Detection of brain micrometastases by high-resolution stereotactic magnetic resonance imaging and its impact on the timing of and risk for distant recurrences

Clinical article

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Objective. The aim of this study was to assess the order of micrometastases that can be detected with high-resolution MR imaging at the time of Gamma Knife surgery (GKS), and to estimate the impact this has on the time until and incidence of distant recurrences.

Methods. A consecutive series of 835 patients with brain metastases treated with GKS in a 7-year period, excluding patients in whom earlier brain metastases were treated with other modalities, were retrospectively analyzed. In all patients GKS was based on high Gd–dose (0.3 mmol/kg), high-resolution stereotactic MR imaging. These images were compared with the standard pretreatment MR images, and the difference in number of metastases found was analyzed. The distant recurrence rate following GKS was compared with that found in a prospective randomized study (Aoyama et al.) comparing radiosurgery to radiosurgery plus prophylactic whole-brain radiation therapy.

Results. New tumors were diagnosed in 40% (95% CI 36%–43%) of all patients as well as in the majority of patients with multiple lesions found on the diagnostic scan. The more tumors there were on the diagnostic scan, the higher the likelihood of detecting additional lesions with high-resolution imaging. It was calculated that approximately 50% of the micrometastases present at the time of GKS could be diagnosed with high-resolution imaging, which decreased the incidence of and delayed the time for the development of distant recurrences.

Conclusions. Additional brain metastases can be diagnosed in 40% of patients by using high-resolution imaging. Thus, radiosurgical treatments based on high-resolution stereotactic MR imaging decrease the incidence of and lengthen the time to distant recurrences. (DOI: 10.3171/2011.4.JNS101832)

Key Words • radiosurgery • whole-brain radiation therapy • brain metastases • high-resolution magnetic resonance imaging • oncology

Abbreviations used in this paper: GKS = Gamma Knife surgery; RS = radiosurgery; WBRT = whole-brain radiation therapy.

GAMMA Knife surgery has become more and more frequently used in the management of cerebral metastases. Multiple institutions have reported a consistently high local tumor control rate of 80%–90% following GKS.⁵,⁷,¹⁰–¹³,¹⁷ Thus, GKS is an efficient and well-documented management option for patients with brain metastases. In addition, prospective randomized studies¹⁶ have shown a prolonged survival time for patients with single brain metastases treated with RS plus WBRT compared with WBRT alone.

In contrast to the high acceptance of GKS for visible brain metastases, there is no generally accepted policy on how to manage the risk for distant recurrences (new lesions developing distant from earlier tumors) following GKS. Historically, the risk for distant recurrences was used as an argument against GKS. The assumption was, especially for patients with multiple brain metastases, that micrometastases were frequent and posed a significant threat to the patient, and thus, WBRT was advocated. These micrometastases were left untreated if GKS was used as the only treatment modality, and thus, the recommendation was WBRT alone for multiple lesions and a combination of WBRT and GKS for single lesions.

A prospective randomized study comparing patients treated with either RS alone or RS plus WBRT showed that the number of distant recurrences is higher when WBRT is omitted.² This has been used as an argument to recommend prophylactic WBRT after RS. The successful use of prophylactic WBRT in patients with small cell lung cancer is another argument for using the same strategy for patients with other primary tumors. Studies of patients with small cell lung cancer have shown prolonged survival⁶ or a decreased risk for developing brain metastases following WBRT⁸ as compared with no treatment.

Andrews et al.¹ found a 71% local tumor control rate of 1 year after WBRT. A fundamental radiobiological principle states that the likelihood of local tumor control
following radiotherapy decreases with increasing numbers of tumor cells. It is therefore reasonable to assume that the likelihood of controlling micrometastases by WBRT is high. It is equally reasonable to assume that the control rate of these lesions will be at least as high following GKS of the micrometastases that can be visualized at the time of GKS. In our institution we have made an effort to visualize as many micrometastases as possible by routinely using high Gd–dose, high-resolution MR imaging. The philosophy has been to treat as many micrometastases as possible at the time of GKS rather than use prophylactic WBRT to control them. It is reasonable, however, to assume that a number of micrometastases are being left untreated when omitting prophylactic WBRT. We therefore tried to assess the percentage of micrometastases that can be detected by high-resolution imaging, and thereby treated, by comparing our data to those from a prospective randomized study.2

**Methods**

**Patient Population**

Data from all 1045 brain metastases in patients treated with GKS in St. Elizabeth Ziekenhuis, Tilburg, the Netherlands between June 1, 2002, and July 1, 2009, were prospectively collected. Excluded from the study were patients in whom the treatment was preceded by a diagnostic MR imaging study showing more than 8 brain metastases (2 patients), individuals who received WBRT in conjunction to GKS (3 patients), those in whom no follow-up information was available (12 patients), and those who had undergone at least one earlier treatment for brain metastases (193 patients). Thus, a total of 835 patients were eligible for and were included in the study.

**Patient Characteristics**

The age of the patients at GKS was between 24 and 92 years (mean and median 62 years). There were 427 (51%) male and 408 (49%) female patients. The primary tumor was known in 780 patients (93%). Of these patients, lung cancer was the primary tumor in 466 (60%), gastrointestinal in 84 (11%), breast cancer in 81 (10%), renal cell carcinoma in 75 (10%), malignant melanoma in 43 (6%), and other primary tumors in 31 (4%) of the patients. Thirteen percent of the patients were alive at the closing of the study.

All patients underwent a conventional MR imaging examination no more than 1 month prior to GKS, and all patients were recommended to undergo follow-up MR imaging examinations every 3 months after GKS, as long as it was considered to be clinically meaningful. Follow-up imaging was available in 505 (91%) of the 556 patients who survived more than 4 months after GKS. The number of brain metastases found on the high-resolution imaging was documented and compared with the number of lesions found on the diagnostic scan. The difference in number of lesions between the studies was related to the number of metastases on the diagnostic scan, tumor pathological characteristics (lung vs non–lung cancer), sex, age of the patient, and primary tumor control.

To assess the fraction of micrometastases that could be detected by high-resolution imaging, we hypothesized that all micrometastases are controlled by prophylactic WBRT. If so, the maximum difference between the number of distant recurrences following RS alone on the one hand and following RS plus WBRT on the other hand represents the incidence of micrometastases. The necessary data for this comparison were extracted from Fig. 2 (the right graph in the figure on p. 2486) in the study by Aoyama et al.2 (hereafter referred to as the “prospective study”).

Data from the prospective study were compared with the incidence of and time for distant recurrences in our patient population. The time for an intracranial distant recurrence to occur was defined as the time between the date of GKS and the date of the first imaging session in which a new lesion could be detected. For the other patients, the time at risk to develop distant recurrences was defined as the time between the date of GKS and the date of the last clinical or radiological information. Neither local recurrences nor intracranial but extracerebral tumor activity were within the scope of this study, and thus were not recorded. As a result, freedom from distant recurrences did not necessarily equal intracranial tumor control.

**Statistical Analysis**

For statistical analysis, the Kaplan-Meier survival statistics was used to analyze survival. The Mann-Whitney U-test was used to compare nominal and continuous data. The Fisher exact test was used for nominal data. A difference was considered to be statistically significant when p < 0.05.

**Results**

**Detection of Additional Lesions and Number of Brain Metastases**

The relationship between number of brain metastases found on the diagnostic scan and the incidence of additional tumors detected on the high-resolution imaging is illustrated in Fig. 1. As seen, new lesions were found in the majority of patients with multiple metastases. New lesions were found significantly more frequently in patients with multiple metastases on the diagnostic scan, compared with patients with single ones (p < 0.0001). In addition, the more tumors on the diagnostic scan, the higher the likelihood of detecting new lesions (p < 0.0001). Finally, significantly more new lesions were found in patients with > 3 tumors on the diagnostic scan, compared with patients with 2–3 tumors (p = 0.009).

**Detection of Additional Lesions and Primary Tumor, Sex, and Age**

The likelihood of detecting additional lesions on high-resolution imaging was related to patient age, sex, primary tumor (lung vs non–lung tumor) as well as primary tumor control. None of the 4 parameters mentioned above was statistically significantly related to the likelihood of finding additional lesions on high-resolution imaging. The p values were 0.83 for primary tumor, 0.14 for sex, 0.99 for age, and 0.15 for primary tumor control.
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Fig. 1. Bar graph showing the relation between number of metastases (1, 2–3, or > 3) found on the diagnostic MR examination and percentage of patients in whom additional lesions were found on the high-resolution stereotactic MR images. The more lesions there are on the diagnostic scan, the higher the likelihood of detecting additional lesions on the high-resolution imaging.

Distant Recurrences Following GKS

Two hundred eighty-four patients (34%) developed distant recurrences. The time of freedom from distant recurrences in our patient population as well as data from the prospective study are illustrated in Fig. 2. It took a longer time to develop a distant recurrence after high-resolution imaging in our patient population, compared with after RS alone in the prospective study. However, the time for a distant recurrence to occur was longest when prophylactic WBRT was given following RS.

The Incidence of Micrometastases That Can be Diagnosed Using High-Resolution Imaging

Micrometastases are responsible for the difference between the incidence of distant recurrences in patients treated with RS alone compared with patients treated with RS and prophylactic WBRT. The incidence of micrometastases cannot be higher than the largest difference between the 2 groups, and is thus most accurately approximated when the difference between the 2 groups is largest. In the prospective study, 21% of patients given prophylactic WBRT had developed new lesions 9 months after RS, compared with 61% of the patients not receiving prophylactic WBRT—a 40% difference. Forty percent of the patients in our study population had developed new lesions 9 months after GKS. Thus, (40 – 21)*2.5 = 48% of the micrometastases could be diagnosed with high-resolution imaging.

Discussion

Benefit of Using High-Resolution MR Imaging

The observation that more brain metastases are diagnosed when higher doses of Gd are used in MR imaging has already been reported by many. The importance of high-resolution imaging in RS has been underlined by Engh et al. They found that at least 1 new metastasis was diagnosed in 29% of the patients harboring up to 5 brain metastases on the diagnostic scan when stereotactic MR imaging was performed using double doses of Gd. We found new tumors in 40% of our patients fulfilling the same criteria, a significant difference (p = 0.018). This occurred in spite of the fact that the patient population studied by Engh et al. had significantly more metastases on the diagnostic scan—an average of 2.2 lesions per patient, compared with 1.6 in our patient population (p < 0.0001). A plausible explanation could be that our patients had not been treated earlier for brain metastases.
metastases, compared with the fact that prior WBRT had been given in 58% and prior RS in 21% of the patients reported by Engh et al. Our use of a triple dose compared with the double Gd dose used by Engh et al., as well as other scanning parameters, may also have contributed to the difference in detecting new lesions.

Incidence of Micrometastases

One consequence of assuming that all micrometastases are controlled by prophylactic WBRT is that distant recurrences that develop following prophylactic WBRT must originate from tumor cells implanted in the brain at a later date than the date of RS (called new tumor cells in the following discussion). If so, we can estimate how many of the distant recurrences originate from micrometastases and how many from new tumor cells by analyzing the graph in the prospective study. Twenty-one percent of the patients who had received prophylactic WBRT did develop distant recurrences within 9 months after RS, compared with 61% of the patients treated with RS only. This means that one-third of the distant recurrences developed from new tumor cells, and the remaining two-thirds from micrometastases in the RS-treated patient population.

Forty percent of the patients in our study population had developed at least one distant recurrence within 9 months after GKS. Assuming the same incidence of distant recurrences developing from new tumor cells in our patient population as in the prospective study’s, 60% of the patients would have developed distant recurrences within 9 months should high-resolution imaging not have been used. However, only 20% of the patients would have developed distant recurrences within 9 months should prophylactic WBRT have been given after GKS.

Micrometastases Versus new Tumors

Little has been discussed about the important conceptual difference between the different sources for distant recurrences: micrometastases and new tumor cells. Micrometastases can be divided into 2 categories: one in which the lesions are possible to diagnose with high-resolution imaging, which is approximately half of the lesions, and one in which this is not possible. It is conceptually possible to prevent all micrometastases from developing into visible distant recurrences by using prophylactic WBRT. Another option to decrease the number of distant recurrences is to use high-resolution imaging and treat them with GKS on the day of RS. The other source of distant recurrences, new tumor cells, is more difficult to address. Any prophylactic treatment of these lesions must prevent new tumor cells from migrating into the brain. Prophylactic WBRT has no role in the management of these lesions, which can only be decreased by successful treatment of the primary lesion.

From a clinical perspective, the 3 different sources of distant recurrences should be managed differently. In reality this is not possible. To optimize the management of the risk for distant recurrences we need to know the relative importance and incidence of each of the sources for distant recurrences. The numbers of micrometastases is definite and will not increase, and most of them that develop into distant recurrences will do so within the first year after GKS. The more micrometastases that have developed into distant recurrences, the fewer that remain to develop into distant recurrences in the future, and micrometastases will no longer contribute to distant recurrences when all of them have grown to a size that can be diagnosed at imaging. The distant recurrences from new tumor cells can be expected to develop at a different pace. It will take a longer time for these tumors to develop, because the growth starts later than for micrometastases. However, this source is indefinite as long as the primary tumor is uncontrolled.

Clinical Consequences of Omitting Prophylactic WBRT

The calculations above imply that we leave micrometastases untreated in one-fifth of the patients following GKS, based on high-resolution imaging, omitting prophylactic WBRT. They also imply that micrometastases are the source of half of the distant recurrences within 9 months after GKS in our patient population. Thereafter, micrometastases become less important and new tumor cells more important as a source for distant recurrences. The number of individuals developing distant recurrences in our patient population was 284 (34%). Of these, 214 (75%) were diagnosed within 9 months, and 70 were diagnosed > 9 months after GKS. The majority of these patients were treated with repeated GKS (154), WBRT (57), or both (1). The primary tumor was progressing and deemed untreatable, and the distant recurrences were asymptomatic in most of the patients (58%) in whom the distant recurrences were not treated. Still, distant recurrences were left untreated in some patients due to a poor clinical and/or neurological condition, which might have been prevented had prophylactic WBRT been given. It is our conclusion that a small minority of patients may suffer from withdrawing prophylactic WBRT. In our opinion this is outweighed by eliminating the risk for neurocognitive impairments found following WBRT (taking into consideration that WBRT can be given at a later date in the vast majority of patients should a clinical indication develop).

Weaknesses of the Study

The present study is based on 2 critical assumptions—the first being that all micrometastases are controlled by WBRT. This might be an overestimation of the
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Conclusions

High-resolution stereotactic MR imaging detects new metastases in 40% of all cases and in the majority of patients with multiple brain metastases diagnosed at a routine MR imaging examination. Approximately 50% of the micrometastases that would have developed into distant recurrences should they have been left untreated can be diagnosed with high-resolution imaging and treated with GKS. The advantages outweigh the disadvantages when prophylactic WBRT is replaced with high-resolution imaging. Further studies are needed to define potential subgroups of patients in whom prophylactic WBRT is justified.

Disclosure

Dr. Karlsson is a consultant for Elekta Instruments. The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Acquisition of data: Karlsson, Hanssens, Beute. Analysis and interpretation of data: Karlsson, Yeo. Drafting the article: Karlsson, Hanssens, Yeo, Beute. Critically revising the article: Hanssens, Yeo, Chou, Beute. Statistical analysis: Karlsson.

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