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Volumetric tumor burden and its effect on brachial plexus dosimetry in head and neck intensity-modulated radiotherapy

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Abstract

To determine the effect of gross tumor volume of the primary (GTV-P) and nodal (GTV-N) disease on planned radiation dose to the brachial plexus (BP) in head and neck intensity-modulated radiotherapy (IMRT). Overall, 75 patients underwent definitive IMRT to a median total dose of 69.96 Gy in 33 fractions. The right BP and left BP were prospectively contoured as separate organs at risk. The GTV was related to BP dose using the unpaired t-test. Receiver operating characteristics curves were constructed to determine optimized volumetric thresholds of GTV-P and GTV-N corresponding to a maximum BP dose cutoff of > 66 Gy. Multivariate analyses were performed to account for factors associated with a higher maximal BP dose. A higher maximum BP dose (> 66 vs 66 Gy) correlated with a greater mean GTV-P (79.5 vs 30.8 cc; $p = 0.001$) and ipsilateral GTV-N (60.6 vs 19.8 cc; $p = 0.014$). When dichotomized by the optimized nodal volume, patients with an ipsilateral GTV-N 4.9 vs < 4.9 cc had a significant difference in maximum BP dose (64.2 vs 59.4 Gy; $p = 0.001$). Multivariate analysis confirmed that an ipsilateral GTV-N 4.9 cc was an independent predictor for the BP to receive a maximal dose of > 66 Gy when adjusted individually for BP volume, GTV-P, the use of a low anterior neck field technique, total planned radiation dose, and tumor category. Although both the primary and the nodal tumor volumes affected the BP maximal dose, the ipsilateral nodal tumor volume (GTV-N 4.9 cc) was an independent predictor for high maximal BP dose constraints in head and neck IMRT.

Keywords

Head and neck cancer; Brachial plexus; Gross tumor volume; Dose-volume histogram

Introduction

Brachial plexopathy after head and neck cancer (HNC) radiotherapy is a rare but potentially devastating complication without an effective cure.¹ A recent report has suggested that brachial plexopathy symptoms may be underreported in the HNC population, with a risk

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approaching 12% correlating with a dose-response relationship for the development of brachial plexus (BP)–related neuropathies among patients treated with radiotherapy for HNC.² Within the past 10 years, intensity-modulated radiotherapy (IMRT) has emerged as the standard radiotherapy approach for treating HNC. The radiation dose to the BP is significantly increased among patients undergoing IMRT compared with conventional radiotherapy for the treatment of HNC.³ IMRT optimization without consideration of the BP can lead to significant dose inhomogeneity within the BP, which may lead to an increased risk of long-term toxicity.⁴

The Radiation Therapy Oncology Group recommends limiting the BP maximum dose to 60 to 66 Gy, depending on the study protocol.⁵ Original data from Emami *et al.*⁶ suggest that the tolerance dose before the conformal radiotherapy era was 60 Gy. Radiologic atlases have been published to improve accuracy and reduce interobserver variability in contouring the BP.^{5,7,8} At our institution, the BP has been routinely contoured as an organ at risk (OAR) since 2004 with the intent to limit the BP maximum dose less than 60 Gy, while achieving tumor coverage with the prescription dose. A recent report of 114 patients with HNC treated with IMRT reported that a significantly higher planned radiation dose was delivered to the BP in patients with laryngeal, hypopharyngeal, and oropharyngeal cancer with locally advanced disease (63.4 vs 58.4 Gy; $p = 0.002$) as compared with more distant sites such as the nasopharynx.⁴ Similarly, it was reported that advanced nodal disease (N2/3) correlated with a higher maximum BP dose than N0/1 disease (60.9 vs 52.8 Gy; $p < 0.0001$).⁴ The maximum dose to the BP in patients receiving IMRT has been shown to be a significant contributing factor in the development of symptomatic brachial plexopathy.² Exploring dosimetric factors that may contribute to a greater risk of brachial plexopathy will help define and determine attainable dose limits to the BP during IMRT optimization, which may subsequently reduce the risk of BP-related complications. Hence, the purpose of this study was to evaluate the influence of volumetric tumor burden on planned BP dose in head and neck IMRT, when the BP is routinely contoured as an avoidance structure for IMRT optimization.

Methods and Materials

Patient population

Between August 2005 and May 2011, 75 patients with HNC were treated with definitive IMRT. Patients undergoing primary surgery and adjuvant postoperative radiation were excluded from this study. All patients were staged according to the 2002 American Joint Committee on Cancer.⁹ The study was conducted as a retrospective review and approved with a waiver of informed consent by the institutional review board.

Patient simulation and immobilization technique

Before receiving radiation therapy (RT), computed tomography (CT) simulation was performed with 2- to 3-mm slice thickness, extending from the vertex of the scalp to at least 5 cm below the clavicle. The patients were immobilized on a carbon fiber Civco “S-frame” with a type S thermoplastic head and neck board.

IMRT planning technique

The following structures were contoured by the physician on the planning CT: gross tumor volume (GTV), clinical target volume (CTV), planning target volume (PTV), and OAR including the bilateral BPs (each contoured as its own separate OAR). Margins of 7 to 15 mm were added to GTV to generate the CTV, followed by 3 to 5 mm expansion to PTV. GTVs were contoured incorporating diagnostic CT, positron emission tomographic, and magnetic resonance images when available from pretreatment scans.

Treatment planning was performed using Pinnacle treatment planning software, version 6.0 to 8.0m (Philips Medical Systems, Fitchburg, WI). The IMRT optimization objectives constrained the BP maximum dose to < 60 Gy if adjacent nodal disease was present or < 56 Gy for patients receiving elective nodal irradiation based on the gradient method. In the cases when the BP overlapped with PTV, priority was given to PTV coverage while keeping hot spots outside of the BP. IMRT plans were normalized such that 95% of PTV was covered with the prescription dose (66 to 69.96 Gy) and no more than 1% of PTV received less than 93% of prescription dose, and no more than 1% or 1 cc of PTV received more than 110% of prescription dose.

All patients were treated with 7 to nine 6-MV photon beam step-and-shoot technique. In 9 patients (12.0%), an upper IMRT plan was matched to a low anterior neck (LAN) field; the remaining patients were treated with full-length IMRT fields. Elective nodal areas and regions at risk for subclinical disease were treated to 54 to 60 Gy using a dose painting technique.

The volume, mean, minimum, and maximum planned doses to the BP were recorded in the dose-volume statistics report generated by the treatment planning system at the time of treatment and retrospectively collected. The volumes of the primary tumor (GTV-P) and nodal disease (GTV-N) were retrospectively collected from the original treatment contours.

Brachial plexus contouring technique

The right BP and left BP were contoured as separate structures in all 75 patients. The contouring methodology has been previously described.^{4,7} The superior and lower limits of the BP, between the C4-C5 and T1-T2 neural foramina, were identified on a sagittal CT view. The ventral rami of C5-T1 exiting through the intervertebral neural foramina were contoured on the axial CT. The BP trunks were contoured between the anterior and middle scalene muscles to the insertion of the scalene muscles into the first rib.

Statistical analysis

Descriptive statistics were calculated for tumor characteristics and dose-volume histogram parameters obtained from the radiation plans. For the analysis of GTV-P with planned radiation dose parameters (maximum and mean dose to BP), the BP (left or right) receiving the higher dosage was used. For the analysis of GTV-N with planned BP radiation dose parameters, dose parameters from the ipsilateral BP were used. Cutoff values of 60, 66, and 70 Gy for maximum dose to BP were used to categorize the cohort into 2 dose groups. Comparisons between the 2 groups were made with the unpaired t-test.

Receiver operating characteristics (ROC) curves were constructed, and optimized sensitivity- and specificity-defined volumetric thresholds of GTV-P and GTV-N were identified as the cutoff values that best predicted delivery of maximum radiation dose of > 66 Gy to either plexus (for GTV-P) and to ipsilateral BP (for GTV-N), respectively. ROC curve analyses were performed to demonstrate overall discriminatory power of a predictive model over the whole range of GTV values.¹⁰ The area under the ROC curve (AUC) was used to assess the predicted validity of GTV-P and GTV-N.¹¹ The closer the AUC value is to 1.0, the more predictive the GTV volume parameters were with respect to delivery of maximum radiation dose of > 66 Gy to BP. Based on these cutoff values, patients were dichotomized into 2 groups (GTV < vs cutoff value) and compared in terms of mean and maximum dose delivered to the BP.

Univariate and multivariate analyses were performed using the general linear model (Proc GLM) of SAS 9.1 system (SAS Institute, Cary, NC), and crude and adjusted maximum and mean dose to BP (with standard errors) were calculated for ROC cutoff-based GTV groups. The following potential confounding variables were explored in these analyses: BP volume (continuous variable), GTV (continuous variable), use of a LAN field (categorical), Tumor category (categorical: T0-T3 vs T4), Nodal category (categorical: N0-N1 vs N2-N3), and total radiation dose (continuous variable). Finally, patients were evaluated for local control, nodal control, and overall survival from conclusion of RT until last available follow-up or death. Patients with a follow-up of less than 3 months were excluded from treatment outcome analysis unless there was a disease recurrence during that period. Actuarial control rates at 2 years were estimated using the Kaplan-Meier product-limit method. A 2-sided hypothesis was used for all tests, and a probability value of less than 0.05 was considered statistically significant.

Results

Patient and treatment characteristics

The median age of study population was 58.0 years (range: 31 to 86 years). Stage III to stage IV disease was present in 65 (86.7%) patients. Four patients had an unknown primary and 3 were treated for nodal disease recurrence, hence there were 7 patients with T0 category disease, without a GTV-P. Complete tumor characteristics are described in Table 1.

Treatment outcome

The median follow-up for the entire patient cohort ($n = 75$) was 24.2 months, (range: 0 to 72.1 months). There were 6 patients who died from unknown or noncancer-related causes within 3 months (range: 0 to 2.4 months) of completing RT, that were excluded from the disease control analysis.

Local and nodal recurrences occurred in 12 (17.4%) and 7 (10.1%) patients, respectively. The median time to recurrence was 3.4 months (range: 1.9 to 19.3 months) and 2.1 months (range: 0.3 to 3.5 months) for local and nodal failure, respectively. The estimated 2-year actuarial local control, nodal control, and overall survival were 80.8%, 89.8%, and 77.9%,

respectively. To date, we have not detected any symptomatic brachial plexopathies, though our median follow-up is short to reliably detect such a potential late toxicity.

Dose and volume statistics for 150 BPs

The mean ($\pm$ standard deviation, SD) BP volume, BP mean dose, and BP maximum dose were 8.5 ± 4.5 cc, 43.7 ± 10.0 Gy, and 59.6 ± 11.5 Gy, respectively (Table 2). There were no statistically significant differences between mean right and left BP volume ($p = 0.958$), mean dose ($p = 0.604$), or maximum dose ($p = 0.646$).

Gross tumor volume

The GTV-P was contoured in 68 patients (mean = 40.8 cc; SD = 51.1 cc). Of 150 BP, 84 BP were adjacent to GTV-N (mean = 30.5 cc; SD = 67.8 cc), with no statistically significant difference between right and left sides ($p = 0.624$). In 66 BP, no adjacent nodes were involved.

Correlating maximum BP dose with primary GTV

Overall, 40 (58.8%), 14 (20.6%), and 11 (16.2%) patients received a maximum dose of > 60 , > 66 , and > 70 Gy, respectively, to at least 1 BP. A higher maximum BP radiation dose correlated with a greater mean GTV-P: 79.5 vs 30.8 cc ($p = 0.001$) and 98.6 vs 29.7 cc ($p < 0.0001$), for > 66 vs ≤ 66 Gy and > 70 vs ≤ 70 Gy, respectively (Table 3). When dichotomized by proximity of the primary site to the BP: oropharynx, hypopharynx, and larynx tumors (in closer proximity to the BP) were compared with nasopharynx, oral cavity, and others (more distant from the BP), a significant difference in mean GTV-P was noted for the 66 and 70 Gy cutoffs (Fig.).

Correlating maximum BP dose with nodal GTV

A total of 55 (65.5%), 22 (26.2%), and 13 (15.5%) individual BP received a maximum dose of > 60 , > 66 , and > 70 Gy, respectively. A higher maximum BP radiation dose correlated with a greater mean ipsilateral GTV-nodal; 60.6 vs 19.8 cc ($p = 0.014$) and 79.0 vs 21.6 cc ($p = 0.004$) for > 66 vs ≤ 66 Gy and > 70 vs ≤ 70 Gy, respectively (Table 3).

ROC curves analysis

ROC curve analysis identified 79.6 cc (AUC = 64.2%; CI: 51.6% to 75.4%) and 4.9 cc (AUC = 65.6%; CI: 54.4% to 75.6%) as the optimized cutoff values of GTV-P and ipsilateral GTV-N, respectively, which best predicted a maximum BP radiation dose of > 66 Gy. When dichotomized by the ROC threshold, a larger ipsilateral GTV-N volume (> 4.9 vs ≤ 4.9 cc) significantly correlated with a higher maximum ipsilateral BP dose (64.2 vs 59.4 Gy; $p = 0.001$) but no difference in maximum BP dose was noted for larger GTV-P volume (63.0 vs 60.8 Gy for > 79.6 vs ≤ 79.6 cc; $p = 0.518$) (Table 4).

Multivariate analysis

The difference in maximum ipsilateral BP dose, when dichotomized by GTV-N of 4.9 cc, retained significance after individually adjusting for BP volume, GTV-P, the use of a LAN field technique, total planned radiation dose, and tumor category. After adjusting for GTV-P,

the maximum BP dose was 64.1 and 59.4 Gy ($p = 0.001$) for GTV-N category < 4.9 and 4.9 cc, respectively.

Discussion

Tumor volume of the primary head and neck disease site and nodal disease in head and neck IMRT influences the BP maximum dose. Our data suggest that ipsilateral GTV-N and rather than the GTV-P predominantly drives the maximum BP dose. Patients with larger nodal GTVs were at significant risk of receiving a greater radiation dose to the BP, with an ipsilateral nodal volume of 4.9 cc identified as the optimized threshold of GTV-N above which the maximum ipsilateral BP dose was more likely to exceed 66 Gy. For the primary head and neck disease site, when dichotomizing by proximity to the BP, oropharynx, hypopharynx, and larynx tumors (which are anatomically in closer proximity to the BP) compared with nasopharynx, oral cavity, and others, have a lower primary tumor volumetric thresholds when using the 60, 66, and 70 Gy BP dose cut points. In our study, we found that the relationship between the GTV-P and BP dose constraints was more significant for patients with oropharynx, hypopharynx, and larynx tumors.

Chen *et al.*² recently reported the first study suggesting a dose-response relationship for the development of brachial plexopathies with a 1.39 times greater odds of developing symptoms with each 1 Gy increase in the maximum BP dose. On multivariate analysis, neck dissection (hazard ratio = 9.55; $p < 0.001$) and maximum BP dose (hazard ratio = 1.87; $p < 0.001$) were independent predictors of brachial plexopathy. This study reported a brachial plexopathy rate of 12%, which was significantly higher than that of previously published reports. This increased rate was likely because of a prospective questionnaire used to identify patients with subjective symptoms suggestive of brachial plexopathy.^{2,12} This questionnaire was adopted from studies on breast cancer and has not been validated in the HNC population. Therefore its sensitivity to detect brachial plexopathy in contrast to other treatment-related upper extremity neuropathies related to head and neck treatment has not yet been determined. The symptoms on the questionnaire may detect the sequelae of head and neck surgery, particularly a neck dissection with or without sacrifice of the spinal accessory nerve, chemotherapy-related peripheral neuropathy, or other treatment-related neuropathies, and may not be purely attributed to the effect of IMRT on the BP. For example, tingling in the hands and fingers could be related to peripheral neuropathy from cisplatin-based chemotherapy regimens, whereas pain in the arm or shoulder may also be related to effect of neck dissection on the spinal accessory nerve or from postoperative fibrosis and not exclusively owing to radiation-induced neuropathy. Despite these limitations, Chen *et al.* have demonstrated the importance of patient-reported outcomes as a measure of toxicity from the patient's perspective with dose correlation of the BP dose in head and neck IMRT.

Multiple studies have demonstrated that a larger GTV-P correlates with increased rates of locoregional recurrence, development of distant metastasis, and mortality.¹³ Given the higher risk of locoregional failure in patients with larger GTVs, a more aggressive approach is justified in giving priority to GTV and tolerating higher levels of BP maximal dose, especially given the potential for cure. As such, it is our preference that priority is given to

tumor coverage, even if this results in exceeding guidelines for BP dose constraints. This approach has maintained high local and regional control rates in this patient population, for whom 87% of patients have locally advanced HNC without brachial plexopathies reported to date in our series. Arguably, we did not perform patient-reported outcomes to determine more subtle patient symptoms relating to upper extremity dysfunction and plan to evaluate this in future studies. Future studies could also examine the influence of primary site on brachial plexopathy risk, as our study demonstrated that tumors in closer proximity to the BP such as the oropharynx, larynx, and hypopharynx generally have lower tumor volume thresholds when correlating to BP dose compared with HNCs of the nasopharynx and oral cavity.

The BP roots and trunks are located between the anterior and middle scalene muscles, which is medial and adjacent to the nodal levels II through IV. In the setting of gross nodal disease, treatment of the involved nodes to 66 to 70 Gy results in overlap of the nodal PTVs on the BP roots and trunks, hence the increased likelihood of exceeding BP dose constraints even when the volume of nodal disease is low. It has been suggested that the BP roots, trunk, divisions, cords, and branches may have differences in radiation dose tolerance given the differences in reported BP radiation dose tolerance in the breast cancer literature,^{14,15} as compared with the HNC literature.^{2,4} Furthermore, BP contouring guidelines in HNC usually do not define the BP outside the IMRT field, and hence the BP traversing the axilla (within the field of breast cancer radiation) is usually outside the region of head and neck IMRT optimization. However, there have been no convincing studies evaluating the differential sensitivity along the length of the BP. This observation warrants further evaluation as it could potentially identify areas at greatest risk.

In this study, we defined an ipsilateral nodal volume threshold of threshold 4.9 cc above which there is a significantly greater risk of prescribing a maximal BP dose of greater than 66 Gy. Methods to reduce BP dose include reducing PTV margins on elective nodal volumes or by reducing CTV and PTV margins on gross nodal disease. Reduction of PTV expansions to 2.5-mm CTVs may be permitted in the context of onboard imaging with cone-beam CT or daily kilovoltage imaging, which allows for improvement in treatment setup reproducibility. In head and neck IMRT, maintaining maximum BP dose constraints within tolerance guidelines can be challenging in patients with gross nodal disease > 5 cc. Although our objective of head and neck IMRT is to achieve 95% of PTV coverage with the prescription dose (66 to 69.96 Gy) as a priority over BP dose constraints, there is the potential that a reduction in nodal CTV and PTV expansions may improve our ability to limit BP dose. Although different optimization algorithms are currently available and clinically implemented, the principles of head and neck IMRT optimization remain similar. Most approaches are based on the gradient method and simulated annealing, which sample and explore the possible solution space with differing strategies. Hence, with the same input parameters, there will be different outputs after a single iteration. Although the treatment planning process is inherently iterative and continuously adapting, the radiation dosimetrist/planner may add additional optimization contours to further shape the dose locally, and subsequently modify the optimization parameters multiple times to achieve the desired dose constraints. In our experience, the results are isodose lines that are sculpted to conform to

the target and avoid adjacent normal tissue, according to the original optimization goals taking into account the treatment delivery capabilities.

The results of this study assist in informing the radiation oncologist of the expected BP dosimetry in head and neck IMRT planning and its relationship to the tumor burden, when the BP is routinely contoured as an avoidance structure. If the BP is not avoided during the IMRT optimization process, the doses to the BP are expected to be higher than the BP dose findings of this study. To understand the clinical implications and true tolerance of the BP in the HNC population in the context of volumetric tumor burden, future studies that enable correlation of tumor and BP dosimetric data with nerve conduction studies or electromyography in treated patients and using a validated patient-reported symptom module would be required.

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Fig.

Correlating maximum dose to brachial plexus (left or right) with primary gross tumor volume devised by tumor subsite (oropharynx, hypopharynx, and larynx compared with nasopharynx, oral cavity, and others).

Table 1

Tumor characteristics of 75 patients with head and neck cancer treated from 2005 to 2011

	<i>n</i> (%)
Primary site	
Hypopharynx	10 (13.3)
Larynx	20 (26.7)
Nasopharynx	4 (5.3)
Oral cavity	7 (9.3)
Oropharynx	28 (37.3)
Other [*]	2 (2.7)
Unknown primary	4 (5.3)
AJCC Stage	
I	4 (5.3)
II	6 (8.0)
III	9 (12.0)
IV	56 (74.7)
Tumor category	
T0	7 (9.3)
T1	10 (13.3)
T2	18 (24.0)
T3	20 (26.7)
T4	20 (26.7)
Nodal category	
N0	18 (24.0)
N1	6 (8.0)
N2	41 (54.7)
N3	10 (13.3)

n = number of patients; AJCC = American Joint Committee on Cancer.*Note:* 3 patients were treated for recurrent disease in nodes (tumor category, T0).^{*} Other sites include sinonasal and external auditory canal tumor.

Table 2

Gross tumor volume and dose-volume histogram statistics of 75 patients with head and neck cancer with 150 brachial plexuses

	<i>n</i>	Mean (SD)	Median (range)
Gross tumor volume (cc) *			
Primary	68	40.8 (51.1)	18.3 (2.9 to 214.4)
Nodal	84	30.5 (67.8)	9.0 (0.37 to 512.1)
Dose-volume histogram			
BP volume (cc)	150	8.5 (4.5)	7.0 (1.8 to 29.6)
BP minimum dose (Gy)	150	26.2 (10.6)	29.6 (0.96 to 40.2)
BP maximum dose (Gy)	150	59.6 (11.5)	60.5 (1.9 to 78.4)
BP mean dose (Gy)	150	43.7 (10.0)	45.8 (0.46 to 61.6)

* Gross tumor volume of primary tumor was contoured for 68 patients while of 150 brachial plexuses (75 on each side), 84 were associated with an ipsilateral nodal disease (gross tumor volume nodal) and 66 were with no nodal disease.

Table 3

Correlating various thresholds of maximum radiation dose to brachial plexus with gross tumor volume

Maximum dose (Gy) *	No. of patients	GTV-Primary (cc)			No. of BP	GTV-nodal (cc)		
		Mean	SD	p Value		Mean	SD	p Value
60	28	27.2	37.8	ref	29	19.7	32.8	ref
> 60	40	50.3	57.1	0.066	55	36.1	80.1	0.292
66	54	30.8	34.6	ref	62	19.8	33.5	ref
> 66	14	79.5	80.8	0.001	22	60.6	116.7	0.014
70	57	29.7	34.0	ref	71	21.6	40.1	ref
> 70	11	98.6	81.4	<0.0001	13	79.0	139.3	0.004

* For the analysis of GTV-Primary, the maximum dose is from the brachial plexus (left or right) receiving the greater amount of radiation dosage; for analysis of GTV-nodal, maximum dose is from the brachial plexus corresponding to the side with nodal disease.

Table 4

Maximum and mean dose to brachial plexus volume by primary and nodal gross tumor volumes

	<i>n</i>	<u>Maximum dose (Gy)[*]</u>		<u>Mean dose (Gy)[*]</u>	
		Mean	SD	Mean	SD
GTV-primary [†]					
< 79.6 cc	57	60.8	6.5	44.5	7.5
79.6 cc	11	63.0	21.4	46.3	16.3
<i>p</i> Value		0.518		0.559	
GTV-nodal [†]					
No nodal disease	66	56.0	14.9	40.8	12.3
Nodal disease	84	62.5	6.7	46.0	7.0
<i>p</i> Value		0.0004		0.002	
< 4.9 cc	29	59.4	4.4	44.1	7.8
4.9 cc	55	64.2	7.1	47.0	6.4
<i>p</i> Value		0.001		0.075	

* For the analysis of GTV-primary, the maximum and mean dose is from the brachial plexus (left or right) receiving the greater amount of radiation dosage; for analysis of GTV-nodal, radiation dose is from the brachial plexus corresponding to the side with nodal disease.

[†] GTV-primary and GTV-nodal volumes of 79.6 and 4.9 cc are the optimized cutoff values which best predicted maximum radiation dose of > 66 Gy to either plexus (for GTV-P) and to corresponding brachial plexus (for GTV-N).