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Comparison of Intensity-modulated Radiation Therapy (IMRT), Uniform Scanning Proton Therapy (USPT), and Intensity-modulated Proton Therapy (IMPT) for Prostate Cancer: A Treatment Planning Study

Kihong Son*†, Seungryong Cho*, Jin Sung Kim†, Youngyih Han†, Sang Gyu Ju†, Sung Hwan Ahn†, Eunhyuk Shin†, Jung Suk Shin†, Won Park†, Hongryul Pyo†, Doo Ho Choi†

*Department of Nuclear and Quantum Engineering, Korea Advanced Institute of Science and Technology, Daejeon, †Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

This study assessed compared photon and proton treatment techniques, such as intensity modulated radiation therapy (IMRT), uniform scanning proton therapy (USPT), and intensity modulated proton therapy (IMPT), for a total of 10 prostate cancers. All treatment plans delivered 70 Gy to 95% of the planned target volume in 28 fractions. IMRT plans had 7 fields for the step and shoot technique, while USPT and IMPT plans employed two equally weighted, parallel-opposed lateral fields to deliver the prescribed dose to the planned target. Inverse planning was then incorporated to optimize IMPT. The homogeneity index (HI) and conformity index (CI) for the target and the normal tissue complication probability (NTCP) for organ at risk (OAR) were calculated. Although the mean HI and CI for target were not significantly different for each treatment techniques, the NTCP of the rectum was 2.233, 3.326, and 1.707 for IMRT, USPT, and IMPT, respectively. The NTCP of the bladder was 0.008, 0.003, and 0.002 respectively. The NTCP values at the rectum and bladder were significantly lower using IMPT. Our study shows that using proton therapy, particularly IMPT, to treat prostate cancer could be beneficial compared to 7-field IMRT with similar target coverage. Given these results, radiotherapy using protons, particularly optimized IMPT, is a worthwhile treatment option for prostate cancer.

Key Words: IMRT, USPT, IMPT, Prostate cancer, Treatment planning

INTRODUCTION

Internationally, prostate cancer rates have increased annually. In 2008, prostate cancer rates were the highest of all cancer rates in the US and UK, fourth in Japan, and fifth in Korea.[1)]

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Corresponding Author: Jin Sung Kim, Department of Radiation Oncology, Samsung Medical Center, 50, Ilwon-dong, Gangnam-gu, Seoul 135-710, Korea
Tel: 02)3410-3771, Fax: 02)3410-2619
E-mail: jinsung.k@gmail.com
Corresponding Author: Youngyih Han, Department of Radiation Oncology, Samsung Medical Center, 50, Ilwon-dong, Gangnam-gu, Seoul, 135-710, Republic of Korea
Tel: 02)3410-2604, Fax: 02)3410-2619
E-mail: youngyih@skku.edu

In recent years, the number of cancer patients treated with external beam radiotherapy has increased. The goal of radiotherapy is to deliver a prescription dose to a tumor while minimizing the dose to surrounding normal tissues and organs at risk (OAR). Conformal radiation techniques, including stereotactic patient positioning, multi-leaf collimation, and intensity modulated radiotherapy (IMRT), allow significantly improved dose distributions.[2)] IMRT can produce complex dose distributions and is capable of delivering a radical radiotherapy dose to the prostate while reducing the volumes of the small and the large bowel irradiated to significant doses.[3)] With a proton beam the dose is largely deposited in the Bragg peak at the end of the particle's range, with no dose delivered beyond a few millimeters past the peak. Therefore, proton beams are a great tool to spare healthy tissue around the target.[4)] These characteristics make possible a substantially reduced dose to

normal tissues while maximizing the dose to the tumor, and give proton therapy an inherent advantage over conformal photon therapy.[5-8] Uniform scanning proton therapy (USPT) can have a large irradiation field, a long-range and spread out Bragg Peak (SOBP), and can improve the beam efficiency more than conventional passive scattering proton therapy, especially in a large irradiation field. Intensity modulated proton therapy (IMPT), with a small beam size, can have a high beam efficiency and conformal irradiation.[9] The intensity of proton beams can also be modulated to optimize the dose.[10-12] This optimization reduces proton beam scattering in the compensator material, upstream from the patient, and reduces degradation of the dose penumbra in tissue.[4] This study assessed treatment planning by comparing the best available photon and proton treatment techniques (IMRT, USPT, and IMPT) as applied to 10 prostate

Table 1. Characteristics of the 10 prostate patients.

Patient	Age	Stage	Target volume
1	61	T3bN0	83.64
2	64	T3bN0	52.98
3	76	T3cN0	81.31
4	64	T3aN0	96.34
5	81	T3aN0	111.98
6	77	T2aN0	137.5
7	60	T3aN0	50.04
8	72	T1cN0	121.52
9	74	T3bN0	89.37
10	65	T3aN0	89.71

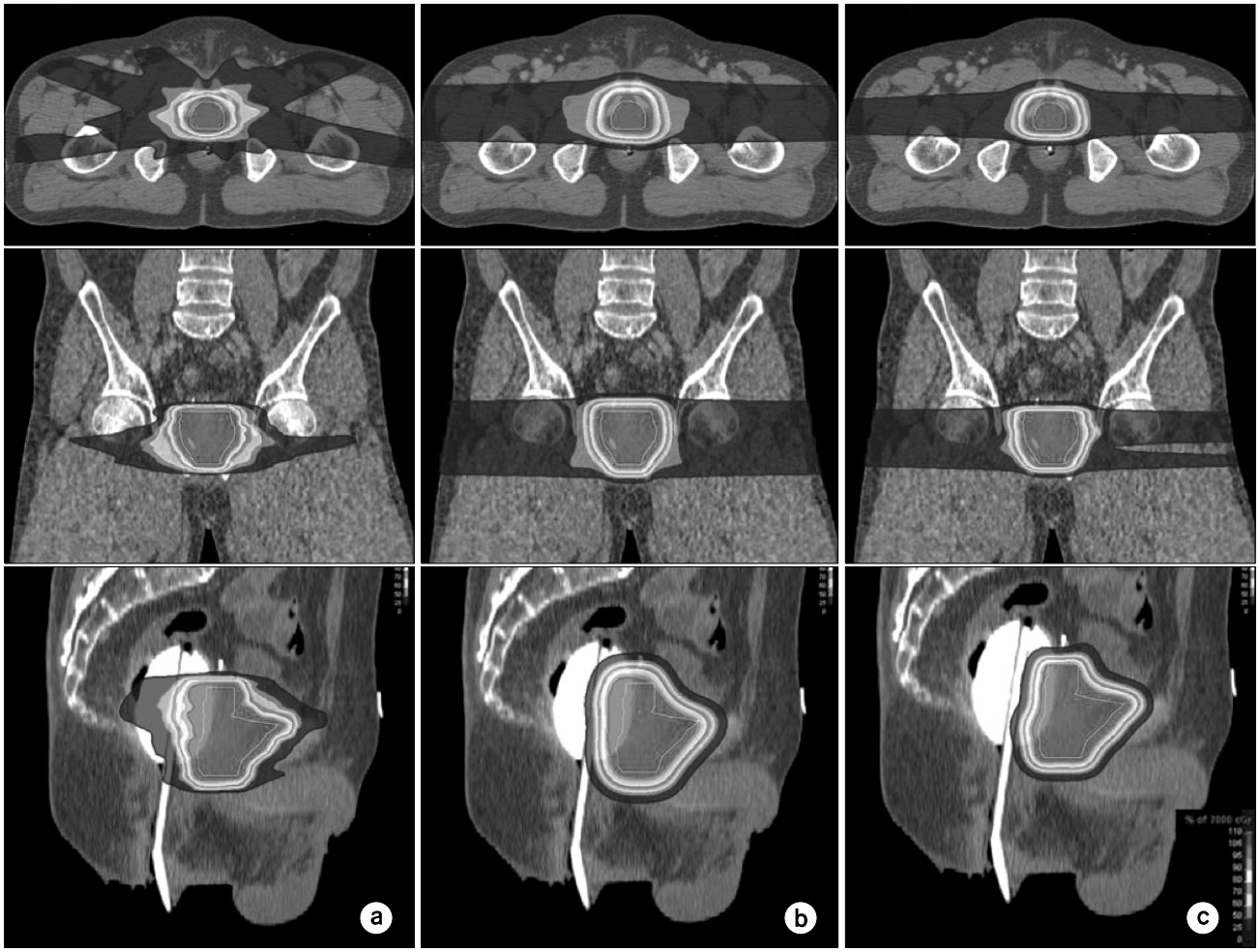

Fig. 1. Color wash IMRT (a), USPT (b), and IMPT (c) dose distribution for the PTV for patient (patient 3) with a prostate cancer. It shows the dose distributions of IMRT, USPT, and IMPT plans for CT image on axial, frontal, and sagittal planes, respectively. IMPT and USPT dose distributions delivered by right lateral (270°) and left lateral (90°) beams.

cancer patients that had received IMRT treatments at Samsung Medical Center in South Korea. Dosimetric parameters of the target and OAR were evaluated by the dose volume histogram (DVH), conformity index (CI), homogeneity index (HI), and normal tissue complication probability (NTCP).

MATERIALS AND METHODS

1. Treatment simulation and volume definition

We selected 10 localized prostate cancer patients. Table 1 shows the characteristics of the 10 patients. All patients underwent simulation using a 16-slice large bore (80-cm) helical computed tomography (CT) scanner (GE, Germany). CT scanning was performed in the supine position with the slice thickness of 2.5 mm. For each patient, the clinical target volume (CTV) was defined as the whole prostate plus the seminal vesicle including a suspected gross tumor by MRI for 4 patients. The prostate gland was contoured in all CT scans and defined as the clinical target volumes (CTVs). On each slice, the bladder, rectum and both femoral heads were defined as OAR. For every CT scan, the planning target volume (PTV) was defined by adding a 1.0-cm margin around the prostate in all direction, except posteriorly at the rectum interface where a 0.7-cm margin was used. All plans delivered 70 Gy to 95% of the planned target volume (PTV) in 28 fractions.

2. IMRT planning

For inverse IMRT treatment planning, we used a 7-coplanar non-opposed beam arrangement at 260^{o}, 290^{o}, 320^{o}, 0^{o}, 35^{o}, 65^{o}, and 100^{o} angles with 6MV photon beam. The IMRT plan was generated on a commercial Pinnacle3 treatment planning system (TPS) (Philips Radiation Oncology Systems, Fitchburg, USA). The PTV dose objectives were attained, and the dose to all critical structures and the external contour was minimized as much as possible without compromising the dose to the PTV or generating hot spots in healthy tissue (Fig. 1a).

3. Uniform scanning proton treatment planning

Proton therapy treatment plans were created for prostate cancer patients using a RayStation V 2.4 treatment planning system (RaySearch Laboratories, Stockholm, Sweden) for IBA Proteus 235 machine and dose kernels are calculated using the pencil beam dose algorithm of the treatment planning system which takes heterogeneities into account also within the cross sections of the spots. The USPT plan stacks uniform fluence energy layers combined with a PMMA compensator. The USPT plan employed two equally weighted, parallel-opposed lateral fields to deliver the prescribed dose to the PTV. We used relatively small margins in planning because various uncertainties had already been included in the PTV. Fig. 1b shows the actual treatment plan for Patient 2, using bilateral beams, and the corresponding coronal and axial views with the dose distribution.

4. Intensity modulated proton treatment planning

The IMPT plan also employed two lateral beams using a RayStation planning system. Each beam was initially generated such that it delivered a flat SOBP to the target volume. To explore improvements to proton therapy treatment, individual pencil beams were not of equal weight. Initially, weighting the individual pencil beams equally led to a gradient SOBP, which gave higher doses proximal to the target than a flat SOBP.[13] Inverse planning was then used to optimize the plan. Dose objectives were prescribed where 95% of the PTV volume received the prescription dose. After the PTV objectives had been achieved, the doses to the rectum, bladder, femoral heads, and the external contour were minimized as much as possible without compromising conformity in the PTV. The optimization constraints shown Table 2 were also used for IMPT planning. Fig. 1c show the actual IMPT plan, using bilateral

Table 2. Optimization constraints for IMRT and IMPT.

ROI	Description
PTV	Uniform Dose 7,000 cGy
	Max Dose 7,100 cGy
Right femoral head	Max Dose 3,700 cGy
	Max DVH 3,000 cGy to 60% volume
	Max DVH 900 cGy to 40% volume
Left femoral head	Max Dose 3,700 cGy
	Max DVH 3,000 cGy to 60% volume
	Max DVH 900 cGy to 40% volume
Bladder	Max Dose 6,900 cGy
	Max DVH 2,500 cGy to 40% volume
Rectum	Max DVH 4,250 cGy to 20% volume
	Max DVH 1,890 cGy to 55% volume

PTV: planning target volume, DVH: dose volume histogram.

beams, and the corresponding coronal and axial views with the dose distribution.

5. Analysis and evaluation

The DVH for the IMRT, USPT, and IMPT plans were compared for the PTV and for OAR, such as the rectum, bladder, and both femoral heads. We evaluated the Homogeneity Index (HI), defined as the ratio of the dose received by 5% of the PTV volume to that received by 95% of the PTV.

$$HI = D_5 / D_{95}$$

Where D_5 and D_{95} are the doses received by 5% and 95% of the PTV volume, respectively. Conformity of high dose around the target was evaluated by calculating the Conformity index (CI). The CI was defined as the ratio between the target volume (TV) and the reference isodose (V_{RI}) volume.[14)]

$$CI = TV / V_{RI}$$

The normal tissue complication probability (NTCP) was calculated for the rectum and bladder using the NTCP model proposed by Lyman, Kutcher, and Burman.[15)]

RESULTS

1. PTV

All DVH curves in Fig. 2a are similar up to a dose of 71.0 Gy. No plan exceeded 113% of the prescription dose. After this point the different techniques cause the curves to separate

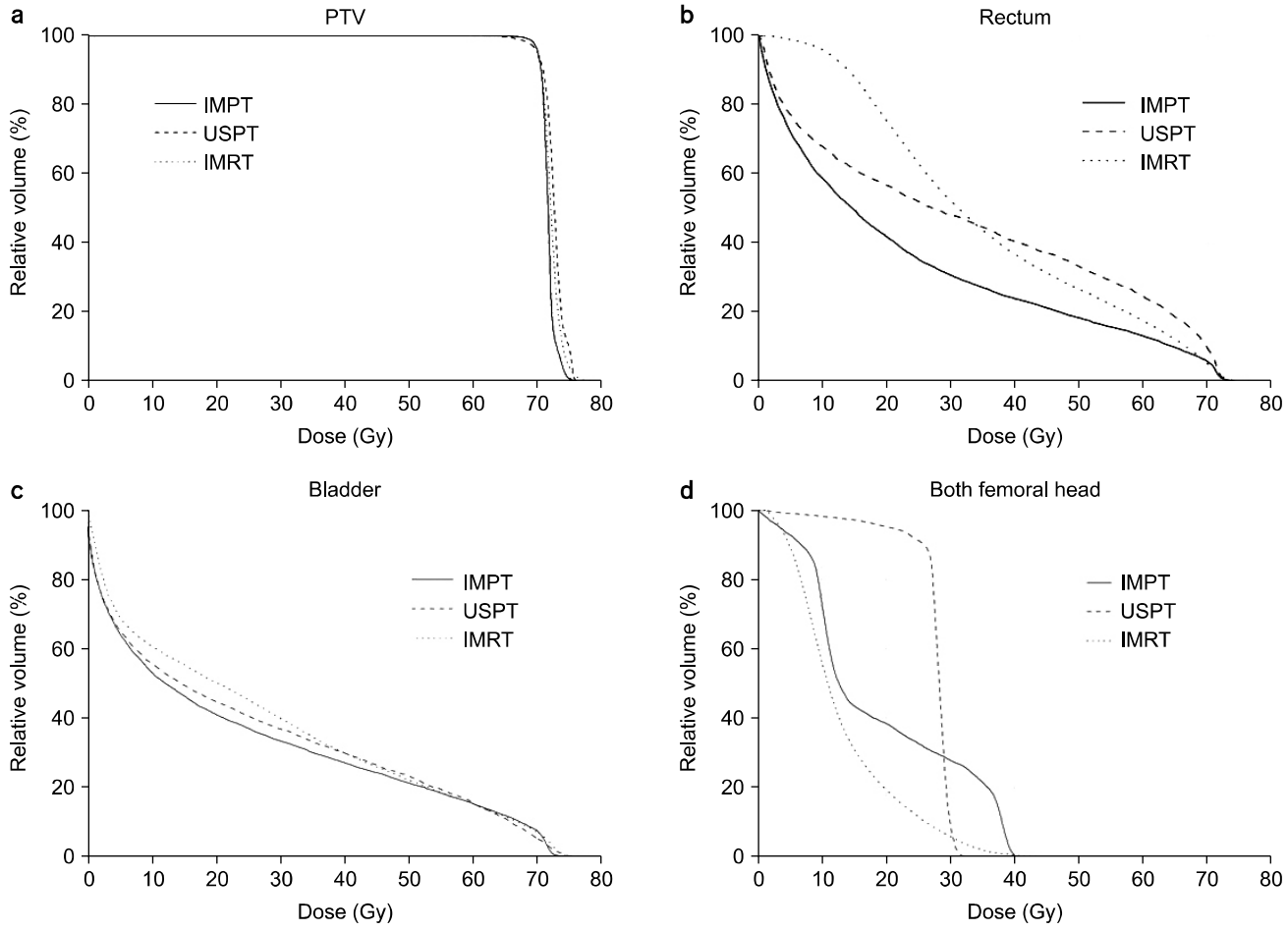

Fig. 2. Mean DVHs of 10 prostate patients for OARs at IMPT, USPT, and IMRT.

Table 3. Conformity indexes (CI) and homogeneity indexes (HI) were represented for IMPT, USPT, and IMRT at PTV.

Patient	CI			HI		
	IMRT	USPT	IMPT	IMRT	USPT	IMPT
1	1.40	1.31	1.16	1.09	1.05	1.04
2	1.18	1.32	1.19	1.09	1.05	1.04
3	1.05	1.16	1.19	1.04	1.06	1.04
4	1.13	1.25	1.12	1.05	1.05	1.02
5	1.08	1.30	1.12	1.05	1.05	1.03
6	1.10	1.51	1.14	1.05	1.04	1.04
7	1.05	1.07	1.18	1.05	1.08	1.05
8	1.18	1.92	1.27	1.06	1.05	1.04
9	1.02	1.15	1.19	1.06	1.08	1.03
10	1.18	1.12	1.34	1.05	1.06	1.07
Mean	1.14	1.31	1.19	1.06	1.06	1.04

Table 4. NTCP values for the rectum and bladder of 10 patients.

Patient	Rectum (%)			Bladder (%)		
	IMRT	USPT	IMPT	IMRT	USPT	IMPT
1	3.823	5.510	2.460	0.000	0.001	0.000
2	3.598	4.492	1.429	0.000	0.000	0.000
3	1.387	1.429	1.243	0.000	0.000	0.000
4	2.919	4.710	2.106	0.000	0.000	0.000
5	2.192	5.042	2.403	0.000	0.000	0.000
6	2.523	2.888	1.946	0.000	0.000	0.000
7	0.388	0.718	0.593	0.000	0.000	0.000
8	0.388	0.718	0.593	0.000	0.000	0.000
9	1.380	3.926	1.739	0.074	0.028	0.023
10	3.728	3.822	2.498	0.000	0.000	0.000
Mean	2.233	3.326	1.701	0.008	0.003	0.002

NTCP: normal tissue complication probability.

slightly. The highest dose was 78.5 Gy for the 7-field step and shoot IMRT plan. The mean dose within the PTV was 72.0 Gy. USPT achieved a dose distribution in the PTV closest to the objectives, with a mean dose of 72.6 Gy and a maximum dose of 76 Gy. IMPT had a maximum dose of 71.6 Gy and a mean dose of 73.6 Gy (Table 3). The CIs and HIs for PTV are given in Table 3. The target dose conformity was determined by comparing the PTV volume with the volume encompassed by the 95% isodose body. The mean CIs were 1.14, 1.31, and 1.19 for IMRT, USPT, and IMPT, respectively. The IMRT dose distributions were more conformal to the target. The mean HIs for IMRT, USPT, and IMPT were 1.06, 1.06, and 1.04, respectively.

2. Rectum and bladder

The principal objective of these plans was to attain similar PTV coverage, which could increase high dose rectal exposure. The average DVH for the rectums of all 10 patients is shown in Fig. 2b. The IMPT plan was the most proficient in sparing the rectum. For doses less than 34 Gy, USPT gave lower dose to the target than IMRT. For doses more than 34 Gy, however, USPT delivered the higher dose. The mean doses for IMPT, USPT, and IMRT were 23.7 Gy, 32.5 Gy, and 36.1 Gy, respectively. Fig. 2c shows the DVH curves for the bladder. The highest mean dose to the bladder was 29.7 Gy from IMRT. The lowest mean dose to the bladder was 23.7 Gy from IMPT. USPT gave a mean dose of 25.5 Gy. The dose sparing qualities of IMPT are apparent, particularly when comparing this dose distribution to step and shoot IMRT and USPT plans. NTCP was calculated for the rectum and bladder (Table 4). The NTCP of the rectum was 2.233, 3.326 and 1.701 for IMRT, USPT, and IMPT, respectively. The NTCP of the bladder was 0.008, 0.003, and 0.002, respectively. NTCP at the rectum and bladder were lowest for IMPT.

3. Femoral heads

IMRT delivered the lowest dose to the right and left femoral heads comparing USPT and IMPT (Fig. 2d). Also, IMRT delivered a mean dose to the femoral heads of 13.4 Gy and a maximum dose of 42.7 Gy. The highest mean exposure was due to USPT (27.5 Gy). Using a variety of angles between the IMRT beams meant no beam passed directly through the femoral heads, unlike the proton plans. Despite the lower mean dose of IMPT (18.9 Gy) compared to USPT (27.5 Gy), the maximum dose of IMPT in the femoral heads was approximately 10 Gy higher for USPT. USPT gave higher levels of low dose exposure principally due to the beam arrangement. Despite this, USPT at doses above 30 Gy exposes the smallest volumes.

DISCUSSION

Several randomized prostate cancer trials have shown that higher doses are associated with significantly improved biochemical control.[16-18] High radiation doses, however, are lim-

ited by the risk of chronic rectal and bladder toxicity.[19,20] Proton therapy has been proposed to deliver elevated doses with potentially lower toxicity to normal surrounding structures. Yet, few reports have compared the dosimetric qualities.[4,21]

Vergas compared dose-volume between proton therapy using double scattering and IMRT for prostate cancer.[21] This study involved examining treatment plans generated for 10 prostate cancer patients. The IMRT plans generated by Vargas used 5 fields. With these plans PT gave a better whole dose than IMRT in the PTV and achieved values closer to the prescribed dose. In contrast to our results, the rectal DVH curve for PT was significantly lower than the IMRT curve for all doses $>$ 80 Gy.

Trofimov[4] showed that IMRT achieved spared the bladder significantly better than 3D double scattering proton therapy, while rectal sparing was similar. The dose to the rectum and bladder could also be reduced with IMPT compared to double scattering proton therapy due to better penumbra characteristics of the lower energy beams. USPT has a large irradiation field and a long-range and large SOBP, and can improve the beam utilization efficiency more than conventional passive double scattering proton therapy with a scanning proton beam. Although several planning studies have been reported for prostate patients, none compared IMPT and USPT.

Although proton therapy appears to be promising to reduce toxic effects, we also face a clinical challenge with dose-escalated radiotherapy using proton therapy. Because of a limited number of treatment fields, delivering ablative doses to targets with complicated shapes or locations, such as tumors curved around sensitive critical structures, is difficult using USPT, as shown in this study. In such cases, compromised dose coverage using optimized IMPT has to be considered to avoid damaging critical normal tissue structures. IMPT using scanning beam therapy can simultaneously optimize the intensities and the energies of all pencil beams using an objective function that account for targets and normal tissue constraints. IMRT plans also can generate irregular shapes of dose distributions by optimizing beam weights and segment weights among multiple beams arranged around PTV. Even for IMPT, multiple beam arrangements should be used by rotating gantry to obtain the best dose distribution. Cella et al[12] used the same 5-beam arrangement for IMPT as IMRT. While the present study uses parallel opposed 2 fields for IMPT, the “concave” dose distributions can be obtained by parallel lateral 2-field arrangement with optimization.

Uncertainty in the particle penetration depth is one of the main factors limiting sparing of healthy tissue with proton therapy. Currently, standard proton treatments for prostate cancer employ parallel-opposed lateral beams, which are considered the least affected by proton range uncertainty. A lateral approach is associated with the largest radiological depth of the target, thus, higher scatter and a wider dose penumbra. Improving range verification would improve proton dose conformity substantially, especially with the possibility to conform to the target proximally using IMPT. Improved dose conformity to the target, in turn, will make target dose escalation feasible while adequately sparing of healthy organs.

In this study, IMRT and IMPT produced equivalent dose distributions in the target volumes, though IMPT provided the best results overall. IMPT dose distributions in OARs were superior for doses from 0 to 60 Gy, in particular in the bladder and penile bulb, with a large benefit at lower doses. The probabilities of late complication, according to NTCP were similar for IMRT, USPT and IMPT. Therefore, we report that unoptimized proton therapy is not always superior to optimized photon radiotherapy, such as IMRT. The treatment technique (radiation source, optimization) should be selected intelligently based on the tumor and OARs to get most efficient treatment Because conformity and homogeneity for dose distributions are high, IMPT can be expected to be more sensitive to organ movement than the uniform scattering technique. Our study did not include effects due to prostrate movement. Although advanced planning and delivery methods, such as IMPT, often provide exquisite dose distributions, the practicalities of the delivery process must also be taken into account when assessing treatment plans.

CONCLUSION

Our study shows that using proton therapy, particularly IMPT, to treat prostate cancer could be beneficial compared to 7-field IMRT and USPT. Homogeneity in the PTV is better using IMPT. Optimized proton therapy also gave better sparing

of the bladder, rectum, and femoral heads, although rectal sparing was similar to IMRT and USPT at high doses. Improved protons techniques have the potential to greatly reduce the dose delivered to healthy tissue, possibly reducing second malignancies. Given these results, radiotherapy using protons, particularly IMPT, represents a worthwhile treatment option for prostate cancer.

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전립선 암 환자의 IMRT, USPT, 및 IMPT 기법에 따른 치료효과 비교

*한국과학기술원 원자력 및 양자공학과, †성균관대학교 의과대학 삼성서울병원 방사선종양학교실

손기홍*† · 조승룡* · 김진성† · 한영이† · 주상규† · 안성환†
신은혁† · 신정석† · 박 원† · 표홍렬† · 최두호†

본 연구는 총 10명의 전립선 암 환자를 대상으로 세기조절방사선치료(IMRT), 균일스캐닝양성자치료(USPT), 그리고 세기조절양성자치료(IMPT)기술을 이용한 치료계획의 결과를 비교, 평가 하였다. 각 치료 계획은 타깃 체적의 95%에 70 Gy가 28회 분할 조사되도록 하였으며 세기조절방사선치료(IMRT)에서는 step-and-shoot 기법을 이용하여 총 7개의 빔을 사용하여 방사선을 조사하였고, 균일세기양성자치료(USPT)와 세기조절양성자치료(IMPT)에서는 동일한 방사선 가중치의 측방향대향조사면(lateral opposing field)를 사용하여 타깃에 처방선량이 전달되도록 하였다. 한편, 세기조절양성자치료(IMPT)의 최적화를 위해 IMRT치료와 유사한 Inverse planning을 수행하였다. 결과 비교를 위해 타깃의 균질성지수(homogeneity index) 및 동형지수(conformity index)와 정상조직의 정상조직합병증확률(NTCP)을 계산하였다. 비록 치료기법간에 균질성지수(homogeneity index), 동형지수(conformity index)차이가 크지 않았지만, 직장의 경우 각 세기조절방사선치료(IMRT), 균일스캐닝 양성자치료(USPT) 및 세기조절양성자치료(IMPT)에서 2.233, 3.326 및 1.707로 계산되었다. 또한 방광의 정상조직합병증확률(NTCP)는 0.008, 0.003, 및 0.002를 나타내었다. 직장과 방광의 NTCP 값이 IMPT을 사용할 때 유의하게 낮은 값을 보이는 것을 확인하였다. 본 연구를 통해 전립선 암의 방사선 치료 시 세기조절방사선치료(IMRT)보다 양성자를 이용한 방사선 치료, 특히 최적화된 세기조절양성자치료(IMPT)가 치료 효과를 높일 수 있는 치료계획이 될 수 있음을 확인할 수 있었다.

중심단어: 세기조절방사선치료, 균일세기양성자치료, 세기조절양성자치료, 전립선암, 방사선치료계획