Quality Improvement Study

Medicine®

OPEN

Dosimetric comparison among cyberknife, helical tomotherapy and VMAT for hypofractionated treatment in localized prostate cancer

Marcello Serra, PhD[a,*], Gianluca Ametrano, PhD[b], Valentina Borzillo, Dr.[b], Maria Quarto, Prof.[a], Matteo Muto, PhD[c], Rossella Di Franco, Dr.[b], Savino Federica, MD[a], Filomena Loffredo, PhD[a], Muto Paolo, Prof.[b]

Abstract

Hypofractionation for localized prostate cancer treatment is rapidly spreading in the medical community and it is supported by radiobiological evidences (lower α/β ratio compared with surrounding tissues). Stereotactic body radiation therapy (SBRT) is a technique to administer high doses with great precision, which is commonly performed with CyberKnife (CK) in prostate cancer treatment. Since the CyberKnife (CK) is not available at all radiotherapy center, alternative SBRT techniques are available such as Volumetric Modulated Arc Therapy (VMAT) and Helical Tomotherapy (HT). The aim of the present study was to compare the dosimetric differences between the CK, VMAT, and HT plans for localized prostate cancer treatment.

Seventeenpatients have been recruited and replanned using VMAT and HT to this purpose: they received the treatment using the CK with a prescription of 36.25 Gy in 5 fractions; bladder, rectum and penis bulb were considered as organs at risk (OAR). In order to compare the techniques, we considered DVHs, PTV coverage, Conformity Index and new Conformity Index, Homogeneity Index, beam-on time and OARs received dose.

The 3 treatments methods showed a comparable coverage of the lesion (PTV 95%: 99.8 ± 0.4% CK; 98.5 ± 0.8% VMAT; 99.4 ± 0.5% HT. $P < .05$) and good sparing of OARs. Nevertheless, the beam-on time showed a significant difference (37 ± 9 m CK; 7.1 ± 0.3 m VMAT; 17 ± 2 m HT. $P < .05$).

Our results showed that, although CK is the best SBRT technique for prostate cancer treatment, in case this technology is not available, it can be replaced by a similar treatment delivered by VMAT technique. VMAT can be administrated only if it has an appropriate Image Guided Radiation Therapy (IGRT) tracking system.

Abbreviations: CI = conformity index, CK = CyberKnife, DVH = dose volume histogram, HI = homogeneity index, HT = helical tomotherapy, IGRT = Image Guided Radiation Therapy, IMRT = intensity modulated radiation therapy, LINAC = linear accelerator, nCI = new Conformity Index, NTCP = normal tissue complicance probability, OAR = organ at risk, PIV = prescribed isodose volume, PTV = planning tumor volume, QoL = quality of life, RT = radiotherapy, SBRT = stereotactic body radiotherapy, TCP = tumor control probability, TIV = tumor isodose volume, VMAT = Volumetric Modulated Arc Therapy.

Keywords: cyberknife, helical tomotherpy, prostate cancer, radiotherapy, stereotactic radiotherapy, VMAT

1. Introduction

Prostate cancer is the second tumor most commonly diagnosed among men around the world.[1] The risk of developing prostate cancer is closely related to aging: about 14% at 50 years old and 50% from 80 years old upward.[2] Indeed, about 1 million men are diagnosed with prostate cancer each year and this number is expected to increase due to general improvement in living conditions and therefore the world population aging.[3] Nowadays is possible to detect such malignancy in its early stages and intervene promptly, by allowing low mortality rate, thanks to screening campaigns, early diagnoses and technological progress.

Exclusive radiotherapy (RT) administered in localized prostate cancer, as an alternative to radical prostatectomy, offers comparable results in terms of overall survival and Quality of Life (QoL), to those ones of surgery.[4] Its use is approximately 25% in patients <65 years old and 40% in patients over 65 years old.[5]

In external beam radiotherapy (EBRT) the standard fractionation is 1.8–2 Gy/fraction, but according to radiobiology knowledge and according to the linear-quadratic model, the α/β ratio differences with healthy tissues surrounding the tumor can dramatically affect the fractionation, Tumor Control

Editor: Jianxun Ding.

The authors have no funding and conflicts of interests to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Dipartimento di Scienze Biomediche Avanzate, Università degli Studi di Napoli Federico II – Napoli, [b] Department of Radiation Oncology, Istituto Nazionale Tumori - IRCCS - Fondazione G. Pascale - Naples, [c] Dipartimento Onco-Ematologico Radioterapia, Azienda ospedaliera San Giuseppe Moscati – Avellino, Italy.

[*] Correspondence: Marcello Serra, Dipartimento di Scienze Biomediche Avanzate, Università degli Studi di Napoli Federico II, Via Pansini 5, 80138, Napoli, Italy (e-mail: serra.emme@gmail.com).

How to cite this article: Serra M, Ametrano G, Borzillo V, Quarto M, Muto M, Di Franco R, Federica S, Loffredo F, Paolo M. Dosimetric comparison among cyberknife, helical tomotherapy and VMAT for hypofractionated treatment in localized prostate cancer. Medicine 2020;99:50(e23574).

Received: 19 June 2020 / Received in final form: 7 October 2020 / Accepted: 5 November 2020

http://dx.doi.org/10.1097/MD.0000000000023574

Probability (TCP) and Normal Tissue Complication Probability (NTCP). The linear quadratic model describes the survival probability of a cell (SF) following dose radiation exposure (d) as $SF = \exp[-\alpha d - \beta d^2]$, where α and β are parameters describing the cells radiosensitivity. Each tissue has a α/β ratio which has units of Gy and reflects the response to a radiation dose (the same dose delivered to 2 different tissues can generate different effects). Moreover, computational models of TCP show how the tumor control varies according to dose/fraction (fx). In particular if the α/β ratio of the tumor is lower than the surrounding healthy tissues, the high dose/fraction (greater than 2 Gy/fx) increases the tumor control probability. On other hand if the α/β ratio of the tumor is higher than the surrounding tissues the standard fractionation (2 Gy/fx) is preferred. Several studies establish that the α/β ratio for prostate cancer is 1.5 Gy, lower than the nearby organs (rectum, bladder), which allowed the physicians to move towards hypofractionated regimes and dose escalation.[6–12]

The hypofractionation has significant advantages in terms of radiobiological effects, outcomes improvement, treatment curse reduction with costs decrease, improvement of patient QoL and compliance to treatment. Thanks to these advantages, the medical community is moving in this direction for prostate cancer treatment and other tumors if radiobiological evaluations consent hypofractionation.[13]

Technological advances in imaging, treatment-planning, dose delivery and dose verification, combined with the results of moderately hypofractionated randomized trials,[14–19] allow higher fraction doses in a low number of fractions (ablative hypofractionation) as in Stereotactic body radiotherapy (SBRT).[20–24]

In SBRT of prostate cancer, dose delivery and target tracking accuracy are important to increase treatment efficacy and decrease side effects, since the prostate is subject to organ motion. There are different SBRT techniques for prostate cancer treatment: non-isocentric techniques that employing robotic arm-based linear accelerators (LINACs) as CyberKnife System (CK, Accuray, Sunnyvale, CA, USA), and helical or volumetric isocentric coplanar techniques with gantry rotation around the body patient such as VMAT and helical tomotherapy (HT Accuray, Sunnyvale, CA, USA). The CyberKnife System is the most common SBRT modality used in localized prostate cancer treatment. CK is 6 MV photon beam linear accelerator installed on a 6 degrees of freedom robotic arm. A wide range of movement allows high conformity by following irregular edges of the lesion and avoids the OARs due to the different entry points of the treatment fields. It is an IGRT where the image system (2 orthogonal kilovoltage X-ray imagers) allows the linear accelerator to follow the lesion, by tracking of golden intraprostatic fiducials markers, and it consents to adapt beams delivery and correct the patient position. The helical tomotherapy is an IMRT (Intensity Modulated Radiation Therapy) coplanar arc with binary multileaf collimator (MLC) and mega-voltage computer tomography (MVCT). Table movement and at the same time a rotating beam around the patient, generate the helical geometry of the treatment. In the VMAT technique, delivered by a LINAC, during the gantry rotation around the isocenter, the field is continuously shaped by a MLC and also the dose rate is modulated, in order to avoid or reduce the delivered dose to the OARs.

In this study, we aim to compare the dosimetric results of CK treatment plans with HT ones and with VMAT ones, for the tumor target and the OARs by delivering 36.25 Gy in 5 fractions (7.25 Gy per fraction).

Table 1

Constraints for OARs considered in the planification process.

OAR	Dmax	Dose limit
Bladder	< 38 Gy	V_{37Gy} <10 cc
		$V_{37.5Gy}$ <5 cc
		V_{18Gy} <15 cc
		$V_{50\%}$ <40%
		$V_{100\%}$ <10%
Rectum	< 38 Gy	V_{36Gy} <1 cc
		V_{25Gy} <20 cc
		$V_{50\%}$ <50%
		$V_{80\%}$ <20%
		$V_{90\%}$ <10%
		$V_{100\%}$ <5%
Penis bulb	< 50 Gy	V_{29Gy} <50%

2. Methods

2.1. Patients and treatment planning

In this study have been involved 17 patients with a localized prostate cancer. They have been treated in the "Instituto Nazionale Tumori - IRCCS Fondazione G. Pascale" with SBRT CK system in the period between June 2015 and October 2017. Four gold fiducials markers had been implanted into prostate and 7/10 days after placement, patients underwent a non-contrast simul-CT scan (1 mm cuts) in supine position with personalized immobilization system and thin-cut MRI scans. Target volumes and OARs delineation has been performed by physicians using a simul-CT scan with MRI fusion. Gross target volume (GTV) was defined as prostate gland, Clinical target volume (CTV) was equal to GTV and Planning target volume (PTV) was CTV with a 3 mm expansion posteriorly and 5 mm in all directions. The rectum, bladder and penis bulb were contoured as OARs. The CK treatment planning was performed using the Precision inverse treatment planning system (Accuray Inc., Sunnyvale, CA) and the prescription dose was 36.25 Gy at 80% isodose line delivered in 5 fractions. The prescription dose covered at least 95% of the PTV and the constraints for OARs are presented in Table 1.

In order to compare the dosimetric results among the different techniques, the CT images and contours (PTV and OARs), for all patients, were exported as DICOM-RT files to the planning systems of HT (Hi-Art 4.2.3 System) and VMAT (TPS Philips, Pinnacle v. 16.0.2) and re-planned.

For the HT plans was selected a field width of 2.5 cm, a pitch of 0.145 and a modulation factor of 3.6. Therefore, all patients had 3 radiotherapy plans each.

VMAT treatment plans were computed with Pinnacle TPS and the treatments geometrical setup was decided by experienced medical physicists: 2 arcs of 360 ° (clockwise/counterclockwise) with a 20° collimator and final gantry spacing 3, in both arches there was a 0° couch kick. VMAT plans were computed for an Elekta Synergy linear accelerator (Elekta, Crowley, UK) equipped with 6 MV photon beam and multileaf collimator with 5 mm leaf.

In both cases the minimum request was that the prescription dose covered at least 95% of the PTV.

2.2. Dosimetric and Statistical analysis

In order to achieve dosimetric information for each patient, the best possible treatment was planned by ensuring an optimal PTV coverage and OARs sparing in accordance with the con-

Table 2

Volumes and dosimetrical paramaters extrapolated by the DVHs for PTV and OARs for the three techniques.

ROI	Parameter	VMAT	CK	HT
PTV	Volume (mean)	90 ± 30 cc	90 ± 30 cc	87 ± 30 cc
	Range	61 – 157 cc	60 – 157 cc	59 – 153 cc
	D_2 (mean; range)	3758 ± 9 cGy [3745–3775] cGy	4500 ± 60 cGy [4425–4598] cGy	3750 ± 50 Gy [3669–3820] Gy
	D_5 (mean; range)	3742 ± 7 cGy [3732–3760] cGy	4463 ± 60 cGy [4372–4569] cGy	3730 ± 40 Gy [3662–3795] Gy
Rectum	Volume (mean)	60 ± 15 cc	57 ± 15 cc	55 ± 16 cc
	Range	29–98 cc	24 – 95 cc	22 – 92 cc
	V_{18} (mean; range)	19 ± 3% [12.9%–25.2%]	35 ± 8% [22.63%–51.46%]	27 ± 3% [23.38%–31.94%]
	V_{29} (mean; range)	6 ± 1% [3.57%–8.58%]	14 ± 4% [7.59%–21.33%]	7 ± 1% [5.26%–9.76%]
	V_{33} (mean; range)	3 ± 1% [1.84%–4.81%]	7 ± 2% [3.46%–10.72%]	4 ± 1% [2.30%–7.28%]
	V_{36} (mean; range)	0.9 ± 0.4% [0.26%–1.68%]	2.3 ± 1.1% [0.15%–4.09%]	2 ± 1% [0.65%–4.47%]
	D_2 (mean; range)	3420 ± 90 cGy [3261–3582] cGy	3620 ± 80 cGy [3501–3757] cGy	3600 ± 100 cGy [3333–3686] cGy
	D_5 (mean; range)	3020 ± 120 cGy [2772–3282] cGy	3420 ± 110 cGy [3129–3552] cGy	3200 ± 200 cGy [2941–3567] cGy
Bladder	Volume	123 ± 60 cc	122 ± 60 cc	128 ± 60 cc
	Range	57–243 cc	57–242 cc	56 – 237 cc
	V_{18} (mean; range)	29 ± 15% [10.30%-75.13%]	35 ± 10% [16.40% - 51.12%]	37 ± 4% [26.46% - 43.1%]
	V_{36} (mean; range)	4 ± 3% [0.98%–13.85%]	6 ± 3% [1.96%–14.21%]	4 ± 2% [0.89%–7.38%]
	D_2 (mean; range)	3640 ± 70 cGy [3506–3742] cGy	3880 ± 160 cGy [3594–4116] cGy	3670 ± 50 cGy [3525–3741] cGy
	D_5 (mean; range)	3430 ± 250 cGy [2865–3708] cGy	3610 ± 240 cGy [3092–3956] cGy	3550 ± 80 cGy [3338–3633] cGy
Penis bulb	Volume	8 ± 4 cc	7 ± 4 cc	7 ± 4 cc
	Range	3 – 17 cc	3 – 17 cc	3 – 17 cc
	V_{29}	1 ± 4% [0%–15.74%]	3 ± 5% [0.34%–3.34%–4.33%–4.94% - 14.51%–16.01%]	4 ± 12% [3.37%–4.87%-46.80%]
	D_2 (mean; range)	1100 ± 900 cGy [237–3458] cGy	2300 ± 700 cGy [1121–3415] cGy	2400 ± 60 cGy [1386–3483] cGy
	D_5 (mean; range)	1000 ± 900 cGy [227–3348] cGy	2100 ± 700 cGy [899–3264] cGy	2340 ± 60 cGy [1103–3468] cGy

CK = CyberKnife; HT = helical tomotherapy, VMAT = Volumetric Modulated Arc Therapy.

straints.[20–27] Expert physicians approved resulting plans. After developing all patients plans, DVHs were extracted and analyzed with Matlab (The MathWorks, Inc., Natick, Massachusetts, United States). In Table 2, are presented the dose received by a specified volume percentage of the respective ROI, the homogeneity index (HI), the conformity index (CI), the new conformity index (nCI). Such parameters are evaluated using the following equations:

$$HI_{95} = \frac{D_{5\%} - D_{95\%}}{D_{90\%}}$$
$$HI_{98} = \frac{D_{2\%} - D_{98\%}}{D_{90\%}}$$
$$CI = \frac{PIV}{TIV}$$
$$nCI = \frac{CI}{coverage}$$

HI is a measure of dose homogeneity inside the tumor volume. HI_{95} and HI_{98} depend on whether the maximum dose is evaluated as a dose received from 5% ($D_{5\%}$) or 2% ($D_{2\%}$) of the tumor volume. In case of high homogeneity these parameters will be close to zero.

PIV (Prescription Isodose Volume) is the volume which receives the prescription dose and TIV (Tumor Isodose Volume) is the volume of the tumor which receives the prescribed isodose. The PIV could be not restricted to the tumor volume but could be larger or smaller, ideally a CI value as close as possible to the unit could be desirable. Nevertheless, low CI values can be obtained also in case of missing target, therefore the coverage must be taken into account and hence nCI is defined. For the sake of completeness, CI and nCI were computed only for CK and VMAT since the beam on time for HT was too long for a treatment where no tracking tumor technology is adopted, therefore the HT plans were evaluated not clinically valid and no further analysis were carried out.

PTV Coverage 95% and 98% indicate the volume of PTV receiving the 95% or 98% of the prescribed dose respectively (Table 3).

Table 3

Dosimetric indeces and beam on time for the three techniques.

Index	VMAT	CK	HT
PTV Coverage 95%	98.5 ± 0.8%	99.8 ± 0.4%	99.4 ± 0.5%
and range	[96.9%–99.6%]	[98.24%–100%]	[98.60%–100%]
PTV Coverage 98%	93.9 ± 1.6%	99.2 ± 0.8%	98.1 ± 1.3%
and range	[90.6%–95.8%]	[97.2%–100%]	[96.1%–99.9%]
HI_{95}	0.055 ± 0.007	0.187 ± 0.016	0.033 ± 0.013
and range	[0.046 – 0.072]	[0.160–0.213]	[0.014–0.051]
HI_{98}	0.08 ± 0.01	0.21 ± 0.02	0.05 ± 0.02
and range	[0.07–0.1]	[0.18–0.26]	[0.02–0.09]
Beam on time (minutes)	7.1 ± 0.3 m	37 ± 9 m	17 ± 2 m
and range	[6.1–7.7] m	[22–55] m	[14.6–21.1] m
CI	1.12 ± 0.01	1.13 ± 0.05	
and range	[1.09–1.14]	[1.06–1.26]	
nCI	1.31 ± 0.06	1.16 ± 0.05	
and range	[1.23–1.42]	[1.09–1.26]	

CI = conformity index, CK = CyberKnife, HI = homogeneity index, HT = helical tomotherapy, nCI = new Conformity Index, VMAT = Volumetric Modulated Arc Therapy.

Beam-on time, reported in Table 3, is the time (in minutes) during the beam is turned on and when it deliveries dose. This not consider the needed time to correctly place the patient on the couch based on markers and laser system.

Anova test was used to analyze differences in dosimetric parameters among the 3 planning modalities with a significance level at $P < .05$ and if only 2 indices were involved in the analysis, a T-test with a significance level at $P < .05$ was used. The statistical analysis was performed with Matlab.

3. Results

Table 2 summarizes mean values, standard deviations and ranges of the PTV volume, bladder volume, rectum volume and penis bulb volume derived from the contouring operation. We expected a single volume value for every organ. On the contrary, because the 3 used TPS gave slightly different volume values, we considered and illustrated 3 results per instance.

For the sake of clarity, since for each TPS the volume percentages are computed by normalizing them for its own whole recovered volume value these values are reported. In addition, the different constraints values for the OARs obtained with the different techniques (CK, VMAT, HT) and the dose received by 2% ($D_{2\%}$) and 5% ($D_{5\%}$) of the volume are shown in Table 2.

In order to give an overview about the treatments, the most meaningful constraints used in hypofractionated radiotherapy for prostate cancer treatment have been reported. The volume of rectum receiving the 50% (35 ± 8%, 19 ± 3%, 27 ± 3%, CK, VMAT, and HT, respectively) and 100% (2.3 ± 1.1%, 0.9 ± 0.4%, 2 ± 1%, CK, VMAT, and HT respectively) of the prescribed dose are noted. The same values are highlighted also for the bladder V_{18} (35 ± 10%, 29 ± 15%, 37 ± 4%, CK, VMAT, and HT, respectively) and V_{36} (6 ± 3%, 4 ± 3%, 4 ± 2%, CK, VMAT, and HT, respectively). From such results, it is possible to deduct that VMAT is able to spare the rectum at the intermediate dose whereas there is not a large differences at high doses $D_{2\%}$ (3620 ± 80 cGy, 3420 ± 90 cGy, 3600 ± 100 cGy, CK, VMAT, and HT, respectively) and $D_{5\%}$ (3420 ± 110 cGy, 3020 ± 120 cGy, 3200 ± 200 cGy, CK, VMAT, and HT, respectively), even if the highest doses are achieved by CK. Regarding the bladder, there are insubstantial differences between modalities nevertheless VMAT reaches the lowest results also in terms of $D_{2\%}$ (3880 ± 160 cGy, 3640 ± 70 cGy, 3670 ± 50 cGy, CK, VMAT, and HT, respectively) and $D_{5\%}$ (3610 ± 240 cGy, 3430 ± 250 cGy, 3550 ± 80 Gy, CK, VMAT, and HT, respectively).

Such findings are validated by the Figure 1, in which the mean DVHs for PTV, bladder, rectum and penis bulb are shown. The DVHs VMAT curves are always lower than those of CK and HT, and VMAT reaches comparable values to the other ones only at high doses, whereas the CK and HT curves are superimposed or intersect.

The data in Table 2 about the volume of penis bulb that received 29 Gy (V_{29}) deserve a clarification: 29 Gy were reached in only one case with VMAT technique, in 6 cases with CK and 3 cases with HT whereas in the remaining other cases the values were 0%.

In Table 3 the 95% and 98% PTV coverage, HI_{95}, HI_{98}, CI, nCI and beam on time for CK, HT, and VMAT are listed. For the 95% PTV coverage (99.8 ± 0.4% CK; 98.5 ± 0.8% VMAT; 99.4 ± 0.5% HT. $P < .05$) and the 98% PTV coverage (99.2 ± 0.8% CK; 93.9 ± 1.6% VMAT; 98.1 ± 1.3% HT. $P < .05$) the differences among the techniques were statistically significant. CK coverage was the highest and VMAT coverage was the lowest of all techniques especially in 98% PTV coverage. Looking at the homogeneity indices, HI_{95} (CK 0.19 ± 0.02; VMAT 0.06 ± 0.01; HT 0.03 ± 0.01. $P < .05$) and HI_{98} (CK 0.21 ± 0.02; VMAT 0.08 ± 0.01; HT 0.05 ± 0.02. $P < .05$) were statically different. CK has the highest value which is not indicating a good dose homogeneity compared to VMAT and HT that has more homogenous dose distribution in both cases.

A not statistically significant difference between CK and VMAT was observed in terms of CI: 1.13 ± 0.05 vs 1.12 ± 0.01 ($P = .26$), whereas significant difference was found focusing on nCI: 1.16 ± 0.05 vs 1.31 ± 0.06 ($P < .05$).

The beam on time among the treatment modalities was statistically different: 37 ± 9 m CK vs 7.1 ± 0.3 m VMAT and 17 ± 2 m HT ($P < .05$).

4. Discussion

Prostate cancer is a fairly common disease among men in the world.[1–3] In recent times, due to scientific progress, several treatment methods became available and in particular hypofractionated radiotherapy is one of the most used.[6–28]

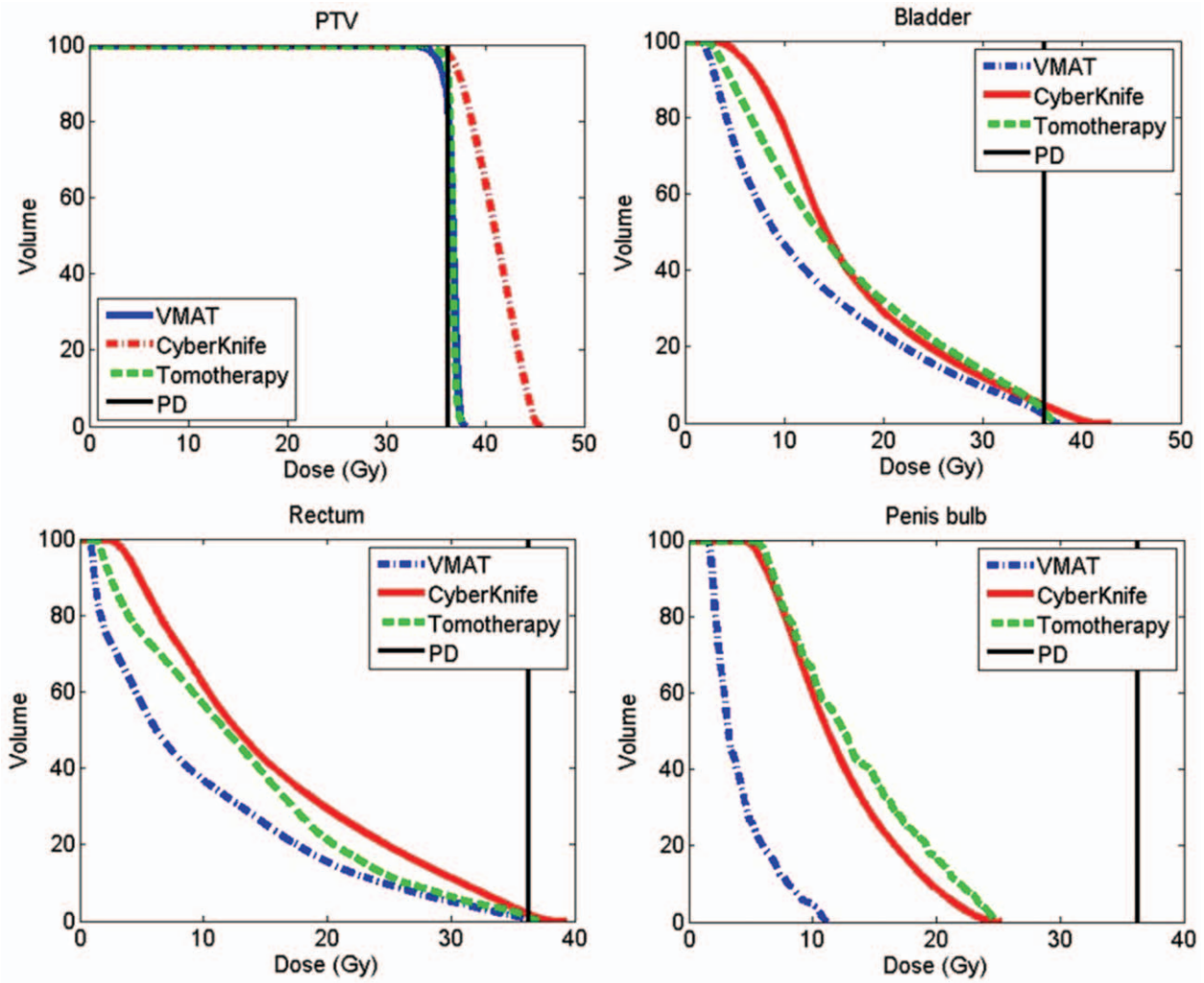

Figure 1. In the figure the DVHs for PTV, bladder, rectum and penis bulb are showed. In each panel there is the mean DVH obtained from the individual DVH for each patient and for the different treatment technique: VMAT in blue, CK in red and HT in green. Moreover, in each panel with the vertical solid black line the prescription dose (PD) (36.25 Gy) is drawn.

Moreover, in hypofractionated radiotherapy field various techniques are available, every of them has its pros and cons and not all of them are available in the same medical center. Therefore, in this study dosimetric results about the treatment of the localized prostate cancer by comparing the CK, VMAT, and HT technique are investigated, in order to understand if comparable goals in terms of tumor coverage and OARs sparing can be achieved.[20–27]

Trough the comparison between such platforms, there is a general satisfaction about the coverage of the PTV in literature, but conflicting results regarding the OARs sparing could depend on the version of the used TPS, the machines and the expansion margins to create the PTV.[29–34] Indeed, in our work the same PTV expansion has been used for each of the 3 techniques, whereas in other cited works authors used larger expansion for HT, VMAT, and IMRT or such parameter is not reported. It is noteworthy that wider margins on one side increase conformity of the used technique but on the other side decrease its sparing capability.

Focusing our attention on the mean DVHs (Fig. 1) and looking at the Table 2, for rectum and bladder the lower doses reached by the VMAT technique and the highest ones by CK are appreciable. However by paying more attention, the maximum sparing is reached at the lowest or intermediate doses whereas comparable values are obtained at high doses. Lower dose is delivered by VMAT to the penis bulb. Even if VMAT allows for the OARs sparing, this does not seem to negatively affect the coverage of tumor volume that is acceptable but the lowest one among the investigated techniques. It is noteworthy that the higher doses reached by CK are expected since this machine is conceived for the SBRT[30,32] and the total dose is prescribed at 80% isodose line. Given this particular feature to dose delivery by CK, it is expected a low dose-homogeneity inside the PTV with respect the other modalities as highlighted by the HI_{95} and HI_{98}. Moreover, to give a visual interpretation of the numerical indexes exposed above and a better dose delivery understanding to the different technologies, we display, in Figure 2, the dose distribution for the 3 different analyzed modalities. Because of dose delivery during the rotation of the treatment field, VMAT and HT slices show that low doses are delivered all around the PTV. Even though it is possible to observe a more jagged dose structure with CK due to the possibility to exploit multiple corridors and at the same saving

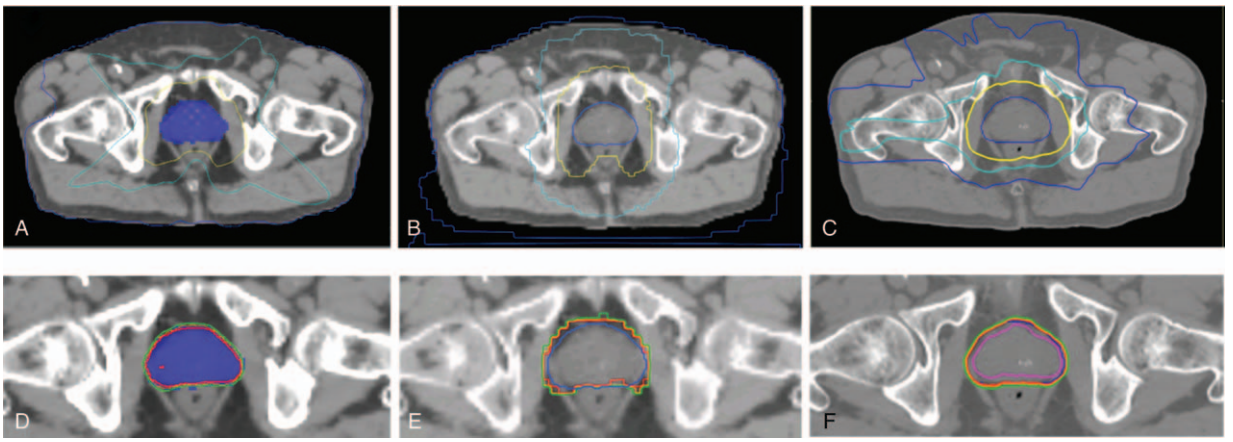

Figure 2. Dose distribution for the same patient in the same slice for the 3 techniques: a) and d) VMAT, b) and e) HT, c) and f) CK. In the panels a) and d) the PTV is showed as a blue shaded region, whereas for HT and CK the PTV is defined by a blue outline. The panels a), b) and c) show the dose distribution at 10% (blue line) 30% (cyan line) and 50% (yellow line) of the prescribed dose (36.25 Gy), the panels d), e) and f) report the dose at 95% (green line) 98% (orange line) 100% (red line) and 110% (magenta line).

from low doses healthy tissues. On the other hand, thanks to the technological progress of the abovementioned systems, the 95%, 98% of the prescribed dose is well confined along the PTV edges, and furthermore the dose in CK plans reaches the 110% of the prescribed dose, therefore justifying the lower values for the HI.

An important parameter is treatment duration: the longest ones are for the CK (37 minutes) whereas the shortest ones are for VMAT (7.1 minutes). Our beam on time are comparable or faster than those found by Lin et al.[33] The beam on time found for HT is 17 minutes considered not clinically deliverable since there is not a specific tool to track the PTV position during the treatment. Indeed in a such long duration, shifts due to organ motions are expected and therefore the probability to deliver high doses to the OARs and to do not cover the PTV increases. The CK has a longer treatment length as it is equipped with a particular IGRT system to track prostate movement through fiducial markers and KV images acquisition during the whole treatment.

Even if the treatment duration for VMAT is the shortest one compared with other techniques, if an imaging dynamic tracking system is not adopted, it could lead to a missing target or an overtreatment of the PTV and OARs, considering that during this time some patient and organ motions are unavoidable. Nevertheless, we can consider it clinically deliverable since in our Institute it is available the IGRT Clarity system, a real time prostate tracking through an ultrasound probe that allows a sub-millimetric accuracy when delivering dose.

In our clinical practice, we use this system for prostate SBRT LINAC based with VMAT technique and we contour targets with the same margin of CK SBRT.[29]

Only CK and VMAT were considered eligible for a real treatment because of dose-delivery time, and for both of them the CI and nCI have been measured. These results showed that CI is not exhaustive enough, to have a more complete information about quality and accuracy of the treatment thus the nCI has to be considered. Indeed, even if the CI are not distinguishable, the information about the coverage contained in the nCI allows to affirm that the CK provides better accuracy.

The 3 techniques offer a satisfactory coverage for the PTV in term of 95% and 98% coverage (Table 3) even if a statistically significant difference was found: CK has the highest coverages and VMAT the lowest ones. Moreover, the CK is confirmed to be the most accurate (CI and nCI), the VMAT technique the most rapid and versatile[32] and the lowest HT performance, in terms of time, it can be attributed to its particular way of delivering the dose and to the particular anatomical conformation of this pathology, the HT is particularly suitable for long sized lesions. The differences of the PTV coverages and OARs sparing between CK and VMAT could be attributable to the technological intrinsic properties of the dose delivery. Therefore, by taking into account that CK and VMAT are available solutions for the treatment of prostate cancer and administration of high doses where a suitable tracking system is required, a further study could involve VMAT treatments with the flattening filter free beam in order to have a steepest beam profile comparable to that of CK. Furthermore, it must be taken into account that although CK is the main tool for the SBRT, it is not available in every radiotherapy centers. Thus, VMAT adaptability satisfies the need of hypofractionated treatment of such a widespread disease.

Finally, it is possible to assert that in general there are not big differences among the analyzed techniques if appropriate systems to track the tumor during the treatment are available. As a consequence, if the clinical or anatomical conditions of the patient do not specifically require one technique rather than another, the abovementioned treatments are interchangeable and the best modality to adopt can be evaluated patient by patient.

5. Study approval and recruiment

This study is part of the Cypro Trial, approved by the Ethics committee of the National Cancer Institute - G. Pascale Foundation - Naples, Protocol Version 1.0; 27th of January 2020. Decision n 105.

Author contributions

Conceptualization: Marcello Serra, Gianluca Ametrano, Matteo Muto, Di Franco Dr Rossella, Muto Prof Paolo.
Data curation: Marcello Serra.
Formal analysis: Marcello Serra.

Investigation: Marcello Serra, Borzillo Dr Valentina, Savino Federica, Filomena Loffredo.
Methodology: Marcello Serra, Gianluca Ametrano, Matteo Muto.
Software: Marcello Serra, Quarto Prof Maria.
Supervision: Muto Prof Paolo.
Visualization: Marcello Serra.
Writing – original draft: Marcello Serra.
Writing – review & editing: Marcello Serra, Gianluca Ametrano, Borzillo Dr Valentina, Quarto Prof Maria, Matteo Muto, Di Franco Dr Rossella, Muto Prof Paolo.

References

[1] Rawla P. Epidemiology of Prostate Cancer. World J Oncol 2019;10: 63–89.
[2] Stangelberger A, Waldert M, Djavan B. Prostate Cancer in Elderly Men. Rev Urol 2008;10:111–9.
[3] Pollock PA, Ludgate A, Wassersug RJ. In 2124, half of all men can count on developing prostate cancer. Curr Oncol 2015;22:10–2.
[4] Lam TBL, MacLennan S, Willemse PM, et al. EAU-EANM-ESTRO-ESUR-SIOG prostate cancer guideline panel consensus statements for deferred treatment with curative intent for localised prostate cancer from an international collaborative study (DETECTIVE Study). Eur Urol 2019;76:790–813.
[5] Siegel R, DeSantis C, Virgo K, et al. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin 2012;62:220–41.
[6] Dasu A, Toma-Dasu I. Prostate alpha/beta revisited - an analysis of clinical results from 14168 patients. Acta Oncol 2012;51:963–74.
[7] Fowler J, Chappell R, Ritter M. Is alpha/beta for prostate tumors really low? Int J Radiat Oncol Biol Phys 2001;50:1021–31.
[8] Fowler J. The radiobiology of prostate cancer including new aspects of fractionated radiotherapy. Acta Oncol 2005;44:265–76.
[9] Arabpour A, Shahbazi-Gahrouei D. Effect of Hypofractionation on Prostate Cancer Radiotherapy. Int J Cancer Manag 2017;10:e12204.
[10] Miralbell R, Roberts SA, Zubizarreta E, et al. Dose fractionation sensitivity of prostate cancer deduced from radiotherapy outcomes of 5969 patients in seven international institutional datasets: a/b = 1.4 (0.9-2. 2) Gy. Int J Radiat Oncol Biol Phys 2012;82:e17–24.
[11] Alongi F, Fiorentino A, De Bari B. SBRT and extreme hypofractionation: A new era in prostate cancer treatments? Reports of Practical Oncology & Radiotherapy Volume 20, Issue 6, November-December 2015, Pages 411-416. https://doi.org/10.1016/j.rpor.2014.09.005.
[12] Nahum AE. The radiobiology of hypofractionation. Clin Oncol (R Coll Radiol) 2015;27:260–9.
[13] Brenner DJ, Hall EJ. Fractionation and protraction for radiotherapy of prostate carcinoma. Int J Radiat Oncol Biol Phys 1999;43:1095–101.
[14] Lukka H, Hayter C, Julian JA, et al. Randomized trial comparing two fractionation schedules for patients with localized prostate cancer. J Clin Oncol 2005;23:6132–8.
[15] Yeoh EE, Botten RJ, Butters J, et al. Hypofractionated versus conventionally fractionated radiotherapy for prostate carcinoma: final results of phase III randomized trial. Int J Radiat Oncol Biol Phys 2011;81:1271–8.
[16] Pollack A, Walker G, Horwitz EM, et al. Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer. J Clin Oncol 2013;31:3860–8.
[17] Arcangeli G, Saracino B, Gomellini S, et al. A prospective phase III randomized trial of hypofractionation versus conventional fractionation in patients with high-risk prostate cancer. Int J Radiat Oncol Biol Phys 2010;78:11–8.
[18] Aluwini S, Pos F, Schimmel E, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): late toxicity results from a randomised non-inferiority phase 3 trial. Lancet Oncol 2016;17:464–74.
[19] Wilkins A, Mossop H, Syndikus I, et al. Hypofractionated radiotherapy versus conventionally fractionated radiotherapy for patients with intermediate-risk localised prostate cancer: 2-year patient-reported outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol 2015;16:1605–16.
[20] Katz AJ, Santoro M, Ashley R, et al. Stereotactic body radiotherapy for organ-confined prostate cancer. Technol Cancer Res Treat 2010;9: 575–82.
[21] King CR, Brooks JD, Gill H, et al. Long-term outcomes from a prospective trial of stereotactic body radiotherapy for low-risk prostate cancer. Int J Radiat Oncol Biol Phys 2012;82:877–82.
[22] Friedland JL, Freeman DE, Masterson-McGary ME, et al. Stereotactic body radiotherapy: an emerging treatment approach for localized prostate cancer. Technol Cancer Res Treat 2009;8:387–92.
[23] Freeman DE, King CR. Stereotactic body radiotherapy for low-risk prostate cancer: five-year outcomes. Radiat Oncol 2011;6:3.
[24] Alongi F, Cozzi L, Arcangeli S, et al. Linac based SBRT for prostate cancer in 5 fractions with VMAT and flattening filter free beams: Preliminary report of a phase II study. Radiat Oncol 2013;8:171.
[25] Timmerman RD. An overview of hypofractionation and introduction to this issue of seminars in radiation oncology. Semin Radiat Oncol 2008;18:215–22.
[26] Grimm J, LaCouture T, Croce R, et al. Dose tolerance limits and dose volume histogram evaluation for stereotactic body radiotherapy. J Appl Clin Med Phys 2011;12:3368.
[27] De Bari B, Arcangeli S, Ciardo D, et al. Extreme hypofractionation for early prostate cancer: biology meets technology. Cancer Treat Rev 2016;50:48–60.
[28] De Bari B, Fiorentino A, Arcangeli S, et al. From radiobiology to technology: what is changing in radiotherapy for prostate cancer. Expert Rev Anticancer Ther 2014;14:553–64.
[29] Seppälä J, Suilamo S, Tenhunen M, et al. Dosimetric comparison and evaluation of 4 stereotactic body radiotherapy techniques for the retreatment of prostate cancer. Technol Cancer Res Treatment 2017;16:238–45.
[30] Chun CY, Lee LM, Yu HW, et al. Dosimetric and radiobiological comparison of Cyberknife and Tomotherapy in stereotactic body radiotherapy for localized prostate cancer. J Xray Sci Technol 2017;25:465–77.
[31] MacDougall ND, Dean C, Muirhead R. Stereotactic body radiotherapy in prostate cancer: is rapidarc a better solution than CyberKnife? Clin Oncol (R Coll Radiol) 2014;26:4–9.
[32] Slosarek K, Osewski W, Grzadziel A, et al. Integral dose: Comparison between four techniques for prostate radiotherapy. Rep Pract Oncol Radiother 2014;20:99–103.
[33] Lin YW, Lin KH, Ho HW, et al. Treatment plan comparison between stereotactic body radiation therapy techniques for prostate cancer: Non-isocentric CyberKnife versus isocentric RapidArc. Phys Med 2014;30:654–61.
[34] Hossain S, Xia P, Huang K, et al. Dose gradient near target-normal structure interface for nonisocentric CyberKnife and isocentric intensity-modulated body radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2010;78:58–63.