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# Upregulation of a kinase interacting protein 1 in tongue squamous cell carcinoma correlates with lymph node metastasis and poor overall survival

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**Abstract**

A kinase interacting protein 1 (AKIP1) is upregulated in cancer cells/tissues and associated with deteriorative tumor features, while it has not been investigated in tongue squamous cell carcinoma (TSCC). The goal of this study was to measure AKIP1 expression and analyze its correlation with clinical feature and prognosis in TSCC patients.

We retrospectively reviewed 194 TSCC patients, whose formalin fixed paraffin-embedded (FFPE) tumor tissue specimens and paired adjacent tissue specimens were accessible for AKIP1 detection by immunohistochemistry (IHC). Whereas only 107 patients whose fresh-frozen tumor tissue and paired fresh-frozen adjacent tissue that were still available in storage were included for AKIP1 mRNA detection by real-time reverse transcription quantitative polymerase chain reaction (RT-qPCR).

AKIP1 expression (both the protein detected by IHC and mRNA detected by RT-qPCR) was higher in TSCC tissue than that in adjacent tissue. In addition, both tumor AKIP1 mRNA and protein expressions were correlated with advanced N stage and TNM stage, while they were not correlated with other clinical features in TSCC patients. As for survival, there was a correlation of AKIP1 mRNA with poor overall survival (OS), while the correlation of AKIP1 protein expression with OS was of limited statistical significance.

There is an upregulation of AKIP1 in TSCC and it correlates with lymph node metastasis as well as unfavorable prognosis in TSCC patients.

**Abbreviations:** AKIP1 = A kinase interacting protein 1, FFPE = formalin fixed paraffin-embedded, IHC = immunohistochemistry, OS = overall survival, RT-qPCR = reverse transcription quantitative polymerase chain reaction, TSCC = tongue squamous cell carcinoma.

**Keywords:** AKIP1, lymph node metastasis, overall survival, TNM stage, tongue squamous cell carcinoma

## 1. Introduction

Tongue squamous cell carcinoma (TSCC) is one of the commonly diagnosed head and neck cancers, and its incidence is experiencing an increment especially in young individuals.[1] The clinical behavior of TSCC is aggressive and the early stage cancer development is non-symptomatic that contributes to high propensity for local invasion and metastasis, resulting in the approximately 40% incidence of lymph node metastasis at diagnosis.[2] Moreover, the treatment for TSCC including surgery, radiotherapy and chemotherapy is uniformed, which lacks individuality for heterogeneity.[3] To note, the mortality of TSCC has been increasing in the recent years with estimated annual deaths over 1,300,000 cases globally.[2] Therefore, novel therapeutic strategies and prognostic biomarkers are essential for TSCC.

A kinase interacting protein 1 (AKIP1) is an intracellular protein localized at the cytoplasm, nucleus, and mitochondria who plays the role as an adaptor of intracellular structural protein.[4] It is also reported to be a potent oncogenic protein in many cancers including breast cancer, cervical cancer, gastric cancer and esophageal cancer etc.[4–8] In laboratory aspects, AKIP1 has been shown to promote cell migration and invasion by activating Slug-induced epithelial-mesenchymal transition in gastric cancer cells, induce epithelial-mesenchymal transition via activating PI3K/Akt/IKKβ pathway in cervical cancer cells, and activate the Wnt/β-catenin/CBP signaling pathway in hepatocellular carcinoma cells.[9–11] Meanwhile, the clinical implication of AKIP1 is revealed, which implicates that AKIP1 is associated with poor clinical features such as advanced tumor stage, and it is potentially a biomarker for unfavorable prognosis in cancer patients.[4–8] Whereas in TSCC, the role of AKIP1 is not yet identified.

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*YS and GS contributed equally to this work.*

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Therefore, we detected the AKIP1 expression by both immunohistochemistry (IHC) and real-time reverse transcription quantitative polymerase chain reaction (RT-qPCR) to analyze the correlation of AKIP1 with clinical feature and prognosis in TSCC patients.

## 2. Methods

### 2.1. Patients

194 TSCC patients who underwent resection and/or combined with radiotherapy in our hospital were retrospectively reviewed. All patients were confirmed as TSCC according to the finding of histopathology. The eligible patients included in this study were aged above 18-years old, had well preserved tumor tissue and adjacent tissue specimens which were suitable for IHC assay, had complete tumor features records before surgery. The patients who received neoadjuvant therapy, had history of or complicated with other cancers, or had no any follow-up data after surgery were excluded. This study was approved by the Ethics Committee of our hospital. Written informed consents were provided by themselves or their family members.

### 2.2. Data collection

Patients' demographics such as age and gender were collected. Patients' tumor features such as pathological grade, T stage, N stage and TNM stage were acquired from their electronic medical records. Whether the patients received adjuvant radiotherapy or not was also collected. Patients' overall survival (OS) was defined as the date of surgery to the data of death.

### 2.3. AKIP1 protein assessment

The formalin fixed paraffin-embedded (FFPE) tumor tissue specimens (N=194) and paired FFPE adjacent tissue specimens (N=194) were obtained from store room of the Pathology Department. The AKIP1 protein level in the tissue specimens was assessed using IHC assay. The IHC staining procedures were as follows: briefly, all specimens were sliced into 4 μm sections, which were then deparaffinized, rehydrated and retrieved the surface antigen. After inhibiting endogenous peroxidase and blocking nonspecific binding, the sections were incubated with anti-AKIP1 antibody (1:100, Abcam, Cambridge, MA, USA) overnight and then in Goat anti-Rabbit IgG H&L (HPR) Secondary Antibody (1:10000, Abcam, Cambridge, MA, USA) for 30 min, and lastly stained and counterstained with diaminobenzidine and hematoxylin, respectively. Rabbit IgG, polyclonal - Isotype Control (ab37415) (1:100, Abcam, Cambridge, MA, USA) was used as isotype control. The IHC score by multiplying staining intensity score (ranging 0–3) and staining density score (ranging 0-4) were assessed referring to a previous study[12] and AKIP1 low (IHC score≤3) or high (IHC score>3) was defined accordingly.

### 2.4. AKIP1 mRNA detection

Among all patients, 107 fresh-frozen tumor tissue and paired fresh-frozen adjacent tissue were available. The AKIP1 mRNA in the fresh-frozen tissues was detected by RT-qPCR. The RNA was firstly reversely transcribed to cDNAs after extracted from the fresh frozen tissues. The RNA extraction kit was TRIzol Reagent (Thermo Fisher Scientific, Waltham, Massachusetts, USA) and reverse transcription kit was ReverTra Ace qPCR RT Master Mix (Toyobo, Osaka, Kansai, Japan). Then, the relative AKIP1 mRNA expression was detected by KOD SYBR qPCR Mix (Toyobo, Osaka, Kansai, Japan). The internal reference was GAPDH, whose median Ct value was 19.21±3.46 (variation 18.0%) in TSCC tumor tissues and 20.66±4.55 (variation 22.0%) in adjacent tissues (under the same amount of cDNA/PCR). Further analysis showed no difference of Ct value between TSCC tumor tissues and adjacent tissues ($P=.683$), indicating that GAPDH expression was similar in tumor tissues and adjacent tissues, and it was suitable to be the internal reference in this RT-qPCR analysis. Relative expression of AKIP1 mRNA was calculated with $2^{-\triangle\triangle Ct}$ method. Primers: AKIP1 mRNA forward primer (5'->3'): AGAACATCTCTAAGGACCTCTACAT; reverse primer (5'->3'): CCAGAATCAACTGCTACCACAT; GAPDH forward primer (5'->3'): GGAGCGAGATCCCTCCAAAAT; reverse primer (5'->3'): GGCTGTTGTCATACTTCTCATGG. AKIP1 mRNA expression was classified as high or low based on the median value of AKIP1 mRNA in tumor tissues.

### 2.5. Statistical analysis

SPSS 24.0 statistical software (IBM, Chicago, Illinois, USA) and GraphPad Prism 8.02 (GraphPad Software Inc., San Diego, California, USA) was applied for data analysis. Paired-samples t test was used to compare the AKIP1 IHC score between tumor tissue and adjacent tissue, and McNemar's test was used for comparison of AKIP1 protein expression. AKIP1 mRNA expression between tumor tissue and adjacent tissue was compared by Wilcoxon signed-rank test. AKIP1 protein expression and AKIPA mRNA expression correlations with clinical features were assessed by Chi-square test or Wilcoxon rank sum test. OS was analyzed using Kaplan-curve, and the difference between groups was compared by log-rank test.

## 3. Results

### 3.1. Study flow

The initial 289 TSCC patients were reviewed initially, whereas 95 of them were excluded, including 37 who had no eligible tumor tissue or adjacent tissue specimens for IHC assay, 35 who were unable to make contact, 14 who received neoadjuvant therapy, 7 who had no follow up data after surgery, and 2 who had history of other cancers (Fig. 1). The remaining 194 TSCC cases were eligible, from whom all 194 FFPE tumor tissue and adjacent tissue specimens were used for AKIP1 protein measurement by IHC assay, while only 107 fresh-frozen tumor tissues and adjacent tissues were available, which were used for AKIP1 mRNA detection by RT-qPCR.

### 3.2. Clinical features

The mean age of total patients was 55.5±12.1 years and the gender composition was 53 (27.3%)/141 (72.7%) female/male (Table 1). There were 39 (20.1%), 86 (44.3%), 69 (35.6%) patients at pathological grade G1, G2, G3, respectively, and 30 (15.5%), 81 (41.8%), 74 (38.1%), 9 (4.6%) patients at TNM stage I, II, III, IV, respectively. In addition, 143 (73.7%) patients received adjuvant radiotherapy. The additional clinical features of TSCC patients could be seen in Table 1.

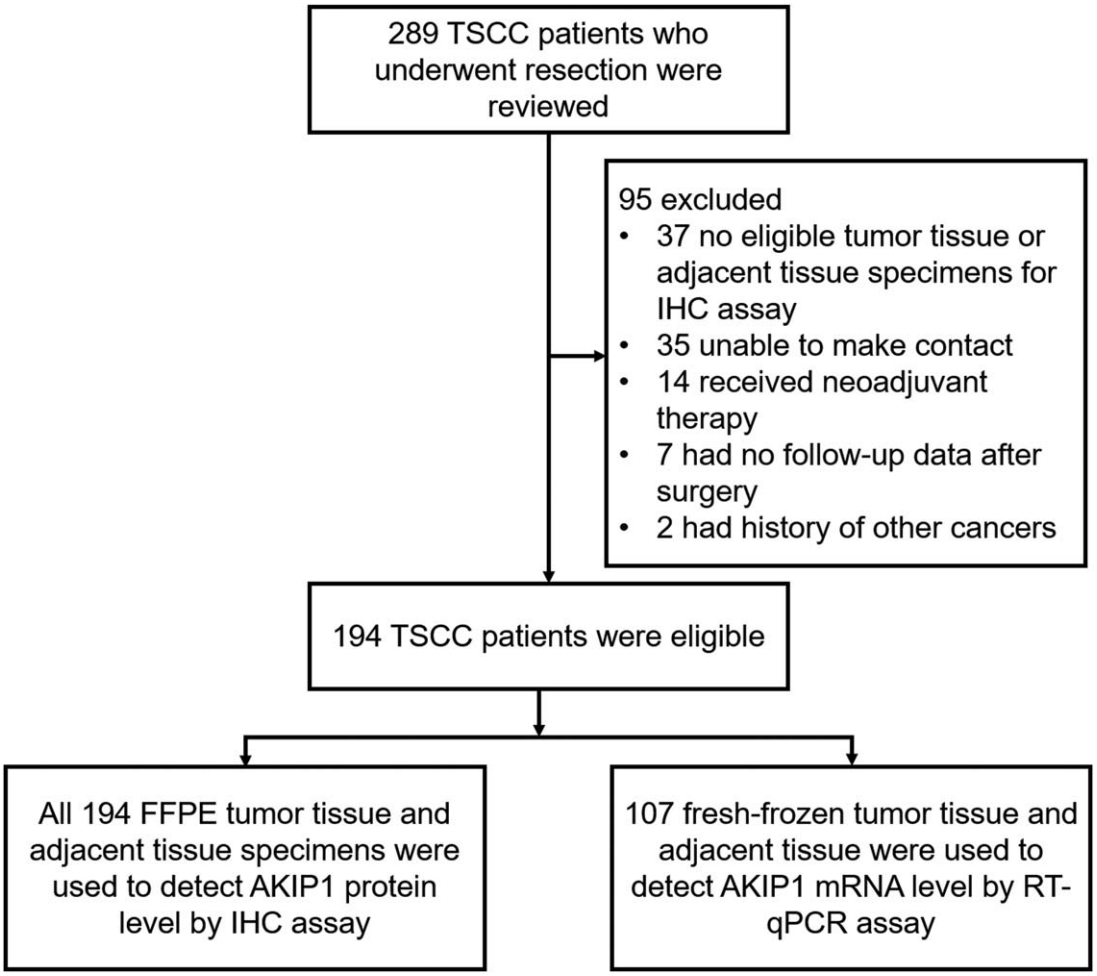


**Figure 1.** Study flow. TSCC, tongue squamous cell carcinoma; IHC, immunohistochemistry; AKIP1, a interacting protein kinase 1; FFPE, formalin fixed paraffin-embedded; RT-qPCR, reverse transcription quantitative polymerase chain reaction.

### *3.3. AKIP1 expression in TSCC*

AKIP1 protein expression (high or low) examples in tumor tissue and adjacent tissue were shown in Figure 2A. The mean AKIP1 IHC score was higher in TSCC tumor tissue compared with adjacent tissue ($P < .001$) (Fig. 2B), and further comparison of AKIP1 protein high/low expression between TSCC tissue and adjacent tissue ($P < .001$) (Table 2) also indicated that AKIP1 protein level was higher in TSCC tumor tissues compared with adjacent tissues. Besides, the comparison of AKIP1 mRNA expression also validated the overexpression of AKIP1 in TSCC tumor tissues ($P < .001$) (Fig. 3).

### *3.4. Correlation of AKIP1 with clinical features*

AKIP1 protein expression was correlated with advanced N stage ($P = .004$) and TNM stage ($P = .010$), but not other clinical features (Table 3). As for AKIP1 mRNA expression, it was also correlated with advanced N stage ($P = .002$) and TNM stage ($P = .005$) as well (Table 4).

### *3.5. Correlation of AKIP1 with survival*

The accumulating OS showed a lower tendency in AKIP1 protein high expression patients than in AKIP1 protein low expression patients ($P = .060$) (Fig. 4A), meanwhile, the OS was decreased in AKIP1 mRNA high expression patients than that in AKIP1 mRNA low expression patients ($P = .049$) (Fig. 4B).

## 4. Discussion

AKIP1 has been considered as a pivotal regulator in carcinogenic progression. The laboratory findings reveal that in cervical cancer, AKIP1 promotes epithelial-mesenchymal transition and metastasis via activating PI3K/Akt/IKKβ pathway and the subsequent NF-κB signaling.[10] Besides, research on gastric cancer also indicates that AKIP1 overexpression promotes cell proliferation, invasion, metastasis in gastric cancer cells.[9] On the other hand, silencing AKIP1 in colorectal cancer cells reduces cell migration ability, indicating that AKIP1 promotes colorectal cancer progression.[4] As for the clinical findings, AKIP1 expression is upregulated in non-small cell lung cancer (NSCLC) tumor tissues, and it positively correlates with lymph node metastasis as well as TNM stage in NSCLC patients.[13] In multiple myeloma, AKIP1 upregulation is correlated with higher pathological stage and unfavorable treatment response in MM patients.[14] In addition, AKIP1 also associates with high tumor stage, size, and lymph node metastasis in breast cancer patients.[6] Enlightened from these existing evidence that AKIP1 is upregulated in cancer cells/tissues and is

**Table 1**

**Clinical features.**

| Items | TSCC patients (N = 194) |
|---|---|
| Age (years), mean±SD | 55.5 ± 12.1 |
| Gender, No. (%) | |
| Female | 53 (27.3) |
| Male | 141 (72.7) |
| Pathological grade, No. (%) | |
| G1 | 39 (20.1) |
| G2 | 86 (44.3) |
| G3 | 69 (35.6) |
| T stage, No. (%) | |
| T1 | 32 (16.5) |
| T2 | 103 (53.1) |
| T3 | 59 (30.4) |
| N stage, No. (%) | |
| N0 | 121 (62.4) |
| N1 | 64 (33.0) |
| N2 | 9 (4.6) |
| TNM stage, No. (%) | |
| I | 30 (15.5) |
| II | 81 (41.8) |
| III | 74 (38.1) |
| IV | 9 (4.6) |
| Adjuvant radiotherapy | |
| No | 51 (26.3) |
| Yes | 143 (73.7) |

TSCC = tongue squamous cell carcinoma, SD = standard deviation.

associated with deteriorative tumor features, while AKIP1 has not been investigated in TSCC, the malignancy with high metastasis rate, we explored the AKIP1 expression by IHC and RT-qPCR in TSCC, as well as analyzed its correlation with clinical features. We observed that AKIP1 was upregulated in TSCC tumor tissues, and it was correlated with lymph node metastasis and advanced TNM stage in TSCC patients. It was consistent with the previous evidence that AKIP1 was upregulated in tumor tissues/cells and could be speculated that AKIP1 is the key regulator for the biological aggressiveness of cancers. These outcomes could be explained by that:

**Table 2**

**Comparison of AKIP1 protein expression between adjacent tissue and tumor tissue.**

| | AKIP1 protein expression | | |
|---|---|---|---|
| Items | Low | High | *P* value |
| Adjacent tissue, No. (%) | 129 (66.5) | 65 (33.5) | <.001 |
| Tumor tissue, No. (%) | 85 (43.8) | 109 (56.2) | |

Comparison was determined by McNemar's test. AKIP1, A-kinase interacting protein 1.

1. AKIP1 was an oncogenic protein which promoted epithelial-mesenchymal transition in cancer cells, and it facilitated proliferation, invasion, metastasis of cancer cells,[10] which contributed to lymph node metastasis and high TNM stage in TSCC.
2. (2) Apart from the function on cell proliferation and metastasis, AKIP1 was also shown to promote angiogenesis in cancer via activating NF-κB and the subsequent CXCL1, CXCL2, and CXCL8 expression,[9] thereby, it was positively correlated with tumor growth.

AKIP1 is recognized as a prognostic marker in a variety of cancers. For instance, colorectal cancer patients with higher AKIP1 level have shorter OS compared with those with AKIP1 low expression.[4] In breast cancer, a strong correlation of AKIP1 with poor OS and recurrence free survival was observed.[6] The same trend is also presented in gastric cancer, cervical cancer, acute myeloid leukemia, and hepatocellular carcinoma, which suggests that AKIP1 is a strong indicator for poor survival in wide range of malignancies.[4–6,8–11,13–15] Therefore, we extracted the follow-up data of TSCC patients from the clinical record and analyzed the association of AKIP1 with TSCC patients' survival, which verified that AKIP1 mRNA expression was correlated with poor OS in TSCC patients, but AKIP1 protein expression did not. This could be explained in several ways:

1. As the regulator in carcinogenesis, AKIP1 activates multiple signaling pathways such as Wnt/β-catenin signaling, Akt/GSK-3β/Snail pathway and PI3K/Akt/IKKβ pathway that contributed to increased cancer cell proliferation, invasion and

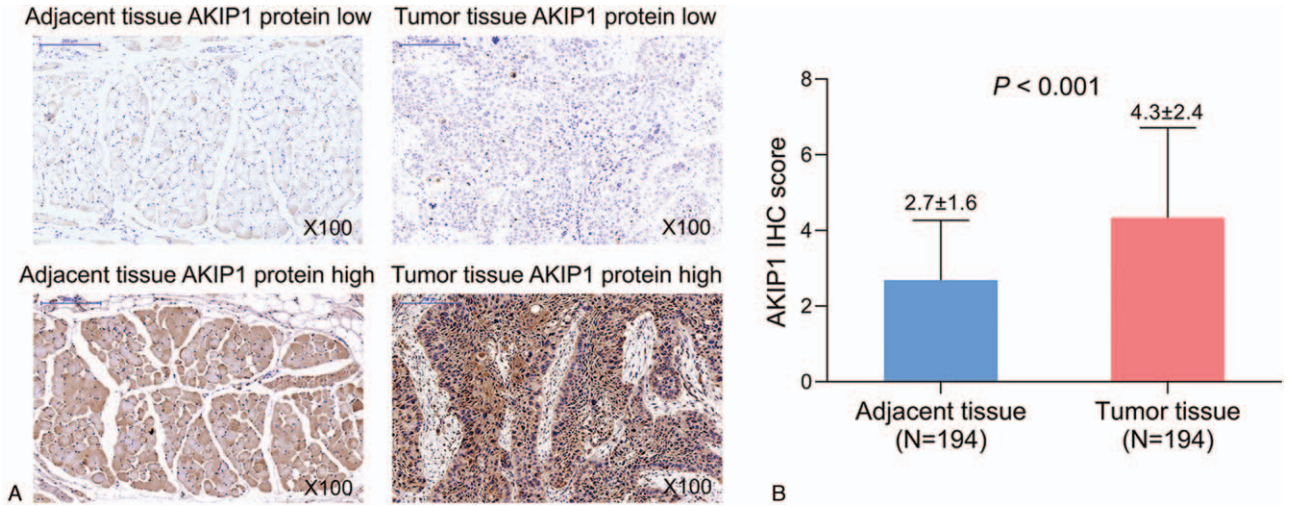


**Figure 2.** The IHC assay for AKIP1 assessment. The IHC examples of AKIP1 expression (high/low) in adjacent tissue and TSCC tumor tissue (A). AKIP1 IHC score between tumor tissue and adjacent tissue (B). IHC, immunohistochemistry; AKIP1, A interacting protein kinase 1.

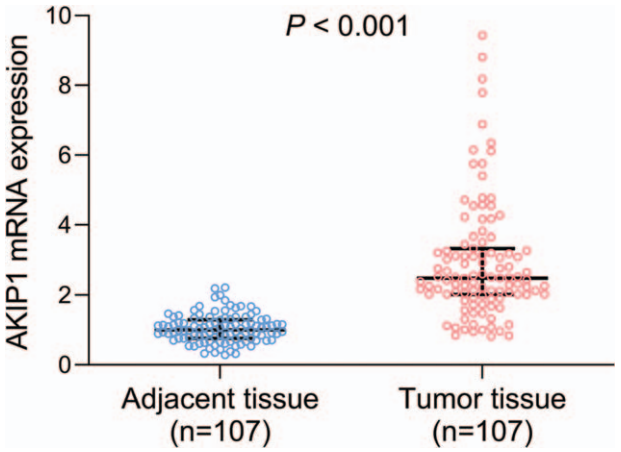


**Figure 3.** Comparison of AKIP1 mRNA expression between tumor tissue and adjacent tissue. AKIP1, a interacting protein kinase 1; mRNA, messenger RNA.

metastasis, therefore, AKIP1 was correlated with advanced tumor features and poor prognosis accordingly.[6,10,11]

2. The metastasis and recurrence of tumor is the main obstacle for TSCC prognosis. As shown previously that AKIP1 promoted tumor metastasis as well as angiogenesis, it might accelerate the TSCC metastasis and recurrence, thus, lead to poor prognosis.
3. (3) The correlation of AKIP1 protein level with overall survival was of limited statistical significance, which might be due to that unlike AKIP1 mRNA, which was a direct reflection of AKIP1 expression at transcription level, the protein expression of AKIP1 might be altered during the transcriptional processes, thus, the correlation of AKIP1 protein expression with survival was mitigated.

The mRNA expression of AKIP1 was a relative value (against the internal reference), whereas the AKIP1 protein expression was absolute value. Since the determination cut-off for AKIP1 high/low expression by AKIP1 mRNA and protein was different, the results from statistical analysis would vary.

We conducted the novel exploration of AKIP1 in TSCC, while there were still some limitations in our study. As a retrospective study, the survival of TSCC patients might be affected by cofounding factors, therefore, the correlation of AKIP1 with survival needed to be validated in prospective studies. In addition, the follow-up duration could be prolonged to see a greater difference in OS between AKIP1 high and low expression patients. Although the regulatory function of AKIP1 has been studied in other cancers, there still lack evidence about the molecular mechanism of AKIP1 in TSCC pathogenesis, which needs further exploration. Besides, the use of single internal reference in RT-QPCR might bring bias to the results, thus, validation using extra house-keeping genes was needed in the future.

In conclusion, AKIP1 is upregulated in TSCC and it correlates with lymph node metastasis as well as poor survival in TSCC patients.

**Table 3.**

**Correlation of tumor AKIP1 protein expression with clinical features.**

| Items | AKIP1 protein expression | | *P* value |
|---|---|---|---|
| | Low (n=85) | High (n=109) | |
| Age, No. (%) | | | .124 |
| <55 years | 35 (41.2) | 57 (52.3) | |
| ≥55 years | 50 (58.8) | 52 (47.7) | |
| Gender, No. (%) | | | .220 |
| Female | 27 (31.8) | 26 (23.9) | |
| Male | 58 (68.2) | 83 (76.1) | |
| Pathological grade, No. (%) | | | .229 |
| G1 | 20 (23.5) | 19 (17.4) | |
| G2 | 38 (44.7) | 48 (44.1) | |
| G3 | 27 (31.8) | 42 (38.5) | |
| T stage, No. (%) | | | .054 |
| T1 | 17 (20.0) | 15 (13.8) | |
| T2 | 48 (56.5) | 55 (50.4) | |
| T3 | 20 (23.5) | 39 (35.8) | |
| N stage, No. (%) | | | .004 |
| N0 | 62 (72.9) | 59 (54.2) | |
| N1 | 22 (25.9) | 42 (38.5) | |
| N2 | 1 (1.2) | 8 (7.3) | |
| TNM stage, No. (%) | | | .010 |
| I | 16 (18.8) | 14 (12.8) | |
| II | 41 (48.2) | 40 (36.7) | |
| III | 27 (31.8) | 47 (43.2) | |
| IV | 1 (1.2) | 8 (7.3) | |
| Adjuvant radiotherapy | | | .830 |
| No | 23 (27.1) | 28 (25.7) | |
| Yes | 62 (72.9) | 81 (74.3) | |

Correlation was determined by Chi-square test or Wilcoxon rank sum test. AKIP1, A-kinase interacting protein 1.

**Table 4.**

**Correlation of tumor AKIP1 mRNA expression with clinical features.**

| Items | AKIP1 mRNA expression | | *P* value |
|---|---|---|---|
| | Low (n=53) | High (n=54) | |
| Age, No. (%) | | | .628 |
| <55 years | 28 (52.8) | 26 (48.1) | |
| ≥55 years | 25 (47.2) | 28 (51.9) | |
| Gender, No. (%) | | | .627 |
| Female | 17 (32.1) | 15 (27.8) | |
| Male | 36 (67.9) | 39 (72.2) | |
| Pathological grade, No. (%) | | | .062 |
| G1 | 16 (30.2) | 6 (11.1) | |
| G2 | 21 (39.6) | 27 (50.0) | |
| G3 | 16 (30.2) | 21 (38.9) | |
| T stage, No. (%) | | | .202 |
| T1 | 11 (20.8) | 6 (11.1) | |
| T2 | 29 (54.7) | 31 (57.4) | |
| T3 | 13 (24.5) | 17 (31.5) | |
| N stage, No. (%) | | | .002 |
| N0 | 41 (77.4) | 27 (50.0) | |
| N1 | 12 (22.6) | 22 (40.7) | |
| N2 | 0 (0.0) | 5 (9.3) | .005 |
| TNM stage, No. (%) | | | |
| I | 11 (20.8) | 6 (11.1) | |
| II | 27 (50.9) | 19 (35.2) | |
| III | 15 (28.3) | 24 (44.4) | |
| IV | 0 (0.0) | 5 (9.3) | |
| Adjuvant radiotherapy | | | .780 |
| No | 14 (26.4) | 13 (24.1) | |
| Yes | 39 (73.6) | 41 (75.9) | |

Correlation was determined by Chi-square test or Wilcoxon rank sum test. AKIP1, A-kinase interacting protein 1.

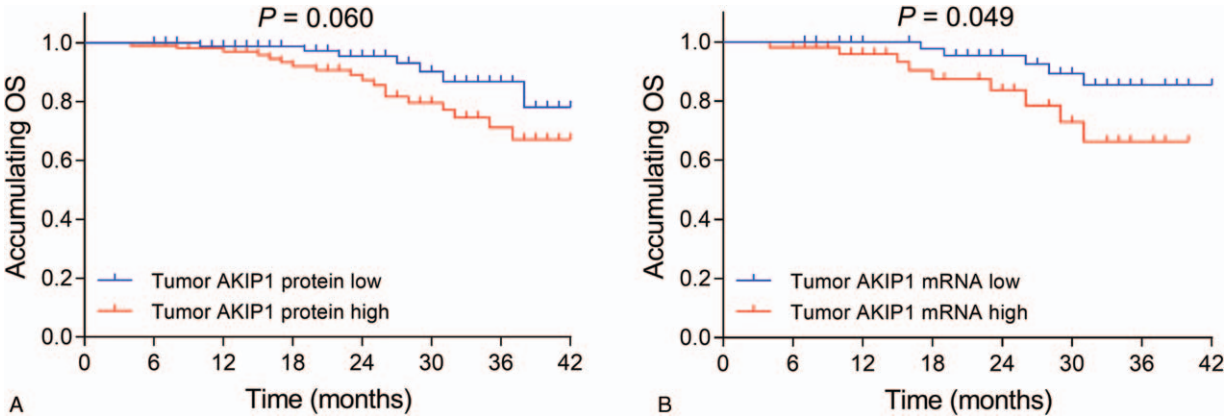


**Figure 4.** Comparison of survival between AKIP1 high and low expression patients. Comparing accumulating OS between AKIP1 protein high and low expression patients (A). Comparing accumulating OS between AKIP1 mRNA high and low expression patients (B). AKIP1, a interacting protein kinase 1; OS, overall survival.

## Author contributions

**Conceptualization:** Guang Shi, Chao Ma.
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**Writing – original draft:** Ying Sun, Guang Shi, Jianjun Jiao, Yingqi Liu.
**Writing – review & editing:** Guang Shi, Chao Ma, Qingling Gao, Xueqiang Zhang, Qiang Feng.

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