Role of Interstitial PDR Brachytherapy in the Treatment of Oral and Oropharyngeal Cancer

A Single-Institute Experience of 236 Patients

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Purpose: To evaluate the role of pulsed-dose-rate interstitial brachytherapy (PDR IBT) in patients with head-and-neck malignancies.
Patients and Methods: From October 1997 to December 2003, 236 patients underwent PDR IBT for head-and-neck cancer at the authors' department. 192 patients received brachytherapy as part of their curative treatment regimen after minimal non-mutilating surgery, 44 patients were treated with irradiation alone. 144 patients had sole IBT (median D_{REF} = 56 Gy), in 92 patients IBT procedures (median D_{REF} = 24 Gy) were performed in combination with external irradiation. The pulses (0.4–0.7 Gy/h) were delivered 24 h a day with a time interval of 1 h between two pulses. The analysis of tumor control, survival and treatment-related toxicity was performed after a median follow-up of 26 months (6–75 months).
Results: At the time of analysis permanent local tumor control was registered in 208 of 236 patients (88%). At 5 years overall survival and local recurrence-free survival of the entire group were 82–73% and 93–83% for T1/2, and 56% and 83% for T3/4, respectively. Soft-tissue necrosis was seen in 23/236 patients (9.7%) and bone necrosis in 17/236 patients (7.2%). No other serious side effects were observed.
Conclusions: PDR IBT with 0.4–0.7 Gy/h and 1 h between pulses is safe and effective. These results confirm that PDR IBT of head-and-neck cancer is comparable with low-dose-rate (LDR) brachytherapy – equally effective and less toxic.

Stellenwert der interstitiellen PDR-Brachytherapie in der Behandlung von Mundhöhlen- und Oropharynxkarzinom

Ziel: Untersuchung des Stellenwerts der interstitiellen Pulsed-Dose-Rate-Brachytherapie (PDR-IBT) bei Patienten mit HNO-Tumoren.
Patienten und Methodik: Zwischen Oktober 1997 und Dezember 2003 wurden insgesamt 236 HNO-Patienten mit PDR-IBT in der eigenen Klinik behandelt. 192 Patienten wurden in kurativer Intention nach einer minimal-invasiven Chirurgie, 44 Patienten mit alleiniger Strahlentherapie behandelt. 144 Patienten erhielten eine alleinige IBT (Median D_{REF} = 56 Gy), bei 92% wurde die Brachytherapie (Median D_{REF} = 24 Gy) mit perkutaner Strahlentherapie kombiniert. Die Pulsdosis (0,4–0,7 Gy/h) wurde stündlich 24 h am Tag verabreicht. Die Analyse der Tumorkontrolle, des Überlebens und der Nebenwirkungen wurde nach einem medianen Beobachtungszeitraum von 26 Monaten (6–75 Monate) durchgeführt.
Ergebnisse: Zur Zeit der Analyse wurde bei 208 von 236 Patienten (88%) eine dauerhafte lokale Tumorkontrolle registriert. Das 5-Jahres-Gesamtüberleben und das rezidivfreie Überleben für alle Patienten betrugen bei T1/2 82–73% und 93–83% und für T3/T4 56% und 83%. Weichteilnekrosen fanden sich bei 23 von 236 Patienten (9,7%) und Osteoradionekrosen bei 17 von 236 Patienten (7,2%). Es wurden keine weiteren schwerwiegenden Nebenwirkungen registriert.
Schlussfolgerung: Die PDR-IBT mit 0,4–0,7 Gy/h und einem Intervall zwischen den Pulsen von 1 h ist eine sichere und effektive Behandlung. Diese Ergebnisse bestätigen, dass die PDR-IBT bei HNO-Tumoren der Low-Dose-Rate-(LDR-)Brachytherapie vergleichbar ist – gleich effektiv und weniger toxisch.

Schlüsselwörter: PDR-Brachytherapie · HNO-Tumoren

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Introduction

Interstitial brachytherapy (IBT) alone or as boost combined with external-beam therapy as definitive treatment modality or as postoperative therapy is indicated in the treatment of both primary and recurrent head-and-neck cancer. The results of low-dose-rate (LDR) brachytherapy with iridium-192 (^{192}Ir) wires using the rules of the Paris system are considered, up to now, the gold standard in the therapy of preferably small head-and-neck tumors, particularly in comparison with high-dose-rate (HDR) brachytherapy results [20, 21, 25, 27, 28, 41]. Pulsed-dose-rate (PDR) brachytherapy as a substitute for LDR brachytherapy is considered a useful option in the treatment of head-and-neck tumors, because here, the biological advantages of LDR brachytherapy meet with the technological advantages of the HDR afterloading method [21, 26, 35, 39].

This paper presents a single-institute experience of 236 patients with a special emphasis on the relative incidence of local control rate and late toxicity in patients with squamous cell carcinoma of the oral cavity and of the oropharynx who underwent PDR IBT preferably after minimal, non-mutilating surgery.

Patients and Methods

From October 1997 to December 2003, 236 patients had PDR IBT for head-and-neck cancer. 192 patients received brachytherapy as part of their curative treatment regimen after minimal non-mutilating surgery, 44 patients were treated exclusively with brachytherapy.

Patient characteristics and distribution in regard to tumor sites and tumor stage (Table 1) show that the majority of the patients had tumors of the oral cavity (72%) and that only a minority of our patients was treated with small tumors (T1 = 38%). In addition, some unfavorable prognostic parameters were presented by a relevant number of our patients: tumor grade G3 in 20% (47/236 patients), lymph vessel invasion present (L1) in 20% (47/236 patients) and close or positive resection margins – microscopic (R1) or macroscopic (R2) residual tumors were found in 11% (26/236 patients) and 17% (41/236 patients), respectively, before we started IBT. As inclusion criteria for IBT after surgery we defined any tumor with a size between 2 and 4–5 cm without significant bone infiltration and all tumors sized < 2 cm (T1) with infiltration depth of > 5 mm or with lymphangiosis (L1) or grading 3. An additional external-beam irradiation was performed in patients with positive neck lymph nodes or unknown lymph node state.

Brachytherapy was preceded by surgery in 192/236 patients (81%). The surgical procedures included different kinds of surgery (for details see Table 2). All patients received PDR IBT with or without external-beam irradiation. All implants were done under general anesthesia using plastic tubes afterloaded with ^{192}Ir with a source strength (air kerma rate, Ka.100) in the range of 1.2 mGy·m^2/h < Ka.100 < 4.8 mGy·m^2/h.

Table 1. T-, N-classification of all 236 patients.

Tabelle 1. T-, N-Klassifikation bei allen 236 Patienten.

Tumor site	Tumor (number of patients) T1	T2	T3	T4	Tx	Total
Lip	4	3	0	0	0	7
Floor of mouth	38	18	2	8	1	67
Oral tongue	36	54	7	2	4	103
Base of tongue	1	13	5	4	2	25
Tonsil	6	9	3	1	0	19
Soft palate	3	3	0	0	0	6
Others	2	3	1	1	2	9
Total	90	103	18	16	9	236

Tumor site	Lymph nodes (number of patients) N0	N1	N2	Nx	Total
Lip	7	0	0	0	7
Floor of mouth	54	6	6	1	67
Oral tongue	69	19	11	4	103
Base of tongue	12	6	6	1	25
Tonsil	7	4	8	0	19
Soft palate	4	0	1	1	6
Others	8	0	0	1	9
Total	161	35	32	8	236

The implant method respecting the rules of Paris system was described in detail earlier [37, 39]. A dose per pulse (d_p) in a median value of 0.55 Gy (range: 0.4–0.7 Gy) was prescribed. For dose specification and prescription the rules were used similar to the Paris system. Thus, the d_p of 0.4–0.7 Gy corresponded to our reference dose (D_{REF}), which was prescribed at 85% of the mean central dose. A d_p > 0.55 Gy was used in exceptional cases for logistic reasons in only 29/236 patients (12%). The pulses were delivered for 24 h per day with a time interval of 1 h between the pulses. The volume of the 85% isodose (V_{85}) was about 24 cm^3 with a 120% and 150% isodose volume (V_{120}, V_{150}) of approximately 6.5 cm^3 and 3.5 cm^3, respectively. The dose homogeneity index (DHI) values and the uniformity index (UI) were about 0.76 and 1.72, respectively (Table 3).

144/236 patients (61%) had IBT procedures alone using a median total dose of 55.6 Gy (range: 50–64 Gy). In combination with external-beam therapy the IBT procedures (92/236, 39%) were performed using a median total dose of D_{REF} = 24 Gy (range: 14–51.7 Gy). The median time interval between external irradiation and brachytherapy was 10 days. External-beam irradiation was performed up to a median reference dose of 51 Gy (range: 4–72 Gy) using a linear accelerator with 6-MV photons. The treatment volume usually included the primary

Table 2a. Type of surgery in all 236 patients.

Tabelle 2a. Art der chirurgischen Eingriffe bei allen 236 Patienten.

Tumor site	Type of surgery (number of patients) Biopsy only (no surgery)	Tumor resection only	Tumor resection and neck dissection	Tumor resection and lymph node sampling	Tumor resection with plastic reconstruction	Tumor resection with plastic reconstruction and neck dissection	Tumor debulking only	Total
Lip	5	0	1	1	0	0	0	7
Floor of mouth	6	9	39	0	4	9	0	67
Oral tongue	19	12	63	2	0	6	1	103
Base of tongue	9	6	9	0	0	1	0	25
Tonsil	3	1	15	0	0	0	0	19
Soft palate	0	2	3	0	0	1	0	6
Others	1	4	3	0	0	1	0	9
Total	43	34	133	3	4	18	1	236

Table 2b. State of resection margins in all 236 patients. Ro: clear resection margins; R1: microscopically positive resection margins; R2: macroscopically positive resection margins (no surgery); Rx: resection margins not known.

Tabelle 2b. Zustand der Resektionsränder bei allen 236 Patienten. Ro: freie Resektionsränder; R1: mikroskopisch positive Resektionsränder; R2: makroskopisch positive Resektionsränder (keine Chirurgie); Rx: Resektionsränder nicht bekannt.

Tumor site	R-state R0	R1	R2	Rx	Total
Lip	2	1	3	1	7
Floor of mouth	54	6	6	1	67
Oral tongue	75	9	19	0	103
Base of tongue	11	4	9	1	25
Tonsil	12	4	3	0	19
Soft palate	6	0	0	0	6
Others	6	2	1	0	9
Total	166	26	41	3	236

tumor site and comprehensive regional lymph nodes, generally using opposed lateral field matched to an anteroposterior supraclavicular field. 21/236 patients (8.9%) with recurrent tumors were treated with additional interstitial hyperthermia (single session, > 40 °C for 1 h). 29/236 patients with recurrent tumors also received simultaneous chemotherapy during brachytherapy – most often, cisplatin/5-fluorouracil (5-FU; 19 patients) or carboplatin/5-FU (five patients) combination was selected; three patients were treated with mitomycin C/5-FU combination and two patients with carboplatin only.

The statistical analysis was performed with SPSS 11.5 software. The actuarial curves were calculated according to the Kaplan-Meier method. The comparisons were made using log-rank test or Cox regression analysis or Kruskal-Wallis test as appropriate. All patients were followed closely to analyze

Table 3. Selected brachytherapy parameters. DHI: dose homogeneity index; UI: uniformity index.

Tabelle 3. Ausgewählte Brachytherapieparameter. DHI: „dose homogeneity index"; UI: „uniformity index".

	V_{85}	V_{100}	V_{120}	V_{150}	DHI	UI
Mean	24.42	15.47	6.79	3.61	0.74	1.73
Median	23.5	15	6.4	3.5	0.76	1.72
Standard deviation	11.94	7.97	3.34	1.52	0.071	0.26
Minimum	0.43	0.35	0.1	0.05	0.34	1
Maximum	58.2	37.9	20.8	8.2	0.92	2.73

local control, survival, acute and late toxicity according RTOG/EORTC criteria. No patient was lost to follow-up. The analysis was performed after a median follow-up of 26 months (6–75 months). The median follow-up was calculated from the first day of radiation therapy to the date of last follow-up.

Results

The 5-year overall and local relapse-free survival rates of the entire group were 71.4% and 85.7%, respectively (Figure 1). At the time of analysis local tumor control was registered in 208 of 236 patients (88%). Most local recurrences developed in the first 18 months after therapy with a plateau apparent after 20 months (Figure 1b), the mean time to local recurrence was 9.2 months (median 9.5 months, 2–34 months).

The 5-year overall survival rates of the entire group according to tumor size and lymph node metastases were: 90.8% for T1 N0, 81.5% for T1 N+, 72.7% for T2 N0, 44.1% for T2 N+, 62.8% for T3/4 N0, and 56.3% for T3/4 N+. The only prognostic factor for overall survival in N+ patients was tumor size ($p = 0.04$).

The 5-year local recurrence-free survival rates of the entire group according to tumor size and lymph node metastases were: 86.2% for T1 N0, 92.9% for T1 N+, 82.9% for T2 N0,

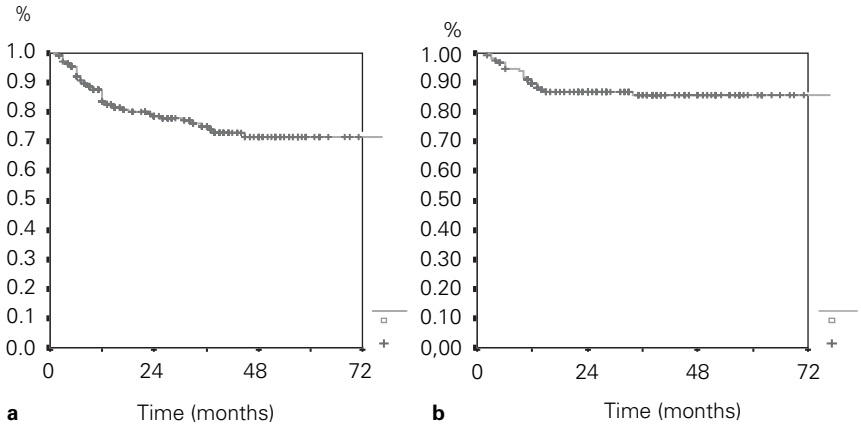
91.9% for T2 N+, 63.5% for T3/4 N0, and 83.3% for T3/4 N+.

The analysis according to tumor site showed, that the 5-year local recurrence-free survival rates for patients with lip carcinoma were 100%; for patients with oral cavity carcinoma: 90.9% for T1 N0, 92.9% for T2 N0, 80% for T1 N+, 75% for T2 N+, 80% for T3/4 N0, and 66.7% for T3/4 N+ (not significant); for patients with oropharynx carcinoma: 80% for T1 N0, 100% for T2 N0, 100% for T1 N+, 100% for T2 N+, 80% for T3/4 N0, and 90% for T3/4 N+. The differences in patients with oropharynx cancer without or with lymph node metastases were also without any statistical significance and, in our opinion, were only due to the small number of patients in these subgroups. In the detailed analysis of subsets of each tumor localization we observed that in oropharynx cancer, the best results were achieved by tonsil cancer and the worst by base of tongue cancer patients (Figure 3), again without significant differences. Also in oral cavity cancer patients the tumor localization did not significantly influence treatment results (Figure 2).

No tumor or treatment factors were significantly correlated with the development of local recurrence. The 5-year local relapse-free survival rates for patients receiving brachytherapy only or external-beam irradiation were 82.6% and 90.0% ($p = 0.16$), respectively. Similarly, the kind of surgery (Tables 2a and 2b) – particularly clear resection margins (R0), R1 resection margins and no surgery (R2) – did not influence the 5-year local relapse-free survival rates (86.8% for R0, 92% for R1, and 76.0% for R2; $p = 0.27$).

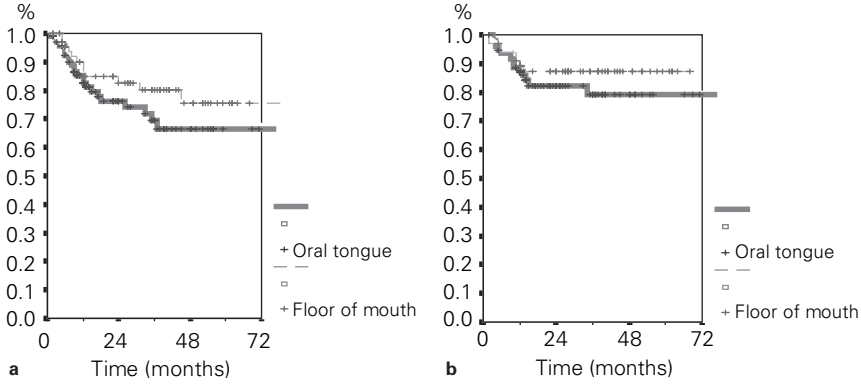
In 15 patients (6.4%) metastases occurred; 8/15 developed neck metastases, the other 7/15 distant metastases. The mean time to metastases was 16 months (median 12 months, 2–46 months). Eleven patients developed a second primary tumor within a mean time of 24 months (range: 12–50 months).

Serious late side effects (Table 4) such as soft-tissue necrosis and bone necrosis were observed in 23/236 (9.7%)



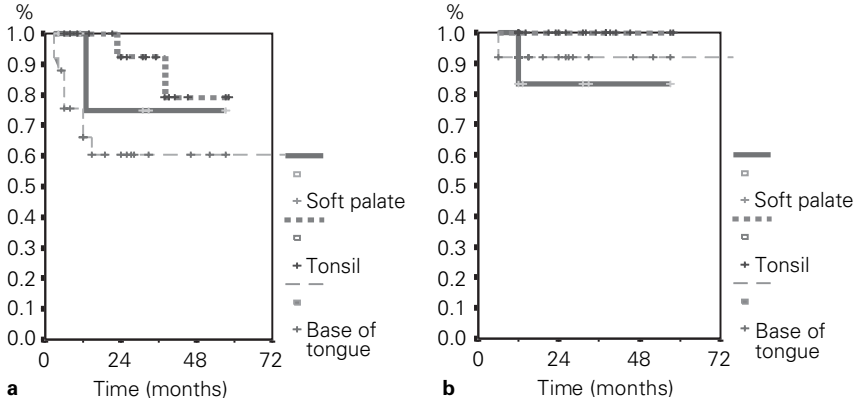
Figures 1a and 1b. 5-year overall (a) and local relapse-free (b) survival rates of the entire group.

Abbildungen 1a und 1b. 5-Jahres-Gesamtüberleben (a) und rezidivfreies Überleben (b) aller Patienten.



Figures 2a and 2b. Overall survival (a) and local control (b) in a series of patients with oral cavity tumors by tumor site.

Abbildungen 2a und 2b. 5-Jahres-Gesamtüberleben (a) und rezidivfreies Überleben (b) von Patienten mit Mundhöhlenkarzinom bei unterschiedlichem Tumorsitz.



Figures 3a and 3b. Overall survival (a) and local control (b) in a series of patients with oropharyngeal cancer by tumor site.

Abbildungen 3a und 3b. 5-Jahres-Gesamtüberleben (a) und rezidivfreies Überleben (b) von Patienten mit Oropharynxkarzinom bei unterschiedlichem Tumorsitz.

Table 4. Serious late side effects.

Tabelle 4. Schwere Spätnebenwirkungen.

	Number of patients	Surgical treatment necessary
Soft-tissue necrosis	23/236 (9.7%)	2/23 [2/236 (0.9%)]
Bone necrosis	17/236 (7.2%)	9/17 [9/236 (3.8%)]

and 17/236 patients (7.2%), respectively. In 2/23 patients with soft-tissue necrosis and in 9/17 patients with osteoradionecrosis, further surgical treatment was necessary. Among all treatment- and tumor-related parameters only V_{150} was significantly different in patients both with or without soft-tissue necrosis (mean V_{150}: 4.98 cm^3 vs. 3.62 cm^3, respectively; $p = 0.018$) and with or without osteoradionecrosis (mean V_{150}: 4.05 cm^3 vs. 3.62 cm^3, respectively; $p = 0.02$). No other treatment or tumor factors correlated with the rate of late side effects.

Discussion

Radiobiological studies showed, that PDR brachytherapy is probably equivalent to LDR brachytherapy models [1, 5, 7, 10, 12, 13, 17, 19, 24, 29, 32, 42]. Initial clinical data for different clinical situations provided some evidence to support this hypothesis [8, 9, 11, 15, 18, 21, 26, 30, 31, 34, 36, 37, 39, 40, 43]. Unfortunately, for head-and-neck cancer only limited experiences with PDR brachytherapy have been presented up to now – mostly only feasibility studies with limited patient numbers [6, 11, 18, 21, 26, 43]. The French experiences with PDR brachytherapy in 30 head-and-neck cancer patients [26] only showed, that PDR brachytherapy is feasible and that 14/28 patients had short or definitive breakdown of therapy due to different problems. Similarly, de Pree et al. [6] showed in 17 patients, that PDR brachytherapy is feasible. Levendag et al. [18] treated 38 patients with head-and-neck cancer with PDR brachytherapy ($d_p = 2$ Gy, four to eight times/day) alone or in combination with external irradiation. The patients showed better local control as compared with a historical control group (87% vs. 61%).

Some centers also introduced daytime PDR schedules to avoid hospitalization and to reduce overall treatment costs. Whether it is possible to restrict PDR irradiation to office hours only without restricting therapy efficacy [3, 34], remains controversial. Until now, no long-term results of any study support this suggestion. We believe, that only the complete 24-h treatment schedule guarantees that PDR brachytherapy will preserve all the radiobiological advantages of LDR brachytherapy. In our experience, we cannot report any logistic or practical problems with the 24-h treatment schedule of PDR brachytherapy administered for 3–6 days.

If we compare our results of PDR IBT in head-and-neck cancer, mostly given as postoperative brachytherapy, with results of LDR postoperative brachytherapy [2, 4, 14, 16], we see prevailing similarities in the results. Local control rates are, depending on tumor size, between 78% and 92% for T1/2 tumors and 57% for T3/4 tumors in the largest study so far [16] and between 93% and 70% in studies with smaller patient numbers [2, 4]. Local control rates in our study also depended on tumor size and ranged between 93% and 64%. The local control rates are also not essentially different from the results of other groups using LDR IBT definitively or postoperatively [2, 4, 14, 16, 20, 22, 27, 28, 33, 38]. Regarding the serious side effects of postoperative brachytherapy, Lapeyre et al. [16] reported complications in 34/82 patients (43%), eight of them (9.8%) grade 3. Beitler et al. [2] reported a high rate of late side effects – severe or moderate chronic sequelae in 12/23 patients (52.2%). Similarly, in the study by Mendenhall et al. [23] 7/15 patients (46.7%) developed serious late complications. In our study we registered serious late side effects in 7.2–9.7% of the patients.

The results of our study on 236 patients, actually the largest series worldwide, suggest, that PDR brachytherapy is really equivalent to LDR brachytherapy, and thus also confirm the radiobiological hypothesis, that PDR brachytherapy is indistinguishable from continuous LDR brachytherapy, if the pulses were given for 3–7 days once per hour with pulse doses (d_p) between 0.4 and 0.7 Gy. Moreover, it seems, that due to the possibility of optimization of the source times, PDR brachytherapy is superior to LDR brachytherapy in terms of its individualization potential and the possibility of a better treatment schedule – in particular regarding late side effects.

Conclusion

The results of PDR IBT in head-and-neck cancer are comparable with earlier experiences using LDR brachytherapy. Our results suggest, that PDR brachytherapy is most probably safer and equally effective compared to LDR brachytherapy.

References

1. Armour EP, White JR, Armin A, et al. Pulsed low dose rate brachytherapy in a rat model: dependence of late rectal injury on radiation pulse size. Int J Radiat Oncol Biol Phys 1997;38:825–34.
2. Beitler JJ, Smith RV, Silver CE, et al. Close or positive margins after surgical resection for the head and neck cancer patient: the addition of brachytherapy improves local control. Int J Radiat Oncol Biol Phys 1998;40:313–7.
3. Brenner DJ, Schiff PB, Huang Y, et al. Pulsed-dose-rate brachytherapy: design of convenient (daytime-only) schedules. Int J Radiat Oncol Biol Phys 1997;39:809–15.
4. Chao KS, Emami B, Akhileswaran R, et al. The impact of surgical margin status and use of an interstitial implant on T1, T2 oral tongue cancers after surgery. Int J Radiat Oncol Biol Phys 1996;36:1039–43.
5. Chen CZ, Huang Y, Hall EJ, et al. Pulsed brachytherapy as a substitute for continuous low dose rate: an in vitro study with human carcinoma cells. Int J Radiat Oncol Biol Phys 1997;37:137–43.
6. De Pree C, Popowski Y, Weber D, et al. Feasibility and tolerance of pulsed dose rate interstitial brachytherapy. Int J Radiat Oncol Biol Phys 1999; 43:971–6.
7. Fowler JF, Van Limbergen EF. Biological effect of pulsed dose rate brachytherapy with stepping sources if short half-times of repair are present in tissues. Int J Radiat Oncol Biol Phys 1997;37:877–83.
8. Freel JH, Speiser BL. Pulsed low dose rate brachytherapy for uterine cervix carcinoma. Int J Radiat Oncol Biol Phys 1999;43:95–100.

9. Fritz P, Berns C, Anton HW, et al. PDR brachytherapy with flexible implants for interstitial boost after breast-conserving surgery and external beam radiation therapy. Radiother Oncol 1997;45:23–32.
10. Fritz P, Frank C, Weber KJ. In-vitro-Untersuchungen zur PDR-Brachytherapie. Strahlenther Onkol 1998;174:365–74.
11. Geiger M, Strnad V, Lotter M, et al. Pulsed-dose rate brachytherapy with concomitant chemotherapy and interstitial hyperthermia in patients with recurrent head-and-neck cancer. Brachytherapy 2002;1:149–53.
12. Hall EJ, Brenner DJ. Pulsed dose-rate brachytherapy [Editorial, Comment]. Radiother Oncol 1997;45:1–2.
13. Harms W, Peschke P, Weber KJ, et al. Dose-dependent differential effects of low and pulsed dose-rate brachytherapy in a radioresistant syngenic rat prostate tumour model. Int J Radiat Biol 2002;78:617–23.
14. Housset M, Baillet F, Dessard-Diana B, et al. A retrospective analysis of three treatment techniques for T1–2 base of tongue lesions: surgery plus postoperative irradiation, external irradiation plus interstitial implantation and external irradiation alone. Int J Radiat Oncol Biol Phys 1987;13:511–6.
15. Jensen PT, Roed H, Engelholm SA, et al. Pulsed dose rate (PDR) brachytherapy as salvage treatment of locally advanced or recurrent gynecologic cancer. Int J Radiat Oncol Biol Phys 1998;42:1041–7.
16. Lapeyre M, Bollet MA, Racadot S, et al. Postoperative brachytherapy alone and combined postoperative radiotherapy and brachytherapy boost for squamous cell carcinoma of the oral cavity, with positive or close margins. Head Neck 2004;26:216–23.
17. Lartigau E. Is "pulse dose rate" curietherapy comparable to low dose rate brachytherapy? Bull Cancer Radiother 1995;82:336–9.
18. Levendag PC, Schmitz PI, Jansen PP, et al. Fractionated high-dose-rate and pulsed-dose-rate brachytherapy: first clinical experience in squamous cell carcinoma of the tonsillar fossa and soft palate. Int J Radiat Oncol Biol Phys 1997:38:497–506.
19. Mason KA, Thames HD, Ochran TG, et al. Comparison of continuous and pulsed low dose rate brachytherapy: biological equivalence in vivo. Int J Radiat Oncol Biol Phys 1994;28:667–71.
20. Mazeron JJ, Grimard L, Raynal M, et al. Iridium-192 curietherapy for T1 and T2 epidermoid carcinomas of the floor of mouth. Int J Radiat Oncol Biol Phys 1990;18:1299–306.
21. Mazeron JJ, Noel G, Simon JM. Head and neck brachytherapy. Semin Radiat Oncol 2002;12:95–108.
22. Mazeron JJ, Simon JM, Le Pechoux C, et al. Effect of dose rate on local control and complications in definitive irradiation of T1–2 squamous cell carcinomas of mobile tongue and floor of mouth with interstitial iridium-192. Radiother Oncol 1991;21:39–47.
23. Mendenhall WM, Parsons JT, Stringer SP. Radiotherapy after excisional biopsy of carcinoma of the oral tongue/floor of the mouth. Head Neck 1989;11:129–31.
24. Niedbala M, Alsbeih G, Ng CE, et al. Equivalence of pulsed-dose-rate to low-dose-rate irradiation in tumor and normal cell lines. Radiat Res 2001; 155:297–303.
25. Nose T, Peiffert D, Lapeyre M, et al. Late effects of post-high-dose-rate brachytherapy for oropharyngeal carcinoma: are they severer than post-low-dose-rate? Strahlenther Onkol 2004;180:776–82.
26. Peiffert D, Castelain B, Thomas L, et al. Pulsed dose rate brachytherapy in head and neck cancers. Feasibility study of a French cooperative group. Radiother Oncol 2001;58:71–5.
27. Pernot M, Hoffstetter S, Peiffert D, et al. Epidermoid carcinomas of the floor of mouth treated by exclusive irradiation: statistical study of a series of 207 cases. Radiother Oncol 1995;35:177–85.
28. Pernot M, Hoffstetter S, Peiffert D, et al. Role of interstitial brachytherapy in oral and oropharyngeal carcinoma: reflection of a series of 1344 patients treated at the time of initial presentation. Otolaryngol Head Neck Surg 1996;115:519–26.
29. Pop LA, van den Broek JF, Visser AG, et al. Constraints in the use of repair half times and mathematical modelling for the clinical application of HDR and PDR treatment schedules as an alternative for LDR brachytherapy. Radiother Oncol 1996;38:153–62.
30. Roed H, Engelholm SA, Svendsen LB, et al. Pulsed dose rate (PDR) brachytherapy of anal carcinoma. Radiother Oncol 1996;41:131–4.
31. Rogers CL, Freel JH, Speiser BL. Pulsed low dose rate brachytherapy for uterine cervix carcinoma. Int J Radiat Oncol Biol Phys 1999;43:95–100.
32. Sethi T, Dixon B, Flynn A, et al. Continuous, pulsed or single acute irradiation of a transplanted rodent tumour model. Radiother Oncol 1997;43:203–9.
33. Simon JM, Mazeron JJ, Pohar S, et al. Effect of intersource spacing on local control and complications in brachytherapy of mobile tongue and floor of mouth. Radiother Oncol 1993;26:19–25.
34. Skowronek J, Piotrowski T. Pulsed dose rate brachytherapy: a method, description and review of clinical application. Przegl Lek 2002;59:31–6.
35. Sminia P, Schneider CJ, van Tienhoven G, et al. Office hours pulsed brachytherapy boost in breast cancer. Radiother Oncol 2001;59:273–80.
36. Strnad V. Treatment of oral cavity and oropharyngeal cancer: indications, technical aspects, and results of interstitial brachytherapy. Strahlenther Onkol 2004;180:710–7.
37. Strnad V, Geiger M, Lotter M, et al. The role of pulsed-dose-rate brachytherapy in previously irradiated head-and-neck cancer. Brachytherapy 2003;2:158–63.
38. Strnad V, Jacobs H. Head and neck cancer. In: Strnad V, Pötter R, Kovács G, eds. State and prospects of clinical brachytherapy. Bremen–London–Boston: UNI-MED, 2004:142–53.
39. Strnad V, Lotter M, Grabenbauer G, et al. Early results of pulsed-dose-rate interstitial brachytherapy for head and neck malignancies after limited surgery. Int J Radiat Oncol Biol Phys 2000;46:27–30.
40. Swift PS, Purser P, Roberts LW, et al. Pulsed low dose rate brachytherapy for pelvic malignancies. Int J Radiat Oncol Biol Phys 1997;37:811–7.
41. Takacsi-Nagy Z, Polgar C, Oberna F, et al. Interstitial high-dose-rate brachytherapy in the treatment of base of tongue carcinoma. Strahlenther Onkol 2004;180:768–75.
42. Visser AG, van den Aardweg GJ, Levendag PC. Pulsed dose rate and fractionated high dose rate brachytherapy: choice of brachytherapy schedules to replace low dose rate treatments. Int J Radiat Oncol Biol Phys 1996;34:497–505.
43. Zienkiewicz J, Ziemlewski A, Serkies K, et al. Preliminary experiences in the treatment of head and neck neoplasms with the use of pulsed brachytherapy. Wiad Lek 2002;55:569–74.

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