Asian Journal of Andrology (2009) 11: 131–137

www.nature.com/aja

Original Article

Correlations between age, Charlson score and outcome in clinical unilateral T3a prostate cancer

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Abstract

According to the European Association of Urology (EAU) guidelines, a life expectancy of > 10 years is considered an important factor in the treatment of prostate cancer. The Charlson score is used to predict mortality based on comorbidities. The purpose of this study was to investigate the relationship between age, Charlson score and outcome in patients with cT3a prostate cancer. Between 1987 and 2004, 200 patients, who were with clinical T3a prostate cancer and who underwent radical prostatectomy (RP), were previously detected by digital rectal examination (DRE). Patients were categorized into two age groups (< 65 and ≥ 65 years old). Patients were also divided into two groups according to Charlson score (= 0 and ≥ 1). Both age and Charlson score were analyzed regarding their predictive power of patients' outcomes. The mean follow-up period was 70.6 months, and the mean age of patients was 63.3 years. In all, 106 patients were < 65 years old and 94 patients were ≥ 65 years old. Age was a significant predictor of overall survival (OS). A Charlson score of 0 was found in 110 patients, and of ≥ 1 in 90 patients. Charlson score was not a significant predictor of biochemical progression-free survival (BPFS), clinical progression-free survival (CPFS) or OS. Cox multivariate analysis showed that margin status was a significant independent factor in BPFS, and cancer volume was a significant independent factor in CPFS. Charlson score does not influence the outcome in patients with clinical locally advanced prostate cancer. Age may influence OS. RP can be performed in motivated healthy older patients. However, the patients need to be counseled regarding possible surgery-related side effects, such as urinary incontinence and erectile dysfunction, which are age- and comorbidity-dependent.

Asian Journal of Andrology (2009) 11: 131–137. doi: 10.1038/aja.2008.35; published online 15 December 2008.

Keywords: age, Charlson score, cT3a prostate cancer

1 Introduction

Locally advanced prostate cancer is defined as a tumor that has extended clinically beyond the prostatic capsule, with invasion into the pericapsular tissue, apex, bladder neck or seminal vesicle, but without lymph node involvement or distant metastases. Possible treatments for T3 prostate cancer include radical prostatectomy (RP), radiotherapy (RT), androgen deprivation therapy (ADT) and combinations of these three. However, the best method of treatment for patients with locally advanced prostate cancer remains unknown. Several authors have reported their surgical experience with locally advanced prostate cancer [1–6]. In these reports, the overall survival (OS) at 5 and 10 years was greater than 75% and greater than 60%, respectively, and the cancer-specific survival (CSS) at 5 and 10 years was 85%–100% and 57%–100%, respectively.

According to the guidelines of the European Association of Urology (EAU), RP can be performed in organ-confined patients with a life expectancy of more than 10 years who accept treatment-related complications. For locally advanced disease, RP can be performed in patients with prostate-specific antigen (PSA) serum levels < 20 ng mL^{-1}, the tumor ≤ cT3a,

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Received: 17 October 2008 Accepted: 20 October 2008
Published online: 15 December 2008

biopsy Gleason score ≤ 8 and a life expectancy of > 10 years [7]. Therefore, a life expectancy of more than 10 years seems to be an important factor in the treatment of prostate cancer. The Charlson index contains 19 categories of comorbidity, which are defined using ICD-9-CM diagnosis codes and are weighted from 1 to 6, on the basis of the relative risk of dying from the condition [8]. The overall comorbidity score is calculated by summing all individual comorbidity scores for a given patient. The categories included are as follows: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease and mild-to-moderate diabetes, all weighted 1; diabetes with chronic complications, hemiplegia, severe renal disease and any malignancy, including lymphoma and leukemia, all weighted 2; moderate or several liver disease, weighted 3; and metastatic solid tumor or AIDS, weighted 6. A higher Charlson score correlates with higher mortality rate. The purpose of this study was to analyze the correlations between age or Charlson score and biochemical progression-free survival (BPFS), clinical progression-free survival (CPFS), CSS and OS in patients with clinical unilateral T3a prostate cancer.

2 Materials and methods

2.1 Patients

Between 1987 and 2004, 2 273 patients underwent RP at our institution. Two hundred and thirty-five patients (10.3%) were assessed as having unilateral cT3 disease by digital rectal examination (DRE). They were selected for operation on the basis of possessing limited, unilateral cT3a, any Gleason score, any PSA level and ECOG performance status 0–1. Thirty-five patients who received neoadjuvant treatment before surgery were excluded. Two hundred patients (8.8%) were included in the final analysis. Patients with clinical unilateral T3a disease assessed by transrectal ultrasound, but not by DRE, were not included. The data were retrieved from patient files, from the computer system of the hospital and from general practitioners, who provided updated clinical and biochemical information by telephone. No patient received ADT or RT before RP. All patients had negative findings on both contrast-enhanced computed tomography (CT) of the pelvis and bone scan.

The patients were categorized into two subgroups according to age at surgery: < 65 and ≥ 65 years old. The patients were also divided into two subgroups according to the Charlson score at surgery: 0 and ≥ 1.

Patients underwent bilateral pelvic lymphadenectomy without frozen section, followed by radical retropubic prostatectomy under general or spinal anesthesia. Surgery was performed by one of two senior surgeons, according to the techniques described earlier [9].

The last PSA value obtained before prostate biopsy was used in the analysis. The RP specimens, including prostate, seminal vesicles and bilateral pelvic lymph nodes, were examined microscopically after routine preparation. The prostate was weighed and cut as a whole mount section at 4-mm intervals. All specimens were scored according to the Gleason grading system. Microscopic extension of malignant cells to the inked surface of the resected specimen was interpreted as a positive surgical margin. The pathology reports were recorded as pT2a, pT2b, pT2c, pT3a, pT3b or pT4, and lymph node status was assigned on the basis of the 2002 TNM classification [10].

BPFS was defined as the time between operation and the moment of biochemical progression. Biochemical progression was defined as any postoperative serum PSA level ≥ 0.2 ng mL^{-1}. All patients who experienced PSA progression below this threshold but received adjuvant or salvage treatment (RT and/or ADT) were censored for BPFS. CPFS was defined as the time between operation and the moment of local or distant progression. Local recurrence was defined as cancer cells in the pelvic area proven by pathological examination. Distant metastases were defined as lesions suspicious for tumor, detected by bone scan, CT or MRI, outside the pelvic area. CSS was defined as the time between operation and death from disease progression or complications caused by the disease. OS was defined as the time between operation and death from any cause.

2.2 Statistical analysis

All categorical variables were analyzed by χ^2 test. Continuous variables were compared by one-way analysis of variance. Kaplan–Meier analysis with the log-rank test was used to analyze the correlation between age, Charlson score and all survival variables (BPFS, CPFS, CSS and OS). Cox proportional hazard regression analysis was used to determine whether age or Charlson score was an independent prognostic indicator of disease progression. MedCalc statistical software, version 8.1.0.0 (MedCalc Software, Belgium) and SPSS v12.0 (SPSS Inc., Chicago, IL, USA) were used for the analysis.

3 Results

The mean age of patients was 63.3 years (range 41–79 years). The mean follow-up period was 70.6 months (range 7–177 months). Forty-seven patients (23.5%) were confirmed to have organ-confined disease (pT2), and 145 (72.5%) were staged as pT3, including 113 (56.5%) with extraprostatic extension alone and 32 (16%) with seminal vesicle invasion. Eight patients (4%) had adjacent structure invasion (pT4). Seventeen patients (8.5%) had lymph node

involvement. No positive lymph nodes were found in any patient with pT2. The mean PSA was 14.9 ng mL^{-1} (range 1–127 ng mL^{-1}). The median surgical Gleason score was 7 (range 4–9). Sixty-seven patients (33.5%) had a positive surgical margin, including all the patients with pathological T4. One hundred and twelve patients (56%) received adjuvant or salvage treatment (ADT, RT or both) after RP.

One hundred and six patients were < 65 years old, and 94 patients were ≥ 65 years old (Table 1). Between the two age subgroups, there were no significant differences in preoperative PSA, node status, pathological stage, surgical Gleason score or cancer volume. Only surgical margin status was significantly different between the groups. In the Cox multivariate analysis, age was a significant predictor of OS (Table 2). In the Kaplan–Meier analysis, there were no significant differences between age groups in BPFS, CPFS or CSS (P = 0.263 for BPFS, 0.192 for

Table 1. Patient characteristics by age group.

Age (years)	< 65	≥ 65	*P* value
Number of patients	106	94	
Preoperative PSA			
Mean (range)	14.0 (1.0–97.0)	15.9 (2.7–127.0)	0.360
+ Node, *n* (%)	12 (11.3%)	5 (5.3%)	0.206
+ Margin, *n* (%)	26 (24.5%)	41 (43.6%)	0.007
Surgical Gleason score			
Mean (range)	7 (4–9)	7 (5–9)	0.499
Cancer volume			
Mean (range)	6.78 (0.20–31.00)	6.38 (0.88–27.70)	0.646
Pathological stage, *n* (%)			
2	33 (31.1%)	14 (14.9%)	0.053
3a	55 (51.9%)	58 (61.7%)	
3b	15 (14.2%)	17 (18.1%)	
4	3 (2.8%)	5 (5.3%)	

Abbreviation: PSA, prostate-specific antigen.

Table 2. Cox univariate and multivariate analyses of BPFS, CPFS and OS.

Survival	Covariates	Univariate			Multivariate		
		HR	95% CI	*P*	HR	95% CI	*P*
BPFS	Preoperative PSA	1.021	1.010–1.032	< 0.001	1.012	0.998–1.025	0.090
	Cancer volume	1.056	1.024–1.090	0.001	1.022	0.985–1.061	0.242
	Node	0.336	0.181–0.624	0.001	0.637	0.314–1.292	0.211
	Margin	0.293	0.187–0.459	< 0.001	0.367	0.226–0.593	< 0.001
	Gleason score ≤ 7(3+4) *vs*. ≥ 7(4+3)	0.882	0.561–1.387	0.588	1.022	0.632–1.653	0.929
	Pathological stage			< 0.001			0.311
	T3a *vs*. T2	1.510	0.777–2.935	0.224	1.114	0.559–2.221	0.759
	T3b–T4 *vs*. T2	3.982	1.956–8.108	< 0.001			
	Charlson score 0 *vs*. ≥1	0.878	0.562–1.369	0.565	1.259	0.787–2.015	0.337
	Age	1.020	0.988–1.052	0.228	1.014	0.983–1.047	0.369
CPFS	Preoperative PSA	1.005	0.979–1.031	0.718	0.991	0.960–1.024	0.596
	Cancer volume	1.124	1.060–1.192	< 0.001	1.080	1.022–1.164	0.045
	Node	2.227	0.073–0.708	0.011	0.864	0.215–3.482	0.838
	Margin	0.329	0.116–0.937	< 0.001	0.476	0.154–1.467	0.196
	Gleason score ≤ 7(3+4) *vs*. ≥ 7(4+3)	0.389	0.144–1.055	0.064	0.581	0.189–1.782	0.342
	Pathological stage			0.018			0.378
	T3a *vs*. T2	2.702	0.334–21.882	0.352	2.205	0.252–19.251	0.475
	T3b–T4 *vs*. T2	8.944	1.102–72.597	0.040	4.700	0.399–55.374	0.219
	Charlson score 0 *vs*. ≥ 1	1.610	0.595–4.355	0.349	1.996	0.706–5.648	0.193
	Age	0.963	0.906–1.025	0.236	0.956	0.897–1.019	0.168
OS	Preoperative PSA	1.015	0.999–1.031	0.062	1.000	0.976–1.024	0.990
	Cancer volume	1.114	1.054–1.178	< 0.001	1.067	0.994–1.146	0.071
	Node	0.258	0.093–0.713	0.009	0.550	0.146–2.079	0.378
	Margin	0.390	0.149–1.019	0.055	0.774	0.276–2.175	0.627
	Gleason score ≤ 7(3+4) *vs*. ≥ 7(4+3)	0.514	0.206–1.283	0.154	0.499	0.176–1.414	0.191
	Pathological stage			0.001			0.207
	T3a *vs*. T2	0.919	0.185–4.559	0.918	0.509	0.096–2.706	0.429
	T3b–T4 *vs*. T2	5.558	1.242–24.883	0.025	1.429	0.240–8.524	0.695
	Charlson score 0 *vs*. ≥ 1	0.860	0.358–2.068	0.736	1.146	0.426–3.083	0.787
	Age	1.111	1.028–1.201	0.008	1.103	1.024–1.189	0.010

Abbreviation: BPFS, biochemical progression-free survival; CI, confidence interval; CPFS, clinical progression-free survival; HR, hazard ratio; OS, overall survival; PSA, prostate-specific antigen.

Table 3. Projected 5- and 10-year survival rates by age group.

Age (years)	Survival	5-year (%)	10-year (%)
< 65	BPFS	64.5	50.8
	CPFS	94.2	79.9
	CSS	98.5	95.7
	OS	98.5	85.9
≥ 65	BPFS	53.8	51.4
	CPFS	97.5	90.3
	CSS	98.8	88.3
	OS	93.4	69.3

Abbreviation: BPFS, biochemical progression-free survival; CPFS, clinical progression-free survival; CSS, cancer-specific survival; OS, overall survival.

Table 4. Patient characteristics by Charlson score group.

Charlson score	0	≥ 1	*P* value
Number of patients	110	90	
Mean age (range)	62.1 (43–75)	64.8 (41–79)	0.010
Preoperative PSA			
Mean (range)	13.9 (1.0–127.0)	16.1 (1.2–97.0)	0.293
+ Node, *n* (%)	7 (6.4%)	10 (11.1%)	0.346
+ Margin, *n* (%)	33 (30.0%)	34 (37.8%)	0.313
Surgical Gleason score			
Mean (range)	7 (5–9)	7 (4–9)	0.789
Cancer volume			
Mean (range)	5.96 (0.20–31.00)	7.36 (0.88–28.00)	0.106
Pathological stage, *n* (%)			
2	31 (28.2%)	16 (17.8%)	0.113
3a	63 (57.3%)	50 (55.6%)	
3b	13 (11.8%)	19 (21.1%)	
4	3 (2.7%)	5 (5.5%)	

Abbreviation: PSA, prostate-specific antigen.

Table 5. Projected 5- and 10-year survival rates by Charlson score group.

Charlson score	Survival	5-year (%)	10-year (%)
0	BPFS	60.7	51.5
	CPFS	95.1	82.3
	CSS	98.7	89.4
	OS	96.1	77.4
≥ 1	BPFS	58.0	50.5
	CPFS	96.9	89.3
	CSS	98.7	94.1
	OS	95.7	75.2

Abbreviation: BPFS, biochemical progression-free survival; CPFS, clinical progression-free survival; CSS, cancer-specific survival; OS, overall survival.

CPFS and 0.325 for CSS). OS was significantly different between the two age groups on the basis of Kaplan–Meier analysis ($P = 0.015$) (Figure 1). The projected 5- and 10-year survival rates for the two age groups are listed in Table 3.

A Charlson score of 0 was found in 110 patients and a score ≥ 1 was seen in 90 patients (Table 4). Preoperative PSA, node status, margin status, pathological stage, surgical Gleason score and cancer volume did not differ significantly between Charlson score 0 and ≥ 1 groups. Only age was significantly different. In the Cox multivariate analysis, Charlson score was not a significant predictor of BPFS, CPFS or OS (Table 2). In the Kaplan–Meier analysis, there were no significant differences between the Charlson score groups in any of the survival outcomes. *P* values were 0.559 for BPFS, 0.344 for CPFS, 0.820 for CSS and 0.736 for OS (Figures 2). The projected 5- and 10-year survival rates for the Charlson score groups are listed in Table 5.

Cox multivariate analysis showed that margin status was a significant independent factor in BPFS, whereas cancer volume was a significant independent factor in CPFS (Table 2).

4 Discussion

It is generally accepted that RP can cure most patients with organ-confined prostate cancer. Patients are selected on the basis of clinical stage, age and comorbidities. Usually, patients are considered to be candidates for radical surgery if life expectancy exceeds 10 years and if they are not affected by major comorbidities. The role of surgery in locally advanced prostate cancer is still subject to debate. Nevertheless, in the past 7 years, a number of centers have convincingly argued for the use of surgery in well-selected patients. However, it remains unclear which selection criteria should be used. According to the EAU guidelines (2008 edition), a patient is considered to be a good candidate for RP if the tumor is ≤ cT3a, Gleason score is ≤ 8 and PSA is < 20. Life expectancy is difficult to estimate. Age is in and of itself not a good predictor of life expectancy. Indeed, more and more patients are surviving to 80 years and older. Age is a risk factor for prostate cancer; thus, it is to be expected that an increasing number of elderly patients (> 65 years) will present with prostate cancer to urologists worldwide. The Charlson score is an instrument that can be used in conjunction with age to improve the estimates of a patient's life expectancy. Locally advanced prostate cancer is expected to have a higher disease-specific mortality rate than localized prostate cancer. In this particular patient group, the impact of age and/or Charlson score on survival has not been studied to date.

In an earlier analysis, we studied the correlations between predictive factors (including surgical Gleason score, margin status, node status, pathological stage, preoperative PSA and cancer volume) and survival outcomes in a group of patients who underwent RP for locally advanced prostate cancer. Margin status was the

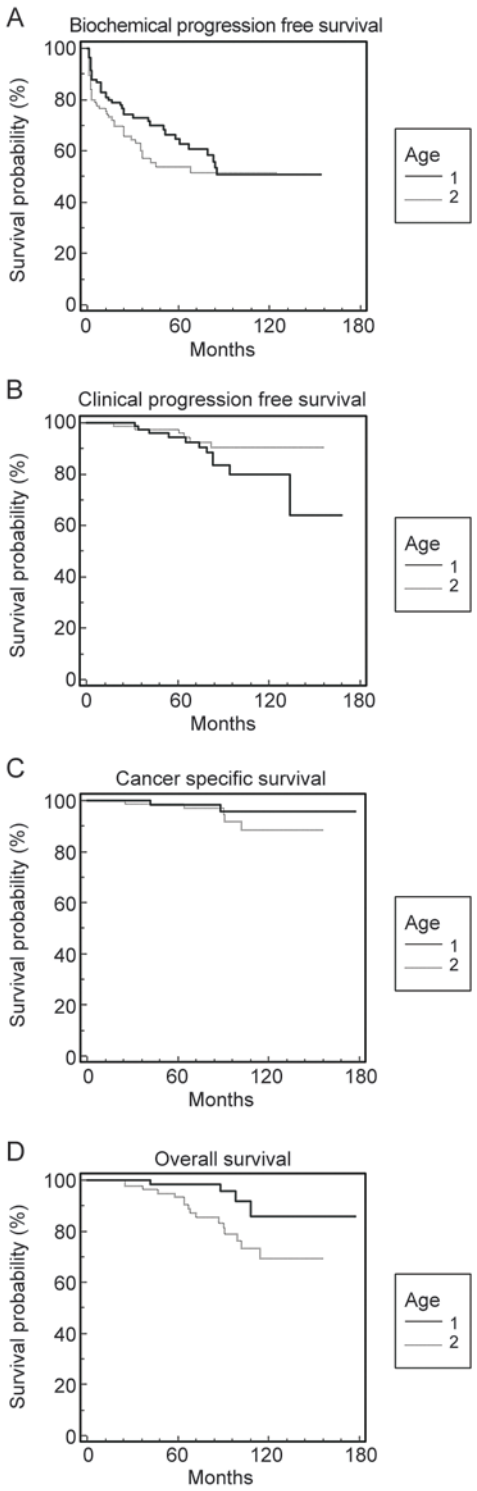

Figure 1. The relationship between age (age group 1: < 65 years, age group 2: ≥ 65 years) and survival outcomes by Kaplan–Meier analysis. The *P* value was 0.263 for BPFS, 0.192 for CPFS, 0.325 for CSS and 0.015 for OS. BPFS, biochemical progression-free survival; CPFS, clinical progression-free survival; CSS, cancer-specific survival; OS, overall survival.

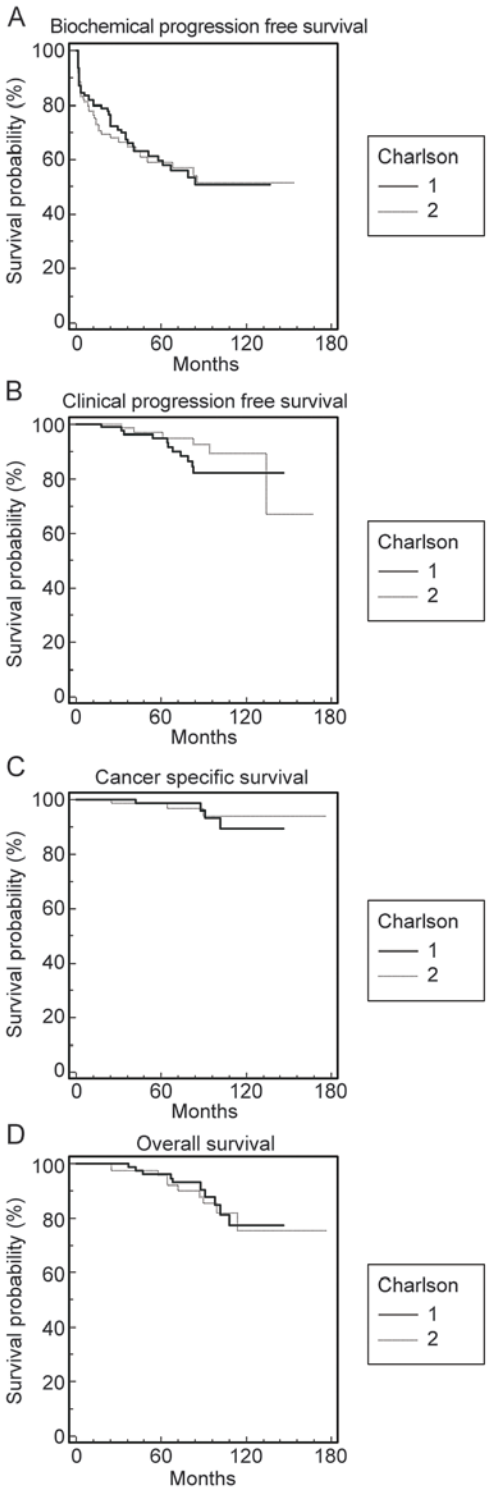

Figure 2. The relationship between Charlson score (1: Charlson score = 0, 2: Charlson score ≥ 1) and survival outcomes by Kaplan–Meier analysis. The *P* value was 0.559 for BPFS, 0.344 for CPFS, 0.820 for CSS and 0.736 for OS. BPFS, biochemical progression-free survival; CPFS, clinical progression-free survival; CSS, cancer-specific survival; OS, overall survival.

only significant independent predictor in BPFS, and cancer volume was the only significant independent predictor in CPFS. Furthermore, only 5 patients (11.4%) developed local recurrence or distant metastasis in the group that received adjuvant treatment, *vs.* 12 patients (17.6%) in the group that received salvage treatment for biochemical recurrence [5]. In this paper, we focus on the impact of age and Charlson score on survival outcomes (BPFS, CPFS, CSS and OS) in patients with T3a prostate cancer.

4.1 The influence of age on survival outcomes

Prostate cancer can be seen in young patients, even in those under 30 years of age [11]. Gronberg *et al*. [12] found that the age-specific relative survival rate did not differ significantly among different age groups, and the authors suggested that younger patients should be offered more aggressive treatment than older patients [12]. A few years later, these authors analyzed the data from 6 514 patients with prostate cancer and found that 85% of these patients died during 7–23 years of follow-up; 55% died of prostate cancer. Patients diagnosed before the age of 60 had an 80% risk of dying of prostate cancer, but patients over 80 years old had a < 50% risk. They concluded that prostate cancer mortality is high but decreases in older patients. Age at diagnosis was found to be a strong predictor of prostate cancer death [13].

Most authors agree that age is a significant predictor of prostate cancer survival. Herold *et al*. [14] found that patients older than 65 years were more likely to have distant failure than younger patients, and that age greater than 65 years was a significant independent predictor of distant metastases. Carter *et al*. [15] described age as a strong predictor of the probability of curable cancer and found that early detection in younger patients could lead to decreased prostate cancer mortality. Ruska *et al*. [16] reported that younger men, particularly if their PSA at the time of diagnosis was less than 10 ng mL^{-1}, had a high possibility of being cured after RP. In a study of 2 897 men with localized prostate cancer who underwent RP, Khan *et al*. [17] found that patients lesser than 50 years old had better long-term cancer control rates.

In their study of 477 men who underwent RP, Smith *et al*. [18] found that younger patients (less than 50 years old) had a better disease-free survival probability (log-rank $P = 0.010$). On multivariate Cox regression analysis, age remained a significant prognostic factor ($P = 0.033$). They concluded that patients younger than 50 years old have a more favorable disease-free outcome [18]. Obek *et al*. [19] studied 489 patients with localized prostate cancer. They reported biochemical recurrence in 12% of patients younger than 70 years old and in 25% of patients older than 70 years old. They concluded that age may be an independent prognostic factor for disease recurrence after RP [19]. However, in our study of patients with cT3a prostate cancer, we found a significant difference in OS between patients younger than 65 and patients 65 years or older ($P = 0.015$).

Freedland *et al*. [20] analyzed 1 753 patients according to age at RP: 50 years old or younger, 51 to 60 years old, 61 to 70 years old and older than 70. They found that men aged 50 years or younger had significantly lower recurrence rates. They concluded that younger men had more favorable outcomes after RP [20]. However, Siddiqui *et al*. [21] categorized 5 509 RP patients into groups < 55, 55 to 59, 60 to 64, 65 to 69 and ≥ 70 years old. They found BPFS was similar across age groups. According to our cT3a data, we found that age was not a significant predictor of BPFS or CPFS.

4.2 The influence of Charlson score on survival outcomes

The Charlson index contains 19 categories of comorbidity, which are defined using ICD-9-CM diagnosis codes. The Charlson score is the most commonly used index for comorbidity in the field of oncology. A recent study by Kastner *et al*. [22] assessed the feasibility of using Charlson score in planning prostate cancer treatment, and the authors concluded that the Charlson score is a superior comorbidity assessment tool for the treatment of prostate cancer. However, Froehner *et al*. [23] compared the American Society of Anesthesiologist (ASA) Physical Status classification and Charlson score in patients who underwent RP. These authors found that ASA classification could improve the classification of prognostic comorbidity and may be used as an alternative to the Charlson score. They also found that only congestive heart failure, vascular disease and severe renal disease were significantly associated with overall mortality [24]. They emphasized that congestive heart failure was an important factor for comorbidity but the conventional Charlson score did not add clinically meaningful information supplementary to congestive heart failure.

Albertsen *et al*. [25] studied the survival probabilities of 767 patients with clinical localized prostate cancer treated by conservative management (either observation or immediate or delayed androgen withdrawal therapy). They found that, with a Charlson score of 0–1, the 15-, 20- and 25-year OS rates were 26%, 15% and 8%, respectively; with a Charlson score >1, the 15-, 20- and 25-year OS rates were 11%, 6% and 3%, respectively. Obviously, in that study, a higher Charlson score was correlated with a worse outcome.

Tewari *et al*. [26] presented lookup tables to estimate survival probability of men with clinically localized prostate cancer stratified by patient age, race, Charlson comorbidity and treatment type. Although the Charlson score is probably the most frequently used measurement of

comorbidities in the context of RP, in our study, Charlson score did not influence the outcome of patients with clinical locally advanced prostate cancer.

5 Conclusion

Charlson score does not influence the outcome of patients with clinical locally advanced prostate cancer. Age may influence OS. Margin status and cancer volume were independent predictors in BPFS and CPFS. RP can be performed in motivated healthy older patients. However, the patients need to be counseled regarding possible surgery-related side effects, such as urinary incontinence and erectile dysfunction, which are age- and comorbidity-dependent.

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