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Daily Setup Accuracy, Side-effects and Quality of Life During and After Prone Positioned Prostate Radiotherapy

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Abstract. *Background/Aim: Exposure of organs at risk with prostate radiotherapy (RT) is lower in the prone position. This study is a prospective evaluation of setup accuracy, side-effects, and quality of life (QOL) during and after prone positioned RT. Patients and Methods: Image-guided (IG) intensity-modulated (IM) RT was administered in prone position on belly-board to 55 high-risk prostate cancer (PC) patients. Rectum diameters were measured in two areas of the symphysis at the beginning of RT and during it. Side-effects, QOL, and prostate specific symptoms (PSS) were evaluated. Results: Setup accuracy was similar to that reported in the literature. In the upper area of symphysis rectal diameters were significantly changed during treatment, but in the prostate region, no difference was detected. No change was detected in patients' QOL and PSS during treatment, but after RT, they improved. Conclusion: Prone positioned IG-IMRT is feasible with tolerable side-effects for high-risk PC patients. Changes in QOL and PSS are insignificant during RT, while improvement after RT suggests a rapid recovery.*

The incidence of prostate cancer (PC) is growing in every industrial country (1). Depending on the stage, surgical therapy, radiotherapy, and hormonal therapy are the potential options in the treatment of localized PC; in case of high risk cancers, administration of androgen deprivation therapy (ADT) is recommended simultaneously with radiotherapy (2). The sort-term and long-term side-effects of therapy are very important as PC patients usually have long survival (2, 3).

The elevation of radiation dose significantly improves biochemical control and disease-free survival independently of the type of radiotherapy, *i.e.*, three-dimensional conformal radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT) (3-5). In case of high risk carcinoma, radiotherapy of the pelvic lymph nodes is also possible besides radiotherapy of prostate and seminal vesicle but may result in more severe side-effects (6). In clinical practice, toxicity can be reduced by the use of modern radiotherapy techniques by decreasing the safety margins (*e.g.* IMRT, IGRT), by advantageous patient positioning and with almost constant fullness of the rectum and the urinary bladder (7, 8).

During radiotherapy the supine position is the most frequently used laying method. Patients can be treated also in a prone position (with the use of belly board - BB), and the use of BB is associated with lower dose burden of intestines in several clinical trials of pelvic cancers formerly in the 3DCRT and nowadays in the IMRT-IGRT era (9-12), which was confirmed in our previous study (in the process for publication) as well. Few publications show that the use of BB is associated with similar or better therapeutic efficiency and significantly lower rectal dose (13, 14), but other articles suggest that the daily positioning of patients might be more difficult (15). Rectal- and urinary bladder walls next to the prostate receive the highest irradiation dose; therefore, providing the constant fullness of these organs is necessary by using standardized bladder preparation protocol, treating patients at a fix daily time and maintaining anti-flatulence diet (5, 8).

Aims of the study were evaluation of daily setup accuracy, determination of the necessary safety margins and analysis of the patients' quality of life and side-effects of the therapy in case of PC patients treated with extended (with therapy of regional lymph nodes) radiotherapy in a prone position by IMRT-IGRT technique.

Patients and Methods

Patients. Patients with histologically-confirmed, localized or locally advanced (T2-4 N0-1 M0) high risk (PSA>20 ng/ml or Gleason score ≥8) PC after the multidisciplinary board's decision and signature of informed consent were enrolled into our prospective

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analysis (number of ethical approval: WHO3856/2016) at the Department of Oncotherapy, University of Szeged, between February 2016 and June 2017. Patients with permanent urinary catheter, or who could not lie in prone position due to any co-morbidities (*e.g.* hip prosthesis, dyspnoea) were excluded. All patients received androgen deprivation therapy. Stage was determined with standard methods (prostate specific antigen (PSA) level, chest X-ray or computer tomography (CT), abdominal and pelvic magnetic resonance imaging (MRI), bone scintigraphy) and TNM 7th edition (16).

Method of radiotherapy

Patient positioning, target volumes and planning. Topometric CT was performed in prone position with BB, All in One (AIO) Solution (ORFIT, Wijnegem, Belgium), with individual immobilization system and six-point thermoplastic mask fixation (Pelvicast system, ORFIT, Wijnegem, Belgium). Polystyrene wedge was placed between the buttocks. The patient's skin was marked in accordance with the laser marks. Standard bladder filling (drinking half litter of liquid during the 30 min before CT) and keep anti-flatulence diet for 7 days before the beginning and during the therapy were recommended. Topometric CT was performed on a Somatom Emotion 6 CT simulator (Siemens, Erlangen, Germany), CT slices were acquired every 5 mm from the diaphragm to an imaginary line 10 cm below the femoral heads.

Target volumes (pelvic lymph nodes, seminal vesicle and prostate) and organs at risk (OARs – bladder, rectum, bones, femur heads, penile bulb, small and large intestine) were delineated after MRI fusion in the ARIA Oncology Information System (Varian Oncology Systems, Palo Alto, CA, USA) with review of an experienced radiologist in all cases, based on the recommendations of RTOG GU Radiation Oncology Specialists Reach Consensus (17). For treatment planning Eclipse planning system was used (Varian Oncology Systems). Isocentric 7 fields IMRT technique was administered with inverse planning according to the RTOG recommendations (17).

Image-guided radiotherapy (IGRT) and determination of safety margins. Therapy was administered five times a week with 6 MV photon beams to 77 Gy total doses. Treatment of patients during the same period of the day was attempted. During therapy, online and offline monitoring and data recording were performed by CBCT. After determining the systematic and random errors the CTV-PTV margin was calculated based on van Herk formula (18) ($A=2.5 \cdot \Sigma pop + 0.7 \cdot \sigma pop$). In this calculated safety zone 90% of patients received 95% of prescribed dose.

Daily evaluation of the rectal fullness. The anteroposterior (AP, 0-180˚), the lateral (LAT, 90-270˚) and the oblique (OBL, 135-315˚) diameters were determined in the upper and lower area of the symphysis on the topometric CT rather than during the radiotherapy on the CBCT in the same regions. The daily alterations of treatment time were analysed.

Evaluation of side-effects and quality of life. Side-effects and quality of life were evaluated based on the European Organization for Research and Treatment of Cancer Quality of Life (EORTC QOL) (19) and the International Prostate Symptom Score (IPSS) (20) before the start of the therapy, during the 3rd or 4th week, after completion of therapy, and 3 and 6 months after it. Side-effects were graded based on the Common Terminology Criteria for Adverse Events (CTCAE, version 4.03) (21).

Statistical methods. Data were reported as mean±SD or median values. Daily changes of rectal fullness were evaluated by the paired samples *t*-test. Statistical analysis (double T-test) of the questionnaires was made with IBM SPSS 20.0 (SPSS Inc., Chicago, IL, USA). A $p<0.05$ was considered significant.

Results

Patient characteristics. A total of 55 patients with high risk or locally advanced PC took part in the study. Mean age of the patients was 65.60 (range=53.33-83.49 years) years. Most of the patients were overweight, mean BMI was 26.96 (range=19.37-41.62kg/m^2) kg/m^2. The number of patients with T2 stage was 41 (74.55%), T3 stage 12 (21.82%) and T4 stage 2 (3.64%). Gleason score was 7 in 27 (48.21%), while 8, 9 and 10 in 5 (9.09%), 19 (33.93%) and 4 (7.14%) cases, respectively. Initial PSA level was lower than 10 ng/ml and was between 10 and 20 ng/ml in 13 (23.21%) and in 9 (16.36%) cases, respectively. In case of 33 (58.93%) patients the initial PSA level was ≥20 ng/ml. A total of 52 (94.55%) patients received the whole prescribed dose (77 Gy). RT had to be completed earlier in 3(5.45%) cases (74 Gy) due to necessity of a urinary catheter during treatment.

Determination of safety margins. CTV-PTV safety margins were the following: lateral: 4.44 mm, longitudinal: 9.69 mm, vertical: 4.98 mm (Table I).

Daily evaluation of the rectal fullness. The data of mean AP, LAT and OBL diameters in the upper and lower area of the symphysis on the topometric CT rather than during the therapy on the CBCT in the same region and the daily alterations of treatment time are recorded in Table II. In the upper area of the symphysis the diameters of the rectal wall were significantly different, but in the lower area of the symphysis - in the region of the prostate - no significant differences were detected (Figure 1).

Side-effects and quality of life. The most common acute side-effects were cysto-urethritis and radiation induced enteritis-proctitis. Almost half and a quarter of the patients complained of GU and GI side-effects, respectively. Temporary urinary catheter was needed in 3 patients. Almost all patients had hot flashes and erectile dysfunction of different grade, but only 40% of them experienced significant complaints. Median (range) period of follow-up was 6 months (range=3-12 months). The most important acute and late (3 and 6 months) side-effects are shown in Figure 2. Based on the EORTC QOL, urination and defecation were significantly worse during the therapy than before. These complaints improved significantly after 3 and 6 months. Erectile dysfunction was

Table I. *Determination of safety margins*.

Number of patients: 55
Number of examinations: 652

	Vertical (cm)	Longitudinal (cm)	Lateral (cm)	3D vectorial (cm)
Random error	0.3249	0.6870	0.2862	0.4495
Systematic error	0.1086	0.1955	0.0995	0.1674
CTV-PTV margin	0.4987	0.9695	0.4491	0.7332

CTV: Clinical target volume; PTV: planning target volume.

Table II. *Analysis of rectal diameter' daily alteration during treatment. Mean difference was counted from the mean results on topometric CT minus the mean results of cone beam CT. In the upper area of the symphysis the diameters of the rectal wall were significantly different, but in the lower area of the symphysis – in the region of the prostate there – could not any significant difference detected.*

Diameters of rectum	Mean results on TCT (cm)	Mean diff. (cm)	SD	95%CI of the difference		*p*-Value
				Lower	Upper	
Upper area of the symphysis						
AP	4.36	0.169	0.407	0.059	0.279	0.003
LAT	3.95	0.193	0.578	0.037	0.349	0.016
OBL	4.12	0.107	0.339	0.016	0.199	0.023
Lower area of the symphysis						
AP	2.80	0.018	0.112	–0.012	0.048	0.239
LAT	2.58	–0.007	0.106	–0.036	0.021	0.621
OBL	2.67	0.029	0.227	–0.032	0.090	0.347

AP: Anteroposterior; LAT: lateral; OBL: oblique; TCT: topometric computer tomography; diff.: difference; SD: standard deviation; CI: confidence interval.

detected in more than one third of patients initially and this rate decreased during the radiotherapy. Evaluation of the patients' sexual life was quite difficult because psychological factors may influence the patients' answers and erectile function can be also worsened by ADT.

Based on total evaluation of the EORTC QOL, the patients' quality of life did not change significantly during therapy, although significant improvements could be detected in 3 and 6 months after therapy (Figure 3). Scores of IPSS questionnaire regarding quality of life were similar to these data, such as prostate specific symptoms: no significant worsening could be detected during the therapy; however significant improvements were registered during the follow-up visits (Figure 4).

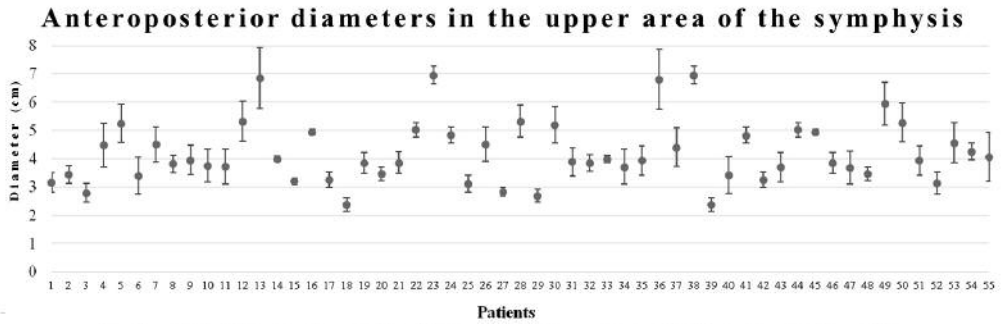
Discussion

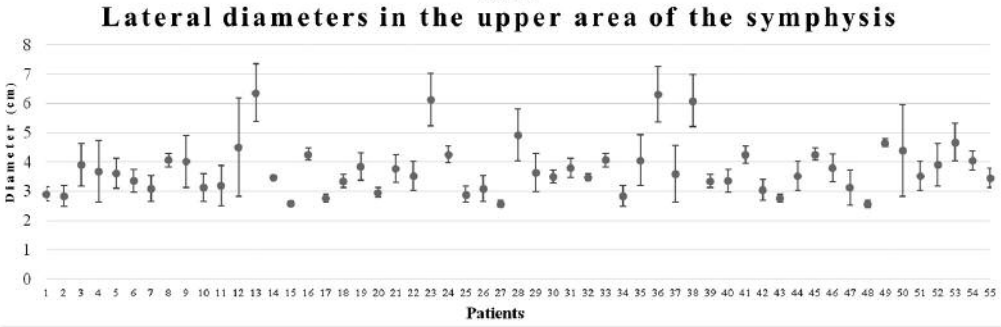
During the last 20 years many prospective randomized clinical studies have proven that local dose escalation significantly improves biochemical control (3, 4, 5). Despite the elevated dose in the target volume, the dose of OARs can be reduced without increased toxicity, using modern RT (7, 8), positioning and immobilization techniques (9-13).

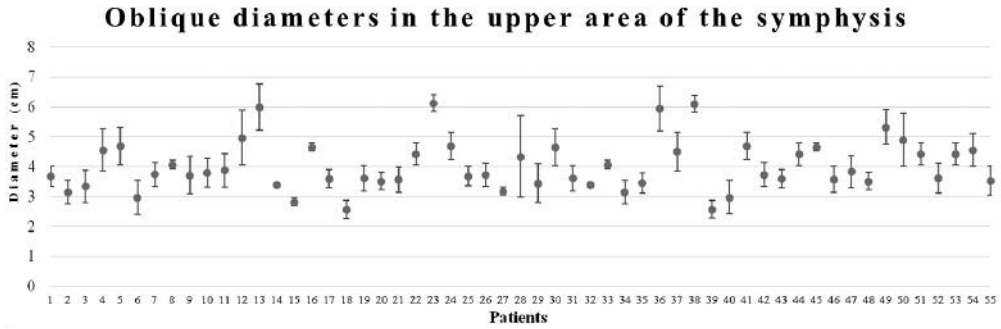
Zelefsky *et al*. (13) and McLaughlin *et al*. (14) have found that significantly lower doses can be administered to the rectum in prone position, but they could not confirm it in the case of urinary bladder. This may be explained by the fact that planning was made with empty urinary bladder and it can be improved by planning and treating with a full bladder, so one part of the bladder can move away from the target volume.

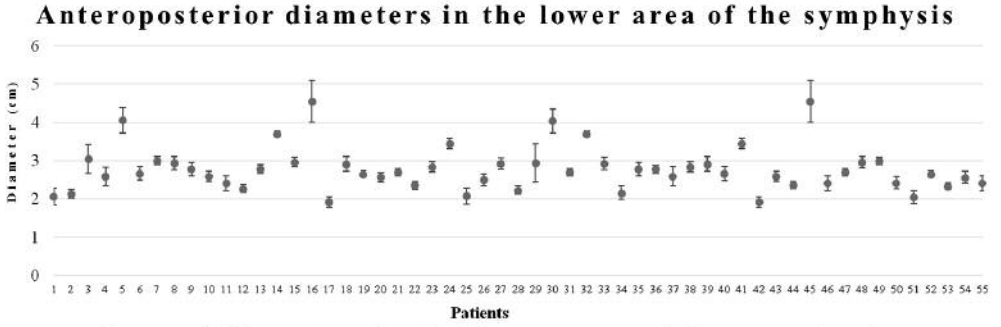
Radiation exposure of intestines is better in prone position with the use of BB, than in supine position, in case of 3D-CRT and IMRT technique, which may decrease the GI morbidity in itself (9). Gonzalez *et al*. (10) found that a significantly smaller volume of the small intestine receives more than 20 Gy dose in prone position with the use of BB, while the interfraction dose variation to the small bowel was similar to the supine position. Bajon *et al*. (11) have shown decreased dose exposure of the urinary bladder in prone position besides sparing the rectum and the small intestine. Chen *et al*. (22) have studied the daily change of the rectal and urinary bladder volume of 19 patients and 314 CBCT pictures. Therapy was administered in supine position with full bladder.

With the use of IG-IMRT patient setting errors can be eliminated, so accuracy of spatial dose delivering can be









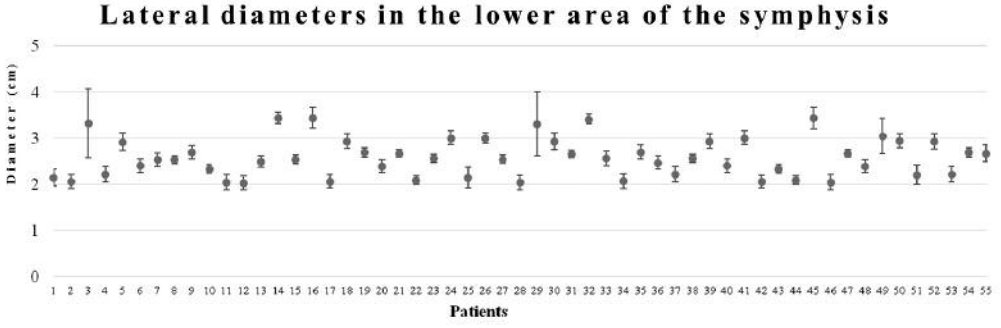


Figure 1. *Continued*

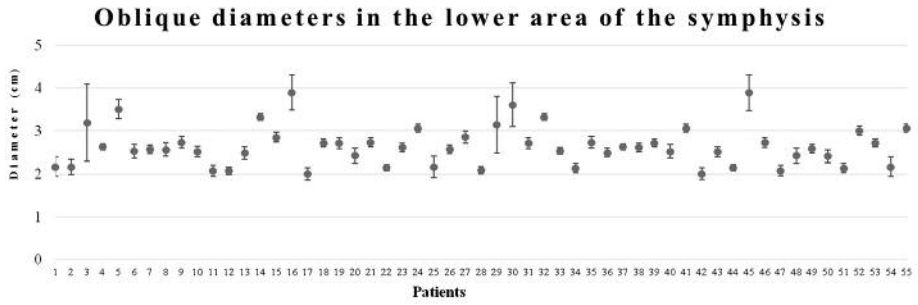


Figure 1. *Rectal diameter alteration in the upper and lower area of the symphysis.*

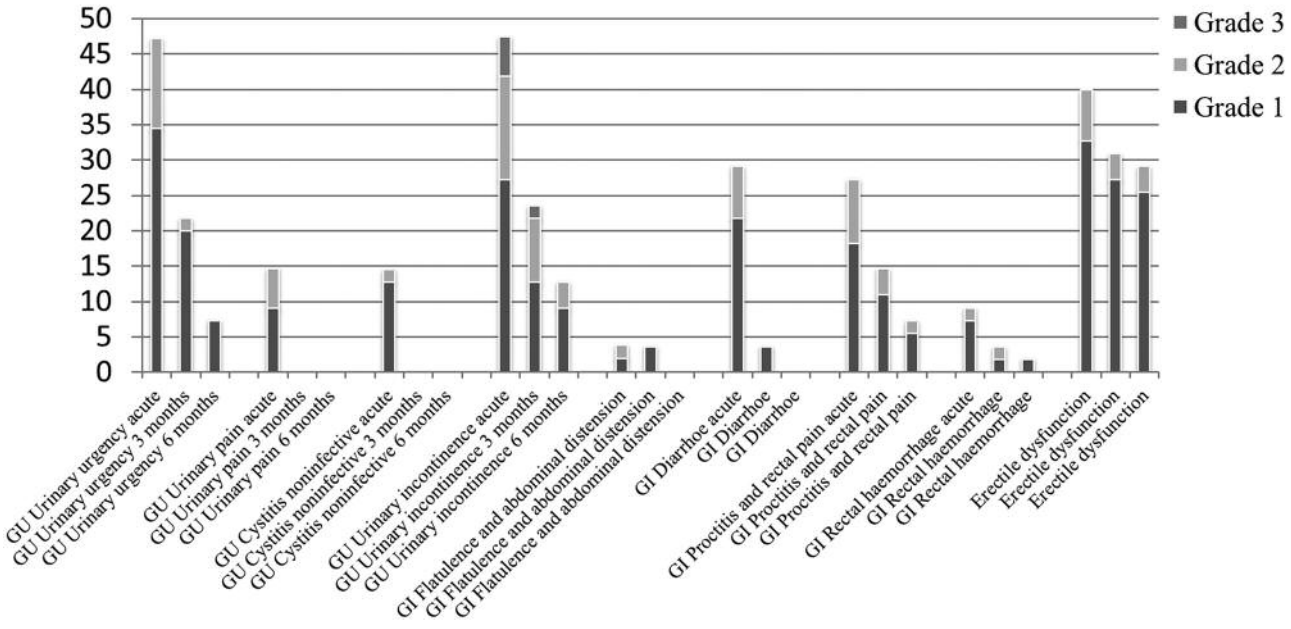


Figure 2. *The most important acute and late (3 and 6 months) genitourinary (GU) and gastrointestinal (GI) side-effects.*

increased, that may lead to improved clinical results (23). In case of prostate cancer patients, the extent of radiotherapy safety zone (CTV-PTV margin) is being studied (recommendations are available from 1 mm to 10 mm) (8). Determination of the proper safety zone has to be estimated by the different institutions taking local conditions into consideration. It can be decreased by marking and mask fixation. For further decrease of the safety zone, besides the precise patient positioning and daily IGRT, the transperineal gold marker implantation was introduced according to Jorgo *et al*. (24).

As the technique of radiotherapy has improved and patient's overall survival has increased, the incidence of side-effects and the way they influence the patients' QOL became important (3, 4). Acute side-effects (mainly cysto-urethritis and radiation induced enteritis-proctitis) develop during radiotherapy (usually from the 6th week) and cease on the first follow-up visit after therapy (2-3 months). Late toxicities usually develop 90 days after completion of radiotherapy and include: chronic cystitis, incontinence, urethral stricture, chronic proctitis and rectal bleeding. In 2007 Dearnaley *et al*. (4) compared side-effects of 64 Gy and 74 Gy dose escalation. Mainly acute and late GI side-effects occurred but were not significant. Late GU side-effects were also common, but there were no significant increases in toxicity frequency and grade. In 2011, Beckendorf *et al*. (3) published the 5-year follow-up study of 70 Gy contra 80 Gy

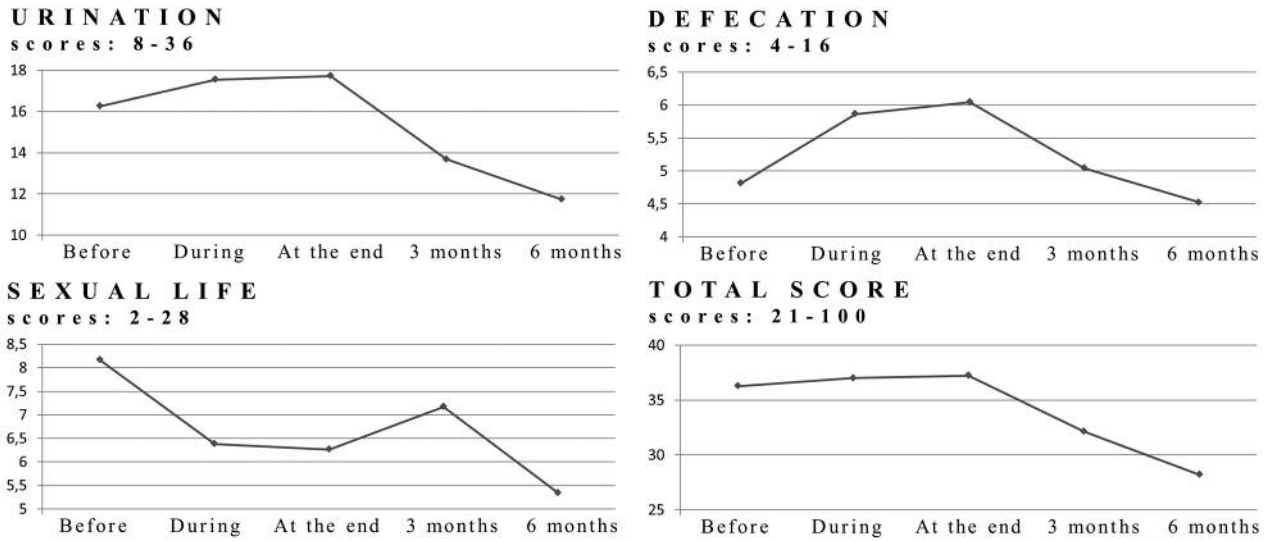


Figure 3. *Evaluation of the EORTC QOL questionnaire: lower score is more favourable.*

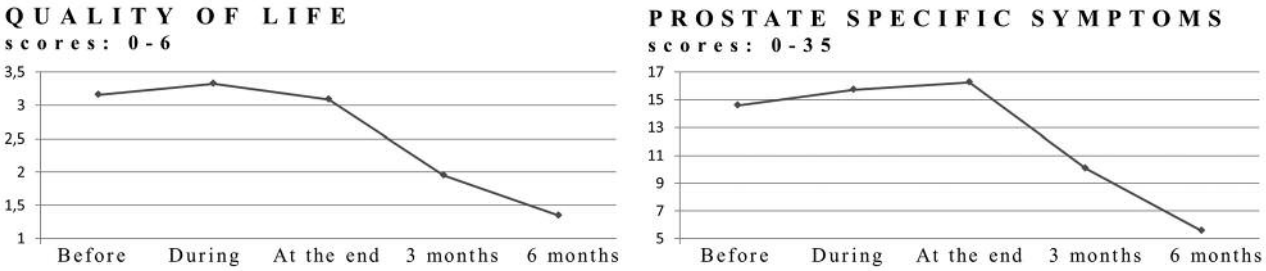


Figure 4. *Evaluation of IPSS questionnaire: lower score is more favourable.*

dose escalations: better 5-year biochemical relapse-free survival was detected in case of high-dose RT. Side-effects were similar in the two arms, however higher proportion of rectal (proctitis, rectal bleeding) and urinary (cystitis, haematuria, urinary obstruction) toxicities were detected in the 80 Gy group. In 2017, Sasaki *et al.* (25) published their long-term outcomes of the effect of fraction dose reduction (2.2 Gy to 2 Gy/fraction) to late GI toxicity by using helical tomotherapy and IM-IGRT. They found that the reduced dose fraction schedule decreased the incidence of late GI toxicity without compromising prostate-specific antigen control.

The limitation of this study is its relatively small number of patients. Regarding the daily reconstruction of the rectum and the accurate patient repositioning on a belly board, further investigations are needed. The late toxicities developed and the quality of life after pelvic IMRT for prostate cancer are under further examination.

Conclusion

IMRT radiotherapy in the prone position can be properly carried out in case of high risk PC patients. Using belly board and mask fixation, vertical and lateral setting accuracy detected with CBCT is similar to the literature. GU/GI side-effects of this therapy were tolerable. Change of patients' quality of life is insignificant during RT, while improvement 3 and 6 months after RT may be due to rapid recovery from side-effects and effectiveness of therapy.

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