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PHYSICS CONTRIBUTION

INTENSITY-MODULATED AND 3D-CONFORMAL RADIOTHERAPY FOR WHOLE-VENTRICULAR IRRADIATION AS COMPARED WITH CONVENTIONAL WHOLE-BRAIN IRRADIATION IN THE MANAGEMENT OF LOCALIZED CENTRAL NERVOUS SYSTEM GERM CELL TUMORS

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Purpose: To compare the sparing potential of cerebral hemispheres with intensity-modulated radiotherapy (IMRT) and three-dimensional conformal radiotherapy (3D-CRT) for whole-ventricular irradiation (WVI) and conventional whole-brain irradiation (WBI) in the management of localized central nervous system germ cell tumors (CNSGCTs).

Methods and Materials: Ten cases of patients with localized CNSGCTs and submitted to WVI by use of IMRT with or without a "boost" to the primary lesion were selected. For comparison purposes, similar treatment plans were produced by use of 3D-CRT (WVI with or without boost) and WBI (opposed lateral fields with or without boost), and cerebral hemisphere sparing was evaluated at dose levels ranging from 2 Gy to 40 Gy.

Results: The median prescription dose for WVI was 30.6 Gy (range, 25.2–37.5 Gy), and that for the boost was 16.5 Gy (range, 0–23.4 Gy). Mean irradiated cerebral hemisphere volumes were lower for WVI with IMRT than for 3D-CRT and were lower for WVI with 3D-CRT than for WBI. Intensity-modulated radiotherapy was associated with the lowest irradiated volumes, with reductions of 7.5%, 12.2%, and 9.0% at dose levels of 20, 30, and 40 Gy, respectively, compared with 3D-CRT. Intensity-modulated radiotherapy provided statistically significant reductions of median irradiated volumes at all dose levels (p = 0.002 or less). However, estimated radiation doses to peripheral areas of the body were 1.9 times higher with IMRT than with 3D-CRT.

Conclusions: Although IMRT is associated with increased radiation doses to peripheral areas of the body, its use can spare a significant amount of normal central nervous system tissue compared with 3D-CRT or WBI in the setting of CNSGCT treatment. © 2010 Elsevier Inc.

Germ cell tumors, Radiotherapy, Intensity modulation, Plan comparison.

INTRODUCTION

Central nervous system germ cell tumors (CNSGCTs) are rare primary intracranial malignancies that account for 2.5% to 4.4% of all pediatric central nervous system (CNS) tumors in Western countries (1–3). In Asian countries they are far more common, accounting for up to 11% of all pediatric CNS tumor cases (4, 5).

Traditionally, radiotherapy alone has been considered the standard treatment for CNS germinomas (6), with long-term disease control and survival rates ranging from 70% to 90% (7–9). For other CNSGCTs, such as mixed germinomas and teratomas, radiotherapy has also played a major role in curative treatment but with lower control rates, varying between 40% and 70% (9–11). Under these circumstances, radiotherapeutic management requires craniospinal irradiation (CSI) as the initial treatment volume and intracranial dose levels of 50 Gy and above as the appropriate doses for obtaining successful tumoricidal effect and local tumor control (7, 12, 13).

Lately, however, irradiation of large volumes and the use of high final doses have been replaced in favor of combined chemotherapy and irradiation treatments that use either

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reduced doses or volumes, or even both (10, 14, 15). These treatments are mainly based on observations of low leptomeningeal recurrence rates (16), good initial response rates to chemotherapeutic agents (17), and the fear that irradiation of the entire CNS could be associated with a wide range of potential late adverse events (18–20). Examples of these recognized late adverse events that are of special interest in pediatric cancer patients are dose- and age-related neurocognitive function decline (19) and the induction of second primary malignancies (SPMs) (20).

Thus, when one is considering radiotherapeutic strategies based on treatment volume reduction and normal CNS tissue sparing, the options currently accepted vary from focal (primary site) irradiation only to whole-ventricular irradiation (WVI).

Similarly, intensity-modulated radiotherapy (IMRT), as a treatment technique with tissue-sparing capacity, can be used to reduce the amount of normal tissue that receives unnecessary radiation (21). As a matter of fact, IMRT is widely used to spare sensitive organs, but in the setting of WVI, its potential ability to reduce the amount of normal CNS receiving different radiation doses is not well established; neither the consequent clinical significance nor the long-term side effects have been adequately studied.

In this study we performed an evaluation of the potential for sparing cerebral hemispheres, using IMRT and three-dimensional conformal radiotherapy (3D-CRT) for WVI, by comparing treatment plans and their dosimetric results with conventional whole-brain irradiation (WBI). Given IMRT's theoretic ability to induce SPM (22), its use in the pediatric population is of special concern. Therefore a secondary evaluation was performed with this study to estimate the dose contributions to peripheral areas of the body that resulted from leakage radiation and from the number of monitor units (MU) generated for each technique.

METHODS AND MATERIALS

Selection of patients

We searched the Department of Radiation Oncology tumor registry and selected 10 cases of children and young adults of the Hospital Israelita Albert Einstein (São Paulo, Brazil) (age range, 7–22 years) with CNSGCTs who were treated with radiotherapy between January 2004 and December 2007. All patients had local intracranial disease only, tumors in the pineal or suprasellar region (or both), and no evidence of cerebrospinal fluid dissemination.

The patients' medical files, radiologic images, and staging examinations were completely reviewed. The median age at the beginning of radiotherapy was 15 years; the male-to-female ratio was 4:1; and the tumor location was pineal in 4 patients, suprasellar in 3, and pineal and suprasellar in 3. Five patients were diagnosed with pure germinoma, four with mixed tumors, and one with teratoma. All patients were treated with curative intent, with chemotherapy and/or surgery preceding the radiotherapeutic management.

Radiotherapy was performed with WVI by use of IMRT with or without ''boost'' to the primary lesion, via IMRT or 3D-CRT. Dose prescription, including the addition of boost irradiation after WVI course, was determined by the physician (Table 1), and daily doses ranged from 150 to 200 cGy, with five daily fractions per week. All patients were able to complete the treatment plan and received the entire radiation dose initially prescribed.

Radiotherapy planning

Before treatment with IMRT, all patients were submitted to a head computed tomography simulation procedure to determine the appropriate target volumes and the organs at risk (OARs) aimed to be spared, such as the optic chiasm, optic nerves, spinal cord, auditory apparatus, and eyes. The gross tumor volume (GTV) corresponded to the primary lesion that was detected with the diagnostic magnetic resonance imaging (MRI) scan, as well as to any possible residual disease that could have remained after initial therapy, detected with a subsequent restaging MRI scan. In case of complete remission after chemotherapy and/or surgery, the GTV corresponded exclusively to the site of the primary lesion, detected with the diagnostic MRI scan. For WVI, the clinical target volume (CTV) corresponded both to the GTV and the entire ventricular system and to additional margins of 1.0 to 1.5 cm. For the boost to the primary lesion, the CTV corresponded to the GTV and to additional margins of 1.0 to 1.5 cm. Margins of 0.3 to 0.5 cm were applied to the CTVs when defining each planning target volume (PTV).

All treatments were performed with a 6-MV linear accelerator (23EX; Varian Medical Systems, Palo Alto, CA), by use of a dynamic IMRT technique (''sliding window''), with a median of 8 isocentric coplanar beam arrangements (range, 5–10) for WVI with IMRT. A median of 5 isocentric coplanar beam arrangements (range, 5–6) was used for the boost to the primary lesion. Inverse planning was calculated with Helios software (Varian Medical Systems), according to the prescription(s) to the target volume(s) and pre-established dose–volume histogram (DVH) constraints to OARs, based on the study of Emami *et al.* (23).

We used the original computed tomography scans to produce new treatment plans, which were obtained using 3D-CRT only (WVI with or without boost to the primary lesion, with 5 isocentric coplanar beam arrangements and using WBI (with or without boost to the primary lesion, with opposed lateral beam arrangements The 3D-CRT plans targeted the same PTVs treated by use of IMRT, with the same beam path arrangements, and all WBI plans targeted the entire CNS and the same PTV for boost to the primary lesion treated by use of IMRT (Fig. 1). All plans were calculated by use of the same linear accelerator parameters as the original IMRT plans, with Eclipse software (Varian Medical Systems).

For DVH analysis purposes, all 3D-CRT plans were produced aiming to provide the same target coverage as their equivalent IMRT plans, with prescription doses covering at least 95% of the PTVs, irrespective of the doses given to previously assigned OARs. Whole-brain irradiation plans, in turn, were produced aiming to ensure that field margins were adequate to provide sufficient target coverage, accounting, for example, for beam penumbra. To evaluate the DVH of the cerebral hemispheres, the entire brain was contoured, but the volumes inside the PTVs were excluded. Dose levels chosen for evaluation were 2, 10, 20, 30, and 40 Gy.

Radiation measurements

The leakage radiation measurements were repeated with the same 6-MV linear accelerator used for all IMRT treatments. By use of a 0.6-cm^3 Farmer ionization chamber (PTW, Freiburg, Germany), lithium fluoride thermoluminescent dosimeters, and a Harshaw TLD Model 3500 reader (Thermo Fisher Scientific, Waltham, MA) for dosimetry, measurements were performed on a supine Alderson-Rando anthropomorphic phantom (Alderson Research Labs, Stanford, CA), based on techniques previously described