

1 **Biological dose summation of intensity-modulated arc therapy and image-guided high-**  
2 **dose-rate interstitial brachytherapy in intermediate and high risk prostate cancer**

3 Georgina Fröhlich, Ph.D.<sup>a,b</sup>, Péter Ágoston, Ph.D.<sup>a,c</sup>, Kliton Jorgo, M.D.<sup>a,c</sup>, Csaba Polgár,  
4 D.Sc.<sup>a,c</sup>, Tibor Major, D.Sc.<sup>a,c</sup>

5 a. National Institute of Oncology, Centre of Radiotherapy, Ráth György Street 7-9, H-  
6 1122 Budapest

7 b. Eötvös Loránd University, Faculty of Science, Pázmány Péter mall 1/A, H-1117  
8 Budapest

9 c. Semmelweis University, Faculty of Medicine, Department of Oncology, Ráth György  
10 Street 7-9, H-1122 Budapest

11 *Corresponding author:* Georgina Fröhlich, National Institute of Oncology, Centre of  
12 Radiotherapy, Ráth György Street 7-9, H-1122 Budapest, Tel: +36-1-224-8600, Fax: +36-  
13 1-224-8620, E-mail: [frohlich.georgina@gmail.com](mailto:frohlich.georgina@gmail.com)

14 **Biological dose summation of prostate tele- and brachytherapy**

15

## Abstract

16 **Objective:** To validate an alternative method for summing the biologically effective doses of  
17 intensity-modulated arc therapy (IMAT) with interstitial HDR brachytherapy (BT) or IMAT  
18 boost in prostate cancer and compare it to the recent Uniform Dose Conception (UDC)  
19 method.

20 **Methods:** Initially 15 IMAT plus interstitial HDR BT plans of patients with intermediate- and  
21 high-risk prostate cancer were included and additional plans of IMAT plus IMAT boost were  
22 created. The prescribed dose was 2/44 Gy for the whole pelvis, 2/60 Gy for the prostate and  
23 vesicle seminals and 1x10 Gy for the prostate gland in BT boost or 2/18 Gy for the prostate  
24 PTV in IMAT boost. CT set of teletherapy was registered with the US of BT, and the most  
25 exposed volume of critical organs in BT were identified on these CT images. The minimal  
26 dose of this volumes was calculated in IMAT plans and summed with the dose from BT using  
27 the linear-quadratic radiobiological model. Biological total doses (EQD) were calculated and  
28 compared between plans with BT and IMAT boost. This method was compared with uniform  
29 dose conception (UDC) in IMAT plus BT boost plans.

30 **Results:** D<sub>90</sub> of the prostate was significantly higher with BT than with IMAT boost: 99.3 Gy  
31 vs. 77.9 Gy, p=0.0034. The dose to rectum and hips were significantly lower with BT boost,  
32 D<sub>2</sub> were 50.3 Gy vs. 76.8 Gy (p=0.0117) and 41.9 Gy vs. 50.6 Gy (p=0.0044), respectively.  
33 The dose to bladder showed the same trend, D<sub>2</sub> were 73.1 Gy vs. 78.3 Gy in BT vs. IMAT  
34 plans, dose to urethra was significantly higher with BT boost, D<sub>0.1</sub> was 96.1 Gy vs. 79.3 Gy  
35 (p=0.0180) using BT vs. IMAT boost technique. UDC overestimates D<sub>2</sub> of rectum by 37%  
36 (p=0.0117) and underestimates D<sub>0.1</sub> of urethra by 1% (p=0.0277) and D<sub>2</sub> of bladder by 7%  
37 (p=0.0614).

38 **Conclusions:** Based on our biological dose summation method, total dose of the prostate is  
39 higher using BT boost, than the IMAT. BT boost yields lower rectum, bladder and hip doses,  
40 but higher dose to urethra. UDC overestimates rectum dose and underestimates the dose to  
41 urethra and bladder.

42 **Keywords:** prostate cancer; dose summation; integrated biological doses; intensity-modulated  
43 arc therapy; interstitial brachytherapy

44

45

## 46 **Introduction**

47 The standard of care in the curative treatment of intermediate- and high-risk prostate cancer is  
48 external beam radiotherapy (teletherapy, TT) and high-dose-rate (HDR) interstitial  
49 brachytherapy (BT) boost with androgen deprivation therapy. Since the  $\alpha/\beta$  value of prostate  
50 tumour is low, dose escalation has an essential role in the development of both radiotherapy  
51 modalities [1,2]. The more complex the techniques, the more they are capable escalating the  
52 dose to the tumour, while sparing the organs at risk (OARs). The state-of-the-art radiotherapy  
53 combination is intensity-modulated arc therapy (IMAT) and image-guided interstitial BT  
54 [3,4]. These complex treatments require reliable reporting of the dose received by tumour and  
55 the critical structures.

56 The use of BT boost has been linked with improved biochemical-progression-free and  
57 overall survival [5,6]. What is more, modern HDR BT approach results in improved quality of  
58 life, as a consequence of lower acute urinary and rectal toxicity [7], with the dose coverage of  
59 the target volume (D90, the minimum dose delivered to 90% of the prostate) correlating with  
60 local tumour control [8], and dose of the OARs with normal tissue toxicity [9].

61 To achieve reporting these dose-volume parameters properly, overall volumetric doses  
62 have to be properly integrated from tele- and brachytherapy. As simple physical dose  
63 summation does not take into consideration the different biological effects, the equivalent  
64 dose given in 2 Gy fractions (EQD2) has to be calculated [10,11]. The dose distribution of the  
65 TT is assumed to be completely uniform in the target volume and OARs (Uniform Dose  
66 Conception, UDC) [12]. However, in the IMAT technique the most exposed 2 cm of the  
67 OARs is not a compact volume, since its voxels are dispersed in the organ, as we have shown  
68 earlier [13]. It was also shown that the most exposed part of the OARs in the integrated plans  
69 is located in the same region that receives the largest dose in BT. Nevertheless, this 2 cm

70 volume is not in the same location, as the most exposed part in TT [14]. So simple DVH  
71 addition sums the dose of two different 2 ccm volumes.

72 In the majority of previous investigations authors did not take into account the real  
73 biological dose of the prostate and the OARs in TT in combined TT and BT treatment.  
74 Pinkawa et al. [15] used the above mentioned UDC method to estimate the doses from TT and  
75 engaged physical BT doses only. Andrzejewski et al. [16] compared different advanced  
76 radiotherapy methods for boosting dominant intraprostatic lesion. They calculated biological  
77 equivalent doses for comparison but did not examine combined therapies. Kikuchi et al. [17]  
78 made a CT series after BT and calculated the biological effective dose of the rectum in TT  
79 and BT. They associated this dose to the pixels of the rectum volume and computed a  
80 summarised dose-volume histogram (DVH) of TT and BT based on this. This was a better  
81 estimation of the rectal dose, than the UDC method, but they could not take into consideration  
82 the quadratic behaviour of the biological dose. This biological dose has to be calculated pixel-  
83 by-pixel in the same organ, but currently in none of the treatment planning systems this  
84 feature is available. The image registration of the TT CT and the CT after BT treatment does  
85 not use the dose values from the real BT plan. The dose gradient is high in BT, so the dose  
86 distribution can be significantly different in a post-BT plan without the needles and the US  
87 probe than in the live plan. Using doses of the live plan, where the needles is in their real  
88 place, is the most adequate method.

89 We have developed an alternative dose summation method in combined radiotherapy  
90 of cervical cancer [14]. The aim of the present study is to validate an alternative method for  
91 summing the biologically effective doses of IMAT with interstitial HDR BT or IMAT boost  
92 in prostate cancer and compare it to the recent UDC method.

93 **Materials and methods**

94 At our institute, fifteen IMAT plus interstitial HDR BT plans of patients with intermediate-  
95 and high-risk prostate cancer were included for this study. Selection criteria were the  
96 following: PSA>10 ng/mL and/or GS 7-10 and/or Stage T2b-T3b. The TT was performed in  
97 supine position, the patients were immobilized with knee and ankle support system. The  
98 prescribed dose was 2/44 Gy for the whole pelvis, 2/60 Gy for the prostate and the vesicle  
99 seminals and was delivered with an energy of 10 MV using 2 full arcs. Based on our local  
100 IGRT protocol, CBCT verification was made from 1<sup>st</sup> to 3<sup>rd</sup> fractions, the systematic error was  
101 calculated and corrected before the 4<sup>th</sup> fraction, then weekly verification was done for patient  
102 positioning. TT was complemented with transrectal US-guided interstitial HDR BT boost,  
103 performed after the 4 weeks TT course, given 1 fraction of 10 Gy [18]. After scanning the  
104 prostate with US, a virtual preimplant plan was generated (Oncentra Prostate v3.1, Elekta  
105 Brachytherapy, Veendendaal, The Netherlands). HIPO optimization method was used, and the  
106 prescribed dose was 10 Gy to the whole prostate gland ( $V_{100} \geq 95\%$ ). Based on this plan,  
107 metal needles were inserted into the prostate through a template under live US guidance. The  
108 optimization procedure was used again for calculating the dwell times in the inserted needles  
109 to achieve the final dose distribution. The detailed description of our treatment method can be  
110 found in our previous publications [19,20]. The total treatment time of TT and BT was 7  
111 weeks (44-54 days). In clinical routine, the EUD method was used to determine the dose  
112 constraints for prostate and OARs in BT implant and their total doses.

113 First, the treatment planning CT for TT was registered with the US set of BT in BT  
114 treatment planning system in every case (Figure 1), then the TT CT with the BT plan was  
115 imported to the TT planning system (Eclipse v13.7, Varian Medical Systems, Palo Alto,  
116 USA).

117 Then, the localisation of the most exposed part of the OARs was investigated in the sum  
118 of TT and BT plans. The most exposed part of hips (femoral heads) is always the nearest  
119 volume to the prostate and the dose contribution from BT is practically zero. So, the most  
120 exposed 0.1 and 2 ccm of hips were calculated only from the TT plan. The most exposed part  
121 of the rectum, urethra and bladder is in the region where the dose maximum is in BT. So, the  
122 most exposed 0.1 and 2 ccm from BT were determined in the TT CTs, and the intersection of  
123 this volumes and the given organ was created (Figure 2). The minimal dose of this  
124 intersection was calculated in TT plans and summed with the dose of this volumes from BT  
125 using the linear-quadratic radiobiological model. The  $\alpha/\beta$  of prostate tumour was assumed 1.5  
126 Gy, while for OARs 3 Gy was used. The following dose-volume parameters were used for  
127 quantitative evaluation of the plans:

128 **D90:** the minimum dose delivered to 90% of prostate (Gy);

129 **D<sub>0.1</sub>(x):** the minimal dose of the most exposed 0.1 ccm of *the critical organ x* (Gy),  
130 where x: *rectum, urethra, bladder or hips*.

131 **D<sub>2</sub>(x):** the minimal dose of the most exposed 2 ccm of *the critical organ x* (Gy),  
132 where x: *rectum, bladder or hips*.

133 To patients, whom BT is not accomplishable, TT boost is performed with additional 18  
134 Gy in 2 Gy fractions for the prostate gland using safety margins of 0.5 cm, if gold markers are  
135 implanted into the prostate, and 0.8 cm, if not [21,22]. For comparison, additional TT boost  
136 plans were created for every patient in the study with the same IMAT technique, and total  
137 EQD2 doses of the most exposed volume of the organs at risks were calculated in these 3-step  
138 TT plans.

139 Wilcoxon-matched pairs test was used (Statistica 12.5, StatSoft, Tulsa, OK, USA) to  
140 compare biological total dose of the combination of TT and BT or TT boost in the treatment

141 of prostate tumour. The comparison of our biological dose summation (BDS) and the  
142 conventional UDC method was also performed with this statistical test.

### 143 **Results**

144 The mean volume of the prostate was 29.8 ccm (21.1-43.0 ccm). We found that EQD2 D90 of  
145 the prostate was 99.3 Gy (96.8-101.9 Gy) using two-step TT and BT boost. The D<sub>0.1</sub> and D<sub>2</sub> of  
146 rectum were 62.8 Gy (41.0-75.6 Gy) and 50.3 Gy (29.8-65.8 Gy). The D<sub>0.1</sub> of urethra was  
147 96.1 Gy (95.5-96.9 Gy), the volume of it was less than 2 ccm in our cases. The D<sub>0.1</sub> and D<sub>2</sub> of  
148 bladder were 85.8 Gy (62.5-169.8 Gy) and 73.1Gy (46.0-140.5 Gy). The D<sub>0.1</sub> and D<sub>2</sub> of hips  
149 were 49.6 Gy (39.8-67.3 Gy) and 41.9 Gy (33.5-58.3 Gy).

150 In TT boost, the volume of the PTV is larger than the prostate, it was 111.7 ccm on  
151 average (range: 71.9-179.5 ccm). In comparison of BT and TT boost techniques, D90 of the  
152 prostate was significantly higher with BT than with TT: 99.3 Gy vs. 77.9 Gy, p=0.0034. The  
153 dose to rectum and hips were significantly lower with BT boost, D<sub>2</sub> was 50.3 Gy vs. 76.8 Gy  
154 (p=0.0117) and 41.9 Gy vs. 50.6 Gy (p=0.0044), respectively. The difference between the  
155 dose to bladder in the case of BT and TT boost showed the same trend, D<sub>2</sub> was 73.1 Gy vs.  
156 78.3 Gy in BT vs. TT plans, but this difference was not significant. Nevertheless, the dose to  
157 urethra was significantly higher with BT boost, D<sub>0.1</sub> was 96.1 Gy vs. 79.3 Gy (p=0.0180)  
158 using BT vs. TT boost technique (Figure 3). The detailed results can be found in Table 1.

159 Comparing our dose summation method to the conventional UDC in the case of  
160 combined TT with BT boost, we found that the UDC overestimates D<sub>2</sub> of rectum by 37% and  
161 underestimates D<sub>0.1</sub> of urethra by 1%. The D<sub>2</sub> of bladder was also 7% smaller using UDC, but  
162 this difference was not significant because of the large standard deviation of this variable  
163 (Table 2).



164 **Discussion**

165 Dose escalation has a fundamental role in the radiotherapy of intermediate- and high-risk  
166 prostate cancer [1,2]. Presently there are no better alternatives of BT boost, however, several  
167 high-tech teletherapy techniques are possible competitors, such as image-guided and  
168 intensity-modulated teletherapy, arc therapy, helical tomotherapy and stereotactic  
169 radiotherapy with linear accelerators or CyberKnife [3,7,16].

170 Vanneste et al. [1] have pointed out the strong correlation between overall survival and  
171 D90 of the prostate target volume in localised prostate cancer, with the best results being  
172 achievable above 75.6 Gy EQD2. Different treatment techniques lead to the same cure rate  
173 but with different toxicity pattern. The EQD2 prescribed dose to the prostate with our  
174 fractionation scheme is 92.9 Gy using BT and 78 Gy with TT boost. At the same time dose to  
175 the OARs is reduced with BT [3,4]. In our study, using IMAT TT with HDR BT boost could  
176 be dose of all OARs kept in a good tolerance level. The EQD2 D90 of the prostate was 99.3  
177 Gy, while D<sub>2</sub> of rectum was 50.3 Gy, approximately the half of the prostate dose. D<sub>0.1</sub> dose to  
178 the urethra was 96.1 Gy on average, less than the prostate dose, in spite of that urethra is  
179 inside the prostate. D<sub>2</sub> dose to the bladder was 73.1 Gy, while for hips it was only 41.9 Gy.  
180 All dose to the hips originates from 60 Gy of TT, BT does not contribute to it.

181 Notwithstanding, in TT larger target volume is used than BT, the total dose to the  
182 prostate is 22% (21.4 Gy) less, D90 was 99.3 Gy using BT and 77.9 Gy with TT boost. D<sub>2</sub>  
183 dose to the rectum, bladder and hips were 35% (26.5 Gy), 7% (5.2 Gy) and 18% (8.7 Gy)  
184 smaller with BT, than using TT boost. 18 Gy IMAT boost to the prostate target volume  
185 instead of BT means extra 9 Gy dose to the hips. Only the dose to the urethra was higher with  
186 BT boost, D<sub>0.1</sub> was 18% (16.8 Gy) higher than using TT boost.

187 In previous publications authors used the recommended UDC method to estimate the  
188 total dose of the prostate and OARs in combined therapy [15]. However, they did not take

189 into account the real biological doses. Kikuchi et al. [17] tried a better estimation of the rectal  
190 dose, than the UDC method, but they used a CT after removing the needles and the US probe  
191 instead of a postimplant CT or a live US imaging in the intraoperative BT plan and they did  
192 not take into account the quadratic behaviour of the biological dose. Since the most exposed  
193 part of the rectum, urethra and bladder is in the region where the dose maximum is in BT, this  
194 most exposed 2 ccm can be used for the calculation of the total biological dose. In this small  
195 volume, the quadratic dependence is negligible. Thus, our dose summation method is simple,  
196 timesaving and there is no interobserver variation. The only more precise method would be a  
197 pixel-by-pixel calculation of the biological dose in the same organ after a deformable  
198 registration of BT and TT images, but no treatment planning systems provides this possibility  
199 at the moment.

200         The effect of the dose summation technique on dose-volume parameters in combined  
201 TT and BT was also investigated in our study. The EQD2 D90 of the prostate was practically  
202 equal in our BDS and the conventional UDC method, but UDC overestimates the dose to  
203 rectum by 37% (18.6 Gy) and underestimates the dose to urethra by 1% (0.7 Gy) and dose to  
204 bladder by 7% (4.9 Gy) compared to BDS method. Besides this, the potential advantage of the  
205 BDS method is that it takes into account the most exposed part of the OARs and thus sparing  
206 these parts from higher doses in TT, as is shown in Figure 4. On the whole, the dose to the  
207 OARs can be reduced using our alternative dose summation method.

208         This study is the starting point of the development of an algorithm for the summation  
209 of TT and BT biologically effective doses, which uses an artificial-intelligence-based DIR  
210 algorithm to match the critical anatomical structures in the two radiotherapy modalities.  
211 Further investigations are needed to assess whether our method predicts toxicity better than  
212 the recent UDC method.

213 **Conclusions**

214 Based on our biological dose summation method in IMAT with interstitial HDR BT or IMAT  
215 boost treatment in prostate cancer, total dose of the prostate is higher using BT boost, than the  
216 IMAT. BT boost results lower rectum, bladder and hip doses, but higher dose to the urethra.  
217 UDC overestimates rectum dose and underestimates the dose to the urethra and to the bladder.

218 *Conflict of Interest statement:*

219 GF: This paper was supported by the János Bolyai Research Scholarship of the Hungarian  
220 Academy of Sciences and the ÚNKP-18-4 New National Excellence Program of the Ministry  
221 of Human Capacities.

222 All other authors: The authors report no proprietary or commercial interest in any product  
223 mentioned or concept discussed in this article.

224 *Contributions:*

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

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

227 KJ: made the contouring.

228 CsP: supported the study.

229 TM: supported the study and discussed the details.

230 **References**

- 231 1. Vanneste BG, Van Limbergen EJ, van Lin EN, van Roermund JG, Lambin P. Prostate  
232 Cancer Radiation Therapy: What Do Clinicians Have to Know? *Biomed Res Int.*  
233 2016;2016:6829875. doi: 10.1155/2016/6829875.
- 234 2. Kuban DA, Tucker SL, Dong YL, Starkschall ZG, Huang EH, Cheung R, Lee AK,  
235 Pollack A. Long-term results of the M. D. Anderson randomized dose-escalation trial  
236 for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2008;70(1):67–74.
- 237 3. Georg D, Hopfgartner J, Gòra J, Kuess P, Kragl G, Berger D, Hegazy N, Goldner G,  
238 Georg P. Dosimetric considerations to determine the optimal technique for localized  
239 prostate cancer among external photon, proton, or carbon-ion therapy and high-dose-  
240 rate or low-dose-rate brachytherapy. *Int J Radiat Oncol Biol Phys.* 2014;188(3):715-  
241 22. doi: 10.1016/j.ijrobp.2013.11.241.
- 242 4. Yang R, Zhao N, Liao A, Wang H, Qu A. Dosimetric and radiobiological comparison  
243 of volumetric modulated arc therapy, high-dose rate brachytherapy, and low-dose rate  
244 permanent seeds implant for localized prostate cancer. *Med Dosim.* 2016;41(3):236-  
245 41. doi: 10.1016/j.meddos.2016.06.002.
- 246 5. Kee DLC, Gal J, Falk AT, Schiappa R, Chand ME, Gautier M, Doyen J, Hannoun-  
247 Levi JM. Brachytherapy versus external beam radiotherapy boost for prostate cancer:  
248 Systematic review with meta-analysis of randomized trials. *Cancer Treat Rev.*  
249 2018;70:265-271. doi: 10.1016/j.ctrv.2018.10.004.
- 250 6. Fu-Min F, Yu-Ming W, Chong-Jong W, Hsuan-Ying H, Po-Hui C. Comparison of the  
251 Outcome and Morbidity for Localized or Locally Advanced Prostate Cancer Treated  
252 by High-dose-rate Brachytherapy Plus External Beam Radiotherapy (EBRT) Versus  
253 EBRT Alone. *Jpn J Clin Oncol* 2008;38(7)474–479. doi:10.1093/jjco/hyn056

- 254 7. Morgan TM, Press RH, Cutrell PK, Zhang C, Chen Z, Rahnama S, Sanda M, Pattaras  
255 J, Patel PR, Jani AB, Rossi PJ. Brachytherapy for localized prostate cancer in the  
256 modern era: a comparison of patient-reported quality of life outcomes among different  
257 techniques. *J Contemp Brachytherapy*. 2018;10(6):495-502. doi:  
258 10.5114/jcb.2018.81024.
- 259 8. Ash D, Al-Qaisieh B, Bottomley D, Carey B, Joseph J. The correlation between D90  
260 and outcome for I-125 seed implant monotherapy for localised prostate cancer.  
261 *Radiother Oncol*. 2006;79(2):185-9.
- 262 9. Murakami N, Itami J, Okuma K, Marino H, Nakagawa K, Ban T, Nakazato M, Kanai  
263 K, Naoi K, Fuse M. Urethral dose and increment of international prostate symptom  
264 score (IPSS) in transperineal permanent interstitial implant (TPI) of prostate cancer.  
265 *Strahlenther Onkol*. 2008;184(10):515-9. doi: 10.1007/s00066-008-1833-3.
- 266 10. Fowler JF. The linear-quadratic formula on progress in fractionated radiotherapy. *Br J*  
267 *Radiol* 1989;62:679-694.
- 268 11. Nag S, Gupta N. A simple method of obtaining equivalent doses for use in HDR  
269 brachytherapy. *Int J Radial Oncol Biol Phys*. 2000;46:507-513.
- 270 12. Niemierko A. Reporting and analyzing dose distributions: a concept of equivalent  
271 uniform dose. *Med Phys*. 1997;24(1):103-10.
- 272 13. Fröhlich G, Lang S, Berger D et al. Spatial relationship of the 3D dose distribution  
273 from brachytherapy and external beam therapy for adding both dose plans in patients  
274 with cervix cancer. *Brachytherapy* 2008;7(2):95
- 275 14. Fröhlich G, Vízkeleti J, Nguyen Anhhong N, Major T, Polgár Cs. Comparative  
276 analysis of image-guided adaptive interstitial brachytherapy and intensity-modulated  
277 arc therapy versus conventional treatment techniques in cervix cancer using biological  
278 dose summation. *J Contemp Brachyther*, 2018;11(1):1–7.

- 279 15. Pinkawa M, Fishedick K, Treusacherr P, Asadpour B, Gagel B, Piroth MD, Borchers  
280 H, Jakse G, Eble M. Dose-volume impact in high-dose-rate Iridium-192  
281 brachytherapy as a boost to external beam radiotherapy for localized prostate cancer- a  
282 phase II study. *Radiother Oncol.* 2006;78:41-46.
- 283 16. Andrzejewski P, Kuess P, Knäusl B, Pinker K, Georg P, Knoth J, Berger D, Kirisits C,  
284 Goldner G, Helbich T, Pötter R, Georg D. Feasibility of dominant intraprostatic lesion  
285 boosting using advanced photon-, proton- or brachytherapy. *Radiother Oncol.*  
286 2015;117(3):509-14. doi: 10.1016/j.radonc.2015.07.028.
- 287 17. Kikuchi K, Nakamura R, Tanji S, Yamaguchi S, Kakuhara H, Yabuuchi T, Inatsu W,  
288 Oikawa H, Ariga H. Three-dimensional summation of rectal doses in brachytherapy  
289 combined with external beam radiotherapy for prostate cancer. *Radiother Oncol.*  
290 2013;107(2):159-64. doi: 10.1016/j.radonc.2013.03.003.
- 291 18. Kovács Gy, Pötter R, Loch T, Hammer J, Kolkman-Deurloo IK, de la Rosette JJ,  
292 Bertermann H. GEC/ESTRO-EAU recommendations on temporary brachytherapy  
293 using stepping sources for localised prostate cancer. *Radiother Oncol.* 2005;74:137-  
294 148.
- 295 19. Fröhlich G, Ágoston P, Lövey J et al. Dosimetric evaluation of high-dose-rate  
296 interstitial brachytherapy boost treatments for localized prostate cancer. *Strahlenther*  
297 *Onkol*, 2010;186(7): 388-395.
- 298 20. Ágoston P, Major T, Fröhlich G, Szabó Z, Lövey J, Fodor J, Kásler M, Polgár Cs.  
299 Moderate dose escalation with single-fraction high-dose-rate brachytherapy boost for  
300 clinically localized intermediate- and high-risk prostate cancer: 5-year outcome of the  
301 first 100 consecutively treated patients. *Brachytherapy.* 2011;10:376-384.
- 302 21. Boehmer D, Maingon P, Poortmans P, Baron MH, Miralbell R, Remouchamps V,  
303 Scrase C, Bossi A, Bolla M; EORTC radiation oncology group. Guidelines for

304 primary radiotherapy of patients with prostate cancer. *Radiother Oncol.*  
305 2006;79(3):259-69.

306 22. Lawton CA, Michalski J, El-Naqa I, Buyyounouski MK, Lee WR, Menard C, O'Meara  
307 E, Rosenthal SA, Ritter M, Seider M. RTOG GU Radiation oncology specialists reach  
308 consensus on pelvic lymph node volumes for high-risk prostate cancer. *Int J Radiat*  
309 *Oncol Biol Phys.* 2009;74(2):383-387. doi: 10.1016/j.ijrobp.2008.08.002.

310

311 **Tables:**

<b>EQD2</b>	<b>TT + BT boost</b>	<b>TT + TT boost</b>	<b>*p-value</b>
<b>D90 (Gy)</b>	99.3 (96.8-101.9)	77.9 (76.4-78.5)	<b>0.0034</b>
<b>D<sub>2</sub>(rectum) (Gy)</b>	50.3 (29.8-65.8)	76.8 (65.8-79.3)	<b>0.0017</b>
<b>D<sub>0.1</sub>(urethra) (Gy)</b>	96.1 (95.5-96.9)	79.3 (78.6-80.4)	<b>0.0180</b>
<b>D<sub>2</sub>(bladder) (Gy)</b>	73.1 (46.0-140.5)	78.3 (77.2-79.8)	0.1614
<b>D<sub>2</sub>(hips) (Gy)</b>	41.9 (33.5-58.3)	50.6 (43.6-58.1)	<b>0.0044</b>

312 **Table 1. The EQD2 total doses of intensity-modulated arc therapy plus interstitial HDR**  
 313 **BT boost (TT + BT boost) and intensity-modulated arc therapy plus teletherapy boost**  
 314 **(TT + TT boost). D90: the minimum dose delivered to 90% of prostate (Gy), D<sub>2</sub>(rectum),**  
 315 **D<sub>2</sub>(bladder), D<sub>2</sub>(hips): the minimal dose of the most exposed 2 ccm of rectum, bladder**  
 316 **and hips (Gy), D<sub>0.1</sub>(urethra): the minimal dose of the most exposed 0.1 ccm of urethra**  
 317 **(Gy). \*Wilcoxon-matched pairs test.**

318

<b>EQD2</b>	<b>BDS</b>	<b>UDC</b>	<b>*p-value</b>
<b>D90 (Gy)</b>	99.3 (96.8-101.9)	100.2 (96.6-104.8)	1.0000
<b>D<sub>2</sub>(rectum) (Gy)</b>	50.3 (29.8-65.8)	68.9 (66.6-70.9)	<b>0.0117</b>
<b>D<sub>0.1</sub>(urethra) (Gy)</b>	96.1 (95.5-96.9)	95.4 (94.4-96.0)	<b>0.0277</b>
<b>D<sub>2</sub>(bladder) (Gy)</b>	73.1 (46.0-140.5)	68.2 (62.9-74.0)	0.0614

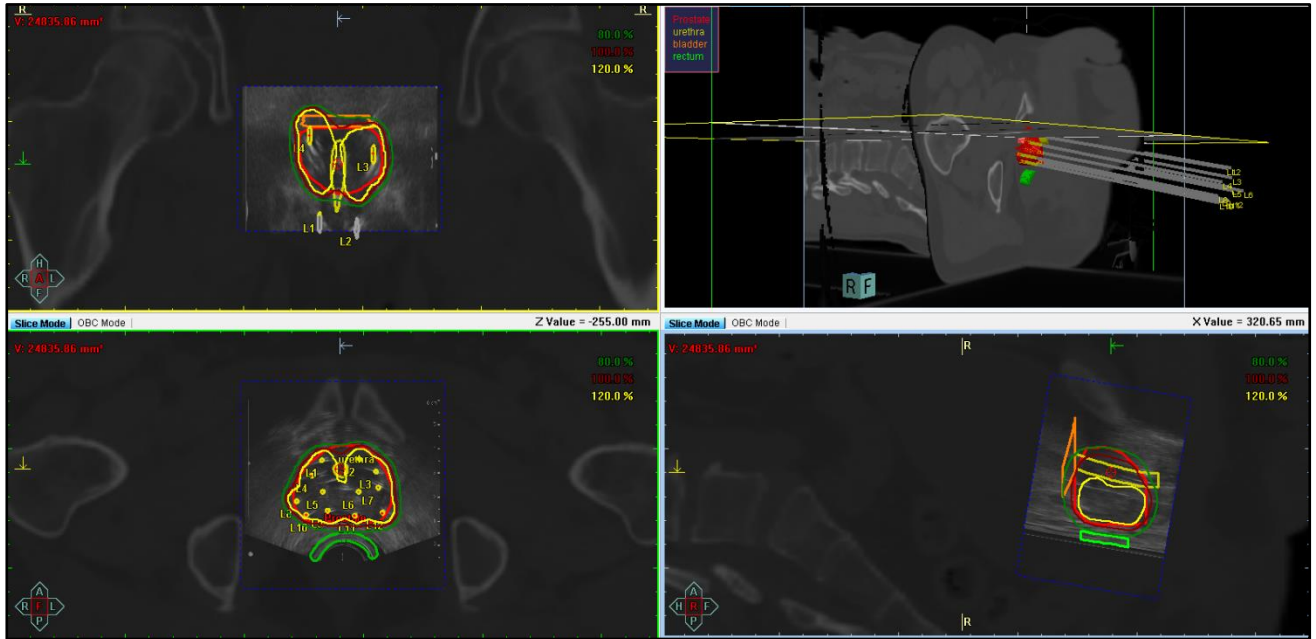
319 **Table 2. The EQD2 total doses of intensity-modulated arc therapy plus interstitial HDR**  
 320 **BT boost calculated by our biological dose summation (BDS) and the uniform dose**  
 321 **conception (UDC) method. D90: the minimum dose delivered to 90% of prostate (Gy),**



322 **D<sub>2</sub>(rectum), D<sub>2</sub>(bladder): the minimal dose of the most exposed 2 cm of rectum and**  
323 **bladder (Gy), D<sub>0.1</sub>(urethra): the minimal dose of the most exposed 0.1 cm of urethra**  
324 **(Gy). \*Wilcoxon-matched pairs test.**

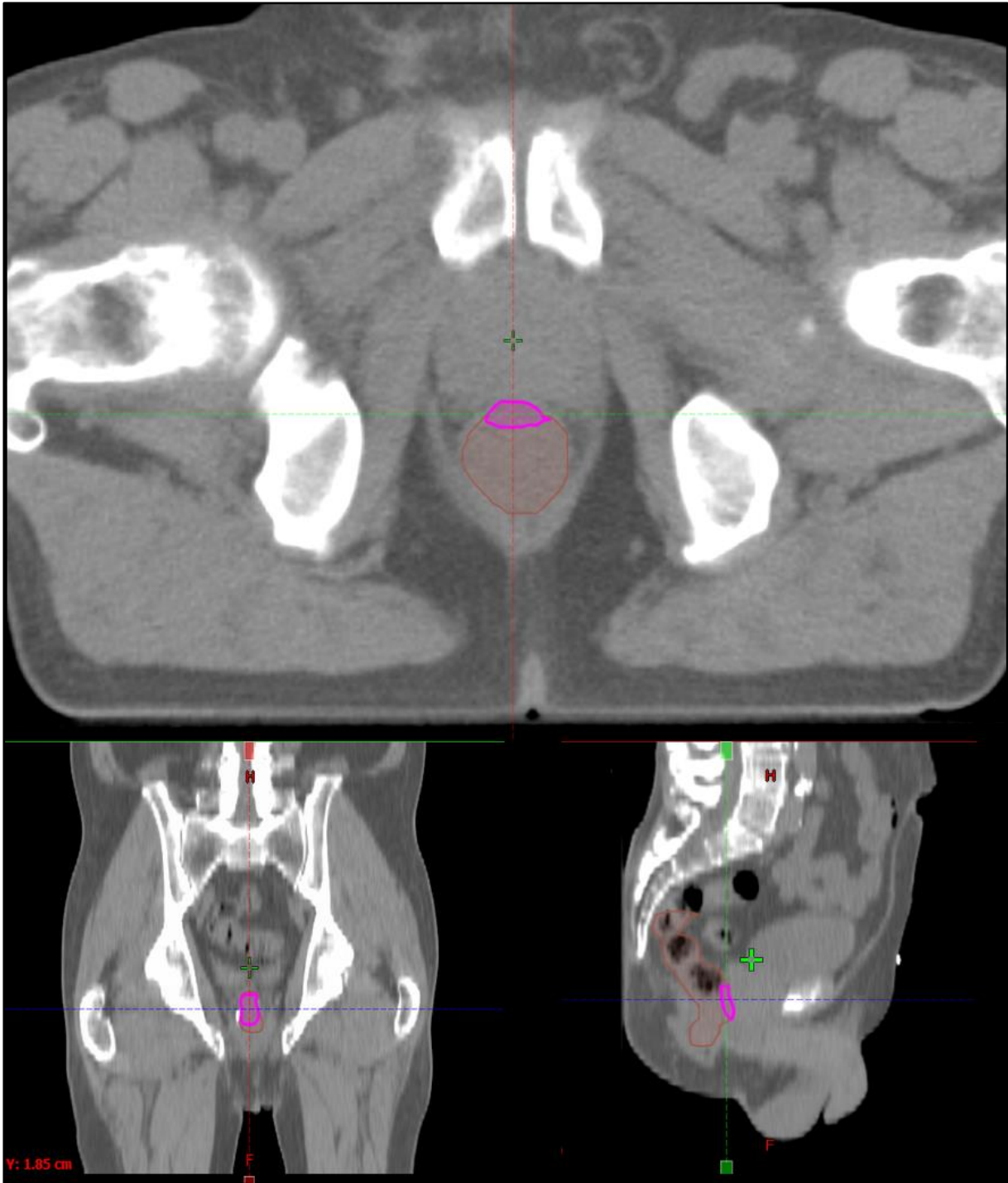
325

326 **Figures:**



327

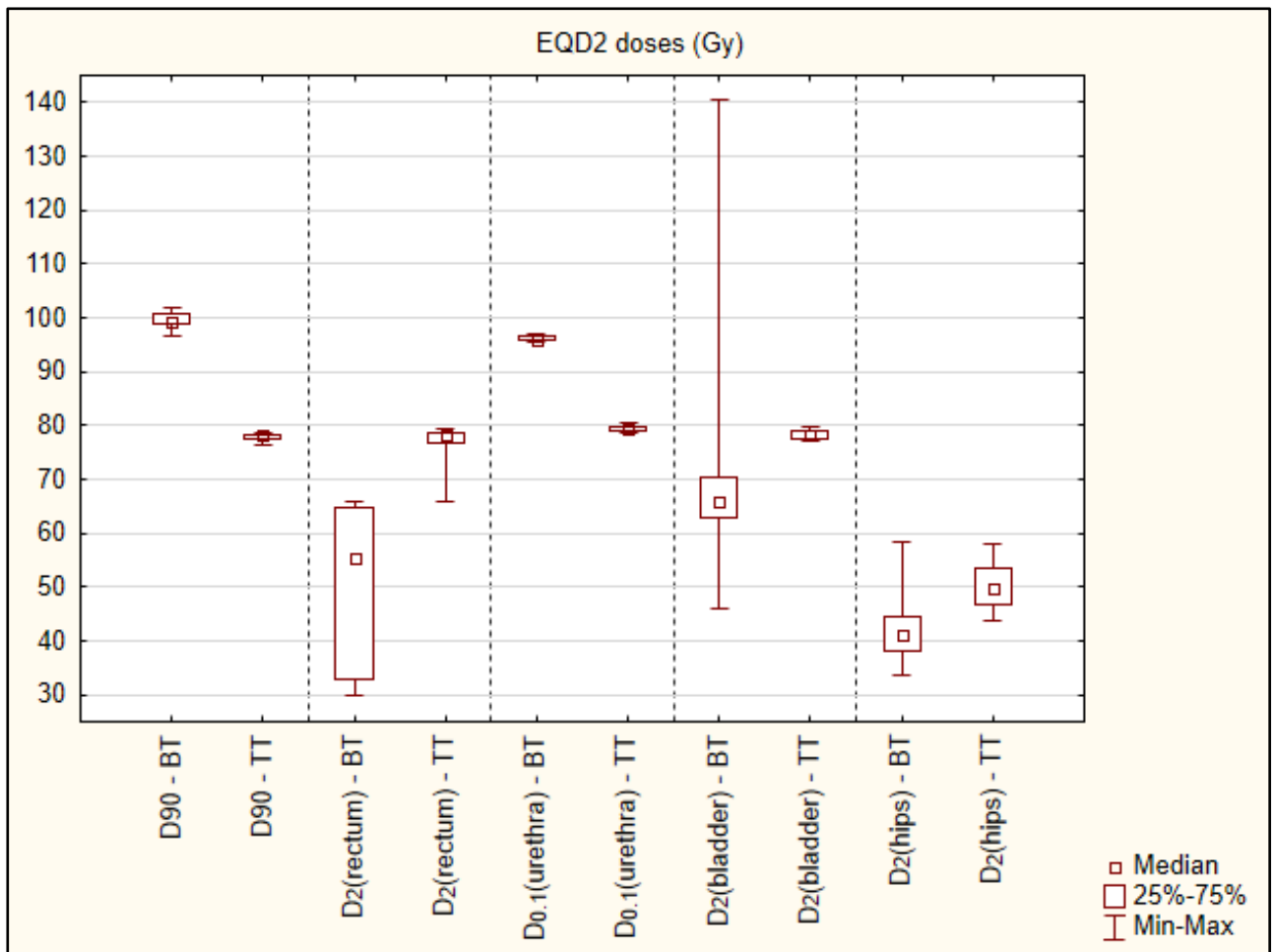
328 **Figure 1.** The BT treatment plan on the registered TT CT and BT US sets. Top left: a  
329 coronal view, top right: 3D reconstruction, bottom left: an axial view, bottom right: a  
330 sagittal view. Thick red: prostate, thick green: rectum, thick yellow: urethra, thick  
331 orange: bladder, green, red and yellow line: the 80%, 100% and 120% isodose line.



332

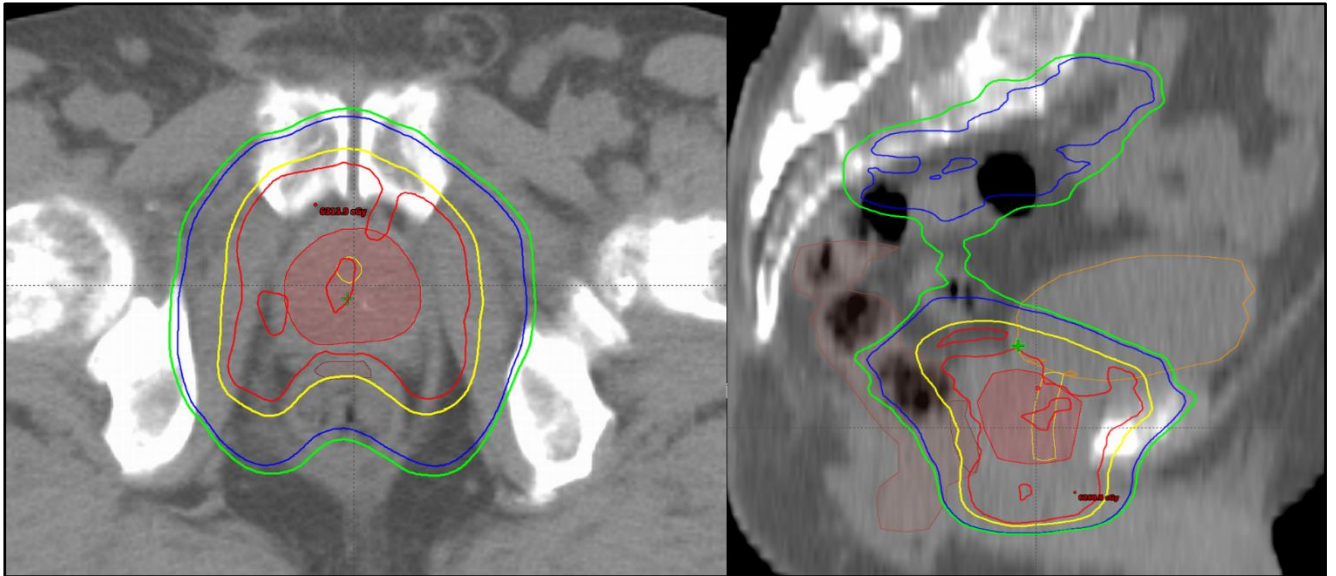
333 **Figure 2. The most exposed 2 ccm part (pink) of the rectum (brown) in an axial (up), in**

334 **a coronal (left) and in a sagittal (right) slice of the TT CT.**



335

336 **Figure 3. The EQD2 total doses of intensity-modulated arc therapy plus interstitial HDR**  
 337 **BT boost (BT) and intensity-modulated arc therapy plus teletherapy boost (TT). D90:**  
 338 **the minimum dose delivered to 90% of prostate (Gy), D<sub>2</sub>(rectum), D<sub>2</sub>(bladder), D<sub>2</sub>(hips):**  
 339 **the minimal dose of the most exposed 2 ccm of rectum, bladder and hips (Gy),**  
 340 **D<sub>0.1</sub>(urethra): the minimal dose of the most exposed 0.1 cm of urethra (Gy).**



341  
342 **Figure 4. The most exposed 2 cm of rectum is indicated with brown, the urethra and**  
343 **the bladder are contoured with yellow and orange and the prostate gland is shown with**  
344 **red (colorwash) in an axial (left) and a sagittal (right) CT slice in a two-step intensity-**  
345 **modulated arc therapy plan. Isodose lines: red: 60 Gy, yellow: 57 Gy, blue: 44 Gy and**  
346 **green: 41.8 Gy.**