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Original article

Beam path toxicity in candidate organs-at-risk: Assessment of radiation emetogenesis for patients receiving head and neck intensity modulated radiotherapy

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ABSTRACT

Background: To investigate potential dose–response relationship between radiation-associated nausea and vomiting (RANV) reported during radiotherapy and candidate nausea/vomiting-associated regions of interest (CNV-ROIs) in head and neck (HNC) squamous cell carcinomas.

Methods and material: A total of 130 patients treated with IMRT with squamous cell carcinomas of head and neck were evaluated. For each patient, CNV-ROIs were segmented manually on planning CT images. Clinical on-treatment RANV data were reconstructed by a review of the records for all patients. Dosimetric data parameters were recorded from dose–volume histograms. Nausea and vomiting reports were concatenated as a single binary "Any N/V" variable, and as a "CTC-V2+" variable.

Results: The mean dose to CNV-ROIs was higher for patients experiencing RANV events. For patients receiving IMRT alone, a dose–response effect was observed with varying degrees of magnitude, at a statistically significant level for the area postrema, brainstem, dorsal vagal complex, medulla oblongata, solitary nucleus, oropharyngeal mucosa and whole brain CNV-ROIs.

Conclusion: RANV is a common therapy-related morbidity facing patients receiving HNC radiotherapy, and, for those receiving radiotherapy-alone, is associated with modifiable dose to specific CNS structures.

Intensity-modulated radiation therapy (IMRT) has become an increasingly common radiation treatment technique for head-and-neck (HN) cancers [1,2]. While 3D-conformal planning is used in many cases internationally [3], the dosimetric superiority of step-and-shoot IMRT [4,5], as well as potential further conformality gains in arc-based variants [6–8], offers the advantage of improved tumor target coverage and critical normal tissue sparing [1], compared to 3D-conformal planning [9–11]. However, IMRT beam paths traverse normal tissues that may not have been directly irradiated in previous 2D and 3D techniques [2,12,13], resulting in distinct toxicity profiles from those seen in the pre-conformal radiotherapy era.

Among these symptom profiles are radiation-associated nausea and vomiting (RANV) symptoms. Radiotherapy alone to the head and neck region, in the pre-IMRT era, was held to have minimal risk of RANV [14,15], However, data suggest that it is commonly encountered in radiation therapy for head and neck cancer patients. Even in the pre-IMRT era, an Italian prospective observational trial demonstrated that radiation-induced emesis occurred in 40% of head and neck patients treated with conventional radiation techniques [16]. Studies have demonstrated that field size, site of disease, and fractionation of radiation therapy are associated with RANV [17]. Compounding this is the degree to which concurrent chemotherapy, which can be highly emetogenic [18], may impact RANV.

Previously, our group presented a pilot evaluation of dosimetric parameters in patients receiving head and neck IMRT for a limited number of candidate structures [12] Building on our preliminary

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experience, we have investigated, in an expanded cohort, additional candidate organs-at-risk (OARs) as part of a larger effort to define candidate organ-at-risk constraints for beam path-attributable symptom reduction in patients receiving IMRT monotherapy.

The specific aims of the current study include:

- interrogation of a potential dose–response relationship between candidate emetogenesis-associated OARs and NV symptoms reported during intensity-modulated radiotherapy (IMRT) for chemotherapy-naive head and neck squamous cell carcinomas,
- identification of OARs predominately associated with NV, for definitive IMRT and cohorts,
- assessment of literature reported candidate OAR constraints in a numerically robust dataset,
- derivation of population-based dose–RANV thresholds CNV-ROIs for future validation for dose constraint/treatment plan selection, and
- generation of hypotheses for future prospective efforts.

Materials and methods

Patient characteristics

A series of patients currently enrolled on a longitudinal patient reported outcome (PRO) assessment study were identified, and those treated with IMRT for squamous cell carcinomas of the head and neck between 2003 and 2013 were extracted from our institutional research database at our institution. Patient characteristics are summarized in Table 1. The original delivered DICOM-RT clinical treatment plan for each patient was imported into a research database (Pinnacle 9.4, Phillips Medical Systems, Andover, MA). Planning CT DICOM files were exported into a commercial deformable registration/segmentation software [19] (Velocity AI 2.8.1, Velocity Medical Solutions, Atlanta, GA). For each patient, candidate emetogenesis-associated regions of interest (CNV-ROIs) (Fig. 1, showing relevant CNV-ROIs; a representative anonymized case as both DICOM and axial slices as a PDF file is included as a supplement file) were segmented manually by a single physician observer [XXX], with serial review by a faculty radiation oncologist [XXX] and a fellowship-trained attending neuroradiologist [XX]. Dose volume histograms (DVHs) were generated for each CNV-ROIs. Therefrom, delivered doses to these specific CNV-ROIs were reconstructed.

Table 1
Patient Characteristics.

Age (years)	
Range	35–83
Median	59
Sex (no. pts)	
Male	98 (75%)
Female	32 (25%)
T stage (no. pts)	
T1	63 (48%)
T2	49 (38%)
T3	7 (5%)
T4	2 (2%)
Tx	9 (7%)
N stage (no. pts)	
N0	33 (25%)
N1	35 (27%)
N2	47 (36%)
N3	4 (3%)
N*x*	11 (8%)
Primary sites (no. pts)	
Base of Tongue	17 (13%)
Tonsil	88 (68%)
Larynx/Nasopharyngeal/Maxillary sinus	25 (19%)
Symptom cohorts (no. pts/percent)	
No nausea/vomiting reported	39 (30%)
Any N/V reported	91 (70%)
CTC-V2+ reported	47 (36%)

Clinical RANV data were reconstructed by a review of records for all 130 patients. At each weekly visit during RT, nausea and vomiting are formally weekly assessed by nursing staff as standard practice. RANV events were defined as the presence of any nursing-staff recorded nausea/emesis events between the start of IMRT and the completion of therapy. Symptoms were evaluated before the start of IMRT and then at least once weekly during patient consultations by nursing assessment. To correlate NV toxicities with radiation doses to the newly added areas of interest, the number and frequency of vomiting episodes were extracted from the electronic nursing record (MOSAIQ, Elekta Medical Systems, Mountain Valley, CA) as CTC-AE (Common Toxicity Criteria for Adverse Events) version 4 vomiting scores recorded during the patient's weekly management visit while on treatment. Nausea was recorded in the treatment record as a binary variable (e.g. was subjective nausea experienced by the patient during the previous week during any week of IMRT). Nausea and vomiting reports were concatenated as a single composite binary "Any N/V" variable (e.g. was any subjective nausea and/or any CTC-AE vomiting event reported at any time during the course of therapy), and as a "CTC-V2+" variable (e.g. was vomiting rated as greater than CTC-AE grade 1, consisting of reported vomiting more than twice in a 24-h period during any week of IMRT, and consistent with moderate-severe RANV).

Statistical evaluation

Statistical assessment was performed using JMP v 11Pro (SAS institute, Cary, NC). Mean dose to CNV-ROIs for those experiencing "Any N/V" or "CTC-V2+" was compared to those without symptoms using the Wilcoxon's rank test for each OAR, with Bonferroni correction for multiple comparisons. Logistic regression was performed using both "Any N/V" and "CTC-V2 + NV" with mean CNV-ROI dose as a continuous variable, to determine whether a dose–response effect might be observed, both for the entire cohort, likewise with Bonferroni correction.

In order to assess the relative contribution to RANV symptoms across multiple CNV-ROIs, and to derive exploratory non-model-dependent CNV-ROI dose–volume constraints recursive partitioning analysis (RPA) was performed. DVH data in 1 Gy bins for pooled CNV-ROIs were evaluated using RPA to allow identification and simultaneous dose–threshold selection of all CNV-ROIs, using "Any N/V" as a discriminant. RPA allows selection of the "thresholds" for continuous variables using a binary categorization variable. RPA is especially suited to scenarios where it is desirable to select and "threshold" continuous variable(s) associated with a categorical variable in the context of a multitude of predictor variables, even in the presence of complex interactions between candidate covariates [20]. Initially, a screen was performed within pooled DVH data for each CNV-ROI using a bootstrap forest methodology to identify candidate thresholds for each OAR. Using "Any N/V" as a discriminator, for each of the 14 CNV-ROIs a boostrap partition was undertaken using a forest of 100 trees after the first RPA split. The dominant column contributors were then selected for each CNV-ROI, and iterative partitions, with a minimum grouping of 20 patients per split/partition were performed until a split demonstrated a logworth value greater than the equivalent Bonferroni-corrrected $p < 0.05$ (e.g. the 1st a priori split criteria was set at a logworth < 1.30/$p < 0.05$, the 2nd split at a logworth < 1.6/$p < 0.025$, 3rd split at a logworth < 1.78/$p < 0.016$, etc.), with pruning after non-significance, to distill candidate

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