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Clinical and Economic Outcomes of Patients With Brain Metastases Based on Symptoms:

An Argument for Routine Brain Screening of Those Treated With Upfront Radiosurgery

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Abstract

BACKGROUND: Insurers have started to deny reimbursement for routine brain surveillance with magnetic resonance imaging (MRI) after stereotactic radiosurgery (SRS) for brain metastases in favor of symptom-prompted imaging. The authors investigated the clinical and economic impact of symptomatic versus asymptomatic metastases and related these findings to the use of routine brain surveillance.

METHODS: Between January 2000 and December 2010, 442 patients underwent upfront SRS for brain metastases. In total, 127 asymptomatic patients and 315 symptomatic patients were included. Medical records were used to determine the presenting symptoms, distant and local brain failure, retreatment, and need for hospital and rehabilitative care. Cost-of-care estimates were based on Medicare payment rates as of January 2013.

RESULTS: Symptomatic patients had an increased hazard for all-cause mortality (hazard ratio, 1.448) and were more likely to experience neurologic death (42% vs 20%; $P<.0001$). Relative to asymptomatic patients, symptomatic patients required more craniotomies (43% vs 5%; $P<.0001$), had more prolonged hospitalization (2 vs 0 days; $P<.0001$), were more likely to have Radiation Therapy Oncology Group grade 3 and 4 post-treatment symptoms (24% vs 5%; $P<.0001$), and required $11,957 more on average to manage per patient. Accounting for all-cause mortality rates and the probability of diagnosis at each follow-up period, the authors estimated that insurers would save an average $1326 per patient by covering routine surveillance MRI after SRS to detect asymptomatic metastases.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

CONCLUSIONS: Patients who presented with symptomatic brain metastases had worse clinical outcomes and cost more to manage than asymptomatic patients. The current findings argue that routine brain surveillance after radiosurgery has clinical benefits and reduces the cost of care.

Keywords

symptoms; brain metastases; stereotactic radiosurgery; surveillance magnetic resonance imaging; economics; cost saving

INTRODUCTION

Patients with brain metastases who undergo upfront stereotactic radiosurgery (SRS) without receiving whole-brain radiotherapy (WBRT) are at an increased risk for experiencing distant brain failure and local recurrence. A phase 3 trial in Japan reported a combined local and distant brain failure rate of 76% at 1 year after radiosurgery alone for patients who had from 1 to 4 brain metastases.[1] Given the high likelihood of recurrence and distant intracranial metastases, it has become standard of practice to use routine surveillance imaging after radiosurgical monotherapy for brain metastases. National Comprehensive Cancer Network (NCCN) guidelines for limited (1-3 lesions) and multiple (>3 lesions) intracranial metastases recommend follow-up with magnetic resonance imaging (MRI) every 3 months for 1 year and clinical follow-up thereafter.[2]

In recent years, some insurers have begun denying reimbursement for surveillance MRI in patients with previously treated brain metastases. These insurers have specified that, in this cohort, imaging should only be performed subsequent to the development of neurologic symptoms. It has been unclear whether the immediate savings incurred from reduced imaging surveillance leads to ultimate cost savings in the overall management of patients. More important, it has been unclear whether forgoing surveillance imaging adversely affects clinical outcomes.

We conducted the current retrospective, single-institution review of patients who received upfront SRS for brain metastases to determine differences in clinical and economic outcomes between asymptomatic and symptomatic patients at presentation. Using these outcomes, we designed a model to determine the costs and savings incurred from using post-SRS routine surveillance imaging on a theoretical cohort of patients. This novel design was predicated on the finding that surveillance brain imaging has been shown to increase the proportion of patients who present asymptomatically.[3-5] To the best of our knowledge, this is the only study to analyze the clinical outcomes and cost-effectiveness of surveillance brain imaging after SRS for brain metastases.

MATERIALS AND METHODS

Data Acquisition

This study was approved by the Wake Forest Institutional Review Board. Data were reviewed and collected from the electronic medical records at our institution on 442 patients who underwent upfront SRS for brain metastases between January 1, 2000 and December 31, 2010. Data gathered included pretreatment clinical characteristics, including age, sex,

histology, pretreatment symptoms, the date of diagnosis of brain metastases, and the receipt of craniotomy. Pretreatment symptom grade was based on the Radiation Oncology Group (RTOG) central nervous system (CNS) toxicity grading system. Recursive partitioning analysis (RPA) class was defined according to the RTOG analysis reported by Gaspar et al.[6] Patient characteristics are summarized in Table 1.

Patient Follow-Up and Salvage Therapy

Patients were monitored with serial MRIs every 3 months for the first year, every 4 months in the second year, every 6 months in the third and fourth years, and annually thereafter. Electronic medical records were used to determine whether patients required hospitalizations, rehabilitation and nursing placement, or salvage therapy for either CNS tumor recurrence or treatment-related sequelae. Patients who developed additional brain metastases after SRS generally underwent further SRS, whereas WBRT generally was reserved for salvage in patients who had either ≥4 total brain metastases over time or short-interval distant brain failure. Patients were considered to have experienced a neurologic death if they died in the setting of stable systemic disease with progressive neurologic disease, in the setting of rapidly progressive systemic and neurologic disease, or if they experienced illness concurrently with severe neurologic dysfunction.[7]

Radiosurgical Technique

Before radiosurgery, each patient underwent a high-resolution, contrast-enhanced stereotactic MRI study of the brain. Treatment planning was performed using the Gamma-Plan treatment planning system (Elekta AB, Stockholm, Sweden). SRS was performed using either the Leksell model B (years 2000-2004), model C (years 2004-2009), or Perfexion (years 2009-2010) Gamma Knife unit (Elekta AB). The median dose delivered to the tumor margin was 19 Gray (Gy) (range, 9-24 Gy), and this was generally prescribed to the 50% isodose line based on the size and volume of each metastasis following the guidelines published by Shaw et al for single-fraction radiosurgical treatment of brain metastases.[8]

Statistical Analysis

Descriptive characteristics were summarized using either the mean and standard deviation or the median and interquartile range, depending on the normality of the data. Continuous variables were compared across groups using the *t*-test, whereas frequency was tested using either the chi-square test or the Fisher exact test. Time to event data were summarized using Kaplan-Meier plots, and the log-rank test was used to determine significance between strata. Primary endpoints included the time to development of new metastases, the incidence of neurologic death, and all-cause mortality. The length of time to recurrence of the original lesion was calculated from the date of SRS to the date of radiographic evidence of recurrence demonstrated by MRI. The results were stratified for symptomatic tumors versus asymptomatic tumors. A univariate analysis of overall survival was completed to estimate the effect of each covariate on the hazard for all-cause mortality. Covariates that met a threshold significance level of $P<.2$ were considered for the multivariate Cox proportional hazards model. Each covariate was tested for proportional hazards assumptions and potential interactions between covariates. All analyses were done using the SAS statistical software package (version 9.2; SAS Institute Inc., Cary, NC).

Estimation of Costs of Care

Costs of care were estimated based on the Medicare payment rate in North Carolina as of January 2013 for craniotomy, hospitalization related to brain metastasis, WBRT, and SRS. Estimates were $24,000 for craniotomy, $21,000 for SRS, $4600 for WBRT, and $300 per hospitalization day. The estimated cost per day for an inpatient stay at a rehabilitation or subacute nursing facility was $150. We computed total costs of care for each patient based on actual services rendered and compared mean differences between the symptomatic and asymptomatic cohorts.

Estimation of the Cost-Effectiveness of Surveillance Magnetic Resonance Imaging

We estimated the cost-effectiveness of routine surveillance MRIs for a hypothetical panel of 5000 patients with characteristics similar to those of our patient cohort. We chose 5000 to represent a rough estimate of the number of individuals with brain metastases covered by any single major insurer; this estimate was approximately 1-25th of the 141,553 individuals in the United States estimated to have brain metastases as of January 1, 2010.[9] By using the all-cause mortality rate for patients in the current cohort, we used Kaplan-Meier curves to estimate how many asymptomatic patients would be expected to survive to the beginning of each follow-up period (months 3, 6, 9, 12, 16, 20, 24, 30, 36, and 42 after initial diagnosis) and, thus, would undergo reimaging. Then, we used the rate of distant failure from our patient series to estimate the number of patients expected to develop brain metastases during each screening interval. On the basis of the reported detection rate of MRI surveillance for asymptomatic metastases after SRS by Lutterbach et al, we assumed that 62% of patients who experienced distant brain failure would be detected with surveillance MRI.[3] We assumed a $662 cost per MRI based on the Medicare payment rate in North Carolina (Healthcare Common Procedure Coding System code 70553), with variations in the sensitivity analyses, to estimate the total cost of routine surveillance MRIs. We compared the result with the estimated cost difference from the early detection of asymptomatic tumors versus symptomatic tumors to evaluate the cost-effectiveness of screening MRIs.

RESULTS

Preradiosurgery Characteristics

Patient characteristics are included in Table 1. Patients who had symptomatic brain metastases received a lesser median marginal dose (18 Gy vs 20 Gy; $P<.0001$), suggesting that patients with symptomatic metastases had larger tumors at the time of diagnosis. The odds of having a symptomatic brain metastases with a median marginal dose <20 Gy was 5.05 (95% confidence interval [CI], 3.15-8.09) relative to patients who received a median marginal dose ≥20 Gy.

Survival

Kaplan-Meier curves for survival and time to distant failure data are provided in Figure 1. In total, 389 patients (88%) had died at the time of the current analysis. The median overall survival was 9.9 months for asymptomatic patients and 8.1 months for symptomatic patients

($P = .3825$). The time to distant failure was 9.4 months for asymptomatic patients and 7.7 months for symptomatic patients ($P = .8037$).

Symptoms Before and After Radiosurgery

Presenting and post-SRS symptoms are listed according to RTOG CNS toxicity grade in Table 2. Of the symptomatic patients, 63% had grade 1 or 2 RTOG CNS toxicity, whereas 37% had grade 3 or 4 RTOG CNS toxicity. Sixty-four percent of patients who had widespread extracranial disease presented with symptomatic metastases, whereas 91% of patients who had no evidence of extracranial disease presented with symptoms ($P<.0001$). Seventy-eight percent of patients who had stable disease presented with symptoms, whereas 62% of patients who had progressive disease presented with symptoms ($P<.0001$).

Chi-square contingency analysis was used to compare symptoms in symptomatic and asymptomatic populations. After initial SRS, 80% of initially asymptomatic patients and 41% of initially symptomatic patients were asymptomatic ($P<.0001$). Sixty-two percent of patients who presented with symptoms had a reduction in the severity of their symptoms (defined as a decrease in RTOG toxicity grade) after SRS, 16% had more severe symptoms (defined as an increase in RTOG toxicity grade) after SRS, and 21% had no change in the severity of their symptoms. Patients with symptomatic metastases were more likely to have RTOG grade 3 and 4 post-treatment symptoms (24% vs 5%; $P<.0001$).

Neurologic Death and Use of Salvage Brain Treatment

Neurologic death, salvage therapies, and hospital/rehabilitation time are listed in Table 3. Forty-two percent of patients who had symptomatic metastases experienced neurologic death compared with 20% of patients who had asymptomatic metastases ($P<.0001$). Forty-three percent of symptomatic patients underwent at least 1 craniotomy, whereas only 5% of asymptomatic patients underwent at least 1 craniotomy ($P<.0001$). Twelve initially symptomatic patients underwent repeat craniotomy for salvage and/or management of tumor/treatment sequelae, whereas only 1 initially asymptomatic patient would undergo subsequent craniotomy ($P = .1210$). There was no difference between groups in requiring salvage therapy with WBRT ($P = .2999$); however, the asymptomatic group more frequently underwent additional SRS (29.6% vs 21%; $P = .0406$).

Hospitalization and Rehabilitation Time

The median time spent in the hospital was 2 days for symptomatic patients and zero days for asymptomatic patients ($P<.0001$). The symptomatic group more commonly required inpatient rehabilitation or placement in a subacute facility ($P = .0177$).

Multivariate Analysis of All-Cause Mortality

Results from the multivariate analysis are displayed in Table 4. Symptomatic patients had an increased hazard for all-cause mortality (hazard ratio [HR], 1.448; 95% CI, 1.128-1.858) when correcting for all other disease-related factors. An increasing number of intracranial metastases at the time of diagnosis, oligometastatic disease relative to no evidence of disease, polymetastatic disease relative to no evidence of disease, and progressive disease relative to stable disease also were associated with an increased hazard for all-cause

mortality (HR, 1.136; 95% CI,1.066-1.210; HR, 1.524;95% CI, 1.126-2.063; HR, 1.633; 95% CI, 1.192-2.238; HR, 1.253; 95% CI, 0.973-1.613). Surgical intervention and repeat SRS were associated with a decreased hazard for all-cause mortality (HR, 0.609; 95% CI, 0.500-0.742; and HR, 0.491; 95% CI, 0.380-0.633, respectively), whereas WBRT was not.

Lifetime Cost Estimates of Interventions

The estimated costs of managing symptomatic and asymptomatic metastases were approximately $41,700 and $29,743, respectively, for a savings of approximately $11,957 per patient when a metastasis was treated asymptomatically. The dominant contributor to the higher costs of managing symptomatic metastases was neurosurgical intervention ($10,919 per patient). Partially offsetting these higher costs was the more frequent use of repeat radiosurgery in the asymptomatic population, which increased the cost of treatment in this cohort by $1506 per patient.

Estimating the Cost-Effectiveness of Routine Surveillance Magnetic Resonance Images

Table 5 compares the expected cost of routine screening MRIs with the expected cost savings from diagnosis of an asymptomatic (vs symptomatic) patient. We incorporated the probability that a patient would survive to each follow-up MRI, the probability of distant brain failure, and the probability that the metastasis would be detected asymptomatically for a hypothetical cohort of 5000 patients, as described above (see Materials and Methods). After 42 months, we estimated that the total cost of surveillance MRIs would be $11,403,374, versus a cost savings from early diagnosis of $18,035,279. Estimated net savings from surveillance MRIs were $6,640,905 (range, $18,035,279-$11,403,374), or $1326 per patient.

In sensitivity analyses, we observed that the net savings from surveillance MRIs persisted until the savings from early detection fell to $7560 (from $11,957 at baseline), the cost of surveillance MRIs rose to $1047 (from $662 at baseline), or the asymptomatic detection rate fell to 41% (from 62% at baseline). At these levels, the total cost of surveillance MRIs exactly equaled the cost savings from early diagnosis, for zero net savings. At more favorable levels (higher savings from early detection, lower cost of surveillance MRIs, or higher asymptomatic detection rate), the net savings from surveillance MRIs were positive.

DISCUSSION

Use of Surveillance Imaging to Detect Metastasis

The current scientific literature supports the finding that the use of MRI surveillance leads to an increased likelihood of detecting brain metastases before patients develop symptoms, which has enabled us to model a population followed with surveillance imaging with a population that presents asymptomatically. Lutterbach et al assessed patients who underwent SRS alone for brain metastasis with MRI surveillance at 2-month intervals for the first 6 months and at 3-month intervals thereafter.[3] Those authors reported that 62% of new metastases were diagnosed by imaging before the development of neurologic symptoms. Sheehan et al observed that patients who received treatment for ≥3 brain metastases were at significant risk of developing new brain metastases within 3 months. Thus, the investigators

recommended that this population undergo thin-slice MRI every 3 months, and they reported that follow-up MRI surveillance performed at 3-month intervals led to the detection of the vast majority of distant brain metastases before the development of symptoms.[4]

Clinical Disparities Between Symptomatic and Asymptomatic Metastases

Neurologic death and overall survival—Patients with asymptomatic metastases were less likely to experience neurologic death, despite a similar median overall survival. However, the presence of symptoms at the time of diagnosis indicated an increased hazard for all-cause mortality. The discrepancy between results from the univariate and multivariate analyses is likely because of the increased proportion of patients with widespread and progressive disease who presented with asymptomatic metastasis, whereas the vast majority of patients who had no evidence of disease presented symptomatically. Patients who presented with asymptomatic metastases were less likely to experience neurologic death, which we attribute in part to the smaller average size of tumors in the asymptomatic group, because these tumors were treated with a greater average marginal dose. Recent series of patients who had brain metastases from small cell lung cancer[10] and patients who had resected brain metastases have demonstrated that patients with larger tumors experienced a greater likelihood of neurologic death.[11] In a series from Poland, investigators prospectively determined that, in patients with HER2-positive breast cancers, early detection of occult intracranial metastases reduced the rate of neurologic death from 48% to 16% ($P = .009$) but did not improve overall survival.[12]

Symptoms after stereotactic radiosurgery—Patients who presented with asymptomatic metastasis also were less likely to experience symptoms after treatment. For patients who were initially asymptomatic but developed symptoms subsequent to treatment, those symptoms were likely to be less severe than the symptoms experienced by patients who were initially symptomatic (5 vs 24% grade 3-4 toxicity, respectively). It has been demonstrated that increasing lesion size is the dominant factor in predicting the development of post-SRS neurologic symptoms,[8,13] which explains how surveillance MRI would improve post-SRS symptom outcomes. Majhail et al prospectively assessed 79 patients who underwent SRS and observed that a maximum target dimension >25 mm and doses >20 Gy were associated with early (defined as within 3 months of radiosurgery) complications.[13] In the RTOG 90-05 trial, Shaw et al observed that patients who had SRS-treated tumors that measured between 21 mm and 40 mm were 7 to 16 times more likely to develop high-grade neurotoxicity compared with patients who had smaller tumors.[8]

Economic Impact of Surveillance

Multiple series have demonstrated that surveillance imaging of high-risk patients increases the likelihood of detecting metastases when they are small and, thus, before they become symptomatic.[3-5,8,13,14] Our series demonstrates that there are significant clinical and economic benefits to the early detection of brain metastasis before patients become symptomatic. To date, no studies have assessed the cost-effectiveness of MRI surveillance of the brain after SRS for brain metastases. In fact, studies of the cost-effectiveness of brain imaging are rare in the scientific literature. Two prior studies analyzed the cost-effectiveness of brain surveillance, including 1 for patients with small cell lung cancer who were not

determined to have metastatic disease[15] and another for pediatric patients after resection of primary CNS tumors.[16] In the first study, the authors calculated that routine brain computed tomography would cost approximately $70,000 per quality-adjusted life year and recommended against its use on that basis. In the pediatric study, the authors compared a surveillance imaging protocol with computed tomography or MRI every 3 months for the first 2 years versus a symptom-prompted imaging protocol. They noted that there was no significant difference in cost between the 2 approaches ($788 symptom-based vs $739 standardized surveillance; $P = .236$), but an increased rate detecting asymptomatic recurrences was observed with routine imaging surveillance. Those investigators also reported that 88% of failures occurred in the first 21 months after treatment. A common theme in both of these studies is that, for imaging surveillance to be cost-effective, sufficient numbers of detectable events are required.

NCCN guidelines empirically recommend surveillance brain imaging every 3 months for the first year for limited metastases (n = 1-3) and multiple metastases (n>3) and clinical follow-up after 1 year.[2] Our analysis indicates that MRI surveillance for 42 months after treatment with SRS was cost saving. Although, per interval, surveillance after 16 months was not cost saving, the net expenditure per interval and cumulatively from 16 months to 42 months was small relative to the upfront savings in the first year. Thus, although the economic advantage of surveillance imaging may diminish after the first 16 months, the improvements in clinical outcomes from surveillance likely continue without a significant change in the overall cost savings over a 42-month period.

Our results indicate that there is a mean cost increase of $11,957 to manage a patient who presents with symptoms compared with a patient who presents asymptomatically. A large portion of this disparity can be attributed to the more frequent use of neurosurgical interventions in the symptomatic population (43% vs 5%). Symptomatic patients also were more likely to undergo multiple craniotomies and/or to require the management of tumor/treatment sequelae (12 vs 1; $P = .1210$), whereas asymptomatic patients were more likely to undergo repeat SRS. Mehta et al previously reported that SRS was significantly less expensive than surgical intervention per week of survival ($270 per week vs $524 per week).[17] Rutigliano and colleagues similarly compared SRS with resection of single brain metastasis and observed that, even if all surgical resection morbidity was excluded from the comparison, SRS was still more cost-effective.[18] Vuong et al performed a similar comparison from the perspective of Germany’s statutory health insurance system and observed that SRS was more cost-effective per year of life saved, which was attributed to a decreased cost for SRS versus resection and an increased in survival for those who underwent SRS (18.4 months vs 13.0 months).[19] In the current analysis, although patients who had asymptomatic metastases also underwent an increased number of additional SRS procedures, this slight difference was a small expense compared with the costs associated with surgery for symptomatic metastases.

There are assumptions and limitations associated with our cost-savings model. We used Medicare payment rates and a $662 price per MRI to estimate costs, which may differ from those faced by a private insurer. However, in sensitivity analyses, our results continued to hold when the price of an MRI rose by 58% (from $662 to $1047) and when the cost savings

from early detection fell by 37% (from $11,957 to $7560). Therefore, our results should be broadly applicable across reimbursement rates. Moreover, our sensitivity analyses varied only 1 parameter at a time. More realistically, if the price of an MRI were to increase, then the cost savings from early detection probably also would be higher because of increases in other associated costs of care, suggesting that cost savings from surveillance MRIs likely will persist even at prices greater than $1047.

In addition, we assumed that the presence or absence of symptoms at presentation would be correlated with symptoms and outcomes in the post-SRS setting. However, it is possible that patients who have disease detected because of a symptomatic presentation in the upfront setting may have more aggressive disease than those who survive long enough to have distant brain failure. Unfortunately, the only way to mitigate such a confounding effect is through the use of a prospective study. Finally, the use of WBRT for salvage after distant brain failure was an endpoint in our study. However, WBRT can be used concurrently with upfront radiosurgery to reduce the probability of distant brain failure,[1] which may reduce the clinical utility of MRI surveillance in the first year, may decrease the cost savings associated with surveillance, but also may limit salvage options if further metastases are detected.

This study employs a novel model in which a retrospectively determined population of asymptomatic patients that presents with brain metastases is used as a surrogate population for a prospective cohort of patients under routine MRI surveillance. This is predicated on the finding that patients who receive imaging surveillance are more likely to present asymptomatically.[3-5,8,13,14] In 1 analysis, routine brain surveillance led to the detection of brain metastases in 62% of patients before they developed symptoms. Although far from ideal, this finding is encouraging considering that, in our study, only 10 of 110 patients (9%) who had no evidence of extracranial disease at the time of diagnosis were asymptomatic. A prospective comparison of a population receiving MRI surveillance versus a population receiving symptom-prompted imaging may be warranted to further delineate the clinical benefit and cost-effectiveness of MRI surveillance in patients who undergo SRS for brain metastasis.

Conclusion

We observed that the presence of symptoms at the time of the diagnosis of brain metastases was associated with increased rates of neurosurgical interventions, longer hospital stays, more inpatient rehabilitation, a greater risk of chronic symptoms and neurologic death, and an increased risk for death from all causes. In our model, surveillance brain imaging after radiosurgery would increase the likelihood of detecting brain metastases before the onset of symptoms and, by our estimation, would save insurers an average of $1326 per patient.

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REFERENCES

1. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA. 2006;295:2483–2491. [PubMed: 16757720]
2. National Comprehensive Cancer Network. Central Nervous System Cancers. Version 2. 2013. Available at: http://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed June 30, 2013.
3. Lutterbach J, Cyron D, Henne K, Ostertag CB. Radiosurgery followed by planned observation in patients with 1 to 3 brain metastases. Neurosurgery. 2008;62:776–784.
4. Sheehan JP, Yen CP, Nguyen J, Rainey JA, Dassoulas K, Schlesinger DJ. Timing and risk factors for new brain metastasis formation in patients initially treated only with Gamma Knife surgery. J Neurosurg. 2011;114:763–768. [PubMed: 20225924]
5. Korones DN, Butterfield R, Meyers SP, Constine LS. The role of surveillance magnetic resonance imaging (MRI) scanning in detecting recurrent brain tumors in asymptomatic children. J Neurooncol. 2001;53:33–38. [PubMed: 11678428]
6. Gaspar LE, Scott C, Murray K, Curran W. Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. Int J Radiat Oncol Biol Phys. 2000;47:1001–1006. [PubMed: 10863071]
7. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA. 1998;280:1485–1489. [PubMed: 9809728]
8. Shaw E, Scott C, Souhami L, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. Int J Radiat Oncol Biol Phys. 2000;47:291–298. [PubMed: 10802351]
9. Howlader N, Noone AM, Krapcho M, et al. eds. SEER Cancer Statistics Review, 1975-2010 [based on November 2012 SEER data submission, posted to the SEER web site 2013.]. Bethesda, MD: National Cancer Institute; 2013.
10. Harris S, Chan MD, Lovato JF, et al. Gamma knife stereotactic radiosurgery as salvage therapy after failure of whole-brain radiotherapy in patients with small-cell lung cancer [serial online]. Int J Radiat Oncol Biol Phys. 2012;83:e53–e59. [PubMed: 22342297]
11. Jensen CA, Chan MD, McCoy TP, et al. Cavity-directed radiosurgery as adjuvant therapy after resection of a brain metastasis. J Neurosurg. 2011;114:1585–1591. [PubMed: 21166567]
12. Niwinska A, Tacikowska M, Murawska M. The effect of early detection of occult brain metastases in HER2-positive breast cancer patients on survival and cause of death. Int J Radiat Oncol Biol Phys. 2010;77:1134–1139. [PubMed: 19932944]
13. Majhail NS, Chander S, Metha VS, Julka PK, Ganesh T, Rath GK. Factors influencing early complications following Gamma Knife radiosurgery. A prospective study. Stereotact Funct Neurosurg. 2001; 76:36–46. [PubMed: 12007277]
14. Elliott RE, Rush S, Morsi A, et al. Neurological complications and symptom resolution following Gamma Knife surgery for brain metastases 2 cm or smaller in relation to eloquent cortices. J Neurosurg. 2010;113:53–64.
15. Colice GL, Birkmeyer JD, Black WC, Littenberg B, Silvestri G. Cost-effectiveness of head CT in patients with lung cancer without clinical evidence of metastases. Chest. 1995;108:1264–1271. [PubMed: 7587427]
16. Kovanlikaya A, Karabay N, Cakmakci H, Uysal K, Olgun N, Ergor G. Surveillance imaging and cost effectivity in pediatric brain tumors. Eur J Radiol. 2003;47:188–192. [PubMed: 12927661]
17. Mehta M, Noyes W, Craig B, et al. A cost effectiveness and cost-utility analysis of radiosurgery vs resection for single-brain metastases. Int J Radiat Oncol Biol Phys. 1997;39:445–454. [PubMed: 9308949]
18. Rutigliano MH, Lunsford LD, Kondziolka D, Strauss MJ, Khanna V, Green M. The cost-effectiveness of stereotactic radiosurgery versus surgical resection in the treatment of solitary metastatic brain tumors. Neurosurgery. 1995;37:445–453. [PubMed: 7501109]
19. Vuong DA, Rades D, van Eck ATC, Horstmann GA, Busse R. Comparing the cost-effectiveness of 2 brain metastasis treatment modalities from a payer's perspective: stereotactic radiosurgery versus surgical resection. Clin Neurol Neurosurg. 2013;115:276–284. [PubMed: 22705458]

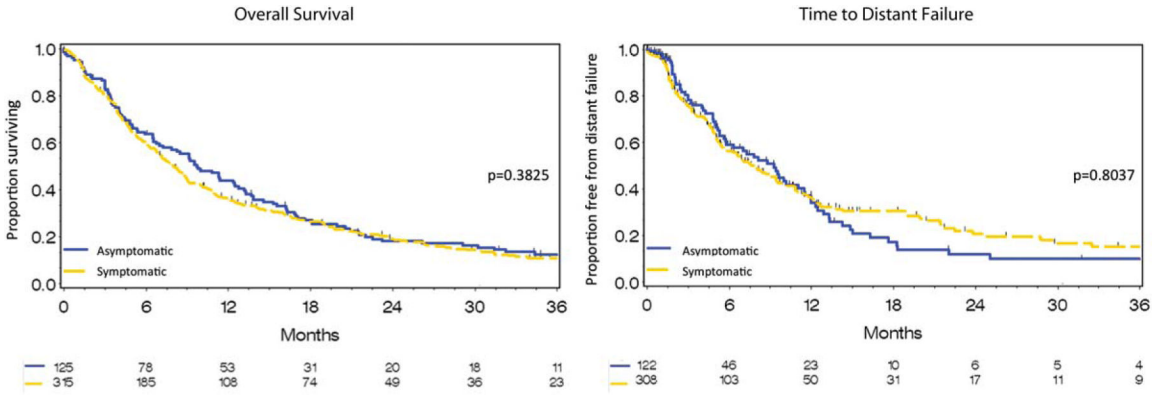

Figure 1.

(*Left*) Overall survival and (*Right*) the time to distant failure are illustrated based on symptoms in patients with brain metastases.

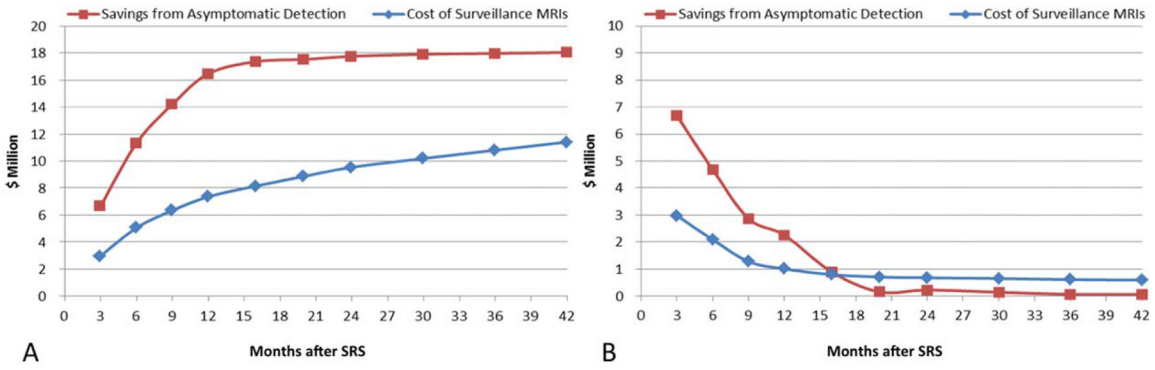

Figure 2.

Cumulative and interval costs and savings from surveillance magnetic resonance imaging (MRI) are illustrated. (A) Cumulative savings and cumulative costs of surveillance MRI are illustrated for a hypothetical cohort of 5000 patients who were under surveillance for months. (B) The interval costs and interval savings for the same cohort are illustrated. Intervals were every 3 months for the first year, then every 4 months for the second year, and every 6 months for the last 18 months. At 16 months, the interval savings from early detection were lower than the cost of surveillance (intersection of curves in B), but the net cost from that time to the completion of the surveillance regimen at 42 months was small relative to the cumulative savings. At 42 months, surveillance with MRI was still cumulatively cost-saving. SRS indicates stereotactic radiosurgery.

TABLE 1.

Baseline Characteristics

Characteristic	No. of Patients (%)		*P*
	Asymptomatic n = 127	Symptomatic n = 315	
Age at diagnosis: Median [range], y	63 [49–69]	61 [51–69]	.7522
Sex			
Women	62 (48.8)	148 (47)	.7813
Men	65 (51.2)	167 (53)	
Primary site			
Lung	64 (50.4)	166 (52.7)	.1108
Breast	24 (18.9)	55 (17.5)	
Melanoma	31 (24.4)	54 (17.1)	
Renal cell	8 (6.3)	40 (12.7)	
Histology			
Adenocarcinoma	40 (45)	97 (43.9)	.2391
Squamous cell	14 (15.7)	29 (13.1)	
Adenosquamous	11 (12.4)	38 (17.2)	
Large cell NE	0 (0)	2 (0.9)	
Her2-negative	6 (6.7)	23 (10.4)	
Her2-positive	13 (14.6)	25 (11.3)	
Breast other	5 (5.6)	7 (3.2)	
No. of metastases			
1	58 (45.7)	169 (53.7)	.2141
2	36 (28.3)	74 (23.5)	
3	21 (16.5)	35 (11.1)	
≥4	12 (9.4)	37 (11.7)	
Extent of disease[a]			
None	10 (7.9)	100 (31.7)	<.0001
Oligometastatic	48 (37.8)	95 (30.2)	
Widespread	54 (42.5)	96 (30.5)	
Unknown	15 (11.8)	24 (7.6)	
Disease status			
Stable	50 (39.4)	177 (56.2)	<.0001
Progressive	60 (47.2)	99 (31.4)	
Unknown	17 (13.4)	39 (12.4)	
RPA class			
1	1 (0.8)	24 (7.7)	.0050
2	117 (93.6)	258 (84.6)	
3	7 (5.6)	23 (7.5)	
Marginal dose: Median [IQR], Gy	20 [20-22]	18 [16.5–20]	<.0001

Abbreviations: Gy, grays; Her2, human epidermal growth factor receptor 2; IQR, interquartile range; NE, neuroendocrine; RPA, recursive partitioning analysis.

[a] Extent of disease was defined as oligometastatic (≤5 extracranial metastases) or widespread (≥5 extracranial metastases).

TABLE 2.

Symptoms From Brain Metastases

RTOG Neurotoxicity Grade[a]	No. of Patients (%)		*P*
	Asymptomatic	Symptomatic	
At presentation			<.0001
0	127 (100)	-	
1	-	52 (16.5)	
2	-	145 (46.0)	
3	-	88 (27.9)	
4	-	30 (9.5)	
After SRS	-		<.0001
0	84 (80.0)	99 (40.7)	
1	10 (9.5)	41 (16.9)	
2	6 (5.7)	45 (18.5)	
3	1 (1.0)	31 (12.8)	
4	4 (3.8)	27 (11.1)	

Abbreviations: SRS, stereotactic radiosurgery; RTOG, Radiation Therapy Oncology Group.

[a]A change in symptoms was defined as a shift in RTOG neurotoxicity by 1 or more grade.

TABLE 3.

Neurologic Death and Interventions

Death or Intervention	No. of Patients (%)		*P*
	Asymptomatic	Symptomatic	
Neurologic death			<.0001
No	78 (80.4)	145 (58.0)	
Yes	19 (19.6)	105 (42.0)	
Surgery			<.0001
None	121 (95.3)	177 (57.1)	
Craniotomy	6 (4.7)	133 (42.9)	
Repeat SRS			.0406
No	88 (70.4)	245 (79.0)	
Yes	37 (29.6)	65 (21.0)	
Salvage craniotomy			.1210
No	126 (99.2)	303 (96.2)	
Yes	1 (0.8)	12 (3.8)	
Salvage WBRT			.2999
No	97 (76.4)	226 (71.7)	
Yes	30 (23.6)	89 (28.3)	
Hospital time: Median [range], d	0 [0-17]	2 [0-34]	<.0001
Rehabilitation time: Median [range], d	0 [0-6]	0 [0-30]	.0177

Abbreviations: SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy.

TABLE 4.

Multivariate Cox Proportional Hazards Model for Overall Survival

Covariate	HR	95% CI	*P*
Age, y	1.010	1.002-1.019	.0203
Sex: Women vs men	0.852	0.690-1.054	.1398
No. of intracranial metastases	1.136	1.066-1.210	<.0001
Oligometastasis vs none	1.524	1.126-2.063	.0064
Extensive metastasis vs none	1.633	1.192-2.238	.0023
Unknown vs none	1.236	0.778-1.965	.3690
Systemic disease status			
Progressive vs stable	1.253	0.973-1.613	.0800
Unknown vs stable	0.732	0.501-1.070	.1069
Symptoms: Yes vs no	1.448	1.128-1.858	.0036
Surgery: Yes vs no	0.609	0.500-0.742	<.0001
WBRT: Yes vs no	0.884	0.697-1.121	.3104
Second SRS: Yes vs no	0.491	0.380-0.633	<.0001

Abbreviations: CI, confidence interval; HR, hazard ratio; SRS, stereotactic radiotherapy; y, year; WBRT, whole-brain radiotherapy.

TABLE 5.

Cost Savings From Routine Surveillance for 5000 Patients[a,b]

Months After SRS	All-Cause Survival/fDBF	No. of Patients Screened/Diagnosed	Cost to Screen, $	Savings from Early Detection, $	Net Savings per Interval, $
0	1.0				
3	0.9/0.8	4500/558	2,979,000	6,672,006	3,693,006
6	0.7/0.6	3154/391	2,087683	4,675,742	2,588,059
9	0.4/0.4	1934/240	1,280,167	2,867,165	1,586,998
12	0.3/0.2	1525/189	1,009,284	2,260,473	1,251,189
16	0.2/0.1	1202/75	795,719	891,078	95,359
20	0.15/0.08	1071/13	709,066	158,808	(550,258)
24	0.12/0.05	1026/19	679,265	228,200	(451,065)
30	0.1/0.03	987/12	653,298	146,318	(506,980)
36	0.05/0.02	926/6	612,937	68,639	(544,298)
42	0.03/0.01	902/6	596,954	66,849	(530,105)
		Total	11,403,374	18,035,279	6,640,905
		Per person	2281	3607	1326

Abbreviations: fDBF, proportion of patients without distant brain failure; SRS, stereotactic radiosurgery.

[a]This table represents the cost savings from magnetic resonance imaging (MRI) surveillance in a model of 5000 patients, which was roughly estimated as the population with brain metastases for a single insurance provider. Savings from early detection are representative of the gross difference in cost between managing asymptomatic versus symptomatic metastases and do not include the cost of screening. A sample calculation is described below.

[b]*Sample calculation:* At the start of month 0, 5000 patients are alive (all-cause survival = 1.0). Based on our Kaplan-Meier curve of the asymptomatic population, all-cause survival at the start of month 3 (the first screening interval) is 0.9, indicating that 500 of 5000 patients are now dead and that 4500 of 5000 patients are able to be screened. The cost to screen is determined by the number of patients screened times the cost of the MRI (4500 × $662 = $2,979,000). Based on the time to distant brain failure, we estimate that 900 of 4500 will develop metastasis within the first interval and that 62% of patients with brain metastasis will be detected asymptomatically by routine surveillance[3] (900 × 0.62 = 558) (see Lutterbach et al[3]). Savings from early detection is determined by the number of patients detected asymptomatically × $11,957, which is the difference in cost between managing a patient who was diagnosed with MRI (asymptomatic) versus a patient who presented with symptoms. Net savings is the difference between the cost to screen and the savings from early detection.