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A dosimetric dnalysis of flattening-filter-free mode linear accelerator-based stereotactic body radiation therapy and HDR brachytherapy for prostate cancer

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Original Article

Abstract

Purpose: Prior studies have reported that linear accelerator (LINAC)-based stereotactic body radiation therapy (SBRT) plans for prostate cancer are unable to achieve comparable intraprostatic doses to high-dose-rate brachytherapy (HDR). However, the utilization of flattening-filter-free (FFF) beams provides superior dose distributions compared with flattened beams. The purpose of this study was to test the feasibility of achieving the high intraprostatic doses observed in HDR by utilizing LINAC - based SBRT with FFF beams. **Methods:** We randomly selected 10 patients with localized prostate cancer previously treated at our institution in 2013. FFF-mode LINAC-based SBRT and simulated HDR (using virtual HDR catheters) plans were generated for each patient. The planning target volume (PTV) V100, V125, V150 and V200 values were compared between the two plans using the two-sided paired samples t-test. **Results:** Regarding the PTV coverage, the mean V100 was slightly higher for SBRT at 96.47% compared with 94.68% for HDR ($p = 0.003$). The V125 (61.69% versus 66.51%, $p = 0.004$) and V200 (15.06% versus 19.66%, $p < 0.001$) were slightly lower for SBRT. There were no significant differences in V150 between the two plans (47.59% versus 49.8%, $p = 0.375$). Rectal and bladder dosimetry were also comparable between the two modalities, though the rectal maximum dose was lower in the SBRT plan (99.6% versus 103.66%, $p = 0.006$) and the dose to 15cc of bladder was lower in the HDR plan (96.34% versus 78.18%, $p = 0.005$). **Conclusion:** Utilization of FFF mode LINAC-based SBRT allows for achievable dosimetry that is very similar to high dose rate brachytherapy. Further studies are warranted regarding the safety and efficacy of this modality.

Keywords: Prostate cancer, High-dose rate brachytherapy, Stereotactic body radiation therapy, Dosimetry, Flattening filter-free

1. Introduction

Localized prostate cancer has been treated with standard course external beam radiation therapy and/or low-dose-rate interstitial brachytherapy for many years. However, with technological advances in the imaging, accuracy and more sophisticated planning software, further buoyed by suggestions of a low alpha-beta ratio for prostate cancer,[1-3] new hypofractionated techniques have been emerging. One such technique is high-dose-rate brachytherapy (HDR). Multiple studies have demonstrated support for this approach with a variety of fractionation schemes.[4-7] A course of 9.5 Gy × 4 fractions is generally accepted as the most appropriate fractionation scheme.[8] At the same time, there has been an increased proliferation of stereotactic body radiotherapy (SBRT) to deliver high dose per fraction without the necessary invasiveness of brachytherapy. There have been several studies supporting the feasibility of this approach as well.[9-13] A course of 7 - 7.25 Gy × 5 fractions has generally been used for this modality.

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Given that most of the clinical data supporting hypofractionation is extrapolated from HDR, one question that has arisen has been whether treatment by SBRT can effectively and safely deliver the same fractionation schemes as HDR. Jabbari *et al.* have reported their early results using the Cyberknife (Accuray Inc, Sunnyvale, CA) using the standard HDR fractionation of 9.5 Gy × 4.[14] Although one typically seeks to achieve homogeneous dose distribution for conventional external beam radiation therapy, dose inhomogeneity within the target volume may be desirable for HDR brachytherapy and SBRT.[15] While one study has suggested that HDR dosimetry can be achieved via the Cyberknife,[15] this has been disputed by subsequent studies due to the inability of Cyberknife, or even linear accelerator (LINAC) based plans to achieve as high intraprostatic doses as can be achieved via HDR.[16-17]

Flattening filter-free beams (FFF) are increasingly becoming available on LINACS. Prior studies have shown increased efficiency of FFF beams[18] as well as dosimetric advantages.[19-20] Furthermore, one comparative study has suggested that even volumetric arc based plans using standard beams on a Varian (Varian Medical Systems, Inc. Palo Alto, CA) LINAC is able to achieve the same or better quality plans compared to the Cyberknife.[21] In this study, we hypothesize that HDR-like dosimetry can be achieved with LINAC-based SBRT by utilizing FFF beams on a Varian Truebeam LINAC.

2. Methods and Materials

Ten randomly selected low- or intermediate-risk patients by National Cancer Care Network guidelines with prostate cancer who were previously treated our institution during the year 2013 with definitive external beam radiation therapy were identified. Our series included 7 men with low risk disease and 3 men with intermediate risk disease.

All patients previously underwent CT simulation for treatment planning with an endorectal balloon (Radiadyne, Houston, TX) inflated with 60 cc of sterile water. The planning target volume (PTV) for all cases was defined as the prostate as was previously contoured with a 4 mm margin all around, excluding the posterior margin, which was 2mm. The rectum, penile bulb and bladder were all previously contoured by the physician. The urethra was not initially contoured. It was placed centrally for the purposes of this study for both the SBRT and HDR plans.

Each patient's identical contours were planned to receive the prescription dose for both the external beam radiation plans as well as the high dose rate brachytherapy plans was 950 cGy per fraction for 4 fractions. The SBRT plans were created using Varian Eclipse V11.02 (Varian Medical Systems Inc, Palo Alto, CA). The corresponding HDR plans were created using Oncentra Master Plan TPS v3.3 SP3 (Nucletron BV, Veenendaal, the Netherlands). Catheters were virtually placed by the physician and subsequently modified as part of the planning process in order to achieve the most optimized plan.

The planning objectives were as follows: Urethral Dmax < 130%, rectal Dmax < 100%, D2cc < 70%, D2cc bladder < 75%. At least 90% of prescription dose coverage was required. For dosimetric analysis of the PTV coverage, we calculated the V100, V125, V150, and V200 representing the volume of the PTV receiving 100%, 125%, 150%, and 200% of the prescription dose, respectively. Variables used for dosimetric comparison of the organs-at-risk (OARs) included: urethral Dmax (maximum point dose to the urethra), rectal Dmax (maximum point dose to the rectum), rectal D2 cc (dose to 2 cc of the rectum), bladder D2 cc (dose to 2 cc of the bladder), and bladder D15cc (dose to 15 cc of the bladder).

Statistical analysis was performed using the SPSS statistical software version 21 (IBM, Armonk, NY). Comparison was made using the simple two-sided paired samples t-test with statistical significance defined as a p-value < 0.05.

Table 1: Summary of planning target volume (PTV) coverage

	Simulated HDR	LINAC FFF SBRT	p-value
Mean PTV V100 in % (95% CI)	94.68 (94.36-95.00)	96.47 (95.82-97.12)	0.003
Mean PTV V125 in % (95% CI)	66.51 (64.18-68.84)	61.69 (59.49-63.89)	0.004
Mean PTV V150 in % (95% CI)	49.8 (46.35-53.25)	47.59 (44.10-51.08)	0.375
Mean PTV V200 in % (95% CI)	19.66 (18.53-20.79)	15.06 (13.88-16.24)	<0.001

Table 2: Summary of rectal dosimetry

	Simulated HDR	LINAC FFF SBRT	p-value
Rectal Dmax in % (95% CI)	103.66 (101.58-105.74)	99.6 (98.65-100.55)	0.006
Rectal D2cc in % (95% CI)	95.14 (92.06-98.22)	94.75 (92.34-97.16)	0.859

Table 3: Summary of bladder and urethral dosimetry

	Simulated HDR	LINAC FFF SBRT	p-value
Bladder D2cc in % (95% CI)	161.00 (152.58-169.42)	148.48 (131.43-165.53)	0.155
Bladder 15cc in % (95% CI)	78.18 (74.74-81.62)	96.34 (86.80-105.88)	0.005
Urethral Dmax in %	135	130	0.05

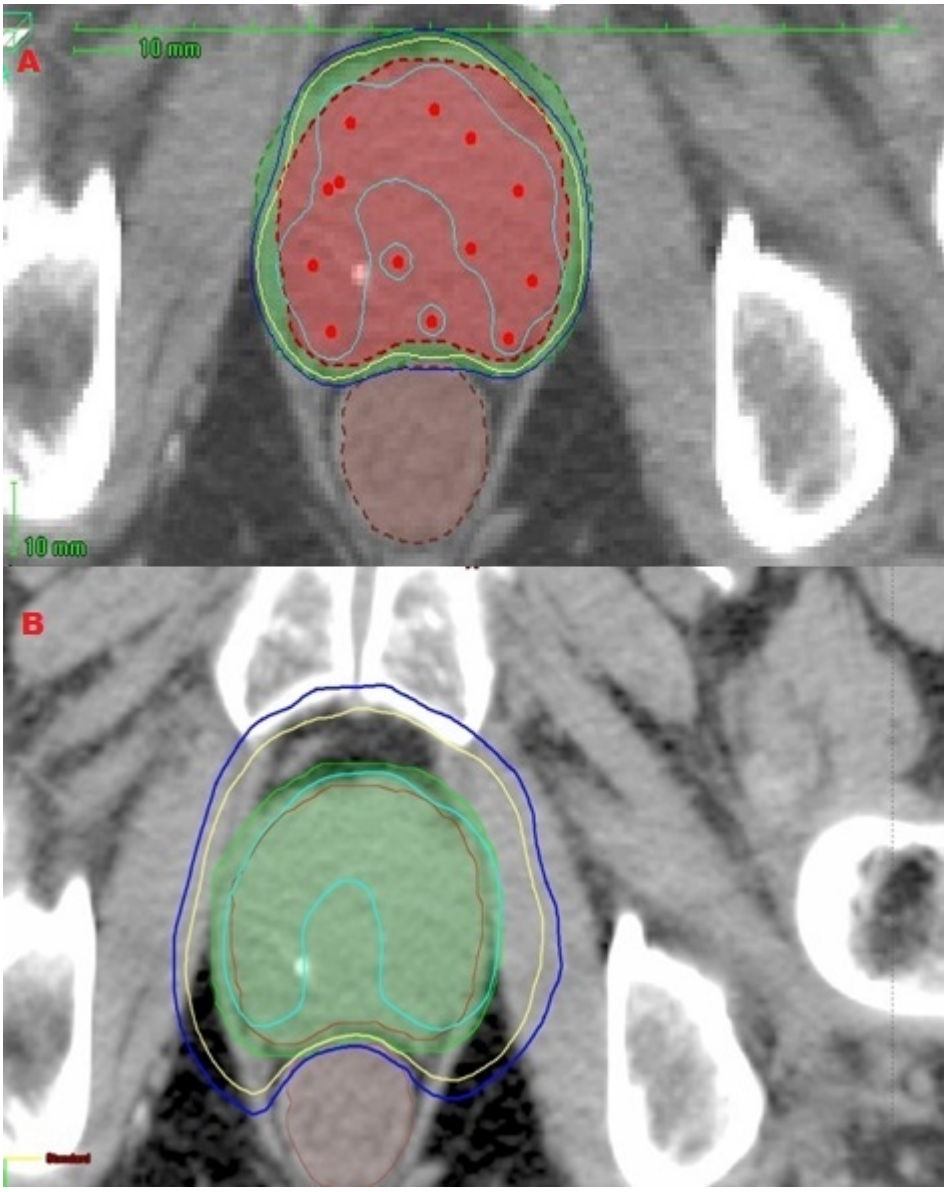

Figure 1: Representative isodose distributions of A) HDR (High-dose-rate) brachytherapy and B) flattening-filter-free SBRT (stereotactic body radiation therapy) plans. Red = PTV, Dark Blue = 90% isodose, Yellow = 100% isodose, Light Blue = 150% isodose

3. Results

3.1. PTV coverage

The analysis of the PTV dose distribution and dose metrics for the LINAC-based SBRT and HDR is shown in Table 1. The V100 was slightly higher with the SBRT plan compared to the HDR plan (96.47% vs. 94.68%, p = 0.003) whereas the V125 (61.69% vs. 66.51%, p = 0.004) and V200 (15.06% vs. 19.66%, p < 0.001) were slightly higher with the HDR plan. The V150 (47.59 % vs. 49.80%, p = 0.375) was similar between the two treatment modalities. Figure 1 shows a comparative plan of the two modalities showing the dose escalation regions (volume receiving at least 100% of the prescription dose), prescription isodose boundaries (V100) and dose falloff regions (V125, V150, V75, V50).

3.2. Rectum

Rectal dosimetry is summarized in Table 2. The rectal Dmax was significantly higher in the virtual HDR plan (99.6% vs. 103.66%, p = 0.006), though this was highly dependent upon the position of the catheters in the HDR plan. The rectal D2 cc (94.75% vs. 95.14%, p = 0.859) and mean rectal doses were very similar between the virtual HDR and HDR. However, rectal D10 and D25 were significantly higher with HDR compared to the SBRT.

3.3. Bladder

Bladder dosimetry is listed in Table 3. As the bladder Dmax for HDR is consistently higher due to proximity of the brachytherapy source, bladder D2 cc was used as a surrogate for the bladder max dose. Although bladder D2 cc was similar for both HDR and SBRT, it varied significantly in the presence of a median lobe or if more than, one catheter was placed in close proximity to the bladder. In those cases the D2 cc was higher for the HDR plan. The bladder D15 cc (96.34% vs. 78.18%, p = 0.005) and bladder dose falloff were significantly lower for the HDR plan.

3.4. Urethra

Table 3 also lists dosimetry values for the urethra. Urethral Dmax was slightly higher with the SBRT plan (135% vs. 130%, p = 0.05). As a caveat, these values for the HDR plan correlate with the placement of the needle, suggesting a correlation between the proficiency of catheter placement and dosimetric quality of plan. As the actual urethra was not identified on the CT scan, but rather placed in the middle of the prostate, the Dmax values for the urethra are more as a proof of concept rather than actual dosimetric value.

4. Discussion

Conventional gantry-based LINACs are an alternative platform to Cyberknife to deliver SBRT and may offer potential advantages over Cyberknife. In addition to wider availability than Cyberknife, gantry-based LINACs offer shorter treatment delivery times and improved dosimetry. Pawlicki *et al*. conducted a dosimetric comparison between Cyberknife SBRT and LINAC-based SBRT delivered via seven-field IMRT. The LINAC-based plans showed improved dose homogeneity with reduced rectal and bladder Dmax.[22] A similar comparative analysis of RapidArc volume - modulated arc therapy and Cyberknife found that RapidArc was able to achieve similar PTV coverage with consistently lower dose to the urethra and small bowel.[21] Furthermore, the average estimated treatment delivery time was substantially shorter with RapidArc (39 minutes vs. 3 minutes).

Given these potential advantages, LINAC-based SBRT may be a more attractive alternative to Cyberknife to perform virtual HDR. Prior studies investigating SBRT dosimetry with the Cyberknife platform have failed to achieve the high intraprostatic dosing seen with HDR. Fuller *et al*. compared Cyberknife SBRT plans for 10 patients with simulated HDR plans.[15] They found that although PTV V100 was similar (median 96.5% Cyberknife vs. 96% HDR), V125 (44% vs. 67.5%), V150 (8.5% vs. 38.8%), and D90 (39.8 Gy vs. 41.3 Gy) were all significantly lower with Cyberknife SBRT. Similarly, Fukuda *et al.* compared HDR brachytherapy plans in 6 patients with corresponding simulated Cyberknife SBRT plans.[16] They also found that HDR had superior intraprostatic dose concentration, with significantly higher V125 (79.4% vs. 48.9%) and V150 (40.8% vs. 3.1%) with the HDR plans. A comparison between actual HDR treatment plans and simulated LINAC-based SBRT plans was performed by Spratt *et al*.[17] They found that HDR and virtual SBRT had comparable PTV V100 (mean 93.08% for SBRT vs. 93.78%) and PTV V150 (42.86% vs. 40.32%), but virtual SBRT was unable to match the high intraprostatic doses of HDR (mean PTV V200 of 0% for SBRT vs. 15.18% for HDR). This is in contrast to our study where with the utilization of FFF beams we are able to attain nearly equivalent high intraprostatic dosing (PTV V200 of 15.06% with SBRT vs. 19.66% with HDR).

Despite the challenges in obtaining the high intraprostatic doses achieved in HDR plans, the early results of studies attempting a dose of 9.5 Gy × 4 via Cyberknife have been favorable. Fuller *et al.*[23] reported their 5 year results of the utilization of this fractionation via Cyberknife and found that the 5 year biochemical disease free survival was 98% for low risk and 92% for intermediate risk, with 6% late grade 3 genitourinary toxicity, similar to those seen in HDR studies.[23] Additionally, a smaller study by Pontoriero *et al.* also revealed favorable 2 year results without any reported Grade 3 toxicities.[24] While these results are promising, they are both single institution studies in highly specialized centers utilizing the Cyberknife. With the ability of the FFF mode in a linac to even more closely mimic HDR dosimetry, it would be expected that this

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fractionation schedule has the potential to be further studied and, if these results are confirmed, eventually offered as a therapeutic option across multiple centers.

Regarding the doses to the normal organs-at-risk, our findings are generally in agreement with previous analyses but differ in some aspects. We found that the bladder D2 cc was higher with the HDR plan compared to the SBRT plan, which is consistent with the experiences of Fuller *et al*.[15] and Fukuda *et al*.[16] However, Spratt *et al*. found the bladder D2 cc was not statistically different with their HDR plan than with their simulated SBRT plan.[17] Rectal dosimetry in these previously mentioned studies was variable as well, with Fuller *et al*. and Spratt *et al*. reporting significantly higher rectal Dmax with SBRT and Fukuda *et al*. reporting non-significantly lower rectal Dmax with SBRT. However, in our study we found that the rectal Dmax was significantly lower in the SBRT arm. These disparate findings may be related to the superiority in efficiency and dosimetry of FFF beams over flattened beams.[18-19] Alternatively, these differences may be operator dependent. For example, the bladder D2 cc and rectal Dmax are both highly dependent on HDR catheter placement. In our study, we attempted to virtually place the catheters in the ideally best location in order to achieve optimal HDR dosimetry results. However, the anatomic insertion of catheters may result in different dosimetric results. Additionally, differences in PTV definition may also account for the discordant findings between studies. As in our analysis, Fuller *et al*. used identical PTVs (2 mm uniform expansion reduced to 0 mm posteriorly) for both the HDR and SBRT plans. However, Fukuda *et al*. used larger PTV margins for their HDR planning (5 mm uniform expansion except posteriorly, which was reduced to 2-5 mm) than their SBRT planning (2 mm uniform expansion). Spratt *et al*.[17] did not explicitly describe the PTV margins used in their study. In this study we tried to select for reasonable margins that are considered acceptable in either the HDR or SBRT setting.

There are several important limitations in our analysis. First, there were a small number of patients in this study. Second, we utilized simulated HDR plans which do not account for changes in anatomy from interstitial catheter placement nor do they account for inaccuracies such as longitudinal catheter displacement. The significance of these effects on dosimetry cannot be accurately estimated. Third, although we demonstrate similar dosimetry between simulated HDR and FFF LINAC-based SBRT, it is unclear whether increasing the intraprostatic dose for SBRT will further improve outcomes. Multiple randomized studies of conventional EBRT have found improved clinical outcomes with dose escalation and retrospective series of patients treated with LDR brachytherapy have similarly established a dose-response.[25-27] However, the clinical relevance of PTV V150 and V200 have yet to be established for either HDR or SBRT. Finally, both SBRT and HDR planning were based on CT simulation with an endorectal balloon. While endorectal balloons are routinely employed for SBRT, they are not standardly utilized for HDR. The effect of an endorectal balloon on rectal dosimetry for either SBRT or HDR is not well-defined. However, a prior study using an endorectal balloon in 3D conformal radiation planning suggests that an endorectal balloon may displace the anterior rectal wall into the high dose regions,[28] which would increase the rectal Dmax for both SBRT and HDR.

5. Conclusion

We have demonstrated the feasibility of virtual HDR using FFF mode LINAC-based SBRT, further supporting the early results from two series supporting this fractionation schedule. Using FFF beams, PTV V150 was similar to HDR with V200 approaching that of HDR while respecting OAR constraints. Further clinical studies are needed to determine the efficacy and safety of high intraprostatic dosing via SBRT on clinical outcomes.

Conflict of interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Brenner DJ, Hall EJ. Fractionation and protraction for radiotherapy of prostate carcinoma. Int J Radiat Oncol Biol Phys. 1999;43:1095-101.
2. Fowler J, Chappell R, Ritter M. Is alpha/beta for prostate tumors really low? Int J Radiat Oncol Biol Phys. 2001;50:1021-31.
3. Brenner DJ, Martinez AA, Edmundson GK, *et al*. Direct evidence that prostate tumors show high sensitivity to fractionation (low alpha/beta ratio), similar to late-responding normal tissue. Int J Radiat Oncol Biol Phys. 2002;52:6-13.
4. Yoshioka Y, Nose T, Yoshida K, *et al*. High-dose-rate interstitial brachytherapy as a monotherapy for localized prostate cancer: Treatment description and preliminary results of a phase I/II clinical trial. Int J Radiat Oncol Biol Phys. 2000;48:675-681.
5. Martinez AA, Pataki I, Edmundson G, *et al*. Phase II prospective study of the use of conformal high-dose-rate brachytherapy as monotherapy for the treatment of favorable stage prostate cancer: A feasibility report. Int J Radiat Oncol Biol Phys. 2001;49:61-9.
6. Corner C, Rojas AM, Bryant L, *et al*. A Phase II study of high-dose rate afterloading brachytherapy as monotherapy for the

treatment of localized prostate cancer. Int J Radiat Oncol Biol Phys. 2008;72:441-6.
7. Demanes DJ, Martinez AA, Ghilezan M, et al. High-dose-rate monotherapy: Safe and effective brachytherapy for patients with localized prostate cancer. Int J Radiat Oncol Biol Phys. 2011;81:1286-92.
8. Hsu IC, Yamada Y, Merrick G, *et al.* ACR Appropriateness Criteria High-dose-rate brachytherapy for prostate cancer. American College of Radiology. Retrieved May 25, 2015, from https://acsearch.acr.org/docs/3082863/Narrative/.
9. 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.
10. McBride SM, Wong DS, Dombrowski JJ, *et al*. Hypofractionated stereotactic body radiotherapy in low-risk prostate adenocarcinoma: preliminary results of a multi-institutional phase 1 feasibility trial. Cancer. 2012;118:3681-90.
11. Bolzicco G, Favretto MS, Scremin E, *et al*. Image-guided stereotactic body radiation therapy for clinically localized prostate cancer: preliminary clinical results. Technol Cancer Res Treat. 2010;9:473–7.
12. Boike TP, Lotan Y, Cho LC, *et al*. Phase I dose-escalation study of stereotactic body radiation therapy for low- and intermediate-risk prostate cancer. J Clin Oncol. 2011;29:2020–6.
13. Katz AJ, Santoro M, Diblasio F, *et al*. Stereotactic body radiotherapy for localized prostate cancer: disease control and quality of life after 6 years. Radiat Oncol. 2013;8(1):118.
14. Jabbari S, Weinberg VK, Kaprealian T, *et al*. Stereotactic body radiotherapy as monotherapy or post external beam radiotherapy boost for prostate cancer: technique, early toxicity, and PSA response. Int J Radiat Oncol Biol Phys. 2012;82:228-34.
15. Fuller DB, Naitoh J, Lee C, *et al*. Virtual HDR CyberKnife treatment for localized prostatic carcinoma: dosimetry comparison with HDR brachytherapy and preliminary clinical observations. Int J Radiat Oncol Biol Phys. 2008;70:1588–97.
16. Fukuda S, Seo Y, Shiomi H, *et al*. Dosimetry analyses comparing high-dose-rate brachytherapy, administered as monotherapy for localized prostate cancer, with stereotactic body radiation therapy simulated using Cyberknife. J Radiat Res. 2014;55:1114-21.
17. Spratt DE, Scala LM, Folkert M, *et al*. A comparative dosimetric analysis of virtual stereotactic body radiotherapy to high dose rate monotherapy for intermediate risk prostate cancer. Brachytherapy. 2013;12:428-33.
18. Thomas EM, Popple RA, Prendergast BM, *et al*. Effects of flattening filter-free and volumetric modulated arc therapy delivery on treatment efficiency. J Appl Clin Med Phys. 2013;14:4328.
19. Hrbacek J, Lang S, Graydon SN, *et al*. Dosimetric comparison of flattened and unflattened beams for stereotactic ablative radiotherapy of stage I non-small cell lung cancer. Med Phys. 2014;41:031709.
20. Navarria P, Ascolese AM, Mancosu P, *et al*. Volumetric modulated arc therapy with flattening filter free (FFF) beams for stereotactic body radiation therapy (SBRT) in patients with medically inoperable early stage non-small cell lung cancer (NSCLC). Radiother Oncol. 2013;107:414-8.
21. Macdougall ND, Dean C, Muirhead R. Stereotactic body radiotherapy in prostate cancer: is rapidarc a better solution than cyberknife? Clin Oncol. 2014;26:4-9.
22. Pawlicki T, Kim GY, Hsu A, *et al*. Investigation of linac-based image-guided hypofractionated prostate radiotherapy. Med Dosim. 2007;32:71-9.
23. Fuller DB, Naitoh J, Mardirossian G. Virtual HDR Cyberknife SBRT for localized prostatic carcinoma: 5-year disease-free survival and toxicity observations. Front Oncol. 2014;4:321.
24. Pontoriero A, Iati G, Mondello S, *et al*. High-dose robotic stereotactic body radiotherapy in the treatment of patients with prostate cancer: preliminary results in 26 patients. Technol Cancer Res Treat. 2016;15:179-85.
25. Zietman AL, Bae K, Slater JD, *et al*. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95-09. J Clin Oncol. 2010;28:1106-11.
26. Kuban DA, Tucker SL, Dong L, *et al*. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phys. 2008;70:67-74.
27. Stone NN, Potters L, Davis BJ, *et al*. Multicenter analysis of effect of high biologic effective dose on biochemical failure and survival outcomes in patients with Gleason 7-10 prostate cancer treated with permanent prostate brachytherapy. Int J Radiat Oncol Biol Phys. 2009;73:341-6.
28. Elsayed H, Bolling T, Moustakis C, *et al*. Organ movements and dose exposures in teletherapy of prostate cancer using a rectal balloon. Strahlenther Onkol. 2007;183:617-24.

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