Commentary

High-Dose MR in the Evaluation of Brain Metastases: Will Increased Detection Decrease Costs?

William C. Black, *Department of Radiology, Dartmouth-Hitchcock Medical Center, Lebanon, NH; and Center for the Evaluative Clinical Sciences, Department of Community and Family Medicine, Dartmouth Medical School, Hanover, NH*

Brain metastases occur in about 25% of patients (1) with cancer and are often diagnosed within the first year after the diagnosis of the primary tumor (2). The treatment of patients with brain metastases usually depends on whether they are solitary or multiple. Surgical resection has been shown to prolong survival by 6 months and improve the quality of life in patients with solitary brain metastases (3). However, surgery is not usually considered appropriate for patients with multiple brain metastases (3, 4). A phase III multicenter trial (5) in this issue demonstrates that the sensitivity of magnetic resonance (MR) in the detection of brain metastases can be increased by increasing the dose of contrast. In this trial comparing high-dose (0.3 mmol/kg) with standard-dose (0.1 mmol/kg) gadolinium, 50% more lesions were detected on the high-dose examinations.

Also in this issue, Mayr et al (6) demonstrate that high-dose MR can reduce the cost of patient treatment by eliminating surgery in certain patients with multiple brain metastases. In their study of 27 patients with suspected brain metastases, three craniotomies and two courses of boost radiation therapy in four patients were avoided because multiple brain metastases were detected on high-dose MR. The savings in treatment costs were much greater than the cost of additional contrast material in the high-dose group, $70 644 versus $9126, so that the total net savings were $61 518 and the net savings per patient, $2278. In addition, four patients were spared the morbidity associated with aggressive treatment for solitary brain metastases.

Should the standard dose of gadolinium in patients with suspected brain metastases be increased from 0.1 mmol/kg to 0.3 mmol/kg on the basis of this study? And if so, should similar savings be expected? A key to answering these questions is a consideration of the study conditions, particularly with regard to patient selection, and the effects of advances in diagnostic testing on the classification of disease (7, 8).

In the study by Mayr et al (6), increasing the dose of gadolinium increased the detection of brain metastases and caused a "migration" (7) of 10 patients into different categories of brain metastases (Table). With one exception, the migration was toward more advanced disease. Of the 6 patients diagnosed as having no brain metastases by the standard-dose examination, 2 were diagnosed with solitary brain metastases by the high-dose examination. Of the 10 patients diagnosed with solitary brain metastases (9) or resectable pair of metastases (1) by the standard-dose examination, 7 were diagnosed with multiple brain metastases by the high-dose examination. Of the 11 patients diagnosed with multiple brain metastases by the standard-dose examination, 1 was diagnosed with a solitary lesion by the high-dose examination.

Increasing the contrast dose will have different effects on cost depending on the case mix of patients. In the study by Mayr et al (6), more patients migrated out of than into the category of solitary brain metastases, and consequently there were substantial savings in treatment costs. However, three patients who migrated into this category did not incur the cost of surgery or boost radiation therapy because they had contraindications to treatment (two of them had terminal cancer, and one had severe congestive heart failure). In contrast, only one patient with contraindications to aggressive treatment migrated out of this category. Thus, had the patients in the study by Mayr et al (6) not had surgical contraindications, as would be expected outside

Address reprint requests to William C. Black, MD, Department of Radiology, Dartmouth-Hitchcock Medical Center, One Medical Center Dr, Lebanon, NH 03756.

Index terms: Brain neoplasms, magnetic resonance; Brain neoplasms, metastatic; Economics; Efficacy studies; Magnetic resonance, contrast enhancement; Magnetic resonance, in treatment planning; Commentaries

AJNR 15:1062–1064, Jun 1994 0195-6108/94/1506–1062

Effect of contrast dose on classification of brain metastases in the study by Mayr et al (6)

0.1 mmol/kg		Stage Migration	0.3 mmol/kg
None	6	4 None 2 Solitary	4 None
Solitary	10[a]	3 Solitary 7 Multiple	6 Solitary
Multiple	11	1 Solitary 10 Multiple	17 Multiple

[a] One patient had two brain metastases in close proximity amenable to resection to the standard-dose MR exam but additional lesions detected on the high-dose exam.

this investigational setting, the actual treatment savings would have been less. One aggressive treatment instead of three would have been avoided in the entire study group, for a total net savings of $14 796 (cost of treatment, $23 922, minus cost of additional contrast, $9126), or $548 per patient.

Nevertheless, if high-dose MR were reserved for those patients without surgical contraindications who would have solitary brain metastases diagnosed with standard-dose MR (assuming that these patients somehow could be identified), then substantial savings per patient could be expected. Applying the pattern of stage migration observed in the study by Mayr et al to this highly selected patient population, as many as 70% might avoid aggressive treatment for a savings of $16 407 per patient (70% of $23 922 minus $338). However, the savings would seem more modest from the population perspective, which is the appropriate perspective for health care policy and decision making under capitation. Considering that about 25% of patients with cancer have brain metastases and about 25% of these are resectable (on standard-dose MR) (3), the savings per patient with cancer undergoing MR would be $1025 (25% of 25% of $16 407).

However, it cannot be assumed that, as a group, patients found to have additional lesions by high-dose MR would benefit from *not* having aggressive treatment, perhaps directed toward the metastases posing the most immediate threat. It is probable that some of the patients in the randomized trial by Patchell et al (3) had additional metastases that would have been detected by high-dose MR, yet, as a group, the patients treated surgically lived 6 months longer. On the other hand, it cannot be assumed that, as a group, patients found to have additional lesions by high-dose MR *would* benefit from aggressive treatment, or that the radiologist and neurosurgeon could reliably distinguish those who would and would not benefit. Regardless of its real effect, however, aggressive treatment probably would appear to prolong survival on the basis of comparisons with historical controls—the only control groups available outside the setting of a prospective trial—because of the stage migration associated with the increased detection of brain metastases (7, 8). In fact, some neurosurgeons do advocate aggressive treatment for patients with multiple brain metastases (9), and three of the nine patients in the study by Mayr et al (6) who migrated out of the solitary brain metastases category had craniotomies anyway, one for diagnosis and two for severe symptoms. Whether similar patients would benefit, the savings from high-dose MR would be reduced.

Without repeating the trial of standard versus high-dose MR on different populations of patients with cancer, the effect of contrast dose on the cost of their management cannot be reliably predicted. However, suppose high-dose MR were used for patients who have cancer without neurologic signs or symptoms of brain metastases, as some have advocated recently for lung cancer (5). Fewer than 10% would be expected to have diagnoses of brain metastases on standard-dose MR, and these patients would be evenly divided between those with solitary and those with multiple lesions (1, 10). If only 10% of patients in the category of no metastases were to migrate to the category of solitary metastases with high-dose MR (the migration rate in the study by Mayr et al was 33%) (Table), more patients would migrate into than out of the category undergoing aggressive treatment, 10% versus 4%. Under these conditions, high-dose MR would increase the cost per patient by $1773 because of the increase in treatment, $1435, and in MR contrast material, $338. Furthermore, because the majority, about 75%, of patients with cancer have no neurologic signs or symptoms of brain metastases, the increased cost per patient undergoing MR also would be substantial, $1330.

Even if it does not reduce the cost of treating patients who have cancer without signs or symptoms of brain metastases, the increased contrast dose might be justified on the basis of the benefit it provides to them. However, it should not be assumed that the benefit from surgical resection of solitary brain metastases detected exclusively by high-dose MR would be the same as that

demonstrated in the earlier randomized trial by Patchell et al (3). In their study, the control group had a median survival of only 15 weeks, and 50% of the deaths were caused by brain metastases, indicating that they were advanced at the time of randomization (although their sizes were not actually reported). In contrast, most of the metastases detected exclusively by high-dose MR are less than 5 mm in diameter (11). Patients with solitary lesions of this size would be much more likely to die of other metastases that would subsequently develop or other diseases than the control group in the randomized trial and thus are less likely to benefit from surgical resection. Regardless of whether the increased contrast dose would actually lead to a prolongation of survival in these patients, it probably would appear to do so because of the stage migration. In addition, the morbidity and mortality from craniotomy in practice probably would be higher than what was reported in the randomized trial (12, 13). Thus, the resection of solitary brain metastases detected exclusively by high-dose MR might not be cost-effective, given that resection was only marginally cost-effective in the randomized trial, $45 600 per year of life saved (cost of craniotomy in the study by Mayr et al, $22 800, divided by 0.5-year prolongation of survival).

It is also unclear how increasing the dose of contrast would affect the confidence of the radiologist and the cost of diagnosis. In a study by Yuh et al (11), high-dose MR improved the radiologists' confidence in 21 of the 22 "possible" lesions (those about which the three radiologists could not agree) seen on standard-dose MR. However, at least 16 possible lesions were seen exclusively on high-dose MR. In fact, the total number of possible lesions was greater on the high-dose than standard-dose MR examinations, 26 versus 22, indicating a "migration" rather than elimination of uncertainty. The possible lesions seen exclusively on high-dose MR probably represent some combination of small brain metastases and enhancing vascular structures, such as small telangiectasias and venous angiomas (6), which may lead to more rather than fewer biopsies.

In conclusion, increasing the dose of MR contrast from 0.1 to 0.3 mmol/kg can lead to a reduction in the cost of treating a select group of patients with cancer, perhaps those with signs or symptoms of brain metastases. However, the standard dose of contrast for patients with cancer in general undergoing MR should not be increased with the expectation that their treatment costs would be reduced. In fact, it is possible that the increased detection of brain metastases would lead to an increase in treatment costs, primarily because of an increase in surgery. Whether this increased intervention actually would improve patients' outcomes could be determined only by well-designed prospective studies, and whether any improvement would be cost-effective would depend on the future availability of health care resources (14). These concerns pertain to other technical refinements that increase the detectability of brain metastases, such as magnetization transfer contrast (15), even if they decrease the cost of the MR examination per se.

Acknowledgment

I thank Dr Alexander C. Mamourian for reviewing the manuscript.

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