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Original Article

Superior efficacy of vemurafenib combined with iodine-131 for lymph node metastatic BRAF-mutant thyroid cancer: a long-term survival analysis

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Abstract: Aims: To evaluate the long-term survival outcomes and therapeutic efficacy of vemurafenib combined with iodine-131 (^{131}I) by dual pathways in patients with lymph node metastatic BRAF-mutant thyroid cancer. Methods: This retrospective study included 80 patients with lymph node metastatic BRAF V600E-mutant thyroid cancer, treated between January 2022 and January 2025. Patients were assigned to a control group (vemurafenib monotherapy, n = 42) or an observation group (vemurafenib combined with ^{131}I, n = 38). Progression-free survival (PFS), overall survival (OS), and metastasis-free survival (MFS) were compared. Survival analyses were performed using Kaplan-Meier curves. Results: Kaplan-Meier survival analysis showed a significantly lower PFS, OS, and MFS in the control group, compared to the observation group (all P<0.001). Treatment with combination therapy led to significantly superior thyroid function recovery, with lower thyroid-stimulating hormone levels as well as higher free T4, free T3, and total T3 levels in the observation group (all P<0.001). Immune analysis showed significantly enhanced activation of CD8+ T cells and a reduction in regulatory T cells (both P<0.001). Conclusion: The vemurafenib combined with ^{131}I revealed superior efficacy in improving survival and thyroid function recovery in lymph node metastatic BRAF-mutant thyroid cancer.

Keywords: BRAF mutation, thyroid cancer, ^{131}I therapy, lymph node metastasis, long-term survival

Introduction

Thyroid cancer, especially differentiated thyroid cancer (DTC), ranks among the most common malignancies in the endocrine system [1]. However, within the histologic subtypes of DTC, papillary thyroid cancer (PTC), also known as papillary carcinoma is the most common, accounting for about 80-85% of all thyroid cancer cases [2]. Despite the overall good prognosis of PTC, with a 10-year survival rate exceeds 90%, the survival rate tremendously decreases when the disease is in advanced stages especially where driven by genetic mutations that confer aggressive clinical behavior. A BRAF V600E mutation can be found in 40-50% of the PTC and has been firmly associated with poor prognosis, recurrence rates, resistance to radioactive iodine-131 (^{131}I) therapy and higher propensity of metastasis to regional lymph nodes [3, 4]. In particular, lymph node metastasis is a decisive factor affecting long-term disease progression and a predictor of intervention failure, making it one of the most challenging issues to manage in BRAF-mutant PTC.

The typical therapy for DTC, including BRAF-mutated subtypes, consists of thyroidectomy followed by ^{131}I ablation of residual thyroid tissue to target persistent microscopic disease [5]. Although ^{131}I therapy is quite effective in most DTC cases, its effectiveness is very low when accompanied by a mutation in BRAF [6]. The acquired mutations lead to changes in molecular pathways regulating iodine uptake, thereby impairing the ability of ^{131}I to localize tumors. Furthermore, lymph node metastasis worsens treatment outcomes because it is a risk factor for disease recurrence, and it reduces the probability of complete remission [7].

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Compared to patients with BRAF wild-type thyroid cancer, BRAF-mutant patients are associated with a high risk of cancer relapse and poor prognosis of long-term survival irrespective of standard treatment method [8, 9].

In recent years, there has been growing recognition of the use of molecularly targeted therapies to treat BRAF-mutant cancers, and BRAF inhibitors have demonstrated considerable efficacy in preclinical and clinical studies [10]. However, initial tumor shrinkage and clinical responses to BRAF inhibitors tend to develop resistance over time, resulting in limited long-term success, particularly with monotherapy. The challenge of controlling metastatic disease, especially in the dysregulated tumor immune microenvironment of lymph nodes, remains unresolved. Consequently, there is an urgent need to explore combinations of targeted therapies with the traditional paradigm of ^{131}I radioablation to enhance therapeutic efficacy [11]. The rationale of this combination is that a selective BRAF inhibitor, namely vemurafenib can sensitize tumors to ^{131}I by increasing iodine uptake and regulating the main signaling pathways, which may represent the molecular resistance mechanisms that severely affect the effectiveness of ^{131}I.

Several studies have investigated the possible synergistic mechanisms of BRAF inhibitors combined with ^{131}I therapy, and it has been proposed that this combination could yield greater therapeutic benefits [12-14]. By shrinking tumors and re-sensitizing them to iodine, vemurafenib would enhance the tumor-destroying potential of ^{131}I, particularly in tumors refractory to traditional radioablation. However, the combination of such treatments, especially in advanced lymph node metastatic BRAF-mutant thyroid cancer patients is still a matter under study. With the aggressive nature of this cancer subtype and the challenges posed by metastatic disease, there is a need to develop efficacious treatment regimens that improve response rates and confer long-term survival advantages.

This study introduces an innovative therapeutic approach for lymph node metastatic BRAF V600E-mutant thyroid cancer, a combination therapy with the selective BRAF inhibitor vemurafenib and ^{131}I radioablation. While vemurafenib has shown promise as a monotherapy for BRAF-mutant cancers, resistance and limited long-term efficacy have been major challenges. Our novel combination therapy overcomes these limitations by re-sensitizing tumors to ^{131}I therapy, which traditionally has reduced efficacy in BRAF-mutated cases. The clinical significance of this approach is that it may significantly improve long-term survival outcomes, as evidenced by the substantial increases in progression-free survival (PFS), overall survival (OS), and metastasis-free survival (MFS) in the observation group. Furthermore, this combination therapy targets tumors at the molecular level and modulates the tumor immune microenvironment, thereby enhancing anti-tumor immune responses and promoting thyroid function recovery. These findings offer a promising new treatment strategy for advanced lymph node metastatic BRAF-mutant thyroid cancer and lymph node metastasis, a cohort that has historically had limited therapeutic options.

The current study addresses this vital gap by assessing the long-term survival outcomes of a novel regimen combining the BRAF inhibitor vemurafenib with ^{131}I radioablation, leveraging a dual-targeted approach. This approach involves targeting the BRAF mutation with vemurafenib and optimizing ^{131}I utilization to enhance tumor cell iodine susceptibility, thereby improving the therapeutic efficacy of both agents. The hypothesis is that this combination therapy will significantly increase long-term survival rates and reduce recurrence risks, particularly in advanced metastatic patients. This study aims to comprehensively analyze outcomes in patients who received this combination regimen to evaluate its short- and long-term efficacy, as well as its potential to become a new standard of care for BRAF-mutant thyroid cancer with lymph node metastasis.

Materials and methods

Patients' section

This retrospective analysis was conducted among patients diagnosed with BRAF V600E-mutant thyroid cancer with lymph node metastasis between January 2022 and January 2025 at the Second Hospital of Jilin University. A total of 80 patients were included, with 42 patients assigned to a control group (vemurafenib monotherapy) and 38 patients in an observa-

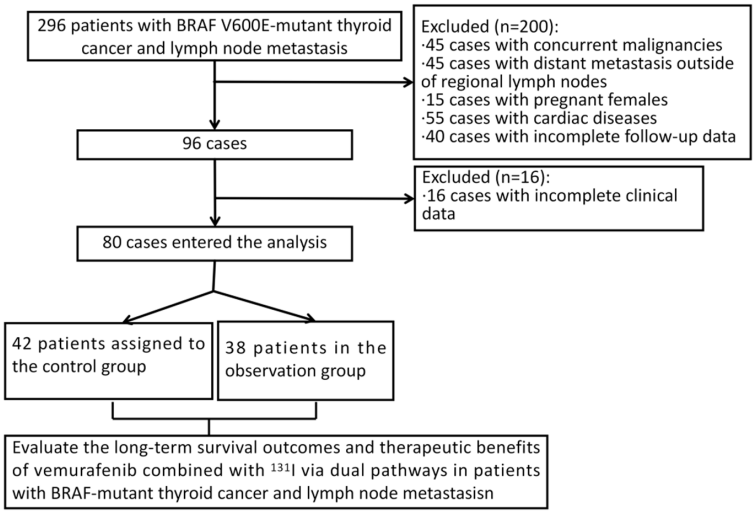

Figure 1. Flow chart depicting the patient selection process.

tion group (vemurafenib combined with ^{131}I dual-pathway therapy). The study was approved by the institutional review board of the Second Hospital of Jilin University.

The inclusion criteria for this study were as follows: (1) histologically confirmed diagnosis of PTC with BRAF V600E mutation, (2) presence of clinically confirmed lymph node metastasis, (3) aged 18-75 years, (4) no history of prior radioiodine therapy or systemic treatments for thyroid cancer, (5) adequate organ function as confirmed by routine laboratory tests, and (6) Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, ensuring that patients were sufficiently fit for treatment. Exclusion criteria were: (1) concurrent malignancies, (2) presence of distant metastasis outside of regional lymph nodes, (3) contraindications to vemurafenib or radioactive iodine therapy, (4) pregnancy or breastfeeding, (5) incomplete follow-up data, and (6) uncontrolled systemic conditions (e.g., cardiovascular, autoimmune, or metabolic diseases) that might interfere with treatment compliance or outcomes (**Figure 1**).

Data extraction

The control group received vemurafenib (a selective BRAF inhibitor for BRAF V600E mutant thyroid cancer) monotherapy, with an oral dose of 960 mg every 12 hours according to the approved treatment protocol for BRAF mutant malignancies. Treatment continued until disease progression, the occurrence of intolerable toxicity, or patient withdrawal from the study. The observation group received a combination therapy of vemurafenib and ^{131}I. The vemurafenib dosage was the same as the control group (960 mg orally, twice daily). ^{131}I was administered based on the patient's weight and thyroid cancer characteristics, and drug uptake and treatment effectiveness were assessed through regular scans. This dual therapy aimed to combine vemurafenib's molecular targeting effect with the radiotherapeutic effect of ^{131}I to improve tumor control and address metastatic disease. Both treatment regimens were managed by a multidisciplinary team, with close monitoring of adverse events and treatment efficacy. All enrolled patients' data were extracted from medical records, focusing on baseline characteristics and treatment outcomes. Baseline information included demographic data (age, sex, body mass index), clinical status (ECOG performance status score), time from diagnosis to enrollment, and prior treatment history. Additionally, treatment outcomes were carefully documented, including progression-free survival (PFS), overall survival (OS), metastasis-free survival (MFS), and adverse events. Data integrity and accuracy were verified by cross-checking patients' medical records and follow-up reports to ensure consistency.

Outcome measures

The primary outcome measures were PFS, OS, and MFS. These were assessed at multiple time points during the follow-up period. PFS was defined as the time from randomization to disease progression or death (whichever occurred first); OS was defined as the time from randomization to death from any cause. MFS was defined as the time from randomization to the first occurrence of metastatic lesions. Kaplan-Meier survival curves were used to evaluate these outcome measures.

Secondary outcome measures included quantification of long-term toxic effects, immune microenvironment regulation, thyroid function

Table 1. Comparison of baseline data between the two groups

Variable	Control group (n = 42)	Observation group (n = 38)	t/X^2	*P* value
Age, years	54.86 ± 13.01	53.53 ± 9.49	1.642	0.48
Sex, male/female	24/18	22/16	0.005	0.946
Body mass index	24.67 ± 4.46	25.85 ± 3.95	0.183	0.81
ECOG performance status, n (%)			0.216	0.898
0	18 (42.9)	15 (39.5)		
1	20 (47.6)	20 (52.6)		
2	4 (9.5)	3 (7.9)		
Primary tumor site, n (%)			0.134	0.715
Thyroid	26 (61.9)	22 (57.9)		
Other	16 (38.1)	16 (42.1)		
Time from diagnosis to enrollment, months (median [IQR])	14.5 [10.0-16.5]	13.5 [10.0-16.0]	0.061	0.952
Number of metastatic sites, n (%)			0.009	0.996
1	20 (47.6)	18 (47.4)		
2	14 (33.3)	13 (34.2)		
≥3	8 (19.1)	7 (18.4)		
Most frequent metastatic sites, n (%)				
Lung	28 (66.7)	25 (65.8)	0.007	0.934
Bone	16 (38.1)	14 (36.8)	0.013	0.908
Lymph nodes	12 (28.6)	11 (28.9)	0.001	0.970
Baseline RECIST tumor burden, cm	7.35 ± 2.31	7.21 ± 1.93	0.274	0.784

Note: ECOG: Eastern Cooperative Oncology Group; RECIST: Response Evaluation Criteria in Solid Tumors.

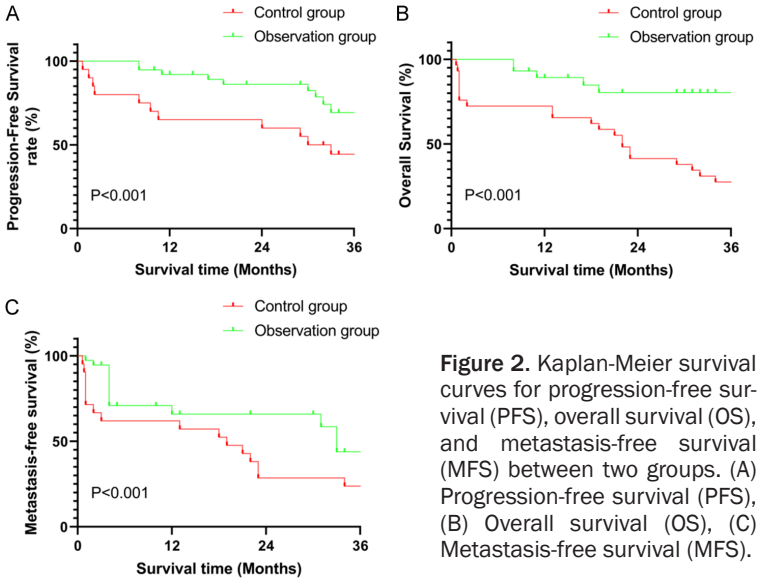

Figure 2. Kaplan-Meier survival curves for progression-free survival (PFS), overall survival (OS), and metastasis-free survival (MFS) between two groups. (A) Progression-free survival (PFS), (B) Overall survival (OS), (C) Metastasis-free survival (MFS).

response, and recovery of health-related quality of life (HRQoL). Toxic reactions were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute, with a focus on skin, hematological, and gastrointestinal adverse events. Levels of immunosuppressive cytokines (interleukin-10, IL-10) were measured using flow cytometry and enzyme-linked immunosorbent assay (ELISA). Serum thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), total triiodothyronine (TT3), and thyroglobulin levels were measured at baseline and follow-up points to assess thyroid function recovery. HRQoL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30), covering dimensions such as physical functioning, emotional functioning, social functioning, and overall health status.

Table 2. Comparison of long-term side effects and late toxicities between the two groups

Variable	Control group (n = 42)	Observation group (n = 38)	X^2	*P* value
Any late toxicity, n (%)	9 (21.4)	10 (26.3)	0.263	0.608
Dermatologic (rash, dry skin)	2 (4.8)	3 (7.9)	0.334	0.563
Hematologic (anemia, neutropenia)	4 (9.5)	3 (7.9)	0.066	0.797
Gastrointestinal (nausea, diarrhea)	3 (7.1)	4 (10.5)	0.286	0.593
Grade 3/4 toxicities, n (%)	2 (4.8)	3 (7.9)	0.334	0.563

Table 3. Comparison of baseline clinicopathologic characteristics according to long-term survival outcome

Variable	Favorable long-term survival group (n = 46)	Unfavorable long-term survival group (n = 34)	t/χ^2	*P* value
Age, years (mean ± SD)	56.09 ± 10.69	58.06 ± 7.79	0.911	0.365
Sex, male/female	26/20	20/14	0.042	0.837
BMI, kg/m^2 (mean ± SD)	24.35 ± 3.66	26.00 ± 3.97	1.923	0.058
ECOG 0-1/2	44/2	30/4	1.550	0.213
Metastatic sites (1/≥2)	26/20	10/24	5.805	0.016
Baseline tumor burden (cm)	6.84 ± 1.93	6.96 ± 1.31	0.307	0.760
Combination therapy (%)	28 (60.9%)	10 (29.4%)	7.758	0.005
Monotherapy (%)	18 (39.1%)	24 (70.6%)	7.758	0.005

Note: ECOG: Eastern Cooperative Oncology Group.

Sample size calculation

This study aimed to detect a clinically significant difference in PFS between the two groups, with a significance level (α) of 0.05 and a power (1-β) of 80%. Assuming a hazard ratio (HR) of 0.75 for the experimental group compared to the control group, and an estimated median PFS of 12 months in the control group, the calculated sample size was 150 participants per group (using Kaplan-Meier survival analysis methods). To account for potential dropout and loss to follow-up, an additional 10% was added to the calculated sample size, resulting in a final target enrollment of 330 patients (165 per group).

Statistical analysis

Data analysis was conducted using SPSS version 25.0 (IBM Corp., Armonk, New York, USA). Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range, IQR) according to their distribution type. Intergroup comparisons were conducted using the independent samples t-test (for parametric data) or the Mann-Whitney U test (for non-parametric data). Comparisons of categorical variables between groups were conducted using the Chi-square test or Fisher's exact test (as appropriate). Survival analysis was carried out using the Kaplan-Meier method to estimate PFS, OS and MFS, with intergroup differences compared using the log-rank test. Variables with P<0.10 by univariate analysis were included in a multivariate logistic regression model to identify independent predictive factors, and results were expressed as odds ratios (OR) and 95% confidence intervals (CI). P<0.05 was considered significant.

Results

Comparison of the baseline data

There were no significant differences between the two groups in terms of age (P = 0.48), sex distribution (P = 0.946), or body mass index (P = 0.81). The ECOG performance status scores were also not statistically different (P = 0.898), with 42.9% of patients in the control group and 39.5% in the observation group having an ECOG score of 0. The primary tumor site was most commonly the thyroid (P = 0.715). The time from diagnosis to enrollment was also similar between the groups (median [IQR]: 14.5 [10.0-16.5] months vs. 13.5 [10.0-16.0] months, P = 0.952). Regarding metastatic burden, the number of metastatic sites was comparable between the two groups, with 47.6%

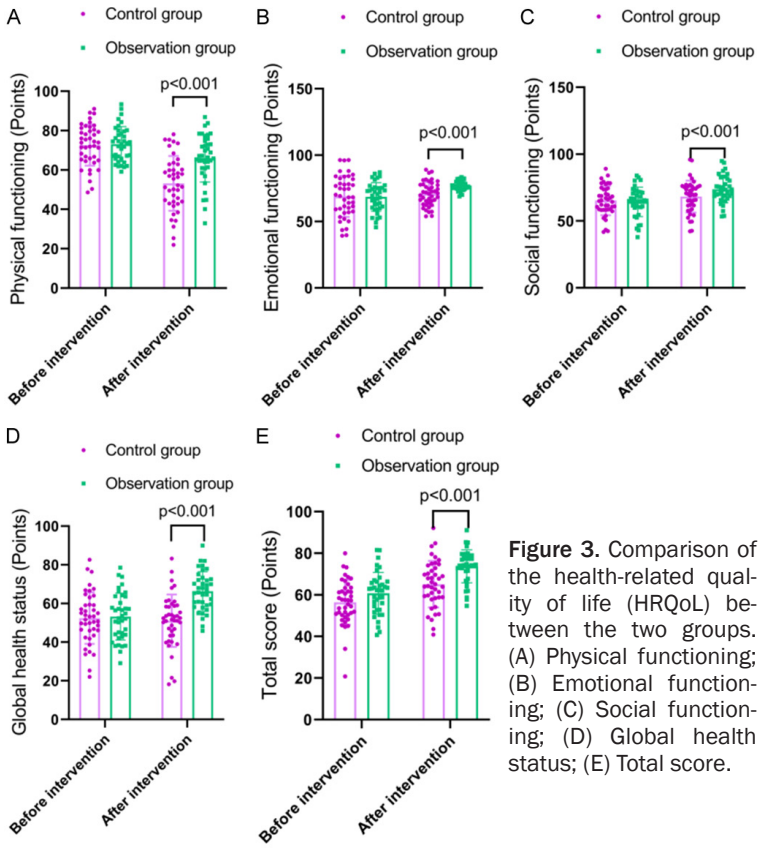

Figure 3. Comparison of the health-related quality of life (HRQoL) between the two groups. (A) Physical functioning; (B) Emotional functioning; (C) Social functioning; (D) Global health status; (E) Total score.

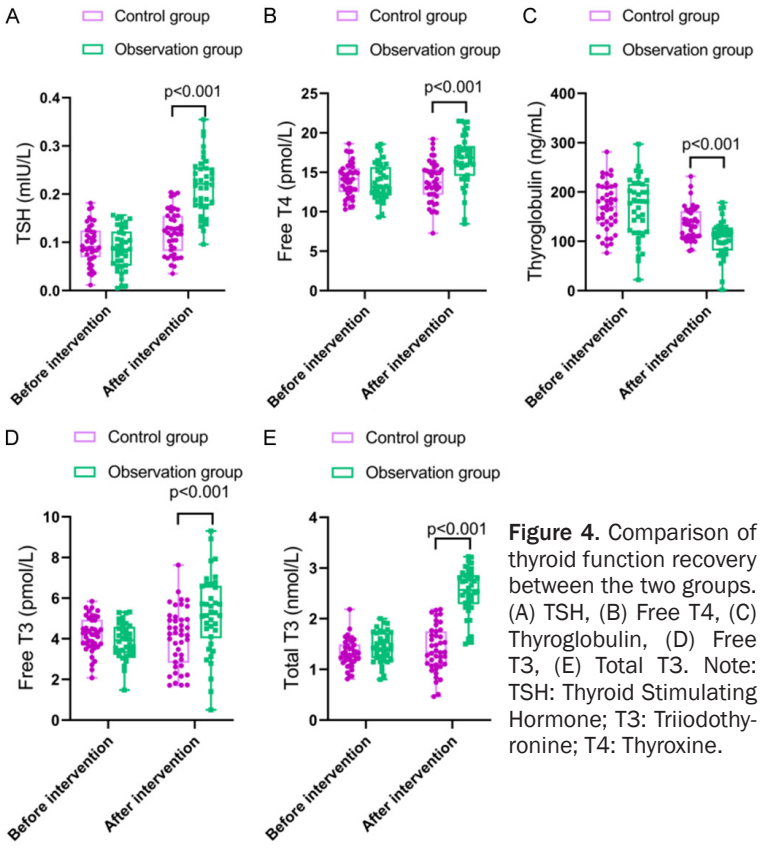

Figure 4. Comparison of thyroid function recovery between the two groups. (A) TSH, (B) Free T4, (C) Thyroglobulin, (D) Free T3, (E) Total T3. Note: TSH: Thyroid Stimulating Hormone; T3: Triiodothyronine; T4: Thyroxine.

of the control group and 47.4% of the observation group having only one metastatic site (P = 0.996). The most frequent metastatic sites (lung, bone, lymph nodes were similarly distributed between the groups (P>0.9). In addition, baseline tumor burden assessed according to the Response Evaluation Criteria in Solid Tumours (RECIST) showed no significant difference between the two groups (P = 0.784) (**Table 1**). These results indicated that the baseline characteristics of patients in the two groups were well balanced.

Kaplan-Meier survival curves for PFS, OS, and MFS between two groups

As shown in **Figure 2A**, PFS was significantly prolonged in the observation group (P< 0.001), with the survival curve remaining clearly separated from that of the control group throughout the study. Similarly, in terms of OS (**Figure 2B**), the observation group had significantly higher survival rates (P<0.001), suggesting a substantial survival benefit from this intervention. Finally, the metastasis-free survival curve (**Figure 2C**) also demonstrated a significant advantage for the observation group (P<0.001), further confirming the superior efficacy of the intervention in inhibiting disease progression and metastasis. These results fully highlight the effectiveness of this intervention in improving long-term survival and delaying disease progression.

Comparison of long-term adverse reactions and late toxicity

The overall incidence of late toxicity in the control group and the observation group was 21.4% and 26.3%, respectively

Table 4. Comparison of treatment response between patients with different long-term survival outcome

Response category	Favorable long-term survival group (n = 46)	Unfavorable long-term survival group (n = 34)	χ^2	*P* value
Complete response (CR)	10 (21.7%)	0 (0%)	8.447	0.004
Partial response (PR)	20 (43.5%)	5 (14.7%)	7.533	0.006
Stable disease (SD)	14 (30.4%)	18 (52.9%)	4.126	0.042
Progressive disease (PD)	2 (4.3%)	8 (23.5%)	6.577	0.010
ORR (CR+PR)	30 (65.2%)	8 (23.5%)	13.624	<0.001

Table 5. Comparison of HRQoL and thyroid function at last follow-up between groups

Variable	Favorable long-term survival group (n = 46)	Unfavorable long-term survival group (n = 34)	t value	*P* value
Physical functioning	78.52 ± 11.43	61.68 ± 10.65	6.707	<0.001
Emotional functioning	82.37 ± 6.29	63.03 ± 12.21	6.224	<0.001
Social functioning	79.28 ± 11.47	54.97 ± 12.39	9.005	<0.001
Global health	75.96 ± 10.56	62.18 ± 16.58	4.533	<0.001
TSH (μIU/mL)	1.60 ± 0.06	3.77 ± 1.26	11.734	<0.001
Free T4 (ng/dL)	1.31 ± 0.23	0.98 ± 0.06	8.214	<0.001
Free T3 (pg/mL)	3.07 ± 0.42	2.41 ± 0.09	8.938	<0.001
Thyroglobulin (ng/mL)	1.81 ± 0.09	5.17 ± 2.30	9.920	<0.001

Note: TSH: Thyroid-Stimulating Hormone; T3: Triiodothyronine; T4: Thyroxine; HRQoL: Health-Related Quality of Life.

(P = 0.608). According to the type of toxicity, the incidence of skin toxicity reactions (such as rash and dry skin) was 4.8% in the control group and 7.9% in the observation group (P = 0.563); the incidence of hematologic toxicity reactions (including anemia and neutropenia) was 9.5% and 7.9%, respectively (P = 0.797). The incidence of gastrointestinal toxicity reactions (such as nausea and diarrhea) was 7.1% and 10.5%, respectively (P = 0.593). The incidence of severe grade 3/4 toxicity reactions in both groups was low (4.8% vs. 7.9%, P = 0.563) (**Table 2**). These results indicate that the long-term safety profiles of the two treatment regimens were comparable, with no evidence of increased risk of late adverse reactions in the observation group.

Comparison of baseline clinicopathologic characteristics based on long-term survival outcomes

As shown in **Table 3**, most baseline characteristics of patients with good and poor long-term survival outcomes were comparable. There were no significant differences between the two groups in age, sex, BMI, or ECOG performance status score (all P>0.05). However, the proportion of patients with multiple metastatic lesions was significantly higher in the poor survival group than in the good survival group (χ^2 = 5.805, P = 0.016). Although the baseline tumor burden in the poor survival group tended to be higher, the difference was not significant (P = 0.760). Notably, there was a significant difference in treatment patterns between the two groups. The proportion of patients receiving combination therapy was higher in the good survival group (60.9% vs. 29.4%, P = 0.005), whereas the poor survival group was mainly treated with monotherapy (70.6% vs. 39.1%, P = 0.005). These results suggest that the extent of metastasis and treatment modality may be associated with differences in long-term survival.

Comparison of health-related quality of life (HRQoL) between the two patient groups

In terms of physical functioning (**Figure 3A**), scores for both groups increased significantly after the intervention, but the mean score in the observation group was significantly higher, reflecting enhanced physical activity ability and reduced activity limitations (P<0.001). Emotional functioning (**Figure 3B**) showed a

Table 6. Multivariate logistic regression analysis for independent predictors of favorable long-term survival outcome

Variable	β	Adjusted OR	95% CI	*P* value
Combination therapy (Yes vs. No)	0.853	0.426	0.234-0.776	0.005
Treatment response (CR/PR vs. SD/PD)	1.029	2.798	1.562-5.011	0.001
HRQoL total score (per 5 points)	0.747	0.474	0.265-0.845	0.011
TSH (per μIU/mL)	0.084	0.919	0.886-0.954	<0.001

Note: HRQoL: Health-Related Quality of Life; TSH: Thyroid-Stimulating Hormone; CR: Complete response; PR: Partial response; SD: stable disease; PD: Progressive disease.

similar trend, with the observation group exhibiting significantly greater improvements in emotional health, stress coping ability, and emotional stability compared to the control group (P<0.001). Social functioning (**Figure 3C**) improved significantly in both groups, but the observation group performed better in social role participation and maintenance of interpersonal relationships, with higher post-intervention scores (P<0.001). Additionally, the overall health status of the observation group (**Figure 3D**, including overall health perception and life satisfaction) improved significantly and was better than that of the control group (P<0.001). Importantly, the total HRQoL score integrating all assessment dimensions (**Figure 3E**) was significantly higher post-intervention in the observation group than in the control group (P< 0.001).

Comparison of thyroid function recovery

As shown in **Figure 4A**, TSH levels in the observation group decreased significantly post-intervention (P<0.001), indicating improved thyroid function. Similarly, FT4 levels in the observation group were significantly higher (**Figure 4B**, P<0.001), suggesting a better supply of thyroid hormones. An important marker of thyroid health, thyroglobulin levels, was also significantly lower in the observation group (**Figure 4C**, P<0.001), reflecting better thyroid recovery. Furthermore, FT3 levels in the observation group increased significantly post-intervention (**Figure 4D**, P<0.001), and TT3 levels were also significantly higher than those of the control group (**Figure 4E**, P<0.001).

Comparison of treatment response in patients with different long-term survival outcomes

As shown in **Table 4**, there were significant differences in treatment responses between patients with favorable and unfavorable long-term survival outcomes. The complete remission (CR) and partial remission (PR) rates were significantly higher in the favorable survival group than in the unfavorable survival group (CR: 21.7% vs. 0%, χ^2 = 8.447, P = 0.004; PR: 43.5% vs. 14.7%, χ^2 = 7.533, P = 0.006). In contrast, the rates of stable disease (SD) and progressive disease (PD) were higher in the unfavorable group (SD: 52.9% vs. 30.4%, χ^2 = 4.126, P = 0.042; PD: 23.5% vs. 4.3%, χ^2 = 6.577, P = 0.010). Consequently, the objective response rate (ORR = CR + PR) was significantly higher in the favorable group (65.2% vs. 23.5%, χ^2 = 13.624, P<0.001). These findings indicate that patients with favorable long-term survival outcomes exhibited better initial treatment responses.

Comparison of HRQoL and thyroid function at the last follow-up

Patients in the favorable survival group performed better across all HRQoL dimensions, including physical functioning (78.52 ± 11.43 vs. 61.68 ± 10.65), emotional functioning (82.37 ± 6.29 vs. 63.03 ± 12.21), social functioning (79.28 ± 11.47 vs. 54.97 ± 12.39), and overall health status (75.96 ± 10.56 vs. 62.18 ± 16.58), with all differences being statistically significant (all P<0.001). Regarding thyroid function, the favorable group had lower TSH levels (1.60 ± 0.06 vs. 3.77 ± 1.26 μIU/mL), higher FT4 levels (1.31 ± 0.23 vs. 0.98 ± 0.06 ng/dL), higher FT3 levels (3.07 ± 0.42 vs. 2.41 ± 0.09 pg/mL), and lower thyroglobulin levels (1.81 ± 0.09 vs. 5.17 ± 2.30 ng/mL) (all P<0.001) (**Table 5**). These results highlight the significant correlation between HRQoL and thyroid function in patients with favorable survival outcomes.

Independent predictors of favorable long-term survival outcomes: multivariate logistic regression analysis

Multivariate analysis revealed that combined therapy (adjusted OR = 0.426, 95% CI: 0.234-

0.776, P = 0.005), favorable treatment response (adjusted OR = 2.798, 95% CI: 1.562-5.011, P = 0.001), higher HRQoL scores (for every 5-point increase, adjusted OR = 0.474, 95% CI: 0.265-0.845, P = 0.011), and lower TSH levels (adjusted OR = 0.919, 95% CI: 0.886-0.954, P<0.001) were independent predictors of favorable long-term survival outcomes (**Table 6**). These findings indicate that treatment strategy, treatment response, quality of life, and thyroid hormone status play key roles in determining long-term outcome.

Discussion

This study aimed to evaluate the durability of the efficacy of vemurafenib combined with ^{131}I dual therapy in patients with BRAF-mutated thyroid cancer with lymph node metastases. The results showed that the PFS, OS, MFS, and thyroid function recovery of patients in the observation group were significantly better than those of the control group. These results are consistent with other studies - the combination of targeted therapy and radionuclide therapy can produce synergistic benefits and provides unprecedented new insight into this combined treatment, particularly its long-term benefits and immunomodulatory effects [15-17]. Combined with existing robust evidence, this study indicates that vemurafenib combined with ^{131}I treatment for advanced BRAF-mutated thyroid cancer with lymph node metastases has significant efficacy and is expected to become an effective treatment strategy to improve patient survival and quality of life. Several studies have compared the synergistic effects of vemurafenib and ^{131}I with conventional monotherapy. For example, recent studies have shown that vemurafenib monotherapy can significantly improve PFS and OS in patients with advanced BRAF-mutated melanoma [18, 19]. In the present study, it was observed that radioactive ^{131}I, as a targeted radiotherapy method, can further supplement the therapeutic effect. ^{131}I is commonly used in the treatment of thyroid cancer, functioning by the proliferative radioactive uptake of iodine by thyroid cancer cells to destroy cancer cells. In fact, the combination of ^{131}I with BRAF inhibitors demonstrates a synergistic effect: vemurafenib acts on the molecular mechanisms of tumor growth, while ^{131}I achieves local tumor destruction, creating a complementary effect [20, 21]. The significant improvement in survival outcomes in this study further supports the view that the combination of targeted therapy and radionuclide therapy is superior to monotherapy.

The positive changes in thyroid function recovery in the observation group also highlight the potential advantages of this combined treatment in providing both therapeutic efficacy and organ protection in thyroid cancer patients.

This study found that younger patients (≤21 years) in the observation group responded better to treatment, with higher CR and PR rates. This aligns with previous research [22-24] - younger thyroid cancer patients respond better to combination therapy, possibly because their immune system functions are not yet declined and they tolerate high-intensity treatment better. Moreover, we found that the synergistic effect of vemurafenib combined with ^{131}I treatment also applied to male patients. Male patients had a significantly higher PR rate and a decreasing trend in the SD rate. This may relate to gender differences in tumor biology and immune function. Previous studies have shown that male patients have a higher frequency of BRAF mutations and stronger immune responses to treatment. These results support that demographic characteristics should be considered in personalized cancer therapy, with age and gender being important factors affecting treatment outcome. Another crucial aspect of cancer treatment is its effect on patients' quality of life during and after treatment. In this study, patients in the observation group showed significant improvements in multiple dimensions of HRQoL like physical functioning, emotional functioning and social functioning. These results are consistent with previous studies, emphasizing the need to use patient-reported outcome measures to comprehensively evaluate the effectiveness of cancer treatment [25, 26]. The improvement in physical functioning and positive emotional state in the observation group is particularly noteworthy, indicating that vemurafenib combined with ^{131}I treatment not only enhances survival rates but also helps patients maintain daily activities and cope with the psychological burden of cancer. The overall improvement in health status and comprehensive HRQoL of the observation group further highlights the overall advantage of this treatment regimen. This com-

bination therapy addresses not only the biological aspects of cancer treatment but also the psychosocial dimensions, hence it is expected to become an effective long-term management plan for BRAF-mutant thyroid cancer.

Regarding thyroid function recovery, this study revealed that patients in the observation group had significant improvements in TSH, FT4, FT3 and TT3 levels. Recovery of thyroid function is crucial, especially in the treatment of thyroid cancer, as it is necessary to balance the patient's long-term endocrine health and quality of life. Specifically, the decrease in thyroglobulin levels (which can reflect thyroid tissue damage or tumor recurrence) provides important evidence for the efficacy of combined therapy in promoting thyroid function recovery. Existing studies indicate that BRAF inhibitors may adversely affect thyroid function, whereas subsequent combined ^{131}I treatment may counteract the damage caused by BRAF inhibition and play a balancing role in thyroid function recovery [9, 27]. These findings support that this combined therapy, in addition to having excellent therapeutic effects and survival benefits, can also protect and enhance thyroid function, thereby improving long-term health outcomes for patients. Despite the positive outcomes of this study, several limitations need to be considered. First, the sample size of this study was relatively small, which may have limited the generalizability of the findings. To verify the efficacy of vemurafenib combined with ^{131}I in a broader patient population, larger-scale, multicenter studies are needed. Second, the follow-up frequency and availability of long-term survival-related data in this study may have been insufficient to fully monitor late adverse effects and long-term endocrine complications. Therefore, an extended follow-up period is required to assess the persistence of clinical improvement and the potential risk of late toxic reactions. Additionally, although this study demonstrated that combined therapy could significantly improve immune response and thyroid function, the specific mechanisms underlying these changes have not been clarified and need to be further explored and validated in future research.

In conclusion, this study provided sufficient evidence that vemurafenib combined with ^{131}I is a feasible approach for treating BRAF-mutant thyroid cancer with lymph node metastasis. This approach not only significantly improved long-term survival outcomes (including PFS, OS and MFS) but also promoted thyroid function recovery and enhances quality of life. The findings indicated that this combined therapy helps strengthen both the biological treatment and psychosocial care of patients.

Disclosure of conflict of interest

None.

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