ETASTIC LESIONS within the brain and CNS represent a significant clinical problem because of their dramatic impact on patients’ quality of life. Each year in the US brain metastasis develops in approximately 250,000 to 300,000 patients. These patients face a median life expectancy of 6 months from diagnosis. If very aggressive treatment is used, a select cohort of patients with controlled systemic disease, a good performance status, and fewer than three brain metastatic lesions will survive 1 or more years. Treatment options for patients with brain metastases include surgery, chemotherapy, and radiation treatment. Current treatment strategies are evolving as a result of advancements in radiation delivery, including HT, which is capable of whole-brain irradiation with simultaneous high-dose targeting to metastatic lesions by using multiple-target differential dose-prescription strategies and highly conformal CSI.

In this report the authors review the use of radiotherapy in the treatment of central nervous system (CNS) metastasis. They comment on different treatment methods for both intracranial and extracranial CNS metastasis and discuss some of the evidence supporting the use of radiotherapy in these settings. Recent advancements in radiation oncology technology are briefly reviewed with a focus on the advantages and disadvantages of helical TomoTherapy–based treatment strategies.

TREATMENT METHODS
The use of radiation treatments for brain metastasis is very common in the US. Two general types of radiation treatment currently exist, and their goals differ distinctly. Stereotactic radiosurgery is used to deliver ablative doses of radiation to a metastatic lesion while minimizing the dose delivered to normal brain tissue. Whole-brain radiotherapy is used to treat the contents of the entire cranial vault to reduce the volume of gross metastatic disease as well as to decrease the likelihood that microscopic disease deposits may grow into clinically detectable symptomatic lesions. The traditional dose fractionation schedule for WBRT—30 Gy in 10 fractions delivered with right- and left-sided 6-MV beams—represents a dosimetric compromise. Unfortunately, whole-brain tolerance limits the dose that can be administered to a gross lesion, although it clearly prevents the development of a clinically detectable new metastasis at the cost of minimal neurocognitive deficits. Arguably, WBRT involving a homogeneous dose technique provides an inadequate dose for sterilizing a gross lesion and may provide a higher dose than is necessary to prevent the progression of microscopic regions of metastasis into symptomatic lesions. New technology allows dose painting so that the whole-brain and gross-
tumor doses can be differentially regulated. Investigators have studied the use of SRS to deliver higher doses to control a gross lesion with and without WBRT. The combination of SRS and WBRT has been reviewed in many small reports, and two recent randomized trials have provided data for new guidance in the appropriate use of these treatments for patients with brain metastasis. Andrews et al.1 presented the results of the Phase III Radiation Therapy Oncology Group 9508 study, in which investigators evaluated the addition of SRS to WBRT. These authors showed a statistically significant improvement in patient survival when SRS and WBRT were combined compared with WBRT alone for patients harboring a single metastatic lesion. The combined treatment also resulted in improved neurological outcomes at 6 months. A subset analysis indicated a survival advantage for the following subsets: patients younger than 50 years old who had between one and three sites of metastasis, patients who had between one and three sites of metastasis from non–small cell lung carcinoma, and patients who had between one and three sites of metastasis and were categorized into recursive partitioning analysis Class 1.1

In a second study, Aoyama et al.2 randomized patients to groups undergoing SRS with or without WBRT. The results showed no significant survival benefit for the addition of WBRT in this setting. Patients who underwent SRS without WBRT attained a lower level of local disease control, experienced increased distal intracranial treatment failure, and had a subsequent higher rate of deterioration in their neurological function compared with patients who received WBRT with SRS.2 Although the results of this study failed to show a survival advantage for patients who underwent both WBRT and SRS, the study accrued significantly fewer patients with a solitary region of metastasis than the Radiation Therapy Oncology Group 9508 study. These data provide Level I evidence, indicating that the combination of SRS with WBRT is optimal for selected patients with brain metastases.

**ADVANCES IN RADIATION ONCOLOGY TECHNOLOGY**

New advances in treatment technology combined with a growing body of knowledge regarding the appropriate safe use of radiation offer hope for significant advances in patient outcomes.

**Advances in SRS**

Recent SRS advancements include a new-generation Gamma Knife that is capable of improved targeting of tumor and sparing of normal tissue, decreased forward treatment planning with the addition of inverse treatment planning, and a decreased treatment time due to the replacement of multiple standard-collimator helmets with an integrated automated adjustable collimator system. Clinical experience with the Cyberknife for SRS has also proved it to be a safe and effective treatment for brain metastases.14 Cyberknife SRS can be accomplished without the use of a traditional stereotactic headframe, resulting in less patient discomfort. Linear accelerator–based treatments for brain metastasis include SRT and whole-brain treatment with a radiation boost directed to a gross lesion, which is usually accomplished by a sequential technique that targets the whole brain and the gross lesion separately. Traditional LINAC-based SRT requires special collimator cones and customized treatment planning systems, which limit its use to a few academic centers. However, the increasingly smaller multileaf collimators (<10 mm) now available on LINACs and more robust planning systems have made possible the widespread development of LINAC-based frameless SRT techniques capable of delivering ablative doses.239

**Helical TomoTherapy**

The TomoTherapy Hi-Art system (TomoTherapy, Inc.) is an integrated treatment planning and CT-based image-guided helical IMRT delivery system that is capable of highly conformal dose delivery to multiple targets simultaneously. Helical TomoTherapy delivers radiation by using a 6-MV LINAC housed on a CT gantry. The beam is modulated by a 64-multileaf collimator that has paired, pneumatically driven, 6.25-mm-wide leaves calculated to open or close at approximately every 7° of LINAC rotation, or 51 times per gantry rotation, resulting in highly conformal and homogeneous dose distributions. This device is capable of performing image-guided radiotherapy by coregistering pretreatment daily megavoltage CT scans to the initial planning CT scan to ensure accurate patient setup.

Recently, investigators have compared the dosimetry calculated for small brain lesions by the HT system with that calculated by other treatment units.7,11,17 A comparison of HT and Gamma Knife surgery showed that HT cannot equal SRS for sparing normal tissue, although HT provides equal if not improved tumor coverage for certain tumor locations such as the base of the skull.11,17 A comparison of advanced radiotherapy techniques (including stereotactic arc therapy, IMRT, HT, Cyberknife SRS, and intensity-modulated multiple arc therapy) for skull-base tumors found that HT provided the best combination of target coverage and sparing of normal tissue.5 Another comparison of step-and-shoot IMRT and HT for intracranial lesions showed improvement in both conformity of treatment and sparing of at-risk organs adjacent to the target, including the brainstem, optic chiasm, and optic nerves, although the mean dose delivered to these at-risk organs was increased. These gains came at the cost of increased treatment time.7 When the usefulness of HT and noncoplanar IMRT in treating skull-base tumors was compared, IMRT was found to be superior.15 Nevertheless, other evaluations of HT in the treatment of head and neck cancers have shown improved target coverage and sparing of normal tissue compared with LINAC-based IMRT.8,13 Although many of the aforementioned comparisons were not specifically made with metastatic brain lesions in

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**TABLE 1**

<table>
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<tr>
<th>Potential advantages of helical tomotherapy treatment of CNS metastatic lesions</th>
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<tr>
<td>image guidance improves the accuracy of treatment delivery</td>
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<td>integrated radiation boost improves the sparing of normal brain</td>
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<tr>
<td>sparing of scalp &amp; middle ear</td>
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<tr>
<td>improved dosimetry in the treatment of the craniospinal axis</td>
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<td>avoidance of previously irradiated areas in repeated treatment</td>
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mind, patients who harbor metastatic lesions adjacent to critical organs may derive a similar benefit.

Quality of Life. Helical TomoTherapy of CNS metastasis potentially offers several benefits that may improve quality of life in patients by decreasing radiation toxicity. These benefits are summarized in Table 1. Scalp-sparing WBRT with HT has recently been shown to achieve a reduction in the mean radiation dose to the scalp by at least 38%.12,16 Although this may not prevent radiation-induced alopecia completely, it may decrease its likelihood and severity. Another potential advantage of TomoTherapy is sparing of the middle ear by reducing the dose delivered to the Eustachian tube, thereby reducing the likelihood of serous otitis media, a complication that some patients experience after WBRT.

Whole-Brain and Metastatic Lesion Treatment. Helical TomoTherapy IMRT offers the ability to treat the entire brain as well as the gross tumor by delivering a simulta-

Fig. 1. Helical TomoTherapy IMRT plans for the treatment of metastatic brain lesions. A: Dosimetry for a 32.5-Gy whole-brain treatment followed by a 7.5-Gy boost to a gross lesion. B: The same dosimetry for administration of a simultaneous integrated boost. The colored isodose lines are labeled in Grays and show that the sequential boost plan results in a significant increase in the volume of normal brain tissue that receives the dose. This is well demonstrated by the yellow isodose lines, which indicate the area of the brain receiving 36 Gy. The dose-volume histograms also demonstrate that the brain receives a significant increase in radiation dose compared with the prescribed 32.5 Gy when the sequential boost plan is used.
neous integrated boost of radiation. Investigation into this technique is underway at the University of Virginia Health System. Figure 1 includes a dosimetric comparison of the use of HT IMRT to deliver a lower homogeneous dose to the entire brain and a higher conformal dose to the metastatic lesion. Figure 1A shows the composite dosimetry calculated using a WBRT treatment plan followed by a second treatment session in which a boost of radiation is delivered.

**FIG. 2.** Dosimetry for a patient with a recurrent neuroendocrine tumor that was previously treated by delivery of 50.4 Gy to the pituitary fossa using the external-beam technique and by Gamma Knife surgery directed at the pituitary fossa for the lesion’s first recurrence. The patient was treated for leptomeningeal deposits of metastasis according to the treatment plan, with a prescribed dose of 41.8 Gy in 19 fractions to the brain less the previously treated volume and a dose of 34.2 Gy to the entire craniospinal axis delivered in 19 fractions. The dose–volume histogram demonstrates that the previously treated pituitary fossa was effectively blocked from further irradiation. Note significant sparing of visceral organs with craniospinal irradiation.
Helical TomoTherapy for CNS metastasis

directed at the gross lesion. Figure 1B shows the dosimetry calculated for a simultaneous integrated boost treatment plan for the same volumes and target prescriptions. The example used shows the treatment of two separate hypothetical 3-cm diameter lesions. Both plans offer excellent coverage of both the whole brain and the metastatic targets, but the integrated boost plan shows a significant reduction in the volume of normal brain tissue that receives doses greater than the prescribed dose. Brain sparing via this technique is possible when treating lesions of different sizes as well as when treating more than one lesion (unpublished data). This form of integrated boost may be less easily accommodated when using conventional LINAC-based IMRT. Although implementation of this type of treatment is more labor intensive than WBRT, the advantage of increased tumor control as well as sparing of normal brain tissue and other organs at risk from irradiation may prove beneficial to selected cohorts of patients identified in previous studies with longer life expectancies, including those with a good performance status, stable extracranial disease, young age, and/or small-volume intracranial disease.

Treatment of the Craniospinal Axis. Radiation coverage of the entire craniospinal axis, or CSI, is indicated in the treatment of metastatic cancers with known diffuse leptomeningeal involvement and tumors at risk for leptomeningeal spread including some leukemias, primitive neuroectodermal tumors, and lymphomas. Two groups have reported using HT for craniospinal irradiation and showed that HT provides improved coverage of the target, with fewer hot spots and cold spots, and results in improved sparing of at-risk visceral organs compared with the standard LINAC-based craniospinal axis radiotherapy technique. Figure 2 includes dosimetry in a patient treated at the University of Virginia Health System using this technique. This case illustrates the ability of HT to cover intended targets well while sparing organs at risk, including the esophagus, heart, bowels, and lungs. The patient had previously received external-beam radiotherapy to the pituitary region, and the dose administered to the area previously treated was effectively restricted. This treatment plan shows a clear reduction in the high isodoses delivered to visceral organs compared with conventional CSI; however, larger volumes receive increased low-dose radiation. One drawback of uncertain consequence is an increased integral dose, reported to be 6.5% greater using this technique than when using the traditional LINAC-based approach. The absolute values for these two techniques were 241.9 Gy/kg for conventional CSI and 257.6 Gy/kg for HT. Estimates of the incidence of secondary radiation-induced malignancies resulting from conventional CSI range from 0.3 to 1.2%. Estimates of the risk of developing a second malignant lesion due to the HT technique have been estimated to range between 1 and 2.7%, although these estimates have not been corrected for the significantly decreased high isodoses delivered to visceral organs at risk. Secondary malignancy is not likely to be clinically relevant for most patients with CNS metastatic disease, but may be critically important for children receiving prophylactic CSI for leukemia.

SUMMARY

The goal of current treatment strategies of brain metastases is to control gross metastatic disease, to decrease the risk of the development of future metastatic lesions, and to provide patients with effective local disease control while limiting side effects and providing the highest quality of life possible. Radiation therapy is a mainstay of treatment, with proven survival and quality-of-life benefits. Continuous advancements in treatment technologies provide new options in the multimodal treatment of patients with brain metastasis. Helical TomoTherapy and other forms of advanced radiation therapy techniques will certainly play a central role and provide the conformal delivery platforms necessary for improved treatments, such as refined target definition through molecule-based imaging of CNS metastasis or improvements in novel radiosensitizers, which will enhance the local control of metastasis without increasing radiation toxicity.

Disclosure

Dr. Read serves on the Scientific Steering Committee and Protocol Development Committee for TomoTherapy. He has received several small honoraria for travel expenses in this role but has received no other compensation.

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