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1 **Radiobiological optimization comparison between pulse-dose rate and high-**
2 **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 $D_{90}CTV_{HR}$ with HDR as with PDR planning after conversion into dose equivalent per 2 Gy-fractions (EQD2) following LQM. Plans were compared for dosimetric variables.

Results: As per study's methodology, the $D_{90}CTV_{HR}$ was strictly identical between PDR and HDR plans: 91.0 Gy (Interquartile: 86.0-94.6 Gy). The median $D_{98}CTV_{IR}$ 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 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 $> 20 Gy$.

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

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

101 **Methods**

102 **Patient population**

103

104 Clinical and dosimetric data of ten consecutive patients receiving intracavitary image-guided
105 adaptive BT after pelvic external beam radiation therapy (EBRT) and concomitant chemotherapy in
106 2016 for a LACC were examined. Only patients with NO disease after an exhaustive pre-treatment
107 workup were included to overcome the issue of potential contribution of simultaneous lymph node
108 boosts.

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

113

114 **Linear-quadratic model**

115

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

125

126 **PDR BT procedure**

127

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

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

141

142 **Conversion to HDR planning treatment**

143

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

151

152 **Data extraction and statistics**

153

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

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

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

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

164 HDR/PDR therapeutic ratio =

165

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

168 **Results**

169 **Patients and EBRT dose contribution**

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

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

178

179 **PDR BT**

180

181 Median number of pulses was 50 (interquartile range (IQR), 47-53). The aforementioned
182 planning aims for CTV_{HR} were reached for seven patients. Among the three others, two were very
183 close with a D₉₀CTV_{HR} of 84.4 Gy_{EQD2} and 84.0 Gy_{EQD2} respectively. The median D₉₀CTV_{HR} and D₉₈CTV_{IR}
184 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
185 aims for OAR were reached for every patient. The median D_{2cc} of bladder, rectum, sigmoid and small
186 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,
187 56.0-67.7 Gy_{EQD2}) and 66.8 Gy_{EQD2} (IQR, 59.2-75.9 Gy_{EQD2}), respectively.

188

189 **HDR BT**

190

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

193 $D_{98}CTV_{IR}$ was 62.9 Gy_{EQD2} (versus 65.0 Gy_{EQD2} with PDR, $p < 0.001$). Conversely, dose to the bladder was
194 increased with HDR-BT for all patients. The median bladder D_{2cc} was 65.6 Gy_{EQD2} (versus 62 Gy_{EQD2},
195 $p = 0.004$). Doses to the rectum, sigmoid and small bowel were higher in 7, 9 and 8 cases with a
196 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}, $p = 0.002$)
197 and 69.4 Gy_{EQD2} (versus 66.8 Gy_{EQD2}, $p = 0.014$) respectively.

198

199 **Linear quadratic model effect**

200

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

203 Regarding the target volumes (α/β ratio = 10 Gy), at same physical dose, EQD2 $D_{90}CTV_{HR}$ was
204 higher for HDR dosimetry, as compared to PDR. To adjust both plans on radiobiologically weighted
205 $D_{90}CTV_{HR}$, the HDR physical dose had to be decreased. Therefore, the physical dose delivered to 98%
206 of the CTV_{IR} was also decreased in the same range. Consequently, for two plans achieving the same
207 EQD2 $D_{90}CTV_{HR}$, the EQD2 $D_{98}CTV_{IR}$ was lower for HDR plan, as a result of radiobiological weighting in
208 this era receiving lower doses. This effect is shown in **Figure 2**.

209 Regarding the OAR (α/β ratio = 3 Gy), lowering the HDR physical dose to adjust both plans on
210 radiobiologically weighted $D_{90}CTV_{HR}$ led to decrease the EQD2, and the extent of decrease depended
211 on the BT contribution. When the dose contribution of BT was very low, the effect of radiobiological
212 weighting was also low, leading to EQD2 D_{2cc} being almost equivalent for PDR and HDR dosimetry.
213 However, when BT contribution increased, the decrease of physical dose caused by the adjustment
214 on $D_{90}CTV_{HR}$ did not counterbalance the radiobiological effect for HDR OARs. Thus, the EQD2 D_{2cc}
215 doses calculated for OARs were always higher for HDR plan (**Figure 2**). Although no firm dose
216 threshold could be identified, the effect of radiobiological weighting became obvious for BT doses \geq
217 20 Gy_{EQD2}.

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

225

226 Radiobiological optimization

227

228 **Figure 4** shows the HDR/PDR therapeutic ratio ($[\text{EQD2}_{\text{HDR}}/\text{EQD2}_{\text{PDR}}]_{\text{D}_{2\text{cc}}}$
229 $_{\text{rectum}}/[\text{EQD2}_{\text{HDR}}/\text{EQD2}_{\text{PDR}}]_{\text{D}_{90\text{ CTVHR}}}$) as a function of the dose per pulse in PDR treatments for an
230 unchanged prescribed dose of 15 Gy. For illustrative purposes, only four representative patients
231 were plotted i.e. the patient with the highest rectal dose, the one with the lowest rectal dose and
232 two with intermediate physical $\text{D}_{2\text{cc}}$ doses. We observed that the impact of modifying dose per pulse
233 in PDR was dependant on the level of dose. Schematically, when rectal physical $\text{D}_{2\text{cc}}$ was low,
234 lowering the dose per pulse in PDR (increasing total number of pulses) was not associated with an
235 expected therapeutic gain. Contrariwise, the differential effect associated with dose per pulse
236 reduction was significant when the physical dose level increased. This observation was particularly
237 substantial when PDR physical dose to the rectal $\text{D}_{2\text{cc}}$ exceeded 20 Gy.

238 Discussion

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

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

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

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

259 Enrolment of patients in large clinical trials comparing both PDR and HDR-BT does not seem
260 feasible or even relevant. The prospective EMBRACE study has included approximately one third of
261 patients treated with PDR-BT. This large study may provide further insights into the dose rate effect
262 in patients treated according to modern standards of IGABT based on dose optimization. However,
263 neither large randomized study nor dosimetric comparison of both BT modalities exists, and it is
264 therefore still difficult to anticipate which patients may get benefit from PDR or from HDR. Our
265 findings suggest a slight difference between HDR and PDR when plans were adjusted on $D_{90CTV_{HR}}$.
266 Both techniques provided acceptable target volume coverage with a slightly higher value with the
267 HDR technique for OAR D_{2cc} while CTV_{IR} received higher dose in the PDR plan. The theoretical
268 radiobiological benefit of PDR over HDR became predominant when doses to OARs were superior to
269 $20Gy_{EQD2}$, although no firm dose threshold could be identified. We found that above this range of
270 dose, the higher the dose, the greater the difference between both BT modalities (**Figure 3**).
271 Similarly, the effect of adjusting both plans on radiobiologically weighted $D_{90CTV_{HR}}$ led to clinically
272 relevant differences in term of bladder EQD2 D_{2cc} , but had only marginal effect in terms of rectal
273 EQD2 D_{2cc} , which is in line with the fact that higher physical doses delivered to the bladder (**Figure 1**).

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

288 Another issue addressed in this study was the possibility to adjust dose per pulse to modify
289 the therapeutic ratio. In some institutions treating patients with PDR-BT, dose rate is corrected by
290 decreasing the dose rate to the isodose prescription and increasing the total number of pulses in
291 order to not exceed the limit of 0.6 Gy/hour to the OARs (11). It was hypothesized that going further
292 in this process could be beneficial in terms of therapeutic index by allowing dose escalation based on
293 radiobiological optimization. Our results suggest that this kind of radiobiological optimization is
294 relevant to decrease relatively more EQD2 D_{2cc} than the $D_{90CTV_{HR}}$, and this effect was the most
295 significant at increasing physical OAR doses. Notably, the benefit of decreasing dose per pulse was
296 particularly important when physical BT dose contribution to rectal D_{2cc} was $> 20\text{Gy}$, which would
297 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,
298 as compared with usual guidelines for OARs dose constraints of 70-75 Gy_{EQD2} , our results suggest that
299 in most cases radiobiological optimization may be relevant to achieve dose escalation (**Figure 4**).

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

317 **Conclusion**

318 In conclusion, our data suggest that radiobiological optimization may have a substantial role
319 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.

322 **Declarations**

323

324 **Ethics approval and consent to participate**

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

327

328 **Competing interests**

329 The authors declare no competing financial interest.

330

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

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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

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

431

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

433

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

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

439

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

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

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







