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Original Research Article

Effect of the combination of radioiodine therapy and euthyrox in BRAF-mutated thyroid cancer post-total thyroidectomy

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Abstract

Purpose: *To investigate the effect of combining radioiodine therapy with euthyrox in treating thyroid cancer with BRAF gene mutation following total thyroidectomy (TT).*
Methods: *This retrospective study analyzed records of 98 differentiated thyroid cancer (TC) patients with BRAF gene mutation who underwent TT between February 2018 and January 2020 at Guangdong Provincial Hospital of Traditional Chinese Medicine, Guangzhou, China. The patients were randomized into control (46 patients) and study groups (53 patients). Control group received euthyrox, while the study group received euthyrox in addition to radioiodine following total thyroidectomy. Efficacy, thyroid function before and after treatment, incidence of adverse reactions, and 3-year recurrence rates were evaluated.*
Results: *The study group showed significantly higher overall response rate (ORR) compared to control group ($p < 0.05$). There were no significant differences in thyrotropin (TSH), free thyroxine (FT4), and free triiodothyronine (FT3) levels between the groups before treatment ($p > 0.05$). After treatment, both groups exhibited significant changes in thyroid function, with decreased TSH, and increased FT4 and FT3 levels ($p < 0.05$). Post-treatment TSH levels were significantly lower while FT4 and FT3 levels were significantly higher in the study group compared to control group ($p < 0.05$).*
Conclusion: *Combining radioiodine therapy and Euthyrox following total thyroidectomy enhances therapeutic outcomes in patients with BRAF-mutated TC, improves thyroid function and reduces recurrent risk without increasing adverse reactions. Further studies will aim to expand the sample size and stratify patients by severity to comprehensively validate these findings.*

Keywords: *Total thyroidectomy, Radioiodine therapy, Euthyrox, BRAF gene mutation, Thyroid cancer*

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INTRODUCTION

Thyroid cancer (TC) is a highly malignant form of head and neck cancer, with steadily increasing global incidence. Differentiated thyroid cancer (DTC) constitutes about 95 % of all TC cases and is the most common subtype [1,2]. The rise in TC rates is attributed to over-diagnosis and radiation exposure [3,4]. Additionally, the presence of BRAF gene mutations has been independently linked to carcinogenesis, affecting cellular functions like proliferation, invasion,

migration, cell cycle regulation, and apoptosis, thereby potentially influencing the prognosis of TC patients [5].

Total thyroidectomy (TT) is increasingly employed as a surgical strategy for TC, effectively eliminating primary tumors and reducing the risk of complications from reoperation [6]. Postoperative radioiodine therapy has been clinically proven to enhance patient prognosis, although not all patients respond adequately to this treatment [7].

Euthyrox is commonly used in endocrine therapy to manage hypothyroidism following thyroid surgery [8]. However, there is currently no consensus on how BRAF gene mutations affect treatment response rates.

This study retrospectively analyzed follow-up data from DTC patients with BRAF mutations who underwent TT and were treated with radioiodine therapy combined with Euthyrox. The findings would guide future clinical research on this treatment modality.

METHODS

Baseline data

Medical records of 98 differentiated thyroid cancer (DTC) patients with confirmed BRAF gene mutations, who underwent total thyroidectomy (TT) at Guangdong Provincial Hospital of Traditional Chinese Medicine, Guangzhou, China from February 2018 to January 2020, were retrospectively analyzed and randomized into control (comprising of 46 patients) and study groups (comprising of 53 patients).

Control group received Euthyrox while study group received Euthyrox in addition to radioiodine following total thyroidectomy.

Ethical approval

Approval for the study was obtained from the Ethics Committee of University Town Hospital, Guangdong Provincial Hospital of Traditional Chinese Medicine (approval no. LL0103512.), and the study conformed with the principles outlined in the Declaration of Helsinki [5].

Inclusion criteria

Patients who underwent TT, and DTC were confirmed by postoperative pathological analysis, had not undergone prior iodine treatment, BRAF gene mutation was confirmed through genetic testing, and adequate clinical case records were available.

Exclusion criteria

Intolerance or allergy to treatment protocols or drugs used in this study, severe liver or kidney dysfunction, uncontrollable endocrine disorders, coexisting mental health conditions, and inability to comply with the treatment protocol.

Therapeutic regimen

Control group received Euthyrox (Merck KGaA, Germany, SFDA approval no.: J20160065) at 25 µg daily, which was increased to 100 µg daily after 3 weeks of treatment, and continued until normal metabolic levels were achieved. The study group received radioactive iodine (HTA Co., Ltd., SFDA approval no.: H10960247) at 3.7 GBq/day for patients without metastasis, and 5.55 GBq/day for patients with metastasis for four weeks in addition to Euthyrox following surgery. Post-treatment consumption of acidic foods was recommended to protect the salivary glands.

Follow-up

All patients underwent a three-year follow-up involving outpatient re-examinations and telephone consultations. Recurrence rates were documented for both groups over this period.

Evaluation of parameters/indices

Treatment efficacy

Treatment efficacy was classified as markedly effective (ME: no metastatic lesions were detectable, and thyroglobulin (Tg) levels significantly decreased below the normal range after treatment), effective (E: reduction in size or number of metastatic lesions and a decrease in serum Tg levels after treatment), ineffective (I: no reduction, or an increase, in size or number of metastatic lesions, with stable or elevated serum Tg levels).

Overall response rate (ORR)

The overall response rate (ORR) was calculated using Eq 1.

$$ORR\ (\%) = ((ME+E)/N)100 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ (1)$$

Incidence of adverse reactions

All adverse reactions during treatment were recorded and compared.

Thyroid function

Prior to and following treatment, 5 mL of venous blood was collected from each patient into a tube with inert separation gel and coagulant. After centrifugation at 3000 rpm for 10 min, serum was analyzed for levels of free triiodothyronine (FT3), free thyroxine (FT4), and thyrotrophin (TSH) using Siemens ADVIA Centaur XP series automatic chemiluminescence immunoassay system.

Recurrence rate

Recurrence rates within three years after treatment were compared between study and control groups using Kaplan-Meier curves.

Statistical analysis

Data were processed using Statistical Packages for Social Sciences (SPSS version 20.0 Co., Ltd., Chicago, USA) and figures were drawn using GraphPad Prism 7 (GraphPad Software Co., Ltd., San Diego, USA). Categorical data were analyzed using chi-square test (χ^2). Continuous data were presented as mean ± standard deviation (SD), and analyzed using independent-sample t-tests for inter-group comparisons and paired T tests for within-group comparisons. Recurrence analysis was done using Kaplan-Meier curve, and $P < 0.05$ was considered statistically significant.

RESULTS

Baseline data

There was no significant difference in gender, age, lesion location, number of lesions, maximum tumor diameter, nodule calcification, T staging and N staging comparisons in study and control groups ($p > 0.05$; Table 1).

Treatment efficacy

There was a significant difference in treatment efficacy, and ORR was significantly higher in study group compared to control group ($p < 0.05$; Table 2).

Thyroid function

Prior to therapy, there was no significant difference in TSH, FT4, and FT3 levels between study and control groups ($p > 0.05$). After treatment, both groups exhibited significant reduction in TSH levels and increase in FT4 and FT3 levels ($p < 0.05$). However, study group demonstrated significantly lower TSH and higher FT4 and FT3 levels compared to control group after treatment ($p < 0.05$; Figure 1).

Table 1: Baseline data (N, %)

Parameter	Item	Control (n=46)	Study (n=53)	χ^2/t	*P*-value
Gender	Male	14(30.43)	21(39.62)	0.910	0.340
	Female	32(69.57)	32(60.38)		
Age (years)	<60	35(76.09)	42(79.25)	0.142	0.706
	≥60	11(23.91)	11(20.75)		
Lesion location	Left	9(19.56)	13(24.53)	1.632	0.442
	Right	25(54.35)	22(41.51)		
	Bilateral	12(26.09)	18(33.96)		
Number of lesions	Single	12(26.09)	16(30.19)	0.204	0.651
	Multiple	34(73.91)	37(69.81)		
Maximum tumor diameter	>1cm	30(65.22)	38(71.70)	0.481	0.488
	≤1cm	16(34.78)	15(28.30)		
Nodular calcification	Yes	15(32.61)	20(37.74)	0.283	0.595
	No	31(67.39)	33(62.26)		
T staging	T1-2	40(86.96)	41(77.36)	1.525	0.217
	T3-4	6(13.04)	12(22.64)		
N staging	N0	7(15.22)	14(26.42)	1.848	0.174
	N1	39(84.78)	39(73.58)		

Table 2: Treatment efficacy (N, %)

Parameter	Markedly effective	Effective	Ineffective	Overall response rate
Control (n=46)	18(39.13)	16(34.78)	12(26.09)	34(73.91)
Study (n=53)	26(49.06)	22(41.51)	5(9.43)	48(90.57)
***T*-value**				4.802
***P*-value**				0.028

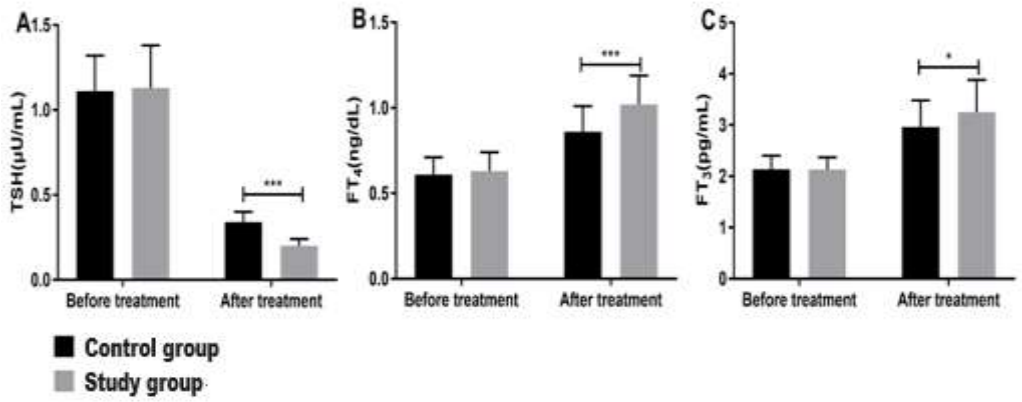

Figure 1: Thyroid function indices in patients before and after treatment. A: Thyrotrophin (TSH) levels B: Free thyroxine (FT4) levels. C: Triiodothyronine (FT3) levels. **P* < 0.05 vs control group, ****P* < 0.001 vs control group

Table 3: Adverse reactions (N, %)

Effect	Control (n=46)	Study (n=53)	χ^2	*P*-value
Chest pain	2(4.35)	3(5.66)		
Insomnia	2(4.35)	2(3.77)		
Parotid swelling and pain	1(2.17)	3(5.66)		
Palpitation	1(2.17)	2(3.77)		
Total adverse reaction	6(13.04)	10(18.87)	0.554	0.457

Adverse reactions

There was no significant difference in incidence of adverse reactions (such as chest pain, insomnia, parotid swelling and pain, and palpitations) in both groups ($p > 0.05$; Table 3).

Recurrence

During the 3-year follow-up, 7 patients (15.22 %) in control group experienced recurrence, compared to 2 patients (3.77 %) in study group. Kaplan-Meier analysis indicated a significantly higher 3-year recurrence rate in control group compared to study ($p < 0.05$; Figure 2).

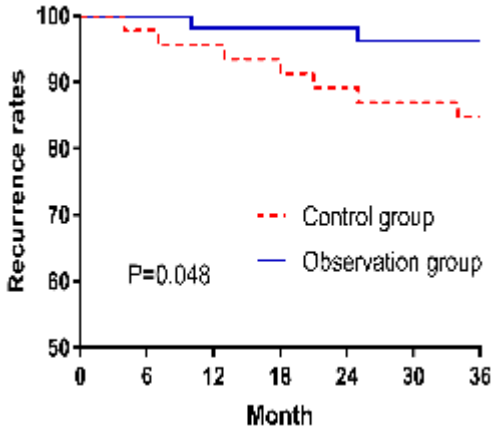

Figure 2: Kaplan-Meier curve for 3-year patient recurrence

DISCUSSION

Differentiated thyroid cancer (DTC) uptake iodine through thyroid follicular epithelial cells and has the capability to secrete thyroglobulin. It also relies on TSH for growth and function [10]. Advances in large-scale genomics and transcriptomics have gradually unveiled the pathogenesis of TC. Several oncogenic drivers have been identified that contribute to the onset, progression, and prognosis of DTC. A significant genetic alteration in DTC is the hyperactivation of MAPK pathway, mainly due to mutations in BRAF and RAS genes [11].

The BRAF gene mutations lead to overactivation of MAPK pathway and phosphorylation of the X-linked apoptosis inhibitor protein, which suppresses tumor cell apoptosis [12]. Previous research indicates that BRAF mutations induce invasive biological and clinical behaviours, loss of thyroid differentiation, reduced response to radioiodine therapy, and decreased overall survival [13].

This study revealed that combined therapy of radioiodine and Euthyrox following total thyroidectomy resulted in higher response rate of 90.75 %, compared to 73.91 % with Euthyrox alone. The incidence of adverse reactions was similar between the two groups, underscoring that radioiodine therapy, targeting both residual and metastatic tumor tissues, offers a more effective treatment outcome without increasing

adverse effects. For patients undergoing near TT or TT, continuous administration of thyroxine tablets is essential to maintain thyroid function and suppress TSH [14]. TSH receptors, found on cell membranes of DTC cells, play critical role in tumor growth through their interaction with TSH. After thyroidectomy, a significant decrease in thyroid hormone levels and a corresponding increase in TSH occur, potentially stimulating thyroid cell proliferation and increasing the risk of recurrence and metastasis [15]. Therefore, suppressing TSH with thyroid hormone therapy after surgery is crucial. Euthyrox, a thyroid hormone medication, is widely used for this purpose [16].

This study evaluated TSH, FT4, and FT3 levels in two groups before and after treatment and the result revealed that study group (received combined radioiodine therapy and Euthyrox) exhibited significantly lower TSH and higher FT4 and FT3 levels after treatment, suggesting that this combination effectively enhances thyroid hormone levels and overall metabolism. Additionally, a three-year follow-up using Kaplan-Meier curve analysis revealed a significantly lower recurrence rate in study group compared to control group. These results indicate that synergistic use of thyroid hormone and iodine-131 effectively eliminates residual thyroid tissue, thus improving prognosis.

Limitations of this study

This study has several limitations. The follow-up period was relatively short, constraining the ability to assess long-term prognosis. Also, the study did not categorize patients by disease severity, which limits the analysis of treatment outcomes across different risk levels.

CONCLUSION

Radioiodine therapy, in addition to euthyrox after total thyroidectomy, enhances efficacy in TC patients with BRAF gene mutations. This therapeutic strategy promotes thyroid function recovery, reduces the risk of postoperative recurrence, and does not significantly increase the incidence of adverse reactions. Further studies should aim to expand the sample size and stratify patients by severity to comprehensively validate these findings.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Qiang Fu and Xueyang Huang conceived and designed the study, and drafted the manuscript. Qiang Fu, Xueyang Huang, Yu Yang, Yalan Huang collected, analyzed and interpreted the experimental data. Yalan Huang revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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