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Clinical Investigation: Head and Neck Cancer

Dose—Volume Modeling of Brachial Plexus-Associated Neuropathy After Radiation Therapy for Head-and-Neck Cancer: Findings From a Prospective Screening Protocol

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Summary

This work, representing the culmination of 6 years of prospective data collection from patients followed after radiation therapy for head-and-neck cancer, proposes dose—volume guidelines for the brachial plexus in an attempt to limit neuropathic symptoms. This research is noteworthy given the popularity of the brachial plexus contouring atlas (available on the Radiation Therapy Oncology Group website) and the limited knowledge of the normal tissue tolerance of this structure.

Purpose: Data from a prospective screening protocol administered for patients previously irradiated for head-and-neck cancer was analyzed to identify dosimetric predictors of brachial plexus-associated neuropathy.

Methods and Materials: Three hundred fifty-two patients who had previously completed radiation therapy for squamous cell carcinoma of the head and neck were prospectively screened from August 2007 to April 2013 using a standardized self-administered instrument for symptoms of neuropathy thought to be related to brachial plexus injury. All patients were disease-free at the time of screening. The median time from radiation therapy was 40 months (range, 6-111 months). A total of 177 patients (50%) underwent neck dissection. Two hundred twenty-one patients (63%) received concurrent chemotherapy.

Results: Fifty-one patients (14%) reported brachial plexus-related neuropathic symptoms with the most common being ipsilateral pain (50%), numbness/tingling (40%), and motor weakness and/or muscle atrophy (25%). The 3- and 5-year estimates of freedom from brachial plexus-associated neuropathy were 86% and 81%, respectively. Clinical/pathological N3 disease ($P<.001$) and maximum radiation dose to the ipsilateral brachial plexus ($P=.01$) were significantly associated with neuropathic symptoms. Cox regression analysis revealed significant dose—volume effects for brachial plexus-associated neuropathy. The volume of the ipsilateral brachial plexus receiving >70 Gy (V70) predicted for symptoms, with the incidence increasing with V70 >10% ($P<.001$). A correlation was also observed for the volume receiving >74 Gy (V74) among patients treated without neck dissection, with a cutoff of 4% predictive of symptoms ($P=.038$).

Conclusions: Dose—volume guidelines were developed for radiation planning that may limit brachial plexus-related neuropathies. © 2014 Elsevier Inc.

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Introduction

Due to concerns of toxicity from excessively high doses, the brachial plexus is increasingly contoured as an organ at risk (OAR) for intensity modulated radiation therapy (IMRT) treatment planning for head-and-neck cancer. However, there are limited data investigating the radiobiological tolerance of this structure, and dosimetric guidelines are practically nonexistent (1). In a previous study, the importance of maximum dose (Dmax) in predicting symptoms including upper-extremity paresthesia, pain, weakness, and motor dysfunction, associated with radiation-induced brachial plexopathy was demonstrated (2). However, volume effects were not specifically analyzed. This is pertinent because data from other neurologic organs such as the spinal cord suggest that parallel architecture may influence dose−volume effects and that the proportion of a neurologic structure exposed to high doses may be significant in predicting complications (3). The purpose of the present study was to therefore perform a dose−volume analysis from a large cohort of patients who underwent prospective screening for brachial plexus-associated neuropathy in an attempt to identify dosimetric parameters that may be of practical use in treatment planning.

Methods and Materials

Data prospectively collected from 352 consecutive patients returning for follow-up between August 2007 and April 2013 after completing radiation therapy for squamous cell carcinoma of the oropharynx, oral cavity, larynx/hypopharynx, nasopharynx, and unknown primary origin requiring bilateral neck irradiation were used for dose−volume modeling of brachial plexus-associated neuropathy. None of the patients complained of any brachial plexus-related symptoms at the time of initial cancer diagnosis. Table 1 outlines patient and disease characteristics. All patients had completed a self-administered standardized symptom questionnaire at a median of 40 months (range, 6-111 months) after completion of radiation therapy. This questionnaire, which was modified from a previously validated instrument initially designed to assess for brachial plexus symptoms among breast cancer patients, was designed to survey patients regarding the presence or absence of upper-extremity pain, sensory loss, motor weakness, and difficulty with manual dexterity (4). The survey was routinely administered at each clinic visit and comprised 5 basic questions requiring a yes or no answer: (*1*) Have you noticed any change in your arm or hand since completing radiation therapy? (*2*) Do you have any pain in your arm or hand? (*3*) Do you have any numbness or tingling of the hand or fingers? (*4*) Do you have any problems carrying and lifting objects with your arm? (*5*) Do you have any problems with your fingers such as with writing or unscrewing a bottle?

All patients who were surveyed for brachial plexus-associated symptoms were clinically without evidence of disease. The median age at the time of screening for the entire population was 59 years (range, 28-92 years). Two hundred patients (57%) were treated by definitive radiation therapy, and 152 (43%) were treated by primary surgery followed by postoperative radiation therapy. One hundred seventy-seven patients (50%) underwent surgical neck dissection at any point during therapy.

The median dose delivered was 70 Gy (range, 38-72 Gy). IMRT was used for 288 (82%) cases. Treatment was delivered at 2-2.12 Gy per fraction. Two hundred twenty-one patients (63%) received cisplatin chemotherapy concurrently during radiation therapy. The brachial plexus was delineated as ipsilateral and contralateral structures using the Radiation Therapy Oncology Group atlas on computed tomography (CT) to allow for generation of dose−volume statistics (5). Beginning in January 2009, the brachial plexus was designated as a low-priority OAR during inverse planning with a generalized assigned constraint of Dmax $<$74 Gy. One hundred ninety-nine patients (57%) had their IMRT plans optimized to reduce dose to the brachial plexus using this planning parameter.

Complication-free survival using the endpoint of any positive brachial plexus-related neuropathy was calculated using the Kaplan-Meier method, with comparisons among groups performed with 2-sided log−rank tests (6). Three separate Cox proportional hazards model were subsequently constructed considering V66, V70, and V74 to identify independent predictors of brachial plexus-associated neuropathy. Selection of patient and disease variables to consider as predictors was based on univariate

Table 1 Clinical and disease characteristics

Characteristic	Total patients (%)
Primary site	
Oropharynx	176 (50)
Oral cavity	52 (15)
Larynx	50 (14)
Unknown	28 (8)
Nasopharynx	25 (7)
Hypopharynx	21 (6)
T-stage	
T0	28 (8)
T1	70 (20)
T2	105 (30)
T3	63 (18)
T4	88 (25)
N-stage	
N0	47 (13)
N1	57 (16)
N2	211 (60)
N3	37 (11)
Sex	
Male	280 (79)
Female	72 (21)
Racial distribution	
White, non-Hispanic	260 (74)
Asian	35 (10)
Black	29 (8)
Hispanic	28 (8)
Diabetes mellitus	
No	309 (88)
Yes	43 (12)
Definitive treatment	
Primary RT	200 (57)
Surgery plus postoperative RT	152 (43)
Neck dissection	
No	175 (50)
Yes	177 (50)
Concurrent chemotherapy	
No	131 (37)
Yes	221 (63)

Abbreviation: RT = radiation therapy.

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