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Original article

Thoracolumbar spinal cord tolerance to high dose conformal proton–photon radiation therapy

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ABSTRACT

Purpose: To evaluate and understand the tolerance of the thoracolumbar spinal cord using equivalent uniform dose (EUD) and dose volume histogram (DVH) analysis after combined high dose photon–proton radiotherapy.

Materials and methods: A total of 68 patients were identified as having high dose radiotherapy, ⩾5900 cGy (RBE) in the region of the thoracolumbar spinal cord, defined as extending inferiorly to L2. Pathological diagnosis for patients in this review included chordoma (50 patients, 53.1%), chondrosarcoma (28 patients, 29.8%), osteosarcoma (3 patients, 3.2%), other sarcoma (11 patients, 11.7%), and other (2 patients, 2.1%). Patient data were reviewed retrospectively, detailed dose volume histogram data (DVH) were available for 23 patients. Composite plans and DVH were constructed for both pre-operative and post-operative radiation therapy courses in MIM-Vista software, as available. Dose constraints to the center and surface of the cord were 5400 cGy (RBE), and 6300 cGy (RBE) respectively, and patients receiving concurrent chemotherapy received an eight percent dose reduction. Spinal cord toxicity was recorded using the RTOG/EORTC late effects scoring system.

Results: Clinical and dosimetric data for each patient were analyzed. Median prescription dose was 7020 cGy (RBE), range (5940–7820 cGy (RBE)). Median follow-up was 12.9 months. Five-year overall survival for all patients in this group was 88.7%, 95%CI (74.7–95.2). One patient suffered from transient paralysis following stem cell transplant for treatment of myelodysplastic syndrome. Other reasons for spinal cord injury following treatment included: local disease progression, noted in 7 patients (10.3%), and direct result of surgery, noted in 8 patients (11.8%). Freedom from neurological injury (RTOG Grade 2 or higher) at 5 years was 92.9%(95%CI: 74.6–98.2), at 6 years was 80.9%(95%CI: 55.3–92.7), and at 8 years 80.9%(95%CI: 55.3–92.7).

Conclusion: Our clinical and dosimetric data suggest that the noted dose constraints are safe and acceptable with regard to spinal cord complications. Pre-existing disease characteristics, surgical complications, as well as tumor progression, appear to be more important factors when it comes to spinal cord toxicity.

The spinal cord is often a dose-limiting structure in the definitive treatment of a number of malignancies. Radiation injury to the spinal cord is characterized histologically by white matter injury and damage to the vascular endothelium [1]. Such injuries can be a catastrophic complication, and therefore understanding the relationship between dose and toxicity is of utmost importance to the radiation oncologist to optimize tumor control and prevent normal tissue toxicity.

The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) associates a dose of 50 Gy with a 0.2 percent risk of myelopathy, a dose of 60 Gy with 6 percent risk of myelopathy, and a dose of 69 Gy with a 50 percent chance of myelopathy [2]. Much of the knowledge with regard to dose constraints to the spinal cord is in the reirradiation setting in patients undergoing palliative radiotherapy [3,4].

Technological advances in radiotherapy delivery including the use of intensity modulated radiotherapy (IMRT), and proton beam radiotherapy (PBRT) using passively scattered or pencil beam scanning allow high doses of radiation to be delivered to tumors adjacent to the spinal cord, while creating a dose gradient resulting in protection of the spinal cord itself.

Nevertheless, there is limited information regarding the tolerance of the spinal cord especially in the era of modern treatment planning [5]. We have previously reported our experience with

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spinal cord toxicity associated with high dose photon–proton therapy for patients treated at the Massachusetts General Hospital for tumors of the cranio-occipital junction [6]. The purpose of this study was to report spinal cord toxicity in patients undergoing high dose proton–photon radiotherapy for tumors involving the thoracolumbar spinal cord.

Materials and methods

An institutional database of patients was queried to review patients who received high dose radiotherapy, ⩾5900 cGy (RBE), to the thoracolumbar spine at the Massachusetts General Hospital between 2002 and 2013.As the thoracolumbar region may include radiation fields involving both the spinal cord as well as the cauda equina, for the purpose of this analysis, the spinal cord was defined as extending inferiorly down to L2.

Complete details of the radiation treatment technique have been previously described [7]. All patients underwent CT simulation using customized immobilization. Intravenous as well as intrathecal contrast was administered to provide optimal delineation of the spinal cord for contouring and treatment planning purposes. All patients had lumbar instillation when the planned dose to spinal cord would exceed 5040 cGy. Patients would not necessarily have lumbar instillation for the pre-operative RT dose which was 5040 cGy, but would have it for the post-operative RT planning CT. Daily kV imaging was used for image guidance during the proton therapy.

Treatment plans were developed with a combination of photons using either 3D conformal radiation therapy or IMRT, and passively scattered protons using shrinking field technique. The exact dose and schedule was determined by the treating radiation oncologist, but generally patients were treated with a photon dose of 1980–3060 cGy, with the remainder of dose delivered by proton therapy. Proton doses were prescribed in radiobiological equivalents (RBE), and a conversion factor of 1.1 was utilized [8]. Daily dose fractionation was between 180 and 200 cGy. Institutional dose constraints to the center and surface of the cord, assessed in prospective clinical trials, were 5400 cGy (RBE), and 6300 cGy (RBE) respectively; patients receiving concurrent chemotherapy had an eight percent dose reduction. Spinal cord toxicity was recorded using the RTOG/EORTC Late Radiation Morbidity Scoring Schema, which has been previously described [9].

Sixty-eight patients were identified as having radiotherapy fields which treated the thoracolumbar spinal cord. Composite plans and dose–volume histograms (DVHs) were constructed by fusing and registering treatment plans using dosimetric information from planning software for both pre-operative and post-operative radiation therapy courses using MIMsoftware (MIM Software Inc. 25800 Science Park Drive – Suite 180 Cleveland, OH 44122). Complete dose distributions were available for 23 patients. Statistical analysis was performed using SAS software (SAS version 9.3; 100 SAS Campus Drive, Cary, NC 27513).

Results

Demographic information for all patients in series is shown in Table 1. The median age of patients in this series was 54 years (range, 6–90 years).Median follow-up for all patients was 12.9 months. Median follow-up for the 40 patients with a follow-up greater than 0 months was 50 months. Median prescription dose to the target was 7020 cGy (RBE), range (5940–7820 cGy (RBE)). Sixteen patients received pre-operative radiotherapy with a median dose of 3600 cGy (range, 1800–7820 cGy). The median post-operative dose and total dose was 7020 cGy (range, 1800–7820 cGy). Five-year overall survival for all patients in this group was 86.9%, 95%CI (74.7–95.2). Kaplan–Meier analysis for overall survival is shown in Fig. 1a. Freedom from neurological injury at 5 years was 92.9% (95%CI: 74.6–98.2).

Table 1
Demographic Information for Patients in this Series.

Variable	Value
No. of patients	68
Dose distributions available	23
Age	
Mean	51.4
Median	54.15
Pre-operative dose (n = 16)	
Mean	3476
Median	3600
Post-operative dose (n = 68)	
Mean	6240
Median	7020
Total dose (n = 68)	
Mean	7059
Median	7020
Dural plaque used	10/68 (14.7%)
History of diabetes	3/68 (4.4%)
Hypertension	17/68 (25%)
History of smoking	27/68 (39.7%)
Chemotherapy used	11/68 (16.2%)
Diagnosis	
Chordoma	29 (42.7%)
Chondrosarcoma	25 (36.7%)
Osteosarcoma	2 (2.9%)
Other sarcoma	10 (14.7%)
Other	2 (2.9%)

One patient was found to have a toxicity that is potentially radiation related. He presented with spinal cord compression, and did not have any direct complications related to the surgery or the radiation initially, but was diagnosed with myelodysplastic syndrome (MDS) approximately two years following the completion of the radiotherapy. At that time, the patient underwent treatment with azacitidine, and followed by bone marrow transplantation (see Fig. 1b). Approximately three years following the completion of radiation, the patient experienced transient paralysis. However, through intensive physical therapy he was able to regain much of his function, and he was able ambulate with the assistance of a walker. The DVH of his composite treatment is shown in Fig. 2. DVH analysis reveals that approximately 5 cc of the cord received more than 4500 cGy, and 2 cc received more than 5000 cGy, and approximately 1 cc received 5200 cGy.

While only 1 patient had toxicity potentially attributable to radiotherapy, other reasons for spinal cord injury following

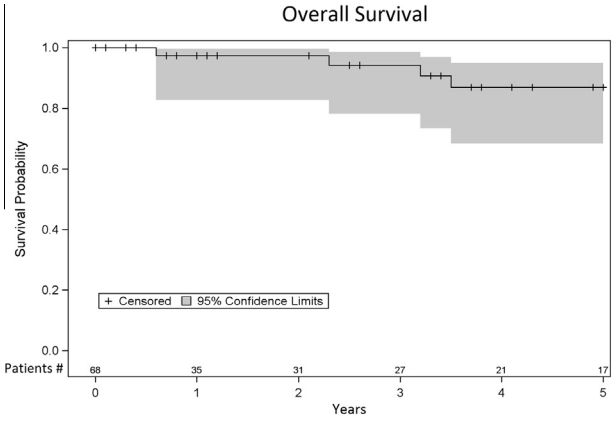

Fig. 1a. Overall survival: five-year overall survival for all patients in this group was 88.7%, 95%CI (74.7–95.2).

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