only palifermin, a recombinant keratinocyte growth factor, has been consistently shown to significantly reduce the severity and duration of radiation-induced mucositis in HNC [14,15]. The disappointment, however, is that the benefit in physician-assessed OM did not translate into better patient-reported outcomes or reduced radiotherapy breaks. Of note, the incidences of treatment breaks in both arms of our study were identical (table 2) and significantly lower than those reported in palifermin studies (4-5% versus 14-15%). This suggests that whilst the incidence of severe OM remained considerable, our current standard oral care regimen provided adequate support for patients to complete their planned treatment.

As there is a clear dose response association for developing severe OM: 50% probability at 51 Gy [16], it is challenging to elicit any additional clinically relevant benefit with anti-mucositis agents alone without radiotherapy dose or volume modifications. Continued efforts to better define target volumes with adaptation during radiotherapy based on image defined response, are required to reduce the volume of normal tissue within the radiation field, thereby reducing rates of toxicity whilst maintaining cure rates. Novel oral mucosal surface delineation [17], functional

imaging-guided target delineation and treatment adaptation [18,19] are areas of ongoing research.

We acknowledge that our study has several limitations. As an open label, non-placebo controlled trial, there was no blinding of the physicians assessing the patients and this may have introduced biases. This may have also influenced the way patients completed their QoL questionnaires. There were significant challenges with manufacturing identically-packaged placebo. Second, whilst our patients were stratified by radiotherapy technique and type of therapy, they were not further stratified by primary site of disease. Consequently, there was a small difference in the distribution of high-risk patients between the two groups. Finally, even though we did not expect a high response rate for QoL questionnaires, the rate was significantly lower than originally projected. This may have been related to the relatively long questionnaires, which some patients found ‘laborious’ and the presence of acute toxicities, especially during the latter part of radiotherapy.

Conclusion

Caphosol did not reduce the incidence or duration of severe OM during and after radiotherapy in HNC.

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Conflict of interest

None.

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Figure legends

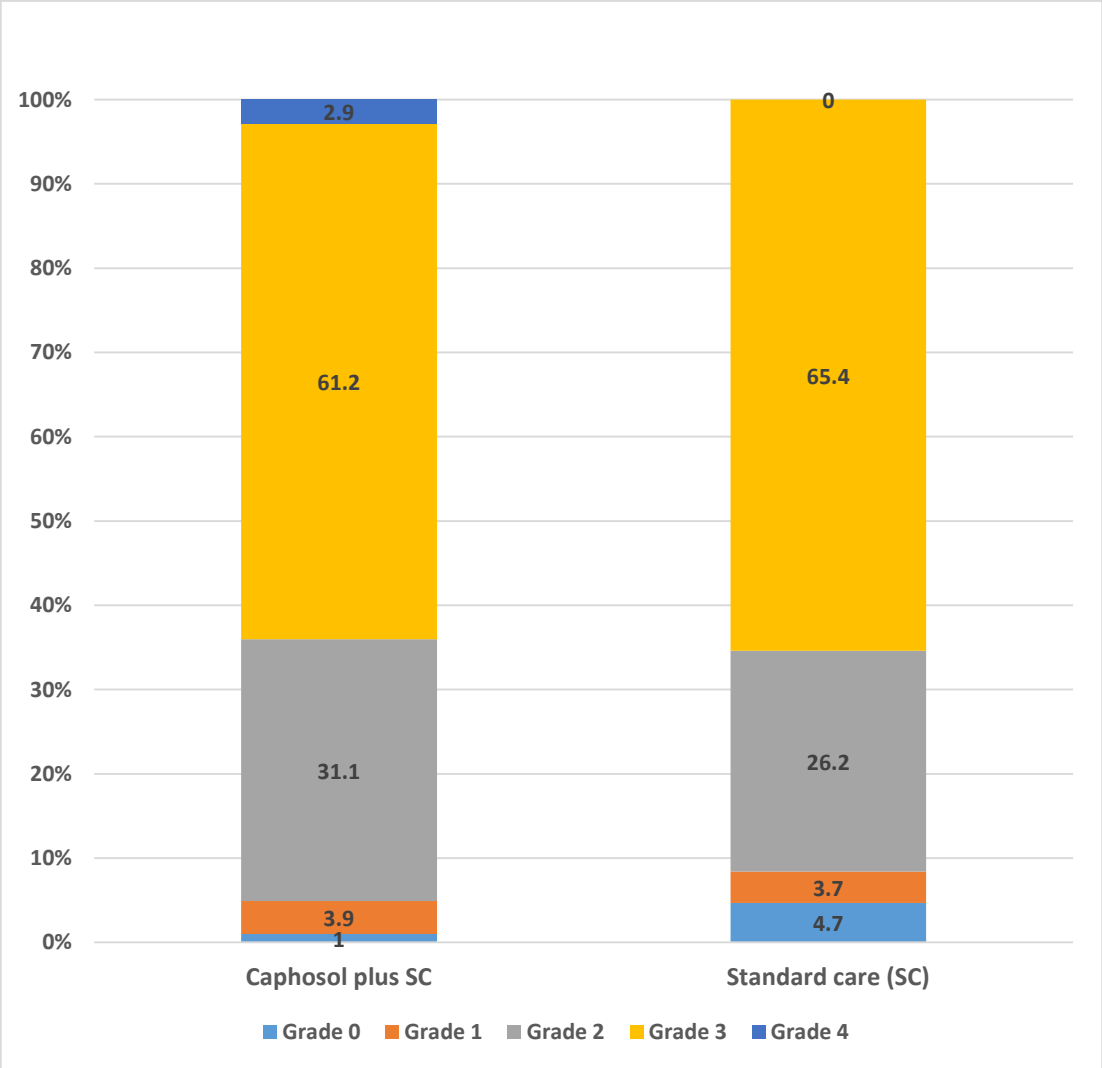
Figure 1. Consort diagram of this study.

Figure 2. Histogram showing percentage of patients using Caphosol at least 4 times a day at weekly intervals during and 1-week post-radiotherapy (n = 105).

Figure 3. Graphical presentations of mean changes (%) at each time point relative to pre-radiotherapy score for core function scales of QLQ-C30 (**A** – Global health status; **B** – Physical functioning; **C** – Social functioning; **D** – Role Functioning; and **E** – Emotional functioning).

Figure 4. Graphical presentations of mean changes (%) at each time point relative to pre-radiotherapy score for QLQ-HN35 components associated with oral symptoms (**A** – Swallowing; **B** – Pain; **C** – Senses problems; **D** – Sticky saliva; **E** – Feeding tube; **F** – Weight loss; **G** – Nutritional Supplement use; and **H** – Dry mouth).

Appendix 1. Maximum severity of oral mucositis



Appendix 2: Summary of core scales (QLQ-C30) including counts and mean changes from pre-treatment scores with 95% confidence intervals

QLQ-C30	Standard oral care								Caphosol							
			Change from Pre-RT (95%CI)								*Change from Pre-RT (95%CI)*					
	Count	Mean at Pre-RT	Count	4 weeks during RT	Count	4 weeks post RT	Count	8 weeks post RT	Count	Mean at Pre-RT	Count	4 weeks during RT	Count	4 weeks post RT	Count	8 weeks post RT
Global health status	58	68.0	36	-24.7 (-32.7, -16.7)	44	-17.0 (-23.9, -10.1)	38	-17.3 (-25.5, -9.2)	61	68.6	39	-21.8 (-28.4, -15.1)	41	-15.2 (-21.7, -8.8)	37	-16.2 (-22.9, -9.5)
Physical functioning	58	84.4	37	-13.9 (-20.8, -7.0)	44	-14.4 (-19.8, -8.9)	38	-14.3 (-21.3, -7.2)	61	87.0	39	-13.4 (-18.6, -8.2)	41	-15.4 (-21.8, -8.9)	38	-14.2 (-19.5, -8.9)
Role functioning	58	72.7	37	-18.9 (-31.0, -6.8)	44	-26.9 (-38.6, -15.2)	38	-17.5 (-29.4, -5.7)	61	79.5	39	-30.3 (-41.0, -19.7)	41	-26.4 (-39.0, -13.9)	38	-23.7 (-33.9, -13.5)
Emotional functioning	58	83.6	37	-9.2 (-16.1, -2.3)	44	-6.6 (-13.5, 0.2)	38	-13.9 (-22.9, -4.9)	61	75.3	39	-1.5 (-6.2, 3.2)	41	-1.2 (-7.1, 4.6)	37	0.7 (-4.3, 5.7)
Cognitive functioning	58	84.8	37	-16.2 (-24.1, -8.2)	44	-6.4 (-11.7, -1.2)	38	-9.6 (-17.2, -2.1)	61	79.0	39	-10.7 (-16.5, -4.8)	41	-2.0 (-8.5, 4.4)	37	-2.3 (-8.8, 4.3)
Social functioning	58	75.6	37	-18.5 (-27.6, -9.3)	44	-22.7 (-31.6, -13.9)	38	-17.5 (-27.4, -7.7)	61	74.6	39	-15.8 (-23.8, -7.9)	41	-15.4 (-23.4, -7.5)	37	-9.0 (-17.0, -1.0)
Fatigue	58	28.7	37	26.1 (17.1, 35.0)	43	22.1 (12.2, 32.0)	38	19.0 (9.7, 28.3)	61	28.2	39	28.7 (19.9, 37.5)	41	21.4 (13.2, 29.6)	38	21.6 (12.9, 30.3)
Nausea and vomiting	58	8.9	37	24.8 (15.7, 33.9)	44	8.3 (0.8, 15.9)	38	10.5 (1.9, 19.2)	61	7.1	39	29.5 (21.4, 37.6)	41	11.8 (6.4, 17.2)	38	10.5 (2.8, 18.3)
Pain	58	20.4	37	27.0 (16.8, 37.1)	44	15.9 (6.4, 25.5)	38	8.3 (1.0, 15.7)	61	21.3	39	25.7 (15.3, 36.1)	41	8.5 (1.1, 15.9)	38	12.7 (4.6, 20.8)
Dyspnoea	58	6.9	37	8.1 (0.8, 15.4)	44	9.8 (3.6, 16.1)	38	10.5 (2.0, 19.1)	61	13.1	39	5.1 (-3.0, 13.2)	41	11.4 (4.0, 18.8)	38	7.0 (1.4, 12.6)
Insomnia	58	30.5	36	2.8 (-6.0, 11.5)	44	4.5 (-6.0, 15.1)	38	1.8 (-11.5, 15.0)	61	35.5	39	-2.5 (-15.1, 10.0)	41	-1.6 (-11.3, 8.0)	38	5.3 (-7.2, 17.7)
Appetite loss	57	18.7	36	55.6 (41.5, 69.6)	43	40.3 (28.5, 52.1)	37	22.5 (9.1, 35.9)	61	24.6	37	47.8 (35.8, 59.8)	40	24.2 (9.6, 38.8)	38	23.7 (10.2, 37.2)
Constipation	58	20.1	37	14.4 (1.1, 27.7)	44	9.8 (0.4, 19.2)	38	7.0 (-4.8, 18.9)	61	24.6	39	27.3 (17.4, 37.2)	41	17.1 (5.9, 28.3)	38	1.8 (-9.8, 13.3)
Diarrhoea	57	4.7	37	9.0 (1.6, 16.4)	43	-0.8 (-4.8, 3.3)	37	0.9 (-6.9, 8.7)	61	6.0	39	3.4 (-4.5, 11.3)	41	4.1 (-1.1, 9.3)	36	7.4 (-1.7, 16.5)
Financial difficulties	58	21.8	37	-0.0 (-7.6, 7.5)	43	2.3 (-5.6, 10.3)	38	3.5 (-6.0, 13.0)	61	24.0	39	0.8 (-6.1, 7.8)	41	2.4 (-5.9, 10.8)	37	7.2 (-0.0, 14.4)

Appendix 3: Summary of Head & Neck scales (QLQ-H&N35) including counts and mean changes of scores from pre-treatment levels with 95% confidence intervals

QLQ-HN35	Standard oral care								Caphosol							
			Change from Pre-RT (95%CI)								*Change from Pre-RT (95%CI)*					
	Count	Mean at Pre-RT	Count	4 weeks during RT	Count	4 weeks post RT	Count	8 weeks post RT	Count	Mean at Pre-RT	Count	4 weeks during RT	Count	4 weeks post RT	Count	8 weeks post RT
Pain	58	20.4	38	33.6 (24.5, 42.6)	44	22.0 (13.1, 30.8)	36	20.1 (10.7, 29.4)	59	22.6	40	36.5 (28.8, 44.1)	41	19.3 (10.2, 28.4)	35	12.6 (4.5, 20.7)
Swallowing	58	13.4	38	40.3 (30.2, 50.4)	44	21.1 (12.2, 30.1)	36	20.4 (10.9, 29.9)	59	14.9	39	33.4 (24.1, 42.6)	40	17.4 (9.1, 25.6)	35	16.2 (8.3, 24.1)
Senses problems	58	12.4	38	47.4 (35.8, 59.0)	44	33.0 (26.1, 39.8)	36	28.7 (19.4, 38.1)	59	12.7	40	42.5 (33.6, 51.5)	41	22.4 (12.8, 31.9)	35	24.8 (16.7, 32.8)
Speech problems	58	11.9	36	29.0 (20.3, 37.8)	43	19.4 (11.1, 27.7)	37	17.3 (8.1, 26.4)	58	14.2	40	25.2 (16.9, 33.5)	42	12.4 (6.8, 18.1)	35	18.4 (11.1, 25.8)
Trouble with social eating	58	13.9	37	54.0 (43.5, 64.5)	42	35.4 (25.0, 45.9)	37	36.6 (25.2, 47.9)	57	16.3	39	42.9 (32.6, 53.3)	41	30.9 (21.2, 40.5)	34	27.2 (17.0, 37.4)
Trouble with social contact	57	6.9	37	18.9 (9.7, 28.1)	43	16.1 (9.4, 22.7)	37	10.9 (3.4, 18.5)	58	9.5	40	8.6 (3.1, 14.0)	42	9.5 (4.0, 15.0)	35	8.8 (2.7, 14.8)
Less sexuality	56	22.6	36	41.6 (28.7, 54.5)	39	39.7 (27.6, 51.8)	33	32.3 (20.1, 44.5)	55	34.2	37	23.4 (11.4, 35.4)	38	18.4 (5.0, 31.8)	34	19.1 (7.8, 30.4)
Teeth	58	17.2	37	0.0 (-9.4, 9.5)	44	-0.0 (-11.2, 11.2)	34	4.9 (-9.7, 19.5)	58	17.8	40	-2.5 (-10.4, 5.4)	41	1.6 (-7.8, 11.0)	35	1.9 (-6.1, 9.9)
Opening mouth	57	19.9	38	18.3 (8.3, 28.4)	44	17.4 (8.3, 26.6)	35	12.4 (-1.0, 25.8)	59	15.8	40	23.3 (9.8, 36.7)	41	21.1 (12.4, 29.9)	35	17.1 (7.3, 26.9)
Dry mouth	58	22.4	38	44.7 (32.3, 57.1)	44	43.2 (33.3, 53.0)	36	51.9 (39.0, 64.7)	59	22.6	40	40.8 (30.0, 51.7)	40	30.8 (21.1, 40.6)	35	47.6 (33.9, 61.4)
Sticky saliva	58	19.0	38	61.4 (50.5, 72.4)	44	43.2 (32.7, 53.7)	36	38.9 (23.4, 54.4)	59	23.7	40	51.7 (39.7, 63.6)	41	26.0 (14.3, 37.8)	35	40.0 (25.9, 54.1)
Coughing	58	19.5	37	24.3 (13.6, 34.9)	44	19.7 (9.0, 30.4)	35	13.3 (2.6, 24.1)	59	22.6	40	19.9 (11.2, 28.6)	41	13.8 (5.3, 22.4)	35	6.7 (-2.5, 15.9)
Felt ill	57	13.5	37	36.1 (26.1, 46.0)	43	8.5 (-0.2, 17.2)	35	9.5 (1.7, 17.4)	59	13.0	40	29.9 (20.0, 39.8)	41	13.0 (4.8, 21.2)	35	11.4 (3.0, 19.9)
Pain killers	56	55.4	36	38.9 (20.9, 56.8)	41	19.5 (-0.1, 39.1)	36	13.9 (-5.5, 33.3)	58	46.6	40	57.5 (42.0, 73.0)	42	40.5 (22.7, 58.2)	35	28.6 (9.6, 47.5)
Nutritional supplement	57	24.6	37	54.1 (36.1, 72.0)	43	48.8 (28.9, 68.8)	35	37.1 (14.3, 60.0)	58	29.3	40	50.0 (34.3, 65.7)	41	39.0 (19.8, 58.2)	35	48.6 (29.9, 67.2)
Feeding tube	57	3.5	37	8.1 (-0.8, 17.0)	43	27.9 (14.3, 41.5)	37	21.6 (8.2, 35.1)	58	8.6	40	7.5 (-3.3, 18.3)	41	19.5 (5.5, 33.6)	35	0.0 (-8.0, 8.0)
Weight loss	56	21.4	36	66.7 (51.0, 82.3)	35	28.6 (8.0, 49.2)	33	24.2 (0.1, 48.4)	55	21.8	38	55.3 (34.8, 75.8)	39	23.1 (3.4, 42.7)	33	45.5 (26.2, 64.7)

Table 1. Patient demographics

Characteristics	Caphosol plus SC (n = 108)		Standard care (SC) (n = 107)		All patients (N = 215)	
	No.	%	No.	%	No.	%
Sex						
Female	23	21.3	31	29.0	54	25.1
Male	85	78.7	76	71.0	161	74.9
Age (years)						
Mean (SD)	57.8 (11.7)		59.9 (9.3)		58.8 (10.6)	
Primary sites						
Oral cavity	15	13.9	11	10.3	26	12.1
Oropharynx	67	62.0	57	53.3	124	57.6
Nasopharynx/Sinonasal	3	2.8	8	7.5	11	5.1
Hypopharynx	3	2.8	9	8.4	12	5.6
Unknown primary	9	8.3	12	11.2	21	9.8
Salivary glands	10	9.3	8	7.5	18	8.4
Others†	1	0.9	2	1.8	3	1.4
Tumour stage (AJCC)						
I	8	7.4	5	4.7	13	6.0
II	13	12.0	13	12.1	26	12.1
III	18	16.7	9	8.4	27	12.6
IV	69	63.9	80	74.8	149	69.3
Histology						
SCC	97	89.8	98	91.6	195	90.7
Others*	11	10.2	9	8.4	20	9.3
Weight loss (kg)						
Mean (SD)	0.7 (2.1)		0.6 (2.1)		0.6 (2.1)	
Pain relief						
No	73	67.6	77	72.0	150	69.8
Yes	35	32.4	30	28.0	65	30.2
Smoker						
No	87	80.6	89	83.2	176	81.9
Yes	21	19.4	18	16.8	39	18.1
Alcohol						
No	38	35.2	41	38.3	79	36.7
Yes	70	64.8	66	61.7	136	63.3
Recreational drug use						
No	104	96.3	105	98.1	209	97.2
Yes	4	3.7	2	1.9	6	2.8

† Include skin and orbital tumour

* Include adenocarcinoma, small cell, acinic cell, mucoepidermoid and adenoid cystic carcinoma

Table 2. Study treatment

Treatment		Caphosol plus SC (n = 108)		Standard care (SC) (n = 107)		All patients (N = 215)	
		No.	%	No.	%	No.	%
Radiotherapy							
RT only		44	40.7	39	36.4	83	38.6
CRT	Carboplatin	22	20.3	31	29.0	53	24.7
	Cetuximab	2	1.9	0	0	2	0.9
	Cisplatin	31	28.7	30	28.0	61	28.4
	Cis/Carbo*	9	8.4	7	6.6	16	7.4
	Total	64	59.3	68	63.6	132	61.4
Induction chemotherapy							
No		69	63.9	57	53.3	126	58.6
Yes	Carbo/5FU	10	9.3	9	8.4	19	8.8
	Cis/5FU	27	25.0	36	33.6	63	29.3
	Cis/5FU & Carbo/5FU	2	1.8	5	4.7	7	3.3
	Total	39	36.1	50	46.7	89	41.4
Technique							
Bilateral		80	74.1	77	72.0	157	73.0
Unilateral		28	25.9	30	28.0	58	27.0
Technique							
3D-Conformal		13	12.0	7	6.5	20	9.3
IMRT		95	88.0	100	93.5	195	90.7
RT breaks							
No		104	96.3	102	95.3	206	95.8
Yes		4	3.7	5	4.7	9	4.2

*Cisplatin Day 1 switched to carboplatin Day 29

Table 3. Efficacy end points (as treated analysis).

End points	Caphosol plus SC (n = 103)		Standard care (SC) (n = 107)		p value
	No.	%	No.	%	
Primary					
Incidence of ≥G3 OM	66	64.1	70	65.4	0.839
Secondary					
Duration of ≥G3 OM (days)					
Mean (SD)	16.8 (17.5)		17.5 (21.9)		0.692
Incidence of ≥G3 PM	59	57.3	68	64.2	0.309
Duration of ≥G3 PM (days)					
Mean (SD)	13.7 (16.7)		18.4 (21.5)		0.187
Incidence of ≥G3 PD	30	29.1	33	31.1	0.752
Duration of ≥G3 PD (days)					
Mean (SD)	8.3 (16.7)		9.7 (19.5)		0.671
Incidence of ≥G3 pain	50	48.5	58	54.7	0.372
Duration of ≥G3 pain					
Mean (SD)	18 (24.7)		20 (24.1)		0.397

OM – oral mucositis, PM – pharyngeal mucositis, PD – pharyngeal dysphagia