

CLINICAL THERAPEUTICS

Stereotactic Radiosurgery for the Management of Brain Metastases

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This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the author's clinical recommendations.

A 50-year-old man with a history of locally advanced non–small-cell lung cancer presents with moderately severe headaches and mild numbness of the right arm. He is functionally independent and has no coexisting medical conditions. His neurologic examination is normal except for some diminished sensation in the right arm. Magnetic resonance imaging (MRI) of the brain reveals a single lesion, 2.5 cm in diameter, in the left parietal region, with a moderate amount of edema. Additional testing shows no evidence of extracranial disease. He is treated with dexamethasone, with rapid improvement of his symptoms. His physicians recommend whole-brain radiation therapy followed by stereotactic radiosurgery.

THE CLINICAL PROBLEM

Brain metastases occur in 20 to 40% of patients with cancer.¹ The incidence is believed to be over 170,000 cases per year in the United States, although exact figures are not known. Recently, a study of a population-based cohort of patients admitted to Swedish hospitals revealed a doubling of the annual age-adjusted incidence rate of hospitalization for brain metastases from 7 to 14 patients per 100,000 population between 1987 and 2006.²

The prognosis of patients with brain metastases is generally poor. The most commonly used prognostic system is the Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).³ This classification scheme stratifies patients on the basis of three prognostic categories (recursive-partitioning-analysis classes 1, 2, and 3, with a higher class indicating a worse prognosis) according to age at diagnosis, absence or presence of extracranial metastases, score on the Karnofsky Performance Status scale (which ranges from 0 to 100, with higher scores indicating improved functional status; Table 2 in the Supplementary Appendix), and status of the primary cancer. On the basis of this analysis, the median survival of patients with brain metastases ranges from 2.3 to 7.1 months. A more recent analysis of the RTOG database of brain metastases led to the development of a revised prognostic scale called the Graded Prognostic Assessment (which ranges from 0 to 4, with higher scores indicating improved survival; Table 3 in the Supplementary Appendix).⁴ Although analysis of the RTOG recursive-partitioning-analysis database showed the status of the primary cancer to be prognostic, the RTOG Graded Prognostic Assessment analysis showed the number of metastatic lesions (one, two to three, or more than three) to be prognostic. Neither system suggests that the type of primary tumor influences outcomes.

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PATHOPHYSIOLOGY AND THE EFFECT OF THERAPY

Lung cancer accounts for 30 to 60% of all brain metastases. Other common primary cancers include breast cancer, melanoma, renal-cell carcinoma, colorectal cancer, and carcinoma of unknown primary origin (Table 4 in the Supplementary Appendix). Parenchymal metastases typically occur at the gray–white junction as a result of arterial hematogenous spread,⁵ and regions of the brain receiving a greater blood supply are more susceptible to developing metastases.⁶ As a result, an estimated 80% of metastases occur in the cerebral hemispheres. Less common sites of metastases are the cerebellum (15% of cases) and the brain stem (<5% of cases). The majority of patients are found to have multiple rather than single metastatic lesions on presentation. Given the superior resolution of brain tumors on MRI as compared with computed tomography (CT), MRI is the preferred imaging method for diagnosing brain metastases.

The goal of radiation therapy is to destroy tumor cells while limiting harmful effects on normal tissue. Radiation therapy for brain metastases is potentially beneficial because tumor cells are more susceptible to radiation, in part because they are undergoing frequent mitosis, than is the surrounding brain.⁷

However, despite the differential susceptibility of tumor cells to radiation, whole-brain radiation therapy is associated with potential neurologic complications. In the short term, headache, erythema, nausea, and vomiting can occur; long-term effects include somnolence, fatigue, memory loss, and in rare cases, dementia.⁸ Unlike whole-brain radiation therapy, stereotactic radiosurgery is designed to deliver a high amount of radiation to a focal target, such as a tumor, while minimizing the dose to normal surrounding brain tissue, which should decrease side effects. The vast majority of brain metastases have distinct pathological and radiographic margins,⁹ which makes it possible to clearly define the desired radiation target.

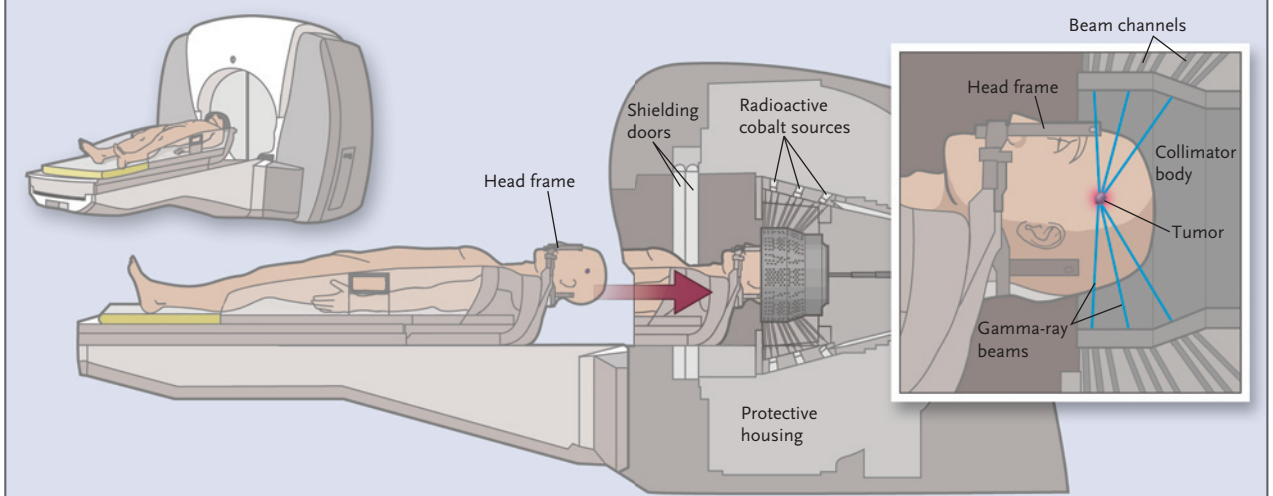
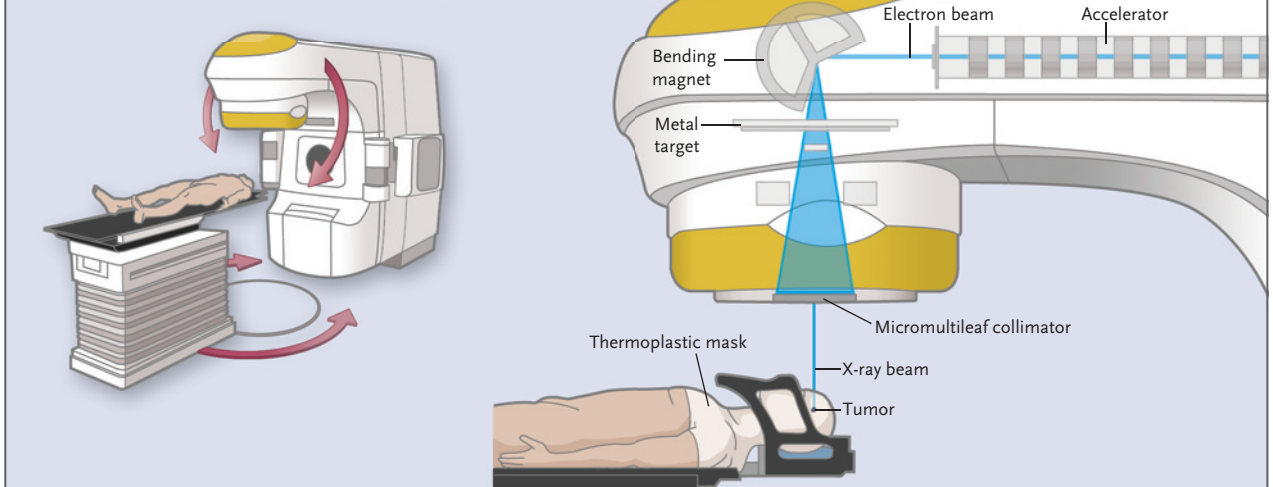
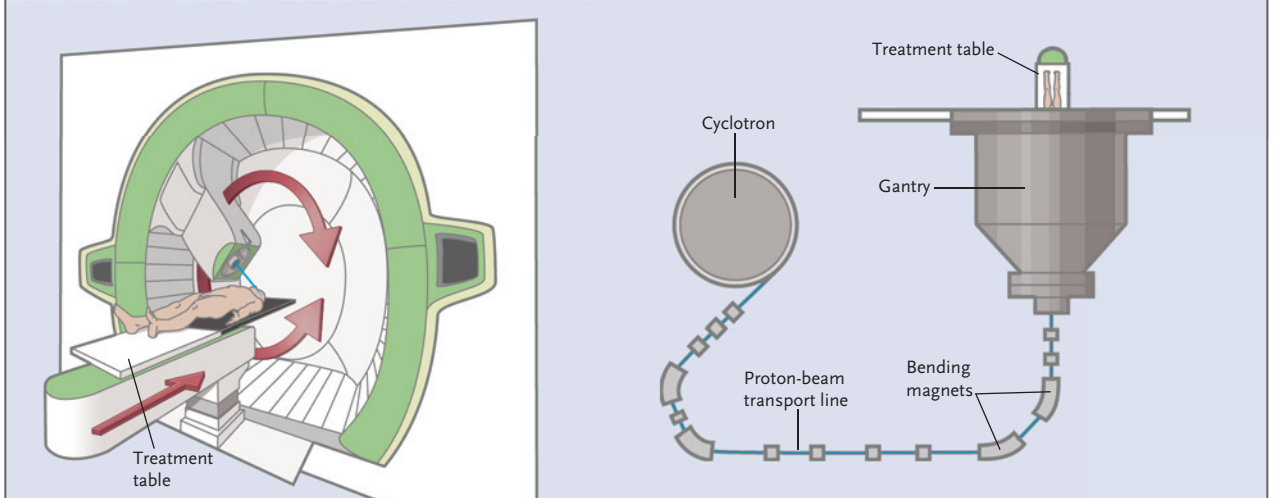
A technique for delivering a high dose of radiation to a precisely defined target is to use multiple intersecting beams of radiation converging on the target (Fig. 1). With this approach, the dose within the tumor is much higher than the dose in the surrounding normal brain tissue, as a re-

Figure 1 (facing page). Stereotactic Radiosurgery with the Use of Various Radiation-Therapy Devices.

Panel A depicts stereotactic radiosurgery involving a cobalt-60–based device (also called a gamma knife). A set of 192 individual cobalt-60 sources is arranged in a conical tungsten shell, with external shielding and internal channels shaped to focus radiation under the control of a treatment computer. Each cobalt-60 source emits gamma rays. The multiple gamma-ray beams converge on the tumor, resulting in the delivery of a much higher dose of radiation to the tumor mass than to the surrounding tissue. Panel B illustrates stereotactic radiosurgery involving a linear-accelerator–based device. A linear accelerator is used to generate a high-energy x-ray beam by accelerating an electron, which is directed at a metal target. The high-energy x-ray beams are focused by means of beam-shaping devices (micro-multileaf collimators) located at the head of the machine. Individual x-ray beams are directed at the tumor sequentially from multiple angles. As with the cobalt-60–based device, this results in the delivery of a much higher dose of radiation to the tumor mass than to the surrounding tissue. Panel C shows stereotactic radiosurgery by means of a cyclotron-based device that uses proton beams. The generation of a proton beam requires a cyclotron. Because such equipment is extremely expensive and requires a great deal of physical space, relatively few institutions use proton-beam–based devices for stereotactic radiosurgery. One potential advantage of such devices is that the proton beam can be precisely focused to control the depth of proton penetration. As a result, it deposits most of its energy within the tumor, with much less irradiation occurring beyond the tumor (Bragg peak effect). As with the linear-accelerator–based device, proton-beam devices can direct individual beams sequentially at the tumor from multiple angles.

sult of the sharp dose gradient (“dose falloff”) achieved by the multiple intersecting beams of radiation. Since the dose falloff is less rapid for larger lesions, the prescribed dose for brain metastases is inversely proportional to the maximum tumor diameter. Since a lower dose is used for larger lesions, local control is generally better with smaller lesions (<2 cm in diameter).

The mechanism of the effect of stereotactic radiosurgery on tumors is not well established but probably involves radiation-induced DNA damage and changes to the tumor vasculature. Pathological studies of tumors removed after radiosurgery suggest that the vascular endothelium may be the primary target.¹⁰ More recent studies suggest that the effect may involve endothelial-cell apoptosis, microvascular dysfunction, or the induction of a T-cell response against the tumor.^{11–13}

A Cobalt-60–Based Device**B Linear Accelerator****C Cyclotron**

CLINICAL EVIDENCE

Two published phase 3 trials have evaluated the combination of stereotactic radiosurgery plus whole-brain radiation therapy as compared with whole-brain radiation therapy alone.^{14,15} The RTOG trial (protocol 9508) was a multi-institutional study of 333 patients with one to three metastatic brain lesions. Among patients with a single lesion, survival was significantly improved in patients assigned to undergo stereotactic radiosurgery after whole-brain radiation therapy (median, 6.5 months, vs. 4.9 months among those undergoing radiation therapy alone; $P=0.04$).¹⁴ For patients with two to three lesions, local control (defined as no increase in lesion size on MRI during the follow-up period) was significantly improved with the combination of whole-brain radiation therapy and stereotactic radiosurgery as compared with radiation therapy alone, but survival was not improved (5.8 vs. 6.7 months, $P=0.98$). In a much smaller study of 27 patients at the University of Pittsburgh, rates of local control were 92% in the group undergoing the combined therapy, as compared with 0% in the group undergoing whole-brain radiation therapy alone ($P=0.002$).¹⁵

Several retrospective series have compared surgical resection with stereotactic radiosurgery.^{16–18} The most recent of these, a matched-pair analysis of 52 patients undergoing whole-brain radiation therapy followed by stereotactic radiosurgery and 52 other patients undergoing surgical resection followed by whole-brain radiation therapy, showed that the stereotactic-radiosurgery group had significantly better 1-year rates of survival (56%, vs. 47% in the surgical-resection group; $P=0.03$), intracerebral control (66%, vs. 50%; $P=0.003$), and local control (82%, vs. 66%; $P=0.006$).¹⁷ Unfortunately, no phase 3 trial comparing surgery with stereotactic radiosurgery has been published, because of the difficulty of randomization between the two treatments (since surgery is invasive whereas stereotactic radiosurgery is minimally invasive). The use of stereotactic radiosurgery as adjuvant therapy and in cases of recurrent disease after surgery has also been reported.^{19,20}

CLINICAL USE

Stereotactic radiosurgery is an appropriate form of therapy for patients who have one to four brain metastases, no larger than 4 cm in diameter, from

metastatic cancer (Table 1, and Table 4 in the Supplementary Appendix). It appears to be effective for all types of primary tumors, even those that have been considered to be resistant to conventional radiation therapy.^{21,22} The ideal candidate for such treatment has controlled extracranial metastases or an absence of such metastases and an excellent performance status (Karnofsky Performance Status score of 90 or 100). Surgery is a better option for patients with larger lesions (>3.5 cm in diameter), no known primary diagnosis, symptomatic mass effect, or clinically significant edema. Table 2 lists the advantages of surgery and stereotactic radiosurgery.

Several types of radiation-therapy devices are used in stereotactic radiosurgery (Fig. 1). The three most common are cobalt-60–based machines, linear accelerators, and cyclotrons, which use gamma rays, x-rays, and protons, respectively. Although these kinds of equipment differ in the type of radiation delivered and in the manner that the radiation is focused on the tumor, randomized trials have not yet been performed to show whether one has clinical advantages over another. Therefore, the decision to use one type of technology rather than another is typically based on physician preference and expertise as well as machine availability.

Effective implementation of stereotactic radiosurgery requires a team of well-trained neurosurgeons, radiation oncologists, and medical physicists who work together as part of a multidisciplinary team.²³ The most commonly used approach for precise localization and immobilization of the target begins with the attachment of a head frame to the skull, while the patient is under local anesthesia, typically with the use of four screws that pierce the scalp and secure the frame to the outer table of the skull (Fig. 2A). The patient is typically given an anxiolytic intravenously to aid with frame placement. A fiducial reference box is then placed on the frame during imaging to provide coordinates for target localization. Frameless approaches have also been developed. For example, one approach uses a thermoplastic mask with bite plate for head positioning; another uses a mask and stereoscopic radiography of the patient's skull before and during treatment to verify the radiation-beam orientation with reference to bony landmarks (Fig. 2B). Such methods may be more comfortable for patients.^{24–26}

MRI or CT is then performed to localize the

target in three dimensions. These data are imported into a high-speed computer to help physicians and the medical physicist to develop an individualized treatment plan that focuses the radiation as precisely as possible on the tumor target. For irregularly shaped targets, individual beams can be selectively blocked or altered to conform to the target's shape and minimize the dose to normal brain tissue.

Once the treatment plan and quality assurance checks have been completed, the patient is brought into the treatment room and positioned, usually supine, on a treatment couch. Since the radiation beams are focused on the tumor, shielding to prevent scatter is not required. In some cases, normal brain structures such as the optic nerves or chiasm should be shielded or avoided to minimize the dose to these sensitive structures. To minimize the risk of complications, patients should be given intravenous dexamethasone before the start of treatment, unless it is contraindicated because of allergy.

During treatment, the number and position of the radiation beams and the position of the treatment couch vary, depending on the type of technology used and the location, size, and shape of the tumor. The doses typically used are 1500 to 2400 cGy, which are biologically equivalent to 5 to 6 weeks of daily conventional radiation therapy. The dose chosen is not based on tumor type, but rather, primarily on the size, number, and location of the brain metastases. The dose may be administered in a single session or in three to five sessions of fractionated radiation therapy over a period of several days to 1 week. If the patient has multiple lesions, the lesions can be treated sequentially on the same day. At some centers, radiation techniques may be able to be used to treat multiple lesions simultaneously.

Depending on the location, number, and size of lesions, the typical treatment time can vary from 30 minutes to 3 hours. After treatment is complete, the head frame is removed and the patient is usually discharged within an hour. Some patients may require pain medication after frame removal, which occasionally delays discharge.

The patient may be sent home with a tapering schedule of dexamethasone, depending on the size, location, and number of metastatic brain lesions. Many patients are able to resume routine activities within 1 week after the procedure. Follow-up office visits and MRI visits are usually scheduled to occur 2 to 3 months after treatment.

Table 1. Characteristics of Brain Metastases That Make Them Ideal Targets of Radiosurgery.*

Well defined on imaging (MRI and CT)
Spherical or pseudospherical shape
Most <4 cm in maximum diameter
Generally noninfiltrative
Located at gray–white junction

* CT denotes computed tomography, and MRI magnetic resonance imaging.

Repeat treatment of a lesion is not generally recommended, given that repeat stereotactic radiosurgery has an increased risk of potential complications and difficulty in differentiating necrosis from radiation and recurrence of tumor.

The costs of stereotactic radiosurgery vary on the basis of the technology used, number of lesions treated, and institutional fee for the procedure. Estimated Medicare costs for stereotactic radiosurgery are \$10,000 to \$27,000 per procedure, as compared with \$2,300 to \$7,650 for whole-brain radiation therapy.²⁷

The role of whole-brain radiation therapy in combination with stereotactic radiosurgery is a subject of controversy. I recommend considering whole-brain radiation therapy as part of the treatment regimen for most patients with brain metastases, since the rates of recurrence of local and distant brain lesions are significantly greater without it.²⁸ Whole-brain radiation therapy may be administered before or after stereotactic radiosurgery.

Since life expectancy is poor for the majority of patients with brain metastases, the quality of life is of paramount importance to patients and their families. The health-related quality of life is influenced by a patient's experience, beliefs, expectations, and perceptions.²⁹ Given the variety of side-effect profiles associated with the various management strategies for brain metastases, the risks and benefits need to be thoroughly discussed with patients and their families.

ADVERSE EFFECTS

Side effects from radiation treatment are typically classified as acute effects (occurring during treatment or shortly after its completion), early delayed effects (occurring weeks or months after completion), and late effects (which can become permanent).

Table 2. Advantages of Surgery and Stereotactic Radiosurgery for Brain Metastases.**Surgery**

Treatment of larger lesions (>4 cm in diameter)
 Rapid resolution of mass effect and edema
 Removal of cancer
 Histologic confirmation of cancer
 Rapid tapering of the dose of corticosteroids used to treat symptomatic lesions
 Less intensive follow-up
 Lower risk of radiation necrosis when combined with whole-brain radiation therapy

Stereotactic Radiosurgery

Treatment of small, deep lesions or eloquent areas
 Minimally invasive or noninvasive approach
 General anesthesia not required
 Outpatient procedure
 Treatment of multiple lesions during same session
 Short recovery time (<1 wk)
 Potential avoidance of whole-brain radiation therapy
 Rapid initiation of systemic therapies

Acute effects from stereotactic radiosurgery include common complications (occurring in >50% of patients) such as screw-site soreness and headache after frame removal, as well as less frequent complications (in <5% of patients) such as screw-site infection, short-term exacerbation of neurologic symptoms, and seizures. Later side effects, either early delayed or late, are uncommon (occurring in <5% of patients) and include brain edema, radiation necrosis, and the worsening of preexisting neurologic deficits or development of new ones. In one trial, 7% of patients in the radiosurgery-only group had seizures and 3% had radiologic evidence of leukoencephalopathy.³⁰ Another prospective trial of stereotactic radiosurgery alone reported acute side effects (including seizures and transient worsening of preexisting neurologic symptoms) in 9% of patients and late side effects (neurologic deficits including paresis and decreased visual acuity) in 4% of patients.³¹ Corticosteroid dependency is also a concern. Since long-term corticosteroid use has a number of side effects, including psychosis, diabetes, insomnia, weight gain, and immunosuppression, whenever possible, the dexamethasone should be tapered off soon after the procedure.

Acute side effects from whole-brain radiation therapy include common effects (occurring in >50% of patients) such as alopecia, fatigue, and erythema and less common effects (occurring in <20% of patients) such as otitis externa, impaired sense of taste, nausea, and headache. Early delayed and late side effects from whole-brain radiation therapy may include tanning of the scalp, alopecia, hearing loss, neurocognitive decline, behavioral changes, the somnolence syndrome, and radiation necrosis. Prospective studies have shown that the majority of patients with brain metastases have neurocognitive deficits before the initiation of radiation therapy³²⁻³⁴ and that the degree of tumor control that can be achieved with radiation therapy appears to be positively correlated with neurocognitive function.³⁵ As a result, the true effect of whole-brain radiation therapy on neurocognitive function is a subject of debate.

AREAS OF UNCERTAINTY

Perhaps the most important area of uncertainty in the use of stereotactic radiosurgery concerns whether or not to include whole-brain radiation therapy in the management plan.³⁶ Two phase 3 trials have examined this issue.^{37,38} Both showed advantages in local control with combined therapy. However, the results of the two trials differed with respect to cognitive outcomes. In one study, mental status, as measured by the Mini-Mental State Examination, began to decline sooner after therapy was completed in patients undergoing stereotactic radiosurgery alone than in patients undergoing stereotactic radiosurgery plus whole-brain radiation therapy. The other study showed that a deterioration in memory, as measured by Hopkins Verbal Learning Test, at 4 months after the completion of therapy was significantly more likely with the combined therapy.

These differing findings have led to controversy over the relative effects of tumor progression and whole-brain radiation therapy on neurocognition. Advocates of treatment with stereotactic radiosurgery alone note the lack of a survival advantage with the addition of whole-brain radiation therapy and, if disease progresses, the opportunity for salvage therapy consisting of further stereotactic radiosurgery or subsequent whole-brain radiotherapy.³⁸⁻⁴⁰ Advocates of combining stereotactic radiosurgery with whole-brain radiation therapy argue that most patients have occult

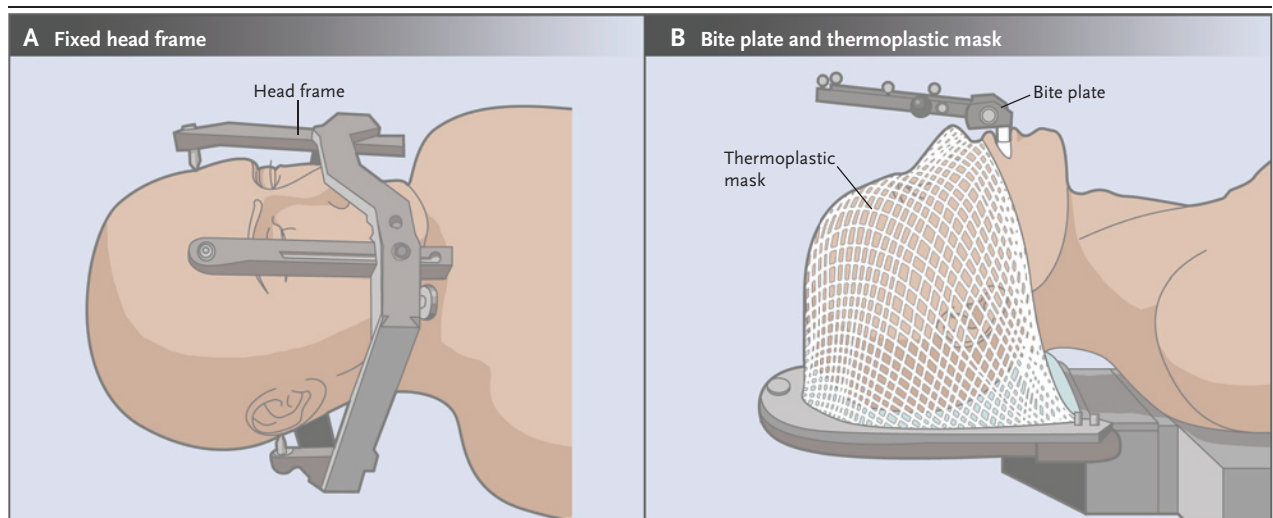


Figure 2. Stereotactic Radiosurgery with the Use of a Head Frame or Frameless Approach.

Stereotactic radiosurgery requires very precise positioning of the patient's head relative to the radiation-delivery system. The conventional method of maintaining stable positioning is to use a rigid head frame, which is secured to the outer table of the patient's skull with screws (Panel A). Local anesthesia is required for this approach, and headache and screw-site pain are common after the procedure. Newer approaches have been developed to try to achieve stable positioning without the need for a head frame. One method involves the molding of a thermoplastic mask over the face and head, together with the positioning of a bite plate with embedded reflective markers against the hard palate (Panel B). Another radiation-delivery system uses a mask and stereoscopic radiography of the patient's skull before and during treatment to verify the radiation-beam orientation with reference to bony landmarks.

disease at diagnosis, that local and distant disease progression is more frequent in the absence of whole-brain radiation therapy, and that tumor recurrence can lead to neurologic deterioration and deficits more severe than those caused by whole-brain radiation therapy.^{30,32,41}

treatment approach (surgery vs. no surgery), the National Comprehensive Cancer Network believes that the best means of management is participation of the patient in a clinical trial.

GUIDELINES

The National Comprehensive Cancer Network has developed clinical practice guidelines with regard to the management of brain metastases.⁴² It recommends that stereotactic radiosurgery be considered for patients with a limited number of brain metastases (one to four) who have stable, systemic disease or reasonable systemic treatment options and for patients who have a small number of metastatic lesions in whom whole-brain radiation therapy has failed. Category 1 evidence for a single resectable metastasis supports the use of surgical resection followed by whole-brain radiation therapy or by stereotactic radiosurgery in combination with whole-brain radiation therapy. Category 2B evidence (less compelling than category 1) supports the use of stereotactic radiosurgery alone. Since institutional practice will help determine

RECOMMENDATIONS

The patient in the vignette has a brain metastasis from non-small-cell lung cancer, with the cancer categorized as class 1 according to recursive partitioning analysis and has a score of 3.5 on the Graded Prognostic Assessment scale. To provide a balanced and thorough discussion of treatment options, the patient should be evaluated by a neurosurgeon, since surgical resection and stereotactic radiosurgery appear to be equally effective options. Because of the controversy regarding which management option is optimal in this patient, I would offer him participation in an ongoing clinical trial. An ongoing phase 3 study (ClinicalTrials.gov number, NCT00377156) by the North Central Cancer Treatment Group (Intergroup N0574) involves the random assignment of patients with one to three brain metastases to undergo stereotactic radiosurgery alone or stereotactic radiosurgery followed by whole-brain radiation therapy.

If the patient is not interested in participating in a clinical study, I would recommend whole-brain radiation therapy followed by stereotactic radiosurgery, rather than stereotactic radiosurgery alone, to minimize the risk of progression of local and distant brain disease.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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