**Clinical
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Review Article

The 1991 George Edelstyn Memorial Lecture*: Needles, Wires and Chips — Advances in Brachytherapy

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Abstract. The majority of quantitative data on the effects of dose-rate come from experiments with cultured cells in vitro. These data are reviewed, and it is concluded that results obtained from the in vitro experience may be carried over, in a quantitative manner, to guide clinical ratiotherapeutic design. As an example, there are contradictory guidelines suggested to compensate for changes in dose-rate in interstitial wire-implant brachytherapy. The Paris group has suggested no dose correction is required for implant times from 3 to 8 days, whilst the Paterson/Ellis school suggests a significant correction. It is shown that, based on known radiobiological principles, this controversy can be resolved. These same radiobiological notions, as well as advances in computer technology, have led to the technique of pulsed brachytherapy, which allows the average dose-rate to be maintained at a constant rate, even when the wire activities have decayed.

Keywords: Brachytherapy; Radiation; Dose rate

INTRODUCTION

The suggestion to treat cancer by direct implantation of radioactive sources was first made by Alexander Graham Bell soon after the turn of the century [1]. The early sources contained radium which, because it involves a decay series that includes a gas (radon), must be encapsulated, and, because the emissions include unwanted α and β rays, must be filtered. Consequently, radium needles are rigid and thick, which is uncomfortable for the patient. There is also the potential hazard of a needle leaking radon gas, or breaking and leaking a whole range of long-lived toxic radioactive materials. A major step forward

came with the development of high specific activity man-made radionuclides, first tantalum-182 and later iridium-192 [2–8]. Thin flexible wires could be cut to any length, allowing greater diversity and flexibility in the design of implants. They also greatly improved patient comfort because the wires were not rigid. Iridium wire is also an improvement from the standpoint of radiation safety because it cannot leak like a radium needle, and is not such a problem if lost because the half-life of the radionuclide is relatively short ($T_{1/2}$ = 70 days). As we discuss later, the short half-life turns out to cause other problems. In addition, the lower energy γ–ray emissions of iridium-192 make shielding a little easier.

Subsequent developments in brachytherapy, made possible by the introduction of iridium wires, included the development of afterloading techniques by Henschke et al. [9] and, finally, computer-controlled remote afterloading devices, characterized by the 'chips' in the title of this paper [10].

RADIOBIOLOGY AND THE DOSE-RATE EFFECT

The most complete dose-rate data for the range of dose-rates of importance in radiotherapy have been obtained for cells cultured in vitro. The earliest studies of this sort were performed by Hall and Bedford [11] using HeLa cells. Many radiobiological principles, including the demonstration of repair of sub-lethal damage, were established with cells of rodent origin, particularly Chinese hamster cells; dose-rate studies with these cells were first performed by Bedford and Mitchell [12]. Hamster cells tend to be characterized by a survival curve for acute doses of X-rays that has a large initial shoulder and there is a correspondingly large dose-rate effect. By contrast, the acute survival curve for HeLa cells has a modest shoulder and the magnitude of the dose-rate effect is correspondingly smaller. It appears to be generally true that a large shoulder is associated with a large dose-rate effect, whereas a smaller shoulder is associated with a modest dose-rate effect. This is not

surprising since the shoulder on the acute dose response curve probably reflects the accumulation of sub-lethal damage, and the dose-rate effect reflects the repair of sub-lethal damage.

As predicted by Lajtha and Oliver [13], and before that by Lea and Catcheside [14], when the dose-rate is progressively reduced, the slope of the survival curve becomes progressively shallower as a greater proportion of sub-lethal damage is repaired. A limiting slope is reached, reflecting complete repair of sub-lethal damage, which is an extension of the initial slope of the acute dose response curve. In cells that are not prevented from dividing, there is a further dose-rate effect due to cell proliferation if the exposure time encompasses several cell cycles.

In some cell systems an inverse dose-rate effect has been demonstrated. For example, Mitchell et al. [15] showed that reducing the dose-rate from 1.54 to 0.37 Gy/hour in HeLa cells results in *more* cell killing for a given absorbed dose. The explanation for this is that a certain dose-rate range can exist which allows cells to move through the cycle, but interposes a block in the phase of the cell cycle, G_2, which is relatively radiosensitive. The well known radiation-induced block in G_2 comes at what is now known to be a 'molecular checkpoint', where cells that have been exposed to any DNA damaging agent pause and assess their chromosomal damage before proceeding into mitosis. Genes that control this checkpoint have been cloned and sequenced in yeast, but their human homologues have yet to be identified [16,17].

An overall picture of the dose-rate effect is illustrated in Fig. 1. As the dose-rate is reduced from that characteristic of an acute exposure, the survival curve gets shallower and the shoulder disappears. A
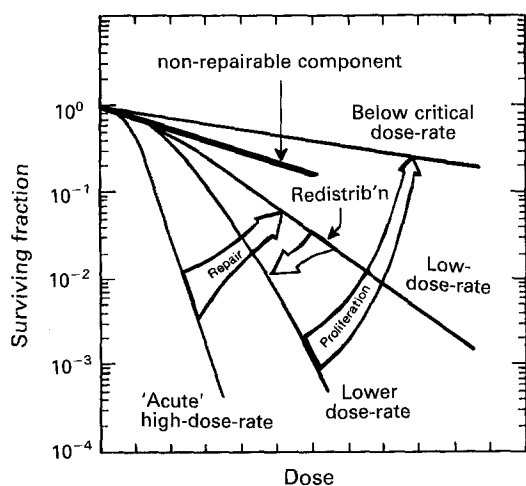
limiting slope is reached when complete sub-lethal damage repair occurs, but the dose-rate is still sufficient to 'freeze' cells in their cycle and prevent progression. A further reduction in dose-rate allows cells to progress through the cell cycle, and accumulate in G_2, which is a radiosensitive phase; this results in the inverse dose-rate effect as described above. As the dose-rate is reduced still further, cells can escape the G_2 block to divide and then a dose-rate effect in the normal direction results from cell proliferation, as cell birth offsets cell killing in a protracted exposure that encompasses several cell cycles.

In the past decade, developments in technique, and particularly the availability of more sophisticated tissue-culture media and growth factors, have combined to make possible the culture of a variety of human cells of both normal and neoplastic origin. As a result, a considerable body of data for cells of human origin has become available.

Detailed data for one particular cell line (derived from an astrocytoma) are shown in Fig. 2 [18]. The results are typical of those found for a number of human cell lines, namely a dose-rate effect between 1 Gy/min and 0.6 Gy/h that is modest compared with that seen for Chinese hamster cells, with little further dose-rate effect below 0.6 Gy/h. A small inverse dose-rate effect is seen here, which is sometimes detectable, but is more often 'swamped' by the effects of sub-lethal damage repair.

About 40 data sets can be identified in the literature for the dose-rate effect in cells of human origin, which include cells of normal and neoplastic origin. These data were summarized and analysed using the linear-quadratic formalism by Brenner and Hall [19]. The expression used to fit the data was

$$S = \exp\left(-\alpha D - G\beta D^2\right)$$

where S is the fraction of cells surviving a dose D, α and β are constants, and G is a factor to allow for the dose-rate or fractionation pattern, as first proposed by Lea and Catcheside [14]. G depends on the temporal pattern of the dose delivery and the half-time for repair of sub-lethal damage ($T_{1/2}$). The fitted curves (without experimental data) for acute and
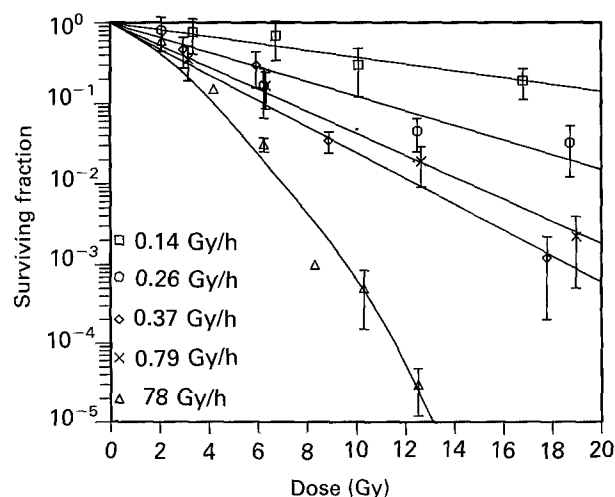

Fig. 1. Revised and updated illustration of the dose-rate effect caused by repair of sub-lethal damage, redistribution within the cycle, and cell proliferation. The dose-response curve for acute exposures is characterized by a broad initial shoulder. As the dose-rate is reduced, the survival curve becomes progressively shallower as more and more sub-lethal damage is repaired, but cells are 'frozen' in their positions within the cycle and do not progress. As the dose-rate is lowered further, and for a limited range of dose-rates, the survival curve steepens again as cells can progress through the cycle and pile up at a block in G_2, which is a radiosensitive phase, but still cannot divide. A further lowering of dose-rate allows cells to escape the G_2 block and divide; cell proliferation may then occur during the protracted exposure and the survival curve becomes shallower as cell birth due to mitosis offsets cell killing due to the irradiation (re-drawn from an idea by Joel Bedford).

Fig. 2. Survival curves for grade 4 astrocytoma cells cultured in vitro and exposed to Caesium-137 gamma-rays at various dose-rates. (Data replotted from Schultz and Geard [18].
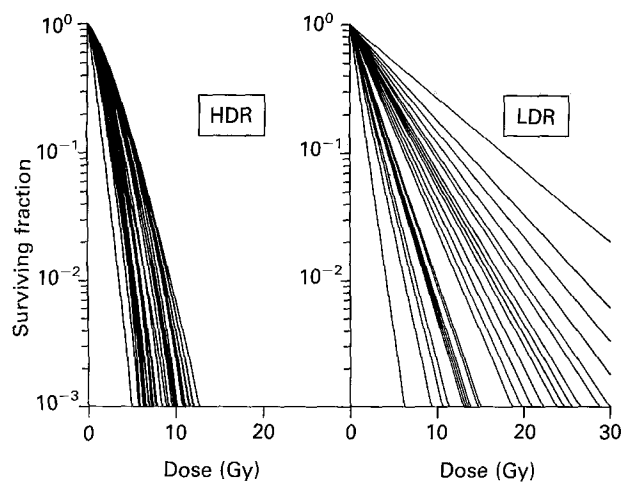
Fig. 3. Dose response curves for 38 data sets for cells of human origin, cultured in vitro and exposed to high or low-dose-rate. Shown are the linear quadratic fits to the experimental data. Note that, at low-dose-rate, the curves fan out because of variations in repair half-times and intrinsic sensitivity.
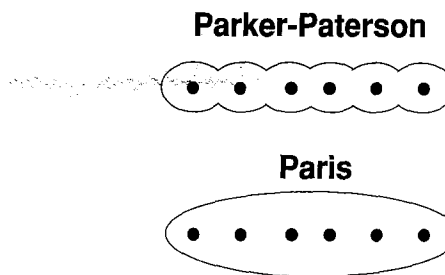

Parker-Paterson

Paris

Fig. 4. Illustrating the differences in dose distribution that result from two of the most widely used sets of rules for interstitial implants. The Parker–Paterson rules [24–26] require that the inner needles have lower linear activity (1/2 if there is one, 2/3 for more than one). As a consequence, the dose in a plane 0.5 cm from the implant is held constant. In the Paris system [28,29] all wires have the same linear activity and so the. isodose lines 'bulge' over the centre of the implant.

INTERSTITIAL IMPLANTS

Rules to distribute radium needles in planar or volume implants were devised by Parker and Paterson, aimed at producing uniform irradiation in a plane parallel to the implanted sources or at a distance outside an implanted volume [24–26]. These rules demanded a variety of needles of different linear activity. The rules were simplified and adapted by Quimby for use in the United States where needles of varying linear activity were less widely available [27].

The introduction of iridium wires demanded a different set of rules and the 'Paris' system of dosimetry was introduced, based on the same linear activity for all sources, and varying the separation of the radioactive wires for different lengths [28,29]. Fig. 4 illustrates the consequences of these different philosophies. The Parker-Paterson system results in an isodose surface that is approximately rectangular in cross-section, while the Paris system produces an isodose surface more closely approximating to an ellipsoid. Another difference, an inevitable consequence of uniform linear activity in the case of iridium wire, is that the dose-rate varies with implant size in the Paris system to a greater extent than in the Parker-Paterson system. This will be discussed later.

very low-dose-rate irradiation are shown in Fig. 3. There is considerable variation in the radiosensitivity of the different cell lines, particularly those derived from tumours. The low dose-rate curves fan out, showing an even greater range of radiosensitivities, reflecting different initial slopes and rates of repair of sub-lethal damage.

The analysis of these data sets by Brenner and Hall [19] shows a large range of values for α/β and $T_{1/2}$, the half-time for repair of sub-lethal damage. The mean values of these parameters are listed in Table 1 [19–22], together with a summary of the limited in vivo data available for late responding tissues in vivo, both for animals and for radiotherapy patients. α/β ratios tend to be large for early responding tissues (which include tumours and cells in culture) and small for late responding tissues [23]. The half-time for repair ($T_{1/2}$) is extremely variable both in vitro and in vivo. In vivo, particularly, estimation of $T_{1/2}$ is difficult, and realistic values are not known with any confidence.

DOSE-RATE VARIATIONS IN INSTERSTITIAL IMPLANTS

Interstitial implants usually involve the range of dose-rates where the variation of biological effect with dose-rate is substantial and important, at least as observed for cells in culture where precise measurements are possible. In the case of interstitial implants with radium needles it was pointed out by Paterson [25] that the limiting factor is the normal tissue tolerance, which should be used fully to maximize the possibility of tumour control. The maximum dose that can be delivered without unacceptable damage to surrounding normal tissue depends critically on the dose-rate as well as on the volume of tissue irradiated. In the 1960s, Paterson published a curve of biological equivalence, based on limiting late
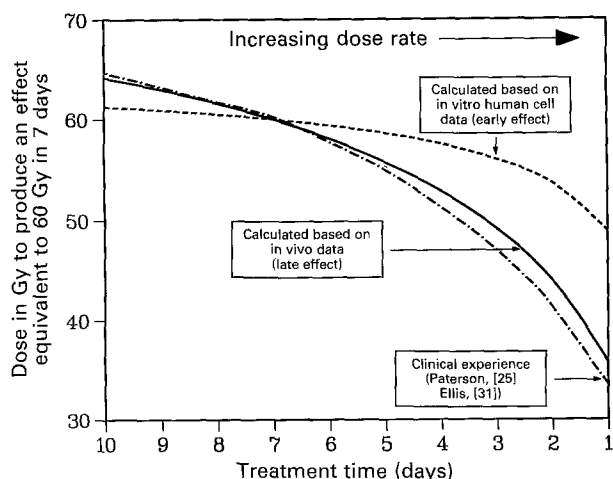
Table 1. Average values of α, β, α/β and $T_{1/2}$

	α (Gy^{-1})	β (Gy^{-2})	α/β (Gy)	$T_{1/2}$ (min)
Early effects in vitro				
Cell survival [19]	0.38	0.051	8.2	30.5
Late effects in vivo				
Human skin (telangiectasia)				
fast repair[a] [20]	0.10	0.024	4.1	24.0
slow repair[a]	0.10	0.024	4.1	210.0
Mouse lung [21] (late damage)	0.31	0.072	4.3	39.0
Rat spinal chord [22] (paralysis)	0.066	0.019	3.4	93.0

[a]The slow and fast components of the repair were roughly equally important.

Fig. 5. Isoeffect curves equivalent to 60 Gy in 7 days calculated in various ways. Based on clinical experience (Dot-dash curve); from α/β and $T_{1/2}$ values related to late effects from Table 1 (solid line); calculated from the average α/β and $T_{1/2}$ values for cells of human origin cultured in vitro – i.e. early effects from Table 1 (dashed line).

effects, for treatments given at different dose-rates (Fig. 5). Regarding 60 Gy in 7 days as the standard, he proposed that an implant of shorter duration should use a slightly lower dose, and an implant of longer duration an augmented dose. The published curve was based on his clinical experience accumulated over many years and was unequivocally based on equalizing late effects in normal tissues. In 1968, Ellis proposed a very similar scheme for use in clinical practice (unpublished data); the data on which his curve was drawn were obtained from clinical experience and are attributed to T. A. Green.

The introduction of iridium wire as a substitute for radium needles in interstitial brachytherapy resulted in a considerably larger variation of dose-rates associated with implants. Two factors are involved:

1. The relatively short half-life of iridium-192 (74 days) means that during the period of several months that the material is clinically useful there will be a range of linear activities.

2. The 'Paris' system of dosimetry, using the same linear activity for all sources and varying the separation of the radioactive wires for different lengths (i.e. greater separation for longer wires and therefore larger treatment volumes) also results in dose-rate variations. Larger volumes contain more activity and are associated with higher dose-rates.

These two factors combined, the short half-life of the iridium-192 and the dosimetry system used, result in practice in a three-fold variation in the total irradiation time for delivery of a given tumour dose [30]. This is a significantly larger range of dose-rates than was characteristic of the radium implants upon which most of the clinical experience of Paterson and Ellis was based. Nevertheless, after analyzing the results of interstitial radiotherapy using iridium-192 in several hundred patients, Pierquin et al. [30] came to the conclusion that the time factor (and therefore the dose-rate) was unimportant, or at least less important than others had suggested.

Consequently, the Paris school recommended the same prescribed dose irrespective of overall time

within the range 3–8 days. They were careful to point out that their conclusions were preliminary but nevertheless concluded [30]:

'We can however say with certainty that the variation in overall treatment time for the same tumour dose from 3 days to 8 days does not appear to influence the frequency of recurrence or necrosis'.

This advice is in direct conflict with the clinical experience of both Paterson [25] and Ellis [31] and does not agree with the experimental radiobiological data that would predict a substantial dose-rate effect over the dose-rate range used in iridium implants. In the next section we attempt to analyse and resolve this apparent conflict, using basic radiobiological notions.

ISO-EFFECT CURVES

Figure 5 shows the variation in tolerance dose with overall treatment time proposed by Paterson [25] and by Ellis [31]. A dose of 60 Gy in 7 days was considered to be a standard treatment; if the overall implant time was shorter, due to a higher dose-rate, then the prescribed dose was to be reduced, and vica versa. Also shown in Fig. 4 are the corresponding isoeffect curves calculated from the α/β and $T_{1/2}$ values for cells in culture and for late effects in vivo, listed in Table 1.

It is interesting to note that the variation in dose with overall time calculated from the α/β and $T_{1/2}$ values relating to late effects in vivo shows remarkably close agreement with the clinical experience of Paterson and of Ellis based on tissue tolerance. The isoeffect curve for any early responding tissue, including tumour control or cells cultured in vitro, is shallower. That is, the isoeffect dose shows *less* dependence on dose-rate or overall time, because the α/β ratio is much larger than in the case of late responding tissues.

As discussed above, a complication and confounding variable in the interpretation of clinical data relating dose to produce an equivalent effect to implant time (and therefore to dose-rate) is the fact that, for interstitial implants, the dose-rate tends to increase as the size of the implant increases. This correlation is particularly true for implants using iridium-192 wires, as used in the Paris system, which are all of the same linear activity, but less so when there is a variation in linear activity, as in the Parker and Paterson system [26]. The bias of larger tumours and larger volumes being associated with higher dose-rates, while smaller tumours and smaller treatment volumes are associated with lower dose-rates, was pointed out by Pierquin and his colleagues [30]. Larger tumours of course require a larger dose for a given level of local control, while the maximum dose that can be tolerated by normal tissues decreases as the volume implanted increases.

This volume/dose-rate bias has an interesting effect on the isoeffect curves as illustrated in Fig. 6. The left hand panel shows isoeffect curves for tumour control, while the right hand panel shows isoeffect curves for late effects in normal tissues. The isoeffect
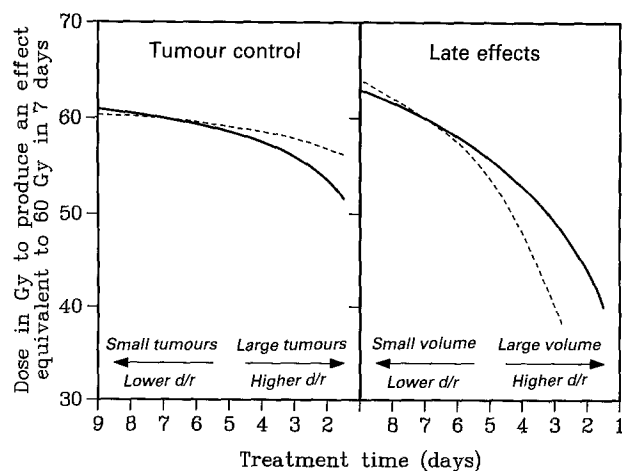
Fig. 6. Illustrating the consequences of the association of dose-rate with tumour size. On the left, the solid line is an isoeffect curve for tumour control, matching to the standard which is taken to be 6000 cGy in 7 days. The dashed line shows qualitatively the effect of the bias that small tumours are associated with lower dose-rate while large tumours are associated with higher dose-rates. The consequence is to flatten the isoeffect curve. On the right, the solid line is an isoeffect curve for normal tissue tolerance matching to 6000 cGy in 7 days. Note that the curve is steeper than for tumour control because of the smaller α/β ratio. The isoeffect curve is made even steeper (dashed curve) by the fact that small treatment volumes are associated with lower dose-rates and large treatment volumes are associated with higher dose-rates.

curve for normal tissues is steeper than for tumour control, showing a greater time dependence (or dose-rate dependence) in keeping with the smaller α/β ratios characteristic of late responding tissues as described by Withers et al. [23]. This is illustrated by the solid lines in both panels of Fig. 6. The dashed lines in Fig. 6 illustrate, in a qualitative way only, the effect of the variation of dose-rate with tumour size. At one extreme, higher dose-rates are associated with large tumours and therefore large implanted volumes. Large tumours require a large dose to produce local control, while larger volumes can tolerate lower doses required to produce a given level of necrosis. The bias of higher dose-rates being associated with larger tumours (and conversely lower doses associated with smaller tumours) has opposite effects on the isoeffect curves for tumour control and for normal tissue tolerance. It will tend to *flatten* the isoeffect curve for tumour control and *steepen* the isoeffect curve for normal tissue tolerance, as shown by the dashed lines in Fig. 6. It should be stressed that the dashed lines are qualitative only, showing a trend, but cannot be quantitative at this time because data relating tumour control dose to tumour volume, or tolerance dose to treatment volume are very limited.

Based on these considerations, then, it is clear why the Paris school and the Patterson/Ellis school differed so radically in their prescriptions for dealing with dose-rate changes. Firstly, the Paterson/Ellis recommendations were based on equalizing only late effects, where there is a clear change of equi-effect dose with dose-rate (solid curves in Fig. 6). However, the Paris recommendations were based on an attempt to equalize late *and early* attempts (with hindsight it certainly seems that when the dose-rate changes it is generally not possible to match both late and early effects). Secondly, as we have seen, the Paterson/

Ellis recommendations were based on a dosimetric system in which there was little correlation between volume and dose-rate. However, the Paris recommendations were based on a system in which the correlation between tumour volume and dose-rate would tend to make the equi-effect curve for tumour control vary even less with dose-rate.

THE DOSE-RATE EFFECT AND CLINICAL INTERSTITIAL BRACHYTHERAPY DATA

The clinical application of iridium-192 wires for interstitial implants, results in a wide range of dose-rates, and therefore of implant times, to achieve a given dose. As discussed above, this is a consequence of two factors. Firstly, the relatively short half-life of iridium-192 means that, during the period of several months that the material is clinically useful, there will be a range of activities. Secondly, the 'Paris' system of dosimetry, using the same linear activity for all sources and varying the separation of the radioactive wires for different lengths, also results in dose-rate variations [29]. These two factors combined result in practice in a potential three-fold variation in the total irradiation time for delivery of a given tumour dose [30].

Two papers have appeared recently that document the importance of the dose-rate effect in clinical brachytherapy. The first describes the analysis of local tumour control and the incidence of necrosis in a large cohort of patients with T_{1-2} squamous cell carcinoma of the mobile tongue and the floor of the mouth, who were treated with interstitial iridium-192 [32]. The data are shown in Fig. 7, where patients were grouped according to dose-rate, either more or
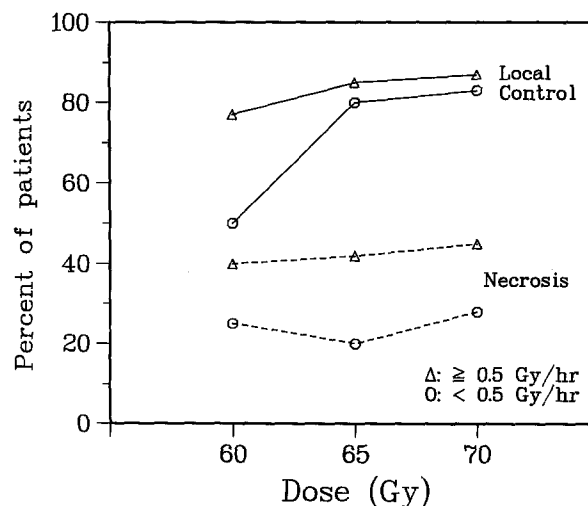

Fig. 7. Local tumour control and necrosis rate at 5 years as a function of dose in patients treated for T_{1-2} squamous cell carcinomas of the mobile tongue and the floor of the mouth with interstitial iridium-192 implants. The patients were grouped according to whether the implant was characterized by a high-dose-rate (above 0.5 Gy/h) or low-dose-rate (below 0.5 Gy/h). The necrosis rate is higher for the higher dose-rate at all dose levels. Local tumour control did not depend on dose-rate provided the total dose was sufficiently large. (Redrawn from the data of Mazeron et al. [32].
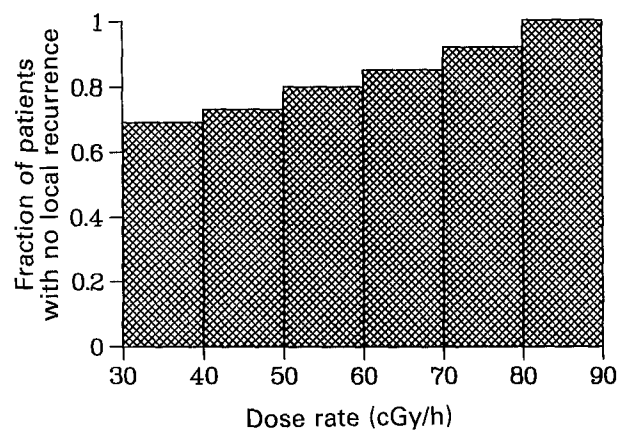
Fig. 8. Percentage of patients who showed no local recurrence as a function of dose-rate in patients treated for breast carcinoma by a combination of external beam radiation plus iridium-192 interstitial implant. The implant was used to deliver a dose of 37 Gy; the dose-rate varied by a factor of 3 due to different linear activities of the iridium-192 wire, and to different size volumes implanted. (Drawn from the data of Mazeron et al. [33].)

Fig. 9. Illustrating the principle of pulsed brachytherapy. The computer controlled remote afterloader controls the pulsing of the single iridium-192 source, which moves from the lead 'safe' to step through the catheters implanted in the patient. The dwell time in each stepped position can be varied to reflect the activity needed to produce the desired dose distribution. Note that this systems allows excellent radiation protection; no source preparation is needed and the source is returned to the safe while the patient is nursed. The computer control station is outside the patient treatment room.

less than 0.5 Gy/h. It is evident that there is a substantially higher incidence of necrosis in patients treated at the higher dose-rate. By contrast, dose-rate makes little or no difference to local control provided the total dose is high enough, namely 65–70 Gy, but there is a clear separation at lower doses (60 Gy), with the lower dose-rate being less effective. These results are in good accord with the radiobiological predictions of Fig. 6, where the isoeffect curve is steep for late effects (necrosis) but shallow for early effects, including tumour control.

The second paper analyses data from a large group of patients with carcinoma of the breast who received an iridium-192 implant as a boost to external beam radiotherapy [33]. These results allow an assessment of the effect of dose-rate on tumour control, but provide no information on the effect of dose-rate on late effects, since there was only one case that involved necrosis. The interstitial implant comprised only part of the radiotherapy, and a fixed standard dose was used, so only limited conclusions can be drawn from these data. However, the results (Fig. 8) show a correlation between the proportion of recurrent tumours and the dose-rate. For a given total dose, there were markedly fewer recurrences when the radiation was delivered at a higher dose-rate rather than a lower dose-rate. The authors conclude that the higher dose-rates should be used. This is a reasonable conclusion in view of the virtual absence of significant late effects. However, an alternative conclusion would be to use a lower dose-rate and increase the total dose with a view to maximizing the therapeutic differential.

PULSED INTERSTITIAL BRACHYTHERAPY

One way of essentially eliminating concerns about the variation of effect with dose-rate as iridium wire decays, is the use of pulsed brachytherapy. The principle of pulsed interstitial brachytherapy is to
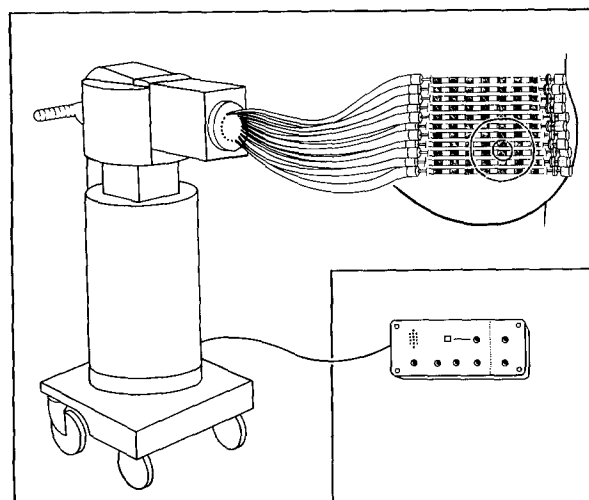
replace the many individual wires or ribbons in a conventional implant by a single iridium-192 source, of about 37 GBq, as in Fig. 9. This source, under computer control from a remote afterloading device, steps through the implanted catheters of the implant with dwell times tailored to accommodate the dose distributions required [19]. More than 25 years ago Hall and Bedford [11] investigated the equivalence of pulsed and continuous low-dose-rate irradiation. Fig. 10 shows some of their data which demonstrate that giving six short pulses per hour is indistinguishable from continuous irradiation. Such frequent pulsing would be inconvenient in a clinical device. Brenner and Hall [19], in analyzing a large body of in vitro data for cell lines of human origin (see above), came to the conclusion that a 10-minute pulse every hour would adequately mimic continuous low-dose-rate irradiation of about 40–60 cGy/hour. They concluded that a reasonable equivalence in terms of both early and late effects would be achieved.

The proposal in pulsed brachytherapy, therefore, is for the source to move through the catheters of the implant for about 10 minutes of each hour, delivering an appropriate dose, before returning to the safe. This strategy allows, as the radioactive source decays over a period of months, the pulse length to be gradually lengthened to offset this decay and so maintain the same dose per pulse. This process is illustrated diagrammatically in Fig. 11. By this means, the average dose-rate is maintained at 42 cGy/h, or whatever dose-rate is desired, as the source strength decays. The principle of pulsed brachytherapy has previously been described in detail [19]. Several advantages were listed which include:

1. Improved radiation safety, since there is no individual source preparation beforehand, and during an implant the source can be returned to the safe while the patient is nursed or examined.
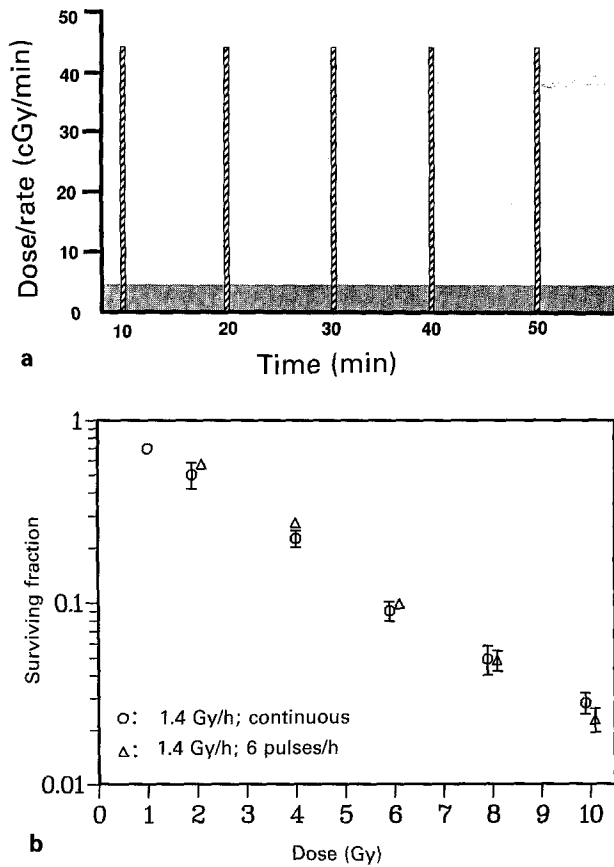2. Only one source needs to be replaced instead of a

Fig. 10. (a) Illustrating the plan of an experiment by Hall and Bedford in 1964 [11] to compare continuous low-dose-rate with pulsed high-dose-rate irradiation (2-37 rad/min = 44-9 rad/min for 31-7 sec/10 min). **(b)** Survival data for HeLa cells treated with continuous low-dose-rate and 6 pulses per hour high-dose-rate. There is no detectable difference in cell survival between the two treatment protocols.

Fig. 11. Illustrating the principle of pulsed brachytherapy and the way in which this innovation makes it possible to keep the overall dose-rate constant. A continuous low-dose-rate of (say) 42 cGy/h is replaced by pulses of 42 cGy delivered in 10 min every hour. As the single iridium-192 source decays with a half-life of 74 days, the pulse length is adjusted to maintain the dose per pulse to precisely 42 cGy. As a consequence the average dose-rate is maintained and the overall treatment times for a given total dose may remain fixed.

whole inventory of sources, which leads to a substantial cost saving.

3. A stepping source under computer control, with variable dwell time in each position, allows improved optimization of the dose distribution.

To these advantages can now be added the ability to keep the average dose-rate constant for implants of different sizes, and for all patients, as the iridium-192 source decays. This turns out to be a most desirable feature since the recent reports discussed above have clearly shown that both tumour control and necrosis incidence are dose-rate dependent.

SUMMARY AND CONCLUSIONS

Radiobiological data for cultured cells of human origin demonstrate clearly that there is a substantial dose-rate effect for cellular lethality over the range of dose-rates used in interstitial brachytherapy. An analysis of dose-rate and fractionation data obtained with cells cultured in vitro, as well as the much more limited data available in vivo from animal experiments and in humans, shows that the ratio α/β, as well the half-time for repair of sub-lethal damage, varies widely from one cell line or tissue to another.

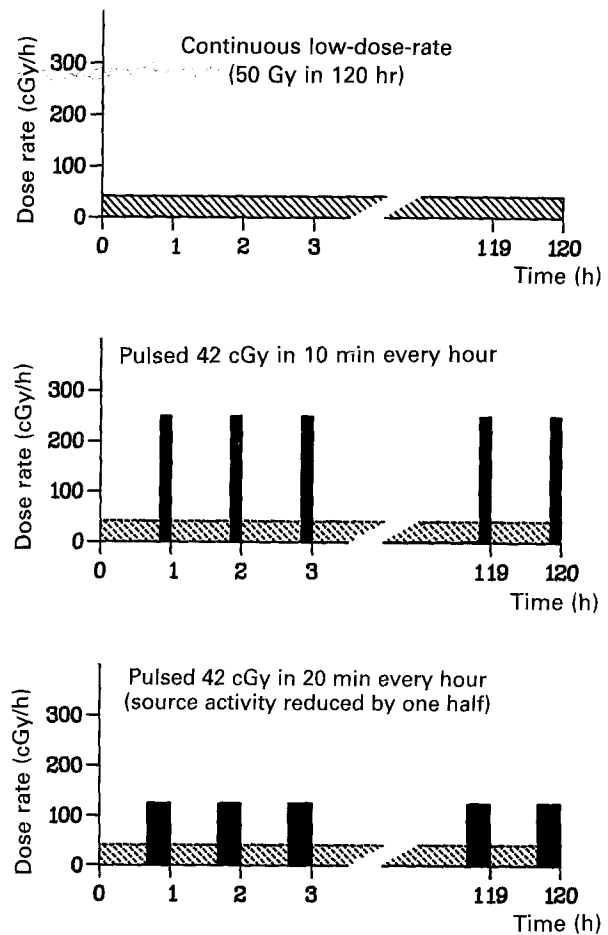Isoeffect curves relating total dose to produce a

given effect as a function of overall time (and therefore dose-rate) are steeper for normal tissue tolerance than for tumour control. The difference is exaggerated by the bias that exists between tumour size and dose-rate, especially in the case of implants with iridium-192 wire, where all lines in an implant have the same linear activity. Large tumours and treatment volumes are associated with higher dose-rates, while small tumours and treatment volumes are associated with lower dose-rates. This *flattens* the isoeffect curve for tumour control, but *steepens* the isoeffect curve for normal tissue tolerance. This observation partly accounts for disagreements in the past between the recommendation that total dose should be varied with overall time [25,31] and the recommendation that total dose should remain the same for implant times between 3 and 8 days [30]. The Paterson recommendation related to implants with radium needles and was based unequivocally on matching normal tissue tolerance. The Paris system recommendations related to iridium-192 implants and were based on a combination of tumour control and necrosis. Recent technological advances, such as pulsed brachytherapy, make it posible to maintain a constant dose-rate as the radioactive sources decay,

an advantage which should greatly facilitate the future analysis of interstitial brachytherapy data.

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