ORIGINAL ARTICLE

Stereotactic Radiotherapy of Central Nervous System and Head and Neck Lesions, Using a Conformal Intensity-Modulated Radiotherapy System (Peacock™ System)

Mario Ammirati, M.D.,[1] Antonio Bernardo, M.D.,[1] Nilam Ramsinghani, M.D.,[2] Richard Yakoob, M.P.,[2] Matthew Al-Ghazi, M.P.,[2] Jeffrey Kuo, M.D.[2], and Giuseppe Ammirati, M.S.[3]

ABSTRACT

The objective of this article is to evaluate single-fraction or fractionated stereotactic radiotherapy of central nervous system (CNS) and head and neck lesions using intensity-modulated radiotherapy (IMRT) with a commercially available system (Peacock™, Nomos Corporation, Sewickley, PA). This system allows tomotherapeutic delivery of intensity-modulated radiation, that is, the slice-by-slice treatment of the volume of interest with an intensity-modulated beam, making the delivery of highly conformal radiation to the target possible in both single or multiple fractions mode. During an 18-month period, 43 (21 males and 22 females) patients were treated, using a removable cranial screw-fixation device. Ages ranged from 10 to 77 years (mean, 52.2; median, 53.5). Intra- and extra-axial lesions, including head and neck malignancies and spine metastases, were treated. Clinical target volume ranged from 0.77 to 195 cm^3 (mean, 47.8; median, 29.90). The dose distribution was normalized to the maximum and was prescribed, in most cases, at the 80% or 90% isodose line (range, 65 to 96%; median, 85%; mean, 83.4%) and ranged from 14 to 80 Gy (mean, 48; median, 50). The number of fractions ranged from 1 to 40 (mean, 23; median, 25). In all but one patient, 90% of the prescription isodose line covered 100% of the clini-

Skull Base, volume 11, number 2, 2001. Reprint requests: Mario Ammirati, M.D., Division of Neurosurgery, UMDNJ–Robert Wood Johnson Medical School, Three Cooper Plaza, Suite 411, Camden, NJ 08103. E-mail: ammirati-mario@cooperhealth.edu. [1]Division of Neurosurgery, University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School, Camden, New Jersey; [2]Department of Radiation Oncology, University of California, Irvine, California; [3]University of California, Irvine. 1531-5010, p;2001,11,02,109,120,ftx,en sbs00221x.

cal target volume. The heterogeneity index (the ratio between the maximum radiation dose and the prescribed dose) ranged between 1.0 and 1.50, whereas the conformity index (the ratio between the volume encompassed by the prescription isodose line and the clinical target volume) ranged between 1.0 and 4.5. There were no complications related to the radiation treatment. With a median follow-up of 6 months, more than 70% of our patients showed decreased lesion size. Stereotactic IMRT of CNS and head and neck lesions can be delivered safely and accurately. The Peacock system delivers stereotactic radiation in single or multiple fractions and has no volume limitations. It has been used to treat intracranial, head and neck, and spinal lesions. The option of fractionation, the lack of volume constraint, and the capability of treating intracranial, head and neck, and spinal pathology make stereotactic IMRT a valuable adjunct to established stereotactic radiotherapy systems delivering convergent-beam irradiation using the Linac or Gamma Knife. In a clinical setting that offers Linac, Gamma Knife radiosurgery, and conformal stereotactic radiotherapy, the latter may have advantages for treating large (> 25-cm^3) and irregular lesions, especially when fractionation is considered useful.

KEYWORDS: Intensity-modulated radiotherapy, intracranial lesions, linear accelerator, stereotactic radiotherapy

Optimal delivery of therapeutic radiation to benign and malignant central nervous system (CNS) lesions relies on maximizing the dose to the target while simultaneously minimizing the dose to the surrounding structures. Three-dimensional (3D) computer planning and convergent-beam irradiation (CBI) techniques using the linear accelerator (Linac), the Gamma Knife (AB Elekta, Stockholm, Sweden), or the proton-beam represent ways of depositing a highly conformal dose of radiation to a target inside the brain with steep dose fall-off at its boundaries. Gamma Knife and Linac-based systems are currently used mainly with single-dose fraction and are best suited for lesions not exceeding 25 cm^3 in volume.[8] Proton-beam therapy can be fractionated and does not have definite volume limitations. However, it is not widely available because of its significant cost. Tomotherapeutic delivery of intensity-modulated radiation, that is, the slice-by-slice treatment of the volume of interest with an intensity-modulated beam, is one way of circumventing these constraints, making the delivery of highly conformal radiation to the target possible in both single or multiple fractions mode. This report describes our experience with such an approach, using a commercially available system (Peacock™, Nomos Corporation, Sewickley, PA).

MATERIALS AND METHODS

System Description

The Peacock system is a Linac-based system capable of delivering to a target and to sensitive structures a dose of radiation that closely matches the amount of radiation set a priori by the planner. Radiation is given in either single or multiple fractions in a slice-by-slice mode. The system does so by continuously changing intensity of the beam as the Linac gantry rotates around the patient describing a single or multiple coplanar arcs encompassing the slice of tissue to be treated. A multileaf intensity-modulation collimator attached to the

Linac makes modulation of the intensity of the radiation beam possible. Radiation therapy (RT) delivered in this manner is referred to as intensity-modulated radiation therapy (IMRT).

The four basic component of the system are as follows:

1. *Patient immobilization and target localization device (Talon™)*: The Talon consists of an adjustable skull mount secured with the skull by two self-tapping screws placed through the inner table of the skull. The Talon is inserted using local anesthesia and can be placed in the operating room or treatment room. During computed tomography (CT), the patient is scanned with the Talon in place and attached to a CT adapter in a set position that is duplicated on the radiation treatment couch during the single or multiple treatments. The Talon is removed after CT and between fractions, leaving the skull screws behind to insure that it is replaced accurately. The Talon and its attachments establish a coordinate system that is used by the planning system to locate exactly in space the target to be treated. The Talon and its attachments form a stereotactic device (Fig. 1).
2. *Treatment planning (Peacock plan)*: The Peacock plan is an intensity-modulated inverse treatment planning system. The planner prescribes a dose to the target while setting dose limits to surrounding structures, and the planning system determines physically deliverable intensity-modulated beam fluence profiles that closely match the clinical prescription. This approach to the planning process is commonly referred to as inverse planning. It is the opposite of forward planning used in conventional RT, including CBI, in which the planner postulates a number of beams and beam weight and the planning system calculates the dose reaching the target and surrounding structures. The plan is delivered in a rotational fashion through a multileaf collimator (vide infra) attached to a Linac.

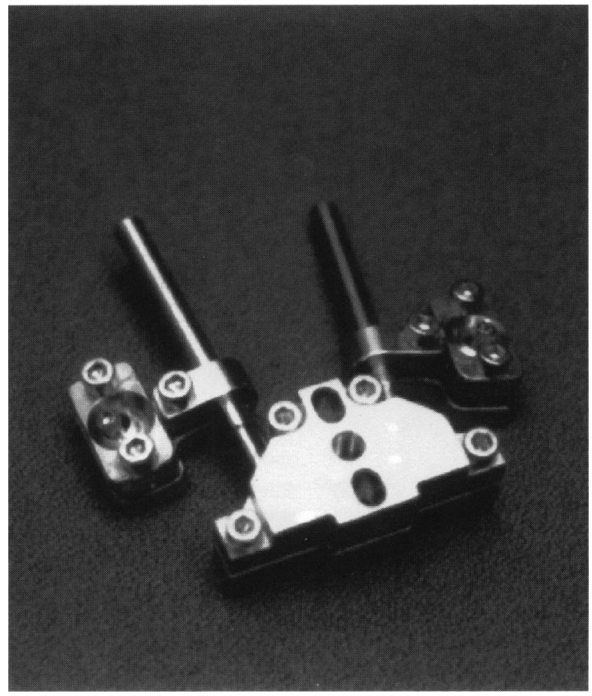

Figure 1 The Talon™ skull mount.

3. *Multileaf intensity-modulating collimator (MIMiC™)*: The MIMiC is a binary temporal modulator consisting of 40 switches, 20 in each of 2 banks (Fig. 2). A half-open switch identifies a 1 × 1 cm^2 vane, whereas a fully open switch identifies a 2 × 1 cm^2 vane, giving the option of treating a 1- or 2-cm thick slice of tissue 20 cm in diameter for each bank. Because there are opposite banks, a slice of tissue up to 4 cm thick may be treated for each arc rotation, usually in the horizontal plane. The MIMiC is attached to the Linac, and therapy is given in a rotational fashion, whereas the gantry describes a 270- to 360-degree arc around the patient (Fig. 3). The configuration of the 40 beamlets of the MIMiC, which creates the modulated beam used for treatment, is updated every 0.25 degrees of gantry rotation. Arc delivery is modeled as if it consisted of a series of fixed fields spaced every 5 or 10 degrees delivered in succession, the equivalent of 55 (5-degree-spaced fields for a 270-degree arc) or 72 (5-degree-spaced fields

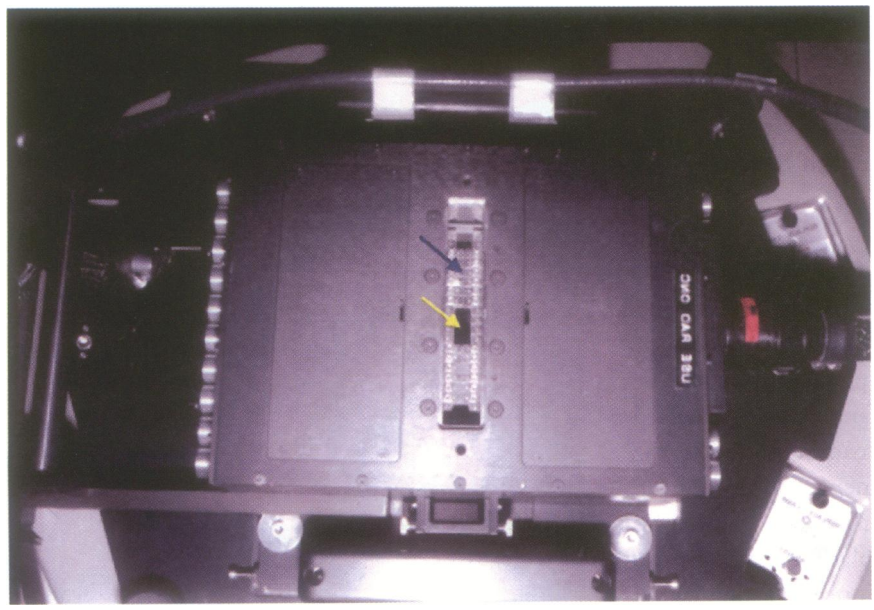

Figure 2 Multileaf intensity-modulating collimator. Some vanes are open (yellow arrow), and some are closed (blue arrow).

for a 360-degree arc) static field treatments. Each slice treatment field consists of 20 independent pencil beams; therefore, 1,100 individual beamlets can be turned on or off during a 270-degree arc modeled as 55 static fields 5 degrees apart. In addition, each beamlet may be on from 1/10 to 10/10 of the 5-degree arc rotation, creating an intensity that can vary from 10% to 100% for each 5-degree arc rotation. This allows each beamlet to be at one of 10 intensity levels for each 5 degrees of gantry rotation, giving more than 10^{13} beam configurations.

4. *Couch indexing device (Crane™)*: Accurate positioning and stability of the treatment couch are essential in a tomotherapeutic (slice-by-slice) treatment and are achieved by using the Crane. This device attaches to the treatment couch to improve the stability of the couch top and provides accurate positioning within 0.01 to 0.05 mm (Fig. 4). The Crane allows the couch to be accurately indexed in steps, so that the whole length (volume) of the target is covered.

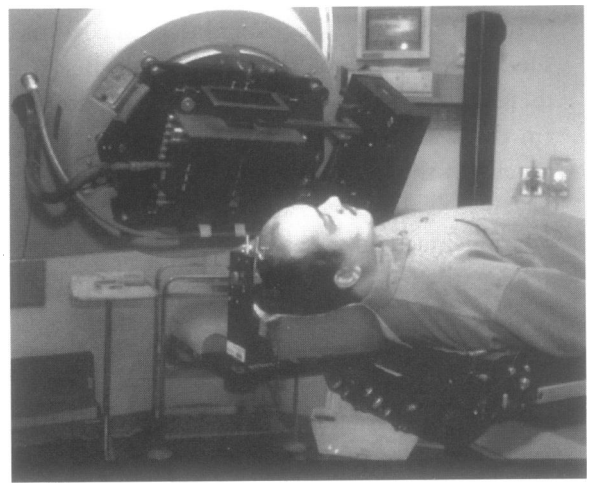

Figure 3 While the patient undergoes treatment, the head is secured to the treatment couch, using the Talon™.

Patients, Treatment Methods, and Radiation Plan Characteristics

During an 18-month period, 43 (21 males, 22 females) patients were treated. Their ages ranged from 10 to 77 years (mean, 52.2; median, 53.5). Pathology included intra- and extra-axial lesions (Table 1). Clinical target volume[3] ranged from

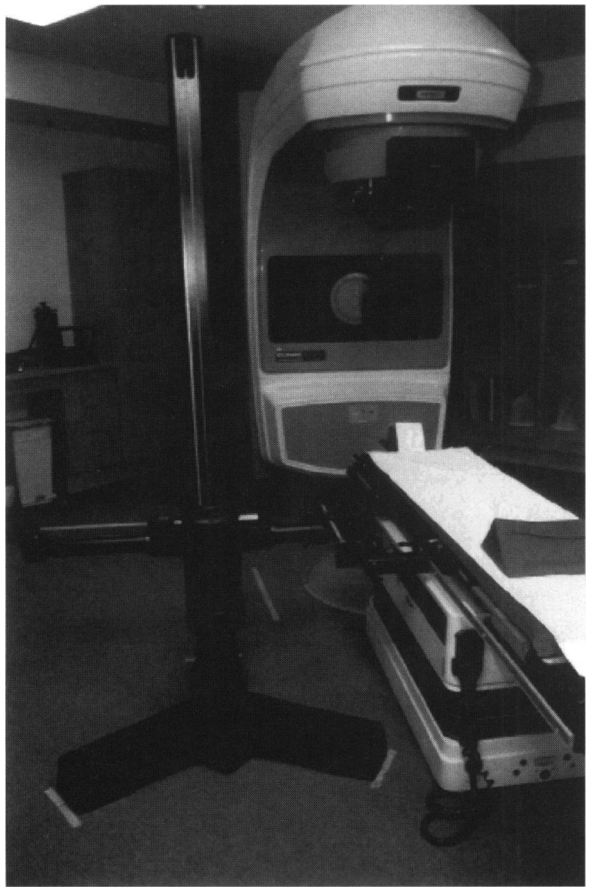

Figure 4 The Crane™ is used to index the table with a submillimetric accuracy.

Table 1 Number and Types of Pathology Treated by IMRY

Type of Pathology	N
Glioblastoma multiforme	4
Anaplastic astrocytoma	4
Low-grade astrocytoma	1
Oligodendroglioma	3
Brain metastasis	5
Head and neck malignancy	5
Esthesioneuroblastoma	1
Chordoma	1
Plasmocytoma	1
Pituitary adenoma	4
Meningioma	7
Craniopharyngioma	1
Acoustic neuroma	1
Arteriovenous malformation	4
Spine metastasis	1

0.77 to 195 cm^3 (mean, 47.8; median, 29.90). A treatment plan was selected that most closely matched our specifications in terms of target minimum dose and sensitive structures maximum dose. The dose was normalized to the maximum and usually prescribed at the 80% or 90% isodose line (range, 65 to 96; median, 85; mean, 83.4) and ranged from 14 to 80 Gy (mean, 48; median, 50). Figure 5 shows an example of a treatment plan. Ninety percent of the prescription isodose line covered 90 to 100% of the target volume in all but one patient in whom it covered 71% of the target. In this patient, 80% of the prescription isodose line covered the entire target. The homogeneity index, the ratio between the maximum dose and the prescribed dose, ranged from 1 to 1.50 (mean, 1.18; median, 1.20) while the conformity index (the ratio between the volume encompassed by the prescription isodose line and the clinical target volume) ranged between 1.0 and 4.5 (mean, 2.8; median, 1.62). The number of fractions ranged from 1 to 40 (mean, 23; median, 25). The number of arcs per treatment ranged from 1 to 7 (mean, 3.3; median, 3). Treatment (beam-on time) lasted from 4.2 to 38 minutes (mean, 10.30; median, 8.75). Setup time averaged 10 minutes and decreased with experience. The biologic equivalent dose (BED), that is, the dose expected to yield the same biologic effect irrespective of number of fractions or dose per fraction, was calculated for the target and structures at risk according to the following formula:

$$\mathrm{BED} = nd\,[1 + d/(\alpha/\beta)]$$

where n is the number of fractions, d is the dose per fraction, and α/β is the ratio between the linear and the quadratic component of cell killing.[5] α/β was given a value of 3 for normal structures and a value of 10 for the lesion.[11] However, the value of α/β is approximate because specific α/β values are not known for all types of tissues. Follow-up ranged from 1 to 23 months

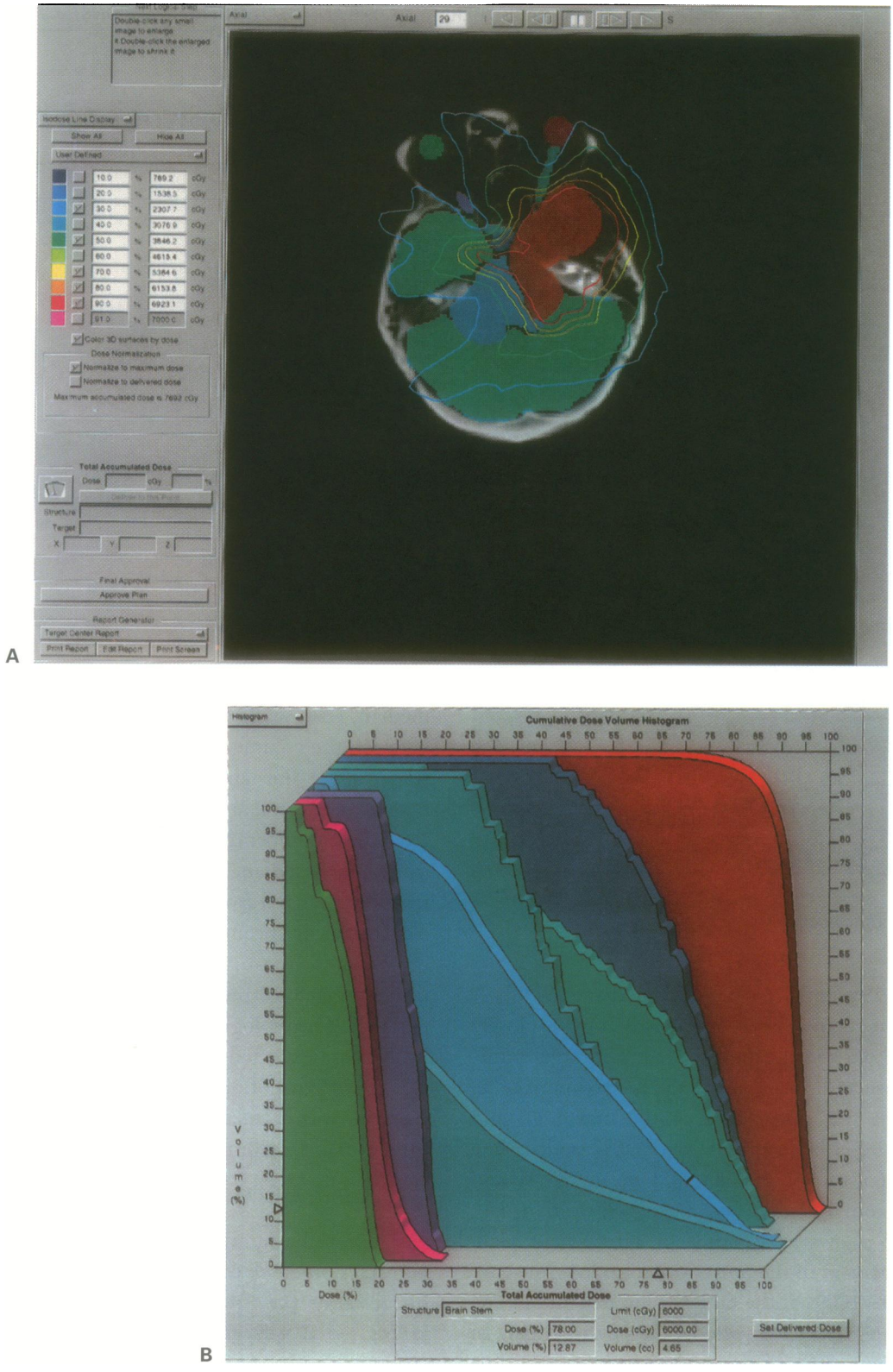

Figure 5 Peacock™ treatment plan of this large malignant petroclival meningioma (A). The treatment plan achieves a high degree of conformality for this large, irregular lesion while significantly sparing the brain stem (A). The dose-volume histogram of the same plan demonstrates that only 4.65 ml of the brain stem receives 60 Gy (B).

(mean, 8.6; median, 6). Lesion size was followed with the appropriate neuroradiologic test (CT, MRI, angiography).

CLINICAL RESULTS

There were no complications related to the radiation treatment. Early in our series, one screw pierced the dura upon removal, necessitating dural repair.

The four patients with anaplastic astrocytomas were treated "up front"; all showed a decrease in tumor size 3 months after treatment. Two patients died 6 months after treatment; one from tumor progression; and one patient with stable disease of an unrelated cause. The other two patients are alive with stable disease, at 9 and 15 months after treatment, respectively. One of the survivors required reoperation 12 months after treatment with pathology showing postradiation changes intermingled with neoplasm.

Of the four patients with a glioblastoma multiforme, three were treated at recurrence after surgery with conventional radiation therapy, and one was treated upfront. Of these three patients, two were available for follow-up and died 6 and 11 months after treatment, respectively, of progressive disease after the size of their tumor decreased 3 months after treatment. The single patient treated up front showed no change in residual tumor 1 month after treatment, but disease had progressed 5 months after treatment. Of the three patients with an oligodendroglioma, two were available for follow-up; one patient exhibited no evidence of neoplasm 28 months after IMRT; 2 months after IMRT, the size of the neoplasm in the other patient was unchanged.

The only patient with a low-grade astrocytoma showed a decrease in the size of the neoplasm 3 months after IMRT and is alive with stable disease 6 months after treatment.

Of the five patients with brain metastases, one progressed despite treatment and four showed decreased lesion size. Of the latter, two patients eventually progressed outside the treated area, at 2 and 5 months after treatment, respectively. One patient with recurrent metastatic fibrosarcoma shows good control of the large right frontoparietal metastasis at 9 months after IMRT (Fig. 6). One patient with a primary lung tumor had multiple metastases treated with IMRT. One metastasis decreased 5 months after IMRT and one metastasis increased 7 months after treatment. She underwent surgery because of an enlarging lesion; pathology showed only postradiation changes. She was well 16 months after treatment.

Of the five patients with head and neck malignancies, one did not respond at all, one responded initially, followed in 6 months by tumor progression, two remain well with decreased tumor size 1 year after IMRT, and one has decreased tumor size 5 months after IMRT. Of the seven patients with meningioma, 3 have a follow-up of less than 2 months; tumor size decreased in 1 patient with 15 months follow-up and is unchanged in two patients with 12 months follow-up and in one patient with 6 months follow-up. The only acoustic neurinoma treated showed no change 18 months after IMRT.

The patient with the esthesioneuroblastoma maintains a decrease in tumor size 22 months after treatment while the patient with the chordoma shows no change 1 year after IMRT; the patient with the plasmocytoma showed a decrease in tumor size 2 months after treatment. Two patients with pituitary tumor have a follow-up of <3 months; the other two patients showed decreased tumor size at 1 and 2 years after IMRT, respectively. The only patient with a craniopharyngioma has a follow-up of <2 months.

Of the four AVM patients, two showed a slight decrease in the size of the AVM at 10 and 12 months after IMRT, respectively, and two showed no change in AVM size at 12 and

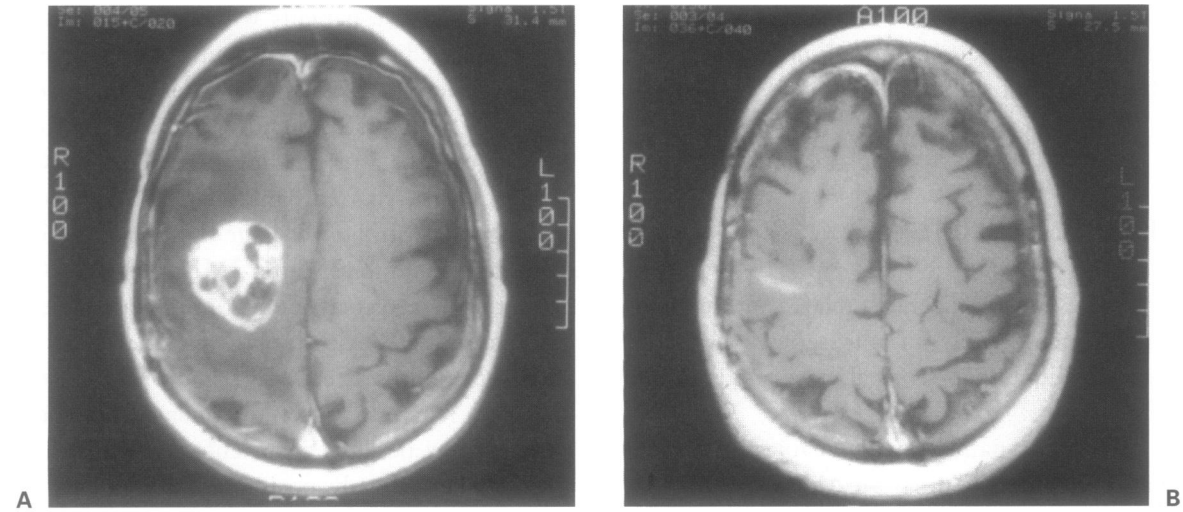

Figure 6 Gadolinium-enhanced MR images of a patient with metastatic fibrosarcoma before (A) and 9 months after treatment (B) showing good local control of the disease.

14 months after IMRT, respectively. The only patient with a spine metastasis showed a decrease in lesion size 5 months after treatment.

DISCUSSION

What Is Intensity-Modulated Radiation Therapy?

Conceptually, intensity-modulated radiation therapy may be better understood as an evolution of 3D conformal radiation therapy (CRT). In 3D-CRT, the target and dose limiting surrounding structures are delineated tridimensionally, and the amount of radiation delivered is better assessed in comparison to 2D RT. 3D-CRT maximizes and minimizes the amount of radiation reaching the target and important structures, respectively. This is achieved by changing the shape of the incident beam to conform to the projection of the target for a set of fixed beam directions or during rotational therapy.[1] However, the intensity of the beam is not modulated temporally across the treatment field.[1] By contrast, IMRT employs intensity modulation of the beam across the treatment field. The modulation is possible because the beam is segmented by the multileaf collimator into multiple beamlets that can be opened or closed independently of each other during rotational treatment. This ability gives rise to 10^{13} possible beam configurations.

IMRT and Convergent Beam Irradiation

Convergent beam irradiation using the Linac and the Gamma Knife is usually given in single treatment although there are recent reports of fractionated stereotactic radiotherapy using the Linac, the Gamma Knife, and cyberknife.[10] The optimal volume limit is approximately 5 cm^3 for the Gamma Knife and about 25 cm^3 for the Linac.[8] Larger volumes are treated using multiple isocenters with an increase in dose inhomogeneity that may be related to a potential increase in complications.[5] For a large intracranial irregular target treated with single-fraction stereotactic radiotherapy, a treatment plan generated using IMRT may have some advantages compared with a multiple-isocenter plan generated using conventional radiosurgery systems.[12] We have used IMRT with single or multi-

ple fractions to treat head and neck lesions in addition to CNS lesions and have found no volume constraint. Therefore, IMRT may have a place in a clinical setting with Linac and/or Gamma Knife radiosurgery for the treatment of large (>25 cm^3) and irregular lesions, especially when fractionation is thought to be advantageous.

Advantages of Fractionation

From a radiobiologic standpoint, dose fractionation has known advantages compared with a single fraction dose, especially in malignant neoplasms.[7] First, the number of hypoxic cells is reduced through cell killing and reoxygenation. Hypoxic cells are less sensitive to radiation than well-oxygenated cells. Second, radiation induces a redistribution of cells within the cell cycle. Fractionation increases the likelihood that a malignant cell will be caught in a radiation-sensitive phase of its cell cycle. In addition to the radiobiological advantages of fractionation for malignant neoplasms, the composition of the target volume also needs to be evaluated. In fact, the normal component of targets that contain normal tissue intermingled with pathological tissue, like low-grade and anaplastic astrocytomas, is more susceptible to damage by the lack of fractionation.[3]

Immobilization/Target Localization System

IMRT is tomotherapy, meaning that the treatment is delivered in a slice-by-slice fashion, and junctioning between treatment slices is critical. Therefore, we use an invasive fixation/localization device (i.e., the Talon) because it offers superior accuracy and reproducibility for repositioning than noninvasive systems.[13] However, a noninvasive relocatable localizing device (face mask) can also be used.[11] The patients tolerated the screws very well; there was no infection at the screw sites, even though they remained in place for >1 month in more than 50% of our patients.

Treatment Plan Evaluation

Optimal dose, dose per fraction, and treatment plan evaluation criteria for IMRT of CNS lesions have yet to be established. We evaluated our plans according to the Radiation Therapy Oncology Group (RTOG) radiosurgical guidelines, which highlight, among other things, the amount of normal tissue included in the prescription isodose volume.[9] These guidelines state that "if 90% of the prescription isodose line completely encompasses the target, if the maximum dose divided by the prescribed dose is ≤ 2, and if the volume of the prescription isodose surface divided by the target volume is 1.0 to 2.0, the case is per protocol."[9] In all but one patient, the whole target was covered by 90% of the prescription isodose line, making the cases per protocol according to RTOG guidelines.[9] Only in one patient was the whole target covered by 80% of the prescription isodose line, making it a minor violation according to the same guidelines. The homogeneity index, the ratio between the maximum and the prescribed dose, was <2 (range, 1 to 1.50), making all the cases per protocol according to RTOG radiosurgical guidelines.[9] The conformity index, the ratio between the prescription isodose volume and the target volume, was 1 to 2 in 30 patients, 2 to 2.5 in 4 patients, and 2.6 to 4.5 in 9 patients. In other words, vis a vis the conformity index, 70% of our plans were per protocol, 9% were minor violations, and 21% were major violations according to RTOG radiosurgical guidelines.[9] Even though our plans fared fairly well according to RTOG recommendations, it is important to recognize that these guidelines were developed for single-fraction stereotactic radiotherapy (radiosurgery) and not for fractionated stereotactic radiotherapy.

The versatility of the system that we used is underscored by the fact that most of our plans were

suitable, according to RTOG guidelines, for use in single-fraction stereotactic radiotherapy (radiosurgery) although, clinically, we used the majority of the plans to deliver fractionated stereotactic radiotherapy. The capability of this planning system, as well as that of other 3D planning systems to define the volume of a structure receiving a specific amount of radiation may help establish an objective tolerance limit for various volumes of irradiated structures. This objective measurement of the volume of a structure at risk receiving a certain dose of radiation may help establish data on organ tolerance that are more reliable than current data largely based on approximations derived from 2DRT.[2]

Consequently, although useful as general guidelines, data on target dose and structure tolerance from conventional RT and from CBI using the Linac and the Gamma Knife must be adapted to IMRT because IMRT is neither conventional RT nor CBI. Our treatment plans have been guided by the goal of giving the target and structures at risk an acceptable BED, according to both conventional external-beam therapy fractionation schedules and stereotactic radiosurgery experience.[11] When our BED for organs at risk was below the reported dose for accepted techniques, we judiciously increased the dose to the target while maintaining the BED to structures at risk within acceptable tolerance limits. When a large dose of radiation is delivered to targets near critical structures, in addition to assuring adequate target coverage, it is paramount that the amount of radiation delivered to the structures at risk is associated with a BED known to have a low probability of complications. Our treatment plans adequately achieved their clinical objectives when evaluated according to isodose distribution and dose–volume histograms.

Cost

IMRT delivered using the system described does not require the capital investment needed for a Gamma knife or proton beam. Furthermore, the lack of volume limitation, the capability of fractionation, and the capability of treating head and neck and spine pathology suggest that a significant number of patients could benefit from this form of stereotactic RT.

CONCLUSIONS

IMRT using the Peacock system can be delivered safely to CNS and head and neck lesions. The optimal dose and dose per fraction using IMRT system need to be established considering the BED for the target and for structures at risk known from other radiation techniques.

IMRT may be of value in a clinical setting that has Linac and/or Gamma Knife radiosurgery for the treatment of large (>25 cm^3) and irregular lesions, especially when fractionation is thought to be useful. Longer follow-up evaluation is needed to assess the clinical effect of IMRT on CNS and head and neck lesions.

REFERENCES

1. Carol MP. IMRT: where we are today. In: Sternick ES, ed. The Theory and Practice of Intensity Modulated Radiation Therapy. Madison, WI: Advanced Medical Publishing; 1997:17–36
2. Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991;21:109–122
3. ICRU. New ICRU Dose specification report for external beam radiotherapy. Technical Report 50. Bethesda, MD: International Commission on Radiation Units and Measurements; 1993
4. Larson DA, Shrieve DC, Loeffler JS. Radiosurgery. In: Leibel SA, Phillips TL, eds. Textbook of Radiation Oncology. Philadelphia: WB Saunders; 1998:391–393
5. Nedzi LA, Kooy H, Alexander E, et al. Variables associated with the development of complications from radiosurgery of intracranial tumors. Int J Radiat Oncol Biol Phys 1991;21:591–599
6. Perez CA, Brady LW, Roti Roti JL. Overview. In: Perez CA, Brady LW, eds. Principles and Practice of Radiation Oncology. 3rd ed. Philadelphia: Lippincott-Raven, 1998: 13–14

7. Perez CA, Brady LW, Roti Roti JL. Overview. In: Perez CA, Brady LW, eds. Principles and Practice of Radiation Oncology. 3rd ed. Philadelphia: Lippincott-Raven; 1998;23–26
8. Phillips MH, Stelzer KJ, Griffin TW, et al. Stereotactic radiosurgery: a review and comparison of methods. J Clin Oncol 1994;12:1085–1099
9. Shaw E, Klin R, Gillin M, et al. Radiation Therapy Oncology Group: radiosurgery quality assurance guidelines. Int J Radiat Oncol Biol Phys 1993;27:1231–1239
10. Shoshan Y, Suh JH, Barnett GH. Fractionated stereotactic radiosurgery. In: Germano IM, ed. Linac and Gamma Knife Radiosurgery. Boston: American Association of Neurological Surgeons; 2000:57–70
11. Wazer DE, Ling M, Kramer B, et al. Clinical application of IMRT for malignant tumors of the CNS. In: Sternick ES, ed. The Theory and Practice of Intensity Modulated Radiation Therapy. Madison, WI: Advanced Medical Publishing; 1997:177–193
12. Woo SH, Grant WH, Bellezza D, et al. A comparison of intensity modulated conformal therapy with a conventional external beam stereotactic radiosurgery system for the treatment of single and multiple intracranial lesions. Int J Radiat Oncol Biol Phys 1996;35:593–597
13. Woo SH, Butler BE, Grant WH. Clinical experience: benign tumors of the CNS and head and neck tumors. In: Sternick ES, ed. The Theory and Practice of Intensity Modulated Radiation Therapy. Madison, WI: Advanced Medical Publishing; 1997:195–198