CENPF as a Potential Biomarker Associated with the immune microenvironment of renal cancer

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Abstract

Purpose:

Our objective is to explore potential biomarkers of renal cancer and their function in tumor progression.

Methods:

We integrated data from the TCGA database, including Kidney Chromophobe(KICH), Kidney renal papillary cell carcinoma(KIRP), and Kidney renal clear cell carcinoma(KIRC), to identify the widespread differentially expressed genes. Molecular Complex Detection (MCODE) was then utilized to screen the most important module among the upregulated genes. Further, univariate and multivariate Cox regression analyses were performed on the hub genes. The results demonstrated that Centromere Protein F(CENPF) overexpression was significantly associated with a worse survival in KIRC patients. To validate the overexpression of CENPF, we conducted qPCR analysis on tissues and plasma samples from KIRC patients. We observed that patients with high expression of CENPF had a poorer prognosis based on KIRC TCGA data. Through single-cell sequencing analysis of KIRC patients in GSE159115, we found that CENPF is predominantly expressed in the T cell cluster. Finally, we used CIBERSORT to analyze the differences in composition of tumor immune infiltrating cell (TIIC) between KIRC patients exhibiting high and low expression of CENPF.

Results:

1. We screen out CENPA, Centromere Protein M(CENPM), Centromere Protein U(CENPU), Centromere Protein E(CENPE), and CENPF as key oncogenic genes upregulated in KIRC, KICH, and KIRP.

2. We found that CENPF expression was significantly associated with KIRC progression.

3. We observed a T-cell sub-cluster that exhibited high expression of CENPF.

4. CENPF displayed a significant negative correlation with resting mast cells, while it exhibited a positive correlation with follicular helper T-cells and memory-activated CD4 T-cells.

5. Prognostic analysis revealed that patients with high expression of follicular helper T-cells had poorer prognosis, while those with high expression of plasma cells had a better prognosis.

Conclusion:

CENPF is upregulated and modulates the immune microenvironment in KIRC.

1. Introduction

Renal cell carcinoma (RCC) is a type of cancer that originates from renal tubular epithelial cells and is among the top ten most prevalent cancers worldwide. RCC accounts for 2% of all cancer diagnoses and
deaths globally, with higher incidence rates observed in developed countries\(^2\). Significant progress has been made in the histopathology and molecular characteristics of RCC in the past two decades, leading to major revisions in its classification by pathology experts\(^3\)–\(^5\). The main subtypes\(^6\), each with an incidence of at least 5%, are KIRC\(^7\), KIRP\(^8\), and KICH\(^9\). Standard treatment typically involves surgical resection of the tumor, including partial or radical nephrectomy for surgically resectable cases. Patients with inoperable or metastatic RCC typically receive systemic treatment with targeted drugs and/or immunotherapy checkpoint inhibitors, with treatment decisions guided by various nomographs\(^10\).

Through comprehensive bioinformatics analysis, a recent study identified and analyzed novel biomarkers associated with chromophobe renal cell carcinoma. The study highlighted CENPA, KNG1, and AGT as the top three hub genes specific to chromophobe renal cell carcinoma\(^11\). Additionally, bioinformatics analysis revealed ADCY1, APLN, FRMD5, GNG4, GREB1, KIF23, CXCL1, CXCL2, GPR84, IRF8, and TLR4 as hub genes specifically associated with clear cell renal cell carcinoma\(^12\). Another investigation demonstrated a significant correlation between CD8\(^+\) T cells and improved overall survival in KICH, while a higher proportion of regulatory T cells were linked to poorer outcomes in KIRC. In the case of KIRP, favorable outcomes were associated with M1 macrophages, whereas worse outcomes were observed with M2 macrophages\(^13\). Furthermore, a separate study integrated CHEK2, PDK4, ZNF304, SNAI2, and SRC genes to develop a risk prediction model for KIRC\(^14\). Notably, there is a gap in research studies integrating single-cell sequencing results with CIBERSORT immune infiltration analysis specifically in KIRC. Therefore, our aim is to conduct comprehensive research in this area.

In this study, we screened for differentially expressed genes (DEGs) in KIRC, KIRP, and KICH by analyzing datasets from TCGA. Subsequently, CENPA, CENPU, CENPM, CENPF, and CENPE were selected using Cytoscape. We found that CENPF was more highly expressed in the collected KIRC tissues and plasma compared with paracancerous tissues or plasma from healthy individuals. The immunological significance of CENPF was explained by single-cell sequencing analysis and immune infiltration analysis. These results reveal that CENPF is upregulated and modulates the immune microenvironment in renal cancer.

### 2. Materials and Methods

#### 2.1 Data sources

We downloaded clinical and gene expression data from the UCSC Xena database (https://xenabrowser.net/datapages/). The downloaded data included normalized count data from KIRC (n = 607), KIRP (n = 321), and KICH (n = 89) datasets of renal cell carcinoma patients. Additionally, we obtained the single-cell gene expression counting matrix data (GSE159115) from the National Center for Biotechnology Information Gene Expression Omnibus.

#### 2.2 Identification of Overlapped Hub Genes in KICH, KIRP, and KIRC
Differential expression analysis between tumor and normal groups was performed using the Wilcoxon test. Subsequently, a protein-protein interaction (PPI) network was constructed using the STRING database to identify hub genes.

### 2.3 Samples source and Real-Time Quantitative PCR (qPCR)

We collected plasma samples from 10 normal patients and 10 KIRC patients, 14 pairs of KIRC tissues and paracancerous kidney tissues from the First Affiliated Hospital of Sun Yat-sen University. Total RNA was extracted using TRIzol™ LS Reagent (Invitrogen™, 10296010CN) according to the manufacturer’s instructions. The cycle threshold (Ct) values were normalized to the expression levels of ACTIN, and the relative amount of mRNA specific to each of the target genes was calculated using the 2^−ΔΔCt method. The primer sequences were as follows:

- CENPF-F: AGCACGACTCCAGCTACAAGGT
- CENPF-R: CATCATGCTTTGGTTTCTTCTG
- ACTB-F: CATGTACGTTGCTATCCAGGC
- ACTB-R: CTCCTTAATGTCACGCACGAT
- CENPA-F: GTGTGGACTTCAATTGGCAAG
- CENPA-R: TGCACATCCTTTGGGAAGAG
- CENPU-F: ACCCACCTAGAGCATCAACAA
- CENPU-R: ACTTCAATCATACGCTGCCTTT
- CENPE-F: ACTCAAGGAAAGCCTGCAAGA
- CENPE-R: GGTTCTGTCGGTCCTGCTTT
- CENPM-F: GCTGTGATGTCGGTGTTGAG
- CENPM-R: CTTTGCCAAGTGGACCTTCAG

### 2.4 Single-cell analyses of KIRC

"Seurat" package in R was applied to identify cell clusters in KIRC samples from GSE159115. Subsequently, we further examined the cells to identify which specific cell types exhibited high expression levels of CENPF.

### 2.5 Filtering CENPF-Related Immune Cells
CIBERSORT is a method primarily used to characterize immune cell composition based on gene expression profiles in different tissues. The KIRC expression matrix were uploaded to the CIBERSORT website (https://cibersort.stanford.edu/) for analysis, using the LM22 reference matrix. The abundance ratio matrix obtained from CIBERSORT. We obtained significant differences TIIICs between the high and low cenpf groups through t-test, which was visually represented using the "barplot" and "pheatmap" functions in R. We then calculated the Pearson correlation coefficients between the TIIICs with significant differences and CENPF using the "cor" function in the R package, followed by visualization with the "corrplot" package. Finally, we performed univariate Cox analysis to filter out the TIIICs related to CENPF. The threshold of significance was set to p < 0.05.

2.6 Statistical Analyses

All statistical analyses were performed using R version 4.2.1. A Spearman test was conducted for correlation analysis. The differences between the groups were analyzed by Student's t-test when two groups were compared. Correlations between two variables were explored with the Spearman's correlation coefficient. All statistical tests were two-sided, and P < 0.05 was considered significant.

3. Results

3.1 Recognition of Overlapped DEGs in KIRC, KICH, and KIRP

To identify DEGs across the three subtypes of kidney cancer (KIRC, KICH, and KIRP), we analyzed the HTSeq-FPKM chip expression dataset (n = 607 for KIRC, n = 89 for KICH, and n = 321 for KIRP) from the GDC Hub. Our analysis used the criteria of adjusted P < 0.01 and |log2 FC| > 2 and revealed 5091 DEGs in KIRC (4085 up-regulated and 1006 down-regulated genes), 3899 DEGs in KICH (785 up-regulated and 3114 down-regulated genes), and 2304 DEGs in KIRP (1036 up-regulated and 1268 down-regulated genes). We visualized the up- and down-regulated genes in KIRC (Fig. 1A), KICH (Fig. 1B), and KIRP (Fig. 1C) with heatmaps. We used a Venn diagram to visualize the overlapped up-regulated (246 genes in red) and down-regulated DEGs (931 genes in blue) among the three datasets (Fig. 1D).

3.2 Construction and Module Analysis of PPI Network

We utilized STRING\textsuperscript{15} to identify interacting genes and construct a protein-protein interaction (PPI) network based on the overlapped DEGs. Subsequently, we visualized the PPI network using Cytoscape\textsuperscript{16}, which consisted of 382 nodes and 1442 edges (Fig. 2A). To identify significant modules among the up-regulated DEGs, we employed MCODE, resulting in the identification of 38 crucial molecules, including UBE2C, TTK, TROAP, TPX2, TOP2A, PLK1, PBK, NDC80, NCAPG, MKI67, MELK, MCM10, KIF4A, KIF20A, KIF18B, KIF14, HJURP, GTSE1, GINS2, FOXM1, DLGAP5, DEPDC1, CENPU, CENPM, CENPF, CENPE, CENPA, CDKN3, CDCA5, CDC45, CDC25C, CCNB2, CCNA2, BUB1B, BUB1, BIRC5, ASPM, and ASF1B (Fig. 2B). From these molecules, we selected the top five, including one H3-related histone, CENP-A, and four constitutive centromere-associated network-related proteins, CENP-M, CENP-U, CENP-E, and CENP-F (Fig. 2C).
3.3 Univariate Cox Regression Analyses of Hub Genes

Furthermore, we conducted univariate regression analysis of hub genes in different subtypes of kidney cancer and utilized the "ggplot2" package to visualize the results in the form of a forest plot. Figure 3A, 3B, and 3C present the outcomes of univariate Cox regression analyses for CENPU, CENPM, CENPF, CENPE, and CENPA across the three renal cancer subtypes. The findings highlight the significant role of hub genes as risk factors in all three types of kidney cancer.

3.4 CENPF Expression is Higher in KIRC and Associated with Poor Prognosis

We validated these 5 hub genes in 10 pairs of KIRC tissues and found that only CENPF matched our anticipated expectations (Fig 4A). Furthermore, we collected a total of 14 paired KIRC tissues, paracancerous kidney tissues, peripheral blood plasma from 10 normal physical examination patients and 10 KIRC patients. We assessed the expression of CENPF using quantitative polymerase chain reaction (qPCR). Our results revealed that CENPF was highly expressed in tumor samples compared to normal samples in both tissues and plasma (Figure 4B). Furthermore, we downloaded mRNA and clinical data of KIRC patients from the UCSC Xena database (https://xenabrowser.net/datapages/) and analyzed the data. Our analysis showed that KIRC patients with high expression of CENPF had a poorer overall survival rate (Figure 4C). Notably, tumors with stage or grade III/IV expressed higher levels of CENPF compared to tumors with stage or grade I/II(Figure 4D,E).

3.5 Analysis of KIRC Single-Cell Sequencing Results

With the aim of further investigating the role of CENPF in the tumor immune microenvironment of KIRC, we conducted an analysis on renal tumor samples from 7 KIRC patients sourced from the GSE159115 dataset. Figure 5A shows the result of cell grouping after single-cell sequencing of KIRC. Our analysis revealed a predominant expression of CENPF within the T cells found in the tumor tissue(Fig. 5B).

3.6 Distinguishing Immune Cells Associated with CENPF

We subdivided the KIRC expression matrix into two groups, one with high expression levels of CENPF, and the other with low expression levels of CENPF. We then employed the reference matrix of immune cells, provided by cibersort (LM22), to further analyze the immune cells that are closely associated with CENPF. Figure 6A illustrates the infiltration levels of 22 immune cells in the KIRC data.

Figure 6B shows a box plot that demonstrates the different immune cell contents of the TIICs resulting from the high and low CENPF groups. We subsequently selected immune cells with a significant difference between the CENPF-high group and the CENPF-low group to perform a correlation analysis with CENPF. The results of this analysis are illustrated in Figure 6C. The findings revealed that CENPF had
a significant negative correlation with resting mast cells, but a positive correlation with follicular helper T cells and memory activated CD4 T cells (Figure 6C).

We conducted an analysis on the association between CENPF and mast cells, follicular helper T cells, and memory activated CD4 T cells in KIRC. Since too few data were available for participation statistics after excluding outliers of memory activated CD4 T cells, we next only analyzed the clinical value of follicular helper T cells and mast cells in KIRC patients. Our results indicate that follicular helper T cells improved overall survival of KIRC patients (Figure 6D) and the infiltration of follicular helper T cells varied based on KIRC grades and stages (Figure 6E-6F). On the other hand, mast cells were negatively correlated with overall survival of KIRC patients (Figure 6D). We found lower infiltration of mast cells in patients with grade 3/4 and stage iii/iv KIRC (Figure 6E-6F).

4. Discussion

Patients with recurrent or metastatic RCC typically experience poor prognosis. In recent years, there has been rapid progress in the research of RCC tumor microenvironments. For instance, one study has revealed the prognostic and predictive value of immune/stromal-related gene biomarkers in renal cell carcinoma. A separate study has confirmed the prognostic value of an immune-associated gene panel for KIRC. In this study, we systematically analyzed TCGA RCC databases and identified five overlapped hub genes across three subtypes of RCC, one of which was CENPF. Centromeric proteins (CENPs) are a family of proteins that consist of immobile structural proteins (CENP-A, CENP-B, CENP-C, CENP-D, CENP-G, CENP-H, CENP-I) and transient centromere proteins (CENP-E, CENP-F).

CENPF is a kinetochore-related protein that controls the process of mitosis, regulates the cell cycle, and participates in the recruitment of spindle checkpoint proteins to maintain checkpoint response. CENPF is closely related to the occurrence and development of many tumors, including gastric cancer, papillary thyroid cancer, breast cancer, adrenocortical carcinoma and others. CENPF is one of the marker genes unique to cancer stem cells and is associated with poor prognosis in collecting duct renal cell carcinoma. A study identified CENPF as a key gene involved in the metastasis of KIRC. We employed multiple methods to confirm the prognostic value of CENPF, including survival analysis, univariate and multivariate Cox proportional risk models, and nomograms. Furthermore, we verified that CENPF was highly expressed in the tissues and plasma of KIRC patients, in contrast to paracancerous tissue or plasma from healthy individuals. These results are also consistent with the results of another study in which CENPF plays a tumor promoting role in KIRC. We then aim to investigate the potential correlation between CENPF and the immune microenvironment in KIRC. Additionally, our single-cell sequencing analysis showed a group of T cells with high expression of CENPF, which we identified as CENPF-T cells. A separate study revealed that CENPF upregulation may cause premature depletion of CD4 + memory T cells and result in immunosuppression in skin cutaneous melanoma. Consequently, we aimed to investigate the impact of CENPF on the immune infiltration microenvironment of KIRC.
The tumor microenvironment (TME) is composed of various cells and factors, including immune cells, that can either support or inhibit tumor growth. A study has revealed that immune checkpoint blockade (ICB) reshapes the RCC microenvironment and changes the interaction between cancer and immune cell population. Tfh cells are specialized CD4+ T cell subsets that provide basic help to B lymphocytes for effective antibody responses against a variety of pathogens, including viruses, bacteria, fungi, and helminths. In most solid organ tumors of non-lymphocyte origin, Tfh cells are associated with better cancer immune responses, improved clinical outcomes, and increased therapeutic responsiveness. A spatial transcriptomic study of KIRC has shown that Tfh cells are associated with mature tertiary lymphoid structures (TLS), which are organized aggregates of immune cells that form postnatally in nonlymphoid tissues. Our CIBERSORT results revealed that follicular helper T cells promote KIRC development while mast cells have a contrasting effect. Furthermore, CENPF demonstrated a positive association with follicular helper T cells and memory activated CD4 T cells, and a negative association with mast cells.

Some studies have shown that Tfh cells play an anti-tumor role in RCC. CD4+ T follicular helper (Tfh) cells provide effective assistance to B cells and can be found in the tertiary lymphatic structure (TLS) of tumors. In many solid organ tumors that exhibit TLS, promoting the number or function of Tfh cells may help enhance anti-tumor immune responses. Tfh can actively coordinate the formation of TLS by secreting CXCL13, and can indirectly enhance CD8+ T cell-mediated anti-tumor immunity by secreting IL-21. However, our analysis has revealed that in KIRC, patients with high levels of Tfh infiltration do not have a favorable prognosis. Therefore, it is worth studying how CENPF affects immune cell infiltration and specific cell types, particularly the role of Tfh cells. A study has demonstrated a negative correlation between the abundance of CXCL13+CD8+ T cells and overall and disease-free survival in KIRC. High-level infiltration of CXCL13+CD8+ T cell subgroups have been shown to elevate fatigue markers (such as PD-1, Tim-3, TIGIT) and reduce the expression of activation markers (TNF-α, IFN-γ). In addition, the abundance of CXCL13+CD8+ T cells within tumors has been linked to immune escape within the tumor microenvironment, characterized by an increase in Th2 cells, tumor-associated macrophages, Foxp3+ regulatory T cells, and TLS, alongside a decrease in natural killer cells and GZMB+ cells. Thus, Tfh cells correlated with high expression of CENPF may promote immune escape in KIRC by interacting with CXCL13+CD8+ T cells.

Mast cells (MCs) are innate immune cells characterized by their expression of FceRI and CD117. They are distinct from bone marrow hematopoietic progenitors and are known for their involvement in coordinating angiogenesis and inflammation. In recent studies, tumor-infiltrating mast cells (TIMs) have garnered attention due to their potential role in shaping adaptive immune responses. The role of mast cells can vary in different tumor immune microenvironments, as they can exhibit both tumor-promoting and anti-tumor properties, which depend on the specific type and anatomical location of the tumor. For instance, MMP-2 and MMP-9 released by MCs can promote tumor angiogenesis and growth. A study has shown that in non-metastatic clear cell renal cell carcinoma, TIMs can directly produce cytotoxic
reactions against tumor cells, thereby leading to significantly longer cancer-specific survival in patients\textsuperscript{48}. However, there are also articles that demonstrate an association between tumor-infiltrating immune cells (TIMs) and the formation of blood vessels in renal cell carcinoma\textsuperscript{49}. Furthermore, these studies indicate that TIMs are negatively correlated with the prognosis of patients\textsuperscript{50}.

In our research, we found that CENPF is negatively correlated with TIMs expression in KIRC and that patients with high TIMs have a better prognosis, which is consistent with the study we mentioned before. Mast cells (MCS) accumulate in the tumor microenvironment with the aid of chemoattractants (such as CXCL2\textsuperscript{51}, VEGF-A\textsuperscript{52}) released by tumor cells\textsuperscript{53}. CENPF may regulate mast cells by affecting cytokine secretion in the TME or through related signaling pathways.

In conclusion, our study confirmed that CENPF is highly expressed in KIRC and is a risk factor for the occurrence and development of KIRC. Significantly, we have identified a group of T cells in KIRC that exhibit elevated expression of CENPF. Notably, CENPF is positively correlated with follicular helper T cells and negatively associated with mast cell in KIRC, indicating that CENPF modulates the immune microenvironment in KIRC. Based on the other studies and our findings, it is suggested that the T cells with high expression of CENPF are CXCL13 + CD8 + T cells or other types of T cells. The interaction between CENPF-expressing T cells and Tfh cells promotes immune evasion. Conversely, the presence of mast cells in the tumor's immune microenvironment exerts a suppressive effect on tumor growth.

\textbf{Declarations}

5.1 Ethical approval and consent to participation

We confirmed that all methods were performed in accordance with relevant guidelines and regulations, and that ethical approval and informed consent from study participants were obtained.

5.2 Consent to publication

All study participants agree to publish their data in the research paper.

5.3 Availability of data and material

Database sources and specimen information have been described in the Materials and methods section.

5.4 Competing interest

There are no potential conflicts of interest associated with this research.

5.5 Funding

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5.6 Acknowledgement
Special thanks to Wang Ruizhi for his guidance in this study, and the Laboratory Department of the First Affiliated Hospital of Sun Yat-sen University for providing the specimens and PCR testing platform.

5.7 Author contribution

Ruizhi Wang and Meilin Chen completed the data analysis. Xiuxin Tang and Tangdan Ding wrote the main manuscript text. Yanping Liang and Meifang He finished all PCR tests and prepared figures. Dong Wang reviewed the manuscript.

5.8 Ethics statement

We guarantee that all experiments conducted in this study complied with the Helsinki Declaration.

All authors and participants in this study confirm that all experiments related to human tissue samples were performed in accordance with relevant guidelines and regulations.

The research obtained ethical approval from the Ethics Committee of the First Affiliated Hospital, Sun Yat-sen University, and informed consent was obtained from all subjects and/or their legal guardians. All participants confirm that all methods were carried out in accordance with relevant guidelines and regulations. We also confirm that all experimental protocols were approved by the Ethics Committee of the First Affiliated Hospital, Sun Yat-sen University.

References


**Figures**
Figure 1

Recognition of DEGs in KIRC, KICH and KIRP

Heatmaps of DEGs in (A) KIRC, (B) KICH and (C) KIRP. Red: up-regulated DEGs; Blue: down-regulated DEGs; Normal: normalsamples; Primary: primary carcinoma. (G) Up-regulated DEGs and down-regulated
DEGs in KIRC, KICH and KIRP were displayed by using the Venn diagram; Red number: up-regulated DEGs; Blue number: down-regulated DEGs.

Figure 2

Construction of PPI network of DEGs and identification of the most significant module of up-regulated DEGs

(A) PPI network of DEGs. The up-regulated genes were marked in pink and the down-regulated genes were marked in blue. (B) The most significant module of up-regulated DEGs. The up-regulated genes were marked in pink. (C) CENPA and four members of CENP-A distal complex (CAD)
Figure 3

Univariate Cox regression analyses of the hub genes

(A) The forest plot displays the results of univariate Cox regression analysis for the five members of the CENP family in KIRP. (B) The forest plot displays the results of univariate Cox regression analysis for the five members of the CENP family in KICH. (C) The forest plot displays the results of univariate Cox regression analysis for the five members of the CENP family in KIRC.
Figure 4

CENPF expression is higher in KIRC and associated with poor prognosis

(A) Comparison of CENPU, CENPM, CENPE, CENPA, CENPF mRNA expression between KIRC tissues and paracancerous kidney tissues from hospital. (B) Comparison of CENPF mRNA expression between KIRC tissues and paracancerous kidney tissues from hospital. Comparison of CENPF mRNA expression between KIRC plasma and healthy people plasma. (C) Kaplan-Meier analysis of OS KIRC patients with low and high CENPF expression. (D) Comparison of CENPF mRNA expression between stage I/II and stage III/IV patients. (E) Comparison of CENPF mRNA expression between grade I/II and grade III/IV patients. *, P<0.05. KIRC, kidney renal clear cell carcinoma; CENPF, centromere protein F; TCGA, The Cancer Genome Atlas; mRNA, messenger RNA; OS, overall survival.
Figure 5

Single cell analysis of KIRC revealed that CENPF is predominantly expressed in T cells.

(A) Single-cell atlas of ccRCC. t-SNE plot of scRNA-seq data from KIRC samples obtained from seven KIRC patients. Cell clusters found there in representing 13 cell types are shown. vSMC, vascular smooth muscle cells; Macro, macrophages; Endo, Endothelial cells; Fibo, fibroblast cells. (B) Expression of CENPF in various cell clusters.
Figure 6

Recognition of three CENPF-related immune cells

(A) Heatmap of the expression of TIICs. (B) Box diagram of TIICs’ abundance in high and low-CENPF groups. (C) Correlation coefficients between abundance ratios of different immune cells and CENPF. The correlation curve between CENPF and follicular helper T cells. The correlation curve between CENPF and
mast cells. (D) Kaplan-Meier analysis of OS KIRC patients with low and high follicular helper T cells. Kaplan-Meier analysis of OS KIRC patients with low and high mast cells. (E) Comparison of follicular helper T cells infiltration between grade I/II and grade III/IV patients. Comparison of mast cells infiltration between grade I/II and grade III/IV patients. (F) Comparison of follicular helper T cells infiltration between stage I/II and stage III/IV patients. Comparison of mast cells infiltration between stage I/II and stage III/IV patients.