PULSED DOSE RATE BRACHYTHERAPY – DESCRIPTION OF A METHOD AND A REVIEW OF CLINICAL APPLICATIONS

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SUMMARY

Pulsed Dose Rate (PDR) treatment is a new brachytherapy modality that combines physical advantages of high-dose-rate (HDR) technology (isodose optimization and radiation safety) with radiobiological advantages of low-dose-rate (LDR) brachytherapy.

Pulsed brachytherapy uses a stronger radiation source than that employed in LDR brachytherapy and provides a series of short 10 to 30 minutes long exposures every hour amounting to approximately the same total dose in the same overall as that administered in the LDR.

Modern afterloading equipment offers some advantages over interstitial or intracavitary insertion of separate needles, tubes, seeds or wires. Isodose volumes in tissue can be created flexibly by a combination of careful positioning of the catheter and by adjusting the dwell times of the computerized stepping source. Automatic removal of radiation sources into a shielded safe eliminates radiation exposures to staff and visitors. Radiation exposure is also eliminated to the staff who previously loaded and unloaded a large variety of radioactive sources into the catheters, ovoids, tubes etc.

This review, based on summarized clinical investigations, analyses the feasibility, differences between methods of brachytherapy and preliminary clinical applications of PDR brachytherapy.

Key words: PDR brachytherapy, method of treatment, clinical applications.

INTRODUCTION

The efficacy of brachytherapy, as compared with the efficacy of external beam alone, is attributable to the ability of radioactive implants to deliver a higher concentrated radiation dose more precisely to tissues, which contributes to improved local control, provided that the tissue is clinically delimitable and accessible. At the same time, the surrounding healthy tissues are spared irradiation. In contrast to external-beam irradiation, brachytherapy is invasive, requiring insertion of site-specific applicators under sedation or anaesthesia. The surgeon who is sometimes involved in these procedures, particularly if laparotomy or craniotomy is required for the insertion of applicators, or if tumour resection is required prior to applicator insertion, should be aware of the indications for brachytherapy and the associated techniques [1,2,3].

Brachytherapy, with modern afterloading equipment, offers three major advantages over interstitial or intracavitary insertion of separate needles, tubes, seeds or wires:

(1) Isodose volumes in tissue can be created at will by a combination of careful placement of the catheter and adjustment of the dwell times of the computerized stepping source. This process is usually called “dose optimization”.

(2) Automatic removal of radiation sources into a shielded safe whenever somebody enters the room eliminates radiation exposures to staff and visitors.

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(3) Radiation exposure is also eliminated to the staff who previously loaded and unloaded a large variety of radioactive sources into catheters, ovoids, tubes etc [1,4,5,6,7].

Low Dose Rate (LDR) remote afterloading systems certainly give radiation protection, but do not provide as much flexibility in the design of alter native isodose volumes as that obtained with higher dose rate sources with adjustable stepping positions and dwell times.

At the other end of the spectrum of brachytherapy methods is the use of High Dose Rate (HDR) afterloading with a single source of 192 Ir moved by computer to a series of dwell positions. In that case the choice of isodose volume is very flexible. Large doses can be given within a few minutes. Sources of that kind require well-shielded bunkers similar to linear accelerator rooms.

One radiobiological disadvantage in the use of such high dose rates, of 1-3 Gy/min (greater ratio of late tissue effects), can in practice be overcome by careful placement of catheters and by good immobility achievable with very short exposures.

Pulsed Dose Rate (PDR) treatment is a recent brachytherapy modality that combines physical advantages of high-dose-rate (HDR) technology (isodose optimization, planning flexibility and radiation safety) with radiobiological advantages of low-dose-rate (LDR) brachytherapy (repair advantages).

DESCRIPTION OF A METHOD

PDR was first used in San Francisco in 1992. There are 4 PDR microSelectrons in use in Poland now: in Gdańsk, Gliwice, Kraków and in Poznań.

PDR uses a single stepping ^{192}Iridium source of 15-37 GBq (0,5 – 1Ci). This produces treatment dose rates of up to about 3 Gy per hour, which can be utilized (pulsed) every hour, 24 pulses per day.

The source is enclosed in a 2,5 mm long capsule 1.1 mm in diameter. Treatment times can be programmed from 0 to 999.9 seconds per position per pulse. The single radioactive stepping source moves through all the implanted catheters during each pulse. A typical pulse length lasts 10 minutes per hour, which may be increased to approximately 30 minutes three month later when the ^{192}Ir source has decayed.

Pulsed brachytherapy uses a stronger radiation source than that employed in LDR brachytherapy and gives a series of short 10 to 30 minute exposure long every hour amounting to approximately the same total dose in the same overall time as that in LDR *(Fig. 1).*

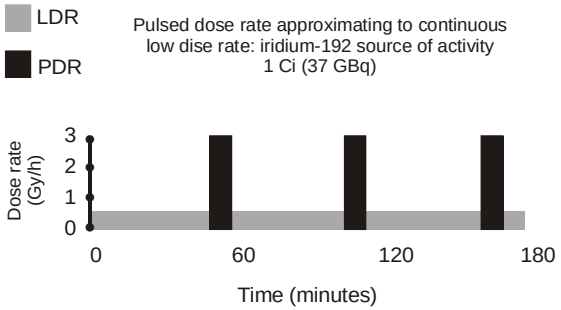


Fig. 1. Illustration of the principle of pulsed brachytherapy. A continuous low dose rate of 0,5 Gy/h is replaced by a pulse of 0,5 Gy delivered in 10 minutes. As a single iridium192 source decays with the half-life of 74 days, the pulse length is adjusted to maintain the dose per pulse to be precisely 0,5 Gy. Thus, the average dose rate is maintained and the overall treatment time for a given total dose remains fixed.

The trajectory of a single high activity source through the implanted catheter can be precisely programmed by a dedicated computer and carried out by a remote source projector.

The resulting isodoses can be optimized by modulating the dwell time of the source as a function of its trajectory within the implanted volume. This allows individualization of dose distributions, while essentially eliminating radiation exposure to the medical staff.

The source strength is 10 to 20 times lower than that used in HDR, and the requirements for shielding are less stringent. An ordinary brachytherapy room would require less than two extra half, value thickness of protection, and an accelerator type bunker is not necessary.

Nursing care is facilitated compared with LDR brachytherapy, since patients can be attended between the treatment sessions, without concern about problems of radioprotection.

RADIOBIOLOGY OF PULSED BRACHYTHERAPY

Gaps between pulses allow greater freedom for the patient and increase safety for nursing staff. However, in principle, any move away from continuous exposure towards treatment with gaps involves some radiobiological disadvantage. Pulsed brachytherapy is equivalent to fractionation with a larger dose per fraction, and the theoretical and experimental evidence that this procedure will lead to a relative increase in the late normal-tissue reactions is strong. The magnitude of this effect has been considered by Brenner and Hall, who concluded that for gaps between pulses of up to 60 minutes the radiobiological deficit may be acceptable [8].

In PDR brachytherapy each pulse delivers a small dose and is followed by an interval which allows some repair, the increase in the radiobiological effect being small. However, the main question is whether the increased effect is greater in late-responding normal tissues than in tumour cell kill.

To reproduce the biological effects of LDR brachytherapy using PDR remote afterloading Brenner i Hall [8] and Fowler i Mount [9] offer the following four recommendations:

(1) same total dose,
(2) same dose rate: typically about 0,5 Gy/hour,
(3) pulse length of 10 minutes or more (or dose rate not exceeding 3 Gy/hour during the pulse), and
(4) pulse repeated each hour: typically 0,4 - 1,0 Gy/ hour.

If these conditions are met, the biological effects of PDR radiation therapy should be equivalent to those of LDR radiation therapy for all tissues.

The above conclusions were drawn from calculations taking into account both the cell repair capacity (estimated by alpha/beta) and the kinetics of repair (estimated by $T_{1/2}$), for tumours and late-reacting normal tissues. The alpha/beta value for tumours and late reacting human tissues have been estimated and are consistent with laboratory results using experimental models. By contrast, due to the lack of clinical data, $T_{1/2}$ has been estimated from experimental data [10].

However, it is likely that early-responding tissues, such as tumours, repair sublethal damage more rapidly than do late-responding tissues. In 1996, Brenner and Hall exploited this difference to design new therapeutic regimens. They estimated, using a $T_{1/2}$ of 0,5 hours for early-responding tissues and 4 hours for late-responding, that PDR brachytherapy delivering series of pulses separated by 3-4 hours should produce better results than LDR brachytherapy [11,12,13].

Advantages of PDR

(1) Full radiation protection,
(2) No source preparation,
(3) No source inventory,
(4) Optimization of the dose rate distribution,
(5) Only one source to replace every three months, and
(6) All brachytherapy feasible with one machine: intracavitary, interstitial, intraoperative, intraluminal.

Limitations of PDR

PDR treatment has a certain number of practical limitations:

(1) The maximum number of needles that can be implanted is limited by the number of afterloading channels: 18 in case of the PDR MicroSelectron,
(2) Only one person per day can be treated,
(3) Another disadvantage of the system compared with LDR is the presence of connecting tubes between the machine and the needles (catheters), the weight of which may cause some discomfort to the patient, and
(4) Finally, the multiple source transfers may result in treatment irregularities due to source blockages, particularly in the case of implanted plastic tubes.

Although the PDR approach has been the subject of numerous theoretical papers, and afterloading machines modified for PDR treatments have been commercially available for several years, very little data have been published

regarding on the clinical experience with these techniques.

CONCLUSIONS

PDR brachytherapy offers several advantages over conventional LDR brachytherapy:

(1) The distribution of radiation doses can be more easily controlled and tailored permitting the following improvements:
   (a) more precise application (then LDR) of the prescribed dose to the treatment volume,
   (b) better reproducibility of treatment plans,
   (c) greater flexibility to change the dose distribution through the course of treatment if necessary,
(2) Improved radiation safety for clinical and physics staff,
(3) Only one source to replace every three months, and
(4) All brachytherapy procedure feasible with one machine: intracavitary, interstitial, intraoperative and intraluminal.

Compared with HDR brachytherapy

(1) PDR offers similar quality of treatment,
(2) Similar treatment procedure and technical verification,
(3) Improved radiation safety for clinical and physics staff,
(4) Requirements for shielding are less stringent - an accelerator type bunker is not necessary,
(5) Theoretical radiobiological advantage: the technique allows some repair in late-reacting normal tissue due to intervals between pulses,
(6) patient comfort is believed to be worse, and
(7) few indications for palliative treatment.

Clinical feasibility studies are in progress. Summarized indications and prescribed doses are presented in Table 1 and 2 *(Table 1, 2).*

Table 1. Clinical applications and proposed doses.

TUMOUR (method of treatment)	TOTAL DOSE	PULSE DOSE	TOTAL TIME
1/ oesophagus: *-palliative* *-combined with EBRT*	*2x 16 - 20 Gy* *20 Gy*	*0,4 - 0,6 Gy* *0,5 Gy*	*40 - 50 h* *20 h*
2/ bronchus: *-palliative* *-palliative (II)* *-combined with EBRT*	*1x,2x 25 Gy* *10 - 15 Gy* *5 - 12 Gy*	*0,5 - 0,6 Gy/0,5 h* *1 - 1,5 Gy* *0,5 - 0,6 Gy/0,5 h*	*25 h* *10 -15 h* *5 - 10 h*
3/ gynaecology: *-radically* *-combined with EBRT*	*4x-5x 60 Gy* *2x 20 - 30 Gy*	*0,4 - 0,5 Gy* *0,4 - 0,5 Gy*	*120 - 150 h* *50 - 60 h*
4/ breast: *-"boost"* *-combined with EBRT in LABC*	*10 - 25 Gy* *20 - 30 Gy*	*0,5 - 1,0 Gy* *0,5 - 1,0 Gy*	*10 - 25 h* *20 - 30 h*
5/ HAN: *-palliative* *-combined with EBRT*	*2x 20 - 30 Gy* *2x 20 Gy*	*0,5 Gy* *0,5 Gy*	*40 - 60 h* *40 h*
6/ anus, rectum: *-radically* *-combined with EBRT*	*4-5x 60 - 70 Gy* *2x 16 - 20 Gy*	*0,4 - 0,5 Gy* *0,4 - 0,5 Gy*	*120 - 140 h* *40 h*

HAN - Head and Neck tumors
LABC - Locally advanced breast cancer
EBRT – External radiotherapy

Table 2. Indications for PDR-brachytherapy in different tumours (based on published researches).

Localization	Indications		Contrindications
	Radical treatment	Palliative treatment	
1/ Esophageal cancer (1, 2, 5, 6, 14)	1st and 2nd clinical stage – patients disqualified from surgical treatment because of: (a) localization (b) medical contrindications (c) loss of patients consent	Patients with: (1) dysphagia (2) in advanced age (3) with cachexia (4) with distant metastases (5) with recurrence after teletherapy (6) with progression after teletherapy	(1) infiltration of cardiae (2) broncho-esophageal fistula
2/ Lung cancer (1, 2, 5, 14)	(1) "boost" after teletherapy (2) clinical stage of T1-2 N1-2 M0	(1) recurrence after teletherapy (2) patients with non squmaous cell cancer disqualified from radical teletherapy, with dyspnoea due to bronchial or tracheal obturation	(1) tumour localized in extern part of the lung (2) Pancoast tumour (3) syndrom of venae cavae superior (4) massive haemoptysis
3/ Gynecological tumors (1, 2, 15, 16, 17)	Indications like those in LDR brachytherapy	Indications like those in LDR brachytherapy	
4/ Breast cancer (1, 2, 18, 19)	**I. "Boost" after teletherapy in breast-sparing surgical treatment (lumpectomy, quadrantectomy)** Condition: separate cutting for tumorectomy and lymphadenectomy (a) brachytherapy as a "boost" after teletherapy (b) brachytherapy before teletherapy (catheters are implanted during surgery) is performed two weeks after surgery **II. Brachytherapy connected with teletherapy in local advanced breast cancer (excluding T4)** Patients previously treated with chemotherapy, disqualified for surgery		Localization of tumour at a shorter distance than 1 cm from skin surface or ribbs - excluding ductal carcinoma "in situ" - in this case treatment plan should include papilla and areola of the mamma
5/ HAN tumours (1, 2, 20, 21, 22)	(1) radical, independent treatment (2) complementary treatment after non radical surgical treatment (3) "boost" after teletherapy	(1) palliative treatment of recurrence after teletherapy	
6/ Rectal, anal cancer (1, 2, 23, 24, 25)	(1) Clinical stage – T1, T2 i N0 – brachytherapy optionally to surgery (2) in more advanced tumours – combined treatment: chemotherapy (5-Fu, Mitomycyna C) + teletherapy (40 – 50 Gy), then brachytherapy after two months interval (due to slow regression of tumour and necrosis prophylaxis)		

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