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Original Article

Role of stereotactic radiosurgery in the management of single or multiple cerebral metastases

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Keywords

Stereotactic radiosurgery; cerebral metastases; efficacy of whole brain irradiation

INTRODUCTION

Cerebral metastases are a common complication of systemic disease occurring in 25% of patients.[1] Left untreated they are often the cause of rapid deterioration and death with an associated survival of around 1 month attributable to progressive central nervous system (CNS) malfunction.[2]

Treatment for extra-cerebral disease has been developed and improved over the last decade resulting in increased survival and consequently leading to an increase in patients presenting with cerebral metastases.[3] Metastatic spread from systemic cancers comprise almost one-half of all intracranial tumours. Approximately 30–40% of brain metastases are single; with the commonest primary tumours giving rise to metastasis being lung, colon, kidney and breast cancers.[4] Patients usually present with a short history of focal neurological symptoms, which vary depending on the site of the metastasis. Generally treatment is palliative as around 50% of patients have uncontrollable systemic disease.[4]

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Of the conventional management approaches available for cerebral metastases (surgery and external beam radiotherapy) no single modality offers effective disease control, either by increasing survival or improving quality of life (QOL). However recent research offers evidence of an alternative management option offering positive results.[4] Providing the systemic disease is under control, high doses of focused radiation can be delivered to individual tumours in the form of stereotactic radiosurgery (SRS).

SRS BACKGROUND

SRS is a technique that delivers a focal dose of high-energy radiation using three-dimensional image processing and is ideally suited for the treatment of small intracranial targets.[5] The characteristic of SRS offers a sharp dose gradient of radiation at the treatment field edges, which markedly reduces the dose of radiation to surrounding normal structures.[6] It is an attractive treatment option as it is minimally invasive and able to reach surgically inaccessible lesions. It offers low complication rates (0% procedure related mortality, and 5% 30-day complication rate) when treating brain metastasis compared with a perioperative complication rate of 3–8% and associated 30-day morbidity rates of 2–6% from surgery.[2]

USE OF WHOLE BRAIN RADIOTHERAPY (WBRT)

In 1995 survival figures published for patients treated with WBRT for cerebral metastases were quoted as 3–6 months.[6] More recent results offered a mean survival for patients treated with WBRT as 15–18 weeks,[7] figures supported by numerous studies. This indicates in the space of 6 years no developments have been made resulting in increased survival for patients with cerebral metastases. Although it must be remembered the aim of treatment may not be to increase survival but to improve QOL.[8] Nonetheless in the current climate of health care it should be possible to devise, research and implement new forms of treatment to improve QOL, control the progression of a disease and ultimately increase survival rates within 6 years. Is it time to explore a new primary treatment option in the management of cerebral metastases?

Historically WBRT was accepted as the treatment of choice in many cases especially where patients were too ill to undergo surgery or where the lesion was surgically inaccessible.[1] Consequently only WBRT could be offered to those not consenting to, or suitable for surgery. The 30 Gy in 10 fraction regime, which is still used clinically today, was devised over 20 years ago following research by Gelber et al. and Kurtz et al. in 1981 (cited in reference 7), once this regime was accepted no further research was published on the subject for well over a decade. This may explain the failure to improve survival figures in patients with cerebral metastases.

As surgical expertise and peri and post operative care improved, three major trials were performed in the 1980's and 1990's demonstrating patients with solitary, operable metastasis appeared to have a better prognosis if surgically removed.[7] If surgery was then combined with WBRT, patients were seen to have an increased survival compared with WBRT alone. These results were taken a step further by the Mayo Clinic in 1987[9] who addressed the problem from a different angle: can surgical resection of an apparently isolated metastasis be all that is needed? Their findings showed the risk of subsequent brain relapse was reduced from 85% to 21% if postoperative radiotherapy was delivered, demonstrating that surgical resection was clearly not enough to control the disease by itself. Consequently aggressive local surgery followed by WBRT became standard practice for the treatment of operable, single metastasis in a patient with controlled systemic disease.[7]

Although classed as a "new" treatment option SRS has been around for over 30 years. Since it's development in the late 1960's it has become established as a primary management option in conditions such as trigeminal neuralgia, arteriovenous malformations and acoustic neuromas.[10] High resolution volume acquisition, highly advanced magnetic resonance imaging (MRI) pulse sequences with contrast enhanced images and powerful 3D computational software enable treatment planning to be highly accurate and sophisticated allowing the true potential of SRS to be realised.[3] Since it is a proven management option in a number of functional, benign and malignant conditions it comes as no surprise that SRS be assessed as to its role in the management of metastases.

Cerebral metastases are physically and biologically ideal lesions to treat with radiosurgery. As metastasis are usually spherical and small, have radiographically distinct margins, are minimally invasive and grow by displacing normal brain tissue, the entire extent of the disease can be targeted in the SRS treatment field while sparing radiation injury to surrounding normal tissue.[10]

One of the earliest publicised studies assessing the role of adjuvant radiation therapy utilising the Gamma Knife (GK) came from Pittsburgh in 1987 where it was concluded that SRS eliminated the surgical and anaesthetic risks of a craniotomy and resection of solitary metastasis.[9] These initial findings prompted much research in this field with varying opinions as to the usefulness of SRS with the most common conclusion being the need for further research.[1–3,7] Since recent advances in technology, results from these early studies hold little value except as an initial indication as to the efficacy of SRS. Conclusions from studies performed prior to the use of MRI must be accepted with caution, the development of such a sophisticated imaging tool which allows much better tumour visualisation and target delineation means it is unrealistic to compare results from the pre

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MRI era with recent ones as they are innately outdated by technology.

In order to try and standardise the management of metastasis and evaluate the role of SRS, the Radiation Therapy Oncology Group (RTOG) Brain Tumour Committee initiated the first clinical trials programme in 1989 defining the study, RTOG protocol 90-05.[11] It was designed to treat patients with recurrent, previously irradiated primary brain tumours and cerebral metastasis using escalating doses of single fraction radiosurgery to establish efficacy and maximum tolerated dose. Patients with cerebral metastasis were chosen for this trial, the first of its kind, as high numbers of patients were anticipated due to the high local failure rates of conventionally fractionated radiotherapy and the fact that few other treatment options exist for these patients.[11] The study addressed some important issues, which became the building blocks for SRS as it is used today.

Dose

Single fraction dose was escalated to 24 Gy without serious CNS toxicity however, the maximum "safe" dose was not reported due to the reluctance of the researchers to further escalate prescribed dose. Clinically, doses have yet to be increased past those set in the trial and are rarely used at such levels except in cases of metastatic melanoma due to the known radioresistance of such tumours.[3,12]

Toxicity

The study highlighted that 22% of patients developed unacceptable CNS toxicity after treatment when following the RTOG radiosurgical protocol, this was seen to be significantly more probable in patients with large tumours (greater than 21 mm in diameter).[11] This can be substantiated with knowledge of Radiosurgical dose gradients, there is much less fall off of dose when treating large volumes resulting in more normal tissue being irradiated, producing a less conformed treatment, nevertheless it must be remembered that toxicity is as proportional to tumour/tissue volume as it is to dose. This finding still heeds the rationale for SRS treatments, limiting many procedures to treating relatively small volumes only.

When assessing cause of death results from numerous studies it is evident that few patients actually die as a result of their cranial metastasis. In most cases cause of death is attributable to progression of systemic disease, highlighting why QOL is such an important factor in disease management. Alexander et al.[6] found that in a large number of patients no tumour cells were identified at autopsy following radiosurgery thus apparent failure of treatment may not indicate biological failure. Chen et al.[2] did however find that patients who died as a result of their CNS disease were 1.65 times more likely to have received WBRT during their treatment course. This raises important issues, highlighting that the role of WBRT in the management of cerebral metastasis needs careful consideration.

Combined therapies

As the debate continues, it remains unclear as to the optimal treatment approach. As discussed it is well accepted and publicised that surgery plus cranial irradiation (WBRT or SRS) increases prognosis and improves QOL but what alternative options are available for patients not suitable for surgery? More recent studies have discussed the role of SRS combined with WBRT as a prophylactic measure for disease control. It is an accepted practice for patients receiving radiotherapy for non-small cell lung cancer (NSCLC) with no confirmed diagnosis of cranial metastasis receive prophylactic cranial irradiation to prevent cranial metastases or eliminate microscopic spread.[13] Similarly, it is thought that WBRT may reduce the incidence of progression of CNS disease if combined with SRS.[14] It has been assumed that this would improve local control, however Flickinger[15] found a higher local control rate but no improvement in median survival time when the two therapies were combined with results, also supported by Kihlström et al.[16] Nonetheless Fuller et al.[17] documented their best results from combined therapy (WBRT and SRS) with a local tumour control rate of 80% for a small number (10) of patients in their study.

It is difficult to fully assess the role of conventional radiotherapy, as applied doses of fractional radiotherapy administered before or after radiosurgery vary among numerous studies leading to an over or under estimation of the efficacy of WBRT. Moriarty et al. (1995) confirmed the failure

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of WBRT to have an impact on survival rates in patients treated with SRS (cited in reference 3). No one has, as yet, defined criteria as to whether SRS should be offered alone or in conjunction with WBRT, nonetheless regardless of survival figures other factors must be considered. Firstly WBRT is not an undemanding treatment option. It is accepted that this approach harbours many unwanted side effects such as epilation and symptoms from raised intercranial pressure,[3] while some reports demonstrate WBRT can cause dementia in long-term survivors.[2] In patients with such a poor prognosis surely QOL should be a major consideration when deciding which therapy to opt for. Many studies report no clinical complications associated with SRS, no procedure related mortalities[2] and no radiation-induced changes in surrounding brain tissue observed via follow up imaging.[14] Research by Muacevic et al.[3] observed a decrease in peritumoural oedema after SRS and dismissed speculation that patients who undergo SRS may require high dose steroids for long intervals post treatment, concluding that it is in fact those patients who receive conventional radiotherapy who need prolonged steroidal therapy to minimise associated side-effects. Remembering that long-term steroid use also has associated risks and side effects which all effect a patient's QOL.

Role of SRS in the management of multiple metastases

Approximately 50% of patients with CT or MR detected brain metastases have multiple lesions.[18] SRS has been believed to play no part in the management of multiple tumours because of the local nature of the therapy, however more recent clinical experience suggests otherwise. Figure 1 illustrates a 3D, MRI reconstructed cut-box image highlighting a patient with 10 metastases (greyscale, reproduced from original colour) from primary breast carcinoma, comprising a total tumour volume of 12.9 cc. The same patient 6 months after radiosurgery (Fig. 2), only six metastases remain visible following triple dose, contrast enhanced MRI with a total tumour volume of 0.6 cc. The patient received further SRS, 2 years after the first treatment for four lesions, two new and two retreats. To date she remains well and free from metastatic disease related symptoms 2.5 years post radiosurgery. It is worth noting that before referral for the initial radiosurgical procedure she was given a survival figure of 3 months.

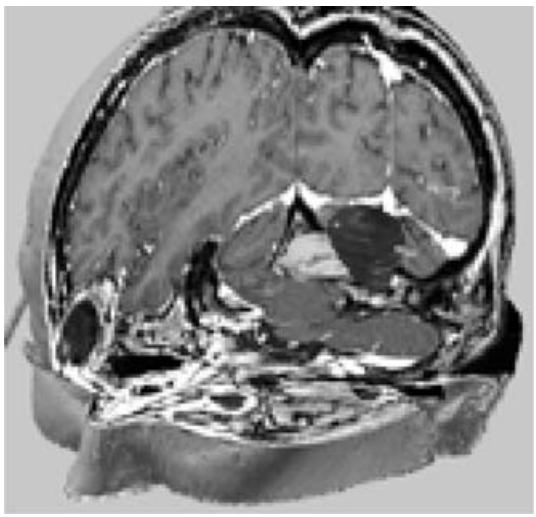

Figure 1. A 3D, MRI reconstructed cut-box image highlighting a patient with 10 metastases (greyscale, reproduced from original colour) from primary breast carcinoma.

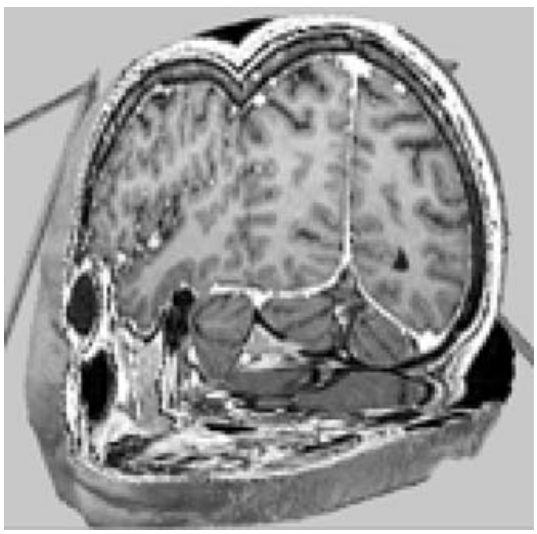

Figure 2. The same patient 6 months after radiosurgery. Only 6 metastases remain visible following triple dose. (Image courtesy of the Cromwell Hospitals Gamma Knife Centre.)

To support this, evidence can be drawn from Serizawa et al's study.[13] They regarded the efficacy of SRS for multiple metastases, assessing patients with up to 10 brain metastases with a maximum diameter of 30 mm. Their results reported good survival figures with a high rate of local control.

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They concluded that prophylactic WBRT had no significant effect on the appearance of new lesions and did in fact hamper treatment, as additional radiation therapy for new lesions is hazardous if a full dose of WBRT was part of the initial management. Further evidence can be drawn from results of a study presented by Sheehan et al.[19] in which one patient is still alive 8 years after SRS despite receiving treatment for multiple metastases. This opens a new issue for debate, how many lesions may be reasonably treated with SRS and where do you draw the line? Whether it is preferable to immediately address only gross lesions or, in addition, potential microscopic disease, which may or may not become symptomatic during the patients lifetime is not entirely clear.

Clinically, the author has experienced successful treatments for multiple metastases (ongoing survival, of 20 months post radiosurgery for a patient treated for 22 metastases and ongoing survival of 6 months in a patient treated for 32 metastases). A study by Yang et al. reported that 25 small lesions could be safely treated with SRS without acute radiation induced side effects (cited in reference 19). There is some consensus in the literature that it is not the number of metastases but the overall combined tumour volume that is of importance[2,13] and patients with more than 3 cc total tumour volume have a significantly increased risk of death, although clinical experience shows this is not necessarily true (Fig. 3).

CONCLUSION

There remains much debate surrounding the management of cerebral metastases. Issues highlighted in the conclusion to Marcou et al's[7] report suggest there may be a more political issue surrounding the debate. A wide difference in opinion exists between oncologists and neurosurgeons as to the application of WBRT and SRS. Oncologists seem reluctant to eschew WBRT with its 30 Gy in 10 fraction "gold standard" and bring focal radiation therapy into primary therapy and are generally more opposed to the use of SRS for multiple metastases, while those from a neurological background "infer a high dissatisfaction" for the WBRT approach. One thing is clear however, the role of WBRT is highly debatable, evidence suggests it does not reduce the risks for further metastatic disease, therefore is it time we redefined this gold standard?

In general, findings confirm that radiosurgery alone can be used to achieve local tumour control rates as good as those found with combined therapies (surgery plus WBRT, or SRS plus WBRT) for patients presenting with single circumscribed metastasis less than 3.5 cm in diameter.[3] SRS is attractive because of its minimal invasiveness and the possibility of withholding adjuvant radiotherapy. There is a general consensus that surgery combined with radiotherapy should be saved for patients with large tumour volumes not suitable for SRS.

One thing is clear, even with the advances in imaging, specifically highly sophisticated MRI it is impossible to detect evidence of microscopic disease.[1] Some would therefore argue the need for prophylactic therapies. However, with the continued debates in the literature and affects on patients QOL perhaps the answer is not to adopt the "what if" therapeutic approach but simply to carry out more stringent follow ups to continually assess the progression of the disease. As Chen et al.[2] described, data on local control after SRS are frequently under represented because of the lack of complete and accurate imaging follow-up. Nevertheless, if there is still a case for prophylactic therapy then perhaps work needs to be done to reassess the dose fraction regimes in conventional radiotherapy.

The lack of efficacy and cognitive behavioural consequences of whole brain radiotherapy have prompted clinicians to select patients for alternative therapies.[12] More attention needs to be paid to the optimal therapy of metastatic brain disease, particularly in those patients with few adverse prognostic factors.[7] So far SRS has proven to be of benefit in controlling and eliminating metastatic cranial disease (both solitary and multiple tumours). It provides an alternative to surgical resection and should be considered as an essential management option in these patients. Results of retrospective studies should be regarded with caution and must be confirmed within the framework of a prospective randomised study. It is essential that the capabilities of radiosurgical facilities to ablate individual and

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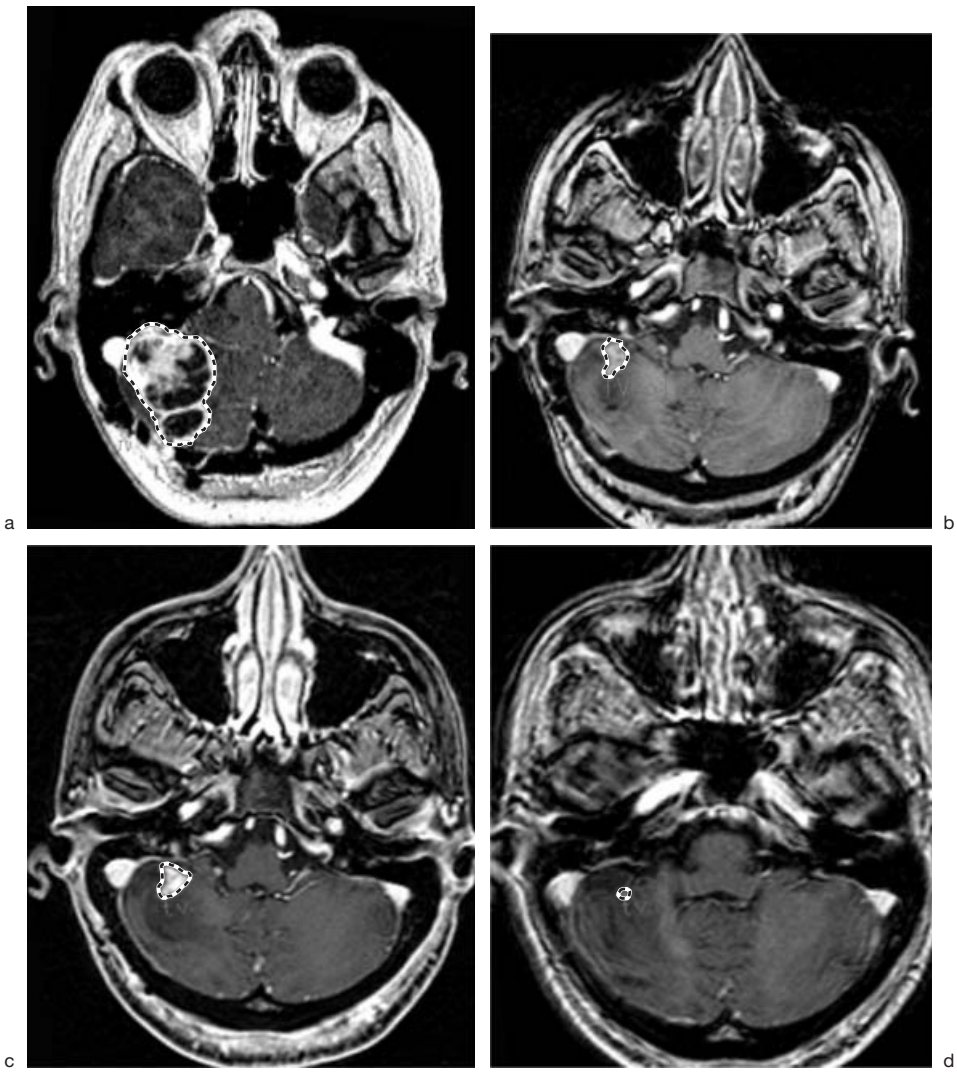

Figure 3. T1 weighted, contrast enhanced, transaxial MR images highlighting a metastatic tumour from a melanoma primary. (a) Pre-treatment scan, tumour volume = 17 cc; (b) 5 months after radiosurgery, tumour volume = 1.0 cc; (c) 12 months post radiosurgery, tumour volume = 1.0 cc; (d) 15 months post radiosurgery, tumour volume = 0.756 cc. Follow up at 21 months post radiosurgery showed further tumour reduction to 0.185 cc. (The patient died 24 months after SRS as a result of progressive systemic disease.) (Images courtesy of the Cromwell Hospitals Gamma Knife Centre.)

multiple metastases successfully be more fully studied and consequently promoted and accepted as a routine, primary management options for all suitable metastasis patients.

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