

Practice parameters for the management of single brain metastasis

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Object. In January 1998 the Guidelines and Outcomes Committee of the American Association of Neurological Surgeons (AANS) issued a charge for the development of evidence-based practice parameters focusing on the treatment of patients with single metastasis to the brain. The charge was imposed in response to the significant controversy surrounding questions relating to the optimal management strategies for patients with single brain metastasis.

Methods. A team consisting of physicians from the AANS, the American Academy of Neurology, and the American Association of Therapeutic Radiation Oncology convened and the literature was reviewed. Methodically drawing from the best of Class I, II, and III levels of available evidence, authors sought to determine how the literature addressed and disposed of the question of the optimal management for an adult with a known history of cancer and a single metastatic brain lesion. Framing the question in this specific manner allowed researchers to focus directly on treatment issues, without having to consider diagnostic issues.

Conclusions. The results of the evidence-based analysis demonstrated that there was insufficient information to establish standards of care. Data from the literature does, however, support a guideline stating that surgical resection accompanied by whole brain radiation therapy is associated with the best survival rate. Additional lower-quality evidence supports an option for management with radiosurgery.

KEY WORDS • practice parameter • metastasis • treatment evaluation

In April 1994, the Guidelines and Outcomes Committee of the AANS issued a charge to develop practice parameters for the treatment of low-grade glioma in adult patients. Research was undertaken in response to this charge and the report of resulting data was published in 1998. Subsequently, a second project was undertaken under the auspices of the AANS–Congress of Neurological Surgeons Joint Tumor Section to develop practice parameters for the treatment of adult patients with known cancer and a single metastatic brain lesion, and the results of that effort form the substance of this report.

Brain metastasis was studied because it is the most common type of intracranial tumor, with an annual incidence rate of more than 100,000 cases. The majority of

patients with brain metastases have either multiple tumors or uncontrolled systemic disease, whereas the remainder have single lesions. Systemic disease status is the single most reliable predictor of survival. The management of the following two groups of patients with single brain metastasis has been controversial: 1) those having uncontrolled systemic disease and predictably shortened survival, but whose brain metastasis, if successfully treated, would allow for the maintenance of a satisfactory quality of life for the duration of expected survival; and 2) those having controlled systemic disease. In this study the following definitions were used: if systemic disease was undocumented, one brain lesion was referred to as a "solitary" lesion, but if systemic disease was documented, one brain lesion was referred to as a "single" lesion. Because issues of diagnosis of both systemic and metastatic diseases are so large and complex, we restricted our research to relate solely to the treatment of patients with diagnosed cancer and a known single or solitary metastatic brain lesion. We then attempted to answer the question of what is the optimal therapy for an adult (> 18 years of age) patient with a single metastasis to the brain from a non-CNS malignancy.

Abbreviations used in this paper: AAN = American Academy of Neurology; AANS = American Association of Neurological Surgeons; ASTRO = American Association of Therapeutic Radiation Oncology; BrdU = bromodeoxyuridine; CNS = central nervous system; CT = computerized tomography; IRS = I-125 seeds; KPS = Karnofsky Performance Scale; MR = magnetic resonance; RS = radiosurgery; RTOG = Radiation Therapy Oncology Group; WBRT = whole-brain radiation therapy.

METHODS

Literature Search

The Brain Metastasis Guidelines Team members of the AANS were invited to participate by the Guidelines and Outcomes Committee of the AANS and the AANS-CNS Joint Tumor Section and included two neurooncologists, one radiation oncologist, and four neurosurgeons. Three members of the AANS Guidelines and Outcomes Committee also joined the research team. Medline and Embase searches for the years 1966 to 1998 and 1974 to 1998, respectively, were performed using the MeSH subject headings "surgery" or "surgical procedures," "operative" (exploded) or "craniotomy" or "radiotherapy" (exploded) plus the unattached subheadings "surgery" or "radiotherapy" or "drug therapy" or "prevention and control" or "therapy" or "radiography" or "gamma knife" plus text words "whole brain radiation therapy" as well as "stereotact" (as a root) within 3 words of "biopsy." These terms were combined with the MeSH terms "brain neoplasms" (exploded) and "neoplasm metastasis" (exploded) plus text words "brain" within 3 words of "metast" (root). The therapy terms were combined with brain metastasis terms. Then the text words "single" or "solitary" within five words of "brain" or "metast" (root) were combined with the therapy of brain metastases terms. The resulting set was limited to those articles concerning humans. A total of 318 articles on Medline and 284 articles on Embase were found. Researchers reviewed the abstracts of each of the 602 articles and selected 75 that directly related to our research.¹⁻⁷⁶

A more complete review of the articles was based on the following criteria: original work published in the peer-reviewed literature; entire manuscript available (no article was reviewed based solely on its abstract); subject matter directly or indirectly addressing the treatment of a single metastasis with surgery, various radiation therapy approaches (including standard radiation, radiosurgery, and brachytherapy), chemotherapy, or various combinations of these treatments. Complete review involved reading and abstracting the materials, methods, and results sections of each article with the aid of a standard form designed by the research team. In addition, the quality of the evidence in each article was classified according to the criteria listed in Table 1. The 75 articles were divided among team members so that at least two individuals reviewed each one. Thirty-one key articles consisted of relevant data and methods that allowed for interpretation of the results. Seven articles contained Class I evidence,^{18,39,40,47-49,67} two articles had Class II evidence,^{3,56} and only 21 of the remaining 67 articles with Class III having evidence

provided relevant data.^{4,6,12-15,23,31,34,36,38,44,46,54,55,59,60,68,72,76} Although many of the other articles with Class III evidence provided similar or sometimes unique information, team members concluded that it was not possible from a methodological standpoint to reliably abstract pertinent data from these studies. Therefore, based on these 26 reports, practice parameters were generated.

The following definitions were considered in forming these practice parameters.¹⁶ Standards are generally accepted principles for patient management, which reflect a high degree of clinical certainty (based on Class I evidence or, when circumstances preclude randomized controlled clinical trials, overwhelming evidence from either Class II studies that directly address the question at hand or a decision analysis that directly addresses all the issues). Guidelines are recommendations for patient management that may identify a particular strategy or range of strategies and reflect moderate clinical certainty (based on Class II evidence or a decision analysis that directly addresses the issue or on strong consensus of Class III evidence). Practice options or advisories include other patient management strategies for which there is unclear clinical certainty (based on inconclusive or conflicting evidence or opinion).

Therapeutic Modality and End Point Selection

Although the end points with which to evaluate the effectiveness of treatment have not been definitively established, we judged efficacy according to the following criteria: 1) local control of the single metastasis; 2) prevention of the development of further CNS disease (distant CNS metastasis); and 3) survival. Although one might assume that the first two findings should result in an increase in survival, this is not certain. Nonetheless, the prevention of CNS morbidity by itself would justify using one therapy over another.

The major treatment strategies with which to attain local control of single metastasis are WBRT, resection, focused radiation (that is, RS or brachytherapy), or a combination thereof. For prevention of distant CNS metastasis, WBRT is the primary modality used. Chemotherapy could be considered an alternative for distant control, but Class I or II data of its effectiveness are lacking at the present. All three methods of treatment (WBRT, resection, and RS) are thought to affect survival. We classified the selected articles according to the combinations of therapeutic modalities studied, as shown in Table 2. A direct comparison of results was limited by the end points used in the various studies and will be discussed later. Unless explicitly stated otherwise, we have assumed that survival is measured from the date of treatment.

RESULTS

Prognosis of Patients Treated Using WBRT Alone

Median survival time for patients treated using WBRT alone ranged from 3.5 to 8.2 months. Among the articles selected, all three classes of evidence relating to this treatment strategy were represented. We found data from six studies^{18,39,40,47-49,67} with Class I evidence which allowed us to consider survival rates for patients treated with WBRT (Table 3).

TABLE 1
Classification of quality of evidence

Class	Type of Evidence
Class I	well-designed randomized controlled clinical trials
Class II	well-designed nonrandomized controlled studies such as case-control or cohort studies
Class III	expert opinion, nonrandomized historical controls, case series, or case reports

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TABLE 2
Combinations of therapeutic modalities in the
26 reviewed studies*

Type of Evidence	Treatment			
	Surgery	RS	WBRT	No WBRT
Class I	Yes	Yes		
	Yes	No	39,47,48,67	
	No	Yes		47
	No	No	18,39,40,48,49,67	
Class II	Yes	Yes		
	Yes	No	3,56	3
	No	Yes		
	No	No	56	
Class III	Yes	Yes		54
	Yes	No	6,12,14,15,36,38,44,46,54,55,59,60,68,72,76	13,16,23,31,59,60,68,73,76
	No	Yes	4,6,23	34†
	No	No	14,36,38,44,46,55	

* Numbers indicate references.

† Brachytherapy is used in this study.

In studies by Mintz and colleagues,³⁹ Patchell and associates,⁴⁷ and Vecht, et al.,⁶⁷ patients with single metastasis to the brain treated using WBRT alone were compared with those treated using resection followed by radiotherapy. Various types of tumors were represented in each series, but radiosensitive tumors were excluded from all. Eligibility criteria were similar among all three studies. In the study conducted by Mintz and colleagues, patients were treated with 30 Gy of WBRT in 10 fractions. Median survival was 6.28 months and death resulting from neurological (27.9%) or combined neurological and systemic progression occurred in 62.8% of patients studied. In the study by Patchell and associates patients were treated using 36 Gy of WBRT in 12 fractions. Median survival in these patients was only 15 weeks. The high percentage of patients with non-small cell lung cancer, a relatively less radiosensitive tumor type, may account for the poorer survival rate in this study. In the Vecht, et al., investigation, patients were treated with 40 Gy administered in daily 2-Gy fractions. Patients with stable extracranial disease had median survival rates of 7 months.⁶⁷

Phillips, et al.,⁴⁹ reported on a randomized study of patients with presumed brain metastasis (no other sites of active disease) treated with either 37.5 Gy administered in 15 2.5-Gy fractions to the whole brain or 37.5 Gy with the radiation sensitizer BrdU 0.8 g/meter²/day for 3 days. Although the overall median survival rate for patients with single and multiple metastases was not significantly different between these two treatment groups (6.12 months for WBRT alone compared with 4.3 months for radiotherapy plus BrdU), the survival rate of patients with single metastasis was 6.98 months. It was not possible to extract data on median survival for patients with single metastases from each treatment arm.

Murray and colleagues⁴⁰ reported on RTOG 9104, a randomized phase III trial of accelerated hyperfractionation in which a treatment strategy of 1.6-Gy fractions twice daily of WBRT administered initially to a total dose of 54.4 Gy was compared with standard radiotherapy of 30 Gy in 10 fractions. Patients with uncontrolled systemic

TABLE 3
Prognosis of patients with single brain metastasis
treated with WBRT*

Authors & Year	No. of Patients	Radiation Dose (Gy)	Survival (mos)
Patchell, et al., 1990	23	36	3.75
Epstein, et al., 1991	30	32/48 AH	4.9
	53	32/54.4 AH	5.4
	44	32/64 AH	7.2
	26	32/70.4 AH	8.2
	31	40	7
Vecht, et al., 1993	31	40	7
Phillips, et al., 1995	30	37.5	6.98
Mintz, et al., 1996	43	30	6.28
Murray, et al., 1997	60	3.2/54.4 AH*	4.5
	60	30	5.3

* AH = accelerated hyperfractionation.

disease were ineligible to participate in the study. Overall median survival including patients with single and multiple metastases in both treatment arms was 4.5 months. Sixty patients with single metastasis were accrued to each treatment arm, and the rate of survival in patients in the standard radiotherapy arm was 5.3 months compared with 4.5 months in those in the accelerated hyperfractionation arm.

In a phase I/II trial, RTOG 85-28, Epstein, et al.,¹⁸ noted improved survival for patients with single brain metastasis treated with accelerated hyperfractionation (1.6 Gy administered twice daily to 32 Gy, with groups determined by boost escalation to total doses of 48, 54.4, 64, and 70.4 Gy). Median survival rates were 4.9 months for patients treated with 48 Gy, 5.4 months with 54.4 Gy, 7.2 months with 64 Gy, and 8.2 months with 70.4 Gy.

Patient Outcome and Resection Combined With WBRT Compared With WBRT Alone

Results from two of three randomized controlled trials demonstrated benefit from resection in patients with single brain metastasis. In these studies Class I evidence demonstrates the effect of resection plus WBRT compared with WBRT alone and permits analysis of the role of surgery.

Patchell and associates⁴⁸ performed a prospective randomized trial of single brain metastasis treatment using either WBRT alone or resection plus WBRT. Patients older than 18 years of age with a KPS score over 70 and a single metastasis were eligible to participate in the study. Other exclusion criteria included having lesions not resectable, leptomeningeal disease, previous cranial radiation, a need for emergency surgery, small cell lung cancer, lymphoma, leukemia, germ cell tumors, or multiple myeloma. All patients underwent postoperative CT to assess the effects of gross total resection of the tumor, and all patients received 36 Gy of WBRT. Baseline characteristics of the patients in each group were comparable. Median survival time was longer in the combined therapy group (40 weeks) compared with that in the WBRT group (15 weeks). In addition, a lower rate of recurrence at the initial site of metastasis and prolongation of time to recurrence (median 59 weeks compared with 21 weeks, respectively, $p < 0.001$) was noted in the resection group. In

analyzing survival as a function of neurological death, we found that patients in the resection group compared favorably (62 weeks compared with 26 weeks). The authors concluded that the overall improvement in survival outcome in the resection group was a result of a reduction in deaths from neurological disease.

Vecht, et al.,⁶⁷ reported a randomized controlled prospective study of 63 patients who were treated with either resection plus radiotherapy compared with radiotherapy alone. Radiotherapy was administered two times per day in 2-Gy fractions to a total of 40 Gy. Patients were stratified according to type of cancer (lung versus nonlung) and status of extracranial disease. Eligible patients were older than 18 years of age and had a histologically verified malignancy and a single lesion demonstrated on cranial CT. Patients with small cell lung cancer, lymphoma, leptomeningeal disease, or more than one brain lesion were excluded. Follow-up data on all 63 patients were recorded. Diagnosis was correct in all patients who underwent surgery. The median survival rate in patients with stable systemic disease was 12 months compared with 7 months for those with progressive systemic disease. Patients were functionally independent longer in the resection group (9 compared with 4 months, $p < 0.06$). In comparing patients having progressive systemic disease, median survival of those in the resection group and the radiotherapy group was equivalent (5 months). Intracranial cause of death as determined clinically was also the same in both groups.

Mintz and associates³⁹ performed a prospective randomized controlled trial in which patients who had a single brain metastasis were treated using either WBRT alone or surgery plus WBRT. Radiotherapy consisted of a total of 30 Gy to the whole brain delivered in 10 fractions. Gross total resection was judged by results of CT performed within the first week postsurgery. Exclusion criteria consisted of a KPS score less than 50, leukemia, lymphoma, small cell lung cancer, skin cancer other than melanoma, meningeal carcinomatosis, previous radiotherapy treatment, comorbid conditions precluding adequate follow-up review, brainstem or basal ganglion lesion, or more than one metastasis. Survival was calculated from the time of randomization, and cause of death was classified as either neurological or systemic. The locations of the brain metastases were considered to be relatively comparable, but details of eloquent compared with noneloquent locations were not included. We found no difference in median survival rate between the two treatment groups (resection plus WBRT 5.6 months compared with WBRT alone 6.3 months, $p < 0.24$). There were no significant differences in morbidities or causes of death. Neurological causes accounted for 14.6% of deaths in the resection treatment arm and 27.9% in the WBRT only arm. In the resection and WBRT only groups, systemic causes of death accounted for 46.3% and 34.9%, respectively. Quality of life outcomes were assessed using the Spitzer quality of life index which assesses five domains: activity, daily life, health, support, and outlook. There was no significant difference in quality of life between the groups by using this measure for 6 months of follow up. In this intention-to-treat analysis, there were protocol violations in both groups. In the resection group four patients died before WBRT, one refused WBRT, two withdrew from the

study before surgery but after having undergone one treatment of WBRT, one had a glioblastoma multiforme and did not undergo WBRT, and 38 of 40 underwent gross total resection. In the WBRT alone group, one patient died several days after randomization and did not receive radiation treatment and 10 patients experienced surgical intervention. Only 2.3% of the patients in the resection group were misdiagnosed, and all nine of the patients who switched from the WBRT group to the resection group were accurately diagnosed.

Two articles with Class II evidence have comments on the value of surgery and radiation therapy.^{3,56} Armstrong, et al.,³ retrospectively reviewed data on 143 patients who were treated using resection between 1974 and 1989. Thirty-two patients who received no postoperative radiation were compared with 32 patients who received 39 Gy per 10 days). Statistically, radiotherapy had no effect on survival or brain failure rates, but did have some impact on local brain control.

Patient Outcome and WBRT Combined With Surgery Compared With Surgery Alone

In the only published randomized controlled trial selected for review, patients receiving radiation postoperatively had a lower rate of brain tumor recurrence. In the study by Patchell, et al.,⁴⁷ a prospective randomized multicenter controlled trial, patients who underwent surgery alone were compared with those who underwent surgery plus postoperative radiotherapy for the management of single brain metastasis. The enrollment criteria were similar to those noted in these authors' 1990 study (Table 4).⁴⁸ Forty-nine patients underwent postoperative radiotherapy and 46 patients received no radiation treatment but were subject to observation. Patients received 50.4 Gy (1.8 Gy in 28 fractions) over 5.5 weeks. Resections were judged to be complete with the aid of postoperative MR images. The primary end point in this trial "the recurrence of brain tumor" was noted in 18% of patients in the radiation group and 70% in the observation group. Patients in the radiotherapy group were less likely to die of neurological disease (14 compared with 44%); however, there was no significant difference in overall survival rate between groups. Postoperative radiotherapy was associated with a lower incidence of recurrence at the primary site (14 compared with 37%).

Prognosis of Patients With Single Brain Metastasis Treated Using RS With or Without WBRT

We found insufficient evidence to reach a conclusion about the prognosis of patients with single brain metastasis who underwent either RS and WBRT or RS alone. Among the articles selected, only those with Class III evidence allowed us to assess the role of RS in the treatment of single brain metastasis. Auchter and colleagues⁴ reported on 122 patients who were treated using a linear accelerator-based procedure. The selection criteria for patients in this retrospective analysis were similar to those in the study of Patchell, et al.⁴⁸ Patients had to be older than 18 years of age and have a single surgically resectable brain metastasis of nonradiosensitive histology and a KPS score greater than 70. The peripheral dose ranged from 10 to 27 Gy and the median dose was 17 Gy. Whole-brain radiation

TABLE 4
Class I evidence of patients treated with WBRT with or without surgery*

Authors & Year	No. of Patients	Radiation Dose (Gy)	Surgery	Overall Survival (mos)	Neurological Survival (mos)	Local Control Rate (%)	Distant Control Rate (%)
Patchell, et al., 1990	25	36	GTR	9.3	14.5	80	92
	23	36	None	3.75	6.1	48	100
Vecht, et al., 1993	31	40	GTR	10			
	32	40	None	4			
Mintz, et al., 1996	41	30	GTR	5.6			
	43	30	None	6.3			

* GTR = gross total resection.

therapy was applied in all but five patients who refused this modality, and the radiation dose ranged from 25 to 40 Gy with a median dose of 37.5 Gy. The median follow-up review of patients was 123 weeks and the local control rate, which was defined as no progression in radiosurgical volume, was 86%. The rate of intracranial recurrence outside of the radiosurgical volume was 22%. The actuarial rate of survival from the time of radiosurgery was 56 weeks, and the 1-year and 2-year survival rates were 53% and 30%, respectively. Patients maintained a KPS score greater than 70 for 44 weeks. Survival analysis included the status of the primary disease and, thus, 25% of deaths could be attributed to CNS progression.

Flickinger, et al.,²³ reported on 116 patients who underwent RS alone (51 patients) and RS plus fractionated large-field radiotherapy (65 patients). Forty-five patients had received no benefit from previous radiotherapy, whereas 71 patients had received no previous radiotherapy. Median follow up after radiotherapy of the entire cohort was 7 months. Minimum radiosurgery dosages varied between 8 Gy and 30 Gy with a mean of 17.9 Gy. Maximum radiosurgical dosages varied between 16 Gy and 66.7 Gy, with a mean of 34.8 Gy. The total dosage of fractionated radiotherapy varied between 20 Gy and 77 Gy, with a mean dose per fraction of 2.5 Gy. The mean dose administered with RS was 33 Gy, with a range between 14 Gy and 55 Gy. Average tumor diameter varied between 3 mm and 36 mm with a mean of 18.7 mm. Patients were older than 24 years of age and all but four cases were found to be nonradiosensitive histologically. For patients who were managed from the time of initial diagnosis, the median survival time was 14 months. Among the entire cohort, the local control rate was 85% with tumor progression in 15%. The 2-year actuarial tumor control rate was $67 \pm 8\%$. According to results of multivariate analysis, local tumor control was better in patients who underwent RS plus fractionated radiotherapy ($p = 0.0111$). In a subset analysis of patients who were treated initially by using RS alone compared with those treated using RS plus radiotherapy, local control was better in those treated with the combination therapy ($p = 0.008$). One patient had symptomatic, pathologically documented radiation necrosis, and four patients developed symptomatic edema requiring reinstitution of steroid therapy.

Bindal and associates⁶ reported on two series of patients: 31 treated using RS and 62 treated using surgery and WBRT. (Although both groups had comparable per-

centages of patients treated using WBRT, circumstances which led to the addition of WBRT in the RS group could bias the results.) Groups were retrospectively matched according to systemic disease status, histology, pretreatment KPS score, time to brain metastasis, number of metastases, and patient age and sex. In patients in the RS group, the median lesion size was 1.96 cm³ (range 0.41–8.25 cm³), and the median dose applied to the isocenter was 20 Gy (range 12–22 Gy). In all cases, only one isocenter was used. In the RS group, 22 of 31 patients received WBRT and 16 of these 22 received pre-RS radiotherapy. (It is unclear how many of these 16 patients received little or no benefit from WBRT, a poor prognostic variable for successful subsequent RS.) In patients in the surgery group, 41 of 62 also received WBRT. The median survival of patients in the surgery group was 16.4 months compared with 7.5 months for those in the RS group. It is impossible to isolate the patients in the RS group who were treated at the time of initial diagnosis from those who were treated with RS after a recurrence or a progression, and directly to compare them with those who were treated surgically (another source of bias for the same reason noted earlier in the discussion of the study by Flickinger, et al.²³). Neurological causes accounted for 50% of deaths in the RS group compared with 19% in the surgery group. Recurrence was local in 8.1% and distant in 21% of patients in the surgery group compared with 38.7% and 9.7%, respectively, in patients in the RS group. In patients in the RS group complications of symptomatic radionecrosis occurred in 12.9% and intratumoral hemorrhage in 9.7% (leading to death in one patient). In patients in the surgery group complications included two postoperative hematomas, which required no reoperation, and one instance of wound infection, which was treated with antibiotics.

Prognosis of Patients With Single Brain Metastasis Treated Using Interstitial Implant Radiotherapy

We found insufficient evidence to reach a conclusion regarding the prognosis of patients with single brain metastasis treated using interstitial implant radiotherapy.

Kreth, et al.,³⁴ conducted a Class III retrospective review in which was studied the survival of patients following stereotactic biopsy and subsequent treatment with temporary low-activity IRS calculated to administer a radiation dose (range 60–100 Gy) to the outer diameter of the contrast-enhancing lesion. The following four groups

were treated: 38 patients (35 with solitary and three with multiple brain metastases) were treated using combined IRS and WBRT (40 Gy administered in 2 Gy fractions every day for 5 days), 49 were treated using WBRT alone (40 Gy administered in 2 Gy fractions every day for 5 days), 22 were treated using IRS alone (60 Gy), and 21 were treated using IRS for recurrent disease. Although subgroup analysis is not provided in the report, the patients who underwent combined treatment had a median survival of 17 months, compared with 12 and 7.7 months for IRS alone and WBRT, respectively. These data compare favorably with those in the literature, but the absence of a cohort analysis and a clear separation of data between patients with solitary metastasis and those with multiple metastases, as well as the inability to relate systemic disease status for individual patients do not allow for valid comparison to other Class III studies in the literature.

DISCUSSION

Prognosis of Patients With Single Brain Metastasis Treated Using WBRT Alone

The survival of patients treated using WBRT in the control arms of various randomized trials ranged from 3.75 to 8.2 months (Table 3). The rate of local control of the tumor was not evident from these studies alone. One must remain cautious while reviewing studies that report survival data on patients with single metastases and stable systemic disease which have been extracted from a larger patient series, including patients with multiple metastases or patients with advanced systemic disease. It can be difficult to determine if certain factors have introduced bias into the analysis of the group of patients with single metastasis. For example, it is common to require that patients entered into randomized trials have an estimated survival of at least 3 months and a minimum KPS. Thus, resulting data in such a trial do not represent the entire patient population with single brain metastases, but represent a population with better than average prognosis.

Patient Outcome and Surgery Combined With WBRT Compared With WBRT Alone

Data from two of three randomized trials that address the question of whether patient outcome is improved in patients treated using surgery combined with WBRT compared with WBRT alone indicated that surgery provided significant benefit. There are several possible explanations for the discrepancy in results. Mintz, et al.,³⁹ assert that improved survival outcomes after surgery in the study conducted by Patchell and associates⁴⁸ may reflect a referral bias because the patients were accrued after referral to a neurosurgical service, whereas the patients in the studies by Vecht and colleagues⁶⁷ and Mintz, et al.,³⁹ were referred by oncologists, neurologists, neurosurgeons, and radiation oncologists. They further assert that survival in the Patchell nonsurgical group (3.75 months) was unusually low and may have resulted from the inclusion of a higher percentage of patients with non-small cell lung cancer (77%), a relatively radioresistant tumor type. On the other hand, the advantage of surgery may be lost in patients with advanced systemic disease. In the Mintz trial 45% of patients, compared with 37.5% in the Patchell and 31.7% in

the Vecht trial, had systemic metastases that may have limited the positive effects of surgery.

Another major difference between the Mintz study and the Patchell and Vecht studies was the administered dose of WBRT. In the Vecht study patients were treated to a total dose of 40 Gy was applied to patients. (Smalley, et al.,⁶⁰ demonstrated that dosages greater than 39 Gy compared favorably with lower doses). In the Patchell study patients received 36 Gy, whereas 30 Gy was administered to patients in the Mintz trial. An interaction between surgery and the dose of WBRT cannot be ruled out with the existing data.

Note that all three studies with Class I evidence were of relatively small sample sizes. Although the additional patient survival time attributed to surgery in both the Patchell and Vecht studies cannot be considered to be definitively proven, the preponderance of Class I evidence indicates that in patients who meet the eligibility criteria in these studies and who receive at least 36 Gy of WBRT, surgical excision of the metastasis can more than double survival time.

Patient Outcome and WBRT Combined With Surgery Compared With Surgery Alone

Data from the study by Patchell, et al.,⁴⁷ demonstrates that the addition of WBRT to surgical excision improves the local control rate (an increase in survival from 43 to 48 weeks). In this study, however, a significant increase in survival was not demonstrated.

Prognosis of Patients With Single Brain Metastases Treated Using RS With or Without WBRT

In contrast to surgical excision, stereotactic RS has not been subjected to a randomized comparison with either WBRT alone or surgery with or without WBRT. As evidenced by the studies reviewed for this report, it is often difficult to isolate from case series patients comparable with those in surgical trials. Therefore, inferences about the comparability of radiosurgery and surgical excision are subject to bias uncontrolled by proper research procedures. For example, in the study by Flickinger and colleagues,²³ it is not possible to separate outcomes of patients who underwent RS as their primary treatment from those who were treated for recurrence. In addition, the radiosurgical studies use stable disease-partial and complete responses combined (local control rate)-as the measure of technical success. Authors of surgery trials consider residual tumor at the surgical site to be technical failure. A 20% increase in the size of the tumor would be considered as stable and therefore a success in a radiosurgical trial-an inconceivable interpretation in a surgery trial. Whether these differences in the measurement of outcome reflect a difference in the biological behavior of the treated tumor is unknown, because the necessary studies have not been done. As a result of these limitations, it is impossible to conclude that RS is comparable with resection in its effect on patient survival or quality of life.

CONCLUSIONS

A distinction must be made between evidence-based practice parameters and algorithms or other consensus-

derived recommendations for clinical practice. The former defines the state of scientific knowledge supporting clinical treatment of a given condition. The latter combines that scientific knowledge with collected experience, interpreted in the context of the individual patient to suggest the most appropriate course of action. Evidence-based practice parameters, by their very nature, will always have limitations when applied to individual patient care decisions, but should form the base from which the practitioner interprets the individual situation and recommends action.

What, then, can be said about the optimal therapy for an adult patient with a single brain metastasis from a non-CNS malignancy? There is insufficient information to establish any recommendations as standards. We can, however, propose a guideline: resection accompanied by WBRT promotes the best survival rate. The available Class I evidence indicates that this guideline applies to patients whose KPS score exceeds 50 (70 in the studies with significant treatment effects) and who have no certain radiosensitive tumors (such as small cell lung, germ cell, myeloma, lymphoma, and leukemia). These criteria are compatible with an average survival of 3.75 to 6.3 months in the control population. In this population, the predominance of Class I evidence suggests that resection of the single metastasis accompanied by WBRT provides the best possibility of survival. Because one trial (Mintz, et al.) does not support this conclusion and raises important questions about the dose of radiotherapy, the pretreatment KPS score, and possible referral bias, we cannot establish a standard.

Class III evidence indicates that radiosurgery for lesions smaller than 2.5 cm accompanied by WBRT may provide an effective alternative to conventional resection plus WBRT. However, the impact on survival and quality of life in comparison to conventional surgery and WBRT is unknown. Other forms of focal therapy have not been sufficiently tested to allow a reasoned assessment of their role in the treatment of solitary brain metastasis.

DISCLAIMER

These practice parameters are provided as an educational service of the AANS, the AAN, and the ASTRO. These sponsoring organizations have not endorsed these guidelines. The guidelines are based on critical analysis of the available evidence in the medical literature. They are not intended to include all possible clinical scenarios in patients with a single brain metastasis. They do not address and are not intended to exclude alternative treatments. The authors representing the AANS, AAN, and ASTRO recognize that patient care decisions are the responsibility of the patients and the physician(s) caring for the patient and must be individualized based on all of the circumstances involved.

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