Identification of a chromatin regulator signature for predicting prognosis of prostate cancer patient

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Abstract. – OBJECTIVE: Prostate cancer is a malignancy with unsatisfactory prognosis. Mounting proofs have verified that chromatin regulators (CRs) participate in the developmental process of tumor. Hence, this research intended to reveal the biofunction and prognosis significance of CRs in prostate cancer patients.

MATERIALS AND METHODS: CRs were obtained from previously finished topic research. The mRNA expression and clinical data were acquired from TCGA and GEO datasets. Molecular subtypes were identified by ConsensusCluster-Plus package. Cox regressive analyses, LASSO regressive analyses and stepAIC were utilized to screen the prognosis-related genes and establish the risk model for forecasting outcomes in prostate cancer. Genomic variation, immune infiltration, drug sensitivity difference and analysis of clinical features were all investigated.

RESULTS: 462 samples in TCGA cohort study were classified into two clusters based on 23 prognosis CRs. Patients in cluster 1 (clust1) presented better overall survival (OS), lower tumor mutation burden (TMB), enhanced immune infiltration, higher immune escape and hyposensitivity to several drugs. Furthermore, our team smoothly established and substantiated a 10 CR-derived model for forecasting the prognostic results of individuals with prostate cancer, which was an independent prognosis indicator. Functional analyses revealed that CRs were predominantly enriched in tumor-associated signal paths. The CR-derived model was related to immunocyte infiltration and sensitive to several drugs.

CONCLUSIONS: Holistically, the present research offered fresh enlightenment regarding the biofunction of CRs in prostate cancer. Our team discovered a dependable prognosis marker for the survival of individuals with prostate cancer.

Key Words: Chromatin regulators, Molecular subtypes, Prostate cancer, The Cancer Genome Atlas, Signature, Prognosis.

Introduction

Prostate carcinoma is one of the most common diagnosed tumors in males and is particularly common in developing nations¹. About 15% of prostate cancer cases are high-risk and potentially fatal². Although radical therapies like prostate excision and radiation treatment have been successful in prostate cancer, there are still problems like determination and localization of prostate lesions, that remain to be solved³. To ameliorate the survival and quality of prostate carcinoma sufferers, further research is needed to personalize treatment, which depends on the knowledge of the developmental process of prostate cancer.

Chromatin regulators (CRs) are indispensable regulatory elements in epigenetics⁴. In healthy mammalian cells, chromatin architecture is modulated by epigene events, like heritable DNA CpG methylation and histone modifications and chromatin remodeling, which ensures normal genetic expressions in reaction to different bio-signals⁵. During tumorigenesis, abnormal regulation of epigenemechanisms induces abnormal chromatin conformation and aberrant stimulation or silencing of genes that control cellular development and death, hence facilitating tumorigenesis and developmental process⁶. CRs have been shown to be aberrantly expressed and correlated to prognosis in different tumor types. HMGA1 is on the short arm of human chromosome 6 (6p21), a region participating in chromosome abnormalities related to mankind tumors. An elevation of the expressing level of HMGA1 is related to high grade cancers and advanced prostate cancer, overexpressed HMGA1 in prostate cancer lineage cells induced chromosomal unsteadiness and structure abnormalities⁷. In prostate cancer, histone demethylase KDM7A controls androgen receptor activity and tumor growth⁸. EZH2, a histone lysine methyl-
transferase, participated in different malignancy phenotypes like programmed cell death and metastases in prostate cancer.

In the present paper, our team highlighted the expression profile of CRs in prostate cancer and their prognostic value through bioinformatics analysis. We intended to construct and demonstrate a prognosis marker on the basis of CRs that can validly forecast the prognosis of individuals with prostate cancer. Moreover, our team explored the association between the prognostic features of prostate cancer and the immune micro-environment, which provides a theory-wise foundation for immuno-checkpoint treatment regimens.

Materials and methods

Raw Data Acquisition

Public prostate cancer RNA-seq data, clinicopathological characteristics, and mutation data (CNV and SNP) were acquired from TCGA database and GEO database (GSE116918). In total, 462 tumor and 52 normal specimens in the TCGA-prostate cancer cohort and 248 tumor specimens in the GSE116918 cohort were utilized for analyses. An overall 870 CRs were acquired from previously finished topic researches.

Cluster Analysis

As per the standards of \(|\logFC| > 1 \) and FDR < 0.05, CRs with differential expression were determined via limma package of R program. Next, above differentially expressed CRs were studied via univariable Cox analysis through the Coxph function of R package survival in TCGA dataset, and \( p < 0.05 \) was considered the liminal value. Then, molecular typing was performed separately for TCGA dataset samples via the R package Consensus Cluster Plus 1.52.0. Pam arithmetic and “Pearson” distance were utilized to complete 500 bootstraps with every bootstrap having specimens (≥ 80%) of TCGA dataset. Cluster number \( k \) was between 2 and 10, and the optimum \( k \) was identified as per cumulative distribution function (CDF) and AUC. The clustering was substantiated in GSE116918 dataset. Survival curves (KM curves) between molecular subtypes were then analyzed for difference. In addition, differences in the distribution of clinical characteristics between molecular subtypes were compared and a Chi-square test was completed; \( p < 0.05 \) had significance on statistics.

Mutation Analysis

Waterfall plot was generated to explore the detailed single-nucleotide variant (SNV) characteristics between molecular subtypes via “oncoplot” function in R software, “maftools” package.

Cell-type Identification by Estimating Relative Subsets of RNA Transcripts (CIBERSORT)

CIBERSORT analyses were utilized to compare diversities in different immunocytes in molecular subtypes. Wilcoxon test analyses were completed to identify the difference of 22 kinds of infiltrating immunocyte score between molecular subtypes. The “ggplot2” package was used to realize the visualization of the distributional status of the diversities in 22 kinds of infiltration immunocytes.

Computation of Immune Score, Stromal Score, and Estimate Score

R software ESTIMATE arithmetic was utilized to compute overall stroma level (Stromal Score), the immunocyte infiltration (Immune Score) and the combination (ESTIMATE Score) of sufferers in the TCGA-prostate cancer cohort using Wilcox.test analysis to determine differences between molecular subtypes.

Tumor Immune Dysfunction and Exclusion (TIDE)

TIDE is a calculation framework designed to assess the potential of cancer immunoescape from the genetic expression profiles of tumor specimens. TIDE was used to predict sample responses in the TCGA-prostate cancer datasets, and to compare the proportion of treatment responses in different subtypes, as well as TIDE scores.

Drug Sensitivity Analysis

pRRoPhetic was used to predict the sensitivity of erlotinib, sunitinib, paclitaxel, VX-680, TAE684 and crizotinib to IC50 in molecular subtypes.

Establishment and Corroboration of a Prognosis Model on the Basis of CRs

Our team completed univariable Cox regressive analyses to identify the prognosis significance of CRs. Then lasso-penalized Cox regressive analyses were leveraged to establish the prognosis risk model via the glmnet R package. Risk scoring was computed via the equation below:
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where Coefficient is lasso Cox regressive model coefficient of the relevant mRNA. Our team separated prostate cancer sufferers into risk_{high} and risk_{low} groups as per the mid-value of risk scoring. Survival analyses were completed via the Kaplan-Meier (K-M) curve to assess the prognoses. Time-associated ROC analyses were utilized to analyze the prognosis significance of our modeling method through the survival ROC package. GSE116918 data set was deemed as the verified set for further validating the prognosis value of the modeling method. In addition, diversities in the distributional status of clinical characteristics between these two groups were compared and a Chi-square test was utilized; \( p < 0.05 \) had significance on statistics.

A predictive Nomogram was Developed

Univariable cox regressive analyses were completed to identify the association between age, T Stage, N Stage, Cluster and Risk Score. Clinical factors which could forecast the prognoses in an independent manner were identified via multivariable cox regressive survival analyses as per Hazard ratio (HR), 95% CI and \( p \)-value. Clinical variables and the CR-derived hallmark risk scoring were utilized to construct a nomograph related to the outcomes for assessing the possibility of 1-, 3-, and 5-year OS for prostate cancer sufferers. The concordance index (C-index) and correction curve were utilized to analyze the prediction capability of the nomograph.

Statistical Analysis

The R program 4.0.3 was utilized for statistic assay. K-M curves were utilized for analyzing survival status via the Survminer R package 2.43-3. \( p < 0.05 \) had significance on statistics (*\( p < 0.05 \); **\( p < 0.01 \); ***\( p < 0.001 \); ****\( p < 0.0001 \)).

Results

Construction of CRs-Related Subtypes

Limma package was used to analyze DEGs between tumor and healthy specimens in TCGA cohort study; and 756 up-regulated and 1,199 down-regulated genes were discovered (Figure 1A). Among them, 58 genes belonged to CRs (Figure 1B). 23 prognosis factors were determined via univariable cox survival analyses (Figure 1C), and they were closely correlated (Figure 1D).

Based on 23 prognostic factors, 462 samples in TCGA cohort study were classified into two clusters using ConsensusClusterPlus package (Figure 2A-C). KM survival curve results revealed that sufferers in clust1 had a better survival duration compared to clust2 in TCGA cohort study and GSE116918 dataset (Figure 2D, E). Of the distributional status of two clusters in diverse clinical characteristics, remarkable diversity in Event in TCGA cohort study were observed (Figure 3).

Functional Enrichment Analysis of CRs-Related Subtypes

To better reveal the value of our sub-types, the function enrichment was analyzed. First, 154 significance pathways between two clusters were obtained using GSVA package (Figure 4A). GSEA analysis in ClusterProfiler package displayed that the majority of pathways were stimulated in clust1; for example, enrich score of ALLOGRAFT_REJETION were higher in clust1 than that in clust2; moreover, this pathway also activated in clust1(Figure 4B).

Analysis of Genomic Variation in CRs Related Subtypes

Genomic variation between two clusters were analyzed in TCGA cohort study. Firstly, we extracted molecular genetic characteristics, including Aneuploidy Score, Nonsilent Mutation Rate, Fraction Altered, Number of Segments and Homologous Recombination Defects, the results showed that those characteristics were higher in cluster2 than in cluster1 (Figure 5A). Moreover, our team identified the top 15 mutation genes based on SNV data using maftools software (Figure 5B). TP53 and SPOP are two top mutation genes in which missense variants facilitated the majority of SNVs.

Immune Infiltration Level Analysis and Drug Sensitivity Analysis in two Clusters

Next, we evaluated the speculated percentage of 22 immunocytes in 2 clusters in TCGA dataset. 8 kinds of immunocytes with significantly different distributions between two clusters were found (Figure 6A). Surprisingly, clust1 had higher score of StromalScore, ImmuneScore and ESTIMATEScore (Figure 6B). Our team afterwards
**Figure 1.** Determination of chromatin regulators with differential expression. A, DEGs between prostate carcinoma and para-carcinoma tissue in TCGA dataset. B, Venn of differentially expressed genes and chromatin regulators. C, Forest map of significant prognostic chromatin regulators. D, Heatmap of significant prognostic chromatin regulators.

**Figure 2.** Identification of chromatin regulators associated molecular subtypes. A, CDF curve of patients in TCGA dataset when K=2-10. B, CDF delta area when K=2-10. C, ConsensusClusterPlus identifies two chromatin regulators associated molecule sub-types. D, K-M curve between C1 and C2 sub-types in TCGA cohorts. Log-rank test was utilized. E, K-M curve between C1 and C2 sub-types in GSE116918 dataset. Log-rank test was utilized.
evaluated the 10 enriched oncogenesis pathways and discovered that 8 of 10 oncogenesis pathways were enriched in a differential manner between two clusters (Figure 6C).

Moreover, the forecasted scores of immune therapy biomarkers were computed via the TIDE arithmetic. TIDE and IFNG were greater in clust1 group vs. clust2 group (Figure 6D). Our team assessed the qualities of TIDE T cell function disorder scores, which were also higher in clust1 group (Figure 6D). T cell exclusion, as well as two cellular types discovered to suppress T cell infiltration in cancers [i.e., myeloid-derided suppressor cells (MDSC) and the M2 subtype of tumor-associated macrophages (TAM, M2)], were all higher in clust1 group (Figure 6D). Those outcomes indicated that sufferers in clust2 were better candidates for immunotherapy.

To ameliorate the treatment efficacy of sufferer prostate cancer, our team explored the susceptibility diversity of commonly seen chemo medicines amongst the two groups. The outcomes of GDSC database analyses revealed that the IC50 results of medicines like Erlotinib, Sunitinib, Paclitaxel, VX-680, TAE684 and Crizotinib were higher in patients of cluster2 than those of cluster1 (Figure 6E). Those outcomes indicated that sufferers in the Cluster2 were remarkably more susceptible to those medicines (Figure 6E).

**Construction and Corroboration of CR-Derived Signature**

An overall 981 CRs, which involved 81 CRs with downregulation and 901 CRs with upregulation, were determined as CRs with differential expression between two clusters in the TCGA dataset (Figure 7A), of which 778 genes belonged to tumor key genes (Figure 7B). Based on 778 CR, our team utilized univariable Cox regressive analyses to investigate the prognosis merit of CR. The outcome revealed that 245 of them exhibited prognosis significance.

Afterwards, LASSO Cox regressive analyses and stepAIC were utilized to establish a prognosis hallmark for prostate cancer sufferers. A risk model was smoothly developed using 10 genes (FCER1A, ZFP36L2, LAPTM4B, TRIM2, SLC22A3, SCUBE2, LCN2, PAQR6, NOXA1 and CDC20) (Figure 7C, D). The risk scoring was computed via the coefficients of 10 CRs according to the following equation: risk score = (0.522*FCER1A expression) + (0.309*ZFP36L2 expression) + (0.365*LAPTM4B expression) - (0.359*TRIM2 expression) - (0.143*SLC22A3 expression) + (0.235*SCUBE2 expression) - (0.347*LCN2 expression) + (0.4*PAQR6 expression) + (0.4*NOXA1 expression) + (0.449* CDC20 expression).

Patients were classified into risk_{high} and risk_{low} groups as per the mid-value of risk scoring. The mortality rates of risk_{high} sufferers were remarkably greater vs. risk_{low} sufferers in TCGA dataset (p < 0.0001) (Figure 8A) and GSE116918 dataset (p < 0.0001) (Figure 8C). The time-reliant ROC analyses revealed that the prognosis accurateness of the CR-derived hallmark was 0.83, 0.83 and 0.8 at 1-, 3-, 5-year separately in the TCGA dataset (Figure 8B) and 0.95, 0.79 and 0.79 at 1-, 3-, 5-year separately in the GSE116918 dataset (Figure 8D).
Figure 4. Functional enrichment analysis of two clusters. A, GSVA analysis identified significant pathways in two clusters in TCGA dataset. B, GSEA analysis identified significant pathways in two clusters in TCGA dataset.
Relationship Between the CR-Derived Signature and Clinical Features

The result (Figure 9A) revealed that remarkable diversities existed between risk high and risk low sufferers in Cluster ($p=0.0011$), T stage ($p=0.0109$), N stage ($p=0$), Age ($p=0.015$), Event ($p=0$) and Cancer status ($p=0$) but no remarkable diversities existed in M stage ($p=1$).

In addition, stratified analyses were completed to explore the prognosis merit of the hallmark in sub-groups. This study discovered that the CR-derived hallmark exhibited splendid ability in forecasting prognoses in clust1 vs. clust2, N0 vs. N1, age > 60 vs. age <=60, T1-T4 stage, Alive vs. Death, Cancer status, except M0 vs. M1 (Figure 9B).
Pathways Characteristics of CR-based Signature

In order to better study the potential regulatory pathways of signature, enrichment scoring of every pathway was computed via the GSVA package of R language, and the correlation between risk scoring and enrichment scores of pathways was analyzed by Rcorr function of Hmisc package. The outcome revealed that 9 pathways were remarkably related to signature (Figure 10A). Among them, 3 pathways were positively correlated with risk score, while 6 pathways were negatively correlated (Figure 10B).

CR-Derived Signature Was an Independent Index of the Prognostic Results of Prostate Cancer

Univariate and multivariate Cox analyses were executed to corroborate if such hallmark could
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**Figure 7.** Establishment of signature. A, DEGs between 2 clusters in TCGA data set. B, Venn of differentially expressed genes and Tumorigenesis gene. C, LASSO coefficients profiles of 245 genes. D, LASSO regressive analysis with 10-fold cross-verification acquired 12 prognosis genes based on the minimal lambda value.

**Figure 8.** Prognostic analysis of signature. A-B, TCGA verifies the K-M and ROC curves of the data set. C-D, K-M and ROC curves of GSE116918 dataset.
Figure 9. The distributional status of diverse clinical characteristics of risk high and risk low sufferers A, which involved Clusters, T staging, N staging, M staging, and Age, Event and cancer status (B). Chi-square test was conducted.

Figure 10. Functional enrichment analyses of risk high and risk low sufferers. A, Heatmap of significant pathway associated with risk scoring. B, Correlative analyses of pathways with risk scoring.
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... independently serve as a prognosis index. Univariable analyses revealed that T stage, N stage, Cluster and Risk type were evidently linked to the survival of prostate cancer sufferers (Figure 11A). Multivariable analyses revealed that T stage, Cluster and Risk type were evidently linked to prognoses (Figure 11B). Those outcomes unveiled that the CR-derived hallmark could independently serve as a prognosis index for prostate cancer sufferers.

**Figure 11.** The hallmark could independently serve as a prognosis indicator. Univariable (A) and multivariable (B) Cox regressive analyses of risk scoring and clinical characteristics. C, Calibration for nomograph based on OS. DCA for assessing the ability of risk scoring, clusters, M staging and nomograph in forecasting prognoses. A nomograph on the basis of risk scoring and T staging for staging 1-, 3- and 5-year OS.
For the sake of predicting the survival of prostate cancer sufferers, our team developed a nomograph comprising T stage, cluster and risk scoring. Nomography predicted the 1-, 3-, 5-year OS of sufferers with prostate cancer (Figure 11C). The correction curve revealed that the actual OS of sufferers coincided with the forecasted results (Figure 11C). The nomogram had the favorable prediction ability (Figure 11C).

**Immune Infiltration Level Analysis and Drug Sensitivity Analysis in CR-Based Signature**

We also evaluated the speculated percentage of 22 immunocytes in risk\textsubscript{high} and risk\textsubscript{low} sufferers in the TCGA data set. 8 kinds of immunocytes with significantly different distributions between risk\textsubscript{high} and risk\textsubscript{low} sufferers (Figure 12A). Surprisingly, risk\textsubscript{high} sufferers had higher score of Stro-

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**Figure 12.** Characterization of tumor microenvironment and immunotherapy between risk\textsubscript{high} and risk\textsubscript{low} sufferers in TCGA dataset. A, Enrichment of 22 immunocytes assessed via CIBERSORT. B, ESTIMATE approach for computing stroma scoring and immunity scoring. C, Differences of 10 oncogenic pathways score between two clusters in TCGA dataset. D, TIDE scoring, IFNG scoring, T cell function disorder scoring, T cell exclusion scoring, MDSC and TAM.M2 scoring of risk\textsubscript{high} and risk\textsubscript{low} sufferers in TCGA data set. E, GDSC database analyses revealed that the IC50 results of medicines like erlotinib, sunitinib, paclitaxel, VX-680, TAE684 and crizotinib were greater in risk\textsubscript{high} sufferers in contrast to risk\textsubscript{low} sufferers.
nalScore, ImmuneScore and ESTIMATEScore (Figure 12B). Our team then evaluated the 10 enriched oncogenesis pathways and discovered that 7 of 10 oncogenesis pathways were enriched in a differential manner between 2 clusters (Figure 12C).

Moreover, the forecasted scoring of immune therapy biomarkers was computed via the TIDE arithmetic. TIDE and IFNG were greater in risk$_{high}$ sufferers vs. risk$_{low}$ sufferers (Figure 12D). We evaluated the quality of TIDE T cell function disorder scoring, which also higher in risk$_{high}$ sufferers (Figure 12D). T cell exclusion and MDSC, except for TAM.M2, were all higher in risk$_{high}$ sufferers (Figure 12D). Those outcomes unveiled that risk$_{high}$ sufferers were better candidates for immunotherapy.

We also explored the susceptible diversity of commonly seen chemo medicines amongst these 2 groups. The outcomes revealed that the IC50 results of medicines like erlotinib, sunitinib, VX-680, TAE684 and crizotinib were greater in risk$_{high}$ sufferers vs. risk$_{low}$ sufferers, which unveiled that vs. risk$_{low}$ sufferers were remarkably more susceptible to those medicines (Figure 12E).

**Discussion**

In this study, 23 CRs with differential expression between prostate cancer tissues and normal tissues and associated with prognosis of prostate cancer were firstly screened from TCGA database. Based on 23 CRs, two molecular subtypes with significant prognostic differences, mutational status, and immune characteristics were identified. We then identified 10 CRs associated with prostate cancer prognosis by univariable and multivariable Cox regressions. Based on those 10 CRs, our team developed and corroborated a risk model related to prognoses. Survival analysis and ROC analysis show that the model has satisfactory prediction merit. Eventually, univariable and multivariable Cox analyses revealed that the risk scoring on the basis of 10 CRs independently serve as a prognosis index of prostate cancer. In addition, our team discovered that this marker was tightly associated with immunocyte infiltration and sensitive to a variety of chemotherapy drugs.

As a core part of the epigenetic mechanism, CRs regulate the transcriptional process of substantial cell genes, like oncogenes. Hence, their changed activity can greatly affect global genetic expression patterns and healthy cell signal transmission networks, facilitating the proliferative ability of oncogenes and eventual oncogenesis. Largesc scale identification research of mankind tumors’ points to epigenetic modulators as hotspots for gene variants in gastric, liver, ovarian, prostate cancer, osteosarcoma, which highlights the significance of gene and epigenetic gatekeepers in the developmental process of tumor. Frequent mutations in genes encoding histones themselves in brain tumors further support the critical role of chromatin structure in tumorigenesis. In this work, our team first identified 2 molecular subtypes of prostate cancer based on CRs and established a 10 CRs-signature.

**FCER1A** is capable of encoding an IgE acceptor, which is primarily expressed on the surfaces of mastocytes. **FCER1A** has been discovered to participate in mammary carcinoma, glioma, ZFP36L2, zinc finger protein 36, CSH type-like 2 (called as Brf2, Erf2 and Tis11D, as well); it also has anti-cancer biofunction in multiple tumor types. Overexpressed ZFP36L2/TIS11D WT gene suppressed the development of HeLa cells. Consequently, studies have confirmed that Lysosomal protein transmembrane 4 beta (LAPTM4B) is aberrantly expressed in diverse malignancies and exerts an effect on tumor development. **LAPTM4B** is related to prostate cancer. Evidence have suggested that the Tripartite motif-containing 2 (TRIM2) protein is related to oncogenesis effects in multiple malignant tumors, like lung adenocarcinoma, colonic and rectal carcinoma, and pancreatic cancer, via modulating cellular proliferative, metastatic, and transcriptional activities, as well as the ubiquitination route.

The expression of SLC22A3 is significantly higher in colorectal cancer, and affects proliferation, migration, invasion, cell cycle and apoptosis. **SCUBE2** increase suppressed the developmental process of cellular cycle, repressed cellular proliferative, metastatic, and invasive abilities, and it facilitates programmed cell death in breast cancer cells. In prostate cancer cells, lipocalin-2 (LCN2) depletion induces attenuated proliferative ability, decreases expressing levels of proinflammation cell factors, lower adherence, and abnormal distributional status of F-actin. Upregulated **PAQR6** is related to androgen receptor signal transmission and unsatisfactory prognoses in prostate carcinoma. **CDC20** with its gene mutations are remarkably related to inferior survival of prostate cancer.
Limitations

Despite the fact that we used bio-informatics methods on a large sample to identify two genetic subgroups of prostate cancer with significant prognostic differences, as well as a 10 CRs signature, we are required to note the limitations of our work. In the future, we plan to place a greater emphasis on research that is both fundamentally experimental and functionally in-depth. Other considerations were not taken into account on our end because the samples lacked essential clinical follow-up information, most notably diagnostic specifics, such as whether or not the patients had other health conditions, when differentiating the molecular sub-types.

Conclusions

In conclusion, we generated two subgroups and a 10 CRs signature based on CRs in order to guide tailored therapy for prostate cancer patients. CRs are vital for forecasting the prognostic results of prostate cancer sufferers and targeting CRs might be a valid strategy to treat prostate carcinoma. This research ought to be corroborated by more studies.

Conflict of Interest

All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare.

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Ethics Approval

Not Applicable.

References


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