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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* $\leq$ 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 $\geq$ 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 $\geq$ 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 $\geq$ 4.9 cc) was an independent predictor for high maximal BP dose constraints in head and neck IMRT.

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 maybe underreported in the HNC population, with a risk 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

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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* $\geq$ 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 $\pm$ 4.5 cc, 43.7 $\pm$ 10.0 Gy, and 59.6 $\pm$ 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.