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Effect of Brain Stem and Dorsal Vagus Complex Dosimetry on Nausea and Vomiting in Head and Neck Intensity Modulated Radiation Therapy

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Abstract

Background—IMRT (Intensity Modulated Radiation Therapy) is becoming the treatment of choice for many head and neck cancer patients. IMRT reduces some toxicities by reducing radiation dose to uninvolved normal tissue near tumor targets; however, other tissues not irradiated using prior 3D techniques may receive clinically significant dose causing undesirable side-effects including nausea and vomiting (NV).⁹ Irradiation of the brainstem, and more specifically, the area postrema and dorsal vagal complex, has been linked to nausea and vomiting.¹⁰ We previously reported preliminary hypothesis-generating dose effects associated with NV in IMRT patients.⁹ The goal of this study is to relate brainstem dose to nausea and vomiting symptoms.

Methods—We retrospectively studied 100 consecutive patients that were treated for oropharyngeal cancer with IMRT. We contoured the brainstem, area postrema, and dorsal vagal complex with the assistance of an expert diagnostic neuroradiologist. We correlated dosimetry for the three areas contoured with weekly NV rates during IMRT.

Results—NV rates were significantly higher for patients who received concurrent chemotherapy. Post-hoc analysis demonstrated that chemoradiation cases exhibited a trend towards the same dose-response relationship with both brainstem mean dose ($p=0.0025$) and area postrema mean dose ($p=0.004$); however, both failed to meet statistical significance at the $p=0.002$ level. Duration of toxicity was also greater for chemoradiation patients, who averaged 3.3 weeks with reported CTC-AE events, compared to an average of 2 weeks for definitive RT patients ($p=0.002$). For definitive RT cases, no dose-response trend could be ascertained.

Conclusion—The mean brainstem dose emerged as a key parameter of interest; however, no one dose parameter (mean/median/EUD) best correlated with NV. This study does not address extraneous factors that would affect nausea and vomiting incidence, including the use of antiemetics, nor chemotherapy dose schedule specifics before and during RT. A prospective study will be required to depict exactly how IMRT dose affects NV.

Keywords

Intensity-modulated radiotherapy; Head and neck cancer; Brainstem; Postrema; Nausea and vomiting

Introduction

IMRT provides a means by which the tumor volume dose can be maintained or even escalated, while the dose to surrounding uninvolved normal tissue can be reduced. The general assumption with IMRT technique is that a higher conformal dose is achieved in the target volume, while critical structures are spared or receive a significantly lower dose than traditional 3D or 2D planning. IMRT uses a circumferential array of beams along with multi-leaf collimators to create the highly conformal dose cloud of radiation (Figure 1). These beams traverse normal tissues that may not have been directly irradiated in prior 2D and 3D techniques. IMRT planning constraints can be used to limit dose to below accepted “tolerance” levels and prevent devastating complications such as brain necrosis and chronic toxicities such as xerostomia. We recently reported that brain stem doses well below traditionally accepted tolerance levels are associated with NV. Radiation-induced NV is considered a lower minimal risk for patients with head and neck cancer who are being treated with radiation therapy only, but these data antedated IMRT.^{2, 10} The area postrema in the medulla oblongata and the dorsal vagus nucleus have been linked to radiation-induced NV.^{6, 8, 10}

Specific aims of this study include:

- Correlation of the presence or absence of nausea/vomiting toxicities with dose to structural CNS components during IMRT of the head and neck.
- Correlation of the presence of severe nausea/vomiting (CTC-AE Grade >2) with dose to said structures.
- Identification of specific dosimetric parameters associated with toxicity for implementation in future prospective series.

Materials and Methods

We reviewed 100 consecutive head and neck cancer IMRT cases treated from 2003 up until 2007 as identified from our institutional research database. This retrospective study was approved by the Institutional Review Board and patient identity was protected. The original clinical treatment plan for each patient was imported into the research database. Each patient was treated with an arrangement of nine intensity modulated beams. The areas of interest were the brainstem, area postrema (AP) and dorsal vagal complex (DVC) (Figure 2). The medulla oblongata is the portion of the brainstem that protrudes through the foramen magnum into the skull and is a continuation of the spinal cord. The brain stem starts at approximately the upper border of the first cervical vertebra and continues superiorly to the pons and mesencephalon.¹

The previously contoured brainstem was recontoured due to contour variations among planning dosimetrists, and AP and DVC contours as well. A group of four dosimetry students trained and instructed by a single expert neuroradiologist and an expert dosimetrist contoured the structures according to common guidelines. These were then reviewed and approved by the neuroradiologist. Dose Volume Histograms (DVH) were generated to include the additional contours. From there, the minimum, maximum, mean, and median radiation doses to these areas were recorded.

To correlate nausea and vomiting toxicities with radiation doses to the newly added areas of interest, the number and frequency of nausea/emesis was extracted from the MOSAIQ database as CTC-AE version 3 scores recorded during the patient's weekly management visit while on treatment. These scores were then transformed into a binary variable indicating patients experiencing CTC-AE grade 3 nausea/vomiting vs. CTC-AE grade 2). Data on concurrent chemotherapy was also recorded as a binary variable (concurrent chemotherapy vs. definitive RT).

Extracted data was analyzed into JMP v6.1 statistical software for analysis. Descriptive statistics for demographic and dosimetric variables were calculated. Between group comparison for binary continuous variables was performed using t-test with post-hoc Tukey's HSD. Weekly CTC-AE toxicity scores were regarded as ordinal variables, and numeric toxicity grade frequency was analyzed using chi-square analysis. Binary logistic regression was performed to ascertain dose-response relationships between composite variables (patients experiencing toxicity vs. no toxicity, and patients experiencing CTC-AE grade 3 nausea/vomiting vs. CTC-AE grade 2).

In order to account for multiple comparison, a Bonferroni correction was applied for the number of logistic regressions performed; this required that for each individual logistic regression, a $p < 0.002$ is required to meet statistical significance. For all other analyses, the standard $p < 0.05$ was utilized.

Results

A total of one hundred IMRT cases were included in the dataset; of these, 51 received concurrent chemoradiation, typically with platin, while 49 were cases were RT alone. The median age of patients was 56 years (range 32-80 years), with 86 male and 14 female patients. All patients were treated with standard fractionation radiotherapy using a median of 66 Gy in a median of 30 fractions (Table 1). T & N staging for each patient is depicted in Table 2.

Table 3 shows the number of patients experiencing nausea and vomiting with IMRT alone and IMRT with concurrent chemotherapy on a weekly basis. Nausea and vomiting is seen less in patients with IMRT alone and with less severity of symptoms. NV also abated more rapidly in IMRT alone patients than compared with concurrent chemo. Toxicity reportage revealed 16 patients with a maximum CTC-AE Grade of 0, 32 with Grade 1, 33 with Grade 2, and 19 with Grade 3. The median number of weeks with CTC-AE scores >0 was 2 weeks (mean 2.7, range 0-7) (Table 4).

Analysis of the entire cohort (n=100) demonstrated multiple dosimetric variables associated with trend towards a dose-response relationship with regard to maximum toxicity; however, all failed to meet statistical significance at the Bonferroni-adjusted threshold ($p = 0.002$). Binary dose-toxicity analysis demonstrated a positive relationship on logistic regression with severe (Grade 3 or greater) toxicity at a statistically significant level for the brainstem mean dose and area postrema mean dose ($p = 0.002$ for, Table 5, Figures 3 and 4).

Patients receiving chemotherapy exhibited a statistically distinct distribution of CTC-AE scores ($p=0.00068$, Table). Duration of toxicity was also greater for chemoradiation patients, who averaged 3.3 weeks with reported CTC-AE events, compared to an average of 2 weeks for definitive RT patients ($p=0.002$). Post-hoc analysis demonstrated that chemoradiation cases exhibited a trend towards the same dose-response relationship with both brainstem mean dose ($p=0.0025$) and area postrema mean dose ($p=0.004$); however, both failed to meet statistical significance at the $p = 0.002$ level. For definitive RT cases, no dose-response trend could be ascertained for the structures/parameters investigated.

Discussion/Conclusion

While the benefit for the use of IMRT for the treatment of HNC is well documented, specifically for the reduction of dose to the parotid salivary glands to lessen the incidence of high-grade xerostomia, it does not come without a cost. The use of multi-beam circumferential IMRT dose arrangement introduces higher integral dose to normal tissues as compared to conventional techniques⁹. It is noteworthy to mention that although the cases reviewed in this study demonstrate a nine beam arrangement, this is not a clinical standard. Planning and delivery of head and neck IMRT can be accomplished utilizing fewer beams to possibly decrease integral dose to normal tissues, however this may come at the expense of dose conformity depending on the target volumes.

Regarding brainstem toxicity in HNC treatment, 54 Gy is a common dose constraint used in clinical practice⁷. This dose limit is beneficial for the prevention of brainstem necrosis, however it does not prevent the occurrence of acute nausea and vomiting resulting from the lower integral doses received from IMRT treatment. Doses to specific areas of the brainstem, the area postrema and dorsal vagal complex, have been correlated to nausea and vomiting based on previous experience in stereotactic radiosurgery and that further limiting those doses could reduce occurrence of those toxicities^{4, 5}. Utilizing DVH analysis in their retrospective study, Rosenthal, et al. detail mean and median brainstem doses below 5 Gy using conventional treatment technique with minimal NV reporting and 25-35 Gy mean and median ranges using IMRT technique with statistically significant NV reporting⁹. Our data suggests that NV developed around week two of treatment indicating a possible 15 Gy to 25 Gy dose correlation to toxicity.

The concurrent use of emetogenic chemotherapy was also considered in this study; however, our limited sample size for RT/chemoRT groups makes elucidation of the effect of chemoRT on dose response difficult. It appears that dose-response thresholds/relationships may be modified substantially with concurrent chemoradiation.

Since this investigation was performed retrospectively, it does not address extraneous factors that could affect toxicity experience. These factors include the use of prophylactic antiemetics or antiemetic medication received during radiation treatment, use of radioprotectants and radiosensitizers before and during treatment, and outside stimuli that may increase sensitivity to nausea and affect baseline levels of toxicity. Such factors warrant a prospective investigation to said structures for radiation-induced NV to determine the true toxicity levels from radiotherapy alone. As with the previous study, mean brainstem dose emerges as a key parameter of interest; however, no one dose parameter (mean/median/EUD) best correlated with NV. In addition, we would like to look at more complex measures of toxicity including use of antiemetics, a more detailed toxicity scoring criteria, and quality of life measures. From these further studies, treatment planning solutions could be identified and integrated into future IMRT HNC treatments.

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Fig. 1.
Nine beam IMRT arrangement.

Fig. 2.
Dorsal vagal complex, area postrema and brainstem delineation on CT.

Logistic Fit of Any Grade 3 Toxicity by area postrema mean

Fig. 3.
Area postrema Grade 3 toxicity

Fig. 4.
Brainstem Grade 3 toxicity

Table 1

Patient population demographics

		# Pts
Age (years)		
	Range	32 - 81
	Median	56
Sex		
	Male	86
	Female	14
Primary Site		
	Base of Tongue	49
	Tonsil	47
	Oropharyngeal	4
Treatment type		
	IMRT alone	49
	Concurrent cisplatin	25
	Other concurrent chemo	26
Dose to primary site (Gy)		
	40 / 20 fx	1
	55 / 29 fx	1
	57 / 30 fx	12
	60 - 63 / 30 fx	1
	66 / 30 fx	54
	66 - 68 / 33 fx	1
	70 / 33 fx	27
	70 / 34 fx	1
	70 / 35 fx	2

Table 2

Population by tumor and nodal staging

T and N staging (n = 100)						
	T0	T1	T2	T3	T4	TX
N0	1	2	7	4	3	1
N1	0	5	10	4	0	1
N2	0	25	18	10	1	4
N3	0	0	1	0	1	0
NX	0	0	1	0	0	1
Total	1	32	37	18	5	7

Table 3

Rates of toxicities for nausea and vomiting by treatment group: IMRT alone or with concurrent chemo

	IMRT alone				Concurrent Chemo			
	0	1	2	3	0	1	2	3
Week 1	38	5	5	1	38	9	4	0
Week 2	31	12	4	2	24	18	8	1
Week 3	30	13	4	2	29	14	4	4
Week 4	33	7	6	1	29	16	5	2
Week 5	30	0	5	1	26	15	7	3
Week 6	23	8	8	0	21	16	9	2
Week 7	15	5	0	0	12	14	5	2
Week 8	0	0	0	1	1	3	3	3

Score
0= None
1= <2 day
2= >2 day
3= Unrelieved

Table 4

Distribution of toxicity by chemotherapy cohort

Cohort	CTC-AE maximum score			
	0	1	2	3
ChemoRT	4	18	14	15
Definitive RT	12	14	19	4

Table 5

Logistic regression

Structure	Parameter	p=	Sig.
Brainstem	Maximum	0.07	n.s.
	Mean	0.02	n.s.
	Median	0.02	n.s.
	EUD	0.5	n.s.
Dorsal vagal complex	Maximum	0.1	n.s.
	Mean	0.05	n.s.
	Median	0.06	n.s.
	EUD	0.3	n.s.
Area postrema	Maximum	0.08	n.s.
	Mean	0.3	n.s.
	Median	0.1	n.s.
	EUD	0.6	n.s.

Structure	Parameter	p=	Sig.
Brainstem	Maximum	0.07	n.s.
	Mean	0.0006	*
	Median	0.004	n.s.
	EUD	0.3	n.s.
Dorsal vagal complex	Maximum	0.02	n.s.
	Mean	0.007	n.s.
	Median	0.009	n.s.
	EUD	0.4	n.s.
Area postrema	Maximum	0.01	n.s.
	Mean	0.001	*
	Median	0.01	n.s.
	EUD	0.7	n.s.

Results of logistic regression evaluation of maximum toxicity distribution.

Results of analysis of binary logistic regression (Grade 3 vs < Grade 3 CTC-AE scores).