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AJNR Am J Neuroradiol 1994, 15 (6) 1053-1061
http://www.ajnr.org/content/15/6/1053

Cost-Effectiveness of High-Dose MR Contrast Studies in the Evaluation of Brain Metastases

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PURPOSE: To investigate the cost-effectiveness of high-dose MR contrast studies in the management of brain metastases. **METHODS:** During the phase III clinical trial of high-dose contrast studies (0.3 mmol/kg), 11 of 27 patients were judged by the reviewers to have potential treatment changes based on the additional information provided by the high-dose studies. We retrospectively evaluated how many of these 27 patients had actual treatment changes because of the results of the high-dose study. Using the fee schedule at our institution, the cost-effectiveness was analyzed based on the cost savings from treatment changes and the additional expense of implementing the high-dose studies. **RESULTS:** A total of 3 craniotomies ($22 800 each) and 2 aggressive courses of radiation therapy ($1122 each) were avoided in 4 patients because of the additional lesions detected by the high-dose studies. This resulted in a treatment cost savings of $70 644. The extra expense for implementing the high-dose study is $9126 for a single injection in all 27 patients, $9295 for 2 separate injections completed in 1 visit in the 11 patients, and $11 154 for 2 separate injections completed in 2 separate visits. The cost savings in management (diagnosis and treatment) therefore ranged from $59 490 to $61 518 for all patients and from $2203 to $2278 per patient. **CONCLUSION:** Based on our limited data, the high-dose study seems to impact positively on the cost-effectiveness in the management of brain metastases. However, because our study had limitations, our results need to be confirmed with a larger patient population and a more standardized treatment approach and fee schedule.

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

AJNR Am J Neuroradiol 15:1053–1061, Jun 1994

The early detection and correct diagnosis of the number and extent of brain metastases (none, one, or multiple) can be essential for the management of patients with cancer. Standard-dose (0.1 mmol/kg) contrast-enhanced magnetic resonance (MR) studies have been reported to be efficacious in the diagnosis of brain metastases (1–19). Recent reports have shown that high-dose (0.3 mmol/kg) contrast-enhanced MR studies of the brain further improve the detection of brain metastases, especially of small lesions (20–25). However, the high-dose contrast study is more expensive than the standard-dose study and further increases the cost of patient care. This fact raises many concerns in a time when cost containment is a major issue in health care reform.

The purpose of this study was to evaluate the cost-effectiveness of the more expensive high-dose study in the overall care of patients with known or clinically suspected brain metastases. This objective was achieved by: (*a*) reviewing the additional information provided by the high-dose contrast studies that was not available from the standard-dose studies; (*b*) assessing potential and actual treatment changes occurring as a result of

Received September 28, 1993; accepted pending revision December 20; revision received January 11, 1994.

This work was supported in part by grants to each participating institution from Squibb Diagnostics.

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AJNR 15:1053–1061, Jun 1994 0195-6108/94/1506–1053

the additional information provided by the high-dose study; (*c*) estimating cost savings from actual treatment changes related to the high-dose studies; and (*d*) investigating various techniques of implementing the high-dose studies and the associated cost related to these techniques.

Patients and Methods

Patient Population

The patient population for this cost-effectiveness analysis of high-dose MR studies was recruited from a phase III clinical trial of a nonionic gadolinium chelate (26). In the phase III protocol, a prospective comparison between high-dose (cumulative 0.3 mmol/kg) and standard-dose (0.1 mmol/kg) MR contrast studies was performed in 31 consecutive patients with radiologic (mostly computed tomography [CT]) evidence and/or clinical suggestion of symptomatic brain metastases. Four patients had previously been excluded from the analysis (2 for excessive motion artifact and 2 for an incomplete study related to machine malfunction). Twenty-seven patients were therefore analyzed in the phase III study.

Review Method: Actual versus Potential Treatment Changes

As part of the protocol of the phase III study, the high-dose and standard-dose MR examinations were independently and prospectively reviewed by a radiologist (W.T.C.Y.), a neurosurgeon (M.G.M.), and a radiation oncologist (N.A.M.). These reviewers were blinded to the contrast dose and clinical history and were not involved in the patient's care. They evaluated the lesion detection rate of the high-dose and standard-dose studies independently and assessed the potential benefit (*potential treatment changes*) that may have been provided by the high-dose studies because of additional information or lesions detected by the high-dose examinations. The results were tabulated, as reported previously (26).

For the purpose of the current cost-effectiveness analysis, the medical records and the MR findings of the 27 patients were retrospectively reviewed by the neurosurgeon (M.G.M.) and the radiation oncologist (N.A.M.) 22 to 26 months after the completion of the high-dose MR examinations during the phase III clinical trial. The reviewers investigated the actual courses of treatment chosen by the referring physicians and whether *actual treatment changes* were made as a result of the additional information provided by the high-dose studies. The following clinical information was recorded: the primary cancer, status of the systemic disease, overall medical condition at the time of the high-dose study, and treatment plan based on the findings of either the standard-dose or high-dose studies. Special attention was directed to those patients with potential treatment changes from the additional information provided by the high-dose studies as judged earlier during the phase III review (26).

Cost-Effectiveness Analysis

The expenses for patient care were calculated from fee schedules and billing records at our medical center. They included: (*a*) the cost of diagnostic procedures (high-dose and standard-dose studies); and (*b*) the cost of treatment of brain metastasis (surgery and radiation therapy). The cost-effectiveness analysis consisted of two components: the additional expense of the diagnostic procedures for a high-dose study and the cost savings or expenses from the actual treatment changes as a result of the high-dose-studies.

Cost of Diagnostic Procedures. The cost of diagnostic procedures at our institution includes the expenses of contrast material and scanning time (pulse sequences). Because the diagnostic procedure for all patients during the Food and Drug Administration clinical trial was free of charge, the cost was estimated by the current fee schedule at our institution. The standard charge for the contrast agent in our institution for the standard dose (0.1 mmol/kg) of gadopentetate dimeglumine or gadoteridol is the same. The charge for a higher dose (two or three times the standard dose) is proportional to the total amount of contrast material administered (0.1, 0.2, or 0.3 mmol/kg).

In a clinical setting, the charge for the high-dose study would vary with the technique of implementing the high-dose study: (*a*) *single injection* of high-dose contrast material (0.3 mmol/kg); (*b*) *two separate injections in one visit*; or (*c*) *two separate injections in two visits*. If the high-dose study were performed using a single-injection technique (0.3 mmol/kg), the additional expense compared with the cost for the standard-dose study (0.1 mmol/kg) would include only the extra dose of 0.2 mmol/kg of contrast material. There would be no additional cost for extra pulse sequences, because the imaging would be the same as in the standard-dose study. If the single-injection technique were applied, the high-dose study would have to be performed in *all* (n = 27) patients with clinical suspicion of brain metastasis.

The advantage of using two separate injections in the high-dose study is that the second injection (0.2 or 0.3 mmol/kg) is given only to those selected patients in whom additional information would be essential for therapy planning (negative study, solitary lesion, or equivocal lesion). Although there would be a cost savings of contrast material in limiting the second injection to selected patients, there would be an additional charge for extra pulse sequences for the selected patients. In the selected patients, an additional contrast dose of 0.2 mmol/kg is needed for the second injection if the high-dose study is completed immediately after review of the standard-dose study by an on-site radiologist (two separate injections in one visit). Otherwise, an additional dose of 0.3 mmol/kg is needed for the return visit for the high-dose study if an on-site radiologist is not available and/or the scheduling does not allow extra scanning time for an immediate second injection (two separate injections in two visits).

Cost of Treatment Procedures. Treatment costs for brain metastases included all the expenses related to surgery and

TABLE 1: Number of lesions and patients in standard- and high-dose contrast studies

0.1 mmol		0.3 mmol	
No. of Lesions	No. of Patients	No. of Lesions	No. of Patients
None	6	None	4
		Solitary	2
		Multiple	0
Solitary	9	None	0
		Solitary	2
		Multiple	7
Multiple	12	None	0
		Solitary	1
		Multiple	11

radiation therapy. Cost for surgical treatment included hospitalization, nursing, operating room, anesthesiology, medications (intravenous solutions, antibiotics, etc), and extra costs related to the treatment of complications (ie, extra days in the intensive care unit, antibiotics). Expenses for laboratory or radiologic tests and medications were included only if they were a direct result of the treatment of brain metastasis (ie, the craniotomy or its complications) and if these procedures or medications would not have been ordered otherwise. The cost for radiation therapy included the number of radiation treatments (10 or more), type of simulation procedures, and related radiation field changes.

Results

Treatment Approach

At our institution, a normal MR brain image warrants the surgical resection of the primary cancer in patients without other significant systemic disease. In patients with multiple brain metastases (two or more lesions), cranial surgery is usually not indicated, and the patient is typically treated with whole-brain irradiation (*short course of brain irradiation*). However, in a patient with multiple brain metastases without a diagnosis of cancer after extensive workup, craniotomy is considered justified to obtain a tissue diagnosis regardless of the number of brain metastases. In addition, craniotomy with tumor resection is offered to patients with brain metastases, if one of the lesions causes severe symptoms that may significantly affect the quality of life, or for large lesions in the posterior fossa that may cause obstructive hydrocephalus. Craniotomy is then followed by palliative whole-brain irradiation to 3000 cGy in 10 fractions in 2 weeks (short course of brain irradiation). In patients with a solitary brain metastasis and a controlled primary tumor, surgical resection is the treatment of choice, followed by a more comprehensive course of brain irradiation to 3000 cGy in 10 treatments and an additional dose (boost) of radiation therapy to the region of the resected tumor (*aggressive course of brain irradiation*). This treatment requires at least 3 more treatment days and more complex radiotherapy planning, simulation of treatment fields, and dosimetry.

MR Findings and Potential Treatment Changes

No complications were observed from the administration of the high-dose MR contrast studies. In the 27 patients studied, the high-dose MR studies confirmed the presence of multiple lesions in 11 of the 12 patients with multiple lesions demonstrated on the standard-dose studies (Table 1). In 1 of the 12 patients, the high-dose study resulted in a change in diagnosis from multiple lesions to a single lesion. The high-dose studies also resulted in a decrease in the number of patients with normal findings from 6 (22%) by the standard-dose (0.1 mmol/kg) study to 4 (15%) by the high-dose (0.3 mmol/kg) study, and in a decrease in the number of patients with single lesions from 9 (33%) by the standard-dose study to 5 (19%) by the high-dose study (Table 1). The high-dose studies therefore increased the number of patients with multiple lesions from 12 (44%) to 18 (67%). This resulted in a change in diagnosis in a total of nine patients (33%) from either normal findings (n = 2) or a single brain lesion (n = 7) on the standard-dose study to a single lesion or multiple lesions, respectively, on the high-dose study (Tables 1 and 2). This accounted for 2 of the patients (33%) with normal findings and 7 of the 9 patients (78%) with solitary brain lesions demonstrated on the stand-

TABLE 2: MR findings on standard- and high-dose studies, treatment changes, and reasons for no treatment changes

0.1 → 0.3 mmol/kg, No. of Lesions Detected	Potential Change, No. of Patients	Actual Change, No. of Patients	No Actual Change, No. of Patients	Reason for No Change (No. of Patients)
0 → 1	2	0	2	Terminal cancer (1) Severe congestive heart failure (1)
1 → m	7	4[a]	3	Severe symptoms from brain lesion (2) Craniotomy for diagnosis (1)
m → m	1[b]	0	1	Terminal cancer
m → 1	1	0	1	Terminal cancer
Total	11	4	7	

Note.—m indicates multiple.

[a] Three craniotomies and two aggressive courses of radiation therapy were not performed because of high-dose study results.

[b] One patient had two lesions in very close proximity amenable to resection on the standard-dose study, but additional lesions remote from the original two lesions were found on the high-dose study.

ard-dose study (Table 1). These 9 patients previously had been judged by the neurosurgeon and the radiation oncologist in the phase III study to have a potential change in the treatment of brain metastasis without considering the overall medical condition or status of their systemic disease (26).

In addition, one patient had two lesions in very close proximity to each other on the standard-dose study. Our independent reviewers also had considered aggressive treatment in this patient similar to that appropriate for a solitary lesion with resection and follow-up radiation plus a radiation boost treatment (26). The high-dose study in this patient, however, demonstrated additional lesions remote from the two lesions in close proximity demonstrated on the standard-dose study. Aggressive treatment was not judged to be indicated because of the results of the high-dose study.

In another patient, the standard-dose study showed multiple lesions, but the high-dose study confirmed only one solitary lesion. The reviewers had judged that the potential treatment change in this patient would consist of more aggressive therapy (resection and aggressive radiation therapy) (26).

Therefore, without consideration of the overall systemic disease or other medical conditions, the high-dose MR studies provided additional information that may have resulted in potential treatment changes in 11 of the 27 patients (41%).

It should be noted that the group of patients (n = 11) with potential treatment changes in this report contains 1 more patient than the previously reported group (26). One of the 27 patients in the phase III review (Table 1, patient 13 in reference 26) had normal findings on the standard-dose study but showed a solitary lesion on the high-dose study. This patient (patient 13) had been accidentally excluded from the evaluation for potential treatment changes (Table 2 in reference 26) and would have been judged to have a potential treatment change by the same neurosurgeon and radiation oncologist. Because the main purpose of the current study was to evaluate the actual treatment changes for all 27 patients, the number of patients with potential changes should not influence the outcome.

Clinical Patient Data

Thirteen of the 27 patients had lung cancer, reflecting the tendency of lung cancer to metastasize to the brain; 3 had renal cell carcinoma; 3 had gastrointestinal cancers; 2 had breast cancer; 1 each had laryngeal cancer and malignant melanoma; and 4 had cancers of unknown primary sites. The patients ranged in age from 43 to 76 years (mean, 61; median, 60 years). Eleven of the 27 patients had evidence of other systemic metastases at the time of the diagnosis of brain metastasis.

Twenty-three of the 27 patients had evidence of brain metastases on the high-dose MR study (Table 1). All but one obtained palliative benefit with improvement in neurologic symptoms from the therapy of the brain metastases. Median survival in the 11 patients with potential treatment changes was 5.5 months (mean, 8.9; range, 1 to 26 months) compared with 4.0 months (mean, 5.7; range, 1 to 21 months) in the 12 remaining

patients who had MR evidence of multiple brain metastases on standard-dose MR ($P = .315$).

Management Cost: Diagnosis and Treatment

Diagnostic Procedures. The cost of diagnostic procedures included a charge for contrast material and a charge for imaging time (pulse sequences). The charge for a routine brain MR excluding contrast dose and additional sequences at our institution is $507. This charge for the standard pulse sequence was not included in the cost comparisons, because it is the same whether the study is performed with standard-dose or high-dose contrast. Patient charges for gadolinium at our institution are $169 for 0.1 mmol/kg (standard dose), $338 for 0.2 mmol/kg, and $507 for 0.3 mmol/kg (high dose). When a single-injection technique is used for the high-dose study, the additional cost per patient for high-dose compared with standard-dose contrast is only the additional 0.2 mmol/kg of contrast agent: $338. No additional pulse sequences are needed. The total additional diagnostic cost for the high-dose study using a single injection for *all 27 patients* would be $9126 ($338 × 27). When the two-injection technique is applied to the high-dose study, the additional cost would include additional contrast material (0.2 mmol/kg if completed within one visit and 0.3 mmol/kg if administered in a second visit) and additional pulse sequences after the second injection *only for the 11 selected patients.* The cost for additional pulse sequences at our institution is $507 per patient. The additional cost for the high-dose study would be $11 154 ([$507 + $507] × 11 patients) for two separate injections in two visits. If the high-dose study can be performed by two separate injections in one visit, with the second injection immediately after the completion of the first injection, the additional cost would be $9295 ([$338 + $507] × 11 patients).

Surgical Treatment. The cost of craniotomy with resection of the metastatic lesion and hospitalization was calculated at $22 800 based on the average cost of cranial surgery in 3 of the 11 patients who underwent craniotomy for symptomatic lesions despite additional information obtained by the high-dose study. One of the three patients had a prolonged intensive care unit admission and received additional therapy (antibiotics, anticonvulsants, vasopressors, respiratory therapy, etc).

Radiation Treatment. A short course of irradiation to 3000 cGy in 10 treatments was calculated at $2302 based on the average of 4 of the 11 patients treated with that dose of whole-brain irradiation at our institution. In the patients who had an aggressive course of brain irradiation (higher total radiation dose and/or boost fields), the additional cost to cover simulation, radiation field placement, dosimetry, and additional radiation treatments averaged $1122. Because not all patients received radiation therapy at our institution, this figure was derived from subtracting the average cost for a short course of whole-brain irradiation (see above) from the average cost in 2 patients with higher-dose aggressive radiation courses and/or boost fields.

Actual Treatment Changes

Despite the fact that 11 patients were judged by the reviewers to have potential treatment changes as a result of the high-dose studies, only 4 of the 11 patients had actual treatment changes.

In the four patients with actual treatment changes, craniotomy and resection of a presumed solitary metastasis based on the results of the standard-dose study were initially planned. The craniotomies were then canceled in three patients by the referring neurosurgeons because of the finding of multiple brain metastases demonstrated by the high-dose MR study. However, an aggressive radiation course was actually abandoned in only one of the three patients whose craniotomies had been canceled. In the other two, the initially planned courses of radiation therapy were not modified because of previously received prophylactic brain irradiation in one and the preference of the patient's oncologist in the other case. In the fourth patient with an actual treatment change, an aggressive course of brain irradiation was substituted by a short course of radiation therapy.

In the other seven patients without actual treatment changes, three underwent craniotomy despite the presence of multiple brain metastases demonstrated on the high-dose study (Table 2). Two of the three had severe symptoms, and one needed craniotomy to establish the cancer diagnosis. All three patients had single lesions on the standard-dose MR study and multiple metastases on the high-dose study. In the other four patients without actual treatment changes, three were terminally ill because of the advanced stages of the malignancies, and one patient had severe congestive heart failure (Table 2).

Cost-Effectiveness Analysis

The cost-effectiveness analysis of the high-dose study consisted of the cost savings from the treatment as a result of the high-dose study and of the additional expenses incurred in performing the high-dose studies.

Based on the cancellation of the three craniotomies and the two courses of aggressive brain irradiation, a total treatment expense of $70 644 ([$22 800 × 3] + [$1122 × 2]) was avoided in the treatment of the 27 patients. The cost-effectiveness analysis therefore showed that the total savings in the care (diagnostic and treatment) of the 27 patients would be $61 518 ($70 644 − $9126) for the single-injection technique; $61 349 ($70 644 − $9295) for two injections in one visit; and $59 490 ($70 644 − $11 154) for two injections in two visits. Based on these calculations, the information provided by the high-dose studies resulted in an average savings in medical-care costs of $2251 per patient (range, $59 490 to $61 518 for 27 patients and $2203 to $2278 per patient).

Discussion

The occurrence of metastatic disease to the brain is not uncommon in patients with known malignancies. Intracranial metastases occur in approximately 25% of patients with cancer and account for up to 40% of all adult brain neoplasms (27, 28). Lung and breast carcinomas, both among the most common malignant tumors in humans, are also the most common primary neoplasms that metastasize to the brain (28). An estimated 80 000 to 100 000 patients are diagnosed with brain metastasis yearly (29). Significant medical costs are expected for the care of patients with metastasis to the brain. The optimal palliative benefit and the cost-effectiveness in the care of these patients depend on early diagnosis and appropriate treatment.

Treatment Approach

The treatment of brain metastases is a factor that may determine survival time (30). Untreated patients with brain metastases have a median survival of less than 3 months. The differentiation between solitary and multiple brain metastases is prognostically important. In patients with multiple brain metastases, the median survival is estimated at 3 to 6 months (31). In these patients, the treatment of choice is usually conservative and typically includes only a very short palliative course of radiation therapy with the goal of temporary improvement of symptoms, because this is considered to afford a better quality of life for the short remaining lifespan. Extensive craniotomy with prolonged hospitalization and considerable patient discomfort—in addition to tremendous medical costs—is frequently not considered (32, 33).

It has been reported that patients with solitary brain metastases and controlled primary tumors who are treated aggressively have a longer survival, a lower recurrence rate, and a better quality of life (28, 30, 34, 35). A median survival of up to 27 months and a 5-year survival of 20% to 30% are reported (36, 37). Therefore, aggressive treatment of the single metastasis, despite the additional cost, may be justified in selected patients (35). The higher cost for aggressive treatment includes expenses for radical surgical resection and postoperative irradiation usually with a higher radiation dose (38), particularly to the area of the tumor resection (boost). Therefore, early and correct diagnosis of brain involvement and the number of metastases are important not only for cost-effectiveness but also for the quality of life.

Diagnostic Dilemma

Because of the exponential growth pattern of malignant tumors and the long doubling time of some, metastatic deposits in the brain may be very small and remain asymptomatic for a long time period (39). It is the detection of small metastases that becomes a challenge for the neuroradiologist. Intracranial metastases are diagnosed before or at the same time as the primary tumors in approximately 20% of patients with cancer (40). Approximately 50% are found within the first year after diagnoses of the primary tumors (40). This suggests that many of the lesions may have metastasized to the brain, but they were too small to be detected by conventional radiologic means at the time of primary tumor diagnosis. In addition, 50% of all patients with intracerebral metastases will have only single lesions demonstrated by CT or MR (35, 41, 42, and Pollei SR, Atlas S, Drayer B, et al, Preliminary Experience with a New Low Osmolar, Nonionic Gadolinium Preparation in Patients with Intracranial Tumors, presented at the Society of Magnetic Resonance in Medicine, 1990). In these 50%, the detection of additional occult lesions that were not evident on routine radiologic examinations

(including CT and standard-dose contrast-enhanced MR) or the confirmation of the diagnosis of a single metastasis by high-dose studies is essential for optimal care.

The detection of these small metastases and the differentiation between no lesions, one lesion, and multiple lesions by radiologic means, such as high-dose MR studies, become essential to patient care because of the grave implications for therapy planning. It may be even more important at the time of the initial cancer diagnosis in asymptomatic patients with cancers with a high probability of metastasizing to the brain (eg, lung cancer).

CT scans of the brain have been used routinely to identify brain metastases. MR, however, particularly contrast-enhanced MR, has been reported to be more sensitive than CT (7, 15). With better lesion detection by higher-contrast dose studies (0.3 mmol/kg), the chance of treatment changes and cost savings further increases (20–23, 25, 43).

Cost Savings with Better Detection

Our results support the proposition that the detection of small brain lesions can result in cost savings in the treatment of those patients with clinical suspicion (symptomatic) of or known brain metastases, despite the high cost of the high-dose studies. The actual cost reduction in our limited patient population resulted primarily from the identification of patients who would not benefit from craniotomy and radical resection ($22 800 average per patient) of presumed "solitary" brain metastases, because multiple brain metastases were found. The omission of a boost field and replacement of aggressive brain irradiation by a short course of radiation therapy also reduced the cost ($1122 average per patient), but their impact was less, because only external radiation boost treatments, not sophisticated stereotactic radiosurgery techniques, were used in our patients.

Our results, however, did not reflect the value of the high-dose study in asymptomatic patients with newly diagnosed primary cancers without clinical evidence of brain metastases, particularly in those with a high probability of developing brain metastases, such as in newly diagnosed cases of lung cancer. Based on the principle that the high-dose study can provide better detection of small metastases, it is possible that high-dose studies may be potentially helpful in the management of this group of asymptomatic patients. However, the actual impact of high-dose studies on cost savings in asymptomatic patients remains to be determined.

Limitations of Our Study

Although the results of our study suggest that high-dose MR studies have a positive impact on the management cost of brain metastases, our findings need to be confirmed by further study. The major limitations of our study include: (*a*) potential errors by using fee schedules and treatment approaches biased toward those implemented at our medical center; (*b*) the discrepancies between the amount billed and the amount collected for a radiologic study; (*c*) the potential for false-positive findings on a high-dose study; and (*d*) the nonideal patient population and/or patient selection.

Errors in cost-saving calculations can result from the differences in the fee schedules among various major medical centers and community hospitals. The fee schedule at our medical center cannot be referred to as the standard charge for the nation, although we think that the differences may be small. Additionally, to exclude variations between patients based on their different insurance carriers, our calculations were based on the amount charged at our institution for a study rather than the amount collected. However, cost savings may be smaller if the data were based on the actual reimbursement rates.

Similarly, the treatment approach at our university teaching hospital should not be used as a standard of practice across the nation. Whether these patients should be treated at all for their brain metastases may be a matter of further controversy. Most of our patients did not survive long after the diagnosis of brain metastasis regardless of the type of treatment. The lack of difference in the survival time between the patients with multiple brain metastases on the standard-dose studies and those with presumed solitary lesions on the standard-dose studies but multiple metastases on the high-dose studies indicates, however, that the high-dose studies may have identified a poor-risk group among the patients with initially presumed limited brain involvement.

It is possible that high-dose contrast studies could show false-positive results in cases of small telangiectasia or venous angioma. Although we had long-term follow-up in most patients, we did not have histologic confirmation in all cases.

However, 9 of the 11 patients with additional lesions identified by the high-dose studies had follow-up CT examinations. In 4 of the 9, CT strongly supported the malignant nature of the new lesions. Additionally, one angiogram prospectively and independently showed abnormal findings suggesting metastasis corresponding to the area of an additionally detected lesion. In 1 other patient, typical neurologic symptoms that developed later correlated with an additionally detected lesion (our unpublished data).

Additionally, the patient population and selection were not ideal. Because our hospital is a major referral center, the patient population is different from that seen in most community hospitals. The inclusion criteria for the phase III clinical trial (25, 26) were designed by the FDA and the manufacturer (Squibb Diagnostics, New Brunswick, NJ) to recruit *consecutive* patients with known or suspected (symptomatic) brain metastases regardless of whether the brain examinations were indicated for the treatment of these patients. This may explain why many of those patients (7 of 10) with additional potentially beneficial information provided by the high-dose study were either terminally ill or needed cranial surgery for the relief of acute neurologic symptoms or for diagnostic biopsy (Table 2). The high-dose study was not needed in these patients because the additional information would not be expected to be helpful in their care, nor would it avoid aggressive therapy. If appropriate selection criteria were applied by using high-dose studies only for those patients with clear indications including normal or equivocal studies, or single lesions demonstrated on standard-dose studies, the results of the cost-effectiveness analysis would be expected to be different.

Implementation of the High-Dose Study

In the calculations of the cost of the high-dose study, we have proposed the following techniques: single-dose injection technique (0.3 mmol/kg) to all patients; or two-dose injection technique (initial standard dose of 0.1 mmol/kg to all patients and second injection of 0.2 or 0.3 mmol/kg to selected patients). The imaging after the second injection can be completed within one visit (0.2 mmol/kg) or in a second visit (0.3 mmol/kg). Using the fee schedule at our medical center, the overall cost (in 27 patients) for the high-dose study among the three different techniques ranged from $9126 to $11 154 for all 27 patients and was not dramatically different when compared with the savings from avoiding aggressive therapeutic procedures ($70 644). There was almost no difference in the cost of a single injections of 0.3 mmol/kg to all patients ($9126, 13% of the treatment savings) and two injections in one visit to selected patients ($9295, 13%). The two-injection technique completed in two separate visits ($11 154, 16%) had the highest cost.

The optimal technique of administration of the high-dose study could not be determined by our limited data. The preferred technique probably will be influenced by the type of practice. The application of a *single injection* of 0.3 mmol/kg to all patients to complete the examination within a single time slot of a brain examination may be the method of choice for some centers. On the other hand, when there is the possibility of flexible scheduling and prompt review of the standard-dose study by an on-site radiologist, the high-dose study could be administered most economically by completing the *two separate injections in one visit*, thus avoiding a second appointment (more time for positioning and tuning at the second visit) and by reducing the dose for the second injection (0.2 rather than 0.3 mmol/kg). In some patients, prolonged examinations and/or return visits may not be possible because of the severity of their symptoms or the immediate need to intervene therapeutically. If patient comfort is taken into account beyond cost considerations, a *single injection* of 0.3 mmol/kg may avoid unnecessary discomfort in these usually symptomatic patients.

In conclusion, despite the many limitations in our study, high-dose examinations seemed to impact positively on the cost of treating patients with known or highly suspected brain metastases, despite the fact that not all the information provided by the high-dose MR study could be used clinically, and many patients had evidence of extensive brain and extracranial metastases. The cost reduction resulted primarily from the identification of patients who would not benefit from expensive craniotomy. Our results did not show a dramatic difference in cost savings among the various techniques of implementing the high-dose studies. Although the mortality rate did not seem to be improved by the high-dose study, a poor-risk group of patients with presumed solitary metastases may have been identified. Our results need to be confirmed by a larger patient population, stricter selection criteria, and more standardized fee schedule and patient treatment.

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