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Radiobiology of Brachytherapy and the Dose-Rate Effect

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1 Introduction

The biological effects of radiotherapy depend on dose distribution, treated volume, dose rate, fractionation and treatment duration. These various factors, however, are of different importance in determining the outcome of external beam radiotherapy or of brachytherapy.

In conventional external beam radiation therapy (EBRT), the volume treated is usually large. Variation in dose is kept minimal inside the target volume, aiming at a homogeneous distribution of dose. Deviations within a range of - 5% to + 7% of the prescribed dose are considered acceptable (40,41).

In brachytherapy, the dose is prescribed to an isodose encircling a small target volume, but in contrast with EBRT, the dose distribution is very heterogeneous. It is minimal at distance of the radioactive sources, but much higher doses and dose rates are delivered in their immediate vicinity. The average dose given to the target volume is therefore always higher than the prescribed dose, prescribed at the periphery of the implant. This is an important point to remember as the treatment report contains information regarding only the dose and dose rate at the reference isodose, i.e. at the periphery of the implant.

Another distinct feature of brachytherapy is that the doses within an implant are higher than the tolerance dose levels accepted in external beam irradiation, yet they are well tolerated because of the volume-effect relationship (very small volumes can tolerate very high dose levels).

Last but not least, time-dose factors differ widely between EBRT and brachytherapy. In external beam radiotherapy, the total dose is delivered in small, daily fractions of a few seconds or minutes, allowing for full repair between exposure. The treatment is protracted over several weeks. In contrast, the dose is delivered continuously, and treatments tend to be short in brachytherapy (several hours to several days). There is however a variety of schedules, depending on the type of equipment used.

According to ICRU report 38, treatment dose rates fall into three categories (39):

- *Low Dose Rate (LDR)* brachytherapy ranges between 0.4 and 2 Gy/h. However, in routine clinical practice, LDR brachytherapy is usually delivered at dose rates between 0.3 and 1 Gy/h. This is compatible with conventional manual or automatic afterloading techniques.
- *Medium Dose Rate (MDR)* brachytherapy ranges between 2 Gy/h and 12 Gy/h. MDR can also be delivered by manual or automatic afterloading, although the latter is far more frequent.
- *High Dose Rate (HDR)* brachytherapy delivers the dose at 12 Gy/h or more, and only automatic afterloading can be used because of the high source activity.

A new category is *pulsed dose rate (PDR)* brachytherapy, which delivers the dose in a large number of small fractions with short intervals, allowing only for incomplete repair, aiming at achieving a radiobiological effect similar to low dose rate over the same treatment time, typically a few days.

Finally, permanent implants deliver a high total dose (for example 150 Gy) at a *very low dose rate*, over several months.

In this chapter we will describe the radiobiological mechanisms which explain the differences between dose rates, based on experimental and clinical results, and provide practical examples and solutions to translate treatment rules between different dose rates.

2 Radiobiological Mechanisms

The biological damage inflicted by irradiation of human cells with ionising radiation can be divided into three consecutive steps:

- A very short initial physical phase (about 10^{-18} s), during which photons interact with orbital electrons, raising them to higher energy levels inside the atoms (excitation), or ejecting some of them from the atoms (ionisation). This is the energy deposition phase.
- A chemical phase, again very short (about 10^{-3} s), during which ionised and excited atoms interact, leading either directly or indirectly through the formation of free radicals to the breakage of chemical bonds. Free radicals are highly reactive and can induce chemical changes in biologically important molecules like DNA. Single-strand or double-strand break in DNA appears to be the basic damage leading to biological effects.
- A biological phase, much longer (seconds to years), during which the cells react to the inflicted chemical damage (46). Specific repair enzymes can successfully repair the vast majority of lesions in DNA. A few lesions however may not be repaired, and may therefore lead to cell death. Cell death is not immediate and usually occurs during the next cell division (apoptosis is a minor process in most human cells). However, death due to a lethal lesion may be delayed for a limited number of mitotic divisions (up to 5 or 6). Because the stem cells are the only cells which divide in normal tissues, the earliest effect observed is a deficit in stem cells. Later, the loss of stem cells will lead to a deficit in differentiated cells, causing the observed clinical reactions. The early reactions are seen during the first days or weeks after irradiation (for example diarrhoea or acute mucositis). They are temporary because the cell deficit is compensated for by the repopulation of stem cells, and subsequently of differentiated cells. Late reactions due to damage to the late-reacting tissues, for instance blood vessel damage, fibrosis, telangiectasia, etc, may be seen after months or years. Damage to these late reacting normal tissues is poorly repaired and is responsible for most severe complications of radiotherapy. Tolerance of these tissues is the limiting factor for radiation therapy.

3 The four Rs of Radiobiology

A number of biological processes take place during irradiation and modify the radiation response. These processes are often described as the 4 Rs of radiobiology (91). Each follows a specific time pattern:

- *Repair of DNA damage* is described above. In older textbook, it is often referred as repair of “sublethal” damage and both terms will by used as synonyms in this chapter. Both experimental and clinical studies have shown that human tumours strongly differ in radiosensitivity and radiocurability (77,78). This is thought to stem from differences in capacity for repair of sublethal damage. Similar differences are seen between normal tissues, the haemopoetic system being, for example, more sensitive than the kidney.

- *Reassortment or redistribution* in the cell cycle. The cell cycle is divided in four consecutive stages: G1, S, G2 and M. G1 is a gap of apparent inactivity after a mitosis (M), before DNA

synthesis (S-phase) resumes in view of the following cell division. G2 is a second gap of apparent inactivity between S phase and M (Fig 4.1).

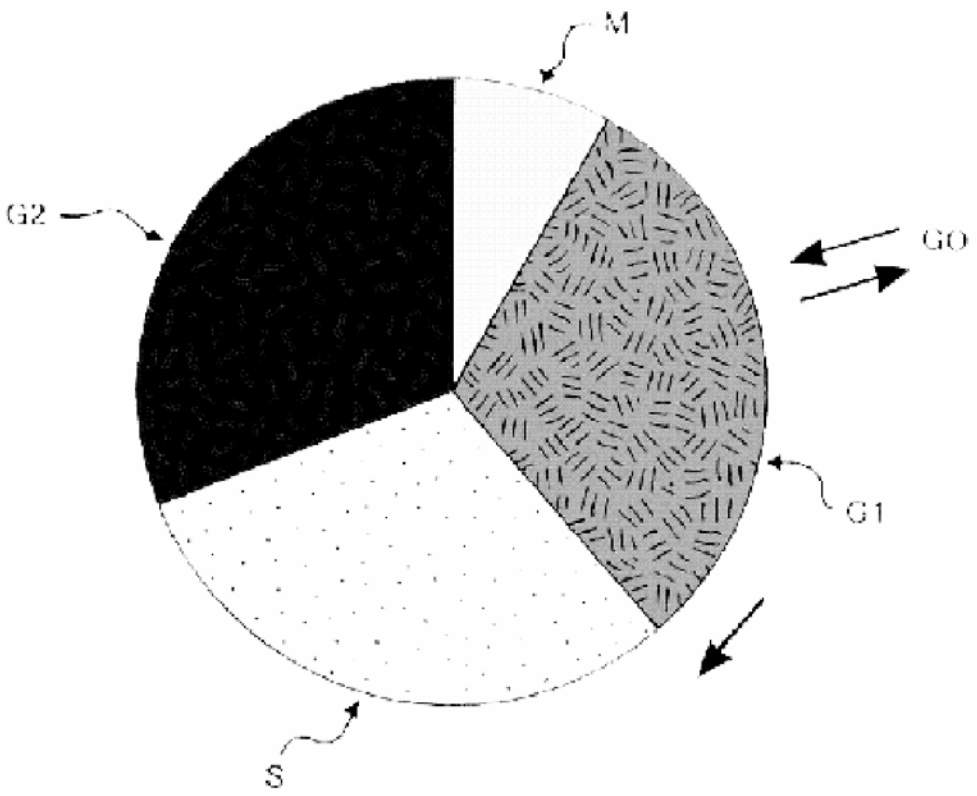

Fig 4.1: The cell cycle.

Radiosensitivity varies along the cell cycle, S being the most resistant phase, and G2 and M the most sensitive. Therefore, cells surviving an exposure are preferentially in a stage of low sensitivity (G1), i.e. synchronised in a resistant cell cycle phase. They progress thereafter together into S and then to the more sensitive G2 and M phases. A new irradiation exposure at this time will have a larger biological effect (more cell kill). However, while this synchronisation effect has explained some experimental results (51), redistribution has never been shown to play a measurable role in the clinic of radiotherapy.

- *Repopulation*. Cells surviving an irradiation keep proliferating. This increases the number of clonogenic cells, i.e. the number that must eventually be sterilised to eradicate cancer. Repopulation therefore has a detrimental effect as far as cancer control is concerned. Stem cells do also proliferate in normal tissues, which has in this case a protective effect (it helps the tissue to recover from radiation damage and it adds to DNA repair in cells).

- *Reoxygenation*. Because of an inappropriate development of intratumoural vasculature, every tumour of clinically detectable size contains a large proportion of poorly oxygenated cells. Also, the proportion of hypoxic cells increases with the tumour size. Acutely hypoxic cells are far more radioresistant than well oxygenated cells. This is expressed by the oxygen enhancement ratio (OER), i.e. the ratio between radiation doses required in hypoxia and air to produce the same biological effect. Its value is 3, and it varies very little with dose or with

the biological system. Hypoxic cells usually survive irradiation, but they progressively (re)oxygenate, due to the better supply of oxygen available after well oxygenated cells have died (fig 4.2). This restores radiosensitivity in the tumour. Several mechanisms are involved, but reoxygenation occurring at long intervals is probably due to tumour shrinkage leading to a reduction of the intercapillar distance.

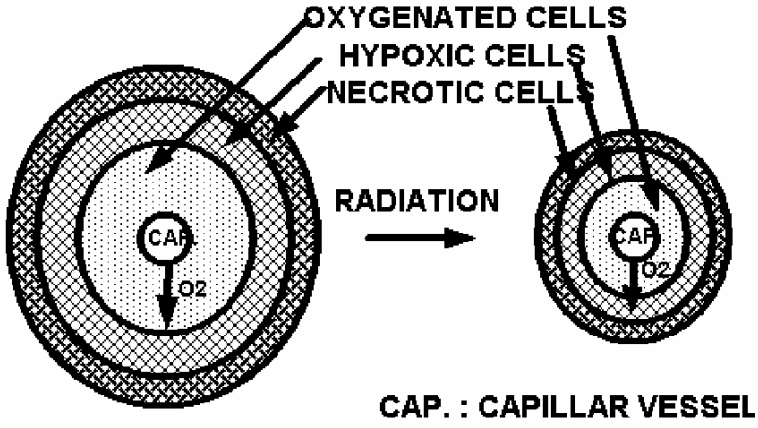

Fig 4.2: Re-oxygenation due to tumour shrinkage.

4 Dose Rate Effects in Brachytherapy

The four R's in high dose rate irradiation

Biological effects of radiation are strongly dependent upon the rate of dose delivery. The radiobiological processes involved in high dose rate brachytherapy are in all respects similar to those involved in fractionated external beam radiation therapy, except for the volume effect, as mentioned earlier.

Repair, repopulation, and reoxygenation, are the main factors determining outcome. They do not occur during the very short duration of irradiation (up to 10-15 minutes), but take place between consecutive fractions, provided the interval is adequate.

Repair. For brief exposures, the survival fraction S of a cell population decreases with increasing dose D. It has been mathematically modelled as the sum of two type of lesions:

- Lethal (non-repairable) lesions, with a survival fraction $S = \exp(-\alpha D)$, represented by the tangent to the survival curve at its origin.
- Sublethal lesions, non-lethal and potentially repairable, but the accumulation of which can cause cell death, with a survival fraction $S = (-\beta D^2)$.

The sum of these two components leads to the classical linear-quadratic (LQ) equation proposed 30 years ago by Chadwick & Leenhouts and Kellerer & Rossi:

$$S = \exp -(\alpha D + \beta D^2) \qquad [1]$$

The survival curve displayed on a semi-logarithmic graph exhibits an initial shoulder (Fig 4.3). The importance of this shoulder varies from one cell population to another. According to the model, it is proportional to DNA repair capacity. Hence, a broad shoulder is associated with a large repair capacity, and conversely. The ratio α/β corresponds to the dose at which the contribution of the two factors to the survival fraction is equal, $\alpha D = \beta D^2$, and $D = \alpha/\beta$. A large α/β corresponds to a small shoulder (small repair capacity) and a small α/β to a broad shoulder (large repair capacity).

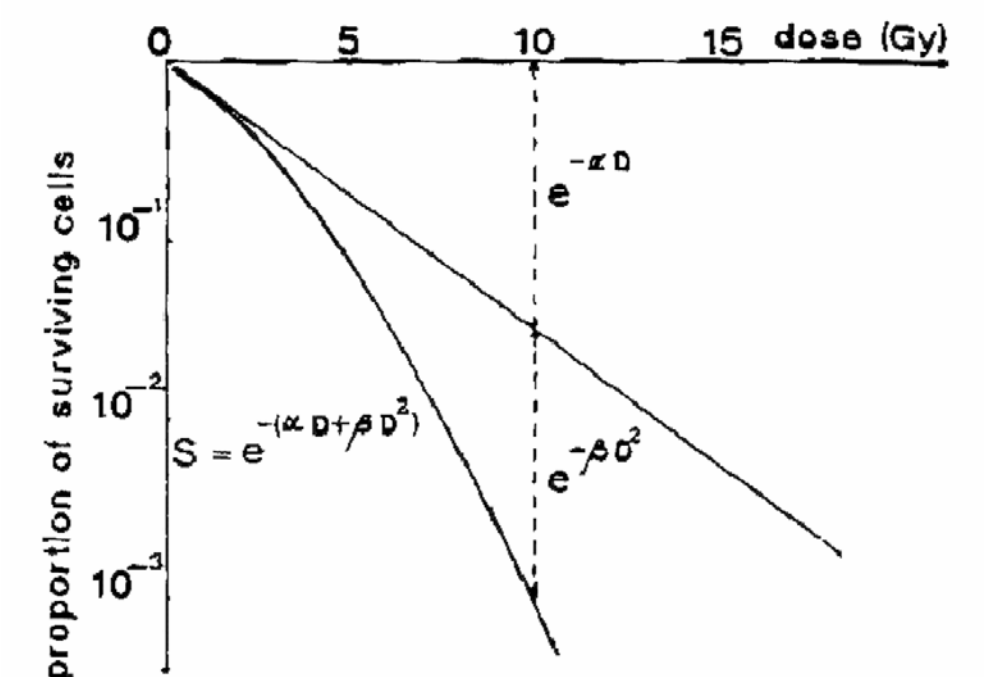

Fig 4.3: Survival curve according to the linear-quadratic model.

Since normal tissue reactions after irradiation depend on radiation effects in a relevant cell population, for example basal cells in the epidermis or marrow progenitors in the blood (82). Radiation effects in these tissues can be described by their target cell survival curve (target cell theory). Therefore, the linear quadratic model can also be applied to tissue effects.

Survival curves for early reacting normal tissues and tumours are less curved than those of late reacting normal tissues (Fig 4.4). Early reacting normal tissues and tumour have a lower sensitivity to dose per fraction and a higher α/β ratio than late responding normal tissues. Biological effects observed increase faster with increasing dose per fraction in late responding tissues than in early reacting tissues and tumour, and small doses per fraction are associated with a lower risk of complications and a better therapeutic ratio. This difference in fractionation sensitivity between early- and late reacting tissues is interpreted as reflecting differences in DNA damage repair capacity and constitutes the basis of the differential effect of fractionation or low dose rate (22).

In summary, a low α/β is characteristic of late-responding normal tissues and some tumours (0.5 to 6 Gy, average 3 Gy), while a higher α/β ratio characterises the early-responding normal tissues and carcinomas (7 to 20 Gy, average 10 Gy) (80,81).

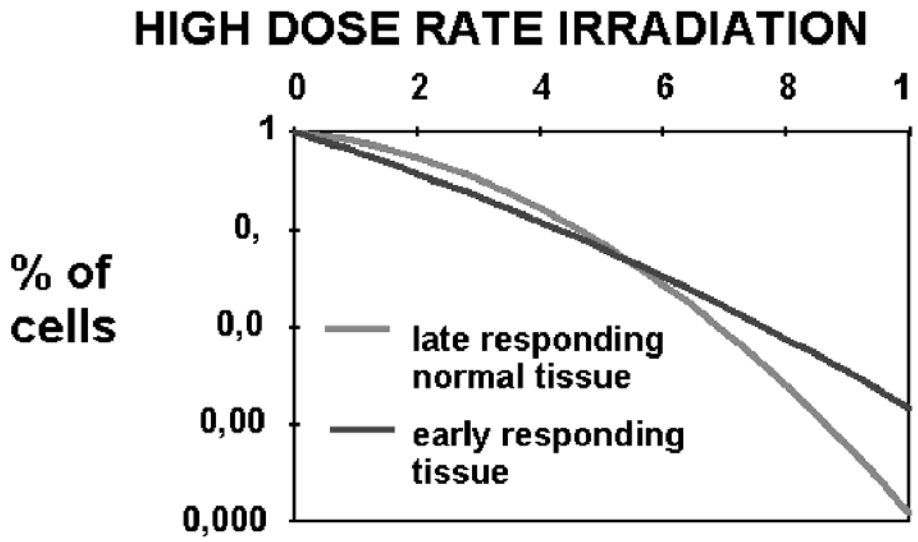

Fig 4.4: Survival curves in early-responsing tissues (normal tissues and carcinomas) and in late-responding normal tissues according to the linear-quadratic model.

Radiobiological studies have shown that each successive fraction in a series is equally effective, so the effect (E) of n fractions of size d can be expressed as:

$$E = -\log (SF)^n$$
$$= n(\alpha D + \beta dD)$$
$$= \alpha D + \beta dD \qquad [2]$$

Where the total radiation dose D = nd.

Reassortment. As explained above, clinical examples of the effects of redistribution are absent. Its role, therefore, remains elusive.

Repopulation does not occur in late responding normal tissue during the course of a 6-7 weeks irradiation, but it plays a role in early reactions and tumour cell killing. Proliferation has little effect in tumours for treatment times shorter than 3-4 weeks (18). After this time, accelerated repopulation of fast-growing tumours may be observed. (9). For early effects on skin and mucosa (desquamation and mucositis), the spontaneous tissue kinetics are unchanged until about 10 days after the initiation of irradiation, when the rate of cell replacement is accelerated (20). It remains very active during the two weeks following irradiation, and then tends to drop quickly, back to its physiological level.

Reoxygenation. Following a large single dose irradiation, most well oxygenated cells are killed, and hypoxic cells survive predominantly. Because aerobic cells have disappeared, the distance between capillary vessels and hypoxic cells decreases. This allows oxygen to reach hypoxic cell, which reoxygenate and become more radiosensitive. The process takes between hours and weeks.

The four R's in low dose rate irradiation

The biological effect of radiation decreases as the dose rate decreases. The relative importance of the four Rs described above at different dose rates are shown in Fig 4.5.

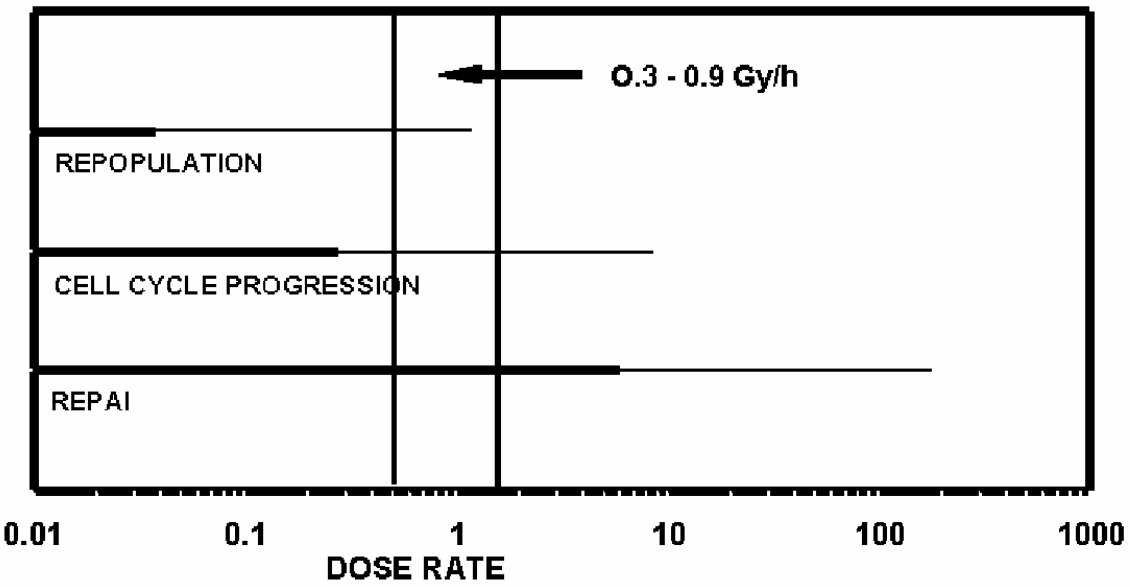

Fig 4.5: The effects of repair of sublethal damage, progression in cell cycle, and repopulation on survival rate, according to dose rate.

Repair of sublethal damage is the fastest process. Its effects can be detected already after 15-30 minutes and it is completed approx. 6 hours after an exposure. It is also the most significant factor altering radiation effect between 1 Gy/min, and 0.3 Gy/h. Repair of DNA damage is a dynamic process, following a specific kinetics (as any enzymatic process). For practical purpose, kinetics has been assumed to follow a simple exponential function of time. It can be described by its half-value $T_{1/2}$, the half time for repair (time during which half of the DNA damage is repaired). In conditions of irradiation where repair already takes place during exposure, i.e. low dose rate irradiation, the LQ model is modified by incorporation of a time factor g (5,15,79):

$$E = \alpha D + \beta g D^2, \qquad [3]$$

g depends upon the half-time for repair ($T_{1/2}$) and the duration of exposure t according to the relation:

$$g = 2\,[1 - (1 - e^{-\mu t}) / \mu t] / \mu t), \qquad [4]$$

where μ is the repair constant, and $\mu = \mathrm{Log}2/T_{1/2} = 0.693/T_{1/2}$ .The value of g is 1 for brief exposures (t tends to 0) and it tends to 0 for very long exposures (t tends to ∞). Therefore, the survival curve is fully linear quadratic for a short irradiation, but as the dose rate is lowered and the duration of

exposure is protracted, the survival curve progressively loses its quadratic term. At very low dose rate, for very protracted irradiation, the survival curve is simply linear (αD). This modified version of the LQ model is called “incomplete repair model” (79).

Repair $T_{1/2}$ for tumours and normal tissues are less well established than α/β. Most $T_{1/2}$ were estimated experimentally (1,33,65,69-71), but dose rates lower than 1 Gy/h (i.e. continuous irradiation lasting longer than 24 hours) have been rarely used. The few available human data are derived from external irradiation in breast cancer or estimated from brachytherapy clinical data (45, 47,48,53,54,81,83,84). The following approximate values are frequently used:

$T_{1/2}$ = 30 min to 1 h for early-reacting normal tissues and tumours.
$T_{1/2}$ = 1.5 h for late-reacting normal tissues.

Actual $T_{1/2}$ are far more variable, within the range of a few minutes to a few hours. In fact, a single-exponential model of kinetics of repair does probably not account for the multiplicity of molecular steps involved in DNA repair. A double-exponential model, with a fast and a slow repair component, often fits better experimental results. The mathematics involved is more complex and, for clinical purpose, the single exponential model appears to offer an acceptable level of accuracy.

Within the time range of conventional low dose rate brachytherapy, somewhere between 3 and 10 days (0.3 to 1 Gy/hr), repair kinetics represent an important factor for calculating treatment equivalencies (70). For a α/β ratio of 10 Gy (acute effects), the slope of the isoeffect curve (see below) critically depends on the repair kinetics value. For a α/β ratio of 3 Gy (late effects), repair kinetics do not play the same central role between 3 and 10 days, and the slope of the isoeffect curve depends much less on $T_{1/2}$ value. However, for longer times, as with permanent implants, repair kinetics become essential for isoeffect calculations.

Reassortment, is a slower process than repair. It might be the most important process below 1 Gy/min. It can lead to cell synchronisation in G2 and M stages (G2 block), and consequently to an increase in radiosensitivity, i.e. a decrease in dose rate (or an increase in treatment duration) would lead to an increase in cell kill. However, while there is some experimental evidence for this process, its role in clinical applications has not been appreciated, so far.

Repopulation is the slowest process and is of significance only for applications lasting more than a few weeks, i.e. with permanent implants.

Reoxygenation is a relatively slow process, and it could be a disadvantage in low dose rate irradiation. The total duration of the treatment usually does not exceed a few days, and reoxygenation due to the elimination of well oxygenated cells and tumour shrinkage cannot occur by the end of the treatment. However, other mechanisms are probably implicated. One of them is recirculation through closed vessels. A temporary increase in blood flow could lead to acute reoxygenation of hypoxic cells, and the OER associated with low dose rate irradiation has been estimated to be as low as 1.6-1.7 (7,49).

5 Experimental Results

Early in vitro studies in the sixties have shown that there is an effect of dose rate on cell survival (33,34). This effect differs with cell type. The dose needed for 1% survival is roughly 1.5-3 times higher at 1Gy/h than it is at 1 Gy/min.

Studies have also been carried out in vivo both on animal tumours and healthy tissues. Compared with an acute exposure, the dose required to produce the same biological effect at 1 Gy/h is increased by a factor of 1.1 to 2 in tumours. For healthy tissues, it is about 2 times higher for early effects (skin, intestine, lip mucosa, etc.), and by a factor 2.5 higher for late effects (skin, rectum, lung, and kidney) (21). This results in a differential effect, i.e. the relative protection of late reacting tissues with low dose rate irradiation, similar to the one observed with fractionation.

Acute reactions of the skin, for instance, were relatively insensitive to alterations in the dose per fraction around 2 Gy to 3 Gy. In contrast, the tolerance of the small bowel, in particular the risk of developing a late radioenteritis, was dramatically dependent on the dose per fraction in the very same range (14). It has been anticipated that a similar differential effect would result from variations in the dose rate of a continuous exposure.

Two sets of experiments at various dose rates were carried out in order to verify this hypothesis (69-71). The mouse lip mucosa was used as a model for acute effects and the rat cervical spinal cord was used as a late effect model. A large differential effect had already been observed between these two models in a previous series of fractionated experiments (1,2,85,87).

Single acute doses were compared with increasingly protracted continuous exposures lasting up to 24 hours. As expected, isoeffect doses had to be increased to compensate for DNA damage repair. However, while protracting the exposure time down to 10 hours, a differential effect could not be demonstrated. Therefore, repair appeared to be of similar magnitude in both tissues during the low dose rate (LDR) experiments, whereas it was different in fractionated irradiation. Similar observations have been obtained from other data sets (83).

This unexpected observation eventually lead to a better understanding of the interplay between repair capacity and repair kinetics during LDR irradiation. A combination of the fractionated and the low dose rate irradiation data sets was used to calculate repair parameters in the two biological models, using the linear quadratic formula adapted by Dale (15) and Thames (79). Repair capacity was actually larger in the spinal cord than in the lip mucosa (α/β values 1.6 and 7.4 Gy, respectively) but repair kinetics was markedly slower in the spinal cord than in the lip mucosa (t1/2 of 1.4 h vs. 0.8 h, respectively). The sparing effect of extending the exposure time expected from its large repair capacity was offset by its relatively slow repair kinetics in the spinal cord. Conversely, repair appeared to be at least as efficient, if not even more, in the lip mucosa because its limited repair capacity was expressed much quicker, due to its fast repair kinetics. This lack of differential effect would have disappeared, of course, if the dose rate had been further decreased.

6 Clinical Results: LDR, MDR, HDR Brachytherapy

Many clinical data have been accumulated over the years in brachytherapy, but very few randomised trials. Nevertheless, these retrospective studies help to better understand the biological background of brachytherapy and devise rules that can be followed in clinical practice.

Brachytherapy versus external beam radiation therapy

While brachytherapy has been a very popular treatment for about a century, most studies are retrospective. In fact, brachytherapy has been used as a standard treatment since the twenties in many tumours, such as cancers of the cervix, oral cavity, lip, penis, etc. It was originally delivered as the only treatment. Later, it was often successfully combined with external beam radiation therapy, acting as boost, notably in cancer of the cervix. In other situations, such as for small cancers of the mobile tongue, attempts to replace exclusive low dose rate brachytherapy by combined external

radiotherapy and brachytherapy boost led to a decrease in local control, and sometimes to an increase in complications (8,60,61,89).

One randomised trial has compared a boost with EBRT or brachytherapy in breast cancer. Fourquet et al. reported on 255 patients presenting with large (3 - 7 cm) breast tumours, who were treated with EBRT to the whole breast (58 Gy) with a 20 Gy boost in the tumour bed, either with conventional cobalt-60 irradiation or with an interstitial iridium 192 implant (mean dose rate: 0.64 Gy/h) (24). The 8-year local control rates were 61% and 76%, respectively ($p = 0.02$).

The interval between external beam radiation therapy and brachytherapy boost

Brachytherapy is often delivered as a boost to residual tumour after wide-field EBRT, typically of 45 to 50 Gy over 5 weeks. Acute reactions may be maximal at this time and persist over a few weeks. The temptation is then to postpone the application for patient comfort. However, repopulation of tumour may also be maximal during these weeks. Therefore, shortening the interval between the two irradiation may maximise local control rates. This has been demonstrated, for example, in oropharyngeal and breast cancers (19,61).

The dose per fraction in high dose rate brachytherapy

It has been seen that the dose per fraction is one of the most important parameters of the therapeutic ratio with high dose rate radiation therapy. In external beam radiation therapy, the risk of developing late injury directly depends on the dose per fraction, for example in small bowel (14). This was confirmed by the results of a survey published by Orton et al. on HDR brachytherapy in carcinoma of the uterine cervix. The rates of severe complications were 3.44% and 1.28% with doses per fraction at point A $\leq$ 7 Gy, and > 7 Gy, respectively ($p < 0.001$) (57).

Low dose rate brachytherapy versus high dose rate brachytherapy

There have been several randomised trials comparing LDR and HDR brachytherapy in cervix cancer and oral tongue cancer (37,38,58,75), and some historical comparisons (57). However, no trial met the criteria of modern randomised studies. In most cases, HDR and LDR brachytherapy produced similar results.

In some specific circumstances, LDR brachytherapy might nevertheless be less toxic for late responding normal tissues, for instance when it is necessary to reach the limit of tolerance to maximise local control rate. Examples are exclusive brachytherapy for small cancers of the oral cavity (45) or treatment with irradiation (or chemoradiation) in locally advanced cancer of the cervix (63).

Dose rate effects in low dose rate brachytherapy

The effects of dose rate on local outcome in low dose rate irradiation have been controversial for several decades. Initially, Paterson proposed that the total dose should be corrected for overall treatment time. In 1952 he published an isoeffect curve (figure 4.6) (59). The standard treatment was 60 Gy in 7 days. The dose had to be decreased to 46 Gy if delivered in 3 days, and increased to 62 Gy if given in 9 days. A clinical analysis published by Mitchell in 1960 tended to confirm Paterson's prediction (55). Clinical data supporting this curve have not been communicated. Later, in the seventies and the eighties, the validity of Paterson's curve was questioned:

Pierquin et al. reviewed the local outcome of 263 squamous cell carcinoma carcinomas of oral cavity, the lower lip, the skin, and the penis, implanted with iridium 192, to deliver a dose of 70 Gy in

3 to 8 days (64). They did not find an effect of overall treatment duration on either probability of local control or complications within this range. Similar conclusions can be drawn by Fu et al. in oral tongue cancers (31). Awwad and Burgers applied the Paterson correction to oral tongue and bladder carcinoma and observed a decrease in tumour control. They concluded that the correction was overestimated (4). Larra et al. did not find an effect of overall time between 1 and 10 days on the control of 121 skin carcinomas implanted to a dose of 60 Gy (44). Van Limbergen at al did not observe a difference in local control between 3 and 6 days with tumours of the uterine cervix treated with a dose of 60 Gy (86). An observation confirmed, later on, by a randomised trial in cervix cancer (32,43). Barkley and Fletcher considered that current dose rates could be multiplied by a factor of 2 to 3 without affecting local outcome (6).

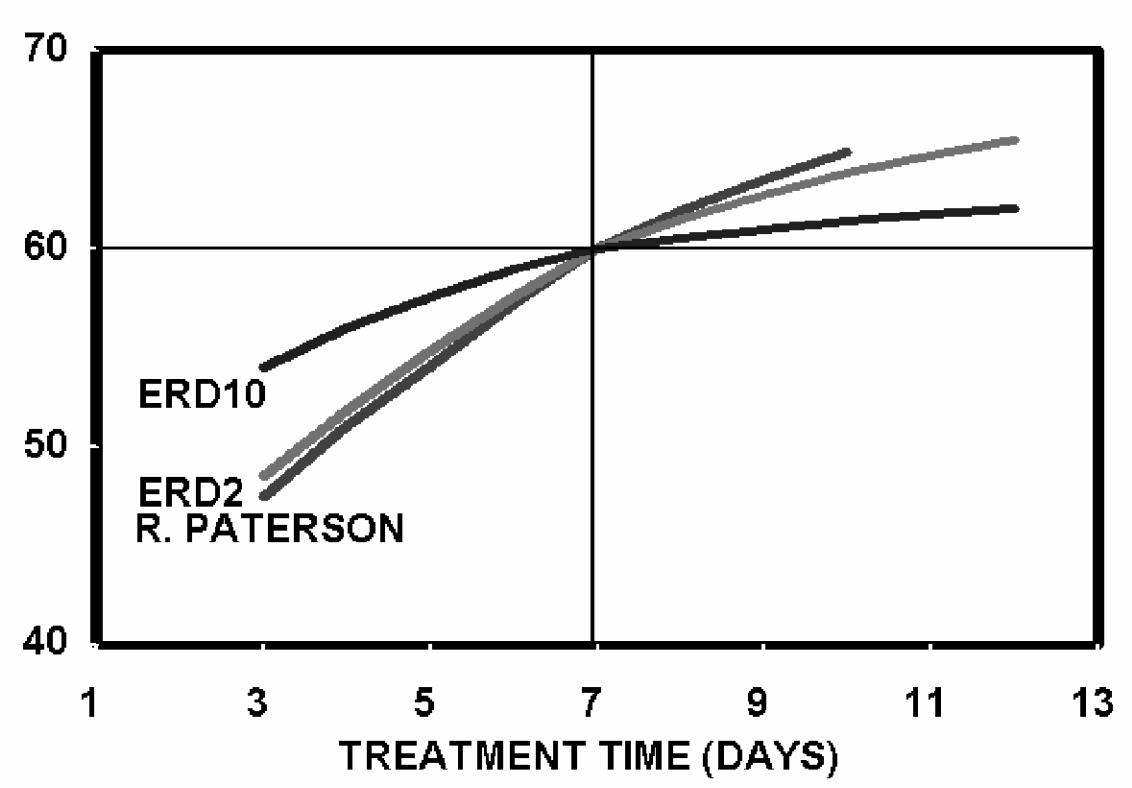

Fig 4.6: Isoeffect curves between 3 and 10 days according to Paterson (58), and to Dutreix (20) in early reacting tissues (ERD_{10}, with α/β = 10 and $T_{1/2}$ = 1 h), and late-reacting tissues (ERD_2, with α/β = 3 and $T_{1/2}$ = 1.5 h).

These conclusions were not supported by radiobiological data, and a reappraisal of the issue was carried out in the nineties, with a more appropriate use of statistics in the analysis of clinical series.

Fontanesi et al. found an effect of dose rate on complications in the re-irradiation of 23 head and neck tumours with iridium 192 (23). Mazeron et al. observed an effect of dose rate between 0.3 and 0.9 Gy/h on local control in a population of 340 patients with a T1-3 adenocarcinoma of breast treated with a 37 Gy iridium-192 boost (53). Sarin et al, in a population of 289 patients treated with conservative surgery and irradiation for early breast cancer, found that higher dose per fraction with teletherapy and higher dose rate with a brachytherapy boost adversely affected cosmesis and contributed to late complications (68).

Mazeron et al. found an effect of dose rate in the range of 0.3-0.9 Gy/h on both probabilities of local failure and necrosis in 279 T1-2 tumours of the oral cavity treated with a 60-70 Gy iridium 192 implant alone (54). Pernot et al. showed that a dose rate in excess of 0.6 Gy/h was associated with an increased rate of complications in a population of 1134 patients who were implanted for a squamous cell carcinoma in oral cavity or oropharynx (62).

A randomised trial compared two dose rates (0.4 and 0.7 Gy/h) in a population of 204 patients with T1-2 of the cervix, treated with a 60 Gy preoperative caesium 137 intracavitary application (32,43). They found that the higher dose rate was associated with an increased probability of late effects and surgical complications.

By the end of the nineties, it became clear that there is an effect of dose rate on local outcome in the range of 0.3-1 Gy/h. These effects seem greater for late reacting tissue than for local control. Indeed, the effect of dose rate in low dose rate brachytherapy can be compared to the effect of dose per fraction in fractionated external beam radiation therapy. Decreasing the dose rate increases the therapeutic ratio, as does lowering the dose per fraction in external radiotherapy.

Isoeffect curves can be drawn for these two types of tissue (Fig 4.6) (21). The isoeffect curve of late responding normal tissue is very close to that previously published by Paterson. In contrast, the isoeffect curve of carcinoma is much less steep (i.e. carcinomas with a large α/β). This means that Paterson's correction is appropriate for late effects, but is overestimated for early effects and cancer control. It is therefore not advisable to adapt the dose to the dose rate in the range of 0.3-1 Gy/h (see practical examples below). It seems more appropriate to keep the total dose high to maximise local control, and the dose rate low (0.3-0.6 Gy/h) to minimise late effects.

However, a dose-correction is usually recommended when the dose rate exceeds 1 Gy/h (36,47,48). Such dose rates have been used for gynecological treatments given with caesium 137 afterloading equipment. The clinical gain is a shorter hospital stay but, to compensate for the higher dose rate, the total dose had to be adapted. Treatment duration usually ranges from 10 to 30 hours with dose rates of 1.5 to 2 $Gy.h^{-1}$. This range of time corresponds to the experimental conditions described above, in which a differential effect was not observed between early and late radiation damage models. The ensuing discussion is thus fully relevant to 1.5 to 2 $Gy.h^{-1}$ brachytherapy. In practice, 1.5 to 2 $Gy.h^{-1}$ brachytherapy is also fractionated. The radiobiological interpretation of clinical data should therefore combine dose rate and dose fractionation parameters. Little differential effect is expected but the fractionation of the treatment (2 or 3 fractions) compensates, to some extent, for this lack of relative protection of late responding normal tissues.

Clinical effects of inhomogeneity of dose

Distribution of dose is far more inhomogeneous in brachytherapy than in EBRT. The inhomogeneity increases with intersource spacing, which has clinical consequences. Simon et al investigated a series of 133 T1 and 141 T2 squamous cell carcinomas of mobile tongue and floor of mouth tumours treated by iridium 192 alone. They found that both the probability of local failure and of necrosis was higher when the intersource spacing was 15 - 20 mm than when it was 9 - 14 mm ($p = 0.055$ and $p = 0.013$, respectively) (76).

The homogeneity of dose distribution can be improved with good geometry of the sources. This is the basic philosophy of both the Manchester and the Paris systems, which have been designed to avoid "cold spots" (underdosage) and limit the size of "hot spots" (overdosage) in interstitial brachytherapy. The latter increases with increasing intersource spacing. Therefore, rules of the Paris system recommend a spacing of 8 - 15 mm for sources up to 5 cm long and 10 – 20 mm for longer sources.

Volume, anatomical site

The volume of healthy tissues included in the planning target volume is one of the major parameter of complication probability. A series of experiments was carried out at GSF, on the tolerance of the rectum in rats irradiated with an oscillating Cs-137 source (42). The ED50 (dose resulting in an effect in 50% of animals) varied from 22.5 to 87 Gy when the irradiated volume was decreased from 100 to 8% of the length of the rectum, a 4-fold increase in tolerance. These experiments were carried out at high dose rate.

Similar effects have been documented in the clinical literature, but they have not been integrated into mathematical models. It is however likely that the total dose required to sterilise carcinomas increases with increasing tumour volume, but that at the same time the tolerance of late responding normal tissues decreases.

The probability of late effects also depends upon the type of tissue involved. For example, the same technique of brachytherapy applied to oral tongue and floor of mouth carcinomas leads to a rate of soft tissue necrosis more than two times higher in the floor of mouth than in the oral tongue [54]. The intracavitary irradiation of cervical cancer delivers a total dose in the centre of the cervix several times higher than that to the rectal and the bladder walls, yet the severe complications are usually observed in rectum and bladder. Again, there is no mathematical model which at present includes this site effect.

Reirradiation

It was believed until recently that it was not reasonably possible to reirradiate normal tissues already exposed at their maximal tolerance level. However, experimental and clinical evidence, notably with brachytherapy of squamous cell carcinoma occurring or recurring in a previously irradiated oropharynx, indicate that a high dose reirradiation can be tolerated if delivered to a limited volume. There is no clear information about the minimal interval necessary between the two irradiations. Recovery after initial irradiation seems however to be less in some tissues, such as the central nervous system.

7 Pulsed Dose Rate Brachytherapy

At the beginning of the 90's, a new technology was developed in order to mimic the biological effect of continuous low dose rate brachytherapy, while taking advantage of the same stepping source technology developed for high dose rate brachytherapy. Source strength was reduced from about 1 Ci (instead of 10 Ci). The total dose is delivered in the same total time as with continuous low dose rate treatment, but with a large number of small fractions (or pulses), typically one per hour, up to one per 4h (Fig 4.7).

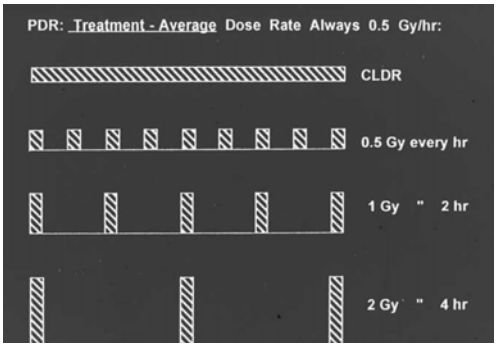

Fig 4.7: Several PDR schedules on the average delivery of 50 Gy/h over the whole treatment time. Biological effects however may be very different.

Theoretical calculations indicate that pulsed dose rate irradiation should be approximately as effective as continuous low dose rate when the same total dose is given in the same overall time (Fig 4.8).

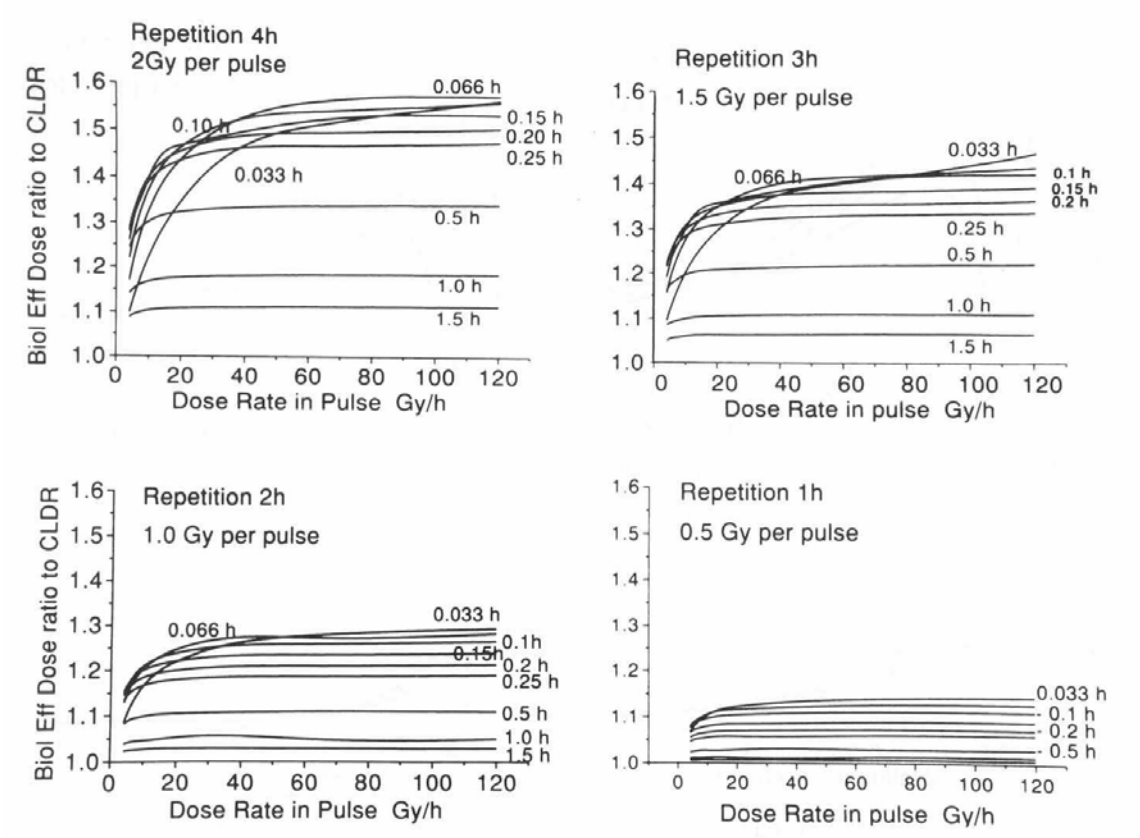

Fig 4.8: Calculated Relative Biological Effect of 4 different PDR schedules, compared to CLDR 50 Gy/h (70 Gy total dose) in function of pulse size (4 diagrams) and different half times of repair. When pulse doses exceed 1 Gy, isoeffect to CLDR is only present when half time of repair is lower than 30 minutes. After Fowler and Van Limbergen (30)

When doses per pulse are small (<0.5 Gy) and repair times larger than 10 min the differential effect to CLDR is less than 10%. This is, however, not the case if large doses per pulse (> 2 Gy) are used and/or there is a non-exponential or very short $T_{1/2}$ (< 0.5 h) (12,28,29). Experimental data are available from a variety of animal experiments.

In the mouse jejunum, Mason et al (52) found continuous LDR at 0.7 Gy/h and PDR with 0.7 Gy hourly pulses to be of equal effectiveness. Pulse duration was around 10 min. Shortening the pulse down to 1 min marginally increased the effectiveness by 3 - 4%. This is due to the fast repair kinetics of jejunum.

Armour et al (3) investigated different PDR schedules in the rat rectum. The endpoint was late rectal stenosis. The reference LDR protocol used a dose rate of 0.75 Gy/h. The PDR schedules were of equivalent effectiveness when pulses of 0.375, 0.75 and 1.5 Gy were given at 30 min, 1h or 2h

intervals, respectively. Larger pulses of 3 Gy every 4h resulted in a 15% increase in effectiveness and pulses of 6 Gy every 8h resulted in a 30% increase in effectiveness. This reference dose rate of 0.75 Gy/h is high. In the clinic it would correspond to a treatment of 3 days 8 hours for a total dose of 60 Gy, i.e. maybe too "hot" for late effects. A lower reference dose rate of 0.4 - 0.5 Gy/h would have been more clinically relevant, though probably not feasible with this model.

Brenner et al. (13) have compared LDR and PDR schedules in the rat cataract model. A dose of 15 Gy was delivered to the rat eye (a) continuously over 24h (0.625 Gy/h) or (b) with hourly pulses of 10min, (c) with 10 min pulses every 4h and (d) with hourly pulses of about 1 min. All schedules were found to be isoeffective.

Haustermans et al (35) attempted to define a pulsed dose rate protocol isoeffective with a continuous low dose rate irradiation in the rat cervical spinal cord. Two different schedules were used, delivering pulses of 0.69 Gy at 1h repetition (9 pulses/day) and of 2 Gy at 3h repetition (4 pulses/day), with overnight intervals of 12-15h. The reference LDR exposure used a range of dose rates up to 0.94 Gy/h. Pulsed dose rate irradiation was more effective than low dose rate by a factor of 10 to 17%. The most likely explanation was that there was a substantial component of repair with very short t1/2 in the spinal cord. Multi-exponential repair has been shown to offer a better fit to spinal cord repair in more recent experiments (65).

These data highlight the shortcomings of using mono-exponential repair models as an approximation to multi-exponential repair, which is particularly critical in pulsed dose rate isoeffect calculations. Data on normal tissue repair characteristics in humans are unfortunately extremely scanty, as has already been mentioned.

The radiobiological modelling of pulsed dose rate is difficult, due to numerous uncertainties regarding DNA repair parameters. Theoretical pulsed dose rate protocols, which could simulate a continuous low dose rate treatment, have been worked out (10-13,27,28,52). Their conclusions were quite similar regarding the need to deliver pulses of at least 10 minutes per hour with a source having the lowest possible activity. It must be emphasised once more that these calculations are based on a hypothesis concerning the repair half time for early and late responding normal tissues as well as tumours (12,27,28). As stated previously, available data on the kinetics of DNA repair are scanty.

An important, yet often forgotten element in theoretical calculations of isoeffects is the reference low dose rate used in the model. Conventional low dose rate in the Paris or Manchester system delivers 10 to 12 Gy per day (0.4 – 0.5 Gy/h). Higher dose intensity, for instance 15 or 17 Gy per day, has a much greater biological effectiveness (33). Therefore, the reference low dose rate is very critical for isoeffect calculations, as critical as the α/β and t1/2 values.

In addition to its limitations as a biological model, the linear-quadratic isoeffect model does not account for the peculiar, stepwise accumulation of absorbed dose throughout the target volume with current PDR afterloading equipment. In order to build up, over 10 minutes, a dose distribution that mimics linear sources, the point source needs to cover a large number of consecutive steps, each one being only briefly, but intensely exposed. Therefore, the dose accumulated in very small volumes, and ultimately at the cellular level, is delivered at a much higher dose rate than the average dose rate calculated for the entire exposure. This has been called the "golf ball" effect by Fowler and Van Limbergen (30). Biological equivalent doses calculated without accounting for this effect are usually overestimating the tissue tolerance and pulsed dose rate appears "hotter" than expected.

In summary, whenever pulsed dose rate brachytherapy departs from its original hourly pulse without interruption at night, it becomes biologically closer to a «hyper fractionated high dose rate » than a continuous low dose rate treatment.

8 Permanent Implants at Very Low Dose Rate

Both paladium-103 and iodine-125 encapsulated sources are widely used in permanent implants of prostate adenocarcinoma. The dose outside the implanted volume falls off very rapidly because both radioactive isotopes emit low energy X-rays in the range 20-30 keV, a major advantage as far as radioprotection is concerned.

The relative biological effectiveness (RBE) of radiation varies with radiation quality because of differences in the spatial pattern of energy deposition. The range of secondary electrons in water depends upon their initial energy. For example, 20 and 350 keV electrons have a LET of 1.3 keVμm and 0.25 keVμm, corresponding to a range of 9.0 and about 1000 μm, respectively. These wide differences account for a measurable variation in biological effectiveness. Compared to cobalt-60, iodine-125 has a RBE in the range 1.4 – 2.0. Although obtained with different biological systems and endpoints, RBE values of 1.15 - 1.2 are in general observed for high dose and high dose rate (72). On the other hand, values up to 2.0 are observed at low dose or low dose rate, which is consistent with microdosimetric data. The former RBE is relevant to temporary implants with high activity iodine-125 seeds and the latter to permanent implants with low activity seeds. Palladium-103 has a slightly larger LET than iodine-125. Its RBE values compared to iodine-125 are increased by about 10% (92).

Practically, the existence of a RBE larger than 1 implies a different biological effectiveness per Gy delivered. In this particular case, iodine or palladium sources are more efficient per Gy than, for example, external beam irradiation with megavoltage equipment.

A second particular feature of permanent implants with iodine and palladium seeds is that the total dose is delivered over an extended period, until the sources are completely decayed. The radioactive half-lives are 60 and 17 days for iodine-125 and palladium-103, respectively. The initial dose rate, at the time of implantation, is about 0.08 to 0.1 Gy/h for iodine and 0.18 to 0.2 Gy/h for palladium and the corresponding total absorbed doses are 160 Gy (over 1 year) and 115 Gy (over 3 months), respectively. Because of the radioactive decay, the dose rate steadily decreases throughout irradiation, with a corresponding increase in RBE. The biological equivalence of the final dose is quite complex to calculate since the decrease in radiation effectiveness due to the reduction in dose rate is partially compensated for by an increase in RBE. Tumour shrinkage, when present, also compensates to some extent for radioactive decay by decreasing the distance between adjacent sources. Complex models are required to describe the interplay of these various factors (16,17).

Experimental data systematically exploring the variation of RBE of palladium-103 and iodine-125 with the dose rate of exposure, relative to iridium-192 and cobalt-60, are not yet available.

9 Practical Applications

To compare the biological effects of two different irradiation schedules a simple iso-effect formula can be used (5). It is based on the linear quadratic model of radiation effect and on the mono exponential model of repair kinetics (see above). It includes the repair parameters α/β and $T_{1/2}$. Equivalence can be calculated for each tissue of interest with the relevant parameters, when they are known, yet most often average α/β and $T_{1/2}$ values are used for early (10 Gy and 1h) and for late reacting tissues (3 Gy and 1.5h).

A preliminary warning is necessary when considering isoeffect models. There are almost no in vivo experimental data exploring the dose rate effect beyond 24 - 30 hours of continuous irradiation. Therefore, the mathematical models, and more particularly the incomplete repair model, have not yet been properly validated at dose rates relevant to classical LDR (73).

Moreover, equivalencies vary widely with α/β and $T_{1/2}$. Thus a simple "magical" formula equating HDR with LDR is probably a dangerous illusion. The clinician has to proceed always with caution. Moreover, calculations have been made with the linear quadratic model assuming first order (mono-exponential) repair kinetics. If repair proves in the future to be more frequently multi-exponential, then equivalencies might have to be recalculated with the appropriate formulae.

Comparison of two HDR irradiations

Using formula [2], and assuming that all sublethal damage is repaired and there is no proliferation between fractions, the following equation can be written:

$$D = D_0 (\alpha/\beta + d_0) / (\alpha/\beta + d) \quad [5]$$

D is the total dose delivered with fractions of size d and D_0 the total dose delivered with fraction of size d_0.

Practical example 1:

- A treatment delivering 30 Gy in 5 fractions of 6 Gy has to be replaced by an equivalent schedule with 7 fractions of 4.3 Gy. What is the total dose with the new fraction size? The answer is 33.5 Gy for early effects, and 37 Gy for late effects.
- Estimate the reduction of dose needed to keep the same biological effect as 30 Gy in 5 fractions when delivering the irradiation in only 4 fractions. The answer is 4 fractions of 7 Gy for early effects, and 4 fractions of 6.85 Gy for late effects.

There are thus two options, overdosing normal tissues to keep the same probability of local control or underdosing the tumour to maintain the same probability of late effects in normal tissues.

Comparison of two LDR irradiations

Using formula [3 and 4], we can write:

$D = D_0 (\alpha/\beta + 2.9 \cdot T_{1/2} \cdot DR_0) / (\alpha/\beta + 2.9 \cdot T_{1/2} \cdot DR)$ [6] where DR is the dose rate in Gy/h.

Practical example 2:

- Estimate the equivalent dose delivered at 0.42 Gy/h (10 Gy / day) to a low dose rate irradiation of 30 Gy at 0.68 Gy/h (15 Gy / day). The answer is 32 Gy for early effects, and 37.5 Gy for late effects.
- Estimate the reduction of dose needed to keep the same biological effect as 30 Gy in 3 days when delivering the irradiation in only 2 days. The answer is 28 Gy for early effects, and 24 Gy for late effects.

Comparison of HDR and LDR irradiation

Combining formulas [2] and [5], we can write the Liversage formula (50):

$N = \mu t/\{2\,[1-1/\mu t\,(1 - e^{-\mu t})]\}$ [7]

Where N is number of fractions into which the HDR treatment must be divided in order to be equivalent to the LDR treatment lasting t hours if both total time and total dose remain constant.

When t exceeds 10 hours, the exponential term becomes negligible and the formula is simplified to:

$N = \mu t/[2\,(1-1/\mu t)]$

When t approaches 100 hours, the last term becomes negligible and the formula can be simplified again; it becomes

$N = \mu t/2$
And $d = 2.9.\ T_{1/2}.\ DR$ [8] with DR = dose-rate

Practical example 3:

- a dose rate DR = 1 Gy/h (24 Gy/day) corresponds to a dose per fraction d = 2,9 Gy for early effects, and d = 4,4 Gy for late effects.
- a dose rate DR = 0.7 Gy/h (16.8 Gy/day) corresponds to a dose per fraction d = 2 Gy for early effects, and d = 3 Gy for late effects.
- a dose rate DR = 0.42 Gy/h (10 Gy/day) corresponds to a dose per fraction d = 1,2 Gy for early effects, and d = 1.8 Gy for late effects.

This may lead to delivery of a considerable number of fractions, with a long interval between fractions (at least 6 hours) and thus long overall treatment time to allow sublethal damage to be repaired. This is not clinically practicable. Practical solutions are :

- HDR brachytherapy, with typically a few fractions delivered at long intervals, during which we can assume that all damage is repaired.
- PDR brachytherapy, with a large number of fractions delivered at short intervals, implying some incomplete repair between consecutive fractions (see further).

Practical example 4:

- estimate the equivalent dose delivered at 0.42 Gy/h for a HDR treatment delivering 30 Gy in 4 fractions.

Using formula [3], the response is 46.9 Gy for early effects, and 65.6 Gy for late effects.

However, treatment with iridium is very often heterogeneous with respect to dose rate because of the frequent re-use of wires for consecutive patients. It is therefore also heterogeneous with respect to biological effectiveness.

Breast cancer has been treated at the Institut Curie with cobalt-60 external beam irradiation (57.6 Gy in 32 fractions), followed by a boost of 20 Gy to the involved breast quadrant with an iridium implant (24)

The mean air kerma rate of the wires was 7.94 $Gy.h^{-1}.m^2/cm$ (range 4.19 - 13.44) and the median dose rate at the reference isodose was 0.64 $Gy.h^{-1}$, with a range of 0.34 to 1.1 $Gy.h^{-1}$, corresponding to a treatment duration of 18 to 58 hours (mean 31 hours). This broad range was the consequence of the Curie Institute policy of purchasing iridium wires of identical activity every 3 months and using them throughout the period. The activity available at the time of the implant depended on the time elapsed since the previous purchase.

Liversage's formulation (50) indicates that a low dose rate irradiation delivering 20 Gy in 31 hours is isoeffective with 20 Gy delivered in 11 fractions (assuming a repair t1/2 of 1 hour for the tissue of interest). This is not far from a conventional boost of 20 Gy in 10 fractions. However, the same calculations for the two extremes, namely 18 and 58 hours of continuous exposure, result in extremely different schedules. Twenty Gy delivered in 58 hours corresponds to 20 Gy delivered in 20 fractions of 1 Gy whereas the same doses, delivered in 18 hours corresponds to 20 Gy in about 7 fractions of 2.8 Gy.

These data deserve several comments. If normalised for 2 Gy per fraction, and assuming an α/β value of 3 Gy for late radiation effects, these three schedules correspond to total doses of about 17, 20 or 25 Gy, respectively, i.e. a dose variation of more than 30%. If one considers the steepness of the dose-response curves for normal tissue effects, one has to admit that such a variation is likely to result in a wide variation in treatment tolerance and possibly in clinical effectiveness.

These theoretical considerations are amply supported by clinical evidence in gynaecological as well as in interstitial therapy (43,53). They are however not limited to the low dose rate category of treatments. Medium dose rate treatments, lasting hours rather than days, may also lead to large differences in biological effectiveness. This is particularly important for centres working with medium dose rate afterloading equipment loaded with cesium-137 sources. The slow decay of caesium implies that gynaecological treatments (or others, such as oesophageal carcinoma) are delivered at dose rates slowly declining with time. It is therefore very important to check the treatment protocols from time to time in order to adapt to this variability. Indeed, the fact that the decay in activity is slow makes it possible that progressive shifts in efficacy/tolerance, spread over a long period of time, remain undetected by the clinician.

It is particularly interesting to consider the Manchester experience with medium dose rate caesium afterloading in light of these specific considerations. Hunter mentioned this steady decline in dose rate, from 180 $cGy.h^{-1}$ in 1978 down to about 138 $cGy.h^{-1}$ in 1992 throughout the various dose-searching studies carried out to try to find an ideal schedule which could replace the old radium prescription [34]. In addition to this steady decline in dose rate, several consecutive dose reductions were tested - 6% to 19% - taking the initial Manchester technique with radium as the control (2 x 3750 cGy at 53 $cGy.h^{-1}$ to point A). These consecutive dose reductions were carried out at a decreasing average dose rate, i.e. both the total dose reduction and the dose rate reduction contributed to the decrease in biological effectiveness. In other words, two fractions of 30 Gy at point A, delivered in about 22 hours (138 $cGy.h^{-1}$) cannot be directly compared to two fractions of 35 Gy delivered in 19 hours (180 $cGy.h^{-1}$). If one normalises for a single dose rate (assuming α/β = 3 Gy and $T_{1/2}$ = 1.5 h), the difference in biological dose was 25 % (30 Gy at 138 $cGy.h^{-1}$ is roughly equivalent to 26 Gy at 180 $cGy.h^{-1}$). This is significantly more than the 14% dose reduction advocated by Hunter.

Clinical data from Eindhoven (66), Bristol (56) and Montevideo (47,48) indirectly support this argument.

It is worth mentioning in this context that there seems to be little differential effect between acute and late reactions in this range of dose rates. This means that the dose rate variations discussed above are likely to affect acute and late reacting tissues to a similar extent (70). It is only at lower dose rates (below 1 $Gy.h^{-1}$) that a decrease in dose rate will preferentially protect the patient from late radiation effects.

As for PDR, the inability of current isoeffect models to account for the "golf ball" effect (30) has led in some case to unexpected clinical toxicities. In a series of patients treated for anal canal cancer with a PDR boost, a higher than expected complication rate was in the form of local necrosis and ulcerations (67) was noted in 13 out of 17 patients. A colostomy was required in 8.

Biological effects of inhomogeneity of dose

In a brachytherapy implant, the dose distribution is also a dose rate distribution. Changes in physical dose rate, near or far from the sources, will result in different biological effects (86). Let us consider a classical low dose rate continuous irradiation of 60 Gy in 6 days and study the variation in biological effectiveness between 30 Gy and 120 Gy; a dose and dose rate gradient of a factor 4:

At the isodose receiving 120 Gy, the dose rate is 0.83 Gy/h. Using formula [3], we can estimate the equivalent dose to be 133 Gy for early reactions, and 165 Gy for late reactions. At the 30 Gy isodose, the dose rate is 0.21 Gy/h. The equivalent doses are 28 Gy and 24 Gy, respectively.

We can then calculate that the biological equivalent doses vary for a physical dose gradient of 4 by a factor 4.7 for early reactions and 6.8 for late reactions. The biological gradient is thus much steeper than the "physical" gradient (86).

Let us now consider a 42 Gy HDR irradiation delivered in 6 fractions. At the 84 Gy isodose, the dose per fraction is 14 Gy, and the equivalent doses are 119 Gy and 143 Gy for early and late effects, respectively. At the 21 Gy isodose, the dose per fraction is 3.5 Gy, and the equivalent dose 17 Gy and 14 Gy. We can then calculate that the equivalent doses vary by a factor 7 for early reactions, and 10 for late reactions.

Fowler and Stitt estimated the relationship between the number of HDR fractions and the late damage to normal tissues, for the same probability of tumour control as a traditional LDR technique of 70 Gy in 140 hours for gynaecological treatments in one or two insertions (26). The purpose of the analysis was to determine the minimal number of fractions to be given to reach the maximal theoretical tolerance of late responding normal tissues (120 Gy Biological Effective Dose, with α/β 3). They concluded that the maximum number of fractions strongly depends upon the isodose in which the critical organ is situated. It is 25 - 30 fractions at the reference isodose (where the Gross Tumour Volume should be), 12 - 15 fractions at the 90% isodose, and 4 to 5 fractions at the 80% isodose (where the rectum, for instance, is supposed to be).

Combined external beam radiation therapy and brachytherapy

Brachytherapy is often delivered as a boost after external beam radiation therapy. The biological effects of combined treatment can be estimated using formulas 4 and 6.

Practical example 5:

A LDR brachytherapy of 30 is delivered in 3 days following external beam conventional irradiation of 50 Gy in 25 fractions over 5 weeks. The effect of repopulation is ignored. Estimate the equivalent dose with a fractionated conventional irradiation.

Answer: using formula [7], it becomes
30 Gy = 25 x 1.2 Gy for early effects
and 30 Gy = 16.7 x 1.8 Gy for late effects

Now, using formula [5], we can estimate the equivalent dose to 28 Gy for early effects, and to 29.5 Gy for late effects. The total equivalent dose is then 78 Gy for early effects and 79.5 Gy for late effects.

These results were estimated, assuming no repopulation throughout the course of irradiation (including a possible interval between combined treatments), which would not be true over a long period for the tumour population. We can assume that a dose M used is compensating for tumour cell multiplication, whose repopulation is constant during irradiation. This dose depends upon the potential doubling time t_{pot}, which is the average time between two divisions of viable cells. T_{pot} usually ranges between 5 and 10 days, while values as low as 2 days have been observed. We can assume that, for compensating for mitotic division, a dose producing a survival fraction of 50% should be delivered for each division, or each T_{pot}. This dose is around 2 Gy, and the total dose M required to compensate for repopulation during the irradiation is therefore (20):

$M = 2\ Gy\ .\ t\ .\ T_{pot}^{-1}$ [7]
$M = 2\ Gy\ .\ T_{pot}^{-1}$ per day

M may then represent a large part of the dose delivered to the tumour volume with fractionated irradiation over several weeks (around 15 Gy), while it is negligible during the short time-frame of LDR brachytherapy, and in late responding normal tissues over the whole course of treatment. Reduction of overall treatment time, including that between the external beam radiation therapy and the brachytherapy boost, increases the probability of tumour control, without a significant increase in probability of late reactions, provided the interval between fractions is sufficiently long to allow complete repair of sublethal damage.

Interruption of treatment

Interruption of treatment may occur during a continuous irradiation of several days, particularly if an afterloading equipment is used. In most cases, it is a short interruption each time the staff enters the room. Partial repair of sublethal damage may occur, but this should not have a significant effect on local outcome, provided that the total duration of these interruptions does not exceed about 10% of the overall treatment time.

Longer interruptions allow more complete repair of sublethal damage. Nevertheless, the consequences are minimal if the interruption lasts for a few hours or days. If the interruption exceeds a week and the potential doubling time is short, accelerated repopulation might occur, and an increase in total dose be needed.

Permanent implants

The total dose is delivered over several months and the dose rate decreases according to the half-life of the radionuclides, as described by the following formula:

$DR = DR_0/2^{t/T}$

with DR = actual dose rate
DR_0 = initial dose rate
T = half-life
t = time

During this long period, repopulation occurs, and the irradiation becomes ineffective when the dose rate has decreased to a "critical value", which is just sufficient to compensate for the effects of repopulation of tumour cells (21).

Let us consider, for example, a permanent implant of ^{125}I sources with an initial dose rate of 0,07 Gy/h. The total dose that will be delivered is 150 Gy. We assume a constant T_{pot} of 6 days. The "critical dose" is 120 Gy, and is reached after 140 days (23.5 times T_{pot}) when the dose rate has decreased to 0.014 Gy/h. We can the estimate the dose used to compensate for the effects of repopulation using formula [7]. It is 47 Gy. The effective dose delivered is then 120 Gy - 47 Gy = 73 Gy. In addition, because the dose rate has been continuously very low, the equivalent dose delivered to late responding normal tissues might also be low, but conclusive data are lacking. Last but not least, corrections are not made for variations in RBE as stated earlier in this chapter.

Pulsed dose rate brachytherapy

We have seen that pulsed dose rate brachytherapy was designed in the early nineties to reproduce the biological effects of low dose rate brachytherapy, while keeping the advantages of a stepping source, namely full radiation protection and the possibility of optimising dose distribution. While the irradiation is delivered over a period of time comparable to low dose rate brachytherapy, it is not continuous. The dose is delivered in pulses, repeated at intervals of 1-4 hours. This interval between fractions is not sufficient to allow complete repair of sublethal damage. Estimation of equivalent dose takes into account an "Incomplete repair factor" Hm, which depends upon the number of fractions per day, the interval between fractions, and $T_{1/2}$ (80,81).

The equation [2] then becomes:

$$D = \exp [-\alpha D - \beta d . (1 + Hm) . D]$$

The lack of knowledge for $T_{1/2}$ values for human tissues in situ is probably the biggest area of uncertainty of these estimations (27,29). Two regimens have been proposed:

- The same total dose as with LDR irradiation, the same total duration, pulses repeated each hour or every two hours with an actual dose rate of not more than 3 Gy/h. This irradiation would reproduce the effects of low dose rate irradiation with a reduction in therapeutic ratio of not more than 10%, whatever the value of $T_{1/2}$ for late reacting normal tissues (27,30).
- A fewer number of pulses per day, with intervals between pulses as long as 3-4 hours (and sometimes a break at night), a similar total duration and reduced total dose. The equivalent dose was estimated to be acceptable, provided $T_{1/2}$ is short for early effects (0.5-1 hour), and long for late effects (3-4 hours) (13,88). In contrast, a big reduction in therapeutic ratio would be observed if an unexpectedly $T_{1/2}$ were observed in late responding normal tissues (compared to tumours) (Fig 4.8).

Estimation of equivalent dose is much more complex for PDR treatment than for LDR and HRD treatments, and cannot be reasonably done manually. It assumes a constant dose rate during pulses, which may be low medium according to ICRU definitions. It does not take into account the fact that the miniaturised source advances step by step inside the catheters. The dose rate in a given point in the target volume therefore varies between low and high values during the pulse, and PDR brachytherapy might behave more like HDR brachytherapy than LDR Brachytherapy (30).

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