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Radical prostatectomy *vs* radiotherapy in high-risk prostate cancer patients: two centre experience

Didelės rizikos prostatos vėžio gydymas taikant radikalią prostatektomiją arba spindulinę terapiją: dviejų centrų patirtis

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Background/objective

There are no randomized trials on the comparative effectiveness of radical prostatectomy (RP) and radiotherapy (RT) for high-risk prostate cancer. Our aim was to compare treatment outcomes of high-risk prostate cancer after RP and RT, including overall survival (OS), biochemical-progression-free survival (bPFS) and disease-progression-free survival (dPFS), using two cancer treatments centers' patient data.

Methods

Data on high-risk prostate cancer patients between 2005 and 2009 were retrospectively reviewed in two cancer centers: National Cancer Institute, Vilnius, Lithuania and N.N. Alexandrov National Cancer Centre of Belarus, Minsk, Belarus; 210 patients were included in the study group treated with RP (n = 174) or RT (n = 36). The mean follow-up time was 5.6 and 6.6 years, respectively.

Results

Lower T stage was an independent predictor of better OS ($p = 0.01$) and bPFS ($p = 0.03$). Only the highest Gleason score ≥8 was significantly predictive of a worse OS ($p = 0.05$), bPFS ($p = 0.02$) and dPFS ($p = 0.001$). A high PSA level was predictive of a worse bPFS ($p = 0.007$ for PSA ≥20) and dPFS ($p = 0.008$ for ≥20). The treatment modality in this study was insignificant after T stage, Gleason score and PSA level adjustment for OS, bPFS survival and dPFS survival ($p = 0.17$, $p = 0.39$, $p = 0.20$).

Conclusions

The T stage, Gleason score and pretreatment PSA level are significant factors for OS, bPFS survival, and dPFS survival of high-risk prostate cancer patients. Treatment option (RP or RT) was not an independent predictor of survival in this study.

Key words: high-risk prostate cancer, radical prostatectomy, radiotherapy

Įvadas / tikslas

Iki šiol nėra atlikta atsitiktinės atrankos klinikinių tyrimų siekiant palyginti radikalios prostatektomijos (RP) ir spindulinės terapijos (ST) efektyvumą gydant didelės rizikos prostatos vėžį. Šio tyrimo tikslas – naudojant dviejų gydymo centrų duomenis įvertinti didelės rizikos prostatos vėžiu sergančių ir RP arba ST gydytų pacientų bendrąjį išgyvenamumą, išgyvenamumą iki biocheminio progresavimo ir iki ligos progresavimo.

Pacientai ir metodai

2005–2009 metų duomenys apie didelės rizikos prostatos vėžio ligonius buvo retrospektyviai surinkti dviejuose gydymo centruose: Nacionaliniame vėžio institute (Vilnius, Lietuva) ir N. N. Aleksandrovo nacionaliniame vėžio centre (Minskas, Baltarusija). Tyrimo grupę sudarė 210 pacientų, iš kurių 174 taikyta RP, 36 – ST. Vidutinis stebėjimo laikas buvo atitinkamai 5,6 ir 6,6 metų.

Rezultatai

Pirminis naviko išplitimas (T) buvo susijęs su geresniu bendruoju išgyvenamumu (p = 0,01) ir geresniu išgyvenamumu iki biocheminio progresavimo (p = 0,03). Esant didžiausiam naviko diferenciacijos laipsniui (pagal *Gleason* ≥8) nustatytas reikšmingai blogesnis bendrasis išgyvenamumas (p = 0,05), išgyvenamumas iki biocheminio progresavimo (p = 0,02) ir išgyvenamumas iki ligos progresavimo (p = 0,001). Blogesnis išgyvenamumas iki biocheminio progresavimo (p = 0,007) ir iki ligos progresavimo (p = 0,008) taip pat buvo susijęs su aukštu PSA lygiu (≥ 20 ng/mL). Šioje tyrimo grupėje taikytas gydymas neturėjo reikšmingos įtakos bendrajam išgyvenamumui, išgyvenamumui iki biocheminio progresavimo ir iki ligos progresavimo (atitinkamai p = 0,17, p = 0,39, p = 0,20) atsižvelgus į pirminį naviko išplitimą, naviko diferenciaciją ir PSA lygį.

Išvados

Pirminis naviko išplitimas (T), naviko diferenciacijos laipsnis (pagal *Gleason*) ir PSA lygis iki gydymo turėjo reikšmingos įtakos bendrajam išgyvenamumui, išgyvenamumui iki biocheminio progresavimo ir iki ligos progresavimo didelės rizikos prostatos vėžiu sergančių pacientų grupėje. Šiame tyrime taikytas gydymas (RP arba ST) nebuvo nepriklausomas išgyvenamumui įtaką darantis veiksnys.

Reikšminiai žodžiai: didelės rizikos prostatos vėžys, radikali prostatektomija, spindulinė terapija

Introduction

Prostate cancer is the most common cancer in men worldwide [1] and the second cause of cancer-related death in men in the Western world [2]. The main treatment options for high-risk prostate cancer are radical prostatectomy (RP) and radiotherapy (RT). However, there is no consensus on which is superior [3], as no decisive large prospective randomised clinical trial comparing the outcomes of the treatments has been done yet. The only two completed trials are inconclusive or underpowered [4, 5], and the results of the ongoing trials might not be available soon [6]. Therefore, the only data sources currently available are retrospective studies. Although they are quite numerous, their results are controversial as well – most of them favor RP [7], but some favor also RT [8–10].

The purpose of this study was to compare treatment outcomes of patients with a high-risk prostate cancer after RP and RT, including overall survival (OS), biochemical-progression-free survival (bPFS), and disease-progression-free survival (dPFS), using two cancer treatment centers' patient data.

Materials and methods

Study population

Data on high-risk prostate cancer patients were collected retrospectively in two oncology centers. The National Cancer Institute, Vilnius, Lithuania (NCI) is one of the biggest prostate cancer treating tertiary health care centers in Lithuania. During the study period, high-risk prostate cancer patients were treated according to the standard hospital treatment protocol which corresponds to the Lithuanian Urologist Association recommendations based on the protocol confirmed by the Lithuanian Ministry of Health (2002-08-14, 422). N.N. Alexan-

drov National Cancer Center of Belarus, Minsk (NCC) is the biggest cancer centre in Belarus, where prostate cancer patients are concentrated. In the NCC, prostate cancer patients were mainly treated surgically, while in the NCI both treatment methods were used.

The medical records of patients who presented to urology departments at the NCI and the NCC between 2005 and 2009 were reviewed. High-risk patients were defined as T3 or the Gleason 8–10 or PSA > 20 ng/mL (one criteria) or those who met two of the following criteria: T2b or greater; the Gleason score 7; PSA 10–20 ng/ml.

Treatment

Prostate cancer patients were treated according to the standard treatment protocols. RP is a typical surgical procedure with a standard protocol. Prostate, seminal vesicles and regional lymph nodes are removed. The bladder and the urethra are then reconnected. RT patients in this study group were treated with external beam radiotherapy to a total dose of 40–72 Gy (for 26 patients 70 Gy) with a daily dose of 2 Gy delivering five fractions per week.

In the RT group, 33 of 36 patients received neoadjuvant antiandrogen therapy 2–3 months before radiotherapy, during the therapy and 6 months to 2 years after. In the surgery group, for 27 of 174 patients adjuvant therapy was used differently in the two centers: in the NCI, neoadjuvant the antiandrogen therapy was used during the study period and in the NCC adjuvant treatment was used if the operation was found to be not radical.

Follow-up

The study population includes only patients with adequate follow-up data (the last standard medical examination no less than 3 years after treatment). In both centers, the PSA level is tested every 3 months for one year, then every 6 months for the next 3 years, then once a year.

The primary endpoint of interest was overall survival (OS). OS was defined as the time from surgery in the RP group and the date of radiotherapy in the RT group to death from any cause or to 31 December 2012. Biochemical-progression-free survival was defined as the time from surgery to the PSA level ≥0.2 ng/mL and after radiotherapy as a rise of PSA more than 2 ng/mL after the nadir had been reached. Disease progression was defined as the development of either local disease recurrence or distant metastases.

Statistical analysis

Survival was estimated by the Kaplan–Meier method, and the Cox regression analysis was used to assess the effects of different variables on patient survival. The survival curves were compared using the log-rank test. $P < 0.05$ indicated a statistically significant difference. All statistical analyses were performed using the Stata Statistical Software version 11.0. (StataCorp. 2009. Stata Statistical Software: Release 11.0. College Station, TX, USA).

Results

Study group characteristics

The mean patient age of the whole group was 62.9 years (range, 44–77 years), and the mean pretreatment PSA level was 20.1 ng/mL (range, 2.0–214.6 ng/mL). The characteristics of the patients by treatment group are shown in Table 1.

In total, 174 patients received RP and 36 patients RT as the definitive prostate cancer treatment. There were no notable imbalances with regard to the mean age, the biopsy Gleason score and the mean pretreatment PSA level. Patients treated with RP were more likely to have the clinical stage T2b–T2c (57.5% vs. 13.9%) and less likely to have stage T3 (42.5% vs. 86.1%) as compared with patients treated with RT. The mean follow-up time was 5.6 years for the RP and 6.6 years for the RT groups.

Treatment outcomes

The outcomes analyzed were the 5-year overall survival (OS), the biochemical-progression-free survival (bPFS), and the disease-progression-free survival (dPFS) rates. The results of the Kaplan–Meier univariate survival analysis as well as the 5-year survival are presented in Table 2. For 210 patients in the study, the mean OS was 92%, bPFS 42%, and dPFS 82%. Age was not a

Table 1. Baseline characteristics of the study group

Parameter	RP(N = 174)		RT (N = 36)	
	N	%	N	%
Mean age (yr) (range)	62.7 (44–77)		64.0 (53–75)	
< 65	95	54.60	17	47.22
>= 65	79	45.40	19	52.78
T stage				
T2b–T2c	100	57.47	5	13.89
T3	74	42.53	31	86.11
Biopsy Gleason				
Gleason ≤6	127	72.99	28	77.78
Gleason 7	33	18.97	7	19.44
Gleason ≥8	14	8.05	1	2.78
Mean PSA level (ng/mL) (range)	21.3 (2.01–214.6)		14.1 (3.1–51.0)	
< 10	83	47.70	15	41.67
10–20	32	18.39	16	44.44
> 20	59	33.91	5	13.89
Treatment centre				
NCC	92	52.87	-	
NVI	82	47.13	36	100.00
Adjuvant therapy				
No	147	84.48	3	8.33
Yes	27	15.52	33	91.67
Biochemical progression	99	56.90	23	63.89
Disease progression	33	18.97	4	11.11
Deaths	18	10.34	2	5.56
Deaths from cancer	11	6.32	1	2.78
Mean followup (yr) (range)	5.6 (1.1–7.9)		6.6 (4.1–8.8)	

significant factor influencing survival in this study. A lower T stage was associated with a better OS (96% vs. 88%, $p = 0.01$) and bPFS (48% vs. 36%, $p = 0.02$), but not dPFS. Similarly, a lower Gleason score was related to a better OS ($p = 0.02$) and dPFS ($p = 0.003$) and not significantly with a better bPFS ($p = 0.07$). The PSA level was important for both bPFS ($p = 0.02$) and dPFS ($p = 0.02$) but not for OS ($p = 0.34$). Treatment outcomes were better in the RT as compared to the RP group: OS – 97% vs. 91%, bPFS – 48% vs. 41%, dPFS – 92% vs. 80%. However, the Kaplan–Meier survival analysis showed no statistically significant difference between patients treated with surgery or radiotherapy. Statistically significant results are presented in Figures 1–3.

The Cox multivariate survival analysis was conducted to determine the prognostic value of the significant clinical and pathological features (Table 3). The variables studied included T stage (T2b–T2c vs. T3), the Gleason score at biopsy (≤6 vs. 7 vs. ≥8), PSA level (<10 vs. 10–20 vs. >20 ng/ml), and treatment modality (RP vs. RT). The variables had an uneven impact on the three outcome measures. A lower T stage was an independent predictor of a better OS ($p = 0.01$) and bPFS ($p = 0.03$). Only the highest Gleason score ≥8 was significantly

Table 2. 5-year survival and results of univariate analysis in high-risk prostate cancer patients

Parameter	OS			log rank, p	bPFR			log rank, p	dPFR			log rank, p
	Rate	95% CI			Rate	95% CI			Rate	95% CI		
Total	91.9	87	94.9		42	34.5	49.4		81.6	74.5	86.8	
Age												
< 65	91.4	84.1	95.5	0.92	45.3	34.8	55.1	0.78	85.7	76.4	91.5	0.32
>= 65	92.4	84.8	96.3		38.6	27.8	49.3		77	65.2	85.3	
T stage												
T2b–T2c	96	89.8	98.5	0.01	48.4	37.5	58.5	0.02	82.3	72	89.1	0.94
T3	87.5	79	92.7		35.7	25.5	46		81.1	70.5	88.2	
Gleason at biopsy												
Gleason ≤6	93.6	88.1	96.7	0.02	44.4	35.3	53	0.07	82.7	74	88.8	0.003
Gleason 7	92.5	78.5	97.5		40.4	24.6	55.7		88.6	72.3	95.6	
Gleason ≥8	70.5	38.9	87.9		25	6.88	48.8		53.3	26.3	74.4	
PSA level (ng/mL)												
< 10	92.6	85.1	96.4	0.34	51.5	39.4	62.2	0.02	90.8	82.4	95.3	0.02
10–20	95.6	83.4	98.9		37.3	22.5	52		78.6	61.4	88.8	
> 20	87.8	76	94		32.2	20.5	44.4		69.8	53.8	81.2	
Treatment												
RP	90.6	84.9	94.3	0.25	40.7	32.4	48.8	0.65	79.8	71.9	85.6	0.15
RT	97.2	81.9	99.6		47.9	29.2	64.3		91.6	69.9	97.9	

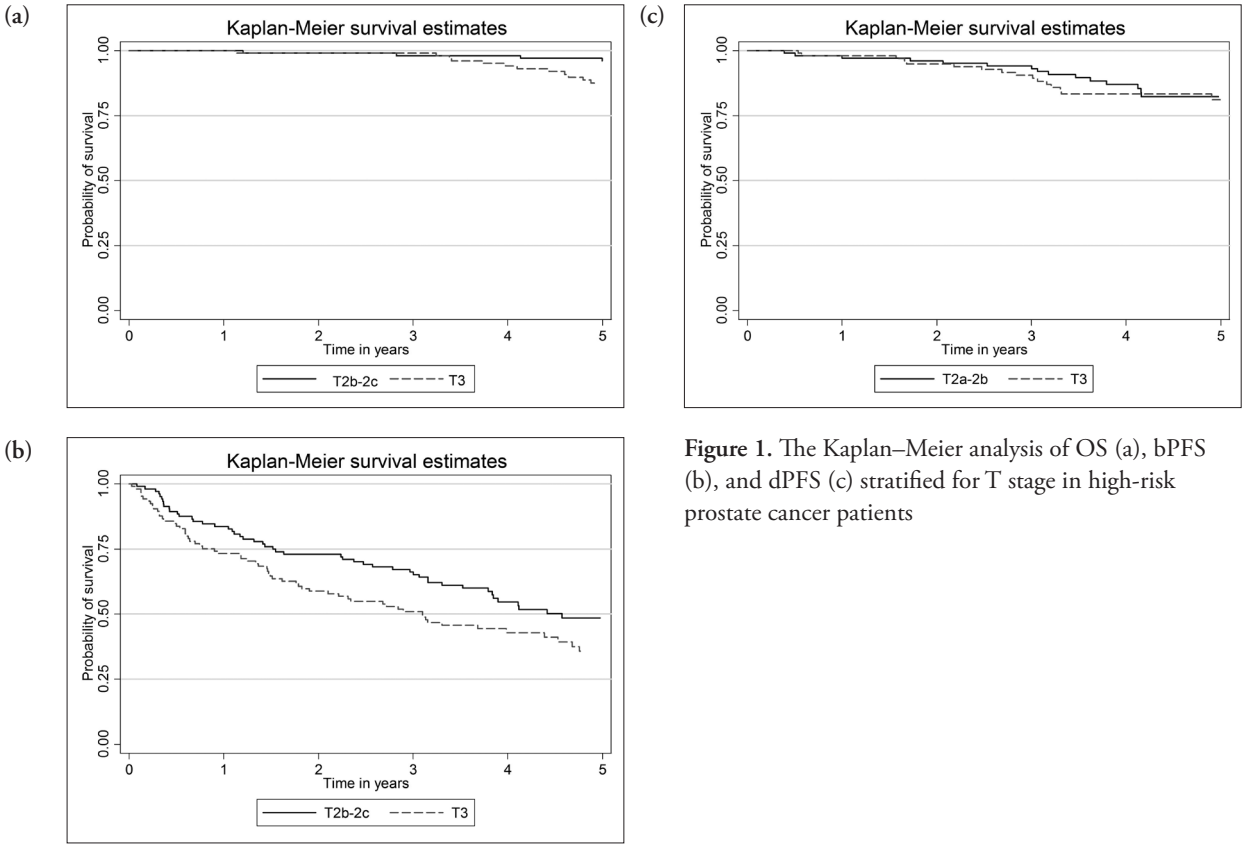

Figure 1. The Kaplan–Meier analysis of OS (a), bPFS (b), and dPFS (c) stratified for T stage in high-risk prostate cancer patients

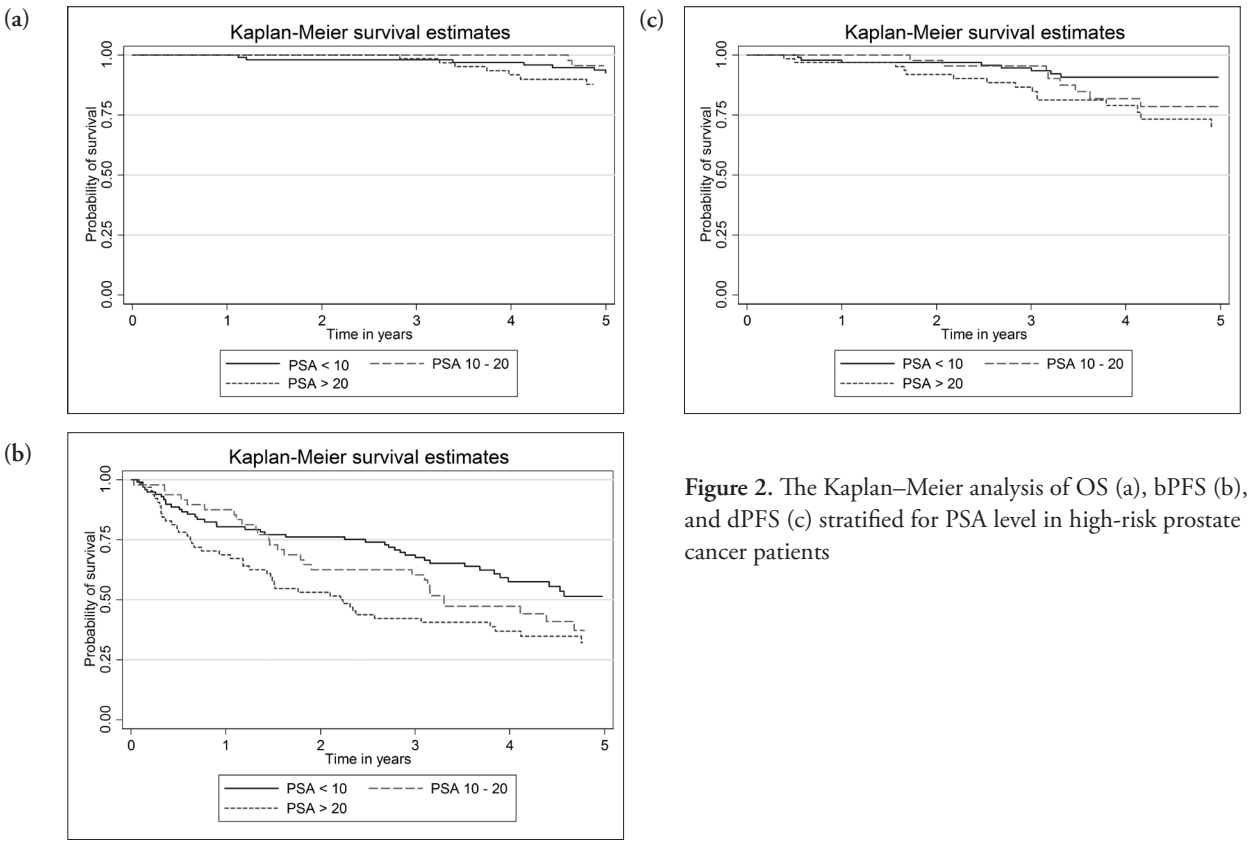

Figure 2. The Kaplan–Meier analysis of OS (a), bPFS (b), and dPFS (c) stratified for PSA level in high-risk prostate cancer patients

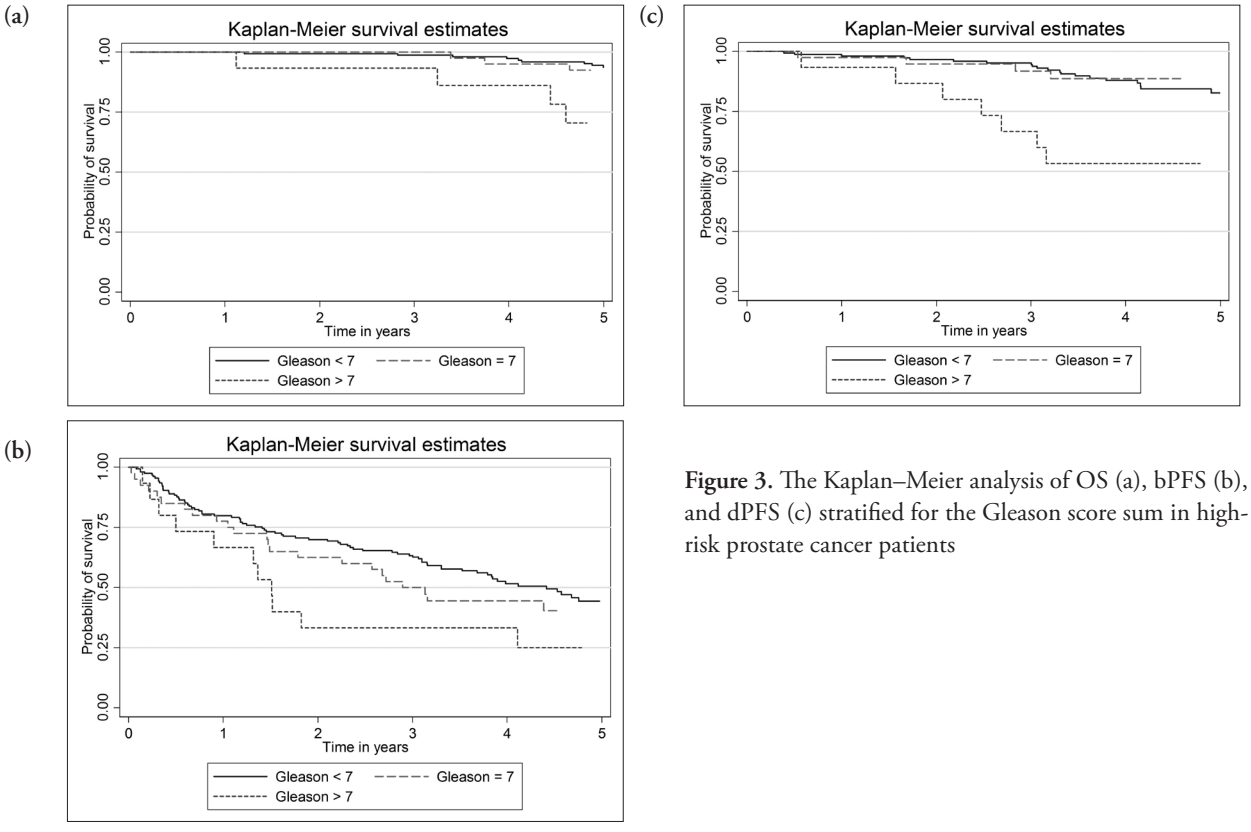

Figure 3. The Kaplan–Meier analysis of OS (a), bPFS (b), and dPFS (c) stratified for the Gleason score sum in high-risk prostate cancer patients

Table 3. Cox multivariate regression analysis of survival in high-risk prostate cancer patients

Parameter	OS			p value	bPFR			p value	dPFR			p value
	HR	95% CI			HR	95% CI			HR	95% CI		
T stage												
T2b–T2c	Ref.	–	–	–	Ref.	–	–	–	Ref.	–	–	–
T3	3.76	1.31	10.78	0.01	1.52	1.04	2.24	0.03	1.14	0.58	2.24	0.71
Gleason at biopsy												
Gleason ≤6	Ref.	–	–	–	Ref.	–	–	–	Ref.	–	–	–
Gleason 7	1.43	0.49	4.20	0.51	1.49	0.94	2.37	0.09	1.59	0.66	3.85	0.30
Gleason ≥8	3.33	1.03	10.79	0.05	2.09	1.13	3.88	0.02	3.84	1.68	8.77	0.001
PSA level (ng/mL)												
< 10	Ref.	–	–	–	Ref.	–	–	–	Ref.	–	–	–
10–20	0.70	0.19	2.63	0.60	1.50	0.94	2.40	0.09	3.20	1.27	8.07	0.01
> 20	1.38	0.52	3.70	0.52	1.85	1.19	2.90	0.007	3.07	1.34	7.07	0.008
Treatment												
RP	Ref.	–	–	–	Ref.	–	–	–	Ref.	–	–	–
RT	0.34	0.07	1.58	0.17	0.80	0.47	1.34	0.39	0.47	0.15	1.49	0.20

predictive of a worse OS (p = 0.05), bPFS (p = 0.02) and dPFS (p = 0.001). The PSA level was not a predictor of OS; however, the high PSA level was predictive of a worse bPFS (p = 0.007 for PSA ≥20) and a worse dPFS (p = 0.01 for the PSA level 10–20, p = 0.008 for ≥20). The treatment modality (RP vs. RT) in this study was insignificant after the T stage, Gleason score and PSA level adjustment for OS, bPFS survival, and dPFS survival (p = 0.17, p = 0.39, p = 0.20).

Discussion

The comparative effectiveness of local prostate cancer treatment is recognized as one of the top 25 research issues by the Institute of Medicine [11]. Despite the need to solve this question, to our knowledge, no convincing randomized clinical trial has been published yet. There are trials comparing outcomes of surgery with watchful waiting [12, 13] and surgery with RT in low-risk prostate cancer [14], but RP vs. RT in high-risk prostate cancer is still a heated debate. Meanwhile, it is possible to shed some light on the question with retrospective studies.

Treatment option was not an independent predictor of outcome in this study. Although the OS, bPFS and dPFS were slightly higher in the RP group, the difference was statistically insignificant. A few explanations could be given: either the treatment modalities are equally effective or there are some drawbacks in our study. Our study population was quite small (N = 210), especially the RT group (N = 36). Although we considered many confounding variables (age, T stage, biopsy Gleason score, pretreatment PSA level), some were left out, e.g., comorbidity. On the other hand, there is some evidence that comorbidity (the Charlson comorbidity index) is not a better predictor of survival than age [15], especially for cancer-specific survival [16]. It would be useful to compare cancer-specific survival (CSS) with overall survival (OS) in both treatment groups to check for significant differences. In this study, CSS was very low (results not shown) because of the moderately small patient population and follow-up time, therefore, it was not analyzed here.

The study found that the T stage, Gleason score and pretreatment PSA level were independent predictors of OS or disease progression. These parameters were found to predict outcome independently of the treatment in other studies as well [16–18]. Particularly predictive of a worse outcome in our study was the Gleason score ≥8. The PSA level was a significant independent predictor of bPFS and dPFS, but not OS. Similarly, Denham et al.

[19] found that the high pretreatment PSA was a strong predictor of biochemical recurrence but not of cancer-specific survival once recurrence had happened. According to the authors, this could be due to the small but significant subgroup of patients with aggressive locally advanced prostate cancer which exhibits low pretreatment PSA levels. In such patients, the low pretreatment PSA could even be a predictor of a worse cancer-specific (and thus overall) survival.

A drawback of our study was rather small and heterogeneous patient population. Patients from two cancer centers were pooled to increase the sample size and the ability to generalize the results, thus rendering the study more valid. It was possible to pool the patients as treatment protocols did not differ in the two centers. However, it could have been more difficult to control for the confounding variables in such a mixed patient population. Again, this problem could be solved with a larger study population.

The mean follow-up time in this study was 5.6 years for RP and 6.6 years for RT groups. It is comparable or a little shorter than the follow-up in similar studies [17, 20]. However, it could be argued that the follow-up for prostate cancer patients should be longer to be sufficient. With a longer follow-up, additional survival benefits could have showed up in one of the treatment groups. Prostate cancer usually progresses particularly slowly, and even after biochemical recurrence only a minority of patients die from cancer-specific causes [21]. Therefore, to track the outcomes of the therapy more accurately, cancer-specific (or overall) survival with a long (e.g., 10 or 15 years) follow-up should be preferred over bPFS with a shorter follow-up.

The quality of life is another issue for high-risk prostate cancer patients. Cancer-specific mortality is very low even in high-risk prostate cancer patients after any radical treatment [22]. As overall survival differs minimally with either treatment (RP or RT), the subsequent quality of life becomes crucially important. We did not analyze the quality of life after a certain treatment in this study; however, there are results from other studies. In a study with patients comparable at baseline [23], RT was found to be at least as good as RP, with even better results in sexual and urinary domains. Nicolaisen et al. [24] found no apparent long-term quality of life difference with respect to treatment modality (RP, RT or RP + RT). The exact outcomes for treatments compared were slightly different (e.g., RT was associated with a better urinary function). Interestingly, pretreatment information and patient education had a more significant improvement on patient quality of life than the treatment option itself. A useful way to quantify the quality of life after treatment is calculating the quality-adjusted life years. Using the constructed model and literature facts, Parikh and Sher [25] found that RT with hormone therapy was superior to RP with RT, resulting in a higher quality-adjusted life expectancy, especially in patients who tolerated hormone therapy well.

Another approach to compare two treatment modalities which yield very similar results is their cost. In a hypothetical model, Cooperberg et al. [26] found that differences in outcomes, expressed in quality-adjusted life years, were small. However, the difference in costs of RT and RP was substantial – the cost for RT was essentially higher. This fact could also be considered, especially if RP and RT prove to have the same efficacy in larger randomized trials as well.

New treatment options have become commonplace since most of the retrospective studies (including ours) had been conducted: primary androgen deprivation, cryotherapy, brachytherapy. Original treatment modalities have been improved too with intensity-modulated or proton beam radiation therapy and laparoscopic or robotic-assisted radical prostatectomy. Therefore, it might be useful to supplement the future comparative effectiveness studies with these new treatment options.

Conclusion

The T stage, Gleason score and pretreatment PSA level are significant factors for OS, bPF survival and dPF survival of prostate cancer patients. Treatment option was not an independent predictor of survival in this study.

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