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A RANDOMIZED TRIAL OF SURGERY IN THE TREATMENT OF SINGLE METASTASES TO THE BRAIN

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Abstract To assess the efficacy of surgical resection of brain metastases from extracranial primary cancer, we randomly assigned patients with a single brain metastasis to either surgical removal of the brain tumor followed by radiotherapy (surgical group) or needle biopsy and radiotherapy (radiation group). Forty-eight patients (25 in the surgical group and 23 in the radiation group) formed the study group; 6 other patients (11 percent) were excluded from the study because on biopsy their lesions proved to be either second primary tumors or inflammatory or infectious processes.

Recurrence at the site of the original metastasis was less frequent in the surgical group than in the radiation group (5 of 25 [20 percent] vs. 12 of 23 [52 percent]; $P<0.02$). The overall length of survival was significantly longer in the surgical group (median, 40 weeks vs. 15 weeks in the radiation group; $P<0.01$), and the patients treated with surgery remained functionally independent longer (median, 38 weeks vs. 8 weeks in the radiation group; $P<0.005$).

We conclude that patients with cancer and a single metastasis to the brain who receive treatment with surgical resection plus radiotherapy live longer, have fewer recurrences of cancer in the brain, and have a better quality of life than similar patients treated with radiotherapy alone. (N Engl J Med 1990; 322:494-500.)

METASTASES to the brain occur in 20 to 30 percent of patients with systemic cancer[1] and are the most common type of intracranial tumor.[2,3] The life expectancy of patients with brain metastases is short, and current treatment of such metastases is not very effective. Whole-brain radiation therapy is the current standard treatment, but patients treated with radiotherapy alone have a median length of survival of only three to six months.[1,4-10] Despite occasional responses in individual patients, chemotherapy has not been shown to improve the survival of most patients with brain metastases.[1,11,12] Approximately half of all metastases to the brain are single[13] and therefore potentially treatable by surgical resection. The role of surgery in the management of brain metastases has been controversial, however, because of the complete absence of controlled clinical trials.

For over 60 years,[14,15] surgery has occasionally been performed in patients with single brain metastases who otherwise have good prognoses. Uncontrolled retrospective studies of the effectiveness of surgical treatment have had conflicting results; several studies[15-21] have shown substantial benefit from surgery, whereas others[6-8,22] have found no benefit. Nonrandomized

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studies have been biased because the patients who received surgical treatment were those with minimal disease, whereas the patients treated with radiation alone were those with more extensive disease and poorer prognoses.

Uncontrolled studies have failed to determine what role, if any, surgery should have in the management of single brain metastases. In order to determine whether the surgical removal of single brain metastases resulted in improved survival and quality of life, we conducted a prospective, randomized trial comparing the effectiveness of surgery plus postoperative radiotherapy with that of radiotherapy alone.

Methods

Eligibility of Patients

Patients at least 18 years old who had radiographic evidence of a single metastasis to the brain were eligible for the study if they had documented systemic cancer (not originating in the central nervous system) that had been diagnosed by examination of tissue within five years of treatment of the brain metastasis. Patients also had to be capable of caring for themselves independently (as indicated by Karnofsky performance scores ≥70 percent[23]). Patients were excluded if they had brain lesions that were not potentially surgically resectable; evidence of leptomeningeal metastases; a history of cranial radiotherapy; a need for immediate treatment to prevent acute neurologic deterioration; or certain radiosensitive primary tumors (small-cell lung cancer, germ-cell tumors, lymphoma, leukemia, and multiple myeloma).

Study Design

The study was a randomized, prospective trial with two treatment groups. The experimental protocol was approved by the institutional review board of the University of Kentucky Medical Center, and written informed consent was obtained from each patient before his or her entry into the study. Before randomization, all patients underwent both computerized tomography (CT scanning) and magnetic resonance imaging of the head to rule out multiple lesions. In addition, the extent of disease was evaluated in all patients; this evaluation consisted of a chest x-ray film, hematologic and chemical profiles, CT scanning of the abdomen or a radionuclide liver–spleen scan and bone scan, as clinically indicated, and other studies considered appropriate to each patient's primary tumor. At the time of the diagnosis of brain metastasis, all patients were given dexamethasone (4 mg every six hours), which was continued throughout the course of radiation therapy and then discontinued. Patients who could not tolerate the cessation of corticosteroids were maintained at the lowest dose possible. Before randomization, the patients were stratified according to the location of the tumor (supratentorial or infratentorial), the extent of disease (brain metastasis, brain metastasis plus cancer in the primary site, or brain metastasis plus cancer in the primary site and at least one additional site), and the type of primary tumor. Computer-generated random numbers were then used to assign patients to one of two treatment groups (one group received surgery plus radiotherapy, and another received radiotherapy alone).

For patients in the surgical group, surgical treatment was undertaken within 72 hours of entry into the study. All patients underwent craniotomy, and the goal of surgery in all cases was the total removal of the metastasis. All patients underwent contrast CT scanning between postoperative days 2 and 5 to determine whether the surgical removal of the tumor was complete.[24] Within 14 days after surgery, the patients began receiving 36 Gy (3600 rad) of whole-brain radiation therapy, delivered through two lateral ports covering the brain and meninges to the foramen magnum. A dose fraction of 3 Gy of cobalt-60 per day was given at a rate of 1 to 2 Gy per minute. A total of 12 dose fractions was given on weekdays.

In the radiation group, patients with supratentorial lesions who were randomly assigned to treatment with radiation alone underwent stereotaxic needle biopsies of the suspected metastasis within 72 hours after entering the study. Patients with infratentorial lesions did not undergo biopsy because of the increased risk posed by biopsy in that area. Within 48 hours of biopsy or study entry (in patients who did not undergo biopsy), patients received radiotherapy according to the same treatment schedule and dosage used for the patients in the surgical group.

After treatment of the brain metastasis, each patient continued to receive appropriate treatment, if needed, for the primary tumor.

Evaluation and Criteria for Response

After the treatment of the brain metastasis, patients were evaluated every three months by means of neurologic examinations and magnetic resonance imaging or contrast CT scanning. If a recurrence was detected and the patient's condition warranted it, further treatment — surgery, repeat radiotherapy, or both — was provided. The nature of the additional treatment depended on the patient's condition.

To compare the efficacy of the two treatments, we evaluated changes in functional independence as indicated by Karnofsky scores, radiographic evidence of changes in tumor size or recurrence of the brain metastasis, the length of time to recurrence, the length of survival, and the causes of death in the two groups. Clinical improvement after treatment was measured by changes in Karnofsky performance scores. Patients who had Karnofsky scores lower than their pretreatment scores 30 days after surgery were considered to have surgical morbidity. The quality of life after the treatment of the brain metastasis was measured by the length of time Karnofsky scores remained ≥70 percent. (A patient with a score of 70 percent can care for himself or herself but is unable to work or maintain a normal level of activity.) The recurrence of brain metastases was identified by CT scanning or magnetic resonance imaging, and the development of leptomeningeal metastases was identified by examination of the cerebrospinal fluid. A recurrence of the original brain metastasis was defined as the reappearance of a metastasis in exactly the same site as the first metastasis. The radiation group included some patients whose original brain tumors never completely disappeared; in those patients, recurrence was defined as an enlargement of the original brain lesion after treatment. The length of time to the recurrence of the original brain metastasis was calculated from the date of the first treatment of the metastasis to the date when a recurrence in the same site was verified by CT scanning or magnetic resonance imaging. 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. The length of survival was calculated from the first day of treatment of the brain metastasis to death or the last follow-up evaluation.

The cause of death was determined for all patients who died; 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 from intercurrent illness (e.g., sepsis) were also included among those with neurologic causes of death, as were patients with both rapidly progressive systemic disease and advancing neurologic dysfunction. Even if these patients had not had progressive systemic disease, they would still have died of neurologic causes and thus represented failures of treatment. The systemic cancer was considered the only cause of death if patients with neurologic improvement or stabilization had fatal infections, hemorrhages, or failure of vital organ systems other than the brain. Deaths within 30 days of surgery were considered operative deaths.

Statistical Analysis

The results obtained in a nonrandomized, retrospective comparison of surgery plus postoperative radiation with radiation alone[20] were used to estimate the sample size needed for our study. In the earlier study, the median length of survival of patients in the surgical group was 19 months, whereas the median length of survival of patients in the radiation group was 9 months; thus, the ratio of the

medians was 19:9, or 2.11. Assuming exponential survival, we estimated that, for a randomized trial, a sample of approximately 24 patients in each group would be required for the study to have a power of 80 percent to demonstrate a significant difference in the overall length of survival at a significance level of $P<0.05$.[25]

Survival curves were drawn by the Kaplan–Meier product-limit method.[26] When the survival curves were based on neurologic causes of death, deaths from other causes were treated as censored data. The log-rank test was applied to evaluate the differences between two or more survival curves. The effects of treatment and of the covariates for length of time to the recurrence of the original metastasis, actuarial survival, neurologic survival (i.e., survival when only deaths from neurologic causes were included), and the length of time Karnofsky scores remained at or above 70 percent were determined in a multivariate analysis with use of Cox regression analysis[27] to determine the best subset of covariates associated with the various time-dependent end points through a stepwise proportional-hazards model. The covariates examined in all cases were the treatment group, age, sex, location of the brain metastasis, type of primary tumor (lung vs. all other types), extent of disease (disseminated vs. undisseminated), initial Karnofsky score (70 percent vs. ≥80 percent), and length of time between the diagnosis of the primary tumor and the development of the brain metastasis. Additional covariates were examined as appropriate (see Results). The chi-square test was used to determine the relation between two categorical variables, and Fisher's exact test was used when the cells in two-by-two contingency tables contained small numbers of patients. A two-tailed t-test was used to compare the means of continuous variables between the two treatment groups.

Results

Enrollment and Characteristics of Patients

Between October 1985 and December 1988, the option of participating in the study was offered to 56 consecutive patients who were referred to the Neurosurgery Division for the resection of suspected single brain metastases and who met the entry requirements. Only two patients declined to participate. Initially, 54 patients were entered in the study, but 6 of them (11 percent) proved on resection or biopsy not to have metastatic brain tumors. The six nonmetastatic brain lesions consisted of two glioblastomas, one low-grade astrocytoma, two abscesses, and one nonspecific inflammatory reaction. Our analyses of the outcome of the trial therefore included the remaining 48 patients, of whom 25 were randomly assigned to the surgical group and 23 to the radiation group. The base-line characteristics of the 48 patients are shown in Table 1. There was no statistically significant difference in the distribution of variables between the two groups. In the surgical group, all the patients appeared to have had complete resections, as assessed by postoperative contrast CT scanning. No patients in either group were lost to follow-up. As of November 1, 1989, 43 of the 48 patients had died (21 of 25 in the surgical group and 22 of 23 in the radiation group), and the median follow-up for living patients was 71 weeks (range, 68 to 196). Because of the high percentage of deaths in both groups, the overall median follow-up was identical to the overall length of survival — 15 weeks in the radiation group and 40 weeks in the surgical group.

Recurrence of Brain Metastasis

Surgical removal of the brain metastasis followed by postoperative radiotherapy resulted in substantially better local control of tumor in the brain than did radiotherapy alone. As shown in Table 2, the rate of recurrence at the site in the brain of the original metastasis (independent of distant brain metastases or leptomeningeal metastases) was significantly lower ($P<0.02$) in the surgical group (5 of 25 [20 percent]) than in the radiation group (12 of 23 [52 percent]). In addition, the length of time from treatment to the recurrence of the original brain metastasis (Fig. 1) was significantly shorter for the patients treated with radiation alone (median, 21 weeks) than in the surgical group (median >59 weeks; $P<0.0001$; relative risk, 7.1; 95 percent confidence interval, 2.4 to 21.5). Multivariate analysis demonstrated that only surgical treatment of the brain metastasis ($P<0.0001$) and the absence of disseminated disease ($P<0.0004$) reduced the risk of a recurrence of the original brain metastasis. Surgical treatment had no effect on the subsequent development of metastases elsewhere in the brain.

Table 1. Patients' Characteristics.

Characteristic	Surgery Group (N = 25)	Radiation Group (N = 23)
Sex (M/F)	18/7	14/9
Age (yr)		
Median	59	60
Range	44–74	49–73
Karnofsky score (%)		
Median	90	90
Range	70–100	70–100
Primary tumor		
Lung (non-small-cell)	18	19
Breast	2	1
Gastrointestinal	2	1
Genitourinary	1	1
Melanoma	2	1
Extent of disease*		
None	6	4
Primary tumor only	10	10
Disseminated	9	9
Median time between diagnosis of primary tumor and development of brain metastasis (wk)	8	4
Location of brain metastasis		
Supratentorial	18	17
Infratentorial	7	6
Treatment for primary tumor† — no. (%)		
Radiation	5 (20)	7 (30)
Surgery	12 (48)	8 (35)
Chemotherapy	5 (20)	3 (13)

*Other than the brain metastasis.

†Before the development of the brain metastasis.

Table 2. Location of Recurrence of Metastatic Cancer in the Brain.

Recurrence	Surgery Group (N = 25)	Radiation Group (N = 23)
	no. (%)	
None	18 (72)	10 (43)
Original (all types)*	5 (20)	12 (52)
Original only	2 (8)	10 (43)
Original and distant	3 (12)	2 (9)
Original and leptomeningeal	0 (0)	0 (0)
Distant only	2 (8)	0 (0)
Leptomeningeal only	0 (0)	1 (4)

*A recurrence of the original brain metastasis is defined as the reappearance of a metastasis in exactly the same site in the brain as the first brain metastasis.

The occurrence of distant brain metastases or leptomeningeal metastases (independent of the recurrence of the original brain metastasis) was similar in both treatment groups (5 of 25 [20 percent] in the surgical group vs. 3 of 23 [13 percent] in the radiation group; P = 0.52).

Survival

The patients treated with surgery plus radiation had a median length of survival of 40 weeks, whereas the patients treated with radiation alone had a median length of survival of only 15 weeks; actuarial survival (Fig. 2) was significantly different in the two groups (P<0.01; relative risk of death, 2.2; 95 percent confidence interval, 1.2 to 4.1). Overall survival was still

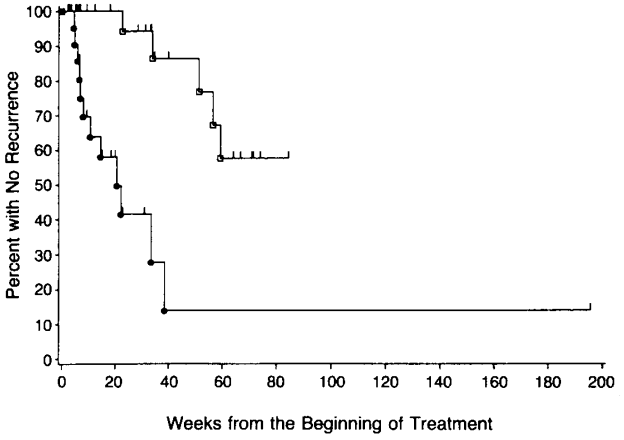

Figure 1. Length of Time to the Recurrence of the Original Brain Metastasis, According to Treatment Group.

The length of time from the beginning of treatment for the original brain metastasis to recurrence was significantly shorter (P<0.0001) in the 23 patients treated with radiation alone (solid circles) than in the 25 in the surgical group (open squares) (median, 21 weeks vs. >59 weeks; relative risk of recurrence, 7.1; 95 percent confidence interval, 2.4 to 21.5). Recurrence of the original brain metastasis was defined as the reappearance of a metastasis in exactly the same site as the first brain metastasis.

Tick marks indicate patients (living or dead) in whom recurrences did not develop.

less than 10 percent in both treatment groups by week 90, however. Multivariate analysis showed that surgical treatment of the brain metastasis and a longer time between the diagnosis of the primary tumor and the development of the metastasis in the brain were associated with increased survival (P<0.04 for both variables), whereas the presence of disseminated disease and increasing age were associated with decreased survival (P<0.02 and P<0.01, respectively). When the treatments (surgery, radiation, or chemotherapy) given for the primary tumor after the treatment of the brain metastasis were entered as variables in the Cox analysis, none was found to be significantly associated with survival.

When the length of time to death from neurologic causes in the two groups was compared (Fig. 3), there was a significant difference between the survival

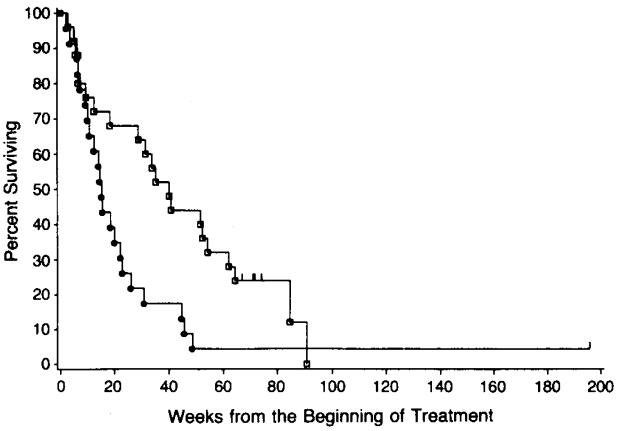

Figure 2. Actuarial Survival According to Treatment Group.

The 25 patients treated with surgery plus radiation (open squares) lived significantly longer (P<0.01) after the beginning of treatment for the original brain metastasis than the 23 patients treated with radiation alone (solid circles) (median length of survival, 40 weeks vs. 15 weeks; relative risk of death, 2.2; 95 percent confidence interval, 1.2 to 4.1).

Tick marks indicate the last follow-up evaluation of living patients.

curves, for which the median was 62 weeks in the surgical group and 26 weeks in the radiation group (P<0.0009; relative risk of death from neurologic causes, 5.2; 95 percent confidence interval, 1.8 to 15.2). Multivariate analysis showed that only surgical treatment of the brain metastasis (P<0.0008) was positively correlated with neurologic survival (i.e., with not dying from neurologic causes), whereas the

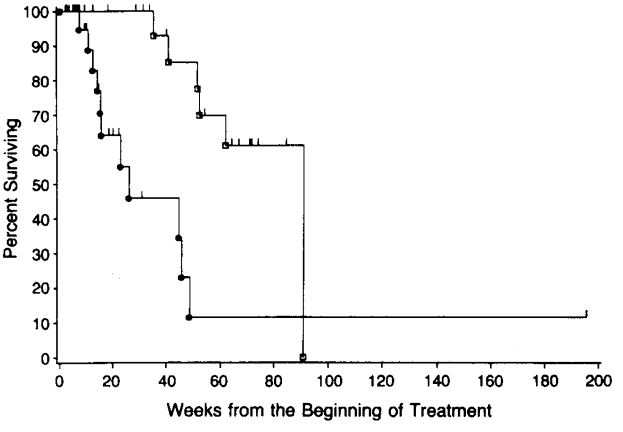

Figure 3. Neurologic Survival According to Treatment Group.

When only deaths due to neurologic causes were used as end points and data on patients who died from non-neurologic causes were censored, there was a significant difference (P<0.0009) in neurologic survival between the two groups. The surgical group (open squares; n = 25) had a median length of survival of >62 weeks, and the radiation group (solid circles; n = 23) had a median length of survival of 26 weeks (relative risk of death from neurologic causes, 5.2; 95 percent confidence interval, 1.8 to 15.2). Survival was measured from the beginning of treatment for the original brain metastasis.

Tick marks indicate patients who did not die of neurologic causes.

presence of disseminated disease ($P<0.002$) was negatively correlated with survival. Additional variables representing the treatments given for the primary tumor after the development of the brain metastasis were not significantly associated with survival. When death from systemic causes ("systemic death") was used as the only survival end point in comparing survival times, there were no significant differences between the two treatment groups ($P = 0.56$); the median length of time to death from systemic causes was 54 weeks in the surgical group and 23 weeks in the radiation group. Of the patients who died, 15 of 21 (71 percent) in the surgical group and 11 of 22 (50 percent) in the radiation group died of systemic causes ($P = 0.26$).

Less than half of all patients who had recurrences of brain metastases (of any type) received further treatment for their brain lesions. In the radiation group, 13 patients had recurrences, of whom 5 received additional treatment. Of these, one had surgery plus further radiation and lived an additional four weeks. Four patients received further radiotherapy only, with a median length of survival (from the start of the second course of radiation to death) of 10 weeks. In the surgical group, seven patients had recurrences; of those, four received additional treatment. One patient had a second operation (and no further radiotherapy) and lived an additional 28 weeks. Four patients received further radiotherapy only, with a median additional length of survival of 14 weeks.

Quality of Life

The patients in the surgical group maintained Karnofsky scores ≥70 percent (Fig. 4) much longer than the patients treated with radiation alone (median, 38 weeks vs. 8 weeks; $P<0.005$; relative risk that a Karnofsky score <70 percent would develop, 2.4; 95 percent confidence interval, 1.3 to 4.6). Multivariate analysis showed that only surgical treatment of the brain metastasis ($P<0.007$) was associated with a better quality of life, whereas increasing age ($P<0.02$) and the presence of disseminated disease ($P<0.04$) were associated with a poorer quality of life.

Complications of Treatment

Operative mortality was 4 percent, and operative morbidity was 8 percent. In the radiation group, the 30-day mortality rate was 4 percent, and the 30-day morbidity rate was 17 percent. After stereotaxic biopsy, one patient had a hemiparesis that resolved within two weeks; no other complications were associated with the biopsies. The median length of the hospital stay for the admission during which the brain metastasis was treated was 27 days in the surgical group and 22 days in the radiation group ($P = 0.48$).

Discussion

The results of this prospective, randomized trial show that the surgical removal of single brain metastases followed by radiotherapy results in substantially longer survival and a better quality of life than treatment with radiotherapy alone. Surgical treatment permits better local control of the brain metastasis, which results in a subsequent reduction in morbidity and mortality from neurologic causes.

The large difference in overall survival in favor of surgical treatment resulted from a reduction in deaths due to the brain metastasis. In determining overall (actuarial) survival, we used both systemic and neurologic causes of death as end points. Surgery and radiotherapy treat only the brain metastasis, and deaths directly attributable to the failure of treatment for the brain metastasis are usually from neurologic causes. Therefore, using death from neurologic causes as the only survival end point is a more accurate way to determine the true effect of treatment for brain metastases. When neurologic survival in the two groups was compared, there was a large, statistically significant advantage associated with surgical treatment. When death from systemic causes was used as the only survival end point, the difference in survival between the two groups was not statistically significant. Therefore, the prevention of death from neurologic causes by the surgical treatment of the brain metastasis was the factor most responsible for the large difference in overall survival between the two groups.

There are several reasons for the failure of treatment of metastatic cancer in the brain. Treatment failures are of two types: recurrences at the original site and new metastases at sites in the brain other than the original one (distant metastases). The reasons for the two types of failure are probably different. Recurrence at the original site is almost certainly due to the failure of the initial treatment to eradicate the original metastasis totally. Recurrences at distant sites in the

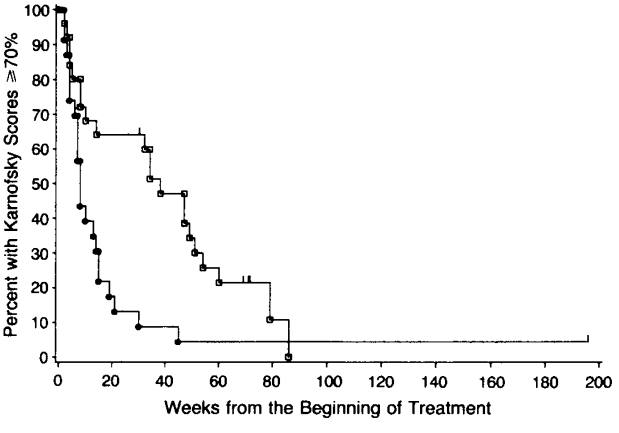

Figure 4. Duration of Functional Independence (Karnofsky Scores ≥70 Percent), According to Treatment Group.

The patients who were treated with surgery plus radiation (open squares; n = 25) maintained independence in self-care (Karnofsky performance scores ≥70 percent) significantly longer ($P<0.005$) than those treated with radiation alone (solid circles; n = 23) (median, 38 weeks vs. 8 weeks; relative risk of having a score <70 percent, 2.4; 95 percent confidence interval, 1.3 to 4.6).

Tick marks indicate the last follow-up evaluation of living patients.

brain may result either from new metastases spreading to the brain after treatment for the original brain tumor has been completed or from the presence of additional (but undetected) brain metastases that were present but not destroyed by radiotherapy at the time the original brain metastasis was treated.

The radiation dose used in our study (36 Gy [3600 rad]) was chosen because that dose was near the high end of the range commonly used in the treatment of metastatic brain tumors. It is possible, but unlikely, that the use of a higher dose of radiation might have altered our results. However, large, multicenter trials conducted by the Radiation Therapy Oncology Group[28-30] have failed to show any significant benefit from either higher radiation doses or different fractionation schemes in the treatment of brain metastases.

With any surgical procedure, operative mortality has to be weighed against any possible benefit from surgery. In earlier series of patients with single brain metastases who were treated with surgery, operative mortality rates were in the range of 10 to 34 percent.[15,16,31-36] However, with improvements in surgical technique, the advent of CT scanning, and the use of corticosteroids, surgical mortality rates in most series reported during the past 10 years have been under 10 percent.[19,20,37,38] The 4 percent rate in the present study was well within the acceptable range and was identical to the 30-day mortality rate in the radiation group. Therefore, there was no excess mortality due to surgery as compared with radiation alone.

An important finding was the high percentage of patients who proved after surgery or biopsy not to have metastatic brain tumors. All patients had tissue-proved primary tumors diagnosed before their entry into the study; 6 of the 54 patients (11 percent) did not have metastatic tumors despite having findings on CT scanning and magnetic resonance imaging that were consistent with single brain metastases. Although it has been standard practice to assume that patients with systemic cancer in whom intracranial lesions develop have brain metastases, there have been previous reports of false diagnosis rates as high as 50 percent with CT scanning.[39] Given the relatively high rate of misdiagnosis of metastatic tumors on the basis of CT scanning, even if resection is not possible, a stereotaxic needle biopsy may still be worthwhile to confirm the diagnosis. This is especially true for patients with controlled systemic cancer whose survival is likely to depend on the treatment of the brain lesion. Half the patients in our study who proved not to have brain metastases had potentially reversible infectious or inflammatory conditions.

Although our study showed that surgery plus radiotherapy was superior to radiotherapy alone in the treatment of single brain metastases, radiotherapy alone remains the treatment of choice for most patients with brain metastases. This is so because only about 50 percent of brain metastases are single and therefore potentially resectable. Unfortunately, nearly half of patients with single metastases are not candidates for surgery because of the inaccessibility of the tumor, the presence of extensive systemic disease, or other factors.[20] This leaves approximately 25 percent of all patients with brain metastases who would benefit from surgical resection; the rest should be treated with radiotherapy alone.

The patients with brain metastases who are most likely to benefit from surgical resection are those with a single surgically accessible lesion, either no remaining systemic disease (true solitary metastasis) or controlled systemic cancer limited to the primary site, and a life expectancy of at least two months. Because the median length of time that Karnofsky scores were maintained at pretreatment levels was about two months in the patients treated with radiotherapy alone, patients with life expectancies of less than two months should receive adequate palliation from radiation alone and are unlikely to gain any benefit from surgery.

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INCREASE IN GLOMERULAR FILTRATION RATE IN PATIENTS WITH INSULIN-DEPENDENT DIABETES AND ELEVATED ERYTHROCYTE SODIUM–LITHIUM COUNTERTRANSPORT

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Abstract Increased sodium–lithium countertransport in erythrocytes is found in patients with insulin-dependent diabetes mellitus (IDDM) and nephropathy. To determine whether such an increase precedes the onset of nephropathy and, if so, whether it is associated with changes in renal function, we measured erythrocyte sodium–lithium countertransport in 52 patients with IDDM but not nephropathy or hypertension and in 32 control subjects.

Seventeen of the 52 patients with IDDM (33 percent) had sodium–lithium countertransport activity that exceeded the maximal activity in the control subjects (0.39 mmol of lithium per hour per liter of cells). Eighteen of the 52 patients with IDDM were studied in more detail. The 7 patients with raised sodium–lithium countertransport values had glomerular filtration rates (median, 159 ml per minute per 1.73 m^2 of body-surface area; range, 134 to 197) that were significantly higher ($P<0.01$) than those in the remaining 11 patients with IDDM and normal sodium–lithium countertransport (median, 126 ml per minute per 1.73 m^2; range, 110 to 176) or in the 10 control subjects (median, 128 ml per minute per 1.73 m^2; range, 93 to 151). In the seven patients with elevated sodium–lithium countertransport, the filtration fraction (median, 0.27; range, 0.22 to 0.37) was also greater ($P<0.01$) than that in control subjects (median, 0.22; range, 0.18 to 0.28). There were no differences in renal function between the patients with IDDM and normal sodium–lithium countertransport and the control subjects.

We conclude that sodium–lithium countertransport is increased in patients with IDDM before the onset of nephropathy and is associated with hyperfiltration. Thus, elevated sodium–lithium countertransport activity may be an early marker of diabetic nephropathy. (N Engl J Med 1990; 322:500-5.)

IT is not clear why diabetic nephropathy develops in approximately one third of patients with insulin-dependent diabetes mellitus (IDDM), usually during the second decade of their illness,[1,2] but it has recently been suggested that this complication is most common in patients with a family history of hypertension.[3-5] Patients with diabetic nephropathy often have an elevation in blood pressure, which has been presumed to be a consequence of renal damage. However, the blood pressure in patients with IDDM and microalbuminuria is often raised before there is evidence of an impairment in renal function.[6-9] In addition, 25 percent of these patients may have renal hemodynamic abnormalities, leading to an increase in the glomerular filtration rate and renal plasma flow early in the course of their disease.[10,11] Any further disturbance in renal hemodynamics in diabetic patients with a family history of hypertension may lead to increased intraglomerular pressure and renal damage.[3,4]

Sodium–lithium countertransport in erythrocytes is increased in some patients with essential hypertension.[12] The activity of this transporter is related to the presence of a family history of hypertension,[13-18] and its increased activity in normotensive persons may in-

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