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Short Report

Does Dose to an Oral Mucosa Organ at Risk Predict the Duration of Grade 3 Mucositis after Intensity-modulated Radiotherapy for Oropharyngeal Cancer?

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Abstract

Various methods have been described to delineate the oral mucosa organ at risk (OAR). This study examined whether dosimetric parameters derived from four different OARs correlated to the duration of acute grade 3 mucositis (G3M) in patients with oropharyngeal carcinoma. In total, 66 patients were included in this study. The duration of CTCAE version 3 G3M and the duration of strong opiate use were prospectively recorded, together with six patient factors. In addition, for each OAR the following dose parameters were derived: mean dose, V55, V50, V45, V40 and V30. No statistically significant correlation of version 3 G3M or duration of strong opiate use was noted with the tested parameters. However, a trend towards significance between duration of strong opiate use and pre-treatment weight was observed ($P = 0.053$), reaching statistical significance on subsequent linear regression. This study failed to show a relationship between dosimetric parameters derived from four oral mucosa OARs and the duration of CTCAE version 3 G3M or duration of opiate use, potentially suggesting serial rather than parallel radiobiological phenomena. The utility of CTCAE version 4 G3M as an end point requires further investigation given its potential relationship to pre-treatment weight.

Key words: IMRT; mucositis; organ at risk; oropharyngeal cancer

Introduction

Radical radiotherapy in head and neck cancer is associated with significant mucositis in most cases [1,2]. Investigators have proposed radiobiological models to predict acute mucosal toxicity [3–6]. Many of these models are based on data from the two-dimensional radiotherapy or conformal planning era and their application to patients treated with intensity-modulated radiotherapy (IMRT) and particle therapy is, therefore, limited.

With the use of IMRT and particle therapy it is possible to reduce dose to the oral mucosa out with of planning target volumes (PTVs) and potentially lower mucosal toxicity. However, in order to achieve this goal an appropriate oral mucosal organ at risk (OAR) needs to be defined. Different methods have been described to delineate the oral mucosal OAR, essentially differing in whether the whole volume of oral cavity structures (excluding bone and air) is contoured or if the OAR is limited to the mucosal surfaces only [7,8].

The purpose of this study was to investigate the relationship between oral mucositis and dosimetric data derived from different methods of delineation.

Materials and Methods

In total, 66 patients with oropharyngeal carcinoma previously treated with IMRT (55 Gy) in 20 fractions over 25 days to the high dose volume; 46 Gy in 20 fractions to areas at risk of harbouring microscopic disease) and synchronous carboplatin or cetuximab were included in this study. The planning technique and outcomes of these patients have previously been described [9]. No attempt was made to

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spare a specific oral mucosa OAR, although a sculpting volume to spare anterior structures was routinely used. Standard protocol for these patients was to be reviewed weekly during treatment and in the post-treatment phase until grade 3 mucositis (G3M) had settled. Symptomatic mouth care was started in most cases in the second week of treatment with benzydamine hydrochloride. The duration of CTCAE version 3 G3M (confluent mucosal ulceration) and the duration of strong opiate (morphine or fentanyl) use (a surrogate for CTCAE version 4 G3M) were prospectively recorded at the time of treatment.

Oral mucosal OARs were contoured in four ways. In the first method (oral cavity contour; OCC), the oral and pharyngeal mucosa was defined as limited by the inner table of mandible and including the tongue, base of tongue, floor of mouth, and palate [7]. In the second method (mucosal surface contours; MSC), mucosa was defined as a 3 mm thick wall of tissue including the buccal mucosa, buccal gingiva, gingiva proper, lingual gingiva, lingual frenulum, alveolar mucosa, labial mucosa, labial gingiva, labial frenulum, mucosal surface of the floor of mouth, mucosal surface of the tongue anterior to the terminal sulcus and the mucosal surface of the hard palate [8]. In the third method (oral cavity surface contour; OCSC) the OCC was defined as above and then restricted to mucosa in the outer 3 mm of this volume [8]. In the fourth method (oral/oropharyngeal surface contour; OOPSC), a 3 mm thick volume comprising the surface mucosa of the oropharynx not included in the OCSC was added to the OCSC. PTVs were not excluded from the mucosal OARs.

For each patient and each method of contouring the oral mucosal OAR the following dosimetric parameters were derived: mean dose, V55, V50, V45, V40 and V30. Initially, Spearman's correlation or the Mann–Whitney test was used to investigate for a relationship between the duration of version 3 G3M or strong opiate use and these dose parameters for each OAR and six additional patient factors: pre-radiotherapy haemoglobin, weight, age, smoking status (ever versus never), use of neoadjuvant chemotherapy and synchronous chemotherapy (carboplatin versus cetuximab). A parametric analysis (simple linear regression) for any identified relationship was then carried out. Statistical analysis was carried out using the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 22.0).

Results

All patients developed version 3 G3M with a median duration of 28 days (7–65). Sixty-one patients required strong opiate use with a median duration in all patients of 7 weeks (0–24).

For the OCC OAR the mean dose was 51 Gy (45–55 Gy), for the MSC OAR 41 Gy (28–53 Gy), for the OCSC 49 Gy (41–55 Gy) and the OOPSC 51 Gy (45–55 Gy).The median values and range for the dosimetric parameters are as shown in Table 1.

No statistically significant correlation of duration of version 3 G3M or duration of strong opiate use was noted with the tested parameters other than a trend towards an association of the duration of strong opiate use with pre-treatment weight ($P = 0.053$). However, in a simple linear regression analysis, the association of the duration of strong opiate use with pre-treatment weight was found to be significant ($P < 0.05$). The duration of opiate use was found be to be approximately proportional to pre-treatment weight.

Discussion

For IMRT and particle therapy to reduce oral mucosal toxicity, dosimetrists need to be provided with an OAR to which a reduction in dose results in less mucosal toxicity. Additionally, the tools with which the mucosal toxicity is measured need to be sensitive enough to detect the achieved reduction in toxicity. Here we investigated the relationship between four OARs and two toxicity measurement tools and failed to show a relationship.

Bhide *et al.* were able to derive a model based on the mean dose to the OCC OAR estimating a MD50 (mean dose predicting 50% probability of version 3 G3M) of 51 Gy [2,10]. It is important to note that in their study the incidence of version 3 G3M was used as the end point. The use of incidence as opposed to duration is problematic as the vast majority of patients undergoing chemoradiation for oropharyngeal mucosa will experience version 3 G3M at some point during or subsequent to chemoradiation [9]. In addition, mucosa within the high dose PTV will probably display confluent mucositis and attempts to reduce the mean dose to the whole OCC OAR will probably be ineffective in reducing its incidence.

Here the duration of version 3 G3M was used as a mucosal end point as this measure might be more sensitive to changes in dose to the OARs. However, no relationship was identified.

To avoid reliance on the visual appearance of the oral mucosa, CTCAE version 4, in which G3M corresponds to severe pain interfering with oral intake, is currently being used in many international studies. Strong opiate use was used in this study as a surrogate for version 4 G3M. The finding that this end point seemed to depend on pre-treatment weight may reflect heavier patients requiring higher doses of opiates and therefore a longer period of time to be weaned off analgesia. This shows a potential weakness of version 4. The duration of version 4 mucositis should be used as a mucosal end point in isolation with caution, particularly in radiotherapy dose escalation studies, where a relationship between the duration of G3M and consequential mucosal damage has been observed [11].

Despite establishing a model relating mean dose to the OCC OAR and incidence of version 3 G3M, Bhide's group subsequently developed the MSC OAR. Dean *et al.* [8] have shown a reduction in mean mucosal doses when the same plan is applied to the MSC OAR as compared with the OCC OAR and showed the increased potential to reduce dose to

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