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Original Article

Role of serum cholinesterase in patients treated with salvage radical prostatectomy

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Abstract

Background: Serum cholinesterase (ChE) a serine hydrolase that catalyses the hydrolysis of esters of choline, is involved in cellular proliferation and differentiation, therefore affecting carcinogenesis. The aim of this study was to understand the prognostic role of preoperative serum ChE in patients with radiation-recurrent prostate cancer (CaP) treated with salvage radical prostatectomy (SRP).

Material and methods: This retrospective study included 214 patients with radiation-recurrent CaP treated with SRP from January 2007 to December 2015 at 5 academic centers. Patients were considered with abnormal/decreased ChE levels if <5 kU/l. Biochemical recurrence-free and metastases-free (MFS) survival analyses were performed.

Results: Median serum ChE level was 6.9 (interquartile range) 6–7.7) kU/l. Serum ChE level (<5 kU/l) was decreased in 25 (11.7%) patients. Decreased serum ChE level was associated with lower body mass index ($P = 0.006$) and metastasis to lymph nodes ($P = 0.004$). In multivariable analysis, continuous ChE was an independent predictor of MFS (hazard ratio [HR] 0.48, confidence interval [CI] 0.33–0.71, $P < 0.001$), overall survival (HR 0.68, CI 0.48–0.96, $P = 0.03$) and cancer-specific survival (HR 0.41, CI 0.2–0.84, $P = 0.01$). Serum ChE improved the C-index (by 2.54%) to 87.8% for prediction of overall survival and (by 3%) to 92% for prediction of MFS.

Conclusion: Preoperative serum ChE is associated with the development of metastasis in patients with radiation-recurrent CaP who underwent SRP. The biological underpinning of this association with the biological and clinical aggressiveness of CaP needs to be further elucidated.

Keywords: Radiation-recurrent; Prostate cancer; Salvage radical prostatectomy; Serum cholinesterase; Biomarker

1. Introduction

Serum cholinesterase (ChE) (or pseudocholinesterase [pChE]/butyrylcholinesterase) is a serine hydrolase that

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catalyses the hydrolysis of esters of choline [1]. pChE is produced in the liver and found in most tissues, with the exception of red blood cells [2]. Congenital pChE deficiency is a rare genetic abnormality which may lead to prolonged duration of action of muscle relaxants that are hydrolyzed by pChe [3]. The gene involved is located on chromosome 3 (3q26.1–q26.2) [4]. pChE deficiency is present in approximately 1 out of every 1,500 to 2,500 persons and it seems to affect male Caucasian Americans almost twice as often as their female counterparts [5].

Recently, ChE has been shown to modulate cellular proliferation and differentiation, suggesting a possible role in carcinogenesis [6,7]. Serum ChE levels have been shown to be decreased in patients with various advanced cancers regardless of hepatic involvement [8]. One of the possible mechanisms underlying the lower ChE activity in cancer patients has been hypothesized to be its association with cancer-specific anorexia [9]. Another mechanism is its association with increased acetylcholine activity which is known to promote the growth and metastasis in various cancers, including prostate cancer (CaP), via its M3 muscarinic receptor [10,11].

Salvage radical prostatectomy (SRP) is performed for local failure after primary radiation therapy (RT) of CaP [12]. Five- and 10-year biochemical recurrence-free survival (BRFS) estimates range from 47% to 82% and from 28% to 53%, respectively; 10-year cancer-specific survival (CSS) and overall survival (OS) estimates range from 70% to 83% and from 54% to 89%, respectively. Pre-SRP prostate-specific antigen (PSA) levels and prostate biopsy Gleason score at time of recurrence are the strongest predictors of disease stage such as organ-confined disease status, progression, and CSS [13].

The aim of our study was to understand the role of serum ChE activity in patients with radiation-recurrent CaP who underwent SRP. To this end, we evaluated the association of preoperative serum ChE with clinicopathologic characteristics and outcomes in patients treated with SRP for biochemically recurrent, advanced CaP [14].

2. Patients and methods

2.1. Patient selection

Five participating centers provided information for men treated with SRP who presented biochemical and clinically localized recurrence after RT for primary CaP with curative intent. Local institutional review board approval was obtained at all centers for the present study and all institutions provided agreement before study initiation. Prior to final analysis, all identified data anomalies were resolved through regular communication with all centers, and the database was frozen to produce the final data set. The study cohort included 214 patients with radiation-recurrent CaP treated with SRP from January 2007 to December 2015. RT modalities included brachytherapy, external beam RT (EBRT), or combination RT techniques (EBRT and brachytherapy, EBRT and intensity-modulated RT, or EBRT and 3-dimensional conformal RT). CaP recurrence after RT was defined as an increase of ≥2 ng/ml greater than the nadir according to the Radiation Therapy Oncology Group American Society for Radiation Oncology Phoenix criteria [15]. All patients underwent a pre-SRP biopsy to confirm radiation-recurrent CaP [16]. No patient had metastases on imaging before SRP. Open surgical SRP with pelvic lymph node dissection was performed in all patients. All prostate specimens were examined by dedicated genitourinary pathologists at each center. The pathologic stage was assigned using the 2007 American Joint Committee on Cancer Tumor Nodes Metastasis (TNM) staging system and the grade according to the 2006 Gleason grading consensus [17].

Serum ChE measurements were routinely taken at each center (normal range 5–12 kU/l). Patients were considered with abnormal/decreased ChE activity if less than normal level <5 kU/l. Serum samples were analyzed using Ortho VITROS 5.1 FS and 5600 Integrated System (Ortho Clinical Diagnostics, Raritan, NJ) assays for ChE. Analytical methods were controlled according to the manufacturer's instructions using preventative maintenance, function checks, calibration, and quality control which passed specifications prior to testing samples. The rate of color loss was monitored by reflectance spectrophotometry (400 nm). The rate of change in reflection density was proportional to the ChE activity in the samples. Each sample was tested in duplicate and the inter-assay coefficient of variation was less than 5%.

2.2. Follow-up protocol

Follow-up examinations were performed in accordance with institutional protocols. Generally, the patients were followed up quarterly within the first 2 years and semiannually thereafter [13]. tPSA level and the presence of urinary and sexual symptoms were evaluated at each visit. Biochemical recurrence (BCR) was defined as 2 consecutive tPSA values of ≥0.2 ng/ml after SRP; the date BCR was assigned to the first date. Distant metastases were identified using radiologic imaging. The cause of death was determined by the treating physicians, corroborated with medical record review and/or death certificates, or by the death certificates alone [18]. In cases for which death certificates were retrieved and reviewed for the cause of death, only men with known BCR after SRP, who had documented metastatic CaP, and who had CaP listed in the death certificate were considered to have died of CaP [19]. The follow-up duration was calculated from the date of surgery to the date of death or the last follow-up visit.

2.3. Statistical analysis

The normal distribution of data was analyzed for each continuous variable using kurtosis and skewness. Associations of serum ChE with categorical variables were assessed using χ^2 tests; differences in continuous variables were analyzed using Mann-Whitney U test. BRFS and

metastases-free survival (MFS) curves were generated using the Kaplan-Meier method. A log-rank test was applied for pair wise comparisons of survival between patients with normal ChE and low ChE serum levels. Cox proportional hazards regression analyses were adjusted for standard clinical and pathologic characteristics. Harrell's concordance index (*c*-index) was used to measure the ordinal predictive power of the model for BRFS, MFS, OS, and CSS. Statistical significance was set at $P < 0.05$. All tests were 2-sided. Analyses were performed using STATA, version 14.1 (StataCorp LP, College Station, TX).

3. Results

3.1. Association of serum cholinesterase with clinicopatological characteristics

The clinical and pathologic characteristics of the 214 men with radiation-recurrent CaP treated with SRP, stratified by ChE serum level, are shown in Table 1. Median age was 69 (interquartile range[IQR] 64−72) years. Median PSA level was 3.82 (IQR 2.05−6.5) ng/ml. Median serum ChE level was 6.94 (IQR 6.06−7.71) kU/l. Serum ChE was decreased (<5 kU/l) in 25 (11.7%) patients. Patients with decreased ChE had significant lower body mass index ($P = 0.006$) compared to those with normal ChE levels ≥5 kU/l. Decreased serum ChE was associated with adverse pathological features (Table 1). Gleason 10 was seen in 9 (36%) patients with ChE <5 kU/l compared to 6 (3.2%) with normal serum ChE ($P < 0.001$). When we stratified according to low and intermediate risk (Gleason 6 and 7) vs. high risk (Gleason 8, 9, and 10), decreased ChE was not statistically associated with Gleason score ($P = 0.07$). A total of 40 (18.7%) patients had positive lymph nodes, of which 10 (25%) had ChE levels below 5 kU/l; this is a 40% rate of lymph node metastases in patients with decreased ChE levels compared to 15.9% in those with normal ChE levels ($P = 0.004$). One hundred and two (47.7%) patients had received luteinizing hormone-releasing hormone (LHRH) agonist before SRP. ChE levels were not different between patients who had LHRH agonist and those who had not ($P = 0.37$).

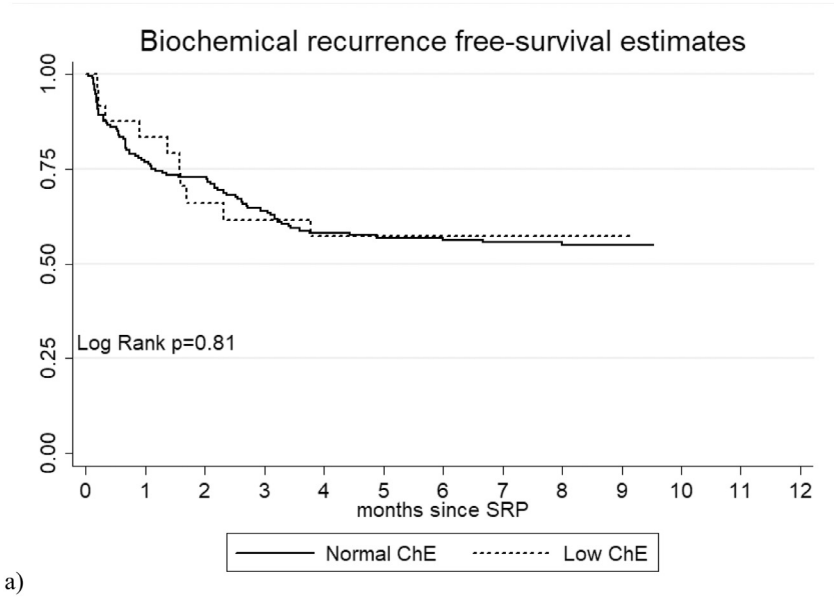
3.2. Association of serum cholinesterase with biochemical recurrence and metastasis after surgery

Within a median follow-up period of 25.3 months (IQR 15−28.5 months), 90 (42.1%) patients experienced BCR after SRP; 80 (42.3%) of these patients had normal ChE levels and 10 (40%) had decreased ChE levels. Kaplan-Meier survival estimates showed no difference in BRFS estimates between patients with normal levels vs. decreased preoperative serum ChE; 1-year BRFS were 54.9% (CI 47.3−62) in patients with normal ChE levels and 57.1% (CI 34.9−74.2) in patients with decreased serum ChE levels, $P = 0.81$ (Fig. 1a). Preoperative serum ChE was associated with BRFS in univariable analysis when we considered it as a continuous variable (hazard ratio [HR] 0.83, CI 0.73−0.94, $P = 0.004$). It did not retain its statistical association in multivariable analysis when adjusted for the effects of established clinicopathologic features. Independent predictors for BRFS

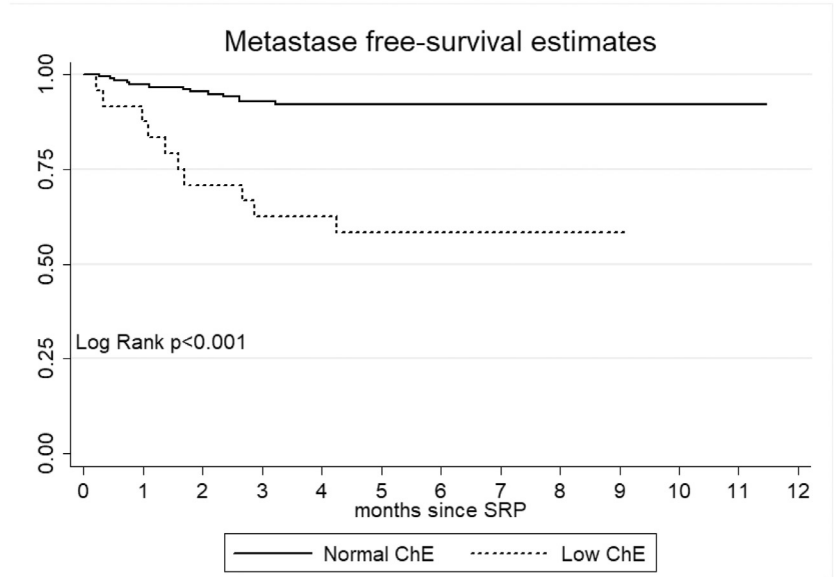
Table 1
Clinicopathologic characteristics of 214 patients treated with salvage radical prostatectomy and lymphadenectomy for recurrence after radiation stratified by preoperative serum cholinesterase level.

Variable	Normal ≥5 kU/l	Low <5 kU/l	*P*
Patients no. (%)	189 (88.3)	25 (11.7)	
Age median (IQR)	69 (64−72)	69 (67−75)	0.22
BMI median (IQR)	24 (24−27)	24 (24−24)	**0.006**
ASA no. (%)			0.53
1	30 (15.9)	6 (24)	
2	100 (52.9)	13 (52)	
3	59 (31.2)	6 (24)	
Preoperative LHRH treatment no. (%)	88 (46.6)	14 (56)	0.37
Prostate volume cm^3 median (IQR)	46 (36−58)	53 (44−62)	0.09
Presurgery PSA median (IQR)	3.8 (2.1−6.39)	4.29 (1.48−9.46)	0.71
Stage no. (%)			0.91
Organ confined	108 (57.2)	14 (56)	
Nonorgan confined	81 (42.8)	11 (44)	
Seminal vesicle invasion			0.59
No	131 (69.3)	16 (64)	
Yes	58 (30.7)	9 (36)	
Gleason score no. (%)			**0.07**
≤7	138 (83.1)	14 (66)	
>7	51 (16.9)	11 (44)	
Lymph node metastasis no. (%)	30 (15.9)	10 (40)	**0.004**

ASA = American Society of Anesthesiologists; BMI = body mass index; IQR = interquartile range;
LHRH = luteinizing hormone-releasing hormone; PSA = prostate-specific antigen.
Statistical significant results are bolded.



a)



b)

Fig. 1. Comparison of biochemical recurrence-free survival (a), metastases-free survival (b) between patients with normal and low serum cholinesterase in 214 patients treated with salvage radical prostatectomy for radiation-recurrent prostate cancer.

were previous LHRH treatment, stage >pT2, Gleason score, and positive lymph nodes (Table 2). During follow-up, 23 (10.7%) patients developed metastasis; 13 (6.9%) in patients with normal ChE and 10 (40%) in patients with decreased ChE. Kaplan-Meier survival estimates showed a significant difference between MFS in patients with normal and decreased serum ChE; 1-year MFS was 92.1% (CI 86.8−95.4) for patients with normal ChE and 58.3% (CI 36.4−74.9) for patients with decreased serum ChE, $P < 0.001$ (Fig. 1b). Serum ChE was a predictor of MFS in univariable analysis as a categorical (hazard ratio [HR] 6.41, CI 2.81−14.62, $P < 0.001$) and as a continuous variable (HR 0.49, CI− 0.39 −0.61, $P < 0.001$). In multivariable analysis, ChE as a continuous variable was an independent predictor of MFS (HR 0.48, CI 0.33−0.71, $P < 0.001$) together with previous LHRH treatment and preoperative PSA. Serum ChE improved the C-index by 3% up to 91.96% for prediction of metastases after SRP (Table 2).

3.3. Association of pretreatment serum cholinesterase with overall and cancer-specific survival

Within a median follow-up period of 25.3 months (IQR 15−28.5 months), 18 (8.4%) patients died after SRP; 13 (6.8%) had normal ChE levels and 5 (20%) had decreased

Table 2
Univariable and multivariable cox regression analyses predicting biochemical recurrence and metastases in 214 patients treated with salvage radical prostatectomy for radiation-recurrent prostate cancer.

Variables	Biochemical recurrence-free survival						Metastases-free survival					
	Univariable			Multivariable[a]			Univariable			Multivariable[a]		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
LHRH yes vs. no	3.01	1.94–4.68	**<0.001**	2.32	1.43–3.76	**0.001**	13.81	3.23–58.96	**<0.001**	5.71	1.25–26.8	**0.03**
PSA cont.	1.04	1.02–1.07	**<0.001**	1.01	0.99–1.04	0.17	1.09	1.06–1.12	**<0.001**	1.04	1–1.08	**0.03**
ECE yes vs. no	2.86	1.86–4.37	**<0.001**	1.93	1.24–3.09	**0.01**	4.45	1.75–11.3	**0.002**	2.03	0.71–5.75	0.18
SVI yes vs. no	2.41	1.58–3.66	**<0.001**	0.92	0.53–1.58	0.77	4.65	1.96–10.99	**<0.001**	1.15	0.35–3.76	0.81
Gleason score 6			Ref.						Ref.			
7	2.33	1.2–4.51	**0.01**	2.5	1.23–5.07	**0.01**	1.78	0.37–8.6	0.46	0.91	0.16–5.01	0.91
8	2.75	1.27–5.94	**0.01**	2.23	0.99–5.05	0.053	1.72	0.24–12.28	0.58	0.71	0.09–5.46	0.74
9	3.27	1.2–8.89	**0.02**	2.53	0.88–7.27	0.08	2.77	0.25–30.6	0.4	2.69	0.22–31.61	0.43
10	7.02	3.06–16.1	**<0.001**	1.79	0.62–5.17	0.27	36.8	8.02–169	**<0.001**	1.25	1.14–10.86	0.83
Lymph node + yes vs. no	3.28	2.07–5.18	**<0.001**	2.33	1.2–4.54	**0.01**	8.94	3.88–20.6	**<0.001**	3.15	0.68–14.54	0.14
Harrell's C-index			**73.85**						**88.96**			
ChE cat. (cut-off 5 kU/l)	0.92	0.47–1.78	0.81	0.45	0.19–1.07	0.07	6.41	2.81–14.62	**<0.001**	1.98	0.47–8.38	0.34
Harrell's C-index			**75.39**						88.65			
ChE cont.	0.83	0.73–0.94	**0.004**	0.92	0.8–1.06	0.3	0.49	0.39–0.61	**<0.001**	0.48	0.33–0.71	**<0.001**
Harrell's C-index			**74.04**						**91.96**			

ChE = cholinesterase; CI = confidence interval; ECE = extra capsular extension; HR = hazard ratio; LHRH = luteinizing hormone-releasing hormone; PSA = prostate-specific antigen; SVI = seminal vesicles invasion.
[a] Adjusted including ChE cont.
Statistical significant results are bolded.

ChE levels. Pretreatment serum ChE was a predictor of OS in univariable analysis when assessed as a categorical (HR 3.79, CI 1.31–10.9, $P = 0.01$) and as a continuous variable (HR 0.64, CI 0.49–0.83, $P = 0.001$). In multivariable analysis, ChE as a continuous variable was an independent predictor for OS (HR 0.68, CI 0.48–0.96, $P = 0.03$) in addition to Gleason score. Serum ChE improved the C-index by 2.54% up to 87.8% for prediction of OS after SRP, while ChE as categorical variable increased the C-index up to 87.9% (Table 3).

During follow-up, 7 (3.3%) patients died of CaP, 4 (2.1%) with normal ChE and 3 (12%) with decreased ChE.

Table 3
Univariable and multivariable cox regression analyses predicting overall and cancer-specific survival in 214 patients treated with salvage radical prostatectomy for radiation-recurrent prostate cancer.

Variables	Overall survival						Cancer-specific survival					
	Univariable			Multivariable[a]			Univariable			Multivariable[a]		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
LHRH yes vs. no	2.37	0.93–6.08	0.07	1.16	0.36–3.65	0.79	9.62	1.14–81	**0.03**	9.55	0.69–131.5	0.09
PSA cont.	1.07	1.02–1.12	**0.006**	1	0.94–1.07	0.78	1.08	1.03–1.14	**0.001**	1.03	0.96–1.12	0.34
ECE yes vs. no	4.05	1.54–10.6	**0.004**	2.16	0.66–7.08	0.19	2.53	0.55–11.5	0.22	0.68	0.08–5.35	0.71
SVI yes vs. no	5.55	2.15–14.29	**<0.001**	2.88	0.86–9.6	0.08	4.52	0.98–20.8	0.053	2.78	0.35–21.97	0.33
Gleason Score 6			Ref.						Ref.			
7	1.43	0.37–5.57	0.59	0.99	0.21–4.62	0.99	1.03	0.09–11.42	0.97	0.59	0.03–11.23	0.73
8	2.14	0.37–12.24	0.39	1.02	0.13–7.54	0.98	-	-	-	-	-	-
9	10.16	0.94–109.6	0.056	16.09	1.23–209.6	**0.03**	11.8	0.66–210	0.09	34.64	1.05–1141	**0.047**
10	121.3	14.1–1040	**<0.001**	6.68	0.39–112.4	0.18	65.08	4.43–954	**0.002**	0.74	0.01–28.38	0.87
Lymph node + yes vs. no	23	4.19–126.2	**<0.001**	14.12	0.97–204	0.052	10.6	1.71–65.6	**0.01**	5.7	0.15–216.98	0.34
Harrell's C-index			**85.26**						**96.56**			
ChE cat. (cut-off 5 kU/l)	3.79	1.31–10.9	**0.01**	2.16	0.48–9.67	0.31	6.04	1.35–27.03	**0.01**	6.10	0.47–79.07	0.16
Harrell's C-index			**87.9**						96.6			
ChE cont.	0.64	0.49–0.83	**0.001**	0.68	0.48–0.96	**0.03**	0.53	0.35–0.8	**0.003**	0.41	0.2–0.84	**0.01**
Harrell's C-index			**87.8**						**97.15**			

ChE = cholinesterase; CI = confidence interval; ECE = extra capsular extension; HR = hazard ratio; LHRH = luteinizing hormone-releasing hormone; PSA = prostate-specific antigen; SVI = seminal vesicle invasion.
[a] Adjusted including ChE cont.
Statistical significant results are bolded.

Pretreatment serum ChE was a predictor of CSS in univariable analysis as a categorical (HR 6.04, CI 1.35–27.03, $P = 0.01$) and as a continuous variable (HR 0.53, CI 0.35–0.8, $P = 0.003$). In multivariable analysis, ChE as a continuous variable was an independent predictor of CSS (HR 0.41, CI 0.2–0.84, $P = 0.01$) in addition to Gleason score (Table 3).

4. Discussion

We found that a decreased pretreatment serum ChE is associated with adverse pathologic features such as higher Gleason score and presence of positive lymph nodes after SRP. This is in agreement with Battisti et al. who found that it was significantly decreased in patients with Gleason ≥7. In patients with radiation-recurrent CaP, we found a significant proportion of patients with decreased pretreatment serum ChE had Gleason 10 (36%) [20]. Besides its association with adverse pathologic features, decreased serum ChE was also associated with lower body mass index. This may be due to the fact that in patients with decreased ChE nutritional status may be compromised as was shown in previous studies [7]. Also there is evidence supporting the influence of radiation on ChE as patients with radiation-recurrent cervical cancer (i.e., stages III and IV) had lower serum ChE [21]. In our study, the median serum ChE level was 6.94 kU/l, which is comparable to the reported value in patients with head and neck squamous cell carcinoma. Moreover, the authors of the latter study demonstrated that patients with squamous cell carcinoma had significantly lower serum ChE levels than healthy controls, suggesting that serum ChE is decreased in some cancer patients [22]. While this association with pathologic features is important, prediction of BCR is more important for clinical decision-making in patients with radiation-recurrent CaP [23].

The present study failed to demonstrate an independent association of preoperative ChE with BCR. This is in contrast to Koie et al. who reported that pretreatment serum ChE was significantly associated with BCR in 535 patients with CaP who underwent RP (5-year BRFS rates were 77.7% and 55.0%, respectively, $P < 0.001$) [24]. However they used a cut-off for serum ChE which was under the lowest normal range reported in their study and also included patients with different characteristics with most patients having localized disease. Their multivariable model included only initial PSA, clinical stage, and Gleason score at biopsy [24]. It may be that ChE measures a phenomenon that may not be of such importance in locally advance CaP. To this, we assessed the prognostic value of ChE with regard to hard endpoints such as MFS, OS, and CSS [25].

We found that patients with decreased pretreatment serum ChE were more likely to develop metastases and to die. Serum ChE as a continuous variable was associated with all 3, MFS, OS, and CSS. In agreement with our findings, Battisti et al. demonstrated that decreased serum ChE is associated with presence of bone metastases at diagnosis in 66 CaP patients [20]. Furthermore, we found that the addition of pretreatment serum ChE to a base multivariable model that includes all established clinicopathologic characteristics [26] increased the accuracy for prediction of metastases by 3%, OS by 2.54%, and CSS by 0.6%.

The biological reason underlying the association of ChE with metastatic phenomenon, especially micrometastasis, remains unknown. This could represent a highly interesting area of research [18,27]. Regarding clinical implications of these findings, patients with decreased pre-SRP serum ChE might benefit from a more extended PLND, multimodal therapy or a closer follow-up.

Results of this study should be regarded with caution as it suffers from several limitations. First are its retrospective design and short follow-up [28]. Second, ChE is a sensitive, but nonspecific, serum biomarker and decreased ChE levels could be influenced by inflammation, physical stress, poor performance status, secondary malnutrition, or previous LHRH treatment. While, this would rather weaken an association with outcomes, this undermines its overall performance as a biomarker [29]. Third, some heterogeneity in laboratory pathology results could be a potential bias as our study included 5 centers. However, the same technique and kits were used for serum ChE determination and we stratified patients according to normal and low range and analyzed it also as a continuous variable to avoid cut-off related bias.

5. Conclusions

Low preoperative serum ChE predicts poor prognosis in patients who underwent SRP for recurrent CaP after RT. As serum ChE is evaluated for anesthesia presurgical work-up, it could represent an easily, available biomarker to help increase the predictive accuracy for oncologic outcomes prediction. The biological underpinning of this association and the value of ChE as a biomarker of micrometastatic disease in locally aggressive CaP needs to be further assessed.

Ethical standards

This study has been approved by the appropriate ethics committee.

Conflict of interest

The authors declare that they have no conflict of interest.

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