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

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Biological dose summation of prostate tele- and brachytherapy

Abstract

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

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

Results: D90 of the prostate was significantly higher with BT than with IMAT boost: 99.3 Gy vs. 77.9 Gy, p=0.0034. The dose to rectum and hips were significantly lower with BT boost, D_2 were 50.3 Gy vs. 76.8 Gy (p=0.0117) and 41.9 Gy vs. 50.6 Gy (p=0.0044), respectively. The dose to bladder showed the same trend, D_2 were 73.1 Gy vs. 78.3 Gy in BT vs. IMAT plans, dose to urethra was significantly higher with BT boost, $D_{0.1}$ was 96.1 Gy vs. 79.3 Gy (p=0.0180) using BT vs. IMAT boost technique. UDC overestimates D_2 of rectum by 37% (p=0.0117) and underestimates $D_{0.1}$ of urethra by 1% (p=0.0277) and D_2 of bladder by 7% (p=0.0614).

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

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

Introduction

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

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

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

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

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

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

Materials and methods

At our institute, fifteen IMAT plus interstitial HDR BT plans of patients with intermediate- and high-risk prostate cancer were included for this study. Selection criteria were the following: PSA>10 ng/mL and/or GS 7-10 and/or Stage T2b-T3b. The TT was performed in supine position, the patients were immobilized with knee and ankle support system. The prescribed dose was 2/44 Gy for the whole pelvis, 2/60 Gy for the prostate and the vesicle seminals and was delivered with an energy of 10 MV using 2 full arcs. Based on our local IGRT protocol, CBCT verification was made from 1^{st} to 3^{rd} fractions, the systematic error was calculated and corrected before the 4^{th} fraction, then weekly verification was done for patient positioning. TT was complemented with transrectal US-guided interstitial HDR BT boost, performed after the 4 weeks TT course, given 1 fraction of 10 Gy [18]. After scanning the prostate with US, a virtual preimplant plan was generated (Oncentra Prostate v3.1, Elekta Brachytherapy, Veendendaal, The Netherlands). HIPO optimization method was used, and the prescribed dose was 10 Gy to the whole prostate gland (V100≥95%). Based on this plan, metal needles were inserted into the prostate through a template under live US guidance. The optimization procedure was used again for calculating the dwell times in the inserted needles to achieve the final dose distribution. The detailed description of our treatment method can be found in our previous publications [19,20]. The total treatment time of TT and BT was 7 weeks (44-54 days). In clinical routine, the EUD method was used to determine the dose constraints for prostate and OARs in BT implant and their total doses.

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

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

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

$D_{0.1}$(x): the minimal dose of the most exposed 0.1 ccm of *the critical organ x* (Gy), where x: *rectum, urethra, bladder or hips*.

D_2(x): the minimal dose of the most exposed 2 ccm of *the critical organ x* (Gy), where x: *rectum, bladder or hips*.

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

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

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

Results

The mean volume of the prostate was 29.8 ccm (21.1-43.0 ccm). We found that EQD2 D90 of the prostate was 99.3 Gy (96.8-101.9 Gy) using two-step TT and BT boost. The $D_{0.1}$ and D_2 of rectum were 62.8 Gy (41.0-75.6 Gy) and 50.3 Gy (29.8-65.8 Gy). The $D_{0.1}$ of urethra was 96.1 Gy (95.5-96.9 Gy), the volume of it was less than 2 ccm in our cases. The $D_{0.1}$ and D_2 of bladder were 85.8 Gy (62.5-169.8 Gy) and 73.1Gy (46.0-140.5 Gy). The $D_{0.1}$ and D_2 of hips were 49.6 Gy (39.8-67.3 Gy) and 41.9 Gy (33.5-58.3 Gy).

In TT boost, the volume of the PTV is larger than the prostate, it was 111.7 ccm on average (range: 71.9-179.5 ccm). In comparison of BT and TT boost techniques, D90 of the prostate was significantly higher with BT than with TT: 99.3 Gy vs. 77.9 Gy, p=0.0034. The dose to rectum and hips were significantly lower with BT boost, D_2 was 50.3 Gy vs. 76.8 Gy (p=0.0117) and 41.9 Gy vs. 50.6 Gy (p=0.0044), respectively. The difference between the dose to bladder in the case of BT and TT boost showed the same trend, D_2 was 73.1 Gy vs. 78.3 Gy in BT vs. TT plans, but this difference was not significant. Nevertheless, the dose to urethra was significantly higher with BT boost, $D_{0.1}$ was 96.1 Gy vs. 79.3 Gy (p=0.0180) using BT vs. TT boost technique (Figure 3). The detailed results can be found in Table 1.

Comparing our dose summation method to the conventional UDC in the case of combined TT with BT boost, we found that the UDC overestimates D_2 of rectum by 37% and underestimates $D_{0.1}$ of urethra by 1%. The D_2 of bladder was also 7% smaller using UDC, but this difference was not significant because of the large standard deviation of this variable (Table 2).

Discussion

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

Vanneste et al. [1] have pointed out the strong correlation between overall survival and D90 of the prostate target volume in localised prostate cancer, with the best results being achievable above 75.6 Gy EQD2. Different treatment techniques lead to the same cure rate but with different toxicity pattern. The EQD2 prescribed dose to the prostate with our fractionation scheme is 92.9 Gy using BT and 78 Gy with TT boost. At the same time dose to the OARs is reduced with BT [3,4]. In our study, using IMAT TT with HDR BT boost could be dose of all OARs kept in a good tolerance level. The EQD2 D90 of the prostate was 99.3 Gy, while D_2 of rectum was 50.3 Gy, approximately the half of the prostate dose. $D_{0.1}$ dose to the urethra was 96.1 Gy on average, less than the prostate dose, in spite of that urethra is inside the prostate. D_2 dose to the bladder was 73.1 Gy, while for hips it was only 41.9 Gy. All dose to the hips originates from 60 Gy of TT, BT does not contribute to it.

Notwithstanding, in TT larger target volume is used than BT, the total dose to the prostate is 22% (21.4 Gy) less, D90 was 99.3 Gy using BT and 77.9 Gy with TT boost. D_2 dose to the rectum, bladder and hips were 35% (26.5 Gy), 7% (5.2 Gy) and 18% (8.7 Gy) smaller with BT, than using TT boost. 18 Gy IMAT boost to the prostate target volume instead of BT means extra 9 Gy dose to the hips. Only the dose to the urethra was higher with BT boost, $D_{0.1}$ was 18% (16.8 Gy) higher than using TT boost.

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

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

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

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

Conclusions

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

Conflict of Interest statement:

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

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

Contributions:

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

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

KJ: made the contouring.

CsP: supported the study.

TM: supported the study and discussed the details.

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Tables:

EQD2	TT + BT boost	TT + TT boost	*p-value
D90 (Gy)	99.3 (96.8-101.9)	77.9 (76.4-78.5)	**0.0034**
D_2(rectum) (Gy)	50.3 (29.8-65.8)	76.8 (65.8-79.3)	**0.0017**
$D_{0.1}$(urethra) (Gy)	96.1 (95.5-96.9)	79.3 (78.6-80.4)	**0.0180**
D_2(bladder) (Gy)	73.1 (46.0-140.5)	78.3 (77.2-79.8)	0.1614
D_2(hips) (Gy)	41.9 (33.5-58.3)	50.6 (43.6-58.1)	**0.0044**

Table 1. The EQD2 total doses of intensity-modulated arc therapy plus interstitial HDR BT boost (TT + BT boost) and intensity-modulated arc therapy plus teletherapy boost (TT + TT boost). D90: the minimum dose delivered to 90% of prostate (Gy), D_2(rectum), D_2(bladder), D_2(hips): the minimal dose of the most exposed 2 ccm of rectum, bladder and hips (Gy), $D_{0.1}$(urethra): the minimal dose of the most exposed 0.1 ccm of urethra (Gy). *Wilcoxon-matched pairs test.

EQD2	BDS	UDC	*p-value
D90 (Gy)	99.3 (96.8-101.9)	100.2 (96.6-104.8)	1.0000
D_2(rectum) (Gy)	50.3 (29.8-65.8)	68.9 (66.6-70.9)	**0.0117**
$D_{0.1}$(urethra) (Gy)	96.1 (95.5-96.9)	95.4 (94.4-96.0)	**0.0277**
D_2(bladder) (Gy)	73.1 (46.0-140.5)	68.2 (62.9-74.0)	0.0614

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

D_2(rectum), D_2(bladder): the minimal dose of the most exposed 2 ccm of rectum and bladder (Gy), $D_{0.1}$(urethra): the minimal dose of the most exposed 0.1 ccm of urethra (Gy). *Wilcoxon-matched pairs test.

Figures:

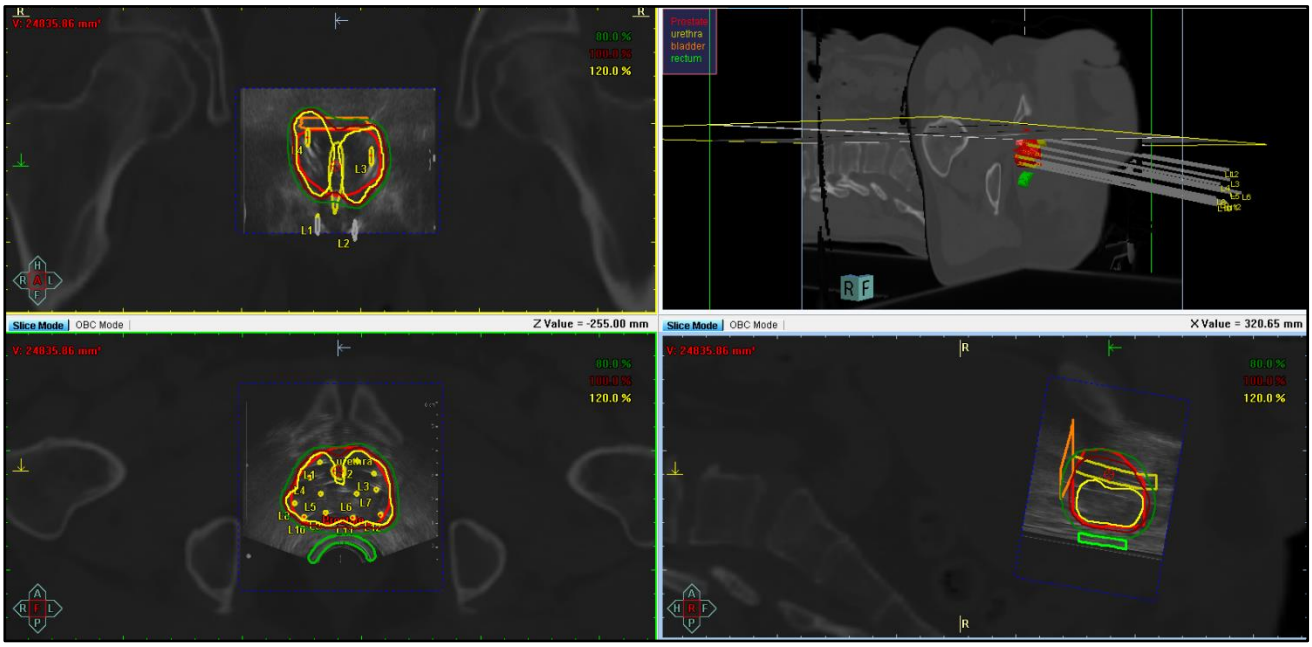


Figure 1. The BT treatment plan on the registered TT CT and BT US sets. Top left: a coronal view, top right: 3D reconstruction, bottom left: an axial view, bottom right: a sagittal view. Thick red: prostate, thick green: rectum, thick yellow: urethra, thick orange: bladder, green, red and yellow line: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

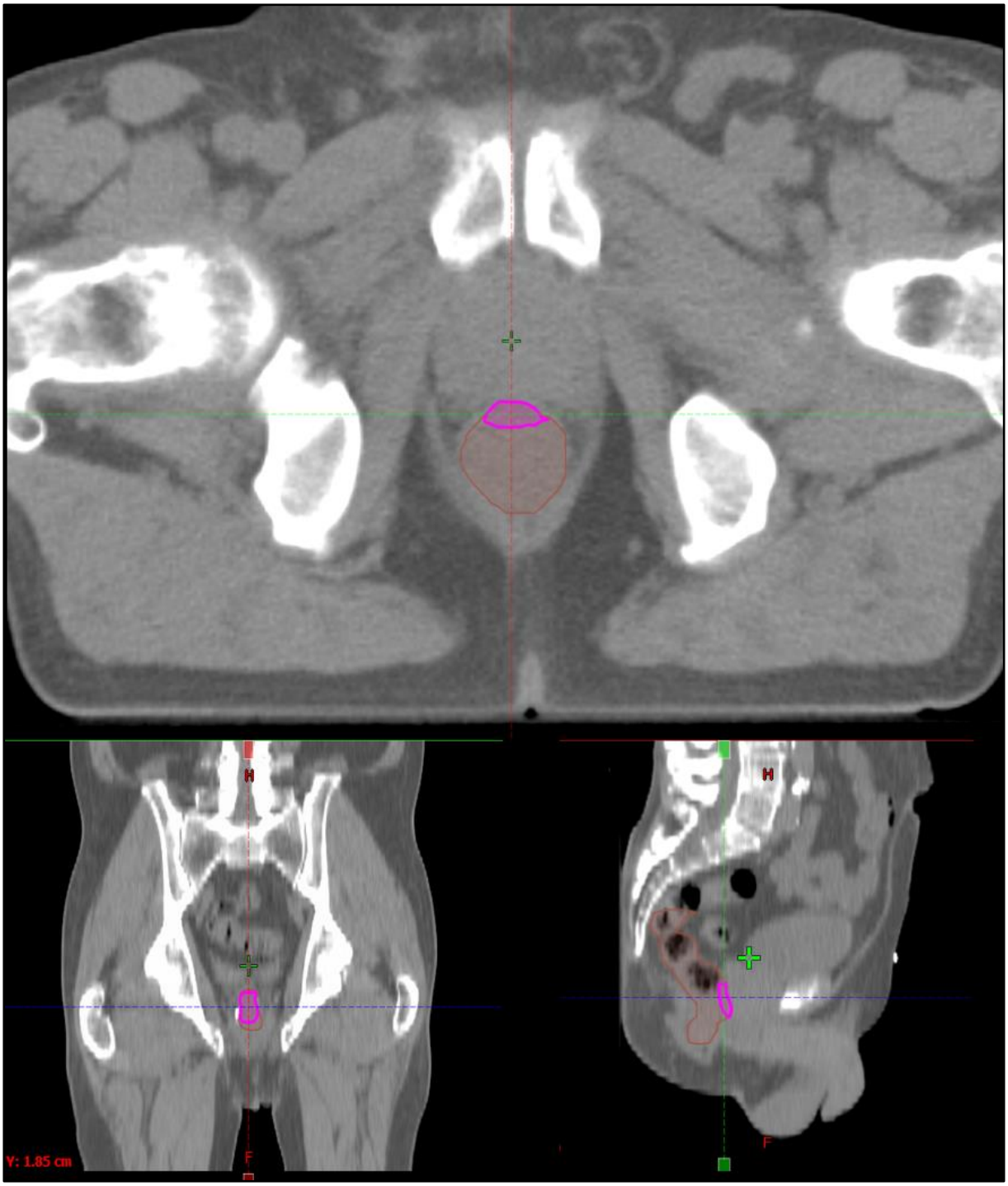
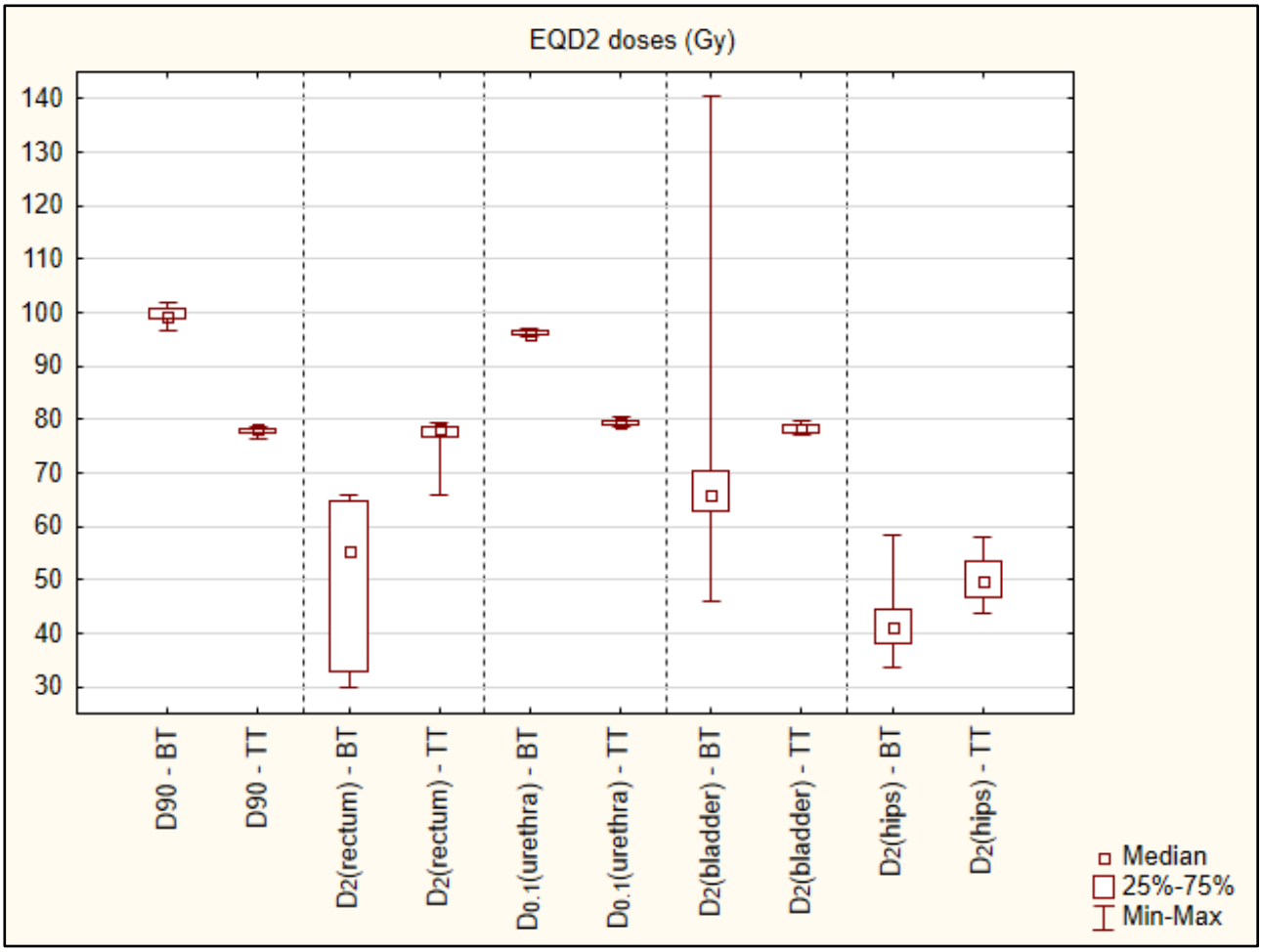


Figure 2. The most exposed 2 ccm part (pink) of the rectum (brown) in an axial (up), in a coronal (left) and in a sagittal (right) slice of the TT CT.



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_2(rectum), D_2(bladder), D_2(hips):**
339 **the minimal dose of the most exposed 2 ccm of rectum, bladder and hips (Gy),**
340 **$D_{0.1}$(urethra): the minimal dose of the most exposed 0.1 ccm of urethra (Gy).**

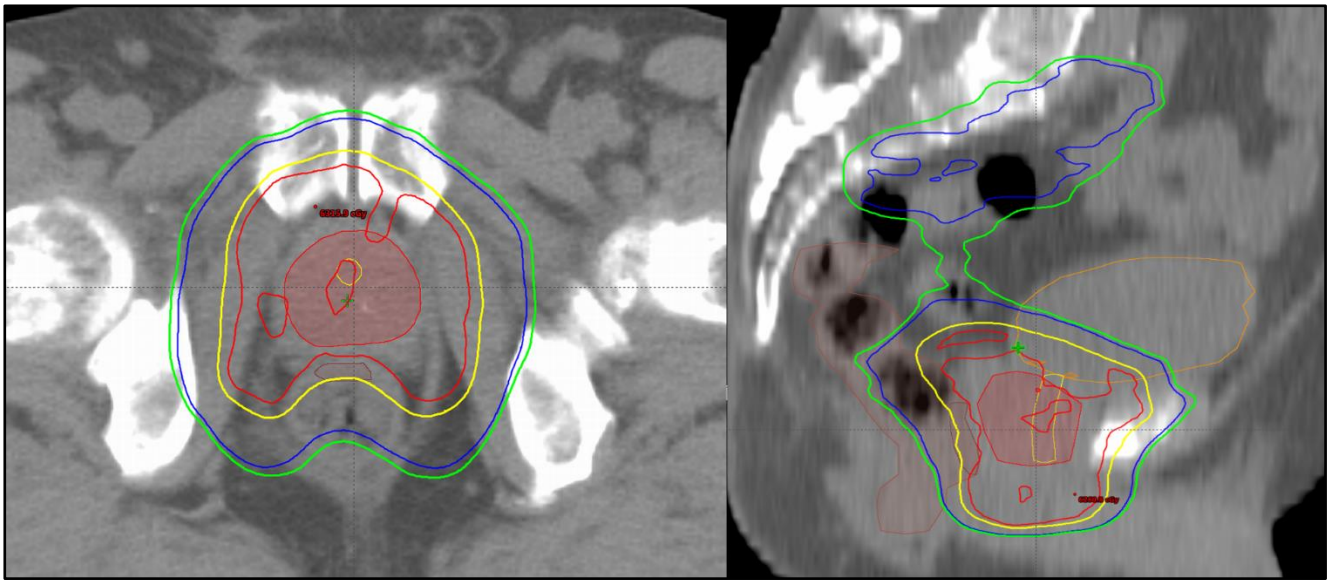


Figure 4. The most exposed 2 ccm of rectum is indicated with brown, the urethra and the bladder are contoured with yellow and orange and the prostate gland is shown with red (colorwash) in an axial (left) and a sagittal (right) CT slice in a two-step intensity-modulated arc therapy plan. Isodose lines: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