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Postoperative Radiotherapy in the Treatment of Single Metastases to the Brain

A Randomized Trial

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Context.—For the treatment of a single metastasis to the brain, surgical resection combined with postoperative radiotherapy is more effective than treatment with radiotherapy alone. However, the efficacy of postoperative radiotherapy after complete surgical resection has not been established.

Objective.—To determine if postoperative radiotherapy resulted in improved neurologic control of disease and increased survival.

Design.—Multicenter, randomized, parallel group trial.

Setting.—University-affiliated cancer treatment facilities.

Patients.—Ninety-five patients who had single metastases to the brain that were treated with complete surgical resections (as verified by postoperative magnetic resonance imaging) between September 1989 and November 1997 were entered into the study.

Interventions.—Patients were randomly assigned to treatment with postoperative whole-brain radiotherapy (radiotherapy group, 49 patients) or no further treatment (observation group, 46 patients) for the brain metastasis, with median follow-up of 48 weeks and 43 weeks, respectively.

Main Outcome Measures.—The primary end point was recurrence of tumor in the brain; secondary end points were length of survival, cause of death, and preservation of ability to function independently.

Results.—Recurrence of tumor anywhere in the brain was less frequent in the radiotherapy group than in the observation group (9 [18%] of 49 vs 32 [70%] of 46; $P<.001$). Postoperative radiotherapy prevented brain recurrence at the site of the original metastasis (5 [10%] of 49 vs 21 [46%] of 46; $P<.001$) and at other sites in the brain (7 [14%] of 49 vs 17 [37%] of 46; $P<.01$). Patients in the radiotherapy group were less likely to die of neurologic causes than patients in the observation group (6 [14%] of 43 who died vs 17 [44%] of 39; $P=.003$). There was no significant difference between the 2 groups in overall length of survival or the length of time that patients remained functionally independent.

Conclusions.—Patients with cancer and single metastases to the brain who receive treatment with surgical resection and postoperative radiotherapy have fewer recurrences of cancer in the brain and are less likely to die of neurologic causes than similar patients treated with surgical resection alone.

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FOR PATIENTS with single metastases to the brain and limited systemic disease, 2 randomized trials[1,2] have shown that surgical resection combined with postoperative whole-brain radiotherapy (WBRT) is superior to treatment with WBRT alone. (Although it should be noted that 1 randomized trial[3] failed to show a benefit from surgery.) Postoperative radiotherapy was used in all of the previous randomized trials assessing the efficacy of surgery in the treatment of single brain metastases because it was felt to be effective both in destroying any tumor left in the operative bed and in eliminating undetected micrometastases elsewhere in the brain. However, the rationale for postoperative WBRT is based on unproven assumptions. Given that most metastases are discrete masses and do not infiltrate diffusely into the brain, it is possible that metastases are capable of being totally removed by surgery. Also, improvements in neuroimaging, especially contrast-enhanced, high-resolution magnetic resonance imaging (MRI), may make it possible to detect small metastases and the residual tumor and make the routine use of postoperative WBRT unnecessary.

See also p 1527 and Patient Page.

The value of postoperative WBRT has not been tested in a randomized trial; however, there have been 6 retrospective series[4-9] analyzed (Table 1). Because of conflicting results, these studies have failed to determine the role, if any, of postoperative radiotherapy. Therefore, we conducted a prospective randomized trial comparing the effectiveness of surgery plus postoperative radiotherapy with that of surgery alone to determine if postoperative WBRT resulted in improved neurologic control of disease and increased survival.

METHODS

Eligibility of Patients

Patients at least 18 years old who had a tissue-proven diagnosis of metastatic brain tumor obtained from a complete re-

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Table 1.—Retrospective Studies Assessing the Value of Postoperative Whole-Brain Radiotherapy*

Source, y	No. of Patients: Receiving RT	No. of Patients: Not Receiving RT	Patients With Brain Recurrence, %: Receiving RT	Patients With Brain Recurrence, %: Not Receiving RT	P	Median Survival Time, mo: Receiving RT	Median Survival Time, mo: Not Receiving RT	P
Dosoretz et al,[4] 1980	12	21	50	52	NS	8	10	NS
Smalley et al,[5] 1987	34	51	21	85	NA	21	12	.02
DeAngelis et al,[6] 1989	79	19	45†	65†	.03‡	21	14	NS
Hagen et al,[7] 1990	12	21	50	52	NS	8	10	NS
Armstrong et al,[8] 1994	32	32	47	38	NS	10	14	NS
Skibber et al,[9] 1996	22	12	32	72	NA§	18	6	.002

*RT indicates postoperative radiotherapy; NS, not significant; and NA, not available.
†Estimated from graphs provided by the original sources.
‡Based on comparison of recurrence rates at 1 year.
§No *P* values were given for comparison of groups as a whole.

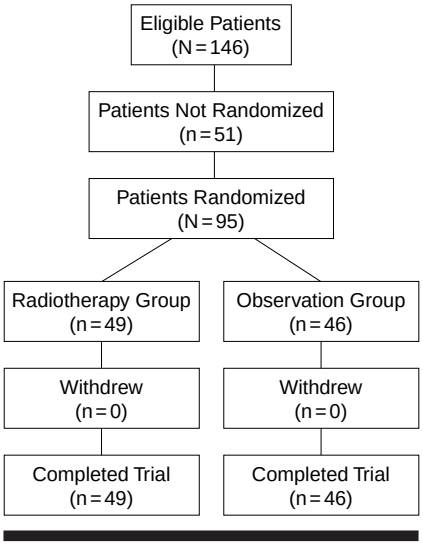

Figure 1.—Randomization of patients into radiotherapy group and observation group.

section of a single brain metastasis were eligible for the study. Patients were excluded if they had brain metastases that had not been completely removed by surgery, evidence of leptomeningeal metastases, a history of previous cranial radiotherapy, a need for immediate treatment to prevent acute neurologic deterioration, concomitant second malignancies, Karnofsky performance scores[10] lower than 70%, or certain radiosensitive primary tumors (small-cell lung cancer, germ-cell tumors, lymphoma, leukemia, and multiple myeloma).

Study Design

The study was a randomized trial with 2 treatment groups (Figure 1). The experimental protocol was approved by the institutional review boards of the University of Kentucky, Lexington, and of the other individual institutions that participated in the trial through the Southwest Oncology Group, the Radiation Therapy Oncology Group, and the Brain Tumor Cooperative Group. Written informed consent was obtained from each patient before entry into the study.

Before randomization, all patients had gadolinium-contrast MRI scan of the head 2 to 5 days after surgery to rule out multiple lesions and to confirm that the brain metastases had been completely resected. The pathologic lesion from the surgical resection was reviewed at a central site to ensure that patients had metastatic tumors. All patients also received an extent of disease evaluation consisting of a chest x-ray film, hematologic and chemical profiles, and other studies deemed appropriate for each patient's particular primary tumor.

Prior to randomization, patients were stratified by (1) extent of disease (brain metastasis only, brain metastasis plus primary site only, and brain metastasis plus primary site plus at least 1 additional site) and (2) primary tumor type (lung, breast, and other). Computer-generated random numbers at a central site were then used to assign patients to 1 of 2 treatment groups. The observation group received surgery only with no further treatment for the brain metastasis. The radiation group received surgery plus postoperative WBRT. At the time of randomization, all patients not already taking corticosteroids began treatment with 4 mg of dexamethasone sodium phosphate every 6 hours (or other corticosteroid in equivalent doses). In the observation group, corticosteroids were tapered and use was discontinued within 2 weeks following surgery, when possible.

For patients in the radiation group, radiotherapy was started within 28 days after surgery. Use of corticosteroids was continued without tapering through the first 2 weeks of radiation therapy and then tapered and stopped, if tolerated. The WBRT was given using lateral ports covering the brain and meninges to the foramen magnum. Patients received 50.4 Gy of WBRT over 5½ weeks (1.8 Gy × 28 fractions) prescribed to the cranial midline. This dose and fractionation scheme were chosen because the total dose was large enough to be effective against micrometastases,[11,12] and evidence from retrospective data[13,14] suggested that low, daily fractionation schemes may result in fewer long-term neuropsychological adverse effects.

In both treatment groups, MRI scans were repeated at 3-month intervals for the first year following treatment and every 6 months thereafter. The MRIs were reviewed at a central site. Patients also had MRI scans at any time they developed symptoms suggesting neurologic progression or recurrence of their brain metastases. If a recurrence was detected, further treatment was given at the discretion of the patient's physicians and was not dictated by the study.

Evaluation and Criteria for Response

To compare efficacy of treatments, we evaluated radiographic evidence of recurrence of the brain metastasis, length of time to recurrence, length of survival, cause of death, and changes in functional performance in the 2 treatment groups. Recurrence of brain metastases was determined by MRI scans, and development of leptomeningeal metastases was verified by examination of cerebrospinal fluid. A recurrence of the original brain metastasis was defined as the reappearance of a metastasis in exactly the same site in the brain as the first metastasis. The length of time to recurrence of the original brain metastasis was calculated from the date of surgery for the metastasis to the date that a recurrence was detected by MRI. A distant recurrence in the brain was defined as the appearance of a new brain metastasis at a site different from that of the original metastasis; leptomeningeal metastases were also considered distant metastases. Length of survival was calculated from the day of surgical removal of the brain metastasis to death or last follow-up evaluation.

For all patients who died, an attempt was made to determine the cause of death. Patients were considered to have died of neurologic causes if they had stable systemic disease and progressive neurologic dysfunction. Patients with severe neurologic disability who died of intercurrent illness were also included among neurologic deaths, as were patients with both rapidly progressive systemic disease and advancing neurologic dysfunction, because these patients also represent brain treatment failures. The systemic cancer was considered the only cause of death if, in the setting of neurologic improvement or stabilization, patients developed fatal infections, hemorrhages, or failure of vital organ systems other than the brain. Patients whose deaths could not be determined to be either neurologic or systemic were classified as unknown.

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Table 2.—Calculation of Estimated Number of Recurrences for Sample Size Determination*

Source, y	Brain Recurrence Rate, %		Estimated No. of Recurrences (No. of Patients)	
	Observation	Whole-Brain Radiotherapy	Observation	Whole-Brain Radiotherapy
Dosoretz et al,[4] 1980	52	50	0.52 (21) = 11	0.5 (12) = 6
Smalley et al,[5] 1987	85	21	0.85 (51) = 43	0.21 (34) = 7
DeAngelis et al,[6] 1989	65	45	0.65 (19) = 12	0.45 (79) = 36

*Estimated brain recurrence rate for observation (11 + 43 + 12) / (21 + 51 + 19) = 73%; postoperative whole brain radiotherapy; (6 + 7 + 36) / (12 + 34 + 79) = 39%.

Table 3.—Patients' Characteristics

Characteristic	Observation Group (n = 46)	Radiation Group (n = 49)	P
Male, No.	27	28	.88
Female, No.	19	21	
Age, median (range), y	58 (38-80)	60 (42-78)	.70
Karnofsky score, median (range), %	90 (70-100)	90 (70-100)	.89
No. of patients with primary tumors			
Lung (non–small cell)	28	29	.97
Breast	4	5	
Other	14	15	
Unknown primary	4	5	
Genitourinary	5	3	
Gastrointestinal	4	4	
Head and neck	0	2	
Melanoma	1	1	
Extent of disease*			
None	16	18	.98
Primary tumor only	18	19	
Disseminated	12	12	
Time between diagnosis of primary tumor and development of brain metastasis, median (range), wk	29 (0-1111)	39 (0-843)	.69
Location of brain metastasis			
Supratentorial	33	32	.50
Infratentorial	13	17	

*Other than the brain metastasis.

Table 4.—Location of Recurrence of Metastatic Cancer in the Brain

Recurrence	No. (%)	
	Observation Group (n = 46)	Radiation Group (n = 49)
None	14 (30)	40 (82)
Original only*	15 (33)	2 (4)
Original and distant†	6 (13)	3 (6)
Distant only	11 (24)	4 (8)

*A recurrence of the original brain metastasis is defined as the reappearance of metastasis in exactly the same site in the brain as the first metastasis.
†A distant brain recurrence is any recurrence not at the site of the original metastasis.

The ability to function independently after treatment of the brain metastasis was measured by the length of time Karnofsky scores[10] remained at 70% or higher.

Statistical Analysis

To estimate the sample size needed, results from the 3 nonrandomized retrospective studies, which were available at the start of our study (1989), were used to derive estimates of overall brain recurrence rates (Table 2). To compare 2 recurrence rates with a 2-tailed test (χ^2) at the .05 α level having an 80% power when one of the recurrence rates was 39% and the other was 73%, a minimum of 40 patients per group were needed.

Survival curves were drawn using the Kaplan-Meier product limit method.[15] When survival curves were based on neurologic causes of death, deaths from other causes were treated as censored. When survival curves were based on nonneurologic causes of death, deaths from neurologic causes were treated as censored. The log-rank test was applied to compare differences between 2 or more survival curves. To determine if censoring deaths due to competing causes affected the comparison of survival curves, cause-specific, survival-failure probability curves were also constructed and compared.[16] Multivariate analyses were based on a Cox regression model[17] in which a stepwise proportional hazards analysis identified the best subset of covariates associated with each time-dependent end point. The covariates examined in all cases were the treatment group, age, sex, location of brain metastasis, primary tumor type, extent of disease, initial Karnofsky score, and the length of time between diagnosis of primary and development of brain metastasis. Additional covariates were examined as appropriate and are noted in the "Results" section. The χ^2 test was used to determine the relationship between 2 categorical variables, and the Fisher exact test was used when small cell sizes were encountered in 2×2 contingency tables. A 2-tailed t test was used to compare the means of continuous variables between the 2 treatment groups.

RESULTS

Enrollment, Patient Flow, and Characteristics of Patients

The study opened in September 1989 at the University of Kentucky. During the years 1992 to 1994, the Southwest Oncology Group, Radiation Therapy Oncology Group, and the Brain Tumor Cooperative Group also contributed patients to the trial. The last patient entered the study in March 1997, and the last follow-up for all patients was November 1, 1997.

A total of 146 patients were eligible for the study and 95 patients, 46 in the observation group and 49 in the radiation group, actually entered the study (Figure 1). The reasons why 51 eligible patients were not randomized included patient refusal and physician preference for a specific treatment. The study patients' baseline characteristics are shown in Table 3. As of November 1, 1997, 82 of the 95 patients had died (39/46 [85%] in the observation group and 43/49 [88%] in the radiation group), and the median follow-up time on living patients was 132 weeks in the observation group and 127 weeks in the radiation group ($P = .77$). The overall median follow-up times were 43 weeks in the observation group and 48 weeks in the radiation group ($P = .58$). No patients were lost to follow-up.

There were 3 protocol violations involving radiotherapy. Two patients who were randomized to receive radiotherapy were given nonprotocol doses (30 Gy and 36 Gy instead of 50.4 Gy). One patient who was randomized to receive no radiotherapy was instead given WBRT (30 Gy). These patients were included in the data analysis and, in accordance with an intention-to-treat analysis, were analyzed along with the treatment group they were originally assigned to by the initial randomization procedure.

Recurrence of Brain Metastases

The addition of postoperative radiotherapy resulted in substantially better control of tumor in the brain than did treatment with surgery alone. As shown in Table 4, the recurrence rate of tumor anywhere in the brain was significantly less ($P<.001$) in the radiation group (9/49 [18%]) than in the observation group (32/46 [70%]). The time to any brain recurrence (Figure 2) was also significantly longer in the radiation group. Multivariate analysis showed that only postoperative radiotherapy lessened the risk of brain recurrence ($P<.001$).

Postoperative radiotherapy reduced the recurrence rate at the original site of operative treatment. Recurrence of the original brain metastases (independent of distant brain metastases or leptomeningeal metastases) was significantly lower ($P<.001$) in the radiation group (5/49 [10%]) than in the observation group (21/46 [46%]). In addition, time from treatment to the development of recurrence of the original brain metastases (Figure 3) was significantly longer in the radiation group (>52 weeks) than in the observation group (median, 27

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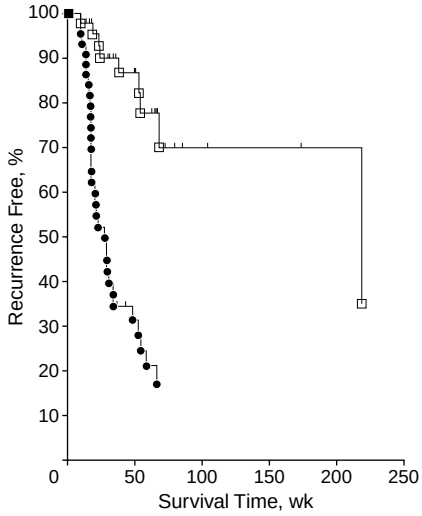

Figure 2.—The length of time to recurrence of tumor anywhere in the brain was significantly ($P<.001$) longer in patients in the radiotherapy group (white squares) than in the observation group (black circles), median 220 weeks vs 26 weeks (relative risk of any brain recurrence, 4.94; 95% confidence interval, 2.36-10.35). Tick marks indicate patients (living or dead) in whom brain recurrences did not develop.

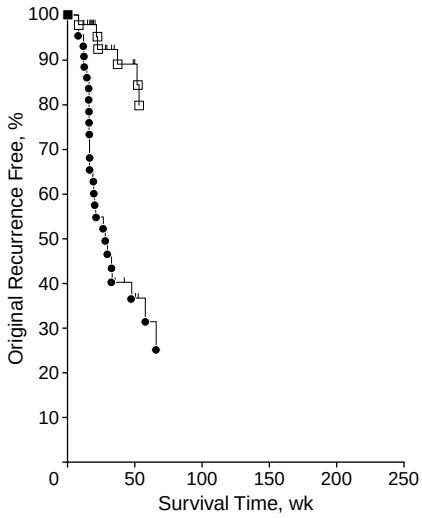

Figure 3.—The length of time from treatment to the development of recurrence of the original brain metastases was significantly ($P<.001$) longer in patients in the radiation group (white squares) than in the observation group (black circles), more than 50 weeks vs median 27 weeks (relative risk of original recurrence, 6.03; 95% confidence interval, 2.48-14.65). Recurrence of the original brain metastasis was defined as the reappearance of a metastasis in the exact site in the brain as the first brain metastasis. Tick marks indicate patients (living or dead) who did not develop recurrences of the original metastasis.

weeks). Multivariate analysis indicated that only postoperative radiotherapy of the brain metastasis ($P<.001$) reduced the risk of developing recurrence of the original brain metastases.

Postoperative radiotherapy also prevented the subsequent development

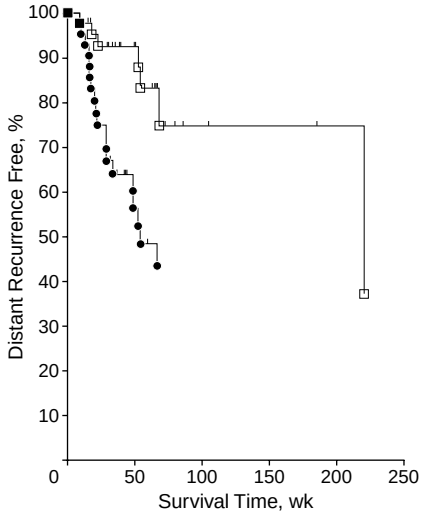

Figure 4.—The length of time to recurrence of distant brain metastasis was significantly ($P=.04$) longer in the 49 patients in the radiation group (220 weeks) (white squares) than in the 46 patients in the observation group (53 weeks) (black circles) (relative risk of distant brain recurrence, 2.77; 95% confidence interval, 1.16-6.59). Recurrence of distant brain metastasis was defined as the appearance of a new metastasis at a site in the brain different from the site of the original brain metastasis. Tick marks indicate patients (living or dead) who did not develop distant brain metastases.

of brain metastases at sites other than that of the original metastasis (distant metastases). The occurrence of distant brain metastases or leptomeningeal metastases (independent of recurrence of the original brain metastases) was significantly less ($P<.01$) in the radiation group (7/49 [14%]) than in the observation group (17/46 [37%]). Radiation significantly delayed the development of distant brain metastases (Figure 4). Multivariate analysis showed that postoperative radiotherapy ($P=.02$) and female sex ($P=.04$) were associated with lower rates of recurrence of distant brain metastases.

Survival

Overall Survival.—The survival times were not significantly different between the 2 groups. The median length of survival in the 49 patients in the radiation group was 48 weeks vs 43 weeks in the 46 patients in the observation group ($P=.39$; relative risk [RR] of death, 0.91; 95% confidence interval [CI], 0.59-1.40). Multivariate analysis showed that the time between the diagnosis of the primary tumor and the development of the brain metastasis was associated with increased survival ($P<.003$).

Death Due to Neurologic Causes.—Postoperative radiotherapy prevented death due to neurologic causes. Of all patients who died, 6 (14%) of 43 in the radiation group and 17 (44%) of 39 in the observation group died neurologic

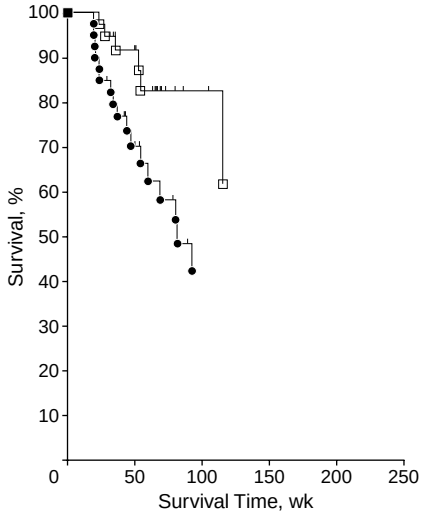

Figure 5.—When only deaths due to neurologic causes were used as endpoints and data on patients who died from nonneurologic causes were censored, there was a significant ($P=.03$) difference between the 2 treatment groups. The radiation group (white squares) had a median survival of more than 115 weeks, and the observation group (black circles) had a median survival of 81 weeks (relative risk of death from neurologic causes, 2.62; 95% confidence interval, 1.03-6.64). Length of survival was measured from the beginning of treatment for the original brain metastasis. Tick marks indicate patients who did not die of neurologic causes or the last follow-up evaluation in living patients.

deaths ($P=.003$). Radiotherapy also delayed death due to neurologic causes. When the length of time to death due to neurologic causes in the 2 groups was compared, there was a significant difference between the survival curves (Figure 5). Construction of cause-specific failure probabilities[16] did not alter this conclusion. Multivariate analysis demonstrated that WBRT was positively correlated with increased neurologic survival ($P<.009$).

Death Due to Systemic Causes.—Patients in the radiation group were more likely to die of their systemic cancer than as a result of neurologic progression. Of all patients who died, 36 (84%) of 43 in the radiation group and 18 (46%) of 39 in the observation group died systemic deaths ($P<.001$). For unknown reasons, patients in the observation group who did not die of neurologic causes appeared to live longer than similar patients in the radiation group. When survival was compared using death due to systemic causes as the only survival end point (systemic death), there was a significant difference between the 2 treatment groups. The median length of systemic survival was 48 weeks in the radiation group and 88 weeks in the observation group ($P=.005$; RR, 0.45; 95% CI, 0.26-0.79). Construction of cause-specific failure probabilities[16] did not alter this conclusion.

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Ability to Function Independently

There was no difference between the 2 groups in how long patients maintained functional independence. The median length of time their Karnofsky scores remained 70% or more after treatment of the original brain metastasis was 37 weeks in the radiation group and 35 weeks in the observation group ($P = .61$; RR, 0.84; 95% CI, 0.61-1.17).

COMMENT

This prospective, randomized trial shows that postoperative radiotherapy given after a complete surgical resection of a single brain metastasis results in substantially better control of disease in the brain and a reduction in the number of deaths due to neurologic causes. We infer from these results that radiotherapy was successful at eradicating microscopic metastases that were undetected at the time of treatment.

The goal of treatment of brain metastasis is to eliminate the metastasis and prevent recurrence of tumor in the brain. Metastases can recur after treatment in 2 ways: (1) there can be recurrence at the original site in the brain or (2) new metastasis at a brain site other than the original one (distant metastasis). The reasons for the 2 types of failure are different. Recurrence at the original site in the brain is almost always due to failure of the initial treatment to completely destroy the metastasis. Our results show that surgery alone does not always eliminate microscopic disease in the operative bed and that postoperative MRI is not reliable for detecting the presence of residual tumor after a "complete" resection. Forty-six percent of patients treated with surgery alone had recurrence at the operative site, but postoperative radiotherapy reduced that recurrence rate to 10%.

Failures at distant sites in the brain may result from either new metastases spreading to the brain after treatment for the original brain tumor has been completed (reseeding) or from the presence of additional (but undetected) brain metastases that were present at the time of treatment of the original brain metastasis. Postoperative WBRT reduced distant brain recurrences. The implication from this is that most of the micrometastases at distant sites were already present in the brain at the time that radiotherapy was given. Radiotherapy would not have had an effect on metastases that were reseeded to the brain after completion of treatment, and there is no evidence that irradiated brain is a less "fertile soil" for subsequent metastases. Therefore, although it is possible that a few recurrences were caused by reseeding, the major mechanism of metastasis to the brain appears to be a single event consisting of a shower of tumor emboli that become lodged at multiple sites in the brain.

An important corollary in the finding of undetected distant brain metastases is that the number of genuine single metastases must be smaller than was previously suspected. Studies[18,19] using computed tomographic scan data suggested that brain metastases were single in slightly less than 50% of cases. However, more recent investigations[20-23] with contrast-enhanced MRI have indicated that the percentage of single metastases detected is only one third to one fourth of patients with cerebral metastases. Our study shows that in more than one third (37%) of patients with only single metastases detected by MRI, additional distant metastases were present. This means that, overall, no more than 10% to 20% of patients with brain metastases have true single metastases.

Despite the reduction in brain recurrence rates and neurologic deaths, postoperative radiotherapy did not result in increased actuarial survival or improve the length of time patients were able to function independently. However, overall survival is determined by death due to both neurologic and nonneurologic causes and is, therefore, not a direct measure of the success of treatment for brain metastases. Patients in the radiotherapy group were more likely to die of systemic than neurologic causes, and so systemic factors were the major determinant of their length of survival. The absence of difference in overall survival times between the 2 treatment groups was a result of the lack of satisfactory treatment for the systemic cancers and not due to a failure of postoperative radiotherapy to control disease in the brain.

Postoperative radiotherapy significantly prevented and delayed death due to neurologic causes, which is all that can be expected of a treatment directed solely at brain disease. The reduction in neurologic death was not present in patients who did not receive radiotherapy in the immediate postoperative period but were instead given WBRT only at recurrence. Neurologic death involves the inexorable loss of mental and physical abilities and is the most difficult type of death for patients and their families to deal with. The prevention of a significant number of neurologic deaths is justification for the routine use of postoperative radiotherapy.

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