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Radiation Dose to the Brachial Plexus in Head-and-Neck Intensity-Modulated Radiation Therapy and Its Relationship to Tumor and Nodal Stage

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Abstract

Purpose—The purpose of this retrospective study was to determine tumor factors contributing to brachial plexus (BP) dose in head-and-neck cancer (HNC) patients treated with intensity-modulated radiotherapy (IMRT) when the BP is routinely contoured as an organ at risk (OAR) for IMRT optimization.

Methods and Materials—From 2004 to 2011, a total of 114 HNC patients underwent IMRT to a total dose of 69.96 Gy in 33 fractions, with the right and left BP prospectively contoured as separate OARs in 111 patients and the ipsilateral BP contoured in 3 patients (total, 225 BP). Staging category T4 and N2/3 disease were present in 34 (29.8%) and 74 (64.9%) patients, respectively. During IMRT optimization, the intent was to keep the maximum BP dose to 60 Gy, but prioritizing tumor coverage over achieving the BP constraints. BP dose parameters were compared with tumor and nodal stage.

Results—With a median follow-up of 16.2 months, 43 (37.7%) patients had 24 months of follow-up with no brachial plexopathy reported. Mean BP volume was $8.2 \pm 4.5 \text{ cm}^3$. Mean BP maximum dose was $58.1 \pm 12.2 \text{ Gy}$, and BP mean dose was $42.2 \pm 11.3 \text{ Gy}$. The BP maximum dose was 60, 66, and 70 Gy in 122 (54.2%), 185 (82.2%), and 203 (90.2%) BP, respectively. For oropharynx, hypopharynx, and larynx sites, the mean BP maximum dose was 58.4 Gy and 63.4 Gy in T0–3 and T4 disease, respectively ($p = 0.002$). Mean BP maximum dose with N0/1 and N2/3 disease was 52.8 Gy and 60.9 Gy, respectively ($p < 0.0001$).

Conclusions—In head-and-neck IMRT, dose constraints for the BP are difficult to achieve to 60 to 66 Gy with T4 disease of the larynx, hypopharynx, and oropharynx or N2/3 disease. The risk of brachial plexopathy is likely very small in HNC patients undergoing IMRT, although longer follow-up is required.

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Keywords

Head and neck cancer; brachial plexus; dose-volume histogram; radiotherapy; intensity-modulated radiation therapy

Introduction

Intensity-modulated radiotherapy (IMRT) has become increasingly prevalent, and is now considered a standard approach in the treatment of head-and-neck cancer (HNC) (1). As a result, a comprehensive knowledge of head and neck (HN) anatomy is required for the accurate delineation of tumor extent and organs at risk (OAR), to optimize tumor control while minimizing the risk of treatment-related morbidities. The brachial plexus (BP) is an OAR that was not traditionally contoured for three-dimensional conformal radiotherapy (3DCRT). With the advent of IMRT, inadvertent hot spots within normal tissues, not previously considered at high risk with 3DCRT, brought the dose tolerance of the BP to the clinician's attention. Brachial plexopathy is a peripheral nerve disorder in which nerve damage occurs at any point from the nerve roots to the terminal branches. Symptoms can vary from subtle to incapacitating shoulder, arm, and hand pain, numbness, paresthesias, weakness, muscle atrophy, and paralysis. Treatment is purely symptomatic and often ineffective (2).

Guidelines have been introduced by the Radiation Therapy Oncology Group (RTOG) to set dose limits to minimize the risk of long-term brachial plexopathies. Recommended dose constraints range from 60 to 66 Gy in 2 Gy per fraction depending on the RTOG protocol (60 Gy in RTOG 0435, 0522, and 0412; 66 Gy in RTOG 0615 and 0617) (3). Radiological contouring atlases have provided a guide to assist the uniformity in contouring using CT and/or MRI imaging (3–5). In a comparative dosimetric study, significant differences in the maximal point dose to the BP was observed between IMRT (68.9 Gy) and 3DCRT (66.1 Gy) ($p = 0.01$) in a cohort of 10 patients with locally advanced HNC for which the BP were contoured in accordance to the RTOG consensus HN atlas (6). To date, studies examining doses to the BP when routinely contoured in clinical practice as an OAR for IMRT optimization are lacking. At our institution, the BP has been routinely contoured as an OAR since 2004 with the intention to keep the maximum BP dose to <60 Gy. In cases where the BP overlapped with the planning target volume (PTV) which was prescribed to 60 Gy, priority was given to the PTV coverage while keeping the hot spots outside of the BP. Also, BP dose–volume constraints were incorporated in the IMRT optimization to keep the BP volume to 60 Gy.

The purpose of this study was to determine tumor factors contributing to the BP dose in patients treated with IMRT when the BP was contoured as an OAR in IMRT optimization.

Methods and Materials

Patient population

The study was conducted as a retrospective review with a waiver of informed consent that was approved by the institutional review board. The study population consisted of 114 HNC

patients treated with IMRT between December 2004 and May 2011. All patients underwent staging workup, including initial evaluation with history and physical examination with a focused HN evaluation, panendoscopy, and biopsy, CT, with or without fluorodeoxyglucose–positron emission tomography/computed tomography (FDG-PET/CT), and magnetic resonance imaging (MRI). All patients were staged according to the 2002 American Joint Committee on Cancer (AJCC) classification (7). Concurrent chemotherapy was also administered in 87.7% of patients (for patients with adequate renal function in Stage III and IV nonmetastatic disease). Patients received 6 to 7 weeks of radiation to a total dose of 66 to 70 Gy (mean total prescription dose was 69.96 Gy in 33 fractions at 2.12 Gy) using IMRT with a simultaneous integrated boost technique. A total of 68 patients received definitive (primary) radiation, and 46 patients received postoperative radiation.

Patient simulation and immobilization technique

Before commencing RT, patients underwent CT simulation in the supine position on a carbon fiber Civco “S-frame” with a type S thermoplastic immobilization HN board (Civco Medical Solutions, Orange City, IA). CT acquisition from the vertex of the scalp to at least 5 cm below the clavicle using 2- to 3-mm slice thickness was performed.

IMRT planning technique

Structures on the planning CT contoured by the physician included the following: gross tumor volume (GTV), clinical target volume (CTV), PTV, and OARs such as the BP, spinal cord, brain, brainstem, bilateral parotid glands, inferior constrictors, larynx, cochleae, esophagus, oral cavity, optic structures, and other critical normal tissue organs adjacent to the target volumes. Volumetric expansions from GTV to CTV were 7 to 15 mm (respecting normal tissue planes) followed by a 3- to 5-mm expansion to the PTV. All patients were treated with 7 to 10 6-MV photon beams. In 17 patients, an upper IMRT plan was matched to a low anterior neck field (LAN); the remaining patients were treated with full-length IMRT fields.

Planning was performed using Pinnacle treatment planning software (version 6.0 to 8.0 m; Philips Medical Systems, Fitchburg, WI). GTVs were contoured incorporating diagnostic CT, PET, and/or MR images. The volume (cm³), mean, minimum, and maximum planned doses to the BP were recorded on the region-of-interest (ROI) dose and volume statistics report generated from the IMRT plan.

During IMRT optimization, the BP ROI was constrained to a maximum dose <60 Gy as a planning objective if adjacent nodal disease was present. In patients receiving elective nodal irradiation, the BP was constrained to 54 to 56 Gy. If the prescription PTV overlapped with the BP contour, then priority was given to covering the target while keeping hot spots outside of the BP.

The IMRT plans were normalized such that 95% of the PTV was covered with the prescription dose (66–70 Gy), with the goal of no more than 1% of the PTV receiving less than 93% of prescription dose, and no more than 1% or 1 cc of the tissue outside the PTV receiving more than 110% of prescription dose. Elective nodal areas and regions at risk for subclinical disease were treated to 54 to 60 Gy using a dose-painting technique.

Brachial plexus contouring technique

The right and left BP were routinely contoured as separate regions of interest (ROI) in 111 patients and the ipsilateral BP was contoured in 3 patients on the planning CT. We have used MRI with CT to establish our contouring methodology to assist identification of the BP. We identified the C4–5 and T1–2 neural foramina on a sagittal-view CT to determine the upper and lower limits of the BP, followed by contouring the ventral rami of C5–T1 exiting through the intervertebral neural foramina on the axial CT. The trunks of the BP were contoured between the anterior and middle scalene muscles to the insertion of the scalene muscles into the first rib (4). Fig. shows an example of our BP-contouring technique.

Statistical analysis

Descriptive statistics were calculated for patient demographics, tumor characteristics, and dose–volume (DV) statistics obtained from the radiation plans. Either the Chi-square test or Fisher's exact test was used to test associations between planned dose to BP and tumor and nodal categories of the disease. Univariate and multivariate analyses were conducted using the general linear model (Proc GLM) of SAS 9.1 system (SAS Institute, Cary, NC), and crude and adjusted means with standard errors were calculated for DV statistics categorized by tumor and nodal categories. The following potential confounding variables were explored in these analyses: BP volume (cm³), use of a LAN field, nodal category (for tumor category analysis), and tumor category (for nodal category analysis), treatment intent (definitive RT vs. postoperative RT), and total radiation dose (Gy). Finally, patients were evaluated for overall survival (OS, death from any cause) from conclusion of RT until last available follow-up or death. The two-year actuarial survival rate was estimated using the Kaplan–Meier product-limit method. A two-sided hypothesis was used for all tests, and a probability value of <0.05 was considered statistically significant.

Results

Patient and treatment characteristics

The mean age of study population was 58 years (range, 31–86 years). Stage 4 disease was present in 86 patients (75.4%). Twelve patients (10.5%) received ipsilateral neck irradiation whereas the remaining 102 patients (89.5%) received bilateral neck irradiation. Patient, tumor, and treatment characteristics are described in Table 1.

Treatment outcomes

The median follow-up for the whole patient cohort was 16.2 months (range, 0–61.8 months). The median follow-up among surviving patients was 20.9 months (range, 2.8–61.8 months). The 2-year actuarial overall survival rate was 71.9%.

A total of 43 patients were followed for at least 24 months, of whom 26 (60.5%), 5 (11.6%), and 2 (4.6%) patients received a maximum dose of >60 Gy, >66 Gy, and >70 Gy, respectively, to at least one of the two BPs. To date we have not reported any brachial plexopathy.

BP dose and volume statistics

The mean BP volume was $8.2 \pm 4.5 \text{ cm}^3$ (left, $8.3 \pm 4.6 \text{ cm}^3$; right, $8.2 \pm 4.4 \text{ cm}^3$), and the mean and maximum doses to the BP were $42.2 \pm 11.3 \text{ Gy}$ (left, $41.4 \pm 12.2 \text{ Gy}$; right, $43.0 \pm 10.3 \text{ Gy}$), $58.1 \pm 12.2 \text{ Gy}$ (left, 57.6 ± 12.6 ; right, $58.6 \pm 11.9 \text{ Gy}$), respectively. There were no statistically significant differences between right and left BP dose or volume. The BP maximum dose was 60, 66, and 70 Gy in 122 (54.2%), 185 (82.2%), and 203 (90.2%) BPs, respectively.

Correlating BP radiation dose with tumor disease

A greater percentage of advanced T4 disease was observed with a maximum brachial plexuses dose threshold of >66 to $>70 \text{ Gy}$. With regard to T category, of the BP with maximum dose of $>70 \text{ Gy}$, 59.1% of plexuses were associated with T4 disease, whereas T4 disease accounted for 26.1% of the plexuses receiving 70 Gy ($p = 0.001$), Table 2. As the maximal BP dose increased from 55 to 60, to 66, and to 70 Gy, the percentage of BP with T4 disease increased from 30.3% to 34.0%, to 42.5%, and to 59.1%, respectively ($p = 0.007$).

No significant differences in maximum and mean BP dose were observed by T stage. Planned minimum dose was lower in T4 group ($22.7 \pm 13.0 \text{ Gy}$) compared with T0–3 group ($26.1 \pm 10.5 \text{ Gy}$) ($p = 0.040$). Tumor category significantly correlated with BP volume as T0–3 and T4 disease had BP volumes of $8.7 \pm 4.9 \text{ cm}^3$ and $7.2 \pm 3.0 \text{ cm}^3$, respectively ($p = 0.022$) (Table 3).

A subset analysis of tumor category by cancer site revealed that higher maximum doses to the BP were seen with T4 disease of the larynx, hypopharynx, and oropharynx compared with T0–3 disease ($63.4 \pm 6.6 \text{ Gy}$ compared with $58.4 \pm 9.5 \text{ Gy}$, respectively; $p = 0.002$). In contrast, there were no differences in BP maximum dose for T0–3 ($55.9 \pm 16.3 \text{ Gy}$) and T4 ($51.8 \pm 17.8 \text{ Gy}$) disease for cancers of the nasopharynx, oral cavity, unknown primary, and others ($p = 0.332$).

Correlation of BP radiation dose with nodal disease

In the analysis of nodal disease, 73.8% of BP receiving $>60 \text{ Gy}$ were classified as N2/3 disease, whereas N2/3 disease comprised 59.0% in the 60-Gy cohort ($p = 0.020$) (Table 2). For advanced nodal disease, maximal BP dose increased from 55 to 60, to 66, and to 70 Gy, as the percentage of BP with N2/3 disease increased from 69.7%, to 73.8%, to 80.0%, and to 81.8%, respectively ($p = 0.095$).

The mean values for BP minimum, maximum and mean dose for group with N0/1 disease were 19.5 ± 14.0 , 52.8 ± 17.3 and $36.5 \pm 15.5 \text{ Gy}$ vs. 28.0 ± 8.4 , 60.9 ± 7.1 and $45.2 \pm 6.7 \text{ Gy}$ in N2/3 disease, respectively ($p < 0.0001$ for all), with no differences noted in the BP volume between cohorts (Table 3).

Multivariate analysis

The differences noted in maximum and mean planned dose to the BP by nodal category remained significant after adjusting individually for BP volume, the use of a LAN field technique, tumor category of the disease, treatment intent, and total radiation dose (Table 4).

Discussion

To our knowledge, this series represents a large cohort of predominantly locally advanced HNC patients with routine BP contouring performed and incorporated into the optimization for IMRT. The current study shows that when the BP is contoured as an OAR for HN IMRT, the dose received to the BP is influenced by disease burden and its proximity to the BP, especially with advanced nodal (N2/3) disease and also in patients with T4 disease of the larynx, hypopharynx, and oropharynx. The BP lies adjacent and medial to the elective nodal levels II through IV. Therefore, when contouring nodal groups and in the setting of gross nodal disease, following CTV and PTV expansions, it is difficult to avoid overlapping of the prescription PTV with the BP. Furthermore, in the postoperative setting, surgical resection of normal structures such as the sternocleidomastoid muscle, or in the presence of extracapsular nodal extension, result in the scalene muscles and BP lying more superficial and adjacent to subcutaneous tissue and the skin and often within the high-dose PTV.

The current RTOG guideline for BP maximal dose is 60 to 66 Gy. In an attempt to create uniformity of contouring, since 2009, RTOG has provided contouring atlases to help identify structures of interest for HNC radiation planning (3). Difficulties in contouring the BP can be caused by difficulty in visualizing the BP with CT alone, especially at the BP roots and trunks, which is often visible only on high-resolution CT or MRI. At our institution, we have used MRI, or MRI/CT fusion, to aid in identification the BP, to improve our understanding of the CT anatomy of the BP for RT contouring (4). The BP is often best visualized with gadolinium-enhanced T1-weighted MRI sequences. However, MRI was not routinely performed on majority of cases because of several limitations: Not all of our patients had a dedicated MRI in treatment planning position with immobilization; some patients could not tolerate MRI, or MRI was contraindicated. Although the BP is best visualized on coronal plane MRI, it is not possible to use these images for RT contouring, as it is done based on axial imaging. Furthermore, rigid fusion of MR and CT images can lead to registration error in the neck, as neck MRIs cannot be performed with treatment immobilization thermoplastic masks, and deformable registration of the MRI with the planning CT is not possible with our current software. Limitations of CT imaging to contour the BP include partial volume artifact, poor resolution between soft tissue including nerve and muscle. As a result, our contouring technique relies on knowledge of bone and soft tissue anatomic relations of the BP including identifying the C4–5 to T1–2 neural foramina and identifying the anterior and middle scalene muscles to the insertion of the scalene muscles into the first rib.

In our study, approximately 20% of the BPs received >66 Gy as a maximum point dose, while delivering 66 to 70 Gy to gross tumor and nodal disease, which raises concern regarding exceeding recommended guidelines despite attempting to keep the BP within tolerance. Alternative methods to reduce BP include using lower RT doses to 60 Gy to

gross nodal disease followed by a planned neck dissection. However, the additional morbidity of planned neck dissections after RT may pose additional brachial plexopathy risk and potentially decrease the tolerance dose of the BP. Moreover; there are no data to support decreasing brachial plexopathy risk by using planned surgery in lieu of RT dose, and this approach may increase nodal recurrence risk if there are delays in surgery or poor patient compliance. As such, our preference is to address gross nodal disease to 70 Gy and optimize the BP to a maximum dose of <66 Gy, however, with preference to preserving target coverage of the prescribed dose. As we have not experienced any brachial plexopathy with this approach, it is likely the risk of brachial plexopathy is very small, even if patients have received high BP doses.

Other methods to potentially reduce the dose to the BP include reducing CTV and PTV margins. In the setting of optimal patient immobilization in conjunction with daily image-guided radiotherapy (IGRT), expansions from GTV to CTV and PTV could potentially be reduced to improve BP sparing. In our study, CTV was created from GTV using uniform 7- to 15-mm expansions with manual alterations made to respect normal tissue planes. Additional 3- to 5-mm expansions from CTV to create PTV were to account for set-up errors. As IGRT evolves, PTV margins may be further reduced which may improve dose constraints of the BP.

Additional benefits of contouring the BP include improving the dose conformity around target PTVs and to keep hot spots outside of the BP, thereby preventing streaking of high-dose radiation in this region. Other methods to minimize high dose to the BP includes the use of matching upper IMRT fields to a LAN field. When matched at the level of the hyoid, this usually coincides with the C5 vertebral level and the upper limit of the BP. In our experience, we prefer to use this method in the setting of node negative disease below the level of the hyoid. When gross nodal disease is present below the level of the hyoid, we prefer to use full-length IMRT to address gross nodal disease within the IMRT fields to avoid matching fields over gross disease.

In 2008, Hall *et al.* published the RTOG guide for the standardization of BP contouring based on 10 patients treated to a median of 70 Gy (range, 60–70 Gy) (3). These investigators reported a mean maximal dose to the BP of 69.9 Gy with 100%, 70%, and 30% of BP exceeding maximal doses of 60 Gy, 66 Gy, and 70 Gy, respectively. Yi *et al.* validated the reproducibility of this RTOG BP contouring atlas when comparing the BP contouring of 5 patients with Stage IV disease among 3 blinded radiation oncologists with no experience in BP contouring (5), although the investigators identified that the majority of discrepancies were noted in contouring the inferolateral BP, and they recommended minor changes to the RTOG guidelines in an attempt to clarify this boundary. All 5 patients received a maximal dose >66 Gy for all three BP contours (range, 69.1–76.9 Gy), when treated with IMRT to 70 Gy (5). The limitation of using standard protocols to contour the BP is that it does not account for normal anatomic variation, whereas 5% to 10% of individuals have a C4 nerve root contributing to the BP (3).

The variability of contouring of the BP was not assessed in this study, and the majority of patients had the BP contoured before the publication of the BP-contouring atlas. We found

significant differences in contouring volume by T stage, which was inversely related to the BP minimum dose; however this was not seen for the other BP dose parameters such as mean and maximum BP dose. This could reflect potential underestimation of the BP in advanced primary disease.

The current study questions the feasibility of BP dose constraint guidelines in the setting of locally advanced disease. The current BP dose recommendations in HNC are derived from scant data from the two-dimensional (2D) and 3DCRT era. Very little information exists regarding brachial plexopathies in patients treated with radiation for HNC (8). Dose limits to the BP are largely based on the work of Emami *et al.*, who evaluated the BP and cauda equina together and suggested a 5% risk at 5 years of 62, 61, and 60 Gy, and a 50% risk at 5 years of 77, 76, and 75 Gy for one-third, two-thirds, and the whole organ, respectively (3, 5, 9). However, more recent studies are lacking.

It is speculated that the BP roots, trunks, divisions, cords, and branches may have differences in radiation tolerance. In HN radiation BP roots and trunks are mainly at risk, whereas in breast cancer, the terminal branches are at risk with additional risk conferred by axillary nodal dissections. The reported incidence of brachial plexopathy in breast cancer patients appears to be higher than that in HNC; yet the BP tolerance dose for breast cancer RT is considerably lower, in the 45- to 54-Gy range (10). We report a median follow-up of 16.2 months, in which 37.7% of patients in our patient cohort had follow-up of >24 months without any reports of brachial plexopathy. It is likely that the risk of brachial plexopathy in HNC patients undergoing IMRT is low. Because HN IMRT has been used routinely in clinical practice for only 5 to 10 years, it may take several years to observe brachial plexopathies with IMRT. Given the lack of radiation toxicity studies involving the BP in HNC, the RTOG guidelines represent a conservative estimate to minimize radiation treatment BP morbidity associated with HN radiotherapy. As the HN IMRT experience matures, data regarding BP toxicity after HN IMRT may be reported, which may guide further refinements in guidelines for BP dose constraints.

Conclusion

Dose constraints for the BP within suggested protocol guidelines are difficult in patients with locally advanced T4 disease of the larynx, hypopharynx, and oropharynx and N2/3 disease without sacrificing adequate PTV coverage for patients undergoing HN IMRT. Contouring the BP for HN IMRT planning is helpful to assist in reducing hot spots in the BP, which otherwise could receive higher doses if the BP was not contoured.

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Summary

This study determines tumor factors contributing to brachial plexus (BP) dose in 114 head-and-neck cancer patients treated with intensity-modulated radiation therapy (IMRT) when the BP is routinely contoured as an organ at risk (OAR) for IMRT optimization. Dose constraints for BP 66 Gy are difficult to achieve in locally advanced nodal (N2/3) and T4 disease of the larynx, hypopharynx, and oropharynx. Contouring the BP is helpful to assist in reducing hot spots in the BP for head-and-neck IMRT.

Fig.
Serial axial planning CT showing the right and left brachial plexus (purple) contours and the anterior (blue) and middle (green) scalene muscles and reference landmarks.

Table 1
Patient and treatment characteristics of 114 head-and-neck cancer patients treated from 2004 to 2011

	Median	Mean $\pm$ SD
Age (y)	58.0	57.9 $\pm$ 9.6
Dose-volume statistics [*]		
Volume (cm ³)	7.0	8.2 $\pm$ 4.5
Minimum dose (Gy)	29.0	25.1 $\pm$ 11.4
Maximum dose (Gy)	59.4	58.1 $\pm$ 12.2
Mean dose (Gy)	44.7	42.2 $\pm$ 11.3
<i>n</i> (%)		
Sex		
Male		78 (68.4%)
Female		36 (31.6%)
Primary site		
Oral cavity		15 (13.2%)
Oropharynx		42 (36.8%)
Nasopharynx		4 (3.5%)
Hypopharynx		10 (8.8%)
Larynx		26 (22.8%)
Unknown primary		9 (7.9%)
Others [†]		8 (7.0%)
AJCC stage		
I		7 (6.1%)
II		8 (7.0%)
III		13 (11.4%)
IV		86 (75.4%)
Tumor category		
T0		10 (8.8%)
T1		18 (15.8%)
T2		28 (24.6%)
T3		24 (21.1%)
T4		34 (29.8%)
Nodal category		
N0		30 (26.3%)
N1		10 (8.8%)
N2		63 (55.3%)
N3		11 (9.7%)
Treatment intent		
Definitive RT (primary)		68 (59.7%)
Postoperative RT		46 (40.3%)

	Median	Mean $\pm$ SD
Radiation technique		
IMRT with LAN match		17 (14.9%)
IMRT only		97 (85.1%)
Treatment type		
Ipsilateral		12 (10.5%)
Bilateral		102 (89.5%)

Abbreviations: AJCC = American Joint Committee on Cancer; IMRT = intensity-modulated radiation therapy; LAN = low anterior neck field; n = number of patients; RT = radiotherapy; SD = standard deviation.

* Dose–volume statistics of 225 brachial plexuses from 114 head-and neck-cancer patients.

[†] Other sites include four parotid gland tumors, two sino-nasal tumors, and two of the auditory canal/temporal bone.

Table 2
Correlation of various thresholds of radiation dose to the brachial plexus with tumor and nodal category

Dose to Brachial plexus	No. of brachial plexuses	Tumor category 4			Nodal category 2+		
		n	%	p Value	n	%	p Value
Maximum dose (Gy)							
55	50	13	26.0		26	52.0	
>55	175	53	30.3	0.557	122	69.7	0.020
60	122	31	25.4		72	59.0	
>60	103	35	34.0	0.160	76	73.8	0.020
66	185	49	26.5		116	62.7	
>66	40	17	42.5	0.044	32	80.0	0.037
70	203	53	26.1		130	64.0	
>70	22	13	59.1	0.001	18	81.8	0.095
Mean dose (Gy)							
45	118	33	28.0		70	59.3	
>45	107	33	30.8	0.636	78	72.9	0.032
50	191	47	24.6		123	64.4	
>50	34	19	55.9	0.0002	25	73.5	0.301
55	214	60	28.0		138	64.5	
>55	11	6	54.6	0.086	10	90.9	0.103

Abbreviation: n = number of brachial plexus with tumor category = 4 or nodal category = 2+.

Table 3

Mean brachial plexus volume and dose by tumor and nodal category

Brachial plexus dose–volume statistics											
	No. of brachial plexuses	Volume (cm ³)		Minimum dose (Gy)		Maximum dose (Gy)		Mean dose (Gy)		SD	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Tumor category											
T0	20	9.6	4.0	29.2	9.7	59.2	8.4	44.3	10.0		
T1	36	9.5	4.8	26.1	9.7	59.6	6.3	45.1	5.6		
T2	55	8.1	4.7	25.6	10.8	57.5	12.3	42.2	10.6		
T3	48	8.3	5.6	25.4	11.1	55.9	15.2	40.6	11.8		
T4	66	7.2	3.0	22.7	13.0	59.2	13.1	41.2	13.9		
<i>p</i> Value for trend		0.006		0.022		0.786		0.074			
T0–T3	159	8.7	4.9	26.1	10.5	57.7	11.8	42.6	10.1		
T4	66	7.2	3.0	22.7	13.0	59.2	13.1	41.2	13.9		
<i>p</i> Value		0.022		0.040		0.404		0.405			
Nodal category											
N0	57	7.5	4.6	20.4	13.8	52.0	18.5	36.4	16.3		
N1	20	8.3	4.1	16.8	14.7	55.0	13.4	36.7	13.7		
N2	126	8.6	4.6	27.9	8.6	61.1	7.2	45.1	6.8		
N3	22	8.1	3.9	28.9	7.0	60.0	6.3	45.5	6.1		
<i>p</i> Value for trend		0.260		<0.0001		<0.0001		<0.0001			
N0–N1	77	7.7	4.5	19.5	14.0	52.8	17.3	36.5	15.5		
N2–N3	148	8.5	4.5	28.0	8.4	60.9	7.1	45.2	6.7		
<i>p</i> Value		0.229		<0.0001		<0.0001		<0.0001			

Abbreviation: SD = standard deviation.

Table 4
Multivariate analysis correlating radiation dose to brachial plexus with nodal category

	No. of brachial plexuses	Univariate		Multivariate*		Multivariate†		Multivariate‡	
		Mean	SE	Mean	SE	Mean	SE	Mean	SE
Minimum dose (Gy)									
N0-N1	77	19.5	1.2	19.5	1.2	21.8	0.99	19.6	1.2
N2-N3	148	28.0	0.88	28.0	0.88	26.8	0.71	28.0	0.87
<i>p</i> Value		<0.0001		<0.0001		<0.0001		<0.0001	
Maximum dose (Gy)									
N0-N1	77	52.8	1.3	53.1	1.3	54.0	1.3	52.7	1.3
N2-N3	148	60.9	0.95	60.7	0.91	60.3	0.93	61.0	0.95
<i>p</i> Value		<0.0001		<0.0001		0.0001		<0.0001	
Mean dose (Gy)									
N0-N1	77	36.5	1.2	36.8	1.2	38.3	1.1	36.5	1.2
N2-N3	148	45.2	0.87	45.0	0.84	44.2	0.78	45.2	0.87
<i>p</i> Value		<0.0001		<0.0001		<0.0001		<0.0001	

Abbreviation: SE = standard error.

^{*} Adjusting for brachial plexus volume.

[†] Adjusting for use of low anterior neck (LAN) field.

[‡] Adjusting for tumor category (note: Analysis retained significance after adjusting for treatment intent and total radiation dose).