Comparative dosimetrical analysis of intensity-modulated arc therapy, CyberKnife therapy and image-guided interstitial HDR and LDR brachytherapy of low risk prostate cancer

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Dosimetric comparison of prostate IMAT, CyberKnife, HDR and LDR BT

Declaration of Interest statement:

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Abstract

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

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

Results: EQD2 total dose of the prostate was significantly lower with IMAT and CK than with HDR and LDR BT, D90 was 79.5Gy, 116.4Gy, 169.2Gy and 157.9Gy ($p<0.001$). However, teletherapy plans were more conformal than BT, COIN was 0.84, 0.82, 0.76 and 0.76 ($p<0.001$), respectively. The D_2 to rectum and bladder were lower with HDR BT than with IMAT, CK and LDR BT, it was 66.7Gy, 68.1Gy, 36.0Gy and 68.0Gy ($p=0.0427$), and 68.4Gy, 78.9Gy, 51.4Gy and 70.3Gy ($p=0.0091$) in IMAT, CK, HDR and LDR BT plans, while $D_{0.1}$ to urethra was lower with both IMAT and CK than with BTs: 79.9Gy, 88.0Gy, 132.7Gy and 170.6Gy ($p<0.001$). D_2 to hips was higher with IMAT and CK, than with BTs: 13.4Gy, 20.7Gy, 0.4Gy and 1.5Gy ($p<0.001$), while D_2 to sigmoid, bowel bag, testicles and penile bulb was higher with CK than with the other techniques.

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

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

Introduction

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

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

Despite the wide-spread application of these state-of-the-art techniques, no detailed analysis of all of these treatment techniques exists. Leszczyński et al. compared the dose distributions of intensity-modulated prostate radiotherapy versus IMAT technique [13]. Yang et al. investigated the dosimetric differences among IMAT, HDR and LDT BT for 10 patients, but HDR BT was not a single fraction monotherapy in their study [14]. Andrzejewski et al. 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].

On the CT series made for CK treatment planning, additional plans using IMAT, HDR and LDR BT were created using the same contour set. Where urethra was not identifiable on CT images, it was contoured between the bladder and the penile channel using a 15 mm pearl. IMAT plans were made in Eclipse v13.7 TPS (Varian Medical Systems, Palo Alto, USA) with a beam energy of 10 MV using 2 full arcs (Fig 1.a). CTV was extended using an isotropic 5 mm margin. The prescribed dose was 70 Gy, the dose of the daily fractions was 2.5 Gy for the PTV. The protocol of our PROMOBRA study was applied for treatment planning in both HDR and LDR BT plans [22]. The prescribed dose in HDR BT was 21 Gy (V100≥95%) to the CTV of the CK plan, as the BT PTV, in a single treatment fraction using Ir-192 radioactive source. HIPO method was used to optimize the plans in the Oncentra Prostate v3.1 TPS (Elekta Brachytherapy, Veendendaal, The Netherlands) (Fig 1.c). In LDR BT the prescribed dose was 145 Gy (V100≥95%) to the same CTV. IPSA optimisation method in the Oncentra Prostate v3.1 TPS (Elekta Brachytherapy, Veendendaal, The Netherlands) was used to calculate the virtual positions of the I-125 isotopes (Fig 1.d). The detailed description of our treatment method can be found in our previous publications [23-26].

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

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

COIN: conformal index [31];

$D_{0.1}$(x), D_2(x): the minimal dose of the most exposed 0.1 and 2 cm^3 of *the critical organ x* (Gy),

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

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

Results

The mean volume of the PTV was 105.7 cm^3 (42.2-189.3 cm^3) in IMAT, 85.5 cm^3 (31.5-159.2 cm^3) in the CK and 61.8 cm^3 (19.8-126.2 cm^3) in both BT plans (which is equal to the original CTV) on average. We found that EQD2 total dose of the prostate was significantly lower with IMAT and CK than with HDR and LDR BT, D90 was 79.5 Gy, 116.4 Gy, 169.2 Gy and 157.9 Gy ($p<0.001$). However, IMAT and CK plans were more conformal than BT plans, COIN were 0.84, 0.82, 0.76 and 0.76 ($p<0.001$).

In our comparison, the D_2 to rectum and bladder were lower with HDR BT than with 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 Gy, 78.9 Gy, 51.4 Gy and 70.3 Gy ($p=0.0091$) in IMAT, CK, HDR and LDR BT plans, while $D_{0.1}$ to urethra was lower with both IMAT and CK than with both BT modalities: 79.9 Gy, 88.0 Gy, 132.7 Gy and 170.6 Gy ($p<0.001$), respectively. D_2 to hips was higher with IMAT and CK, than with BTs: 13.4 Gy, 20.7 Gy, 0.4 Gy and 1.5 Gy ($p<0.001$), while D_2 was higher to other organs with CK, than with the other techniques: 1.1 Gy, 17.9 Gy, 0.8 Gy and 2.8 Gy ($p<0.001$) 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 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 penile bulb in IMAT, CK, HDR and LDR BT plans. The detailed results can be found in Table 1.

Discussion

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

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

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

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

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

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

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

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

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

Conclusions

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

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

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 and discussed the details of this study.

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

CsP: supported the study**.**

TM: supported the study and discussed the details.

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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
D_2(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
D_2(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
D_2(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
D_2(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
D_2(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
D_2(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
D_2(p) (Gy)	4.9	10.3	1.7	3.2	**0.0057**	IMAT,CK

Table 1. Mean EQD2 total doses of intensity-modulated arc therapy (IMAT), CyberKnife (CK), high-dose-rate (HDR) and low-dose-rate (LDR) brachytherapy of prostate cancer. D90: the minimum dose delivered to 90% of prostate, COIN: conformal index, $D_{0.1}$(x), D_2(x): the minimal dose of the most exposed 0.1 and 2 cm^3 of 'x' organ at risk, where x are rectum (r), urethra (u), bladder (b), hips (h), sigmoid (s), bowel bag (bb), testicles (t) and penile bulb (p). *Friedman ANOVA **Fisher-LSD post-hoc test.

Figures:

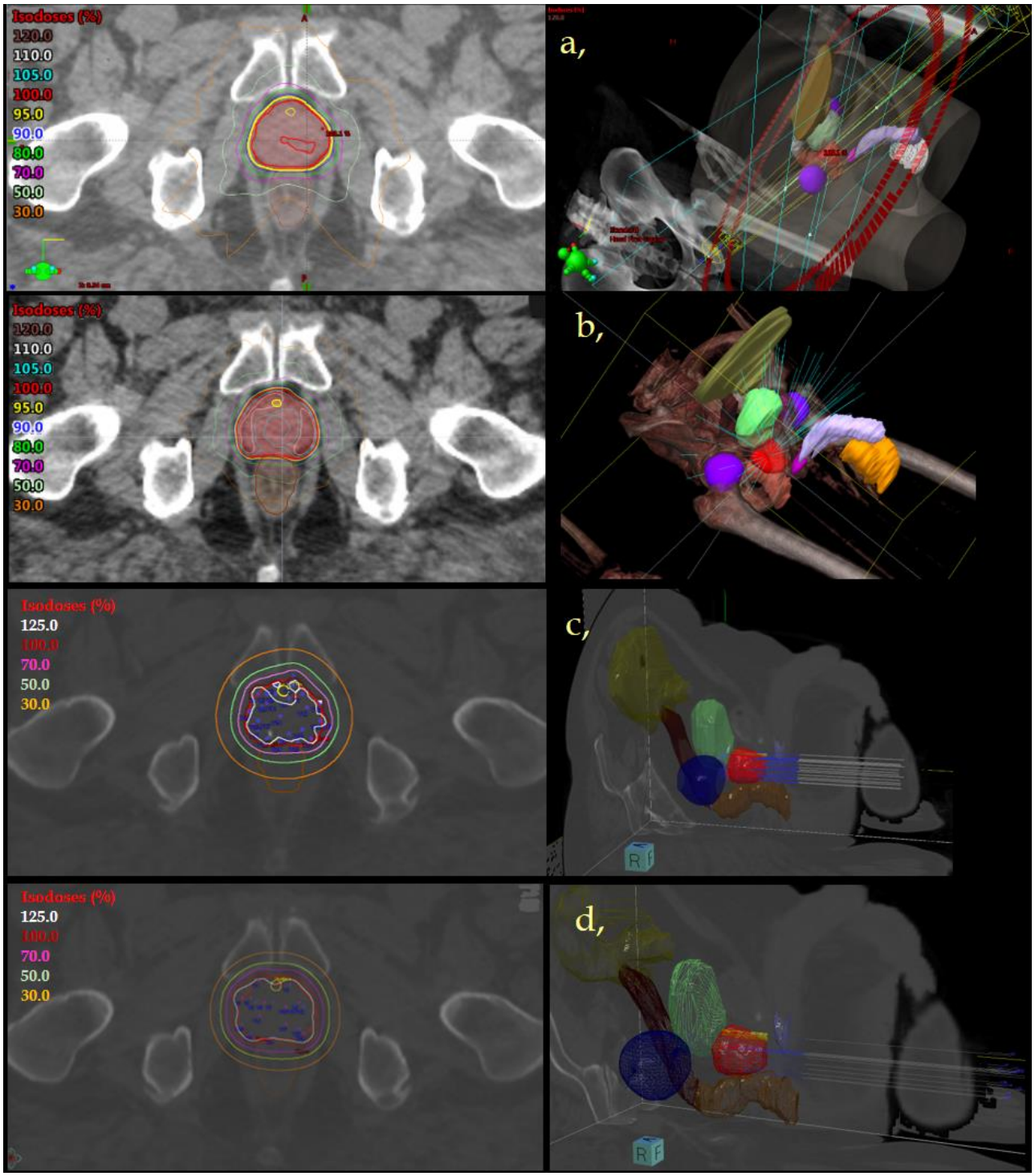

Figure 1. Axial CT slide (left) and 3D reconstruction (right) of a prostate intensity-modulated arc therapy (a,), a CyberKnife (b,), an interstitial high-dose-rate prostate brachytherapy (c,) and an interstitial low-dose-rate prostate brachytherapy plan (d,).

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