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Radiobiological optimization comparison between pulse-dose rate and high-dose rate brachytherapy in locally advanced cervical cancer patients

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Abstract

Objective: Only scarce data are available on the possibility to include radiobiological optimization as part of the dosimetric process in cervical cancer treated with brachytherapy (BT). We compared dosimetric outcomes of pulse-dose rate (PDR) and high-dose rate (HDR)-BT, according to linear quadratic model (LQM).

Methods: 3D dosimetric data of 10 consecutive patients with cervical cancer undergoing intracavitary image-guided adaptive PDR-BT after external beam radiation therapy (EBRT) were examined. A new HDR plan was generated for each patient using the same method as for the PDR plan. The procedure was intended to achieve the same $D_{90CTV_{HR}}$ with HDR as with PDR planning after conversion into dose equivalent per 2 Gy-fractions (Gy_{EQD2}) following LQM. Plans were compared for dosimetric variables.

Results: As per study's methodology, the $D_{90CTV_{HR}}$ was strictly identical between PDR and HDR plans: 91.0 Gy (Interquartile: 86.0-94.6 Gy). The median $D_{98CTV_{IR}}$ was 62.9 Gy_{EQD2} with HDR, versus 65.0 Gy_{EQD2} with PDR ($p<0.001$). The median bladder D_{2cc} was 65.6 Gy_{EQD2} with HDR, versus 62 Gy_{EQD2} with PDR ($p=0.004$). Doses to the rectum, sigmoid and small bowel were higher with HDR plans with a median D_{2cc} of 55.6 Gy_{EQD2} (versus 55.1 Gy_{EQD2} , $p=0.027$), 67.2 Gy_{EQD2} (versus 64.7 Gy_{EQD2} , $p=0.002$) and 69.4 Gy_{EQD2} (versus 66.8 Gy_{EQD2} , $p=0.014$) respectively. For organs at risk (OARs), the effect of radiobiological weighting depended on the dose delivered. When OARs BT contribution to D_{2cc} doses was $<20 Gy_{EQD2}$, both BT modalities were equivalent. OARs Gy_{EQD2} doses were all higher with HDR when BT contribution to D_{2cc} was $\geq 20 Gy_{EQD2}$.

Conclusion: Both BT modalities provided satisfactory target volume coverage with a slightly higher value with the HDR technique for OARs D_{2cc} while CTV_{IR} received higher dose in the PDR plan. The radiobiological benefit of PDR over HDR was predominant when BT contribution dose to OARs was $> 20Gy$.

Keywords: linear quadratic model; pulse dose rate brachytherapy; high dose rate brachytherapy; cervical cancer; radiobiological effect.

67 **Background**

68 Intracavitary brachytherapy (BT) delivered after concurrent chemoradiation plays a major role in the
69 treatment of locally advanced cervical cancer (LACC) and represents the standard of care (1). To date
70 the diverse treatment approaches derived from historical BT schools (e.g. Manchester, Paris,
71 Stockholm) still dominate the basic dosimetric principles. In addition, many new developments such
72 as new applicators, image-guided adaptive BT (IGABT) and the high-dose (HDR) and pulse-dose rate
73 (PDR) remote control afterloading systems, have contributed further to increase optimization
74 capabilities.

75 HDR brachytherapy was initiated in the late 1950s with ^{60}Co and has been increasingly used
76 for the treatment of LACC. Currently, HDR is widely used instead of low-dose rate (LDR) and has
77 substantial advantages in terms of physics properties and convenience (dose optimization, radiation
78 safety, and short treatment time). Radiobiologically, LDR is considered advantageous over HDR in
79 terms of late tissue effects, although not reflected in randomized trials reporting that probabilities of
80 local control and overall survival were similar for LDR and HDR treatments (2–5). However, those
81 trials have been criticized for a number of methodologic limitations (patients and tumors
82 heterogeneity, utilization of different radiation techniques, follow-up limitations) (6). In a
83 randomized comparison of two LDR dose rates (0.4 versus 0.8 Gy/h), prevalence of complications
84 over time was increased in the higher dose rate group, without difference in terms of local control,
85 confirming that dose rate had a differential impact between tumor and normal tissue response (7).

86 PDR-BT was developed in the 1990s, theoretically combining physical advantages of HDR and
87 radiobiological advantages of LDR brachytherapy. With PDR-BT, instead of delivering the dose
88 continuously as in LDR, a series of continuous hourly pulses is delivered, few minutes each hour.
89 Typically, the overall dose and treatment time are the same as corresponding LDR schedule. PDR
90 compared to LDR has many specific advantages such as isodose optimization capability, better
91 therapeutic ratio attributed to multiple fractionation regimens leading to cell cycle redistribution, as
92 well as excellent radiation protection(8,9). From a logistic point of view, the main disadvantage of the
93 PDR compared to HDR is the need for a dedicated hospital room equipped with a remote
94 afterloading system. Therefore the possible number of BT procedures that can be performed daily is
95 limited. On the other hand, the number of applications is reduced.

96 To date, only scarce data are available on the possibility to include radiobiological
97 optimization as part of the dosimetric process, although this strategy has been pointed out in the last
98 International Commission on Radiation Units and Measurements (ICRU) guidelines dedicated to BT

(10). The aim of this study was to explore the radiobiological impact of BT modality on dosimetric outcomes, according to linear quadratic model (LQM).

Methods

Patient population

Clinical and dosimetric data of ten consecutive patients receiving intracavitary image-guided adaptive BT after pelvic external beam radiation therapy (EBRT) and concomitant chemotherapy in 2016 for a LACC were examined. Only patients with NO disease after an exhaustive pre-treatment workup were included to overcome the issue of potential contribution of simultaneous lymph node boosts.

The EBRT radiation procedure has been reported in detail before (11). Briefly, all patients received a pelvic EBRT, with a normal fractionation delivering 45 Gy in 25 daily fractions over 5 weeks, delivered through intensity modulated radiotherapy (Helical TomoTherapy®, Accuray, California).

Linear-quadratic model

For radiobiological weighting, the LQM for incomplete repair was used (12). As an input for the model, the GEC-ESTRO (Groupe Européen de Curiethérapie – European Society for Radiotherapy & Oncology) recommendations suggest a uniform value of alpha/Beta ratio (α/β) = 10 Gy for tumour and clinical target volume (CTV) and α/β = 3 Gy for all OARs. The modelling of PDR requires a value for the half time of tissue repair ($T_{1/2}$), although $T_{1/2}$ is not as consolidated as the previous biological parameters, the GEC-ESTRO refers that 1.5 h is the “best estimate” for this parameter, therefore this value was used for all tissues involved. With these parameters, the biological equivalent dose in 2-Gy fractions EBRT (EQD2) was calculated (12). Cumulative dose volume histograms (DVH) were generated, by adding the contribution of EBRT (45 Gy in 25 fractions) with that of BT.

PDR BT procedure

The implantation technique description is available in a previous publication (11). After the implantation, based on the vaginal mould applicator technique, a pelvic MRI was acquired, with T2

sagittal, axial, and coronal sequences, which were transferred to BrachyVision (Varian Medical Systems, Palo Alto) platforms in order to perform contouring of the gross target volume (GTV), high risk CTV (CTV_{HR}), intermediate risk CTV (CTV_{IR}) and organs at risk (OAR) according to European recommendations from the GEC-ESTRO (12). The planning process started with an activation of the dwell positions in regard to the CTV_{IR}, and a standard physical dose of 15 Gy in 30 pulses of 0.5 Gy (corresponding to an EQD2 dose of 15 Gy_{EQD2} according to LQM) was prescribed and normalized to Point A. The optimization process was aimed at achieving the following planning objectives: D₉₀ (minimum dose delivered to 90% of the volume) to the CTV_{HR} ≥ 85 Gy_{EQD2}, D₉₈ CTV_{IR} ≥ 60 Gy_{EQD2}, D_{2cc} (minimum dose delivered to most exposed 2cc) of the bladder ≤ 85 Gy_{EQD2}, D_{2cc} of the rectum and sigmoid ≤ 75 Gy_{EQD2}. Dwell times and positions were adjusted manually by the same pair of radiation oncologist and physicist, in an iterative way until DVH constraints were fulfilled as best as possible.

Conversion to HDR planning treatment

A new Iridium 192 HDR dosimetry was performed for each patient using the same image set than for the PDR plan. In the same way, the treatment planning process started with an activation of the same dwell positions as in the PDR planning treatment. A standard physical dose of 13.48 Gy in four fractions of 3.37 Gy (corresponding to an EQD2 dose of 15 Gy_{EQD2} according to LQM) was prescribed and normalized to point A. Then, the dwell time for each dwell position was optimized manually in an iterative way following the same pattern as for the PDR optimization. The procedure aimed to reach the same coverage of D₉₀CTV_{HR} than in the PDR plan with a margin of error ≤ 0.1 Gy.

Data extraction and statistics

PDR and HDR plan were compared using dosimetric variables for the CTVs and OAR. CTV metrics included D₉₀CTV_{HR} (control variable) and D₉₈CTV_{IR}. OAR metrics included D_{2cc} of the bladder, rectum, sigmoid and small bowel. Differences in dosimetric variables were evaluated for statistical significance (p<0.05) using the two-tailed Student's paired t-test. Prior to application of the Student's t-test, the data were verified to be normally distributed using a Shapiro-Wilk test.

Finally, the double ratio EQD2_{RECTUM}/EQD2_{CTVHR} (derived from the BED_{NT}/BED_{TUM} ratio described by Sminia et al.), was applied as a function of the overall BT duration in PDR plan, which is directly correlated to the number of pulses and inversely correlated to the dose per pulse (13). This

$$\frac{D_{2cc \text{ rectum EQD2 (HDR)}} / D_{2cc \text{ rectum EQD2 (PDR)}}}{D_{90 \text{ CTV}_{HR} \text{ EQD2 (HDR)}} / D_{90 \text{ CTV}_{HR} \text{ EQD2 (PDR)}}$$

double ratio represents the therapeutic ratio of HDR relative to PDR depending of the dose per pulse applied in the PDR plan:

HDR/PDR therapeutic ratio =

Data management and statistical analyses were performed using R 3.4.1 software (The R Foundation for Statistical Computing Platform, Vienna, Austria).

Results

Patients and EBRT dose contribution

Data from 10 patients treated with endocavitary BT only were analysed. Tumor FIGO stages were as follows: 2 stage IB2, 6 stage IIB, 1 stage IIIA and 1 stage IIIB. Tumor involved the lower third of vagina in 2 patients; the middle and the upper third of the vagina were involved in two patients.

Regarding pelvic EBRT, for all patients, dose delivered to the planning target volume (PTV) was 45 Gy with dose per fraction of 1.8 Gy. Following ICRU guidelines (10), the contribution of EBRT to CTV and OAR metrics assessed in BT plan were therefore considered equal to 44.3 Gy_{EQD2} and 43.2 Gy_{EQD2} respectively (all doses in 2-Gy equivalents, applying the linear quadratic model with a α/β ratio of 10 for CTVs and 3 for OAR). Dosimetric data for both treatment modalities are listed in **Table 1**.

PDR BT

Median number of pulses was 50 (interquartile range (IQR), 47-53). The aforementioned planning aims for CTV_{HR} were reached for seven patients. Among the three others, two were very close with a D₉₀CTV_{HR} of 84.4 Gy_{EQD2} and 84.0 Gy_{EQD2} respectively. The median D₉₀CTV_{HR} and D₉₈CTV_{IR} were 91.0 Gy_{EQD2} (IQR, 86.0-94.6 Gy_{EQD2}) and 65.0 Gy_{EQD2} (IQR, 62.9-65.5 Gy_{EQD2}) respectively. Planning aims for OAR were reached for every patient. The median D_{2cc} of bladder, rectum, sigmoid and small bowel were 62 Gy_{EQD2} (IQR, 58.8-70.2 Gy_{EQD2}), 55.1 Gy_{EQD2} (IQR, 54.3-55.6 Gy_{EQD2}), 64.7 Gy_{EQD2} (IQR, 56.0-67.7 Gy_{EQD2}) and 66.8 Gy_{EQD2} (IQR, 59.2-75.9 Gy_{EQD2}), respectively.

HDR BT

According to the study's methodology, the D₉₀CTV_{HR} coverage was strictly identical to that of obtained with PDR plan. The CTV_{IR} coverage was lower with HDR-BT for all patients. The median

D₉₈CTV_{IR} was 62.9 Gy_{EQD2} (versus 65.0 Gy_{EQD2} with PDR, p<0.001). Conversely, dose to the bladder was increased with HDR-BT for all patients. The median bladder D_{2cc} was 65.6 Gy_{EQD2} (versus 62 Gy_{EQD2}, p=0.004). Doses to the rectum, sigmoid and small bowel were higher in 7, 9 and 8 cases with a median D_{2cc} of 55.6 Gy_{EQD2} (versus 55.1 Gy_{EQD2}, p=0.027), 67.2 Gy_{EQD2} (versus 64.7 Gy_{EQD2}, p=0.002) and 69.4 Gy_{EQD2} (versus 66.8 Gy_{EQD2}, p=0.014) respectively.

Linear quadratic model effect

As shown in **Figure 1** the impact of the LQM was different according to the dose level and the alpha/beta ratio value considered.

Regarding the target volumes (α/β ratio = 10 Gy), at same physical dose, EQD2 D₉₀CTV_{HR} was higher for HDR dosimetry, as compared to PDR. To adjust both plans on radiobiologically weighted D₉₀CTV_{HR}, the HDR physical dose had to be decreased. Therefore, the physical dose delivered to 98% of the CTV_{IR} was also decreased in the same range. Consequently, for two plans achieving the same EQD2 D₉₀CTV_{HR}, the EQD2 D₉₈CTV_{IR} was lower for HDR plan, as a result of radiobiological weighting in this era receiving lower doses. This effect is shown in **Figure 2**.

Regarding the OAR (α/β ratio = 3 Gy), lowering the HDR physical dose to adjust both plans on radiobiologically weighted D₉₀CTV_{HR} led to decrease the EQD2, and the extent of decrease depended on the BT contribution. When the dose contribution of BT was very low, the effect of radiobiological weighting was also low, leading to EQD2 D_{2cc} being almost equivalent for PDR and HDR dosimetry. However, when BT contribution increased, the decrease of physical dose caused by the adjustment on D₉₀CTV_{HR} did not counterbalance the radiobiological effect for HDR OARs. Thus, the EQD2 D_{2cc} doses calculated for OARs were always higher for HDR plan (**Figure 2**). Although no firm dose threshold could be identified, the effect of radiobiological weighting became obvious for BT doses ≥ 20 Gy_{EQD2}.

The interaction between dose level and the LQM is summarized in **Figure 3**. Converting PDR dosimetry to HDR had quite a similar impact on EQD2 CTV_{IR} for the range of doses reported in our population, decreasing the dose uniformly for all patients. For OARs, the effect of radiobiological weighting depended on the dose delivered. For implants in which BT contribution was low, schematically D_{2cc} < 20 Gy_{EQD2}, there was equivalence between both BT modalities. However, when OARs D_{2cc} doses were ≥ 20 Gy_{EQD2}, conversion of PDR to HDR led to systematically increase OAR doses.

Radiobiological optimization

Figure 4 shows the HDR/PDR therapeutic ratio ($[\text{EQD2}_{\text{HDR}}/\text{EQD2}_{\text{PDR}}]_{\text{D}_{2\text{cc}} \text{ rectum}}/[\text{EQD2}_{\text{HDR}}/\text{EQD2}_{\text{PDR}}]_{\text{D}_{90 \text{ CTVHR}}}$) as a function of the dose per pulse in PDR treatments for an unchanged prescribed dose of 15 Gy. For illustrative purposes, only four representative patients were plotted i.e. the patient with the highest rectal dose, the one with the lowest rectal dose and two with intermediate physical $\text{D}_{2\text{cc}}$ doses. We observed that the impact of modifying dose per pulse in PDR was dependant on the level of dose. Schematically, when rectal physical $\text{D}_{2\text{cc}}$ was low, lowering the dose per pulse in PDR (increasing total number of pulses) was not associated with an expected therapeutic gain. Contrariwise, the differential effect associated with dose per pulse reduction was significant when the physical dose level increased. This observation was particularly substantial when PDR physical dose to the rectal $\text{D}_{2\text{cc}}$ exceeded 20 Gy.

Discussion

Most studies comparing radiobiology of HDR versus LDR found a better therapeutic ratio in favour of LDR (14–16). Although there is a theoretical risk of increased complications with HDR compared to LDR, this has not been seen in properly randomized trials or meta-analysis (2,4,17,18). The main explanation is that HDR-BT offers the possibility to optimize by adjusting dwell times and positions, counterbalancing its radiobiological disadvantage.

PDR-BT offers the possibility to combine the radiobiological advantage of LDR and isodose optimization, as allowed by HDR-BT. Indeed, it was published from radiobiological studies that PDR appeared to be functionally equivalent to a continuous irradiation regimen, for both early and late effects (19). However, to our knowledge PDR-BT and HDR-BT have not been compared properly in radiobiological studies. The theoretical benefit of PDR, if any, should theoretically vary according to several factors such as dose rate or tissue's characteristics (half-time repair, α/β ratio) (19,20).

In the scientific literature there are very few data available comparing PDR-BT and HDR-BT. The only randomized prospective study was conducted by Kumar et al. on 37 patients with locally advanced carcinoma of cervix (9). Patients were randomized to receive either HDR (7 Gy each in three fractions, repeated weekly) or PDR (70 cGy hourly pulses for 39 hours, total 27 Gy) BT after EBRT. Toxicity rate did not differ significantly in this low power study although a trend in favour of PDR was observed. In the PDR arm, the rate of late rectal toxicity grade ≥ 2 was 21.1% (vs. 16.7% in

HDR) and 0% (vs.10.5%) for grade ≥ 3 , the rate of late bladder toxicities grade ≥ 2 was 0% (vs. 10.5%), and the rate of late vaginal toxicities grade ≥ 2 was 5.6% (vs. 15.8%). The four-year disease-free survival rate was 67.1% vs. 71.8% ($p = 0.195$).

Enrolment of patients in large clinical trials comparing both PDR and HDR-BT does not seem feasible or even relevant. The prospective EMBRACE study has included approximately one third of patients treated with PDR-BT. This large study may provide further insights into the dose rate effect in patients treated according to modern standards of IGABT based on dose optimization. However, neither large randomized study nor dosimetric comparison of both BT modalities exists, and it is therefore still difficult to anticipate which patients may get benefit from PDR or from HDR. Our findings suggest a slight difference between HDR and PDR when plans were adjusted on $D_{90CTV_{HR}}$. Both techniques provided acceptable target volume coverage with a slightly higher value with the HDR technique for OAR D_{2cc} while CTV_{IR} received higher dose in the PDR plan. The theoretical radiobiological benefit of PDR over HDR became predominant when doses to OARs were superior to $20Gy_{EQD2}$, although no firm dose threshold could be identified. We found that above this range of dose, the higher the dose, the greater the difference between both BT modalities (**Figure 3**). Similarly, the effect of adjusting both plans on radiobiologically weighted $D_{90CTV_{HR}}$ led to clinically relevant differences in term of bladder EQD2 D_{2cc} , but had only marginal effect in terms of rectal EQD2 D_{2cc} , which is in line with the fact that higher physical doses delivered to the bladder (**Figure 1**).

Although PDR use is decreasing worldwide, it is still being proposed in several large institutions, and its radiobiological advantages are consensual for treatment of highly sensitive area, such as anal canal, penile glans, vagina, oral mucosa, or in paediatrics indications (21, 22). The results of this study provide new insights to guide future study searching for LACC patients who could benefit from PDR-BT versus HDR-BT, notably those with significant exposure to OARs and those with large CTV_{IR} . Indeed, according to our results most of patients had an equivalent dosimetry whatever the BT modality. The possibility to perform virtual pre-planning for IGABT applications has been reported in the literature (23). A pre-selection of patients based on the expected contribution of BT to OARs and the CTV_{IR} volume might increase the chance to optimize the therapeutic effect in these patients through radiobiological optimization, and to give centres having both BT modalities available the possibility to decide which treatment will be the most appropriate. Next step will be to anticipate which patients may benefit more from PDR-BT than from HDR-BT, if any, based not only on the expected OARs dose but also on tumors characteristics such as the size, the CTV_{HR} volume, or the expected contribution to lymph node dose.

Another issue addressed in this study was the possibility to adjust dose per pulse to modify the therapeutic ratio. In some institutions treating patients with PDR-BT, dose rate is corrected by decreasing the dose rate to the isodose prescription and increasing the total number of pulses in order to not exceed the limit of 0.6 Gy/hour to the OARs (11). It was hypothesized that going further in this process could be beneficial in terms of therapeutic index by allowing dose escalation based on radiobiological optimization. Our results suggest that this kind of radiobiological optimization is relevant to decrease relatively more EQD2 D_{2cc} than the $D_{90CTV_{HR}}$, and this effect was the most significant at increasing physical OAR doses. Notably, the benefit of decreasing dose per pulse was particularly important when physical BT dose contribution to rectal D_{2cc} was $> 20\text{Gy}$, which would lead to a total $D_{2cc} > 63.2\text{ Gy}_{EQD2}$ (43.2 Gy_{EQD2} EBRT + 20 Gy_{EQD2} BT). As this is still quite a low D_{2cc} dose, as compared with usual guidelines for OARs dose constraints of 70-75 Gy_{EQD2} , our results suggest that in most cases radiobiological optimization may be relevant to achieve dose escalation (**Figure 4**).

This study has some limitations. Direct comparison of different BT treatment plans is quite complicated because of the heterogeneity of dose parameters for EQD2 calculation used in publications and the lack of widely accepted optimization methodology. Although there are recommendations by professional societies (12), no consensus exists regarding optimal parameters in the setting of radiobiological model since no validation study on large prospective cohort exists. Thus, the EQD2 given by radiological models cannot be considered as perfectly accurate. Furthermore, only patients with NO disease were included and therefore the contribution of simultaneous lymph node boosts to the total EQD2 dose remains to be investigated. Finally, the dosimetric results reported here may not be extrapolated identically for other applicators, or other loading patterns. However, it should be highlighted that in patients with large CTV_{HR} , the effect of radiobiological optimization might be still higher. In the EMBRACE 2 study, highly stringent dose constraints have been provided in terms of CTV_{HR} dose objectives, as well as for OARs sparing (e.g. planning aim for rectal D_{2cc} dose $< 65\text{ Gy}_{EQD2}$) (24). In the most advanced tumors or in case of poor response, such stringent objectives will be achievable only by means of a more frequent use of interstitial implantations, which were shown to give more capabilities in terms of dose escalation, without exceeding OARs dose constraints (25). Our study did not address the question of interstitial applications, and this is another limitation.

Conclusion

In conclusion, our data suggest that radiobiological optimization may have a substantial role as part of the optimization process in these very advanced tumors, either by identifying patients who

320 may be treated with PDR-BT rather than with HDR-BT, or by giving the possibility to make dose
321 escalation by adjustments of dose per pulse.

Declarations

Ethics approval and consent to participate

Ethics approval was obtained from our Institutional Review Board and consent was waived for retrospective research.

Competing interests

The authors declare no competing financial interest.

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Table 1: Dosimetric data for target volumes and organs at risk (median with interquartile ranges).

Table 1. Dosimetry of targets volume and organs at risk (median with interquartile ranges)			
	PDR BT	HDR BT	P-value
Target volume			
D90 CTVHR (Gy)	91.0 (86.0-94.6)	91.0 (86.0-94.6)	NA
D98 CTVIR (Gy)	65.2 (62.9-65.5)	62.9 (60.9-63.7)	< 0.001
Organs at risk			
D2cc Bladder (Gy)	62.9 (58.8-70.2)	65.6 (59.7-76.3)	0.004
D2cc Rectum (Gy)	55.1 (54.3-55.6)	55.6 (54.5-56.3)	0.027
D2cc sigmoid (Gy)	64.7 (56.0-67.7)	67.2 (56.7-71.9)	0.002
D2cc small bowel (Gy)	66.8 (59.2-75.9)	69.4 (59.8-85.5)	0.014
BT: brachytherapy; HDR: high-dose rate; LDR: low-dose rate, Dx: minimum dose delivered to x% of the volume, Dx cc: minimum dose delivered to most exposed x cc			

Figure 1: Paired boxplot of target and normal tissue metrics following BT modality.

Figure 2: Linear quadratic model for organs at risk and target volumes.

Figure 3: Comparison of 2 Gy equivalent dose (EQD2) between high dose rate and pulse dose rate brachytherapy.

Each point represents a dosimetric variable for one patient. The abscissa represents the EQD2 of the PDR plan while the ordinate represents the EQD2 of HDR plan. When the point is above the dashed line, this means that the dose EQD2 is higher in the HDR plan.

Figure 4: Therapeutic ratio of HDR relative to PDR, according to total number of hourly pulses

When the ratio is superior to 1 (above the dashed line), PDR allowed a better therapeutic ratio over HDR.

D2cc rectum indicates the physical dose to the rectum in the PDR plan.