Efficacy and Safety of Fuzheng Yiqi Kang-Ai Decoction Combined with External Irradiation in the Treatment of Undifferentiated Thyroid Carcinoma and Its Influence on Antiangiogenesis

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Objective. To explore the efficacy and safety of Fuzheng Yiqi Kang-ai (FZYQKA for short) decoction with external irradiation in the treatment of undifferentiated thyroid carcinoma (UTC) and its influence on antiangiogenesis.

Methods. In this retrospective study, the clinical data of 120 patients with UTC admitted to Zibo Central Hospital (February 2019-February 2020) were retrospectively analyzed, and the patients were equally divided into the experimental group (EG) and the control group (CG) according to the order of admission. All patients received external irradiation, and the EG received FZYQKA decoction additionally. FZYQKA decoction was taken orally 1 dose daily in 3 times with a total of 100 ml, for a total of 2 months. Short-term efficacy, incidence of acute radiotoxic responses, levels of matrix metalloproteinases (MMPs), indexes of immune function, and level of vascular endothelial growth factor (VEGF) were compared between both groups.

Results. Compared with the CG, the disease control rate of the EG was obviously higher (73.3% vs. 40.0%, \( P < 0.001 \)). The acute radiotoxic responses of the two groups were mainly grade I-II oral mucositis, radiodermatitis, pharyngitis, esophagitis, and myelosuppression, and only three patients (5.0%) had grade III-IV toxic reactions. Compared with the CG, the incidence of grade I-II oral mucositis, radiodermatitis, pharyngitis, and esophagitis in the EG was obviously lower (\( P < 0.05 \)). After treatment, compared with the CG, levels of MMPs and VEGF of the EG were obviously lower (\( P < 0.001 \)). After treatment, compared with the CG, indexes of immune function of the EG were obviously higher (\( P < 0.001 \)).

Conclusion. For patients with UTC, FZYQKA decoction combined with external irradiation can exert the antiangiogenesis effect, reduce levels of MMPs, and optimize the short-term efficacy. The safe treatment method has mild toxic and side effects, which should be popularized in practice.

1. Introduction

Thyroid carcinoma is the most common malignant solid tumor of endocrine system, of which undifferentiated thyroid carcinoma (UTC) accounts for 5%-10% [1, 2], and UTC has incomparable severity and invasive ability in thyroid carcinoma [3]. Patients usually present with hoarseness, cough, and dysphagia and are prone to have local fatal invasion and distant metastasis [4–7]. In recent years, the concept of holism and the dialectical theory of Traditional Chinese medicine (TCM) has achieved remarkable results in the treatment of various cancers [8–10]. Scholars Sun and Respiration applied Fuzheng Yiqi Kang-ai (FZYQKA for short) decoction in patients with advanced non-small-cell carcinoma, which found that the levels of vascular endothelial growth factors (VEGFs) were remarkably reduced, while levels of matrix metalloproteinases (MMPs) were greatly increased [11]. The high expression of MMPs is associated with invasion, metastasis, and poor prognosis of tumors, indicating that the drug can reduce...
the possibility of distant metastasis of lung cancer and reduce the invasive ability of malignant tumors. The FZYQKA decoction contains Mongolian milkvetch root, largehead atractylodes rhizome, tuckahoe, cassia twig, and other herbs. Among them, tuckahoe and cassia twig can downregulate HIF-1α expression in lesions and then inhibit the combination of HIF-1α and VEGF under hypoxia, decrease the rate of angiogenesis by regulating the HIF-1α-VEGF signaling pathway, and avoid the acceleration of tumor growth through transcription and posttranscriptional control after HIF-1 binds to target genes. Pinellia tuber, Fritillaria, and Chinese peony also have the effect of antiangiogenesis [12], which is speculated to be the important mechanism of reducing the VEGF level in patients with advanced non-small-cell carcinoma. According to the previous literature, no scholars have applied FZYQKA decoction in the treatment of UTC, but the positive role of this drug in the treatment of other cancers has been confirmed. Therefore, this paper combined FZYQKA decoction with external irradiation to explore the efficacy and safety of the combined method in the treatment of UTC and its influence on antiangiogenesis.

2. Materials and Methods

2.1. Research Design. This retrospective study was performed in the Zibo Central Hospital (February 2019-February 2020) to explore the efficacy and safety of FZYQKA decoction combined with external irradiation in the treatment of UTC and its influence on antiangiogenesis.

2.2. Research Subjects. Clinical data of 120 patients with UTC admitted to Zibo Central Hospital (February 2019-February 2020) were retrospectively analyzed. Inclusion criteria were as follows. (1) After pathological and imaging examination, patients were diagnosed with UTC [13]. (2) Patients received the whole treatment in the hospital, and no one died, transferred halfway, and stopped treatment. (3) The clinical data of patients were complete. Exclusion criteria were as follows. (1) Patients had psychiatric diseases or could not be communicated with. (2) Patients withdrew the experiment halfway. (3) Patients had severe heart, brain, liver, and kidney dysfunction and were complicated with other malignant tumors.

2.3. Procedures. A total of 120 patients were included in this study and equally divided into the experimental group (EG) and the control group (CG) according to the order of admission. On the day that the patients agreed to participate in the study, the study group collected sociodemographic data and clinical data. After analysis, no obvious difference was found in general data between both groups ($P > 0.05$) (see Table 1).

2.4. Moral Consideration. The study conformed to the principles of Declaration of Helsinki [14] and was approved by the Ethics Committee of the Zibo Central Hospital. After enrollment, patients were informed of the purpose, significance, content, and confidentiality of the experiment by the study group.

2.5. Withdrawal Criteria. For patients who were in the following situations and inappropriate to continue the experiment according to the research group, their medical record sheets were kept, but the data was not analyzed. (1) Patients experienced adverse events or serious adverse events. (2) Patients presented with deterioration during the experiment. (3) Patients had severe comorbidities or complications. (4) Patients were not willing to continue the clinical trial and asked the study group for withdrawal.

2.6. Methods. External irradiation was performed with 6 MC X-ray, three dimensional conformal radiotherapy (3DCRT), or intensity modulated radiation therapy (IMRT). Varian Trilogy accelerator [NMPA (I) 20152062178] was used for treatment. The dose fractionation was as follows: (1) patients with recurrent UTC received IMRT with 50-60 Gy/25-28 times (1.8-2 Gy/time) and (2) patients with metastatic UTC. Patients with bone metastasis received 3DCRT or IMRT with 24-50 Gy/25-28 times (1.8-4 Gy/time). Patients with liver, brain, and lung metastasis received stereotactic radiotherapy (SRT) with 48-64 Gy/7-8 times (6-8 Gy/time).

The EG was treated with the FZYQKA decoction additionally, and the prescription was as follows: Astragalus membranaceus 30 g, largehead atractylodes 30 g, Poria cocos 30 g, Codonopsis pilosula 25 g, Rehmannia glutinosa 25 g, lily 25 g, dried tangerine peel 15 g, Pinellia ternata 15 g, Fritillaria 10 g, almond 10 g, guar 10 g, Angelica sinensis 10 g, Chinese peony 10 g, Radix Bupleuri 10 g, Cinnamomi ramulus 5 g, Fructus Aurantii Immaturus 5 g, Sphenanthera 10 g, Schisandra 5 g, licorice 5 g, jujube dates 5 g, and fresh ginger 5 g. FZYQKA decoction was taken orally 1 dose daily in 3 times with a total of 100 ml, for a total of 2 months.

2.7. Observation Criteria

(1) General data. The general data table was fulfilled by patients themselves.

(2) Short-term efficacy. According to the Response Evaluation Criteria in Solid Tumors (RECIST) [15], the patients’ condition was divided into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). $CR + PR = Objective Response Rate$ (ORR). $CR + PR + SD = Disease Control Rate$ (DCR). The therapeutic effect of the patients was compared.

(3) Incidence of acute radiotoxic responses. Acute radiotoxic responses of patients were recorded in line with the Performance and Evaluation Criteria for Acute and Subacute Toxicity [16] by the World Health Organization (WHO).

(4) Levels of MMPs. Serum MMP-2 and MMP-9 levels were measured before treatment ($T_0$), 1 month after treatment ($T_1$), and 2 months after treatment ($T_2$).

(5) Indexes of immune function. Levels of NK, CD4+ Th17, CD4+CD25+Treg, and Th17/Treg were detected by a flow cytometer (ACEA Biosciences.
2.8. **Statistical Processing.** In this study, the data were processed by SPSS20.0 and graphed by GraphPad Prism 7 (GraphPad Software, San Diego, USA). Including enumeration data and measurement data, the study used $X^2$ test and $t$ test. The differences were statistically significant at $P < 0.05$.

3. **Results**

3.1. **Comparison of General Data of Patients.** No significant difference was found in the general data of patients between both groups ($P > 0.05$) (see Table 1).

### Table 1: Comparison of general data.

| Group                      | EG ($n = 60$) | CG ($n = 60$) | $X^2/t$ | $P$  |
|----------------------------|---------------|---------------|---------|------|
| Gender                     |               |               |         |      |
| Male                       | 25            | 26            | 0.034   | 0.853|
| Female                     | 35            | 34            |         |      |
| Age (years old)            |               |               |         |      |
| Range                      | 30-76         | 33-74         |         |      |
| Average age                | 56.21 ± 5.68  | 56.28 ± 5.10  | 0.071   | 0.944|
| Mean body mass (kg)        | 56.98 ± 2.68  | 56.89 ± 2.54  | 0.189   | 0.851|
| BMI (kg/m²)                | 22.58 ± 1.65  | 22.62 ± 1.70  | 0.131   | 0.896|
| Pathological stages        |               |               |         |      |
| I                          | 20            | 22            | 0.147   | 0.702|
| II                         | 24            | 23            | 0.035   | 0.852|
| III                        | 13            | 10            | 0.484   | 0.487|
| IV                         | 3             | 5             | 0.536   | 0.464|
| Marital status             |               |               |         |      |
| Married                    | 42            | 40            | 0.154   | 0.695|
| Unmarried, divorced, or widowed | 18       | 20           |         |      |
| Pulmonary metastasis       |               |               |         |      |
| Bone metastasis            | 40            | 42            | 0.154   | 0.695|
| Brain metastasis           | 2             | 3             | 0.209   | 0.648|
| Liver metastasis           | 1             | 1             | 0.000   | 1.000|
| Location of tumors         |               |               |         |      |
| Unilateral                 | 56            | 54            | 0.436   | 0.509|
| Bilateral                  | 4             | 6             |         |      |
| Living habits              |               |               |         |      |
| Smoking history            | 32            | 30            | 0.134   | 0.715|
| History of drinking        | 26            | 28            | 0.135   | 0.714|
| Monthly income (yuan)      |               |               |         |      |
| ≥4000                      | 25            | 24            | 0.035   | 0.853|
| <4000                      | 35            | 36            |         |      |
| Medical payment            |               |               |         |      |
| Medical insurance          | 32            | 33            | 0.034   | 0.855|
| Commercial insurance       | 20            | 20            | 0.000   | 1.000|
| Public medical care        | 8             | 7             | 0.076   | 0.783|
| Education degree           |               |               |         |      |
| High school degree and below | 36        | 37            | 0.035   | 0.852|
| University degree and above | 24           | 23            |         |      |
3.2. Comparison of Short-Term Efficacy. Compared with the CG, DCR in the EG was obviously higher ($P < 0.001$) (see Table 2).

3.3. Comparison of Incidence of Acute Radiotoxic Responses. The acute radiotoxic responses of the two groups were mainly grade I-II oral mucositis, radiodermatitis, pharyngitis, esophagitis, and myelosuppression, and only 3 patients had grade III-IV toxic reactions. Compared with the CG, the incidence of grade I-II oral mucositis, radiodermatitis, pharyngitis, and esophagitis in the EG was obviously lower ($P < 0.05$) (see Table 3).

3.4. Comparison of Levels of MMPs. After treatment, compared with the CG, levels of MMPs of the EG were obviously lower ($P < 0.001$) (see Figure 1).

### Table 2: Comparison of short-term efficacy [n (%)].

| Group | Complete response (CR) | Partial response (PR) | Stable disease (SD) | Progressive disease (PD) | Objective response rate (ORR) | Disease control rate (DCR) |
|-------|------------------------|----------------------|--------------------|--------------------------|------------------------------|---------------------------|
| EG    | 2 (3.3)                | 18 (30.0)            | 24 (40.0)          | 16 (26.7)                | 20 (33.3)                    | 44 (73.3)                 |
| CG    | 0 (0.0)                | 12 (20.0)            | 12 (20.0)          | 36 (60.0)                | 12 (20.0)                    | 24 (40.0)                 |
| $X^2$ | 2.034                  | 1.600                | 5.714              | 13.575                   | 2.727                        | 13.575                    |
| $P$   | 0.154                  | 0.206                | 0.017              | 0.000                    | 0.099                        | 0.000                     |

### Table 3: Comparison of incidence of acute radiotoxic responses [n (%)].

| Group                        | EG ($n = 60$) | CG ($n = 60$) | $X^2$ | $P$  |
|------------------------------|---------------|---------------|-------|------|
| Oral mucositis               |               |               |       |      |
| I-II                         | 30 (50.0)     | 42 (70.0)     | 5.000 | 0.025|
| III-IV                       | 0 (0.0)       | 1 (1.7)       | 1.008 | 0.315|
| Radiodermatitis              |               |               |       |      |
| I-II                         | 25 (41.7)     | 36 (60.0)     | 4.035 | 0.045|
| III-IV                       | 0 (0.0)       | 2 (3.3)       | 2.034 | 0.154|
| Pharyngitis and esophagitis  |               |               |       |      |
| I-II                         | 24 (40.0)     | 35 (58.3)     | 4.035 | 0.045|
| III-IV                       | 0 (0.0)       | 0 (0.0)       | —     | —    |
| Myelosuppression             |               |               |       |      |
| I-II                         | 6 (10.0)      | 10 (16.7)     | 1.154 | 0.283|
| III-IV                       | 0 (0.0)       | 0 (0.0)       | —     | —    |

**Figure 1:** Comparison of levels of MMPs ($\bar{x} \pm s$, ng/mL). Note: in (a) and (b), the abscissa was $T_1$, $T_2$, and $T_3$ from left to right, respectively. The line with dots was the EG, and the line with squares was the CG. # indicated $P < 0.001$. 

### Figure 1: Comparison of levels of MMPs ($\bar{x} \pm s$, ng/mL). Note: in (a) and (b), the abscissa was $T_1$, $T_2$, and $T_3$ from left to right, respectively. The line with dots was the EG, and the line with squares was the CG. # indicated $P < 0.001$. 

#### 3.4. Comparison of Levels of MMPs. After treatment, compared with the CG, levels of MMPs of the EG were obviously lower ($P < 0.001$) (see Figure 1).

Figure 1(a) was the MMP-2. No obvious difference was observed in MMP-2 at $T_1$ in both groups ($912.65 \pm 30.15$ vs. $913.68 \pm 30.65$, $P > 0.05$). Compared with the CG, MMP-2 at $T_2$ and $T_3$ in the EG was obviously lower ($756.21 \pm 35.68$ vs. $876.68 \pm 35.21$ and $685.98 \pm 30.50$ vs. $762.68 \pm 32.68$, $P < 0.001$).

Figure 1(b) was the MMP-9. No obvious difference was observed in MMP-9 at $T_1$ in both groups ($297.65 \pm 25.65$ vs. $296.68 \pm 26.85$, $P > 0.05$). Compared with the CG,
MMP-9 at $T_2$ and $T_3$ in the EG was obviously higher ($245.98 \pm 25.68$ vs. $274.35 \pm 25.41$ and $210.58 \pm 26.98$ vs. $240.98 \pm 23.98$, $P < 0.001$).

### 3.5. Comparison of Indexes of Immune Function

After treatment, compared with the CG, indexes of immune function of the EG were obviously higher ($P < 0.001$) (see Figure 2).

Figure 2(a) was NK. No obvious difference was observed in NK at $T_1$ in both groups ($7.86 \pm 0.31$ vs. $7.87 \pm 0.30$, $P > 0.05$). Compared with the CG, NK at $T_2$ and $T_3$ in the EG was obviously higher ($10.14 \pm 1.20$ vs. $7.80 \pm 1.08$ and $11.02 \pm 0.98$ vs. $7.65 \pm 1.00$, $P < 0.001$).

Figure 2(b) was CD4$^+$ Th17. No obvious difference was observed in CD4$^+$ Th17 at $T_1$ in both groups ($2.51 \pm 0.78$ vs. $2.53 \pm 0.74$, $P > 0.05$). Compared with the CG, CD4$^+$ Th17 at $T_2$ and $T_3$ in the EG was obviously higher ($1.45 \pm 0.35$ vs. $2.30 \pm 0.36$ and $1.15 \pm 0.23$ vs. $1.82 \pm 0.30$, $P < 0.001$).

Figure 2(c) was CD4$^+$CD25Treg. No obvious difference was observed in CD4$^+$CD25Treg at $T_1$ in both groups ($4.41 \pm 0.35$ vs. $4.43 \pm 0.36$, $P > 0.05$). Compared with the CG, CD4$^+$CD25Treg at $T_2$ and $T_3$ in the EG was obviously higher ($7.65 \pm 0.68$ vs. $5.11 \pm 0.54$ and $8.89 \pm 0.74$ vs. $5.16 \pm 0.65$, $P < 0.05$).

Figure 2(d) was Th17/Treg. No obvious difference was observed in Th17/Treg at $T_1$ in both groups ($10.68 \pm 1.65$ vs. $10.70 \pm 1.54$, $P > 0.05$). Compared with the CG, Th17/Treg at $T_2$ and $T_3$ in the EG was obviously higher ($23.68 \pm 2.10$ vs. $15.44 \pm 1.69$ and $25.98 \pm 2.54$ vs. $16.10 \pm 1.68$, $P < 0.05$).

### 3.6. Comparison of Patients’ VEGF Levels

At $T_1$, no statistical difference in VAGF (pg/mL) levels between EG and CG was observed ($27.65 \pm 2.14$ vs. $27.44 \pm 2.10$, $P > 0.05$), and at $T_2$ and $T_3$, the VEGF levels were obviously lower in EG than in CG ($15.98 \pm 1.65$ vs. $20.65 \pm 1.77$ and $14.10 \pm 1.65$ vs. $18.68 \pm 1.78$, $P < 0.001$).

### 4. Discussion

Thyroid carcinoma arises from the thyroid gland [17], and UTC is of the highest degree of malignancy [18]. Patients present with invasion and metastasis at an early stage, and the diameter of the tumor is observed as above 5 cm at the time of diagnosis [19]. Due to generally poor prognosis, rapid treatment measures should be taken once diagnosed so as to improve the survival period of patients. Because UTC is closely related to thyroid stimulating hormone, there is a high prevalence of p53 mutations [20]. With low sensitivity of conventional chemotherapeutic drugs, only less than 10% of patients have a weak reaction to clinical common drugs such as doxorubicin [21]. Nowadays, with the continuous upgrading of radiotherapy technology, external irradiation has been used in the treatment of UTC. Mild toxic reaction is shown in some studies, which is conducive to relieving the clinical symptoms of patients. In this study,
it was found that the acute radiotoxic responses of the two
groups were mainly grade I-II oral mucositis, radiodermatitis,
pharyngitis, esophagitis, and myelosuppression, and only 3
patients had grade III-IV toxic reactions, which indicated
that external irradiation had ideal safety and could ensure
the quality of life of patients. However, radiotherapy is the
palliative care, which is usually effective only in a short term.
Sensitivity still fails to make 80% of patients obtain long-
term therapeutic effect [22]. A large number of international
literature have confirmed that radiotherapy alone has no
remarkable effect on the long-term survival rate of patients
with UTC [23], so it is essential to adopt other treatment
methods.

Recently, the advantages of TCM in the treatment of
malignant tumors have become increasingly prominent. It
has been confirmed that self-made Shugan Sanjie Qudu
decotion, Jiawei Suanzaoren decoction, and self-made Chaizhi
decotion can relieve the clinical symptoms of thyroid
carcinoma [24], improve organismal tolerance, and
enhance the comprehensive treatment effect. TCM believes
that patients with thyroid carcinoma have Yin and Yang dis-
orders due to disorder of Qi and dysfunction of Zang-fu
organs. Meanwhile, the disease is characterized by deficiency
in the Ben (root) and excess in the Biao (branch), which
results in Qi-yin deficiency and especially toxin retention
and Qi and Yin disorders in patients with UTC, so
FZYQKA decoction should be used in the treatment. Astragal-
us membranaceus, largehead atractylodes, Poria cocos, and
Codonopsis pilosula in FZYQKA decoction have the ef-
cfect of invigorating Qi and can inhibit the metastasis and inva-
sion of malignant tumors. Therefore, compared with the
CG, levels of MMPs in the EG after treatment were obvi-
sously lower ($P < 0.001$), indicating that the invasion ability
of UTC was obviously reduced. In addition, Astragalus poly-
saccharide can also improve the immune function of
patients and especially the regulation of T-lymphocyte sub-
sets, and Poria cocos can also improve the nonspecific
immunity. The combination of all herbal medicine can effec-
tively improve the immunity of patients. Therefore, com-
pared with the CG, indexes of immune function of the EG
after treatment were conspicuously higher ($P < 0.001$).

Meanwhile, the growth of thyroid cancer is closely
related to VEGF, and the positive expression rate of VEGF
in thyroid cancer with different pathological types and clin-
ical stages is significantly different, indicating that VEGF is
an important marker of active biological behavior of thyroid
cancer cells. VEGF can elevate tumor vascular permeability
and create a fibrin matrix structural basis for stromal inva-
sion, while multiple herbs in FZYQKA decoction have anti-
angiogenic effects. In the formula, Pinellia tuber contains
rich baikalen, a substance that is able to downregulate
VEGF level and upregulate Rb-1 expression, resulting in
inhibition of tumor angiogenesis, and the stigmasterol in
Pinellia tuber can destroy the TNF-α-VEGFR-2 axis and
then inhibit the proliferation of endothelial cells. Paniculate
bolbostemma can also induce the apoptosis of endothelial
cells, inhibit VEGF expression, and reduce capillary vessel
density, and cassia twig and tuckahoe can inhibit the VEGF
expression under hypoxia. On this basis, Chinese Angelica
and tuckahoe can further exert the effect of nourishing
blood. Chinese thorowax root, cassia twig, immature orange
fruit, dried tangerine peel, and other herbs have the effects of
removing blood stasis and resolving hard mass, and in com-
bination with Rehmannia root, lily bulb, Fritillaria, bitter
apricot seed, etc., the effects of clearing heat and promoting
diuresis as well as removing blood stasis and expelling pus
can be exerted. The decoction can remarkably improve the
short-term efficacy of patients. The research of scholars
Huiyun et al. shows that Saikosaponin D in Radix Bupleuri
can inhibit the activity of malignant tumor cells and improve
the induction of apoptosis. At the same time, Saikosaponin
A can inhibit the growth of cancer cells and the metastasis
and invasion of cancer cells, which is conducive to control-
ling the development of UTC. Therefore, the short-term effi-
cacy of patients with pancreatic cancer treated with Radix
Bupleuri has been obviously improved [25]. This study also
found that compared with the CG, the DCR of the EG was
conspicuously higher ($P < 0.001$), indicating that FZYQKA
decotion could work on UTC and improve the comprehen-
sive effect of external irradiation.

In conclusion, for patients with UTC, FZYQKA decoc-
tion combined with external irradiation can exert the effect
of antiangiogenesis, reduce levels of MMPs, and optimize the
short-term efficacy. The safe treatment method has mild
toxic and side effects, which should be popularized in
practice.

Data Availability

Data to support the findings of this study is available on rea-
sonable request from the corresponding author.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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