

*Technology Assessment Program*

Report No. 7

**Stereotactic Radiosurgery for  
Metastases to the Brain:**

A Systematic Review of Published  
Studies of Effectiveness

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Report Date: December 1997



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Released March 1998

## ACKNOWLEDGEMENTS

The contributions of the following reviewers are gratefully acknowledged. The MDRC takes full responsibility for the views expressed herein. Participation as a reviewer does not imply endorsement.

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The MDRC Technology Assessment Program wishes to thank Jennifer Cheslog, Stephanie Piper, Kevin Rys, and the staff of the Information Dissemination Program for their help with the report.

# Stereotactic Radiosurgery for the Treatment of Metastases to the Brain

## EXECUTIVE SUMMARY

### **Purpose**

This report was written by the Management Decision and Research Center (MDRC) Technology Assessment (TA) Program in response to requests for information about the effectiveness of stereotactic radiosurgery for the treatment of metastases to the brain.

### **Background**

Metastases to the brain (herein referred to as “brain metastases”) are a major cause of disability and death in cancer patients. Treatment options are limited, particularly for patients with surgically inaccessible or recurrent brain metastases.

Stereotactic radiosurgery (SRS) is a specialized form of radiation therapy that delivers precisely focused beams of radiation to a targeted lesion in the brain. The intent is to destroy the lesion, or control its growth, without harming nearby healthy tissue. This technology has been used to treat a variety of functional and benign brain abnormalities, and indications for its use are now being expanded to include metastases to the brain.

### **Key Findings**

#### ***Cost and Reimbursement***

SRS *uses fewer resources than open cranial surgery*. Relative to surgery, radiosurgery reduces the length of hospital stay by nearly 7 days, to approximately 3 to 4 days. SRS can often be done as an outpatient procedure. Medicare has reimbursed SRS at the same rate as open cranial surgery, but a 30% reduction in reimbursement for SRS was proposed for 1998. This was based on the HCFA estimate of reduced procedure costs.

#### ***Regulation***

Commercially available SRS units are approved for therapeutic use by the Food and Drug Administration (FDA). Facilities must comply with federal standards and guidelines for radiation safety and quality control.

#### ***Evidence of effectiveness***

The best published evidence is from case series, a relatively weak study design that does not provide strong evidence of effectiveness. The studies treated different types of patients and reported outcomes in non-comparable ways. Studies frequently combined outcomes from different patient or treatment groups, making effectiveness data difficult to interpret. While the

findings about the effectiveness of SRS were fairly encouraging and consistent for comparable groups of patients, they should be considered preliminary and interpreted with caution:

- Evidence *suggested* that SRS was a relatively safe and effective technology for the definitive treatment of newly diagnosed and recurrent metastases to the brain in selected patients. Most of the reported side effects of SRS were mild, temporary, and could be relieved by medication. Treatment resulted in very few major complications and very rare deaths.
- All of the *types* of cancers treated responded to therapy. The spread of melanomas, breast cancers, and kidney cancers was controlled for a longer period of time than for other cancers. For breast cancers, this improved tumor control was accompanied by an increased length of survival.
- Median survival after SRS ranged from 26 to 56 weeks. This compared favorably with outcomes from other treatments.
- *Patients with limited numbers of relatively small tumors, and who had well-controlled systemic cancer, may have gained the greatest benefits from treatment.* SRS treatment was equally effective for patients with two metastases as for patients with solitary metastases; SRS treatment was as effective for recurrent metastases as for initially untreated metastases. The effectiveness of SRS treatment and survival benefit in patients with three or more metastases remain undetermined. The absence of active systemic cancer was strongly associated with survival, as was good baseline functional status.
- *Valid comparisons of the relative effectiveness of treatment options are not possible using existing research.* Available data *suggested* that for patients with smaller solitary metastases, SRS (alone or + radiotherapy) appeared to be as effective as surgery + radiotherapy in prolonging survival. SRS may have been more effective than surgery in postponing recurrences, and SRS caused fewer complications. Outcomes from both surgery and SRS were considerably better than those from radiotherapy alone. Optimal management of patients with multiple metastases is yet to be determined.
- It is too early to draw definite conclusions about optimal treatment parameters (including radiation dose, the use of whole brain radiotherapy in addition to SRS, and maximum treatable tumor size). The Radiation Therapy Oncology Group (RTOG) will continue to study the optimal dose planning and maximal possible treatable tumor volume in ongoing or planned RTOG radiosurgery trials.

### **Conclusions**

In the absence of data from high quality studies, uncertainty remains about the true effectiveness of SRS for the treatment of metastases to the brain. One randomized clinical trial is in progress (See Table 7, page 15), and further trials are needed, to address the many unanswered questions about the use of SRS for this application. Such trials will provide stronger evidence on which to base clinical and policy decisions.

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## **I. INTRODUCTION AND BACKGROUND**

### **A. Purpose**

This report was written by the Management Decision and Research Center (MDRC) Technology Assessment (TA) Program in response to requests for information about the effectiveness of stereotactic radiosurgery for the treatment of metastases to the brain.

### **B. Metastases to the Brain**

Metastases to the brain (herein referred to as “brain metastases”) are a significant and increasing health problem in the aging population (Sperduto et al. 1996; Loeffler et al. 1993). About 100,000 cancer patients developed brain metastases in 1997 (Parker et al. 1997). Any primary cancer can spread to the brain, but the most common are *melanomas*, and cancers of the *lung, breast, colorectum, or kidney* (Kihlstrom et al. 1993; Posner 1993). Nearly half of the patients diagnosed with brain metastases have one lesion, and 20% have two metastases (DeAngelis 1994).

As many as half of patients dying from cancer are found to have brain metastases on autopsy (Flickinger et al. 1994). Despite improvements in the treatment of systemic cancers, brain metastases remain a major cause of disability and death in cancer patients, including the estimated 170,000 American veterans who have cancer (Kizer 1997).

### **C. Standard Treatments**

Untreated, patients with brain metastases usually survive for 1 to 2 months (Posner 1974). Most die from the uncontrolled systemic spread of their primary cancer, but one-quarter to one-half die from complications associated with the spread of their brain metastases (Borgelt et al. 1980).

Steroids were found to reduce symptoms and prolong survival by about 1 month (Weissman 1988). With few exceptions, chemotherapy has a limited role in the treatment of brain metastases (NCI September 1997).

Whole brain radiotherapy (WBRT) reduces symptoms and prolongs life more effectively than steroids alone. Median survival in randomized clinical trials of WBRT ranged from 15 to 18 weeks (Borgelt et al. 1980). WBRT retreatment for recurrent brain metastases is controversial, but additional survival benefits have been reported in case series studies (Kurup et al. 1980; Hazuka et al. 1988). For most patients, re-irradiation seldom produces clinically significant benefits, and it is known to cause damage to healthy brain tissue (DeAngelis 1994; Arbit et al. 1995).

For selected patients with a solitary brain metastasis, adding open cranial surgery to whole brain radiotherapy greatly prolongs life. In two randomized clinical trials, median survival for patients treated with surgery + WBRT was 40-43 weeks, compared to 15-26

weeks for WBRT alone. Quality of life was significantly improved in the surgical groups (Patchell et al. 1990; Noordijk et al. 1994). No randomized clinical trials have been done to assess the effectiveness of surgery for the removal of 2 or more metastases, or for the surgical retreatment of recurrent metastases. Surgery for these patients is controversial, and infrequently done. Case series data from surgical studies for selected patients with multiple or recurrent lesions are promising (Lang et al. 1996).

Only about 30% of patients with brain metastases are eligible for surgery (DeAngelis, 1994). Definitive treatment options are limited for patients who are not surgical candidates, and for those with recurrent brain metastases. If these patients have well-controlled systemic cancer, death from neurological causes is likely.

Treatment of brain tumors remains an active area of research. Radiosurgery has been used to treat a variety of functional and benign brain abnormalities, and its effectiveness for the treatment of brain metastases is now being investigated (Flickinger et al. 1994).

## II. DESCRIPTION OF STEREOTACTIC RADIOSURGERY

Stereotactic radiosurgery (SRS) is a specialized form of radiation therapy that delivers precise, small, and focused beams of radiation to a targeted lesion in the brain. The intent is to destroy the lesion, or control its growth, without harming nearby healthy tissue. Treatment is minimally invasive. It requires no surgical incision, causes little discomfort, and can be performed on an outpatient basis, or with a very brief inpatient admission.

Originally developed in 1951, SRS has since incorporated advanced medical imaging and computerized localization systems to refine the technology (Phillips et al. 1994; De Salles et al. 1993).

Three different systems can be used to perform SRS: *Gamma Knife*; heavy charged particles from a *cyclotron or synchrotron*; or a *modified linear accelerator*. There are over 200 stereotactic radiosurgery facilities in the United States (Shrieve et al. 1995), including 27 Gamma Knife centers (Elekta 1997), and 2 cyclotrons or synchrotrons (Pakuris 1996; Sisterson 1997). Most of the remaining centers perform radiosurgery using specialized add-on equipment with linear accelerators (LINACS). LINACS are used to deliver conventional radiotherapy treatment to cancer patients, and are available at many major health care facilities. A few centers have LINACS that are only used for SRS.

The Tampa VA Medical Center recently purchased a LINAC-based system called Peacock. It can be used to perform SRS on brain tumors or prostate tumors. It can also be used to perform specialized forms of radiotherapy for brain, lung, or prostate cancers (DVA 1997). This system has the unique ability to fractionate treatments.



### III. REGULATION AND REIMBURSEMENT

Commercially available SRS units are approved for therapeutic use by the Food and Drug Administration (Jones et al. 1995; FDA 1997). Radiosurgery facilities must comply with Nuclear Regulatory Commission standards and guidelines for radiation safety and quality control. Cyclotron and synchrotron facilities must comply with Department of Energy quality assurance protocols.

No formal training guidelines exist for neurosurgeons or radiotherapists performing SRS (Jones et al. 1995). However, professional organizations have promoted strict guidelines and quality assurance measures (Larson et al. 1994).

SRS is reimbursed by Medicare. Although reimbursement is presently set at the same rate as open cranial surgery, the Health Care Financing Administration (HCFA) proposed a 30% reduction in SRS reimbursement for 1998. This is based on a recent HCFA analysis which concluded that, when compared to open cranial surgery, SRS used fewer resources, and reduced the length of stay from 7-10 days (for open cranial surgery) to 1-3 days (for SRS). SRS can often be done on an outpatient basis. HCFA recommended no national coverage policy for radiosurgery and indicated that payment decisions are at the discretion of local carriers (DHHS 1997).

The Veterans Health Administration reimbursement policy has been to pay for all medically necessary procedures that have FDA approval or come under an approved clinical protocol. Patients requiring radiosurgery can be referred to the Tampa VAMC, the only facility presently housing SRS equipment, or can be referred to academic affiliates or other health care facilities.

### IV. METHODS FOR THE SYSTEMATIC REVIEW

Information about the effectiveness of SRS for the treatment of metastases to the brain was obtained by conducting a *systematic review* of the published literature. A systematic review uses a scientific approach to limit bias and to improve the accuracy of conclusions based on the available data (Guyatt 1995).

A search of the English-language medical literature was performed using the following computer databases for the years 1991 through July, 1997: MEDLINE, PREMEDLINE, HEALTH Planning & Administration, HealthSTAR<sup>1</sup>, and EMBASE<sup>2</sup>, and Current Contents<sup>3</sup> (All Sections, 1994 to July, 1997). An updated search of PREMEDLINE was conducted in November, 1997. Terms for the search included: *radiosurgery* or *stereotactic radiosurgery* or *Gamma Knife*. These were combined with *brain neoplasm*, *controlled clinical trials*, *meta-analysis*, *multi-center*

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<sup>1</sup> Computer databases maintained by the National Library of Medicine.

<sup>2</sup> Elsevier Science Publishers.

<sup>3</sup> Institute for Scientific Information.

*studies* or *practice guidelines*. End references from retrieved articles and listings of English language, public domain technology assessments were also searched.

Titles and abstracts of 748 references were screened. 90 references were determined to be relevant, and their full text articles were reviewed for potential inclusion in the systematic review. Additional articles were retrieved to provide background materials about stereotactic radiosurgery and brain tumor therapy. References were reviewed and were included in the review if they met the criteria in Figure 1.

### Figure 1: Inclusion Criteria for the Systematic Review

- Studies evaluating the effectiveness of SRS for brain metastases
- English language journal articles reporting primary data obtained in a clinical setting, or analyses of primary data maintained in registries or institutional databases
- Study design and methods clearly described
- Case series including  $\geq 10$  patients, or studies with a more powerful design
- Study not superseded by a later publication, with the same purpose, by the same group
- Published 1990 or later, to reflect the current status of diagnostic and treatment technologies

Studies were selected for inclusion if they provided the strongest available evidence of effectiveness. The strength of the evidence is based on how well bias and confounding factors are controlled in the design and conduct of a study. Attributes that strengthen the validity of findings include: **randomized** (vs. nonrandomized), **controlled** (vs. uncontrolled), **blinded** (vs. unblinded), **prospective** (vs. retrospective), **large** (vs. small), **multi-site** (vs. single site), and **contemporaneous controls** (vs. historical). Based on these attributes, common study designs are listed in order, from the most to the least rigorous, for internal validity and strength of evidence (Figure 2).

### Figure 2: Study Designs to Assess Effectiveness

*Ranked according to decreasing strength of evidence provided*

- Large randomized controlled trial, systematic reviews of RCTs
- Small randomized controlled trial
- Nonrandomized trial with contemporaneous controls
- Nonrandomized trial with historical controls
- Surveillance (database or register)
- Case series, multi-site
- Case series, single site
- Case report, anecdote

Sources: Adapted from Ibrahim 1985, and Goodman 1993.

## V. APPRAISAL OF THE LITERATURE

No direct comparisons of the effectiveness of different SRS systems were identified. Published reviews based on comparisons of case series data for the different systems suggest that their treatment outcomes are similar. Lacking strong data to the contrary, the MDRC combined studies using different SRS systems in this report.

### A. Application of the Inclusion Criteria

Table 1 summarizes the findings from the review of the 90 potentially eligible articles.

**Table 1: Eligible Studies, Effectiveness of SRS for Brain Metastases**

STUDY DESIGN	# ELIGIBLE STUDIES
Randomized controlled trials, or systematic reviews of RCTs	0 (RCTs underway) 0 relevant systematic reviews
Nonrandomized trial with contemporaneous controls	0
Nonrandomized trial with historical controls	0
Surveillance (database or register)	0
Case series, multi-site	2 (retrospective)
Case series, single site	2 (prospective) 9 (retrospective or unclear)
Case report, anecdote	Excluded
TOTAL	134

Study characteristics and outcomes were extracted by the authors, summarized in Tables 2 and 3, and discussed below. Differences in study design and quality were noted among the studies. No studies were judged to be of sufficiently high quality that they could be used, to the exclusion of the remaining case series, as the basis for this report.

Despite their design differences, all thirteen studies that met the inclusion criteria for the report were classified as case series. A case series is a relatively weak study design that does not provide strong evidence of effectiveness. Case series studies contain useful information about the clinical course and prognosis of patients, can *suggest* relationships between interventions and outcomes, and can help generate ideas for further research.

### B. Data Synthesis

This report presents a qualitative overview to synthesize the best available evidence. A quantitative synthesis (meta-analysis) was not attempted. The methodological weakness

<sup>4</sup> The majority of excluded articles were discussions or overviews that did not report primary data. The overviews failed to meet the criteria established for systematic reviews. 19 reports of primary data were excluded because they were superseded by more recent publications, had fewer than 10 patients, or were uninterpretable because of unclear reporting. One cost-effectiveness analysis was excluded because of the preliminary nature of the effectiveness data for SRS upon which the analysis was based, and uncertainty about comparability of the populations studied.

of case series, combined with present differences in design and analysis among the eligible studies, argued against the validity and usefulness of pooling study results (Eysenck 1994).

Two eligible studies (Flickinger et al. 1994, and Auchter et al. 1996) did synthesize *some* of the case series data. Using explicit inclusion criteria, both studies identified radiosurgery patients from multiple institutions, and conducted multivariate analyses to identify patient and treatment factors that appeared to be associated with improved outcomes.

## **VI. PUBLISHED FINDINGS**

The synthesis of evidence from eligible studies includes a summary of patient and treatment characteristics and an overview of treatment outcomes. Eight studies performed statistical analyses to identify patient and treatment characteristics that appeared to be associated with improved outcomes. Their findings are included in this report.

### **A. Description of Patients, Treatments, and Outcomes**

The 13 case series that met the inclusion criteria for this report are summarized in Table 2<sup>5</sup>. Additional details relevant to the studies follow. Note that patient characteristics, incompletely described in some studies, may have had a large impact in determining patient response to treatment.

Patients ranged in age from 14 to 87, with a median age in the mid-50s (no data reported by Kihlstrom). Men and women were approximately equally represented in all but the Engenhart study (72% male).

The baseline health status of patients was sometimes difficult to assess because of incomplete reporting. Data suggested that most studies were fairly selective, and included highly functional patients. Kihlstrom, Engenhart, Valentino, and Breneman appeared to have been less selective, and to have included some patients with more advanced disease.

The characteristics of metastases varied among studies. All of the case series included a mix of primary tumor types; the histology of treated tumors generally included those most frequently found in brain metastases. Auchter and Engenhart treated only radioresistant tumors. Auchter, Valentino, and Flickinger included only patients with solitary metastases. Chamberlain and Buatti included only patients with 1-3 metastases. All other studies included patients with solitary or multiple metastases. Tumor size,

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<sup>5</sup> Table 2 includes only radiosurgery patient data from the Bindal study (1996). The study also reported outcomes from a selected series of surgical patients.

reported as either tumor volume (cm<sup>3</sup>) or tumor diameter (cm or mm), varied and was reported inconsistently across studies. Most of the treated tumors were relatively small with tumor diameters of  $\leq 2$  cm or tumor volumes of  $< 3$  cm<sup>3</sup>. Flickinger and Shiau treated several patients with large tumors. Joseph, Valentino, and Engenhart reported no tumor size data. Auchter, Bindal, and Kihlstrom treated only newly diagnosed metastases. Davey treated only recurrences.

Studies used single, or multiple, treatment protocols. Radiosurgery (SRS) was used as a boost to radiotherapy (WBRT), or as the solitary treatment modality. Gamma Knife units were used to perform radiosurgery by Kihlstrom, Flickinger, and Shiau. LINACs were used in all other studies. Radiation dosage planning varied across institutions.

Studies included some measures of baseline patient status, tumor response, and survival (Figure 3). Eligible studies differed in how, and when, these parameters were measured.

### Figure 3: Definitions of Outcome Measures for Cancer Treatment

Actuarial control or survival: the probability of local control or survival at the defined time. It is calculated using available data, and becomes less meaningful as patient numbers decline.

Karnofsky Performance Score (KPS): a measure of functional independence. 100 = normal; 80-90 = mild symptoms; 70 = independent self care, but cannot work;  $\leq 50$  = needs progressively more help; 0 = dead. The KPS can be used to describe patient status at baseline (as in Table 2). Change from baseline can be used as a quality of life measure of treatment outcome.

Local control: lack of significant sustained increase in tumor volume ( $\geq 25\%$ ) for at least 30 days, as measured by follow up imaging. Reported figures often represent crude measures based on patients who were alive and available for follow up, and are subject to many biases.

Median survival: median period of time that patients live after treatment. Many studies exclude from these calculations the patients who died within 30 days of treatment.

Because of the competing risks of mortality from the spread of systemic cancer, follow up times after treatment were limited. Published case series reported only small numbers of patients who were followed for more than a year.

#### B. Reported Outcomes of Stereotactic Radiosurgery

Outcome data from Table 2 are summarized in Table 3.

Ten studies reported crude local control rates. These ranged from 47% to 100%. Overall, approximately 86% of treated tumors had disappeared, decreased in size, or grown less than 25%, when assessed several weeks after treatment. Actuarial local control at one year ranged from 75% to 85%. Good tumor response to treatment, as reflected in high rates of local control, was not necessarily reflected in an increased length of survival.

**Table 2: Summary of the Evidence: Effectiveness of Stereotactic Radiosurgery (SRS) for the Treatment of Brain Metastases**

Note: All studies included patients who had a mix of primary tumor type.

#, STUDY	TREATMENT PLAN (I = initial, R = recurrence)	PATIENT CHARACTERISTICS (N = metastases/cases)	CRUDE CONTROL	ACTUARIAL CONTROL	MEDIAN SURVIVAL	ACTUARIAL SURVIVAL	FACTORS ASSOCIATED WITH IMPROVED LOCAL CONTROL / SURVIVAL (from statistical analyses of outcomes)
1. Shiau, 1997	- SRS, or SRS + WBRT (I) - SRS (R)	N = 219/100 - any brain metastases - KPS = 90	47%	82% (6 mo.) 77% (1 yr.)	48 weeks		<u>Local control:</u> - melanomas (vs. adenocarcinomas) - pre-treatment tumor image suggesting no damaged or dead cells - longer time interval between primary cancer diagnosis and SRS - higher radiation dose
2. Breneman, 1997	- SRS (I, 1 metastasis) - SRS + WBRT (I, ≥ 2 met) - SRS (R)	N = 177/84 - 1-6 metastases - ½: no active systemic cancer	Time to failure: 35 weeks		43 weeks (35 wks., ≥ 3 mets.)		<u>Local control:</u> - melanoma (vs. other tumor histologies) - higher radiation dose <u>Survival:</u> - no active systemic cancer - 1-2 brain metastases (vs. ≥ 3 metastases)
3. Auchter, 1996	- SRS, or SRS + WBRT (I)	N = 122/122 - 1 metastasis - systemic cancer controlled - KPS ≥ 70	86%	85% (1 yr.) 77% (2 yr.)	Actuarial median: 56 weeks	53% (1 yr.) 30% (2 yr.)	<u>Local control:</u> - breast cancer (vs. other tumor histologies);- presence of systemic disease <u>Survival:</u> - no systemic metastases - high baseline KPS ; - local control of primary tumor
4. Chamberlain, 1996	- SRS + WBRT (I) - SRS (R)	N = 74/50 - 1-3 metastases - systemic cancer controlled - KPS = 90 (all ≥ 70)	68%		26 weeks (R) 28 weeks (I)		Not analyzed
5. Joseph, 1996	- SRS, or SRS + WBRT	N = 189/120 - 1-4 metastases - systemic cancer controlled - KPS = 82 (all ≥ 50)			32 weeks	37 wks., 1-2 mets., 14 wks., 3-4 mets. (both at 1 yr.)	<u>Survival:</u> - 1-2 brain metastases (vs. ≥ 3 metastases) - baseline KPS ≥ 70
6. Bindal, 1996	- SRS (I), or SRS + WBRT (I)	N = NS/31 (77% had 1 met.) - small metastases - systemic cancer controlled - KPS = 80	Time to failure: 26 weeks		32 weeks	27% (1 yr.)	Not analyzed
7. Alexander 1995	- SRS + WBRT (I) - SRS (R)	N = 421/248 - any metastases - systemic cancer controlled - KPS ≥ 70	89%	85% (1 yr.) 65% (12 yr.)	40 weeks (91 weeks if no active systemic cancer)		<u>Local control:</u> - smaller brain metastases, or location above the tentorium - initial (vs. recurrent) tumor <u>Survival:</u> - no active systemic cancer - 1-2 brain metastases (vs. ≥ 3 metastases) - age < 60, or female sex
8. Valentino, 1995	- SRS (I or R), or for residual tumor after surgery	N = 139/139 - 1 metastasis - KPS = 65	86%		Actuarial median: 54 weeks (SRS) 74 weeks (SRS + surgery)	12% (2 yr.)	Not analyzed
9. Buatti, 1995	- SRS + WBRT (I) - SRS (R)	N = 28/25 - 1-3 metastases - systemic cancer controlled - KPS ≥ 50	84%		52 weeks	28.3% (1 yr.)	<u>Survival:</u> - development of brain metastases > 1 year after cancer diagnosis, or recurrence > 1 year after treatment (vs. more aggressive cancer)
10. Flickinger, 1994	- SRS [usually (R)] - SRS + WBRT [usually (I)]	N = 116/116 - 1 metastasis	85%	75% (1 yr.) 67% (2 yr.)	47 weeks 22 wks. [SRS (I)] 146 wks. [SRS (R)]		<u>Local control:</u> - melanomas and kidney cancer (vs. other tumor histologies) - combined SRS + WBRT vs. to SRS alone for initial therapy <u>Survival:</u> - breast cancer (vs. other tumor histologies)
11. Davey, 1994	- SRS (R)	N = 20/12 - symptomatic metastases	100%		26 weeks	40% (1 yr.)	Not analyzed
12. Engenhardt, 1993	- SRS (I or R) - SRS + WBRT (multiple mets.)	N = 102/69 - inoperable radioresistant metastases - some had active systemic cancer	95%		26 weeks	28.3% (1 yr.)	<u>Survival:</u> - no active systemic metastatic cancer - good local control of brain metastases
13. Kihlstrom, 1993	- SRS (I)	N = 235/160 - 1-5 metastases	94%		30 wks. (cases followed > 1 yr.)		Findings: - tumor histology did not predict response to treatment

The median length of survival after treatment with SRS (with or without WBRT) ranged from 26 weeks to 56 weeks. For studies that only treated patients with solitary metastases, median survival ranged from 47 to 56 weeks. Actuarial survival at one year ranged from 28.3% (initial and recurrent tumor treatment, 1-3 metastases) to 53% (initial tumor treatment, 1 metastasis).

Treatment-related morbidity and mortality were uncommon. Most of the adverse effects reported in these studies were related to radiation-induced injury, and many were reversible with medication. These included increased intracranial pressures, seizures, transient headaches, nausea and vomiting, increased confusion, hemiparesis, and dysphagia. Alopecia, tumor hemorrhage, and discomfort with the head frame were also reported. Radiation necrosis, a serious form of delayed brain tissue damage, had a median rate of 3% (range: 0%-17%). The median rate of deaths occurring within 30 days of treatment was 1.3% (range: 0%-8%).

**Table 3: Summary of Outcomes Data, based on Case Series Reports in Table 2**

*Studies 3 and 10 (highlighted columns) analyzed data collected in several case series that were conducted at different sites. All other studies were single-site case series.*

	Solitary Metastases			Solitary or Multiple Metastases Treated in the Study									
		Multi-site											
Study # from Table 2	8	3	10	1	2	4	5	6	7	9	11	12	13
Median Survival (weeks) <sup>2</sup>	54	56	47	48	43	26-28	32	32	40	52	26	26	30
% 1-year Actuarial Survival		53					37; 14 <sup>1</sup>	27		28.3	40	28.3	
% Local Control or Weeks to Failure of Control	86	86	85	47	35 weeks	68		26 weeks	89	84	100	95	94
% 1-year Actuarial Control		85	75	77					85				

<sup>1</sup> The two figures represent findings for patients with 1-2 metastases, and 3-4 metastases, respectively.

<sup>2</sup> Expected survival of patients with untreated brain metastases is 4 to 8 weeks. Expected survival with the use of steroids increases to about 12 weeks. Median survival of WBRT ranged from 15-18 weeks. Median survival of WBRT+ surgery ranged from 40-43 weeks (See Page 4.)

### C. Factors Associated with Improved Treatment Outcomes

Eight retrospective studies, including the two multi-site studies, used statistical analyses to interpret their findings and to determine associations with improved treatment outcomes. Results from these analyses are presented in Tables 4 and 5.

Local control of tumor growth was sustained longer for metastases of melanomas (3 studies), breast cancer (1 study), and kidney cancer (1 study included with melanomas) compared to other tumor histologies. The use of higher radiation doses (*a factor inversely associated with tumor size*) was associated with longer local control (2 studies).

An association between local control and one of several other factors was reported by five of the studies. However, the following reported associations were not corroborated by other studies in the group: WBRT + SRS vs. SRS alone, supratentorial location, indolent

cancer spread, size and location of the metastasis, presence of systemic metastasis, initial (vs. recurrent) tumor status, and tumor images suggesting the absence of damaged cells. No associations were found between local tumor control and the following factors: age, gender, functional status, primary tumor site, or number of metastases.

**Table 4: Potential Predictive Factors Associated with Local Control of Tumor Growth**  
(L= positive predictor; X= no association)

#, STUDY	AGE	GENDER	FUNCTIONAL STATUS (KPS)	TREATMENT PLAN	RADIATION DOSE	HISTOLOGY	CHARACTERISTICS OF PRIMARY TUMOR		CHARACTERISTICS OF METASTATIC TUMOR					
							LOCATION	AGGRESSIVENESS	LOCATION	SIZE	PRESENCE OF EXTRACRANIAL METASTASIS	NUMBER	INITIAL VS. RECURRENCE	IMAGING CHARACTERISTICS
1. Shiau, 1997	X			X	L	L	X	L <sup>1</sup>	X	X		X		L
2. Breneman, 1997	X	X			L	L	X	X <sup>2</sup>			X	X		
3. Auchter, 1996	X	X	X		X	L	X	X <sup>3</sup>	X	X	L			
7. Alexander, 1995	X	X		X					L	L			L	
10. Flickinger, 1994	X			L	X	L			X	X			X	

<sup>1</sup> defined as time interval between diagnosis of primary tumor and SRS date.

<sup>2</sup> defined as time interval between diagnosis of brain metastases and SRS date.

<sup>3</sup> defined as time interval between diagnosis of primary tumor to brain metastases.

**Table 5: Potential Predictive Factors Associated with Improved Survival**  
(S= positive predictor; X= no association)

#, STUDY	AGE	GENDER	FUNCTIONAL STATUS (KPS)	TREATMENT PLAN	RADIATION DOSE	HISTOLOGY	CHARACTERISTICS OF PRIMARY TUMOR		CHARACTERISTICS OF METASTATIC TUMOR					
							LOCATION	AGGRESSIVENESS	LOCATION	SIZE	PRESENCE OF EXTRACRANIAL DISEASE	NUMBER	RESPONSE TO RADIATION	INITIAL VS. RECURRENCE
2. Breneman, 1997	X	X				X	X	X <sup>1</sup>			S	S		
3. Auchter, 1996	X	X	S		X		X	X <sup>2</sup>	X	X	S			X
5. Joseph, 1996	X	X	S	X		X					S	S		
7. Alexander, 1995	S	S				X					S	S		X
9. Buatti, 1995	X		X		X	X	X	S <sup>3</sup>		X		X		
10. Flickinger, 1994	X			X	X	S			X	X				X
12. Engenhardt, 1993						X	X				S	X	S	

<sup>1</sup> defined as time interval from diagnosis of brain metastases to SRS date.

<sup>2</sup> defined as local control of primary site.

<sup>3</sup> defined as time interval from diagnosis of primary disease or initial treatment of brain metastases to the development or recurrence of brain metastases.



The strongest predictors of improved survival were the *absence of active systemic cancer* (4 studies), *patient functional status before treatment* (2 studies), and the *presence of a limited number of metastases (1 or 2 vs. 3 metastases)* (3 studies). An association between increased length of survival and one of several other factors was reported by one of the seven studies. However, the reported associations were not corroborated by other studies in the group. Factors included: younger age, female, breast cancer vs. other histologies, indolent cancer spread, and good local control of metastases. No associations were found between increased length of survival and the following factors: the use of WBRT (in addition to SRS), treatment dose, tumor size, location, or initial (vs. recurrent) tumor status.

*Most of the factors associated with improved local control were not associated with increased survival.* Breast cancer histology and lack of aggressiveness of tumor spread were the only factors associated with *both* improved local control and prolonged survival.

## VII. DISCUSSION

### A. Effectiveness of Stereotactic Radiosurgery for Brain Metastases

As more effective methods of controlling systemic cancers are becoming available, definitive treatments for brain metastases are being sought. Whole brain radiotherapy (WBRT) offers only modest benefits to patients. The addition of cranial surgery can increase the duration of survival two to three-fold (relative to radiotherapy) in selected patients. However, surgery + WBRT does not completely eradicate cancers, and about 20% of treated tumors recur at the same location (Patchell et al. 1990). Not all patients are good surgical candidates, not all tumors are surgically accessible, and the use of repeat surgery for recurrences remains controversial. Treatments that are applicable to a broad range of patients, and that provide better outcomes, are still needed.

**The lack of randomized clinical trials and the heterogeneity in the case series studies that provide the only available data preclude definitive assessment of the effectiveness of stereotactic radiosurgery and prevent generalization of the available findings to the larger oncology population.**

However, the overall trends reflected in case series data were encouraging. Findings suggested that selected patient groups derived considerable benefit from treatment with stereotactic radiosurgery. Local control of tumor growth was achieved for most patients, at least for a period of time. This can be expected to reduce the symptoms of intracranial disease, improve the quality of life of the patient, and possibly forestall death from neurological causes. Most side-effects were mild, temporary, and treatable. The median length of survival after SRS treatment ranged from 26 weeks to 56 weeks. This compares quite favorably with outcomes from other treatments.

SRS was sometimes used for patients who were surgical candidates. A more common use of SRS has been for patients who were not surgical candidates, and for whom radiotherapy or palliative care were the available options.

A review of the findings from the multivariate analyses conducted by eight studies included in this report provides some guidance about significant prognostic factors.

- Findings did not support limiting the use of SRS to patients with solitary metastases. Available data reported *no difference in outcomes for patients treated for a solitary metastasis or for two metastases*.

Relatively few patients with 3 or more metastases were treated in the case series included in this report. Treatment outcomes were conflicting and provided little guidance for clinical decision-making. Findings suggested that this group derived significantly less benefit from radiosurgery than patients with 1-2 metastases, and it is uncertain if they derived any clinically important benefits.

- Patients treated for *recurrences of brain metastases appeared to derive as large a survival benefit from SRS as did those for whom radiosurgery was used as the initial treatment for metastases*. This finding is particularly promising, since patients with recurrences are not often candidates for definitive therapies.
- Breast cancer histology (vs. other tumor types) was associated with both improved local control and prolonged survival after treatment with stereotactic radiosurgery.
- The absence of active systemic cancer, along with good baseline functional status and younger age, were associated with improved survival for patients treated with SRS. These findings are mirrored in an analysis of radiotherapy outcomes (Gaspar et al. 1997), as well as in analyses of surgical outcomes (Patchell et al. 1990; Noordijk et al. 1994.) *Note that all surgical patients had a good baseline functional status.*

The presence of cancer that spread rapidly was associated with poor survival in a radiosurgery case series and also in a surgical trial (Patchell et al. 1990).

These findings strongly suggest that *severely debilitated patients, or those with actively progressing systemic cancers, are unlikely to derive significant survival benefit from definitive treatment of their brain metastases*.

- Radiation dose calculations were often based on multiple factors that were difficult to separate in analyses of case series data. The Radiation Therapy Oncology Group (RTOG) is evaluating the optimal dose planning and maximal possible treatable tumor volume in ongoing or planned RTOG radiosurgery trials (Shaw et al. 1996).

## B. Effectiveness of Stereotactic Radiosurgery vs. Traditional Treatments

The weakness of the data also precludes any definitive assessment of the effectiveness of stereotactic radiosurgery relative to other treatment options.

The strongest comparison that can be made is for the treatment of patients with solitary metastases. Table 6 lists outcomes from three treatment options. Data suggest that SRS outcomes were comparable to those of surgery + WBRT, and that SRS caused fewer complications than surgery. Both surgery and SRS had significantly better outcomes than WBRT alone. This comparison must be interpreted with caution, since patient selection and study designs varied. *Biases inherent in case series data tend to overestimate the effectiveness of the therapy being studied* (Pocock, 1991).

**Table 6: Radiotherapy, Radiosurgery, and Surgery for Solitary Brain Metastases**

TREATMENT (study)	DESIGN	N	MEDIAN SURVIVAL (weeks)	FUNCTIONAL INDEPENDENCE (weeks maintained)	CNS DEATH <sup>2</sup>	MORTALITY <sup>3</sup> & MORBIDITY
WBRT (Patchell)	RCT	48	15	8	50%	4%, 17%
WBRT (Noordijk)	RCT	63	26	15	33%	0%, 33% (mild-moderate)
Surgery + WBRT (Patchell)	RCT	48	40	38	29%	4%, 8%
Surgery + WBRT (Noordijk)	RCT	63	43	33	35%	9%, 6% (major)
SRS or SRS + WBRT (Auchter)	Combined Case Series	122	56	44	25%	1.6%, 0%
SRS or SRS + WBRT (Flickinger)	Combined Case Series	116	47	NS	NS	NS, 1%
SRS (Valentino) <sup>1</sup>	Case Series	119	54	NS	NS	NS

**Abbreviations:** NS, not stated by authors      RCT, randomized clinical trial

<sup>1</sup> Only data for SRS patients are reported. SRS + Surgery patients were not comparable.

<sup>2</sup> Percent of deaths considered to have been caused by the effects of uncontrolled growth of brain metastases.

<sup>3</sup> Percent of patients who died within 30 days of treatment, or who were diagnosed with radiation necrosis.

Comparison data to assess the effectiveness of stereotactic radiosurgery for the treatment of multiple metastases are absent, or of such poor quality as to preclude meaningful interpretation. Optimal treatment for patients with multiple metastases remains to be determined.

## VIII. CONCLUSIONS

Lack of data from high quality studies precludes any definitive assessment of the relative effectiveness of SRS to standard treatment for brain metastases. It also precludes any definitive assessment of optimal equipment selection, treatment parameters, or patient selection criteria.

The available data from case series reports *suggest* that SRS is a relatively safe and effective technology for definitive treatment of brain metastases in selected patients. It appears to offer considerably greater survival benefits than traditional whole brain radiotherapy. SRS may be comparable to surgery plus radiation therapy for the treatment of patients with smaller solitary metastases. SRS can be used to treat patients whose metastases recur after traditional therapies, a group for whom definitive treatment options are frequently unavailable. As with other definitive therapies for patients with brain metastases, highly functional patients with well-controlled systemic cancers derive the greatest benefit from treatment.

Uncertainty remains about the true effectiveness of this technology and the appropriate indications for its use in patients with metastatic brain tumors. A randomized clinical trial is in progress (see next page), and further trials are needed, to address the many of the unanswered questions about SRS and about the treatment of brain metastases. Such trials will provide stronger evidence on which to base health care treatment and policy decisions.

## IX. ONGOING TRIALS AND CLINICAL TRIAL RESOURCES

The National Cancer Institute, Physician Data Query (PDQ) System lists eighty three ongoing clinical trails for the assessment of treatments of adult brain cancers. Thirty four of the trials include some form of radiation therapy. Of those, three employ radiosurgery as part of the treatment plan, one of which is for brain metastases. Table 7 lists the NCI stereotactic radiosurgery trial for metastases to the brain in adults (as of March, 1998).

**Table 7: Clinical Trial of Stereotactic Radiosurgery in Adults for Brain Metastases**

TRIAL	DESCRIPTION
RTOG-95-08 Multi-site NCI-sponsored NCI cooperative group program study	Phase III Randomized Study of Fractionated External Beam Whole-Brain Radiotherapy with vs. Without a Stereotactic Radiosurgery Boost in Patients with One to Three Unresected Brain Metastases  start date 1/31/96 status active for 2.5-3.75 years  A companion piece to this trial surveys the insurance industry preapproval decisions for SRS.

The INFORMATION NETWORK, maintained by Johns Hopkins Medical Institutions, surveyed major brain tumor facilities, and identified 11 additional trials of stereotactic radiosurgery for the treatment of primary or metastatic brain tumors. These trials are designed and conducted by the individual treatment centers (INFONET, 1997).

As part of continued efforts to gain expanded access to promising treatments for cancer, VA entered into an agreement with NCI. VA will provide coverage for eligible veterans to participate in a broad range of NCI clinical trials across the country. Medical care costs of veterans who enroll in NCI trials in non-VA facilities will be covered in selected cases (NCI, 1997).

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INFONET. *Al Musella's list of clinical trials and noteworthy treatments for brain tumors* [website]. Available: <http://www.virtualtrials.com> [September 1997].

National Cancer Institute, Information about NCI programs. *NCI and VA make it easier for veterans to enter studies* [website]. Available: [http://icicsun.nci.nih.gov/clinpdq/nci/NCI\\_and\\_VA\\_Make\\_It\\_Easier\\_for\\_Veterans\\_to\\_Enter\\_Studies.html#1](http://icicsun.nci.nih.gov/clinpdq/nci/NCI_and_VA_Make_It_Easier_for_Veterans_to_Enter_Studies.html#1) [September 1997].

## **REFERENCES**

## X. REFERENCES

### STUDIES INCLUDED IN THIS REVIEW

Alexander E, III., Moriarty TM, Davis RB, Wen PY, Fine HA, Black PM, et al. Stereotactic radiosurgery for the definitive, noninvasive treatment of brain metastases. *Journal of the National Cancer Institute* 1995; 87(1): 34-40.

Auchter RM, Lamond JP, Alexander E, Buatti JM, Chappell R, Friedman WA, et al. A multi-institutional outcome and prognostic factor analysis of radiosurgery for resectable single brain metastasis. *International Journal of Radiation Oncology, Biology, Physics* 1996; 35(1): 27-35.

Bindal AK, Bindal RK, Hess KR, Shiu A, Hassenbusch SJ, Shi WM, et al. Surgery versus radiosurgery in the treatment of brain metastasis. *Journal of Neurosurgery* 1996; 84(5): 748-754.

Breneman JC, Warnick RE, Albright RE, Jr., Kukiatinant N, Shaw J, Armin D, et al. Stereotactic radiosurgery for the treatment of brain metastases. Results of a single institution series. *Cancer* 1997; 79(3): 551-557.

Buatti JM, Friedman WA, Bova FJ, Mendenhall WM. Treatment selection factors for stereotactic radiosurgery of intracranial metastases. *International Journal of Radiation Oncology, Biology, Physics* 1995; 32(4): 1161-1166.

Chamberlain MC, Kormanik P, Barba D, Fuller BG, Smith DE, Shea WMC. Stereotactic radiosurgery for metastatic brain tumors. *International Journal of Oncology* 1996; 8(3): 617-624.

Davey P, O'Brien PF, Schwartz ML, Cooper PW. A phase I/II study of salvage radiosurgery in the treatment of recurrent brain metastases. *British Journal of Neurosurgery* 1994; 8(6): 717-723.

Engenhart R, Kimmig BN, Hover KH, Wowra B, Romahn J, Lorenz WJ, et al. Long-term follow-up for brain metastases treated by percutaneous stereotactic single high-dose irradiation. *Cancer* 1993; 71(4): 1353-1361.

Flickinger JC, Kondziolka D, Lunsford LD, Coffey RJ, Goodman ML, Shaw EG, et al. A multi-institutional experience with stereotactic radiosurgery for solitary brain metastasis. *International Journal of Radiation Oncology, Biology, Physics* 1994; 28(4): 797-802.

Joseph J, Adler JR, Cox RS, Hancock SL. Linear accelerator-based stereotaxic radiosurgery for brain metastases: the influence of number of lesions on survival. *Journal of Clinical Oncology* 1996; 14(4): 1085-1092.

Kihlstrom L, Karlsson B, Lindquist C. Gamma Knife surgery for cerebral metastases. Implications for survival based on 16 years experience. *Stereotactic & Functional Neurosurgery* 1993; 61(Suppl 1): 45-50.

Shiau CY, Sneed PK, Shu HK, Lamborn KR, McDermott MW, Chang S, et al. Radiosurgery for brain metastases: relationship of dose and pattern of enhancement to local control. *International Journal of Radiation Oncology, Biology, Physics* 1997; 37(2): 375-383.

Valentino V. The results of radiosurgical management of 139 single cerebral metastases. *Acta Neurochirurgica Supplementum* 1995; 63: 95-100.



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**STUDIES EXCLUDED FROM THIS REVIEW**

Adler JR, Cox RS, Kaplan I, Martin DP. Stereotactic radiosurgical treatment of brain metastases. *Journal of Neurosurgery* 1992; 76(3): 444-449.

Brada M, Laing R. Radiosurgery/stereotactic external beam radiotherapy for malignant brain tumours: the Royal Marsden Hospital experience. *Recent Results in Cancer Research* 1994; 135: 91-104.

Caron JL, Souhami L, Podgorsak EB. Dynamic stereotactic radiosurgery in the palliative treatment of cerebral metastatic tumors. *Journal of Neuro-oncology* 1992; 12(2): 173-179.

Coffey RJ, Flickinger JC, Bissonette DJ, Lunsford LD. Radiosurgery for solitary brain metastases using the cobalt-60 gamma unit: methods and results in 24 patients. *International Journal of Radiation Oncology, Biology, Physics* 1991; 20(6): 1287-1295.

Coffey RJ, Flickinger JC, Lunsford LD, Bissonette DJ. Solitary brain metastasis: radiosurgery in lieu of microsurgery in 32 patients. *Acta Neurochirurgica Supplementum* 1991; 52: 90-92.

Coffey RJ, Lunsford LD, Flickinger JC. The role of radiosurgery in the treatment of malignant brain tumors. *Neurosurgery Clinics of North America* 1992; 3(1): 231-244.

De Salles AA, Hariz M, Bajada CL, Goetsch S, Bergenheim T, Selch M, et al. Comparison between radiosurgery and stereotactic fractionated radiation for the treatment of brain metastases. *Acta Neurochirurgica Supplementum* 1993; 58(8): 115-118.

Flickinger JC, Loeffler JS, Larson DA. Stereotactic radiosurgery for intracranial malignancies. *Oncology* 1994; 8(1): 81-86; discussion 86, 94, 97-88.

Fukuoka S, Seo Y, Takanashi M, Takahashi S, Suematsu K, Nakamura J. Radiosurgery of brain metastases with the Gamma Knife. *Stereotactic & Functional Neurosurgery* 1996; 66(1): 193-200.

Gerosa M, Nicolato A, Severi F, Ferraresi P, Masotto B, Barone G, et al. Gamma Knife radiosurgery for intracranial metastases: from local tumor control to increased survival. *Stereotactic & Functional Neurosurgery* 1996; 66(1): 184-192.

Gerosa MA, Nicolato A, Berlucchi S, Piovan E, Zampieri PG, Pasoli A, et al. Gamma knife radiosurgery of primary and metastatic malignant brain tumors, a preliminary report. *Stereotactic & Functional Neurosurgery* 1995; 64(Suppl 1): 56-66.

Jokura H, Takahashi K, Kayama T, Yoshimoto T. Gamma knife radiosurgery of a series of only minimally selected metastatic brain tumours. *Acta Neurochirurgica Supplementum* 1994; 62: 77-82.

Kihlstrom L, Karlsson B, Lindquist C, Noren G, Rahn T. Gamma knife surgery for cerebral metastasis. *Acta Neurochirurgica Supplementum* 1991; 52(9): 87-89.

Loeffler JS, Alexander Ed. The role of stereotactic radiosurgery in the management of intracranial tumors. *Oncology* 1990; 4(3): 21-41.

Loeffler JS, Kooy HM, Wen PY, Fine HA, Cheng CW, Mannarino EG, et al. The treatment of recurrent brain metastases with stereotactic radiosurgery. *Journal of Clinical Oncology* 1990; 8(4): 576-582.

Martens F, Verbeke L. Stereotactic radiosurgery of cerebral metastases: preliminary results. *Acta Clinica Belgica* 1993; 48(4): 228-233.

Rutigliano MJ, Lunsford LD, Kondziolka D, Strauss MJ, Khanna V, Green M, et al. The cost effectiveness of stereotactic radiosurgery versus surgical resection in the treatment of solitary metastatic brain tumors. *Neurosurgery* 1995; 37(3): 445-455.

Shirato H, Takamura A, Tomita M, Suzuki K, Nishioka T, Isu T, et al. Stereotactic irradiation without whole-brain irradiation for single brain metastasis. *International Journal Of Radiation Oncology Biology Physics* 1997; 37(2): 385-391.

Simpson JR, Rich KM, Drzymala RE, Wasserman TH, Klein EE, Michaletz-Lorenz M, et al. Stereotactic external beam irradiation using a linear accelerator: the Washington University experience. *Missouri Medicine* 1995; 92(4): 188-192.

Sturm V, Kimmig B, Engenhardt R, Schlegel W, Pastyr O, Treuer H, et al. Radiosurgical treatment of cerebral metastases. Method, indications and results. *Stereotactic & Functional Neurosurgery* 1991; 57(1-2): 7-10.

Valentino V, Mirri MA, Schinaia G, Dalle Ore G. Linear accelerator and Greitz-Bergstrom's head fixation system in radiosurgery of single cerebral metastases. A report of 86 cases. *Acta Neurochirurgica* 1993; 121(3-4): 140-145.

Voges J, Treuer H, Erdmann J, Schlegel W, Pastyr O, Muller RP, et al. Linac radiosurgery in brain metastases. *Acta Neurochirurgica Supplementum* 1994; 62(6): 72-76.

**ADDITIONAL REFERENCES CITED IN THE TEXT (Background and Methodology)**

(1997). *State-of-the-art information on adult brain tumor prognosis and treatment*. [Online database]. Available: CancerNet, [July 1997].

(1997). *Description and Treatment Trial Protocols for brain metastases*. [Online database]. Available: CancerNet, [September 1997].

Alexander E, Moriarty TM, Loeffler JS. Radiosurgery for metastases. *Journal Of Neuro Oncology* 1996; 27(3): 279-285.

Arbit E, Wronski M, Burt M, Galicich JH. The treatment of patients with recurrent brain metastases - a retrospective analysis of 109 patients with nonsmall cell lung cancer. *Cancer* 1995; 76(5): 765-773.

Borgelt B, Gelber R, Kramer S, Brady LW, Chang CH, Davis LW, et al. The palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. *International Journal of Radiation Oncology, Biology Physics* 1980; 6(1): 1-9.

Cook DJ, Guyatt GH, Laupacis A, Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest* 1992; 102(4 Suppl): 305s-311s.

De Salles A, Goetsch S, Shaker L. Radiosurgery. Integration of radiation therapy, surgery & radiology. *Administrative Radiology* 1993; 12(1): 33-34.

DeAngelis LM. Management of brain metastases. *Cancer Investigation* 1994; 12(2): 156-165.

Department of Health & Human Services. Health Care Financing Administration. Medicare program; changes in the hospital inpatient prospective payment systems and fiscal year 1998 rates. *Federal Register* 1997; 62(168): Part IV:45966.

Department of Veterans Affairs. Medical centers pioneer new equipment. New radiotherapy struts its stuff. *Vanguard* 1997; XLIII(3): 8.

Elekta Home Page. (1996). *Gamma Knife worldwide locations as of January 1996*. [Website]. Available: <http://www.elekta.com/usasites.html>, [October 2, 1997].

Eysenck HJ. Meta-analysis and its problems. *BMJ* 1994; 309(6957): 789-792.

Flickinger JC, Loeffler JS, Larson DA. Stereotactic radiosurgery for intracranial malignancies. *Oncology* 1994; 8(1): 81-86; discussion 86, 94, 97-88.

Food and Drug Administration. Center for Devices and Radiological Health. (1997). *Information on releasable 510(k)s*. [Website]. Available: <http://www.fda.gov/cdrh/510khome.html>, [September 3, 1997].

Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *International Journal of Radiation Oncology, Biology, Physics* 1997; 37(4): 745-751.

Goodman C. *Literature searching and evidence interpretation for assessing health care practices*. Stockholm: SBU. Swedish Council on Technology Assessment in Health Care; 1993.

Guyatt GH, Sackett DL, Sinclair JC, Hayward R, Cook DJ, Cook RJ. Users' guides to the medical literature. IX. A method for grading health care recommendations. Evidence-Based Medicine Working Group. *JAMA* 1995; 274(22): 1800-1804.

Hazuka MB, Kinzie JJ. Brain metastases: results and effects of re-irradiation. *International Journal of Radiation Oncology, Biology, Physics* 1988; 15(2): 433-437.

Ibrahim MA. *Epidemiology and health policy*. Rockville, Md: Aspen Systems Corporation; 1985.

Jones ED, Banks WW, Fischer LE. *Quality assurance for gamma knives*. NUCREG/CR-6324. 1995, Lawrence Livermore National Laboratory for the United States Nuclear Regulatory Commission: Washington, DC.

Kihlstrom L, Karlsson B, Lindquist C. Gamma Knife surgery for cerebral metastases. Implications for survival based on 16 years experience. *Stereotactic & Functional Neurosurgery* 1993; 61(Suppl 1): 45-50.

Kizer KW. *National cancer strategy*. VHA Directive 97-050. 1997, Department of Veterans Affairs. Veterans Health Administration: Washington, DC.

Kurup P, Reddy S, Hendrickson FR. Results of re-irradiation for cerebral metastases. *Cancer* 1980; 46(12): 2587-2589.

Lang FF, Sawaya R. Surgical management of cerebral metastases. *Neurosurgical Clinics of North America* 1996; 7(3): 459-484.

Larson DA, Bova F, Eisert D, Kline R, Loeffler J, Lutz W, et al. Current radiosurgery practice: results of an ASTRO survey. Task Force on Stereotactic Radiosurgery, American Society for Therapeutic Radiology and Oncology. *International Journal of Radiation Oncology, Biology, Physics* 1994; 28(2): 523-526.

Laws ER, Jr., Thapar K. Brain tumors. *CA: Cancer Journal for Clinicians* 1993; 43(5): 263-271.

Loeffler JS, Alexander E. Radiosurgery for the treatment of intracranial metastases. In: Alexander E, Loeffler JS, Lunsford LD, Eds. *Stereotactic Radiosurgery*. New York: McGraw-Hill; 1997.

Luxton G, Petrovich Z, Jozsef G, Nedzi LA, Apuzzo ML. Stereotactic radiosurgery: principles and comparison of treatment methods. *Neurosurgery* 1993; 32(2): 241-259; discussion 259.

Noordijk EM, Vecht CJ, Haaxma-Reiche H, Padberg GW, Voormolen JH, Hoekstra FH, et al. The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age. *International Journal of Radiation Oncology, Biology, Physics* 1994; 29(4): 711-717.

Pakuris E. (1996). *Clinical trials updates: Proton Radiation Oncology Group (PROG). Particles NewsLetter, Number 18.* [Website]. Available: <http://neurosurgery.mgh.harvard.edu/hcl/ptles.htm>, [July 1996].

Parker SL, Tong T, Bolden S, Wingo PA. Cancer statistics, 1997. *CA: Cancer Journal for Clinicians* 1997; 47(1): 5-27.

Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *New England Journal of Medicine* 1990; 322(8): 494-500.

Phillips MH, Stelzer KJ, Griffin TW, Mayberg MR, Winn HR. Stereotactic radiosurgery: a review and comparison of methods. *Journal of Clinical Oncology* 1994; 12(5): 1085-1099.

Posner JB. Diagnosis and treatment of metastases to the brain. *Clinical Bulletin* 1974; 4(2): 47-57.

Posner JB. Brain tumors. *CA: Cancer Journal for Clinicians* 1993; 43(5): 261-262.

Shaw E, Scott C, Souhami L, Dinapoli R, Bahary JP, Kline R, et al. Radiosurgery for the treatment of previously irradiated recurrent primary brain tumors and brain metastases - initial report of radiation therapy oncology group protocol 90-05. *International Journal Of Radiation Oncology Biology Physics* 1996; 34(3): 647-654.

Shrieve DC, Loeffler JS. Advances in radiation therapy for brain tumors. *Neurologic Clinics* 1995; 13(4): 773-793.

Sisterson J. (1997). *World wide charged particle patient totals, January 1997. Particles NewsLetter, Number 20.* [Website]. Available: <http://neurosurgery.mgh.harvard.edu/hcl/ptles.htm>, [July 1997].

Sperduto PW, Hall WA. Radiosurgery, cost-effectiveness, gold standards, the scientific method, cavalier cowboys, and the cost of hope. *International Journal of Radiation Oncology, Biology, Physics* 1996; 36(2): 511-513.

Weissman DE. Glucocorticoid treatment for brain metastases and epidural spinal cord compression: a review. *Journal of Clinical Oncology* 1988; 6(3): 543-551.