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Clinical Investigation

Ultrahypofractionated Proton Radiation Therapy in the Treatment of Low and Intermediate-Risk Prostate Cancer-5-Year Outcomes

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Purpose: To analyze the 5-year biochemical disease-free survival (bDFS) and late toxicity profile in patients with prostate cancer treated with pencil beam scanning (PBS) proton radiation therapy.

Methods and Materials: Between January 2013 and March 2016, 284 patients with prostate cancer were treated using intensity modulated proton therapy (IMPT), with an ultrahypofractionated schedule (36.25 GyE in 5 fractions). Five patients were immediately lost from follow-up and thus were excluded from analysis. Data for 279 patients were prospectively collected and analyzed with a median follow-up time of 56.5 (range, 3.4-87.5) months. The mean age at time of treatment was 64.5 (40.1-85.7) years, and the median prostate-specific antigen (PSA) value was 6.35 μg/L (0.67-17.3 μg/L). A total of 121 (43.4%) patients had low-risk, 125 patients (44.8%) had favorable, and 33 (11.8%) unfavorable intermediate-risk cancer. In addition, 49 (17.6%) patients underwent neoadjuvant hormonal therapy, and no patients had adjuvant hormonal therapy. bDFS and late toxicity profiles were evaluated.

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Results: The median treatment time was 9 days (range, 7-18 days). The 5-year bDFS was 96.9%, 91.7%, and 83.5% for the low-, favorable, and unfavorable intermediate-risk group, respectively. Late toxicity (Common Terminology Criteria for Adverse Events v.4) was as follows: gastrointestinal: grade 1, 62 patients (22%), grade 2, 20 patients (7.2%), and grade 3, 1 patient (0.36%); genitourinary: grade 1, 80 patients (28.7%), grade 2, 14 patients (5%), and grade 3, 0 patients. PSA relapse was observed in 17 patients (6.1%), and lymph node or bone recurrence was detected in 11 patients. Four (1.4%) local recurrences were detected. Nine patients (3.2%) died of causes unrelated to prostate cancer. No deaths related to prostate cancer were reported.

Conclusion: Ultrahypofractionated proton beam radiation therapy for prostate cancer is effective with long-term bDFS comparable with other fractionation schedules and with minimal serious long-term GI and GU toxicity.

Introduction

Proton radiation therapy is an accepted method in the treatment of prostate cancer. Compared with intensity modulated photon radiation therapy (IMRT), it has lower urogenital toxicity, lower rates of erectile dysfunction, and higher gastrointestinal (GI) toxicity.[1] Normofractionated or slightly accelerated proton radiation therapy is highly effective in the treatment of low- and intermediate-risk prostate cancer.[2,3] Most of the long-term data stems from the era of proton radiation therapy using the passive scattering (PS) technique.

Ultrahypofractionated photon radiation therapy has been used to treat prostate cancer for many years, and its effectiveness is high with low late toxicity rates.[4] Results of ultrahypofractionated radiation therapy were published many times (eg, Kishan et al[5]) and it can be considered a standard treatment approach as stated, for example, in the National Comprehensive Cancer Network (NCCN) guidelines.

During the last decade, proton radiation therapy using the pencil scanning technique (PBS) has begun to replace the PS technique. PBS achieves improved dose distributions over PS in various clinical situations owing to the application of a spot weighted dose.[6,7] This improved dose distribution also permits the use of PBS for ultrahypofractionated prostate cancer radiation therapy, while maintaining the principal advantage of proton radiation therapy (ie, lower integral dose and better sparing of critical organs in the range of medium to low doses). However, to date no comparison has shown a clinical advantage of PBS in prostate cancer compared with PS.

The use of a small number of therapeutic fractions helps solve 1 of the pitfalls of proton radiation therapy—its higher cost compared with IMRT. It also increases patient comfort and throughput within the radiation therapy department.

The aim of this work is to evaluate the therapeutic effectiveness and late toxicity profile in the first 279 patients treated with ultrahypofractionated proton radiation therapy between January 2013 and March 2016 in a prospective clinical registry.

Methods and Materials

The study was performed on the first 284 patients treated with proton radiation therapy for low- and intermediate-risk prostate cancer between January 2013 and March 2016. Five patients were lost to follow-up immediately after completing treatment and were thus excluded from analysis; 279 patients were analyzed. The study was approved by an institutional ethics committee and was conducted according to local ethical standards. All patients provided signed informed consent before inclusion in the clinical registry.

Patients with biopsy-confirmed low- or intermediate-risk prostate cancer were included in the study. Pretreatment clinical examination, prostate-specific antigen (PSA) collection, biopsy, and prostate magnetic resonance imaging (MRI) were performed. Bone scan or positron emission tomography/computed tomography (PET/CT) with F-choline was performed at the discretion of the attending physician. A baseline PSA <15 μg/L was chosen as an inclusion criterion to reduce the risk of including patients with subclinical metastatic disease. Furthermore, patients whose planning target volume (PTV) volume exceeded 150 cm^3 at planning time were excluded from the ultrahypofractionated regimen. These patients were treated with a slightly accelerated regimen of 63 GyE in 21 fractions and are not included in this study. No International Prostate Symptom Score exclusion criteria were used.

Neoadjuvant hormonal therapy was indicated only in patients with intermediate-risk prostate cancer based on the decision of the referring urologist or attending radiation oncologist, and our protocol considers this approach to be optional in this group. Follow-up time was determined as the time from the last fraction of radiation therapy to the last follow-up visit. Follow-up was based on monitoring the PSA level at regular 3- to 6-month intervals and was performed within our facility.

Acute and late toxicity were evaluated based on Common Terminology Criteria for Adverse Events v. 4.0. Any medication or argon laser coagulation after 3 months was considered as grade 2 late toxicity. The Phoenix criterion of biochemical failure was used. Pelvic MRI and PET/CT

scan with F-choline for recurrence localization were performed in the case of biochemical failure (nadir PSA + 2 ng/mL). Demographic and treatment parameters are shown in Table 1.

Planning procedures

All patients underwent transrectal insertion of 3 fiducial markers (GoldAnchor, Naslund Medical AB, Huddinge, Sweden) into both lobes of the prostate before planning CT; these were used for image guided radiation therapy (IGRT). MRI was performed for fusion with CT and contouring for the vast majority of patients. Patients were treated in the supine position. Whole-body fixation with a BlueBag (Elekta, Stockholm, Sweden) vacuum mattress was used for immobilization during the initial period; however, starting in 2014, Pelvicast (Orfit Industries, Wijnegem, Belgium) fixation was used. Planning CT was performed with 2.5-mm slice distance. Patients were instructed to follow a bloating diet regimen very carefully for planning CT and for all radiation therapy fractions, to take mild laxatives, and to follow the same bladder filling. Rectal balloons, spacers, and rectal saline instillation were not used.

Contouring

Contouring was performed using Focal software (Elekta, Sweden). The prostate was first contoured on MRI scans, and the contour was adjusted on CT images. Organs at risk were contoured: bladder, bladder wall (outer contour minus 5-mm thickness, intentionally overestimated for safety reasons), rectum (within 1 cm up and down in the craniocaudal direction away from the PTV), bulbus of the penis, and femoral heads. Furthermore, fiducial markers were contoured. The prostate was considered the gross tumor volume (GTV), and a clinical target volume (CTV) was not defined for low-risk prostate cancer. For intermediate-risk prostate cancer, CTV was generated by 5-mm GTV expansion with exclusion of the rectum and bladder and in such cases included the proximal 5 mm of seminal vesicles. The PTV margin was 5 mm in all cases.

Treatment planning/dose prescription

The treatment plan consisted of 2 opposite laterolateral fields (left-side and right-side field). Each field delivered exactly half of the prescribed dose, and single field uniform dose (SFUD) optimization was used. The team found it to be the most robust solution. Moreover, these 2 opposite fields are robust enough to avoid range uncertainty. Planning objectives were

the volume of CTV receiving 36.25 GyE higher than 99% (CTV $D_{99\%}$ >36.25 GyE), PTV $D_{98\%}$ >36.25 GyE, and PTV maximum dose (D_{max}) ≤37 GyE. Organ at risk tolerance levels were as follows: rectum D_{mean} <27.5 GyE and D_{20ccm} <25 GyE; bladder wall D_{15ccm} <18.3 GyE; bulbus penis D_{3ccm} <30 GyE; and femoral head D_{3ccm} <30 GyE. The robustness of this planning approach was thoroughly evaluated at the beginning of this study by evaluating possible shift scenarios and range uncertainties (usually used evaluation of shifts of ±2 mm in all major axes and CT calibration curve shifts of ±3.5%). Used treatment plans are able to compensate for shifts up to 5 mm in each orthogonal direction. The IGRT approach for each fraction guarantees fulfilling the aforementioned presumptions of acceptable shift ranges. The total dose prescription was 36.25 GyE (physical dose 32.95 Gy) and was delivered in 5 fractions, every other day. The final dose distribution was very homogeneous, in each case up to ±5% of the prescribed dose.

Table 1 Demographic and treatment parameters of patient group

	n	%
N	279	100.0
Adenocarcinoma	279	100.0
Risk group 1, low risk*	121	43.4
Risk group 2, favorable intermediate risk*	125	44.8
Risk group 2, unfavorable intermediate risk*	33	11.8
T stage		
T1a-c	151	54.1
T2a-b	84	30.1
T2c	44	15.8
Gleason score		
7	69	24.7
<7	208	74.6
Not specified	2	0.7
PSA		
<10 ng/mL	232	83.1
10-20 ng/mL	47	16.9
Neoadjuvant hormonal treatment†	49	17.6
Adjuvant hormonal treatment	0	0.0
Radiation therapy, total dose (GyE)	36.25	100.0
Radiation therapy, overall treatment time, median, d	9	
Radiation therapy, overall treatment time, range, d	7-18	

Abbreviation: PSA = prostate-specific antigen.

* Risk group (according to National Comprehensive Cancer Network).

† Neoadjuvant hormonal treatment (androgen therapy—Luteinizing Hormone Releasing Hormone analog, androgen).

Set-up procedures

All patients underwent x-ray imaging in 2 orthogonal planes before each fraction. In the first step, position was corrected for bone structures and treatment couch adjustments were performed. The position of fiducial markers on

the planning CT and on current images then was evaluated. If the difference in position was less than 5 mm, a second correction of the table position according to fiducials was performed. If the displacement was greater than 5 mm, irradiation was not performed and the patient was advised to improve the recommended preparation (bladder filling, rectal emptying using glycerin suppositories) within 1 hour. Setup was repeated after that period.

Statistical analysis

Continuous and categorical data are summarized as medians with ranges and as frequencies with percentages, respectively. Biochemical disease-free survival (bDFS), overall survival (OS), and incidence of maximum cumulative late genitourinary/GI toxicities were estimated using the Kaplan-Meier survival curves and compared with the log-rank test. The Cox proportional hazards model was applied to analyze the impact of Gleason score, initial PSA value, age, T-stage, neoadjuvant hormonal treatment, and overall radiation therapy treatment time on bDFS. $P < .05$ was considered statistically significant. These statistical analyses were performed using R software.[8]

Results

Patients

The median follow-up period was 56.5 months (range, 3.4-87.5 months). A total of 252 (90.3%) patients had a follow-up of more than 48 months, and 121 (43.4%) and 158 (56.6%) of patients were classified as having low- and intermediate-risk prostate cancer according to NCCN, respectively. All patients were treated with a total dose of 36.25 GyE in 5 fractions. Mean and median overall treatment time was 10 and 9 days (range, 7-18), respectively. A total of 49 (17.6%) patients received neoadjuvant hormonal treatment, and no patients received adjuvant hormonal treatment.

Disease control

The 5-year bDFS was 96.9% (95% confidence interval [CI], 93.3-100.0), 91.7% (95% CI, 86.0-97.7), and 83.5% (95% CI, 71.1-98.1) for the low-, favorable intermediate-, and unfavorable intermediate-risk groups, respectively (Fig. 1A). Biochemical relapse was found in 17 (6.1%) patients. In patients with biochemical relapse, 4 recurrences were detected in patients with low-risk cancer (1 PSA relapse only, 2 metastases to the lymph nodes and 1 local relapse). A total of 13 recurrences were detected in the group of medium-risk patients (8 favorable intermediate risk and 5 unfavorable intermediate risk). Localization of relapses for favorable/unfavorable IMD risk patients were as follows: PSA relapse only, 2/1; lymph node, 1/1; lymph node plus bone, 4/1; local relapse, 1/1; and local relapse plus lymph node, 0/1. Five-year OS was 98.3% (95% CI, 96%-100%), 94.9% (95% CI, 91%-99%), and 100.0% (95% CI, 100%-100%) for the low, favorable intermediate-, and unfavorable intermediate-risk groups, respectively (Fig. 1B). Statistical analysis identified Gleason score and initial PSA value <10 μg/L as a significant prognostic factor for biochemical relapse. Age, T-stage, neoadjuvant hormonal treatment, and overall radiation therapy treatment time did not significantly influence bDFS (Table 2). During the follow-up period, 9 (3.2%) patients died; however, none died of prostate cancer.

Late toxicity

Cumulative grade 2 GI toxicity was observed in 20 (7.2%) patients and grade 3 GI toxicity in 1 (0.4%) patient (patient was without diabetes or anticoagulation treatment). The 5-year probability of grade 2+ GI toxicity was 7.8%. No grade 4 toxicity was observed. Most patients with grade 2 toxicity temporarily used local anti-inflammatory medications (corticoids or mesalazine). One patient with grade 3 toxicity experienced bleeding that required transfusion. In all cases, the toxicity was temporary and resolved within 3 years of the end of radiation therapy. The cumulative incidence of maximal GI toxicity is shown in Figure 2A.

Cumulative grade 2+ genitourinary toxicity was observed in 14 (5%) patients, and the 5-year probability of grade 2+ toxicity was 5.7%. No grade 3 or higher toxicity was observed. Most patients with grade 2 toxicity had new medication for weak urinary stream or urinary urgency. No patient was classified as having grade 2 bleeding toxicity. The cumulative incidence of maximal genitourinary toxicity is shown in Figure 2B.

Discussion

Comparison with photon SRT

A comparison of the treatment results of our group of patients with photon stereotactic radiation therapy is possible, for example, with a pooled analysis of 1100 patients published by King et al.[9] The estimated 5-year survival without biochemical relapse for low- and intermediate-risk disease was 95.2% and 84.1%, respectively. Late toxicity data are not available. However, the median follow-up was only 30 to 36 months. Five-year data published by Katz and Kang[10] reviewed a cohort of 477 patients with a median follow-up of 72 months—the 7-year bDFS for low- and intermediate-risk disease was 95.6% and 89.6%, respectively. Late toxicity was low, with grade 2 rectal and urinary toxicity of 4% and 9.1%, respectively, and grade 3 urinary toxicity of 1.7%. Most recently, Kishan et al[11] published results for 2142 patients treated with 33.5 to 40 Gy in 4 to 5 fractions. At median follow-up, 7-year bDFS for low-, favorable intermediate-, and unfavorable intermediate-risk patients was 95.5%, 91.4%, and 85.1%, respectively, with late grade 3+

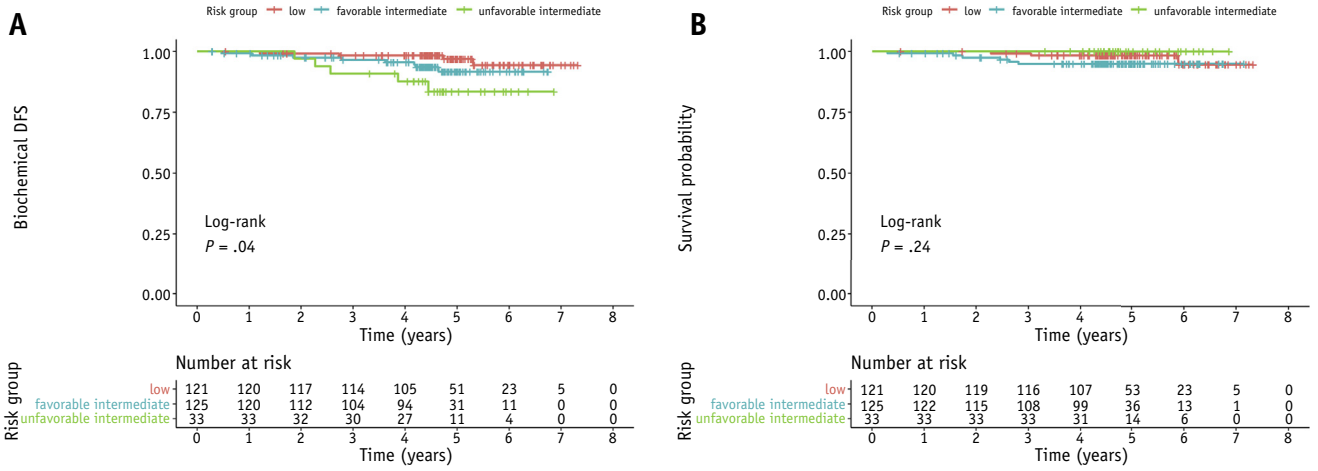

Fig. 1. Kaplan-Meier curves for biochemical disease-free survival (A) and overall survival (B). *Abbreviation:* DFS = disease-free survival.

genitourinary and GI toxicity of 2.4% and 0.4%. Compared with these results, in this work the presented bDFS is comparable with a favorable late toxicity profile.

Comparison with normofractionated or mildly accelerated proton radiation therapy

The results of proton radiation therapy in normofractionated or slightly accelerated schedules published by Bryant et al[2] showed that, at a median follow-up of 66 months, 5-year bDFS was 99%, 94%, and 74% for low-risk, intermediate-risk, and high-risk prostate cancer, respectively. Late grade 3 or higher toxicity was detected in 0.6% of patients for GI toxicity and 2.9% of patients for genitourinary toxicity. Similar results were published by Takagi et al,[3] who reviewed a cohort of 1375 patients treated with normofractionated proton radiation therapy at a dose of 74 GyE at a median follow-up of 70 months; 5-year bDFS was 98.7%, 90.8%, 85.6%, and 65.6% for low-risk, intermediate-risk, high-risk, and very high-risk prostate cancer, respectively. Grade 2+ toxicity was 4.1% for the GI tract and 5.4% for the genitourinary tract. Iwata et al[12] described a cohort of 1291 patients treated with fractionated proton radiation therapy (70-80 GyE in 35-40 fractions or 63-66 GyE in 21-22 fractions). With a median follow-up of 69 months, 5-year bDFS was 97%, 91.1%, and 83.1% for low-, intermediate-, and high-risk prostate cancer, respectively. Grade 2+ toxicity was 4.1% for the GI tract and 4.0% for the genitourinary tract. Grewal et al[13] published 4-year data for low- and intermediate-risk prostate cancer patients treated with 70 GyE in 28 fractions. They found 4-year bDFS of 94.4%, 92.5%, and 93.8% for low-, favorable intermediate-, and unfavorable intermediate-risk patients, with grade 2+ GI and genitourinary toxicities of 7.6% and 13.6%, respectively. The 5-year bDFS for our group of patients is comparable to published results, as is the GI toxicity rate. Genitourinary toxicity is lower in our group—the reason may be the use of PBS within our patient group instead of passive scattering, which was used in the publications by the aforementioned authors.

Table 2 Data analysis of factors influencing outcome

Variable	Value	No. of patients	HR	95% CI	*P*
Initial PSA, ng/mL	<10	232			
	10-20	47	4.818	1.707-13.597	.003*
Gleason score	<7	208			
	7	69	3.205	1.142-8.990	.027*
Age, y	<65	149			
	65+	130	1.894	0.702-5.113	.207
Duration of RT, d	<10	142			
	10+	137	0.850	0.313-2.307	.750
Neoadjuvant	No	230			
Hormonal treatment	Yes	49	0.921	0.287-2.957	.889
T stadium	Stadium I	203			
	Stadium II	76	0.785	0.252-2.451	.677

Abbreviations: HR = hazard ratio; RT = radiation therapy.
* Statistically significant.

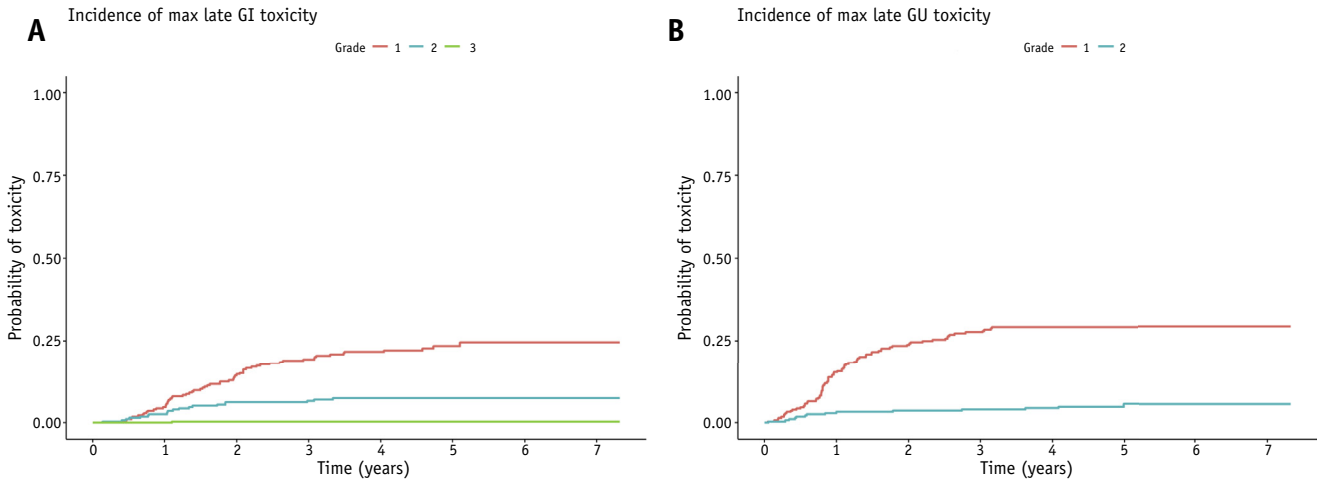

Fig. 2. Cumulative gastrointestinal (A) and genitourinary (B) toxicity. *Abbreviations:* GI = genitourinary; GU = genitourinary.

Comparison with accelerated proton radiation therapy

Comparison of treatment results with accelerated proton radiation therapy is possible when considering the work of Henderson et al.[14] However, this is only a slightly accelerated schedule of 70 GyE in 28 Fr. For 215 patients with a median follow-up of 5.2 years, the 5-year bDFS for low- and intermediate-risk patients was 98.3% and 92.7%, respectively. The genitourinary and GI grade 3+ toxicity was 0.5% and 1.7%, respectively. There are few publications describing the results of extreme proton hypofractionation in prostate cancer. Vargas et al[15] describe an initial comparison of toxicity and quality of life for extremely hypofractionated and normofractionated proton radiation therapy. When comparing a schedule of 38 GyE in 5 fractions and 79.2 GyE in 44 fractions, they had low toxicity in both arms and a temporarily worse genitourinary score in the ultrahypofractionated arm. To the best of our knowledge, this is the first time that 5-year results for ultrahypofractionated proton therapy have been published

Robustness of treatment plans

Using full IMPT planning techniques allows the creation of conformal dose distribution and achieves the most effective dose delivery to the treatment volume while minimizing the dose to surrounding tissues. Nonetheless, this solution is not necessarily best for clinical usage. Full IMPT plans tend not to be robust enough to account for patient setup errors, CT calibration uncertainty, and patient-setup protocol used. Taking into account these uncertainties results in significant perturbation of the planned dose distribution. Using the 2 opposite lateral fields with the SFUD planning technique is much more advantageous for prostate cancer irradiation. Kirk et al[16] evaluated the robustness of 2 SFUD lateral fields and found this solution to be extremely robust.

Comparison of pencil beam scanning and passive scattering

PBS is a promising method of proton delivery, but few clinical data about differences between PBS and PS are available for any clinical diagnosis. Chuaong et al compared the dosimetric differences between PBS and PS in pancreatic cancer and found only better PTV coverage.[17] Yoo et al compared the clinical results between PS and PBS in hepatocellular carcinoma and found no differences.[18] For prostate cancer, so far only Mishra et al[19] have performed such a comparison and found that acute genitourinary toxicity was significantly higher for PBS (21.9% and 15.1%; $P < .01$). Regarding the advantage of PBS in prostate cancer, it is necessary to wait for further data.

Intrafraction motion

Intrafraction motion of the prostate could pose a problem. Setup procedures at our center consist of patient fixation with a thermoplastic mask on the treatment couch, x-ray imaging from the side of the first irradiation field, and irradiation of the first field. Before delivery of the second field, the position of fiducials is verified again with x-ray imaging and position corrected as required, and only then is the second treatment field irradiated. The time between x-ray imaging is typically a few minutes. PBS has such good dosimetric parameters that it allows for the fulfilment of stereotactic constraints for critical organs even with larger PTV margins, in our case 5 mm. Xie et al[20] reported that 5-mm displacement of fiducials occurs in images taken after 120 seconds in 2.8% of patients, and Curtis et al[21] reported that, by using a 3-mm PTV margin, 95% of the target volumes is covered after 240 seconds. Combined with thorough dietary preparation and properly instructing patients on the need for rectal emptying, this approach appears to be sufficient.

Dose homogeneity in PTV

Another possible drawback may be the use of a schedule commonly used for stereotactic photon radiation therapy without correction for inhomogeneous dose distribution, which is typical for photon SBRT due to dose prescription to 75% to 85% isodose. Dosimetric comparison of proton passive scattering and photon SBRT was performed by Kole et al.[22] They found that the dosimetric parameters V90%, V100%, V105%, and D_{mean} for PS and SBRT are 99.8% versus 99.99%, 95.9% versus 95%, 21.99% versus 78.99%, and 37.6 Gy versus 39.6 GyE. Due to the high degree of local control achieved at these doses, this dose difference between PBS and the photon SRT is unlikely to play a role.

In the discussion about dose homogeneity, LET-based variability of RBE should be mentioned. Model-based calculations[23] suggest that equivalent dose may be changed owing to LET dependence, manifested especially in tumors with low α/β. This dependency is, however, in the early stage of research, and therefore no compensation for this effect was taken into account.

Study strengths and limitations

One limitation of this study is possible selection bias due to the different approach of patients to proton radiation therapy, considering their socioeconomic status, which is generally higher than within the general population. Another limitation is the lack of data on quality of life before and after treatment and the effect of treatment on patients' sexual activity (reported only as feedback from patients). Another limitation is the possible overestimation of local control. In PSA relapses, the localization of relapse was determined using PET/CT; however, prostate biopsies were not performed. The strength of the study is the homogeneity of the group of patients who were treated in 1 institution according to the same treatment and follow-up protocol, which did not change over time. Another strength of the study is the fact that the treatment was managed by our facility even after the completion of radiation therapy, and treatment results were not affected by the application of adjuvant hormonal therapy.

Conclusion

Ultrahypofractionated proton radiation therapy using the PBS technique is highly effective in the treatment of low- and intermediate-risk prostate cancer, with a favorable profile of late GI and genitourinary toxicity. The use of this fractionation scheme increases the treatment capacity of proton therapy facilities for these patients; increases, in our experience, the acceptance of this treatment by care providers; and thus increases overall the availability of proton radiation therapy to patients. However, more patients and longer follow-up times are needed to confirm these data.

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