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Management of Brain Metastases: Patient Selection for Aggressive Local Management and the Role of Stereotactic Radiosurgery

The management of brain metastases remains challenging for oncologists. Brain metastases affect up to 40% of patients with cancer and, with improvements in systemic anti-cancer treatment and more sensitive imaging, this incidence appears to be rising [1]. Historically, the majority of patients with brain metastases were treated with whole brain radiotherapy (WBRT), but in recent years that conventional wisdom has been increasingly questioned. For many patients, prognosis is poor and there may be little or no benefit from subjecting them to the morbidity of WBRT if their symptoms can be controlled with corticosteroids alone. This is currently being investigated in lung cancer patients within the MRC QUARTZ trial, which is comparing WBRT with best supportive care [2]. Unfortunately, recruitment into this trial has been slow, suggesting that many oncologists may still have fixed ideas regarding the likely benefits, or otherwise, of WBRT. Interim results have been reported, with no apparent difference in overall survival.

On the other hand, there is a small group of patients with brain metastases in whom aggressive local management is very appropriate, either with neurosurgical resection or stereotactic radiosurgery (SRS), perhaps even a combination of both. Recognition of those patients who have a more favourable prognosis and are likely to benefit from a more aggressive approach is a regular challenge for neurosurgery and neuro-oncology teams.

Prognostic indices

In recent years, a number of prognostic scoring systems have been developed to facilitate management decisions in patients with brain metastases. The recursive partitioning analysis (RPA) score is determined by age, Karnofsky performance status (KPS) and status of systemic disease (Table 1) [3]. Based on these factors, patients are grouped into one of three prognostic groups, which were originally developed using retrospective data from the RTOG database, but have since been validated prospectively. The more recent Graded Prognostic Assessment (GPA) expands this to include the number of metastases as a fourth variable, and has four prognostic groups rather than three (Table 2) [4]. Other prognostic indices have been described, including the score index for radiosurgery (SIR) [5] and the basic score for brain metastases (BSBM) [6], but GPA was derived from the largest dataset (n = 1,960) and has been most widely used. Regardless of the index used, the proportion of patients in the most favourable prognostic groups, unfortunately, is small. Since the GPA index was first described, there have been a number of tumour-specific modifications to the system, most notably in breast cancer [7]. An eloquent comparison of the different prognostic indices noted that some tumour types are not well represented and gave ideas for future refinements [8].

Aggressive local management

With appropriate patient selection, there does appear to be a significant advantage in those managed with surgery or SRS. The benefits of neurosurgical resection have been demonstrated in a number of randomised trials, showing improved local control and overall survival [9,10,11]. More recent trials have

Table 1: RPA classification and prognosis

RPA Class	Description	Median OS
1	KPS >70, age <65, controlled primary disease	7.1 months
2	KPS >70, age >65 or uncontrolled primary disease	4.2 months
3	KPS <70	2.3 months

Table 2: GPA classification

GPA Score	0	0.5	1
Age	>60	50-59	<50
KPS	<70	70-80	90-100
Number of brain metastases	>3	2-3	1
Extracranial metastases	Present	-	None

Table 3: Prognosis according to GPA score

GPA Score	Median OS
0-1	2.6 months
1.5 – 2.5	3.8 months
3	6.9 months
3.5 – 4.0	11.0 months

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shown similar benefits with SRS. The RTOG 95-08 randomised trial, comparing SRS and WBRT with WBRT alone, for patients with 1 to 3 brain metastases and KPS greater than 70, demonstrated an overall survival benefit with SRS in patients with a single metastasis (6.5 v 4.9 months, $p = 0.0393$), regardless of other factors [12]. Those in the SRS arm were also more likely to have a stable or improved KPS at six months. In those with multiple metastases, only patients of RPA class 1 appeared to benefit. An earlier trial comparing SRS and WBRT to WBRT alone for 2-4 metastases used local control as the primary endpoint and was stopped early as a significant difference emerged. The local control rate was 92% with SRS with WBRT, but 0% for WBRT alone. Median time to local failure was 36 months in the SRS with WBRT group, compared with only six months with WBRT alone [13].

Those patients deemed suitable for aggressive local management of brain metastases are ideally younger patients with good performance status, 1 to 3 metastases and controlled systemic disease. A further group includes those with synchronous presentation with the primary or other metastatic disease, in whom there is a radical treatment option for the primary lesion, or treatment with a reasonable expectation of longer-term survival for metastatic disease. A good example of the latter is hormone-sensitive breast cancer, with which many patients can expect to survive for several years with appropriate systemic treatment.

The choice of neurosurgery versus SRS should be considered in the multi-disciplinary setting, with appropriate information sought regarding likely prognosis from extra-cranial disease. Neurosurgery and SRS have distinct advantages and disadvantages, with no evidence of superiority with either modality, as concluded by a Cochrane review in 2010 which found no suitable randomised trial comparing the two modalities in the context of metastatic non-small cell lung cancer [14]. For larger lesions, particularly those greater than 3.0cm diameter, surgical resection is generally considered to be the preferred option. Similarly, when there is a need for histological confirmation then resection should be favoured. On the other hand, for smaller or deep-seated lesions, or those in or near eloquent areas of the brain, the risks of surgical resection may be such that the non-invasive option of SRS is recommended. In some patients who undergo surgical resection, there may be an advantage in offering post-operative radiosurgery to the surgical bed, as discussed below. Neurosurgical resection is not discussed in any further detail here.

Stereotactic radiosurgery

Stereotactic radiosurgery (SRS) was developed, in 1951, by Swedish neurosurgeon Lars Leksell [15]. It utilises external three-dimensional reference points to locate small targets within the brain, allowing precise delivery of a single large fraction of radiation, or in some cases several smaller fractions. Leksell described radiosurgery initially using a 200kV x-ray machine, but in 1968 developed a Cobalt-60 gamma source unit, the Leksell gamma knife. Modern gamma knife units employ the same basic principles. Radiosurgery can also be delivered using a linear accelerator (LINAC), retro-fitted with micoMLC (multi-leaf collimator), or modern purpose-built radiosurgery equipment. LINAC-based SRS can be delivered using fixed beams, intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT).

Traditionally radiosurgery has required fixation of the head using screws, thus requiring patients to be planned and treated in one visit. Newer technologies allow treatment to be delivered using a removable thermoplastic shell and even frameless SRS is now becoming widely available. Whatever technique is used, the aim of SRS is to deliver a necrotising dose of radiation to a small volume of tissue, containing the target lesion and a minimal volume of surrounding normal tissue.

Metastatic brain lesions, first treated using radiosurgery in the early 1980s, have a number of characteristics which make them particularly suitable for SRS. They are usually discrete, well-circumscribed, spherical lesions. In most cases, they enhance vividly with intravenous contrast, facilitating target definition during treatment planning. Furthermore, in potentially radioresistant tumours with a low α/β ratio, such as melanoma, the large fraction size can overcome much of this radioresistance. There is even some evidence that some traditionally radioresistant tumours may actually respond better to SRS than so-called radiosensitive tumours [16].

Smaller lesions can safely be given higher doses, but with increasing diameter of the target lesion, the target volume and penumbra region increase significantly, resulting in a higher dose to surrounding brain. In lesions greater than 3.0cm many of the advantages of SRS are lost, although fractionated stereotactic radiotherapy may still be considered. SRS doses vary between centres and according to local protocols, but doses of 15-24Gy are typical, depending on the size and number of lesions being treated. The RTOG 95-08 protocol stated a marginal dose (to the 50% isodose line) of 24Gy for lesions up to 2.0cm, 18Gy for 2.1-3.0cm and 15Gy for lesions greater than 3.0cm [10].

Although most commonly used to treat single or oligo-metastases, some centres are now treating larger numbers of lesions, using triple-dose gadolinium MRI to maximise detection of smaller lesions. Even when large numbers of lesions are treated simultaneously, usually using gamma knife, the dose to surrounding normal brain can be kept low, when compared with WBRT [17].

Acute toxicities of SRS are usually mild and may include hair loss, local skin reactions, headache and nausea. Late toxicity needs to be carefully discussed with patients in advance, particularly in asymptomatic patients in whom SRS can trigger seizures, or cause pressure symptoms due to persistent oedema or radionecrosis. Earlier papers reporting outcomes following SRS for metastases tended to focus on tumour control and survival, undoubtedly under-reporting complication rates. A prospective review of 316 cases conducted at the M.D. Anderson Cancer Center, specifically to address complications, demonstrated a complication rate of 40%, the most common being new-onset seizures which occurred in 13% of cases [18]. Other important complications included haemorrhage (3%), the vast majority of which had melanoma, and hydrocephalus (1%), usually following treatment of cerebellar lesions near the fourth ventricle. The majority of severe complications occurred more than 30 days after SRS treatment. This 40% complication rate is much greater than previously reported in smaller case series and trials. Predictably, those with lesions in functional regions of the brain were more likely to develop complications. Patients with uncontrolled primary disease seem to be at more risk of complications. The toxicity and morbidity of SRS also appears to be greater in those patients receiving adjuvant WBRT following SRS.

Adjuvant whole brain radiotherapy

The next question, therefore, is that of adjuvant WBRT after local management

with either resection or SRS. Based on the older trials mentioned above, conventional wisdom has been to offer all patients adjuvant WBRT. However, the EORTC 22952-26001 trial compared WBRT with surveillance imaging in 359 patients following resection or SRS for 1 to 3 metastases and found that, although WBRT reduced the frequency of intracranial relapse, it failed to improve overall survival or functional independence [19]. Since WBRT adds significant morbidity, it has been suggested that after complete resection or successful SRS ablation, particularly of a single metastasis, many patients can be followed-up with regular brain imaging rather than immediate WBRT. A number of centres have adopted this approach, which requires careful discussion with the patient and a programme of regular imaging. The optimal imaging regimen has not been established, but an MRI scan at six weeks then every three months seems reasonable, with WBRT offered at relapse. This surveillance approach may be less attractive in those with multiple treated metastases and the authors of the EORTC trial continue to recommend adjuvant WBRT after local treatment of oligo-metastases. They also suggest that the surveillance option would be inappropriate in those who have had incomplete resection, those with a high risk of further intracranial disease (such as small cell lung cancer) or those who are having potentially curative treatment for their primary disease.

Surgery followed by radiosurgery

Recently there has been interest in treating highly-selected patients in a very aggressive manner with surgical resection followed by post-operative SRS or fractionated stereotactic radiotherapy (SRT) to the resection cavity. A retrospective review of 30 patients who underwent resection of 1-4 cerebral metastases, followed by adjuvant SRS or SRT, found that only 13% developed recurrence in the resection cavity [20]. However, 63% recurred elsewhere in the brain, the majority of whom received salvage WBRT at relapse. The 1-year overall survival was 51%. This approach of local management appears feasible, but patient selection is clearly going to be critical. In view of the high rate of recurrence elsewhere in the brain, perhaps there may even be a select group of patients who benefit from a triple modality approach of resection, followed by SRS to the resection cavity and adjuvant WBRT.

Summary

Appropriate management of brain metastases remains a significant and regular challenge for neurosurgeons, neuro-oncologists and general oncologists. While many patients are unlikely to benefit from any active intervention, and may be best managed conservatively with corticosteroids alone, there remains a role for WBRT in younger, fitter patients, particularly those for whom effective systemic treatment options remain. Furthermore, there is clearly a smaller, select group who benefit from aggressive local management with surgical resection or SRS and all potential cases should be discussed at a neuro-oncology multi-disciplinary meeting.

The choice of treatment will depend on the age and fitness of the patient, co-morbidities, the presence or absence of other sites of disease, the number and location of brain metastases and the nature of the underlying tumour. Patients deemed suitable for aggressive local management, i.e. those who have lesions less than 3.0cm, multiple lesions, surgical contra-indications, or with lesions in deep or eloquent parts of the brain, are likely to be offered SRS. Patients with single lesions greater than 3.0cm, in non-eloquent brain, or posterior fossa lesions, are more likely to be offered resection. Resection may also be preferred where there is a need to confirm the histological diagnosis. Even in less fit or older patients, SRS may be worthwhile for a single brain metastasis, although it is probably inappropriate for multiple metastases in such patients.

The role of adjuvant WBRT remains contentious and needs careful discussion with the patient – those who do not receive adjuvant WBRT will need an agreed surveillance imaging schedule, such as that described above. The utility of post-operative SRS to the resection cavity is also debatable, but may be considered on an individual patient basis.

SRS is, therefore, an important part of the armoury in the battle to effectively treat brain metastases, and all oncology units should have access to this treatment option for appropriate patients. ■

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