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FULL PAPER

A review of the clinical experience in pulsed dose rate brachytherapy

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ABSTRACT

Pulsed dose rate (PDR) brachytherapy is a treatment modality that combines physical advantages of high dose rate (HDR) brachytherapy with the radiobiological advantages of low dose rate brachytherapy. The aim of this review was to describe the effective clinical use of PDR brachytherapy worldwide in different tumour locations. We found 66 articles reporting on clinical PDR brachytherapy including the treatment procedure and outcome. Moreover, PDR brachytherapy has been applied in almost all tumour sites for which brachytherapy is indicated and with good local control and low toxicity. The main advantage of PDR is, because of the small pulse sizes used, the ability to spare normal tissue. In certain cases, HDR resembles PDR brachytherapy by the use of multifractionated low-fraction dose.

INTRODUCTION

Pulsed dose rate (PDR) brachytherapy is a treatment modality that combines physical advantages of high dose rate (HDR) brachytherapy, such as isodose optimization, planning flexibility and radiation safety, with the radiobiological advantages of low dose rate (LDR) brachytherapy. Mathematical and *in vivo* studies determined biological equivalence between PDR and LDR after correction of total dose with the linear quadratic model.^{1–3} Since normal tissue repair times differ from tumour cell repair times, the adjustment of pulse dose and time between pulses can be employed to enlarge the therapeutic window between tumour cure and damage to normal tissues.⁴ When keeping the pulse size <1 Gy, PDR has a radiobiological advantage on late effects compared with HDR.⁵ Therefore, PDR brachytherapy has been proposed and introduced as a method to replace continuous LDR, assuming radiobiological equivalence.

Some of the advantages of PDR brachytherapy compared with LDR are full radiation protection for caregivers, no source preparation necessary, no extensive source inventory, that is, only one iridium-192 source per afterloader to be replaced every 2 or 3 months, better reproducibility of treatment plans and greater flexibility to change the dose distribution through the course of treatment if necessary. Compared with HDR brachytherapy, PDR offers similar quality of dose distribution,

and similar treatment procedure and technical verification, both being stepping source technologies.⁶ In addition, with the introduction of CT scan and MRI, treatment planning shifted gradually from two dimension to three dimension (3D), and planning optimization became based on delineated target and organs at risk (OARs).⁷

The brachytherapy practices in Europe for HDR and PDR have increased markedly over the last 2 decades. HDR is the most commonly used technique overall. PDR brachytherapy showed a much slower development, representing up to 16% of the patients treated with brachytherapy in Europe, while the use of LDR brachytherapy has decreased considerably since the introduction of stepping source technology.⁸ By now, LDR iridium-192 and caesium-137 sources are not available anymore in Europe. The aim of this review was to describe the effective clinical use of PDR brachytherapy worldwide in different tumour locations.

METHODS AND MATERIALS

For this review, a search for clinical articles on PDR brachytherapy was performed. An electronic search was performed in MEDLINE using the PubMed database and EMBASE. Search terms used were “pulsed dose rate brachytherapy” or “PDR brachytherapy”. The search was performed on 9 January 2015.

Table 1. Pulsed dose rate (PDR) brachytherapy in cervical cancer (technique and dose)

Author	<i>n</i>	Primary/ recurrence	Stage (FIGO)	Procedure	Type of applicator	Planning	Optimization	Source activity	Pulse size (Gy)	Period (h)	Dose (Gy)	EQD2 (a/b = 10) (Gy) ^a
Boyrie et al ^{9,b}	110	Primary	IB1–IIIB	Intracavitary + interstitial	Tandem/ovoids/ mould/ring	CT/MRI	Geometric	TRAK: 184 Gy cm ²	NR	1	15 (IR-CTV), 40 (HR-CTV)	–
Refaat et al ¹⁰	40	Primary	IB2–II	Intracavitary	Tandem/ovoids	MRI	MRI based	NR	0.5	1	15 (IR-CTV), 35 ± 5 (HR-CTV)	15
Refaat et al ¹⁹	95	Primary	IB–III	Intracavitary	Tandem/ovoids	X-ray	Geometric	NR	0.5	1	20	20
Petit et al ¹¹	226	Primary	IB–IVA	Intracavitary	Tandem/ovoids	X-ray/CT	2005: Geometric	TRAK: 1.2 cGy m ²	0.65	1	16	17
Nomden et al ¹²	39	Primary	IB–IVB	Intracavitary	Tandem/ovoids	MRI	Geometric	NR	0.6	1	17.4–19.2	20
Charra-Brunaud et al ^{13,b}	362	Primary	IB–IIIB	Intracavitary + interstitial	Tandem/ovoids/ mould/ring	X-ray/ CT/MRI	Geometric	TRAK: 137–470 cGy m ² h ^{–1}	Centre specific	Centre specific	15	–
Rath et al ¹⁴	48	Primary	IB–IVA	Intracavitary	Tandem/ colpostats	X-ray	No	NR	0.7	1	27	29
Chargari et al ¹⁵	45	Primary	IB–IVA	Intracavitary	Tandem/mould	MRI	MRI based	TRAK: 1.94 cGy m ² h ^{–1}	NR	1	15	–
Bachtiary et al ¹⁶	57	Primary	IB–IIIB	Intracavitary	Tandem	X-ray	No	0.4–1 mCi	0.7	1	20–45	48
Rogers et al ¹⁷	46	Primary, recurrence	IB–IVA	Intracavitary + interstitial	Tandem/ ovoids/tubes	X-ray/CT	No	NR	0.55	1	30	31
Swift et al ¹⁸	42	Primary	IA–IVA	Intracavitary + interstitial	Tandem/ ovoids/tubes	X-ray	Geometric	0.28–0.95 Ci	0.4–0.8	1	Individual	–

CTV, clinical target volume; EQD2, equivalent 2 Gy dose; HR, high risk; IR, intermediate risk; NR, not reported; TRAK, total reference air kerma.

^aHighest EQD2.^bSame study [Soutien aux Techniques Innovantes et Coûteuses (STIC-PDR)].

Table 2. Pulsed dose rate (PDR) brachytherapy in cervical cancer (outcome and toxicity)

Author	<i>n</i>	Primary/ recurrence	Other treatment modalities	Follow-up (months)	LC	OS	Late toxicity	Sort of toxicity specified
Boyrice et al ^{9,a}	110	Primary	EBRT (45 Gy)/weekly cisplatin	24.2	2-year LC: 78%	2-year OS: 74%	NR	
Refaat et al ¹⁰	40	Primary	EBRT (45 Gy)/weekly cisplatin	30	2.5-year LC: 90%	2.5-year OS: 100%	≥Grade 3 GI: 2.5%; GU: 2.5%	
Refaat et al ¹⁹	95	Primary	EBRT (45 Gy)/weekly cisplatin	45	3-year LC: 84%	3-year OS: 84%	≥Grade 3 GI: 3.2%; GU: 4.2%	
Petit et al ¹¹	226	Primary	EBRT (45 Gy)/weekly cisplatin/surgery	81.7	5-year LC: 80%	5-year OS: 67%	≥Grade 3 GI: 3%; GU: 5.1%	
Nomden et al ¹²	39	Primary	EBRT (45 Gy)/weekly cisplatin	41	3-year LC: 93% ^b	3-year OS: 65% ^b	≥Grade 3 in four patients ^b	GI: enteritis, bleeding, fistula, diarrhoea; GU: ureter stenosis, vaginal stenosis/mucositis/necrosis/ bleeding, fibrosis
Charra-Brunaud et al ^{13,a}	362	Primary	EBRT (45 Gy)/weekly cisplatin/surgery	24	2-year LC: 78.5–100% ^c	2-year OS: 74–96% ^c	≥Grade 3 GI: 0–1.2%; GU: 1.2–5.5% ^c	
Rath et al ¹⁴	48	Primary	EBRT (50 Gy)/weekly cisplatin	15	1.25-year LC: 80%	NR	≥Grade 3: 6%	1 × fistula, 1 × cystitis, 1 × severe lymphoedema
Chargari et al ¹⁵	45	Primary	EBRT (45 Gy)/weekly cisplatin/surgery	26	No local failures	2-year OS 78%	One patient: Grade 3 (vaginal fistula)	
Bachtiary et al ¹⁶	57	Primary	EBRT (45 Gy)/weekly cisplatin	50.4	LC in 46%	3-year OS: 83%	≥Grade 3 GU: 9%; GI: 3.5%	1 × fistula, 1 × proctitis, 1 × haematuria, 1 urge
Rogers et al ¹⁷	46	Primary, recurrence	EBRT (45–50 Gy)/weekly cisplatin/surgery	25	4-year LC: 86%	4-year OS: 55%	≥Grade 3: 7%	1 × vesicovaginal fistula, 1 × rectovaginal fistula
Swift et al ¹⁸	42	Primary	EBRT (45–54 Gy)	17.3	2-year LC: 86%	2-year OS: 65%	≥Grade 3: 14%	4 × rectovaginal fistula, 2 × necrosis

EBRT, external beam radiotherapy; GI, gastrointestinal; GU, genitourinary; HDR, high dose rate; LC, local control; LDR, low dose rate; NR, not reported; OS, overall survival.

^aSame study [Soutien aux Techniques Innovantes et Côuteuses (STIC-PDR)].^bData on PDR and HDR.^cData on PDR and LDR.

Table 3. Pulsed dose rate brachytherapy in breast cancer (technique and dose)

Study	<i>n</i>	Primary/ recurrence	Stage	Procedure	Type of applicator	Planning	Optimization	Source activity	Pulse size (Gy)	Period time (h)	Dose (Gy)	EQD2 (<i>a/b</i> = 5) (Gy) ^a
Hannoun-Levi et al ²⁰	88	Recurrence	Median size 12.5 mm	APBI/ interstitial	Plastic tubes	CT	NR	NR	0.7–1	1	50.4	66
Kauer-Dorner et al ²¹	39	Recurrence	T1	APBI/ interstitial	Plastic tubes	X-ray/CT	NR	NR	0.8	1	50.1	60
Ott et al ^{22,b}	175	Primary	T1–T2	APBI/ interstitial	Plastic tubes	CT	No	Air kerma 1.2–4.8 mGy m ² h ^{−1}	0.6	1	49.8	54
Johansson et al ²³	50	Primary	T1–T2	APBI/ interstitial	Plastic tubes	X-ray	Geometric	TRAK: 0.64 mGy	0.833	2	50	49
Niehoff et al ²⁴	17	Recurrence	T1–T4	Interstitial	Plastic tubes	CT	Geometric	NR	1	2	10–45	46.5
Strnad et al ^{25,b}	132	Primary	T1–T2	APBI/ interstitial	Plastic tubes	CT/IBU	No	Air kerma: 1.2–4.8 mGy m ² h ^{−1}	0.6	1	49.8	54
Ott et al ^{26,b}	57	Primary	T1–T2	APBI/ interstitial	Plastic tubes	CT	No	Air kerma: 1.2–4.8 mGy m ² h ^{−1}	0.6	1	49.8	54
Ulutin et al ²⁷	35	Primary	T1–T3	Interstitial	Plastic tubes	X-ray	No	NR	NR	NR	25 (boost)	–
Resch et al ³²	17	Recurrence	T1–T2	Interstitial	Plastic tubes	X-ray/CT	No	NR	0.5–1	1	Minimum 12.5 (boost)/ minimum 40.2	53
Harms et al ²⁸	113	Primary	T1–T3	Interstitial	Plastic tubes	CT	Geometric	37 GBq	1	1	15–25	32
Harms et al ²⁹	58	Recurrence	NR	Interstitial	Chest wall mould	X-ray	Geometric	37 GBq	0.5–1	1	2 × 20	52
Fritz et al ³⁰	46	Recurrence	NR	Interstitial	Chest wall mould	X-ray	Geometric	37 GBq	1	1.2	2 × 20/20 + 25	54
Fritz et al ³¹	65	Primary	T1–T3	Interstitial	Plastic tubes	X-ray	Geometric	37 GBq	1	1	20 (boost)	25

APBI, accelerated partial breast irradiation; EQD2, equivalent 2 Gy dose; IBU, integrated brachytherapy unit; NR, not reported; TRAK, total reference air kerma.

^aHighest EQD2.^bGerman-Austrian APBI Phase II study.

Table 4. Pulsed dose rate (PDR) brachytherapy in breast cancer (outcome and toxicity)

Study	<i>n</i>	Primary/ recurrence	Other treatment modalities	Follow-up (months)	LC	OS	Late toxicity	Sort of toxicity specified
Hannoun-Levi et al ²⁰	88	Recurrence	BCS/AH/ chemotherapy	46	5-year LC: 94%; 10-year LC: 93% ^a	5-year OS: 89%; 10-year OS: 76% ^a	≥Grade 3: 11%; cosmesis ≥good: 85% ^a	Fibrosis, telangiectasia
Kauer-Dörner et al ²¹	39	Recurrence	BCS/AH/ chemotherapy	57	5-year LC: 93%	5-year OS: 87%	≥Grade 3: 17%; cosmesis ≥good: 63%	Fibrosis, breast pain
Ott et al ^{22,b}	175	Primary	BCS/AH/ chemotherapy	64	5-year LC: 97.7% ^c	NR	NR	
Johansson et al ²³	50	Primary	BCS/AH/ chemotherapy	86	5-year LC: 96%	5-year OS: 88%	≥Grade 3: 20%; cosmesis ≥good: 50%	Fibrosis, fat necrosis
Niehoff et al ²⁴	17	Recurrence	Local excision/AH/ chemotherapy	19	LR in 47% ^c	1-year OS 75% ^c	≥Grade 3 in one patient	Wound healing
Strnad et al ²⁵	132	Primary	BCS/AH/ chemotherapy	12	1-year LC: 100%	1-year OS: 100%	≥Grade 3: 0.6%; cosmesis ≥good: 92–95%	Telangiectasia
Ott et al ²⁶	57	Primary	BCS/AH/ chemotherapy	24	2-year LC: 100%	2-year OS: 100%	≥Grade 3: 2.8%; cosmesis ≥good: 92%	Breast pain, telangiectasia
Ulutin et al ²⁷	35	Primary	BCS/EBRT (40 Gy)/ AH/chemotherapy	80	6-year LC: 87.7% ^d	6-year OS: 91.1% ^d	NR	
Resch et al ³²	17	Recurrence	BCS/EBRT/AH/ chemotherapy	59	LR in 24%	NR	≥Grade 3: 0%; cosmesis ≥good: 30%	
Harms et al ²⁸	113	Primary	BCS/EBRT (50 Gy)/ AH/chemotherapy	61	5-year LC: 95%; 8-year LC: 93%	5-year OS: 93%; 8-year OS: 82%	≥Grade 3: 15%; cosmesis ≥good: 90%	Fibrosis, telangiectasia, skin
Harms et al ²⁹	58	Recurrence	Surgery	NR	1-year LC: 89–96%; 3-year LC: 71–75%	1-year OS: 70–92%; 5-year OS: 17–48%	≥Grade 3: 67%	Fibrosis (10%), telangiectasia (50%), necrosis (7%)
Fritz et al ³⁰	46	Recurrence	Surgery	NR	1-year LC: 87%	2-year OS: 35%	≥Grade 3: 100%	Telangiectasia 100%, reirradiation group: necrosis 12%, fibrosis 12%
Fritz et al ³¹	65	Primary	BCS/EBRT (50 Gy)/ AH/chemotherapy	30	NR	NR	Cosmesis ≥good: 87%	

AH, antihormonal therapy; APBI, accelerated partial breast irradiation; EBRT, external beam radiotherapy; HDR, high dose rate; LC, local control; LDR, low dose rate; LR, local relapse; NR, not reported; OS, overall survival.

^aHDR + PDR + LDR.

^bGerman-Austrian APBI Phase II study.

^cHDR + PDR.

^dLDR + PDR.

Table 5. Pulsed dose rate brachytherapy in head and neck cancer (technique and dose)

Author	<i>n</i>	Primary/ recurrence	Stage	Procedure	Type of applicator	Planning	Optimization	Source activity	Pulse size (Gy)	Period time (h)	Dose (Gy)	EQD2 (a/b = 10) (Gy) ^a
Strnad <i>et al</i> ⁴⁸	104	Recurrence	T1–T4	Interstitial	Plastic tubes	CT	No	NR	0.4–0.7	1	60, if EBRT: 27	89
Haddad <i>et al</i> ³⁶	36	Primary	T1–T4	Interstitial	Plastic Tubes	CT	No	NR	0.5–1	1	15–62	73
Strnad <i>et al</i> ⁴¹	51	Recurrence	T1–T4	Interstitial	Plastic tubes	CT	No	NR	0.4–0.7	1	60, if EBRT: 27	89
Serkies <i>et al</i> ⁴⁰	32	Primary/ recurrence lip	T1–T4	Interstitial	Plastic tubes	X-ray	Geometric	NR	1	1	60–70	83
Strnad <i>et al</i> ⁴²	385	Primary	T1–T4	Interstitial	Plastic tubes	CT	Geometric/ graphical	NR	0.4–0.7	1	57, if EBRT: 24	62
Bartochowska <i>et al</i> ³⁴	16	Recurrent larynx	T1–T4	Interstitial	Plastic tubes	CT/MRI	Geometric	NR	0.6–0.8	1	20–40	45
Bartochowska <i>et al</i> ³³	106	Recurrence	T1–T4	Interstitial	Plastic tubes	CT	Geometric	NR	0.6–0.8	1	20–40	45
Johansson <i>et al</i> ⁴⁷	43	Primary/ recurrence lip	T1–T3	Interstitial	Plastic tubes	X-ray	Geometric	TRAK: 0.15 mGy	0.82	2	60	61
Ziemlewski <i>et al</i> ⁴⁶	45	Primary/ recurrence	T1–T4	Interstitial	Plastic tubes	X-ray/CT	Geometric	NR	1, 0.6, ^b 2.5 ^c	1	70, if EBRT: 20	83
Krempien <i>et al</i> ³⁷	14	Recurrence	T2–T4	Interstitial	Plastic tubes	CT	Geometric	NR	0.5	1	10–20 after EBRT	20
Peiffert <i>et al</i> ³⁹	30	Primary	T1–T3	Interstitial	Plastic tubes	X-ray	No	18.5 Gbq	0.5	1	≥45, if EBRT: 22	46
Levendag <i>et al</i> ³⁸	19	Primary	T1–T4	Interstitial	Plastic tubes	X-ray	NR	37 Gbq	1–2	3	60–70, if EBRT: 20–28	77

EBRT, external beam radiotherapy; EQD2, equivalent 2 Gy dose; NR, not reported; TRAK, total reference air kerma.

^aHighest EQD2.^bFor reirradiation.^cFor elderly lip cancer.

Table 6. Pulsed dose rate (PDR) brachytherapy in head and neck cancer (outcome and toxicity)

Author	<i>n</i>	Primary/ recurrence	Other treatment modalities	Follow-up (months)	LC	OS	Late toxicity
Strnad et al ⁴⁸	104	Recurrence	Surgery/EBRT (46 Gy)/ chemotherapy/ hyperthermia	60	2-, 5-, 10-year LC: 92.5%, 82.4%, 58.9%	5-year OS: 21% (54% other causes)	STN: 17.3%; ORN: 9.6%
Haddad et al ³⁶	36	Primary	Surgery/ EBRT (48–50 Gy)	30	3-year LC: 94%	3-year OS: 90%	ORN: 3%; STN: 8%
Strnad et al ⁴¹	51	Recurrence	EBRT (46 Gy)/ chemotherapy/ hyperthermia	58	2-year LC: 71%; 5-year LC: 57%	NR	ORN: 11.8%; STN 2%
Serkies et al ⁴⁰	32	Primary/ recurrence lip	Surgery	NR	5-year LC: 94%	5-year OS: 73%	Mucositis Grade 3: 3%; ≥good cosmesis: 90%
Strnad et al ⁴²	385	Primary	Surgery/EBRT (55 Gy)/ chemotherapy	63	5-, 10-, 15-year LC: 85.8%, 83.1%, 80.2%	5-, 10-, 15-year OS: 68.9%, 52.2%, 44.1%	ORN: 4.9%; STN: 10.2%
Bartochowska et al ³⁴	16	Recurrent larynx	Surgery/ chemotherapy/ hyperthermia	NR	NR	2-year OS: 22%	STN: 9%
Bartochowska et al ³³	106	Recurrence	Surgery/ chemotherapy/ hyperthermia	NR	6-month LC: 37.7% ^a	1-year OS: 40%; 2-year OS: 17% ^a	STN: 15%; ORN: one patient ^a
Johansson et al ⁴⁷	43	Primary/ recurrence lip	Surgery	54	2-, 5-, 10-year LC: 97.6%, 94.5%, 94.5%	2-, 5-, 10-year OS: 88.0%, 58.9%, 39.1%	STN: 2%
Ziemlewski et al ⁴⁶	45	Primary/ recurrence	Surgery/ EBRT (50 Gy)	22	LC: 88.6%	5-year OS lip cancer: ~85%; other: ~25%	STN and ORN: 15.6%; severe late mucositis: 23%
Krempien et al ³⁷	14	Recurrence	EBRT (36 Gy)/ chemotherapy	35	1-, 2-year LC: 78%, 57%	1-, 2-year OS: 83%, 64%	STN: one patient
Peiffert et al ³⁹	30	Primary	Surgery/ EBRT (45–60 Gy)	23	LC: 83%	NR	STN: 13%; ORN: 3.3%
Levendag et al ³⁸	19	Primary	EBRT (46 Gy)/ neck dissection	31	3-year LC: 87% ^a	3-year OS: 82% ^a	2 patients ulcer, 2 patients severe pain ^a

EBRT, external beam radiotherapy; HDR, high dose rate; LC, local control; NR, not reported; ORN, osteoradionecrosis; OS, overall survival; STN, soft tissue necrosis.

^aHDR + PDR.

The articles were further selected by reading the title and abstracts. Only articles with clinical information and published in English were included for the review. In addition, articles were selected based on the reviewed articles, which were not found by the search term itself, but by hand search of the reference list or published by our own study group. The search was repeated in March 2015 to see whether additional articles had been reported in the interim period. If necessary, articles from the same study were excluded.

RESULTS

Our search resulted in 268 articles in PubMed. After reviewing these articles, 58 articles referred to the use of PDR brachytherapy in clinical practice. The EMBASE search resulted in 255 articles of which 28 articles were relevant for this review, 2 were unique compared with the PubMed search. In addition, 6 articles were

added, of which one was published just after the search, 2 were added based on the references from the other articles and 2 articles were published by ourselves, and the last one was known by us, since they referred to one of our articles. 11 articles were on cervical cancer, 13 on breast cancer, 16 on head and neck (HN) cancer, 5 on prostate cancer, 4 on bladder cancer, 3 on anal cancer, 2 on sarcomas of the extremities and 12 articles on other tumour sites. Most articles reported on the applicator used, applicator procedure, treatment plan optimization, pulse frequency, pulse dose and prescription dose. Source activity was reported, but not in all articles. Also, data on survival and toxicity were reported depending on follow-up time.

Cervical cancer

11 articles reported on PDR in cervical cancer (Tables 1 and 2).^{9–19} Articles were published between 1997 and 2013 and mostly

Table 7. Pulsed dose rate brachytherapy in prostate cancer (technique and dose)

Author	n	Primary/ recurrence	Stage	Procedure	Type of applicator	Planning	Optimization	Source activity	Pulse size (Gy)	Period time (h)	Dose (Gy)	EQD2 (a/b = 3) (Gy) ^a
Lahmer et al ⁵⁰	18	Recurrence	T2b–T4	Interstitial	Needles	Transrectal ultrasound	Geometrical	NR	0.6	1	2 × 30	2 × 33
Lettmaier et al ⁵¹	130	Primary	T1c–T3	Interstitial	Needles	Transrectal ultrasound	Geometrical	NR	0.6–0.7	1	25–35	41.5
Pieters et al ⁵²	110	Primary	T1c–3	Interstitial	Self-anchoring flexible catheters	Transrectal ultrasound/CT	NR	NR	1.04–1.2	2.0–2.2	24.96–28.80	31.3
Pieters et al ⁵³	106	Primary	T1c–T3	Interstitial	Self-anchoring flexible catheters	Transrectal ultrasound/CT	NR	NR	1.04–1.2	2.0–2.2	24.98–28.80	31.3

EQD2, equivalent 2 Gy dose; NR, not reported.

^aHighest EQD2.

concern primary tumours of the cervix. Only Rogers *et al*¹⁷ reported on recurrent cervical cancer in 13% of their cases. Boyrie *et al*⁹ and Charra-Brunaud *et al*¹³ reported data of the same study [Soutien aux Techniques Innovantes et Coûteuses (STIC-PDR)], although Boyrie *et al*⁹ reported data only for a subset of patients for whom optimization was performed on CT scan or MRI. In all studies, intracavitary PDR was performed with a tandem and ovoids, but occasionally a mould was used in the STIC-PDR study.^{9,13} The prescribed dose ranged from 15 to 40 Gy with a pulse size of 0.4–0.8 Gy given every hour. The STIC-PDR study did not report the pulse size in their articles.

PDR was most often preceded by external beam radiotherapy (EBRT), with doses of 45–50 Gy in combination with weekly cisplatin (Table 2). In some articles, the treatment was combined with surgery. Although follow-up time was short, most studies showed a local control (LC) of 80–90% and overall survival (OS) ranged from 4-year OS of 55% reported by Rogers *et al*¹⁷ in 1999 to a 2.5-year OS of 100% with MRI-based brachytherapy as reported by Refaat *et al*.¹⁰ With PDR, ≥Grade 3 gastrointestinal (GI) and genitourinary (GU) late toxicity was low, and when 3D optimization was performed with dose restriction on the OARs, this incidence became even less.^{9,12}

Breast cancer

13 articles reported on PDR in breast cancer (Tables 3 and 4).^{20–32} Three articles were results of the German–Austrian accelerated partial breast irradiation (APBI) Phase II study.^{22,25,26} Because the most recent data published by Ott *et al* did not include data on toxicity, we included the other two articles in our analysis. PDR in the primary breast cancer was reported in six articles, whereas the other seven articles reported on recurrence, including three on chest wall recurrence.

In the primary breast cancer,^{22,23,25–28,31} PDR was used as APBI or as a boost to EBRT. Interstitial tubes were used and treatment planning was performed on X-ray or CT scan. In three studies, a geometric optimization was performed.^{23,28,31} Pulse dose ranged from 0.6 to 1 Gy given every hour, except by Johansson *et al*²³ who applied a period time of 2 h. Both the German–Austrian APBI study and the study by Johansson *et al*²³ gave a total dose of approximately 50 Gy. After EBRT (40–50 Gy), a boost with PDR of 15–25 Gy was given. LC, 95% after 5 years, was excellent for both treatment modalities (Table 4). Although Grade 3 toxicity, *i.e.* fibrosis and telangiectasia, was reported in 15–20%, still patients reported a good cosmesis. The toxicity figures of the German–Austrian APBI study were lower, but follow-up time was short.^{25,26}

In recurrent breast cancer, most studies^{20,21,24,29,30,32} treated only locally with interstitial tubes or a chest wall mould. Resch *et al*³² and four patients in the study of Niehoff *et al*²⁴ combined brachytherapy with EBRT. Treatment planning was performed on X-ray or CT scan, and some studies performed a geometrical optimization. Pulse dose ranged from 0.5 to 1 Gy every 1 or 2 h. Hannoun-Levi *et al*²⁰ and Kauer-Doner *et al*²¹ reirradiated with 50 Gy after a dose of approximately 50 Gy at primary diagnosis. For chest wall recurrences, a split treatment of 2 times 20–25 Gy was given.^{29,30} Both Hannoun-Levi *et al* and Kauer-Doner *et al* reported 5-year LC of 90–95% and 5-year OS of 85–90%.

Table 8. Pulsed dose rate brachytherapy in prostate cancer (outcome and toxicity)

Author	<i>n</i>	Primary/ recurrence	Other treatment modalities	Follow-up (months)	LC	Progression-free survival	OS	Late toxicity
Lahmer et al ⁵⁰	18	Recurrence	AH	21	LC: 94.4%	3-year bPFS: 57%	3-year OS: 89%	≥Grade 3 GU: 16.7%
Lettmaier et al ⁵¹	130	Primary	EBRT (50.4 Gy)/AH	60	NR	5-, 9-year bPFS: 85.6%, 79%	5-, 9-year OS: 85.7%, 80.3%	≥Grade 3 GI: 0.8%
Pieters et al ⁵²	110	Primary	EBRT (46 Gy)/AH	32	NR	NR	NR	≥Grade 3 GU: 4.5%; GI: 0%
Pieters et al ⁵³	106	Primary	EBRT (46 Gy)/AH	34.6	NR	3-, 5-year bPFS: 92.8%, 89.5%	3-year, 5-year OS 99%, 96%	≥Grade 3 GI: 0%; GU: 7.3%

AH, antihormonal; bPFS, biochemical progression-free survival; EBRT, external beam radiotherapy; GI, gastrointestinal; GU, genitourinary; LC, local control; NR, not reported.

However, all reirradiation studies showed impaired cosmetic results. Grade 3 toxicity was comparable with primary studies, except for chest-wall reirradiation. Fritz et al³⁰ reported telangiectasia in all and skin contractures or necrosis in 12% of their patients.

Head and neck cancer

We identified 14 articles on PDR in HN cancer.^{33–46} Based on these articles, we added the article by Johansson et al,⁴⁷ which was not found in both searches, and the article of Strnad et al,⁴⁸ which was published after our search. We excluded four articles of the Erlangen group since these were the previous results from the same studies with shorter follow-up time (Tables 5 and 6). Four articles were on primary HN cancer, whereas Ziemlewski et al⁴⁶ reported on primary and recurrence. Two studies reported data on primary or recurrent lip carcinoma.^{40,47} The other five articles reported on recurrence in HN cancer, whereas

Bartochowska et al³⁴ also did a subanalysis on recurrence in specifically larynx carcinoma.

PDR was performed with interstitial tubes. Geometric treatment plan optimization was performed on X-ray or CT, and in one article, MRI was also used. Pulse dose ranged from 0.4 to 1 Gy was given mostly every hour. Ziemlewski et al⁴⁶ gave a pulse dose of 2.5 Gy in elderly patients with lip carcinoma. Johansson et al⁴⁷ gave pulse dose of 0.8 Gy every 2 h, and Levendag et al³⁸ gave 1–2 Gy every 3 h.

In primary HN cancer, the PDR dose was dependent on other treatment modalities, ranging from 15 Gy, when combined with surgery and EBRT, to 70 Gy, when PDR was given as monotherapy. LC was >80%, and even 94%, in both lip carcinoma studies. Outcome varied between the studies and was mainly due to other prognostic factors. The most common toxicities in these studies

Table 9. Pulsed dose rate brachytherapy in bladder cancer (technique and dose)

Author	<i>n</i>	Primary/ recurrence	Stage	Procedure	Type of applicator	Planning	Optimization	Source activity	Pulse size (Gy)	Period time (h)	Dose (Gy)	EQD2 (a/b = 10) (Gy) ^a
Aluwini et al ⁵⁷	102	Primary	T2–T3	Interstitial	Plastic tubes	X-ray	Dose point	37 Gbq	1	3	30	29
Nap-van Klinken et al ⁵⁴	77	Primary	T1G3–T2	Interstitial	Plastic tubes	CT	Standard	NR	1–2.5	NR	25–28	
Koning et al ⁵⁵	184	Primary	T1–T4	Interstitial	Plastic tubes	NR ^b	NR ^b	NR ^b	NR ^b	NR ^b	25–40 of 50–60	
Blank et al ⁵⁶	23	Primary	T1–T4	Interstitial	Plastic tubes	CT	Standard	0.2–0.8 cGy m ² h ^{−1}	1.04	2	20.8–59.3	61

EQD2, equivalent 2 Gy dose; NR, not reported.

^aHighest EQD2.

^bCentre specific.

Table 10. Pulsed dose rate (PDR) brachytherapy in bladder cancer (outcome and toxicity)

Author	<i>n</i>	Primary/ recurrence	Other treatment modalities	Follow-up (months)	LC	OS	Late toxicity
Aluwini <i>et al</i> ⁵⁷	102	Primary	Surgery/EBRT (40 Gy)	NR	5-, 10-year LC: 80%, 73% ^a	5-, 10-year OS: 75%, 65% ^a	≥Grade 3 GU: 5.8%; GI: 1% ^a
Nap <i>et al</i> ⁵⁴	77	Primary	Surgery/EBRT (40 Gy)	NR	NR	NR	Asymptomatic ulcers, one patient abscess of TUR cavity
Koning <i>et al</i> ⁵⁵	184	Primary	Surgery/ EBRT (10–55 Gy)	50	1-, 3-, 5-year LC: 91, 80, 75% ^a	1-, 3-, 5-, 10-year OS: 91%, 74%, 62%, 44% ^a	4 patients: fistula, 26 patients: necrosis, 19 patients: other complications ^a
Blank <i>et al</i> ⁵⁶	23	Primary	Surgery/EBRT (3 × 3.5 Gy or 20 × 2 Gy)	60	5-year LC: 76% ^a	5-, 10-year OS: 73%, 49% ^a	≥Grade 3: 0%

EBRT, external beam radiotherapy; GI, gastrointestinal; GU, genitourinary; LC, local control; LDR, low dose rate; NR, not reported; OS, overall survival.
^aPDR + LDR.

were soft tissue necrosis (STN) and osteoradionecrosis (ORN), both ranging from 3% to 15%. Haddad *et al*³⁶ showed that toxicity was significantly correlated with a pulse dose >0.75 Gy.

In recurrent HN cancer, the Erlangen group gave 60 Gy with PDR and approximately 25 Gy when combined with EBRT (approximately 50 Gy).^{41,48} Bartochowska *et al*³³ gave 20–40 Gy in their recurrence study. Krempien *et al*³⁷ boosted with 10- to 20-Gy PDR after 36-Gy EBRT. Strnad *et al*⁴¹ reported better 5-year LC if surgery was performed (82% with surgery *vs* 57% without surgery). Adding chemotherapy to the treatment also improved LC, but with more toxicity.⁴⁸ Again STN and ORN were the most common toxicities in these patients with almost the same frequency as in primary HN cancer.

Prostate cancer

PDR treatment for prostate cancer was reported in five articles.^{49–53} We excluded the article of Izard *et al*,⁴⁹ since they performed “HDR” with 18 Gy in three fractions (Tables 7 and 8).

The other two studies were by us (primary) and the group of Erlangen (primary and recurrence). We applied interstitial PDR after EBRT (46 Gy) with self-anchoring flexible catheters, and treatment planning was performed based on transrectal ultrasound (pre-planning) and CT.^{52,53} All patients received 24 pulses with a pulse dose ranging from 1.04 to 1.2 Gy in 2.0–2.2 h. The prescribed dose was approximately 25 Gy. Lettmaier *et al*⁵¹ used needles for interstitial PDR, and treatment planning was performed on transrectal ultrasound with geometrical optimization. A dose of 25–35 Gy in pulse doses of 0.6–0.7 Gy every hour was applied after EBRT (50.4 Gy). For recurrence, Lahmer *et al*⁵⁰ applied the same PDR technique but with a dose of 2 times 30 Gy without EBRT.

Outcome in the primary prostate was approximately 85–90% for 3-year biochemical progression-free (bPFS) survival and 5-year OS ranged from 85% to 96%. There was a significant better bPFS reported for 35 Gy PDR by Lettmaier *et al*.⁵¹ Late toxicity in both studies was low for GI and GU Grade 3 toxicity. Pieters *et al*⁵² reported no Grade 3 GI toxicity.

Table 11. Pulsed dose rate brachytherapy in anal cancer (technique and dose)

Author	<i>n</i>	Primary/ recurrence	Stage	Procedure	Type of applicator	Planning	Optimization	Source activity	Pulse size (Gy)	Period time (h)	Dose (Gy)	EQD2 (a/b = 10) (Gy) ^a
Bruna <i>et al</i> ⁵⁸	71	Primary	T1–T4	Interstitial	Ring template/ needles	X-ray	NR	63–763 mCi	0.5–1	1	17.8	20.8
Gerard <i>et al</i> ⁵⁹	19	Primary	T1–T4	Interstitial	Ring template/ needles	X-ray	No	18 GBq	0.5	1	10–25	25.2
Roed <i>et al</i> ⁶⁰	17	Primary	T1–T4	Interstitial	Ring template/ MUPIT/ needles	X-ray/CT	No	14.3 GBq and 33.7 GBq	0.6	1	25.2	26.2

EQD2, equivalent 2 Gy dose; MUPIT, multiple-site perineal applicator; NR, not reported.

^aHighest EQD2.

Table 12. Pulsed dose rate brachytherapy in anal cancer (outcome and toxicity)

Author	<i>n</i>	Primary/ recurrence	Other treatment modalities	Follow-up (months)	LC	OS	Late toxicity
Bruna et al ⁵⁸	71	Primary	EBRT (44–50 Gy)/ chemotherapy	28	LC: 90%	2-year OS: 90%	≥Grade 3: 17% (pain, bleeding, faecal incontinence or necrosis, temporary colostomy, abdominal pelvic resection)
Gerard et al ⁵⁹	19	Primary	EBRT (44–50 Gy)/ chemotherapy	>12	LC: 95%	OS: 100%	One patient incontinent
Roed et al ⁶⁰	17	Primary	EBRT (46 Gy)	NR	LC: 83%	NR	76% necrosis, 47% colostomy

EBRT, external beam radiotherapy; LC, local control; NR, not reported; OS, overall survival.

Lahmer et al⁵⁰ reported LC in almost 95% after PDR in recurrent prostate cancer, with 3-year bPFS of 57% and 3-year OS of 89%. They reported Grade 3 toxicity in 16.7% and had less morbidity than did salvage prostatectomy.

Bladder cancer

Four articles reported on PDR in bladder cancer after EBRT (10–55 Gy) (Tables 9 and 10).^{54–57} Koning et al⁵⁵ included the data of Blank et al but did not report on technique and planning specifically since this was a multicentre trial where every centre used their own technique and planning. Brachytherapy dose varied between 25 and 40 Gy for high-dose EBRT and 50–60 Gy for low-dose EBRT with centre-specific pulse dose. Aluwini et al⁵⁷ and Nap-van Klinken et al⁵⁴ used interstitial PDR after 40 Gy EBRT. Aluwini et al used 1 Gy per pulse every 3 h to a total dose of 30 Gy, and 5-year OS was 62–65%. Koning et al reported a significantly better LC for PDR than for continuous LDR (cLDR). No clear explanation for this observation was given. This difference between cLDR and PDR was not found in the study of Aluwini et al. This study also showed that this approach led to a bladder preservation of 85% after 10 years. Late toxicity was low. However, Koning et al reported necrosis in 15% of their patients. This was mainly caused if a higher EBRT dose was given.

Anal cancer

PDR in anal cancer was reported in three articles (Tables 11 and 12).^{58–60} The two French studies used a template with needles, whereas Roed et al used the multiple-site perineal applicator template.⁶¹ Treatment planning was performed on X-ray or CT with no optimization. Pulse dose varied from 0.5 to 1 Gy every

hour to a total dose of 10–25 Gy as a boost after 44–50 Gy EBRT. LC ranged from 83% to 95% with a 2-year OS rate of 90% reported by Bruna et al. Roed et al reported 76% necrosis and 46% had a colostomy. The toxicity in the French studies was lower, and they discussed that the higher dose and the larger treated volume could explain the high rate in toxicity.

Sarcomas of the extremities

Muhic et al⁶² reported on PDR in primary adult sarcomas of the extremities, whereas Lazzaro et al⁶³ also reported on recurrence (Tables 13 and 14). Interstitial PDR with plastic tubes was planned on X-ray or CT scan with no further optimization. Pulse dose ranged from 0.3 to 1 Gy every hour to a total dose of 15–20 Gy after EBRT (50–60 Gy) or 45 Gy if no EBRT was given. 3- to 5-year LC was from 83% to 89%, and 3- to 5-year OS was from 76% to 84%. Muhic et al reported 49% decrease of muscle force and function, 41% oedema, 31% pain and 21% wound complications.

Other tumour sites

12 articles reported on PDR on other tumour sites (Tables 15 and 16). Four articles were found on gynaecological malignancies. Vanneste et al⁶⁴ reported on PDR with a Ring applicator in post-operative endometrial cancer applying 28 Gy in pulse dose of 1 Gy every hour to the vaginal vault. Outcome was excellent with 3-year LC of 97% and 5-y OS of 84% comparable to the healthy population of that age. No Grade 3 toxicity was seen. Fokdal et al⁶⁵ included vaginal and recurrent endometrial and cervical cancer in their study. After EBRT (45–50 Gy), they applied PDR with a total dose of 30 Gy to the high-risk clinical target volume, with a 3-year LC of 97% and 5-year OS of 84% with only 3.5% late Grade 3 toxicity. Seeger et al⁶⁹ included

Table 13. Pulsed dose rate brachytherapy in sarcoma (technique and dose)

Author	<i>n</i>	Primary/ recurrence	Size (cm)	Procedure	Type of applicator	Planning	Optimization	Source activity	Pulse size (Gy)	Period time (h)	Dose (Gy)	EQD2 (a/b = 10) (Gy) ^a
Muhic et al ⁶²	39	Primary	3.6–15	Interstitial	Plastic tubes	X-ray/CT	NR	0.5–1 Ci	0.6	1	20	20.6
Lazzaro et al ⁶³	42	Primary/ recurrence	NR	Interstitial	Plastic tubes	CT	No	0.25–1 Ci	0.3–1	1	45, if EBRT: 15	53

EBRT, external beam radiotherapy; EQD2, equivalent 2 Gy dose; NR, not reported.

^aHighest EQD2.

Table 14. Pulsed dose rate brachytherapy in sarcoma (outcome and toxicity)

Author	<i>n</i>	Primary/recurrence	Other treatment modalities	Follow-up (months)	LC	OS	Late toxicity
Muhic <i>et al</i> ⁶²	39	Primary	Surgery/EBRT (50–60 Gy)	42	5-year LC: 83%	5-year OS: 76%	49% decreased force/function, 41% oedema, 31% pain, 21% wound complication
Lazzaro <i>et al</i> ⁶³	42	Primary/recurrence	Surgery/EBRT (50 Gy)/chemotherapy	34	3-year LC: 89%	3-year OS: 83.9%	3× oedema, 1× femoral artery stenosis

EBRT, external beam radiotherapy; LC, local control; OS, overall survival.

vulvar and vaginal cancer (primary and recurrence) with or without EBRT. Their LC was 89% for vulvar cancer and 100% after a median follow-up time of 41.5 months, and they reported late Grade 3 toxicity in only 4.5%. Jensen *et al*⁷² gave 30 Gy after EBRT in all types of gynaecological tumours. LC of 53% was lower than that of the more recent studies,^{10–12,65} with GI, GU and gynaecological Grade 3 toxicity approximately 15%.

Blank *et al* reported PDR in paediatric rhabdomyosarcoma (RMS) of the HN, which was combined with pre-operative chemotherapy, and after surgery, an adjustable silicon mould or thermoplastic material (Gutta-percha and FastForm-percha) to fit the cavity with plastic tubes was placed. After brachytherapy, reconstruction took place [the ablative surgery, mould technique brachytherapy and reconstruction (AMORE) procedure]. This was reported in two articles, *i.e.* orbital RMS and non-orbital RMS.^{66,67} A pulse dose of 1.25 Gy every 2.1 h was applied to a total dose of 40–45 Gy. Outcome in orbital RMS was good with a LC of 80% and 5-year OS of 92%. This was lower in non-orbital RMS with a LC of 75% and a 5-year OS of 73%. Late toxicity was reported in 4 of the 20 orbital RMS cases (cataract 2 ×, ptosis and retinopathy), although it is difficult to attribute toxicity to only brachytherapy because these patients underwent also surgery.

Crook *et al*^{73,74} reported on PDR in penile cancer in two articles, of which the last one is an update of the same study. Therefore, we excluded the first study. PDR was performed for organ preservation. Two or three parallel planes of needles were inserted using pre-drilled lucite templates for guidance and fixation. They applied 0.5–0.612 Gy per pulse every hour with the use of needles to a total dose of 60 Gy. 5-year and 10-year LCs were 88% and 73% with 5-year and 10-year cause-specific survival of 84% both. STN was found in 12% of patients and 9% had a meatal stenosis.

Skowronek *et al*⁶⁸ used PDR brachytherapy as a palliative treatment in bile duct cancer to alleviate jaundice. Interstitial tubes were transhepatically placed under fluoroscopic guidance. Pulse dose of 0.8 Gy every hour was given to a total dose of 20 Gy, and if rapid progression occurred after a week, another 20 Gy was applied. In 76.5% of the patients, improvement of jaundice was seen with no other toxicity.

Tepel *et al*⁷⁰ studied the feasibility of adjuvant PDR in recurrent colorectal cancer after resection. Pulse doses of 1 Gy were given every 2 h, 5 times a day to a total dose of 5–35 Gy. 5-year LC was

37% and 5-year OS was 38%, with late toxicity in 22% of the patients (perineal necrosis, fistula and urethral stenosis). There was a trend in favour of PDR compared with HDR. Harms *et al*⁷⁵ performed PDR in recurrent oesophageal cancer after primary radiotherapy (median 50 Gy). However, only an abstract could be obtained for this review. Treatment was carried out on an outpatient basis applying a weekly 5-Gy daytime schedule (0.5 Gy per pulse per hour, total dose 15–20 Gy). The dose was prescribed 10 mm from the mid-dwell position and encompassed the clipped tumour extension with 2-cm margins. After a median follow-up of 8 months, 50% had a partial or complete response. 4 out of 16 patients had a Grade 3 or higher toxicity and restricting the dose to <15 Gy was recommended in this palliative treatment.

Strege *et al*⁷¹ reported on PDR in primary and recurrent skull base tumours. They applied the same PDR scheme as Tepel *et al* to a total dose of 10–30 Gy. Owing to the diversity of the tumours, conclusions were not made.

DISCUSSION

Since PDR combines the physical advantages of HDR and the radiobiological advantages of cLDR, it has been applied for different tumour sites, *e.g.* cervical cancer, breast cancer and HN cancer. The data presented in this review show overall high tumour control and low toxicity. In time, optimized 3D treatment plans resulted in better sparing of OARs and high dose to the tumour, improving tumour control.^{12,13} With the introduction of MRI-guided brachytherapy, this can be even further improved.^{76,77} In cervical cancer, this is further being investigated in the EMBRACE study.⁷⁸

Disadvantages of cLDR were exposure to staff and employees and the absence of 3D optimized image-based treatment plans. With PDR, patients can have medical care between the pulses avoiding radiation hazard risks for employees. Interruptions in PDR treatment were hardly reported in the reviewed studies, although this does not indicate that the frequency was low. We reported a frequency of 0.6–14.9% disturbed pulses depending on tumour site and version 1 or version 2 afterloader in 1300 clinical treatments.⁷⁹ Of all patients treated, 98% received their dose as planned. Safety is further addressed by the use of correct applicators. For example, in prostate cancer, needle displacement is a common technical problem in HDR brachytherapy and a verification before treatment is necessary.⁸⁰ Checking every pulse in PDR is time consuming and unacceptable. Therefore, we developed

Table 15. Pulsed dose rate brachytherapy in other cancers (technique and dose)

Authors	Tumour type	<i>n</i>	Primary/ recurrence	Stage	Procedure	Type of applicator	Planning	Optimization	Source activity	Pulse size (Gy)	Period time (h)	Dose (Gy)	EQD2 (<i>a/b</i> = 10) (Gy) ^a
Vanneste et al ⁶⁴	Endometrium	74	Primary	FIGO IA-B	Intercavitary	Ring	CT	No	NR	1	1	28	32.8
Fokdal et al ⁶⁵	Vagina, recurrent endometrium and cervix	28	Primary/ recurrence	NR	Intercavitary/ interstitial	MUPIT + needles	CT	Geometric	TRAK: 1.16 cGy	0.6	1	30 (HR-CTV)	31.3
Blank et al ⁶⁶	Paediatric orbital RMS	10	Primary/ recurrence	I–III	Interstitial	Silicon moulds	CT	NR	NR	1.25	2.1	40–45	47.5
Blank et al ⁶⁷	Paediatric non-orbital RMS	13	Primary/ recurrence	I–III	Interstitial	Silicon moulds	CT	NR	NR	1.25	2.1	40–45	47.5
Crook et al ⁷³	Penile	41	Primary	T1–T3	Interstitial	Needles	No	No	0.3–1 Ci	0.5–0.612	1	60	63
Skowronek et al ⁶⁸	Bile duct	17	Primary	NR	Interstitial (transhepatic)	Plastic tubes	X-ray	NR	1 Ci	0.8	1	20 or 40	44.5
Seeger et al ⁶⁹	Vulva/vagina	22	Primary/ recurrence	FIGO I–III	Interstitial	Plastic tubes/ needles/ templates	X-ray	Geometric	TRAK: 0.16–0.17 mGy	0.4–0.7	1	10–63	68.2
Tepel et al ⁷⁰	Colorectal	23	Recurrence	I–IV	Interstitial	Plastic tubes	CT/MRI	Geometric	37 Gbq	1	² (5× a day)	5–35	–
Harms et al ⁷⁵	Oesophagus	16	Recurrence	NR	NR	NR	NR	NR	37 Gbq	0.5	¹ (daytime)	15–20	–
Strege et al ⁷¹	Skull base	15	Primary/ recurrence	IVa	Interstitial	Plastic tubes	CT/MRI	Geometric	NR	1	² (5× a day)	10–30	–
Jensen et al ⁷²	Gynaecological	34	Primary/ recurrence	FIGO II–III	Interstitial	MUPIT + needles	CT	Geometric	15–32 Gbq	0.6	1	30	31.3

CTV, clinical target volume; EQD2, equivalent 2 Gy dose; HR, high risk; MUPIT, multiple-site perineal applicator; NR, not reported; RMS, rhabdomyosarcoma; TRAK, total reference air kerma.

^aHighest EQD2.

Table 16. Pulsed dose rate (PDR) brachytherapy in other cancers (outcome and toxicity)

Authors	Tumour type	n	Primary/ recurrence	Other treatment modalities	Follow-up (months)	LC	OS	Late toxicity
Vanneste et al ⁶⁴	Endometrium	74	Primary	Surgery	37	3-year LC: 97% ^a	5-year OS: 84% ^a	≥Grade 3: 0%
Fokdal et al ⁶⁵	Vagina, recurrent endometrium and cervix	28	Primary/ recurrence	EBRT (45–50 Gy)/ chemotherapy	18	2-year LC: 92%	2-year OS: 74%	≥Grade 3: 3.5% obliteration of vagina
Blank et al ⁶⁶	Paediatric orbital RMS	10	Primary/ recurrence	Chemotherapy/ surgery	NR	LC: 80% ^a	5-year OS: 92% ^a	20% (amblyopia, ptosis, keratopathy/ retinopathy ^a)
Blank et al ⁶⁷	Paediatric non-orbital RMS	13	Primary/ recurrence	Chemotherapy/ surgery	NR	LC: 75% ^a	5-year OS: 73% ^a	2/11 bone, 3/11 secondary tumour ^a
Crook et al (2008)	Penile	41	Primary	None	48	5-, 10-year LC: 87.5%, 73%	5- to 10-year CSS: 84%	STN 12%, meatal stenosis 9%
Skowronek et al ⁶⁸	Bile duct	17	Primary (palliative)	EBRT (40 Gy)	NR	76.5% improvement jaundice	Median OS: 10 months	No late complications
Seeger et al ⁶⁹	Vulva/vagina	22	Primary/ recurrence	Surgery/EBRT (40–50 Gy)/ chemotherapy	41.5	LC vulva: 89%, vagina: 100%	NR	≥Grade 3: 4.5% necrosis
Tepel et al ⁷⁰	Colorectal	23	Recurrence	Surgery/EBRT (45 Gy)/ chemotherapy	20.6	5-year LC: 37%	5-year OS: 38%	22% (perinael necrosis, fistula, urethral stenosis)
Harms et al ⁷⁵	Oesophagus	16	Recurrence	None	8	NR	NR	Grade 3: 1/16; Grade 4: 3/16 (fistula, arterial bleeding)
Strege et al ⁷¹	Skull base	15	Primary/ recurrence	Surgery/ EBRT (40 Gy)	14.5	NR	Median OS: 16 months	No injuries to the eye
Jensen et al ⁷²	Gynaecological	34	Primary/ recurrence	Surgery/EBRT (46 Gy)/ chemotherapy	14	LC: 53%	1-, 2-year OS: 71%, 63%	≥Grade 3 GI: 15%; GU: 18%; Gyn: 15%

CSS, cancer-specific survival; EBRT, external beam radiotherapy; GI, gastrointestinal; GU, genitourinary; gyn, gynaecological; LC, local control; LDR, low dose rate; NR, not reported; OS, overall survival; RMS, rhabdomyosarcoma; STN, soft tissue necrosis.

^aPDR + LDR.

a self-anchoring catheter, which showed less absolute displacement of no clinical importance. However, a deviation in planned dose to the OAR was still reported based on the anatomical variation and organ motion of the OAR.^{81,82} In cervical cancer, the same results were found for the tandem/ovoid applicator.^{83,84}

Still PDR is only used in 16% of the brachytherapy centres in Europe. Moreover, the studies reviewed are only from a few centres across Europe or North America. In India, with a high frequency of cervical cancer, predominantly HDR brachytherapy is performed.⁸⁵ In France, the debate is on how to continue (PDR or HDR) since low dose rate iridium-192 wires are no longer available.⁸⁶ Technically, PDR and HDR do not differ. The same applicators, plastic tubes or needles are used in both techniques. The same is true for treatment planning optimization. The question remains why PDR has not been adopted more extensively on a global scale in the last two decades.

It has been theoretically suggested that PDR has a better radiobiological effect on OARs than HDR had. However, no data

are present that compared late toxicity for PDR vs HDR to investigate this hypothesis. If we compare the studies in this review, none of them that used both PDR and HDR reported less late toxicity in PDR. Late toxicity data in literature⁸⁷ on HDR is scarce and if reported show low morbidity as for example in prostate cancer.

Moreover, the management to facilitate PDR brachytherapy has a complete different approach compared with HDR. For PDR, treatment takes a couple of days and therefore hospitalization is often required. By contrast, HDR can be performed in an outpatient setting since treatment time is short and more patients can be treated with the same afterloader in the same time as one patient receiving a PDR treatment. This plays an important role if we take cost-effectiveness into account. Guedea et al⁸ showed that 59% of the brachytherapy clinics in Europe have only one afterloader and perform HDR. In less developed countries such as India, it is likely to treat with a high patient load with HDR instead of PDR taking into account the total cost.

The question remains if all tumour sites can be effectively treated with HDR only. For cervical cancer, a Cochrane review showed no difference in outcome, control or toxicity with HDR compared with cLDR.⁸⁸ When considering the relative dose distribution PDR is comparable to HDR. For a better understanding of the efficacy of PDR compared with HDR with contemporary MRI-guided brachytherapy in cervical cancer, the results of ongoing studies and in particular the EMBRACE study should be awaited.⁷⁸ In breast cancer, HDR was used as a boost and a higher grade of fibrosis was expected. However, only <5% of the patients had severe fibrosis.^{89,90} HDR brachytherapy has also been implemented in prostate cancer⁹¹ and soft tissue sarcoma.⁹² In HN cancer, HDR can be applied based on tumour site and current evidence, *i.e.* oropharynx and nasopharynx, although more multifractionated schemes were applied for the same arguments as PDR to decrease normal tissue effects. For other HN sites, studies with HDR are scarce.⁹³ However, in bladder cancer, HDR brachytherapy resulted in less LC and more late toxicity than did cLDR.⁹⁴ Pos et al attributed the observed treatment outcome owing to the wrong choice of high-fraction HDR dose for bladder carcinoma cells having a high α - p ratio of 10–15 Gy. Therefore, also in this situation, a multifractionated low-dose HDR schedule or PDR schedule is preferable.

Only scarce data are available on paediatric brachytherapy. The most elaborate studies with long follow-up have used LDR schedules.⁹⁵ The preferable use of PDR for the treatment of children originates from the radiobiological fact to spare normal tissue comparable to LDR. This sparing of tissue in children is particularly important because when cured, they will survive for a long time. Studies that have used HDR advocate low-dose multifractionated HDR schedules to reduce the risk of late sequelae.⁹⁵ In fact, the dose rate within a PDR pulse is given at HDR, but it is the pulse size that determines the radiobiological effect.⁵

CONCLUSION

PDR brachytherapy can be used for different tumour sites with good LC and low toxicity. PDR brachytherapy has been applied in almost all tumour sites for which brachytherapy is indicated. For certain institutes and in some countries, HDR is more often adapted as treatment strategy with duration of the treatment and cost-effectiveness as an argument. The main advantage of PDR is, because of the small pulse sizes used, the ability to spare normal tissue. In certain cases, HDR resembles PDR brachytherapy by the use of multifractionated low-fraction dose.

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