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SHORT COMMUNICATION

Clinical surveillance compared with clinical and magnetic resonance imaging surveillance for brain metastasis: a feasibility survey

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ABSTRACT

Introduction After stereotactic radiosurgery (SRS) for brain metastases, patients are routinely monitored with magnetic resonance imaging (MRI). The high rate of new brain metastases after SRS treatment alone might not be as concerning with modern MRI and target localization treatment. Intensive surveillance might induce anxiety, lowering the patient's quality of life (QOL). The present work is the feasibility component of a prospective study evaluating the role of surveillance MRI on QOL in patients with limited (1–3) brain metastases.

Methods Patients with limited brain metastases treated with SRS alone, an Eastern Cooperative Oncology Group performance status of 2 or less, and documented stability in treated lesions, with no new lesions seen on MRI at weeks 6–10 after SRS, were eligible. All were asked about their interest in participating in the control (MRI and clinical surveillance) or the experimental arm (symptom-directed MRI and clinical surveillance). If 33% or more agreed to participate in the experimental arm, it would be considered feasible to conduct the prospective study.

Results From November 2014 to July 2015, 45% of patients (10 of 22) agreed to participate in the experimental arm. Subgroup analyses found that the decision to participate has no statistically significant association with time of presentation ($p = 0.696$), display of symptoms ($p = 0.840$), age ($p = 0.135$), or number of lesions ($p = 0.171$).

Conclusions Results show that it is feasible to conduct the prospective cohort study. Because of the small sample size, we are limited in the conclusions able to be drawn in the subgroup analyses. However, the future study would allow for a better understanding of the attitudes of patients toward MRI and its effect on QOL.

Key Words Clinical surveillance, magnetic resonance imaging, quality of life

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INTRODUCTION

With the continual improvement in medical technologies, physicians are now able to detect changes in a patient's body even before any symptom arises. Patients can then receive the appropriate treatment in a timely manner, preventing disease from progressing further and lowering the risk of death.

Taking advantage of such modern technologies, radiologic surveillance is currently incorporated into the follow-up routine for cancer patients who have undergone radiosurgery for brain metastases[1]. That approach is expected because this population consists of high-risk patients with cancers that have metastasized. The literature shows a high rate of reseeding when stereotactic radiosurgery (SRS) is used[2]. Whether there is a quality of life (QOL) or survival advantage to detecting asymptomatic recurrent brain metastases after SRS remains unknown[3]. We therefore sought to conduct a nonrandomized prospective study to observe the effect on QOL for patients who received both clinical and radiologic follow-up and for those who received clinical follow-up only. However, before conducting the prospective study, we elected first to perform a feasibility survey to determine the recruitment rate for the experimental arm. In the present study, participation in the control arm consisted of clinical and MRI follow-up every

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3 months for 1 year. Participation in the experimental arm consisted of clinical follow-up alone every 3 months for 1 year. In the latter group, MRI would be used only should an indication of change in symptoms and control arise.

Not only is inappropriate and excessive use of imaging harmful to a patient's QOL, it is also very costly to the health system. With the allocation of limited health care resources being a long-standing problem in medicine, it is crucial to provide imaging to patients only by necessity. That goal is clearly reflected in the Health System Funding Reform led by the Ontario Ministry of Health and Long-Term Care (http://www.health.gov.on.ca/en/pro/programs/ecfa/funding/hs_funding.aspx). Having determined that the current rate of growth is not sustainable with an increasing and aging population, Ontario's Health System Funding Reform program aims to make smarter use of limited resources by ensuring that funding is used to providing quality care that is needed. The first step in our evaluation was the feasibility survey presented here. We sought to comprehensively evaluate the utility of surveillance MRI after SRS alone for brain metastases.

METHODS

We conducted this feasibility study at the Juravinski Cancer Centre (Hamilton, ON) from November 2014 to July 2015. The Juravinski Cancer Centre is a comprehensive institution for cancer care and research. Our feasibility study will be used to determine whether it is appropriate to conduct the proposed larger nonrandomized prospective study. We assessed expected recruitment rates and refusal rates for participation by potential study subjects. As a statistical decision, it was determined *a priori* that a 33% participation rate in the experimental group was needed at minimum to consider the study feasible.

Eligible participants included all patients seen in a neuro-oncology follow-up clinic who had undergone SRS for 1–3 brain metastases within the preceding 6–10 weeks, who had stable disease (all treated lesions controlled and no appearance of new lesions), who had no lesion larger than 3.0 cm, who had received no treatment for brain metastases before the initial SRS treatment, and who had a Karnofsky performance status greater than 60. The eligibility criteria in the feasibility study mirrored those of the proposed prospective study.

Patients would attend their follow-up appointment and then afterward be invited to complete a survey (Table I). The student investigator would explain the purpose and details of the cohort study and ask whether the patient would like to participate in the experimental arm of the study should it occur. The study would require the participant to attend follow-up appointments every 3 months and to complete a set of surveys at each appointment. The 3 month follow-up appointments were based on the surveillance scheme used in similar SRS studies for brain metastases[1,4]. If the patient declined to participate in the experimental arm, they were further prompted, using a list of pre-determined statements, to elaborate on their decision. Any reasons mentioned by the patient in addition to the pre-determined statements were also recorded at the end of the survey.

Because the control arm of the study would consist of usual follow-up, we expected to have no trouble recruiting patients into that arm. However, the experimental arm constituted a novel intervention that differs from the standard care plan, and we therefore aimed to use the feasibility study to gauge patient interest in participating in the experimental arm. We expected to recruit 60 patients for the survey, with a target of 30 patients per arm.

Hypothesis-generating subgroup analyses were also conducted to determine whether any particular factors were associated with the decision to participate in the experimental arm. The subgroups that were selected *a priori* for investigation were time of presentation ("early presentation" defined as within 3 months of systemic metastatic presentation, and "late presentation" defined as more than 3 months after systemic metastatic presentation), display of symptoms, age, sex, and number of lesions (1–3).

The chi-square statistical test was used in the subgroup analyses for sex, metastatic presentation, symptoms, and number of lesions. Simple logistic regression was used in the subgroup analyses for age and Karnofsky performance status. Results were considered to be statistically significant when $p \leq 0.05$.

RESULTS

Of the 22 patients who were eligible and participated in the survey, 45% (n = 10) agreed to participate in the experimental arm. To further understand and explore the reasoning of the patients who declined to participate in the experimental arm, we reviewed the various explanations given. The most common reason was worry that the lack of radiologic surveillance would compromise the patient's health. Some patients further elaborated their concern about not undergoing MRI by using statements such as "not getting a full picture without the MRI" or "having a constant fear of the unknown."

In the subgroup analyses (Table II), we observed no statistically significant differences in the responses given by patients in the two subpopulations. However, the sample size for the survey was quite small, and therefore significant differences might not be detected. We believe that, with a larger sample population, significant differences could be detected because our data seem to suggest an increasing trend in decline of participation with an increasing number of lesions.

DISCUSSION

Because of the high rate of outfield failure after brain SRS (48% as demonstrated at 2 years in the study by Kocher *et al.*[1]), the practice of quarterly MRI surveillance after initial SRS and the salvage of new out-of-field lesions as proposed by international randomized controlled trials were adopted as clinical standards. The current literature also demonstrates that MRI surveillance can negatively affect a patient's QOL. Schneble *et al.*[5] emphasized that surveillance techniques should not only strive for improved patient survival, but also attend to the patient's QOL; the implementation of unnecessary interventions can result in increased patient anxiety, needless testing, and increased cost of care and utilization of resources.

TABLE I Patient survey

Name: _____ Patient ID: _____
Date of birth: _____ Gender: _____
The Karnofsky Performance Status Index allows patients to rate their functional impairment with a corresponding score. Please refer to the scale in the appendix.
Karnofsky Performance Status (KPS): _____
Brain metastatic presentation (please select one):
☐ Early presentation of brain metastases (within 3 months of systemic metastatic presentation)
☐ Late presentation of brain metastases (after 3 months of systemic metastatic presentation)
Presentation of symptoms (please select one):
☐ Symptomatic
☐ Asymptomatic
Number of lesions treated (please circle one): 1 2 3
Willingness to participate in study (please circle one): Yes No
If no, please specify (check all that applies):
☐ I am worried that participating in the experimental arm (only clinical follow-up and not the radiological follow-up) would compromise my health.
☐ I am anxious about participating in the control arm due to the inclusion of radiologic MR assessments in the follow-up plan.
☐ I cannot invest time and commit to following up every 3 months for up to a year.
☐ I do not wish to have a detailed medical history, physical examination, and quality of life measures completed every 3 months.
☐ I am concerned about the possible side effects (anxiety or unnecessary treatment) that would incur should I participate in the study.
☐ I am not interested in the study topic.
☐ It is inconvenient for me to travel the distance to the hospital for the measurements and tests.
☐ I am concerned about any costs that may incur should I participate in the study.
☐ I feel overwhelmed with the inquiries and questionnaires.
☐ I do not wish to participate due to personal problems.
☐ I am afraid that the care that I would receive would be compromised.
☐ Other (please specify): _____

Although the Schneble *et al.* study targeted patients at high risk of recurrence from breast cancer, its conclusions about surveillance are applicable to our study, given the similarity in the intensity of the surveillance schemes. Common complaints about MRI surveillance include claustrophobia and anxiety because of the narrowness of the bore, associated movement restrictions, length of the procedure, loud noise from the machine, or simply worry about the next MRI[6–8]. To demonstrate the extent of the impact of MRI on the general patient population, claustrophobia is experienced by an average of 2.3% of all patients who undergo MRI (95% confidence interval: 2.0% to 2.5%), and up to 37% experience moderate-to-high levels of anticipatory anxiety[9–11]. Given the noncurative nature of brain metastases and the potential problems that arise from MRI, it is important to evaluate the potential impact of clinical surveillance alone.

Contrary to our generalized assumption about the detrimental effects on a patient's QOL caused by MRI surveillance, it is interesting to note that some patients were more worried and anxious about not receiving regular MRI exams as part of their follow-up. Radiologic surveillance provides patients with updated visual knowledge that they would not otherwise have. Results from our preliminary investigation show that patient attitudes are variable and that the efficacy of surveillance will be determined by the

TABLE II Subgroup analyses examining correlations between various patient characteristics and response to an invitation to participate in a clinical trial

Characteristic	Response		*p* Value
	Yes	No	
Age (years)			
Median	65.5	61	0.135
Range	51–91	40–81	(two-tailed)
Median KPS score	75	80	0.891 (two-tailed)
Sex (*n*)			
Women	7	5	0.571
Men	3	5	
Metastatic presentation (*n*)			
Early	7	5	0.696
Late	5	7	
Symptoms (*n*)			
Symptomatic	8	10	0.840
Asymptomatic	2	2	
Lesions (*n*)			
1	7	4	0.171
2	2	3	
3	1	5	

KPS = Karnofsky performance status.

future prospective study at the conclusion of the present feasibility cohort.

The participation rate for the experimental arm was much higher than the threshold set *a priori,* with nearly half the patients agreeing to participate in the experimental arm. We believe that the achieved interest in participation is a strong enough positive indicator for the feasibility of the prospective cohort study. It was therefore decided to terminate the feasibility study early, as soon as the sample size reached 20 patients.

Little is known about the attitudes and reasoning of patients with respect to their decision about participation in trials. Therefore, in the process of creating the survey for the study, we put much effort into compiling a comprehensive list of possible rationales. Had we continued the feasibility study, it would have been beneficial to revise the list and include common reasons provided in the "Others" section, together with pre-established statements.

The results of our feasibility study might not be easily applied elsewhere, such as at other cancer institutions in the United States or European countries, because the financial cost of undergoing MRI would have to be taken into consideration. In Canada, MRI exams are covered by universal health insurance; however, in other countries, many patients would have to pay out of pocket for this service. Because the procedure is not affordable for many patients, a higher percentage of patients might be expected to opt into the control arm, because they would thereby gain access to resources not otherwise accessible.

CONCLUSIONS

Our study shows that it is feasible to conduct the proposed prospective cohort study, because the participation rate in the experimental arm exceeded our pre-determined threshold of 33%. Further research into the utility of MRI in follow-up and its effect on patient QOL would allow us to provide the best oncology care possible for patients who have undergone SRS for 1–3 brain metastases.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

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Stopeck et al. study[2]
Phase 3, randomized, double-blind, double-dummy, active-controlled study. Patients with breast cancer and bone metastases (n=2046) received either 120 mg XGEVA SC Q4W (once every 4 weeks) (n=1026) or 4 mg zoledronic acid IV Q4W (n=1020). The primary outcome measure was to demonstrate non inferiority of time to first on-study SRE as compared to zoledronic acid. The secondary outcome measures were superiority of time to first on-study SRE and superiority of time to first and subsequent SREs. An SRE is defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone or spinal cord compression.

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