Indications of Stereotactic Irradiation for Brain Lesions

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Acta Oncologica Vol. 39, No. 5, pp. 597–603, 2000

Stereotactic radiosurgery (SRS: single-fraction stereotactic irradiation) was originally developed to treat benign lesions in the brain, and has been adopted for the treatment of small primary or metastatic brain tumours. It has recently been recommended that stereotactic radiotherapy (SRT: fractionated stereotactic irradiation) be applied to the treatment of brain tumours; however, it requires much more time and work than SRS, and sufficient radiobiological evaluations of these techniques have never been carried out. Biologically effective doses were calculated to determine the indications for SRS and SRT, and to decide on an effective SRT schedule, incorporating the factors of 'repair' and 'cell proliferation'. The results suggest that SRS would be recommended for arteriovenous malformations and benign tumours that have distinct margins separating them from surrounding normal tissue and SRT would be recommended for benign or malignant brain tumours without clearly defined boundaries. The recommended SRT schedules would be 7 Gy × 7 fractions every other day for malignant tumours and 3.5 Gy × 12 fractions every other day for benign tumours. However, clinically, these schedules should be modified according to many other factors in individual cases.

Received 9 December 1999
Accepted 10 May 2000

Stereotactic radiosurgery (SRS: stereotactic irradiation (STI) delivered in a single high dose-rate fraction) was initially developed by Leksell (1) for the treatment of non-malignant lesions in the brain. There is increasing interest in its use to treat small primary brain tumours or metastases (2–6). In more recent years, stereotactic radiotherapy (SRT: fractionated STI) has been developed; however, sufficient radiobiological evaluations have not been carried out on these techniques. Larson and colleagues categorized potential STI targets into four categories 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 (7). We actually calculated the biologically effective dose (8, 9) for these categories to make clear applications of SRS and SRT, and to determine a reasonable SRT schedule. Factors of 'repair' and 'cell proliferation' have been neglected in the radiobiological considerations for STI reported to date, mainly because of complexity of calculation. 'Half-time repair' (10, 11), which is one of the key values in the 'repair' factor, might be larger for the nervous tissue than many other normal tissues because nerve cells have poor ability to recover from various types of damage. 'Cell proliferation' should be a very important factor when the total radiation period would be extended by applying SRT. In this study, we made the models by assuming the values of 'half-time repair' and 'cell doubling time', and investigated the ideal SRT schedules for benign and malignant brain tumours.

MATERIAL AND METHODS

Calculation of the biologically effective dose (BED)

We calculated BEDs from equation 1 (8, 9) to compare the radiobiological effect of different STI schedules.

$$BED = D\left(1 + \frac{Gd}{\alpha/\beta}\right) \quad [1]$$

where D is the total dose and d the dose of one fraction, and α and β are the linear-quadratic coefficients, respectively. α/β is a characteristic value for each tissue or organ and in this study we assumed it to be 10 Gy for an early effect and 2 Gy for a late effect on central nervous tissue,

 ISSN 0284-186X

the same as in many other reports (7, 12). G is a value that incorporates the repair factor of the sublethal damage during irradiation (13, 14), but little attention has been given to the G-value in the past, and many studies on STI have calculated BEDs from the following equation, assuming that G = 1 (7, 12, 15):

$$BED = D\left(1 + \frac{d}{\alpha/\beta}\right) \quad [2]$$

In this study, we paid particular attention to the G-value and calculated it from following equation (14, 16):

$$G = \frac{2}{\mu T}\left\{1 - \frac{1}{N\mu T}(NY - SY^2)\right\}$$

$$Y = 1 - \exp(-\mu T)$$

$$S = \frac{NK - K - NK^2Z + K^{N+1}Z^N}{(1 - KZ)^2}$$

$$K = \exp(-\mu X)$$

$$Z = \exp(-\mu T)$$

R = dose rate; μ = time constant, $\mu = \ln 2/t_{\frac{1}{2}}$ ($t_{\frac{1}{2}}$: half-time repair); N = number of fractions; T = exposure period per fraction; X = interval period.

The value of $t_{\frac{1}{2}}$ has been assumed to be about 3 h in some reports (10–16), but we also calculated the G-value at various $t_{\frac{1}{2}}$ values (from 1 to 9). We used a constant dose rate (R) of 120 Gy/h.

When we also incorporated the cell proliferation factor, the equation for BED became (15):

$$BED = D\left(1 + \frac{Gd}{\alpha/\beta}\right) - \left(\frac{\ln 2}{\alpha} \times \frac{T_{all} - T_k}{T_{eff}}\right)$$

T_{all}: overall radiation period; T_{eff}: effective doubling time; T_k: kick-off time for the change in tumour kinetics.

Little is known about the T_{eff} of brain tumours. Clinically, the period required for a tumour diameter to double on CT scans or MRI images averages several weeks for malignant tumours and several months for benign tumours. In this study, we assumed it to range from 20 to 200 days, and thus the T_{eff} should be 5 days ($20/2^2$) for malignant tumours and 50 days ($200/2^2$) for benign tumours. The values for parameters T_k and α were used as estimated by Fowler (15): 14 days and 0.35 Gy^{-1}, respectively. Accordingly, BEDs should be calculated by the following equations when the overall irradiation period exceeds 14 days.

For malignant tumours:

$$BED = D\left(1 + \frac{Gd}{\alpha/\beta}\right) - \left(\frac{0.693}{0.35Gy^{-1}} \times \frac{T_{all} - 14}{5}\right)$$

$$= D\left(1 + \frac{Gd}{\alpha/\beta}\right) - 0.396(T_{all} - 14) \quad [5]$$

For benign tumours:

$$BED = D\left(1 + \frac{Gd}{\alpha/\beta}\right) - \left(\frac{0.693}{0.35Gy^{-1}} \times \frac{T_{all} - 14}{50}\right)$$

$$= D\left(1 + \frac{Gd}{\alpha/\beta}\right) - 0.396(T_{all} - 14) \quad [6]$$

Classification of STI targets

Larson and colleagues classified potential STI targets into four categories 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 (7), as follows (Fig. 1):

(A) Late-responding target embedded within late-responding normal tissue: Abnormal arteriovenous malformation (AVM) vessels often interlaced within a matrix of glial cells. In this case, both the target tissue and the normal tissue have low α/β values ($\alpha/\beta = 2$) and are exposed to the same radiation dose (estimated ratio of normal tissue dose to target dose: 100%).

(B) Late-responding target surrounded by late-responding normal tissue: Meningioma usually does not invade normal brain parenchyma. In this case, both the target tissue and the normal tissue have low α/β values ($\alpha/\beta = 2$), but are exposed to different radiation doses (estimated ratio of normal tissue dose to target dose: 80%).

(C) Early-responding target embedded within late-responding normal tissue: Both normal glial cells and

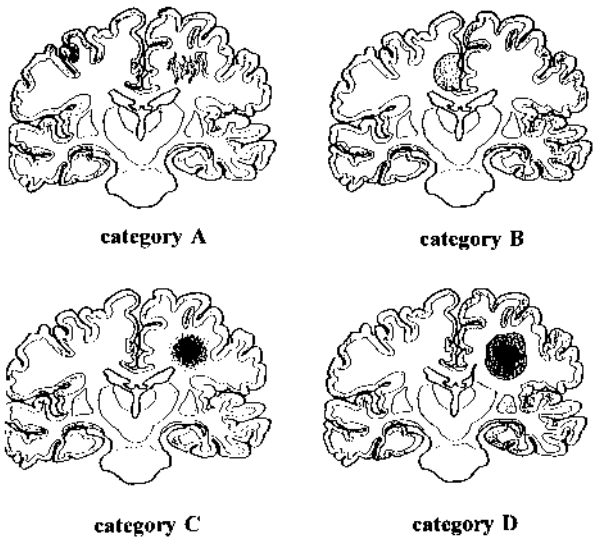

Fig. 1. Classification of potential stereotactic irradiation targets according to whether the target tissue is early- or late-responding and whether it is embedded within or only surrounded by normal tissue. (A) Late-responding target embedded within late-responding normal tissue. (B) Late-responding target surrounded by late-responding normal tissue. (C) Early-responding target embedded within late-responding normal tissue. (D) Early-responding target surrounded by late-responding normal tissue.

malignant glial cells reside within the target volume in the form of an astrocytoma. In this case, the target tissue ($\alpha/\beta = 10$) and the normal tissue ($\alpha/\beta = 2$) are exposed to the same radiation dose (estimated ratio of normal tissue dose to target dose: 100%).

(D) Early-responding target surrounded by late-responding normal tissue: The radiographically apparent target volume contains mainly malignant cells in the form of a metastatic brain tumour. In this case, the target tissue ($\alpha/\beta = 10$) and the normal tissue ($\alpha/\beta = 2$) are exposed to different radiation doses (estimated ratio of normal tissue dose to target dose: 80%).

We calculated BEDs for each category to determine the indications for SRT and to be able to choose a suitable SRT schedule.

RESULTS

Indications for SRT

SRT has been recently adopted to treat small brain lesion; however, it requires much more time and work than SRS. Thus, it is necessary to decide the indications for SRT. Over the last few years, several studies have been devoted to the assessment of SRS at a dose of 15–20 Gy in one fraction, and for the most part satisfactory results of treatment have been obtained without severe chronic complications. To calculate the optimal SRT schedules we considered 220 Gy_2, which is equivalent to the late-effect dose of SRS at a dose of 20 Gy calculated from equation 2 $[20(1 + 20/2) = 220\ Gy_2]$, to be the limiting late-effect dose. The subscript '2' means that this BED value is calculated by using an α/β ratio of 2 Gy. We evaluated the indications for SRT by classifying STI t1argets into four groups (A–D; Fig. 1), as described by Larson and colleagues (7). The estimated α/β values of the targets and the ratios of normal tissue dose to target dose (N/T ratio) in these four groups are described above. The STI schedules with 220 Gy_2 as the limiting dose for categories A and C (N/T ratio = 100%) and categories B and D (N/T ratio = 80%) are shown in Table 1 (calculated by using equation 2). We calculated the early-effect BEDs for each schedule using the estimated α/β values, and the results are shown in Fig. 2. The values in this figure clearly demonstrate that fractionation (SRT) should be applied to categories C and D and SRS should be recommended for categories A and B.

SRT schedule

SRT should be recommended for category C and this category might be primary tumours with all grades of malignancy from low to high (benign to highly malignant). Conventional external-beam radiotherapy schedules for these tumours are generally 2 Gy × 25 fractions, 2 Gy × 30 fractions or 2 Gy × 35 fractions, selected according to the grade of malignancy. Total sterilization of all clonogenic cells in the target volume should be the aim of treatment for the malignant brain tumours, whereas total tumour sterilization is not always necessary for the benign tumours because long-term survival is expected in patients with benign tumours when the tumour cells are sufficiently damaged and lose their invasive nature. Thus, the doses of SRS should be set lower for benign brain tumours than for malignant brain tumours. In this study, we considered 15 Gy to be the standard SRS dose for benign tumours and 20 Gy for malignant tumours. The BEDs of the schedules were calculated from equations 1 and 3, in which $t_{\frac{1}{2}}$ was assumed to be 3 h. The early-effect BEDs for SRS irradiated with 15 Gy and 20 Gy were 37.3 Gy_{10} and 59.5 Gy_{10}, respectively, and while the late-effect BEDs for these schedules were 126.4 Gy_2 and 217.5 Gy_2.

Table 1

Stereotactic irradiation schedules conditioned on a dose limit of 220 Gy_2, the late-effect dose of stereotactic radiosurgery at the dose of 20 Gy

No. of fractions	Dose/fractions (Gy)	Total dose (Gy)
Categories A and C		
1	20.00	20.00
3	11.15	33.45
6	7.62	45.72
9	6.06	54.54
12	5.13	61.56
15	4.50	67.50
Categories of B and D		
1	25.00	25.00
3	13.94	41.81
6	9.53	57.15
9	7.58	68.18
12	6.41	76.92
15	5.63	84.38

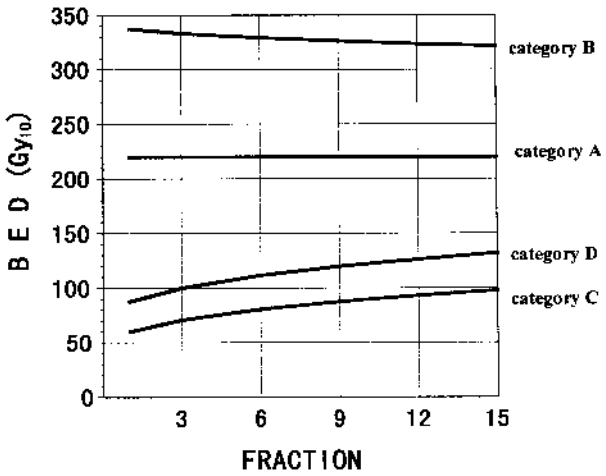

Fig. 2. Biologically effective doses (BEDs) for the target categories in figure 1 delivered in 1, 3, 6, 9, 12 or 15 fractions that would produce late-effects equivalent to SRS (single fraction) in each category.

Table 2

Stereotactic radiotherapy schedules for malignant brain tumours that produce a late-effect of 217.5 Gy_2, which is equivalent to a late-effect BED of stereotactic radiosurgery at a dose of 20 Gy

No. of fractions	Dose/fraction (Gy)	Total dose (Gy)	Early-effect BED Gy_{10}
1	20.00	20.00	59.50
2	13.86	27.27	66.14
3	11.15	33.45	70.75
4	9.53	38.12	74.45
5	8.43	42.15	77.68
6	7.62	45.72	80.56
7	6.99	48.93	83.13
8	6.48	51.84	85.43
9	6.06	54.54	87.59
10	5.70	57.00	89.49
12	5.13	61.56	93.14
15	4.50	67.50	97.88

SRT schedule for malignant brain tumours. SRT schedules producing a late-effect BED of 217.5 Gy_2, which is equivalent to a late-effect BED of SRS at a dose of 20 Gy, are shown in Table 2 ($t_{\frac{1}{2}}$ was assumed to be 3 h), and the early-effect BEDs for each schedule are shown in the last column of the table. The early-effect BED for a conventional external beam irradiation schedule for malignant brain tumours of 2 Gy × 35 fractions is calculated roughly as $70(1 + 2/10) = 84$ Gy_{10}, and the SRT schedule that would produce an equivalent early-effect BED is 7 Gy × 7 fractions. We chose this schedule for further consideration of the factors of repair and cell proliferation. The results of calculating late-effect BEDs and early-effect BEDs from equations 1 and 5, with $t_{\frac{1}{2}}$ values ranging from 1 to 9, for SRT schedules with irradiation every day (7-day schedule), every second day (13-day schedule), every third day (19-day schedule), and every fourth day (25-day schedule), are shown in Fig. 3. When the irradiation period was 7 days, late-effect BED rose steeply as the value of $t_{\frac{1}{2}}$ increased (Fig. 3A). Early-effect BEDs decreased by 2.0 Gy and 4.3 Gy when the radiation periods were 19 days and 25 days, respectively (Fig. 3B). Considering the factors of repair and cell proliferation, the recommended schedule for malignant brain tumours should be 7 Gy × 7 fractions every other day. This schedule should be considered as one example conducted under several assumed values, so that it must be modified in various clinical conditions.

SRT schedule for benign brain tumours. The same consideration is also extended to benign brain tumours. SRT schedules producing a late-effect BED of 126.4 Gy_2 (equivalent to 15 Gy SRS) and its early-effect BEDs are shown in Table 3. We chose the SRT schedule of 3.7 Gy × 12 fractions for further consideration because it would produce an early-effect BED equivalent to that of the conventional 2 Gy × 25 fractions external beam irradiation schedule [$50(1 + 2/10) = 60$ Gy_{10}]. The late- and early-effect BEDs for SRT schedules for 1- to 4-day intervals are shown in Fig. 4. When the irradiation period was 12 days, the late-effect BED rose steeply as the value of $t_{\frac{1}{2}}$ increased (Fig. 4A). Early-effect BEDs decreased by only 0.5 Gy_{10}, 1.0 Gy_{10} and 1.5 Gy_{10} during the 23-, 34- and 45-day radiation period, respectively (Fig. 4B). Thus, the 3.7 Gy × 12 fractions SRT schedule, with fractions administered at 2- to 4-day intervals, would be theoretically acceptable; however, we recommend the shortest schedule (irradiation every other day) to make treatment more convenient for patients and because of the relative high BED of the early effect.

DISCUSSION

There is increasing interest in the use of STI to treat small brain lesions because it can concentrate very high doses on the target. However, late complications involving damage to normal glial cells just beyond the periphery of the target (17, 18), such as facial nerve dysfunction after STI for acoustic neurinoma (2, 19), are a constant concern. SRT is replacing SRS for certain targets for radiobiological reasons (20, 21); however, sufficient radiobiological evaluation of these techniques has not been performed. With STI, multiple narrow radiation beams are stereotactically directed to produce a radiobiological effect within a carefully defined small intracranial volume. Many clinicians do not yet have a 'feel' for the magnitude of the biological effects generated by this procedure. Therefore, it is useful to calculate the BED, which was introduced by Barendsen (8) and reviewed by Fowler (15), to use for reference. BED is a useful concept for the summation of different fractionated schedules, and has the dimensions of dose. It is the quickest way to see if the total dose must be reduced when large doses per fraction are used. Brenner and colleagues discussed the SRT schedule theoretically (22), based on the results of low dose-rate ^{125}I brachytherapy of brain tumours and experimentally obtained α/β and $t_{\frac{1}{2}}$ values. However, the cell proliferation factor was not considered in their report, and they did not mention the total radiation period. SRT requires much more time and work than

SRS, and thus clear indications for STR would need to be present to select it over SRS. A radiation period of at least a few weeks should be necessary for SRT, and the repair and cell proliferation factors should be incorporated for radiobiological factors to be considered in selecting effective SRT schedules.

Indications for STI in the clinical setting

We evaluated indications for STI by classifying STI targets into four categories (Fig. 1) and showed that SRS should be recommended for categories A and B, and that SRT should be recommended for categories C and D. However, there are other factors to take into consideration when STI is used clinically.

1. Category A: Arteriovenous malformations (AVMs) are an example of a target in this category, in which both SRS and SRT would have an equivalent therapeutic effect based on our calculations (Fig. 2). Because the abnormal vasculature of the AVM nidus does not provide nourishment to immediately adjacent tissue, some glial cells may be in a hypoxic state, which may in turn decrease their radiosensitivity. One might argue for a single fraction rather than multifraction treatment to avoid irradiating re-oxygenated normal tissue. Little information is available concerning this point; however, no therapeutic gain would be expected from fractionating the treatment of AVMs.
2. Category B: Meningiomas are an example of a target in this category, and SRS is recommended based on our calculations. Meningiomas have a clear-cut boundary and do not usually invade normal brain parenchyma; however, their borders are not always smooth. When tumours have an intricate boundary, normal glial cells may be exposed to radiation doses equivalent to those of the target, and reduction of the total dose and/or a fractionated STI schedule should be considered.
3. Category C: Astrocytomas are an example of a target in this category and an SRT schedule is recommended to treat them based on our calculations (Fig. 2). In this category, it is important to draw the margin of the target. Overestimation of the target would lead to increased late complications and underestimation would result in treatment failure. A further point that needs to be clarified is modification of the biological effect by repair and cell proliferation. This is a very important point, and is discussed below in detail.
4. Category D: Metastases are an example of a target in this category and SRT is recommended based on our theoretical considerations. Many patients with brain metastasis cannot be expected to have a long-term survival. In such cases, a treatment schedule that is immediately effective is preferable, and late complications of irradiation would not be a major consideration. Thus, SRS should be recommended for some cases in this category.

Factors of repair and cell proliferation for SRT schedule

It has been established that the '4 Rs', repair, repopulation, reassortment and reoxygenation, are the important radiobiological principles in fractionated radiotherapy. It has not been possible to calculate the actual values for reassortment and reoxygenation by a generally accepted formula. Over the last few years, evaluation of repair and repopulation has been the subject of controversy, but little attention has been given to this point when considering STI schedules. New values are needed to evaluate these factors: half-time repair ($t_{\frac{1}{2}}$) for 'repair', kick-off time for the change in tumour kinetics (T_k), and cell-doubling time (T_{eff}) for 'cell proliferation'. Little information is available

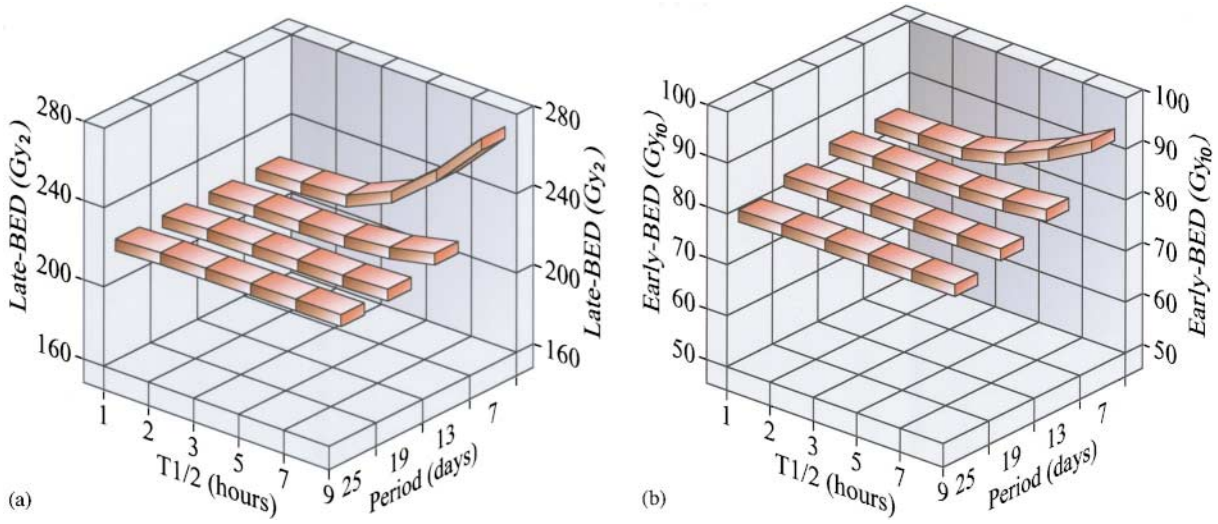

Fig. 3. Late- (A) and early- (B) effect biologically effective doses (BEDs) of the 7 Gy × 7 fractions schedule for malignant and benign brain tumours delivered over 7, 13, 19 and 25 days, assuming a half-time repair value ($t_{\frac{1}{2}}$) of 1, 2, 3, 5, 7 and 9 h.

Table 3

Stereotactic radiotherapy schedules for benign brain tumours that produce a late-effect BED of 126.4 Gy_2, which is equivalent to a late-effect BED of stereotactic radiosurgery at a dose of 15 G

No. of fractions	Dose/fraction (Gy)	Total dose (Gy)	Early-effect BED (Gy_{10})
1	15.00	15.00	37.29
2	10.30	20.60	41.76
4	7.01	28.04	47.72
6	5.56	33.36	51.96
8	4.70	37.60	55.34
10	4.12	41.20	58.25
12	3.69	44.28	60.70
14	3.36	47.04	62.93
16	3.09	49.44	64.80
18	2.87	51.66	66.57
20	2.69	53.80	68.30

on these values, and introducing these factors adds several stages of complexity and potential error, but the procedure is useful for comparing new schedules, where the assumptions for the schedules to be compared are kept the same.

Repair. Many different values make up the repair factor, as shown in the complex equation 3, but the most important may be $t_{\frac{1}{2}}$, the half-time for repair of sublethal damage, which has been estimated to be about 3 h in some reports (10, 11). However, the value of $t_{\frac{1}{2}}$ is still a matter of controversy and little is known about it in the central nervous system (CNS). Evidence that recovery of CNS function after several types of damage, such as brain trauma or embolism, takes a very long time or never occurs at all may indicate that repair from radiation damage is slower and that $t_{\frac{1}{2}}$ would be too long. In this study we calculated BED at various $t_{\frac{1}{2}}$ values from 1 to 9 h, and showed that the late-effect BED rose steeply as the value of $t_{\frac{1}{2}}$ increased when the period of treatment was short, and thus the incidence of late complications of radiation exposure would increase. We must extend the radiation period to prevent late complications but it drives us to the matter of cell proliferation of the tumour.

Cell proliferation. Only a few studies of the cell proliferation factor have been made thus far (15). Values for α, T_k and T_{eff} must be chosen to use equations 5 and 6. In this study, we estimated α to be 0.35 and T_k to be 2 weeks (15) and T_{eff} for benign and malignant tumours to be 50 days and 4 days, respectively. Radiotherapy for malignant tumours should be completed in 2 weeks because prolongation of the irradiation period would result in a reduced early-effect BED. Little attention needs to be paid to cell proliferation of benign tumours, and extended schedules (3–4 weeks) may be acceptable. However, a 2-week schedule is recommended for patients' convenience.

Other factors affecting SRT schedules

When repair and cell proliferation factors are taken into consideration, a 7 Gy × 7 fractions every other day SRT

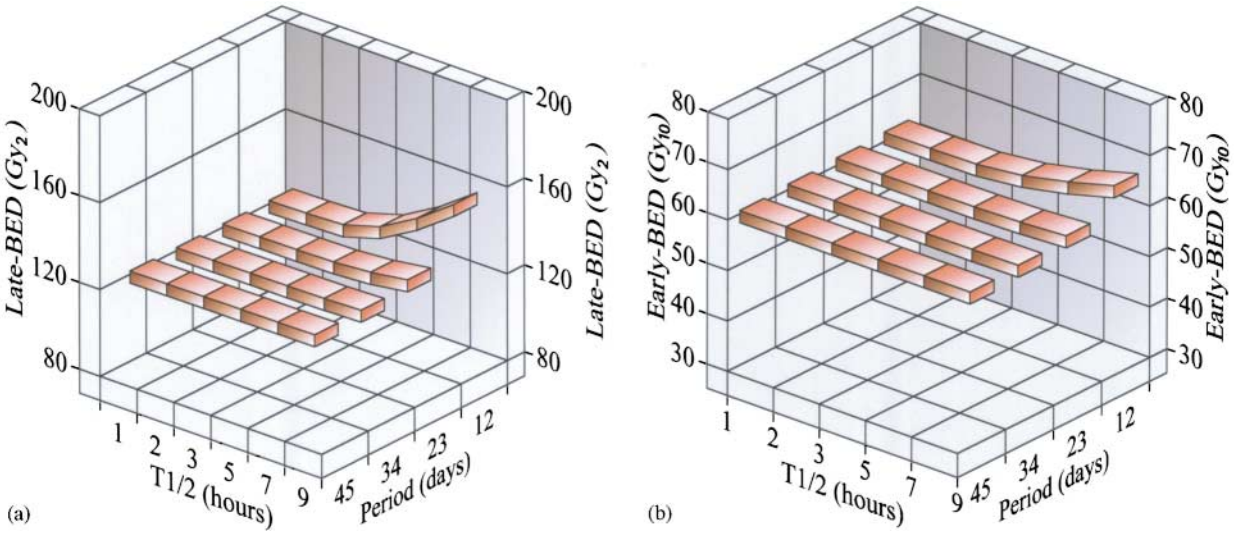

Fig. 4. Late- (A) and early- (B) effect biologically effective doses (BEDs) of the 3.7 Gy × 12 fractions schedule for benign brain tumours delivered over 12, 23, 34 and 45 days, assuming a half-time repair value ($t_{\frac{1}{2}}$) of 1, 2, 3, 5, 7 and 9 h.

schedule should be recommended for malignant tumours, and a 3.5 Gy × 12 fractions every other day schedule for benign tumours. Clinically, however, these schedules should be modified based on many other factors in the individual patient. When the tumour is very small, two interpretations are possible: the tumour dose can be decreased because of the small tumour volume, or it can be increased because only a small volume of normal tissue would be irradiated. When the tumour margin is distinct, it should be possible to increase the tumour dose and/or to decrease the number of fractions. When the central necrosis of the tumour exists, the fraction number should be increased considering reoxygenation. The schedule should also be modified according to the patient's general condition and prognosis.

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