STEREOTACTIC RADIOSURGERY AND RADIOTHERAPY. RADIOBIOLOGY AND TREATMENT PLANNING.

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INTRODUCTION

Stereotactic radiosurgery (SR) is the treatment of small lesions in the brain using external beams of radiation. The treatment is performed in one single fraction with the use of high dose. The beams are guided to the desired point within the brain using very accurate, 3-dimensional imaging procedures (Leksell, 1951).

Stereotactic radiotherapy (SRT) is the treatment of small or medium lesions in the brain with fractionated regimes employing stereotactic method. This procedure differs from conventional radiotherapy in that the volume of tissue is usually smaller, the number of fractions delivered is much smaller, and the dose per fraction is much larger. The strategy of radiosurgery or stereotactic radiotherapy is to use the localisation of a high radiation dose to the volume of the target lesion to effect the desired biological sequalae, while sparing adjacent normal tissues.

Although stereotactic radiosurgery has traditionally been kept distinct from radiotherapy, the two fields are rapidly converging. In SR and SRT, improved dose localisation is achieved by using stereotactic apparatus to pinpoint the target volume, and by using special irradiation schemes and technology to deliver it precisely. Dose distributions with steep fall-off have been achieved primarily by a large number of ports or arcs (photon SR or SRT) or by improved depth dose characteristics (charged particle SR and SRT). Radiotherapy, too, is riding a wave of technological achievements that is carrying it to ever better dose distributions. Multileaf collimators, sophisticated 3-dimensional treatment planning programs for conformal therapy, computerised delivery systems, on-line portal imaging systems and megavoltage X-rays are all components of this effort. Improved diagnosis and better target localisation with CT and MRI are helping to heighten confidence in the volume needed to be treated. In the future, then, the advantages and techniques of radiosurgery and stereotactic radiotherapy will become of more interest and use to the radiotherapist, and they will take their place alongside the other, more established, methods.

STEREOTACTIC TREATMENT PROCEDURE

The flowing chart diagram showing the stereotactic procedure for SR or SRT is shown in Fig. 1. The individual procedures are closely connected and must be performed consequently, usually, in one day.

Indication criteria for SR or SRT are beyond the scope of this paper. Shortly speaking, the aim of SR and SRT is a choice of the most effective and most delicate treatment for the patient. Although neurosurgery disposes with many refined techniques, especially of microsurgery, and remains the standard treatment when both patient and the physician are willing to undertake the risks of such procedure, sterotactic radiosurgery or radiotherapy offers an excellent alternative to this.

There are some very important advantages for SR and SRT such as shortening of hospitalisation, sparing of social position, avoidance of operational risks and unexpected lowering of cost of the treatment, as well. Between disadvantages of SR and SRT belong delayed time of cure (0.5-3 years), lesion control instead of removal, insufficiency to resolve acute states, limitation by radiosensitivity of critical structures.

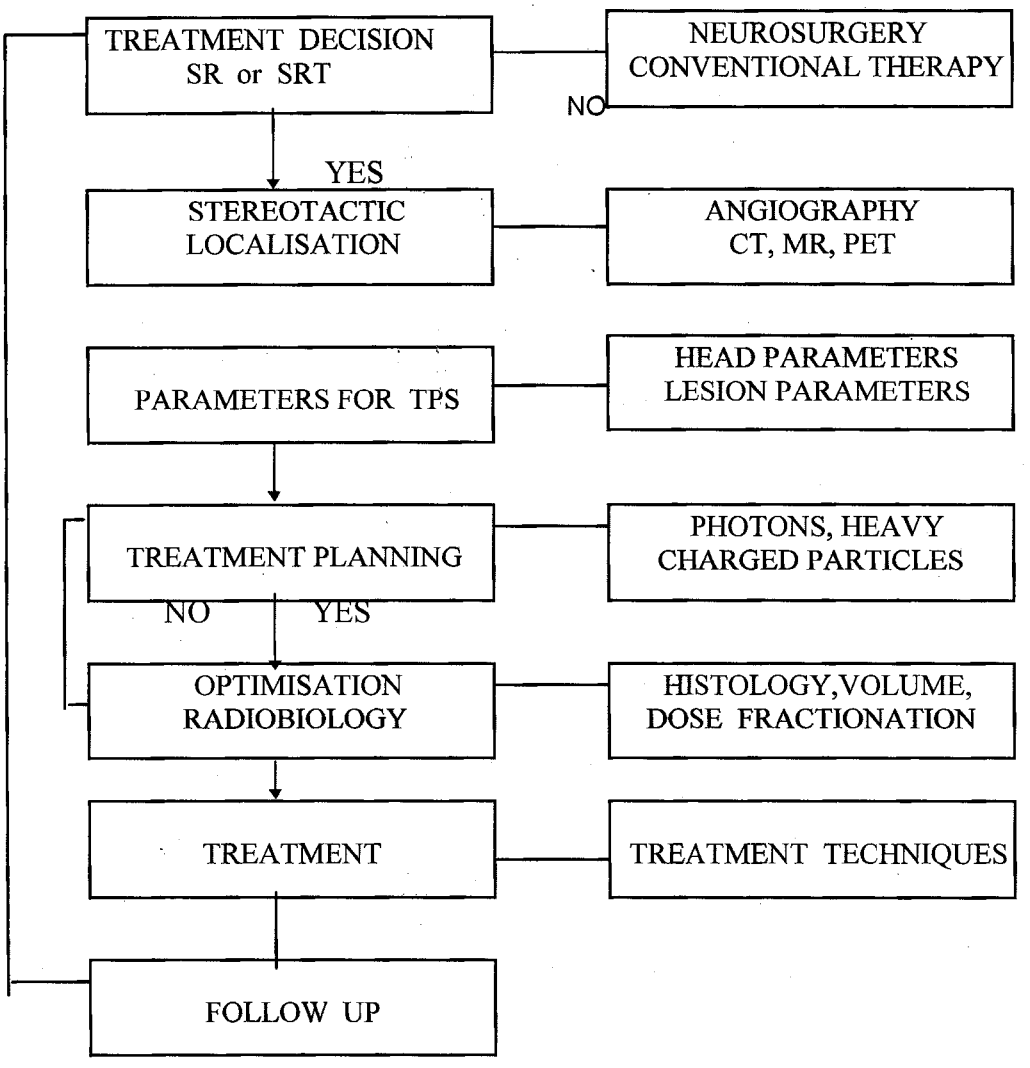

Fig. 1. : Flowing chart diagram for the stereotactic radiosurgery or stereotactic radiotherapy procedure.

Criteria for the choice of patient for SR and SRT depend mainly on the histology, volume and location of lesion, health condition of patient, etc. In principle four main groups can be identified in SR and SRT treatment: (a) functional ; (b) benign tumours; (c) malignant tumours; and (d) vascular malformation. Number of treated malignant tumours is increasing with the development of linac stereotactic technology very rapidly and it is expected that in near future it will be competitive with other three groups.

RADIOBIOLOGY OF RADIOSURGERY AND STEREOTACTIC RADIOTHERAPY

At radiosurgery or stereotactic radiotherapy narrow radiation beams are directed stereotactically to produce radiobiological effects within a carefully defined small intracranial volume. The desired effects within this target volume following a single treatment include blood vessel thrombosis and/or reproductive cell death. The common experience indicate that one can usually avoid delivering clinically significant dose beyond the target volume, in part because of the steep dose gradient at the target periphery and in part because most practitioners require the minimum dose to target isodose contour often as low as 50% of maximum-to closely conform to the 3-D target configuration. Interior to the target contour,

therefore, radiosurgery doses are often high and inhomogenous and results in larger variations in radiobiologic effect within and adjacent to the target volume than would be expected following a course of fractionated treatment. This is due to the degree of curvature of cell survival curves obtained with X-rays or gamma rays, which may be very large for normal human glial cells and for many radiosurgery targets. Therefore, interior to the target periphery, small increments of dose often have a disproportionate radiobiological effect, which is accentuated by the steep gradient, and may increase likelihood of cure of complication. Beyond the target tissue, on the other hand the isodose curves would suggest, possibly decreasing normal tissue effects or decreasing the response of infiltrative cells beyond the apparent target periphery.

The first radiobiological principle of importance here is that malignant tumors, even of those of limited size, usually contain a proportion of *hypoxic cells* that, because of their deficiency in oxygen, are resistant to killing by X rays or gamma rays (Larson et all., 1993; Hall and Brenner, 1993). The cellular survival curve for malignant cells is characterised by having two components; the slopes of the two components differ by factor of 2.5 to 3. Up to doses of several Gy, the response is dominated by killing of aerobic cells, while for higher dose, the killing of hypoxic cells dominates. It is immediately apparent that irradiating these tumor cells with single large dose of several tens of Gy will not kill all the cells, because the dose of this size will not be adequate. However, it is well known fact, that tumors exhibit a characteristic known as *reoxygenation* whereby, between fractionated doses of X rays and gamma rays, tumors tend to re-establish their original pattern and proportion of oxygenated and hypoxic cells. In a fractionated regime, therefore, each dose of X-rays or gamma rays predominately kills aerobic cells, and the interval between treatments allows hypoxic cells to re-establish their oxygenated state.

The second radiobiological principle is based upon a wealth of experimental evidence that indicate that there is a difference in shape between the dose response relationship characteristic of *early responding tissues and tumors, and late responding tissues.* In mathematical terms, if the dose-response relationship is expressed with a linear-quadratic relation where cellular survival, S, is then the ratio of a/b tends to be small for late responding tissues (< 3 Gy) and larger (> 8 Gy) for early responding tissues. The practical consequence of the difference in shape between the dose-response curves for early and late responding tissues is a marked difference in the response to fractionation of these two types of tissues. Late-responding tissues are more sensitive to changes in fractionation than early-responding tissues.

The linear-quadratic formalism is now a generally accepted and proven tool in the field of radiation oncology for comparing the early and late effects of different fractionation schemes. The magnitude of different effects obtained from radiosurgery and fractionated radiotherapy can be seen from Fig. 2 where is a plot of radiosurgery dose versus total fractionated dose at 2 Gy per fraction necessary to produce the same radiobiological effects, both for late responding tissue (a/b=2.5, upper curve) and for early responding tissue (a/b =10, lower curve) This figure is based on biologically effective dose (BED) formalism recently reviewed by Fowler (1992) in which:

$$BED = RSD * (a/b + RSD)/ (a/b)$$
$$= TFD *(a/b + d)/ (a/b) - n* 0.693 /a,$$

where RSD - radiosurgery dose, TFD - total fractionated dose , d - daily dose,
n -number of cell doublings.

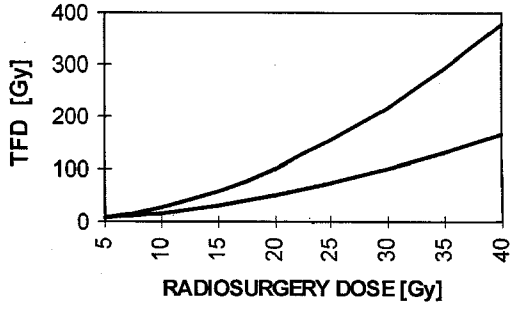

Fig. 2: Radiosurgery dose (RSD) versus total fractionated dose (TFD) at 2 Gy per fraction necessary to produce the same radiobiological effects.

Calculation has been simplified by assuming that the last term in the above equation is negligible. Without this approximation, the total fractionated dose corresponding to a given RSD would be somewhat large. It is obvious that using this formalism it is possible to construct curves for different values of a/b and/or to calculate different fractionated or protracted stereotactic regimes.

It is useful to categorise potential radiosurgery target according to whether the target tissue is early or late responding and according to whether it is embedded within or only surrounded by normal tissue. It is assumed that normal relevant tissue consists mostly of low a/b, late responding tissue (glial cells, for example) and it is also distinguished target volumes that contain only abnormal tissue from those containing both abnormal and normal tissues. All radiosurgical target can be attributed to one of the categories given in the Table 1.

Table 1: Definition of different categories of radiosurgical targets.

Category	Description	Example	$(a/b)_{TU}/(a/b)_{NT}$	Fractionation
I.	late-responding target embedded within late-responding normal tissue	AVM	low/ low	NO
II.	late-responding target surrounded by late-responding tissue	meningeoma	low/low	POSSIBLE
III.	early-responding target embedded within late-responding tissue	low grade astrocytoma	high/low	YES
IV.	early-responding target surrounded by late-responding tissue	metastases	high/low	YES

Radiosurgery volumes are usually less than a few centimetres in maximum dimension. This target size limitation is based on clinical experience showing that radiosurgery *complications* are much strongly *associated with target size* than with dose, and thus related to the volume of normal tissue-receiving significant radiation dose. For radiosurgery targets surrounded by normal tissue and for those embedded in normal tissue the dose is delivered to a thin rim of normal tissue just beyond the target periphery. The volume of the rim is proportional to the square of target radius. For radiosurgery of targets embedded in normal tissue, significant dose is delivered additionally to any normal tissue within the target volume. This volume is proportional to the cube of the target radius. For either type of target, therefore, unavoidable *geometrical factors* results in a rapid increase in the volume of normal tissue receiving significant dose as target size increases.

Regarding AVM, it is clear that the radiobiological principles do not imply any particular radiobiological advantage if one fraction scheme over another. Generally it is accepted that radiosurgery for small AVM is better than fractionated irradiation. It is not recommended to treat, either by the radiosurgery or by the fractionated irradiation, large AVM because doses likely to be curative are to cause clinically unacceptable levels of normal tissue damage.

Regarding malignancy, it is clear that fractionated schemes are potentially superior to radiosurgery for small malignancies, at least in principle, especially if one ignores the possible effects of radiosurgery on vessels within the target volume. On the basis of basic radiobiological principles applicable to tumor radiotherapy, it would seem important that, when stereotactic fractionated radiotherapy for treatment of malignancies situated in the brain is used, moderate number of fractions (around five to six) should be used. By contrast, single-fractionated treatment of a malignancy would be expected to give suboptimal therapeutic ratio between tumor control and late complications. Fractionated regimes using five or six fractions can be calculated using above equations for early and late responding tissues to produce the same radiobiological effects. Examples are given in tab. 2 (ignoring proliferation during treatment).

It is worth mentioning that stereotactic fractionated techniques have several advantages over conventional fractionated techniques, chief of which is that the desired target volume-and only the target volume-receive full dose irradiation in a highly reproducible manner. This can only improve the therapeutic ratio.

Table 2: Radiosurgery dose and corresponding total radiotherapy dose to produce a similar radiobiological effect, for late (a/b =2.5) and early responding tissue (a/b =10) .

	Total fractionated dose [Gy]			
	2.5 Gy/fraction		6 Gy/ fraction	
Radiosurgery dose	a/b=2.5	a/b =10	a/b=2.5	a/b =10
10 Gy	27.8	16.7	14.7	12.5
20 Gy	100	50	53	37.5
30 Gy	216.7	100	114.7	75

TREATMENT PLANNING

Treatment planning procedure consists in principle from three components: target volume delineation in 3D using stereotactic images and evaluation of co-ordinates, dose distribution calculation in 3D and treatment time or monitor unit calculation for selected dose. The aim of dose distribution calculation is to tailor isodose curves around the target volume, that is the spatial dose distribution must be shaped so that the maximum dose volume always is located within target volume. Generally it is ambition to shape the dose distribution so that the border of the target is circumscribed by a dose surface of 80 to 50 % of the dose maximum. This reflects the ambition to combine a homogenous distribution within the target and rapid fall off at its periphery.

Criteria for selection of absorbed dose levels for individual cases are based on three major factors: a) *histology* of the surgical target; b) *target volume,* and c) by proximity of *critical structures* close to the target. The dose is usually prescribed at the periphery of the target but sometimes, and particularly for functional disorder treatment the maximum dose is used. Sometimes the dose to maximum is limited by the tolerance of dose to critical structure, for example to brain stem.

The treatment planning system depends on the treatment techniques used in the department. There are available commercial treatment planning system, like GAMAPLAN or KULA for Gamma Knife, X-KNIFE from RADIONIX for Varian stereotactic system, STEREPLAN PLUS for Leibinger system,etc. It is quite obvious that special stereotactic techniques require special input data for therapy machine and patient's input data. It is therefore impossible to explain here even different systems used, and therefore only basic ideas of treatment planning procedure will be outlined.
The safe administration of the large single or multiple fraction doses of irradiation used in SR or SRT is made possible by a combination of the small size of the treatment fields used and the close matching of the treatment volume with the target volume facilitated by stereotactic localisation techniques. Circular collimators are used with Gamma Knife and with most linear accelerator stereotactic techniques. The use of circular collimators results in treatment volumes which are fairly spherical in shape. Depending on the techniques used and the position of target volume within skull, the treatment volume may be elongated diameter in one particular direction or can be quite irregular. When the target volume to be treated deviates significantly from the shape of the roughly spherical treatment volume for SR or SRT with a single isocenter it is helpful to change the shape of the treatment volume to limit the amount of high dose irradiation to surrounding tissues. The shape of treatment volumes can be basically modified by (Phillips, 1993):
a) combination of different collimators in one isocenter; b) selective blocking; c) using multiple isocentric irradiation; d) using different weights for different shots; e) change of "gamma angle", i.e. different position of patient's head; f) change of dose rate for different entrance angles.

The use of selective blocking makes a treatment of irregular target volumes more conformal and provides less dose to critical structures. Selective beam blocking appears to be useful technique for shaping radiosurgical dose distributions for all stereotactic techniques, especially when treating a target volume situated directly underneath and important and/or radiosensitive structure as optic chiasm. The combination of multiple isocenter treatment techniques with selective beam blocking is a particularly useful for irregular tumors such as acoustic neurinomas.
Optimisation of alternative results of treatment planning within one medical centre and the increasing interest of various centres in stereotactic SR or SRT make it necessary that a basis of evaluation and comparison be found. Two-dimensional isodose contours overlaid on the main anatomical structures and dose volume histograms may possibly provide such a basis. Evaluation of such treatment planning results is frequently done merely by qualitative analysis by an experienced neurosurgeon. A more quantitative evaluation is facilitated by dose-volume histograms. The problem of evaluation as a whole, however, is not yet sufficiently solved and remains to be done in the future.

Each treatment plan has to be optimised from three basic aspects: firstly from the point of absorbed dose conformation including absorbed dose level used for treatment; secondly, for critical structures near the target volume; thirdly, for radiobiological aspects. It is necessary to optimise the expected outcome of the treatment and possible risk having consequences in increased morbidity. Optimisations of treatment plan, mostly based on previous experience, is a fundamental part of the treatment, but patient's radiation protection safety should be considered as well.

FUTURE DIRECTIONS

Stereotactic radiosurgery and stereotactic radiotherapy is an attractive therapy because a)it is efficacious for treating lesions in

inaccessible regions of the brain; b) morbidity and mortality are low (there is almost no risk of infection or haemorrhage);c) treatment is quick and precise.

In future, it is likely that the previously sharp distinction between radiosurgery and radiotherapy will become increasingly blurred. Radiotherapists are expeditiously applying the well-confined dose distributions available with stereotactic methods. While appropriating the dose localisation characteristic of radiosurgery, they must acknowledge the biological characteristics of each specific lesion being treated. New fractionation schedules are being explored, and new methods for tailoring the dose distribution to the target volume are being developed. From the neurosurgical side, radiosurgery has become one more tool in the neurosurgeon's stereotactic toolkit whose role in the treatment of various diseases is being explored. Another trend in the use of SR and SRT as but one step in a multi-modality treatment that can include surgery, chemotherapy, and embolization.

Development in the physics of stereotactic SR and SRT will, no doubt, parallel those occurring in radiation therapy. Namely, better improvements in treatment will rely on better treatment planning algorithms; precise, reliable and for patient more confortable positioning techniques will be developed and used.

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