An Overview of Radiotherapy Trials for the Treatment of Brain Metastases

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A review of the English literature was undertaken to (1) determine the efficacy of radiation therapy for the treatment of brain metastases, (2) identify prognostic factors, and (3) ascertain whether there is an effect of treatment technique on outcome. Critical analysis of relevant randomized trials indicated that radiation therapy can effectively palliate the symptoms of brain metastases.

Introduction

Brain metastases are a common site of distant failure for epithelial malignancies. They are often a harbinger of the final phase of the cancer patient's course. The appropriate management approach for a patient with a brain metastasis depends on the patient's clinical status, the extent of the disease, and the patient's wishes. Very few prospective or randomized studies have evaluated the best treatment approach for a patient with a brain metastasis. For example, no study has prospectively compared radiation therapy to best supportive care. However, the clear efficacy of radiation therapy in controlling, at least temporarily, the neurologic symptoms of brain metastases makes it difficult to advocate withholding radiation, except in the most extreme of situations [1]. Corticosteroids alone, although a temporizing measure, quickly lose their efficacy, and their side effects may negatively impact on the patient's quality of life.

With these issues in mind, a review of the English language literature was undertaken in an attempt to (1) determine the efficacy of radiation therapy for the treatment of brain metastases, (2) identify patient factors that have prognostic significance, and (3) ascertain whether treatment technique has any effect on outcome. Using Medline and journal references, relevant articles were reviewed and abstracted. Randomized trials were preferentially selected. The chosen articles were analyzed for treatment techniques, response, and survival.

Treatment of Multiple Brain Metastases

Several randomized trials have looked at the effect of fractionation and dose on response and survival. Harwood and Simpson of the Princess Margaret Hospital in Toronto randomized 108 patients to receive either 30 Gy in ten 3-Gy fractions over 2 weeks or 10 Gy in one fraction [2]. Among the 101 evaluable patients, there was no statistically significant difference in median survival between the single-fraction and multiple-fraction arms (132 vs 121 days). Nor was there a difference in the frequency of response between the two arms. Death from cerebral metastasis was reported in 70% of patients, with no difference seen in the recurrence rate between the two arms.

RTOG Trials of Whole-Brain Irradiation

The Radiation Therapy Oncology Group (RTOG) completed a series of protocols designed to optimize palliative whole-brain radiation therapy. The first trial, open from January 1971 to November 1973, randomized 993 patients to one of four treatment regimens: 40 Gy in 4 weeks, 40 Gy in 3 weeks, 30 Gy in 3 weeks, or 30 Gy in 2 weeks [3]. A total of 910 patients were evaluable. A follow-up study, which ran from November 1973 to February 1976, randomized 1,001 patients to treatment with 40 Gy in 3 weeks, 30 Gy in 2 weeks, or 20 Gy in 1 week.

The results of these two trials were published together [4]. The response to treatment was equivalent among all of the arms, even when patients were stratified by initial performance status. In both studies, patients with the shortest treatment regimens responded more quickly. For example, in the second study, 64% of the patients receiving 20 Gy in 1 week responded within 2 weeks, as compared with only 54% of the patients on the other arms.

There was no difference in the duration of improvement among the dose schedules. Similarly, there was no difference by treatment group for the time to progression. Overall, median survival was 18 weeks in the first study and 15 weeks in the second study. Death was attributed to brain metastasis...
in 49% of the patients in the first trial and 31% of the patients in the second. The authors defined a "palliative index," which was the percentage of remaining life spent in an improved or stable neurologic state. For all patients in the study, 75% to 80% of the remaining life was palliated, using this marker. Again, there was no time or dose effect.

**Ultra-Rapid High-Dose Arms**—At the same time that these two studies were run, individual participating centers had the option to also randomize patients to ultra-rapid high-dose arms [5]. In the first study, 26 patients were offered 10 Gy in a single fraction, and in the second study, 33 patients were treated with 12 Gy in two fractions. The percentage of these patients showing neurologic improvement was the same as those receiving more protracted fractionation (46%). The promptness of improvement was also consistent with the previous studies. In contrast, the duration of improvement was less satisfactory. In the first study, the median duration of improvement (time to failure or death) was 10 weeks for the longer-fractionation arms and 4 weeks for the single 10-Gy fraction. However, in the second study, patients given 12 Gy in two fractions had a 10-week duration of improvement, which was the same as that seen in patients given the other fractionation schemes. The response of symptoms to treatment and treatment morbidity were the same on all arms. Median survival times for all of the arms also were equivalent, as was the percentage of deaths attributed to the brain metastases.

The authors concluded that the duration of improvement, time to progression, and complete disappearance of headache was generally poorer in both the 10-Gy arm and the 12-Gy arm. A review of the data indicates that this conclusion appears to hold true for the 10-Gy arm but is more equivocal with regard to the 12-Gy-in-two-fraction arm.

**Factors Predicting Improved Survival**—The complete study was analyzed to identify patients having a favorable survival [6]. Patients with breast cancer and no soft-tissue metastases, ambulatory lung cancer patients with an absent primary or no extracerebral metastases, and other ambulatory patients with no extracerebral metastases had a median survival of 28 weeks, as compared with 11 weeks for the remaining patients (see Table 1). There was no outcome advantage to any fractionation scheme among even this selected subgroup of patients. The median time to progression was 24 weeks for the breast cancer patients and 13 weeks for the lung cancer patients.

**Follow-up of Favorable Patients**—A follow-up study by the RTOG enrolled 309 patients with a favorable prognosis (ie, those who had a positive brain isotope scans with no other evidence of disseminated disease, no severe neurologic impairment, and a controlled primary) [7]. These patients were randomized between 30 Gy in ten 3-Gy fractions and 50 Gy in twenty 2.5-Gy fractions. The primary tumor was located in the lung in 80% of patients and in the breast in 7%. (In the remaining patients, the primary was either unknown or at another site.) Of the patients in the 30-Gy arm, 93% completed treatment. In contrast, 21% of the patients in the 50-Gy arm failed to get full therapy, receiving a median dose of 30 Gy (range, 2.5 to 47.5 Gy).

The median survival of patients in the 30-Gy arm was 18 weeks and that of patients in the 50-Gy arm was 17 weeks. The 1-year survival rates of both arms were approximately 25%. The two arms were equivalent with regard to the percentage of patients achieving response, time to achieving response, duration of response, and time to progression. Overall, 47% of the patients died with an improved or stable neurologic function.

**Radiation With and Without a Radiosensitizer**
Between 1979 and 1983, the RTOG then randomized 859 patients between 30 Gy in 10 fractions and 30 Gy in 6 fractions over 3 weeks, with or without the administration of the putative radiosensitizer misonidazole. Again, among the 779 analyzable cases, there were few differences in outcome among the arms [8]. The overall median survival was 3.9 months, with 60% of patients alive at 3 months, 35% at 6 months, and 15% at 1 year. Brain metastases were considered the cause of death in one-third of the patients.

As a measure of a palliative index, 44% of the patients spent 90% to 100% of their remaining survival time in a stable or improved Karnofsky status, and 65% maintained a stable or improved neurologic function. The median time to deterioration of performance status was 1.8 months.

**Analyses for Prognostic Factors**—Two papers have been published analyzing the patients who participated in this study (see Table 1). The first paper, by Diener-West and colleagues, identified four factors associated with improved survival: Karnofsky performance status of 70 to 100, an absent or controlled primary, age less than 60 years, and metastatic spread limited to the brain [9]. Patients with all four characteristics had a 200-day survival of 52%; those with three characteristics, a survival of 38%; those with two characteristics, 24%; those with one characteristic, 18%; and those with no characteristics, 8%.

The second paper, by Swift and colleagues, looked at the CT characteristics of patients in the study.
in an attempt to identify a favorable subgroup [10]. Pretreatment CT scans were available for over 750 patients. CT scan quality was variable, with 7% judged excellent; 45%, good; 34%, fair; 11%, poor; and 3%, absent or useless. Among the 408 patients who had at least one follow-up scan, 50% were responders and 21% were complete responders. Of the patients without a follow-up CT scan, 59% died within 6 weeks of initiation of treatment and 80%, within 12 weeks. The only prognostic factors that were statistically correlated with increased survival were one to three lesions (median survival of 4.0 months, vs 3.2 months in those with more than three lesions) and the absence of mid-line shift (4.3 months, vs 3.7 months in those with such a shift).

**Phase I/II Trial of Accelerated Fractionation**

A subsequent RTOG phase I/II trial of accelerated fractionation enrolled patients with a controlled or absent primary and stable extracerebral metastases, or an uncontrolled primary and no extracerebral metastases [11]. The entire brain was treated twice daily with 1.6-Gy fractions to a total dose of 32 Gy, and then the entire diseased area was given a radiation boost, also in 1.6-Gy fractions twice daily. The dose was increased in successive groups from 16 Gy to 22.4 Gy to 32 Gy to 42.4 Gy.

Among the 345 patients accrued, there was no increased toxicity with increasing dose. Median survival increased from 4.2 months at a total dose of 48 Gy to 5.3 months at 54.4 Gy, 4.8 months at 60 Gy, and 6.4 months at 70.4 Gy. Patients in the 48-Gy arm had a 1-year survival rate of 15%, whereas those in the other arms had a survival rate of 30%. Approximately 65% of the patients in all of the treatment arms showed tumor clearance by CT scan.

A subgroup analysis of the 153 patients with an unresected solitary brain metastasis showed a statistically significant increase in survival with increasing dose, as shown in Table 2 [12]. Within this subgroup, 36% of the patients died from their brain metastasis.

**Trial of Second Planned Radiation Course**

Between November 1986 and September 1989, the Institute Gustave Roussy randomized 216 patients to receive either 18 Gy in 3 fractions over 3 days or 18 Gy in 3 fractions over 3 days followed, 4 weeks later, by the same dose or 25 Gy in 10 fractions over 2 weeks [13]. The decision of which second course to give was made clinically, with patients with poorer performance status receiving the shorter course. Of the patients randomized to single-course therapy, 16% received a second course at the time of neurologic deterioration. Among the patients randomized to two courses, 25% did not receive their planned second course due to poor general health status or death.

The overall median survival was 4.7 months and the 1-year survival rate was 20%, with no statistical difference between the two groups. Among patients analyzable for follow-up at 4 to 8 months, the median duration of performance improvement or stabilization was 3 months. The authors concluded that a planned second course of radiation did not benefit the patient.

**Two Trials from Japan**

Two series have been published from Osaka, Japan. In the first trial, open from 1980 through 1983, 70 patients were randomized between 30 Gy in 10 fractions over 2 weeks and 50 Gy in 20 fractions over 4 weeks [14]. One-quarter of the patients in both groups experienced neurologic improvement, and 6% in each group worsened.

Median survival of the patients receiving 30 Gy was 4 months, vs 3 months for those receiving 50 Gy. The 1-year survival rates of the 30- and 50 Gy groups were 20% and 6%, respectively (a statistically nonsignificant difference). The investigators did not analyze the durability of the response. They found that the lactic dehydrogenase (LDH) level was predictive of survival. Therefore, in the second trial, patients were stratified according to whether their LDH level was above or below 250 U/L [15]. The 96 patients with the lower LDH level were randomized to either 30 Gy in 10 fractions or 50 Gy in 20 fractions (the same treatment arms as in the previous trial). The 70 high-LDH patients were randomized to 30 Gy in 10 fractions or 20 Gy in 5 fractions.

The low-LDH group had a median survival of 5 months, as compared with 3 months in the high-LDH group. Rates of 1-year survival for the two groups were 19% and 5%, respectively. Treatment dose did not affect survival. Overall median survival was 4.1 months, and 1-year survival rate was 13%. There was no significant dose effect for neurologic response (43% for the low-LDH group vs 29% for the high-LDH group). Significantly more acute side effects, such as nausea, vomiting, and headache, were observed in the 20-Gy arm.

**Favorable Prognostic Factors**

Table 1 reviews the favorable prognostic factors from the randomized trials. It is clear that patients with higher performance status have longer survival. Patients with controlled primaries and limited intracerebral disease also do better. In the analysis of RTOG 7916 by Diener-West et al, patients with
four of four favorable prognostic signs (see Table 1) had a 52% probability of surviving 200 days, whereas those with no favorable signs had an 8% probability of surviving for that length of time. It is worth noting that even in the most favorable prognostic group, the median survival of patients with brain metastases is on the order of 7 months.

Role of Surgery in Solitary Brain Metastases

Two randomized studies have assessed the addition of surgery to radiation for single brain metastases.

University of Kentucky Trial

A trial from the University of Kentucky randomized 48 patients to either biopsy and 36 Gy of radiation in 3-Gy daily fractions or surgical resection followed by the same radiation therapy scheme [16]. Histologic study showed that 11% of the patients did not have a metastatic tumor, but rather an inflammatory process or a primary brain lesion. There was a statistically significant improvement in survival in the surgically treated patients, with median survival increasing from 15 to 40 weeks. The rate of recurrence, as determined by CT or MRI, was 20% in the surgery group and 52% in the radiation-only group, and the median time to recurrence was 59 weeks for combined treatment vs 21 weeks for radiation only.

On multivariate analysis, the factors significant for increased survival were surgical treatment of the metastasis, absence of disseminated disease, longer time to the development of the brain metastasis, and younger age. Surgery also markedly decreased the risk of dying from a neurologic cause.

The researchers concluded that the patients most likely to benefit from resection were those with a single surgically accessible lesion, either no remaining systemic disease or controlled systemic cancer limited to the primary site, and a life expectancy of at least 2 months.

Dutch Trial

A Dutch trial randomized 66 patients with single brain metastases to surgery and radiotherapy or radiotherapy alone [17,18]. The radiotherapy was given as 40 Gy in 2-Gy fractions twice daily for a total of 2 weeks. Sixty-three patients were evaluable. All of the patients in the surgery group were found to have metastatic disease, and one patient in the radiotherapy group was found to have a malignant glioma at surgery for recurrence.

Median survival was 10 months in the combined-treatment group and 6 months in the radiotherapy group. The largest difference in survival was observed in the patients with inactive extracranial disease, with median survivals of 12 and 7 months for combined treatment and radiotherapy alone, respectively. Patients with active extracranial disease had equal median survivals of 5 months regardless of treatment. Among all the patients, the strongest prognostic factor for increased survival was younger age (equal to or less than 60 years). The cause of death was considered intracranial in 32% of the combined-treatment group and 33% of the radiotherapy-alone group.

These researchers also concluded that surgery combined with radiotherapy should be considered for patients with a good performance status, controlled extracranial disease, and a surgically accessible lesion.

RTOG-SWOG Trial

A third study, conducted by the RTOG and the Southwest Oncology Group (SWOG) [19], was intended to be a randomized trial of surgery and radiotherapy vs radiotherapy alone for solitary brain metastases. However, it had poor patient accrual and was continued as a prospective physician preference trial. Data on 80 of the 97 patients entered into the trial could be analyzed. These data were consistent with the studies described above, showing an advantage for the combination of surgery and radiation over radiation alone.

Role of Radiation in Solitary Brain Metastases

A question that has not been answered in a randomized trial is whether surgery combined with radiation is superior to surgery alone for a solitary brain metastasis. This question is important in light of the findings of DeAngelis of an estimated 19% risk of radiation-induced dementia within 5 to 36 months (median, 14 months) of whole-brain irradiation [20]. This was correlated with use of higher daily fraction sizes (3 Gy or more). The Dutch trial discussed above, which used 2 Gy twice daily, noted no dementia in their nine long-term survivors. No other trial has addressed this issue. There have been several retrospective reviews of surgery alone vs surgery and radiotherapy. Retrospective reviews must be viewed with caution due to inherent selection biases.

Mayo Clinic Review
A review of the Mayo Clinic experience showed 229 patients had been operated on for solitary brain metastases between January 1972 and December 1983 [21]. The authors analyzed the patients by the extent of surgery, extent of extracranial disease, and whether postoperative radiotherapy was given.

Table 3 outlines the results of this review. Patients with systemic disease did poorly whether or not they received radiation therapy. In contrast, patients who had controlled systemic disease and who received radiotherapy did better, even when adjusted for prognostic factors, than did those who received no radiation.

**MSKCC Results**

The Memorial Sloan-Kettering Cancer Center (MSKCC) has twice published their results. In the first paper, 89 patients treated between January 1, 1978, and December 31, 1985, were reviewed [22]. The authors found that the 70 patients who received radiotherapy had a 20.6-month median survival and 48% 1-year survival. The 19 patients who did not receive radiation therapy had a 14.4-month median survival and a 47% 1-year survival. These numbers are not statistically different. However, the authors noted that 11% of the patients who received radiation and survived for 1 year showed evidence of dementia, and all of these had been treated with a high daily fraction size. They concluded that postoperative radiation may be indicated, but it should be given in small fractions.

The second report from Memorial Sloan-Kettering reviewed 143 patients with non-small-cell lung cancer without prior cranial radiotherapy who underwent resection of brain metastases between 1974 and 1989 [23]. Of the 143 patients, 32 did not receive whole-brain radiotherapy (group A), and these were prognostically matched with 32 patients who did receive radiotherapy (group B). Also evaluated were 79 additional patients who received radiotherapy after surgery but were not included in the patient group designed to match group A (these were designated group C). Most patients received 30 Gy in ten 3-Gy fractions.

The median survivals of the three groups were: group A, 14 months; group B, 10 months; and group C, 15 months. These differences were not statistically significant. Survival rates at 1 year and beyond were also statistically equivalent. Focal failure (failure at the primary brain site) occurred in 34% of group A patients and 23% of combined groups B and C \( (P = 0.07) \). However, failure elsewhere in the CNS occurred in 7% of the group A patients and in 21% of combined group B and C \( (P = 0.07) \). The MSKCC investigators concluded that whole-brain radiation therapy has no discernible impact on survival.

As yet, there is no clear indication as to whether postoperative radiation is needed or how morbid it may be. These questions are being studied in an ongoing RTOG trial.

**Radiosurgery for Intracerebral Metastases**

Radiosurgery is the use of highly focused x-ray beams centered onto a small volume of tumor. It is useful to give higher doses of radiation to tumors while minimizing the dose to surrounding normal tissues. There are no completed randomized trials comparing the combination of radiosurgery and whole-brain radiation to whole-brain radiation alone or radiosurgery alone, although several trials are ongoing.

Flickinger et al reported on the experience of several major centers with stereotactic radiosurgery for solitary brain metastases [24]. They reviewed 116 patients, 65 of whom also received whole-brain radiotherapy. Combined treatment achieved better local control but did not improve survival. The results of the prospective randomized trials should provide better insights into the future role of radiosurgery in the treatment of brain metastases.

**Role of Chemotherapy**

Only one randomized trial has evaluated the use of combined chemotherapy and radiotherapy for brain metastases [25]. In this trial, 100 patients with brain metastases from lung cancer (only 10 of whom had small-cell lung cancer but another 12 of whom were described as having other or unknown primaries) were randomized to receive radiotherapy alone (group A); radiotherapy and lomustine (CCNU, CeeNu) or ACNU, a nitrosourea available in Japan (group B); or radiotherapy, lomustine/ACNU, and tegafur, an orally administered fluorouracil precursor (group C). Surgery was allowed if clinically indicated. Eighty-eight patients could be evaluated.

The median survivals for groups A, B, and C were 27, 29, and 30.5 weeks, respectively. Complete resolution of the tumor, as indicated by CT scan (excluding those who had had complete surgical resections), was noted in 29%, 69%, and 63% of patients in groups A, B and C, respectively.
Conclusions

Radiation therapy is effective in controlling of brain metastases. Most patients treated with this modality can expect to maintain a stable or improved neurologic status throughout the majority of their survival. However, as many as a third of patients can be expected to die from complications related to the progression of the brain metastases. Despite this, no survival advantage to increasing doses of radiation has been found in randomized trials. In a prospective study using twice-daily radiation in patients with minimal systemic disease, a slight advantage was seen in the higher-dose groups. A subset analysis suggested that this effect was most prominent in patients with unresected solitary metastases.

Table 4 summarizes the survival results of the randomized trials involving unselected patients. A remarkably consistent pattern is evident. Over 2 decades of treatment, with all of the changes in systemic treatments made during that time, there has been no change in the median survival of 4 months or the 20% 1-year survival for patients with brain metastases.

Subgroup analyses have shown that a favorable subgroup of patients can be identified (Table 1). The best prognostic group are young patients with good performance status and no active systemic disease. With standard treatment, patients with these characteristics have, at best, a median survival of 7.5 months and a 1-year survival of 25%. More aggressive therapy, such as twice-daily treatments, in patients with similar characteristics yields a median survival of 5 months and a 1-year survival of 30%--a minimal gain over far less aggressive treatments.

Two randomized studies have shown a survival benefit among patients with solitary brain metastases and no active systemic disease treated with surgery and radiotherapy rather than radiotherapy alone. No study, either retrospective or prospective, has clearly shown that radiotherapy is not needed after resection. Therefore, at present, whole-brain radiotherapy should be offered to patients after resection. Because 50% of these patients, if properly selected, may be alive at 1 year, consideration should be given to the use of smaller daily fractions to minimize toxicity. The appropriate dose for treating brain metastases remains controversial. Patients with extremely limited expected survival can be treated with 2,000 cGy in five fractions, and some studies indicate that even faster fractionation schemes can be used. Above all, it must be remembered that radiation is palliative. The goal of the treatment of brain metastases should be to maximize the quality of life of the patient. Small gains in survival at the expense of a decrease in quality of life should be avoided. Among the appropriately selected subgroups of patients who may enjoy long-term survival, more aggressive treatment options should continue to be explored.

References:


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