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Iodine-131: An Effective Method for Treating Lymph Node Metastases of Differentiated Thyroid Cancer

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Background: The aim of this study was to assess the efficacy of radioactive iodine-131 (¹³¹I) therapy for lymph node metastasis of differentiated thyroid cancer (DTC) and to identify influential factors using univariate and multivariate analyses to determine if identified factors influence the efficacy of treatment.

Material/Methods: This study included a retrospective review of 218 patients with histologically proven DTC in the post-operation stage. After thyroid tissue remnants were eliminated with ¹³¹I therapy, patients' lymph node status was confirmed by ultrasound and by ¹³¹I whole body scan regarding lymph node metastasis, and then patients were treated with ¹³¹I as appropriate. The treatment efficacy was assessed and possible influencing factors were identified using univariate and multivariate analyses.

Results: The total effective rate of ¹³¹I therapy was 88.07% (including a cure rate of 20.64% and an improvement rate of 67.43%). The non-effective rate was 11.93%. Of the total 406 lymph nodes of 218 patients, 319 lymph nodes (78.57%) were judged to be effectively cured, including 133 (32.75%) lymph nodes that were totally eliminated and 186 (45.82%) lymph nodes that shrank. Eighty-seven (21.43%) of the 406 lymph nodes had no obvious change. No lymph nodes were found to be in a continuously enlarging state. Distant metastasis, size of lymph node, human serum thyroglobulin (HTG) level, and condition of thyroid remnants ablation were identified as the independent factors influencing the efficacy of treatment using univariate and multivariate analyses.

Conclusions: The use of ¹³¹I is a promising treatment for lymph node metastasis of DCT. Distant metastasis, size of lymph nodes, HTG level, and condition of thyroid remnant ablation were independent factors influencing the treatment efficacy.

MeSH Keywords: **Iodine Isotopes • Lymph Nodes • Thyroid Neoplasms**

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Background

Differentiated thyroid cancer (DTC) includes papillary thyroid cancer and follicular thyroid cancer. DTC incidence tops the list of cancers of the human endocrine system and DTC rates are increasing every year [1,2]. Studies have confirmed the efficacy of ^{131}I in ablation of thyroid remnants, treatment of metastasis after ablation operation, and as a prognostic indicator [3–5]. Three stages of treatment of DTC have been suggested as optimal treatment strategies: the total or subtotal ablation of thyroid tissues, the postoperative ablation of thyroid remnants with ^{131}I therapy, and the administration of thyroid hormone suppression treatment. Follow-up metrics for DTC patients include thyroglobulin (HTG) levels, single-photon emission computed tomography (SPECT)/CT, ultrasound, chest CT, and ^{131}I whole body scan. DTC generally has a good prognosis, but lymph node metastasis may occur at an early stage, which can have a negative impact on the prognosis of DTC. Many studies have shown that the metastasis rate of cervical lymph nodes ranges from 15% to 80% [7–9]. Nevertheless, ^{131}I is still regarded as a common method for treating lymph node metastasis of DTC. Due to the lack of studies about ^{131}I treatment efficacy and its influencing factors, our study aimed to analyze these two aspects of ^{131}I therapy of lymph node metastasis of DTC.

Material and Methods

Clinical materials

We conducted a retrospective analysis of 218 patients with histologically proven DTC after thyroidectomy, of which 187 patients had papillary thyroid cancer and 31 patients had follicular thyroid cancer. Of the 218 patients, 64 were male and 154 were female; the average age ranged from 32 to 56 (43.73 ± 12.12) years. Treatment for 94 patients was with total thyroidectomy or subtotal thyroidectomy, while the remaining 124 patients underwent a combination of total thyroidectomy and cervical lymph node dissection (of which 76 patients had unilateral lymph node dissection and 48 patients had bilateral lymph node dissection). After treatment with ^{131}I for ablation of thyroid remnants (with a dosage of 3.7 GBq), 406 lymph nodes of 218 patients were found to have metastases using ultrasound and therapeutic-dosage ^{131}I whole body scan. Three hundred and forty-seven lymph nodes were < 2 cm and 59 lymph nodes were ≥ 2 cm; the largest lymph node was $3.4 \times 2.5 \times 1.9$ cm.

Treatment methods

Lymph node metastasis in DTC patients were treated with 5.55 GBq ^{131}I . Before the ^{131}I therapy, all patients were asked to

stop taking Euthyrox for at least 3 weeks prior to ^{131}I therapy to ensure thyroid-stimulating hormone (TSH) levels were > 30 uIU/mL. All patients had routine blood tests (TSH, HTG, and HTGAb), and chest radiograph, cervical neck ultrasound, and ^{131}I whole body scan (185 MBq). After a week of ^{131}I therapy, the patients were given prednisone and vitamin C to mitigate local symptoms as well as to protect their salivary glands and parotid glands [12]. On the sixth day of ^{131}I therapy, the patients were given a therapeutic-dosage ^{131}I whole body scan, and if the patients showed no signs of getting better after the first course of treatment, the second therapeutic activity was administered under the same conditions only with 5.55 GBq ^{131}I . All patients had ≤ 2 treatments.

Criteria of treatment efficacy

Methods to assess the efficacy of ^{131}I for treating lymph node metastasis of DTC include HTG level, ultrasound, and therapeutic-dosage ^{131}I whole body scan. The criteria for treatment efficacy were as follows:

- (1) Cure Rate (CR). The lymph nodes disappeared after ^{131}I therapy as seen by ultrasound; former lesions showed no ^{131}I uptake on whole body scan; and HTG level was < 2 $\mu\text{g}/\text{mL}$.
- (2) Improvement Rate (PR). The shrinkage and removal of lymph nodes were shown on ultrasound; the ^{131}I whole body scan showed images of lesions that were faded; and the HTG level decreased, but was still ≥ 2 $\mu\text{g}/\text{mL}$.
- (3) Non-effective Rate (NR). The lymph nodes did not shrink but tended to enlarge in size or increase in number; no obvious changes or no signs of densification were shown on ^{131}I whole body scan; and no changes were seen in HTG level. If a patient presented with several metastatic lymph nodes, the ineffectiveness of treatment was defined as either of the following: enlargement of any single lymph node, or increase in lymph node number.

Observation factors

The influences of nine factors on treatment efficacy were analyzed and included: age, gender, pathological type of cancer (papillary cancer or follicular cancer), operation methods, condition of distant metastasis, number of metastatic lymph nodes, number of lymph nodes, HTG level, and condition of thyroid remnant ablation. All tissue samples were provided and recorded by clinical doctors with over 10 years experience treating lymph node metastasis of DTC with ^{131}I therapy.

This study was approved by the Hebei Medical University Ethical Committee, Hebei, China. The nature, purpose, and potential risks of the study were explained to each participant prior to enrollment. Written informed consent was obtained from all enrolled patients.

Table 1. Results of univariate analysis.

Influencing Factors		Number of patients	χ^2	P
Age	≥45 years old	124	4.436	0.035
	<45 years old	94		
Gender	Male	64	0.024	0.878
	Female	154		
Pathological types	Papillary cancer	187	2.956	0.086
	Follicular cancer	31		
Operation methods	Total or subtotal thyroidectomy	94	2.589	0.108
	Total thyroidectomy and lymphadenectomy	124		
Distant metastasis	Yes	40	30.574	0.000
	No	178		
Number of lymph nodes	>1	116	4.756	0.029
	≤1	102		
Size of lymph node	≥2 cm	53	9.387	0.002
	<2 cm	165		
HTG	≥5 µg/L	157	54.497	0.000
	<5 µg/L	61		
Condition of thyroid remnants ablation with ¹³¹ I	Total ablation	177	12.501	0.000
	Subtotal ablation	41		

Statistical analysis

All statistics were analyzed using the SPSS 17.0 statistical software package. The univariate analysis was conducted through chi-square test, and the multivariate analysis through logistic regression analysis.

Results

Treatment efficacy of ¹³¹I to lymph node metastasis

The 218 patients with lymph node metastasis of DTC underwent ¹³¹I therapy once or twice. Of these, 45 patients became free of disease with a cure rate of 20.64%; 147 patients had improved conditions, for an improvement rate of 67.43%; and 26 patients were treated non-effectively; thus, the total effective rate (cure plus improvement) for ¹³¹I therapy was 88.07%, and the non-effective rate was 11.93%. Of the total 406 lymph nodes, 319 (78.57%) were treated effectively: 133 (32.75%) were totally removed after ¹³¹I therapy, and 186 (45.82%) had shrunk. In addition, 87 (21.43%) of the 406 lymph nodes had

no obvious changes, and none of lymph nodes were found to be in a continuously enlarged state.

Results of univariate analysis

The univariate analysis showed that age, condition of distant metastasis, size of lymph nodes, number of lymph nodes, HTG level, and condition of first-time thyroid remnant ablation had statistical significance, while gender, pathological type, and operation method had no statistical significance (Table 1).

Results of multivariate analysis

Factors from the univariate analysis that showed significant influence on treatment efficacy were then used in a logistic multivariate regression analysis model; the factors used were: age, condition of distant metastasis, size of lymph nodes, number of lymph nodes, HTG level, and condition of thyroid remnant ablation with ¹³¹I. As a result, the condition of distant metastasis, size of lymph nodes, HTG level, and condition of thyroid remnant ablation with ¹³¹I were defined as independent factors influencing the efficacy of treatment ($p < 0.05$) (Table 2).

Table 2. Results of multivariate analysis.

Influencing Factors	B	S.E.	Wald	P	Exp(B)	95.0% CI for EXP(B)
Distant metastasis	-2.209	0.564	15.333	0.000	0.110	0.036~0.332
Size of lymph node	-1.232	0.557	4.894	0.027	0.292	0.098~0.869
HTG	-2.377	0.553	18.511	0.000	0.093	0.031~0.274
Condition of first-time remnants ablation	-1.116	0.566	30887	0.049	0.328	0.108~0.993

Discussion

The differentiated thyroid has a good prognosis, but the occurrence of lymph node metastasis and distant metastasis is an important factor influencing prognosis. Therapy with ^{131}I can be used to treat metastasis of DTC, lower the recurrence and mortality rates of patients, and prolong patients' longevity, which is generally considered an effective method of treatment for this disease [7–9,13].

In our study, an analysis of 406 lymph nodes of 218 DTC patients was conducted. We found that the effective rate of ^{131}I therapy was 88.07%, and the average accumulation dosage of ^{131}I required for treatment was quite low, which is in agreement with other study reports [14,15]. This may be because the basic feature of thyroid cells' iodine uptake was sustained in both metastases of papillary thyroid cancer and metastases of follicular thyroid cancer. Our study found that ^{131}I internal radiation can be used to kill metastatic cancer cells effectively.

This study showed that ^{131}I could effectively treat lymph node metastasis of DTC, but there are many influencing factors. The study looked at nine clinical factors that might influence the treatment efficacy of ^{131}I , and found that distant metastasis, size of lymph nodes, HTG level, and condition of thyroid remnant ablation with ^{131}I were independent factors influencing the efficacy of treatment. In a univariate analysis, age and the number of lymph nodes were also included as influencing factors, but were eliminated in a multivariate analysis, which might be correlated with the small number of clinical cases available and interference of other confounding factors. Of the confounding factors, thyroid tissue remnants and distant metastasis were found to be important in influencing the efficacy of treatment, likely because both remnant thyroid tissues and

metastasis have the ability to uptake iodine, and thus reduce the effectiveness of iodine uptake of metastatic lymph nodes, especially under conditions where the iodine-uptake ability of remnant thyroid tissues is over 1,000 times that of metastatic tissue [16]. The HTG level is a specific marker used to identify the recurrence or metastasis of DTC [17–20]. It has also been proven to be an important factor influencing ^{131}I treatment efficacy on metastasis of DTC, which is in line with the thyroid tissue remnants and distant metastasis. The size of the lymph node is also an important factor and when the diameter of metastatic lymph nodes is >2 cm it is difficult for ^{131}I to totally eliminate them.

There were some limitations to our study. First, the sample size was small, and no detailed research or analysis was conducted based on age, staging, or other factors. Second, the follow-up was only short-term, and there was no analysis that showed the influence of ^{131}I therapy on the survival period of DTC patients. Third, the retrospective design may have lead to unstable results due to the non-integrality of the data and the bias of inclusion and exclusion.

Conclusions

This study showed the efficacy of ^{131}I for treating lymph node metastasis of DTC, but a comprehensive evaluation is needed on patients' influencing factors to select optimal therapeutic schedules.

Competing interests

The authors have declared that no competing interests exist.

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