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Particle therapy

Helical tomotherapy and intensity modulated proton therapy in the treatment of dominant intraprostatic lesion: A treament planning comparison

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ABSTRACT

Purpose: To compare helical tomotherapy (HT) and intensity modulated proton therapy (IMPT) for prostate cancer irradiation while concomitantly boosting dominant intraprostatic lesions (DILs).
Methods and materials: Treatment plans of seven patients were designed for HT and IMPT (pencil beam size: 3 mm sigma). The prescribed median PTV/DIL doses were 71.4/100 Gy in 28 fractions, while satisfying "safe" dose constraints for organs at risks (OARs) including rectum, bladder, femoral heads, penile bulb and urethra. The planner could further reduce the dose to OARs if PTV/DIL constraints were reached.
Results: IMPT achieved better dose conformity (CI = 1.11 vs 1.31, $p < 0.05$) and coverage (V95% = 97.3% vs 95.3%, $p < 0.05$) in PTV. Concerning DIL volumes, both techniques delivered the prescribed dose (Dmedian: HT = 100 Gy, IMPT = 102.1 Gy) with similar dose conformity (CI: HT = 1.49, IMPT = 1.44) and same dose homogeneity, D99%, D1%, while satisfying the OARs constraints.
Excepting urethra, the sparing of OARs was significantly better with IMPT; in general, the lower the dose, the greater the benefit of IMPT. Normal tissue complication probabilities for the rectum were in favor of IMPT with an absolute reduction of 3–8%, depending on the NTCP model ($p < 0.05$).
Conclusions: Both techniques allowed delivering 100 Gy to DILs, while complying with the OARs constraints. IMPT was superior in sparing OARs for doses up to approximately 70 Gy, with larger benefit at lower doses.
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Prostate cancer is predominantly a multi-focal disease [1] and, consequently, the whole gland is traditionally irradiated. A higher treatment dose improves the biochemical control [2] but dose escalation to the whole prostate may be limited by the proximity of organs at risk (OARs) such as rectum and bladder.

Several investigations [3,4] have highlighted that local relapses after radiotherapy are mainly located in the so-called dominant intraprostatic lesions (DILs). There is therefore a rationale for selective dose escalation to DILs, typically identified via MRI techniques such as T2 weighted MRI [5] and diffusion-weighted MRI (DWI) [5,6], allowing a better sparing of OARs compared to the whole prostate dose escalation.

As local control could depend on radioresistant tissues within the DIL [7,8], the need for 2 Gy equivalent (EQD_2) doses in excess of 100 Gy was suggested [8].

Following a previous planning study assessing the potential of helical tomotherapy (HT) in achieving such dose levels [9], in this study we investigated whether proton therapy dose distributions delivered with pencil beam scanning (PBS) can at least match, and possibly improve, HT dose distribution for the treatment of prostate DIL.

Materials and methods

Patients and imaging

Seven consecutive patients (median PSA: 6.26 ng/ml; median age: 76 years) with intermediate/high risk prostate cancer previously treated at San Raffaele Scientific Institute with HT were considered. All patients underwent T2-weighted, T1-weighted and DWI MRI, which showed evidence of DIL in the peripheral zone. Patients had comfortably full bladder and empty rectum for CT and MRI acquisitions. CT (GE Medical Systems) and MRI (1.5-Tesla Achieva, Philips Medical System) images were performed with 4 mm and 3 mm slice thickness, respectively; details of MRI acquisition protocols and matching between MRI and CT images were previously reported [9].

Volumes of interest and planning objectives

For each patient, two clinical target volumes (CTV) were defined: CTVp (prostate plus seminal vesicles) and CTVDIL (intraprostatic lesions).

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CTVp had a planning target volume (PTV) generated with 8–8–10 mm expansion, in agreement with our clinical protocol [10,11]; PTVDIL was a 5 mm expansion of CTVDIL. A reduced margin was chosen in this case in order to limit the fraction of the rectum potentially exposed to very high doses as much as possible: the value of 5 mm was previously found to be as the "minimum" safe margin in the case of daily image-guidance with HT [9].

All CTVDIL volumes were located in the peripheral zone of the prostate, never in the middle of it: the minimum distance between rectum and DIL ranged between 0.7 and 22 mm (average value: 7.4 mm). Three patients had multi-focal disease but the PTVDIL was always a single one because the dominant lesions were close to one another.

The dose prescription was 71.4 Gy (2.55 Gy/fr) for the PTV volume not including PTVDIL and a median dose of 100 Gy (3.57 Gy/fr) for PTVDIL. The target volumes were to be irradiated simultaneously in 28 fractions, according to the protocol in use at HSR [10].

Planning objectives required that: (a) at least 95% of PTV, and possibly the 98%, received 95% of the prescribed dose, (b) 95% of the overlap volume between rectum and PTV received 64 Gy with an average dose of 65.5–66 Gy and (c) PTVDIL received a median dose of 100 Gy. Specific objectives of conformity and homogeneity were not defined for the DIL volumes.

The following organs at risk (OAR) were defined: rectum, bladder, urethra, femur heads and penile bulb. Urethra was manually drawn on each slice as an about 4 mm diameter circular structure with the center put in the center of the prostate.

The main limitation to dose escalation was the dose to OARs close to prostate and DIL volume (rectum, bladder and urethra). Due to the lack of detailed knowledge about the risk of very high doses (>80–90 Gy) to small volumes, we defined constraints for the OARs based on both external radiotherapy and brachytherapy practice, translating them with the linear-quadratic model to our daily dose scenario [9]. Table 1 shows a summary of the dosimetry constraints for the organs at risk.

In three patients the PTVDIL was overlapping with the rectum volume. In these areas, priority was given to the rectum constraints.

Additionally, the planner could further reduce to the OARs if all constraints were satisfied.

Planning and plan evaluation

HT plans were performed using a 2.5 cm field, pitch of 0.3 and modulation factor of 4.

IMPT plans were optimized with the Hyperion software [12]: they consisted of five fields (55°, 120°/130°, 180°, 230°/240° and 305° gantry angles). A pencil beam algorithm with heterogeneity and large-angle scatter correction was used for dose calculation [13]. Each proton pencil beam was assumed to have a gaussian shape in the transversal plane with a 3 mm sigma in air at patient entrance (regardless of beam energy). Initial energies could range from 65 to 240 MeV; 4 mm water equivalent distance between energy layers and a 5×5 mm scanning pattern was simulated. The proton plans were optimized assuming a constant relative biological effectiveness (RBE) of protons equal to 1.1. All proton doses are therefore in Gy equivalent (GyE). However, to improve readability, doses are indicated in Gy throughout the paper regardless whether they are from protons or photon plans.

DVHs were evaluated with the dosimetric indices of the clinical protocol plus additional parameters.

PTV dose homogeneity and dose conformity were quantified with an homogeneity index (HI) and a conformity index (CI). CI was calculated for PTV as $\frac{V_{67.8\ Gy\ WholeBody}}{V_{PTV}}$ and for PTVDIL as $\frac{V_{95\%\ PTVDILi\ in\ WholeBody}}{V_{PTVDIL}}$; HI was calculated for PTV as $\frac{D_{5\%\ PTV}-D_{95\%\ PTV}}{D_{prescription}}$ and for PTVDIL as $\frac{D_{5\%\ PTVDIL}-D_{95\%\ PTVDIL}}{D_{median}}$.

Since the rectal wall is the main organ at risk, rectal normal tissue complication probability (NTCP) values were calculated using three different sets of published parameters [14–16].

The statistical significance of the differences was assessed by Wilcoxon matched pair tests.

Results

Target volumes

In general, HT and IMPT generated satisfactory dose distributions in PTV and PTVDIL (see Fig. 1). Target coverage parameters for the PTV (V95% and D99%) were on average significantly better in IMPT. In all patients but one, D99% was in favor of protons by 1.5–3 Gy; V107% and D1% were in favor of IMPT by 0–6.5 Gy ($p > 0.05$) and 1.5–2.5 Gy ($p < 0.05$), respectively.

Both techniques reached a median PTVDIL dose of 100 Gy and similar conformity (CI: HT = 1.49, IMPT = 1.44) and homogeneity (HI: HT = 0.24, IMPT = 0.24), with protons showing about 1 Gy increase in all patients ($p < 0.05$).

In the overlap the average dose and D95% were within 1 Gy for all patients but in one, where they were in favor of protons by about 2 Gy. Tomotherapy plans showed a lower maximum dose ($p < 0.05$).

Further details of the average results for HT and IMPT for the most important dosimetric indices analyzed and the associated standard deviation (SD) for target volumes and overlap region are shown in Table 2.

Organs at risk

In all cases but one HT and IMPT plans complied with all OARs dose–volume objectives, except in one patient where HT slightly missed the rectal dose constraints for V70 and V80 (for more details on OARs dosimetric values see Table 2).

In general, the lower the dose, the larger the dosimetric benefit of IMPT: all Vx values from 0 to 70 Gy for all OARs showed a difference in favor of IMPT (the average DVHs of the OARs are shown in Figs. 3 and 4).

The largest differences between IMPT and HT were found for bladder and penile bulb. IMPT allowed in all patients a statistically significant bladder sparing up to 70 Gy, with an average reduction of the mean dose by 17.3 Gy (range 9–22 Gy, $p < 0.05$).

In the penile bulb, IMPT reached a statistically significant and large reduction of dose in all patients, with a decrease in mean dose ranging from 8.5 to 29 Gy. From 20 to 50 Gy, IMPT reduced the irradiated volume by 30–45% compared to HT ($p < 0.05$).

Table 1
Main dose objectives for the organs at risk.

Organ at risk	Objective
Rectum	V40 $\leqslant$ 60% V65.5 $\leqslant$ 20% 68.5 $\leqslant$ 5% V70 $\leqslant$ 2 cc V75 $\leqslant$ 1 cc Dmax $\leqslant$ 80 Gy
Bladder	V75 $\leqslant$ 0.1 cc As low as possible outside the PTV
Urethra	V80 $\leqslant$ 1 cc V90 $\leqslant$ 0.1 cc
Femur heads	Dmax $\leqslant$ 40 Gy
Penile bulb	V52 $\leqslant$ 50%