Calculated Effects of Displacement Errors in External Beam Radiotherapy of Prostatic Adenocarcinoma

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In order to evaluate the impact on the biological effective dose (BED) of irradiation delivered to a tumour with large displacement errors (LDE) and to estimate the effect on local control, simulated treatment of prostatic adenocarcinoma was performed. The calculation of BED in combination with the critical-voxel model and the LQ model was used to evaluate the effect of different combinations of LDEs. The model is called the Dose Volume Inhomogeneity Corrected BED (DVIC-BED) model. The dose-response curve was assumed to follow Poisson statistics. Different combinations of radiobiological parameters were used to test the model. A simulated clinical treatment with a dose of 66–80 Gy in 2 Gy fractions was carried out to evaluate displacement errors and non-optimal dose distributions. Five random LDEs excluding 33% of the target volume corresponded to an overall dose reduction of 3–5 Gy compared with a 10 Gy reduction if 100% of the target is missed five times. A 5 Gy decrease in dose corresponds to a reduction in clinical or chemical control up to 10–25% in the interval 65–85 Gy. LDEs in different directions are less deleterious than errors occurring in the same direction. Different α/β-ratios (3–15) had little effect on the DIC-BED, but the effect of different α values (0.05, 0.2 and 0.5) was large. However, the results depend on radiobiological parameters for prostatic adenocarcinoma, which not are well known, and further studies in the field should be encouraged.

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Radiotherapy is an established method for the curative treatment of prostatic adenocarcinoma (PAC) (1–8). Local control seems to be an important factor for survival (5).

In external beam radiotherapy, much attention has been focused on the use of three-dimensional conformal therapy and the possibility of increasing the dose to the target, without increasing the complication frequency (3, 6–8). When using conformal therapy, there is an increased risk of underdosage of the target volume due to either small margins or tumour mobility (9). Generally speaking, it has been suggested that missing the target by as few as 1–2 times during a treatment course can reduce the dose by 10% or more (10) with any potentially serious impact on local control and survival. The average and maximum displacement errors expressed in millimetres presented by different authors are recorded in Table 1. The maximum values differ considerably, but these extreme values are usually rare. To this, the potential motion of the prostate should be added (9). LDE (large displacement error) is, from this point on, defined as actual target volume misses, irrespective of the cause and size.

The aim of the study was to evaluate the effects on doses delivered to the tumour target volume of different LDE combinations. The results are related to the estimated effects on local control and the frequency of side effects.

This study focuses on the effect of large displacement errors (LDEs) on local control. For ethical reasons, this cannot be done in a randomized study and in our study we therefore applied a model combining the linear-quadratic (LQ) formula and the critical volume (tissue-rescuing unit) model (11–13), called the Dose Volume Inhomogeneity Corrected Biological Dose Equivalent (DVIC-BED).

There are at least two possible fields of application for the model presented in this article. First, the model can be used in conjunction with the treatment plan in the dose-planning system to display the impact of certain LDEs in the evaluation of a treatment plan. Second, the model can be used during the external beam radiotherapy course in conjunction with a portal imaging device to evaluate the impact of detected LDEs.

Since PAC has infrequently been characterized from a radiobiological point of view in the literature, the study

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was divided into two parts. In the first section, the effects of different α/β-ratios and α-values on the model were presented. In the second section the impacts of one or several large displacement errors, volume misses and combinations were simulated.

MATERIAL AND METHODS

Calculation model

The survival of a tumour is assumed to follow Poisson statistics (14, 15). If the number of clonogenic cells before start of treatment is M and the number of fractions is n (with a dose d delivered to a total dose D), the following expression for P_{tot} (according to the α/β-model) can be derived. (11):

$$P_{tot} = e^{-((e^{(-\alpha d-\beta d2)^n})\times M)} = e^{-(e^{(-\alpha d-\beta dD)}\times M)} \quad [1]$$

$$E = -\ln(e^{(-\alpha D-\beta dD)}) \quad [2]$$

$$P_{tot} = e^{-e^{-E}\times M} \quad [3]$$

If we assume that the clonogenic cells are homogeneously distributed in the tumour from the outset, then the tumour can be divided into several subvolumes. The probability for cure will then depend on the number of clonogenic cells in each volume according to (12, 13):

$$P_{tot} = e^{-((M/vn\times e^{-E})+\ \ldots\ +(M/vn\times e^{-Evn}))} = e^{-(M/vn\times(e^{-E}+\ \ldots\ +e^{-Evn}))} \quad [4]$$

where vn is the number of subvolumes. The solution of this equation, which clarifies how P_{tot} is dependent on E (or dose), is represented by the dose-response curve.

Table 1

Comparison of displacement errors in different studies (28–38)

Author	Year	Displacement error (mm)	
		Mean	Max
Richards & Buchler	1977	–	In 6% > 30 mm
Byhardt et al.	1978	15	40
Rabinowitz et al.	1985	5.6	24
Kihlén & Rudén	1989	4	6
Griffiths et al.	1991	0.8–3.3[1]	9–17[1]
Soffen et al.	1991	3.3–8[2]	7–15[2]
Rosenthal et al.	1993	4–6[2]	14–21[2]
Gilderslave et al.	1994	2–4.3[3]	6.4–11[3*]
Lennernäs et al.	1995	5.4	27

In Richards & Buchler (1977) (33), no mean displacement errors were presented and the data were separated into intervals, e.g. > 30 mm.
[1] with or without laser positioning.
[2] with or without cast fixation.
[3] with or without on-line portal verification.
* value from figure.

Isoeffect

Fowler introduced the concept of the biologically effective dose in 1989, which is one of the methods of expressing an isoeffect, and this is described as (11):

$$BED = E/\alpha = D(1 + d/(\alpha/\beta)) \quad [5]$$

The advantage of using this formula is that it contains the α/β-ratio and that BEDs from different treatments can be added.

In the BED calculation above it is assumed that complete repair occurs between two consecutive fractions. It contains no correction for the proliferation that might occur during treatment. This is acceptable in the case of the late-reacting tissue. In our opinion this is also applicable to prostatic adenocarcinoma in the current situation since most studies show no correlation between treatment times on local control (16–19), at least when the treatment time is less than 8 weeks.

In order to calculate the DVIC-BED in a target in which an inhomogeneous dose distribution occurs, the exponent in equation 4 becomes:

$$DVIC\text{-}BED = -(\ln(e^{-E_1} + e^{-E_2} + \ldots e^{-E}vn/vn))/\alpha \quad [6]$$

These calculations depend on several underlying assumptions, such as the validity of Poisson statistics, the homogeneous distribution of clonogenes in and between different subvolumes and the validity of the LQ formula.

If the method is applied to tumours that proliferate during treatment, Poisson statistics may underestimate the cure rate (15) and, a time factor should be included (11). The model is not, so far, evaluated for normal tissue effects.

Treatment

The treatments simulated in parts 1 and 2 are administered daily, 5 days a week external beam radiotherapy with 2 Gy fractions to a total dose of 66–80 Gy. This interval covers standard doses and more novel doses in different dose escalation studies.

Large displacement errors

In the first section, external beam treatments with one to six 33% target misses were simulated with both different α/β-ratios and α-values. The effects were expressed as the ratio between DVIC-BED of an optimal treatment without any displacement errors, and the actual achieved DVIC-BED in a treatment with large displacement errors ($DVIC\text{-}BED_a$/$DVIC\text{-}BED_o$).

In the second section, 0–5 LDEs with 0–100% misses of the target volume were investigated. In the case of 33% of volume misses, different combinations of the displacement errors in the three 33% subvolumes were presented.

The α/β-ratios

The α/β-ratio and α-values have been published by Eklöv (4.14, $\alpha = 0.12$) and Stenelöv (7.5 ± 2.5, $\alpha = 0.189$) for

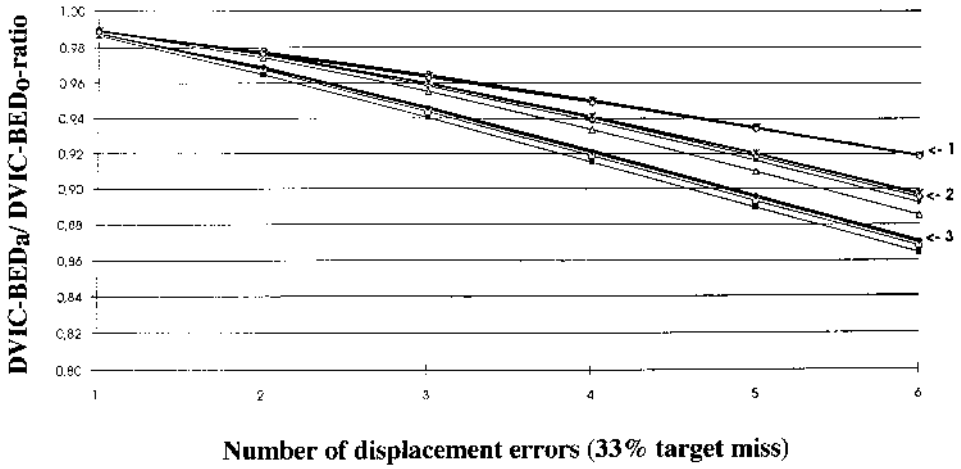

Fig. 1. The effect on the DVIC-BED$_a$/DVIC-BED$_o$-ratio (a = actual, o = optimal) in external beam irradiation (2 Gy fractions to 80 Gy). The α-value is different in each cluster of lines (cluster 1 = 0.05, 2 = 0.2 and 3 = 0.5) and the α/β-ratio (3–15) varies in each cluster. The lowest line represents the lowest ratio.

^{60}Co and DeWeese (3.7–10.9, $\alpha = 0.064$–0.115) for both high and low dose rate irradiation (20–22).

In the first section α/β-ratio = 3, 6, 9, 12, 15, 18 and $\alpha = 0.05$, 0.2 and 0.5 were used.

In the second section the ratios 4.14 and the $\alpha = 0.12$ were implemented.

Estimation of dose levels required for local control and that cause side effects

The dose required to achieve local control of prostatic adenocarcinoma has been suggested by Hanks (6, 8), Perez (3) and Zelefsky (7). Hanks's data are presented in four 5 Gy intervals from < 60 to > 70 Gy (6) and as two curves, depending on the pretreatment prostate-specific antigen (PSA) value (8).

Kabalin (23) and Ljung (24) have reported biopsy-proven local cure rates of 9–35% after irradiation to 70 Gy (in Kabalin, 4 patients had an additional ^{125}I implantation).

Zietman has reported local failure rates of 6–26% in different PAC studies and microscopic local control in 38–100% (25).

RESULTS

In Fig. 1 the relative effects of 1–6 displacement errors on DVIC-BED during external beam radiotherapy, missing 33% of the target with different α/β-ratios and α-values, are presented. The effect of the different ratios is small, but the effect of α-value increments on the DVIC-BED$_a$/DVIC-BED$_o$ ratio is greater.

Fig. 2 shows the effect of 0–5 displacement errors in 0–100% of the target volume. The effect on the DVIC-BED increases with the size and the number of the displacement errors. The relationship in the curves is more or less the same with increasing α/β-ratios (with the same fraction size). However, the α-value has a greater impact on the effect of the displacement errors.

The effects of LDEs in different subvolumes are presented in Table 2. Both the DVIC-BED and the corresponding dose in Gy are listed. A 30% miss is not as serious, in terms of DVIC-BED decrease, as a 100% miss. Although this is an obvious conclusion, the effect on local control can be astonishingly high, and this will be discussed in the next section.

LDE direction has a moderate effect on DVIC-BED. LDEs consistently occurring in the same direction and involving the same subvolume have a larger impact on the DVIC-BED than those occurring in several different directions. If five LDEs occur in the same subvolume, the DVIC-BED will decrease by 7% (113 → 105) and if the LDEs are scattered the decrease will be 5.5% (113 → 108).

DISCUSSION

We present a formula for calculating the effect of LDEs by combining the LQ formula, the tissue-rescuing unit and BED concepts, called DVIC-BED. These calculations indicate that a 30% target miss during fractionated external radiotherapy is less important than a 100% miss and that the direction of the displacement error has a moderate effect, although the absolute figures are dependent on the parameters implemented.

However, the effect of LDEs on local control is dependent on the steepness of the dose-response curve at the current dose level. The dose required for the local control of a PAC is not self-evident, nor is the gradient of the dose-response curve. Higher doses seem to increase clinical and microscopic local control. Since local control seems to be important for the outcome of the disease (5, 7, 8), higher doses in the target volume are desirable and most authors today recommend that PAC patients should re-

ceive doses of 70 Gy or more (7, 8, 26, 27). In dose escalation studies doses above 80 Gy have been used (7, 8).

Unfortunately, the current literature provides little guidance about the shape of the dose-response curve. In Perez's work post-irradiation biopsies were performed infrequently, but data on microscopic control rates after 70 Gy are discouraging. The BED estimate in treatments using a combination of 20 Gy ^{192}Ir brachytherapy in two fractions, together with 50 Gy external beam radiotherapy in 2 Gy fractions, is at least 142, which corresponds to an external beam irradiation in 2 Gy fractions of 96 Gy. Porter has reported negative biopsies in 75–85% of ^{192}Ir brachytherapy-treated patients and a 5-year survival of 82% (4).

Recently, Hanks (8) and co-workers presented dose-response curves based on the pretreatment PSA and clinical and biochemical disease-free patients (bNED), which clearly indicates the steep dose-response relationship in the 70–80 Gy interval and the impact of dose escalation on bNED.

It can be estimated from Perez's data that a dose reduction of 5 Gy results in a decrease in clinical local control of approximately 10% in the interval 65–70 Gy and 20–25% in the interval 75–80 Gy using data presented by Hanks (8). However, dose escalation will force the BED to a flatter section of the dose-response curve, and the probability for cure will be less dependent on BED fluctuations.

Data on α/β-ratios in PAC are also limited. Different α/β -ratios (3–15) had little effect on the DVIC-BED, but the effect of different α values (0.05, 0.2 and 0.5) was large. The data presented by Eklöv are based on the cell-line DU 145 and 4.14 is generally regarded as rather low for tumour tissue. However, the external beam LDE calculations are less dependent on α/β-ratios, but the impact of LDEs in conjunction with high α-values is strong.

Although these values are determined in vitro, PAC can be assumed to have both a low α-value and a low α/β-ratio. There are indications that PAC behaves more like late-reacting tissue rather than acute-reacting tissue with little or no proliferation occurring during a 6–8-week treatment course (16–19). This is also the reason why no compensation for proliferation has been made in the BED calculation.

As mentioned above, we suggests that the DVIC-BED model can be used in conjunction with the dose-planning system or a portal imaging device to evaluate the effect of possible or detected LDEs. The DVIC-BED model could also be used as a uniform reporting analysis for dose distributions similar to the equivalent uniform dose (EUD) concept reported by Niemierko (37).

Models such as tumour control probability (TCP) and normal tissue complication probability (NTCP) are based on dose volume histograms (DVH), and incorporating the motion of the target in the DVH and the TCP/NTCP models is a well-known problem (38). The DVIC-BED model can take dose inhomogeneities in the planned dose distribution into consideration and compensate for dose inhomogeneities occurring in different subvolumes of the tumour at different times during a course of radiotherapy. Furthermore, TCP/NTCP models are based on the physical dose distribution, whereas DVIC-BED is based on radiobiological parameters and there are differences in the calculated effects between the two strategies (for a review, see Wheldon et al. (38)). However, although it is possible to add other radiobiological parameters to a BED calculation, such as proliferation of tumour cells, it is important to note that all models are simplifications and a great deal of information about the tumour is still not known.

The results of our study advise against treatments with large LDEs. Small errors may have a large impact on local control if the dose-response curve is steep. There is a need for a good fixed positioning of the patients in order to

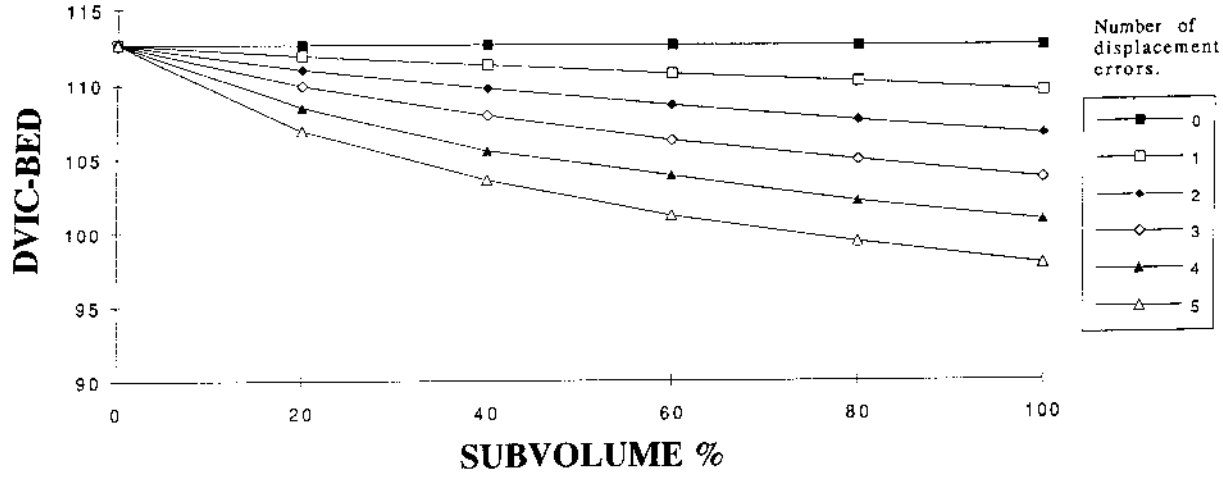

Fig. 2. The effect on DVIC-BED of different large displacement errors (0–5) and different sizes of missed subvolumes (0–100%).

Table 2

Different combinations of subvolumes (A–C) leading to a miss of the target volume by 33% and the resulting DVIC-BED for 1–5 LDEs. A 100% miss is presented for comparison. The corresponding dose in Gy for each DVIC-BED, if the treatment is given without LDE, is also shown

Total number of large displacement errors and numbers of errors in each of subvolumes A–C				Total DVIC-BED and Gy for different volume misses, (Gy)			
	A	B	C	33%	(Gy)	100%	(Gy)
0	0	0	0	113	76	113	76
1	0	0	1	112	75	110	74
2	0	0	2	110	74	107	72
2	0	1	1	111	75	107	72
3	0	0	3	109	73	104	70
3	0	1	2	109	73	104	70
3	1	1	1	110	74	104	70
4	0	0	4	107	72	101	68
4	0	1	3	108	73	101	68
4	0	2	2	108	73	101	68
4	1	1	2	109	73	101	68
5	0	0	5	105	71	98	66
5	0	1	4	106	72	98	66
5	1	1	3	107	72	98	66
5	1	2	2	108	73	98	66

reduce the dose to the surrounding tissues and for overall security. This study also advocates a better determination of radiobiological parameters, including the elaboration definition of the dose-response curve, for PAC.

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