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Long-term management of patients with multiple brain metastases after shaped beam radiosurgery

Case report and review of the literature

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The role of radiosurgery in the treatment of patients with advanced-stage metastatic disease is currently under debate. Previous randomized studies have not consistently supported the use of radiosurgery to treat patients with numbers of brain metastases. In negative-results studies, however, intracranial tumor control was high but extracranial disease progressed; thus, patient survival was not greatly affected, although neurocognitive function was generally maintained until death. Because the future promises improved systemic (extracranial) therapy, the successful control of brain disease is that much more crucial. Thus, for selected patients with multiple metastases to the brain who remain in good neurological condition, aggressive lesion-targeting radiosurgery should be very useful. Although a major limitation to success of this therapy is the lack of control of extracranial disease in most patients, it is clear that well-designed, aggressive treatment substantially decreases the progression of brain metastases and also improves neurocognitive survival. The authors present the management and a methodology for rational treatment of a patient with breast cancer who has harbored 24 brain metastases during a 3-year period.

KEY WORDS • palliative care • imaging software • whole-brain radiation • dose distribution • systemic therapy

THE role of radiosurgery in the treatment of patients with advanced-stage metastatic disease is a topic being debated. Previous randomized studies have not consistently supported the use of radiosurgery to treat patients with large numbers of brain metastases.[15,27,33,35] In negative-results studies, however, intracranial tumor control has been high but extracranial disease has progressed; thus, survival was not greatly affected.[35] Importantly, the patient's neurocognitive function was generally maintained until death. Since these studies were performed, there have been important advances in the care of patients with metastatic disease, which have greatly improved the quality of life and survival durations of those with extracranial metastases. These advances include better treatment of neutropenic sepsis,[12] bisphosphonate treatment for bone metastases,[31] combination chemotherapy and radiation therapy for head and neck cancers and lung cancer,[32] and better imaging to allow preemptive treatment of disease (such as cord compression) and antibody therapy.[43] The future promises improved systemic (extracranial) therapy, making the successful control of brain disease that much more crucial. Thus, for selected patients with multiple metastases to the brain who are still in good neurological condition, aggressive radiosurgery to those lesions should be very efficacious. The planning and long-term evaluation of patients with multiple brain metastases is extremely complex and requires careful and systematic documentation. Here we present the management and a methodology for rational treatment of a patient with breast cancer who has had 24 brain metastases during a 3-year period.

Abbreviation used in this paper: MR = magnetic resonance.

Case Report

Radiosurgery Technique

Planning for shaped beam radiosurgery involves obtaining a series of MR images to locate and assess targets for treatment. These images were all fused using the Novalis (BrainSCAN; BrainLAB) treatment planning software. Prior to each patient visit, the MR images, obtained using a standard method, were then fused to all previously obtained images (spoiled gradient recalled acquisition, 1.5-

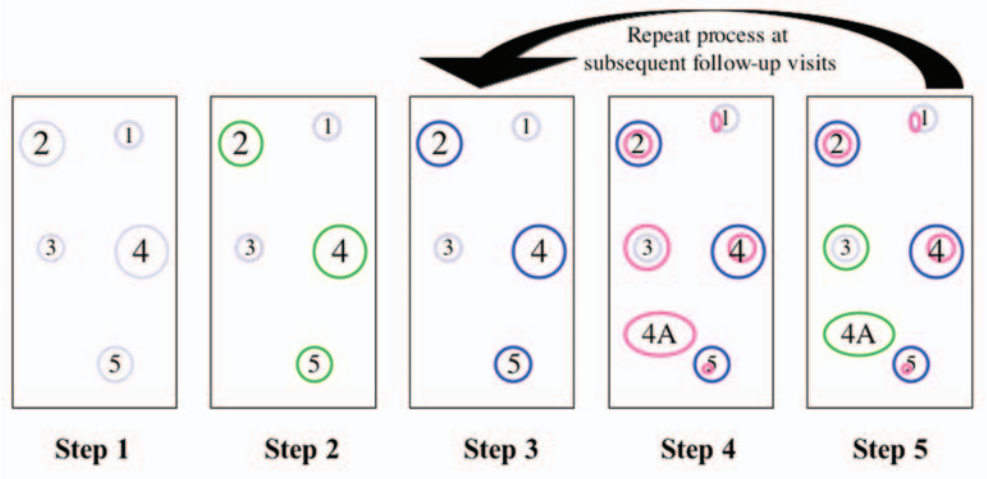

FIG. 1. Schematic drawings illustrating the technique used to follow and identify treatment targets for radiosurgery. *Step 1:* Outline all tumors, number them, and color them light blue. Patient will receive 24-Gy whole-brain irradiation and shaped beam surgery. *Step 2:* Identify target lesions (green) based on size, eloquence, and geographical distribution. Three are seen here: 2, 4, and 5. Typically no more than five tumors should be treated in a single shaped beam surgery session. *Step 3:* Code shaped beam surgery–treated lesions with dark blue for easier follow-up examination. *Step 4:* Fuse follow-up MR images and draw all lesions again by using light red. Note that all lesions are stable or smaller except for a new tumor (4A) and a light blue former tumor (3). *Step 5:* The two growing or new tumors receive shaped beam surgery (green). They will then be colored dark red. The process returns to *Step 3* at subsequent follow-up visits.

mm thickness, no skip, with 20 ml of Gd contrast [TE 2 msec, TR 9 msec]). An MR image was obtained prior to whole-brain irradiation and fused with those acquired for routine follow up (Fig. 1). All tumors were contoured during each visit. Appropriate colors were used to differentiate targets for treatment, targets treated in the past by radiosurgery, and targets that had received only whole-brain irradiation as therapy. New lesions were also indicated by color coding. Tumor size and responses to treatment were thereby easily evaluated over time using the volumetry features available in the Novalis treatment planning software package. Over time, identification of all lesions by this color-coding technique simplified decision making regarding further radiosurgery.

Patient History and Technique Application

This professional woman in her mid-40s with two young children developed a high-grade, her2neu-positive, T2N2M0 breast cancer with more than 10 positive nodes. She underwent a mastectomy, and six dose-intense cycles of adjuvant Cytoxan, Adriamycin, and Taxol were administered followed by chest wall irradiation including the supraclavicular and internal mammary nodes. A dose of 50.4 Gy was administered to all sites with a 10-Gy boost to the mastectomy scar. Near the completion of radiation treatment (12 weeks after completion of chemotherapy), the patient developed a headache; an MR study of the brain demonstrated 10 metastatic lesions. Systemic metastatic workup included chest and abdominal computerized tomography scanning and nuclear bone scanning, all of which were negative. Whole-brain radiation was delivered to a total of 30 Gy at 3-Gy per dose. The original axial spoiled gradient recalled acquisition MR study (designated MR1) was loaded into the treatment planning software along with the MR study performed 1 month after whole-brain irradiation (designated MR2). The tumors were outlined on MR1, and the fusion with MR2 demonstrated four lesions that had not diminished in size. These lesions were targeted for radiosurgery. A dose of 12 Gy was given at the 100% isodose line, with a minimum of 10 Gy at the tumor periphery. Approximately 98% of each lesion received more than 11 Gy.

At 6 months, the follow-up study (MR3) demonstrated no new lesions and no growth of the previous four stereotactic radiosurgery–treated lesions, but it also revealed that the remaining six tumors had progressed since MR2 (Fig. 2). The patient was asymptomatic but now had systemic bone disease that was well-controlled by Herceptin. The growing lesions were treated with radiosurgery. Shaped beam arcing fields were used with a central tumor dose of 14 Gy and a minimum peripheral dose of 12 Gy. Ninety-eight percent of each lesion received more than 13 Gy.

The patient continued to undergo imaging every 3 months, and the image obtained 9 months after the second radiosurgery (MR4) demonstrated five new metastases (Fig. 3). The original 10 lesions were all stable or smaller in size. Relevant to this discussion, the official reading of the image was initially incorrect. Specifically, due to complexity, the initial reading of MR4 indicated growth of the original lesions rather than the actual result, namely five new lesions and stable (or smaller) preexisting disease. The difference between the neuroimaging report and the true situation was elucidated by fusion of MR2, MR3, and MR4. The five new tumors were treated with radiosurgery. Again shaped beam arcing fields were used with a central tumor dose of 14 Gy and a minimum peripheral dose of 12 Gy. Ninety-eight percent of each lesion received more than 13 Gy.

After the third radiosurgery, the patient entered a protocol study that featured tumor vaccine therapy for breast cancer at another institution. Normally, the possibility of any tumor growth in the brain would have made her inel-

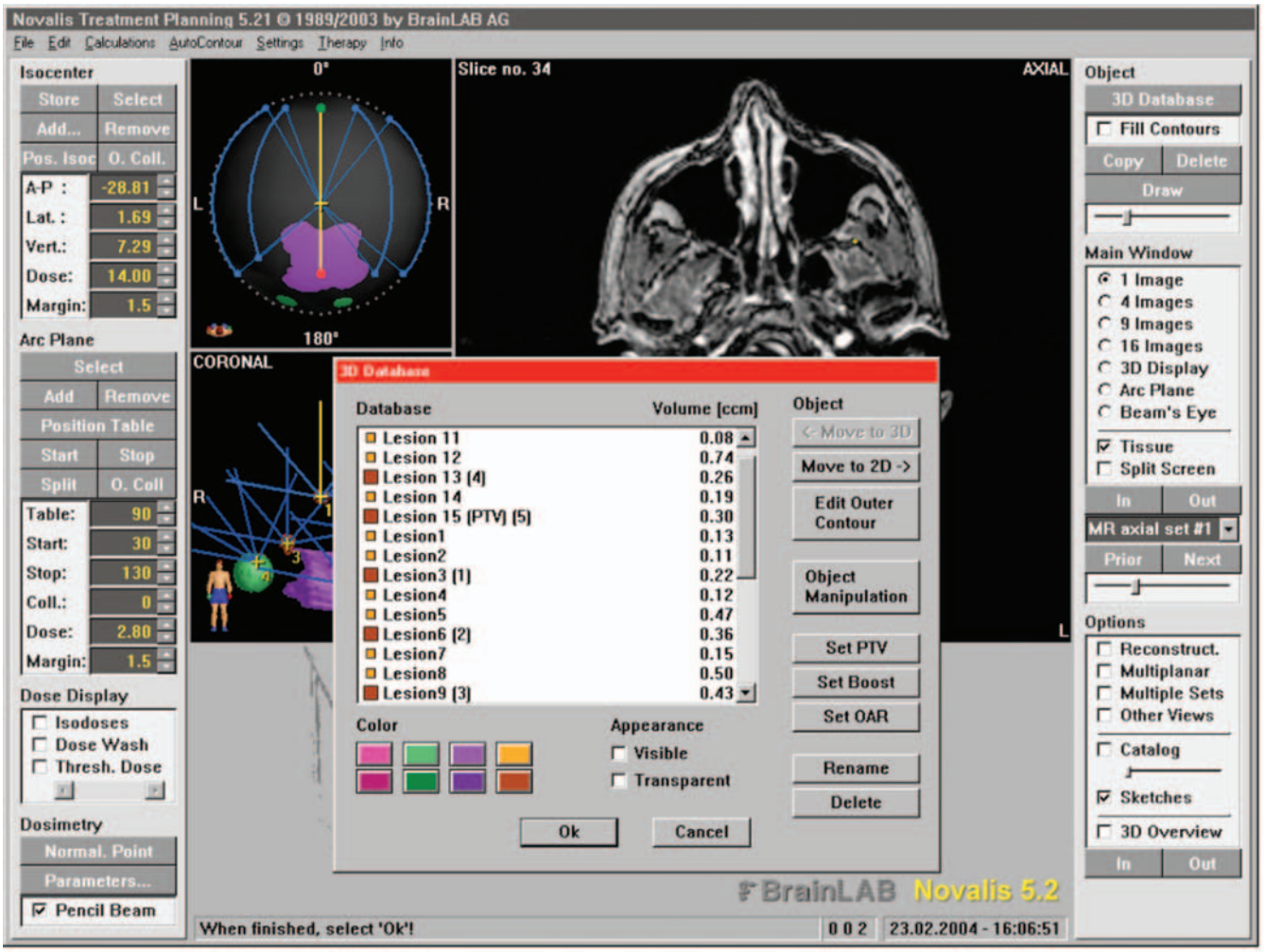

FIG. 2. Typical view of Novalis BrainSCAN treatment planning screen. There are 15 tumors outlined including five newly treated with radiosurgery (dark brown), and 10 others treated in the past (light brown). They are numbered sequentially from superior to inferior. The volume of each tumor can be easily compared over time because this image is fused with all previous treatment and follow-up images.

igible for the vaccine protocol, but because she had received comprehensive brain treatment, she was permitted to enroll in the study. She did very well on the bisphosphonates and vaccine therapy for the year, during which she did not undergo MR imaging (her preference). At completion of the study, 1 year after the third radiosurgical procedure and 2 years and 2 months after the first radiosurgical procedure, the patient had no neurological symptoms but did have a headache. An MR image was obtained (MR5), which demonstrated that 12 of the tumors already treated by radiosurgery had increased in size. In addition, there were nine new lesions. Five of the 21 active lesions were more than 4 ml in volume and nine were more than 0.7 ml in volume. The three largest and two other tumors were treated by radiosurgery. The doses and techniques used were identical to the procedure performed 1 year earlier. This was followed by repeated whole-brain irradiation of 1.8 Gy per dose for a total of 18 Gy. The patient's neurological performance remained normal. Five more lesions were treated 1 month after whole-brain irradiation. The targets were the four lesions that had been growing and one lesion that did not decrease in size after whole-brain treatment. This cohort of tumors included all lesions that were 0.5 ml or greater in residual size. The patient's systemic disease remains in excellent control and, remarkably and more importantly, the patient has no identifiable neurological deficits.

Discussion

Treatment Efficacy

The goal of palliative therapy is to enhance the patient's quality of life and to achieve increased median survival time, while simultaneously ensuring that the benefits of treatment outweigh the detriments. Randomized clinical studies in most adults with solid tumors show how difficult it is to make major improvements in median survival time with most available palliative or adjuvant therapies; improving quality of life, however, is commonly achieved.[28,29,42] Our

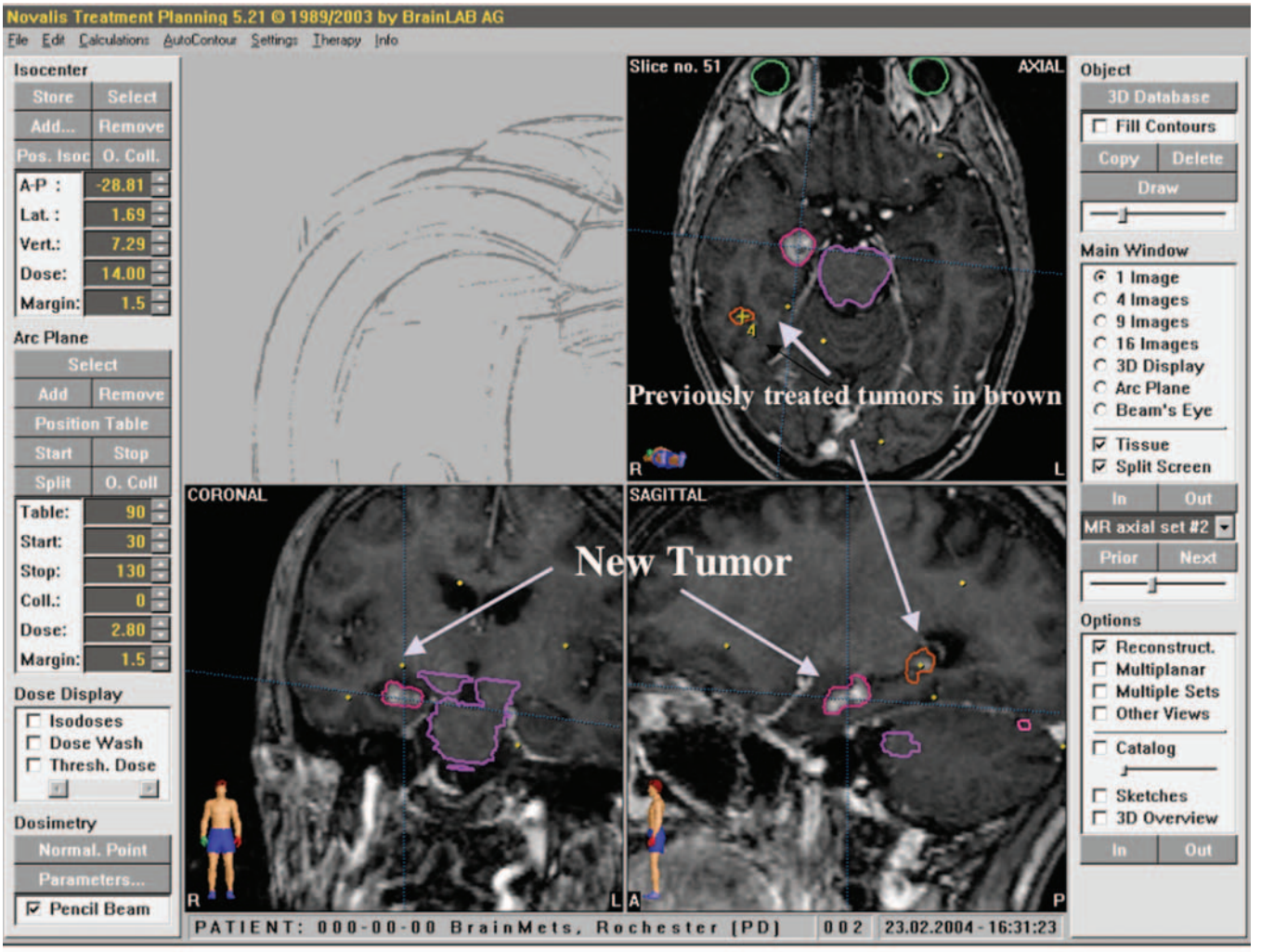

FIG. 3. Typical view of Novalis treatment planning screen. The tumors that were treated (dark brown) are now absent *(top right)* or smaller *(lower panels)*. There is a new tumor that will be targeted for radiosurgery (red).

particular patient underwent two standard whole-brain radiation treatments and five separate radiosurgical treatments (total number of lesions treated 20), including retreatment of four large lesions.

The subsequent growth of the remaining lesions within 6 months of the first radiosurgical treatment suggests that whole-brain irradiation alone would have resulted in a much shorter survival time for this patient. Indeed, even if the duration of her survival was not increased by shaped beam radiosurgical treatment, then certainly her neurocognitive state, critical for quality of life, was dramatically enhanced. Moreover, this patient cannot tolerate steroid therapy due to steroid psychosis, and therefore, without palliative radiosurgical intervention, the edema that her tumors were likely to cause would have greatly affected her quality of life. Although we concede that shaped beam radiosurgery is not appropriate for many patients with multiple brain metastases, based on our experience, we can only conclude that some patients with multiple brain metastases gain great advantage from aggressive radiosurgery, including both better and longer survival periods. Indeed, others have come to this same conclusion.[27,33,39] Although there is no fully satisfactory method for choosing appropriate cases for this treatment, recursive partitioning analyses have identified several classes of patients:[11,27] patients with a Karnofsky Performance Scale score greater than or equal to 70, controlled primary lesions, age younger than 65 years, with only brain disease were those who most benefited from radiosurgery; patients with a Karnofsky Performance Scale score less than 70 had limited benefit.

Role of Whole-Brain Irradiation

Whole-brain irradiation is needed in most patients with multiple brain metastases;[24,25,28,29,38,39,42] however, some patient groups might derive less benefit from whole-brain irradiation. For example, it is questionable whether patients with tumor histological types not prone to produce brain metastases (colon cancer, ovarian cancer) or those with three or fewer lesions need whole-brain irradiation.[6] This is particularly true if the metastases occur solely in

the brain, are few in number, or occur after a long disease-free interval. Questions related to this issue are being posed in active protocols.[2]

Irradiation of the whole normal brain often prevents development of metastases. For example, in adjuvant studies in which patients at risk of developing brain metastases are randomized, metastases are commonly prevented.[1,3,7,13,14,16,18,30,41] Likewise, authors have examined patterns of failure in patients after whole-brain irradiation for metastases. Approximately 40 to 80% of patients with brain metastases will develop subsequent lesions without whole-brain irradiation. Whole-brain irradiation reduces this risk of new lesions to about 10 to 20%.[24,38,39] Whole-brain irradiation is also reported to control the existing lesions until death in approximately 50% of patients and improve the local control rates after radiosurgery.[5,37,38]

The minimum required dose and fractionation for the whole-brain treatment is unknown. Doses used range from a low of 20 Gy in five fractions to a high of 50 Gy in 25 fractions. A large variety of treatment schedules seems to have yielded equivalent results,[1,3,7,13,14,16,18,22,30,41] although those that feature fraction sizes over 3 Gy may consequently produce long-term dementia.[8] The prevention of new metastases by whole-brain radiation therapy might therefore be related more to a poisoning of the normal tissue than killing of occult tumor foci. This poisoning phenomenon, called tumor bed effect, is long lasting after irradiation but not permanent.[20,21,23,26,44] Thus, if the role of the whole-brain field is primarily to control future metastases, low total doses should be sufficient. Our choice of 30 Gy in 10 fractions at the time of initial presentation was based on the standard of care. For patients selected for aggressive brain management, we would now use 24 to 30 Gy in 12 to 15 fractions. This schedule should produce similar tumor kill rates with less normal tissue damage for any tissue with an α/β over 2 Gy, when compared with the usual schedule of 20 Gy in five fractions or 30 Gy in 10 fractions. As mentioned, the tumor bed effect is not permanent and requires a lesser dose than does tumor control. Our subsequent dose of 18 Gy was based on our concurrent plan to undertake two radiosurgery procedures and a goal of again poisoning the tumor bed: the additive effect of the radiation doses was carefully considered. When treating large numbers of metastases, the radiosurgery procedures can result in median brain doses of 2 to 3 Gy. Eighteen Gy to the whole brain therefore allows the cumulative whole-brain dose over the 3 years to be maintained at less than 60 Gy.

Radiosurgery Dose

Our patient was treated with central and peripheral radiation doses of 12 and 10 Gy, respectively, immediately after 30-Gy whole-brain irradiation, and then, at later time points, the patient received central and peripheral doses of 14 and 12 Gy, respectively. Although the Radiation Therapy Oncology Group has established higher maximally tolerated doses than that which we prescribed for our patient, most radiosurgical series have shown high levels of in-field control even for large lesions treated to minimum doses of 10 Gy; therefore, we have routinely used conservative doses even for small tumors. We have had only four patients develop in-field recurrences. Ultimately, most of this patient's tumors subsequently regrew but the recurrence required 12 to 24 months. It is interesting to note that brain metastases from breast cancer are reported to be more resistant to radiosurgery than brain metastasis from lung cancer or melanoma.[9,17] The difference in local tumor control, however, may be more a result of duration of patient survival. That is, systemic therapy is associated with longer survival in patients with breast cancer compared with those who have lung cancer or melanoma. We nevertheless now believe that the conservative radiosurgical doses are not fully sufficient for long-term tumor control in patients being treated aggressively. Based on radiobiological principles, the dose increase required is probably small.[40] We have therefore raised our standard dose by 10 to 20%. Specifically, central and margin doses are now 15 and 12 Gy, respectively, immediately after whole-brain irradiation, and 16.5 and 13.5 Gy, respectively, when whole-brain irradiation is not planned.

Choice of Targets for Radiosurgery

When whole-brain radiation is delivered, the literature suggests that half the lesions subsequently will not grow. It has become our practice to treat tumors that have not decreased in size, as well as those that are larger than 1 ml following whole-brain irradiation. At periods of more than 6 months after whole-brain radiation therapy, we have chosen to treat tumors that have grown. Indeed, larger tumors may not actually be viable and smaller tumors may have very active growth. The use of fluorodeoxyglucose positron emission tomography does not appear to differentiate viable from successfully treated tumors reliably.[4] Two years after irradiation there can be MR imaging changes, such as increased enhancement, that mimic recurrence.[9,10] This issue becomes even more confusing when considering the large number of MR imaging pulse sequences available and their differential anatomical accuracy and specificity for active tumor. Until there are reliable methods for identifying targets, we may over- and undertreat the disease in some patients. In addition to the biological choice of targets, there are technical limitations. Dosimetrically, tumors that are close together can have regions of overlap; therefore, dispersed geographical distribution is advantageous when choosing targets on any one radiosurgical procedure. As mentioned previously, only a limited number of tumors can be treated during any one procedure because the falloff dose in the remainder of the brain builds up with the number of targets. It is usually difficult to treat more than five lesions during any one procedure.

Technological Limitations

Although technological advances allow us to analyze carefully and accurately the number, location, and growth of metastases, the process remains slow and time consuming when considering that these analyses have to be performed at each 3-month follow-up visit. Automation of labeling of targets and automatic volumetry of targets are critical to making possible routine aggressive radiosurgical treatment of multiple brain metastases. Likewise, the ability to generate composite treatment plans is critical when multiple retreatments are performed over a long period of time. This is especially true if repeated whole-

brain irradiation is desired. Finally, the contoured tumors should be coded for date of scan and whether a target was treated or is being followed. The coding should be simple and immediately recognizable because the number of contours will be large. Until automated procedures to contour, size, locate, and label tumors are consistently available, aggressive therapy of metastases will be difficult to test in clinical trials. The Novalis treatment planning system is now the most suitable system available for this process; however, users and patients alike would benefit from additional software tools.

New Therapies

The treatment of metastases in the brain is likely to improve through the use of agents aimed at either selectively reducing the toxicity of radiation or those that selectively enhance the effects of radiation on tumor. Studies in which both these questions are examined are in progress worldwide. Some protective agents include pentoxifylline, vitamin E, corticosteroids, anticoagulants (warfarin, and low molecular weight heparin), oxygen-carrying agents, antioxidants (melatonin), erythropoietin, and other growth factors. None of these interventions has yet distinguished itself. Regarding sensitizers, interesting data have emerged based on the use of Motexafin gadolinium,[19] temozolamide,[34] and Efaproxiral (RSR-13).[36] Studies are underway featuring Gefitimib and thalidomide. Ultimately, it may be possible to offer improved efficacy of both whole-brain and stereotactic irradiation.

Conclusions

Clear benefit is observed in some individual patients who have undergone aggressive treatment with radiosurgery for multiple metastases. A major limitation to the success of this therapy is the lack of control of extracranial disease in most patients. It is clear that aggressive well-designed treatment substantially decreases the progression of brain metastases and also improves neurocognitive survival. Indeed, Sneed and colleagues[38,39] concluded that the neurological consequences of metastatic recurrence in the brain were greater than the consequences of radiation therapy to the brain.

Evaluation of patients who have undergone multiple complex treatments is technically demanding. The Novalis treatment planning system, at present, is the only software solution for radiosurgery that satisfactorily facilitates the comprehensive follow up of patients who have undergone several and repeated radiosurgeries over a long period of time. Progress is still required in software design to facilitate further the clinical application of this treatment; such software development would allow for rigorous testing of this treatment modality in clinical trials.

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