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Regular paper

Dynamic changes of serum miR-105-3p expression and prognostic value evaluation of postoperative thyroid cancer

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Objective. To explore the dynamic changes of serum miR-105-3p expression after thyroid cancer surgery and its correlation with clinicopathological manifestations and to evaluate its clinical value as a potential biomarker after surgery. Methods. A total of 100 thyroid cancer patients admitted to Shaanxi Provincial People's Hospital from November 2020 to August 2021 were selected as the research objects. The aim was to detect the expression of serum miR-105-3p in patients and its correlation with tumor pathological characteristics (pathological type, tumor differentiation, TNM stage, lymph node metastasis), and to detect the dynamic changes of postoperative serum miR-105-3p in patients to evaluate its prognostic value as a potential biomarker. Results. The level of serum miR-105-3p increases in patients with well-differentiated thyroid cancer and lymph node metastasis; the level of serum miR-105-3p gradually decreases with the passage of time after surgery, and there is a significant difference between 4 d after surgery and before surgery; serum miR-105-3p level can significantly distinguish between patients with poor prognosis and good prognosis within 2 years after the operation, and it can predict the improvement of the prognosis of thyroid cancer after surgery. Conclusions. The level of serum miR-105-3p is closely related to the degree of differentiation and lymph node metastasis in patients with thyroid cancer. Its level gradually decreases with the passage of time after surgery. It has a good diagnostic value for the prognosis of thyroid cancer after surgery and when it is expected to become a thyroid cancer surgery. Potential biomarkers for post-diagnosis.

Keywords: thyroid cancer, serum miR-105-3p, dynamic changes, diagnosis, prognosis

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Abbreviations: miRNA, microRNA

INTRODUCTION

Thyroid cancer originates from thyroid epithelial cells and is one of the common malignant tumors in the endocrine system (Asamoah *et al.*, 2021). It has the characteristics of slow growth and low malignancy (Di Cristofano *et al.*, 2021). It has no obvious symptoms when rising early; in the middle and late stages, it can be manifested as hard masses, dysphagia, vocal cord compression, and neck intercourse (Bourlon *et al.*, 2021). Symptoms such as compression of nerve nodules seriously affect the quality of life of patients. Epidemiological surveys show that thyroid cancer accounts for 1.3% of the world's cancer incidence and 0.5% of cancer mortality. In recent years, the incidence of thyroid cancer in China has also been on the rise (Cheng *et al.*, 2021). The number of new cases of thyroid cancer accounts for 15.6% of the total number of thyroid cancers in the world, and the number of deaths accounts for 13.8% of the world's total (Lin *et al.*, 2021; Wirth *et al.*, 2021). A large number of clinical research data show that thyroid cancer is a malignant tumor with a low degree of malignancy and relatively slow development, and the patient has a long survival period and a good prognosis (Creff *et al.*, 2021). However, it is worth noting that thyroid cancer has the characteristics of easy recurrence after surgery, which seriously affects the prognosis of patients (Puttergill *et al.*, 2021). Therefore, effective risk stratification of patients with thyroid cancer after surgery, so as to timely intervene in patients with high-risk prognosis, can effectively reduce tumor metastasis and recurrence. The probability of improving the prognosis can also effectively save medical resources (Moosa *et al.*, 2021). The current clinical predictive identification of recurrence/metastasis of thyroid cancer after surgery mainly depends on the detection of relevant serum tumor markers (Zahra *et al.*, 2021; Mironska *et al.*, 2019). It depends on the patient's age, gender, endocrine status, intraoperative tumor tissue invasion, and whether to receive radionucleus after surgery. Interference of multiple factors such as thyroid therapy, related markers are not satisfactory for early judgment of recurrence/metastasis of thyroid cancer after surgery and for risk stratification (Ratajczak *et al.*, 2021; Iesato *et al.*, 2021).

In recent years, the relationship between microRNA (miRNA) and thyroid cancer has gradually attracted the attention of academic circles. miRNA is a type of small (19-25 nucleotides) non-coding single-stranded RNA with a variety of biological functions (Cao *et al.*, 2020). As a potential oncogene and tumor suppressor gene, it inhibits the expression of target genes through a post-transcriptional regulatory mechanism, and plays an important role in the occurrence and development of tumors (Nan *et al.*, 2021; Jiang *et al.*, 2020). Studies have shown that, compared with unaffected thyroid tissue, a variety of miRNAs have been transcriptionally dysregulated in thyroid cancer (Zhang *et al.*, 2021; Rogucki *et al.*, 2020; Toraih *et al.*, 2021). Among them, miR-105-3p is a highly conserved miRNA in humans, cattle, horses and many other species, indicating that it has a variety of potential biological effects (Li *et al.*, 2019). Recent studies have shown that miR-105-3p is closely related to the occurrence and development of tumors, including ovarian cancer, prostate cancer, colon cancer and hepatocellular carcinoma (Shen *et al.*, 2014; Cui *et al.*, 2019; Li *et al.*, 2021; Gao *et al.*, 2020). In addition, miR-105-3p can be used as an oncogene to affect various biological behaviors of tumor growth by regulating the expression of different proteins (Sirotkin *et al*., 2010). However, to date, little is known about the expression pattern and biological functions of miR-105-3p in thyroid cancer. This study aimed to investigate the dynamic changes of serum miR-105-3p expression after thyroid cancer surgery and its correlation with clinicopathological manifestations, and to evaluate its clinical value as a potential biomarker.

MATERIALS AND METHODS

General information

This study collected 100 patients with thyroid cancer that were admitted to Shaanxi Provincial People's Hospital from November 2020 to August 2021, all of whom underwent a radical resection of thyroid cancer and were treated with thyroid-stimulating hormone inhibitory drugs after the surgery. Patients general information (age, gender), pathological type (papillary carcinoma, follicular carcinoma, and medullary carcinoma), tumor differentiation degree (well-differentiated, moderately differentiated, and poorly differentiated), TNM staging, and lymph node metastasis data were all collected. This study complies with the Declaration of Helsinki and the relevant laws and regulations of China's clinical trial research. All subjects signed an informed consent form or authorized family members to sign before being selected. The research was approved by the Shaanxi Provincial People's Hospital ethics committee and complied with the quality management standard requirements of clinical trial research.

Inclusion and exclusion criteria

Inclusion criteria: (1) The diagnostic criteria for thyroid cancer refer to the criteria in the 2015 NCCN diagnostic guidelines (Lodewijk *et al*., 2016) for thyroid cancer; (2) age 20-70 years; (3) confirmed by pathological examination; (4) patient has no history of radiotherapy or chemotherapy and endocrine disease. Exclusion criteria: (1) patients with other thyroid surgery; (2) patients with other malignant tumors; (3) patients with immune function diseases; (4) pathological data missing.

Serum miR-105-3p detection

Fasting peripheral venous blood, 5 mL, was collected from all patients 1d before operation and 1d, 2d, 4d, 8d, 14d after operation, centrifuged at 3000g/min for 10 min, and then collected the serum. The MagMAX™ RNA isolation kit (A33899, Thermo Fisher Scientific, Inc. USA) and VetMAX™-Plus One-Step RT-PCR kit (4415328, Thermo Fisher Scientific, Inc. USA) were applied to isolate total RNA and miRNAs according to the instructions. After total RNA extraction, a TaqMan microRNA assay (4427975, Thermo Fisher Scientific, Inc., USA) was carried out to measure the expression of miR-105-3p. After referring to the PrimeScript™ II Reverse Transcriptase kit (2690A, Takara Biomedical Technology Co., Ltd., Japan) instruction manual, reverse transcription of RNA into cDNA was performed. The reagent components in the reaction system were as follows: 20×TaqMan miRNA assay (1 μL), 2×TaqMan Universal PCR Master Mix (10 μL; USA; Thermo Fisher Scientific, Inc.), cDNA (1.33 μL), forward primer (1 μL) and reverse primer (1 μL) and double distilled water (5.67 μL). miR-105-3p: Forward primer: 5'-CCACGGACGTTTGAGCAT-3'; Reverse primer: 5'-TATGGTTGTTCACGACTCCTTCAC-3'. Control U6 snRNA forward primer: 5'-ATTGGAACGATACAGAGAAGATT-3'; Reverse primer: 5'-GGAACGCTTCACGAAT TTG-3'.

RT-qPCR was performed on the ABI 7500 Real-Time PCR System, and the results of the threshold cycle (Ct) were calculated by the $2-\Delta\Delta Ct$ method after normalization to U6.

Follow-up study

After the patient was discharged from the hospital, follow-up was conducted every 6 months, and serum was collected to detect the level of miR-105-3p. All patients were followed up for 2 years after surgery. Recurrence or metastasis was regarded as a poor prognosis, otherwise, the prognosis was good.

Statistical analysis

All data were statistically analyzed using SPSS 22.0 software (SPSS, Inc., Chicago, IL, USA). The measurement data that conformed to a normal distribution are shown as the mean ± standard deviation. The difference between two groups was analyzed by Student's *t*-test. One-way ANOVA was used to analyze the differences among groups. The diagnostic value of serum miR-105-3p level on the prognosis of thyroid cancer was analyzed by ROC curve and AUC. GraphPad 8.0 software (GraphPad software Inc., La Jolla, CA, USA) was used for drawing. $p<0.05$ is considered statistically significant.

RESULTS

General information

Among all 100 patients with thyroid cancer, 29 were males and 71 were females; aged 20–70 years, with an

Table 1. General information of patients with thyroid cancer

Category	N
Gender	
Male	29
Female	71
Age	
≥60 years old	29
<60 years old	71
Pathological Type	
Papillary carcinoma	38
Follicular carcinoma	33
Medullary carcinoma	29
Differentiation	
Well differentiated	43
Moderate differentiation	28
Poorly differentiated	29
TNM Staging	
Stage I	28
Stage II	42
Stage III	30
Whether Lymph Node Metastasis	
Yes	58
No	42

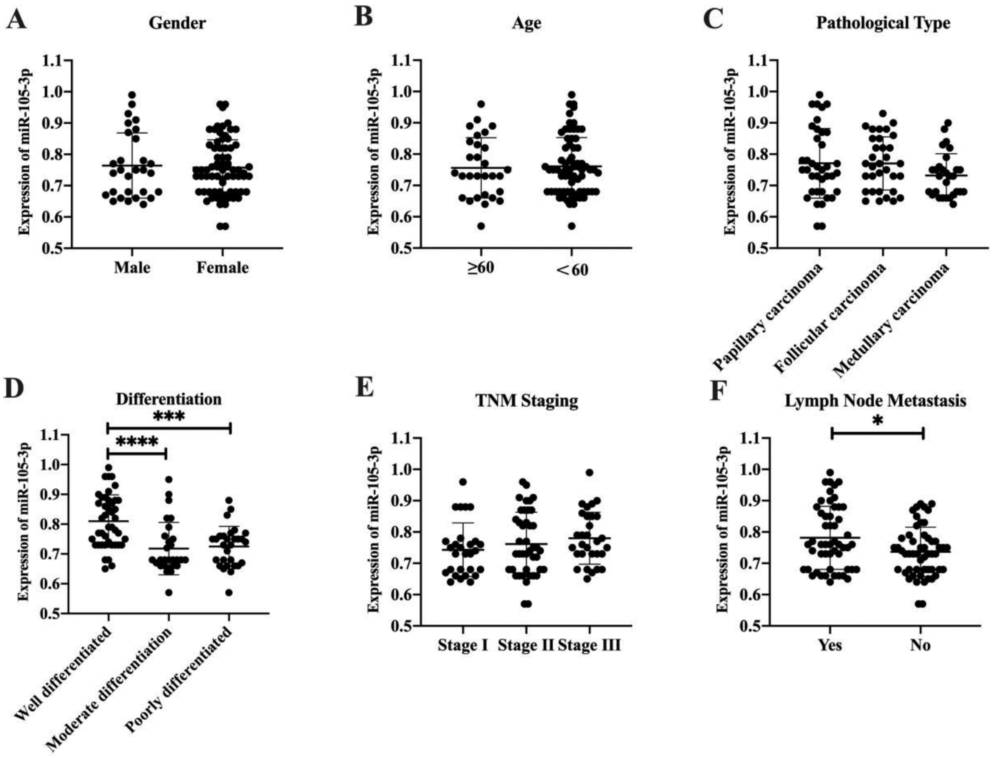

Figure 1. The relationship between preoperative serum miR-105-3p levels and pathological features of thyroid cancer.
(**A**) The relationship between preoperative serum miR-105-3p level and gender in thyroid cancer; (**B**) The relationship between preoperative serum miR-105-3p level and age in thyroid cancer; (**C**) The relationship between preoperative serum miR-105-3p level and pathological types of thyroid cancer; (**D**) The relationship between preoperative serum miR-105-3p level and differentiation of thyroid cancer; (**E**) The relationship between preoperative serum miR-105-3p level and TNM staging of thyroid cancer; (**F**) The relationship between preoperative serum miR-105-3p level and lymph node metastasis in thyroid cancer. Data are expressed as mean ± standard deviation; **p*<0.05, ****p*<0.001, *****p*<0.0001.

average 51.92±12.62 years old; pathological types: 38 cases of papillary carcinoma, 33 cases of follicular carcinoma, 29 cases of medullary carcinoma; differentiated degree: 43 cases of high differentiation, 28 cases of moderate differentiation, 29 cases of poor differentiation; TNM staging: 28 cases of stage I, 42 cases of stage II, 30 cases of stage III; lymph node metastasis: 58 cases of lymph node metastasis, 42 cases of no lymph node metastasis (Table 1).

The relationship between preoperative serum miR-105-3p levels and pathological features of thyroid cancer

We tested the serum miR-105-3p level of all patients 1 day before surgery. The results showed that there was no significant difference in serum miR-105-3p levels in patients with thyroid cancer of different genders, ages, pathological types and TNM stages (Fig. 1A–C and Fig. 1E); the serum miR-105-3p level of well-differentiated patients was significantly higher than that of moderately differentiated and poorly differentiated patients (Fig. 1D); the serum miR-105-3p level of patients with lymph node metastasis was significantly higher than that of non-metastatic patients (Fig. 1D and Fig. 1F).

Changes in serum miR-105-3p levels after thyroid cancer surgery

In order to study the expression pattern of the changes in miR-105-3p levels after thyroid cancer surgery, we detected the serum miR-105-3p levels of all patients on the 1d, 2d, 4d, 8d, and 14d post-operatively. The results showed that compared with preoperatively, serum miR-105-3p levels in patients with thyroid cancer showed a decreasing trend after surgery; and with the passage of time after surgery, serum miR-105-3p levels gradually decreased; 4 d after surgery, the patient's serum miR-105-3p level was significantly different from that before surgery (Fig. 2).

The relationship between serum miR-105-3p level and prognosis after thyroid cancer

In order to further explore the relationship between the changes in serum miR-105-3p levels after thyroid cancer surgery and the patient's prognosis, we conducted a 2-year follow-up of all patients and collected patients' serum for miR-105-3p levels every 6 months, 4 times in total. The results showed that 47 patients had recurrence

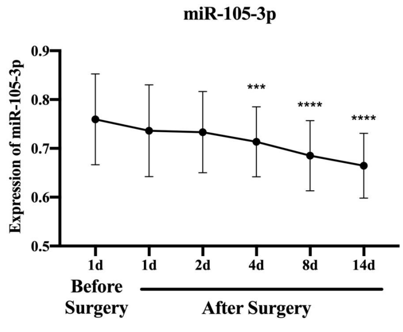

Figure 2. Changes in serum miR-105-3p levels after thyroid cancer surgery.
Data are expressed as mean ± standard deviation; ****p*<0.001, *****p*<0.0001, compared with 1d before surgery.

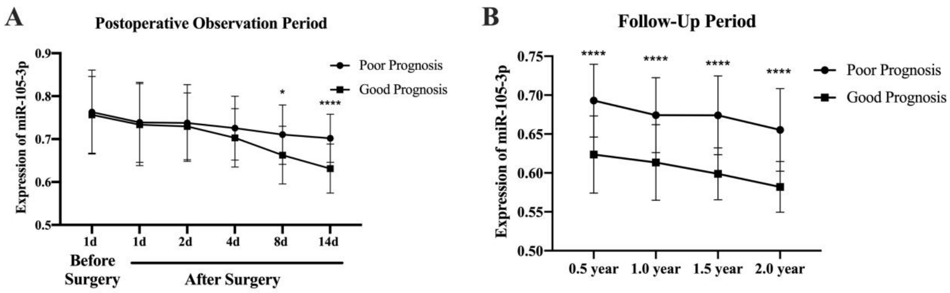

Figure 3. The relationship between serum miR-105-3p level and prognosis after thyroid cancer surgery.
(**A**) The relationship between serum miR-105-3p level and prognosis within 14 d after thyroid cancer surgery; (**B**) The relationship between serum miR-105-3p level and prognosis during the 2-year follow-up period after thyroid cancer surgery. Data are expressed as mean ± standard deviation; *p<0.05, ****p<0.0001, compared with patients with good prognosis.

or metastasis 2 years after surgery, which was a poor prognosis; 53 patients had a good prognosis. Comparing the changes in serum miR-105-3p levels of postoperative patients, it was found that from 8 d after thyroid cancer surgery, serum miR-105-3p levels can significantly distinguish between patients with poor prognosis and patients with good prognosis (Fig. 3A), and during the 2-year follow-up period, the serum miR-105-3p level of patients with poor prognosis was significantly higher than that of patients with good prognosis (Fig. 3B).

The diagnostic value of serum miR-105-3p level in the prognosis of thyroid cancer

The diagnostic value of serum miR-105-3p level on the prognosis of thyroid cancer was analyzed by ROC curve and AUC. The results showed that the diagnostic prognostic sensitivity of serum miR-105-3p at 1d, 2d, 4d, 8d, 14d after operation were 98.11, 96.36, 98.18, 98.18, 96.36, and the specificity were 97.87, 97.96, 97.96, 97.96, 97.96, the AUC were 0.53, 0.53, 0.58, 0.68, 0.79, and the 95% confidence intervals were 0.41–0.64, 0.41–0.64, 0.47-0.69, 0.57–0.78, 0.71–0.88, respectively (Fig. 4); the diagnostic and prognostic sensitivities of serum miR-105-3p within 2 years were 98.18, 96.36, 98.18, 98.18, and the specificity were 97.96, 97.96, 97.96, 97.96, the AUC were 0.82, 0.80, 0.89, 0.88, and the 95% confidence interval were 0.74–0.90, 0.71–0.88, 0.82–0.95, 0.81–0.94, respectively (Fig. 5), suggesting that serum miR-105-3p levels have a diagnostic value for the prognosis of thyroid cancer after surgery.

DISCUSSION

Thyroid cancer is currently one of the fastest-growing malignant tumors, and its specific pathogenesis is not clear (Prete *et al.*, 2020; Haroon *et al.*, 2019). It can

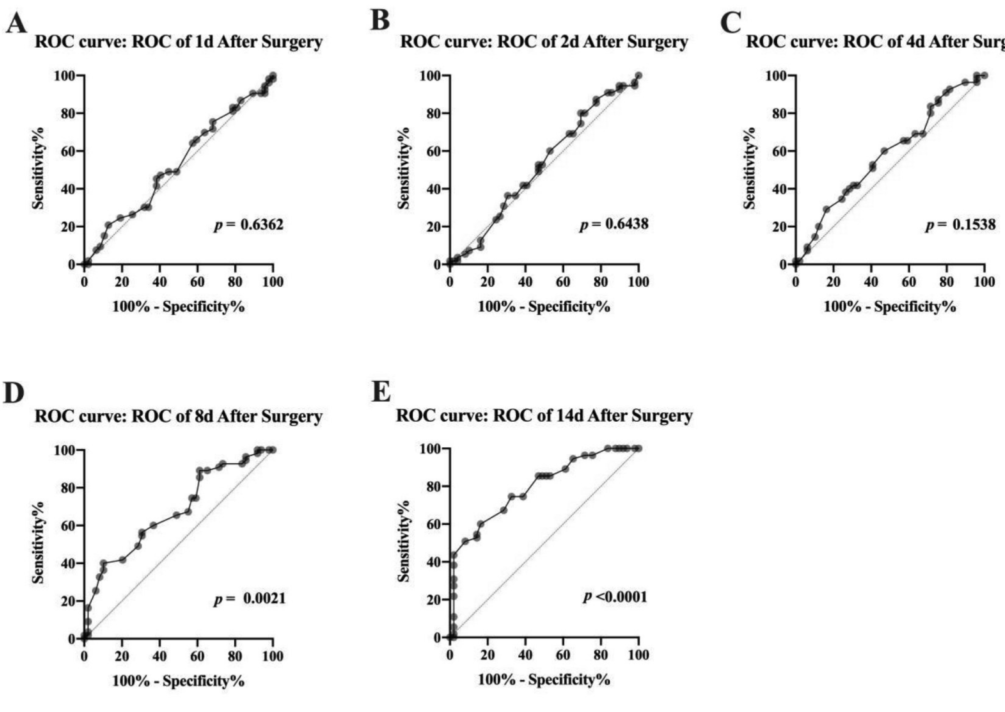

Figure 4. The prognostic value of serum miR-105-3p level after thyroid cancer surgery.
(**A**) The prognostic value of serum miR-105-3p levels at 1 d after thyroid cancer surgery; (**B**) The prognostic value of serum miR-105-3p levels at 2 d after thyroid cancer surgery; (**C**) The prognostic value of serum miR-105-3p levels at 4 d after thyroid cancer surgery; (**D**) The prognostic value of serum miR-105-3p level 8 d after thyroid cancer surgery; (**E**) The prognostic value of serum miR-105-3p levels at 14 d after thyroid cancer surgery.

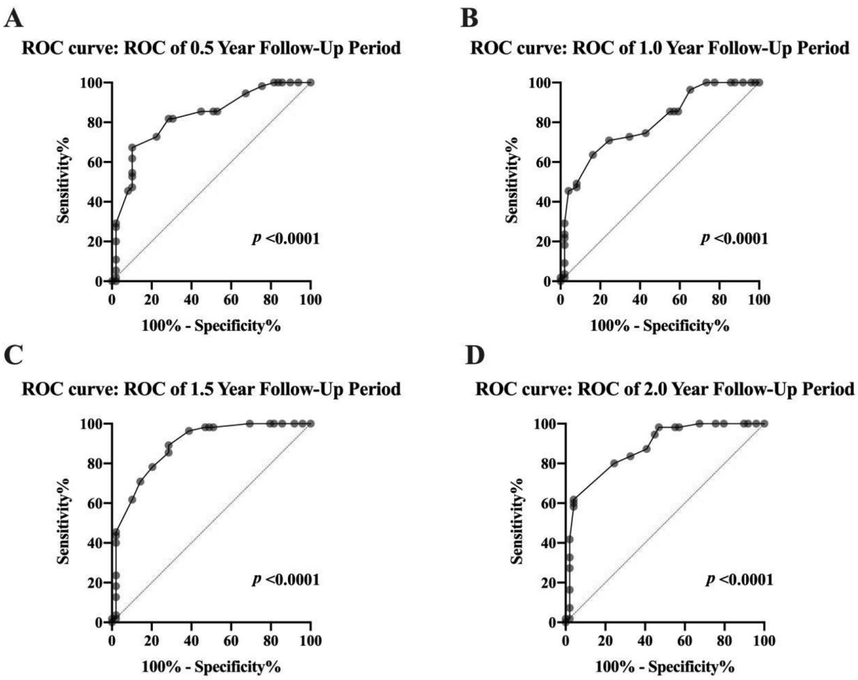

Figure 5. The diagnostic value of serum miR-105-3p level in the follow-up period after thyroid cancer surgery for the prognosis. (**A**) The prognostic value of serum miR-105-3p levels in patients with thyroid cancer during the 0.5-year follow-up period after surgery; (**B**) The prognostic value of serum miR-105-3p levels in patients with thyroid cancer during the 1.0-year follow-up period after surgery; (**C**) The prognostic value of serum miR-105-3p levels in patients with thyroid cancer during the 1.5-year follow-up period after surgery; (**D**) The prognostic value of serum miR-105-3p levels in patients with thyroid cancer during the 2.0-year follow-up period after surgery.

be related to many factors such as diet, genetic inheritance, ionizing radiation and chemical substances (Zhang *et al.*, 2021). Current studies believe that the occurrence of thyroid cancer is related to environmental factors and genetic factors, involving the inactivation of tumor suppressor genes and the excessive activation of oncogenes, and multiple signal transduction pathways cause excessive proliferation and apoptosis of tumor cells, thereby promoting the occurrence and development of tumors, and the signal transduction pathways in tumor cells are regulated by multiple factors (Wang *et al.*, 2020). With the gradual development of diagnosis and treatment methods, studies have found that the prognosis of thyroid cancer is relatively good, but its postoperative evaluation of the prognosis still lacks specific non-invasive detection markers (Qin *et al.*, 2021). Therefore, this study explored the dynamic changes of serum miR-105-3p expression after thyroid cancer surgery and its correlation with clinicopathological manifestations and evaluated its clinical value as a potential biomarker after thyroid cancer surgery.

miRNA is an important molecule that regulates gene expression discovered in recent years (Park *et al.*, 2021). Its properties are relatively stable in tumors and the expression of miRNA in different tumor cells or tumor tissues may be different, but they are the same in the same individual. In different tumors, miRNA plays a role of promoting or suppressing cancer, which mainly depends on the downstream transcription RNA, and the relationship between miRNA and its target gene in the body is regulated by various factors (Tabatabaeian *et al.*, 2020). The diagnostic value of miRNA in thyroid cancer has been confirmed by a number of studies (Ghafouri-Fard *et al.*, 2020). It can not only distinguish malignant tissues from normal tissues, but also has a differential expression in different stages of thyroid cancer. Assessing serum miRNA levels is a practical method for follow-up patients after noninvasive thyroidectomy (Franco *et al.*, 2020). Our study found that serum miR-105-3p levels were significantly increased in patients with well-differentiated thyroid cancer and lymph node metastasis, suggesting that serum miR-105-3p levels are closely related to the degree of differentiation of thyroid cancer patients and lymph node metastasis. Within 14 d after the surgery, the serum miR-105-3p level gradually decreased over time, suggesting that the reduction of serum miR-105-3p level can predict the improvement of the prognosis of thyroid cancer.

Postoperative recurrence or metastasis not only increases the difficulty of the treatment of the disease and causes the body to be injured twice, but it is also the main reason for the decrease in the survival rate of patients (Xiang *et al.*, 2021; Luo *et al.*, 2019; Kim *et al.*, 2021; Takedani *et al.*, 2021). Early prediction of the risk of postoperative recurrence or metastasis of thyroid cancer helps clinicians to formulate effective preventive measures, thereby significantly improving the prognosis of patients and improving the quality of life after surgery (Kang *et al.*, 2019). Our study found that serum miR-105-3p levels can significantly distinguish patients with poor prognosis and good prognosis 4 d after thyroid cancer surgery, and the diagnostic value of serum miR-105-3p levels gradually increases with the passage of time after surgery, suggesting that serum miR-105-3p level has a good diagnostic value for the prognosis of thyroid cancer after surgery, and can be used as a potential biomarker for the diagnosis of thyroid cancer after surgery.

Limitations

The study has some limitations. This study focuses on the dynamic changes of serum miR-105-3p expression after thyroid cancer surgery and its correlation with clinicopathological manifestations. Therefore, we did not consider the inclusion of the normal control group in the design of the experiment. Meanwhile, this study did not further explore the downstream target and mechanism pathway of miR-105-3p. Future studies should focus on the comparison of miRNA expression levels and downstream targets and pathways of miR-105-3p between healthy participants and patients with thyroid cancer to further determine the specificity of miR-105-3p as a biomarker for thyroid cancer.

CONCLUSION

The miR-105-3p serum level is closely related to the degree of differentiation and lymph node metastasis in patients with thyroid cancer, and its level gradually decreases with the passage of time after surgery. It has a good diagnostic value for the prognosis of thyroid cancer after surgery and when it is expected to become a thyroid cancer surgery. It proves to be a potential biomarker for post-diagnosis.

Declarations

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Competing interests. All authors declare that there is no conflict of interest.

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