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Morbidity dynamics in proton–photon or photon radiation therapy for locally advanced prostate cancer

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ABSTRACT

Aim: This study evaluated the frequency and long-term dynamics of early and late post irradiation damage after proton–photon or photon therapy for locally advanced prostate cancer.

Background: The results of a randomized study of proton–photon or photon therapy using several fractionation regimes were analyzed in 272 patients with high and intermediate risk of progression.

Materials and methods: Three variants of proton boost fractionation were studied sequentially: 3.0 (8 daily fractions), 4.0 (5 fractions, 3 or 5 fractions/week), and 5.5 (3 fractions, 3 fractions/week) Gy(RBE).

Results: A significant decrease in the severity of both acute and late gastrointestinal injuries is achievable with a proton beam. The dynamics of late gastrointestinal and genitourinary toxicity over a 10-year period were generally characterized by a decrease in severity of morbidity by 30% and 15%, respectively.

Conclusions: Local irradiation with a fractional dose of 3.0–5.5 Gy(RBE) and a cumulative dose of 28.0–28.8 Gy(RBE) for protons significantly reduces the early and late rectitis severity, but does not reduce the risk of lower urinary tract injuries. Fractionation regimens do not significantly differ in toxicity levels.

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1. Background

High-dose external radiation therapy is a widely used and evolving treatment method for locally advanced prostate cancer. One of its most advanced modalities, proton therapy, is the subject of ongoing research at major centers, mainly in the USA and Japan.[1–4] At the same time, active search is being performed to increase the therapeutic interval using various hypofractionation models.[5–11] However, it is impossible to adequately determine the treatment interval without a thorough understanding of the acute and late toxicities of new treatment methods. In addition, there has been significant interest in identifying new ways to predict the frequency and severity of post irradiation injuries, including our previously applied clinical-dynamic method.[12] The unique feature of this method is the continuous monitoring of the rate of progression and the reduction of early and late post irradiation injuries.

2. Aim

We used this approach for a comparative evaluation of the quality of new hypofractionated proton–photon methods and traditional photon irradiation in prostate cancer patients with a high risk of pelvic lymph node involvement.

3. Materials and methods

The clinical efficacy of proton–photon irradiation using various methods of proton boost hypofractionation was evaluated in randomized studies.[1] Patient allocation to the main and control groups was performed according to arrival time for treatment.[2] This method of randomization was adopted due to the operating schedule of the Institute for Theoretical and Experimental Physics (ITEP) synchrotron: 3–4 cycles for 3 weeks during the calendar year, and intervals between cycles of 2–4 months. The main group was formed when the medical proton beam was operational. Patients received a preliminary photon dose of 44 Gy in 22 fractions to the small pelvis. Three variants of proton boost fractionation were studied sequentially: 3.0, 4.0, and 5.5 Gy(RBE).[3] New regimens were adopted no earlier than 3 years after initiation of a prior regimen, i.e., only after preliminary estimation of the severity of late toxicity. The control group consisted of all patients with locally advanced prostate cancer who were treated with standard conformal photon therapy.

From 2000 to 2011, 289 patients with T1-3N0-1M0 prostate cancer were included in the study. The main group consisted of 116 patients who had undergone combined proton–photon therapy and the control group consisted of 173 patients who had undergone standard conformal 8-field photon irradiation. In most cases, radiation therapy was preceded by 3–12 months of androgen deprivation.

3.1. *Methods of radiation therapy*

The main group received 4–6 field photon irradiation (1.2–6.0 MeV) to the entire volume of the small pelvis or only the prostate and seminal vesicles (this group only included those with T1-2N0-M0 disease, an initial prostate-specific antigen [PSA] level < 20 ng/ml, and a Gleason score ≤ 6), up to an overall dose of 44.0–46.0 Gy in 22–23 daily fractions. The overall dose of subsequent local proton therapy was 28.0–28.8 Gy(RBE) to the prostate in 8 daily fractions, with 3.0 Gy(RBE) in 46 patients, 5 fractions with 4.0 Gy(RBE) and 3 or 5 fractions/week in 44 patients, or 3 fractions with 5.5 Gy(RBE) and 3 fractions/week in 24 patients. Thus, considering the photon component, at $\alpha/\beta = 3$ Gy, the dose to the prostate was 72.8, 72.0, or 72.0 Gy(RBE). The prostate in the control group was irradiated with local 4-field photon boost, in 12–14 fractions at 2 Gy, up to 68.0–72.0 Gy.

Preliminary computed tomography (CT) was performed with intravenous contrast enhancement of the bladder. CT was performed from the anus to the upper border of the sacroiliac joint. Tumor volume planning was developed with a 5-mm margin from the target in the rectal zone and a 10-mm margin in the other zones. At the same time, in sagittal reconstruction, the geometrical center was established and its position was defined by the rectal marker (endostate). Three-dimensional (3D) planning was performed. Patients were irradiated with 2 lateral individual fields. Individual collimators made of Wood's lead-containing alloy were used.

The proton beam energy was 220 MeV. For 2D scanning, a water degrader with a changeable depth was used to create a spread-out Bragg peak. Dose inhomogeneity in the target generally did not exceed 5%.

To calculate equivalent doses, a linear-quadratic model was used with a modification by Withers et al.,[13] regardless of total irradiation time. The ratio α/β for a prostate tumor was defined as 3 Gy in 2000, i.e., at the beginning of the investigation, regardless of the tumor malignancy stage. RBE for protons was defined as 1.1.

Before every proton irradiation, after endostate was introduced into the rectum and the patient was immobilized on the table, X-ray positioning was performed until the desired relative positions of the marked beam center and the radiodense endostate marker were identified.

[1] According to the Decision of the Federal Service for Surveillance in Healthcare, Health Ministry of Russian Federation #NES-296(p)-06, Moscow leading medical institutions, among them P.A. Herzen Moscow Scientific and Research Oncological Institute, have a right to perform clinical investigations, among them clinical trials, at the ITEP Proton Therapy Center.

[2] According to the Federal law of the Russian Federation #323-FZ, all patients involved in the treatment gave their informed consent.

[3] Gy(RBE) – radiobiological equivalent of Gray, the unit of biological dose, previously Cobalt Gray equivalent GyE.

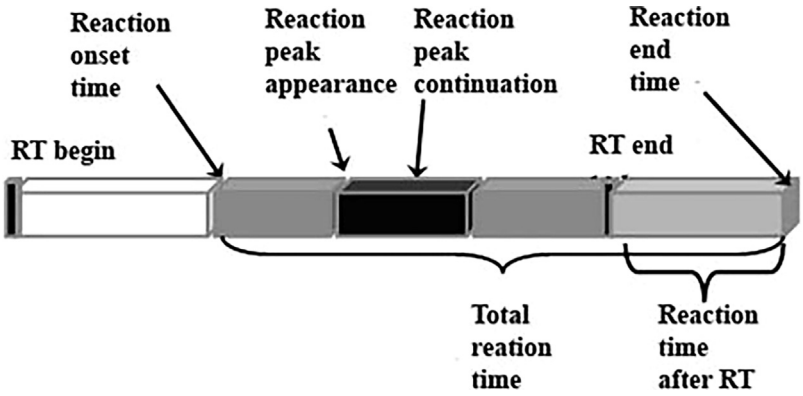

Fig. 1 – Clinical and dynamic methods of acute post irradiation injury evaluation: parameters (days) recorded during progressive gastrointestinal (GI) and genitourinary (GU) toxicity.

3.2. *Criteria of efficacy*

Treatment efficacy was defined by overall and recurrence-free survival and locoregional progression rate. Biochemical relapse was defined as an increase in PSA level higher than the nadir on 3 consecutive evaluations at 3–4 week intervals (the American Society for Therapeutic Radiology and Oncology criterion). Toxicity was evaluated using the standard Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer scale. For early complications we signed intensity, appearance time, duration of reaction peak, and time of reparation (Fig. 1). For late complications the degree of injury and its dynamics were examined.

3.3. *Statistics*

Statistical evaluations were performed with STATISTICA 6.0 (StatSoft Inc., USA). For differences in validation criteria, Student's *t*-test and Fisher's *F*-test were performed. The actuarial survival and locoregional progression rate were calculated by means of the Kaplan–Meier method, and identification of independent prognostic factors and post irradiation injuries

Table 1 – Distribution of 272 patients with prostate cancer from the main and control groups according to separate prognosis factors.

Criterion		Group		Diff. reliability (p)
		Main (protons + phot.)	Control (photons)	
Mean age (years)		66.9 ± 6.4	69.0 ± 5.8	$p > 0.05$
Stage	T1N0M0	11.2 ± 4.1%	16.6 ± 4.7%	>0.05
	T2N0M0	41.1 ± 3.9%	39.3 ± 3.6%	>0.05
	T3-4N0M0	47.6 ± 3.6%	44.0 ± 3.4%	>0.05
	T2-3N1M0	6.1 ± 1.8%	5.1 ± 1.7%	>0.05
PSA	Mean init. (ng/ml)	28.7 ± 3.5	28.0 ± 2.7	>0.05
	pts with PSA > 50 ng/ml	15.8 ± 4.4%	11.4 ± 2.9%	>0.05
Gleason index (mean)		6.33 ± 0.12	6.31 ± 0.1	$p > 0.05$
Progress risk group	Low[a]	7.0 ± 3.1%	3.8 ± 1.2%	>0.05
	Intermediate[b]	36.0 ± 4.0%	46.5 ± 6.6%	>0.05
	High[c]	57.0 ± 5.2%	49.7 ± 5.0%	>0.05
Neoadjuvant HT	Carried out	95.4%	94.9%	>0.05
	Mean time (mon)	6.39 ± 1.0	6.37 ± 0.66	>0.05
Mean irradiation doses	Prostate	71.8 ± 0.1 Gy(RBE)	68.6 ± 0.4 Gy	**<0.01**
	Small pelvis	44.9 ± 0.4 Gy(RBE)	44.8 ± 0.3 Gy	>0.05
Without whole small pelvis irradiation		14.0 ± 4.2%	13.9 ± 3.0%	>0.05
Previous surgeries at urinary tracts	TUR	14.3 ± 4.1%	16.6 ± 4.7%	>0.05
	Adenomectomy	6.3 ± 3.3%	8.9 ± 2.8%	>0.05
	Cystostomy	2.7 ± 2.3%	5.2 ± 1.7%	>0.05
Observation median (months)	Group (at whole)	67.8 ± 3.1	71.6 ± 2.9	>0.05
	Boost: 3.0 Gy(RBE) × 8 fr	97.9 ± 2.1		
	Boost: 4.0 Gy(RBE) × 5 fr	56.4 ± 2.3		
	Boost: 5.5 Gy(RBE) × 3 fr	25.4 ± 1.8		

[a] T1-2N0, G < 6, PSA ≤ 10.
[b] T3N0, or G-6–7, or PSA-10–20.
[c] T4N0, T1-4N1, or G > 7, or PSA > 20.

were performed with the Cox regression model of proportional risks.

4. Results

No significant differences in patient distributions of tumor prevalence and other prognostic factors were noted, except for the equivalent local dose value, which was higher ($p < 0.05$) in the proton therapy group (Table 1).

4.1. *Acute toxicity*

Acute gastrointestinal (GI) toxicity of maximum grade 2 severity was a little lower in the main group after proton–photon therapy than in the control group (54.4 ± 5.4% vs. 69.2 ± 5.7%; $p < 0.01$). No grade 3–4 complications were observed in the main or the control group. No difference was found in the frequency and severity of acute genitourinary (GU) injuries in the proton–photon and photon therapy groups: 33.3 ± 4.6% vs. 36.1 ± 3.5%, respectively, for grade 2 severity, and 0% vs. 1.9 ± 1.8% for grade 3–4 severity.

With an increase in the fractional dose of local proton boost from 3 to 4 Gy(RBE), the frequency of acute grade 2 GI injuries significantly increased ($p < 0.05$) at first (from 41.3 ± 14.2% to 68.2 ± 13.7%, $p < 0.05$), but with further fractional dose escalation to 5.5 Gy(RBE) the frequency decreased (to 50.0 ± 20.0%, $p > 0.05$). The frequency of acute Gr.2 GU complications that depends on the proton boost fractionation regime is following: 30.4 ± 13.2% for 3.0 Gy(RBE), 38.6 ± 14.4% for 4.0 Gy(RBE), and 29.2 ± 18.1% for 5.5 Gy(RBE), ($p > 0.05$).

It should be noted that the use of a 4 Gy(RBE) fractional dose was initiated in daily irradiation mode. However, because the frequency of acute grade 2 rectitis increased to 88.2%, we were forced to change to a regimen with 3 fractions/week; this led to a reliable decrease in frequency to 55.6% ($p < 0.01$). A fractional dose of 5.5 Gy(RBE) was used only every other day.

4.2. *Late toxicity*

Late grade 2 GI injuries (generally presenting with rectal bleeding being stopped conservatively) were seen 3 times less often in the main group after proton–photon irradiation. Severe grade 3–4 injuries occurred in 1 patient in the main group and in 2 patients in the control group. GU injuries were seen with equal frequency after proton–photon and photon-only irradiation. Moreover, grade 3 or 4 injuries were diagnosed in 3 and 5 cases, respectively (Table 2).

Table 2 – Probability of progression and intensity of late gastro-intestinal (GI) and genito-urineal (GU) toxicity depending on irradiation method.

Treatment method	GI toxicity		GU toxicity	
	Gr. 2	Gr. 3–4	Gr. 2	Gr. 3–4
Protons + photons	10.2 ± 5.5%[a]	0.9 ± 1.7%	8.3 ± 5.0%	2.8 ± 2.6%
Photons	34.8 ± 7.4%[a]	1.3 ± 1.8%	9.1 ± 4.5%	3.8 ± 3.0%

[a] $p < 0.01$.

Table 3 – Mean values reduction of the late gastro – intestinal (GU) and genito – urineal (GI) morbidity during the whole observation period as a "reversibility" criterion at the proton–photon and the photon therapy of the prostate cancer.

Damages pattern	Group	Mean values of damage degree		Relative reduction
		Maximal	Final	
GI	Main (prot–phot)	0.49 ± 0.07	0.35 ± 0.06	28.6% ($p > 0.05$)
	Control (phot)	1.0 ± 0.07[a]	0.69 ± 0.06[a]	31.0% ($p < 0.01$)
	At whole	0.79 ± 0.06[a]	0.55 ± 0.05[a]	30.3% ($p < 0.01$)
GU	Main (prot–phot)	0.38 ± 0.07	0.30 ± 0.07	21.1% ($p > 0.05$)
	Control (phot)	0.43 ± 0.07	0.38 ± 0.06	11.6% ($p > 0.05$)
	At whole	0.41 ± 0.05	0.35 ± 0.05	14.6% ($p > 0.05$)

[a] $p < 0.05$.

The proton boost fractionation regimen did not significantly affect the frequency or severity of late GI and GU complications, although the frequency of late grade ≥2 rectitis was appreciably lower with a fractional dose of 4 Gy(RBE): 2.4% for 4 Gy (RBE) vs. 17.8% for 5.5 Gy (RBE), ($p = 0.06$). Noticeable differences between groups with different regimes (Table 3) cannot be observed because the follow-up of these groups is not so far sufficient, although the advantage of proton boost over conformal photon radiation therapy seems obvious.

The long-term dynamics of late post irradiation injuries during the entire observation period (12–132 months) in the main and control groups are presented in Table 3 as a mean values reduction for late GU and GI injuries. The "maximum" level of an injury was accepted for the entire observation period, and the "final" level of injury was determined at the time of last follow-up.

Overall, the reversibility of late post irradiation rectitis injury after proton–photon and photon irradiation was comparable: the reduction rate was about 30%. The reduction of late complications in the lower urinary tract was not significant, i.e., 14.6% overall, but higher after proton–photon therapy (21.1% vs. 11.6%; $p > 0.05$).

Fig. 2 shows survival without GI and GU grade 3–4 complications in the main and control groups.

Despite the mean value of late complications decreased in the mean group (Table 3), the cumulative frequency of grade 3–4 morbidity increased. In the main and control groups, the cumulative actuarial frequency of GI and GU grade ≥3 complications increased equally, reaching 1.7% and 8.7%, respectively, at 10 years.

To determine the independent risk factors for severe (grade ≥ 3) post irradiation complications of the lower urinary tract, a Cox regression model was used (Table 4).

Thus, only prior prostate transurethral resection (TUR) significantly increased the progressive risk of severe (grade 3–4)

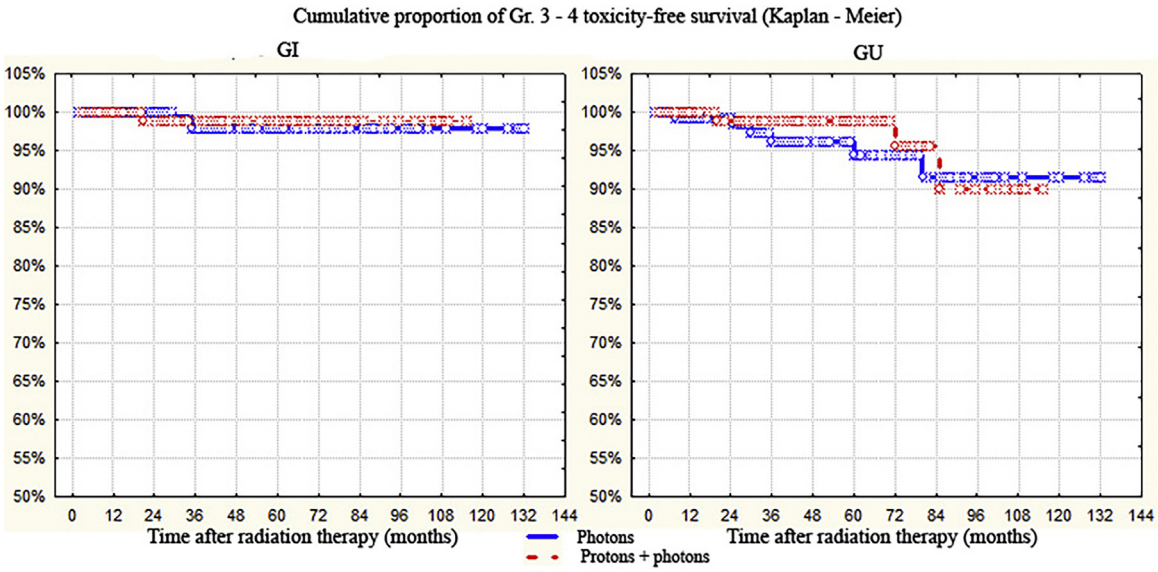

Fig. 2 – Actuarial survival without GI and GU grade 3–4 morbidity after proton-photon and photon therapy.

Table 4 – Influence of various factors on progress risk of late GU Gr. ≥3 morbidity.

Independent risk factors of GU Gr. ≥3 morbidity	Influence	Reliability level (p)
Age	No	0.59
Duration of neoHT (months)	No	0.24
Previous TUR (yes, no)	Yes	0.018
Intensity of acute post-irradiation GU morbidity (grade)	±	0.055
Appearance time of acute GU morbidity (days)	No	0.09
Appearance time of peak acute GU morbidity (days)	No	0.28
Duration of peak acute GU morbidity (days)	No	0.48
Recovery time from acute GU morbidity (days)	±	0.064
Disease relapse risk (yes, no)	No	0.47
Whole small pelvis irradiation (yes, no)	No	0.50
Group (main, control)	No	0.88

late GU morbidity. At the same time, the severity (grade 2 vs. grade 0–1) and repair duration (≥14 days vs. <14 days) following acute post irradiation cystitis-urethritis was significant on univariate analysis ($p < 0.05$). Other dynamic factors of acute toxicity, such as the reaction appearance time, and the duration of peak severity, had no prognostic significance. Due to the small number of cases (3), it was impossible to identify independent risk factors for severe (grade ≥ 3) late GI morbidity. At the same time, late grade 2 rectitis was consistently seen 1.2 times more frequently in patients with acute grade 2 rectitis than in those with less apparent acute changes ($p < 0.02$). Moreover, along with other dynamic factors of acute toxicity, the repair duration, in contrast with the GU morbidity, did not have any prognostic significance.

4.3. *Survival*

No reliable difference was found between recurrence-free and overall survival rates after proton–photon and photon only radiation therapy: the 5-year actuarial biochemical relapse-free survival rates in the main and control groups were 60.0 ± 5.4% and 61.9 ± 4.4%, and, for 10-year survival, the rates were 45.5 ± 8.5% and 42.8 ± 7.1%, respectively ($p > 0.05$). After 5 years, 74.0 ± 5.0% of patients were alive after proton–photon irradiation and 78.8 ± 4.1% were alive in the control group; after 10 years, the rates were 55.9 ± 9.0% and 60.6 ± 5.7%, respectively ($p > 0.05$).

The factors that significantly influenced recurrence-free and overall survival were the risk group ($p < 0.01$) and the duration of neoadjuvant hormone therapy ($p < 0.01$).

Proton boost (the fractional dose 3.0–5.5 Gy(RBE) and the overall dose 28.0–28.8 Gy(RBE)) that was added to photon irradiation of the entire small pelvis volume for locally advanced prostate cancer led to a significant decrease ($p < 0.05$) of acute and late post irradiation GI morbidity, and did not alter GU toxicity and antitumor treatment efficacy in comparison with traditional conformal photon radiation therapy.

Proton boost regimens of 8 daily fractions with 3 Gy(RBE), 5 every-other-day fractions with 4 Gy (RBE), and 3 every-other-day fractions with 5.5 Gy (RBE), did not significantly differ in toxicity level, but final conclusions about relatively late toxicity and antitumor efficacy of these regimens requires a longer observation period.

The dynamics of late GI and GU toxicity during a 10-year period were characterized by a decrease in the severity of morbidity by 30% and 15%, respectively. At the same time, against the background of generally positive dynamics that were largely determined by a reduction in toxicity of grade 1 or 2, an increase in the risk of grade 3–4 GU morbidity to 8% during the 10-year follow-up was observed. The cumulative rate of late GU morbidity in the same time interval did not change from a level of 1.5%. It is worth noting that practically

all cases of morbidity were associated with various mechanical (generally surgical) interventions in the lower urinary tract or rectum in the pre- or post irradiation period.

5. Discussion

Reports of the use of a proton boost after photon irradiation of the entire small pelvis are lacking. There were only few reported observations.[14] Obviously, it is very difficult to determine a marked gain with a proton boost after photon irradiation. Nevertheless, as our results show, a reliable decrease of both acute and late Gr.2 GI complications is achievable with the use of a proton beam. However, it should be stressed that this effect is only comparable with a 3D-conformal radiotherapy photon boost variant, and cannot be directly compared with intensity-modulated radiation therapy (IMRT). The modern technologies of pencil beam scanning (PBS) therapy and IMRT work better for further escalation of a fractional dose and of an overall local dose due to their precision in irradiation that allows an increase in the dose.

A reduction in severity of post irradiation injuries with adequate long-term observation has already been reported by some investigators.[6,14] Kupelian et al. reported that the grade ≥2 GI injury rate decreased two-fold over a 5-year period, from 11 to 5%, and that GU injuries decreased by one-third, from 12 to 8%.[6] Johansson et al. reported that in patients without urodynamic disorders before irradiation, the reduction in grade ≥2 GU injuries was more than 90% (from 13% to 1%) during the 3rd to 5th years of post irradiation observation. However, in the presence of initial GU single-level disorders, only one-half exhibited positive dynamics. But the grade ≥3 GU complications regressed insignificantly, from 10 to 8%.[14]

Our data indicate that after irradiation of the entire small pelvis by a proton technique or photon boost, the average GI and GU toxicity decrease over a 10-year period was 30% and 15%, respectively. The grade 1–2 injuries were reversible and mainly occurred during the second and third observation years. However, the grade ≥3 GU cumulative rate increased, reaching almost 9% in the 10th year. The analysis of all cases of grade 3–4 toxicity showed that mechanical trauma during the pre- or post irradiation period is the most important factor in late irreversible injuries, and the risk of occurrence does not decrease over time.

The role of previous trauma (particularly TUR) in the development of late GU injuries has been reported[15–17]; however, it remains unclear whether there was a correlation between the degree of increased risk and the fractionation regimen, and whether quantitative estimation of this risk in the context of the linear-quadratic model was possible. We did not observe an increase in late GU injury risk; rather, the nearly doubled reduction after a large fractional proton boost indirectly showed that the α/β value for tissues of the lower urinary tract did not decrease after trauma.

6. Conclusion

Local proton irradiation with a single dose of 3.0–5.5 Gy(RBE) and a cumulative dose of 28.0–28.8 Gy(RBE) significantly reduced early and late rectitis severity, but did not reduce the risk of lower urinary tract injuries. Different fractionation regimens did not significantly differ in toxicity levels.

Conflict of interest

None declared.

Financial disclosure

None declared.

REFERENCES

1. Mayahara H, Murakami M, Kagawa K, et al. Acute morbidity of proton therapy for prostate cancer: the Hyogo Ion Beam Medical Center experience. *Int J Radiat Oncol Biol Phys* 2007;**69**:434–43.
2. Nihei K, Ogino T, Onozawa M, et al. Multi-institutional phase II study of proton beam therapy for organ-confined prostate cancer focusing on the incidence of late rectal toxicities. *Int J Radiat Oncol Biol Phys* 2011;**81**:390–6.
3. Vargas C, Falchook A, Indelicato D, et al. Proton therapy for prostate cancer treatment employing online image guidance and an action level threshold. *Am J Clin Oncol* 2009;**32**:180–6.
4. 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.
5. Collins CD, Lloyd-Davis RW, Swan AV. Radical external radiotherapy localized carcinoma of the prostate using of the hypofractionated technique. *Clin Oncol* 1991;**3**:127–32.
6. Kupelian PA, Thakkar VV, Khuntia D, Reddy CA, Klein EA, Mahadevan A. Hypofractionated intensity-modulated radiotherapy (70 Gy at 2.5 Gy per fraction) for localized prostate cancer: long-term outcomes. *Int J Radiat Oncol Biol Phys* 2005;**63**:1463–8.
7. Leborgne F, Fowler J, Leborgne JH, Mezzera J. Later outcomes and alpha/beta estimate from hypofractionated conformal three-dimensional radiotherapy versus standard fractionation for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2012;**82**:1200–7.
8. Madsen BL, Hsi RA, Pham HT, Fowler JF, Esagui L, Corman J. Stereotactic hypofractionated accurate radiotherapy of the prostate (SHARP), 33.5 Gy in five fractions for localized disease: first clinical trial results. *Int J Radiat Oncol Biol Phys* 2007;**67**:1099–105.
9. Miralbell R, Mollà M, Rouzaud M, et al. Hypofractionated boost to the dominant tumor region with intensity modulated stereotactic radiotherapy for prostate cancer: a sequential dose escalation pilot study. *Int J Radiat Oncol Biol Phys* 2010;**78**:50–7.
10. Miralbell R, Roberts SA, Zubizarreta E, Hendry JH. Dose-fractionation sensitivity of prostate cancer deduced from radiotherapy outcomes of 5,969 patients in seven international institutional datasets: $\alpha/\beta = 1.4$ (0.9–2.2) Gy. *Int J Radiat Oncol Biol Phys* 2012;**82**:17–24.
11. Yeoh EE, Botten RJ, Butters J, Di Matteo AC, Holloway RH, Fowler J. 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.

12. Khmelevsky EV, Panshin G. Early radiation reactions of skin in patients with breast cancer: the modifying effect of retinol and neoadjuvant polychemotherapy. *Med Radiol Rad Saf* 1996:55–9 (Russian).
13. Withers H, Thames H, Peters L. A new isoeffect curve for change in the dose per fraction. *Radiother Oncol* 1983;**1**: 187–92.
14. Johansson S, Åström L, Sandin F, Isacsson U, Montelius A, Turesson I. Hypofractionated proton boost combined with external beam radiotherapy for treatment of localized prostate cancer. *Prostate Cancer* 2012;**2012**:14, http://dx.doi.org/10.1155/2012/654861. Article ID 654861.
15. Devisetty K, Zorn KC, Katz MH, Jani AB, Liauw SL. External beam radiation therapy after transurethral resection of the prostate: a report on acute and late genitourinary toxicity. *Int J Radiat Oncol Biol Phys* 2010;**77**:1060–5.
16. McGee L, Mendenhall NP, Henderson RH, et al. Outcomes in men with large prostates (≥60 cm(3)) treated with definitive proton therapy for prostate cancer. *Acta Oncol* 2013;**52**:470–6.
17. Sandhu AS, Zelefsky MJ, Lee HJ, Lombardi D, Fuks Z, Leibel SA. Long-term urinary toxicity after 3-dimensional conformal radiotherapy for prostate cancer in patients with prior history of transurethral resection. *Int J Radiat Oncol Biol Phys* 2000;**48**:643–7.