

REVIEW ARTICLE

Radiation Biology in Brachytherapy

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The biological rationale for the use of brachytherapy, which is undergoing a significant resurgence in the United States, is reviewed with emphasis on low dose rate (LDR brachytherapy). Some of the newer alternatives that have recently been developed, such as pulsed dose rate (PDR) brachytherapy, are discussed. *J. Surg. Oncol.* 1997;65:66-70. © 1997 Wiley-Liss, Inc.

KEY WORDS: radiobiology; dose rate; sublethal damage repair**INTRODUCTION**

The first suggestion to treat cancer by direct implantation of radioactive sources was apparently made by Alexander Graham Bell soon after the turn of the century [1] (Fig. 1). Various groups in different countries adopted different names for this technique, using either the prefix *brachy* from the Greek for "short" or *endo* from the Greek for "within."

Early brachytherapy sources used radium, which involves a decay series that includes a gas (radon), and therefore must be encapsulated, and because the emissions include unwanted α - and β -rays, must be filtered. Consequently, radium needles were rigid and thick, making implantation very painful. There was also a potential hazard of a needle leaking radon gas or of breaking and leaking a range of long-lived toxic radioactive materials. A major advance came with the development of high specific activity man-made radionuclides—first tantalum-182 [2] and, more recently, iridium-192 [3]. These thin flexible wires can be cut to any length, allowing greater flexibility in the design of implants, greatly decreasing patient discomfort.

Subsequent advances on the technological side of brachytherapy, made possible by the introduction of iridium wires, have been the development of afterloading techniques by Henschke et al. [4], and subsequently the introduction of computer-controlled remote afterloading devices [5]. Essentially, an afterloader implant consists of a thin tube, rather than the radioactive source itself; the source is then remotely shuttled in the tube, and thus into the appropriate locations, at a later time. This afterloading technique has the potential to reduce drastically the radiation dose to which staff and visitors are exposed.

The biological rationale for the use of brachytherapy, which is undergoing a significant resurgence in the United States, and continues to be used extensively in Europe, is reviewed with emphasis on low dose rate (LDR) brachytherapy. Some of the newer alternatives that have recently been developed, such as pulsed dose rate (PDR), are discussed.

WHY BRACHYTHERAPY?

There are three key advantages of LDR brachytherapy: (1) positioning of the source a short distance from, or in, the tumor, allowing good dose distributions; (2) short overall treatment times, to counter tumor repopulation; and (3) low dose rate, which results in an increased therapeutic advantage between tumor control and damage to late-responding tissues. Each of these three aspects is briefly discussed.

Good Dose Distribution

Good radiation dose distribution speaks for itself. In many instances, the ability to locate radioactive sources in or close to the tumor, either by topical mold or by intracavitary or interstitial implant, represents the optimal conformal dose delivery system; specifically, it is generally easier (relative to external beam radiotherapy) to deliver high doses of radiation to target tissues, while minimizing radiobiological damage to normal adjacent tissues.

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Dear Dr. Sowers:

I understand from you that the Röntgen rays, and the rays emitted by radium, have been found to have a marked curative effect upon external cancers, but that the effects upon deep-seated cancers have not this far proved satisfactory.

It has occurred to me that one reason for the unsatisfactory nature of these latter experiments arises from the fact that the rays have been applied externally, thus having to pass through healthy tissues of various depths in order to reach the cancerous matter.

The Crookes' tube, from which the Röntgen rays are emitted, is of course too bulky to be admitted into the middle of a mass of cancer, but there is no reason why a tiny fragment of radium sealed up in a fine glass tube should not be inserted into the very heart of the cancer, thus acting directly upon the diseased material. Would it not be worth while making experiments along this line?

[Signed] Alexander Graham Bell

Fig. 1. Alexander Graham Bell [1], suggesting the concept of brachytherapy.

In summary, good dose distributions spare: (1) *early-responding normal tissues*, which, in external beam radiotherapy, typically produce the complications that force treatments to be prolonged over more than 1 month; and (2) *late-responding normal tissues*, which, in external beam radiotherapy, often represent the dose-limiting endpoint.

Short Overall Treatment Times

It is now generally accepted that long overall treatment times can be a significant cause of local failure in radiotherapy, because accelerated repopulation during the treatment means that tumor cells start to divide more rapidly than they can be killed [6–8] (Fig. 2). However, generally speaking, the optimal strategy for any radiotherapeutic regimen requires: (1) short overall times to limit tumor repopulation; and (2) long overall times to reduce early normal-tissue sequelae, especially to the skin and mucosa. Prima facie, requirements 1 and 2 are mutually exclusive; therefore, in most radiotherapeutic situations, the overall treatment time represents a compromise between short treatment times to minimize tumor repopulation and long treatment times to prevent unacceptable early complications.

On the other hand, brachytherapy, because of its good dose distribution, inherently produce less early normal tissue damage. Thus, the compromise on overall time does not have to be made, and much shorter times are tolerable in brachytherapy than could conceivably be employed in external-beam radiotherapy for a comparable effective tumor dose.

Low Dose Rate

It has been known for many decades that lowering the dose rate generally results in a reduction in radiobiological damage [9]. The explanation, relating to sublethal

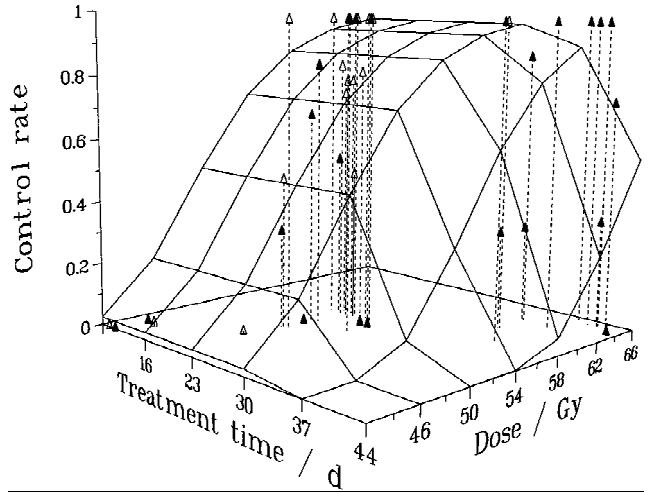


Fig. 2. Tumor control rate for T_{2+3} laryngeal cancer as a function of overall treatment time and overall dose. (Adapted from Brenner [8].) The data points, at the top of the dashed vertical lines, are the clinical results reported by Slevin et al. [7]; open data points represent T_2 tumors; and closed points are for T_3 tumors. The surface is the result of a model fit to these data. Note, in this example from external-beam radiotherapy, how tumor control does not worsen with increasing overall time until the treatment is extended beyond about 30 days.

damage repair, has also been long understood [10]. It has also been clear since the pioneering work of Coutard [11] in France that fractionating or protracting a radiotherapeutic exposure can yield a therapeutic advantage between tumor control and normal tissue sequelae. However, the exact link between these observations was not clearly made until the 1970s [12].

To understand their insight, consider the isoeffect curves in Figure 3, representing “equivalent” schemes for either early- or late-responding endpoints, as a function of treatment time. It is clear that, if the dose rate is increased (i.e., move toward the right in Fig. 3), the dose reduction needed to match late effects is larger than the dose reduction needed to match tumor control. Put another way, for a given dose, increasing the dose rate will increase late effects much more than it will increase tumor control. Conversely, decreasing the dose rate will decrease late effects much more than it will decrease tumor control. Thus, the *therapeutic ratio* (i.e., the ratio of tumor control to complications) will increase as the dose rate decreases.

Based on these notions, the lower the dose rate, the better the differential response that can be achieved between tumor control and late sequelae. Having made this observation, there has been a trend in the past few years toward high dose rate (HDR) brachytherapy, in which much higher activity sources are inserted or implanted, but for much shorter periods of time [13]. These HDR implants are sometimes given in a single fraction or, more often, with a few separate insertions.

Generally speaking, the rationale for HDR implants is based on logistical considerations, particularly the ability

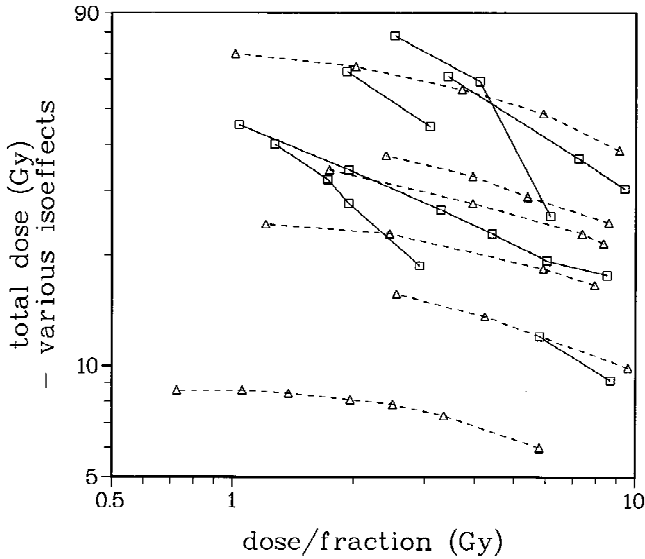


Fig. 3. Isoeffect curves showing the total dose to produce a given endpoint, plotted against dose per fraction, a surrogate, within this context, for dose rate (Adapted from Withers [12]). The triangles, joined by dashed lines, refer to a variety of different early-responding endpoints (e.g., tumor control), while the squares, joined by solid lines, refer to a variety of different late-responding sequelae. Note the generally steeper slopes of the solid lines, suggesting that late-responding tissues are more sensitive than early-responding tissues to changes in the protraction of a given radiation dose.

to treat on an outpatient basis, with the understanding that some therapeutic advantage will be lost. In many situations, such as palliative or intraoperative brachytherapy, the therapeutic ratio between tumor control and late sequelae is not a prime consideration.

In fact, there is one situation (intracavitary implants for cancer of the uterine cervix) in which, for theoretical reasons relating to the extreme insensitivity of the vaginal mucosa, HDR brachytherapy might, in principle, be as good as, or better than, LDR brachytherapy [14], and the clinical results may well bear this out [15,16]. This, however, is a single exception to the general rule that, the lower the overall dose rate, the more efficacious the treatment.

NEW DEVELOPMENTS IN BRACHYTHERAPY

The one major advance that has had the greatest influence on the re-emergence of brachytherapy in recent years has been the introduction of remote afterloaders, which have enabled implants to be given without unnecessary radiation dose to the radiotherapy and nursing staff. Fueled by this resurgence, and by our better understanding of the mechanistic rationale of brachytherapy, there have been a number of suggestions, some proposed, some now in use, to modify standard brachytherapy techniques to produce an even larger therapeutic advantage between tumor control and late sequelae.

Pulsed Brachytherapy (PDR)

The general idea here, as illustrated in Figure 4, is to simulate a continuous LDR interstitial treatment lasting

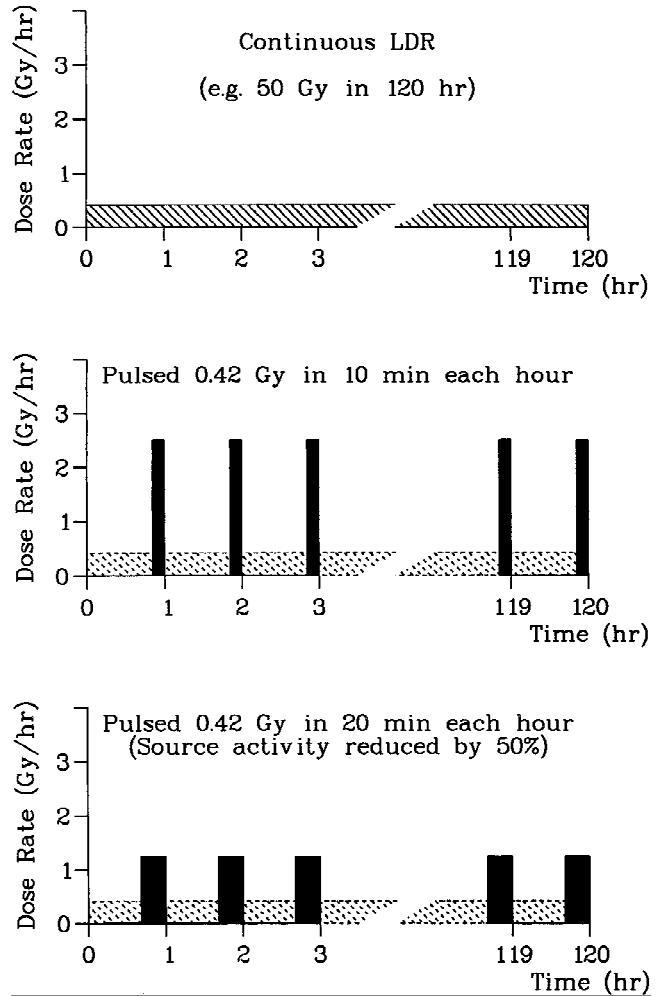


Fig. 4. Illustration of the principle of pulsed brachytherapy (PDR) and the way in which this innovation makes it possible to keep the overall dose rate constant. A continuous low dose rate of (say) 0.42 Gy/hr is replaced by pulses of 0.42 Gy delivered in (say) 10 min every hour. As the single iridium-192 source decays with a half life of 74 days, the pulse length is adjusted to maintain the dose per pulse at precisely 0.42 Gy. As a consequence, the average dose rate is maintained, and the overall treatment times for a given total dose may remain fixed.

several days with a series of short (~10 min) HDR irradiations, say, every hour. This technique is known as pulsed low dose rate (i.e., PDR). The motivation for the development of pulsed dose-rate brachytherapy (i.e., PDR), originally proposed in 1991 [17], was to exploit the advantages made possible by a computer-controlled remote afterloader technology. An irradiator based on this principle consists of a single high-activity radioactive source that, typically once each hour, steps, under computer control, through the catheters of an implant, with dwell times in each position adjusted to obtain the required dose distribution. When the source is not stepping through the implant (typically most of the time), it is retracted into its safe. PDR has a number of advantages: (1) the patient is free of radiation, typically for, say, 50 min each hour; (2) the clinic needs a much

smaller inventory of sources; (3) computer control of traversal of the source through the tumor allows for optimization of the tumor dose; and (4) it is easy to correct for radioactive source decay (e.g., change from 5-min pulses each hour to 6-min pulses), while keeping the overall treatment time fixed.

This last point is of some significance because the half-life of the radioactive isotope that is now most commonly used, iridium-192, is about 74 days. So after, say, 74 days of use, the dose rate produced by that source is halved, and thus the time to produce the same dose would be doubled. The significance here lies in the conclusion [18] that overall dose rate does have a significant effect on, particularly, late-responding normal tissues. Thus, a dose correction is needed as the overall dose rate goes down. The complication of estimating such dose correction factors can be avoided with PDR, in that a compensation for decreasing activity can simply be made by increasing the width of each hourly pulse, a change that will not affect the overall dose rate.

While PDR has prospered in Europe and elsewhere, in the United States, it has foundered on the Nuclear Regulatory Commission requirement that a physicist and/or radiotherapist be present throughout treatment.

Recent studies, however, suggest that it may well be possible to use PDR only during "office hours," by minor adjustments to the overall dose and time [19,20]. If such suggestions turn out to be practical and efficacious, PDR may well exhibit a major emergence in the United States.

Temporal Optimization

So far, the aim of PDR has been to achieve equivalence with continuous low dose rate (CLDR) in terms of cell survival and tissue response, while enjoying all the advantages of PDR enumerated earlier, such as dose optimization, radiation protection, and constant overall dose-rate.

However, it may be possible to achieve a *therapeutic gain* for PDR compared with CLDR by giving more dose in early and late pulses, and less in the intervening pulses [21]. Three developments have come together that may allow significant increases in the therapeutic ratio (tumor control versus normal tissue sequelae) in brachytherapy: (1) the development of PDR brachytherapy, discussed above, in which CLDR is replaced with a series of pulses; (2) increasing evidence that late-responding normal tissues repair sublethal damage more slowly (have a larger half-life) than early-responding tissues, such as tumors [22]; and (3) the theoretical demonstration that a difference in half-life can be exploited to increase the therapeutic ratio by temporal optimization of the dose, that is, delivering an optimized nonuniform dose rate, conveniently achievable with PDR, to the same overall dose and time as the CLDR [21].

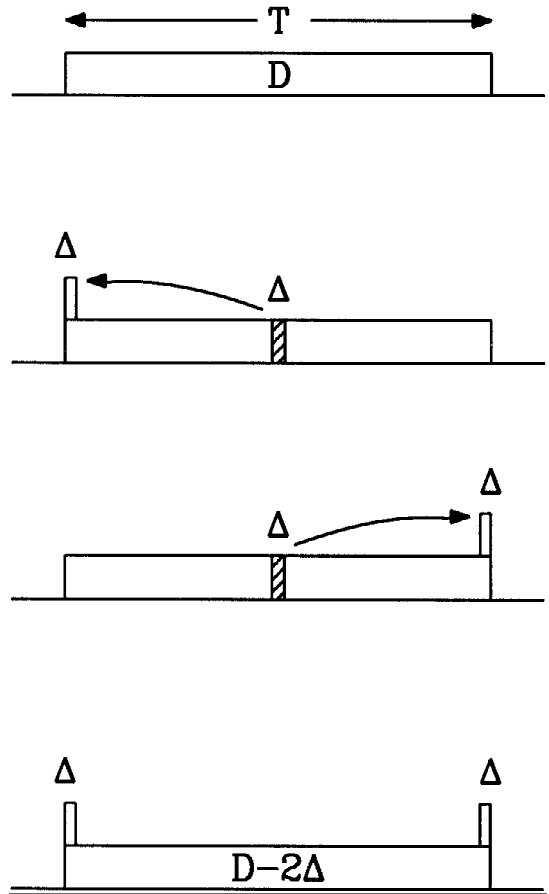


Fig. 5. Technical details of designing a maximally sparing regimen, for a given overall time and dose. Consider first a continuous low dose rate regimen (top). Now move a small amount (Δ) of the dose from the middle and put it acutely at the beginning. Whereas before, the sublethal damage produced by dose Δ could interact with sublethal damage and produced both before and after treatment, to produce lethal damage, now there is no sublethal damage produced before, so there is less chance of lethal damage. A similar argument applies to moving a small dose (Δ) to the end of treatment. This is the most sparing possible regimen for a given overall dose delivered in a given time. The value of Δ , the dose at the beginning and end of the treatment, depends on the total dose, the total time, and the half-time for sublethal damage repair ($t_{1/2}$). Because $t_{1/2}$ is likely to be different for early- and late-responding tissues, a regimen can be optimized for maximum sparing of late sequelae. This optimized regimen will produce less than maximal sparing of the tumor, producing a therapeutic advantage between tumor control and late sequelae.

Consider a CLDR protocol shown in Figure 5. An increment of dose, ΔD , in the middle of the protocol, produces sublethal damage that interacts with damage produced before and after. Suppose this increment of dose ΔD is moved to a pulse at the end of treatment: the damage produced can still interact with sublethal damage produced before, but not after. The same is true of dose moved to a pulse at the beginning of CLDR. Moving dose to pulses at the beginning and end results in "sparing" compared with CLDR. This sparing is greater for late- than for early-responding tissues (e.g., tumors) because of the slower repair rate of late-responding tissues.

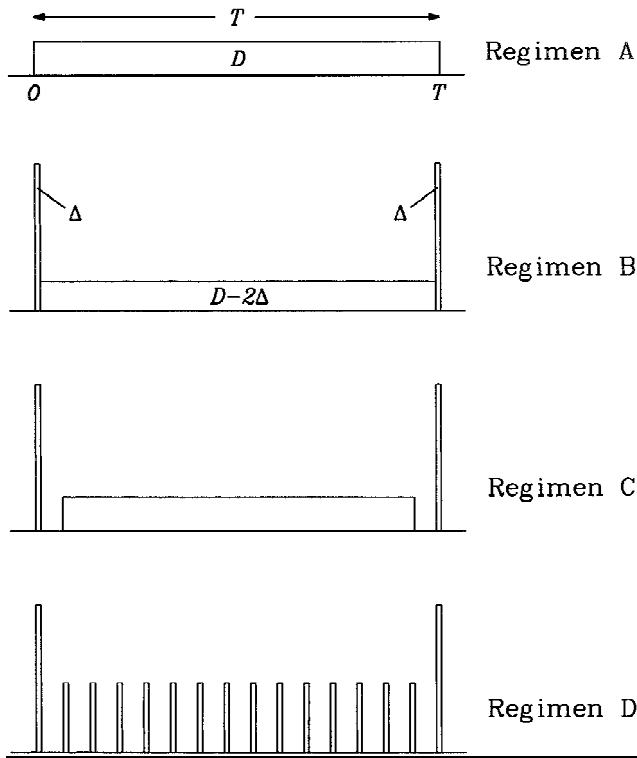


Fig. 6. Schematic representation of four different brachytherapy regimens, all of which deliver the same total dose in the same overall time. **Regimen A:** Continuous low dose rate (CLDR). **Regimen B:** CLDR with dose 2Δ removed from the CLDR portion, and an additional two dose fractions, each of magnitude Δ , delivered acutely at the beginning and end of treatment. **Regimen C:** Acute-fraction/delay/CLDR/delay/acute fraction. **Regimen D:** Multiple acute fractions (PDR), the first and last being larger than the others.

Thus, moving dose to pulses at the beginning and end of CLDR results in differential sparing of late- compared with early-responding tissues (including tumors). This technique is called *temporal optimization* [21].

The obvious strategy in practice would be to use the flexibility of the computer-controlled PDR device to replace CLDR with a series of pulses—a larger dose in the first and last pulses, and smaller doses in the intervening pulses, as shown in Figure 6. The idea has potential applications in all uses of brachytherapy, by appropriate programming of the computer-controlled pulsing afterloader. This would include interstitial implants to the breast, head, neck, or prostate, as well as intracavitary applications, such as for carcinoma of the cervix.

CONCLUSIONS

Looking to the future of brachytherapy in the United States, it is clear that (1) the use of brachytherapy is very much on the increase; (2) the stimulus was the development of remote afterloaders, but brachytherapy is the treatment of choice in many sites where there is practical access; and (3) radiobiologically, brachytherapy has significant advantages over external-beam therapy, and re-

cent developments suggest that it may have the potential to yield significantly better clinical outcomes than currently achieved.

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