Controlling Nutritional Status score: A new prognostic indicator for patients with oligometastatic prostate cancer

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ABSTRACT

The Controlling Nutritional Status (CONUT) score is associated with prognosis in a variety of cancers, but the association with prognosis in oligometastatic prostate cancer has not been reported. And the effect of the CONUT score on the prognosis of prostate cancer was not compared with the platelet to lymphocyte ratio (PLR) and the neutrophil to lymphocyte ratio (NLR). A total of 94 patients who underwent surgery for oligometastatic prostate cancer from January 2015 to December 2017 were retrospectively analyzed. The appropriate cut-off values of CONUT, PLR, and NLR were determined by X-tail. CONUT scores were statistically significant for Gleason scores, T-stage, tumor margin, NLR, and PLR ($P < 0.05$). We evaluated the effect of CONUT scores on PSA progression-free survival. Univariate and multivariate analyses were performed to determine the independent predictors of CONUT scores. On univariate analysis, CONUT scores, NLR, and PLR were significantly associated with PSA progression-free survival ($P < 0.05$). Multivariate analysis showed that the CONUT score was an independent prognostic factor ($P < 0.05$). The present study indicates that the CONUT score is an independent prognostic factor for patients with oligometastatic prostate cancer.

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Introduction

Prostate cancer is one of the most common malignancies in men. In 2016, prostate cancer ranked first in the incidence of male cancer in the United States. Moreover, its mortality is second only to lung cancer.[1] Due to changes in lifestyle and dietary structure, the incidence and mortality of prostate cancer have increased significantly in China.[2] However, most newly diagnosed patients in China are diagnosed with advanced or distant metastases with a poor prognosis and have lost the opportunity to undergo early radical surgery.

In recent years, Hellman et al[3] proposed the concept of oligometastasis. The oligotransfer state is a period of mild tumor invasiveness. It is a transitional phase between localized disease and extensive metastasis. The number of metastases is limited, and the transferred organs are specific but do not yet have a tendency to spread throughout the body. At the present, there is no clear definition of the oligometastasis status in prostate cancer. Singh et al[4] retrospectively analyzed the number and type of metastases in patients with metastatic prostate cancer and found that the survival rate of patients with metastatic lesions ≤5 was significantly better than those with >5 metastases. Oligometastatic cancer can achieve long-term survival through local treatment of the primary tumor. Systemic treatment and the removal of primary tumors can significantly increase the overall survival of patients with gastric cancer[5] and colorectal cancer.[6] In recent years, a number of studies[7] have also found that cytoreductive surgery by primary resection can benefit patients with oligometastatic prostate cancer.

However, there are still significant differences in the prognosis of patients undergoing oligometastasis cytoreductive surgery. Fossati and Löppenberg et al[8,9] analyzed data from 81,971 patients with metastatic prostate cancer in the SEER database from 2004 to 2011 and established a 3-year specificity death risk model based on age, PSA level, Gleason score, and TNM staging. The analysis found that when the 3-year overall risk of death in patients with metastatic prostate cancer was >72%, local treatment of primary tumors did not benefit patients. Therefore, it is imperative to find biomarkers that can stratify oligometastatic patients to determine treatment decisions and predict prognosis. The long-term prognosis of patients with malignant tumors is closely related to systemic nutritional status and immune-inflammatory response.[10] The development, metastasis, and prognosis of oncological diseases depend not only on the type of tumor cells but also on nutrition and immunity, which play an important role in these processes. A variety of nutritional and inflammation-related biomarkers have been used to assess tumor prognosis, such as neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR). The CONUT (Controlling Nutritional Status) score is presented as an emerging concept, which is calculated from serum albumin concentration, total peripheral lymphocyte count, and total cholesterol concentration, and is used to pre-assess the patient's preoperative nutritional status.[11] The use of the CONUT score has the advantages of simplicity of operation and low cost. In recent years, a number of studies have shown that the CONUT score is a new predictor of prognosis for patients with malignant tumors and has been shown to correlate with the prognosis of patients with gastric cancer, colorectal cancer, lung cancer, and liver cancer.

In this study, we aimed to investigate whether the CONUT score is an independent prognostic factor compared to NLR and PLR in oligometastatic prostate cancer and to assess its clinical value in prognosis.

Materials and methods

Study patients

A retrospective analysis of 94 patients diagnosed with metastatic prostate cancer (metastasis ≤5) between January 2015 and December 2017 in Shanghai Tenth People's Hospital was conducted. Case inclusion criteria were set as follows: (1) Patients were diagnosed with prostate cancer by prostate biopsy or transurethral resection of the prostate, and after a rigorous as-

Table 1

Assessment of undernutrition status by the CONUT score.

Undernutrition degree	None	Light	Moderate	Severe
Serum albumin (g/dL)	≥35	30-34.9	25-29	<29
Score	0	2	4	6
Total lymphocyte count (/mm^3)	≥1600	1200-1599	800-1199	<800
Score	0	1	2	3
Total cholesterol (mg/dL)	≥180	140-179	100-139	<100
Score	0	1	2	3

sessment of imaging studies (including CT, MRI, Bone Scan, and 68-Ga-PSMA-ligand PET/CT), a multidisciplinary team at the Shanghai Tenth People's Hospital confirmed the diagnosis as oligometastasis prostate cancer; (2) Serum albumin levels, peripheral blood lymphocyte counts, and cholesterol concentrations were measured 3 days before surgery(For patients with neoadjuvant therapy, we also measure these indicators before surgery); and (3) Clinical and follow-up data were complete.

Data collection

A doctor who did not participate in the surgery was responsible for collecting medical history data, recording data, and analyzing data. Follow-up surveys of patients after surgery included serum concentrations of PSA, testosterone, glucose, and alkaline phosphatase. Because of the small number of deaths from prostate cancer, we cannot assess the overall survival as the study endpoint, so we used PSA progression-free survival (PSA-PFS) as the study endpoint. PSA-PFS was defined as the time from the beginning of ADT to the first evidence of biochemical progression. All data were obtained through outpatient follow-up or by telephone.

Statistical analyses

Using X-tile software v3.6.1 (Yale University),[12] the best cut-off value of the CONUT score, NLR, and PLR was obtained. SPSS v24.0 (SPSS Inc., Chicago, IL) was used for all statistical analyses. The medians and interquartile ranges are used to assess continuous variables, while frequencies and proportions are used to classify variables. The correlation with PSA-PFS was evaluated using the Kaplan-Meier curve with log-rank statistics. Univariate and multivariate Cox regression analyses were used to calculate the respective hazard ratio and 95% confidence intervals (CIs). For all analyses, a *P* value of <0.05 was considered statistically significant.

Results

The optimal cut-off value for the CONUT score, NLR, and PLR

The serum albumin concentration, total peripheral lymphocyte count, and total cholesterol concentration were used to obtain the CONUT score. Blood samples were obtained within 1 week before surgery to calculate the CONUT score. The CONUT scoring system was normal (0-1), mild (2-4), moderate (5-8), and severe (Table 1). Using the X-tile software[12] as a PSA-PFS state variable, the cutoff for the CONUT score was determined (Fig 1A). The best CONUT cutoff was found to be 3. Therefore, 94 patients with oligometastatic prostate cancer were grouped into a low CONUT score (0, 1, and 2) and a high CONUT score (≥3) group. Similarly, we used
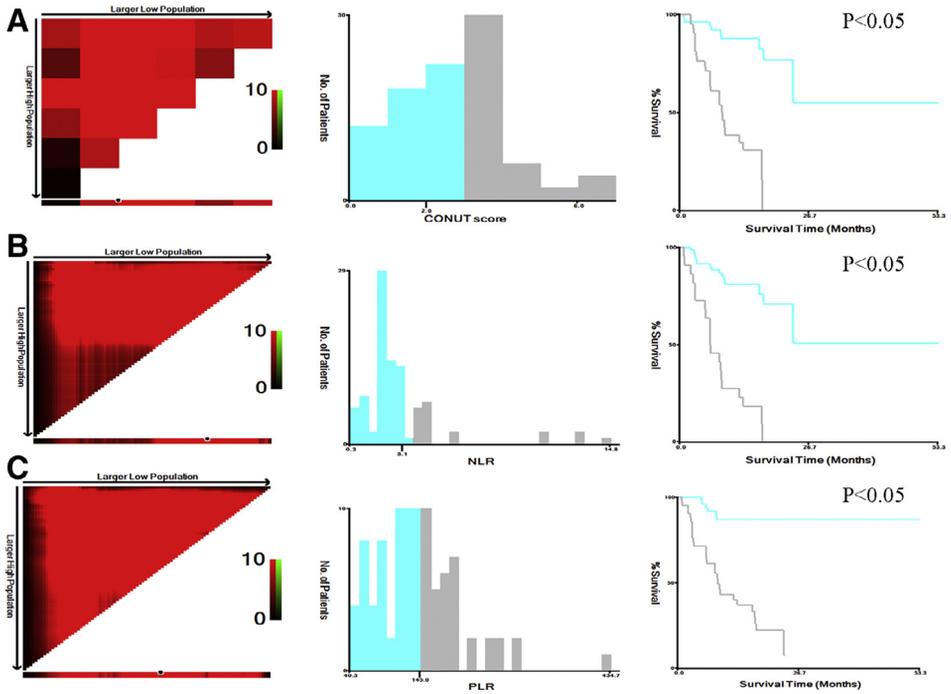
Fig. 1. X-tile analyse of PSA-PFS was performed using patients' data to determine the optimal cut-off values for CONUT score, NLR, and PLR. The optimal cut-off value highlighted by the black circles in left panels is shown in histograms of the entire cohort (middle panels) and Kaplan–Meier plots are displayed in right panels.

X-tile to calculate the optimal cut-off value of NLR and PLR to be 3.1 and 145, respectively (Fig 1B, C).

Clinicopathologic features of patients

Table 2 shows the clinicopathologic features of the 94 patients included in this study. The median age of the patients was 71 years (53-84 years), and the number of patients with BMI $\geq$24 and <24 was 36 (21.73%) and 58 (78.27%), respectively. In terms of T stage, there were 2 patients in T1 (2.13%), 14 patients in T2 (14.89%), 56 patients in T3 (59.57%), and 22 patients in T4 (23.41%). The CONUT score was 0, 1, 2, 3, 4, 5, and 6 for 12 patients (12.77%), 18 patients (19.15%), 22 patients (23.4%), 30 patients (31.91%), 6 patients (6.38%), 2 (2.13%) patients, and 4 (4.26%) patients, respectively. All 94 patients underwent oligometastasis cytoreductive surgery. The prostate and seminal vesicles were completely resected. Routine intraoperative removal of the external iliac, intraorbital, and obturator lymph nodes in the bilateral pelvis was performed, and neurovascular bundles were properly treated. As shown in Table 2.

The relationship between the CONUT score and the clinicopathologic features of patients

As shown in Table 3, when the clinicopathologic parameters in the cohort were divided into the high CONUT group and the low CONUT group by the CONUT score cut-off value (CONUT score = 3), we found that the Gleason score, T stage, tumor margin length, NLR, and PLR in the preoperative high CONUT group were significantly different from those in the low CONUT group

Table 2
Patient characteristics.

Factors	Value or number of patients ($n = 94$)
Age (years)	
Median	71
Range	53-84
BMI (kg/m^2)	
≤24	58
>24	36
PSA	
≤20	14
>20	80
CONUT	
0	12
1	18
2	22
3	30
4	6
5	2
6	4
T stage	
T1	2
T2	14
T3	56
T4	22
N stage	
0	34
1	60
Margins	
Positive	52
Negative	42
Neoadjuvant ADT	
Yes	46
No	48

Abbreviations: BMI, Body Mass Index.

($P < 0.05$). There was no statistically significant difference between the high CONUT group and the low CONUT group among other clinicopathologic features.

PSA Progression-free survival according to the CONUT score

The median follow-up time for all patients was 16.31 months (range: 4.6-55.10 months). Comparing the 2 groups of patients in terms of PSA-PFS, the overall survival time of the high CONUT group was 35.54 ± 7.22 months, and the overall survival time of the low CONUT group was 9.54 ± 1.34 months. Based on Kaplan-Meier curve analysis, high CONUT scores were significantly associated with a decrease in PSA-PFS before surgery (Fig 1A). There was a statistically significant difference in survival curves between the 2 groups ($P < 0.05$). When we divided the patients into 2 subgroups according to whether they received preoperative neoadjuvant ADT, there was a significant difference between the high CONUT group and the low CONUT group ($P < 0.05$, Fig 2A, B).

Univariate and multivariate analysis of PSA-PFS based on the CONUT score

By analyzing the univariate and multivariate results to determine prognostic factors, as shown, univariate Cox regression analysis showed that NLR, PLR, and CONUT scores were considered potential predictors of prognosis in prostate cancer patients ($P < 0.05$). Multivariate Cox

Table 3

Patient characteristics according to the CONUT score.

Factor	Conut score		P value
	Low (52)	High (42)	
Age (years)	70.07 ± 6.58	66.90 ± 7.16	0.12
BMI	23.50 ± 3.23	24.06 ± 3.37	0.56
PSA			
≤20	8	6	
>20	44	36	0.916
Gleason score			
≤7	16	2	0.02
≥7	36	40	
T stage			
≤t3a	26	8	0.02
>ta3	26	34	
Margins			
Positive	22	30	<0.001
Negetive	30	12	
Neoadjuvant ADT	52	42	0.671
Yes	28	20	
No	24	22	
Serum albumin (g/L)	42.5 ± 3.85	39.38 ± 5.19	0.02
Total lymphocyte	2089.62 ± 803.19	1324.76 ± 389.02	0.001
Total cholesterol (mg/dL)	187.98 ± 49.20	139.69 ± 27	0.001
PLR	112.1 ± 45.83	186.89 ± 78.09	<0.001
NLR	2.03 ± 0.99	4.56 ± 3.72	<0.001

Abbreviations: PLR, plateletlymphocyte ratio; NLR, neutrophil to lymphocyte ratio.

Table 4

Univariate and multivariate analyses of prognostic factors.

Factors	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age (≤65,>65)	1.194	0.462-3.085	0.715			
BMI (≤24,>24)	1.767	0.694-4.499	0.232			
NLR (≤2.85, >2.85)	3.897	1.506-10.084	0.005	1.625	0.487-5.419	0.429
PLR (≤147.84, >147.84)	6.36	2.08-19.44	0.001	3.49	0.988-13.888	0.076
T stage (≤t3a.>t3a)	1.942	0.673-5.607	0.22			
PSA						
≤20						
>20	1.481	0.404-5.429	0.554			
Gleason score						
≤7 (3 + 4)						
≥7 (4 + 3)	2.248	0.78-6.477	0.134			
Positive margins	1.264	0.485-3.293	0.632			
Neoadjuvant ADT	1.257	0.484-3.263	0.639			
Conut score (≥3)	7.517	2.353-24.015	0.001	3.972	1.048-11.432	**0.004**

The bold value indicates that this data is statistically significant in multivariate analysis ($P < 0.05$).

regression analysis showed that NLR and PLR were not considered to be independent prognostic factors after cytoreductive surgery in patients with oligometastasis. However, as shown in Table 4, the CONUT score can be considered an independent prognostic factor.

Discussion

In the present study, we evaluated the ability of the CONUT score to predict prognosis in patients undergoing oligometastasis cytoreductive surgery. From the data, it can be concluded
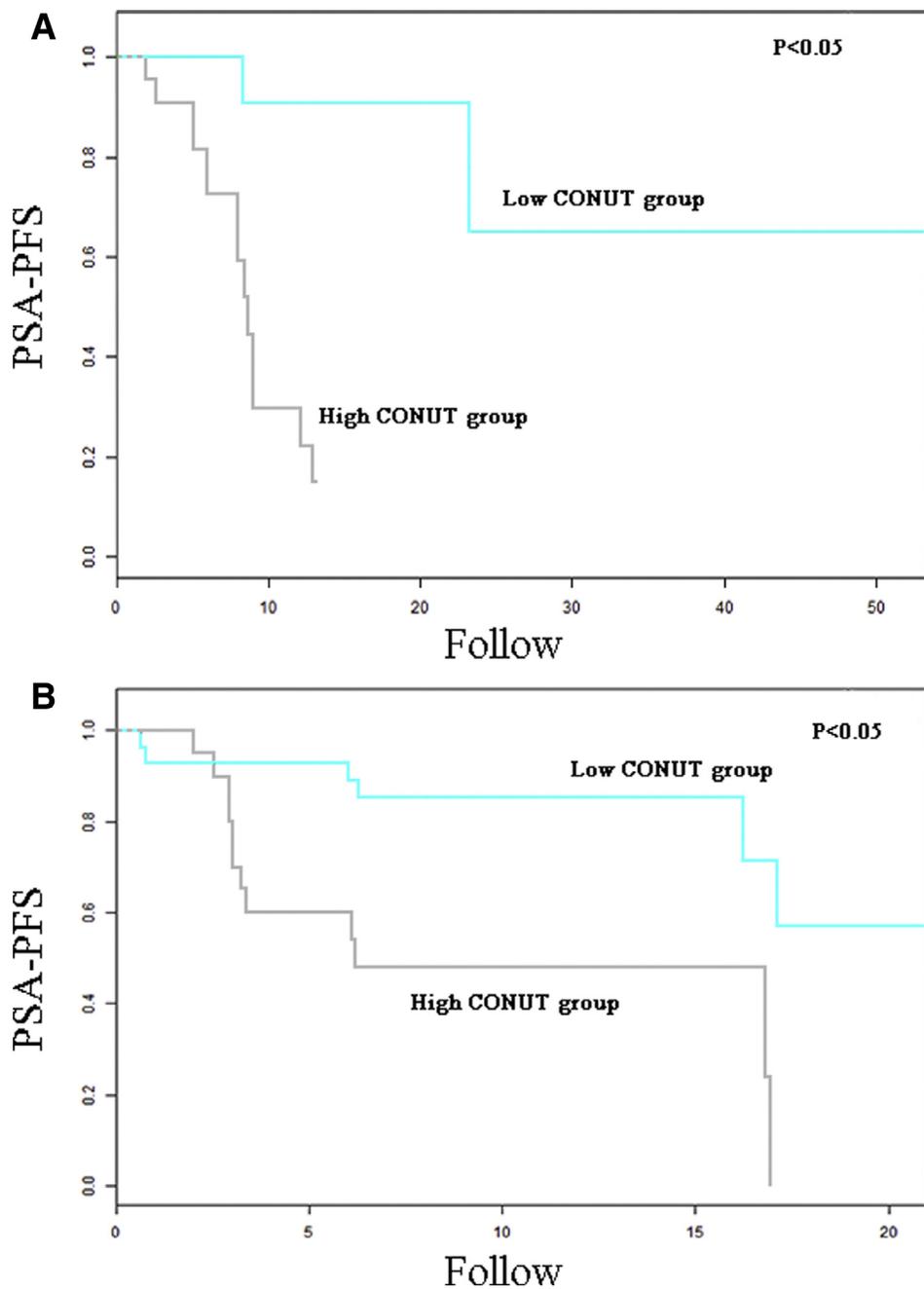
Fig. 2. (A) Kaplan-Meier survival curves of PSA-PFS in patients with neoadjuvant ADT. (B) Kaplan-Meier survival curves of PSA-PFS in patients without neoadjuvant ADT.

that the CONUT score is an independent risk factor for the prognosis of oligometastatic prostate cancer surgery. A high CONUT score is significantly associated with tumor progression. Simultaneously, for the comparison between CONUT scores and clinical parameters, we found that there were differences between the groups in CONUT scores and Gleason scores, t-stages, and tumor margin length ($P < 0.05$). At the same time, we found that neoadjuvant ADT did not cause any differences between the high CONUT and low CONUT groups. In each group, the CONUT score was still significant for evaluating the prognosis. These results also show that the CONUT score cut-off value of 3 is significant. Therefore, we hypothesized that the predictive significance of the CONUT score will help clinicians identify high-risk patients in a timely manner and provide reasonable treatment decisions after surgery. This study is the first to evaluate the clinical value of the CONUT score in predicting prognosis in patients with oligometastatic prostate cancer.

In recent years, the role of nutrition and immunity in predicting the prognosis of cancer patients has received increasing attention.[13] The CONUT score was developed to make it easier and more objective to assess the patient's nutritional status. Serum albumin concentration is considered a reliable indicator of systemic immunity and inflammation.[14] It has been reported that serum albumin levels are significantly associated with the survival of cancer patients.[15] Peripheral lymphocyte counts simultaneously reflect systemic inflammation, which is also a tumor immune response that also plays an important role. Raycoquard [16] et al found that lymphopenia in patients with advanced cancer leads to a microenvironment suitable for cancer cell proliferation and metastasis, resulting in a poor prognosis. While the total cholesterol concentration represents the patient's energy reserve state, Yang[17] et al showed that cholesterol metabolism enhances the antitumor immune response of CD8+ T cells. Upon immune activation of CD8+ T cells, metabolic reprogramming of intracellular cholesterol occurs, leading to significant changes in cholesterol levels. Thus, higher scores not only reflect poor nutritional status but also reflect systemic inflammation and impaired immune responses, suggesting that these patients may have poor treatment tolerance, resulting in poor prognosis. Nutritional Risk Screening 2002[18] and Subjective Global Assessment[19] are the most widely used tools for evaluating the nutritional status of malignant tumors. However, these 2 evaluation scales are cumbersome and subjective; they can only reflect the patient's nutritional status but cannot clearly reflect the patient's immune status. Conversely, the CONUT score is calculated from clinical data, which is objective and can simultaneously reflect the patient's nutritional and immune status.

In this study, we found that PLR and NLR are not independent prognostic factors compared to the CONUT score. Shu et al showed that PLR and NLR can predict biochemical recurrence of prostate cancer.[20] However, another study showed that PLR and NLR do not predict biochemical recurrence of prostate cancer.[21] Therefore, PLR and NLR are controversial in evaluating the prognosis of prostate cancer. Toyokawa et al compared CONUT scores with NLR, PLR, and the Glasgow Prognostic Score in esophageal cancer, and they found that in the univariate analysis, all 4 were significantly associated with 3-year overall survival. In multivariate analysis, only the CONUT score was associated with prognosis.[22] These results also indicate that the CONUT score may be more suitable for predicting prognosis in a variety of cancers than other inflammatory markers, as it integrates not only inflammation-related indicators but also nutrient-related indicators, which makes it more persuasive.

CONUT scores have been found to correlate with the prognosis of patients in a variety of cancers. Ishihara et al[23] reported the predictive value of the CONUT score for the prognosis of patients with upper urinary tract tumors and indicated that the score can independently predict the overall survival, disease-specific survival, and recurrence-free survival of patients with upper urinary tract tumors before surgery. Toyokawa[24] et al found that patients with a CONUT score of ≥2 had significantly shorter DFS and OS than patients with low CONUT scores and that CONUT scores were an independent prognostic factor. In addition, the CONUT score can also evaluate the occurrence of adverse events in cancer treatment.

For advanced prostate cancer, ADT is currently the main treatment and has been shown to improve the survival rate of advanced PCa. Although ADT has been shown to improve survival outcomes, it may cause multiple interrelated adverse effects, such as increased depression, arteriosclerosis, and decreased bone density. In this study, whether or not patients were undergoing

neoadjuvant ADT before surgery led to no statistically significant difference in prognosis for patients undergoing oligometastasis and cytoreductive surgery.

Oligometastatic prostate cancer is a late-stage cancer with mild biological behavior. Radical resection of the primary tumor is important for reducing tumor burden,[25] reducing linear metastasis,[26] and cutting off the connection between the primary tumor and metastatic lesions.[27] Preoperative evaluation of the CONUT score may help predict prognosis and individualized treatment. Based on the above data, patients with high CONUT scores, due to impaired immune and inflammatory responses, micrometastases and residual cancer cells that are more active, may enter biochemical recurrence faster and should be followed more closely than patients with a low CONUT score. At the same time, proper nutritional interventions for patients with high CONUT scores before surgery may affect patient prognosis. Ravasco[28] et al found that early nutritional intervention can significantly improve treatment tolerability and patient survival. Takagi[29] et al proposed that the application of enhanced recovery after surgery, a new nutritional management strategy, before liver resection may improve the patient's nutritional status and, thus, have a significant impact on prognosis.

Conclusion

In conclusion, the CONUT score is a new serum biomarker to evaluate the prognosis of oligometastasis cytoreductive surgery and is simple, convenient, fast, and economical. We suggest that the CONUT score should be calculated before the initial treatment and be used as an assessment tool and reliable indicator of metastatic prostate cancer and immune inflammation. There are several limitations to this study. First, this is a retrospective study conducted in a single center, and there may be a bias in the selection. Second, because the oligometastatic prostate cancer tumor reduction surgeries were performed in recent years, the sample size was small, and the follow-up time was short. Third, this study failed to compare preoperative and nutritional screening tools. Therefore, more multicenter research should be conducted in the future.

Acknowledgments

Disclosure

The author reports no conflicts of interest in this work.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.currproblcancer.2019.02.001.

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