

High-dose-rate and pulsed-dose-rate brachytherapy for oral cavity cancer and oropharynx cancer

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Abstract

Interstitial brachytherapy represents the treatment of choice for small tumours, regionally localized in the oral cavity and the oropharynx. In the technical setting, continuous low-dose-rate (LDR) brachytherapy represented for many years the gold standard for administering radiation in head and neck brachytherapy. Large series of head and neck cancer patients treated with LDR brachytherapy have been reported, constituting an invaluable source of clinical data and the gold standard to compare results of new techniques. Nowadays, LDR brachytherapy competes with fractionated HDR and hyperfractionated PDR. In the paper an overview of the different time-dose-fraction alternatives to LDR brachytherapy in head and neck cancer is presented, as well as the radiobiological basis of different dose-rate schedules, the linear-quadratic model, interconversion of fractionation schedules and the repair half-times for early- and late-responding tissues. In subsequent sections essentials of switching from LDR to HDR and from LDR to PDR are discussed. Selected clinical results using HDR and PDR brachytherapy in oral cavity and oropharynx cancer are presented.

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Purpose

Interstitial brachytherapy represents the treatment of choice for small tumours, regionally localized in the oral cavity and the oropharynx. In the technical setting, continuous low-dose-rate (LDR) brachytherapy represents the gold standard for administering radiation in head and neck brachytherapy [1, 2]. Large series of head and neck cancer patients treated with LDR brachytherapy have been reported, constituting an invaluable source of clinical data and the gold standard to compare results of new techniques [3, 4]. The experience in LDR brachytherapy can be summarized as a quest to optimize the therapeutic ratio by exploiting the differential response of the tumour and the surrounding organs at risk to the delivery of a tumouricidal dose of radiation over a short period of time.

Nowadays, LDR brachytherapy competes with fractionated HDR and hyperfractionated PDR. In the next section we will overview the different time-dose-fraction alternatives to LDR brachytherapy in head and neck cancer.

Radiobiological basis of different dose-rate schedules

The term dose-rate effect refers to the change in sensitivity or tissue response when the dose rate of

irradiation is modified [5]. The response of tissues to radiation is complex, depending in part on the radio-sensitivity of the clonogenic cells of the tissue, but also on the modifying effects of cell proliferation and tissue kinetics, including oxygenation and growth factors. Efforts to model radiation response and therefore predict treatment effects led to the development of the linear-quadratic method, which is the current state of the art tool to interconvert different fractionation schedules.

The linear-quadratic model

Following the Lea and Catcheside quantification of radiation action in an "in vitro" model, Barendsen's seminal paper introduced the linear-quadratic (LQ) model for calculations in radiotherapy [6, 7]. Following this first description other methods for predicting alternative fractionation schedules (nominal standard dose, time dose factor, etc.) were largely replaced by the LQ model. Following the LQ formalism, the effect (survival fraction) is written as:

$$S(D) = \exp(-\alpha D - \beta D^2) \quad (\text{eq. 1})$$

Eq. 1 reflects the mechanistic notion that cell killing results from the interaction of two units of sublethal

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damage (DNA double stand breaks), which can cause cell lethality. The two terms in eq. 1 indicate that the sublethal damage may be produced by the passage of the same track of radiation (linear component in dose) or by two different tracks (quadratic component in dose).

Recent research in radiobiology is questioning this classic assumption. However, the linear-quadratic model fits very well with the survival clonogenic assay, and is the dominant model currently available in radiotherapy.

The linear component (αD) of this dose survival relationship dominates the response at low doses and, with radiation therapy delivered in doses per fraction of the order of 2 Gy, the linear component is of major significance because little opportunity exists for accumulating β -type injury. If a series of small dose fractions is given with sufficient time for repair (a few hours or longer, depending on the tissue) between each, accumulation of sublethal injury will become insignificant. Likewise, exposure to LDR continuous irradiation results in predominantly α -type lethality because of continuous repair. Under these circumstances, the effective survival curve is linear and defined by α .

The dose range over which the linear component dominates in a linear quadratic relationship depends on the relative values of α and β . The α/β ratio defines the dose at which cell killing by linear and quadratic components are equal. The higher the relative value of α to β (the α/β ratio) the more linear is the response at low doses and the less sensitive it is to dose fractionation. If the α/β coefficient is low, the survival curve will bend down after a relatively small initial linear region; there will also be a marked sparing effect of dose fractionation on cell survival.

If some time elapses between the passage of one track and a second, sublethal damage from the first may be repaired before the production of damage from the second. This repair will result in a reduction of the quadratic term in eq. 1, which then transforms into:

$$S(D) = \exp(-\alpha D - G\beta D^2) \text{ (eq. 2)}$$

Where G is the Lea and Catcheside factor [6] denoting the possibility of the damage being repaired as a function of the temporal distribution of the dose. For acute exposures $G \rightarrow 1$ and for very long exposures $G \rightarrow 0$. In this context "acute" and "long" are defined relative to the half-time of repair of sublethal damage ($T_{1/2}$). As we will see later, knowledge of repair half-times is central for the correct usage of alternative HDR-PDR schedules.

The factor G depends on the dose per fraction, interval between fractions, dose rate at which dose is delivered and repair half-times ($T_{1/2}$). This factor G has been calculated for specific cases, but a general method for calculating G for a completely general case is also available [8].

$$G = \frac{2to/(nc)^2}{((n/(1-y)) - ((y(1-yn))/(1-y)^2))} + to \left(x + \frac{1}{x} - 2 \right) \text{ (eq. 3)}$$

Where:

$$x = \exp(-c/to)$$

$$y = \exp(-T/to)$$

$$T_{1/2} = 0.693 \text{ to}$$

$$n = \text{number of fractions}$$

$$c = \text{irradiation time (duration)}$$

$$T = \text{period between fractions}$$

Interconversion of fractionation schedules

Based on equation 2, we can try to equate schemes (produce a regimen with either the same tumour response or the same normal tissue complication rate), and thus, assuming tumour repopulation is negligible, to match a new fractionation schedule (denoted "n") to a given reference fractionation schedule (denoted "r"). Dose (D_n) can be calculated as:

$$\alpha D_r + G_r \beta D_r^2 = \alpha D_n + G_n \beta D_n^2 \text{ (eq. 4)}$$

$$\alpha/\beta D_r + G_r D_r^2 = \alpha/\beta D_n + G_n D_n^2 \text{ (eq. 5)}$$

In the design of new fractionation schedules for HDR and PDR brachytherapy, as compared to LDR brachytherapy it is important to realize the impact of the assumed values of the repair facts in the calculations of isoeffect doses. Caution must be taken in order to make calculations for alternative new time-dose-fraction patterns to be used in the clinical arena.

The repair half-times for early- and late-responding tissues

The suggestion that repair rates might be slower in late-responding compared to early-responding tissues originated from the work of Thames *et al.* [9]. In animal models they concluded that $T_{1/2}$ for the late-responding tissues were significantly greater than 1 h, whereas for the early-responding tissues, the $T_{1/2}$ were less than 1 h. This suggestion was subsequently corroborated in the clinic by analyzing the results of hyperfractionated radiotherapy. Cox *et al.* reported a definitive analysis of the results of RTOG 8313 protocol; this protocol allowed hyperfractionation intervals of 4 to 8 h, for treatment of cancers of the upper respiratory and digestive tracts [10]. The results were divided into interfraction intervals of ≤ 4.5 h vs. > 4.5 h. Both acute toxicity and tumour control were unaffected by the interfraction interval, suggesting a relatively short $T_{1/2}$ of roughly < 100 min. On the other hand, the ≤ 4.5 h group showed a significant increase in late toxicity, suggesting that repair was not complete between fractions, implying a $T_{1/2}$ of roughly > 200 min.

Further evidence from the clinic comes from the results of Turesson on early and late responding skin damage after fractionated radiotherapy [11]. The average estimated $T_{1/2}$ for moderate and severe telangiectasia was 3.4 h with 95% CI (2.8-4.2 h). In addition, they found a two-component repair process, both early and late responding damage having an estimated fast repair component of ~ 25 min. However, the slow repair for early-responding damage had an estimated $T_{1/2}$ of ~ 75 min, while the corresponding estimated slow repair for late-responding tissue was ~ 250 min, with 95% CI from 210 to 320 min.

The most recent estimation of repair rates comes from the analysis of the CHART (Continuous Hyperfractionated Accelerated Radiotherapy) protocol [12]. CHART delivered with 1.5 Gy per fraction, three fractions a day, on 12 consecutive days including the weekend, a total dose of 54 Gy. The prescribed interfraction interval of 6 h was strictly adhered to. The recently published analysis of late normal tissue morbidity for the three fractions per day CHART regimen found that repair half-times for these normal tissues are considerably longer than previously envisaged. Using Monte Carlo simulation, the estimated $T_{1/2}$ with 95% CI were between 3.8 h (2.5-4.6 h) and 4.9 h (3.2-6.4 h), depending on the endpoint evaluated. Calculations showed that those repair half-times are consistent with the observations from two published randomized trials of altered fractionation in head and neck cancer, the EORTC 22791 and 22851. These results are extremely important in the design of multiple fractions-per-day brachytherapy schedules.

Switching from LDR to HDR

The dose-rate effects for LDR brachytherapy can be derived from retrospective analysis from the iridium implant era data. Mazon *et al.* studied the local control and toxicity (necrosis) in a large series of patients treated for oral tongue and floor of the mouth cancer using a standardized implantation technique based on the Paris system [13, 14]. For prescribed doses in the range of 65-70 Gy, there was little or no difference in local control regardless of the dose rate, but there is a clear separation at lower doses (around 60 Gy) with lower dose rates (below 0.5 Gy/h) being significantly less effective. On the other hand, over the entire range of prescribed doses, there was a higher incidence of necrosis in the range of higher dose rate (above 0.5 Gy/h).

It is currently accepted that the migration from LDR to HDR must generally involve a loss in the therapeutic ratio. Invoking the LQ formalism, if an HDR dose is calculated using equation 4, based on producing equal tumour control to an LDR regime, that HDR dose will not be iso-effective in terms of late effects, but it will produce increased late injuries. Conversely, if an HDR dose is calculated to produce less tumour control than the corresponding LDR regime, the HDR dose would be expected to produce less tumour control than the corresponding LDR regime. To overcome this loss in the therapeutic ratio, fractionation has been advocated and has become the standard practice when prescribing HDR brachytherapy, in order to keep the dose-response curves for LDR and HDR closer, exploiting the differences in the α/β ratios in normal and tumour tissues. A number of theoretical papers have been published, trying to compare from a radiobiological point of view the differences between LDR and HDR.

Orton *et al.* used the LQ model to compare late-effect biologically effective doses (BEDs) of LDR and HDR, for constant BED to the tumour [15]. The effects of dose rate (for LDR) and fractionation (for HDR) were considered. Repair half-times observed in the CHART study were used to investigate the potential impact of long repair times on

the comparison of LDR and HDR. They show that, for a repair half-time of 1.5 h for tumour cells, if the repair half-time for late-reacting normal tissue cells exceeds about 2.5 h, LDR becomes radiobiologically inferior to HDR. Even with the least HDR-favourable combinations of parameters, HDR at over about 5 Gy/fraction ought to be radiobiologically superior to LDR at 0.5 Gy/h, so long as the time between HDR fractions is long compared to the repair half-time. Some limitations are however pointed out in this article. First is the possibility that repair is not a simple monoexponential function of time, but is either biphasic, with a fast and a slow component, or is a second order process, which gradually slows as treatment time (and dose) increases. The second limitation to this analysis is the lack of clinical data supporting these data in interstitial brachytherapy.

Sminia *et al.* further investigate the existence of a "window of opportunity" for HDR [16]. They used the LQ model for incomplete mono-exponential repair for constant α/β for tumour and normal tissues of 10 Gy and 3 Gy respectively. Different repair half-times were tested both for normal tissues and tumours. Therapeutic gain (TG), expressed as the ratio BEDHDR/BEDLDR, for normal tissues (NT) and tumours (TUM) was calculated and compared. They found that TG is dependent on the HDR fraction size (or number of fractions), overall treatment time and repair characteristics (α/β and repair half-time) of the exposed tissues. These latest parameters can only be estimated from experimental and clinical data. In conclusion, the "window of opportunity" for fractionated HDR (or PDR) depends both on whether half-times are really longer in the relevant normal tissues than in tumours, which is not definite, and on adequate planning of fraction size and interfraction interval, which is under our control.

Pop *et al.* introduce a note of caution regarding mathematical modelling based on uncertain knowledge of tissue kinetics [17]. They stressed the impact on isoeffect dose calculations of using parameters (repair half-times) derived from cells in culture or hyperfractionated external beam irradiation and the potential pitfall of adopting radiobiological parameters and applying these values in current models for the design of new treatment schedules to be used in clinical practice.

Clinical results using HDR brachytherapy in oral cavity and oropharynx cancer

Reports of the use of HDR brachytherapy for radical treatment of head and neck cancer are scarce, and no consensus exists about safety of dose fractionation schedules and results in terms of local control and toxicity. The American Brachytherapy Society has recognized that only limited experience exists with HDR brachytherapy in patients with head-and-neck cancers. Therefore, some of the suggested fractionation schedules have not been extensively tested in clinical practice [18]. We will review the available experience of the use of HDR brachytherapy in oral cavity and oropharynx cancer.

Donath *et al.* reported their experience using HDR for head and neck cancer either as exclusive treatment or

postoperatively [19]. Exclusive brachytherapy was used in 13 patients with T1-2 N0 malignancies. A total of ten fractions of 4.5-5.0 Gy each were delivered twice a day with a minimum of 5-6 h between treatments. Brachytherapy was applied in a post-operative adjuvant setting (16 cases) following wide local excision of tumours in patients who presented with recurrent disease or a second primary in the head and neck. All patients had previously received external irradiation to the head and neck. The treatment schedule consisted of eight fractions of 3.0 Gy each, for a total of 24 Gy over a period of 4 days. Reported results for the two groups were preliminary. No actuarial analysis was reported.

A Phase I/II protocol using high-dose-rate (HDR) interstitial brachytherapy for early stage node-negative squamous cell carcinoma of the mobile tongue to assess the toxicity and efficacy of this modality was reported by Lau *et al.* [20]. A total of 27 patients were treated: T1 – 10 patients, T2 – 15 patients, and T3 – 2 patients. Seven fractions of 6.5 Gy of HDR brachytherapy were given on a twice-daily schedule, with a minimum interval time of 6 h, over a period of 3.5 days. The actuarial tumour control probability after HDR brachytherapy was 53% at 5 years. Local control rates for the T1 and T2 tumours were lower than comparable historical controls treated at the same institution using low-dose-rate (LDR) radium or caesium needle implants and iridium wire implants. This is despite the fact that the HDR schedule was calculated by the linear quadratic formula to have equal tumour killing effects as 60 Gy in 6 days of LDR radiation. In addition, there was a trend towards higher incidence of severe complications for the HDR patients compared to historical controls treated with LDR.

Levendag *et al.* reported the results in soft palate and tonsillar fossa tumours of 38 patients using fractionated high-dose-rate (fr.HDR, 19 patients) and pulsed-dose-rate (PDR, 19 patients) brachytherapy (BT) regimens, which simulate classical continuous low-dose-rate (LDR) interstitial radiation therapy (IRT) schedules [21]. The fr.HDR schedule entailed twice-daily fractions of ≥ 3 Gy. PDR consisted of pulses of ≤ 2 Gy delivered 4-8 times/day. The median cumulative dose of IRT \pm ERT series was 66 Gy (range 55-73). The results in these patients treated by brachytherapy were compared to 72 patients with similar tumours treated in the same institute with curative intent, using ERT alone. The median cumulative dose of ERT-only series was 70 Gy (range 40-77). Excellent locoregional control was achieved with the use of IRT \pm ERT, with only 13% (5 of 38) developing local failure. Neither BT scheme (fr.HDR vs. PDR) nor tumour site (TF vs. SP) significantly influenced local control rates. The type and severity of the side effects observed are comparable to those reported in the literature for LDR-IRT. Using Cox proportional hazard analysis, T stage and BEDcor10 (biological effective dose with a correction for the OTT) were significant prognostic factors for local relapse-free survival (LRFS) and overall survival (OS) at 3 years. When compared with the historical (ERT-only) controls, the patients treated with IRT had superior local control.

Combined external beam radiotherapy plus HDR brachytherapy proved to be feasible in a study involving 55 patients with oral cavity and oropharynx tumours [22]. Median HDR prescribed dose was 16.8 Gy. Forty-two patients were treated at 1.2 Gy per fraction, 3 patients at 1.5 Gy, 8 patients at 2 Gy and 1 each at 2.5 Gy and 5 Gy. One patient received one fraction per day, 39 received two fractions per day and 15 patients received tid (tri-fractionated). After a median follow-up of 2.7 years crude osteoradionecrosis rate was 7% and actuarial 2-year control for the entire cohort was 79%.

Inoue *et al.* reported the only phase III trial comparing exclusive LDR vs. HDR brachytherapy in head and neck neoplasms [23]. They reported 51 eligible patients (LDR: 26 patients, HDR: 25 patients). LDR brachytherapy was administered using Ir192 with a median dose rate of 0.6 Gy/h. Median prescribed dose was 70 Gy. For the HDR group the fractionation schedule was 6 Gy per fraction, two fractions a day with interfraction interval > 6 h, for a total dose of 60 Gy. Five and seven year local control rates for LDR and HDR groups were 84% and 87% and 77% and 87% respectively ($p = \text{NS}$).

Retrospective non-randomized comparisons between LDR and LDR brachytherapy for T3 oral tongue cancers showed no differences between the two groups [24]. For patients treated with brachytherapy alone, the total dose was 59-94 Gy (median 72 Gy) within one week in LDR and 60 Gy in 10 fractions over 5 days in HDR. For combination therapy the total dose was 12.5-60 Gy (median 30 Gy) of EBRT and 50-112 Gy (median 68 Gy) within 1 week in LDR or 32-60 Gy (median 48 Gy) in 8-10 fractions over 5-7 days in HDR. The 2- and 3-year local control rates of all patients were both 68%. The 2- and 3-year local control rates of patients treated with LDR were both 67%, and those with HDR were both 71%. Toxicity profile was similar in both treatment groups.

Leung *et al.* evaluate the outcomes of 19 patients (T1N0: 10 patients, T2N0: 9 patients) with early stage oral tongue cancer treated exclusively by HDR interstitial implant [25]. The median dose given was 55 Gy in 10 fractions over 6 days. The minimal interfraction interval was 7 hours for the first 7 patients and was extended to 8 hours for the others. After a median follow-up time of 43 months (range 6-78 months) one patient had local failure, and the 4-year local failure-free survival rate was 94.7%.

Nose *et al.* reported the experience with high-dose-rate interstitial brachytherapy in oropharyngeal squamous cell carcinomas [26]. Eighty-two patients (83 lesions) were reported; 76 were previously untreated and 6 displayed previous history of head and neck cancer. External radiotherapy of 46 Gy was combined with 21 Gy/3-5 fractions/2 days HDRIB for 68 lesions, and 48 Gy/8 fractions/5 days HDRIB alone was used for 15 lesions. Involved nodes were either boosted by external radiotherapy or resected. Using this schedule, five-year local control, regional control, cause-specific and overall survival rates were 82%, 84%, 88%, and 64%, respectively. Local control rates for early (T1/T2) and advanced (T3/T4) tumours were 89% and 66%, respectively ($p = 0.02$). The authors reported no excess of toxicity using HDR

interstitial brachytherapy: transient soft tissue necrosis was experienced in 29% of patients. No bone sequelae were observed in previously untreated patients.

Petera *et al.* evaluated preliminary results in a small group of oral cancer patients treated by HDR BT [27]. The treatment schedule for exclusive brachytherapy (10 treatments, for T1-2N0 tumours and recurrences) was 18 fractions of 3 Gy twice daily. The treatment schedule for combined treatment (7 patients, for T2-3 N0-2 tumours) was external beam radiotherapy (40-68 Gy) and brachytherapy (2-6 fractions of 3 Gy twice daily). After a median follow-up of 17 months (8-46), 15 patients were disease free.

Interstitial high-dose-rate brachytherapy has been studied recently in patients with recurrent head and neck cancers [28]. The dose and fractionation schedules used were 3.4 Gy twice per day (b.i.d.) to 34 Gy for post-operative cases, 4 Gy b.i.d. to 20 Gy when combined with 40-50 Gy external beam, and 4 Gy b.i.d. to 40 Gy for definitive treatment. Good local control was achieved. The 2-year LC and overall survival outcomes for the entire group were 71% and 63%, respectively. Patients treated with surgical resection and HDRBT had an improved 2-year LC compared to the patients treated with HDRBT \pm external beam radiation alone (88% vs. 40%, $p = 0.05$). Six grade II and four grade III complications were noted in five patients, all observed in the postoperative HDRBT group.

The combination of perioperative HDR brachytherapy with external beam radiotherapy for the treatment of squamous carcinoma of the oropharynx and oral cavity has been explored in a recent paper by Martínez-Monge *et al.* [29]. The treatment schedule was 4 Gy b.i.d. \times 4 fractions (16 Gy) for R0 resections and 4 Gy b.i.d. \times 6 fractions (24 Gy) for R1 resections, respectively. External beam radiotherapy (45 Gy in 25 fractions) was added postoperatively. Patients with stage III, IVa tumours, and some recurrent cases received concomitant cisplatin-paclitaxel chemotherapy during EBRT. After a median follow-up of 50 months for living patients (range 2.5-86.1), the 7-year actuarial rates of local and locoregional control were 86% and 82%, respectively; and the 7-year disease-free survival and overall survival rates were 50.4% and 52.3%, respectively. Severe complications were more frequent in posteriorly located implants than in anterior implants. Eleven patients (27.5%) developed RTOG grade 3 or greater toxicity. Four patients (10%) presented complications requiring a major surgical procedure (RTOG 4), and one patient died of bleeding (RTOG 5). Three complications (7.5%) occurred in the perioperative period, and 8 (20.0%) occurred more than 3 months after the completion of the treatment programme.

Another recent paper evaluated efficacy and toxicity associated with external beam radiation therapy (EBRT) and interstitial high-dose-rate brachytherapy (IHDRBT) for the treatment of squamous carcinoma of the oropharynx and oral cavity [30]. EBRT (median dose of 50 Gy) to the primary tumour and regional lymph nodes was followed by brachytherapy. Node-positive patients with residual neck disease also underwent neck dissection. Brachytherapy dose (HDR) varied from 14 to 21 Gy,

3-3.5 Gy per fraction, two fractions daily. Local control (including surgical salvage) was 100% and 78% for early and advanced disease, respectively ($p < 0.108$). No major toxicity was associated with this treatment schedule.

In conclusion, from the available evidence it seems that HDR brachytherapy is a feasible and effective way to deliver a dose to treat oral cavity and oropharynx cancer. However, there are some considerations to be made with HDR literature: first, dose prescription and fractionation schedules are very heterogeneous, making comparison very difficult, even with the use of the LQ formalism to calculate equivalences. Second, toxicity reporting is often expressed in crude rates, without actuarial analysis, making comparison with the reference LDR series difficult.

Switching from LDR to PDR

With adaptation to the mechanics developed for high dose rate (HDR), pulsed-dose-rate brachytherapy (PDR) was proposed as a method to replace continuous low dose rate (LDR) assuming radiobiological equivalence. PDR brachytherapy theoretically combines the isodose optimization and physical advantages of high-dose-rate brachytherapy with the biological advantages of continuous low-dose-rate brachytherapy.

Pulsed-dose-rate brachytherapy creates a dose-rate condition that is different from both HDR and LDR. The first assumption which remains to be tested is that a dose delivered to a given volume as a brief pulse of a single stepping source, at a very high instantaneous dose rate, is biologically equivalent to the same average dose delivered continuously by a series of static sources at a much lower instantaneous dose rate. The second assumption is that the dose is relatively equivalent in terms of its effect both on early-reacting tissues (including tumour) and on late-reacting tissues. Are these total doses (one continuous, one pulsed) equivalent over the range of half-times of tissue repair that are clinically relevant in the surrounding normal tissues?

Calculations on the basis of the LQ model have been focused on the possible radiobiological equivalence between common continuous low-dose-rate irradiation (LDR) and superfractionated irradiation (PDR) provided that the same total dose will be prescribed in the same overall time as with the low dose rate [31-33]. A clinically usable fractionation scheme for brachytherapy was recommended by Brenner and Hall [31] and should replace the classical LDR brachytherapy with line sources with an afterloading technique using a stepping source. Using biological data of 36 cell lines of human origin and the linear-quadratic model, it was calculated that a pulse width of 10 min with a period between the pulses of 60 min would be appropriate and that for late effects this method might produce a negligible 2% increase in late-effect probability. Based on these mathematical models, if the repair half-time for late effects were a few hours and repair half-time for early effect a few minutes, PDR would produce a better therapeutic ratio between tumour control (early effect) and late effects than would LDR [34].

Other authors have reached similar conclusions [33]. Assuming monoexponential repair for the beta component,

various pulse regimes were calculated (with dose rates in the pulse varying from 0.5 to 1.2 Gy per hour and pulses delivered every 1-4 h) on early-responding and late-responding tissues, using a wide range of possible half-times of repair from 0.1 to 3 h. Duration and total dose of the implant were kept at 70 Gy in 140 h, and all effects were considered relative to a continuous regimen at 0.5 Gy/h. Looking first at early-reacting (normal and tumour) tissues, biological effectiveness would not be expected to increase by more than 3% if dose rates remained in the 0.5-3 Gy/h range and pulses were given hourly, regardless of the assumed $T_{1/2}$. As the dose per pulse and interval duration increase, the biological effectiveness also increases for all $T_{1/2}$. This is true for late-reacting tissues as well. If intervals increase to one pulse per 4 h, the biological effect in late tissue may increase as much as 15%. Tissues with the shortest $T_{1/2}$ of repair would be at greatest risk. This would necessitate a decrease in the overall dose to sustain levels of late effects similar to those seen with LDR regimens, a decrease which would result in a less-than-desired effectiveness for tumour control. They show that there is no significant loss of therapeutic ratio, defined as tumour damage for a given level of late damage. When dose per pulse is increased, some loss of therapeutic ratio would be expected, but even though repair is not usually complete between pulses, the relative increase of late damage (in units proportional to log cell kill) is less than 10% more than the increase of tumour damage, except in some conditions far removed from clinical practice. Their calculations suggest that pulsed brachytherapy should be safe for pulse repetition frequencies up to about 2 h, using dose rates not exceeding about 3 Gy/h.

Fowler and Van Limbergen [35] expounded further upon the conditions of equivalence between pulsed and continuous low-dose-rate brachytherapy. They emphasized that a volume of tissue around a PDR source receives doses radiobiologically within the high-dose-rate range. This varies, according to the activity of the source, from a radius of 11 mm around a 0.3 Ci source, to 20 mm around a 1 Ci source. This is the approximate range of source strengths we employed (0.28 to 0.95 Ci). This condition would be expected to increase the radiobiological effect, both in tissues with short repair half-times and in tissues with small alpha-beta ratios. One could imagine this volume of high-dose-rate brachytherapy around a pulsed-dose-rate source causing either more damage to a tumour with rapid repair, or more damage to late-responding normal tissues. They compared 70 Gy delivered over 140 h at a continuous dose rate of 0.5 Gy/h (standard treatment) with several pulsed schedules. They concluded that about 75% of the total dose is delivered at HDR in a PDR implant of moderate volume, decreasing to 40% when the source decays from 1 to 0.3 Ci. Even so, restricting the dose per pulse to 0.5-0.6 Gy should avoid ratios of increased effect larger than about 10%.

Daytime-only schedules that would result in the same tumour control probability as a given continuous regimen have been reported [36]. The "daytime" schedule concept was compelled by a Nuclear Regulatory Commission requirement that a physician, physicist, or other qualified

person be present throughout treatment. The models base their predictions upon linear-quadratic and sublethal damage repair rate parameters, and provide evidence that PDR brachytherapy could even result in an improved therapeutic ratio (similar control rate with fewer complications) over corresponding continuous schedules. This appears to be particularly true if the relevant late-effect sublethal damage repair rates are more than 1 hour, a condition for which persuasive evidence exists.

Clinical results using PDR brachytherapy in oral cavity and oropharynx cancer

Although theoretical and experimental evidence suggests that under certain conditions PDR and LDR irradiation are biologically equivalent, articles reporting clinical results in head and neck cancers treated with PDR brachytherapy are scarce in the literature. The investigators reported limited series of cancer patients with clinical outcomes apparently comparable to those of previous series using LDR brachytherapy. However, it is worthy of mention that the reported follow-up in most PDR series is too short in comparison with LDR standard treatments.

A French multicentric study to evaluate the feasibility of pulsed-dose-rate (PDR) brachytherapy to mimic the continuous low-dose-rate (LDR) iridium wire technique in head and neck carcinomas has been reported [37]. A series of 30 patients was evaluated: oral cavity (four T1, seven T2 and two T3), velotonsillar arch (eight T1 and eight T2) and the posterior wall (one T3). Thirteen were irradiated by exclusive brachytherapy (dose ≥ 45 Gy). The PDR delivered 0.5 Gy/pulse, one pulse/h, day and night, to mimic LDR irradiation. The implantation was feasible for all the patients, usually easy and of good quality. Patient tolerance was poor in nine cases. Sixteen patients could receive the whole PDR treatment with a total ranging from 30 to 120 pulses without any problem. Seven had short breakdowns (≤ 6 h). Seven had definitive breakdowns, but could end the irradiation by manual afterloading of iridium 192 wires. The radioprotection was better (or complete), except for one patient. Most of the breakdowns were related to kinking or fluttering of the tube. The authors conclude that PDR is feasible in head and neck carcinomas, but necessitates improvement of the quality and control of the plastic tube technique.

Levendag *et al.* [21] reported the experience with fractionated high-dose-rate (fHDR) and pulsed-dose-rate (PDR) brachytherapy alone or in combination with external beam radiotherapy (EBRT) in squamous cell carcinoma of the tonsillar fossa (TF) and/or soft palate (SP). Of 38 patients, 19 were treated with fHDR, which involved twice-daily fractions of ≥ 3 Gy. The other 19 patients were administered PDR, which consisted of pulses of ≤ 2 Gy delivered 4-8 times/day. The median cumulative dose (BT + EBRT) was 66 Gy (range, 55-73 months). The results in these patients were compared to 72 patients with similar characteristics treated at the same institution, using EBRT only (with a median dose of 70 Gy), which served as a control. The results show local control of 87% in the BT-EBRT group vs. 61% in the EBRT only group. Multivariate analysis showed tumour stage (T in the TNM classification)

and BEDcor10 (biological effective dose corrected for overall treatment time) significant for local relapse-free survival. Toxicity was comparable to those reported in the literature for LDR.

In Germany, the Erlangen group published their extended experience using PDR in the treatment of head and neck tumours. In the first series they reported the results of 40 patients treated with PDR brachytherapy after limited surgery [38]. Of this group, 24 patients received exclusive PDR brachytherapy (prescribed dose, 50 Gy) and 23 patients received combined EBRT and PDR brachytherapy (prescribed dose, 24 Gy; dose per pulse 0.5-0.7 Gy, hourly, day and night). After a median follow-up of 12 months (range 5-18 months) one patient developed soft tissue necroses and another patient mandible necroses. Local control was achieved in 37 out of the 40 patients.

In a second paper the authors evaluate the efficacy of a combination of PDR brachytherapy with chemotherapy and hyperthermia in patients with local relapse from a head and neck neoplasm [39]. Fifteen patients treated with PDR brachytherapy (median dose 55 Gy, dose per pulse 0.46-0.55 Gy) concomitant with CDDP (20 mg/m² daily) and 5-FU (800 mg/m² continuous infusion for the duration of brachytherapy). After finishing brachytherapy, a single session of interstitial hyperthermia was administered. Treatment was well tolerated. One patient developed soft tissue necroses. After a median follow-up of 6 months, local control rate was 80% (12 of 15 patients) and 2-year actuarial overall survival was 67%.

Ziemlewski *et al.* [40] report the experience using PDR brachytherapy in 45 head and neck cancer patients. All underwent interstitial or contact PDR at a median dose of 70 Gy with a dose per pulse ranging between 0.6 and 1.0 Gy per pulse, hourly. Forty-two patients were administered BT as part of their curative treatment; 32 of them had sole BT. Three re-irradiated patients with recurrent tumour had palliative BT. Grade 3 toxicity of skin and oral mucosa occurred in three (6.8%) and six patients (13.6%), respectively. At a median follow-up of 22 months (range 2-67 months), late serious toxicity (grade 4, for soft tissue and bone) was seen in seven patients (15.9%). Late toxicity was correlated with larger irradiated volumes.

In conclusion, PDR brachytherapy seems to be a feasible technique, but more studies and longer follow-up are needed in order to adequately validate this technique.

Conclusions

LDR brachytherapy plays a major role in the management of head and neck cancer: the local control rate is high and the complication rate is low, achieving a good therapeutic ratio. This treatment is well tolerated by the patient and can be delivered in a short period of time. Hundreds of patients successfully treated are the benchmark to which other treatment modalities have to be compared. New technological developments now offer new modalities for delivering brachytherapy. Those new technologies exploit the use of a single high-activity stepping source controlled by a computer. Radiation protection is complete for the patient, family and staff and

dosimetry can be optimized in a new way not possible with classic linear iridium wires. However, high activity sources create dose-rate conditions that are different from LDR, making necessary new, more precise radiobiological tools for schedule inter-comparison and longer follow-up for the clinical series, in order to assess the exact role of these new modalities in the management of head and neck neoplasms.

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