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Open retropubic radical prostatectomy versus external beam radiation therapy for localized prostate cancer – patient-reported outcomes

Отворена ретропубична радикална простатектомија наспрам спољашње зрачне терапије за локализовани карцином простате – исходи које пријављују пацијенти

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SUMMARY

Introduction/Objective Active treatment options for localized prostate cancer (LPCa) include surgery and radiotherapy with androgen deprivation therapy (ADT) in selected cases, but all options have side effects, mainly addressed to urinary, sexual and bowel function.

Our study aimed to assess and compare patient-reported outcome measures (PROMs) after retropubic radical prostatectomy (ORRP) or external beam radiotherapy (EBRT).

Methods Between June 2019 and May 2021, a total of 120 patients, with LPCa had undergone active treatment, as follow: open retropubic radical prostatectomy (ORRP) - 60 patients and external beam radiotherapy (EBRT) - 60 patients. A validated questionnaire, the Expanded Prostate Cancer Index Composite Short Form (EPIC-26) instrument was used to assess PROM, through the following domains: urinary, sexual and bowel. Patients completed a questionnaire at baseline and six, 12 and 24 months after primary treatment.

Results All urinary scores had statistically significant time x group interaction. After six, 12 and 24 months, all urinary scores were statistically significantly lower in the ORRP group. After 12 and 24 months, bowel score values were statistically significantly lower in patients in the ERBT group. Sexual scores change statistically significant during the follow-up period, without difference between the groups ($p < 0.05$).

Conclusion both ORRP and EBRT are associated with decline of sexual scores. ORRP showed significant variations in all urinary scores, with more pronounced negative impact on urinary symptoms compared to EBRT during the entire follow-up period. Bowel scores are lower in EBRT.

Keywords: localized prostate cancer; open retropubic radical; external beam radiotherapy; patient-reported outcomes

САЖЕТАК

Увод/Циљ Активне опције лечења локализованог рака простате (ЛПЦа) укључују операцију и радиотерапију са андроген-депривационом терапијом (АДТ) у одабраним случајевима, али све опције имају нежељене ефекте, углавном усмерене на уринарну, сексуалну и цревну и функцију.

Наша студија је имала циљ да процени и упореди мере исхода које су пријавили пацијенти (ПРОМ) након ретропубичне радикалне простатектомије (ОРРП) или спољашње зрачне терапије (ЕБРТ).

Методе У периоду од јуна 2019. до маја 2021. године, укупно 120 пацијената са ЛПЦа је подвргнуто активном лечењу, и то: ОРРП - 60 пацијената и ЕБРТ - 60 пацијената. За процену ПРОМ-а коришћен је валидирани упитник, композитни кратка форма са проширеним индексом рака простате (ЕПИЦ-26), кроз следеће домене: уринарни, цревни и сексуални. Пацијенти су попуњавали упитник на почетку и шест, 12 и 24 месеца након примарног лечења.

Резултати Сви резултати уринарног домена имају статистички значајну интеракцију време х група. После шест, 12 и 24 месеца, сви уринарни резултати били су статистички значајно нижи у ОРРП групи. После 12 и 24 месеца, вредности цревног скора биле су статистички значајно ниже код пацијената у ЕРБТ групи. Сексуални резултати се мењају статистички значајно током периода праћења, без разлике међу групама ($p < 0,05$).

Закључак И ОРРП и ЕБРТ повезани су са падом сексуалних скорова. ОРРП је показао значајне варијације у свим резултатима уринарног скора, са израженијим негативним утицајем на уринарне симптоме у поређењу са ЕБРТ током читавог периода праћења. Резултати цревног скора нижи су код ЕБРТ.

Кључне речи: локализовани карцином простате; отворени ретропубични радикал; екстерна радиотерапија; исходи пријављених пацијената

INTRODUCTION

Prostate cancer represents the most common noncutaneous malignancy in men [1]. Its annual share accounts for 7.1 % of all cancers detected, with rising trend nowadays [2, 3].

According to the latest epidemiological data for the male population, in 2023 the most common malignancies were prostate, lung and colorectal cancers, which accounted for 48% of all cases, while prostate cancer alone had shared with 29% [4]. At the time of prostate cancer diagnosis, 77% of patients have localized disease [5]. However, it was observed that since 2014, a 3% annual increase in the incidence of prostate cancer has been associated with a 4.5% annual increase in cases of higher grade, with locally advanced or high-stage disease [6].

Nevertheless, prostate cancer screening and other improvements in the diagnostic and therapeutic procedure has led to sustained declining trend in annual prostate cancer mortality rates, from 4% in 1994 to 0,6% nowadays [7]. Recent data demonstrated that 5-year relative survival rate of prostate cancer is 97%, and is one of the highest among all malignancies [8]. Since the prostate cancer has a long natural history and is age-related, it has become evident that non-cancer comorbidities in patients with prostate cancer represent important danger, causing 57% of all deaths [9, 10].

Active treatment options for localized prostate cancer (LPCa) include surgery (radical prostatectomy) and radiotherapy (external beam radiotherapy - EBRT, or brachytherapy) with androgen deprivation therapy (ADT) in selected cases, but all options have side effects, mainly addressed to urinary, sexual and bowel function [11]. Despite the fact that cancer-free survival is an essential measure of therapeutic success, the patient's perception of health-related quality of life (HRQoL) represents important issue [12]. Various patient-reported outcome measures (PROMs) are used to assess side effects and symptoms, and to evaluate HRQoL [9]. Our study aimed to assess and compare HRQoL in patients with who underwent open retropubic radical prostatectomy or EBRT, using Expanded Prostate Cancer Index Composite (EPIC) PROM.

METHODS

Between June 2019 and May 2021, a total of 120 patients, with LPCa had undergone

active treatment through the following procedures:

1. Group ORRP - 60 patients, mean age 64 (48–73) years, who underwent open retropubic radical prostatectomy (ORRP)

2. Group EBRT - 60 patients, mean age 71 (63–80) years, who underwent EBRT

All of 120 patients were diagnosed with clinically LPCa, through the following procedures: prostate-specific antigen (PSA) testing, digital rectal examination of the prostate, transrectal ultrasound-guided biopsy of the prostate, histopathological examination of specimens, multislice computerized abdomino-pelvic tomography and bone scintigraphy.

Indications for ORRP were: PSA ≤ 20 ng/ml, or GS ≤ 7 (ISUP grade ≤ 2/3), or clinical stage ≤ T2b (for low- and intermediate-risk PCa); PSA > 20 ng/ml, or GS > 7 (ISUP grade ≤ 4/5), or clinical stage ≤ T2c (for high-risk PCa), ECOG performance status 0 or 1, age ≤ 70 years (except in selected cases with life expectancy of > 10 years) [11]. Contraindications were: life expectancy ≤ 10 years, medical history of malignancies, end-stage renal disease, kidney transplantation and advanced cardiovascular or respiratory diseases. Indications for EBRT included high-risk PCa, Gleason > 8 or PSA > 20 ng/mL, patient's motivation, contraindications for ORRP and advanced age.

After the histopathological confirmation of prostate cancer, all patients were examined at the uro-oncology Council, when the appropriate therapeutic procedure was proposed. Upon acceptance of the proposal, the patients received the Council's decision and an informed consent form. Treatment began 6–8 weeks after the council's decision. We used the Walsh operative technique in all patients in the ORRP group [13]. EBRT was delivered at a dose of 74 Gy, in 37 fractions over six weeks, with three-dimensional conformal radiation therapy (3D-CRT).

A validated questionnaire, the Expanded Prostate Cancer Index Composite Short Form (EPIC-26) instrument was used to assess PROM, through the following domains: urinary,

sexual and bowel [14]. Patients completed a questionnaire regularly before prostate biopsy and 6, 12 and 24 months after primary treatment.

Statistical data processing was performed in the R software package. Data are presented as arithmetic mean and standard deviation. The comparison of the values of the tested scores in the monitoring period in relation to the groups was performed by ANOVA for repeated measures. If a statistically significant time x group interaction was obtained, the t test or Mann-Whitney test was used to compare simple effects. The null hypothesis was tested with a significance threshold of $p < 0.05$.

This work is conducted according to the Declaration of Helsinki ethical principles, with guaranteed discretion of personal data, and was approved by the Ethics Committee of the Faculty of Medicine of the University of Niš (No. 12-8818-2/8).

RESULTS

According to the results of the t-test (Table 1) it is noticed that there is a statistically significant difference in the age between observed groups of patients (*t*-statistics = 2.421; p-value = 0.017), in favor of EBRT group. Table 1 shows mean age of patients in study groups.

Table 2 shows the values of urinary scores in relation to the examined groups during the follow-up period. It was found that for all investigated urinary scores there is a statistically significant time x group interaction ($p < 0.05$). Before treatment, all urinary scores differed between the groups, except for incontinence and UIO. After 6, 12 and 24 months, all urinary scores were statistically significantly lower in the ORRP group compared to ERBT ($p < 0.05$). Values of urinary score in relation to the studied groups during the 24 month-follow-up are shown in Figure 1.

Table 3 shows the values of bowel scores in relation to the examined groups during the follow-up period. It was found that there is a statistically significant time x group interaction

for all examined bowel scores ($p < 0.05$). Before treatment, bowel score values did not differ between groups ($p = 0.422$, $p = 0.304$, $p = 0.528$). Even after 6 months, the values of bowel scores do not differ between the groups ($p = 0.228$, $p = 0.136$, $p = 0.329$). After 12 months, bowel score values were statistically significantly lower in patients in the ERBT group compared to the ORRP group ($p = 0.014$, $p = 0.006$ and $p = 0.029$). After 24 months, bowel score values were statistically significantly lower in patients in the ERBT group compared to the ORRP group ($p = 0.011$, $p = 0.003$ and $p = 0.029$). Values of bowel score in relation to the studied groups during the 24 month-follow-up are shown in Figure 2.

The total sexual score, sexual function and sexual bother change statistically significant during the follow-up period ($p < 0.001$ for all) (Table 4). There is no statistically significant difference between the groups ($p = 0.800$, $p = 0.634$, $p = 0.856$) and there is no significant interaction time x group ($p = 0.164$, $p = 0.312$, $p = 0.104$). The movement of the total scores in relation to the examined groups in a period of 24 months is shown in Figure 3.

DISCUSSION

In the present study, we evaluated patients' PROMs using the EPIC-26 instrument, which has been most frequently applied in clinical practice [9].

Barocas et al. analyzed PROMs based on the EPIC instrument, after observation, EBRT or RP in 2750 patients with localized PCa [15]. The effects of RP were associated with lower urinary incontinence and sexual function scores compared to EBRT, except for the bowel score which was better at 12 months. In a recently published study on PROMs after surgery or irradiation in LPCa, Hashin et al. reported significantly lower urinary scores in operated patients and significantly lower bowel scores in irradiated patients, while in the follow-up period there was a decrease in the difference in both domains. In the sexual domain, a decrease in the score after surgical treatment was reported, while the score was unchanged after

irradiation [16]. Analyzing PROMs in 1141 patients after RP, EBRT, permanent prostate brachytherapy (PPB) and AS, Chen et al. concluded that the urinary incontinence score was the lowest after RP, urinary bother and bowel scores after EBRT, while after 3 months the sexual score was worse after RP compared to EBRT. After 24 months, there were no statistically significant differences in relation to the analyzed domains [17].

However, the curative potential of RP and EBRT is to some extent compromised by post-interventional complications and consequent symptoms, with urinary, sexual and intestinal most pronounced. Symptoms of erectile dysfunction (ED) and urinary incontinence (UI) have been adressed to surgery, while bowel and irritative urinary symptoms are predominantly associated with EBRT [18-20]. In the ProtecT trial, Donovan et al. analyzed PROMs for 1643 patients who underwent AS, operative treatment or radiation therapy, with a follow-up period of 72 months [21]. The authors state that operative treatment is associated with a reduction in urinary incontinence and sexual function scores, to a greater extent compared to EBRT, and that despite the variability of symptom scores in terms of improvement after 12 months, the difference between the mentioned groups remains during 72 months of follow-up. As in our study, the difference in urinary incontinence scores in RP versus EBRT remains approximately the same during the follow-up period. The same authors reported that bowel scores were lower in the EBRT group, which is consistent with the results of our study.

Analyzing the effects of individual therapeutic modalities on the outcome of PCa treatment, it is worth mentioning that the recent meta-analysis by Cheng et al. showed that the OS in RP is significantly higher compared to EBRT, with a similar cancer-specific survival (CSS), and that the risk of cancer-specific mortality (PCM) is higher in EBRT [22]. A recent systematic review by Greenberger et al. on the effects of surgery, radiation, and ADT for the primary treatment of LPCa showed that there is still no strong evidence to favor any of these therapies in terms of overall mortality (OM) and PCM [23]. In a study that using the

International Prostate Symptom Score (IPSS) PROM instrument, analyzed the impact of ORRP on postoperative voiding quality, ORRP was associated with a significant reduction in IPSS score and improvement in quality of life, over a 12-month follow-up period [24]. Hoffman et al. conducted a prospective PROMs study for AS, surgery, PPB, EBRT or ADT, of 1386 men with LPCa, using the EPIC-26 instrument, with a 5-year follow-up. In the sexual domain, there is a continuous decrease, both with RP and EBRT. Overall, the authors found no statistically significant differences in HRQoL between RP and EBRT, combined with ADT [20]. The urinary incontinence score declines with RP until month 6 and recovers slightly afterwards, but is significantly lower than with EBRT during follow-up. Urinary symptoms were more pronounced with EBRT during the entire follow-up period. During the 1st year, the bowel score is slightly lower with EBRT compared to RP, but without a statistically significant difference. According to our results, this study, as well as the ProtecT trial, showed that RP significantly affects the reduction of urinary and sexual scores during the follow-up period, and that RP has the greatest negative effect on sexual scores [20, 21].

Our results in terms of sexual scores show a continuous trend of reduction during the follow-up period in both studied groups, at 6 and 12 months, after which a slight improvement is noticeable at 24 months. However, the overall reduction is statistically significant compared to baseline ($p < 0.001$).

Unlike the previously mentioned studies [20, 21], no statistically significant difference was found among the observed groups in our study, in any of the sexual score categories, at 6, 12 and 24 months, which can be explained by a statistically significant difference in age at EBRT. Compared to the baseline, in our study group ORRP showed statistically significant variations in all urinary scores, during the entire follow-up period. The incontinence score shows a significant decline at 6 months, followed by a statistically significant improvement that is most pronounced at 24 months. It is interesting that the urinary summary score shows

variations, starting with a significant decrease in the 6th month, with a continuous statistically significant improvement over time, approaching the values from the baseline. This result is consonant with the results of most of other studies [20, 25].

In our study, the incontinence score was also significantly reduced in EBRT at 6 months, with an additional reduction at 12 months. Urinary function score decreases after treatment and maintains approximately the same values at 6, 12, and 24 months. It is interesting that the increase in the urinary bother score and the urinary irritative/obstructive (UIO) score was recorded only in the 24th month. In this group, the urinary summary score was reduced at 6 and 12 months, but after 24 months it was increased. It should be noted that many patients from this group are on chronic drug therapy for LUTS. During follow-up in at 6, 12, and 24 months, urinary summary, urinary function, urinary bother, urinary incontinence and UIO, were lower in ORRP, showing that the negative effect of ORRP on urinary symptoms was more pronounced compared to EBRT, and this difference is statistically significant. However, the recovery of the same score in ORRP after 24 months in our patients may be due to the preserved muscle mass of the urethral rhabdosphincter (younger patients), with its good preservation during the performance of vesicourethral anastomosis. When it comes to bowel scores, both bowel function and bowel bother and bowel summary scores at ORRP show no variation during the follow-up period ($p>0.01$). With EBRT, these scores progressively decrease statistically significantly and are the lowest in the 24th month. All three bowel scores are lower in EBRT compared to ORRP at 6, 12 and 24 months, and this difference is statistically significant ($p > 0.05$).

In our study, the use of PROMs for assessing of the urinary, intestinal and sexual domains after ORRP or EBRT in LPCa, clearly established the set parameters, even their temporal variability in each of the set categories. Certain conclusions are relevant, such as that urinary incontinence and sexual dysfunction are more prevalent in ORRP, and intestinal dysfunction

in EBRT. However, since these PROMs are personalized instruments, the question of objectification and validation of certain conditions (e.g. personal interpretation of urinary complaints without urodynamic findings, etc.) can be raised, taking into account the adaptability of patients to side effects. Also, it is necessary to expand the profiles of PROMs towards psychometric aspects in the quantitative evaluation of the results, and in this respect the Consensus-based Standards for the Selection of Health Measurement Instruments (COSMIN) methodology is promising [9, 26]. The issue of evaluating the results of multimodal treatment also arises. In this regard, it is necessary to conduct multi-institutional and prospective studies, as well as equalize inclusion criteria and research methodology in order to obtain data of a high level of coherence. For the synthesis and processing of data, it is necessary to expand the information network, based on the PIONEER Consortium [27].

CONCLUSION

In our study group, both ORRP and EBRT are associated with decline of sexual scores, while ORRP showed significant variations in all urinary scores, with more pronounced negative impact on urinary symptoms compared to EBRT, during the entire follow-up period. Bowel scores are lower in EBRT. Future research should include a more extensive consideration in terms of the psychometric domain of the PROM, which would greatly improve the synthesis and quantitative evaluation of the data.

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Table 1. Independent samples t-test for equality of means

Variable	Mean of group ORRP (N = 60)	Mean of group EBRT (N = 60)	Difference	Std. Error Difference	*t*	df	p-value	95% confidence interval	
								Lower	Upper
Age	64 (48–73)	71 (63–80)	7.000	2.891	2.421	118	0.017	1.2749	12.7251

ORRP – open retropubic radical prostatectomy; EBRT – external beam radiation therapy

Table 2. Urinary score values in relation to the examined groups in the follow-up period

Score	Group	Before treatment	Six months	12 months	24 months	p
Urinary summary	ORRP group	78.27 ± 6.82	69.57 ± 13.09	72.53 ± 11.15	76.07 ± 12.05	$< 0.001^{1}$ $< 0.001^{2}$ $< 0.001^{3}$
	ERBT group	82.76 ± 6.16	81.79 ± 7.83	81.41 ± 8.74	85.54 ± 7.67	
Urinary function	ORRP group	98.04 ± 4.29	78.4 ± 20.83	79.4 ± 19.6	79.06 ± 19.78	$< 0.001^{1}$ $< 0.001^{2}$ $< 0.001^{3}$
	ERBT group	95.71 ± 6.54	93.37 ± 11.09	93.71 ± 11.13	93.71 ± 11.13	
Urinary bother	ORRP group	64.15 ± 10.42	63.26 ± 9.98	67.62 ± 8.54	73.93 ± 8.51	$< 0.001^{1}$ 0.002^{2} $< 0.001^{3}$
	ERBT group	73.51 ± 7.87	73.51 ± 7.87	72.62 ± 9.61	79.7 ± 7.88	
Incontinence	ORRP group	96.4 ± 9.02	62.27 ± 34.92	65.29 ± 32.29	65.91 ± 32.24	$< 0.001^{1}$ $< 0.001^{2}$ $< 0.001^{3}$
	ERBT group	95.26 ± 10.31	92.34 ± 16.22	90.99 ± 18.46	92.03 ± 17.8	
Urinary irritative / obstructive	ORRP group	75.05 ± 7.72	79.63 ± 5.92	83.1 ± 7.61	87.74 ± 5.23	$< 0.001^{1}$ $< 0.001^{2}$ 0.008^{3}
	ERBT group	77.14 ± 5.63	77.14 ± 5.63	77.56 ± 8.37	84.52 ± 6.92	

Repeated measures ANOVA, [1] time effect, [2] interaction time x group, [3] group effect;
ORRP – open retropubic radical prostatectomy; EBRT – external beam radiation therapy

Table 3. Bowel score values in relation to the examined groups in the follow-up period

Score	Group	Before treatment	Six months	12 months	24 months	p
Bowel Summary	ORRP group	95.18 ± 14.59	95.18 ± 14.59	95.18 ± 14.59	95.18 ± 14.59	0.003[1]
	ERBT group	92.83 ± 17.24	91.28 ± 20.17	85.83 ± 25.07	85.48 ± 24.94	0.003[2] 0.052[3]
Bowel function	ORRP group	95.95 ± 12.66	95.95 ± 12.66	95.95 ± 12.66	95.95 ± 12.66	0.002[1]
	ERBT group	93.39 ± 14.42	91.73 ± 17.77	86.61 ± 22.3	85.89 ± 22.06	0.002[2] 0.020[3]
Bowel bother	ORRP group	94.4 ± 16.61	94.4 ± 16.61	94.4 ± 16.61	94.4 ± 16.61	0.005[1]
	ERBT group	92.26 ± 20.29	90.83 ± 22.85	85.06 ± 28.13	85.06 ± 28.13	0.005[2] 0.101[3]

Repeated measures ANOVA, [1] time effect, [2] interaction time x group, [3] group effect,
ORRP – open retropubic radical prostatectomy; EBRT – external beam radiation therapy

Table 4. Sexual score values in relation to the examined groups in the follow-up period

Score	Group	Before treatment	Six months	12 months	24 months	p
Sex Summary	ORRP group	58.94 ± 28.76	47.63 ± 26.79	39.51 ± 19.69	42.76 ± 21.47	< 0.001[1]
	ERBT group	53.64 ± 28.02	47.26 ± 25.19	41.41 ± 22.59	42.45 ± 22.04	0.164[2] 0.800[3]
Sex function	ORRP group	57.63 ± 29.32	45.98 ± 27.45	35.91 ± 19.74	40.42 ± 22.89	< 0.001[1]
	ERBT group	51.92 ± 29.5	44.42 ± 26.59	37.73 ± 22.66	38.4 ± 22.89	0.312[2] 0.634[3]
Sex bother	ORRP group	61.88 ± 28.83	51.35 ± 27.16	47.60 ± 25.08	48.02 ± 25.12	< 0.001[1]
	ERBT group	57.5 ± 27.49	53.65 ± 29.46	49.69 ± 30.06	51.56 ± 29.15	0.104[2] 0.856[3]

Repeated measures ANOVA, [1] time effect, [2] interaction time x group, [3] group effect,
ORRP – open retropubic radical prostatectomy; EBRT – external beam radiation therapy

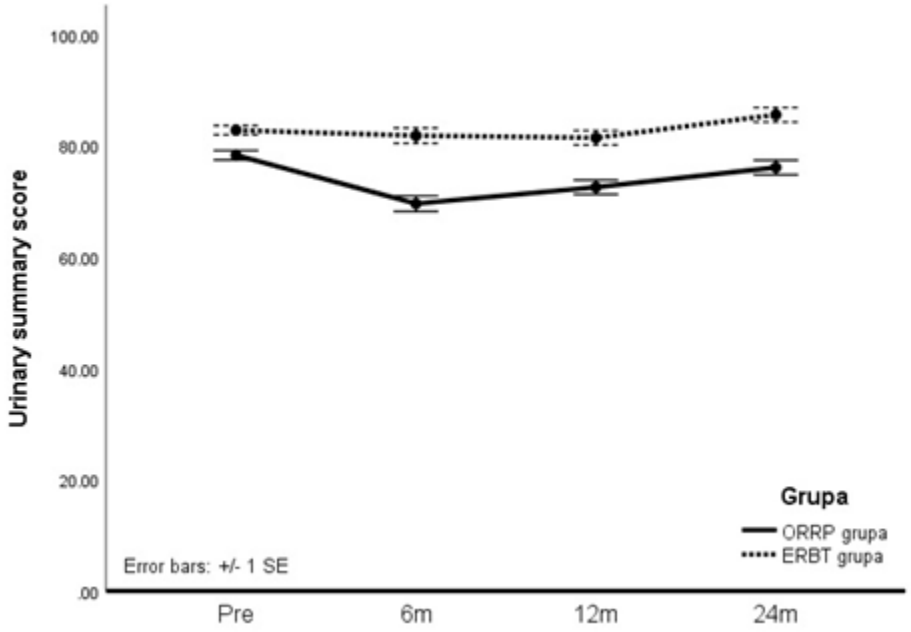

Figure 1. Values of urinary score in relation to the studied groups during the 24 month-follow-up; ORRP – open retropubic radical prostatectomy; EBRT – external beam radiation therapy

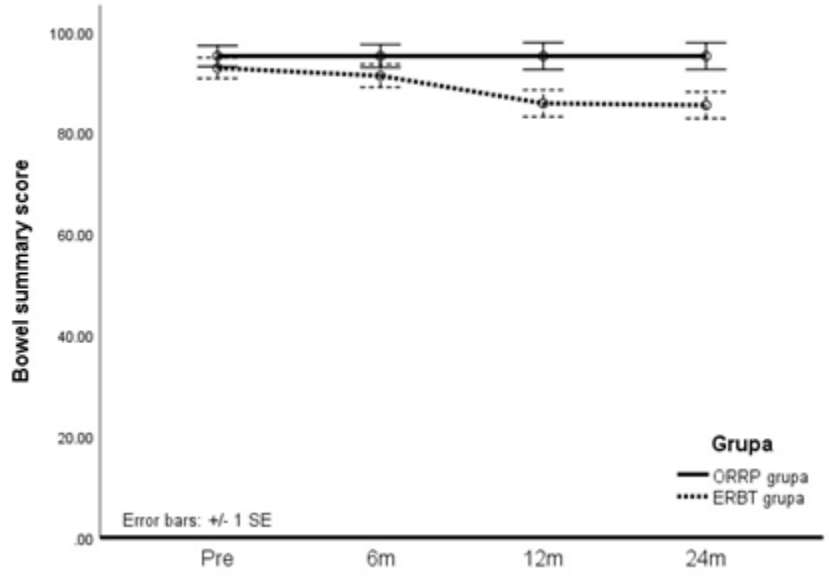

Figure 2. Values of bowel score in relation to the studied groups during the 24 month-follow-up; ORRP – open retropubic radical prostatectomy; EBRT – external beam radiation therapy

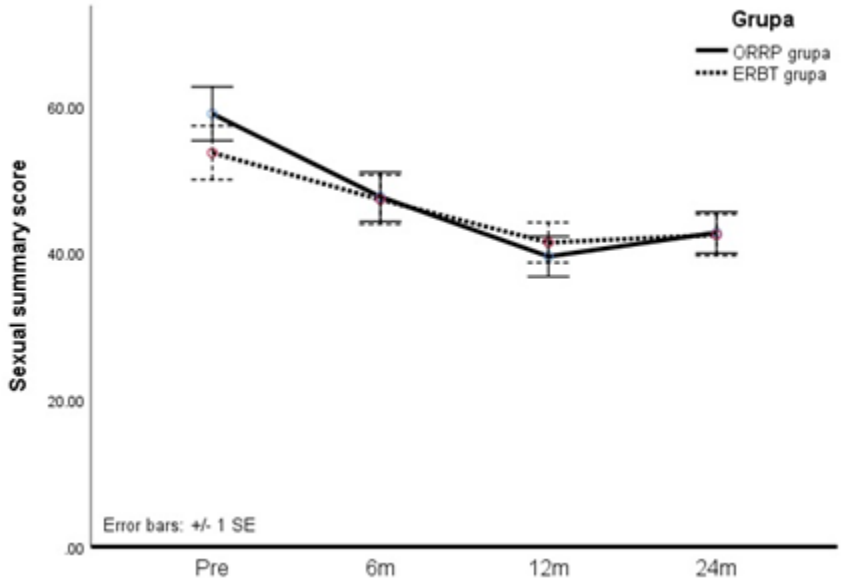

Figure 3. Values of sexual score in relation to the studied groups during the 24 month-follow-up; ORRP – open retropubic radical prostatectomy; EBRT – external beam radiation therapy

