Five-Year Outcomes of Stereotactic Body Radiation Therapy (SBRT) for Prostate Cancer-The Largest Experience in China

Xianzhi Zhao
Changhai Hospital
Yusheng Ye
Changhai Hospital
Haiyan Yu
XUanhan County People's Hospital
Lingong Jiang
Changhai Hospital
Chao Cheng
Changhai Hospital
Xueling Guo
Changhai Hospital
Xiaoping Ju
Changhai Hospital
Xiaofei Zhu
Changhai Hospital
Huojun Zhang (wang_juan_2015@163.com)
Changhai Hospital https://orcid.org/0000-0002-7644-4674

Research Article

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Abstract

Objective

To evaluate the efficacy and toxicity of SBRT for localized prostate cancer (PCa). Moreover, it is the largest-to-date pilot study to report 5-year outcomes of SBRT for localized PCa from China.

Methods

In this retrospective study, 133 PCa patients in our center were treated by SBRT with CyberKnife (Accuray) from October 2012 to July 2019. Follow-up was performed every 3 months for evaluations of efficacy and toxicity. Biochemical progression-free survival (bPFS) and toxicities were assessed using the Phoenix definition and the Common Terminology Criteria for Adverse Events (CTCAE) v.5.0 respectively. Factors predictive of bPFS were identified with COX regression analysis.

Results

133 patients (10 low-, 21 favorable intermediate-, 31 unfavorable intermediate-, 45 high-, and 26 very high risk cases on the basis of the NCCN risk classification) with a median age of 76 years (range: 54–87 years) received SBRT. The median dose was 36.25Gy (range: 34-37.5Gy) in 5 fractions. Median follow-up time was 57.7 months (3.5–97.2 months). The overall 5-year bPFS rate was 83.6% for all patients. The 5-year bPFS rate of patients with low-, favorable intermediate-, unfavorable intermediate-, high-, and very high risk PCa was 87.5%, 95.2%, 90.5%, 86.3%, and 61.6% respectively. Urinary symptoms were all alleviated after SBRT. All the patients tolerated SBRT with only 1 (0.8%) and 1 (0.8%) patient reporting grade-3 acute and late genitourinary (GU) toxicity, respectively. There were no grade 4 toxicities. Gleason score ($P < 0.001$, HR = 7.483, 95%CI: 2.686–20.846) was the independent predictor of bPFS rate after multivariate analysis

Conclusion

SBRT is an efficient and safe treatment modality for localized PCa with high 5-year bPFS rates and acceptable toxicities.

Introduction

PCa is the most common cancer in men and the leading cause of death among malignancy entities [1]. For localized PCa, daily target location with image-guided radiotherapy (IGRT) is essential with intensity-modulated radiotherapy (IMRT) for target margin reduction and treatment accuracy, which has been recommended as one of the standard therapy [2]. Conventionally fractionated IMRT with 1.8-2.0Gy per

fraction has been used increasingly in practice. What's more, radiotherapy combined with androgen deprivation therapy (ADT) is adopted for unfavorable intermediate, high and very high risk groupings [2].

PCa is thought to be with a unique radiobiological feature, namely the relatively slow proliferation, characterized by a low α/β ratio compared to the normal organs around the target [3–4]. The α/β ratio of PCa is about 1.5Gy, while that of the rectum and bladder is about 3.0 Gy. Owing to the characteristic, extremely hypofractionated radiotherapy would offer favourable tumor control without increased risk of late toxicity.

Recently, due to the advantages of SBRT with highly conformal and precise image-guided delivery, growing evidence has confirmed its pivotal role in tumor control. Moreover, it has been commonly used in localized PCa patients, showing excellent bPFS rates and tolerable toxicities, especially when operation can't be tolerated or declined [5–7]. Majority of studies using SBRT indicated that the 5-year bPFS for patients with low-, intermediate-, and high-risk PCa was 95%, 84% and 81% respectively [8]. However, these studies were performed in Caucasians. Therefore, different races may impact efficacy. Compared with Western patients, the genomic alteration signatures in Chinese cohorts were obviously different [9]. In fact, SBRT clinical utility for PCa has been rarely reported in Chinese. So, we performed this study to assess the toxicity and efficacy of SBRT for localized PCa.

Material And Methods

Patient selection:

All patients were screened for eligibility by an oncologist before the study. The inclusion criteria included histologically confirmed adenocarcinoma of the prostate, at least imaging examinations with enhanced pelvic magnetic resonance imaging (MRI) and emission computed tomography (ECT), a Eastern Cooperative Oncology Group (ECOG) score≦1, no involvement of regional lymph nodes or distant metastasis. Patients who refused or were not suitable for surgery because of underlying diseases were enrolled for screening. All patients signatured informed consent before the treatment. The study was performed based on the Declaration of Helsinki and the institutional review board of XXXXXXX reviewed and ratified the study protocol.

SBRT protocols:

Before radiotherapy planning, fours gold fiducials were placed into the prostate. Thermoplastic body mask immobilized the enrolled patients in supine position with arms by their sides. Approximately 1 week after fiducial placement, enhanced computed tomography (CT) scan was performed with a slice thickness of 1.5 mm, with the scan range of at least 10cm below and above the prostate. Patients underwent MRI imaging thereafter. Fused MRI and CT mages were then used for guiding target and organs at risk (OARs) delineation. For low risk PCa cohorts, the gross tumor volume (GTV) only included the whole prostate. For favorable and unfavorable intermediate risk grouping, GTV included the whole prostate and 1 cm of the seminal vesicles. However, GTV included the whole prostate and 2 cm of the

seminal vesicles for high and very high risk grouping. SBRT was delivered by CyberKnife (Accuray Corporation, Sunnyvale, CA, USA). Planning target volume (PTV) was delineated with a 5 mm margin expansion but a 3 mm in posterior direction from GTV to decrease the excessive radiation of the rectum. The treatment parameters were presented in table-1. Prescription doses of 34–37.5 Gy in 5 fractions were given to the PTV every other day with a median prescription isodose line of 79%. The dose-volume constraints for OARs were as follows: rectum: V18.1Gy<50%, V29Gy<20%, V36Gy<1cc; bladder: V18.1Gy<40%, V37Gy<10cc (optimal V37Gy <5cc); prostatic urethra: V42Gy<50%; femoral head: V14.5Gy<5%; penile bulb: V29.5Gy<50%; bowel: V18.1Gy<5cc, V30Gy<1cc [10].

Response evaluation and follow-up:

The prostate-specific antigen (PSA) and testosterone levels of the patients checked every month. Biochemical progression was defined as PSA increase ≥ 2 ng/mL from nadir [11]. LC was defined as local prostate lesions without progression. OS was defined as the time from the beginning of radiation therapy to the last follow-up or death. Disease progression free survival (DPFS) was defined as the time from the date of the beginning of radiation therapy to any sites clinical tumor progressions or death. Acute and late toxicity was scored according to CTCAE v 5.0.

Statistical analysis:

bPFS rates were calculated by the Kaplan-Meier method. Potential factors associated with bPFS were identified with univariate and then multivariate COX proportional hazards regression model. SPSS 18.0 (IBM Corporation, Armonk, NY, USA) was used for statistical analyses. P-value <0.05 was considered as statistics significance.

Results

A. Patient characteristics

SBRT was delivered to 133 localized PCa patients (10 low-, 21 favorable intermediate-, 31 unfavorable intermediate-, 45 high-, and 26 very high risk cases according to the NCCN risk classification) with a median age 76 years (range 54 to 87 years) from October 2012 to July 2019 in XXXXXX. The median pre-treatment PSA was 12.05 ng/mL (range 0.03 to 104.8 ng/mL). Of all patients, 18 (13.5%) patients had two primary cancers and 1 (0.8%) patient had three primary cancers. Their baseline characteristics were summarized in Table 2.

Table 1
Treatment parameters used for SBRT

Parameters	All lesions	Lesions with local control
GTV (ml)	50.0 (10.0–182.7)	50.0 (10.0–182.7)
Maximum dose (Gy)	45.9 (42.7–58.6)	45.9 (42.7–58.6)
Total prescribed dose (Gy)	36.25 (34–37.5)	36.25 (34–37.5)
Number of fractions	5 (5)	5 (5)
Dose per fraction (Gy)	7.25 (6.8–7.5)	7.25 (6.8–7.5)
$BED_{1.5}$ (Gy)	211.5(188.1–225)	211.5(188.1–225)
Number of fiducials	4 (2–5)	4 (2–5)
Prescription isodose line (%)	79 (65–85)	79 (65–85)

Table 2
Patient demography and clinical presentation

Characteristics	Values	Characteristics	Values
Age (years)	76 (range 54–87)	Pre-treatment Hormone treatment	
Gleason score			
▪ 1 + 3	1 (0.8%)	▪ Yes	36 (27.1%)
▪ 3 + 2	2 (1.5%)	▪ No	97 (72.9%)
▪ 3 + 3	41 (30.8%)	Stage	
▪ 3 + 4	25 (18.8%)	▪ T2a	43 (32.3%)
▪ 4 + 3	22 (16.5%)	▪ T2b	9 (6.8%)
▪ 4 + 4	23 (17.3%)	▪ T2c	49 (36.8%)
▪ 3 + 5	1 (0.8%)	▪ T3a	1 (0.8%)
▪ 5 + 3	2 (1.5%)	▪ T3b	6 (4.5%)
▪ 4 + 5	9 (6.8%)	▪ T4	25 (18.8%)
▪ 5 + 4	6 (4.5%)	▪ Tx	16 (12.0%)
▪ 5 + 5	1 (0.8%)	NCCN risk grouping	
Pre-treatment PSA (ng/ml)		▪ Low	10 (7.5%)
▪ < 10	52 (39.1%)	▪ Favorable intermediate	21 (15.8%)
▪ 10–20	47 (35.3%)		
▪ > 20	34 (25.6%)	▪ Unfavorable intermediate	31 (23.3%)
Symptoms			
▪ Presented	59 (44.4%)	▪ High	45 (33.8%)
▪ None	74 (55.6%)	▪ Very high	26 (19.5%)
ECOG score		Pre-treatment TURP	
▪ 0	5 (3.8%)	▪ Yes	25 (18.8%)
▪ 1	128 (96.2%)	▪ No	108 (81.2%)

B. Outcomes:

All patients were followed up until July 2020 or death. The median follow-up was 57.7 months (3.5–97.2 months). 10 patients (7.5%) were dead, and others were survival to the end of the follow-up. Non cancer-

specific death was found in 4 patients (2 cerebral infarction, 1 pneumonia, 1 Parkinsonian syndrome), while 4 patients died of PCa metastasis and 2 patients died of progressions of other tumors. The 2- and 5-year OS rates were 99.2% and 93.0% respectively. The 2- and 5-year LC rates were 99.2% and 96.1% respectively. The 2- and 5-year DPFS rates were 96.1% and 88.1% respectively.

Furthermore, the 2- and 5-year bPFS rates were 96.9% and 83.6% respectively (Fig. 1a). In details, the 2 and 5-year bPFS rates for patients with low-, favorable intermediate-, unfavorable intermediate-, high-, and very high risk PCa were 100% and 87.5%, 95.2% and 95.2%, 100% and 90.5%, 100% and 86.3%, 96.2% and 61.6% respectively ($P = 0.007$, Fig. 1c). In the univariate analysis, patients with Gleason score < 8 had a high bPFS rate than those with Gleason score ≥ 8 ($P < 0.001$, Fig. 1b). However, only Gleason score ($P < 0.001$, RR = 7.483, 95%CI: 2.686–20.846) was the independent predictors of bPFS rate after multivariate analysis. No significant correlation was found between bPFS rate and GTV volume ($P = 0.985$), pre-treatment PSA ($P = 0.253$), symptoms ($P = 0.773$) or age ($P = 0.903$), Table 3. Additionally, an illustrative case was shown in Fig. 2.

Table 3
Univariate analysis for bPFS rate

Factors	2-year b-PFS rate (%)	5-year b-PFS rate (%)	P Value
GTV (ml)			
<50	95.4	85.3	0.985
≥ 50	98.5	82.2	
Gleason score			
<8	98.9	92.5	**< 0.001**
≥ 8	92.5	64.5	
Pre-treatment PSA (ng/ml)			
< 10	94.0	88.4	0.253
10–20	97.8	87.1	
> 20	100	74.2	
Symptoms			
Presented	98.2	85.9	0.733
No	95.8	81.5	
NCCN risk grouping			
Low	100	87.5	
Favorable intermediate	95.2	95.2	
Unfavorable intermediate	100	90.5	**0.007**
High	97.7	86.3	
Very high	92.1	61.6	
Age (years)			
< 70	93.4	80.0	0.903
≥ 70	98.0	84.7	

The symptoms of urethral obstruction and irritative symptoms were most commonly found in patients, which included dysuria, frequency of micturition, nocturnal frequency of micturition, urodynia and urgency of urination. Fifty-nine patients complained of one or more urinary symptoms. All of them (100.0%) had alleviation of symptoms after radiotherapy.

C. Treatment toxicity:

SBRT was well-tolerated with only 1 (0.8%) and 1 (0.8%) patient reporting grade 3 acute and late genitourinary (GU) toxicity with radiation cystitis. No grade 4 or higher adverse reaction was observed. Two (1.5%) patients had grade 2 acute GU toxicity, 1 (0.8%) with grade 2 acute gastrointestinal (GI) and 3 (2.3%) with grade 2 late GU toxicity. Hematuria, frequent urination, increased frequency of nocturia, painful urination and difficult urination were the most common adverse effects during treatment. All the acute toxicities were transitory, reversible and improved by medication, which did not prevent patients to complete SBRT (Table 4).

Table 4
Acute and Late rinary and rectal toxicity on the RTOG scale for prostate cancer patients after SBRT.

Toxicities	Grade 1	Grade 2	Grade3	Grade4
Acute GU	10 (7.5%)	2 (1.5%)	1 (0.8%)	0 (-)
Acute GI	3 (2.3%)	1 (0.8%)	0 (-)	0 (-)
Late GU	5 (3.8%)	3 (2.3%)	1 (0.8%)	0 (-)
Late GI	0 (-)	0 (-)	0 (-)	0 (-)

Discussion

The research investigated the efficacy and toxicity of SBRT for localized PCa. Overall, SBRT may offer a high 5-year bPFS rate of 83.6% and effective symptom relief without severe adverse effects. Additionally, no grade 4 or above adverse reactions were reported. Thence, it may provide evidence that SBRT was also a promising treatment for localized PCa in Chinese. To our knowledge, this is the longest follow-up and largest study to report SBRT for localized PCa from China.

Theoretically, due to low α/β of the prostate cancer, a high single dose could improve tumor control and reduce the risk of late toxicity in bladder and rectum. Three large studies identified the average α/β ratio of PCa was less than 2Gy: (1) analyzing 5093 patients, α/β = 1.55 (95%CI = 0.46–4.52)Gy [12]; (2) analyzing 5969 patients, α/β = 1.4 (95%CI = 0. 0.9–4.2) Gy [13]; (3) analyzing 14168 patients, α/β = 1.7 (95%CI = 1.4–2.2)Gy by the ASTRO and α/β = 1.6 (95%CI = 1.2–2.2)Gy by Phoenix criteria [14, 15]. Although SBRT has been confirmed as an effective option, it still remains controversial whether SBRT has an advantage over conventional fractionated radiotherapy, a current standard of care, in the case of outcomes and toxicities. Two important ongoing phase 3 clinical trials, HYPO trial and PACE study, tried to provide answers. Intermediate to high risk PCa patients were recruited in the HYPO trial, which compared 78 Gy in 39 fractions daily with 42.7 Gy in 7 fractions given in every other day [16]. The 5-year outcomes supported the use of SBRT for radiotherapy of PCa. On one hand, 5-year failure-free survival in SBRT group and conventional fractionation group were 84% (95% CI 80 − 87) and 84% (95% CI 80 − 87) respectively (p = 0·99). Hence, for intermediate-to-high risk PCa, the failure-free survival in SBRTgroup was

non-inferior to conventionally fractionated radiotherapy group. On the other hand, no obvious differences between SBRT group (11 [5%] patients) and conventional fractionation group (12 [5%] patients) in frequencies at 5 years of RTOG grade 2 or higher GU adverse reaction (p = 1.00) was observed. And there was no difference in GI adverse reaction (3 [1%] patients vs 9 [4%] patients; p = 0·14) between two groups. Late toxicities were similar in both groups whereas early adverse effects were more common with SBRT compared with conventional fractionation [17]. Regarding the PACE study, low and intermediate risk PCa patients were enrolled [18, 19]. It included two trials: PACE-A and PACE-B. In PACE-A study, patients candidates for prostatectomy were randomized into laparoscopic surgery and SBRT. In PACE-B study, patients were randomized into image-guided IMRT and SBRT. The prescription dose of IMRT was 78 Gy in 39 fractions, while the prescription dose of SBRT was 36.25 Gy in 5 fractions or 38 Gy in 4 fractions. So far, the acute toxicity of PACE-B was reported in 2019. There was no significant statistical difference with grade 2 or more GI toxicity between conventionally fractionated radiotherapy group and SBRT group (12% [53/432] patients vs 10% [43/415] patients, p = 0.38), while no significant differences in grade 2 or worse GU toxicity were also observed in both groups (27% [118/432] patients vs 23% [96/415] patients, p = 0.16). The results suggested that substantially shortening treatment courses with SBRT didn't increase either acute GI or GU toxicity [20].

Regarding a comprehensive understanding of safety and efficacy of SBRT for localized PCa, King et al [8] recruited 1100 localized PCa patients (58% low-, 30% intermediate-, and 11% high-risk) with a median follow-up of 3 years in a pooled analysis of prospective clinical trials. The median prescription dose was 36.25Gy/ 4–5 fractions in SBRT treatment. The results were promising with a 5-year bPFS rate of 93% for all patients. Furthermore, the 5-year bPFS rates for patients with low risk, intermediate risk and high risk disease were 95%, 84% and 81%, respectively (p < 0.001). Besides, another study including 12 phase 2 trials analyzed 2142 PCa patients. Among all the patients, 1185 (55.3%) had low-risk disease, while 692 (32.3%) had favorable intermediate-risk PCa, 265 (12.4%) unfavorable intermediate-risk PCa. After a median follow-up of 6.9 years, 7-year bPFS rates were 95.5% for low-risk disease, 91.4% for favorable intermediate-risk disease, 85.1% for unfavorable intermediate-risk PCa, and 89.8% for all intermediate-risk PCa. Only 0.60% patients had grade 3 or worse acute GU toxicity, while 0.09% experienced grade 3 or worse acute GI adverse reaction. Additionally, 2.4% and 0.4% patients had grade 3 or worse late GU and GI toxicity, respectively [21]. The results were consistent with our study. In our study, 133 patients (10 low-, 21 favorable intermediate-, 31 unfavorable intermediate-, 45 high-, and 26 very high risk cases) received SBRT. After a median follow-up of 57.7 months, the 5-year bPFS rate was 83.6% for all patients. What's more, the 5-year bPFS rates for low-, favorable intermediate-, unfavorable intermediate-, high-, and very high risk PCa patients were 87.5%, 95.2%, 90.5%, 86.3% and 61.6% respectively. Due to more high and very high risk PCa cases included in this research, the 5-year bPFS rate was slightly lower than that in previous studies. It should be stressed that the 5-year bPFS rate for low risk patients needed further validations due to small number of cases. The treatment toxicity was mild with 0.8% patients reporting grade 3 acute GU adverse reaction and 0.8% patient experiencing grade 3 late GU toxicity.

There were some limitations of this study. First, because of the retrospective nature and a small sample size, generalization of the results should be cautious. Second, this study only evaluated the safety and

feasibility of SBRT for PCa patients. Hence, further comparisons with conventional fractionated radiotherapy are required. In addition, the baseline of patients was heterogeneous with a wide range of ages and GTV volumes. Therefore, a longer follow-up in larger prospective studies is warranted to compare patients' outcomes and adverse effects of surgical resection with those of SBRT and conventional fractionated radiotherapy, which may be beneficial for accurate decision making of treatment modality. .

Conclusion

SBRT is a safe and effective treatment with an encouraging bPFS rate and tolerable toxicity for localized PCa patients. Patients with a Gleason score < 8 and relatively low risk disease had a better biochemical control rate. Moreover, patients with a large prostate volume had a similar outcome comparing to those with a small prostate volume. Notably, more prospective clinical trials need to validate the efficiency and safety of SBRT for patients with localized PCa.

Abbreviations

SBRT: Stereotactic body radiation therapy; PCa: Prostate cancer; bPFS: Biochemical progression-free survival; CTCAE: Common terminology criteria for adverse events; LC: Local control; OS: Overall survival; DPFS: Disease progression-free survival; GU: Genitourinary; IGRT: Image-guided radiotherapy; IMRT: Intensity-modulated radiotherapy; ADT: Androgen deprivation therapy; MRI: Magnetic resonance imaging; ECT: Emission computed tomography; ECOG: Eastern Cooperative Oncology Group; CT: Computed tomography; GTV: Gross tumor volume; PTV: Planning target volume; OARs: organs at risk; PSA: Prostate-specific antigen; GI: Gastrointestinal.

Declarations

Data availability statement

The datasets generated for this study are available on request to the corresponding author.

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Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by the Ethics Committee of the XXXXXX. The patients/participants provided their written informed consent to participate in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

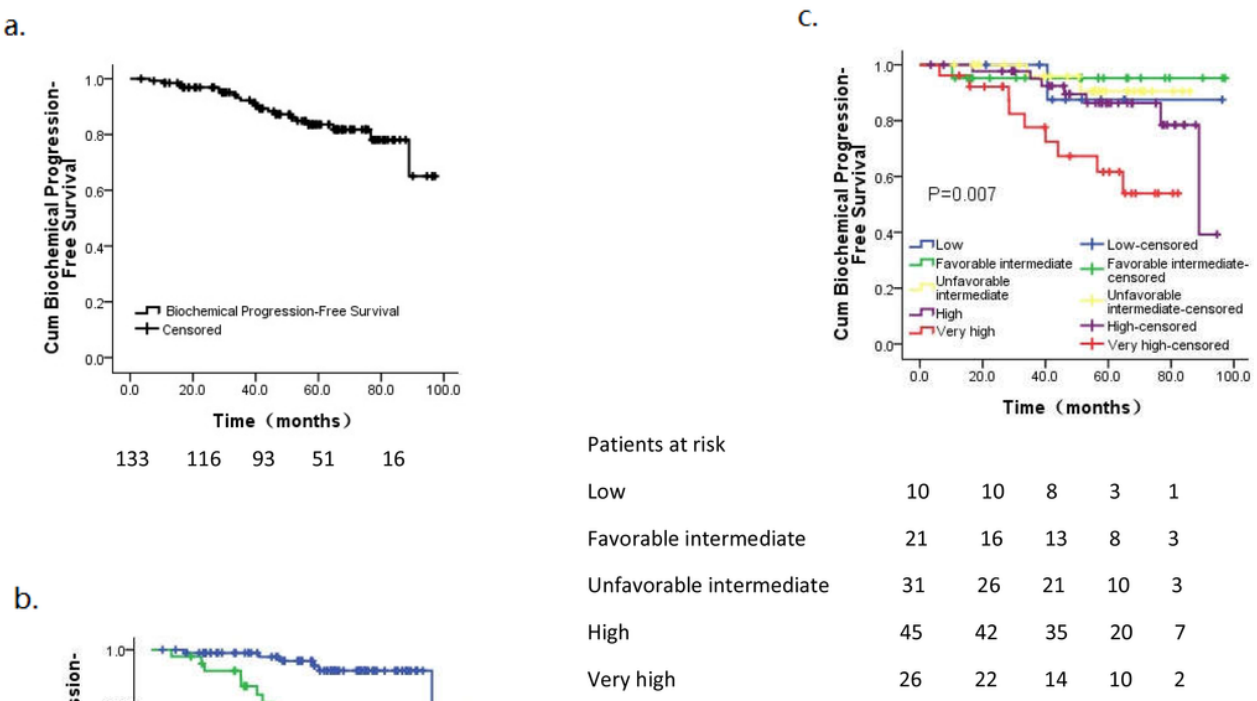

Figure 1

Actuarial survival analysis of patients. (a) Overall bPFS. (b) bPFS in different Gleason score. (c) bPFS in different NCCN risk groupings. bPFS: biochemical progression-free survival. Cum, cumulative

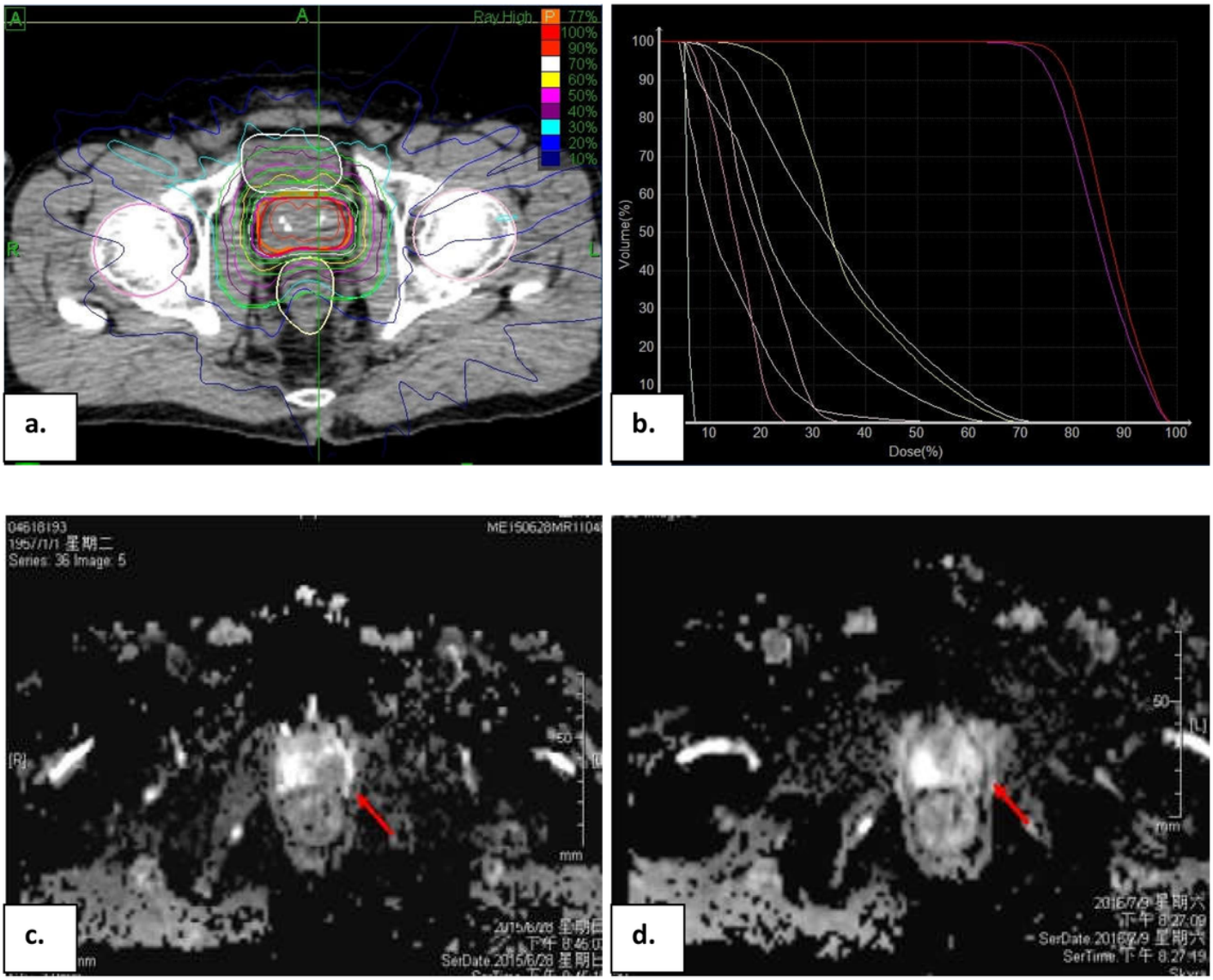

Figure 2

An introductive patient with 58 years old of successful SBRT for an unfavorable intermediate risk prostate cancer. (a) CT scan before SBRT and 36.25 Gy/5 fractions was delivered for prostate cancer. (b) A typical DVH for Cyberknife treatment is shown, revealing doses to the GTV, PTV, and surrounding normai organs. (c) Enhanced MRI scan before SBRT. (d) Enhanced MRI scan 1 year after SBRT. SBRT: stereotactic body radiation therapy; CT: computed tomography; DVH: dose-volume histogram; GTV: gross tumor volume; PTV: planning tumor volume. Note: The red arrows indicate tumor location before and after SBRT.