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Radiation related prognostic factors in radiation oncology

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Introduction

The title indicates that there are many factors determining the outcome of a course of radiation therapy.

Biological factors include the stage of disease. Advanced disease is difficult to control, metastatic disease often impossible. The pathology is of prime importance, and the histogenesis of the tumour is very relevant. For instance, the sarcomatous lesions from fibroblastic/mesenchymal origin, are often very radioincurable, whereas the tumours of lymphocytic or germ cell origin are very radiosensitive and radiocurable.

Some tumours, like that of the salivary glands, are probably more treatable by neutrons than by protons or photons due to the specific radiobiological qualities of neutrons, which are quite different to those of X-rays.

Other factors are the ploidy of tumours, the potential tumour doubling time, genetic make-up and perhaps the facility with which apotosis is induced by radiation or hormone deprivation plus irradiation, such as may be the case in carcinoma of the prostate.

I am not going to address these issues further, but instead I am going to concentrate on the very useful concept of the biologically equivalent dose (BED), which is familiar to many if not all radiation oncologists, but perhaps it is not applied widely enough by radiation oncologists.

Whereas it is imperative for radiation oncologists to be intimately and inextricably married in daily practice to the BED, it is also strongly recommended that non-radiation oncologists familiarise themselves with this simple but extremely useful concept and formula.

Other simple concepts having an impact on the outcome of a course of radiation therapy will also be discussed. These factors, if applied, should help the patient to have a more favourable outlook both in terms of the probability of cure, with a bonus of fewer complications.

Early and late reacting tissues

Epithelial coverings, like the bronchus, vagina and skin, respond to radiation damage by losing the basal cells, and a denudation or excoriation of the relevant epithelium, exposing the capillary loops and supporting matrix. These cells are decimated during the course of radiation, and the effects of irradiation are experienced during or shortly after the exposure to radiation and are classed as acute effects. The connective tissues, neural tissue, skin fibrosis and other such phenomena are not dependent on decimation of cells, but rather upon "stored accumulated latent" damage. The clonogenic cells here do not have to replenish cells at a feverish rate, but when the challenge arises for them to divide, as after trauma or infection, the latent damage manifests.

This can happen months to years later.

Withers (1982) has shown that the dose response curve for late reacting tissues curves more than the dose response curve for early reacting tissues, with the result that the curves tend to cross each other (Fig. 1).

The effect of this is that in the low dose, small fraction zone before the crossover takes place, small fractions cause less damage to the late reacting tissues than to early reacting tissues. A fractional dose beyond the crossover region will cause more damage to the late than the early reacting tissues.

Typical dose effect curves are depicted in figure 2. Dose effect curves are sigmoid with a sharp increase in cell death on the linear portions of the curve.

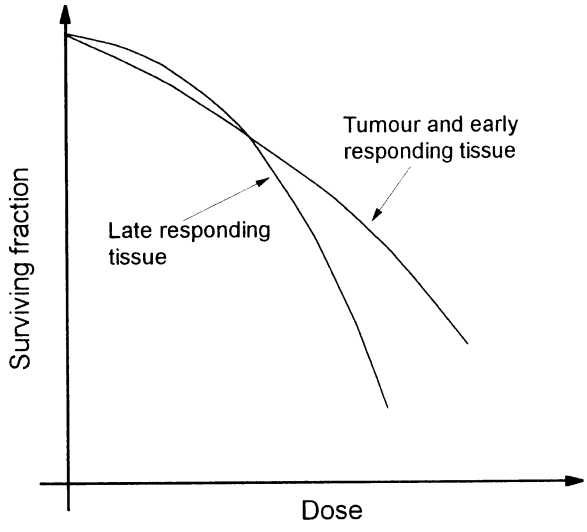

Figure 1. — The dose-response relationship for late-responding tissues is more curved than for early-responding tissues (HR Withers, 1982).

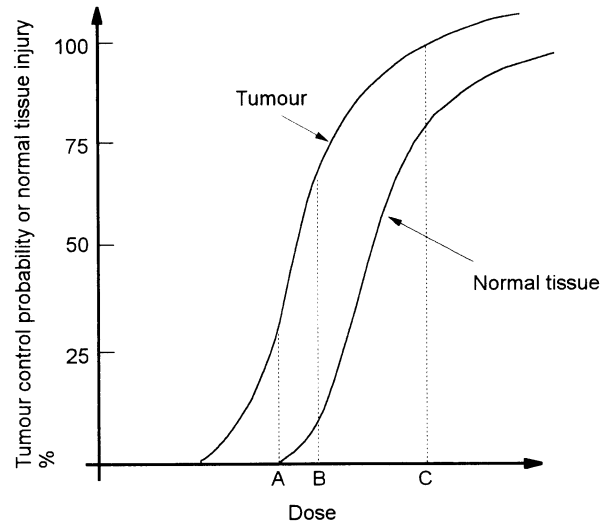

Figure 2. — Illustrative threshold-sigmoid dose response curves for tumour control probability and normal tissue sequelae. This therapeutic situation illustrates that dose prescription nevertheless involves selecting a risk benefit ratio appropriate to the clinical situation. A, B and C illustrate doses which would yield different ratios of tumour control to complications (HR Withers, 1994).

A tumour is assumed to be more sensitive than normal tissues, for example seminoma of the testis, and is represented by the curve on the left. From the figure it follows that a dose delivered at A will result in zero complications but a very low probability of cure. At dose B the complication rate will be low, as will be the cure rate. The cure rate can be high by giving a very large dose, as at C, but then the complication rate will be totally unacceptable.

An important practical, ethical and medico-legal implication of figure 2 is that some incidence of complications is inevitable in the best practice of radiotherapy (Withers, 1994).

An example of a typical dose response curve for cells in culture is shown in figure 3, illustrating that increasing radiation doses kill increasing numbers of cells, and also that cells in different phases of the cell cycle have different sensitivities to the same radiation doses.

The importance of fractionation

However, tissues irradiated in vivo (as opposed to cells in culture) respond in different ways, depending on the tissue type and the fractionation pattern. As mentioned previously some tissues, including tumours of epithelial origin, are early reacting and not very sensitive to dose per fraction. Some tissues are late reacting and very sensitive to fraction size.

Withers (1982) has identified this phenomenon, based on clinical data, and could separate tissues into "early reacting tissues" and "late reacting tissues".

Large doses per fraction are invariably unkind to late reacting tissues, including tissues like brain, lung, kidney, eye and the spinal cord, whereas small doses per fraction spare the normal tissues.

Fractionation is a key strategy in radiotherapy where it has proved its ability to spare normal tissues whilst simultaneously doing optimal damage to malignant tumours. This is due to several radiobiological effects associated with fractionation, like re-oxygenation of anoxic components in tumour tissue, re-entry of tumour cells into a more radiosensitive phase of the cell cycle, and fundamental differences in the DNA repair patterns of tumour cells and "late reacting" normal tissue cells. Repopulation between fractions can negatively influence tumour control (especially in malignant tumours), and the repopulation potential of tumours needs to be taken into account, for example in the treatment of primary and secondary malignant tumours. Shortening the overall treatment time helps to counteract rapid repopulation.

All of the above concepts can be unified into a simple formula that stands up remarkably well to clinical results: the biologically equivalent dose or BED.

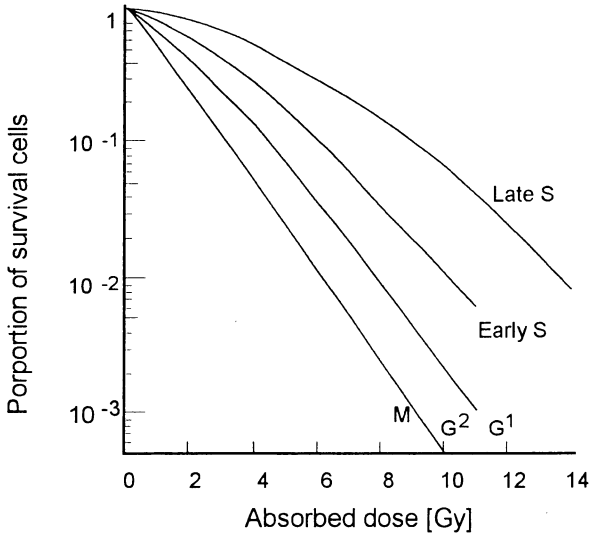

Figure 3. — Survival curves of Chinese hamster cells irradated in different phases of the mitotic cycle, showing that cells have different sensitivities to irradiation in different phases of the cell cycle (M. Tubiana *et al.*, 1990).

Table 1. — *Dose analysis for "optimised" geometry for tandem/ovoid (T/O) and Tandem/Ring (T/R) and Tygerberg (TBH) systems at various points in the pelvis for the nominal dose, biologically effective dose for the tumour (BED_{10}); and late effects (BED_2); all doses in GY.*

	Point M(A)	Point E/(B)	Vaginal Surface	Bladder	Anterior rectum
Nominal Dose (Gy)					
T/R	9.1	1.9	12.4	12.6	8.1
T/O	9.1	2.0	11.7	8.8	5.8
TBH	9.1	1.7	9.1	4.8	6.7
BED_{10} *(Biologically effective dose for tumour control)*					
T/R	17.4	2.26	27.8	65.5	29.98
T/O	17.4	2.4	25.4	16.5	9.2
TBH	17.4	2.0	17.4	7.1	11.2
BED_2 *(Biologically effective dose for late effects)*					
T/R	50.5	3.7	90.5	92.0	41.0
T/O	50.5	4.0	80.1	47.5	22.6
TBH	50.5	3.1	50.5	16.3	29.1

The table illustrates the important point that in terms of BED_{10} expectation of tumour control is high with well fractionated HDR, whereas the complication probability is low. It also illustrates an insignificant contribution of biologically useful doses to lymph nodes and parametria.

The Biologically Effective Dose and Fractionation

The biologically effective dose (BED) is a clinically essential yardstick for the clinician involved in radiotherapy of any kind to reconcile the effects of various treatment schedules. The BED replaced the TDF (time dose fractionation factors), CRE (cumulative radiation effect) and NSD (nominal standard dose) (Fowler 1989).

The BED is based on the linear-quadratic model of cellkill.

For a formal discussion on the LQ model, the α/β ratio and the BED, the reader is referred to several excellent textbooks on radiobiology, and the excellent review article by Fowler (1989).

A mathematical equation that describes these observations quite well is the LQ model briefly discussed below.

Lea and Catcheside (1942) first introduced the LQ model describing the effect of radiation on cells and tissues. The model is used widely in day-to-day radiotherapy practice to predict the biological impact of different total doses and changing doses per fraction.

Shortly, low LET radiation causes single DNA strand breaks. The usual repair enzymes easily repair these. Single strand breaks are associated with the β (quadratic) part of radiation damage of the LQ equation.

The more rarely induced double DNA strand breaks are not easily repaired and such damage is associated with the linear α part of the equation. Nonetheless the damage will manifest either early or late, depending on which tissue type and what tissue architecture has been insulted.

The basic LQ formula is:

$E = \alpha D + \beta D^2$.

E is the effect of a dose of radiation.

D is the dose

The equation can be manipulated to give the following very useful formula:

$BED = nD \times 1 (1 + \{D\} / \{\alpha/\beta\})$

BED is the biologically effective dose which indicates the amount of damage that a particular fractionation schedule is likey to inflict on a tissue with a particular α/β ratio.

n is the number of fractions

D is the dose per fraction

α/β is a ratio defining the sensitivity of tissues to the dose per fraction, and can be determined by radiobiological experimentation for specific cell/tissue systems (Hall 1994).

This formula is very easy to use and can often be done by mental arithmetic but should preferably always be controlled by a second person (Fowler 1989).

Some commonly used values for the α/β ratio are 10 Gy for acutely reacting, proliferating tissues like tumours; and 2 Gy for late reacting tissues.

Some specific α/β ratios:

desquamation of the skin	8.6 Gy - 12.5 Gy
small intestine (jejunum clones)	6 Gy - 10.7 Gy
colon	8 Gy - 13 Gy.

Some quoted values for late reacting tissues include:

cervical spinal cord	1.8 Gy - 2 Gy
lumbar spine	2.3 Gy - 4.9 Gy (Fowler 1989)
eye for cataracts	about 1.2 Gy
retina	1.6 Gy

For early effects, a time factor may be included in the calculation of the BED, but that is not necessary for late effects.

BEDs for tissues with different α/β ratios are not to be compared; for example if a given fractionation schedule gives a BED = 100 Gy for an α/β ratio = 10, the effects of a BED = 100 Gy for an α/β ratio of 2, are not at all identical.

Throughout this article, the relevant α/β ratio is indicated as a subscript, for example, BED_2 for an α/β ratio = 2, or BED_{10} for an α/β ratio = 10.

The BED is expressed in Gy.

The BED formula should be used with caution and circumspection, and it should not override clinical judgement. For example, BED values for brain tolerance for various fractionation schemes agree well (including single large fractions) but interestingly, tolerance values for the optic nerve have widely divergent BED values.

The BED and the therapeutic ratio

Inflicting damage to a tumour whilst minimising damage to the normal tissues can be expressed as the "therapeutic ratio" (TR) is defined as:

TR = {lethal dose to the target tissues} / {tolerance dose to the normal tissues}

The value of this ratio, to be clinically acceptable, should always be greater than 1 (Paterson, 1963).

The important fact about the therapeutic ratio that may be overlooked is that the differential effect of the dose to the target relative to the dose to the normal tissues is far higher than the numerical dose suggests.

For example, if the dose is normalised to 100% over the tumour area for a four field "box" technique for carcinoma of the cervix, and the dose to the tumour prescribed is 2 Gy per fraction, the BED_2 to this area will be equivalent, for 50 Gy total dose, to 100 Gy. If the dose to the normal tissues outside of this area is 1 Gy per fraction then effect on the normal tissues will not be halved (25 Gy/50 Gy = 100% lower) but the relevant BED_2 doses will be 37.5 Gy / 100 Gy or 166.6% lower. If the tumour is sloppily covered by the 100% isodose line, a lot of normal tissues entrapped in the "target area" will be exposed to 66.6% more irradiation than necessary, with complications to match. This makes a strong case for 3-D "conformal" radiotherapy planning.

The BED, inhomogeneity of dose and the volume effect

According to Withers (1994), significant heterogeneity of dose distribution leads to an increased risk of injury, particularly in late responding normal tissues. This increased risk reflects the "double trouble" of both a higher total dose and a higher dose per fraction in the treatment volume. For example, if a tumour dose is prescribed at the 80% isodose contour, then the total dose and dose per fraction in tissues receiving Dmax would be 25% (not 20%) higher. A tumour dose per fraction of 2 Gy would deliver 2.5 Gy at Dmax. The BED, for an α/β ratio of 2 Gy would be equal to 100 Gy for a homogeneous dose of 2 Gy of 25 fractions, but for 25 fractions of 2.5 Gy a part of the lesion would receive a biologically equivalent dose of 158.6 Gy for an α/β ratio of 2 Gy. In large volumes of irradiated tissue, the severity of the late effect may then be wrongly ascribed to some vague volume effect, whereas it is in fact an effect of inhomogeneity of dose.

A specif gynaecological example of applying the BED

The BED probably helps to explain that a single line source is no worse than tandem ovoid systems.

Intracavitary therapy (ICT) plays a major role in the radiotherapeutic management of cervical carcinoma of all stages (Hanks *et al.*, 1993). Interstitial therapy (IT) is not frequently practised and will not be discussed further.

HDR is a fine treatment as long as fractionation is practised. ICT in general should not be seen as anything but a boost for central disease and its contribution to parametrial disease control is very small. A very simple line source technique to deliver fractionated HDR appears to be as good as optimised "tandem ovoid" or "tandem ring" systems (Table 1).

Ovoids (colpostats) versus a single line source

The multitude of ovoid sizes and shapes used, for example in the Fletcher Suit system, leads to a confusing array of isodoses, and depth doses and were implicitly criticised. (Stitt-Haas *et al.*, 1985).

Colpostats may cause either hot or cold spots on the cervix with the latter especially hazardous as already shown by BED application in the example by Withers (1994). Cold spots cannot occur with a line source. The main dose delivered by colpostats is to the vaginal walls and the paracolpos. A line source technique has previously been described by us (Smit *et al.*, 1989). This technique allows multiple small fractions to be given without discomfort to the patient and is significantly less harsh on the vaginal walls (Table 1) and treats more of the parametrium and less of the paracolpos, and there is a high dose gradient from the cervical canal to point A which is highly tumoricidal and not functionally detrimental to the cervix or corpus.

Dosimetry

Computerised tomography (CT) based dosimetry made it possible, with the aid of diode dosimeters, to determine the dose distributions around applicator systems in situ (Wilkinson *et al.*, 1983), (Noyes *et al.*, 1995). I have done the same in 12 patients with our system. Table 1 shows our results next to the published figures of Noyes *et al.*

For early stage disease (stage IB) Noyes *et al.* (1995) report the use of 5 fractions of 9.1 Gy (45.5 Gy, BED_{10} = 87 Gy at point M(A) which contributes to the tandem ovoid optimised system 29 Gy (BED_2 = 113.1) Gy to the anterior rectum. However, because we can easily use 10 fractions of 5.6 Gy (BED_{10} of also 87 Gy) at point A with the TBH system (Smit *et al.*. 1989), this would give a BED_2 of only 62.2 Gy to the anterior rectum, which is far superior for ameliorating late effects than 5 fractions of 9.1 Gy. It follows from table 1 that:

1. The optimised tandem/ovoid system is better than the optimised tandem/ring system, but not significantly better than the TBH system.

2. ICT/HDR cannot contribute a significant biologically effective dose to ensure tumour control to the parametria and lymph glands lateral to point M(A), and one should not add the dose from external therapy to the nominal dose of ICT. Rather the BED should be calculated at several points to get an idea of the effects on the tumour and late reacting tissues.

The clinical results with the TBH technique for IIIB are 38.7% absolute 5-year survival with less than 6% grade I-II rectal and bladder complications (Du Toit and Smit, 1997), with a whole pelvis dose of 50 Gy in 2 Gy fractions plus 4 fractions of 4 Gy each at point M(A).

In summary

1. The outcome of a course of radiotherapy is very dependent on the dose per fraction. The smaller the dose per fraction, as a general rule, the better the sparing of the late reacting normal tissues.

2. Overall treatment time is important, especially for tumours with a rapid doubling time. In such a case, the ideal of small doses per fraction (to save late reacting tissues) as well as a short overall treatment time (to offset the effect of repopulating) can be achieved by small doses per fraction applied two to three times per day, including Saturdays or weekends.

3. The BED (biologically effective dose) is a simple to use formula indicating the effects of fractionation. The most important term in the formula is the α/β ratio which is available from experimental work for

many tumours and tissues and can be looked up. As a guide, an α/β ratio of 10 for early (acute) reaction and for tumour effects, and an α/β ratio of 2 for late effects plus normal tissue complications can be used.

4. The application of the BED demonstrates that for HDR intracavitary therapy for cervical carcinoma, the biologically relevant dose lateral to point M(A) falls very much more rapidly than the nominal dose. Line sources are shown by comparison with other published reports, not to be intrinsically inferior to tandem ring/tandem ovoid systems and may have advantages the more cumbersome systems do not have, and may have the large advantage of allowing multiple small fractions without anaesthesia.

For the particular line source system under discussion, water in a 40 cm^3 Foleys bulb is used as the protecting medium for the posterior bladder wall and the anterior rectum. This particular system allows fraction sizes far smaller than 9.1 Gy at point (M)A, e.g. 3 Gy, which bestows an even greater benefit in terms of the therapeutic ratio according to BED_{10} and BED_2 calculations.

References

Du Toit G. C., Smit B. J.: *SAMJ*, 1997, *87*(10), 1434.

Fowler J. F.: "The linear-quadratic formula and progress in fractionated therapy". *BJR*, 1989, *62*, 679.

Hall Eric J. (ed.): In: "Radiobiology for the Radiologist". Fourth edition. J. B. Lippincott Company, 1994, 64.

Hanks G. E., Herring D. F., Kramer S.: "Pattern of care outcome studies: Result of the National Practice in carcinoma of the cervix". *Cancer*, 1993, *51*, 959.

Lea D. E., Catcheside D. G.: "The mechanism of the induction by radiation of chromosome aberrations in tradescantia". *J. Genet.*, 1942, *44*, 216.

Noyes W. R. *et al.*: "Impact of 'optimised' treatment planning for tandem and ring, and tandem and ovoids, using high dose rate brachytherapy for cervical cancer". *Int. J. Radiat. Oncol. Biol. Phys.*, 1995, *31*(1), 79.

Paterson R.: "The treatment of malignant disease by radiotherapy". 2nd ed., 1963, 14.

Smit B. J., Du Toit J. P., Groenewald W. A.: "An indwelling intra-uterine tube to facilitate high dose rate intracavitary brachytherapy for carcinoma of the uterine cervix". *BJR*, 1989, *62*, 68.

Stitt-Haas J., Dean R. D., Mansfield C. M.: "Dosimetric comparison of the Fletcher Family of gynaecologic colpostats". *Int. J. Radiat. Oncol. Biol. Phys.*, 1985, *11*, 1317.

Tubiana M., Dutreix J., Wambersie A. (eds): In: "Introduction to radiobiology. Cellular effects of ionising radiation". *Cell survival curves*, 1990, 86.

Wilkinson J. M., Moore C. J., Notley H. M., Hunter R. D.: "The use of the Selectron afterloading equipment to simulate and extend the Manchester System for intracavitary therapy of the cervix uteri". *BJR*, 1983, *56*, 409.

Withers H. R., Thames H. D., Peters L. J.: "Differences in the fractionation response of acutely and late responding tissue". In: "Progress in Radio-Oncology". Vol. II, 1982, Eds. Karcher Kogelnik & Reinartz (Raven Press New York, 287).

Withers H. R.: "Biology of radiation oncology". In: "Current Radiation Oncology". Eds. Tobias J. S. and Thomas P. R. M., Vol. 1, 1994, 5.

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