PDR BRACHYTHERAPY: A REPORT ON ONE – YEAR CLINICAL EXPERIENCE AT THE MEDICAL UNIVERSITY OF GDAŃSK

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Received January 26th, 2001; received in a revised form Jule 2nd, 2001; accepted August 30th, 2001

SUMMARY

Purpose: One-year clinical experience with pulse dose rate (PDR) brachytherapy is presented.
Material and methods: Between March 1999 and June 2000 intracavitary, intraluminal, and interstitial PDR brachytherapy was performed in 119 patients with a variety of malignancies. The dose per pulse of 0.5-4 Gy, repeated each hour, or 6 Gy per application was administered, up to the total dose of 6-70 Gy, using a microSelectron-PDR remote afterloading system with a ^{192}Ir source of 1 Ci nominal activity. The planning system PLATO BPS (version 13) was used for dose calculations. Depending on individual applications, the algorithms of the dose point, the geometrical volume, or the geometrical point dose distribution optimization in PDR treatment planning were performed. In 40 patients therapy was given with a curative intent, and 74 cases were treated palliatively. In the remaining five patients PDR was applied as salvage therapy in the previously irradiated area.
Results: With a median follow-up of 11 months (range 1-18 months) local control was maintained until the last follow-up or death in 39 out of 40 patients treated with radical intent. The subjective improvement was achieved in more than a half of patients with advanced esophageal and lung carcinomas presenting dysphagia and dyspnoe. Significant acute toxicity (severe esophagitis precluding subsequent PDR application) occurred in only one patient. Delayed vaginal cuff necrosis was observed in one woman who received prior pelvic irradiation for gynaecological cancer.
Conclusion: The PDR brachytherapy is a safe and clinically effective method in a variety of malignancies. The possibility of programme optimization combined with the use of relatively wide range of pulse doses makes it possible to deliver an optimal brachytherapy scheme.

Key words: Pulsed dose rate brachytherapy, toxicity, palliative treatment, radiotherapy.

INTRODUCTION

Recent technical and radiobiological developments have led to the improvement of brachytherapy methods.
This progress is particularly due to the development of modern afterloading equipment and miniaturisition of ^{192}Ir stepping sources for afterloading machines. Moreover, advances in the threedimentional (3D) treatment planning software incorporated computerized tomography information which helped to define target and critical volumes in conformal brachytherapy. Another advantage was improved radiation protection of the staff and visitors.

Modern brachytherapy uses remote afterloading devices with a single cable-driven radioactive source, moved through a series of positions within an implanted volume, or a set of intracavitary instruments. The source stops for a specified period of time, at a selected number of locations during its transit, and delivers a cumulative dose to the entire volume. In pulsed dose rate (PDR) brachytherapy this cumulative dose consists of a series of small doses (pulses) delivered at a given frequency over a period of hours or days.

Proceedings of the Conference "Brachytherapy 2000", Jurata, Poland, 6 – 7 October 2000.
This study was performed as a part of "MARIA 98" Project supported by a grant from the Foundation for Polish Science (contract no. 1/98).

PDR remote afterloading systems arose as a compromise between low dose rate (LDR) and high dose rate (HDR) remote afterloading systems. This method offers several advantages. Radiobiologically it resembles LDR brachytherapy but at the same time, it helps to optimize isodose distributions. The latter aim is achieved by manipulating the location and number of source-stopping ("dwell") positions, as well as by various periods the source spends at each dwell position within the implanted array.

The nominal activity of a single ^{192}Ir source is 1 Ci or less, which enables a PDR remote afterloading system to be installed in existing or only modified shielded rooms suitable for LDR brachytherapy. Radiobiologic data suggest that PDR therapy and traditional continuous LDR therapy, if delivered with the same total dose and dose rate, produce similar biological effects for both acute- and late-reacting tissues [1, 4, 7]. According to these theoretical calculations and in vitro studies, the recommended dose rate should be lower than 1 Gy (typically 0.5 – 0.6 Gy/hr), the pulse duration should be 10 minutes or more (or a dose rate not exceeding 3 Gy/hr during a pulse), and the pulses should be repeated every hour [3, 9, 10].

PDR brachytherapy was initiated at the Department of Oncology and Radiotherapy, Medical University of Gdańsk, in March 1999. We have been using a microSelectron-PDR remote afterloading machine with a ^{192}Ir stepping source enclosed in a capsule 1.1 mm in diameter and 2.5 mm long, and of 1 Ci activity at installation.

Here we report on our own early experience with this technique.

MATERIALS AND METHODS

Between March 16, 1999 and June 30, 2000 intracavitary, intraluminal and interstitial PDR brachytherapy was performed in a total of 119 patients *(Table 1)*. PDR treatments were prescribed as an exclusive modality or in combination with external beam therapy (EBRT). In 40 patients, PDR was given with a curative intent, and 74 cases were treated palliatively. In the remaining 5 patients, PDR was applied as a salvage therapy in the previously irradiated area. PDR procedures were performed using one pulse per hour with the dose per pulse of 0.5-3 Gy in cases treated with definitive irradiation and re-irradiated, and 1-4 Gy per pulse in cases treated palliatively. Another method used a total dose of 6 Gy in one prolonged pulse. The pulse duration was 5-90 minutes, depending on the volume of the implant or insertion, prescribed dose, and the source activity at the time of the procedure. Source-dwell interval in the applicator was usually 2.5 mm, whereas 5 mm interval was used only occasionally.

Table 1. Tumor site distribution and PDR treatment characteristics.

Site	Indication/intent	Number of cases	Dose/pulse (Gy)	Target dose (Gy)
Esophagus	Palliative	31	1	12-40
Lung	Palliative/Radical	20	3, 6	6-27
Breast	Boost after EBRT	20	1	10-20
Gynecological	Radical/Postoperative	13	1-6	6-50
	Palliative	5	0.6-6	12-45
Head and neck	Radical	8	0.6-1	15-70
Miscellaneous	Palliative/Postoperative	15	0.5-1	9-30

Computer-assisted treatment planning was performed based on orthogonal radiographs, with the applicator(s) in place. The planning system PLATO BPS (version 13) was used to obtain satisfactory dose distributions. The treatment plan was optimized for each application based on the algorithm

of the dose point, the geometrical volume, or the geometrical point dose distribution. The Paris system rules for interstitial implants were used. The clinical target volume was determined with at least 1 cm safety margins around the gross tumour volume, as detected by clinical findings and additional imaging data.

Intra-operatively placed interstitial implants using plastic catheters were used in three cases of abdominal/pelvic cancer. In these situations, the PDR procedure started one to two days after the catheter implantation. A CT-guided stereotactic navigation system was used for interstitial implants in five cases of intracranial tumours. The breast implant templates were placed under both local or general anaesthesia. All patients were carefully supervised by a dedicated nurse during the entire time of application.

Treatment toxicity was scored with the use of an RTOG/EORTC scale.

Lung and esophageal cancer

All but one of the 20 patients with lung cancer and 31 patients with esophageal cancer were treated palliatively to control troublesome symptoms, in particular dysphagia and dyspnoe. Fifteen patients with lung cancer and ten patients with esophageal cancer received external beam radiotherapy (EBRT), usually hypofractionated. The laser therapy prior to PDR was applied in 12 cases of esophageal carcinoma. In most cases, two weekly (range 1-3) intraluminal applications were used. Standard treatment programmers were employed for a single intraluminal catheter. This policy enabled the PDR treatment take started imme-diately after the installation of the appli-cator and after checking the radiographs. The dose was normalized to the dose point at 10 mm distance from the center of the active part of the applicator.

One patient with intraepithelial bronchial carcinoma received three PDR intraluminal placements with a dose of 9 Gy each (3Gy/pulse/h), as a part of planned definitive radiotherapy. This patient refused further treatment.

Breast cancer

Breast cancer PDR interstitial breast implantations with doses of 10-20 Gy (1 Gy/pulse/hr) as a boost to EBRT with the dose of 50-60 Gy, were applied in four patients with locally advanced breast cancer, and in 16 patients with early breast cancer as a part of breast-conserving therapy. Typically, double-plane interstitial breast implants with both flexible or rigid tubes were made. Dose calculation and specification followed the rules of the Paris system, in which rigid tubes are used. In cases with flexible tubes, volume optimized dose distributions was applied.

Gynaecological malignancies

PDR brachytherapy was applied in 18 patients including seven patients, with cervical cancer, and 11 with endometrial cancer. The PDR technique, instead of LDR caesium applications routinely used by us in gynaecological malignancies, was employed in cases with medical contraindications to prolonged immobilization and in patients who refused LDR brachytherapy due to the longer treatment time. PDR was also applied in all patients reirradiated to the pelvis, with increased risk of radiation-induced morbidity. In 11 cases PDR was a part of definitive radiotherapy; two endometrial cancer cases received postoperative vaginal cuff irradiation, and the remaining five patients were irradiated for vaginal recurrence of endometrial or cervical cancer. Four cases of the latter group received prior radical irradiation to the pelvis. The carefully prescribed total doses of 6-50 Gy (median 25 Gy), and the dose per pulse of 0.6, 1.0, 2.0 or 2.5 Gy, were typically used. In four cases, in order to shorten the overall treatment time, a dose of 4 or 6 Gy per pulse was administered. A total of 10 applications using Simon catheters (four to nine in each insertion) at a dose of 7.5 Gy or 10 Gy were made in four endometrial cancer patients, either applied alone or combined with EBRT. The Simon catheter applications were used weekly or twice a week.

Head and neck cancer

PDR implants were made in five patients with lip carcinoma and in two patients with buccal carcinoma. Two or three flexible catheters were used, and 1 Gy/pulse

to 60-70 Gy total dose was given. The PDR boost of 15 Gy (0.6 Gy/pulse) was administered in one patient with a residual tumour after 60 Gy EBRT squamous carcinoma of the hard palate. The mould was constructed to accommodate three flexible tubes.

Re-irradiation

A total of five PDR procedures of 30-35 Gy (0.6 Gy/pulse) were performed in previously irradiated sites. These included four gynaecological vaginal applications and one intra-operatively placed pelvic implant in a patient with rectal cancer. Prior definitive radiotherapy in this group included EBRT and intracavitary brachytherapy in three, and EBRT alone in two cases. Earlier therapy was performed 2, 4, and 18 years earlier.

Miscellaneous tumours

These included cranial tumours, both primary and metastastic, urethral cancer, prostate cancer, bile duct cancer, rectal cancer, and malignant melanoma. Different techniques of application and different doses were used in this group of patients.

RESULTS

At the time of this analysis (January 2001), all breast cancer patients were alive, with no evidence of disease for a median of 11 months (range of 6 to 15 months). Postirradiation skin changes in the boost area (minimum teleangiectasia at puncture sites) appeared in only one patient. Six of the eight head and neck cancer patients were alive with no evidence of disease at 9 to 17 months follow-up. One patient developed nodal recurrence without local recurrence 3 months after the PDR treatment. This patient is alive without evidence of disease after 60 Gy EBRT to the region of disease recurrence. Local disease progression was observed in one patient 6 months after combined EBRT and PDR therapy for hard palate cancer. Eleven of the 18 gynaecological cancer patients remained free of disease for a period of 6-13 months, three patients died of disease progression 7, 10, and 15 months after treatment, respectively, two patients died due to intercurrent disease, and one was lost to in the follow-up. No local recurrence during the follow-up of 7 and 11 months was observed in three out of five re-irradiated patients. The remaining two patients died due to a progressive pelvic disease. The palliative effect was achieved in 61% and 50% of cases with esophageal and lung cancer, respectively. This effect lasted for 1 to 8 months. The subsequent PDR application for symptomatic recurrence was given in three patients (one lung cancer and two esoghageal cancers). The second application was made 6, 9 and 11 months after the first PDR treatment. No evidence of cancer for a period of 8 months was observed in a patient treated for the intraepithelial bronchial carcinoma.

In most instances, PDR brachytherapy was well tolerated and in all but one case there were no severe acute reactions. One patient developed esophageal mucositis (grade 4 RTOG/EORTC scale) precluding subsequent PDR application. Mild confluent mucositis and moderate desquamation were seen in patients treated for lip and buccal carcinomas. This damage resolved after 2-3 weeks. In one patient previously irradiated to the pelvic region with a dose of 60 Gy the vaginal cuff necrosis occurred after the PDR treatment and has persisted for 11 months.

Displacement of the intraluminal tube occured in two patients with esophageal carcinoma. Additionally, there were relatively frequent minor problems and breakdowns during PDR treatment. The most common problem was related to the great curvature of plastic tubes which did not make it possible to load check cable. Because of major failures we had to seek occasionally the manufacturers advice.

DISCUSSION

Due to the small number of cases in cohorts and the short follow-up, this study has focused on acute reactions, technical feasibility and patient tolerance of PDR brachytherapy. No severe acute toxicity was observed in all but one patient who had PDR intracavitary, intraluminal and interstitial brachytherapy administered with radical and palliative intent.

The possibility of disconnecting the patient from the machine during the "quiescent" period is of great importance for patient's comfort.

The first pulsed LDR Selectron from Nucletron Corporation was installed at the University of California, San Francisco in early 1992. Since then several studies have been reported on PDR brachytherapy in many cancer sites including pelvis, head and neck, and breast [9, 11, 13, 14, 15, 16]. These studies confirmed that PDR may replace traditional continuous LDR brachytherapy. No significant increase in toxicity above that seen with the standard continuous LDR approach, and excellent local control in patients treated with PDR have been reported, although the need for a longer follow-up required for full assessment of this modality has been recognized [13,16]. This technique is expected to be at least as clinically efficacious (in terms of both tumor control and late sequelae) as the continuous LDR regimen [6].

As the damage to late reacting tissues is closely related to the brachytherapy dose rate, the PDR technique should be taken into consideration in all patients who had been re-irradiated [5, 12]. To minimize the risk of complications the dose rate of 0.4 – 0.6 Gy per pulse is preferable in such patients.

The PDR system makes it possible to change the dose rate from a pulsed low dose rate to a continuous medium/high dose rate. As our institution is equipped with only one additional LDR/MDR unit for gynaecological applications, PDR treatment was also performed in an attempt to minimize the duration of the treatment time. Short immobilization is particularly useful in elderly and frail gynaecological patients. Moreover, the PDR system provides the delivery of a relatively high dose in a short time in cases treated with palliative intent.

The relatively high source activity requires the assistance of additional staff, and this economic aspect should be taken into the account. Daytime- only schedules (i.e. "extended office hours" – 8 a.m. to 8 p.m., with no irradiation overnight) are therefore considered [2].

To achieve equivalence between the LDR and PDR irradiation regimens, the total dose using both techniques should be administered with the same overall time [1, 8]. This involves the need for prolonged installation of applicators and, in consequence, – extended patient immobilization. The intermittent nature of the radiation leads, however, to greater patients comfort, and closer contacts with his or her family and the staff.

A common technical problem accompanying PDR applications is kinking or flattening of the tubes inside or outside the patient (including the connection between the catheter and the transfer tube). We have also experienced several situations when the incorrect transfer of the check cable occurred, which resulted in a delay in the treatment onset or subsequent breakdowns. To alleviate this problem, semi-rigid catheters have been introduced. Another technical problem accompanying PDR therapy involves large curvature of plastic tubes precluding transfer of the source. This problem may appear in cases treated with a loop technique, commonly used in head and neck cancer patients.

CONCLUSIONS

The PDR brachytherapy has been shown to offer a reliable, safe and clinically effective method for both radical and palliative management. This procedure is suitable in almost all tumor localizations. The optimization of treatment planning programs combined with the possibility of using a relatively wide range of doses delivered per pulse help to obtain adaptation of brachytherapy to specific needs. No major problems are encountered while using a micro-Selectron PDR unit. For the evaluation of clinical results a longer follow-up is needed.

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