[9]. Elderly patients are less often included in clinical trials [10]. It is a well-known fact that patients treated according to a protocol have a significant survival advantage over those treated according to the free choice of the clinician [11].

Proper staging of the patients is mandatory. Stratification and randomisation is obligatory for a balance in prognostic factors and to exclude selection bias. Good definitions of what is aggressive, what is conventional and what is gentle treatment are needed. Is single drug treatment as effective as multiple drug chemotherapy? Is oral treatment as effective as intravenous? Is treatment in elderly patients more schedule dependent than in younger patients? Is it possible to predict the haematological reserve of these patients? Should haematopoietic growth factors be given routinely or only on indication? How disturbing are the concomitant illnesses these patients have, for a adequate chemotherapy? Is the reponse similar to that seen in the younger population?

These questions can only be answered in proper designed phase III studies with a large enough number of patients to draw valid conclusions. Only multicentre studies seem appropriate for this. Treatment of elderly patients should be part of the mainstream of oncological practice [12].

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Radiosurgery for Brain Tumours

THERE ARE many examples in medicine where advances in treatment are led by technology and not by intellectually satisfying pursuits. Nevertheless, the emergence of new techniques does not guarantee progress and the indiscriminate use of new and fashionable treatment methods has to be checked by careful clinical evaluation. Stereotactic radiotherapy (SRT) (or radiosurgery when in the hands of neurosurgeons) has hit the headlines as a new hope for brain tumour patients. It is undoubtedly a technologically advanced method of radiation delivery, but is it the clinical breakthrough often claimed?

What is SRT?

The principle of SRT is simple. It is a high precision technique of localisation and delivery of external-beam radiotherapy at present applicable to the treatment of intracranial lesions. Patients are immobilised in a neurosurgical-type stereotactic frame which acts as a point of reference for three-dimensional localisation on multimodality imaging. This allows for the precise localisation of a region of interest.

Irradiation is highly focused by arranging sources of radiation in a spherical distribution around the patient's head converging onto a small central point. This started life as "radiosurgery" delivered by a dedicated multiheaded cobalt unit with focused sources arranged in a hemisphere around a patient (so-called gamma unit or knife) [1]. Similar high-precision delivery can be achieved with a modern linear accelerator by multiple beams either as multiple arcs of rotation [2–6] or multiple fixed non-coplanar beams [7]. An alternative means of localised irradiation utilises the property of Bragg peak of heavy particles as cyclotron generated protons [8] or heavy charged particles [9]. All of these techniques represent stereotactically guided, conformal external-beam radiotherapy.

How does it help in practice? The high precision of tumour localisation makes it possible to irradiate a smaller volume of normal tissue with less margin for inaccuracy and highly focused treatment delivery reduces the amount of radiation to normal brain [7]. This may allow for a higher dose of radiation to the target while reducing or maintaining the dose to the surrounding normal tissue. Providing that the limitation of conventional technique is the radiation tolerance of normal brain surrounding the tumour, it may be possible with the use of SRT to give a higher dose to the tumour without increasing damage to normal brain. In any case this is the theory. In practice single-fraction SRT/radiosurgery has been successfully developed for the treatment of small inoperable intracranial arteriovenous malfor-

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mations (AVM). Certainly in this setting high radiation doses to the AVM are effective and cause minimal toxicity [10].

STEREOTACTIC RADIOTHERAPY IN BRAIN TUMOURS

The high precision of SRT is unquestionably a technological advance in external-beam radiotherapy. However, with current technology, the advantage over conventional treatment in terms of normal tissue sparing is limited to smaller tumours [7]. At present, SRT is also time-consuming and has been given either as a high single dose of radiation or with unconventional fractionation, situations in which both radiation tolerance and "equivalence" in terms of tumour control are not clearly defined. The enthusiastic initial application of SRT has been largely limited to small lesions treated with single-fraction SRT/radiosurgery. However, in tumours where conventional treatment is known to produce excellent local control with little toxicity the use of SRT is difficult to justify and has on occasions bordered on unethical. It would therefore seem prudent to suggest that the use of SRT, which may carry higher toxicity as well as uncertainty in its efficacy, should not be guided simply by tumour size. As any new therapy it should be assessed by its potential for clinical benefit either as improved tumour control (and hopefully survival) or as reduced toxicity, or preferably both.

Undoubtedly, reducing toxicity by irradiating less normal brain is a laudable objective but this is unlikely to be achieved with single-fraction treatment which negates all the advantages gained through fractionated radiotherapy. The advent of relocatable fixation devices [11–13] heralds a new era in SRT with much wider application, combining the potential advantages of fractionation as well as the increased precision of the technique. However, even in its fractionated form, SRT should strive to satisfy the criteria for clinical benefit.

Acoustic neuromas and meningiomas

Success with single-fraction radiosurgery (mostly with the gamma knife) has been reported in over 80% of patients with acoustic neuroma. However, computed tomography (CT) of 91 patients with unilateral acoustic neuroma treated with radiosurgery showed a reduction in the size of the lesion in 49% of patients and no change in 42% at an unspecified time [14]. The results appear worse in bilateral acoustic neuromas [14]. A smaller series of 40 patients with shorter follow-up suggests a reduction in size in 55% and no change in 43% at a minimum follow-up of 1 year [15]. This treatment is not without complications. It produces hearing loss [16] with more frequent deficit in larger tumours [15] and it is debatable whether it provides any advantage over conventional surgery.

A total of 67 patients with meningiomas treated with radiosurgery have also been reported [17, 18]. The selection criteria of these patients are not clear and there has been some mortality associated with the high-dose single treatment in one centre [17]. The good early results in terms of control rate are insufficient proof of effectiveness, as small meningiomas are indolent tumours with a long natural history.

Solitary brain metastases

Single-fraction SRT can effectively control solitary brain metastases [19] even after previous irradiation [20]. It is non-invasive and at the doses studied carries little toxicity [19, 20]. Providing it can be shown to be as effective as excision [21], SRT may become the future treatment of choice.

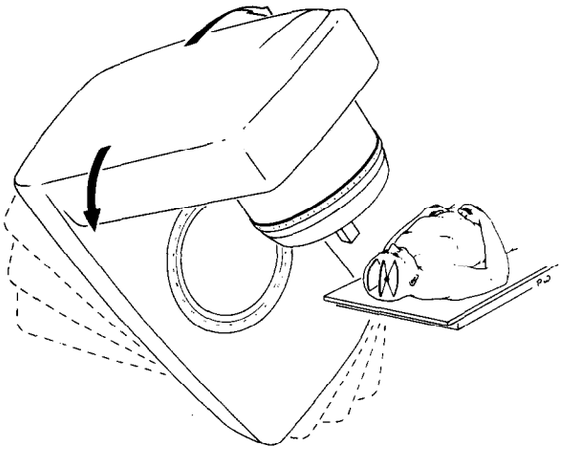

Fig. 1. Stereotactic external beam radiotherapy – highly focused irradiation of a small lesion is achieved by isocentric rotation of a linear accelerator in number of arcs around a precisely localised tumor. Patient is usually immobilised in a stereotactic fixation device (not shown).

Pituitary tumours

Pituitary adenomas and small pineal tumours are examples of localised small intracranial tumours which at first sight seem ideal for SRT. The current results of conservative surgery and radiotherapy in pituitary tumours are excellent with approximately 90% 10-year control rates [22, 23]. The toxicity of conventional treatment includes optic nerve and chiasmal damage, second intracranial tumours and late pituitary failure. The risk of damage to the optic pathway is under 1% and is usually associated with incorrect technique or fractionation. The risk of second brain tumours (assumed to be radiation induced) is 1.3% at 10 years, 1.9% at 20 years (our data). This is an approximately 10-fold increase in risk compared with the normal population. With these figures in mind it is difficult to see how SRT could improve tumour control and reduce toxicity. Unconventional fractionation may increase the toxicity to the optic pathway, particularly as the difficulty of controlling pituitary adenomas largely relates to tumours with suprasellar extension, a situation in which the optic chiasma is usually within or close to the mass. A reduction in the dose and volume of normal brain irradiated may reduce the risk of second tumours but a reduction of such low risk events will be almost impossible to prove. Second tumours have been reported within the pituitary fossa and it is therefore unlikely that the risk will be completely eliminated. It is also unlikely that SRT will avoid radiation induced late pituitary failure.

The results of conventional radiotherapy in acromegaly and pituitary Cushing's disease uncontrolled with surgery and medical treatment are less than satisfactory. Although hormonal control can be achieved, there is considerable delay in the normalisation of hormone levels [24–26]. To assess the potential benefit of SRT it is possible to draw on the experience of proton therapy in acromegaly [27]. At first sight it would appear that following proton therapy a higher proportion of patients reach normal growth hormone (GH) levels earlier than with conventional radiotherapy. Such results are entirely dependent on pretreatment GH levels and there is no published data demonstrating a faster decline in individual GH levels with protons. In addition, recent evidence suggests that lower radiation doses than conventionally used may be effective in the control of

acromegaly [26]. Patients with pituitary Cushing's disease have been treated with radiosurgery [28, 29] and protons [8] but it is difficult to prove that the results are superior to conventional treatment.

At present, it is difficult to justify the routine use of single-fraction SRT in the treatment of pituitary adenoma. However, conventional methods, even though effective, are not ideal and SRT technology continues to evolve. It is likely that in the future the combination of high precision of stereotactic localisation, delivery, conformal therapy and fractionation will be utilised to treat such localised tumours with higher accuracy and potentially lower toxicity.

Pineal tumours

The current results of conventional wide-field irradiation for histologically verified pineal germinoma are extremely good with a near 100% cure rate [30]. Although the toxicity of such treatment could be reduced, this could be achieved by selectively avoiding wide-field irradiation [31] and possibly by the use of chemotherapy (e.g. in large tumours) [32, 33]. There is uncertainty about the extent of tumour invasion around the pineal region and the toxicity of the current treatment technique is minimal. At present it would seem unwise to use SRT in pineal germinoma.

The control rate of non-seminomatous pineal germ cell tumours is poor with radiotherapy alone [30]. It can be envisaged that residual masses in the pineal region following chemotherapy and radiotherapy could be treated with an additional boost of SRT to reduce the relatively high risk of recurrence at this site. The role of SRT in rare pineal tumours such as pineocytoma is difficult to define.

High-grade gliomas

Undoubtedly there is a need for improvement in the local control of high grade astrocytomas [34] but few of these tumours are small and there is considerable evidence of their infiltrative potential [35]. Despite the theoretical objections to an aggressive approach in the treatment of small recurrent gliomas, re-operation [36] or interstitial radiotherapy [37, 38] have resulted in respectable survival of selected patients in a situation with otherwise dire prognosis. Small series of patients with recurrent high-grade gliomas have been treated with single fraction or fractionated SRT and the reported results are similar to those obtained with interstitial radiotherapy [2, 39–41]. The clear advantage of SRT over interstitial radiotherapy is its non-invasive nature and the possibility, if it is fractionated, of avoiding the high risk of necrosis and the need for reoperation associated with brachytherapy. At present it is not clear if the encouraging results of high dose localised therapy are due to the selection of patients with favourable prognosis and the results have also not been compared with those of other salvage programmes.

High-dose irradiation is being incorporated as a boost in the initial treatment of high-grade gliomas. Comparison of patients treated with an interstitial boost with historical controls (which may not be appropriate) suggests a survival advantage [42]. SRT seems a reasonable alternative and, as in the case of interstitial radiotherapy [38], it should be tested in a randomised prospective study. Such studies will not only have to show prolongation of survival but also improvement in quality of life, particularly as high-dose local treatment may result in localised neurological damage and possible functional impairment.

Low-grade gliomas

The role of localised treatment either in the form of surgery or radiotherapy is as yet unproven in patients with low-grade glioma and conventional radiotherapy is under investigation in randomised studies of the EORTC, MRC and BTCG. In addition few patients have localised disease of appropriate size suitable for high-precision focal treatment. Nevertheless, patients have been treated with either interstitial radiotherapy [43] or with one or two fractions of SRT [44]. Although the results are reasonable, these patients are highly selected and may fall into the best prognostic category of patients with low-grade glioma who achieve excellent long-term local control and survival with conventional treatment [45, 46]. Aggressive local approaches in patients with such indolent disease will also have to be tested in prospective randomised trials and the results of uncontrolled series cannot be accepted as evidence of efficacy.

Other tumours

There are a number of intracranial tumours where the poor results of conventional treatment are due to inadequate local control. Clivus tumours (chordoma/chondrosarcoma) are one example. Major advances in neurosurgery with skull-base approaches have improved resection rates although small tumour masses often remain and these may be amenable to treatment with SRT. Results of fractionated proton therapy in skull-base tumours would support such optimism [47]. Another example is medulloblastoma where despite recent improvements 30–40% of patients fail [48, 49] and the majority do so at the primary site in the posterior fossa [50]. A stereotactically guided localised boost of radiation away from sensitive structures in the brain stem may further improve the control of incompletely excised tumours beyond that achieved with adjuvant chemotherapy [48, 49, 51]. SRT may also be of value in patients with locally recurrent medulloblastoma who are rarely salvaged with other forms of therapy [52]. Undoubtedly there will be other potential indications for SRT and they should be considered in an impartial risk-benefit analysis.

CONCLUSION

Stereotactic radiotherapy is a major technological advance particularly when used in a fractionated form. It improves the precision of radiotherapy and new developments in the technology, especially advances in conformal therapy, are likely to widen its application. Prior to widespread use of SRT in neuro-oncology, its role should be carefully studied in selected tumour types so that it does not become discredited as a dangerous radiotherapy toy.

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