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27

Abstract

28 **Objective:** To dosimetrically compare the intensity-modulated-arc-therapy (IMAT),
29 CyberKnife therapy (CK), single fraction interstitial high-dose-rate (HDR) and low-dose-rate
30 (LDR) brachytherapy (BT) in low-risk prostate cancer.

31 **Methods:** Treatment plans of ten patients treated with CK were selected and additional plans
32 using IMAT, HDR and LDR BT were created on the same CT images. The prescribed dose was
33 2.5/70Gy in IMAT, 8/40Gy in CK, 21Gy in HDR and 145Gy in LDR BT to the prostate gland.
34 EQD2 dose-volume parameters were calculated for each technique and compared.

35 **Results:** EQD2 total dose of the prostate was significantly lower with IMAT and CK than with
36 HDR and LDR BT, D90 was 79.5Gy, 116.4Gy, 169.2Gy and 157.9Gy ($p<0.001$). However,
37 teletherapy plans were more conformal than BT, COIN was 0.84, 0.82, 0.76 and 0.76 ($p<0.001$),
38 respectively. The D₂ to rectum and bladder were lower with HDR BT than with IMAT, CK and
39 LDR BT, it was 66.7Gy, 68.1Gy, 36.0Gy and 68.0Gy ($p=0.0427$), and 68.4Gy, 78.9Gy, 51.4Gy
40 and 70.3Gy ($p=0.0091$) in IMAT, CK, HDR and LDR BT plans, while D_{0.1} to urethra was lower
41 with both IMAT and CK than with BTs: 79.9Gy, 88.0Gy, 132.7Gy and 170.6Gy ($p<0.001$). D₂
42 to hips was higher with IMAT and CK, than with BTs: 13.4Gy, 20.7Gy, 0.4Gy and 1.5Gy
43 ($p<0.001$), while D₂ to sigmoid, bowel bag, testicles and penile bulb was higher with CK than
44 with the other techniques.

45 **Conclusions:** HDR monotherapy yields the most advantageous dosimetrical plans, except for
46 the dose to urethra, where IMAT seems to be the optimal modality in the radiotherapy of low-
47 risk prostate cancer.

48 **Keywords:** prostate cancer; intensity-modulated arc therapy; Cyberknife therapy; interstitial
49 high-dose-rate brachytherapy; interstitial low-dose-rate brachytherapy

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51

52 **Introduction**

53 Prostate cancer is the second most common cancer in men worldwide and the fourth most
54 commonly occurring cancer overall. There were 1.3 million new cases in 2019. It is estimated
55 that 33.000 deaths from this disease will occur this year [1]. The standard of care in the curative
56 treatment of low- and selected intermediate-risk prostate cancer is external beam radiotherapy
57 with intensity-modulated arc therapy (IMAT) or with CyberKnife (CK) technique or interstitial
58 high-dose-rate (HDR) or low-dose-rate (LDR) brachytherapy (BT) [2].

59 Since the α/β value of prostate tumour is low, dose escalation has an essential role in the
60 development of all radiotherapy modalities [3-5]. The more complex the techniques, the more
61 they are capable of escalating the dose to the tumour, while sparing the organs at risk (OARs).
62 The IMAT technique results improved OAR sparing with acceptable planning target volume
63 (PTV) coverage [6]. Stereotactic radiotherapy with CyberKnife demonstrated favourable
64 tumour control, better patient-reported quality of life and lower levels of toxicity [7]. The use
65 of BT, as a boost has been linked with improved biochemical-progression-free and overall
66 survival [8,9]. What is more, modern LDR monotherapy approach results in improved quality
67 of life, as a consequence of lower acute urinary and rectal toxicity [11], with the dose coverage
68 of the target volume (D90, the minimum dose delivered to 90% of the prostate) correlating with
69 local tumour control [11], and the dose of the most exposed part of the OARs with normal tissue
70 toxicity [12].

71 Despite the wide-spread application of these state-of-the-art techniques, no detailed
72 analysis of all of these treatment techniques exists. Leszczyński et al. compared the dose
73 distributions of intensity-modulated prostate radiotherapy versus IMAT technique [13]. Yang
74 et al. investigated the dosimetric differences among IMAT, HDR and LDT BT for 10 patients,
75 but HDR BT was not a single fraction monotherapy in their study [14]. Andrzejewski et al.
76 studied the feasibility of dominant intraprostatic lesion (DIL) boosting using IMAT, proton

77 therapy or HDR BT for 12 patients [15]. Georg et al. examined the optimal radiotherapy
78 technique among IMAT, proton-, carbon-ion therapy and HDR or LDR BT, but HDR BT was
79 not a single fraction monotherapy for the 10 studied patients [2]. Morton et al. studied HDR
80 and LDR BT techniques against IMAT external beam therapy [16]. Fuller et al. dosimetrically
81 compared CK and HDR BT plans for their first 10 patients treated with CK, but not all of the
82 OARs relevant to CK treatment were evaluated [17]. King examined HDR versus LDR BT as
83 monotherapy and boost in a radiobiological model [18]. Skowronek made a practical
84 comparison between HDR and LDR prostate BT [19].

85 At our institute, all of the four widely used treatment techniques are available. To take
86 the advantage of this situation, the aim of the present study is a detailed dosimetric comparison
87 of intensity-modulated-arc-therapy, CyberKnife therapy, interstitial high-dose-rate and low-
88 dose-rate brachytherapy, as monotherapy in low-risk prostate cancer.

89 **Materials and methods**

90 Ten CK plans of patients with low- and selected intermediate-risk prostate cancer treated at our
91 institute were included in this study. Selection criteria for treatment were the following:
92 PSA<15 ng/mL and/or GS≤7 and/or Stage T≤2c [20].

93 CK treatments were performed with non-coplanar fields using CyberKnife M6 linear
94 accelerator (Accuray, Sunnyvale, CA, USA). Gold fiducial markers were implanted into the
95 prostate gland to guide the placement of radiation beams during treatment. The CTV was
96 extended by an isotropic 3 mm margin, 8 Gy was delivered to this prostate PTV in each fraction.
97 A total of 5 fractions (total dose 40 Gy) were given every second working day. For treatment
98 planning Accuray Precision 1.1 treatment planning system (TPS) (Accuray, Sunnyvale, CA,
99 USA) was used. The dose was prescribed to the 80–85% isodoses (Fig 1.b). The relative volume
100 of the PTV receiving at least the prescribed dose (V100) had to be at least 95%. The detailed
101 description of our treatment method can be found in our previous publication [21].

102 On the CT series made for CK treatment planning, additional plans using IMAT, HDR and
103 LDR BT were created using the same contour set. Where urethra was not identifiable on CT
104 images, it was contoured between the bladder and the penile channel using a 15 mm pearl.
105 IMAT plans were made in Eclipse v13.7 TPS (Varian Medical Systems, Palo Alto, USA) with
106 a beam energy of 10 MV using 2 full arcs (Fig 1.a). CTV was extended using an isotropic 5
107 mm margin. The prescribed dose was 70 Gy, the dose of the daily fractions was 2.5 Gy for the
108 PTV. The protocol of our PROMOBRA study was applied for treatment planning in both HDR
109 and LDR BT plans [22]. The prescribed dose in HDR BT was 21 Gy ($V_{100} \geq 95\%$) to the CTV
110 of the CK plan, as the BT PTV, in a single treatment fraction using Ir-192 radioactive source.
111 HIPO method was used to optimize the plans in the Oncentra Prostate v3.1 TPS (Elekta
112 Brachytherapy, Veendendaal, The Netherlands) (Fig 1.c). In LDR BT the prescribed dose was
113 145 Gy ($V_{100} \geq 95\%$) to the same CTV. IPSA optimisation method in the Oncentra Prostate
114 v3.1 TPS (Elekta Brachytherapy, Veendendaal, The Netherlands) was used to calculate the
115 virtual positions of the I-125 isotopes (Fig 1.d). The detailed description of our treatment
116 method can be found in our previous publications [23-26].

117 The equivalent dose given in 2 Gy fractions (EQD2) was calculated for each technique
118 using the linear-quadratic radiobiological model [27,28]. The α/β of prostate was assumed 1.5
119 Gy, while for OARs 3 Gy was used [29,30]. 1 year was estimated in LDR BT as overall
120 treatment time, as during this time 89% of the prescribed dose is delivered. The following dose-
121 volume parameters were used for quantitative evaluation of plans:

122 **D90:** the minimum dose delivered to 90% of PTV (Gy);

123 **COIN:** conformal index [31];

124 **D_{0.1(x)}, D_{2(x)}:** the minimal dose of the most exposed 0.1 and 2 cm³ of *the critical organ*
125 *x* (Gy),

126 where x: *rectum (r)*, *urethra (u)*, *bladder (b)*, *hips (h)*, *sigmoid (s)*, *bowel bag (bb)*, *testicles (t)*
127 *and penile bulb (p)*.

128 Friedman ANOVA and Fisher-LSD (Least Significant Difference) post-hoc tests were used
129 (Statistica 12.5, StatSoft, Tulsa, OK, USA) to compare EQD2 dose-volume parameters of
130 IMAT, CK, HDR and LDR BT techniques.

131 **Results**

132 The mean volume of the PTV was 105.7 cm³ (42.2-189.3 cm³) in IMAT, 85.5 cm³ (31.5-159.2
133 cm³) in the CK and 61.8 cm³ (19.8-126.2 cm³) in both BT plans (which is equal to the original
134 CTV) on average. We found that EQD2 total dose of the prostate was significantly lower with
135 IMAT and CK than with HDR and LDR BT, D90 was 79.5 Gy, 116.4 Gy, 169.2 Gy and 157.9
136 Gy (p<0.001). However, IMAT and CK plans were more conformal than BT plans, COIN were
137 0.84, 0.82, 0.76 and 0.76 (p<0.001).

138 In our comparison, the D₂ to rectum and bladder were lower with HDR BT than with
139 IMAT, CK and LDR BT, it was 66.7 Gy, 68.1 Gy, 36.0 Gy and 68.0 Gy (p=0.0427), and 68.4
140 Gy, 78.9 Gy, 51.4 Gy and 70.3 Gy (p=0.0091) in IMAT, CK, HDR and LDR BT plans, while
141 D_{0.1} to urethra was lower with both IMAT and CK than with both BT modalities: 79.9 Gy, 88.0
142 Gy, 132.7 Gy and 170.6 Gy (p<0.001), respectively. D₂ to hips was higher with IMAT and CK,
143 than with BTs: 13.4 Gy, 20.7 Gy, 0.4 Gy and 1.5 Gy (p<0.001), while D₂ was higher to other
144 organs with CK, than with the other techniques: 1.1 Gy, 17.9 Gy, 0.8 Gy and 2.8 Gy (p<0.001)
145 for sigmoid; 0.9 Gy, 11.2 Gy, 0.7 Gy and 0.8 Gy (p<0.001) for bowel bag; 0.4 Gy, 20.7 Gy, 0.6
146 Gy and 4.2 Gy (p=0.0017) for testicles; and 4.9 Gy, 10.3 Gy, 1.7 Gy and 3.2 Gy (p=0.0057) for
147 penile bulb in IMAT, CK, HDR and LDR BT plans. The detailed results can be found in Table
148 1.

149 **Discussion**

150 Dose escalation has a fundamental role in the radiotherapy of low- and selected
151 intermediate-risk prostate cancer [3-5]. Several high-tech teletherapy and BT techniques are
152 widely used, such as image-guided and intensity-modulated teletherapy, arc therapy,
153 stereotactic radiotherapy with linear accelerators or CyberKnife and interstitial HDR or LDR
154 BT [2,3,6-9,11,12]. In the present study, all of the four widely used radiotherapy techniques
155 (IMAT, CK, HDR and LDR BT) were compared dosimetrically using the linear-quadratic
156 radiobiological model.

157 Although these techniques rapidly developed parallely, the dosimetrical differences
158 were conspicuous from the beginning. Leszczyński et al. have pointed out that the treatment
159 delivery time is significantly reduced using IMAT technique compared to intensity-modulated
160 radiotherapy [13]. Yang et al. [14] concluded that HDR and LDR BT significantly reduce the
161 dose to rectum, bladder and femoral heads compared with IMAT. The mean EQD2 dose to
162 urethra was 80.3 Gy in IMAT, 70.2 Gy in HDR and 104.9 Gy in their LDR BT plans. They
163 stated that for localised prostate cancer, HDR BT provides the advantage in sparing of urethra
164 compared with IMAT and LDR, however HDR BT was not a single-fraction treatment in this
165 study. Our results are not in agreement with this, the EQD2 dose to the urethra was the lowest
166 in IMAT plans, $D_{0.1}$ was 79.9 Gy. It was higher, 88.0 Gy with CK technique, while more higher
167 using HDR or LDR BT: 132.7 Gy and 170.6 Gy (all of the differences are significant). In the
168 terms of the other OARs sparing, HDR resulted the lowest dose. The explanation of this
169 difference between the studies can be the different fractionation and prescribed dose. Yang et
170 al. used 78 Gy physical dose in 39 fractions in IMAT, 34 Gy in 4 fractions in HDR and 145 Gy
171 in 1 fraction in LDR BT plans and calculated only mean dose of the OARs instead of volumetric
172 doses.

173 Andrzejewski et al. studied the feasibility of DIL boosting and concluded that higher
174 boost doses were achieved using proton therapy compared to IMAT, keeping doses of major
175 OARs at similar levels, but HDR BT was superior to IMAT and proton therapy, both in terms
176 of OAR sparing and boosting of the DIL [15]. EQD2 D50 to DIL were 110.7 Gy, 114.2 Gy and
177 150.1 Gy in IMAT, proton therapy and HDR BT plans, while the mean dose of the rectal wall
178 was 30.5 Gy, 16.7 Gy and 9.5 Gy, and the mean dose to the bladder wall were 21.0 Gy, 15.6
179 Gy and 6.3 Gy, respectively. Georg et al. examined the optimal radiotherapy technique in the
180 radiotherapy of localised prostate cancer and stated that HDR and LDR BT techniques were
181 clearly superior in terms of bladder and rectal wall sparing, in contrast with IMAT, proton- and
182 carbon-ion therapy, with lowest values for HDR BT [2]. However, they did not examine the
183 dose to the urethra. Based on our comparison, also single fraction HDR monotherapy yields the
184 most advantageous plans, except in terms of the dose to urethra where IMAT proves to be the
185 optimal modality.

186 Morton et al. investigated HDR BT against LDR BT and IMAT external beam therapy
187 in clinical point of view [16]. They concluded that HDR BT enables more consistent implant
188 quality than LDR BT, with evidence of lower acute and late toxicity. Higher disease control
189 rates are also reported with HDR monotherapy than with IMAT technique. These clinical results
190 are in good agreement with our dosimetrical results. HDR BT resulted the most optimal
191 treatment plans in terms of both dose coverage of the prostate and the dose to OARs, except for
192 urethra.

193 Fuller et al. pointed out that urethra dose is lower for virtual CK than for virtual HDR
194 BT plans, suggesting that CK technique may more effectively limit urethra dose [17]. Bladder
195 maximum point doses were higher with HDR BT, but bladder dose fall-off beyond the
196 maximum dose region was more rapid with this technique than using CK therapy. Our study

197 added a new result to this conclusion, specifically using IMAT the dose to the urethra is lower
198 than CK and both BT modalities.

199 Based on the radiobiological examination of King, HDR and LDR BT achieve superior
200 tumour control when compared with IMAT using conventional doses, and HDR BT might
201 achieve superior tumour control compared with LDR [18]. This result supports the clinical
202 evidence for equivalent outcomes in localised prostate cancer with either HDR or LDR BT.
203 However, HDR BT dose escalation regimens might be able to achieve higher biological
204 effectiveness and hence improved outcomes in contrast to IMAT. In the same manner, in our
205 plans, higher EQD2 total doses can be reached to the prostate with BT techniques than with
206 external radiation techniques, and this dose is the lowest using IMAT.

207 Skowronek [19] demonstrated that all available clinical data regarding HDR and LDR
208 BT suggests that they are equally effective, stage for stage, in providing high tumour control
209 rates. The important difference in dosimetric control allows HDR doses to be escalated safely
210 providing such a flexibility that does not exist for LDR BT. Our examination also gave one vote
211 for HDR BT, as the most appropriate technique of dose escalation in prostate radiotherapy.

212 It has to be mentioned, that in our study, the virtual BT plans were made on the planning
213 CT of the CK, and this anatomy is not optimal for BT planning. Furthermore, the EQD2
214 prescribed dose was higher in both BT techniques than in IMAT and CK plans, as the
215 recommended, clinically used fractionation was applied in our plans. Despite of that, HDR BT
216 proved to be the optimal choice in the aspects of sparing most of the OARs beside dose coverage
217 of the prostate. LDR BT resulted in higher dose to the OARs with approximately equivalent
218 prescribed dose to the prostate.

219 **Conclusions**

220 Using single fraction HDR and LDR BT, total dose of the prostate is higher than with IMAT or
221 CK techniques, and accordingly dose to urethra is also higher with both BT modalities using

222 the recommended fractionation scheme. Dose to rectum and bladder is lower with HDR BT
223 than with IMAT, CK and LDR BT, while dose to sigmoid, bowel bag, testicles and penile bulb
224 are higher with CK than using the other examined techniques. Overall, HDR monotherapy
225 yields the most advantageous plans in the radiotherapy of low- and intermediate risk prostate
226 cancer, except in terms of the dose to urethra where IMAT proves to be the optimal modality.

227 *Contributions:*

228 GF: worked out the concept, did the analysis and wrote this paper.

229 PÁ: made the contouring and discussed the details of this study.

230 KJ: made the contouring and discussed the details of this study.

231 GS: performed the treatment plans of the CK and discussed the details of this study.

232 CsP: supported the study.

233 TM: supported the study and discussed the details.

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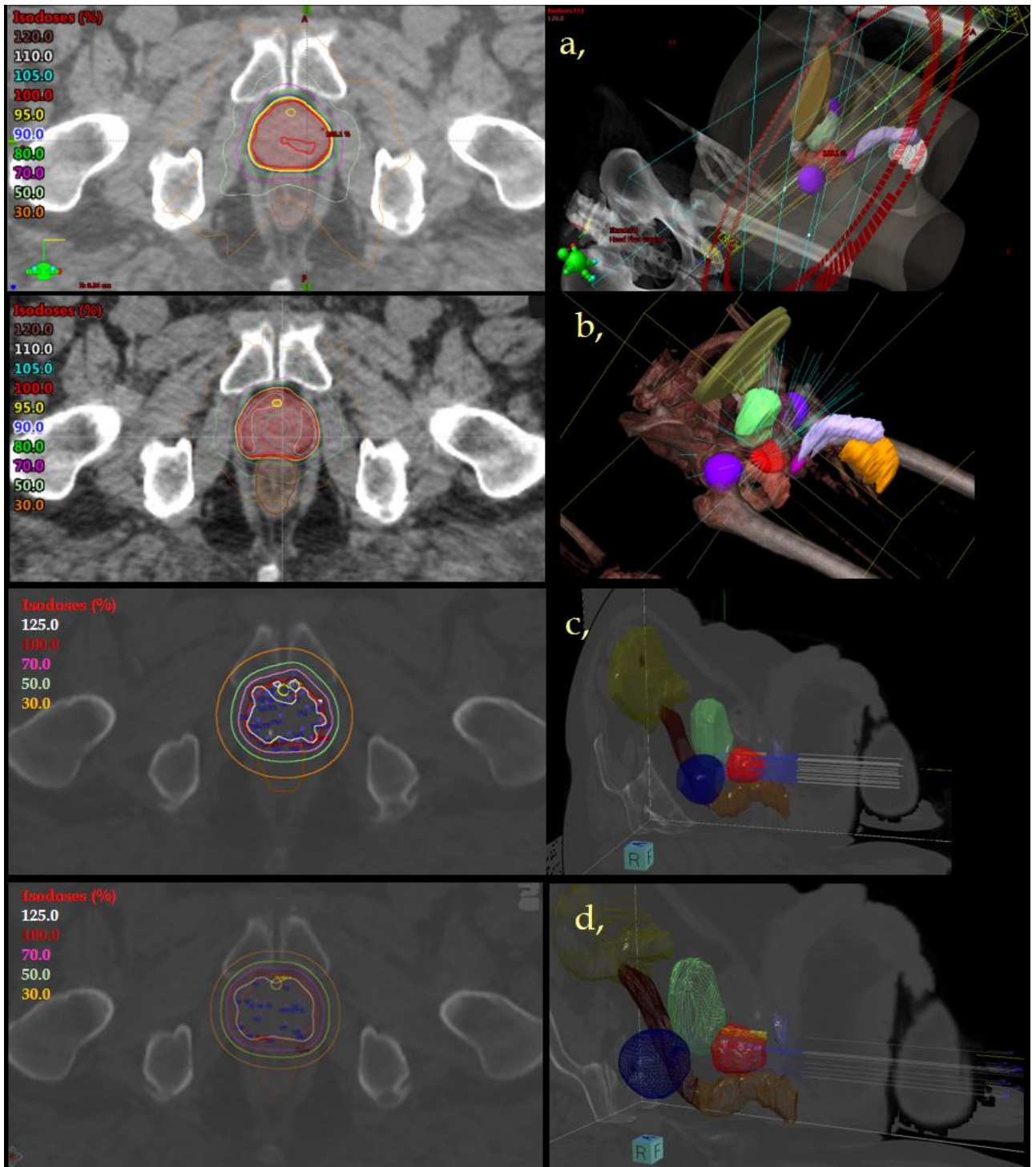
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330 **Tables:**

EQD2	IMAT	CK	HDR	LDR	p*	**post hoc
D90 (Gy)	79.5	116.4	169.2	157.9	<0.001	IMAT,CK
COIN	0.84	0.82	0.76	0.76	<0.001	IMAT-LDR,HDR
D_{0.1}(r) (Gy)	86.4	80.0	55.3	93.5	0.0280	HDR,LDR
D₂(r) (Gy)	66.7	68.1	36.0	68.0	0.0427	HDR
D_{0.1}(u) (Gy)	79.9	88.0	132.7	170.6	<0.001	all
D₂(b) (Gy)	68.4	78.9	51.4	70.3	0.0091	HDR
D_{0.1}(h) (Gy)	17.3	26.5	0.6	2.1	<0.001	IMAT, CK
D₂(h) (Gy)	13.4	20.7	0.4	1.5	<0.001	IMAT, CK
D_{0.1}(s) (Gy)	1.3	20.7	0.9	3.8	<0.001	CK
D₂(s) (Gy)	1.1	17.9	0.8	2.8	<0.001	CK
D_{0.1}(bb) (Gy)	1.1	12.1	1.1	1.3	<0.001	CK
D₂(bb) (Gy)	0.9	11.2	0.7	0.8	<0.001	CK
D_{0.1}(t) (Gy)	0.4	23.0	0.7	4.7	0.0006	CK,LDR
D₂(t) (Gy)	0.4	20.7	0.6	4.2	0.0017	CK,LDR
D_{0.1}(p) (Gy)	15.2	23.7	3.2	5.0	0.0014	IMAT,CK
D₂(p) (Gy)	4.9	10.3	1.7	3.2	0.0057	IMAT,CK

331 **Table 1. Mean EQD2 total doses of intensity-modulated arc therapy (IMAT), CyberKnife**
 332 **(CK), high-dose-rate (HDR) and low-dose-rate (LDR) brachytherapy of prostate cancer.**
 333 **D90: the minimum dose delivered to 90% of prostate, COIN: conformal index, D_{0.1}(x),**
 334 **D₂(x): the minimal dose of the most exposed 0.1 and 2 cm³ of ‘x’ organ at risk, where x**
 335 **are rectum (r), urethra (u), bladder (b), hips (h), sigmoid (s), bowel bag (bb), testicles (t)**
 336 **and penile bulb (p). *Friedman ANOVA **Fisher-LSD post-hoc test.**

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340 **Figure 1. Axial CT slide (left) and 3D reconstruction (right) of a prostate intensity-**
341 **modulated arc therapy (a), a CyberKnife (b), an interstitial high-dose-rate prostate**
342 **brachytherapy (c) and an interstitial low-dose-rate prostate brachytherapy plan (d).**

343 **Red: prostate, yellow: prostatic urethra, light green: bladder, brown: rectum, dark**
344 **brown: sigmoid, khaki: bowel bag, slate blue: femoral heads, lavender: penis, purple:**
345 **penile bulb, orange: testicles.**