Humidification mitigates acute mucosal toxicity during radiotherapy when factoring volumetric parameters. Trans Tasman Radiation Oncology Group (TROG) RadioHUM 07.03 substudy

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A R T I C L E   I N F O

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A B S T R A C T

Purpose/Objective(s): To model in a subset of patients from TROG 07.03 managed at a single site the association between domiciliary based humidification use and mucositis symptom burden during radiotherapy (RT) for head and neck cancer (HNC) when factoring in volumetric radiotherapy parameters derived from tumour and normal tissue regions of interest.

Materials/Methods: From June 2008 through June 2011, 210 patients with HNC receiving RT were randomised to either a control arm or humidification using the Fisher & Paykel Healthcare MR880 humidifier. This subset analysis involves patients recruited from Auckland City Hospital treated with a prescribed dose of ≥70 Gy. Regression models included control variables for Planning Target Volume 70 Gy (PTV70Gy); Equivalent Uniform Dose (EUD) MOIST and TSV (surrogates of total mucosal and total swallowing volumes respectively).

Results: The analysis included 39 patients (humidification 20, control 19). There was a significant odds reduction in CTCAE v3.0 functional mucositis score of 0.29 associated with the use of humidification (p < .001). Within the parameters of the model therefore, the risk of a humidification patient being scored as experiencing a one-step increase in functional mucositis was 3.45 times lower (1/0.29) than for control patients. A control patient was 4.17 times more likely to receive an unfavourable nutritional mode score (p < .001). The risk of being admitted to hospital decreased by a factor of 11.11 for humidification patients (p = .013).

Conclusion: The results support the hypothesis that humidification can help mitigate mucositis symptom burden. Radiotherapy dosimetric parameters assist in the evaluation of toxicity interventions.

Introduction

The rationale for domiciliary humidification during head and neck radiotherapy to ameliorate symptoms associated with mucositis using a high flow rate humidifier with nasal prong interface is based on principles of moist wound care, or in other words to reduce the impact of wound desiccation on tissue injury. This may help mitigate the intense pro-inflammatory environment characteristic of mucositis pathobiology [1,2]. Moisturisation aids nutrient delivery and facilitates migration of cells across epithelial surfaces during wound healing. A moist environment provides a cushioning effect to nerve endings, which can attenuate pain. Changes to the oral microbiome composition during radiotherapy which allow micro-organism species with virulence characteristics to become more dominant may be exacerbated by the desiccated environment [3]. Moisturisation may contribute to more favourable host-microbiome interactions that influence mucositis [4]. Patients with bulky pharyngeal tumours may also experience mass effect symptoms similar to sleep apnoea syndrome, and overnight high flow rate humidification may provide some of the symptomatic benefits associated with continuous positive airways pressure (CPAP) therapy [5].

The TROG 07.03 RadioHUM study was a phase 3 multi centre trial
evaluating the role of domiciliary humidification using the Fisher & Paykel Healthcare MR880 humidifier. The primary analysis has been previously reported [6]. Although the results were negative for the primary endpoint involving CTCAE version 3.0 clinical mucositis scores, there were several positive secondary endpoints suggestive of a benefit from humidification in reducing symptom burden. In compliant (per protocol; PP) patients, the area under the curve for CTCAE v3.0 functional mucositis was significantly reduced (p = .009). Mean total inpatient hospital days (p = .006) and proportion of patients requiring acute hospital admission (p = .013) were also reduced in the PP population. Estimates of McMaster University Head & Neck questionnaire patient reported symptom burden in the PP population were also in the direction favouring humidification with less symptom severity, although differences at most time points did not reach significance. The influence of humidification compliance on the results moderated recommendations regarding its practical utility.

There is evidence that mucositis symptom burden for individual patients correlates with dosimetric and volumetric radiotherapy parameters derived from tumour and normal tissue regions of interest (ROI) [7]. In this report we have modelled the association between humidification use and mucositis symptom burden when factoring in radiotherapy parameters, using a subset of patients from TROG 07.03 managed at a single institution. Radiotherapy parameters used include the Planning Target Volume 70 Gy (PTV70) as a surrogate of tumour volume, and two normal tissue regions of interest (ROI) centred on the oral cavity (MOIST), and oropharynx and supraglottic larynx (TSV).

The primary objective of this study is to use an ordinal regression model to investigate the effect of humidification on CTCAE v3.0 functional mucositis score when factoring in these tumour and normal tissue dosimetric variables. Secondary objectives are to investigate the effect of humidification on nutritional mode and hospitalisation events when factoring in dosimetric variables.

Methods

TROG 07.03 RadioHUM study was a phase 3 multi centre trial in which patients receiving radiotherapy (RT) for head and neck cancer were randomised 1:1 to receive either their institutional standard of care for managing mucositis, or the standard of care plus domiciliary based humidification (clinical trials. gov; NCT01917942). Eligibility criteria were the presence of pathologically confirmed cancer involving the nasopharynx, oropharynx, oral cavity, larynx, hypopharynx, or squamous cell carcinoma unknown primary provided eligible mucosal sites were irradiated. This subset analysis involves patients enrolled on TROG 07.03 recruited from Auckland City Hospital and treated with a prescribed dose of ≥70 Gy. This subset study was approved by the local hospital and university ethics committees.

A humidifier (model MR880 and HC211 flow source; Fisher & Paykel Healthcare, Auckland, New Zealand), set at 37 °C and 100% relative humidity, delivered 44 mg of water suspended in a vapour state per litre of air via nasal prongs. Humidification commenced at flow rates of 25 L/min, increasing if tolerated to 30 L/min. The aim was to just exceed inspiratory demand, thus avoiding entrainment of non-humidified air and promoting some mouth leakage to moisturise the oral cavity.

Humidifiers were provided for home use with instructions to start on day 1 of RT; the recommendation was to use the humidifier overnight with additional usage throughout the day. Humidification continued until week 12 after RT commencement. In those patients with CTCAE version 3.0 clinical mucositis > 2 at week 12 (persistent ulceration), humidification continued until the resolution of ulcerative component of mucositis or week 16, whichever occurred earlier.

Study endpoints

Acute toxicity was evaluated weekly using CTCAE version 3.0, from the commencement of radiotherapy until week 12. Both clinical mucositis and functional mucositis endpoints were recorded. As previously reported in the TROG 07.03 primary analysis, there was significant variability and range in clinical mucositis scoring across individuals and institutions. The low intra-class correlation reported in several studies for clinician scoring of the presence and severity of mucosal ulceration has resulted in the clinical mucositis score being removed from CTCAE version 4.0 [8]. The mucositis endpoint in CTCAE version 4.0 is classified by mucosal site but otherwise resembles functional mucositis score in CTCAE version 3.0. This subset analysis has used CTCAE version 3.0 functional mucositis scores only as the clinician assessment of mucosal toxicity.

Nutritional mode is a clinician reported assessment of nutritional status including feeding tube use employing a 6 point scale (supplementary online table). Nutritional mode was assessed weekly until week 8, and at weeks 10, 12, 16 and 20.

Hospitalisation events up to 20 weeks beyond the commencement of radiotherapy were recorded.

Structure definitions

Two normal tissue ROIs were used in the analysis.

1. MOIST volume (minor oral including sublingual salivary tissue) has been proposed as an ROI to encompass minor salivary glands within the mucosa of the oral cavity and anterior oropharynx (MOIST volume includes the floor of mouth, tongue, base of tongue, hard palate, soft palate, uvula, buccal mucosa, inner lips, retromolar trigone, lateral alveolar margin and anterior faucial pillars) [9]. MOIST was used as a surrogate for total mucosal volume of the oral cavity and anterior oropharynx.

2. Total swallowing volume (TSV) was defined as a composite ROI including the superior pharyngeal constrictors, middle pharyngeal constrictors, inferior pharyngeal constrictors, cricopharyngeus muscle, supraglottic larynx and glottic larynx.

Structure definition was performed by a head and neck Radiation Oncologist (AM) using RayStation version 4.0 treatment planning system (RaySearch Laboratories AB, Stockholm, Sweden). Atlas based segmentation was used within RayStation 4.0 to develop a template for these volumes from the first 20 patients. Subsequent patients thereafter had the template initiated to automatically generate ROI volumes which were then manually adjusted. A second head and neck Radiation Oncologist (GS) audited the normal tissue ROI volumes in 5 randomly chosen cases (Fig. 1).

Planning Target Volume 70 Gy (PTV70) was generated by a 3 mm expansion of the 70 Gy clinical target volume (the expansion was limited peripherally by a contour reduced by 3–5 mm from the external contour). In 2 patients treated to a total of 72 Gy, the PTV 72 was generated.

Statistical methods

Three regression models were established to explore the association of humidification use with dosimetric and volumetric parameters, and the influence of other control variables described below and in Table 1. The coefficient variance estimates were adjusted to account for additional variation from the imputation.

1. Functional mucositis was analysed using an ordinal regression model (also known as cumulative link model) [10].

2. Given the unreliability of the categorisation of the ordinal regression model with nutritional mode data, the 6 levels within the scale were combined into 2 categories (levels 1–3 representing more unfavourable nutritional mode involving feeding tube use, and levels 4–6 without feeding tube use). This reduced the data to a binary
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