Clinical Oncology 29 (2017) 263–273

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

Normal Tissue Complication Probability (NTCP) Modelling of Severe Acute Mucositis using a Novel Oral Mucosal Surface Organ at Risk

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Received 12 July 2016; received in revised form 20 October 2016; accepted 1 November 2016

Abstract

Aims: A normal tissue complication probability (NTCP) model of severe acute mucositis would be highly useful to guide clinical decision making and inform radiotherapy planning. We aimed to improve upon our previous model by using a novel oral mucosal surface organ at risk (OAR) in place of an oral cavity OAR.
Materials and methods: Predictive models of severe acute mucositis were generated using radiotherapy dose to the oral cavity OAR or mucosal surface OAR and clinical data. Penalised logistic regression and random forest classification (RFC) models were generated for both OARs and compared. Internal validation was carried out with 100-iteration stratified shuffle split cross-validation, using multiple metrics to assess different aspects of model performance. Associations between treatment covariates and severe mucositis were explored using RFC feature importance.
Results: Penalised logistic regression and RFC models using the oral cavity OAR performed at least as well as the models using mucosal surface OAR. Associations between dose metrics and severe mucositis were similar between the mucosal surface and oral cavity models. The volumes of oral cavity or mucosal surface receiving intermediate and high doses were most strongly associated with severe mucositis.
Conclusions: The simpler oral cavity OAR should be preferred over the mucosal surface OAR for NTCP modelling of severe mucositis. We recommend minimising the volume of mucosa receiving intermediate and high doses, where possible.

Key words: Head and neck radiotherapy; machine learning; mucositis; NTCP modelling; OAR delineation; oral mucosa

Introduction

Mucositis is a common and important acute toxicity of head and neck radiotherapy, which may result in pain, dysphagia [1] and weight loss, and, hence, reduced quality of life [2,3]. Mucositis may lead to missed treatment fractions [4] and is frequently dose limiting in dose-escalation and accelerated fractionation regimens designed to improve tumour control [5–7]. Furthermore, severe acute reactions have been implicated in the subsequent development of 'late' radiation toxicity [8–10]. A normal tissue complication probability (NTCP) model for severe mucositis, with sufficient predictive performance, could be used for clinical decision-support [11]. Associations between radiotherapy dose metrics and mucositis could inform changes to the radiotherapy planning dose objectives to reduce the incidence of severe mucositis. It has previously been shown that intensity-modulated radiotherapy can be used to spare the oral mucosa in oropharyngeal radiotherapy patients [12].

Our group has previously generated and internally validated an acute mucositis NTCP model, with modest-to-good discriminative ability (mean area under the receiver operating characteristic curve [AUC] = 0.71, standard deviation = 0.09 on internal validation) [13]. The below-perfect predictive performance was attributed to limitations of the organ at risk (OAR) segmentation, limitations of the toxicity scoring instrument and not having data on

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http://dx.doi.org/10.1016/j.clon.2016.12.001

relevant clinical and biological parameters. Only the first of these can be addressed retrospectively. We hypothesised that the discriminative ability could be improved through a more accurate description of the dose distribution to the oral mucosal surfaces, which were previously described by the oral cavity volume contours (OCC) method [14]. The OCC OAR predominantly describes the dose to the musculature of the tongue and floor of mouth, which are not expected to be relevant for mucositis, and does not incorporate the buccal mucosa or mucosa of the lips. We, therefore, developed a novel oral mucosal surface contours (MSC) OAR structure that includes the mucosal surfaces of the oral cavity and excludes the musculature of the tongue and floor of mouth [15]. It was expected that this novel OAR would be more relevant to NTCP modelling of mucositis. To aid implementation of this OAR to a large cohort of patients, we showed that the segmentation of this structure could be fully automated using atlas-based segmentation [16].

The aims of this study were to: (i) improve the discriminative ability of our, previously reported, acute mucositis NTCP model [13] and (ii) gain greater insight into the radiotherapy dose–response relationship of the oral mucosa, through the application of our novel, automatically segmented MSC structure [15,16].

Materials and Methods

Patient Data

A cohort of 351 head and neck radiotherapy patients, enrolled in six different clinical trials [17–23] (with institutional review board approval and signed patient consent; summarised in Appendix A), diverse in terms of primary disease site, radiotherapy treatment technique and use of concurrent chemotherapy, was used. The prescribed dose to the primary planning target volume was either 65 Gy in 30 fractions, 60 Gy in 30 fractions, 67.2 Gy in 28 fractions or 63 Gy in 28 fractions (described in Appendix A). Toxicity was consistently scored for all studies using the mucositis score from the Common Terminology Criteria for Adverse Events (CTCAE) versions 2 (mucositis due to radiation) [24] or 3 (mucositis/stomatitis [clinical examination]) [25] instruments, which are near equivalent. Toxicities were recorded prospectively before the start of radiotherapy, weekly during radiotherapy, and at 1–4 and 8 weeks after radiotherapy. The toxicity end point of interest chosen for analysis was the maximum reported mucositis grade. Patients were dichotomised into severe (maximum toxicity score of grade 3 or worse) and non-severe (maximum toxicity score of less than grade 3) mucositis. Patients with baseline toxicity or any missing toxicity scores and a maximum score below 3 were excluded from the analysis. Our missing data handling strategy is discussed in Appendix B. Complete DICOM radiotherapy data were available for 351 patients. After removing patients who had both missing toxicity data and a maximum toxicity of grade 2 or lower, 182 patients were available for analysis. MSC atlas-based segmentation failed for three patients (for no obvious reasons), so these were excluded from the analysis, leaving 179. Severe mucositis incidence was 74%. Note that excluding the patients removed due to missing toxicity data skews the incidence values to higher than the actual incidences.

Induction chemotherapy ($n = 89$), concurrent chemotherapy regimen (cisplatin [$n = 64$], carboplatin [$n = 10$], one cycle of cisplatin followed by one cycle of carboplatin [$n = 6$] or none [$n = 99$]; administered in two cycles, on days 1 and 29 of radiotherapy), definitive ($n = 149$) versus postoperative radiotherapy, age (median = 57 years, range = 17–88 years), gender ($n_{male} = 114$) and primary disease site (nasopharynx [$n = 18$], oropharynx [$n = 100$], hypopharynx/larynx [$n = 18$], unknown primary [$n = 8$] or parotid gland [$n = 35$]) were also included as covariates in the models. Unilateral versus bilateral irradiation was not explicitly included as a covariate in the models as it correlates perfectly with parotid gland primary disease site.

Radiotherapy Dose Data

The oral mucosa was contoured on computed tomography using two different techniques: the current guidelines (OCC) method [14] and our novel MSC technique [15,16]. Mucositis of the portion of the pharyngeal mucosa visible on clinical examination was included in the scoring of mucositis. Therefore, the pharyngeal mucosa was manually delineated from the roof of the nasopharynx to the level of the inferior border of the oral mucosa structure (OCC or MSC as appropriate) and combined with the OCC or MSC structure (denoted OCC-PM and MSC-PM). The inferior extents of the OCC and MSC structures were very similar. Figure 1 shows an example of these structures. Clinical oncologists carried out the OCC and PM contouring, following the same guidelines, using the RayStation research version 4.6.100.12 treatment planning system (RaySearch Laboratories AB, Stockholm, Sweden). MSC contouring was carried out manually for 41 patients (those included in the atlas and test cohort in [16]). For the remaining patients the MSC was delineated fully automatically. The automatically generated OARs were visually assessed for gross errors. Three patients were excluded due to failure of the automatic segmentation, as previously described in the patient data section. The techniques for manual and automatic MSC segmentation are described in [16].

The physical dose distribution was converted to the fractional dose distribution (physical dose delivered in each fraction), as recommended for modelling of acute toxicity by Tucker *et al.* [26]. The fractional dose distribution was described by the dose-volume histogram (DVH) in 20 cGy intervals from 20 to 260 cGy per fraction. There may be regional variations in radiosensitivity across the oral mucosa that cannot be detected by describing the dose distributions using only DVHs. For example, keratinised areas of the oral mucosa might be expected to be associated with lower mucositis scores [27] than non-keratinised regions of the oral mucosa [28]. Therefore, three-dimensional