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Original Research Article

Brachytherapy boost in anal canal cancer – A GEC ESTRO PDR task force meta-analysis

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ABSTRACT

Purpose: A meta-analysis is presented comparing clinical outcomes and toxicities between high dose rate (HDR) and pulsed dose rate (PDR) brachytherapy (BT) for anal cancer.
Methods and material: Retrospective or prospective clinical trials were identified on electronical databases. Data were collected per Preferred Reporting Items for Systematic Reviews and meta-Analyses guidelines. Pooled effect size for HDR and PDR BT were compared using subgroup analyses.
Results: Nine retrospective studies with a total of 481 patients treated were included of which 219 with HDR and 262 with PDR. Significant differences were observed between the two groups for baseline characteristics and treatment. The cumulative proportion of stage T3-T4 was lower in the HDR group, 0.15 [95 % confidence interval (CI) 0.07–0.29] vs 0.27 [95 %CI 0.09–0.57] in the LDR group, $p < 0.001$. Lower BT doses (in equivalent 2-Gy fraction dose) were given for patients in the HDR group, 11.9 Gy [95 %CI 8.2–15.5] vs 19.5 Gy [95 %CI 15.0–24.0] in the PDR group, $p < 0.001$. No significant differences were found for clinical outcomes or toxicities. The pooled effect size of the overall survival at 5 years for HDR and PDR was respectively 0.82 [95 %CI 0.70–0.94] and 0.82 [95 %CI 0.73–0.91], $p > 0.99$. The 5 years local control was 0.86 [95 % confidence interval (CI) 0.81–0.91] and 0.83 [95 %CI 0.77–0.89], $p = 0.62$. Cumulative toxicity-related colostomy proportion was 0.04 [95 %CI 0.02–0.09] and 0.03 [95 %CI 0.02–0.07], $p = 0.85$.
Conclusion: Both modalities provided a good profile of tolerance and are effective organ conservative strategies for patients with anal canal cancer. In parallel with ongoing developments to better determine the optimal fractionation and dose for HDR-BT treatments, especially in large tumors, PDR BT still has a crucial role for dose escalation strategy in advanced cases.

Introduction

Definitive radiotherapy and concomitant chemotherapy plays a major role in the treatment of anal canal cancer and represents the standard of care of cancer stage II-III of anal margin and stage I-III of anal canal [1]. However, the dose for a boost after 50 Gray (Gy) as well as the place and the modality of brachytherapy (BT) are still under debate.

BT gives the possibility to focally increase the dose to the tumor while sparing organs at risk, including non-involved parts of the anal canal [2]. Historically, BT boost was delivered through continuous low dose rate (LDR) irradiation, because of radiobiological grounds allows for optimal normal tissue sparing. High-dose rate (HDR) brachytherapy and pulsed-dose rate (PDR) BT have progressively replaced LDR BT. HDR BT shows physical advantages, compared to Iridium 192 wires (better dose optimization, radiation safety, and short treatment time)

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[3]. Pulsed-dose rate (PDR) BT combines physical advantages of HDR and radiobiological advantages of LDR brachytherapy. In PDR, instead of delivering the dose continuously as in LDR, a series of hourly HDR pulses, continuing few minutes each hour, is delivered. Typically, the overall dose and treatment time are same as corresponding LDR schedule. PDR compared to LDR has many distinct advantages such as isodose optimization, better therapeutic ratio attributed to multiple fractionation regimens as well as excellent radiation protection [4,5]. From a logistic point of view, the main disadvantage of the PDR compared to the HDR is the need for a hospital room equipped with a remote control afterloading system. Therefore it should increases cost and limits the possible number of BT procedures that can be performed daily.

Since no large randomized trial exist, it is difficult to compare efficacy and toxicity profile of PDR BT and HDR BT. The aim of this study was to explore the literature performing a systematic review and meta-analysis.

Materials and methods

Protocol

We conducted this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and meta-analysis (PRISMA) statement [6].

A systematic search was conducted by two investigators in Cochrane Central Register of Controlled Trials, PubMed, and Google Scholar until July 2021 for studies assessing the treatment outcomes of HDR and PDR BT boost for patients with anus neoplasm. We have used the following terms:

((“anus neoplasms” [MeSH Terms]) OR ((“anal” [All Fields] OR “anus” [All Fields]) AND (“cancer” [All Fields] OR “neoplasm” [All Fields]))) AND (“brachytherapy” [MeSH Terms] OR “brachytherapy” [All Fields]).

Study selection

To be included, studies should be prospective or retrospective, with more than 20 patients by BT modalities (e.g. HDR or PDR) and with at least 24 months of median follow-up time. In all cases, patients received BT as a boost. Studies without details on baseline characteristics, survival and toxicity provided separately for each BT modalities were excluded. Were also excluded: groups undergoing local excision prior to RT, intra-luminal BT and association with other experimental treatment. In the studies with other groups of treatments (i.e. EBRT boost), we included only the groups that fulfilled the criteria above mentioned. Flowchart in Fig. 1. Studies included are listed in Table 1.

Outcomes

Primary outcome was the proportion of toxicity-related colostomy. Secondary outcomes included proportion of toxicity grade 3 or more, 5-

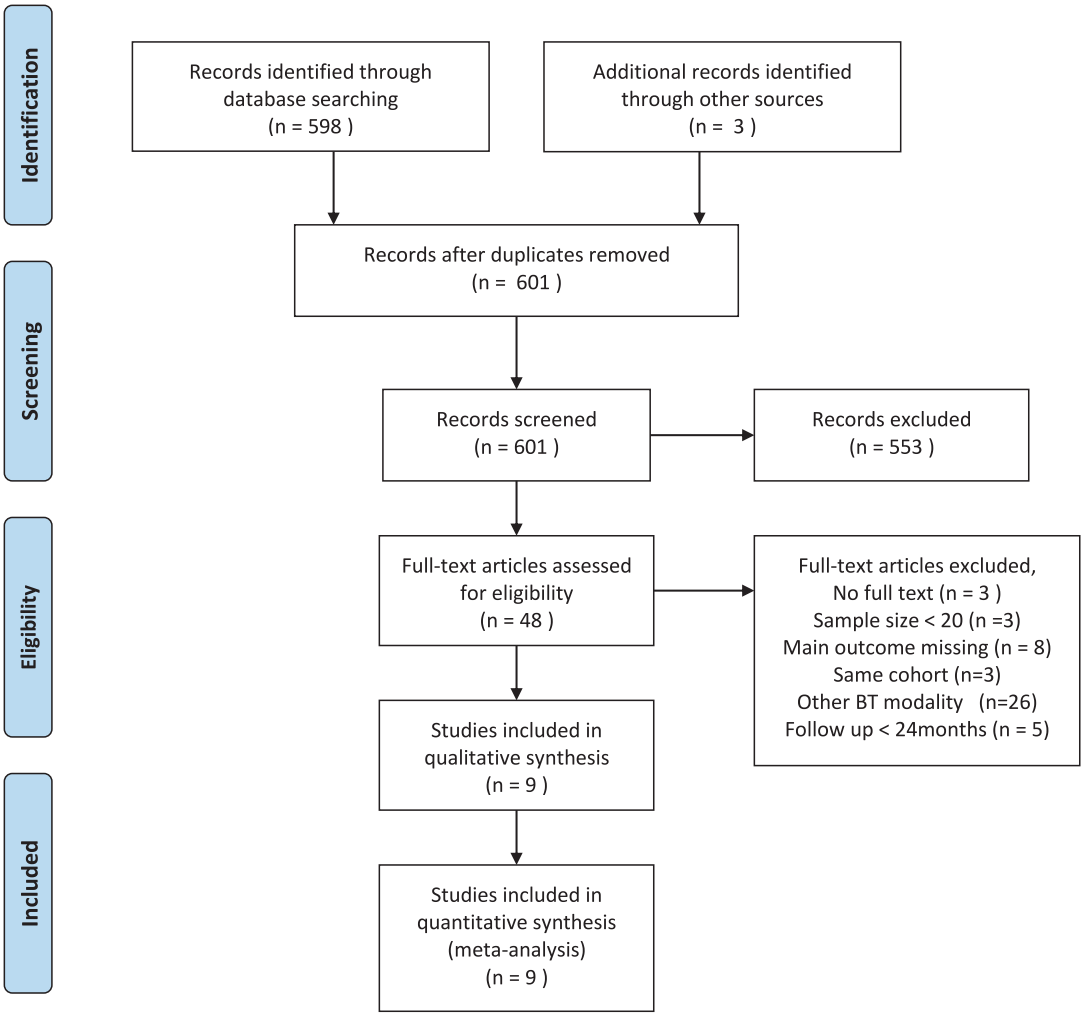

Fig. 1. PRISMA flow diagram illustrating the systematic process conducted to select data. BT: brachytherapy.

Table 1
Patient and tumor characteristics.

Authors, year of publication	BT modality	Country	Mono/multicentric	Median FU (years)	Patients' characteristics			Tumor characteristics	
					Number	% male	Age (median)	% T_3-T_4	% N_1-N_3
Karin Sigrid Kapp, 2001	HDR	Austria	monocentric	31	39	23.1	59	25.6	20.5
Julius Marek Doniec, 2006	HDR	Germany	monocentric	34	50	20.0	64	16.0	30.0
Christoph Oehler-Jänne, 2007	HDR	Switzerland	monocentric	60	34	11.8	60.4	29.4	26.5
Emilien Bertin, 2018	HDR	France	monocentric	61	46	19.6	65	4.3	13.0
Leonel Varela Cagetti, 2019	HDR	France	monocentric	33	50	16.0	67	6.0	6.0
Antoine Bruna, 2006	PDR	Belgium, France	multicentric	28.5	71	15.5	61.2	22.5	26.8
Thomas Gryc, 2016	PDR	Germany	monocentric	60	47	29.8	60	55.3	34.0
Alessandra Arcelli, 2019	PDR	Italy	monocentric	71	102	29.4	61	38.2	52.0
Remi Bourdais, 2021	PDR	France	monocentric	60.4	42	16.7	69	4.8	11.9

BT: brachytherapy, FU: follow-up, HDR: high dose rate, PDR: pulsed dose rate.

years colostomy-free survival rate, 5-years local recurrence-free survival rate, 5-years disease-free survival rate and 5-years overall survival rate. Survival data were extracted from the Kaplan Meier curve for each study using WebPlotDigitizer [7].

Clinical & treatment data

The variables that were likely to affect clinical outcomes were collected such as 1) patient's characteristics: gender, mean age, mean follow-up time; 2) tumor's characteristics: T and N classification according to the Union for International Cancer Control (UICC), histology; 3) treatment characteristics: mean BT dose, volume related to the prescription dose, rate of concurrent chemotherapy and EBRT technics. If not available, mean and standard deviation (SD) were estimated following the method described by Hozo et al. [8] EQD2 dose was estimated using the linear quadratic model (LQM); i.e. α/β ratio = 10 Gy (for tumor), repair halftime ($T_{1/2}$) = 1.5 h.

Data synthesis and analysis

Proportions were logit-transformed before the meta-analysis and then pooled using a random effect model. Between-group mean differences were pooled with an inverse variance method using a random effect model. Pre-calculated effect sizes of survival data were estimated for each study and then pooled using a random effect model. To explore the differences between HDR and PDR groups, a subgroup analysis method was performed. In all analyses, a p-value$<$0.05 was considered statistically significant. The meta-analysis was performed using the RStudio open software with "meta" and "metafor" R packages [9–11].

Results

Patient and tumor characteristics

Nine retrospective studies with a total of 481 patients were included of which 219 treated with HDR and 262 treated with PDR [12–20]. The overall time period for all included studies ranged from 2001 to 2021. Mean follow-up time was significantly shorter in the HDR group, 51 months [IC95%, 33–68] versus (vs) 71 months [IC95%, 20–122] in the PDR group, $p < 0.001$. Mean age was respectively 61 years [IC95%, 59–63] and 60 years [IC95%, 58–62], $p = 0.84$. Gender ratio (male/female) was respectively 0.19 [IC95%, 0.13–0.26] and 0.24 [IC95%, 0.18–0.30], $p = 0.22$.

Proportion of stage T3 and T4 was significantly lower in the HDR group, 15 % [IC95%, 7–29] vs 27 % [C95%, 9–57] in the PDR group, $p < 0.001$. Patient and tumor characteristics are described in Table 1.

Treatment characteristics

Eight studies reported a prescription to the 85 % reference isodose. One study didn't report it [15]. No study reported the volumes of the prescription isodose. Mean BT EQD2 dose was significantly lower in the HDR group, 11.9 Gy [IC95%, 8.2–15.5] vs 19.5 Gy [IC95%, 15.0–24.1] in the PDR group, $p < <0.001$. Alternative EQD2 estimation, with another α/β ratio and $T_{1/2}$, is detailed in Table 2. Proportion of IMRT treatment was significantly higher in the HDR group, 15 % [IC95%, 3–51] vs 4 % [IC95%, 0–61] in the PDR group, $p < 0.01$. Proportion of concomitant chemotherapy was significantly lower in the HDR group, 70 % [IC95%, 61–77] vs 81 % [IC95%, 33–97] in the PDR group, $p < 0.01$. Treatment characteristics are described in Table 3.

Survival outcomes

All but one study reported survival data of local recurrence. Five-years local recurrence-free survival rates for HDR and PDR groups were respectively 85.6 % [IC95%, 80.7–90.5] and 83.0 % [IC95%, 77.0–89.1 %], $p = 0.52$. Corresponding forest plot in Fig. 2. Six studies reported the colostomy-free survival rate. Five-years colostomy-free survival rates were respectively 79.6 % [IC95%, 71.4–87.8] and 76.4 % [IC95%, 53.6–99.2], $p = 0.79$. Six studies reported the disease-free survival rate. Five-years disease-free survival rates were respectively 73.5 % [IC95%, 66.1–81.0] and 72.4 % [IC95%, 55.6–89.3], $p = 0.90$. Seven studies reported the overall survival rate. Five-years overall survival rates were respectively 81.9 % [IC95%, 70.3–93.5] and 82.0 % [IC95%, 72.6–91.4], $p < 0.99$.

Toxicities

All studies reported the number of toxicity-related colostomies. Proportion of toxicity-related colostomy in the HDR group was 4 % [IC95%, 2–9] vs 3 % [IC95%, 2–7] in the PDR group, $p = 0.67$. Corresponding forest plot in Fig. 3. Seven studies reported the number of pelvic late toxicity grade 3 or more (including colostomy). Proportion of pelvic late toxicity grade 3 or more was respectively 7 % [IC95%, 4–12] vs 10 % [IC95%, 4–26], $p = 0.25$.

Discussion

PDR and HDR BT are both excellent treatment modalities to boost residual disease and spare uninvolved parts of the anus in treatment of anal canal carcinoma. From a radiobiological point of view, the therapeutic ratio should theoretically be better for PDR BT and to reach the same local control probability, HDR should lead to more frequent and/or severe toxicities than PDR [21]. Clinical data however do not confirm this hypothesis and there is growing evidence that both PDR and HDR-BT provided excellent clinical outcome, if properly applied. In a recent pooled analysis, limited toxicity and excellent local control with HDR BT in combination with external radiotherapy and chemotherapy was found [22].

The basic premise to design this meta-analysis was to gather high-quality studies reporting the treatment outcomes. Guided by this assumption, we included only studies with more than 20 patients by BT

Table 2
Alternative EQD2 estimation.

HDR studies	α/β (Gy)	3			7			10		
Karin Sigrid Kapp 2001		17.6			13.3			12		
Julius Marek Doniec 2006		14.2			12.0			11.4		
Christoph Oehler-Jänne 2007		14			14			14		
Emilien Bertin 2018		18.2			16.3			15.8		
Leonel Varela Cagetti 2019		21.5			18.1			17.1		
PDR studies	**α/β (Gy)**	**3**			**7**			**10**		
	$T_{1/2}$ (h)	**0.5**	**1.5**	**4**	**0.5**	**1.5**	**4**	**0.5**	**1.5**	**4**
Antoine Bruna 2006		18.0	26.2	43.2	19.6	24.2	33.6	20.1	23.6	30.6
Thomas Gryc 2016		11.1	14.6	21.9	12.9	14.8	18.9	13.4	14.9	18.0
Alessandra Arcelli 2019		16.1	22.2	35.5	18.1	21.5	28.9	18.8	21.3	26.9
Remi Bourdais 2021		14.6	19.0	29.0	17.0	19.4	25.0	17.7	19.6	23.7

HDR: high dose rate, PDR: pulsed dose rate, **α/β**: alpha/beta ratio, $T_{1/2}$: repair halftime.

Table 3
Treatment characteristics.

Authors, year of publication	BT			EBRT		
	Dose rate	Mean eqd2 (Gy) with sd	Median EBRT to BT gap (day)	Median total/fraction dose (Gy)	% IMRT	% Concomitant chemotherapy
Karin Sigrid Kapp, 2001	HDR	8 (1.5)	17	50.4/1.8	0	71.8
Julius Marek Doniec, 2006	HDR	9.3 (1.0)	42	45/1.8	0	–
Christoph Oehler-Jänne, 2007	HDR	14 (0.7)	21	45/1.8	0	79.4
Emilien Bertin, 2018	HDR	14 (0.8)	17	45/1.8	54.3	71.7
Leonel Varela Cagetti, 2019	HDR	14 (2.0)	16	45/1.8	74.0	60.0
Antoine Bruna, 2006	PDR	21.1 (2.0)	29	45/1.8	–	–
Thomas Gryc, 2016	PDR	15.1 (7.6)	40	53.5/1.8	2.1	89.4
Alessandra Arcelli, 2019	PDR	20.7 (2.3)	–	45/1.8	0	94.1
Remi Bourdais, 2021	PDR	20 (5.8)	23	44/2	45.2	38.1

BT: brachytherapy, EBRT: external beam radiation therapy, HDR: high dose rate, PDR: pulsed dose rate, sd: standard deviation, IMRT: Intensity-modulated radiation therapy.

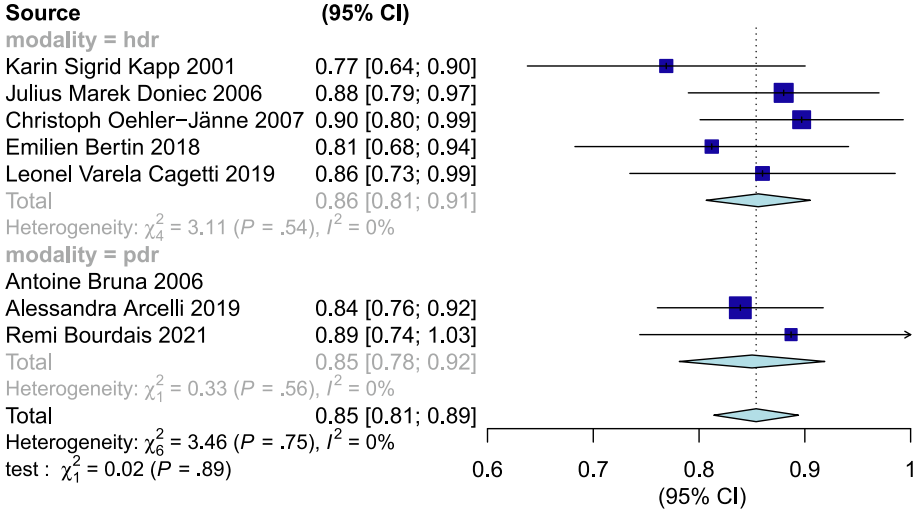

Fig. 2. Forest plot of five-year local recurrence-free survival rate. HDR: high dose rate, PDR: pulsed dose rate, CI: confidence interval.

modalities (e.g. HDR or PDR) and with at least 24 months of median follow-up time. Using these criteria, we identified nine uncontrolled studies reporting on retrospective data. To date, this is the only meta-analysis evaluating the toxicities and treatment outcomes according to BT modality in anal canal cancer. In analyzed papers there were no significant difference between BT modalities regarding the rate of toxicity-related colostomy or pelvic toxicity grade 3 or more. Also the results show excellent local control and toxicity data as compared to external beam radiotherapy series. For T1-T2 tumors, both HDR and PDR-BT use yield to high local control rate and low morbidity. We observed that patients treated with PDR had significant more advanced tumors (T3/T4 and/or cN + tumors) and longer follow-up. Secondly, patients treated with PDR had more aggressive treatment as they were more likely to receive higher brachytherapy dose and concurrent chemotherapy. In this meta-analysis, patients had more advanced tumors in the PDR group, but the survival results did not significantly differ from those in the HDR group. This observation is in accordance with tumor control probability models suggesting that lower doses may

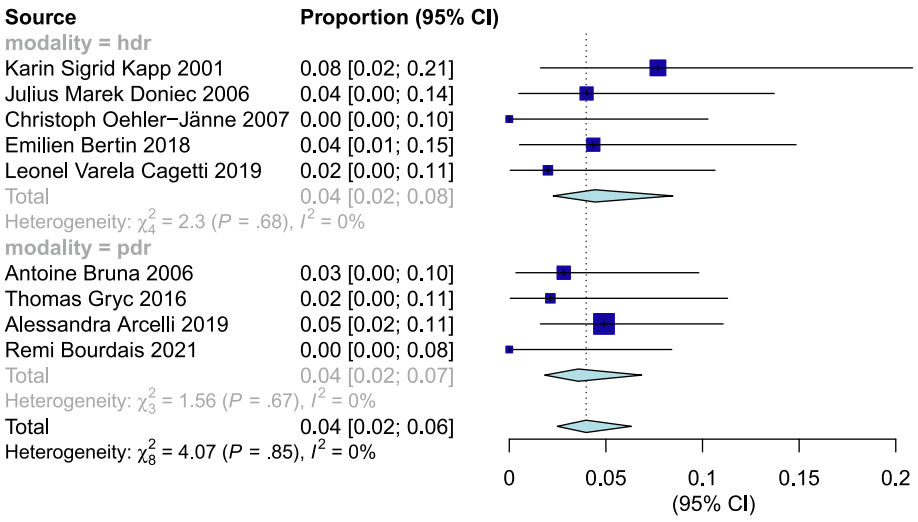

Fig. 3. Forest plot of the proportion of colostomy related to toxicity.

be sufficient for small tumors such as T1-T2, while higher doses may be required for more advanced tumors [23,24]. To date, regarding evidence based medicine the optimal total dose including the boost vary between physical doses of 50.4 Gy (ACT II trial) and 55–59 Gy for T3-T4 or node-positive (RTOG 98–11 trial) [25,26]. European Society of Medical Oncology (ESMO) guidelines recommended total doses of at least 45–50 Gy for T1–2 N0 while higher doses may be required for more advanced or poor responding tumors, using boost doses to the primary tumor ranging from 15 to 25 Gy EQD2 [1]. In the studies included in the meta-analysis, all the HDR studies reported a median BT dose lower than 15 Gy EQD2 while in all PDR studies the median BT dose was higher than 15 Gy EQD2. Thus, while the boost of 15 Gy or higher provided with PDR appeared safe and effective, additional clinical data are needed to refine the optimal fractionation and dose for HDR-BT treatments in advanced cases.

This analysis is subject to the inherent selection bias of the retrospective studies, but given the rarity of centers performing BT boost, randomized data will likely never be acquired. There were discrepancies in the quality, size, and selection processes within the studies included in the meta-analysis. Most of the studies didn't provide details on toxicities, however every study reported the number of toxicity-related colostomy. Only seven studies reported the late pelvic toxicity grade 3 or more. Late toxicities Grade 2 or more were not detailed in most of the studies. This is why we chose toxicity-related colostomy as the main criteria. Regarding local control, data extraction from Kaplan Meier curve was available for all but one study and overall survival for all studies. There was also the possibility of a selection bias. The most evident was the tumor stage that was more advanced in the PDR group. Because HDR BT was applied more recently than PDR-BT, there are fewer published data, especially for advanced tumors. Moreover, the study published by Gryc et al. included patients selected for poor tumor responses after EBRT, but despite this selection bias, survival outcomes and toxicities in this study were in the range of the other PDR studies. Another limitation is the low number of studies included in the meta-analysis, which didn't allow us to adjust for confounding factors by performing a meta-regression analysis. As well the minimum sample size of the selected studies is low therefore the bias caused by sampling error should be strongly considered. In addition, there is in the literature heterogeneity in dose reporting among series and in next studies, a reproducible target and appropriate dose reporting concept will be mandatory for accurate dose/response and dose finding analysis. There are scarce data on modern approaches involving the possibility to include MRI based target concepts in brachytherapy for anal canal cancer, as well as transrectal ultrasound guided implantations with MRI-compatible applicators and careful dose optimization based on the ground rules of the Paris system. To date, dose/effect relationships to guide treatment planning and optimization are lacking. Beyond the question of comparing PDR and HDR, further studies are warranted to better identify dose/response effects and therefore guide total dose and fractionation choice. The observation that higher levels of EQD2 doses were used with PDR BT may question the clinical relevance of LQM to provide reliable comparison tools for the biological effect in all clinical scenarios. In retrospective series of patients treated for lip cancer with BT, equieffectiveness was shown with LDR BT at 70 Gy EQD2, and HDR BT schemes delivering 45 Gy in 9 fractions of 5 Gy (EQD2 = 56.3 Gy [27]. These observations suggest that choice of fractionation should rely on published clinical data, not only on EQD2 calculation derived from LQM. A limitation is the use of 1.5 h half time of repair as a standard value. In case of lower half time of repair the calculated PDR EQD2 values would be lower, which could explain such observed equieffectiveness. Lower EQD2 values explaining tumor control of PDR would not directly lead to a substantially reduced therapeutic window, as the half time of repair could be also lower for late reactions in OARs.

In conclusion, it is not possible to draw conclusions on the superiority of one BT modality over another, because of the study design and limitation highlighted above. Both PDR and HDR BT modalities provided a high efficacy for boosting anal canal cancer, with good profile of tolerance, but using significant different dose levels according to the EQD2 model (mean BT EQD2 dose 11.9 Gy with HDR BT vs 19.5 Gy with PDR BT, $p < <0.001$) and with PDR BT more frequently used for advanced cases (T3/4N + tumors). These higher doses were not associated with higher incidence of late side effects in reported retrospective analyses. For now, PDR BT still has a crucial role to increase the dose in advanced cases, in parallel with ongoing developments to better determine the place of HDR for large tumors and with dose escalation strategies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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