# ESTIMATION OF $\alpha/\beta$ RATIO FOR BENIGN TUMOR OF THE BRAIN FROM CLINICAL DATA

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Thesis
Entitled

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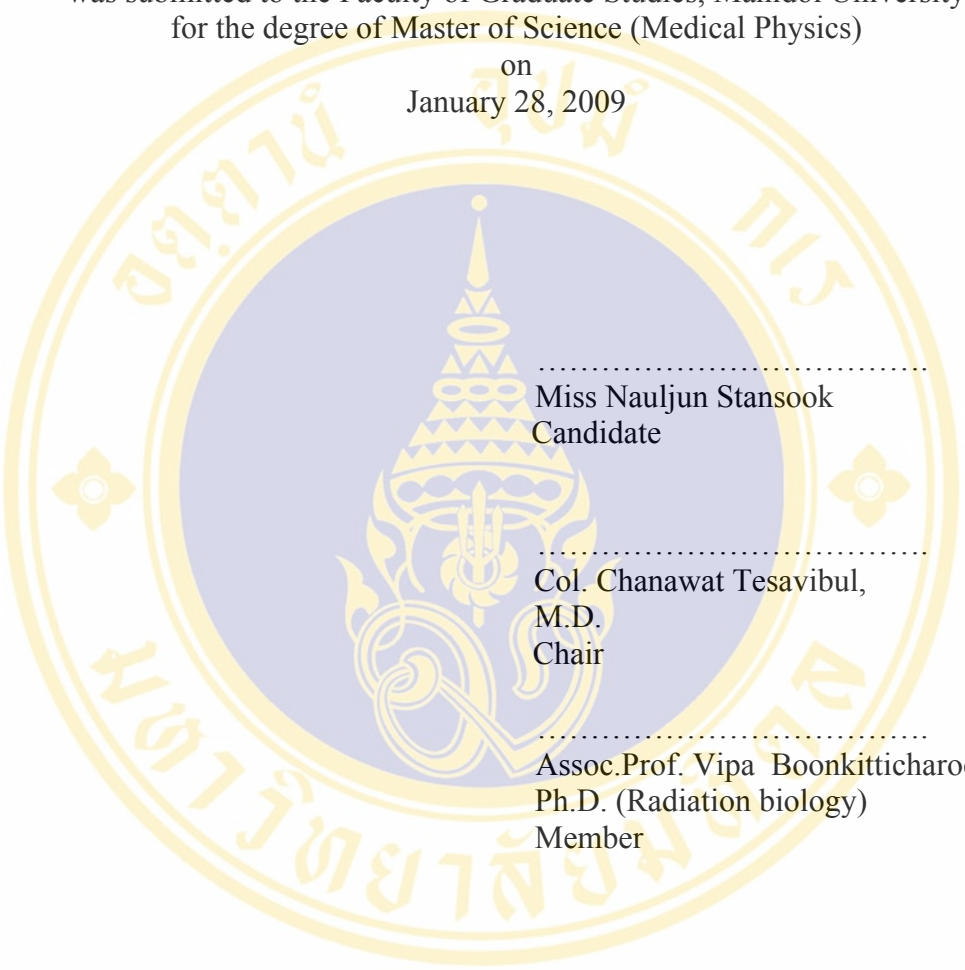

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ESTIMATION OF α/β RATIO FOR BENIGN TUMOR OF THE BRAIN FROM CLINICAL DATA

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ABSTRACT

The aim of this study was to estimate a plausible α/β value for benign tumor of the brain from clinical data. Recently, fractionated stereotactic radiotherapy has been recommended for management of large benign brain tumor or tumor locating next to the dose limiting structure. The knowledge of α/β value would be of great help in the design of an alternative fractionated scheme.

Forty-five articles published between 1997 and 2008 were selected for analysis. These included publications on conventional external beam radiotherapy, fractionated stereotactic radiotherapy and stereotactic radiosurgery. Reports on combined radio-chemotherapy were excluded. Three methods for α/β estimate were employed. These included two iso-effect scheme matching, reciprocal iso-effect dose plotting and two-step graphical matching. A 5-year tumor control rate (TCR) % was chosen as an end point for α/β analysis. The α/β values estimated by different methods were tested for their differences by t-test.

The α/β values obtained from reciprocal iso-effect dose plotting, two iso-effect scheme matching and two-step graphical matching were 3.53 Gy (95% CI 2.08-4.98 Gy), 2.71 Gy (95% CI 2.67-2.75 Gy ) and 2.67 (95% CI 1.87-3.47 Gy), respectively. Statistical analysis showed no significant difference among α/β values obtained from these methods ($p \geq 0.14$). Noteworthily, plausible estimates of α/β determined by two iso-effect scheme matching and two-step graphical matching could be obtained only when the size of dose fraction differed by at least a factor of seven. In conclusion, the α/β estimates for benign brain tumor obtained in this study were in remarkable agreement with the typical value of 2-3 Gy for late responding tissue.

KEY WORDS: ALPHA/BETA VALUE/ BENIGN TUMOR/BRAIN/
CLINICAL DATA

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การประเมินอัตราส่วนของค่าแอลฟ่าต่อเบต้าสำหรับเนื้องอกชนิดไม่ร้ายแรงของสมองจากข้อมูลทางคลินิก
(ESTIMATION OF $\alpha/\beta$ RATIO FOR BENIGN TUMOR OF THE BRAIN FROM CLINICAL DATA)

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บทคัดย่อ

วัตถุประสงค์หลักของการศึกษาคือ เพื่อหาค่า $\alpha/\beta$ ของเนื้องอกชนิดไม่ร้ายแรงของสมองจากข้อมูลทางคลินิก เนื่องจากในปัจจุบันได้มีการนำ fractionated stereotactic radiotherapy มาใช้ในการรักษาผู้ป่วยเนื้องอกชนิดไม่ร้ายแรงของสมองที่มีขนาดใหญ่หรืออยู่ใกล้กับส่วนของสมองที่มีความไวต่อรังสี ค่า $\alpha/\beta$ จะเป็นประโยชน์ต่อการคำนวณแผนการฉายรังสีแบบใหม่จากข้อมูลการรักษาแบบมาตรฐาน

การศึกษานี้ได้ทำการวิเคราะห์หาค่า $\alpha/\beta$ จากผลการรักษาทางคลินิกของผู้ป่วยที่ได้รับการฉายรังสีชนิด conventional external beam radiotherapy, fractionated stereotactic radiotherapy และ stereotactic radiosurgery โดยไม่รวมผู้ป่วยที่ได้รับการฉายรังสีร่วมด้วยเคมีบำบัด จากวรรณกรรมที่ตีพิมพ์ระหว่างปี พ.ศ.2540 และ พ.ศ.2551 จำนวน 45 ฉบับ ด้วยวิธี two iso-effect scheme matching, the reciprocal iso-effect dose plot และ two-step graphical matching ค่า $\alpha/\beta$ จะวิเคราะห์จากอัตราการควบคุมโรคที่ 5 ปี ความแตกต่างของค่า $\alpha/\beta$ ที่คำนวณได้จากวิธีดังกล่าวข้างต้นจะวิเคราะห์ด้วย t-test

ค่า $\alpha/\beta$ ที่ได้จากวิธี reciprocal iso-effect dose plot, two iso-effect scheme matching และ two-step graphical matching เท่ากับ 3.53 Gy (95% CI 2.08-4.98 Gy), 2.71 Gy (95% CI 2.67-2.75 Gy ) and 2.67 (95% CI 1.87-3.47 Gy), ตามลำดับ เมื่อทำการวิเคราะห์ความแตกต่างทางสถิติของค่า $\alpha/\beta$ ที่ได้จากทั้ง 3 วิธีพบว่าไม่แตกต่างกันอย่างมีนัยสำคัญ ($p \geq 0.14$) นอกจากนี้ยังพบว่าค่า $\alpha/\beta$ ที่ได้จากวิธี two iso-effect scheme matching และ two-step graphical matching จะมีค่าใกล้เคียงความเป็นจริงก็ต่อเมื่อแผนการฉายรังสีที่นำมาเปรียบเทียบมีขนาดของรังสีที่ฉายต่อครั้งมีค่าต่างกันอย่างน้อย 7 เท่า ผล

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| Abbreviations | Term |
|---|---|
| AVM | Artriovenous malformation |
| BED | Biologically effective dose |
| CI | Confidence interval |
| cm | Centimetre |
| Eq | Equation |
| $EQD_2$ | Equivalent dose to 2 Gy |
| FSRT | Fractionated stereotactic radiotherapy |
| fx | Fraction |
| Gy | Gray |
| LQ | Linear-quadratic model |
| No. | Number |
| Ref. | Reference |
| SD | Standard deviation |
| SRS | Stereotactic radiosurgery |
| SRT | Stereotactic radiotherapy |
| TCP | Tumor control probability |
| TCR | Tumor control rate |
| vs. | Versus |
| VS | Vestibular schwannoma |
| Yrs | Years |

# CHAPTER I
# INTRODUCTION

According to cancer statistics in Thailand, tumors of the brain are relatively rare. [1]. From Ramathibodi Cancer Registry Annual Reports (2001 – 2005), patients with tumor of the brain account for 5.45 % of the total cancer patients (average yearly total of 1,943 cases) [2,3]. Approximately 47 % of the brain tumors are benign tumors including meningiomas, vestibular shwannomas, pituitary adenomas, etc [2,3]. Radiotherapy is the most effective adjunctive therapy for some benign tumors following surgery [4-7]. Good to excellent long term survival rates were reported in patients with benign menigiomas [8,9,10], pituitary adenoma [7]. Radiation alone becomes are appropriate treatment of choice when the tumor is located in the inoperable site such as skull base. Although, radiation is reasonably effective in control of the benign brain tumors, there have been concerns regarding to the treatment related morbidity including neuropsychological deficit or brain necrosis and endocrine dysfunction [11,12].

Stereotactic radiosurgery (SRS) is a high precision technique of radiotherapy in which multiple collimated beams delivers a single high dose fraction to a well-circumscribed intracranial target volume (usually less than 3 cm in diameter) with a steep dose gradient outside the target volume allowing minimal dose to normal tissue. SRS is commonly used for the treatment of selected patients with benign tumors at the skull base [13]. The effectiveness of SRS is base on the well-circumscribed nature of the benign tumor which allows a specific target irradiation with steep fall off into other surrounding structures and on the radiobiological property of benign tumor as a late responder which is susceptible to large dose fraction [13,14].

As the radiation tolerance of normal tissue is volume-dependent, SRS is prohibited in treating benign tumor of diameter greater than 3 cm for the risk of brain necrosis [14]. SRS is not recommended to treat the tumor locating next to radiosensitive structures, such as the optic nerve, brain stem which can tolerate a dose

8-10 Gy [15,16] far below the treatment dose of 15 Gy [14,16]. Fractionated stereotactic radiotherapy (FSRT) is introduced to improve the normal tissue sparing in the clinical context as mentioned above [7]. Excellent local control with a high rate of preserving the cranial nerve function was reported in series treating meningioma and acoustic neuroma [7,17] with FSRT.

Since there have been indication for choosing FSRT instead of SRS management large benign brain tumor or tumor locating next to the dose limiting structures as brain stem, various cranial nerves. Biologically effective dose (BED) based on linear quadratic (LQ) model is a tool used for the design of new FSRT from the established SRS [16]. For slow-proliferating benign tumor, only one parameter, i.e. $\alpha/\beta$, is needed for the calculation of dose/ fraction for the new FSRT scheme. The knowledge of $\alpha/\beta$ for benign tumor of the brain is limited. There is only one publication by Shrieve et al [16] on the $\alpha/\beta$ value of 3.28 Gy for meningioma estimated by assuming a 15 Gy SRS to be equivalent to the fractionated doses of 54 Gy in 30 fractions [16]. The reliability of $\alpha/\beta$ estimate would have an impact on the validity of the new FSRT schedule. Qi et al [18] noted that a slight difference in $\alpha/\beta$ between arteriovenous malformation (AVM), 2.2 Gy, and brain, 1.5-2 Gy, justified the use of FSRT over the SRS in management of AVM having a lower fractionated sensitivity ($\alpha/\beta$= 2.2 Gy). Substantial clinical data on treatment of benign brain tumors with SRS, FSRT and conventional external beam therapy are compiled for at least 10 years and serve as data-data for determination of a plausible $\alpha/\beta$ value.

There are several methods for estimate of $\alpha/\beta$ value from clinical data for instance, reciprocal dose plot [19], two-scheme matching [20], two-step graphical matching [21], direct analysis [22], etc. The reciprocal dose plot requires a number of iso-effect data sets to fit the LQ equation, $E = D(\alpha+\beta d)$, linearized by the reciprocal rearrangement of D and E to obtain $1/D = (\alpha/E) + (\beta/E)d$. The $\alpha/\beta$ value is determined from the intercept and slope of the linear regression equation [19]. The two-scheme matching of two sets of iso-effect data allows the calculation of the $\alpha/\beta$ from the equation $\alpha/\beta = (D_1d_1-D_2d_2)/(D_2-D_1)$ [20]. The two-step graphical matching involves firstly, the construction of a series of curves relating the equivalent dose of 2 Gy fraction ($EQD_2$) versus tumor control rate at different assumed $\alpha/\beta$ values from

conventional fraction data. Iso-effect BED is obtained from the coinciding point of the curves. Secondly, the iso-effect tumor control rate from brachytherapy is used to read out the equivalent $EQD_2$ from the established dose response curve. This allows the construction of iso-effect BED versus $\alpha/\beta$ curves for equivalent external beam and brachytherapy data. The value of $\alpha/\beta$ at which the curves cross gives a best estimated of tumor $\alpha/\beta$ [21]. Direct analysis method [22] use the maximum likelihood technique to estimate $\alpha$ and $\beta$ from the mathematical function based on Poisson probability. This is accomplished by use of specific computer program.

In this study, three method including reciprocal dose plot, two-scheme matching, and two-step graphical matching were used for the estimate of $\alpha/\beta$ value for benign brain tumor because of their simplicity and do not require specific computer program. This study was conducted to answer the question whether $\alpha/\beta$ values obtained from different methods were equal and in line with the $\alpha/\beta$ for the typical late responding tissue.

# CHAPTER II
# OBJECTIVE

**Objective**

The objective of this research is to estimate a plausible $\alpha/\beta$ value for benign tumor of the brain from clinical data.

**Sub-objective**

1. To decide the range of iso-effect 5-year tumor control rate (TCR).
2. To evaluate the $\alpha/\beta$ value obtained from the matching of single versus single fraction iso-effect schemes, fractionated versus fractionated iso-effect schemes and single fraction versus fractionated iso-effect schemes.
3. To compare the $\alpha/\beta$ value estimated from reciprocal dose plot, two iso-effect scheme matching and two-step graphical analysis.

# CHAPTER III
# THEORETICAL BACKGROUND
# AND
# LITERATURE REVIEWS

**Methods in estimation of α/β value from clinical data**

**1. Reciprocal plot of iso-effect dose**

The reciprocal iso-effect dose plot is derived from the LQ equation for fractionation scheme

$$S = e^{-D(\alpha+\beta d)} \quad (1)$$

Where S is the survival fraction, D is total treatment dose and is equal to number of fractions multiplied by d (dose per fraction). Logarithmic transformation of Eq.1 yields

$$E = -\ln S = D(\alpha + \beta d) \quad (2)$$

Eq.2 can be linearized by reciprocal arrangement of D and E

$$1/D = (\alpha/E) + (\beta/E)d \quad (3)$$

The α/β value is obtained from the magnitude of intercept (α/E) and slope (β/E).

The reciprocal dose plot was firstly presented by Douglas and Fowler in the determination of α/β of skin reactions in mouse [19]. The method requires many iso-effect data to fit the reciprocal dose equation. Therefore, this method was mostly used in animal studies [23,24,25]. The α/β determined from clinical data using the reciprocal dose-plot is limited small. Only one publication involving the determination

of α/β for AVM obliteration was reported by Kocher et al using data from fractionated treatment and single-dose radiosurgery [26].

**2. Matching of two iso-effect scheme**

The α/β value can be calculated from two iso-effect scheme according to the following equation. The fractionated treatment scheme is generally described in terms of biologically effective dose (BED)

$$BED = D\left(1+\frac{d}{(\alpha/\beta)}\right) \tag{4}$$

When two treatment schemes are observed to be equivalent, it follows that

$$BED_1 = BED_2$$

That is

$$D_1\left(1+\frac{d_1}{(\alpha/\beta)}\right) = D_2\left(1+\frac{d_2}{(\alpha/\beta)}\right) \tag{5}$$

$$\alpha/\beta = \frac{(D_1 d_1 - D_2 d_2)}{D_2 - D_1} \tag{6}$$

Withers et al [20] proposed the use of two iso-effect clinical data in calculation of α/β for organs or diseased tissues of interest. The method is simple and has been widely found to be used successfully in many clinical calculations [27,28]. Plausible estimates of α/β have been documented for early or late reaction of the lung, intestine, spinal cord and also many tumors such as head and neck cancer, cervical cancer [28].

**3. Two-step graphical matching**

This method was proposed by Fowler et al [21] in the estimation of α/β value for prostate tumors. It is a two step procedure. Firstly, a series of dose response curves describing the relationship between 5-year tumor control rate (TCR) versus the $EQD_{2,\alpha/\beta}$ are constructed to allow the approximation of the range of iso-effect 5-year

TCR. The curves coincide only at equivalent 5-year TCR. The $EQD_{2,\alpha/\beta}$ is calculated from equation below[29].

$$EQD_{2,\alpha/\beta} = D\left[\frac{d+(\alpha/\beta)}{2+(\alpha/\beta)}\right] \tag{7}$$

The dose response curves, 5-year TCR versus $EQD_{2,\alpha/\beta}$ is constructed based on the logistic function

$$TCR = \frac{e^{(a+bEQD_{2,\alpha/\beta})}}{1+e^{(a+bEQD_{2,\alpha/\beta})}} \tag{8}$$

Since $\alpha/\beta$ is unknown, different values of $\alpha/\beta$ are assigned to allow the calculation of $EQD_{2,\alpha/\beta}$ for different sets of clinical data. In fractionation scheme of similar dose per fraction, the 5-year TCR is weighted according to the number of patients treated (n) in each series with respect to the total number (N) of the pooled series.

$$5-\text{year}\,TCR_{\text{weighted}}(\%) = \frac{1}{N}\sum_{i=1}^{N} n_i TCR_i \tag{9}$$

The parameters of fit, a and b, are predetermined from the logit transformed equation 10

$$\ln\left[\frac{TCR}{1-TCR}\right] = a + bEQD_{2,\alpha/\beta} \tag{10}$$

The second step involves the determination of the fractionated $EQD_2$ which is equivalent to the 5-year TCR of implant treatment. The $EQD_2$ will be read out from the established dose-response curve at control rate equivalent that of the implant treatment. The iso-effect $EQD_2$ is used for the writing of iso-effect BED equation for fractionated treatment and implant treatment. This $EQD_2$ allows the calculation of $BED_{\text{fractionated}}$.

$$BED_{fractionated} = EQD_2\left[1+\frac{2}{\alpha/\beta}\right]$$

This $BED_{fractionated}$ is equivalent to

$$BED_{implant} = D_{implant} \times RE$$

$$RE(\text{relative effectiveness}) = 1+\frac{R_0}{(\mu+\lambda)} \bullet \frac{1}{\alpha/\beta} \quad (11)$$

Where $R_0$ is the initial dose-rate of the radioactive implant with an $\lambda$ as its physical decay constant, $\mu$ is the rate constant of sub-lethal damage repair for prostate cancer. Different values $\alpha/\beta$ are assumed to allow the calculation of $BED_{fractionated}$ and $BED_{implant}$. Curves of BED versus $\alpha/\beta$ are plotted to find the crossing point between the $BED_{fractioned}$ curve and the $BED_{implant}$ curve. The value of $\alpha/\beta$ at which the curves cross yields the best estimate of $\alpha/\beta$ for prostate tumor. This method gives an $\alpha/\beta$ value ranging from 1.4 to 1.9 Gy which is in line with the value of 1.5 Gy estimated by Brenner and Hall [30].

# CHAPTER IV
# MATERIALS AND METHODS

## 4.1 Data sources

The data were search via MEDLINE (1997-2008) and Google (1997-2008) for articles published in English using key words as *benign tumor of the brain* and *radiotherapy.* To ensure that all studies on radiation treatment of benign brain tumor had been identified, the second search was conducted including terms *meningioma* or *vestibular schwannoma* or *acoustic neuroma* or *pituitary adenoma* or *conventional radiotherapy* or *stereotactic radiotherapy* or *stereotactic radiosurgery*.

Inclusion criteria

1. Benign tumor of the brain including meningioma, vestibular schwannoma and pituitary adenoma that underwent conventional radiation therapy technique (EXBT), stereotactic radiotherapy (SRT), stereotactic radiosurgery (SRS), hypofractionation.
2. Clinical data with a mean follow-up time longer than 2 years, a tumor control rate (TCR) of 5 years and a sample size greater than 10 cases.

Exclusion criteria

1. Childhood benign brain tumor.
2. Patients who received chemotherapy or combined radiation and chemotherapy

## 4.2 Clinical data

The totals of 45 articles were selected for this study. Altogether, there were 4,863 patients suffering from benign tumor of the brain including meningioma, vestibular schwannoma and pituitary adenoma. The patient were treated by conventional radiation therapy (670 cases) with a total dose of 47.2-57 Gy in 1.8-2 Gy/fx; stereotactic hypofractionation (141 cases) with a total dose 18-25 Gy in 3-5 fractions; stereotactic radiotherapy (1,161 cases) with a total dose of 48-57.6 Gy in 1.8-2 Gy/fx and stereotactic radiosurgery (2,891 cases) with a marginal dose of 12-20.8 Gy (median 16 Gy) as detailed in Table 4.1, 4.2 and 4.3.

Table 4.1.Treatment of benign brain tumor by conventional multiple fraction

| Authors | No. of patients | Type of tumor | Total dose (Gy) | Dose/fx (Gy) | Median of follow up (yrs) | TCR (%) 5yrs |
|---|---|---|---|---|---|---|
| Conventional technique external beam radiation therapy (EBRT) | | | | | | |
| McCord M,1997[31] | 141 | pituitary | 47.2 | 1.8 | 9.20 | 94.0 |
| Nutting C, 1999[8] | 82 | meningioma | 57 | 1.8 | 9.00 | 92.0 |
| Dufour H,2001[32] | 31 | meningioma | 52.0 | 1.9 | 6.10 | 92.8 |
| Pourel N, 2001[33] | 45 | meningioma | 56.0 | 2.0 | 2.50 | 95.0 |
| Mandelhall W,2003 [34] | 101 | meningioma | 54.0 | 1.8 | 5.40 | 95.0 |
| Metellus P, 2005 [35] | 38 | meningioma | 52.0 | 1.8 | 7.38 | 94.7 |
| Colin P,2005 [36] | 110 | pituitary | 50.4 | 1.8 | 6.83 | 99.0 |
| Maire P, 2006 [37] | 46 | VS | 51.0 | 1.8 | 6.67 | 86.0 |
| Alfons C.M.,2007 [38] | 76 | pituitary | 50.4 | 1.8 | 7.75 | 95.0 |
| Stereotactic Radiotherapy (SRT) | | | | | | |
| Fuss M, 2000[39] | 51 | VS | 57.6 | 1.9 | 3.50 | 95.0 |
| Shirato S, 2000[40] | 65 | VS | 50.0 | 1.9 | 2.65 | 92.0 |
| Debus J, 2001[41] | 189 | meningioma | 56.8 | 1.8 | 2.92 | 98.0 |
| David A, 2001[42] | 56 | VS | 50.0 | 2.0 | 9.58 | 97.0 |
| Szumacher E, 2002[43] | 39 | VS | 50.0 | 2.0 | 2.00 | 95.0 |
| Sawamura Y, 2003[44] | 101 | VS | 48.0 | 2.0 | 3.75 | 91.4 |
| Milker S, 2004[45] | 20 | pituitary | 52.2 | 1.8 | 4.98 | 100 |

Table 4.1.Treatment of benign brain tumor by conventional multiple fraction (continued)

| Authors | No. of patients | Type of tumor | Total dose (Gy) | Dose/fx (Gy) | Median of follow up (yrs) | TCR (%) 5yrs |
|---|---|---|---|---|---|---|
| Milker S, 2005 [46] | 317 | meningioma | 57.6 | 1.8 | 5.70 | 94.7 |
| Sun H, 2005[47] | 68 | pituitary | 50.0 | 2.0 | 4.30 | 98.0 |
| Combs E., 2005[48] | 106 | VS | 57.6 | 1.8 | 4.04 | 93.0 |
| Klaus D, 2006[49] | 65 | meningioma | 55.8 | 1.9 | 3.75 | 100 |
| Henzel M,2006[50] | 84 | meningioma | 56.0 | 1.9 | 2.50 | 100 |

Table 4.2.Treatment of benign brain tumor by hypofractionation (3-5 fractions)

| Authors | No. of patients | Type of tumor | Total dose (Gy) | Dose/fx (Gy) | Median of follow up (yrs) | TCR (%) 5yrs |
|---|---|---|---|---|---|---|
| Muijer O. | 12 | VS | 20 | 4 | 2.75 | 94.0 |
| 2003 [51] | 68 | | 25 | 5 | 2.75 | |
| Chang S., | 47 | VS | 18 | 6 | 4.00 | 98.0 |
| 2005 [52] | 14 | | 21 | 7 | 4.00 | |

Table 4.3.Treatment of benign brain tumor by stereotactic radiosurgery (SRS)

| Authors | No. of patients | Type of tumor | Marginal dose (Gy) | Median of follow up (yrs) | TCR (%) 5yrs |
|---|---|---|---|---|---|
| Kondziolka D,1999[53] | 99 | meningioma | 16.00 | 5.10 | 93.0 |
| Subach B,1999[54] | 40 | VS | 15.00 | 3.00 | 98.0 |
| Stafford S, 2001[55] | 168 | meningioma | 16.00 | 3.33 | 93.0 |
| Hasekawa T, 2001[56] | 115 | meningioma | 13.00 | 5.16 | 94.0 |
| Flickinger J, 2001[57] | 190 | VS | 13.00 | 2.50 | 91.0 |
| David A,2001[42] | 69 | VS | 12.00 | 9.92 | 98.0 |
| Foote K, 2001[58] | 149 | VS | 14.00 | 2.80 | 87.0 |
| Antonio N, 2002[59] | 122 | meningioma | 14.60 | 4.15 | 96.0 |
| Spiegelmann R, 2002[60] | 42 | meningioma | 14.00 | 3.00 | 97.5 |
| Muijer O,2003[51] | 42 | VS | 12.50 | 2.75 | 100 |
| Kondziolka D, 2003[61] | 28 | pituitary | 20.80 | 9.10 | 81.1 |
| Kondziolka D, 2003[61] | 85 | meningioma | 16.50 | 9.10 | 91.5 |
| Kondziolka D, 2003[61] | 157 | VS | 16.70 | 9.10 | 96.9 |
| Pollock B, 2003[62] | 281 | meningioma | 16.00 | 3.58 | 93.0 |
| Flickinger J ,2003[63] | 219 | meningioma | 14.00 | 2.42 | 93.2 |
| Steven J, 2004[64] | 137 | meningioma | 14.00 | 4.50 | 91.7 |
| Yoshiyasu I, 2005[65] | 34 | pituitary | 14.00 | 4.98 | 93.0 |
| Friedman W, 2005[66] | 181 | meningioma | 13.14 | 3.25 | 96.0 |
| Dong G, 2005[67] | 23 | meningioma | 16.00 | 2.75 | 96.0 |
| Guenther C, 2005[68] | 127 | meningioma | 13.80 | 2.44 | 96.4 |

Table 4.3.Treatment of benign brain tumor by stereotactic radiosurgery (SRS) (continued)

| Authors | No. of patients | Type of tumor | Marginal dose (Gy) | Median of follow up (yrs) | TCR (%) 5yrs |
|---|---|---|---|---|---|
| Okunaga T, 2005[69] | 46 | VS | 14.00 | 4.70 | 100 |
| Metellus P, 2005[35] | 36 | meningioma | 14.00 | 5.30 | 88.9 |
| Pouratian N, 2006[70] | 28 | pituitary | 18.90 | 4.80 | 89.0 |
| Zachenhofer I, 2006[71] | 20 | meningioma | 16.83 | 8.58 | 94.0 |
| Dong L, 2006[72] | 112 | VS | 12.27 | 5.69 | 95.9 |
| Friedman W,2006[73] | 390 | VS | 12.50 | 3.33 | 90.0 |
| Kollova A, 2007[74] | 368 | meningioma | 12.55 | 5.00 | 97.9 |

**4.3 Assess and validate the range of iso-effect 5-year TCR.**

Since most of the articles (i.e. 88 %) reporting a 5- year TCR of greater than 90% with a mean (SD) of 94.46 % (3.88), it was uncertain whether these findings were truly different or actually equivalent with a certain degree of statistically variation. To answer this question, different iso-effect data sets (i.e. D versus d) were fitted to the reciprocal dose equation below [19,26,29].

$$\left(\frac{1}{D}\right)=\left(\frac{\alpha}{E}\right)+\left(\frac{\beta}{E}\right)d \qquad (3)$$

To search for the best estimate of α/β from the fitted equation that yielded the highest $R^2$. The iso-effect schemes yielding the best estimate of α/β served as a frame of reference for the determination of α/β for other schemes with different 5-year TCR by

two scheme matching [16,26,75] presuming that they were equivalent as equation below

$$\frac{\alpha}{\beta} = \left( \frac{Dd - D_{ref} d_{ref}}{D_{ref} - D} \right) \quad (12)$$

The α/β thus obtained was tested for its different from $\alpha/\beta_{ref}$ by t-test. TCR of fractionation scheme that yielded non-significant different α/β from the reference value was regarded as iso-effect to the reference 5-year TCR.

**4.4 Determination of the α/β value**

**4.4.1 Matching of two iso-effect scheme** [16,26,75]

$$\frac{\alpha}{\beta} = \left( \frac{D_2 d_2 - D_1 d_1}{D_1 - D_2} \right) \quad (6)$$

The α/β value was calculated by equation 6. the iso-effect scheme were matched between conventional fraction versus conventional fraction (different dose per fraction and different total dose); conventional fraction versus hypofractionation; conventional fraction versus single fraction; hypofractionation versus hypofractionation; hypofractionation versus single fraction; single fraction versus single fraction (different dose per fraction ).

**4.4.2 Analysis of reciprocal of iso-effect dose plot**

Fit iso-effect D and d to equation (3) [19,26,29] with dose per fraction (d) as x-axis and the reciprocal dose (1/D) as y-axis. By linear ligression line analysis, y-intercept and slope were calculated. The α/β value was determined by dividing the y-intercept with the slope.

**4.4.3 Two step graphical matching** [21]

This method was divided in two step graphical analysis. The first step involved was to establish a dose response curves (5-year TCR versus $EQD_{2,\alpha/\beta}$) at different presumed values of α/β. The second step involved the determination of fractionated $EQD_2$ that equivalent to the single dose treatment by using the dose response curve established previously.

**Step 1 Establishment of dose response curves**

1. Data management (21). The data were grouped according to size of dose per fraction (Tables 4.4,4.5,4.6,4.7). For each dose per fraction, the total dose was the arithmetic mean of all clinical reports and the 5-year TCR was weighted by the number of patients as follow.

$$5\text{-year TCR}_{\text{weighted}}(\%) = \frac{1}{N}\sum_{i=1}^{N} n_i \, TCR_i \qquad (9)$$

Where $n_i$ was number of patients in series i, N was the total number of patients treated by the same dose fraction.

Table 4.4.Conventional external beam radiotherapy (EXBT) of benign brain tumor classified according to size of dose per fraction.

| Dose/fx (Gy) | No.of patients | Total dose (Gy) | TCR(%) | Weighted TCR(%) | Type of tumor | Reference |
|---|---|---|---|---|---|---|
| 1.8 | 82 | 57.0 | 92.0 | 12.70 | meningioma | 8 |
| | 38 | 52.0 | 94.7 | 6.06 | meningioma | 35 |
| | 101 | 54.0 | 95.0 | 16.15 | meningioma | 34 |
| | 141 | 47.2 | 94.0 | 22.31 | pituitary | 31 |
| | 110 | 50.4 | 99.0 | 18.33 | pituitary | 36 |
| | 76 | 50.4 | 95.0 | 12.16 | pituitary | 38 |
| | 46 | 51.0 | 86.0 | 6.66 | VS | 37 |
| Total | 594 | 51.7[a] | | 94.37 | | |
| 1.9 | 31 | 52.0 | 92.8 | 92.80 | meningioma | 32 |
| 2.0 | 45 | 56.0 | 95.0 | 95.00 | meningioma | 33 |

a = Average

Table 4.5.Stereotactic radiotherapy (SRT) of benign brain tumor classified according to size of dose per fraction.

| Dose/fx (Gy) | No.of patients | Total dose (Gy) | TCR(%) | Weighted TCR(%) | Type of tumor | Reference |
|---|---|---|---|---|---|---|
| 1.8 | 189 | 56.8 | 98.0 | 29.31 | meningioma | 41 |
| | 317 | 57.6 | 94.7 | 47.50 | meningioma | 46 |
| | 20 | 52.2 | 100 | 3.16 | pituitary | 45 |
| | 106 | 57.6 | 93.0 | 15.60 | VS | 48 |
| Total | 632 | 56.1[a] | | 95.57 | | |
| 1.9 | 84 | 56.0 | 100 | 31.70 | meningioma | 50 |
| | 65 | 55.8 | 100 | 24.53 | meningioma | 49 |
| | 51 | 57.6 | 95.0 | 18.28 | VS | 39 |
| | 65 | 50.0 | 92.0 | 22.57 | VS | 40 |
| Total | 265 | 54.9[a] | | 97.08 | | |
| 2.0 | 68 | 50.0 | 98.0 | 25.24 | pituitary | 47 |
| | 101 | 48.0 | 91.4 | 34.97 | VS | 44 |
| | 56 | 50.0 | 97.0 | 20.58 | VS | 42 |
| | 39 | 50.0 | 95.0 | 14.03 | VS | 43 |
| Total | 264 | 49.5[a] | | 94.82 | | |

a = Average

Table 4.6.Fractionated treatment of benign brain tumor classified according to size of dose per fraction.

| Dose/fx (Gy) | No.of patients | Total dose (Gy) | TCR(%) | Weighted TCR(%) | Type of tumor | Reference |
|---|---|---|---|---|---|---|
| 1.8 | 82 | 57.0 | 92.0 | 6.15 | meningioma | 8 |
| | 38 | 52.0 | 94.7 | 2.94 | meningioma | 35 |
| | 101 | 54.0 | 95.0 | 7.83 | meningioma | 34 |
| | 141 | 47.2 | 94.0 | 10.81 | pituitary | 31 |
| | 110 | 50.4 | 99.0 | 8.88 | pituitary | 36 |

Table 4.6 Fractionated treatment of benign brain tumor classified according to size of dose per fraction. (continued)

| Dose/fx (Gy) | No.of patients | Total dose (Gy) | TCR(%) | Weighted TCR(%) | Type of tumor | Reference |
|---|---|---|---|---|---|---|
| 1.8 | 76 | 50.4 | 95.0 | 5.89 | pituitary | 38 |
| | 46 | 51.0 | 86.0 | 3.23 | schwannoma | 37 |
| | 189 | 56.8 | 98.0 | 15.11 | meningioma | 41 |
| | 317 | 57.6 | 94.7 | 24.49 | meningioma | 46 |
| | 20 | 52.2 | 100 | 1.63 | pituitary | 45 |
| | 106 | 57.6 | 93.0 | 8.04 | VS | 48 |
| Total | 1226 | 51.71[a] | | 94.99 | | |
| 1.9 | 31 | 52.0 | 92.8 | 9.72 | meningioma | 32 |
| | 84 | 56.0 | 100 | 28.38 | meningioma | 50 |
| | 65 | 55.8 | 100 | 21.96 | meningioma | 49 |
| | 51 | 57.6 | 95.0 | 16.37 | VS | 39 |
| | 65 | 50.0 | 92.0 | 20.20 | VS | 40 |
| Total | 296 | 54.28[a] | | 96.63 | | |
| 2.0 | 45 | 56 | 95.0 | 13.84 | meningioma | 33 |
| | 68 | 50 | 98.0 | 21.57 | pituitary | 47 |
| | 101 | 48 | 91.4 | 29.88 | VS | 44 |
| | 56 | 50 | 97.0 | 17.58 | VS | 42 |
| | 39 | 50 | 95.0 | 11.99 | VS | 43 |
| Total | 309 | 50.8[a] | | 94.85 | | |

a = Average

2. Calculation of $EQD_{2,\alpha/\beta}$. Each dose fractionation scheme was converted into an equivalent total dose of 2 Gy [27] fraction as the equation below.

$$EQD_{2,\alpha/\beta} = \frac{D(d + \alpha/\beta)}{(2 + \alpha/\beta)} \quad (7)$$

By assigning different α/β values varying from 0.5 to 6 Gy (Tables 4.7, 4.8, 4.9). These presumed α/β values fall in the range which characterizes the late responding tissue [27]

3. Determination of the parameter of fit for the logistic equation. Generally, a logistic function as shown below is used for fitting the tumor control curve in radiotherapy [76, 77]

$$p = \frac{e^{(a+bx)}}{1+e^{(a+bx)}} \tag{13}$$

By logit transformation, equation 13 can be linearized as follow.

$$\ln\left(\frac{TCP}{1-TCP}\right) = a + bEQD_{2,\alpha/\beta} \tag{14}$$

Data set of $EQD_{2,\alpha/\beta}$ and 5-year $TCR_{weighted}$ for different α/β values were fitted to equation 14 in order to estimated a and b using SPSS program version 11.5. (Tables 4.10, 4.11, 4.12)

4. Plotting of 5-year TCR versus $EQD_{2,\alpha/\beta}$ curves. The 5-year TCR versus $EQD_{2,\alpha/\beta}$ curve was plotted by using equation 15. For different pairs of a and b as shown in Tables 4.10, 4.11 and 4.12. $EQD_{2,\alpha/\beta}$ was varied from 20-120 Gy.

$$TCP = \frac{e^{\left(a+bEQD_{2,\alpha/\beta}\right)}}{1+e^{\left(a+bEQD_{2,\alpha/\beta}\right)}} \tag{15}$$

Table 4.7 The $EQD_{2,\alpha/\beta}$ of conventional external beam radiotherapy (EXBT) from converting mean total dose (Gy) and varied α/β (Gy)

| Dose/fx | Total dose | Assumed α/β (Gy) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (Gy) | (Gy) | 0.5 | 1 | 1.5 | 2 | 2.5 | 3 | 3.5 | 4 | 4.5 | 5 | 5.5 | 6 |
| 1.8 | 51.71 | 47.57 | 48.26 | 48.76 | 49.12 | 49.41 | 49.64 | 49.83 | 49.99 | 50.12 | 50.23 | 50.33 | 50.42 |
| 1.9 | 52.00 | 49.92 | 50.27 | 50.51 | 50.70 | 50.84 | 50.96 | 51.05 | 51.13 | 51.20 | 51.26 | 51.31 | 51.35 |
| 2.0 | 56.00 | 56.00 | 56.00 | 56.00 | 56.00 | 56.00 | 56.00 | 56.00 | 56.00 | 56.00 | 56.00 | 56.00 | 56.00 |

Table 4.8 The $EQD_{2,\alpha/\beta}$ of stereotactic radiotherapy technique (SRT) from converting mean total dose (Gy) and varied α/β (Gy)

| Dose/fx | Total dose | Assumed α/β (Gy) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (Gy) | (Gy) | 0.5 | 1 | 1.5 | 2 | 2.5 | 3 | 3.5 | 4 | 4.5 | 5 | 5.5 | 6 |
| 1.8 | 56.05 | 51.57 | 52.31 | 52.85 | 53.25 | 53.56 | 53.81 | 54.01 | 54.18 | 54.33 | 54.45 | 54.65 | 54.80 |
| 1.9 | 54.85 | 52.66 | 53.02 | 53.28 | 53.48 | 53.63 | 53.75 | 53.85 | 53.94 | 54.01 | 54.07 | 54.16 | 54.24 |
| 2.0 | 49.50 | 49.50 | 49.50 | 49.50 | 49.50 | 49.50 | 49.50 | 49.50 | 49.50 | 49.50 | 49.50 | 49.50 | 49.50 |

Table 4.9 The $EQD_{2,\alpha/\beta}$ of conventional fraction from converting mean total dose (Gy) and varied α/β (Gy)

| Dose/fx | Total dose | Assumed α/β (Gy) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (Gy) | (Gy) | 0.5 | 1 | 1.5 | 2 | 2.5 | 3 | 3.5 | 4 | 4.5 | 5 | 5.5 | 6 |
| 1.8 | 51.71 | 47.57 | 48.26 | 48.76 | 49.12 | 49.41 | 49.64 | 49.83 | 49.99 | 50.12 | 50.23 | 50.42 | 50.56 |
| 1.9 | 54.28 | 52.11 | 52.47 | 52.73 | 52.92 | 53.07 | 53.19 | 53.29 | 53.38 | 53.44 | 53.50 | 53.60 | 53.68 |
| 2.0 | 50.80 | 50.80 | 50.80 | 50.80 | 50.80 | 50.80 | 50.80 | 50.80 | 50.80 | 50.80 | 50.80 | 50.80 | 50.80 |



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Table 4.10 The coefficient (a,b) of logistic regression formula from convention external beam radiotherapy (EXBT)

| Alpha/beta (Gy) | Constant (a) | Slope (b) | $R^2$ |
|---|---|---|---|
| 0.5 | 1.5124 | 0.0246 | 0.2931 |
| 1 | 1.3546 | 0.0275 | 0.3120 |
| 1.5 | 1.2149 | 0.0301 | 0.3298 |
| 2 | 1.1043 | 0.0321 | 0.3419 |
| 2.5 | 1.0016 | 0.0340 | 0.3545 |
| 3 | 0.9151 | 0.0356 | 0.3639 |
| 3.5 | 0.8356 | 0.0371 | 0.3737 |
| 4 | 0.7656 | 0.0383 | 0.3817 |
| 4.5 | 0.7072 | 0.0394 | 0.3877 |
| 5 | 0.6558 | 0.0403 | 0.3928 |
| 5.5 | 0.6057 | 0.0413 | 0.3984 |
| 6 | 0.5574 | 0.0421 | 0.4045 |

Table 4.11 The coefficient (a,b) of logistic regression formula from stereotactic radiotherapy (SRT)

| Alpha/beta (Gy) | Constant (a) | Slope (b) | $R^2$ |
|---|---|---|---|
| 0.5 | -5.6718 | 0.1724 | 0.8220 |
| 1 | -3.8693 | 0.1362 | 0.6904 |
| 1.5 | -2.7979 | 0.1148 | 0.6067 |
| 2 | -2.1372 | 0.1017 | 0.5549 |
| 2.5 | -1.6922 | 0.0929 | 0.5183 |
| 3 | -1.3711 | 0.0865 | 0.4914 |
| 3.5 | -1.1381 | 0.0819 | 0.4722 |
| 4 | -0.9566 | 0.0784 | 0.4580 |
| 4.5 | -0.8019 | 0.0753 | 0.4443 |
| 5 | -0.6864 | 0.0730 | 0.4347 |
| 5.5 | -0.5004 | 0.0694 | 0.4176 |
| 6 | -0.3760 | 0.0669 | 0.4077 |

Table 4.12 The coefficient (a,b) of logistic regression formula from conventional fraction

| Alpha/beta (Gy) | Constant (a) | Slope(b) | $R^2$ |
|---|---|---|---|
| 0.5 | -0.5491 | 0.0722 | 0.4637 |
| 1 | -1.4381 | 0.0893 | 0.5840 |
| 1.5 | -2.1615 | 0.1031 | 0.6828 |
| 2 | -2.6935 | 0.1131 | 0.7570 |
| 2.5 | -3.1125 | 0.1210 | 0.8152 |
| 3 | -3.4224 | 0.1268 | 0.8591 |
| 3.5 | -3.6548 | 0.1311 | 0.8926 |
| 4 | -3.8185 | 0.1341 | 0.9185 |
| 4.5 | -3.9617 | 0.1367 | 0.9370 |
| 5 | -4.0514 | 0.1383 | 0.9513 |
| 5.5 | -4.1837 | 0.1406 | 0.9720 |
| 6 | -4.2401 | 0.1415 | 0.9838 |

**Step2 Single and multifraction graphical matching**

1. Weighted 5-year TCR from single fraction treatments with different marginal doses (Table 4.13) were used to read out the $EQD_2$ from dose response curves established in step 1.

Table 4.13 Single fraction of benign brain tumor classified according to size of dose per fraction

| Marginal dose (Gy) | No.of patients | TCR(%) | Weighted TCR (%) | Type of tumor | Reference |
|---|---|---|---|---|---|
| 12.00 | 69 | 98.0 | 98.00 | VS | 42 |
| 12.27 | 112 | 95.9 | 95.90 | VS | 72 |
| 12.50 | 42 | 100 | 9.72 | VS | 51 |
| | 390 | 90.0 | 81.25 | VS | 73 |
| Total | 432 | | 90.97 | | |

Table 4.13 Single fraction of benign brain tumor classified according to size of dose per fraction (continued)

| Dose/fx (Gy) | No.of patients | TCR(%) | Weighted TCR (%) | Type of tumor | Reference |
|---|---|---|---|---|---|
| 12.55 | 368 | 97.9 | 97.90 | meningioma | 74 |
| 13.00 | 190 | 91.0 | 56.69 | VS | 57 |
| | 115 | 94.0 | 35.44 | meningioma | 56 |
| Total | 305 | | 92.13 | | |
| 13.14 | 181 | 96.0 | 96.00 | meningioma | 66 |
| 13.80 | 127 | 96.4 | 96.40 | meningioma | 68 |
| 14.00 | 34 | 93.0 | 4.77 | pituitary | 65 |
| | 137 | 91.7 | 18.95 | meningioma | 64 |
| | 219 | 93.2 | 30.79 | meningioma | 63 |
| | 36 | 88.9 | 4.83 | meningioma | 35 |
| | 42 | 97.5 | 6.18 | meningioma | 60 |
| | 46 | 100 | 6.94 | VS | 69 |
| | 149 | 87.0 | 19.55 | VS | 58 |
| Total | 663 | | 92.00 | | |
| 14.60 | 122 | 96.0 | 96.00 | meningioma | 59 |
| 15.00 | 40 | 98.0 | 98.00 | VS | 54 |
| 16.00 | 99 | 93.0 | 16.12 | meningioma | 58 |
| | 281 | 93.0 | 45.77 | meningioma | 53 |
| | 23 | 96.0 | 3.87 | meningioma | 62 |
| | 168 | 93.0 | 27.36 | meningioma | 67 |
| Total | 571 | | 93.12 | | |
| 16.50 | 85 | 91.5 | 91.50 | meningioma | 61 |
| 16.70 | 157 | 96.9 | 96.90 | VS | 61 |
| 16.83 | 20 | 94.0 | 94.00 | meningioma | 71 |
| 18.90 | 28 | 89.0 | 89.00 | pituitary | 70 |
| 20.80 | 28 | 81.1 | 81.10 | pituitary | 61 |

2. Construct the iso-effect BED curves for varying α/β values from 0.5 to 6 Gy using the equations 16 and 17

$$BED_{multifraction} = EQD_2\left(1+\frac{2}{\alpha/\beta}\right) \quad (16)$$

$$BED_{single\ fraction} = D_{marginal}\left(1+\frac{D_{marginal}}{\alpha/\beta}\right) \quad (17)$$

3. The crossing point of the two iso-effect lines yielded the best estimate of α/β.

**4.4. Statistical analysis**

Student t-test was used to test for the difference between α/β values obtained by different method of estimation. All of the statistical tests were 2-tailed, and $p \leq 0.5$ was considered statistically significant.

# CHAPTER V
# RESULTS

## 5.1 Determination of the iso-effect range for 5-year TCR

Because of the small variation in 5-year TCR (94.66 ± 3.88) reported in most articles (40 out of 45), it was important to ascertain whether these clinical findings were truly different or actually equivalent. Fitting series of iso-effect data to reciprocal dose plot, it was observed that iso-effect data for 5-year TCR 93% yielded the best fit with an $R^2$ of 0.9448 (Table 5.1.1). The α/β obtained from this fitting was used as a frame of reference in the determination of α/β for other schemes with different 5-year TCR using a two-scheme matching method. It was assumed that the test scheme was equivalent to the reference scheme when the α/β calculated from their matching was not significantly different from the $\alpha/\beta_{reference}$. Values of α/β for different 5-year TCR are shown in Table 5.1.2. Data in Table 5.1.2 have shown the 5-year TCR ranging from 89% to 100% are not statistically different from the 93% except for 90% 5-year TCR. This significant difference observed at 90% 5-year TCR was possibly a by-chance observation and was less reliable because of fewer numbers of data available for matching. A cut-off for range of equivalent effect was chosen at 91% on the basis of number of iso-effect data for matching of greater than 2. Therefore, 5-year TCR ranged from 91% to 100% were regard as an iso-effect endpoint.

Table 5.1.1.Reciprocal dose plot fitting for different fraction

| TCR (%) | Regression line | α/β(Gy) | $R^2$ | Reference |
|---|---|---|---|---|
| 92 | 0.0034x+0.0134 | 3.94 | 0.9164 | 8,40,61,64 |
| 93 | 0.0036x+0.0122 | 3.39 | 0.9448 | 32,48,53,55,62,63,65 |
| 94 | 0.0026x+0.0287 | 11.04 | 0.6741 | 31,56,71 |
| 98 | 0.0041x+0.0173 | 4.22 | 0.8480 | 41,42,47,54,60,74 |
| 100 | 0.0043x+0.0159 | 3.70 | 0.6832 | 45,49,50,51,69 |

Table 5.1.2.The α/β values for different TCRs matching against the TCR of 93%

| TCR (%) matching | No. of matching | No. of patients | α/β (Gy) | %Deviation from reference α/β | P-value (t-test) | Reference |
|---|---|---|---|---|---|---|
| 93vs 81 | 2 | 165 | 9.82±1.24 | -208.81 | 0.03 | 32,48,61 |
| 93 vs 86 | 2 | 847 | 3.76±1.33 | -18.24 | 0.65 | 37,53,55,62,63,65 |
| 93 vs 87 | 2 | 249 | 2.34±0.31 | 26.42 | 0.21 | 32,48,72 |
| 93 vs 89 | 4 | 203 | 4.76±2.85 | -49.69 | 0.36 | 32,35,48,70 |
| 93 vs 90 | 2 | 527 | 1.31±0.20 | 58.81 | 0.03 | 32,48,73 |
| 93 vs 91 | 4 | 1227 | 2.80±1.60 | 11.95 | 0.71 | 32,44,48,53,55,57 ,62,63,65 |
| 93 vs 92 | 8 | 1288 | 3.39±1.12 | -6.60 | 0.75 | 8,32,37,48,53,55 ,61-65 |
| 93 vs 93 | 4 | 938 | 3.18±1.03 | 0.00 | Reference | 32,48,53,55,62,63 ,65 |
| 93 vs 94 | 8 | 1214 | 3.50±1.48 | -10.06 | 0.67 | 31,32,48,53,55,56 ,62,63,65,71 |
| 93 vs 95 | 14 | 1369 | 3.26±0.99 | -2.52 | 0.89 | 33-35,38,39,43,46 ,55,62,63,65 |
| 93 vs 96 | 10 | 960 | 2.38±1.06 | 25.16 | 0.24 | 32,48,59,62,66,68 ,72 |
| 93 vs 97 | 4 | 1151 | 4.16±1.05 | -30.82 | 0.23 | 32,42,48,53,55,61 ,62,63,65 |
| 93 vs 98 | 10 | 1814 | 2.68±1.03 | 15.72 | 0.45 | 32,41,42,47,48,53, 54,55,60,62,63,65, 74 |
| 93 vs 99 | 2 | 630 | 3.85±1.35 | -21.07 | 0.61 | 36,53,55,62,63,65 |
| 93 vs 100 | 9 | 1175 | 2.65±0.94 | 20.13 | 0.34 | 32,48,49,50,51,53 ,55,62,63,65,69 |

## 5.2 Determination of the α/β values

### 5.2.1 Matching of two iso-effects scheme

In principle, α/β is the radiation dose which induces equivalent α kill (small dose response) and β kill (large dose response) [76]. Question arose as whether any

type of iso-effect matching yielded the reliable estimate for α/β. Equivalent schemes were matched as follows: single fraction versus single fraction, hypofraction versus hypofraction, conventional fraction versus conventional fraction, hypofraction versus single fraction, conventional fraction versus hypofraction, and conventional fraction versus single fraction (Tables 5.2.1.1, 5.2.1.2, 5.2.1.3, 5.2.1.4, 5.2.1.5, 5.2.1.6). Matching of iso-effect scheme with ratio of fraction sizes ranges between 1-3 yielded unrealistic α/β estimates which do not represent late responding organ [27] (Table 5.2.1.7). However, when conventional scheme was matched to the single fraction scheme of which the $d_2/d_1$ ratio was 7.46 (Table 5.2.1.7), a reasonable estimated of 2.71 Gy was obtained.

Table 5.2.1.1 The α/β values estimated by matching of two iso-effect scheme between single fraction and single fraction

| Scheme 1 | Scheme 2 | | α/β±SD | |
|---|---|---|---|---|
| Marginal dose (Gy) | Marginal dose (Gy) | d2:d1[b] | (Gy) | Reference |
| 12.00 | 16.83 | 1.40 | -28.83 | 41,60 |
| 12.27 | 16.70 | 1.36 | -28.97 | 50,69 |
| 12.50 | 16.50 | 1.32 | -29.00 | 47,50 |
| 12.55 | 16.00 | 1.27 | -28.55 | 53,55-57,63 |
| 13.00 | 15.00 | 1.15 | -28.00 | 62,65,66 |
| 13.14 | 14.60 | 1.11 | -27.74 | 51,54 |
| 13.80 | 14.00 | 1.01 | -27.80 | 49,52,58,59,61,67 |
| 14.00 | 13.80 | 0.99 | -27.80 | 49,52,58,59,61,67 |
| 14.60 | 13.14 | 0.90 | -27.74 | 51,54 |
| 15.00 | 13.00 | 0.87 | -28.00 | 62,65,66 |
| 16.00 | 12.55 | 0.78 | -28.55 | 53,55-57,63 |
| 16.50 | 12.50 | 0.76 | -29.00 | 47,50 |
| 16.70 | 12.27 | 0.73 | -28.97 | 50,69 |
| 16.83 | 12.00 | 0.71 | -28.83 | 41,60 |
| Mean±SD | | 1.08±0.23 | -28.33±0.53 | |

b = The ratio of dose/fx for scheme 2 and dose/fx for scheme 1

Table 5.2.1.2 The α/β values estimated by matching of two iso-effect scheme between hypofraction and hypofraction

| Scheme 1 | | Scheme 2 | | | | |
|---|---|---|---|---|---|---|
| Dose/fx (Gy) | Total dose (Gy) | Dose/fx (Gy) | Total dose (Gy) | d2:d1[b] | α/β±SD (Gy) | Reference |
| 4 | 20 | 7 | 21 | 1.75 | -67.00 | 51,52 |
| 5 | 25 | 6 | 18 | 1.20 | -2.43 | 51,52 |
| 6 | 18 | 5 | 25 | 0.83 | -2.43 | 51,52 |
| 7 | 21 | 4 | 20 | 0.57 | -67.00 | 51,52 |
| Mean±SD | | | | 1.09±0.51 | -34.71±37.28 | |

b = The ratio of dose/fx for scheme 2 and dose/fx for scheme 1

Table 5.2.1.3.The α/β values estimated by matching of two iso-effect scheme between conventional fraction and conventional fraction

| Scheme 1 | | Scheme 2 | | | | |
|---|---|---|---|---|---|---|
| Dose/fx (Gy) | Total dose (Gy) | Dose/fx (Gy) | Total dose (Gy) | d2:d1[b] | α/β±SD (Gy) | Reference |
| 1.8 | 47.2 | 1.8 | 57.6 | 1.00 | -1.80 | 31,46,48 |
| | 50.4 | | 57.0 | | -1.80 | 8,36,38 |
| | 52.0 | | 56.8 | | -1.80 | 35,41 |
| | 52.2 | | 54.0 | | -1.80 | 34,45 |
| | 54.0 | | 52.2 | | -1.80 | 34,45 |
| | 56.8 | | 52.0 | | -1.80 | 35,41 |
| | 57.0 | | 50.4 | | -1.80 | 8,36,38 |
| | 57.6 | | 47.2 | | -1.80 | 31,46,48 |
| | 47.2 | 1.9 | 57.6 | 1.06 | -2.35 | 31,39 |
| | 50.4 | | 56.0 | | -2.80 | 36,38,61 |
| | 52.0 | | 55.8 | | -3.27 | 35,49 |
| | 54.0 | | 52.0 | | 0.80 | 32,34 |
| | 57.0 | | 50.0 | | -1.09 | 8,40 |
| | 50.4 | 2.0 | 56.0 | 1.11 | -3.80 | 33,36,38 |
| | 56.8 | | 50.0 | | -0.33 | 41-43,47 |
| | 57.6 | | 48.0 | | -0.80 | 44,46,48 |

b = The ratio of dose/fx for scheme 2 and dose/fx for scheme 1

Table 5.2.1.3.The α/β values estimated by matching of two iso-effect scheme between conventional fraction and conventional fraction (continued)

| Scheme 1 | | Scheme 2 | | | | |
|---|---|---|---|---|---|---|
| Dose/fx (Gy) | Total dose (Gy) | Dose/fx (Gy) | Total dose (Gy) | d2:d1[b] | α/β±SD (Gy) | Reference |
| 1.9 | 50.0 | 1.9 | 57.6 | 1.00 | -1.90 | 39,40 |
| | 52.0 | | 56.0 | | -1.90 | 32,50 |
| | 56.0 | | 52.0 | | -1.90 | 32,50 |
| | 57.6 | | 50.0 | | -1.90 | 39,40 |
| | 50.0 | 2.0 | 56.0 | 1.05 | -2.83 | 33,44 |
| | 55.8 | | 50.0 | | -1.04 | 42,43,47,49 |
| | 57.6 | | 48.0 | | -1.40 | 39,44 |
| 2.0 | 48.0 | 2.0 | 56.0 | 1.00 | -2.00 | 33,44 |
| | 56.0 | | 48.0 | | -2.00 | 33,44 |
| Mean±SD | | | | 1.04±0.05 | -1.8±0.91 | |

b = The ratio of dose/fx for scheme 2 and dose/fx for scheme 1

Table 5.2.1.4 The α/β values estimated by matching of two iso-effect scheme between hypofraction and single fraction

| Scheme 1 | | Scheme 2 | | α/β±SD | |
|---|---|---|---|---|---|
| Dose/fx (Gy) | Total dose (Gy) | Dose/fx (Gy) | d2:d1[b] | (Gy) | Reference |
| 4 | 20 | 13.9 | 3.55±0.44 | 27.00±20.25 | 51,54-68, 70-72,74 |
| 5 | 25 | (10-16.83)[c] | 2.84±0.35 | 8.34±6.52 | 52,54-68, 70-72,74 |
| 6 | 18 | | 2.37±0.29 | 45.22±49.98 | 51,54-68, 70-72,74 |
| 7 | 21 | | 2.03±0.25 | 11.27±11.97 | 52,54-68, 70-72,74 |
| Mean±SD | | | 2.48±0.02 | 10.76±5.48 | |

b = The ratio of dose/fx for scheme 2 and dose/fx for scheme 1, c = Range of dose

Table 5.2.1.5 The α/β values estimated by matching of two iso-effect scheme between conventional fraction and hypofraction

| Scheme 1 | | Scheme 2 | | | | |
|---|---|---|---|---|---|---|
| Dose/fx (Gy) | Total dose (Gy) | Dose/fx (Gy) | Total dose (Gy) | d2:d1[b] | α/β±SD (Gy) | Reference |
| 1.8 | 47.20 | 5.5(4-7)[c] | 21(18-25)[c] | 3.06±0.62 | 1.19±0.98 | 31,51,52 |
| | 50.40 | | | | 0.86±0.86 | 36,38,51 ,52 |
| | 52.00 | | | | 0.72±0.81 | 35,51,52 |
| | 52.20 | | | | 0.70±0.80 | 45,51,52 |
| | 54.00 | | | | 0.57±0.75 | 34,51,52 |
| | 56.80 | | | | 0.38±0.69 | 41,51,52 |
| | 57.00 | | | | 0.37±0.68 | 8,51,52 |
| | 57.60 | | | | 0.33±0.67 | 46,48,51 ,52 |
| 1.9 | 50.00 | 5.5(4-7)[c] | 21(18-25)[c] | 2.89±0.59 | 0.72±0.86 | 40,51,52 |
| | 52.00 | | | | 0.55±0.80 | 32,51,52 |
| | 55.80 | | | | 0.28±0.70 | 49,51,52 |
| | 56.00 | | | | 0.27±0.70 | 50,51,52 |
| | 57.60 | | | | 0.17±0.67 | 39,51,52 |
| 2.0 | 48.00 | 5.5(4-7)[c] | 21(18-25)[c] | 2.75±0.56 | 0.74±0.93 | 44,51,52 |
| | 50.00 | | | | 0.55±0.85 | 42,43,47, 51,52 |
| | 56.00 | | | | 0.11±0.69 | 33,51,52 |
| Mean±SD | | | | 2.89±0.34 | 0.47±0.19 | |

b = The ratio of dose/fx for scheme 2 and dose/fx for scheme 1

c = Range of dose

Table 5.2.1.6 The α/β values estimated by matching of two iso-effect scheme between conventional fraction and single fraction

| Scheme 1 | | Scheme 2 | | α/β±SD | |
|---|---|---|---|---|---|
| Dose/fx (Gy) | Total dose (Gy) | Marginal dose (Gy) | d2:d1[b] | (Gy) | Reference |
| 1.8 | 47.20 | 14.2 | 7.89±0.97 | 3.71±1.76 | 31,54-68,70-72,74 |
| | 50.40 | (12-16.83)[c] | | 3.22±1.58 | 36,38,54-68, 70-72,74 |
| | 52.00 | | | 3.00±1.50 | 35,54-68,70-72,74 |
| | 52.20 | | | 2.98±1.49 | 45,54-68,70-72,74 |
| | 54.00 | | | 2.76±1.41 | 34,54-68,70-72,74 |
| | 56.80 | | | 2.45±1.31 | 41,54-68,70-72,74 |
| | 57.00 | | | 2.43±1.30 | 8,54-68,70-72,74 |
| | 57.60 | | | 2.37±1.28 | 46,48, 54-68, 70-72,74 |
| 1.9 | 50.00 | 14.2 | 7.48±0.92 | 3.13±1.59 | 40,54-68,70-72,74 |
| | 52.00 | (12-16.83)[c] | | 2.86±1.49 | 32,54-68,70-72,74 |
| | 55.80 | | | 2.42±1.34 | 49,54-68,70-72,74 |
| | 56.00 | | | 2.40±1.33 | 50,54-68,70-72,74 |
| | 57.60 | | | 2.24±1.27 | 39,54-68,70-72,74 |
| 2.0 | 48.00 | 14.2 | 7.10±0.87 | 3.30±1.40 | 43,54-68,70-72,74 |
| | 50.00 | (12-16.83)[c] | | 2.99±1.59 | 42,43,47,54-68, 70-72,74 |
| | 56.00 | | | 2.27±1.28 | 33,54-68,70-72,74 |
| Mean±SD | | | 7.46±0.53 | 2.71±0.35 | |

b = The ratio of dose/fx for scheme 2 and dose/fx for scheme 1

c = Range of dose

Table 5.2.1.7 The summary of α/β values estimated by matching of two iso-effect scheme

| Matching of two iso-effect schemes | $d_2/d_1$[b] | α/β (Gy) |
|---|---|---|
| Single fraction vs single fraction | 1.08±0.23 | -28.33±0.53 |
| Hypofraction vs hypofraction | 1.09±0.51 | -34.71±7.28 |
| Conventional fraction vs conventional fraction | 1.04±0.05 | -1.80±0.91 |
| Hypofraction vs single fraction | 2.48±0.02 | 10.76±5.48 |
| Conventional fraction vs hypofraction | 2.89±0.34 | 0.47±0.19 |
| Conventional fraction vs single fraction | 7.46±0.53 | 2.71±0.35 |

b = The ratio of dose/fx for scheme2 and dose/fx for scheme 1

**5.2.2 Analysis of reciprocal iso-effect dose plot**

Result from section 5.2.1 suggests that only the conventional fraction versus single large dose fraction yields a reasonable estimate of α/β. In this section, different sets of iso-effect data from conventional fractionation with 1.8, 1.9 and 2 Gy/fx and single fraction with marginal dose varying from 12 to 16.80 Gy were selected to fit the reciprocal iso-effect dose fraction (Equation 3). A straight line curve was obtained with an $R^2$ of 0.8619 (Figure 5.2.2.). The α/β value calculated from the intercept and slope was 3.53 ± 4.74 Gy.

Table 5.2.2.The different sets of iso-effect dose fraction 5-year TCR 91-100 %

| Dose/fx (Gy) | Total dose (Gy) | 1/Total dose (1/Gy) | Treatment fraction | Reference |
|---|---|---|---|---|
| 1.80 | 47.20 | 0.0212 | 26 | 31 |
| | 50.40 | 0.0198 | 28 | 36,38 |
| | 52.00 | 0.0192 | 29 | 35 |
| | 52.20 | 0.0192 | 29 | 45 |
| | 54.00 | 0.0185 | 30 | 34 |

Table 5.2.2 The different sets of iso-effect dose fraction 5-year TCR 91-100 % (Continued)

| Dose/fx (Gy) | Total dose (Gy) | 1/Total dose (1/Gy) | Treatment fraction | Reference |
|---|---|---|---|---|
| 1.80 | 56.80 | 0.0176 | 32 | 41 |
| | 57.00 | 0.0175 | 32 | 8 |
| | 57.60 | 0.0174 | 32 | 46,48 |
| 1.90 | 50.00 | 0.0200 | 26 | 40 |
| | 55.80 | 0.0179 | 29 | 49 |
| | 56.00 | 0.0179 | 29 | 50 |
| | 57.60 | 0.0174 | 32 | 39 |
| 2.00 | 48.00 | 0.0208 | 24 | 44 |
| | 50.00 | 0.0200 | 25 | 42,43,47 |
| | 56.00 | 0.0179 | 28 | 33 |
| 12.00 | 12.00 | 0.0833 | 1 | 42 |
| 12.27 | 12.27 | 0.0815 | 1 | 72 |
| 12.50 | 12.50 | 0.0800 | 1 | 73 |
| 12.55 | 12.55 | 0.0797 | 1 | 74 |
| 13.00 | 13.00 | 0.0769 | 1 | 56,57 |
| 13.14 | 13.14 | 0.0761 | 1 | 66 |
| 13.80 | 13.80 | 0.0725 | 1 | 68 |
| 14.00 | 14.00 | 0.0714 | 1 | 60,63-65 |
| 14.60 | 14.60 | 0.0685 | 1 | 59 |
| 15.00 | 15.00 | 0.0667 | 1 | 54 |
| 16.00 | 16.00 | 0.0625 | 1 | 53,55,62,67 |
| 16.50 | 16.50 | 0.0606 | 1 | 61 |
| 16.70 | 16.70 | 0.0599 | 1 | 61 |
| 16.80 | 16.80 | 0.0594 | 1 | 71 |

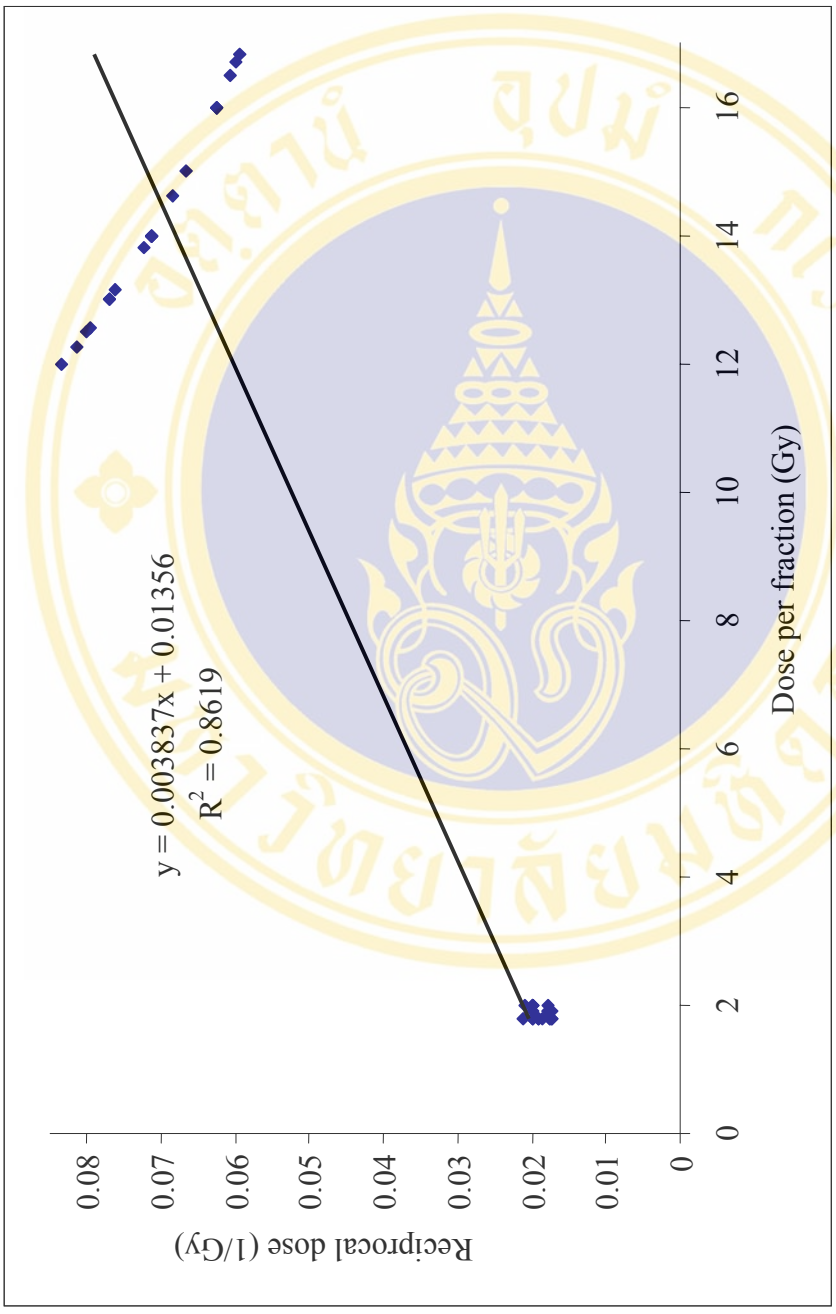


Figure 5.2.2. Reciprocal iso-effect dose plot for estimated the α/β value data with the conventional fractionation data and the single fraction data.

### 5.2.3 Two-step graphical matching

#### 5.2.3.1 Dose response curves established from fractionated treatment data

Fractionated treatment data from conventional external beam therapy (EXBT), stereotactic radiotherapy (SRT) were fitted to the logistic function (Equation 15) which was linearized by logit transformation (Equation 14). The parameters of fit obtained were used to plot the dose response relationship, i.e. tumor control probability (TCP) versus $EQD_2$, at different presumed α/β values (Figures 5.2.3.1 and 5.2.3.3). It was noted that all curves conformed an S-shaped as predicted by the logistic function. Therefore, the data were combined to plot a series of dose response curves as shown in Figure 5.2.3.5.

#### 5.2.3.2 Determination of α/β by single and multifraction graphical matching

The weight TCR of single fraction scheme was used to read out the iso-effect $EQD_2$ from the 5-year TCP versus $EQD_2$ curve established in the previous section. Two iso-effect lines, i.e. single fraction versus multifraction, describing the relationship of α/β and BED were plotted to derive the best estimation of α/β at the cross point data are shown in Table 5.2.3.1, 5.2.3.2 and 5.2.3.3. Representative curves were shown in Figure 5.2.3.2, 5.2.3.4 and 5.2.3.6

As depicted in Figures 5.2.3.1 and 5.2.3.3, the SRT data yielded better S-shaped curves than the EXBT data but the α/β values obtained by these data were not statistically different (Table 5.4).

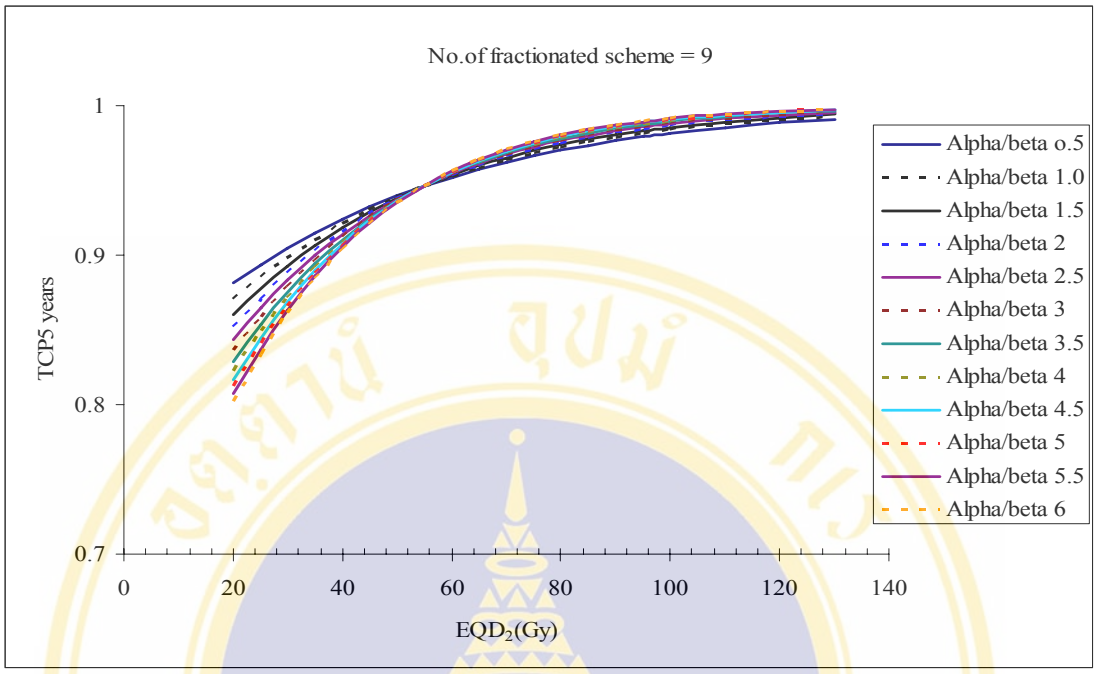


Figure 5.2.3.1 Dose response curve for TCP at 5 years versus equivalent total dose in 2 Gy per fraction at different presumed α/β values (Data from external beam therapy (EXBT) )

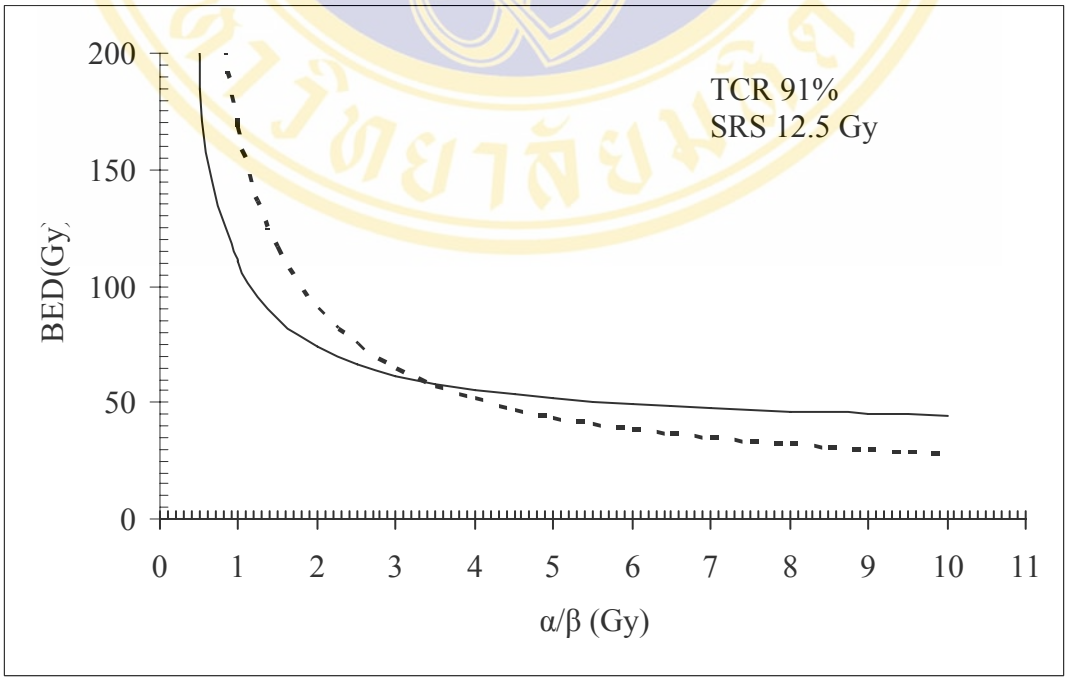


Figure 5.2.3.2 Representative BED versus α/β curves derived from single fraction data (dotted line) and EXBT data (solid line)

Table 5.3.2.1 Alpha/beta values estimated from the crossed point of single fraction and EXBT graphical matching

| Input factor | | Output variable | |
|---|---|---|---|
| TCP | Marginal dose (Gy) | BED (Gy) | α/β (Gy) |
| 0.96 | 12.27 | 380.00 | 0.48 |
| 0.91 | 12.50 | 59.14 | 3.20 |
| 0.92 | 13.00 | 69.33 | 3.10 |
| 0.96 | 13.14 | 221.16 | 0.83 |
| 0.96 | 13.80 | 204.24 | 1.10 |
| 0.92 | 14.00 | 60.67 | 4.20 |
| 0.96 | 14.60 | 143.79 | 1.65 |
| 0.98 | 15.00 | 330.00 | 0.51 |
| 0.93 | 16.00 | 63.85 | 5.35 |
| 0.97 | 16.70 | 143.47 | 2.20 |
| 0.94 | 16.83 | 70.58 | 5.27 |
| Mean±SD | | | 2.55±1.83 |

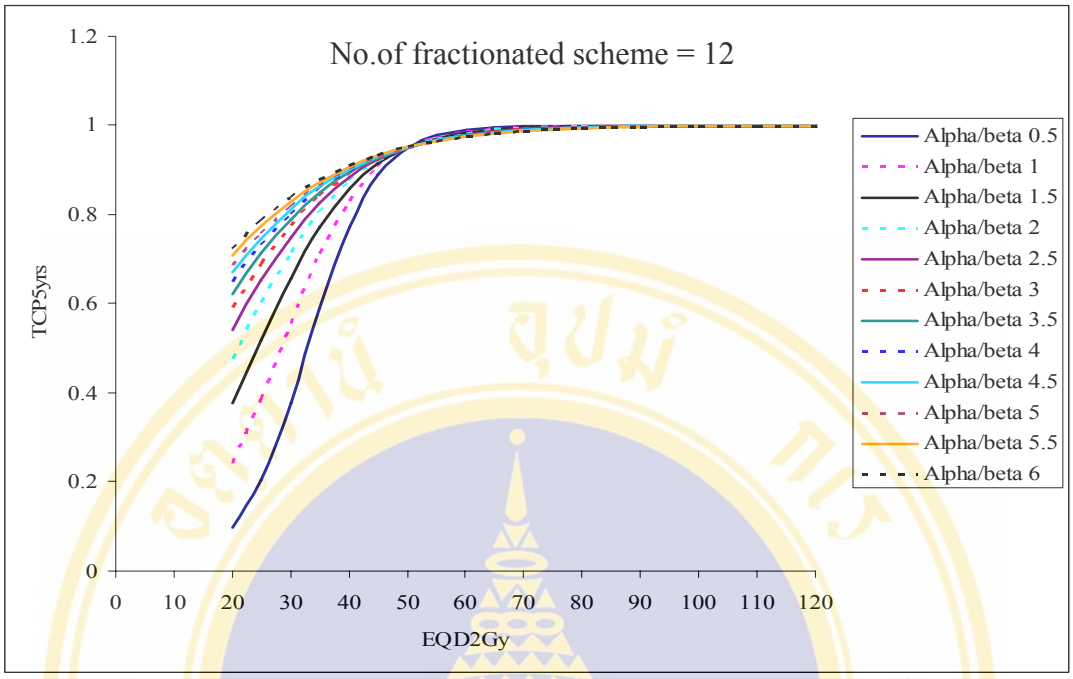


Figure 5.2.3.3 Dose response curve for TCP at 5 years versus equivalent total dose in 2 Gy per fraction at different presumed α/β values (Data from stereotactic radiotherapy (SRT))

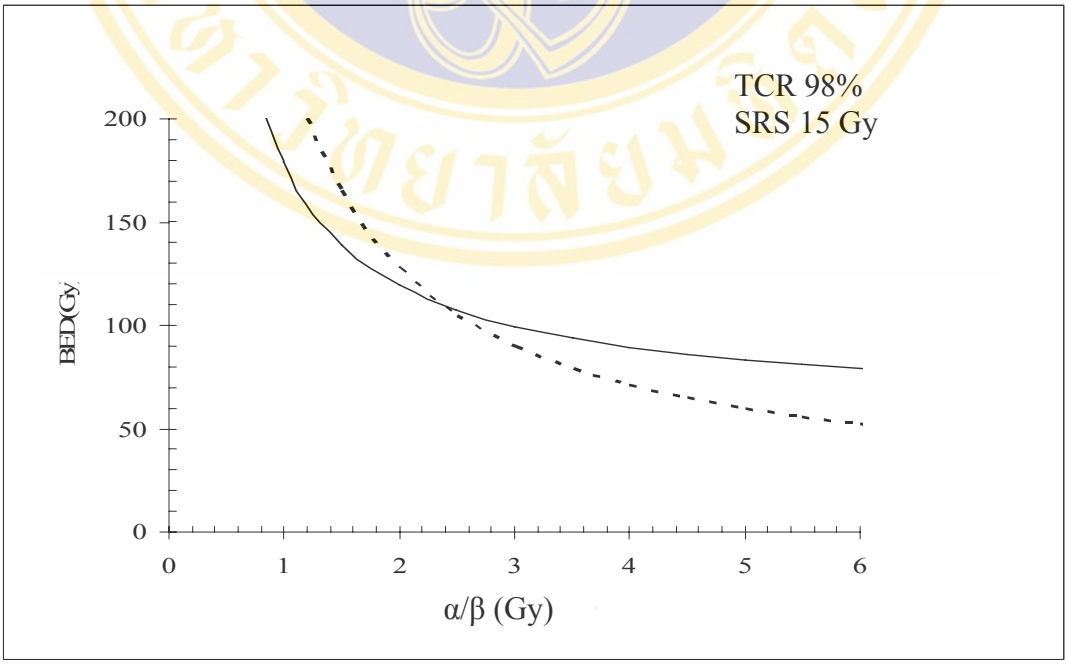


Figure 5.2.3.4 Representative BED versus α/β curves derived from single fraction data (dotted line) and SRT data (solid line)

Table 5.3.2.2 Alpha/beta values estimated from the crossed point of single fraction and SRT graphical matching

| Input factor | | Output variable | |
|---|---|---|---|
| TCP | Marginal dose (Gy) | BED (Gy) | α/β (Gy) |
| 0.96 | 12.27 | 137.73 | 1.20 |
| 0.91 | 12.50 | 83.20 | 2.21 |
| 0.98 | 12.55 | 209.43 | 0.75 |
| 0.92 | 13.00 | 80.60 | 2.50 |
| 0.96 | 13.14 | 112.37 | 1.74 |
| 0.96 | 13.80 | 104.47 | 2.24 |
| 0.92 | 14.00 | 70.00 | 3.50 |
| 0.96 | 14.60 | 88.36 | 2.89 |
| 0.98 | 15.00 | 109.94 | 2.37 |
| 0.93 | 16.00 | 63.41 | 5.40 |
| 0.97 | 16.70 | 79.94 | 4.40 |
| 0.94 | 16.83 | 64.04 | 6.00 |
| Mean±SD | | | 2.93±1.61 |

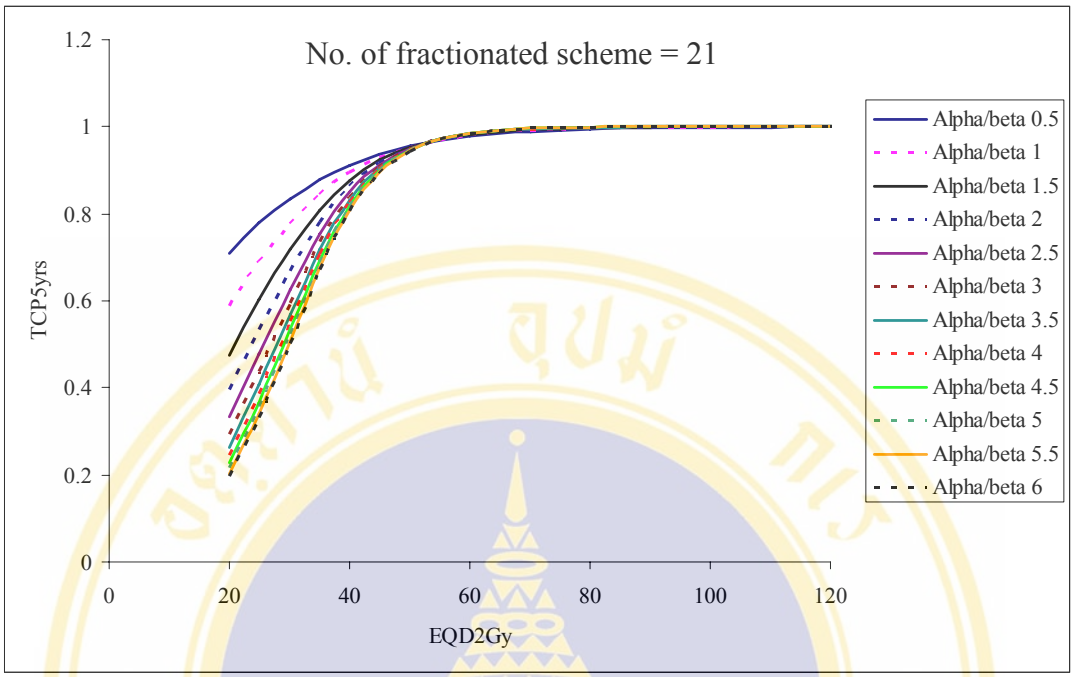


Figure 5.2.3.5 Dose response curve for TCP at 5 years versus equivalent total dose in 2 Gy per fraction at different presumed α/β values (Data from combined EXBT and SRT)

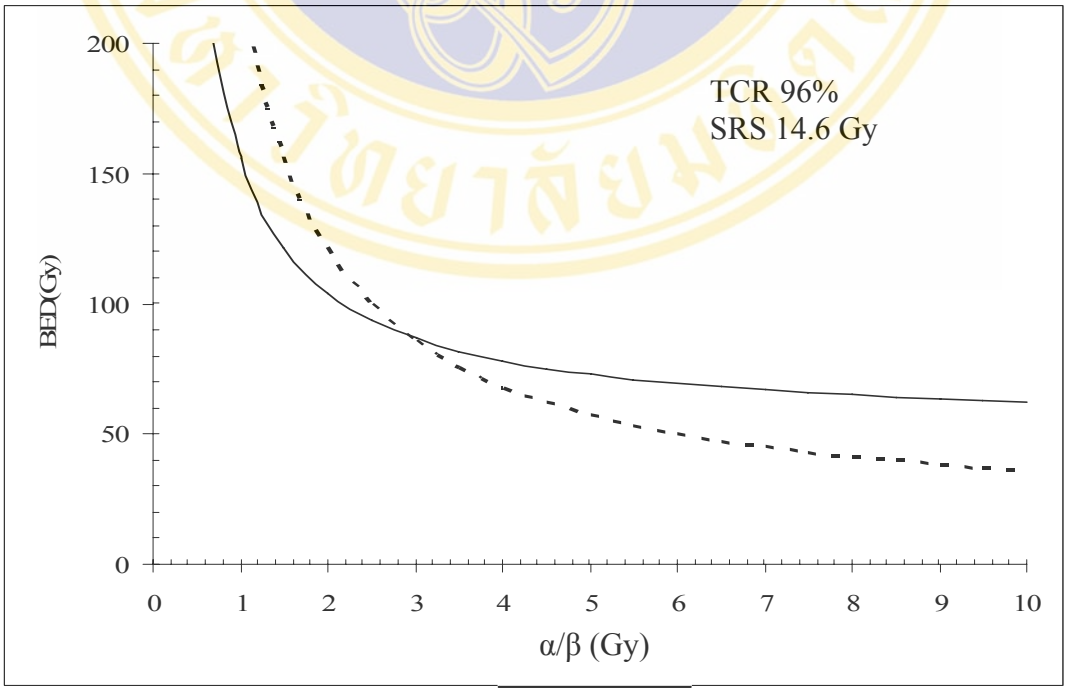


Figure 5.2.3.6 Representative BED versus α/β curves derived from single fraction data (dotted line) and combined EXBT and SRT data (solid line)

Table 5.3.2.3 Alpha/beta values estimated from the crossed point of single fraction and combined EXBT and SRT data graphical matching

| Input factor | | Output variable | |
|---|---|---|---|
| TCP | Marginal dose (Gy) | BED (Gy) | α/β (Gy) |
| 0.96 | 12.27 | 138.79 | 1.18 |
| 0.91 | 12.50 | 80.43 | 2.30 |
| 0.98 | 12.55 | 209.43 | 0.77 |
| 0.92 | 13.00 | 80.60 | 2.50 |
| 0.96 | 13.14 | 111.24 | 1.76 |
| 0.96 | 13.80 | 103.21 | 2.26 |
| 0.92 | 14.00 | 70.00 | 3.50 |
| 0.96 | 14.60 | 88.10 | 2.90 |
| 0.98 | 15.00 | 109.54 | 2.38 |
| 0.93 | 16.00 | 62.97 | 5.45 |
| 0.97 | 16.70 | 80.08 | 4.40 |
| Mean±SD | | | 2.67±1.36 |

Student t-test for different of α/β derived from different data sets revealed no significant variation (Table 5.2.3.4)

Table 5.3.3 Summary of statistics and test for α/β values derived from different data sets

| Matching | α/β(Gy) Mean ±SD | T-test | P-value |
|---|---|---|---|
| A. Single fraction vs EXBT | 2.55±1.83 | A vs B | 0.60 |
| | | A vs C | 0.86 |
| B. Single fraction vs SRT | 2.93±1.61 | B vs A | 0.60 |
| | | B vs C | 0.68 |
| C. Single fraction vs combined EXBT and SRT | 2.67±1.36 | C vs A | 0.86 |
| | | C vs B | 0.68 |

Table 5.4 Summary of statistics and test for α/β values derived from different method

| Method | No.of Matching | α/β (Gy) | SE | 95%CI | T-test | P-value |
|---|---|---|---|---|---|---|
| I. Reciprocal iso-effect dose plot | 41 | 3.53 | 0.74 | 2.08-4.98 | I vs II | 0.14 |
| | | | | | I vs III | 0.14 |
| II. Two iso-effect scheme matching | 224 | 2.71 | 0.02 | 2.67-2.75 | II vs I | 0.14 |
| | | | | | II vs III | 0.41 |
| III. Two-step graphical matching | 11 | 2.67 | 0.41 | 1.87-3.47 | III vs I | 0.14 |
| | | | | | III vs II | 0.41 |

# CHAPTER VI
# DISCUSSION AND CONCLUSIONS

The linear-quadratic (LQ) survival equation is the most commonly used model for calculating iso-effect dose in the design of new fractionation scheme and for the evaluation of treatment plan. The model is described by two parameters, i.e. α or the irreparable component and β or the repairable component. The α/β ratio which is defined as the radiation inducing equivalent α-kill and β-kill is the parameter that governs the shape of the cell survival curve and can be extracted from clinical data [27,76]. For the diseases of the brain, a number of reasonable clinical estimates for α/β values were reported for malignant brain tumor (10-12 Gy) [78,79], arteriovenous malformation or AVM (0.2-5 Gy) [ 18,26,80] but none for benign brain tumor.

Stereotactic radiosurgery (SRS) has been used to treat benign tumor at the skull base for at least 20 years with tumor control rates comparable to those rates induced by fractionated radiotherapy [81]. By allowing a 10% dose error, Shrieve et al [16] calculated the α/β for meningioma as 3.28 Gy by assuming 15 Gy SRS equivalent to the fractionated scheme of 54 Gy in 30 fractions. This estimate appears to be in line with the α/β value of 2-3 Gy for an average late responding tissue [82,83]. However, Qi et al [18] have demonstrated that a slight difference in α/β between brain (1.5- 2 Gy) and AVM (2.2 Gy) justifies the use of fractionated scheme over single-dose scheme in the treatment of AVM for its lower fractionation sensitivity. Fractionated stereotactic radiotherapy (FSRT) has been recommended for treating benign brain tumor as well [84]. Several years of experiences indicate the FSRT is efficacious and safe for acoustic tumors [85]. In the design of a new scheme of FSRT, a more accurate estimate of α/β value based on clinical data should be of great help in deciding on an effective SRT schedule.

In this study, 45 published reports were gathered for the analysis of α/β value for benign brain tumors including meningioma (24 papers), vestibular schwannoma (18 papers), and pituitary adenoma (8 papers). Three methods were used for the estimation

of α/β, i.e. reciprocal of iso-effect dose plot [19], two iso-effect scheme matching [20] and two-step graphical matching [21]. At the iso-effect 5-year TCR (%) (95.5±3.03), α/β determined by reciprocal-plot and two iso-effect scheme matching were 3.53 Gy (95% CI 2.79-4.27 Gy) and 2.71 Gy (95% CI 2.67-2.75 Gy ) respectively. For the two-step graphical matching, the value was 2.67 (95% CI 1.87-3.47 Gy). No statistical difference could be observed for the α/β values obtained these three methods (Table 5.4). On average, the α/β was 2.97 (95% CI 2.42-3.52) which was in good agreement with the 2-3 Gy for the late responding tissue.

All methods used in this study yielded a reasonable estimate of α/β for benign tumor of the brain. However, each method was its strength and limitation. To obtain a plausible estimate for α/β by reciprocal-plot, large numbers of iso-effect data are required for the analysis. The α/β estimate was obtained from the intercept α/E and slope β/E which were subject to uncertainties in both the ordinate (1/D) and abscissa (d). A large 95% CI could be observed for α/β determined by this method. On the other hand, the two iso-effect scheme needs only two sets of equivalent data but the reliable α/β value is obtained only when the size of dose fraction differs by at least a factor seven folds. Equivalent schemes of equal size gave an α/β value outside the 2-3 Gy for late responding tissue. For the two-step graphical matching, iso-effect data is not prerequisite for the analysis but sufficient data are required for the meaningful analysis. However, data for graphical matching must follow the same criterion as the two iso-effect scheme. That is the size of dose per fraction should differ by a factor of at least seven-folds.

In the design of a FSRT scheme (i.e. 5 dose fractions) from the single dose fraction of 15 Gy, the value of α/β would have an impact on the magnitude of BED. The BED calculated by assuming α/β at the range of 2-3 Gy would be overestimate by 40.50% at 2 Gy and underestimated by 0.83% at 3 Gy compared to the α/β of 2.97 Gy obtained in this study. Alternatively, the BED calculated for the α/β of 3.28 Gy based on a theoretical guess [16] was 7.88% underestimated compared with the BED calculated from the α/β of 2.97 Gy extracted from clinical data. Nevertheless, α/β in this study was specified from an average TCR of 95.5 % at 5-year. The validity of 2.97 Gy remains to be elucidated if the TCR significantly drops over longer follow-up period.

**Conclusion**

1. The iso-effect 5-year TCR (%) of 95.5 ± 3.03 was used of α/β value for benign brain tumor.
2. The α/β values obtained from reciprocal of iso-effect dose plot, two iso-effect scheme matching and two-step graphical matching were 3.53 Gy (95% CI 2.08-4.98 Gy), 2.71 Gy (95% CI 2.67-2.75 Gy ) and 2.67 (95% CI 1.87-3.47 Gy), respectively.
3. Plausible estimate of α/β determined by two iso-effect scheme matching and two-step graphical matching was obtained only when the size of dose fraction differed by at least a factor of seven folds.

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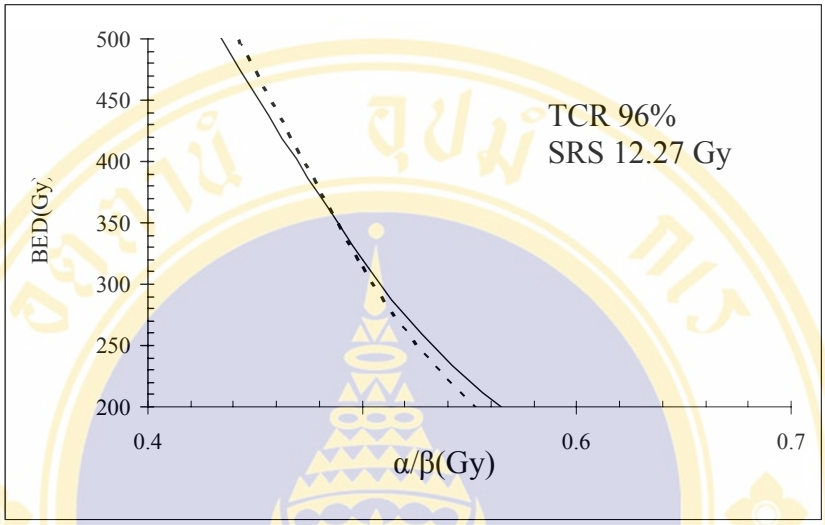
# APPENDIX

**Result A. Determination of α/β by single and EXBT graphical matching**

(a.)




(b)

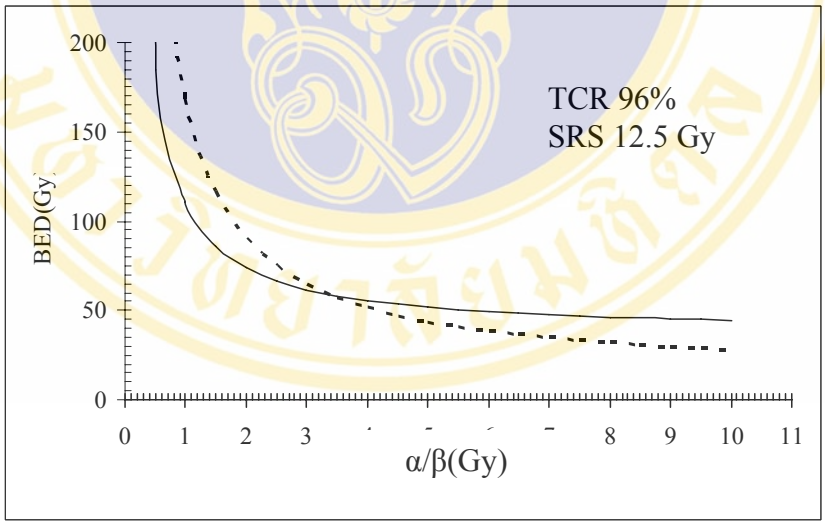
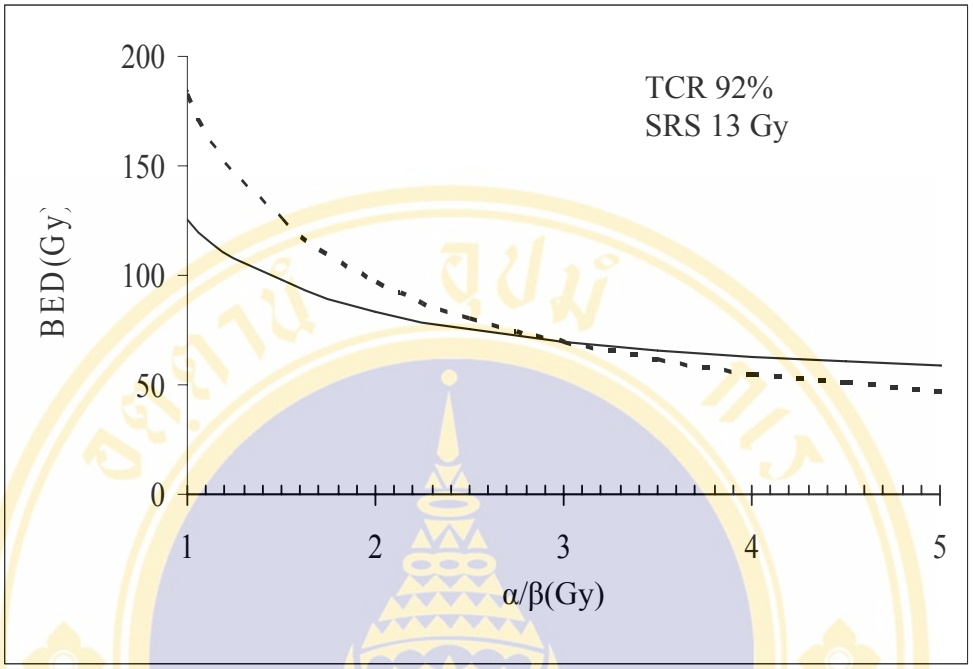



Figure 1. Representative BED versus α/β curves derived from single fraction data (dotted line) and EXBT data (solid line)

(c)




(d)

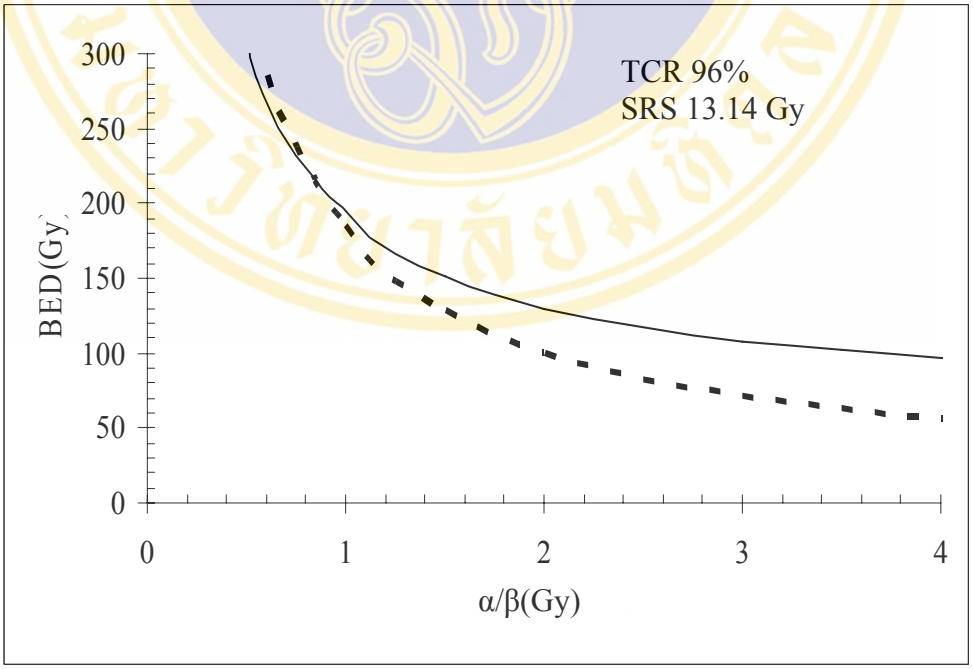
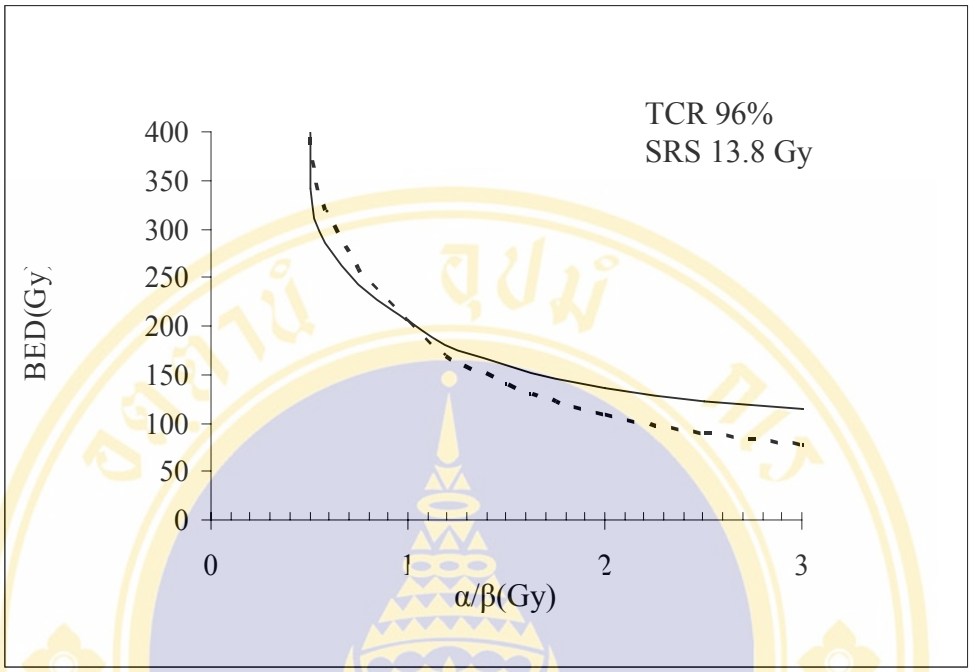



Figure 1. BED versus α/β curves derived from single fraction data (dotted line) and EXBT data (solid line)

(e)




(f)

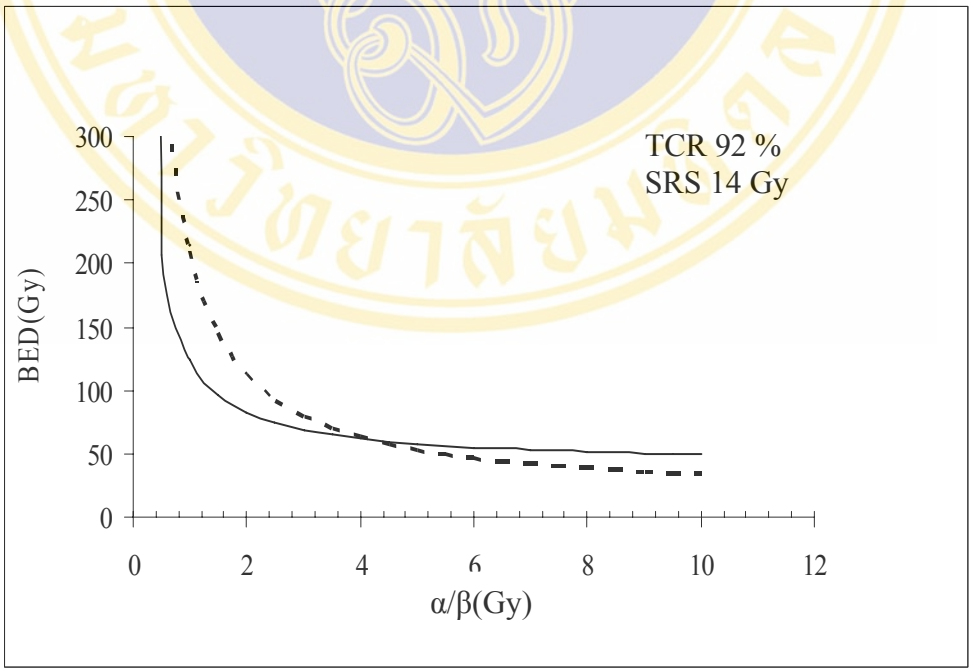
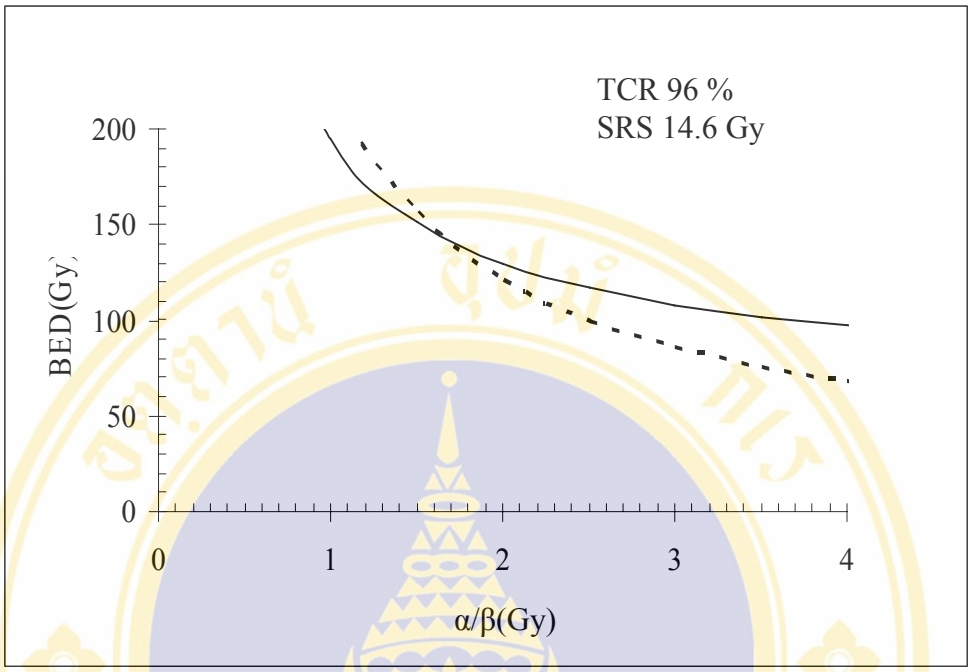



Figure 1. BED versus α/β curves derived from single fraction data (dotted line) and EXBT data (solid line)

(g)




(h)

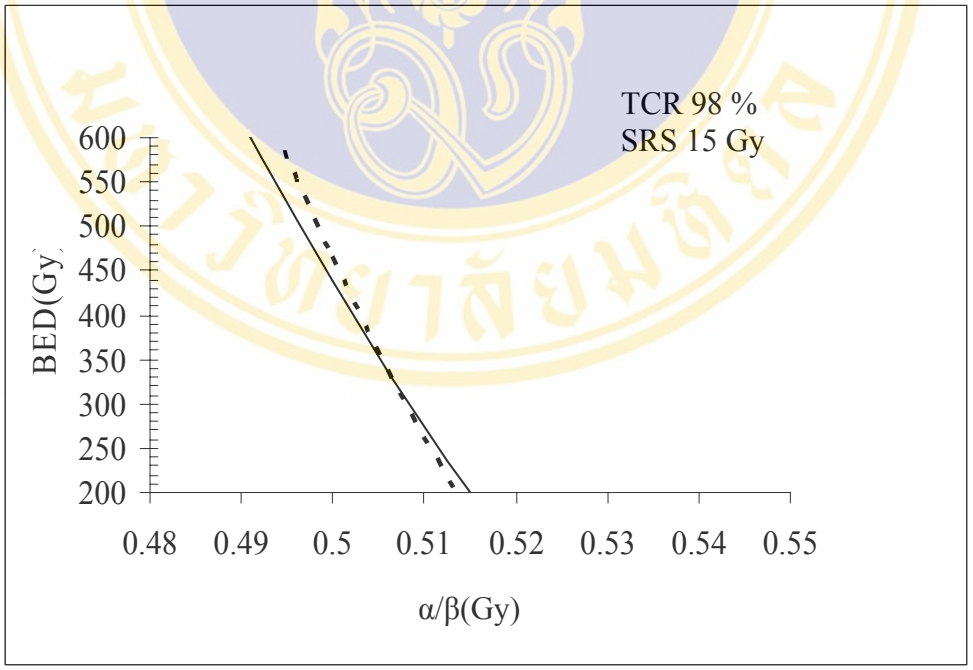
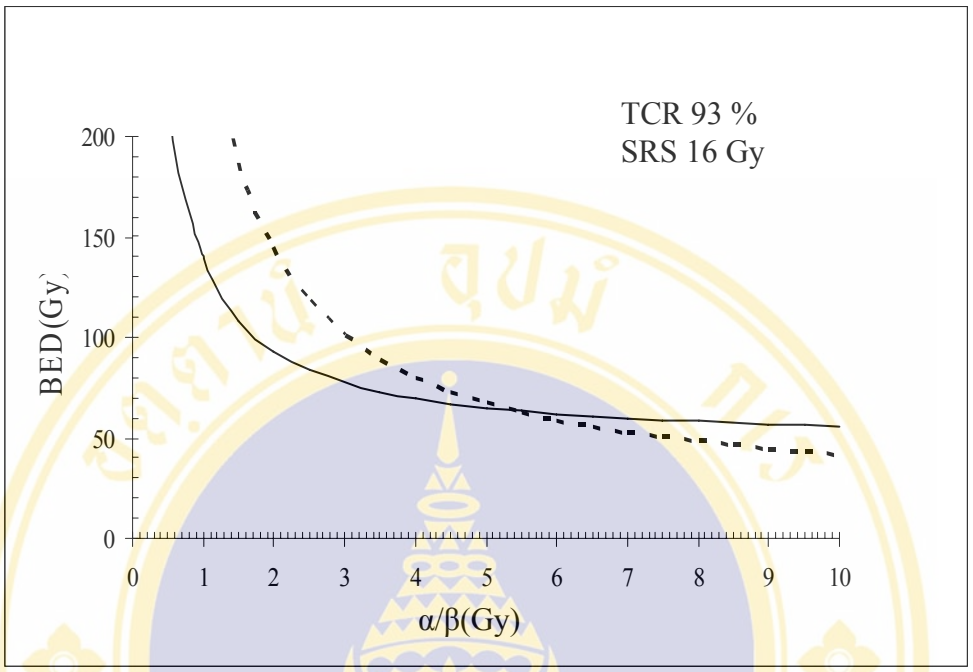



Figure 1. Representative BED versus α/β curves derived from single fraction data (dotted line) and EXBT data (solid line)

(i)




(j)

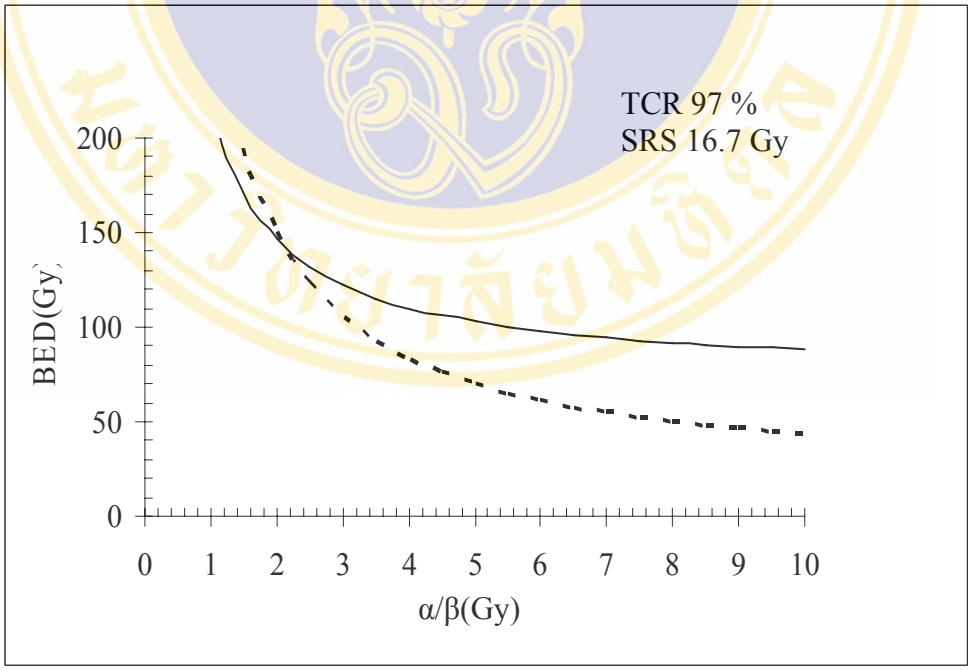



Figure 1. Representative BED versus α/β curves derived from single fraction data (dotted line) and EXBT data (solid line)

(k)

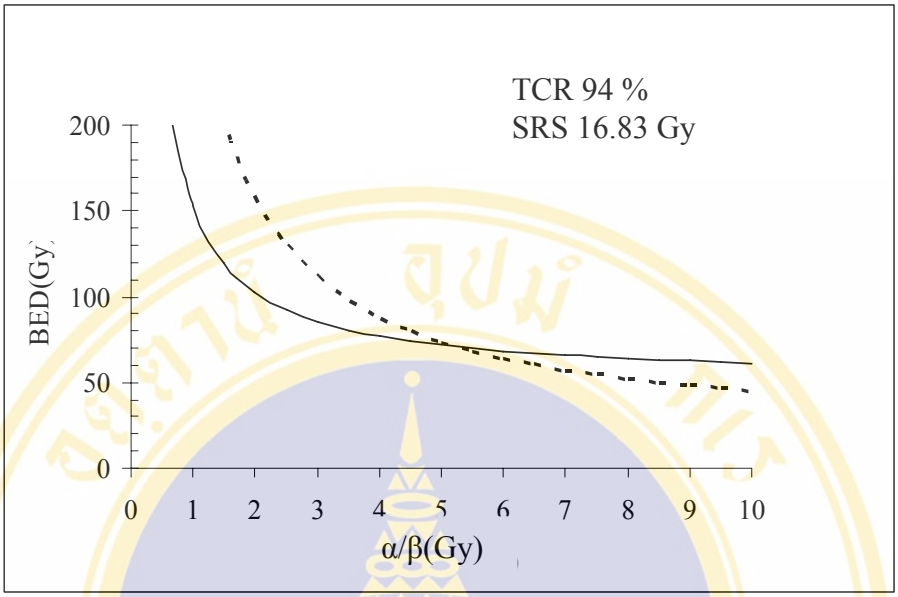



Figure 1. BED versus α/β curve derived from single fraction data (dotted line) and EXBT data (solid line)

**Result B. Determination of α/β by single and SRT graphical matching**

(a)

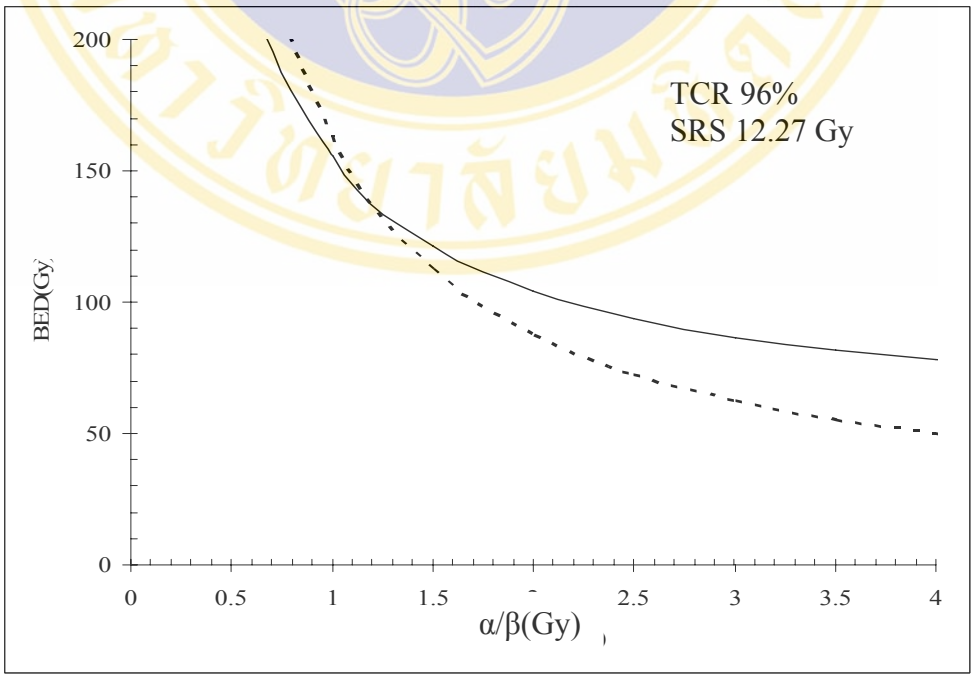
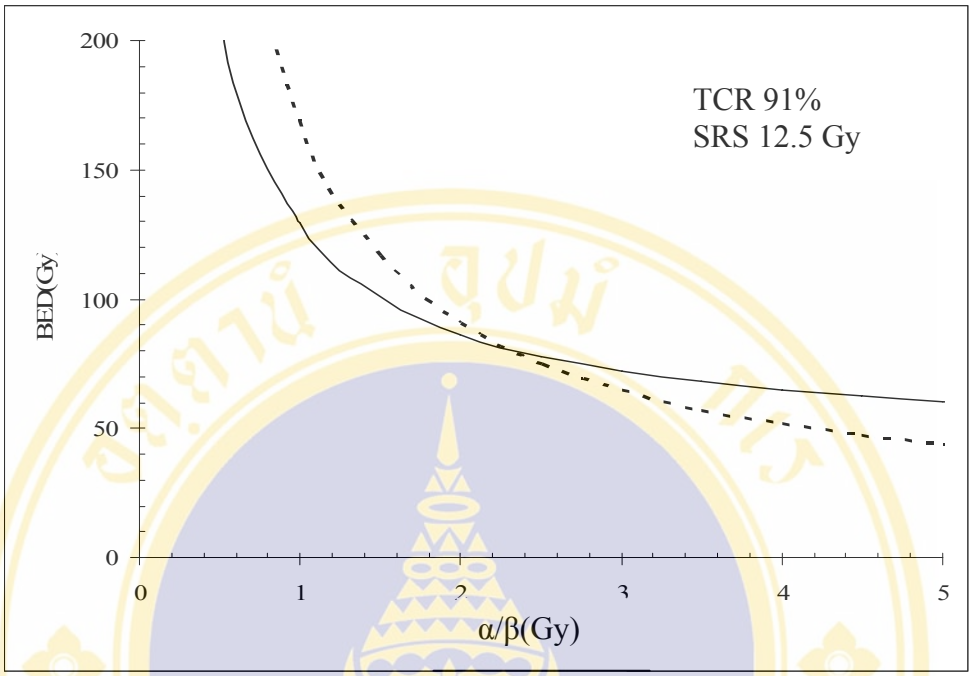



Figure 2. BED versus α/β curve derived from single fraction data (dotted line) and SRT data (solid line)

(b)




(c)

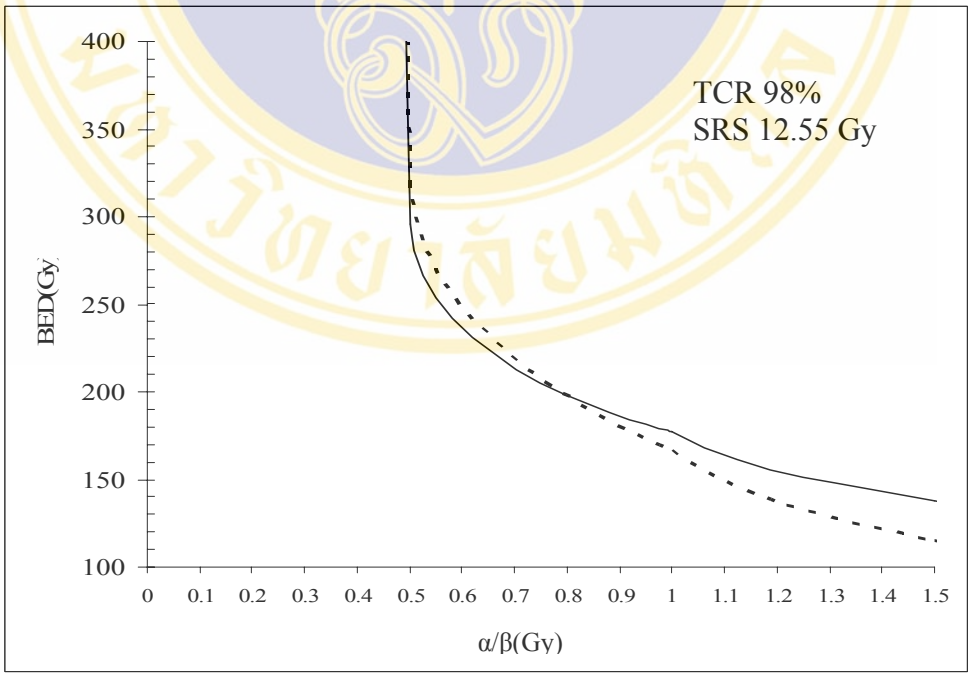
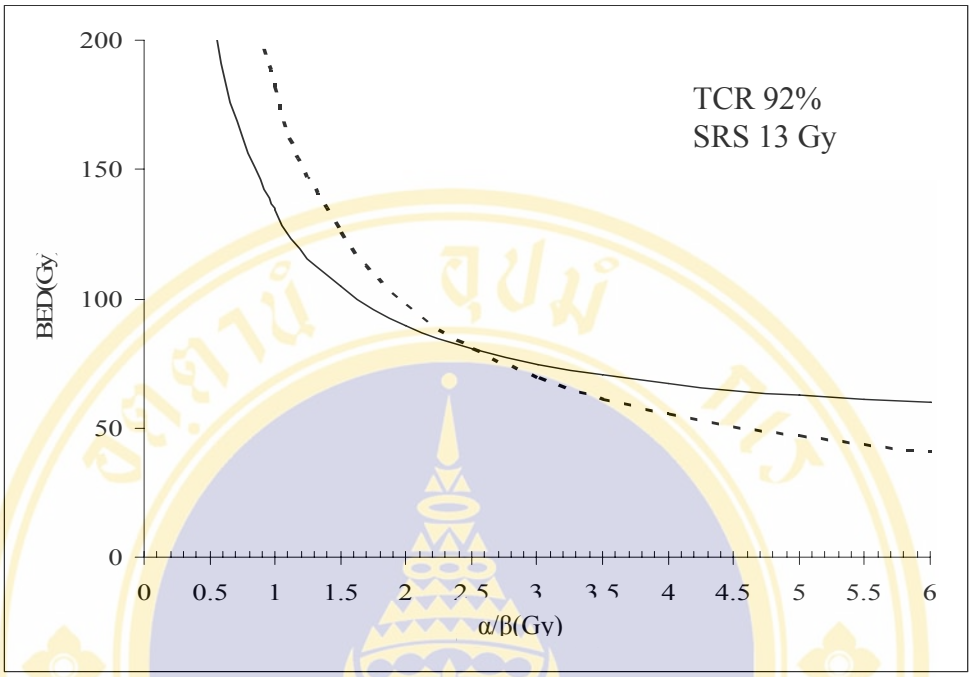



Figure 2. BED versus α/β curve derived from single fraction data (dotted line) and SRT data (solid line)

(d)




(e)

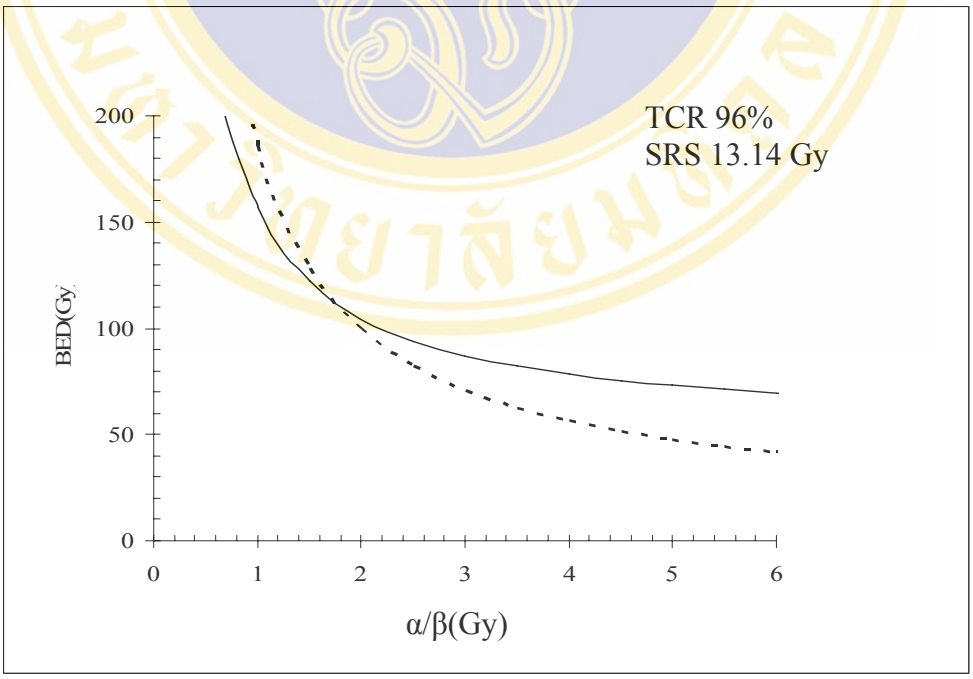
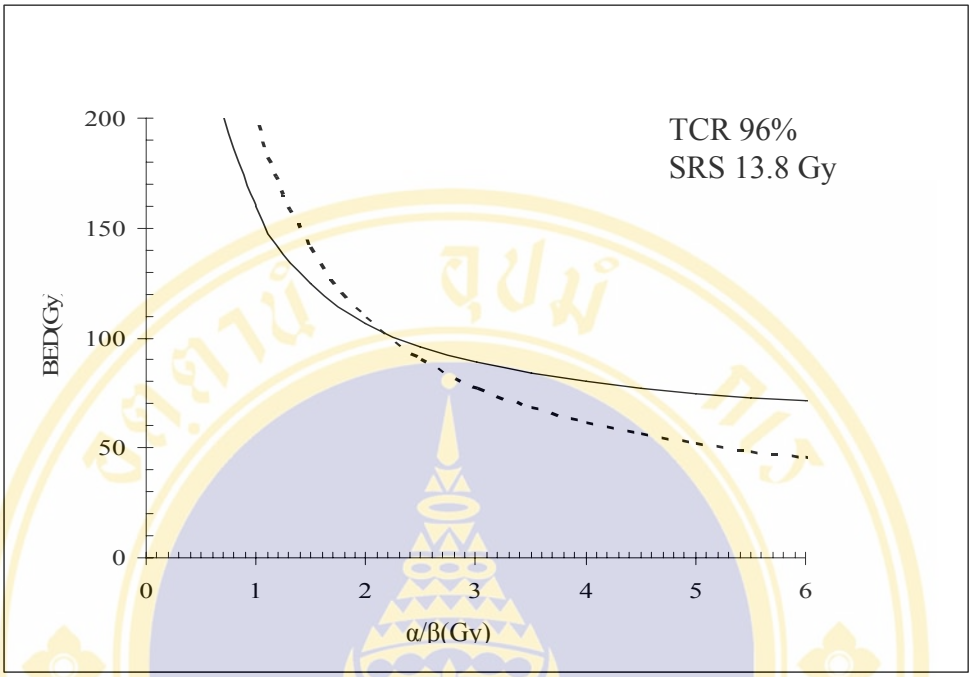



Figure 2. BED versus α/β curve derived from single fraction data (dotted line) and SRT data (solid line)

(f)




(g)

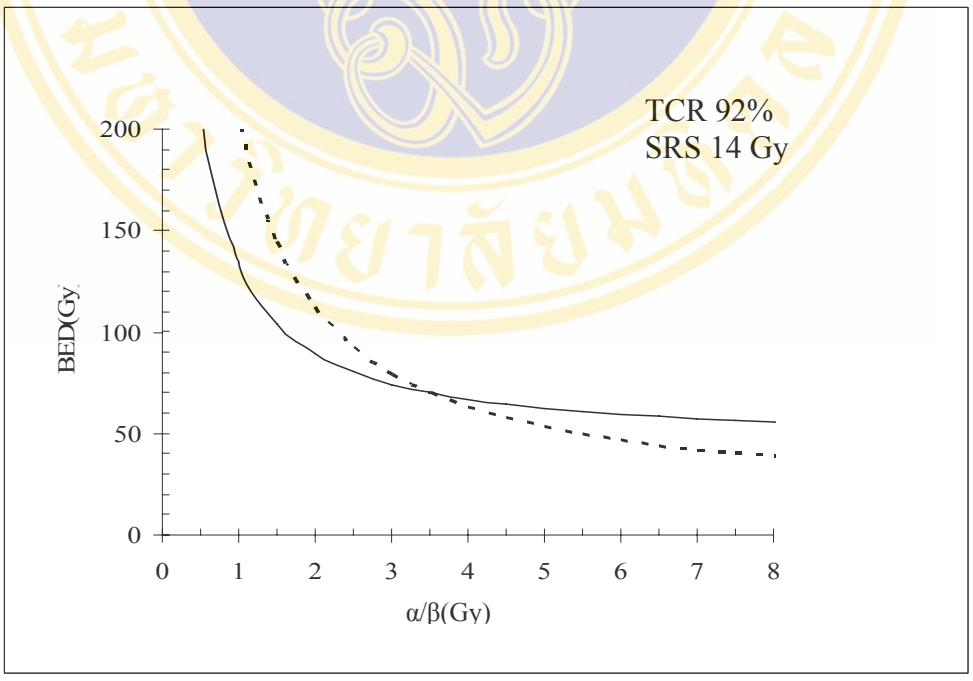
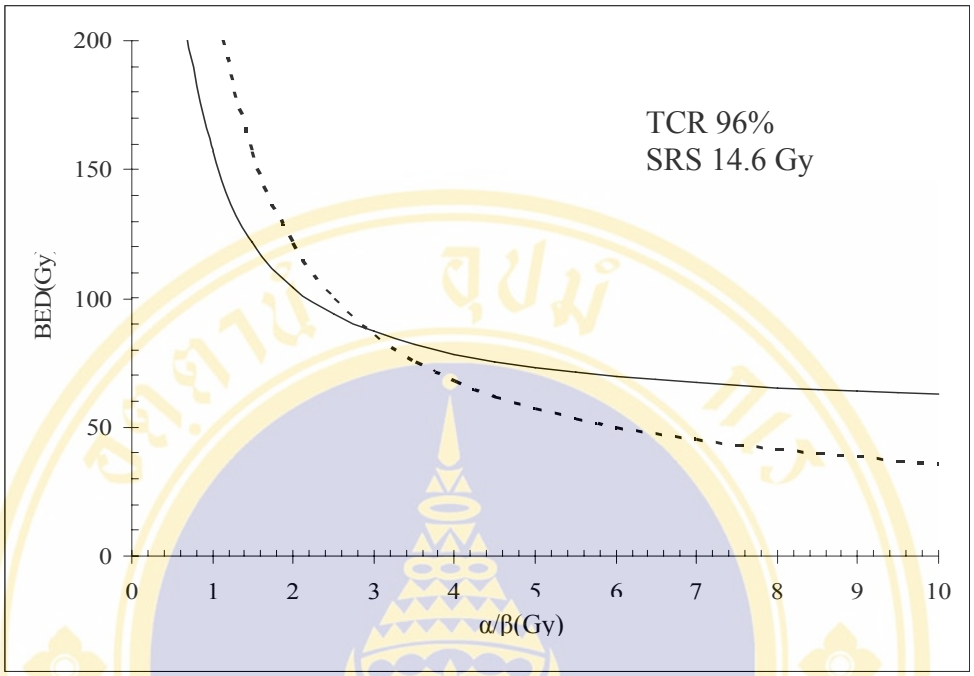



Figure 2. BED versus α/β curve derived from single fraction data (dotted line) and SRT data (solid line)

(h)




(i)

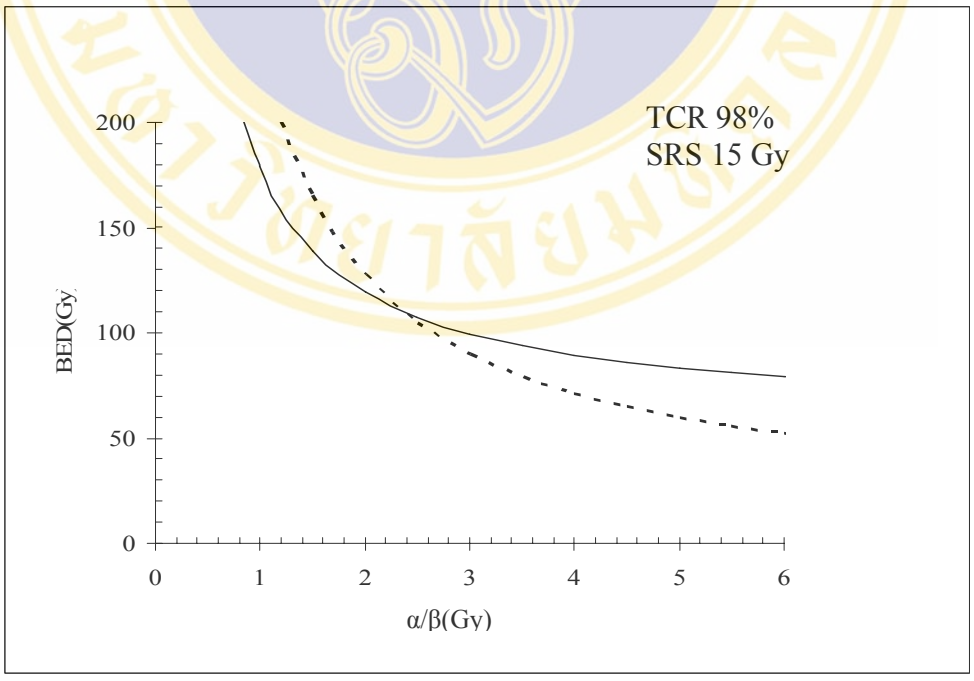
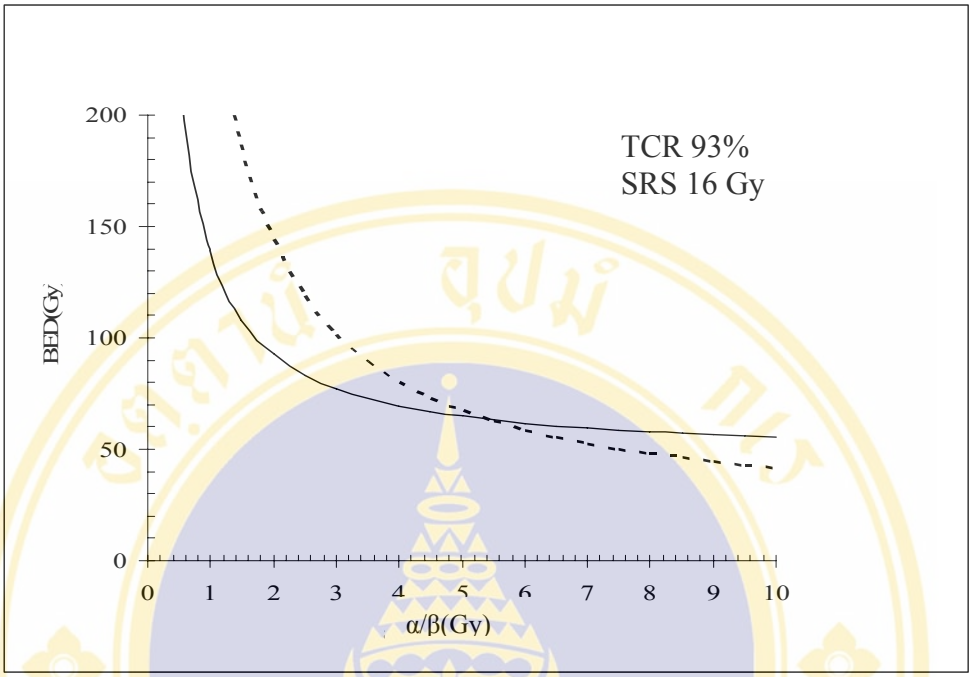



Figure 2. BED versus α/β curve derived from single fraction data (dotted line) and SRT data (solid line)

(j)




(k)

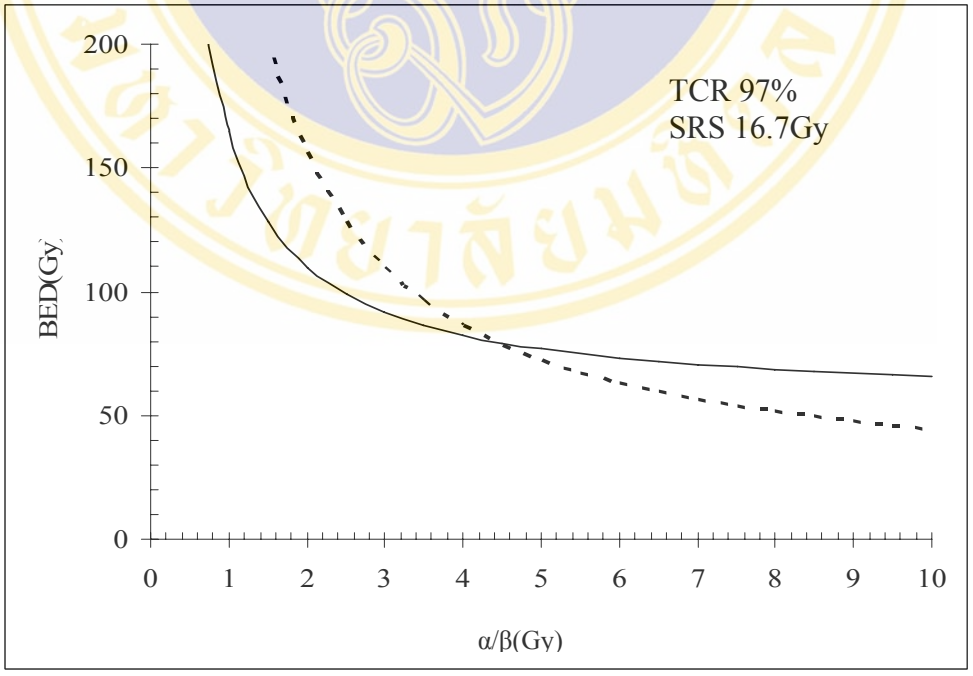



Figure 2. BED versus α/β curve derived from single fraction data (dotted line) and SRT data (solid line)

(l)

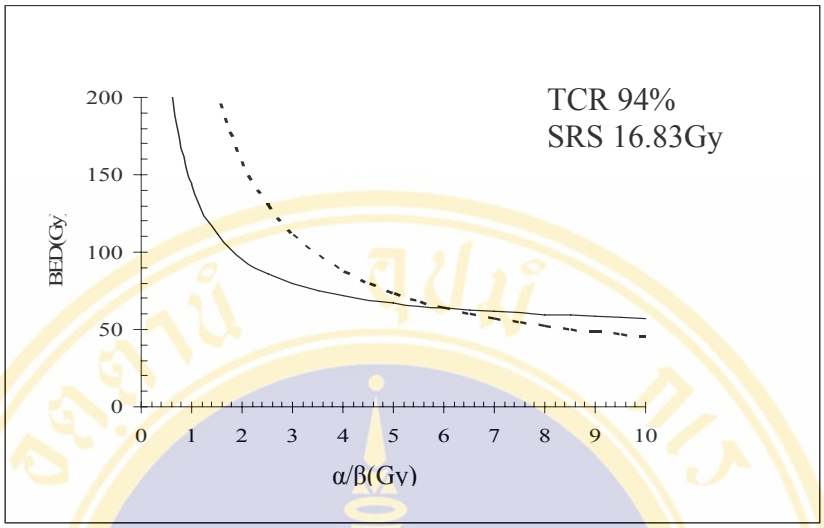



Figure 2. BED versus α/β curve derived from single fraction data (dotted line) and SRT data (solid line)

**Result C. Determination of α/β by single and combined EXRT and SRT data graphical matching**

(a)

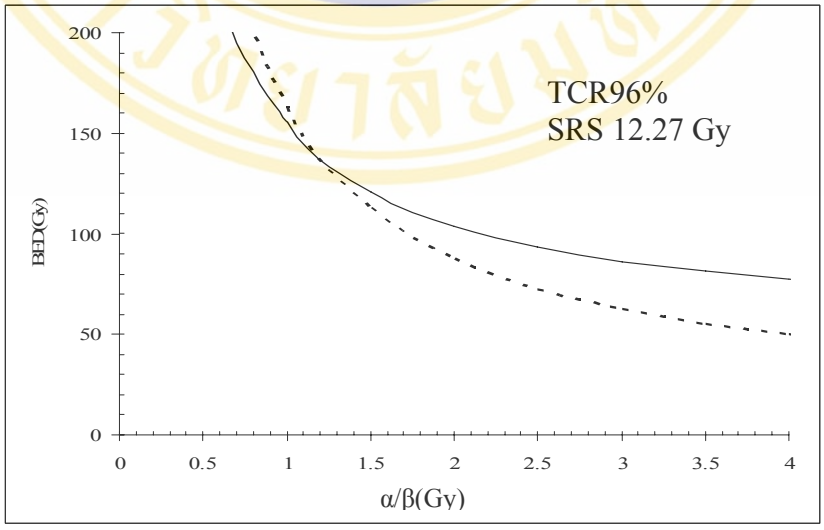
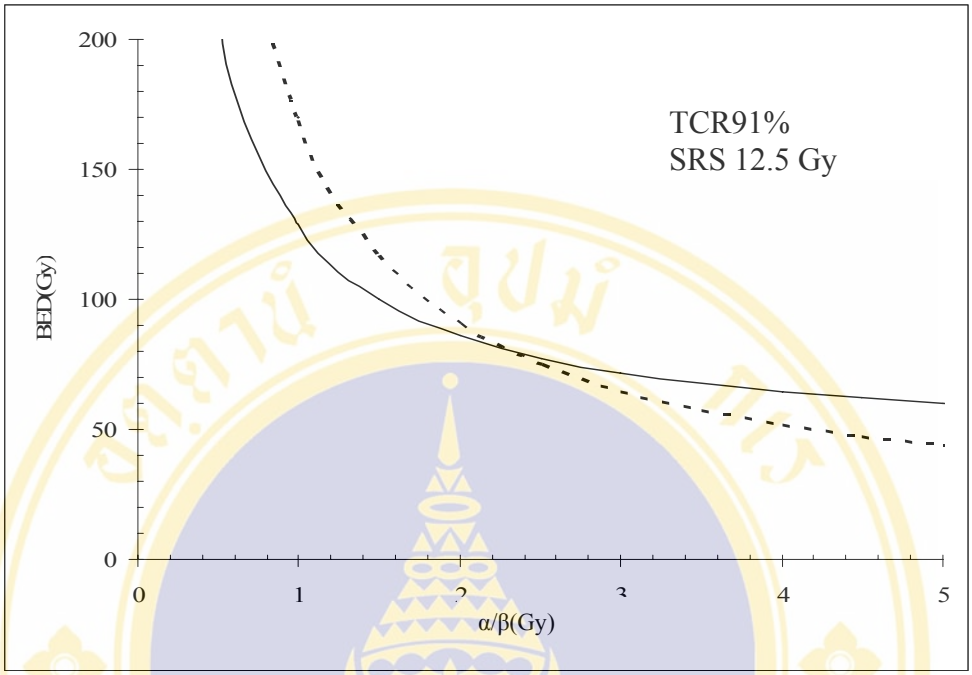



Figure 3. BED versus α/β curve derived from single fraction data (dotted line) and combined EXBT and SRT data (solid line)

(b)




(c)

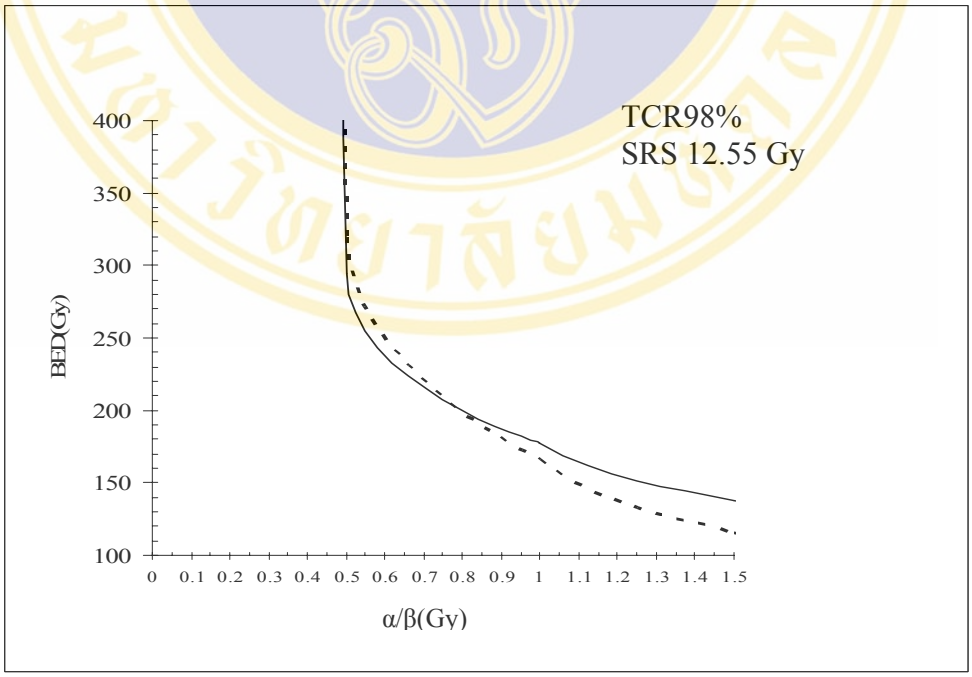
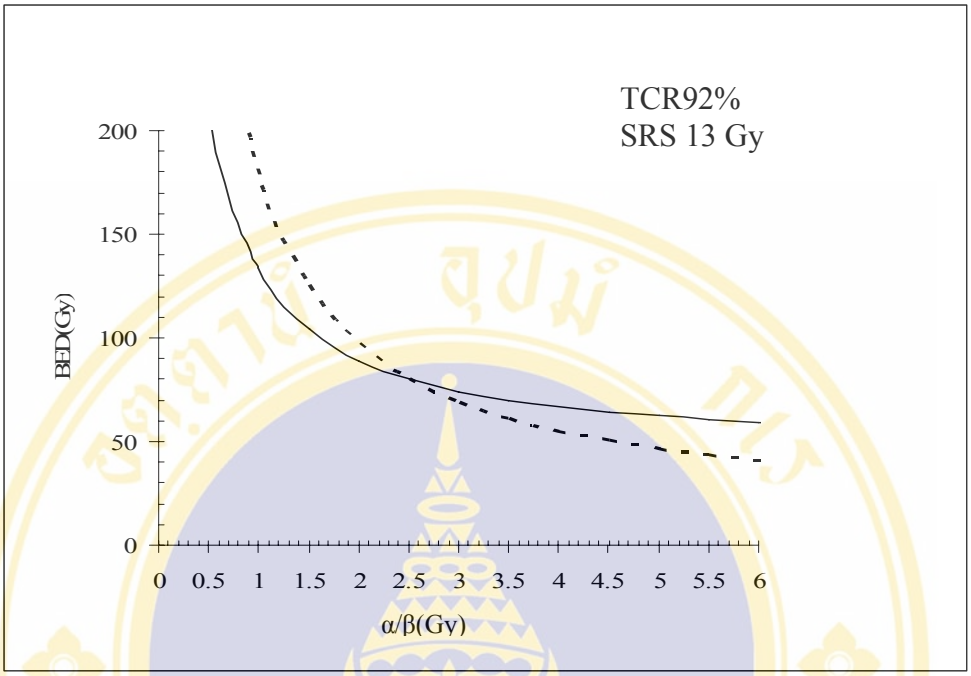



Figure 3. BED versus α/β curve derived from single fraction data (dotted line) and combined EXBT and SRT data (solid line)

(d)




(e)

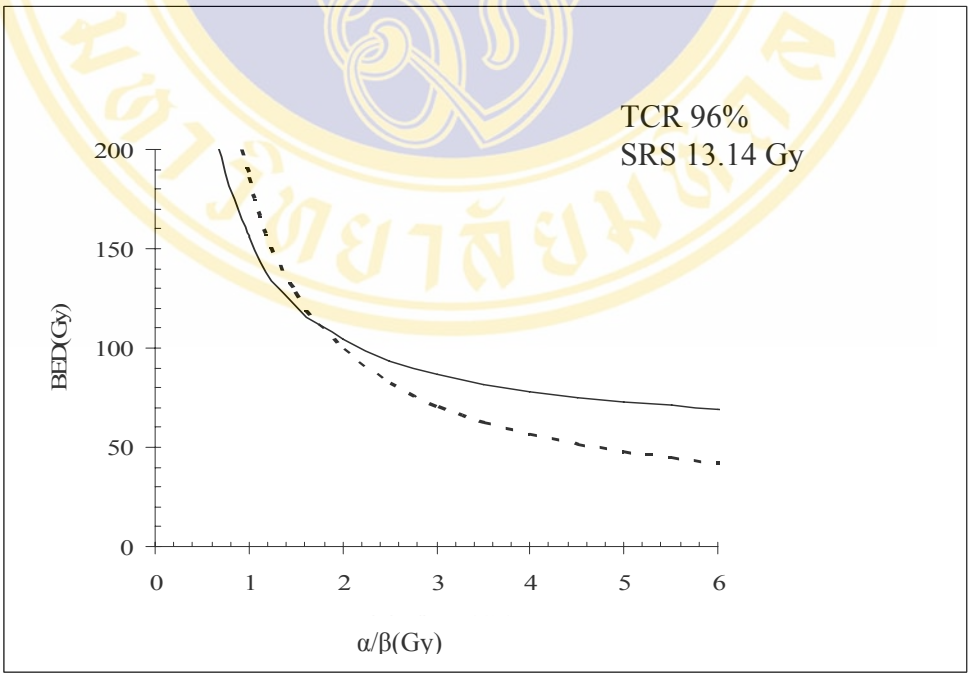
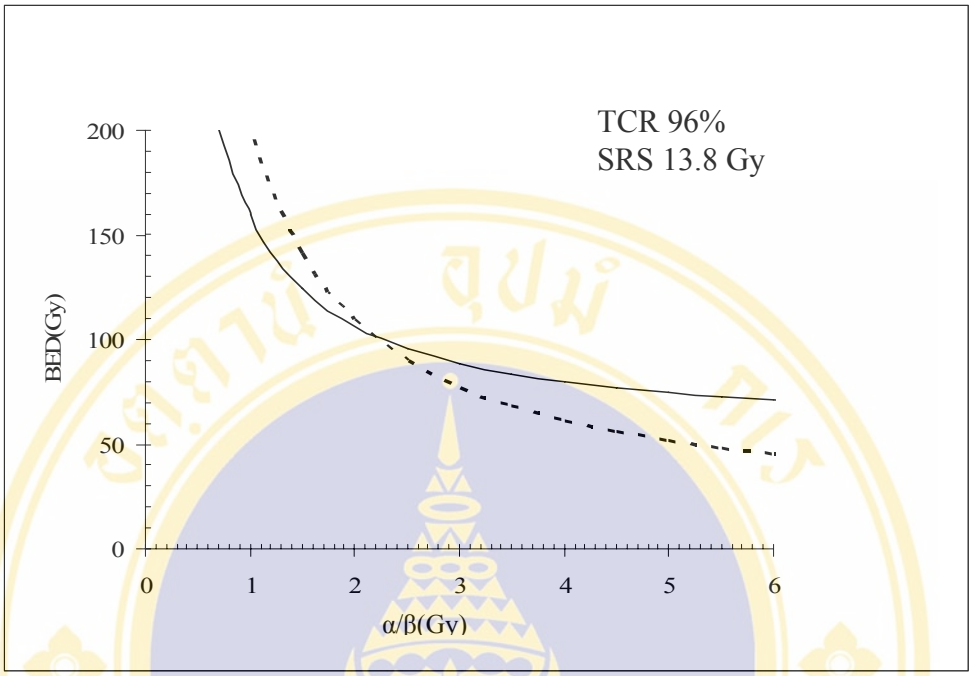



Figure 3. BED versus α/β curve derived from single fraction data (dotted line) and combined EXBT and SRT data (solid line)

(f)




(g)

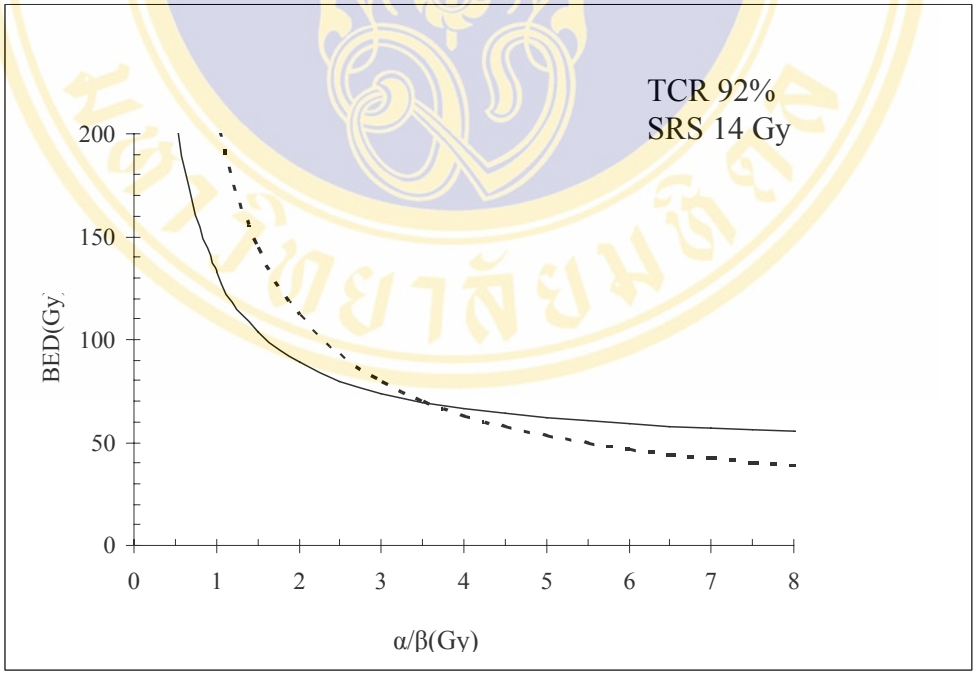
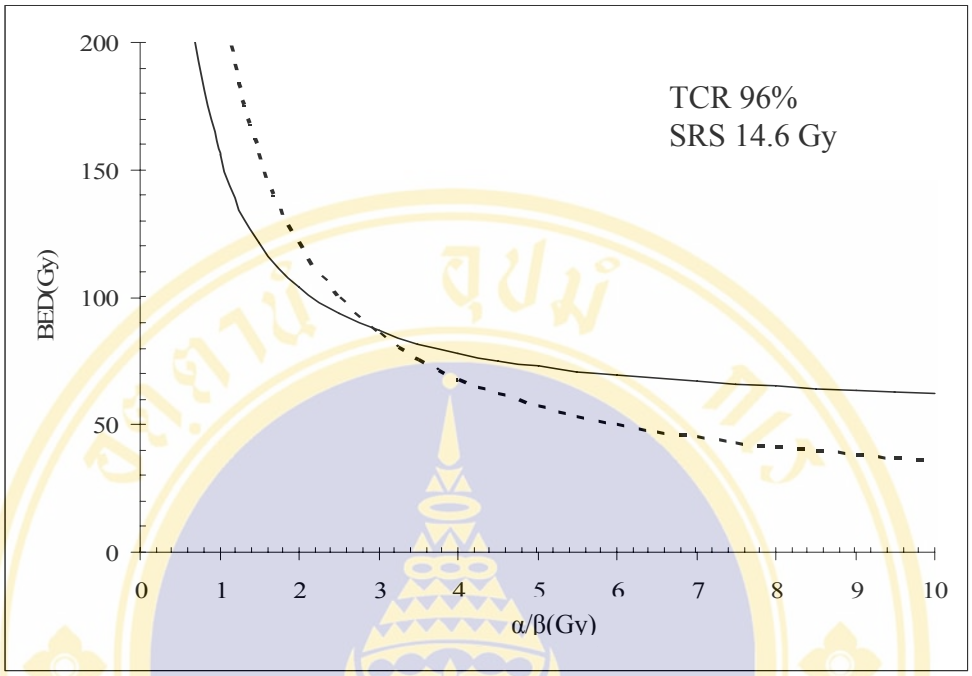



Figure 3. BED versus α/β curve derived from single fraction data (dotted line) and combined EXBT and SRT data (solid line)

(h)




(i)

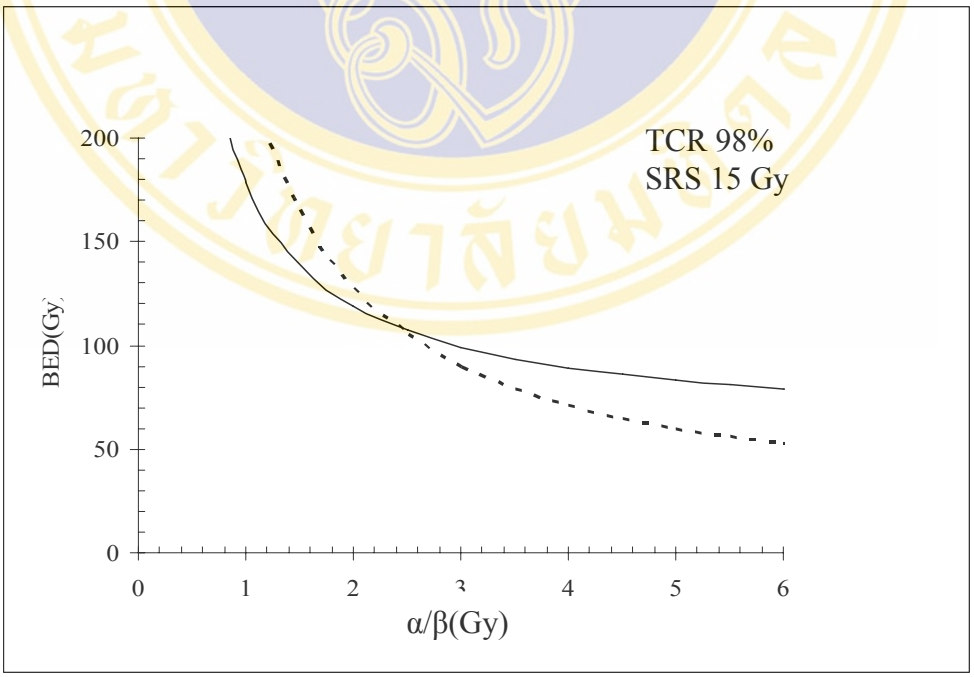
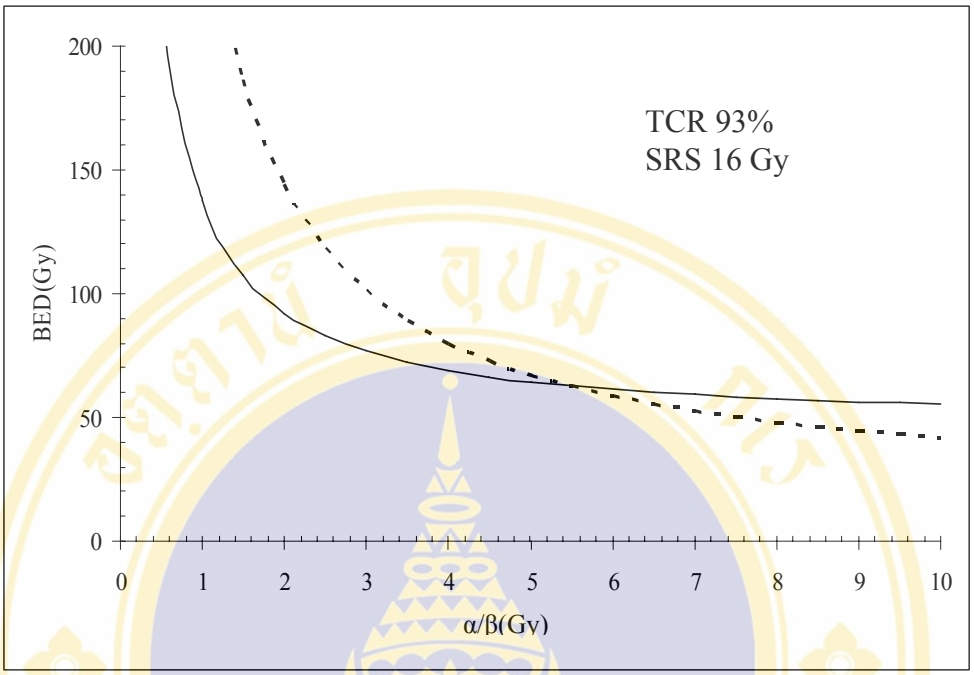



Figure 3. BED versus α/β curve derived from single fraction data (dotted line) and combined EXBT and SRT data (solid line)

(j)




(k)

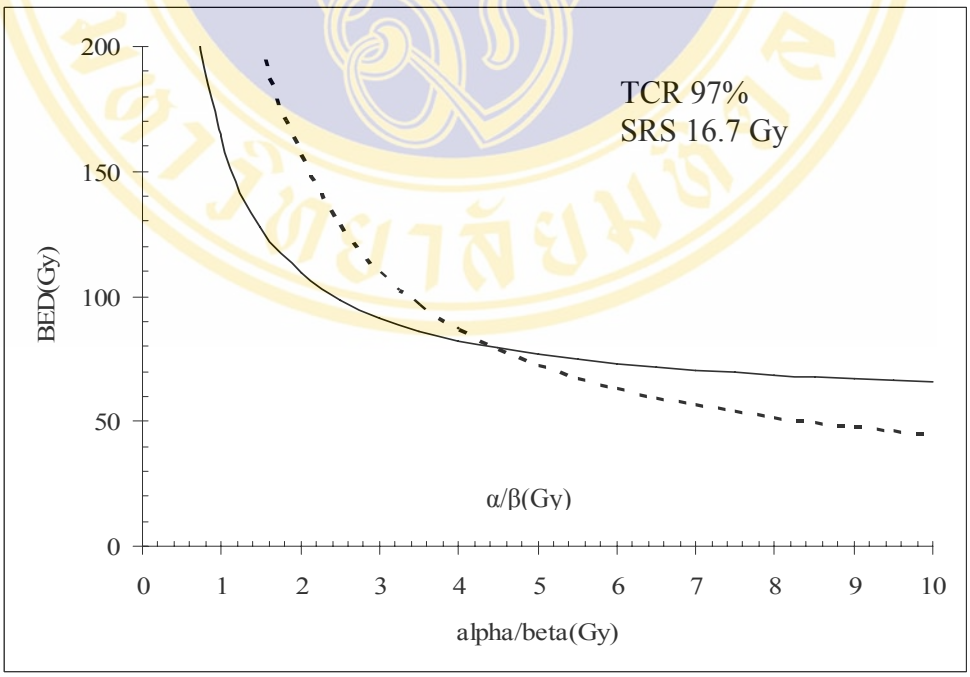



Figure 3. BED versus α/β curve derived from single fraction data (dotted line) and combined EXBT and SRT data (solid line)

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