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Correlation of Planned Dose to Area Postrema and Dorsal Vagal Complex with Clinical Symptoms of Nausea and Vomiting in Oropharyngeal Cancer (OPC) patients treated with radiation alone using IMRT

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Abstract

Objective—To correlate the planned dose to the nausea center (NC) - area postrema (AP) and dorsal vagal complex (DVC) - with nausea and vomiting symptoms in OPC patients treated with IMRT without chemotherapy. We also investigated whether it was possible to reduce doses to the NC without significant degradation of the clinically accepted treatment plan.

Methods—From 11/04 to 4/09, 37 OPC patients were treated with definitive or adjuvant IMRT without chemotherapy. Of these, only 23 patients had restorable plans and were included in this analysis. We contoured the NC with the assistance of an expert board-certified neuroradiologist. We searched for correlation between the delivered dose to the NC and patient-reported nausea and vomiting during IMRT. We used one-paired t-test: two-sample assuming equal variances to compare differences in dose to NC between symptomatic and asymptomatic patients. We then replanned each case to determine if reduced dose to the NC could be achieved without compromising coverage to target volumes, increasing unwarranted hotspots or increasing dose to surrounding critical normal tissues.

Results—Acute symptoms of nausea were as follows: Grade 0 (n=6), Grade 1 (n=13), Grade 2 (n=3), and Grade 3 (n=1). Patients with no complaints of nausea had a median dose to the DVC of 34.2 Gy (range 4.6-46.6 Gy) and AP of 32.6 Gy (range 7.0-41.4Gy); whereas those with any

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complaints of nausea had a median DVC dose of 40.4 Gy (range 19.3-49.4 Gy) and AP dose of 38.7 Gy (range 16.7-46.8 Gy) (p=0.04). Acute vomiting was as follows: Grade 0 (n=17), Grade 1 (n=4), Grade 2 (n=1), and Grade 3 (n=1). There was no significant difference in DVC or AP dose among those with and without vomiting symptoms (p=0.28).

Upon replanning of each case to minimize dose to the NC, we were, on average, able to reduce the radiation dose to AP by 18% and DVC by 17%; while the average dose variations to the PTV coverage, brainstem, cord, temporal lobes, and cochlea were never greater than 3%. Hotspots increased by 2% for 3 patients while hotspots for remaining patients were less than 2% variation.

Conclusion—For OPC cancer patients treated with IMRT without chemotherapy, dose to AP and DVC may be associated with development of nausea. We were able to show that reducing doses substantially to the NC is achievable without significant alteration of the clinically accepted plan and may reduce the incidence and grade of nausea. As symptoms of nausea can be devastating to patients, one can consider routine contouring and constraining of the NC to minimize chances of having this complication.

Keywords

Radiation-induced nausea and vomiting; intensity modulated radiation therapy; area postrema; dorsal vagal complex; head and neck

Introduction

Head and neck cancer patients receiving radiation therapy commonly suffer nausea and vomiting, a symptom that if severe enough may interrupt or delay radiotherapy treatment course. In a recent study from Italy, it was found that radiation-induced emesis occurred in 30% of head and neck patients treated with conventional radiation techniques (1). This study reported their results with concurrent use of chemotherapy and it was unclear whether intensity-modulated radiation therapy (IMRT) was performed, which has now become routinely used for radiotherapy in patients with head and neck cancer (2). IMRT improves dose conformality to the target volume but results in higher integral doses of radiation to surrounding normal tissue structures (3). For head and neck patients, IMRT techniques generally deliver a potentially significant dose to the area postrema (AP) and the dorsal vagal complex (DVC), even though care is taken to constrain dose to the brainstem. The AP and the DVC have been considered to be areas that regulate nausea and vomiting (4, 5). Whether radiation dose-response to these structures exists in relation to nausea and vomiting remains unclear.

Two studies examined IMRT doses to these structures and its relationship to nausea and vomiting (6, 7). In one retrospective study, it was found that radiation dose to the dorsal vagal complex may play a role in the development of nausea during head and neck IMRT (7). Patients with an acute nausea of grade 0 had a median dorsal vagal complex dose of 6.5 Gy while patients with grades 1 to 2 had a median dorsal vagal complex dose of 26.9 Gy. However, 23 of 43 patients (53%) received chemotherapy and 15 of these patients (35%) received multiagent chemotherapy. On multivariate analysis, only amifostine use and chemotherapy appeared to showed significance for nausea.

Similarly, a study by Ciura *et al.* examined 100 patients treated for oropharyngeal cancer with IMRT to relate brainstem dose to nausea and vomiting symptoms (6). All patients were treated using a 9-beam IMRT arrangement. *Post hoc* analysis demonstrated that chemoradiation cases exhibited a trend towards dose response relationship with area postrema mean dose and brainstem mean dose. Fifty one percent of patients in this study received chemotherapy and the authors stated that the limited sample size made it hard to elucidate the effect of concurrent chemotherapy.

It is clear that many chemotherapy agents are emetogenic and contributes to these symptoms with concurrent radiation therapy. However, we found no studies that examined specifically whether radiation therapy alone, in the absence of chemotherapy, to the AP and DVC is correlated with nausea and vomiting. Therefore, we sought to retrospectively examine the relation of nausea and vomiting with doses to the AP and DVC for head and neck patients treated with definitive or adjuvant radiation therapy in the absence of chemotherapy. We also sought to determine whether it was possible to reduce doses to the NC without compromising a clinically accepted treatment plan.

Methods

Study design

From November 1, 2002 to April 2, 2009, 439 consecutive patients with newly diagnosed squamous cell carcinoma of the oropharynx treated with definitive or adjuvant radiotherapy at Memorial Sloan-Kettering Cancer Center or one of its satellites were reviewed. Patients were then excluded for any of the following reasons: induction chemotherapy, concurrent chemotherapy, or adjuvant chemotherapy (n = 402). Of the 37 patients who were eligible for our study, 23 patients had restorable plans that could be included in this analysis. Every effort was exhausted to obtain the treatment planning and those with irrestorable plans we found utilized an older Alpha system. Patient and treatment characteristics are listed in Table 1.

The original clinical treatment plan for each patient was imported into the research database. The areas of interest were the brainstem, AP, and DVC (Figure 1). One radiation oncologist (T.J.W.) contoured the AP and DVC which were then reviewed and approved by an expert board-certified radiologist holding a certificate of added qualification in neuroradiology (R.J.Y.). These contours were then reviewed again by an expert head and neck radiation oncologist (N.Y.L.). Dose-volume histograms were generated to include the additional contours. From there, the hottest 5% (D05), maximum (Dmax) and mean radiation doses (Dmean) to these areas were computed and recorded. Additionally, each case was replanned (S.F. and P.M.) to attempt dose reduction to the NC without compromising coverage to critical organs. We analyzed the doses given to the surrounding critical organs including the cord, brainstem, cochlea, and temporal lobes.

Treatment

All patients received dental care followed by intensity-modulated radiation therapy (IMRT) using two, three, or four dose painting levels. For definitive treatment, we delivered 70 Gy at

2.12 Gy per fraction to the planning target volume (PTV) associated with the gross tumor volume (GTV), 59.4 Gy or 56.0 Gy at 1.8 Gy or 1.7 Gy per fraction to the PTV associated with the high-risk clinical target volume (CTV), and 54 Gy at 1.64 Gy per fraction to the PTV associated with the low-risk CTV. For adjuvant treatment, we delivered 66 Gy at 2 Gy per fraction to the PTV of the high-risk CTV, 60 Gy at 1.81 Gy per fraction to the PTV of intermediate-risk CTV, and 54 Gy at 1.64 Gy per fraction to the PTV of the low-risk CTV. The GTVs and CTVs were each expanded 3 to 5 mm to generate their respective PTVs.

Toxicity

Patients were assessed for acute complications by chart review using the Common Terminology Criteria for Adverse Events v4.0 (CTCAE). The maximum weekly nausea and vomiting grade during the entire radiotherapy course was recorded for each patient (Table 2). Additionally, weekly on-treatment evaluation notes were assessed to determine toxicity.

Statistical Analysis

We investigated the presence of nausea or vomiting of any grade. We correlated nausea and vomiting to the dose that the area postrema and dorsal vagal complex received. One-paired t-test: two-sample assuming equal variances to compare differences in dose to NC between symptomatic and asymptomatic patients was performed.

Results

Seventeen patients (74%) reported acute nausea symptoms (Table 3). Fourteen patients (57%) developed grade 1 nausea, 3 patients (13%) developed grade 2 nausea, and 1 patient (4%) developed grade 3 nausea. Six patients (26%) reported no acute nausea symptoms. Four patients (17%) developed grade 1 vomiting, 1 patient (4%) developed grade 2 vomiting, and 1 patient (4%) developed grade 3 vomiting. Seventeen patients (74%) reported no acute vomiting symptoms.

The median dose to the DVC and AP was significantly higher in patients with grade 1 to 3 nausea (Table 4). Patients without nausea symptoms had a median maximum dose to the DVC of 34.2 Gy (range 4.6-46.6 Gy) and AP of 32.6 Gy (range 7.0-41.4 Gy); while those with a nausea grade of 1 to 3 had a median DVC dose of 40.4 Gy (range 19.3-49.4 Gy) and AP dose of 38.7 Gy (range 16.7-46.8 Gy) (p=0.04). The median maximum dose to the DVC and AP was not different in patients with or without vomiting symptoms. Patients without vomiting symptoms had a median maximum dose to the DVC of 39.1 Gy (range 4.7-46.6 Gy) and AP dose of 35.6 Gy (range 4.3-46.8 Gy); while those with a vomiting grade of 1 to 3 had a median DVC dose of 44.7 Gy (range 19.4-49.4 Gy) and AP dose of 39.5 Gy (16.7-48.8 Gy) (p=0.28).

All 23 patients' treatment plans were replanned to minimize dose to the NC. On average, we were able to reduce the mean dose to the AP by 18% and DVC by 17% (Table 5). The average reduction of D05 to the AP was 18% and DVC by 17%. The average dose variations to the PTV coverage, brainstem, cord, temporal lobes, and cochlea were less than 3%. Hotspots increased by 2% for 3 patients while hotspots for remaining patients varied by less than 3%.

Discussion

IMRT can result in higher integral dose to regions outside of the target volume, and is directly proportional to the number of beams used (8). Many studies have reported dose constraints to organs at risk, particularly the parotid gland, cord, brainstem, pharyngeal constrictors, larynx, optic nerves, and optic chiasm (8-13). It is reasonable to assume that sparing of functional anatomical sites may be achieved with current technologies. It is not always clear, however, whether sparing organs at risk function will compromise PTV coverage and degrade plan quality. In our study, we were able to achieve an average dose reduction of 16% to 18% to the NC after replanning without compromising coverage to target volumes or increasing dose to surrounding normal tissues. Interestingly, the median dose of the NC in symptomatic patients after replanning would be similar to, if not less, than the median dose of asymptomatic patients. However, it is unclear if intentional sparing of the NC will result in reduced toxicity. Our findings suggest that radiation dose alone, in the absence of chemotherapy, to the AP and DVC may be associated with nausea.

Monroe *et al.* suggested that radiation dose to the dorsal vagal complex was associated in the development of nausea during IMRT. They reported a median dose of 26.9 Gy to the DVC for grade 1 to 2 nausea and 6.5 Gy for grade 0 which is lower than our results of 40.4 Gy and 34.2 Gy, respectively. One possible explanation for this finding is that the majority of their patients concurrently received chemotherapy, which may have required a smaller radiation dose to induce symptoms. These results were also consistent with Ciura *et al.* who suggested that 15-25 Gy dose to the nausea center correlated with toxicity where majority of patients received chemotherapy (6).

We acknowledge this study is retrospective with small patient numbers, and thus selection bias and sample size have to be taken to account. Furthermore, although we excluded chemotherapy in our study, medications other than chemotherapy may also induce nausea and confound our results. Narcotics are well known to have emetogenic properties. In a study from Taiwan, 23.9% and 16.6% of patients reported vomiting and nausea, respectively, when transdermal fentanyl was given to head and neck cancer patients treated with radiotherapy (14). We also did not assess whether patients received anti-nausea medications which could have influenced the data. Additionally, higher doses to the AP and DVC may also have been a result of more extensive dose distributions which may have given rise to nausea for entirely unrelated reasons. For example, more extensive xerostomia and mucositis generally leads to more problems with ropy mucous, which can lead to nausea and vomiting. Our numbers were too small to determine if correlation between nausea and vomiting and dose to the AP were independent to mucositis and/or xerostomia. Our data is suggestive and that perhaps cooperative efforts are needed among institutions so that we can have adequate statistical power to describe an effect due to radiation.

We acknowledge that the AP and DVC are not easily identified (13). There are no clear guidelines on contouring these structures as there are for other critical head and neck normal structures (15-17). In our study, we relied on the expertise from a board-certified neuroradiologist to help review the AP and DVC (18). Many radiation oncology facilities are unlikely to have this resource available. Still, contouring the DVC or AP precisely may not

be absolutely necessary as long as the posterior medulla oblongata is spared as much dose as possible.

Historically, many head and neck cancer patients received radiation therapy using two-dimensional radiotherapy. Significant portions of the brainstem likely received doses greater than IMRT techniques. A retrospective study by Rosenthal et al. showed that nausea and vomiting was associated with a brainstem mean dose of ≥ 36 Gy (8). In their study, they reported 76% and 38% of patients treated with IMRT without chemotherapy had nausea and vomiting, respectively. These rates are similar to our small series of 74% and 26% that developed nausea and vomiting, respectively. One of the major differences compared to our study was rather than the entire brainstem dose, we focused on the AP and DVC which has been well known to regulate nausea and vomiting.

Avoidance of dose to the AP and DVC may reduce nausea and vomiting symptoms. Whether this is true will require a prospective study of how IMRT dose affects nausea and vomiting.

Conclusion

For head and neck cancer patients treated with IMRT without chemotherapy, dose to AP and DVC may be associated with development of nausea. Our data shows significant difference in the NC doses for asymptomatic versus symptomatic patients. We were also able to show that reducing doses substantially to the NC is achievable without significant alteration of the clinically accepted plan and may reduce the incidence of nausea. As symptoms of nausea can be devastating to patients, one can consider routine contouring and constraining of the NC to minimize chances of having this complication.

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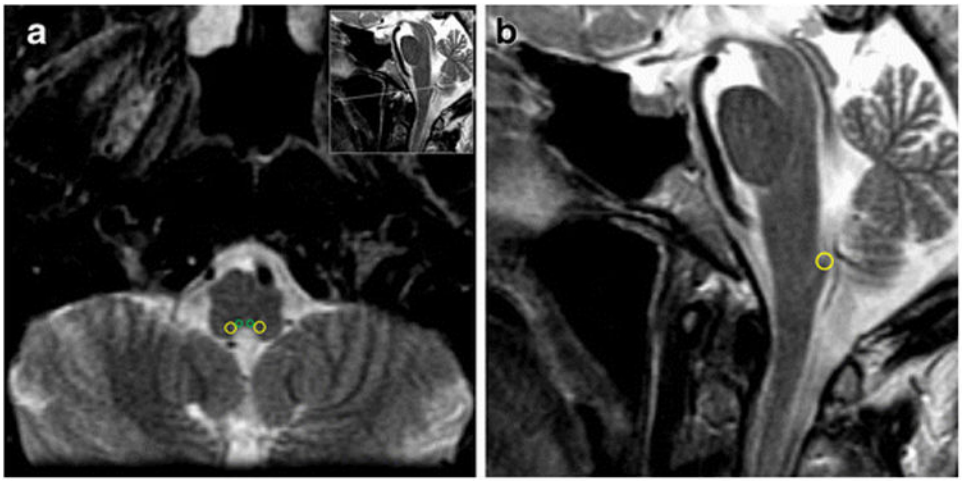

Fig. 1.

(A) T2 MRI axial contour of the area postrema (green) and dorsal vagal complex (yellow)

(B) T2 MRI sagittal contour of the dorsal vagal complex (yellow).

Table 1

Patient characteristics

Characteristic	[n (%)]
Sex	
Male	15 (65%)
Female	8 (35%)
Age	
Range	34-84
Median	57
Primary Site	
Base of tongue	6 (26%)
Tonsil	17 (74%)
Treatment type	
Definitive IMRT	15 (65%)
Adjuvant IMRT	8 (35%)
T stage	
T1	10 (43%)
T2	12 (52%)
T3	1 (4%)
T4	0 (0%)
N stage	
N0	17 (74%)
N1	2 (9%)
N2	4 (17%)
N3	0

Table 2

Acute Nausea and Vomiting Grade, CTCAE v3.0

Acute nausea grade	
Grade 0	None
Grade 1	Loss of appetite without alteration in eating habits
Grade 2	Oral intake decreased without significant weight loss, dehydration or malnutrition
Grade 3	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated
Acute vomiting grade	
Grade 0	None
Grade 1	1 to 2 episodes in 24 hrs
Grade 2	3 - 5 episodes in 24 hrs
Grade 3	≥ 6 episodes in 24 hrs; tube feeding, TPN or hospitalization indicated
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death

Table 3

Acute nausea and vomiting results

	Nausea (percent)	Vomiting (percent)
Grade 0	6 (26%)	17 (74%)
Grade 1	13 (57%)	4 (17%)
Grade 2	3 (13%)	1 (4%)
Grade 3	1 (4%)	1 (4%)

Table 4

Average and median dose delivered to asymptomatic and symptomatic patients.

	Grade 0 nausea patients (n=6)		Grades 1-3 nausea patients (n=17)		Grade 0 vomiting patients (n=17)		Grades 1-3 vomiting patients (n=6)	
	Average (cGy)	Median (cGy)	Average (cGy)	Median (cGy)	Average (cGy)	Median (cGy)	Average (cGy)	Median cGy)
Area Postrema								
Dmax	2956	3261	3716	3871	3434	3558	3765	3949
Dmean	2518	2943	3277	3311	2905	2960	3571	3673
D05	2816	3143	3600	3669	3269	3349	3755	3958
Dorsal Vagal Complex								
Dmax	2901	3420	3937	4041	3544	3910	4028	4469
Dmean	2845	3177	3472	3564	3186	3363	3654	3834
D05	3156	3412	3744	3812	3525	3742	3777	4063
Tempora l Lobe								
Dmax	1602	754	2492	571	2140	1600	3199	3664
Dmean	290	195	346	136	330	308	644	411
D05	723	352	826	301	860	635	1245	1017
Cochlea								
Dmax	2616	2576	3614	810	3113	3062	3747	3832
Dmean	1561	1174	2227	326	1978	1839	2545	2407
D05	2194	1972	3074	635	2702	2334	3183	3007

Table 5

Overall percent average increase and decrease in critical organ doses after replanning

	Average change in dose after replanning (percent)
Area Postrema	
Dmax	-18%
Dmean	-17%
D05	-18%
Dorsal Vagal Complex	
Dmax	-16%
Dmean	-17%
D05	-17%
Brainstem	-2%
Cord	-1%
Temporal Lobe	
Dmax	-3%
Dmean	-1%
D05	-2%
Cochlea	
Dmax	-1%
Dmean	-1%
D05	0%