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# Optimization of dose distribution in stereotactic HDR brachytherapy of brain tumours – an analysis of the physical and radiobiological parameters of dose distribution

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This paper is a shortened version of the PhD Thesis „Optimization of dose distribution in stereotactic HDR brachytherapy of brain tumours – an analysis of the physical and radiobiological parameters of dose distribution.

## Summary

**Aim** Dose distribution was compared between two alternative methods for the brachytherapy of tumours of the CNS: conventional implants which complied with the regulations of the Paris system and stereotactic implants. A biological model was analysed in stereotactic implants.

**Materials/Methods** 31 sequential stereotactic CNS tumour implants were analysed. The analysed implants were compared with appropriate hypothetical implants designed according to the classic standards of the Paris system. Physical parameters of Dose distribution were analysed, including: coverage index (CI), conformity factor (CF), high dosage treatment volume ($V_{200}$), and minimum dose. A value for the radiobiological parameter – Equivalent Uniform Dose (EUD) – was calculated.

**Results** In comparison with classic Paris System implants, stereotactic implants affected only half the volume of healthy tissue within the area of the reference isodose, though the high dose volume was greater. EUD was sensitive to changes in minimal dose and coverage index CI.

**Conclusions** This parameter may be a criterion in the optimization of dose distribution in radiotherapy.

**Key words** **brachytherapy of brain tumours • optimization of dose distribution • EUD**

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## Background

Optimal radiotherapy is a treatment, which gives individual patients the highest likelihood of a localised cure (TCP) and the lowest risk of injury to healthy tissues (NTCP). The parameters TCP and NTCP should be ideal criteria for the optimization of dose distribution, however the models thus far proposed are mathematically complex and difficult to apply. In clinical practice the bases on which treatment plans are assessed are the physical parameters of dose distribution. Niemierko proposed a uniform dose distribution parameter for radiotherapy – the Equivalent Uniform Dose (EUD) which may be acceptable as a biological model suitable for use in irradiation [1].

In classic brachytherapy, implants comprising of radium needles or iridium wire are introduced into the tissues, implants are limited and regulated by the brachytherapy systems. Brachytherapy using a radiation source of high activity (HDR) and stereotactic technique represent important progress in comparison to the classic form. Thanks to stereotactic equipment, isotopes may be precisely introduced to the area to be irradiated, under control of computed tomography (CT) or magnetic resonance imaging (MRI). Altering the times for which the source is held at each consecutive position allows the modelling of dose distribution. CNS tumour brachytherapy is a specific form of interstitial brachytherapy used when protection of nearby healthy tissues in critical organs is necessary.

## Aim

The purposes of the study are:

1. To compare physical dose distribution in the brachytherapy of tumours of the nervous tissues by two alternative methods:
   a) conventional implants which comply with the specifications of the Paris System;
   b) stereotactic implants.
2. To define radiobiological parameters for the assessment of a model reaction of the tissues in stereotactic implants.

## Materials and Methods

31 consecutive stereotactic implantations in cases of brain tumours were analysed in the years 1998–2000. Implantation was carried out using two guides. The therapeutic dose in planning target volume amounted to 15 Gy (5 fractions at 3 Gy daily). The median volume of tumours, including 5 mm margins ($V_{PTV}$) amounted to 78 $cm^3$. The minimum planning target volume was 33 $cm^3$, and the maximum was 177 $cm^3$.

### Implants compliant with the Paris System

Based on the shape of the area to be irradiated, which was defined on the basis of CT and MRI images, a hypothetical implant was designed, according to the classical rules of the Paris System [2]. The internal volume of the reference isodose of the Paris System implant ($V_{PS}$) was calculated on the basis of a cuboid placed in the region to be irradiated. Figure 1 illustrates the ideal definition of the reference volume of a "Paris" implant (simplified for presentation in two dimensions).

### Stereotactic implants

The shape of the tumour was reconstructed on the basis of MRI images. Thanks to fusion of MRI and CT images (CT tests carried out using stereotactic methods) the positions of all anatomical points could be entered into the coordinates of the stereotactic frame, thus allowing for the positioning of isotopes along the planned trajectory.

Stereotactic implants were planned according to the following rules:

1. At least 95% of the planning target volume must receive the therapeutic dose.
2. Bordering volumes of healthy tissues should not receive doses higher than the therapeutic dose and should not have been more than minimally damaged surgically.
3. Areas receiving higher doses, such as those receiving doses greater than twice the therapeutic dose must be limited.

Figure 2 (left side) shows the implanted guide of the source, the contours of the planning target volume, the eyeballs and stereotactic markers. On the right, the guide are presented, with the source positions marked.

### Physical parameters of stereotactic and Paris System implants

*Minimal dose*

In agreement with the rules of the Paris System, it was accepted that the reference isodose consists of the whole planning target volume and the minimum dose in a hypothetical "Paris" implant should be equal to the therapeutic dose, amounting to 15 Gy.

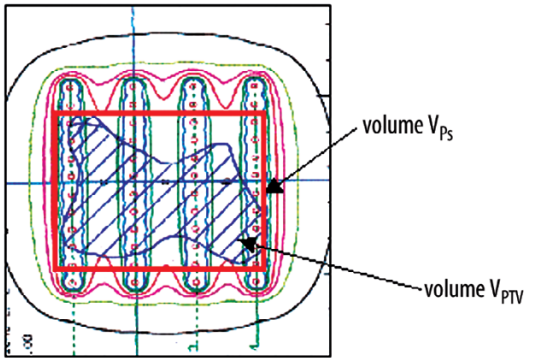


**Figure 1.** A diagram showing the reference volume of a Paris System implant ($V_{PS}$) based on planning target volume ($V_{PTV}$).

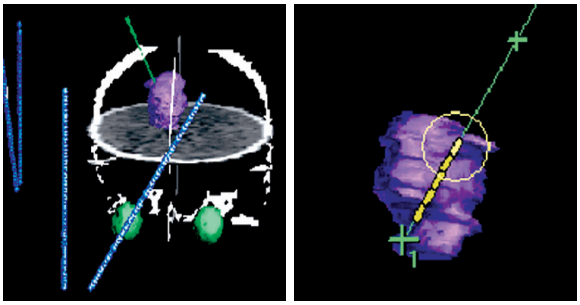

**Figure 2.** Diagram of a planned implantation: left side: guide on a background with the tumour, eye balls and stereotactic markers; on the right: guides with marked source positions, arranged along the longest axis of the tumour.

For the calculation of dose distribution with stereotactic implants, the PLATO (version 14.1 – Nucletron) and Target (version 16 – BrainLab) treatment planning systems were used. The minimum dose in planning target volume is the smallest dose in an element 1 mm$^3$ in volume ($D^{mm}_{min}$). Also defined were doses characteristic for every 1 cm$^3$ of the planning target volume, within the area of the lowest dose ($D^{cm}_{min}$). Values for 1 cm$^3$ volumes were calculated by addition of values for 1000 volume elements of 1 mm$^3$, receiving the smallest dose, $D^{cm}_{min}$, as follows:

$$D^{cm}_{min} = \frac{\sum_{i=1}^{1000} D_{(mm)i}}{1000}$$

*Coverage Index (CI)*

The coverage index (CI) parameter shows the fraction of the planning target volume which will receive at least the therapeutic dose [3]. The CI of hypothetical "Paris" implants has been established as an even 100%.

*Conformity Factor (CF)*

The conformity factor (CF) of dose distribution describes the volume of healthy tissue which is irradiated with a dose not less than the therapeutic dose [3]. CF is defined as the volume of healthy tissue receiving a dose not less than the therapeutic dose divided by the total planning target volume and receiving a dose not less than the therapeutic dose. The conformity factor $CF_{PS}$ of a hypothetical Paris System implant is defined as the estimated reference volume of the "Paris" implant ($V_{PS}$) divided by the planning target volume ($V_{PTV}$).

*High dosage volume*

The high dosage volume is the volume receiving a dose at least twice as great as the therapeutic dose. The high dosage volume is annotated as $V_{200}$ (for stereotactic implants) or $V_{PS}200$ (for "Paris" implants). On the basis of analysed dose distribution from Paris System implants, it was assumed that the high dosage volume, of "Paris" implants investigated, amounted to 18% of the reference volume $V_{PS}$.

**Equivalent Uniform Dose (EUD)**

EUD of non-uniform dose distribution is defined as the uniform dose which gives the same fraction of surviving tumour cells as the non-uniform dose (we set up an identical fractionation scheme for both dose distribution). Knowing the dependency between the fraction of surviving tumour cells from dose SF(D) and differential histograms for dosage spread {Di,Vi} in the planning target volume V, EUD can be calculated as:

$$SF(EUD)=\Sigma(Vi/V)*SF(Di) \quad (1)$$

EUD may be determined by two methods, taking into consideration two SF(D) models.

*$EUD_1$ ("one shot" model)*

In accordance with the most simple model, the relationship between the fraction of surviving neoplastic cells and radiation dose is [4]:

**Table 1.** Dosage parameters $D_{min}^{mm}$ and $D_{min}^{cm}$ in stereotactic implants. Dose expressed as a percentage of the total therapeutic dose.

| | Minimum | Maximum | Average | SD |
|---|---|---|---|---|
| $D_{min}^{mm}$ | 45.0% | 84.0% | 66.6% | 9.2% |
| $D_{min}^{cm}$ | 72.0% | 106.2% | 86.6% | 8.4% |

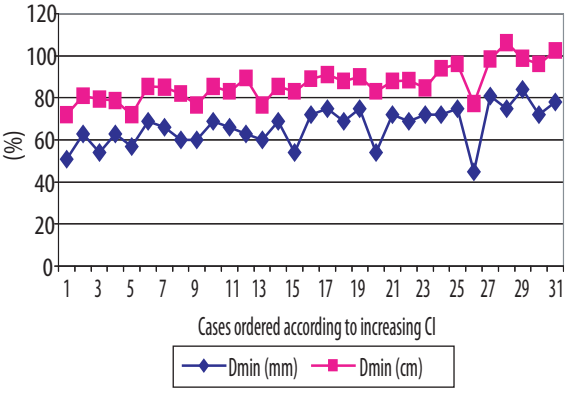


**Figure 3.** $D_{min}^{mm}$ and $D_{min}^{cm}$ values of stereotactic implants, sorted according to increasing coverage index.

$$SF(D) = \exp(-D/Do) \quad (2)$$

where Do is the dose after which 37% of cells survive. This relationship may be represented as $SF(D)=SF(2)^{D/2Gy}$ because $SF(2)=\exp(-2Gy/Do)$. SF(2) is the fraction of cells surviving a radiation dose of 2 Gy. Thus:

$$SF(EUD) = SF(2)^{EUD/2Gy} \quad (3)$$

From relationship (1) we obtain:

$$SF(2)^{EUD/2Gy} = \Sigma(Vi/V)SF(Di) = \Sigma(Vi/V)SF(2)^{Di/2Gy} \quad (4)$$

$$EUD_1 = 2Gy*\ln(\Sigma(Vi/V)SF(2)^{Di/2Gy})/\ln SF(2) \quad (5)$$

The value for $EUD_1$ was accepted as SF(2)=0.5.

*$EUD_2$ (linear-quadratic model)*

According to the linear-quadratic model, and considering dose fractionation, the function SF(D) is defined as follows:

$$SF(D)= \exp(-\alpha D -\beta D^2/n)) \quad (6)$$

where n is the number of fractions and α and β are parameters for a given tissue.

$$SF(EUD)= \exp(-\alpha EUD -\beta EUD^2/n)$$

From relationship (1) we obtain:

$$-\alpha EUD -\beta EUD^2/n = \ln( SFtotal) \quad (7)$$

where the total fraction of surviving cells in the given area SFtotal amounts to:

$$SFtotal=\Sigma(Vi/V)SF(Di))=\Sigma(Vi/V)\exp(-\alpha Di -\beta Di^2/n)) \quad (8)$$

Relationship (7), on the basis of which EUD is defined, is a quadratic equation. Resolving this equation we obtain:

$$EUD2 = n/2\ [-\alpha/\beta+(\alpha^2/\beta^2-4\ln(SFtotal)/n\beta)^{1/2}] \quad (9)$$

For the purpose of defining $EUD_2$ the values for α and β were accepted as 0.35 and 0.035. For calculation purposes, it was accepted that the dose immediately around the source is no greater than 600% of the therapeutic dose. Preliminary calculations proved that this assumption does not alter the values of $EUD_1$ and $EUD_2$.

## Results

### Coverage index and minimal dose

In "Paris" implants, the minimal dose amounts to 15 Gy and the coverage index is accepted as 100%.

Median CI for stereotactic implants amounted to 96%. Table 1 shows the basic parameters of spread $D_{min}^{mm}$ and $D_{min}^{cm}$ for these implants. The correlation coefficient between $D_{min}^{mm}$ and $D_{min}^{cm}$ was r=0.83 (p<0.001). The average minimal dose for internal $D_{min}^{mm}$ volumes irradiated was 67% of the therapeutic dose. In one case the dose barely reached 45% of the therapeutic dose. The average minimal dose, characteristic for 1 $cm^3$ – $D_{min}^{cm}$ volumes – was significantly greater and amounted to 87% of the therapeutic dose.

Figure 3 shows values for $D_{min}^{mm}$ and $D_{min}^{cm}$ from 31 analysed stereotactic implants, sorted according to increasing coverage index. The relationship between the parameters CI and $D_{min}^{cm}$ (r=0.82,

**Table 2.** Average values, intervals and standard deviation for CF and $CF_{PS}$.

| | Minimum | Maximum | Average | SD |
|---|---|---|---|---|
| CF | 1.37 | 2.37 | 1.79 | 0.22 |
| $CF_{PS}$ | 1.94 | 3.69 | 2.71 | 0.40 |

**Table 3.** Average values, intervals and standard deviation for parameters $V_{200}$ and $V_{PS}200$.

| | Minimum | Maximum | Average | SD |
|---|---|---|---|---|
| $V_{200}$ ($cm^3$) | 20.0 | 105.0 | 54.6 | 19.5 |
| $V_{200}$PS ($cm^3$) | 11.2 | 81.2 | 41.8 | 15.5 |

**Table 4.** Average values, intervals and standard deviations for parameters $EUD_1$ and $EUD_2$.

| | Minimum | Maximum | Average | SD |
|---|---|---|---|---|
| EUD1 (Gy) | 18.3 | 23.0 | 20.6 | 1.1 |
| EUD2 (Gy) | 15.1 | 20.4 | 18.3 | 1.1 |

$p<0.001$) is stronger than that between CI and $D_{min}^{mm}$ ($r=0.61$, $p<0.001$), though the difference between these two correlation coefficients is not statistically significant.

## Conformity Factor

Table 2 shows conformity factor values for stereotactic and Paris System implants. The average CF value was 1.79 (SD±0.23), and the average $CF_{PS}$ value was 2.71 (SD±0.40). There was a positive correlation between the parameters CF and $CF_{Ps}$ ($r=0.39$, $p=0.03$).

*High dosage volume*

The parameters $V_{200}$ and $V_{PS}200$ showed normal distribution, which is shown in the histogram in Figure 4. Table 3 shows the basic spread parameters $V_{200}$ and $V_{PS}200$. The average size of the high dosage volume for clinical implants is greater than the average high dosage volume for "Paris" implants by 31%. The correlation coefficient between parameters $V_{200}$ and $V_{PS}200$ was found to be $r=0.88$, ($p<0.001$).

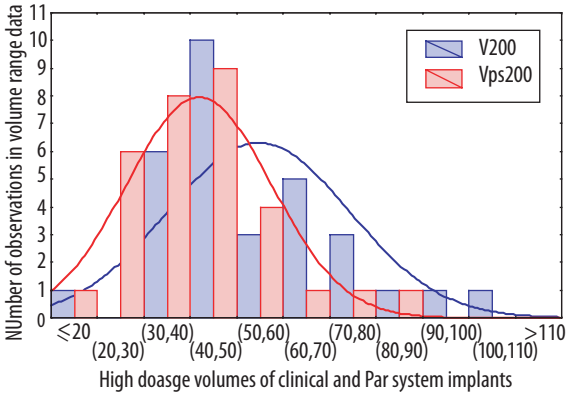


**Figure 4.** A histogram showing high dosage volumes for stereotactic implants ($V_{200}$), Paris System implants($V_{PS}200$) and normal distribution for these parameters.

## Equivalent Uniform Dose (EUD)

Table 4 shows the average values, ranges and standard deviations for the parameters $EUD_1$ and $EUD_2$. The average value for $EUD_1$ was 13% higher than the average value for $EUD_2$. Both

**Table 5.** Linear correlation coefficients r between parameters CI, $D_{min}^{mm}$, $D_{min}^{cm}$, EUD1 and EUD2 for stereotactic implants, ($p<0.001$ in all cases).

| | CI | EUD1 | EUD2 | $D_{min}^{mm}$ | $D_{min}^{cm}$ |
|---|---|---|---|---|---|
| CI | 1.00 | 0.82 | 0.90 | 0.61 | 0.82 |
| EUD1 | 0.82 | 1.00 | 0.97 | 0.77 | 0.87 |
| EUD2 | 0.90 | 0.97 | 1.00 | 0.73 | 0.89 |
| $D_{min}^{mm}$ | 0.61 | 0.77 | 0.73 | 1.00 | 0.83 |
| $D_{min}^{cm}$ | 0.82 | 0.87 | 0.89 | 0.83 | 1.00 |

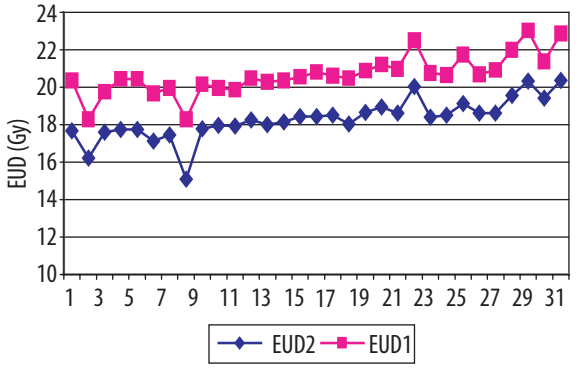


**Figure 5.** $EUD_1$ and $EUD_2$ for analysed cases, sorted according to increasing minimal doses $D_{min}^{mm}$.

these average values ($EUD_1$ and $EUD_2$) are greater than the appropriate therapeutic dose of 15Gy by 37% and 22% respectively.

Figure 5 shows the parameters $EUD_1$ and $EUD_2$ for analysed cases, sorted according to increasing minimal doses.

Table 5 shows values for the linear correlation coefficient r between physical dose distribution parameters CI, $D_{min}^{mm}$ and $D_{min}^{cm}$ and the radiobiological parameters $EUD_1$ and $EUD_2$; all values are statistically significant ($p<0.001$).

From Table 5 it can be seen that the parameters $EUD_1$ ind $EUD_2$ both show a greater correlation with dose $D_{min}^{cm}$ than with minimal dose $D_{min}^{mm}$. The correlation coefficients between $EUD_1$, and minimal dose and between $EUD_1$ and dose $D_{min}^{cm}$ were r=0.77 and r=0.87 respectively. The difference between these two correlation coefficients was not statistically significant, however. Likewise, the dependency of $EUD_2$ on $D_{min}^{cm}$ (r=0.89) was stronger than the association between $EUD_2$ and $D_{min}^{mm}$ (r=0.73).

## Discussion

### Analysis of the physical parameters of stereotactic and Paris System implants

Coverage Index and Conformity Factors allow us to assess a basis of radiotherapy; CI defines the proportion of a volume of tissue receiving a suitable radiation dose and CF represents the quantity of healthy tissue irradiated. For external radiotherapy, in accordance with ICRU report 50, the parameter CI may be less than 100% [5]. CI is associated with the minimal dose in the planning target volume. Years of radiotherapy have led to the formation of a hypothesis that, in the case of dose distribution with a high degree of non-uniformity, effective dose is dependent on the settling of minimum dose [6]. In brachytherapy, owing to dosage gradients, the value for "minimal dose" is associated with the size of analysed "voxel" elements. The correlation between the parameters $D_{min}^{mm}$ and CI for analysed implants ($r=0.6$, $p<0.001$) fixed CI as a criterion for optimising dosage spread. $D_{min}^{mm}$ amounted to an average of 67%, though in one case the dose attained hardly reached 45% of the therapeutic dose, resulting in the definition of criterion CI as ≥95% and a large dosage gradient. Values for $D_{min}^{mm}$ do not fulfil the criteria of ICRU report number 50, which is used in external radiotherapy [5].

3D interstitial brachytherapy planning is the subject of the AAPM report of 1997 [7]. The authors claim that, in traditional brachytherapy planning, the red minimal dose. received by an irradiated volume is, on average, half the dose assumed as minimum dose. This is in agreement with the results of our study. The report suggests limits on CI values, which are historically linked with doses and volumes applied before.

Because parameters CI and CF are normalized to the planning target volume, the range of values for $V_{PTV}$ is wide (33–177 $cm^3$) and, therefore, the same CI or CF values may have different clinical significance for different implants.

Parameters CI and CF are used to assess dose distribution – though only from discreet points on the histograms for planning target volume and healthy tissues. In spite of having full DVH histograms at our disposal, we did not use this information.

From a comparison of conformity factors for stereotactic implants (average value: CF=1.79) and hypothetical Paris System implants (average value$CF_{PS}$=2.71) it can be seen that "Paris" implants deliver the therapeutic dose to twice as much volume of healthy tissue as do stereotactic implants. Because the average value for $V_{PTV}$ amounts to 91 $cm^3$, classic Paris System implants can not possibly be acceptable for CNS brachytherapy.

The high dosage volume for stereotactic implants is greater than in equivalent "Paris" implants, which results from uneven positioning of guides. Many publications underline that the likelihood of necrosis is increased in the high dosage volume [8,9], although authors of other works claim there are positive effects of high doses in the centre of tumours in case of hypoxic tissues [10,11].

**Analysis of radiobiological parameters in stereotactic implants**

Various methods are used, for the reduction of data contained in histograms, in order to define TCP and NTCP and for transforming physical dosage to its biological effects. It is important to point out that TCP and NTCP are mathematically complicated and therefore attempts to optimize dosage spread in relation to these parameters have limited usefulness [12]. An alternative could be optimisation on the basis of EUD [13]. The parameter EUD "reduces" histogram DVH and, at the same time, allows for assessment of dose distribution according to biological effects. EUD is highly sensitive to minimum dose (for implants analysed r=0.8), and therefore may be used to assess effective dose. EUD is always greater than the minimal dose. For dose distribution analysed, EUD was always greater than the planned therapeutic dose of 15 Gy – average $EUD_1$ and $EUD_2$ amount to 20.6 Gy and 18.3 Gy respectively. Niemierko defined EUD for dose distribution in external radiotherapy and, in the majority of cases, EUD was less than the therapeutic dose [1]. Fowler suggests, however, that EUD should also be compared with therapeutic doses [14].

Therapeutic doses in analysed implants amounted to 15Gy and EUD values (defined on the basis of the LQ model) range from 15.1 Gy to 20.4 Gy. EUD could be suitable for settling the therapeutic dose in brachytherapy, where "hot" areas appear in the high dose volume. EUD, like TCP, has limited sensitivity to maximum dose. This is the result of the sigmoid shape of the function formed by TCP ~ exp (-exp (-D)).

It is an interesting fact that EUD shows a greater correlation with minimal dose, characterised by 1 $cm^3$ volumes analysed (r=0.9), than with minimal doses in 1 $mm^3$ (r=0.8) volumes. Could it be that discreet "cold points" of minimal size have no fundamental influence on total biological effects? Intuitively we may assume that the effects of irradiation depend, not only on the minimal dose, but also on the size of the "cold" volume.

The correlation coefficient between EUD and coverage index CI (r=0.9) is greater than that between EUD and minimum dose (r=0.8). Could it be that coverage index is a more suitable criterion for optimisation than minimal dose?

Values for the parameter EUD depend on the accepted function for dose – effect. The value $EUD_2$, defined with regard to dosage fractionation and the linear-quadratic relationship, averages 11% less than $EUD_1$, which is defined on the basis of the model SF(D) = exp(-D/Do).

Any possible use of EUD as a criterion for the optimisation of dose distribution must be preceded by the convinced application of this parameter in clinical practice. The parameter EUD has aroused great interest and many authors believe that EUD values are connected to clinical results [15,16].

In 1999 Niemierko proposed the general concept of EUD [17]. According to that idea, EUD may be shown as a pure phenomenological expression:

$$EUD = \left(\sum_i V_i D^{\alpha}_i\right)^{1/\alpha}$$

where $V_i$ is the fraction of the total irradiated volume, dose is $D_i$ and the parameter $\alpha$ (not to be confused with the LQ parameter) is specific data

for neoplastic tissue, healthy tissues or organs at risk and is associated with the effects on those tissues in the volume to be irradiated. This formula for EUD is applicable equally for tumours and for healthy tissues. EUD for neoplastic tissue behaves as already discussed while in healthy tissues it is the uniform dose, which gives the same likelihood of complications as analysis of non-uniform dose. For $\alpha$=1, EUD is the arithmetical average of dose distribution.

## CONCLUSIONS

The definition of rules for planning implants in CNS brachytherapy, based on values of coverage index and conformity factors is justified. Stereotactic implants, in comparison with classic Paris System implants, affect only half as much healthy tissue in the region of the reference isodose. The high dose volume, however, is greater. The EUD model is a realistic alternative to the TCP and NTCP models. The parameter EUD, which is associated with the fraction of surviving cells in an irradiated volume, is a measure of the effectiveness of dose distribution. However, before optimisation of dose distribution can be based on EUD in practice, convincing clinical data must confirm that EUD is better than other parameters for describing the effects of radiotherapy.

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