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Physician reported toxicities and patient reported quality of life of transperineal ultrasound-guided radiotherapy of prostate cancer

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A B S T R A C T

Purpose: This study aims to address therapy-related toxicities and quality of life in prostate cancer patients undergoing transperineal ultrasound (TPUS) guided radiotherapy (RT).

Methods: Acute and late gastrointestinal (GI) and genitourinary (GU) toxicities were assessed by physicians using CTCAE v5.0. Patient-reported quality of life outcomes were evaluated using EORTC QLQ-C30, -PR25 and IPSS. We utilized Volumetric Modulated Arc Therapy (VMAT) or intensity modulated radiation therapy (IMRT) as the RT technique for this study. The assessments were carried out before RT, at RT end, 3 months after RT and subsequently at 1-year intervals. Prostate-specific antigen (PSA) was also evaluated at each follow-up.

Results: In this study, a total of 164 patients were enrolled, while among them, 112 patients delivered quality-of-life data in a prospective evaluation. The median pre-treatment PSA was 7.9 ng/mL (range: 1.8–169 ng/ml). At the median follow-up of 19 months (3–82 months), the median PSA decreased to 0.22 ng/ml. Acute grade II GI and GU toxicities occurred in 8.6 % and 21.5 % patients at RT end. Regarding late toxicities, 2.2 % patients experienced grade II GI toxicities at 27 months and only one patient at 51 months, whereas no grade II GU late toxicities were reported at these time points. Quality of life scores also indicated a well-tolerated treatment. Patients mainly experienced acute clinically relevant symptoms of fatigue, pain, as well as deterioration in bowel and urinary symptoms. However, most symptoms normalized at 3 months and remained stable thereafter. Overall functioning showed a similar decline at RT end but improved over time.

Conclusion: The outcomes of TPUS-guided RT demonstrated promising results in terms of minimal physician-reported toxicities and satisfactory patient-reported QoL.

Introduction

External beam radiotherapy (EBRT) represents nowadays a mainstay for curative therapy of localized prostate cancer. Accurate localization of the prostate is critical for good clinical outcomes of radiotherapy (RT). In recent years, hypofractionated radiotherapy have been investigated in several phase 3 clinical trials, including CHHIP [1] and HYPRO [2] for moderate hypo-RT, as well as HYPO-RT-PC [3] and PACE-B trial [4] for ultra-hypo-RT. While non-inferiority of such concepts could be proven, higher single dose and longer irradiation time of each fraction require higher precise dose delivery techniques.

For that purpose, image-guided radiotherapy (IGRT) has been widely integrated in clinical routine, which improves the accuracy of radiotherapy and facilitates precise dose delivery [5]. Besides X-ray-based IGRT techniques, such as Cone-beam computed tomography (CBCT) and portal imaging, ultrasound imaging is an alternative option for IGRT of prostate cancer [6]. It provides better soft tissue contrast and was reported to be functionally equivalent to CBCT for inter-fractional prostate re-positioning [7]. Moreover, its latest generation Clarity® Autoscan Transperineal Ultrasound system (TPUS) is a non-invasive system, enabling to track intra-fractional prostate motion in real-time during treatment without additional exposure to ionizing radiations [8].

Several studies [9–11] have reported the initial experience with TPUS system and shown that, using phantom, the precision of TPUS

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exhibited high accuracy with a deviation of less than 1 mm under ideal conditions. It was further concluded that TPUS system represents a reliable method for IGRT for prostate patients [12,13]. Previously, our group also evaluated the TPUS system performance in patients under treatment and found that the system compared favorably with seed-match using CBCT for inter-fractional alignment [14]. Furthermore, some new observations of TPUS in clinical practice were found that moderate pressure should be applied to improve image quality and spare organs at risk [15]. In addition, the prostate intra-fractional motion can be modeled as a time-dependent "random walk" [16,17] and the corresponding prostate deviation is less with shorter fractions [18], which allows for better dose delivery during RT.

Given that TPUS system improves the accuracy of target does delivery and decreases extra dose on organs at risk, it is worthwhile to explore side effects and quality of life (QoL) in patients underwent TPUS-guided RT. However, previous studies have focused on the accuracy of TPUS system in clinical practice [19–21]. There is rare evidence for physician-reported toxicities and patient-reported QoL. In this manuscript, we reported acute and late toxicities and QoL of prostate cancer patients who received TPUS-guided RT.

Patient and methods

Patients

All prostate cancer patients treated with TPUS-guided radiotherapy between May 2016 and March 2023 in our department were included. All these 164 patients received radiotherapy of prostate and/or seminal vesicle without pelvic irradiation. Patients with positive nodal disease or distant metastasis were excluded.

We conducted QoL investigation in this study within a prospective clinical trial ''PANDORA'' (Prospective evaluation of the effectiveness and side effects of modern radiotherapy of prostate carcinoma) in which 112 patients were recruited. This trial was approved by the local institutional ethical committee on 01.08.2019 (No.19-351) and was conducted in accordance with the Helsinki Declaration in its current version.

Radiotherapy

Patients were treated with a 6MV linear accelerator (Elekta Synergy; Elekta, Stockholm, Sweden) in volumetric-modulated arc therapy (VMAT) or intensity modulated radiation therapy (IMRT) techniques. Positioning was performed by one of several trained users (two radiation oncologists and five radiotherapy technologists, all with user training courses for CBCT and TPUS). 126 patients received moderate hypofractionated radiotherapy (57–60 Gy in 19–20 fractions). 38 patients were treated with normo-fractionated RT (72–76 Gy in 36–38 fractions). The median dose for normo-fractionated RT is now reported as 76 Gy, while the median dose for moderately hypofractionated radiation therapy is reported as 60 Gy. The dose has been prescribed following the International Commission of Radiation Units (ICRU 83). The clinical target volume (CTV) to planning target volume (PTV) margin was 6 mm in all directions except posteriorly 3 or 5 mm. Androgen deprivation therapy (ADT) was prescribed to 70 out of 164 patients (42.7 %).

Image guidance procedure with CBCT and TPUS

To increase the daily reproducibility in terms of bladder and rectum, all patients underwent daily preparation protocol to ensure a moderately and comfortably filled bladder and an empty rectum before simulation and each treatment fraction. All patients underwent CT simulation with TPUS. Before each fraction, TPUS were performed following the initial alignment of skin marks to room lasers. Subsequently, setup errors were measured and calculated based on TPUS images. In addition, a CBCT scan was acquired immediately after TPUS registration. Daily manual image registration was preformed through visualization of the soft tissues in both TPUS and CBCT images. Fig. 1 shows a comparison of prostate position control using CBCT and TPUS.

For intra-fractional alignment, all patents used TPUS to monitor intra-fractional prostate motion with a 3 mm threshold, from its verified position in 3 degrees of freedom (anterior-posterior, superior-inferior, left–right). The TPUS automatic scan was acquired every 2–3 s during treatment. If the prostate motion exceeds the predefined threshold in any axis and persists more than 5 s, the system will issue an alert signal in workstation, turning off radiation beam automatically. After correcting the setup errors, radiation can proceed.

In terms of inter-fractional alignment, both CBCT and TPUS were used to control the first 84 patients. TPUS imaging was performed for each fraction while CBCT imaging was conducted daily for the first 5 fractions. When the deviation verified by TPUS and CBCT was comparable, then only TPUS was utilized to correct the inter-fractional error in subsequent treatment fractions. For the following 80 patients, compensation for inter-fractional setup error relied on CBCT imaging, which was conducted daily before each fraction.

Assessments and follow-up

Biochemical control

According to recommendation, patients underwent regular PSA measurements, commencing 6 weeks after RT and continuing every 3 months by his urologist. We gathered the latest PSA values at each follow-up time point for analysis.

Physician-reported outcomes: acute and late toxicities

Gastrointestinal (GI) and genitourinary (GU) adverse events were evaluated and scored by physicians, using the Common Terminology Criteria for Adverse Events (CTCAE v5.0). GI toxicities encompassed diarrhea, constipation, bloating, fecal incontinence and proctitis. GU toxicities included urinary tract pain, urinary frequency, urinary urgency, urinary incontinence, and urinary tract obstruction. Besides GI and GU, other toxicities were also taken into consideration, including fatigue, erectile dysfunction, and dermatitis.

Acute and late toxicities were defined as adverse events occurring within the first 90-days after RT and later, respectively. If a patient presented with the toxic event in the same domain several times, only the highest-grade event was counted.

Patient-reported outcomes: quality-of-life

Patient reported quality-of-life (QoL) outcomes were evaluated within a prospective clinical trial "PANDORA", which enrolled a total of 112 patients. Within this trail, patients were assessed using three validated QoL questionnaires: European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core Module (QLQ-C30), EORTC QoL Questionnaire Prostate Module (QLQ-PR25), and the International Prostate Symptom Score (IPSS). Each patient was requested to complete all these three questionnaires before RT, at RT end, 3 months after RT and subsequently at 1-year intervals, respectively. EORTC QLQ-C30 and -PR25 questionnaires enabled the assessment of diverse functions, with 100 representing the best and 0 the worst; and symptom scores, with 100 indicating the strongest and 0 the absence of symptoms. A minimal clinically relevant difference for each domain was defined as a change from baseline of at least 5 points [22]. 5–10 points changes from baseline were categorized as small, 10–20 points changes as moderate, or more than 20 points as large, following the criteria established by Osoba et al. [22]. The corresponding percentage of each category at follow-up was calculated. Specifically, the symptoms extracted from the QLQ-C30, and PR-25 subdomains were meticulously classified into three distinct groups: GI, GU, and other symptoms. IPSS is calculated as the sum scores of 7 questions, consisting of incomplete emptying, frequency, intermittency, urgency, weak stream, straining and nocturia. The scores range from 0 to 35, with high

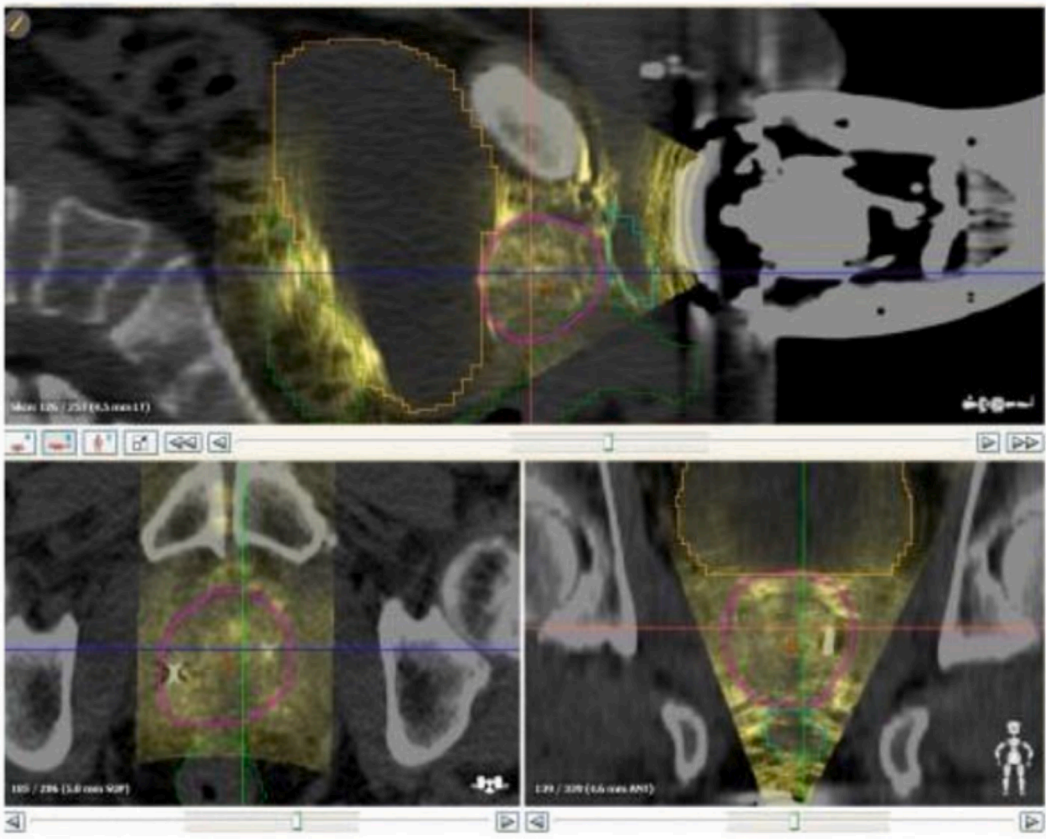

Fig. 1. Comparison of prostate position control using CB-CT and TPUS. This figure is based on previous work conducted by our team, published in 2016 [14].

scores indicating severe urinary symptoms.

Data analysis and statistics

Statistical analysis and plots were conducted using Microsoft Excel and PowerPoint, version 2010 (Microsoft Corporation, Redmond, WA, USA).

Results

Patient characteristics

Between May 2016 and March 2023, a total of 164 prostate patients underwent TPUS-guided RT were enrolled. Among them, a subset of 112 patients underwent QoL assessment, with an average response rate for questionnaires was 72 % (range: 62–84 %). A total of 3949 treatment fractions were performed, with 3133 fractions being monitored by TPUS. The median follow-up duration for all patients was 19 months (interquartile range: 12.75–30 months).

A detailed description of the clinical characteristics of patients at baseline is summarized in Table 1. All patients in this study exhibited an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. The median age was 75 years, ranging from 47 to 88 years. Additionally, 48.5 % of patients were classified as overweight based on the report of a WHO Consultation on Obesity [23]. Median initial prostate-specific antigen (iPSA) was 7.9 ng/mL (range: 1.8–169 ng/mL), and the median IPSS was 9 (range: 0–30) at baseline. Patients presented with low, intermediate, and high-risk advanced prostate cancer in 12.2 %, 50.6 % and 37.2 %, respectively. The median prostate volume was 36 cc (range: 21–160 cc).

Physician-reported outcomes: acute and late toxicities

Acute toxicities

Supplementary Fig. 5 provides an overview of prevalence of GI and GU toxicities at each follow-up. Before RT, no grade 2 GI and 6.1 % patients presented with grade 2 GU were reported. At RT end, 8.6 % grade 2 GI and 21.5 % grade 2 GU toxicities were observed, with one patient reporting grade 3 urinary frequency. At 3 months follow-up, no patient reported grade 2 GI and 11.8 % reported grade 2 GU.

Among all GI toxicities, grade 1 diarrhea and proctitis were the most frequently observed. The corresponding rates for grade 1 diarrhea was 3.7 %, 30.1 % and 9.2 % at baseline, at RT end and at 3 months after RT. Similarly, grade 1 proctitis were observed as 1.2 %, 23.3 %, and 9.8 % at these three time points, respectively.

In patients experiencing fatigue, most of them also reported grade 1, with 4.3 %, 27.0 % and 22.9 % at baseline, at RT end and at 3 months. Whereas grade 2 fatigue was observed in three patients at RT end and one patient at 3 months. An increasing trend of ≥grade 2 erectile dysfunction was observed, with 17.7 %, 24.0 % and 31.4 % at baseline, RT end and 3 months.

Late toxicities

Toxicities assessments up to 51 months showed minimal occurrence of ≥grade 2 GI and GU toxicities. At 51 months, only one patient reported grade 2 diarrhea, while no ≥grade 2 GU were reported. Throughout the late follow-up, the most commonly reported GU toxicity was the grade 1 urinary frequency, contributing to the high prevalence of GU toxicities. Complete details of acute and late toxicities at each time point can be found in Supplementary Table 1A./B. and Supplementary Figs. 1–3.

Table 1
General patient characteristics at baseline (n = 164).

Baseline characteristics of patients		
Characteristic	Number	%
Age (years)		
Median	75	
Range	47–88	
Body-Mass-Index (BMI)		
Median	25	
Overweight	80	48.5 %
T stage		
T1, T2a	109	66.5 %
T2b	13	7.9 %
T2c	22	13.4 %
T3	19	11.6 %
T4	1	0.6 %
N1	0	0.0 %
M1	0	0.0 %
ECOG		
0	146	89.0 %
1	18	11.0 %
IPSS		
median	9.00	
average	9.95	
iPSA (ng/ml)		
<10	102	62.2 %
10–20	48	29.3 %
>20	14	8.5 %
median iPSA	8.00	
Gleason score		
6	31	18.9 %
7a	80	48.8 %
7b	28	17.1 %
8	19	11.6 %
9/10	4	2.4 %
x	2	1.2 %
Risk group (D'Amico risk score)		
Low	20	12.2 %
Intermediate	83	50.6 %
High	61	37.2 %
Androgen-deprivation therapy		
yes	70	42.7 %
no	92	56.1 %
x	2	1.2 %
Prostate volume (ccm)		
median	36	
average	47.5	
Comorbidity		
Smoking	26	15.9 %
Anticoagulation	67	40.9 %
Diabetes mellitus	20	12.2 %
Hypertension	86	52.4 %
Cardiovascular medication	50	30.5 %
Symptomatic haemorrhoid	7	4.3 %
Inflammatory bowel disease	15	9.1 %
Previous pelvic surgery	39	23.8 %
Urinary track and bladder disorder	6	3.7 %
Hyperlipidemia	9	5.5 %
Hypercholesterolemia	38	23.2 %
Hyperuricemia	13	7.9 %
Allergy	40	24.4 %
Neurology	13	7.9 %
Respiratory diseases	19	11.6 %
Previous transurethral resection of prostate (TURP)	26	15.9 %
Prostatitis	16	9.8 %
Other cancer	19	11.6 %
Depression	6	3.7 %

Patient-reported outcomes: quality-of-life

QLQ-C30 and PR-25 function scores

The function scores of QLQ-C30 before RT were deemed satisfactory, as depicted in Fig. 2A. Generally, patients reported a slight decrease of all function scores at RT end, which partially recovered at 3 months. For instance, role functioning exhibited a noticeable decline at RT end, with a baseline score of 88.5 decreasing to 71.7. However, it subsequently recovered to 82.4 and remained stable in the following time. Similarly, global health status (GHS) also exhibited a similar dynamic (74.2, 63.8, 70.3, 70.0 and 71.9 at baseline, RT end, 3, 15 months and 27 months after RT). The baseline sexual functioning and activity scores were modest, probably attributable to the advanced age (median 75) and use of anti-hormone therapy (ADT) in 42.7 % patients. Sexual activity demonstrated normalization during the following months (Fig. 2B).

The changes in QLQ-C30 and PR-25 function and symptom scores, categorized as GI, GU symptoms, and other symptoms, from baseline to follow-up of 15 months and 27 months are presented in Fig. 3. The majority of patients reported no clinically relevant difference in QoL at these two time points. Fig. 4 provides summarized changes of QLQ-C30 and PR-25 function scores at RT-end, 15 and 27 months after treatment compared to baseline. The incontinence aid was excluded from this figure due to the small number of patients (n = 8) who utilized pads at baseline.

QLQ-C30 and PR-25 symptom scores

In general, the symptom scores of QLQ-C30 and PR-25 were sparse (range: 1.95–24.4) at baseline. At RT end, patients reported a discernible deterioration in almost all symptom scores and mostly recovered at 3 months after RT, while nausea and financial difficulties remained stable. (Fig. 2, C–E) A remarkable escalation in symptom scores was observed for diarrhea (score change: 26.5), utilization of incontinence aid (score change: 28.3), urinary symptoms (score change: 23.4) and fatigue (score change: 19.5) at RT end.

To facilitate the understanding of temporal evolution, Fig. 3(C–E) provided a visual representation of these changes. At the 15 and 27-months, the symptom scores remained stable after the initial recovery at 3 months. However, substantial impairments were observed specifically in hormonal treatment-related symptoms during the follow-up, probably attributable to the long-term use of ADT. Fig. 5 provides incidence of clinically relevant deterioration in partial typical symptom scores.

For this analysis, three time points were selected to represent the acute and late phase, with RT end representing the acute phase, 15 and 27 months representing the late phase. At RT end, 49.5 % of patients experienced large deterioration in fatigue, which decreased to 38.3 % at 15 and 36.8 % at 27 months. It is worth noting that the prevalence of large deterioration in bowel symptom decreased obviously in follow-up (27.3 %, 13 %, 6 % at baseline, at 15 and 27 months). Similarly, there was a decrease in moderate deterioration, with the corresponding percentage 21.6 %, 22 %, 6 % at these three time points.

Notably, large deterioration in urinary symptoms increased substantially at RT end, which dramatically declined to zero in follow-up. For hormonal treatment-related symptoms, most patients exhibited no difference and only small deterioration, in a total of 56 %, 55 %, 61 % at

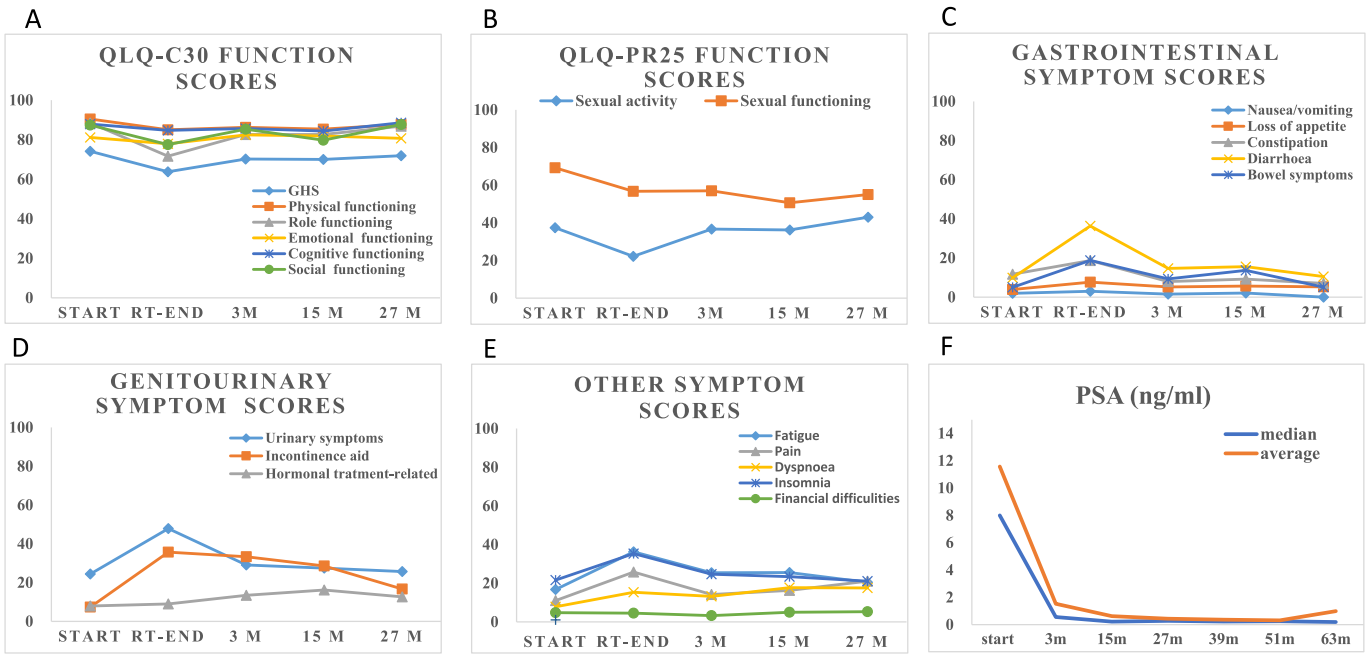

Fig. 2. PSA values and mean scores of the QLQ-C30 and PR-25 function and symptom scores (classified as GI, GU and other symptoms) at each follow-up time point. (A,B) derived from the QLQ-C30 and PR-25 function scores. (C,D,E) derived from QLQ-C30 and PR-25 symptom scores. (F) Change of PSA values over time. Abbreviation: PSA = Prostate Specific Antigen.

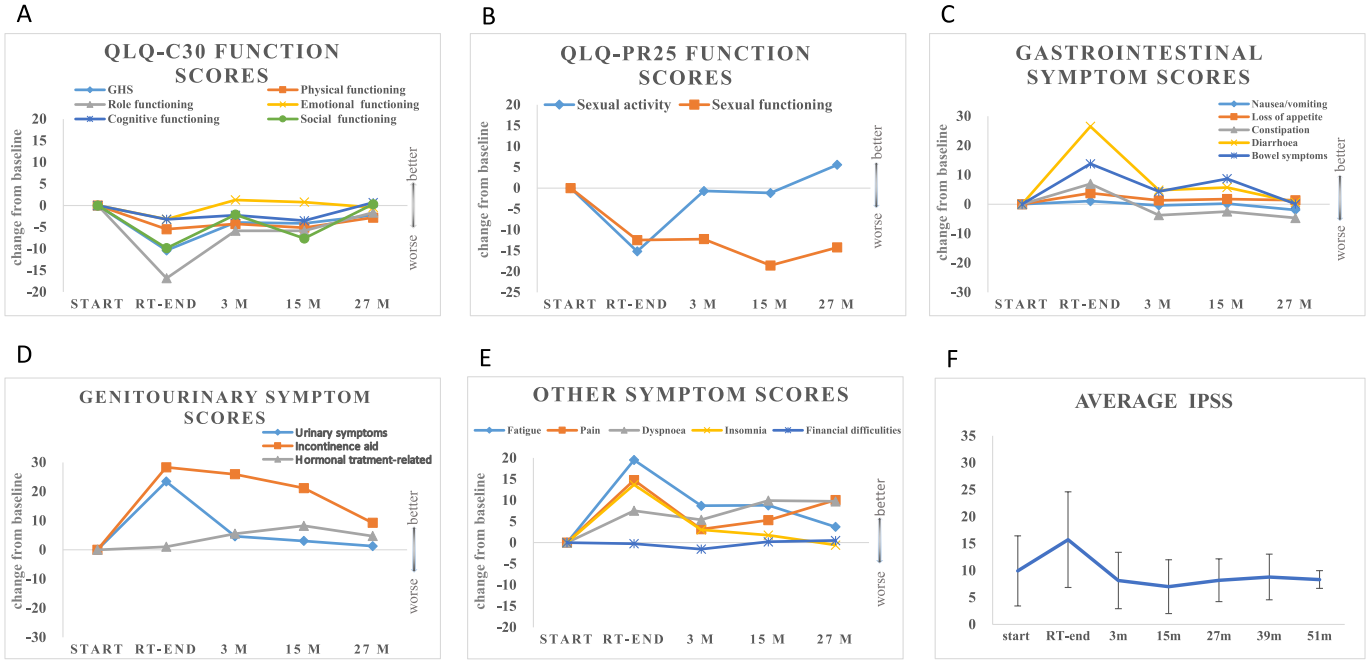

Fig. 3. IPSS values and change in QLQ-C30 and PR-25 functional and symptom scores (classified as GI, GU and other symptoms) at each follow-up time point. (A,B) derived from the QLQ-C30 and PR-25 functional scores. (C,D,E) derived from QLQ-C30 and PR-25 symptom scores. (F) Average IPSS values over time. Abbreviation: IPSS = International Prostate Symptom Score.

RT end, 15 and 27 months after RT. Intriguingly, constipation demonstrated improvement beyond baseline at 3 months and sustained thereafter (11.7 at baseline and 8.0 at 3 months). In addition, nausea/vomiting, and loss of appetite remained unaffected throughout the course of RT and the subsequent follow-up period.

The details of QLQ-C30 and PR-25 function and symptom scores were summarized in Supplementary Table 2/3. Respectively, the score changes of GI, GU, and other symptoms were compiled in Supplementary Table 4 and Supplementary Fig. 4.

International prostate symptom score (IPSS)

The average IPSS at baseline, at RT end, at 3, 15, 27, 39 and 51 months after RT were 9.0, 18.0, 8.5, 6.5, 9.0, 11.0 and 7.0, respectively (Fig. 3F).

Urinary symptoms exhibited a transient exacerbation, characterized by a discernible escalation in IPSS values at the end of radiotherapy, and returned to baseline levels within 3 months following the completion of radiotherapy.

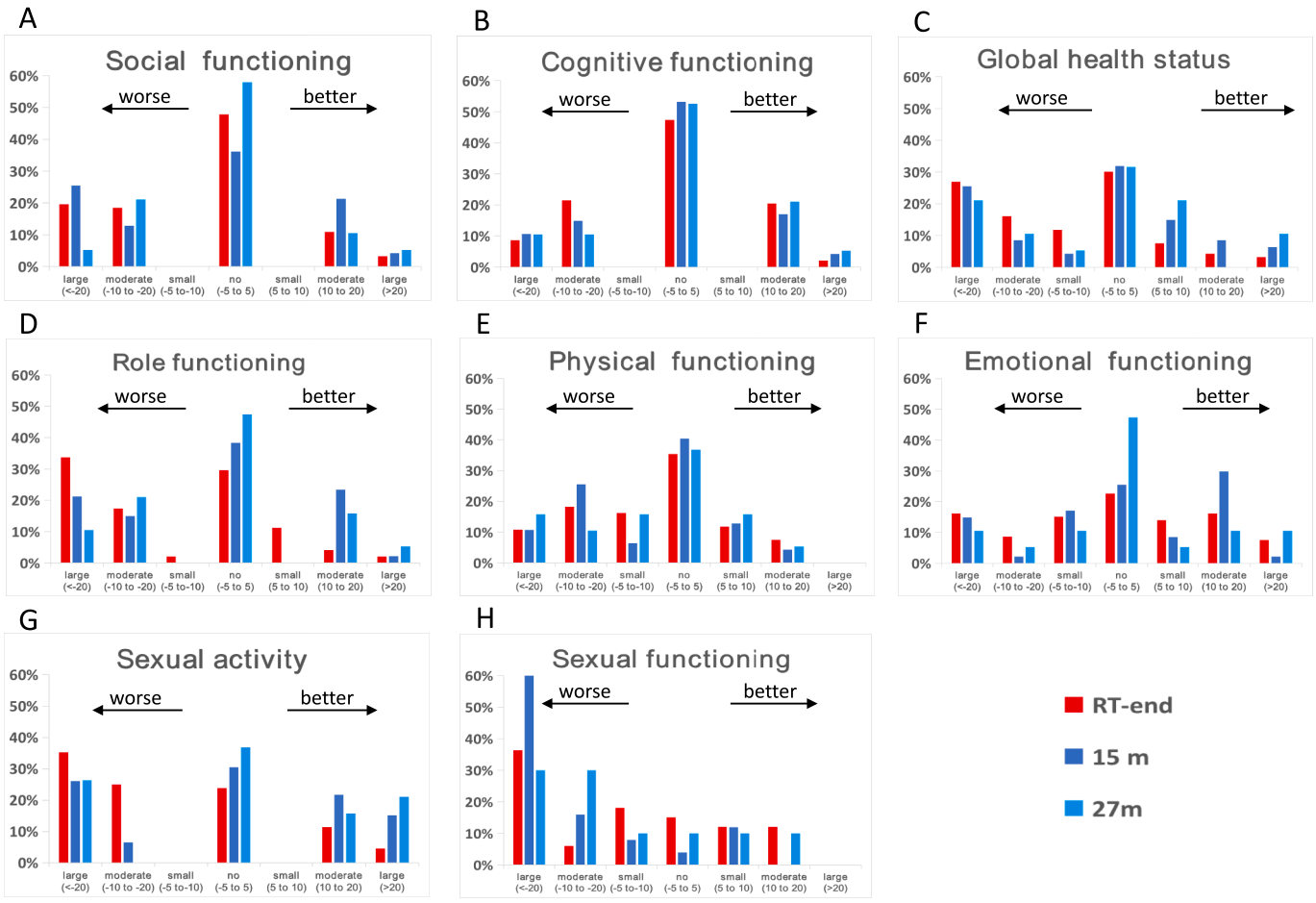

Fig. 4. Distribution of patient numbers according to changes of QLQ-C30 and PR-25 functional subscale scores from baseline to RT-end, 15 months and 27 months. Differences from baseline were considered small (5–10 points difference), moderate (10–20 points difference) or large (>20 points difference) in accordance with Osoba et al. A difference from baseline of at least 5 points was considered clinically relevant (Osoba et al).

Discussion

To our best knowledge, this study is the first comprehensive analysis of physician-reported toxicities and patient-reported QoL in prostate cancer patients undergoing TPUS-guided RT. The assessment utilized CTCAE v5.0 to evaluate toxicities and QLQ-C30, PR-25, IPSS questionnaire to evaluate QoL. This investigation demonstrated a temporary mild deterioration both in toxicities and QoL, with the most pronounced decline at RT end. However, substantial recovery of most items occurred at 3 months after RT, lasting in the further follow-up.

In current clinical practice, image-guided intensity-modulated radiotherapy (IMRT) has become the state-of-the-art for prostate cancer radiotherapy. However, in most institutions, CBCT was utilized for inter-fractional alignment without implementing intra-fractional motion management. In this study, all 164 patients underwent TPUS-based management of intra-fractional motion. And inter-fractional setup errors were daily corrected using either CBCT or TPUS.

Previous studies [1,2,24–30] have provided evidence of toxicities and quality-of-life outcomes in patients underwent moderate hypo-fractionated RT with or without image guidance. In CHHiP trial, bowel and bladder symptoms in the acute phase peaked at 4–5 weeks, with 38 % patients experiencing grade 2 bowel toxicities and 49 % with grade 2 bladder toxicities in the 60 Gy group. Compared to that, our results appeared more favorable, with corresponding toxicities 8.6 % for grade 2 GI and 21.5 % for grade 2 GU at RT end. A possible explanation might be the well-defined IGRT approach in our study, including both inter-fractional alignment and intra-fractional motion management, as well as the relatively small PTV margin of 6 mm (except 5 mm posteriorly). Indeed, in the IGRT subgroup evaluation of CHHiP trial, patients in IGRT-R group with reduced PTV margin of 6 mm (except 3 mm posteriorly) showed the lowest toxicities, in comparison with no-IGRT and IGRT with standard PTV margin of 10 mm (except 5 mm posteriorly). Along with the results in IGRT substudy of CHHiP trial [24], our results also indicated that advanced image guidance with a smaller PTV margin was able to reduce acute GI and GU toxicities. Regarding late toxicities, the CHHiP trial reported that most patients recovered to around baseline, with minimal incidence of 3 % and 2 % for ≥grade 2 bowel and urinary toxicities, respectively. Being in line with them, 2.2 % patients in our study experienced ≥grade 2 GI and no patient ≥grade 2 GU, indicating favorable recovery of GI and GU toxicities at long term follow-up [1].

As for QoL, CHHiP trial [25] reported the deterioration from baseline in bowel and urinary bother to be approximately 10 and 8 points at 10 weeks. Similarly, our study showed a mean decline of 4.3 in bowl and 4.6 points in urinary symptoms at 3 months. At 2 years, 24.4 % patients presented with any bowel bother in CHHiP study, whereas 40 % patients in our study at 27 months. The overall urinary bother showed a similar pattern, with 19.6 % experiencing urinary symptoms in CHHiP study and 28 % in our study. The moderate and severe bowel bothers in CHHiP trial, with more clinically relevant implications, were 7 % at 2 years, while similar results were found in our study, with 12 % patients at 27 months [24].

HYPRO trial [26] is another phase 3 clinical study that also evaluated adverse events of hypo-fractionated RT, using implanted fiducial-based

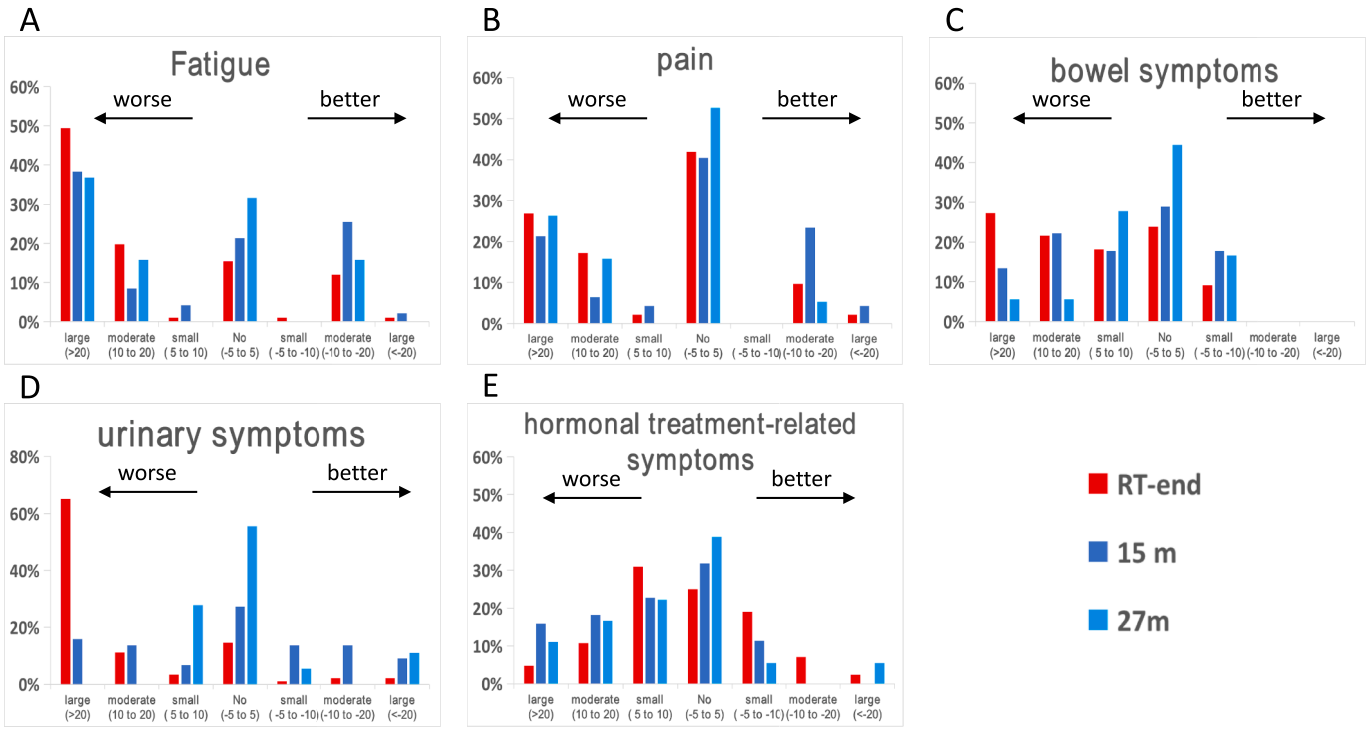

Fig. 5. Distribution of patient numbers according to changes of representive QLQ-C30 and PR-25 symptom scores from baseline to RT-end, 15 months and 27 months. Differences from baseline were considered small (5–10 points difference), moderate (10–20 points difference) or large (>20 points difference) in accordance with Osoba et al. A difference from baseline of at least 5 points was considered clinically relevant (Osoba et al).

image guidance. 32 % patients experienced ≥grade 2 GI and 42 % ≥grade 2 GU at RT end, whereas in our study the incidence was lower, with 8.6 % for ≥grade 2 GI and 22.1 % ≥grade 2 GU toxicities. Concerning late toxicities, HYPRO reported 21.9 % patients presenting ≥grade 2 GI and 41.3 % ≥grade 2 GU toxicities at 3 years, while in our study, no patient reported ≥grade 2 GI and 3.6 % for ≥grade 2 GU at 39 months after RT [27]. Regarding QoL outcomes, HYPRO trial also used QLQ PR-25 to evaluate QoL. Mean decline was reported as 2.0, 2.1, and 5.3 points for urinary symptom, bowel symptom, and ADT-related symptom, respectively at 6 months. Similar deterioration for each domain was also observed in our study, with the corresponding change of 4.5, 4.3 and 5.5 at 3 months after RT, respectively. In HYPRO trial, late QoL showed mean change of 0.9, 2.5, 2.8 for urinary, bowel and ADT-related symptom at 3 years. The mean worsening in our study was 1.3, 0.1, 4.7 at 27 months for the respective symptoms. Clinically relevant deterioration (change of at least 5 points) was observed in 33 %, 38 %, and 46 % of patients for urinary, bowel and ADT-related symptom in HYPRO trial, whereas in our study, the corresponding percentage was 28 %, 40 %, and 50 %, respectively [2].

In RTOG 0415 trial [28], toxicities and QoL were investigated on patients receiving moderate hypo-fractionated RT. The incidence of early and late ≥grade 2 toxicities were 10.7 % and 22.4 % for GI, and 27 % and 29.7 % for GU. While in our study, the corresponding incidence was 8.6 % and 8.4 % for GI, and 22.1 % and 7.2 % for GU. Regarding QoL, the RTOG trial reported a mild decline in bowel domains (7.5) at 12 months. Similarly, the corresponding change in all GI-related items in QLQ-C30 and PR-25 was 7.6 in our study. However, the urinary change scores in the RTOG trial showed a deterioration of 1.8 at 12 months, while in our study it was 6.8, seems to be higher [29]. One possible reason for that may be the higher proportion of elderly patients (≥75 years, 52 %). The median age was 67 years in RTOG trial, compared to 75 years in our study. It has been well documented that elderly patients are more susceptible to side effects from RT [31,32]. This notion was further supported by the subgroup study of older patients (≥75 year) in CHHiP trial [15], which demonstrated general higher incidences of urinary and bladder toxicities and more urinary and bladder bother in the older group [30].

Additionally, we also observed high incidence of urinary side effects at baseline. One possible explanation might be the larger prostate volume. The average prostate volume at baseline in our study was 47.5 cc, suggesting a potential influence of age-related benign prostatic hyperplasia (BPH) on urinary symptoms. Another factor might be the occurrence of TURP before RT, which was observed 15.9 % in our study, also contributing to the high urinary symptoms.

To date, there is limited evidence on toxicities and QoL in patients treated with TPUS-guided RT. Some groups of relatively small patient numbers [33–35] have investigated the side effects of a comprehensive IGRT approach, using CBCT for Inter-fractional alignment and TPUS for intra-fractional motion management. Patients in these investigations tolerated the treatment well, and reported minimal side effects, which were comparable to those observed in our study. Notably, most patients in these studies were treated with SBRT, highlighting the well-designed TPUS-based IGRT approach with reduced PTV margin may facilitate the use of SBRT of prostate.

Limitations and future directions

This study acknowledges several limitations. First, a portion of the toxicity data was collected retrospectively, which may introduce some inherent limitations in data completeness and accuracy. Moreover, heterogeneity in the treatment regimens could potentially affect the comparability of the results.

Despite these limitations, our study adds some evidence for the potential advantages of TPUS-guided RT, showing promising results of treatment-related toxicities and QoL outcomes. For future investigation, we plan to analyze the predictors for the toxicities and QoL in prostate cancer patients treated with a definitive radiotherapy.

Conclusion

In this study, we have demonstrated that a comprehensive TPUS-based IGRT contributed to minimal side effects and favorable QoL in prostate patients, supporting its utilization for high precise RT.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2024.100868.

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