

Value of ^{99m}Tc -MIBI SPECT-CT fusion tomography combined with therapeutic iodine scan in RAIR-DTC evaluation

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Abstract: Investigation of the diagnostic efficacy of ^{99m}Tc -MIBI SPECT/CT imaging combined with therapeutic iodine scan in iodine-refractory differentiated thyroid carcinoma (RAIR-DTC) patients. A total of 26 suspected RAIR-DTC patients who underwent ^{131}I therapy from March 2019 to December 2022 were collected. All patients had completed total thyroidectomy and subsequent radioiodine ablation therapy. They underwent ^{99m}Tc -MIBI SPECT/CT imaging (on admission day 1) followed by therapeutic iodine scan (^{131}I -WBS, on admission days 2-5). RAIR-DTC diagnosis was confirmed pathologically or by comprehensive clinical assessment. Chi-square test was used to evaluate the diagnostic performance of the two imaging methods. One patient was lost to follow-up, leaving 25 patients included in the study, with 18 diagnosed as RAIR-DTC based on pathology or clinical evaluation. Among the 25 suspected RAIR-DTC patients, 15 showed positive ^{99m}Tc -MIBI imaging and 10 showed negative imaging, with corresponding stimulated thyroglobulin (Tg) levels of 89.00 ng/ml (3.19-268.00) and 1.60 ng/ml (0.64-3.10), respectively, showing statistically significant difference ($P = 0.002$). Among the 18 confirmed RAIR-DTC patients, 8 showed complete lack of ^{131}I uptake and 10 showed partial uptake, with stimulated Tg levels of 55.60 ng/ml (3.04-229.00) and 0.80 ng/ml (0.17-1.80), respectively, showing statistically significant difference ($P < 0.01$). When using a stimulated Tg cutoff value of 2.55 ng/ml, the sensitivity and specificity for diagnosing RAIR-DTC were 83.3% and 100%, respectively, with an area under the curve of 0.93. Among the 18 confirmed RAIR-DTC patients, 37 lymph node metastases were found, with 30 lymph nodes showing positive ^{99m}Tc -MIBI imaging and 14 lymph nodes showing positive ^{131}I -WBS imaging, demonstrating statistical difference ($P < 0.001$). ^{99m}Tc -MIBI imaging combined with therapeutic ^{131}I -WBS, along with stimulated Tg, improves the diagnostic efficacy for RAIR-DTC. ^{99m}Tc -MIBI imaging is highly valuable in identifying cervical lymph node metastases in RAIR-DTC patients.

Keywords: ^{99m}Tc -MIBI; Iodine-refractory differentiated thyroid cancer (RAIR-DTC); Therapeutic iodine scan; thyroglobulin

1. Introduction

Thyroid cancer is the most common malignant tumor in the head and neck region, ranking seventh in incidence among all malignancies, and fourth among common malignancies in females. In recent years, its incidence has been increasing annually [1]. Approximately 80-90% of cases histologically classify as differentiated thyroid cancer (DTC), which originates from thyroid follicular epithelial cells and retains biological characteristics typical of normal thyroid tissue, such as expression of sodium-iodine symporter (NIS) and thyroglobulin. DTC typically exhibits low malignancy and slow progression, with relatively favorable prognosis due to retained ability to uptake iodine-131. However, about one-third of patients progress to radioactive iodine-refractory differentiated thyroid cancer (RAIR-DTC), where iodine-131 therapy is ineffective, leading to shortened survival [2].

^{99m}Tc -MIBI is a tumor-seeking radiopharmaceutical characterized by stable physicochemical properties and low radiation absorption dose. It is used as an adjunct diagnostic tool for thyroid cancer, lung cancer, breast cancer, etc. Increased uptake of MIBI occurs in malignant tumor cells due to heightened metabolism, rich blood supply, and enhanced capillary permeability within the tumor. In RAIR-DTC patients, tumor cells exhibit dedifferentiation and increased metabolic activity, resulting in negative iodine scans and heightened accumulation of ^{99m}Tc -MIBI.

This study explores the value of ^{99m}Tc -MIBI imaging combined with therapeutic iodine scan (^{131}I -WBS) in identifying RAIR-DTC lesions.

2. Materials and Methods

2.1 General Information

This study involved patients diagnosed with differentiated thyroid carcinoma (DTC) who underwent successful ablation therapy and were pathologically confirmed between March 2019 and December 2022. The inclusion criteria were stringent to ensure the reliability and validity of the study: (1) Patients who had undergone total or near-total thyroidectomy with confirmed DTC pathology, (2) Those who had completed ablation therapy, and (3) Patients with stimulated serum thyroglobulin (Tg) levels greater than 1 ng/ml or showing a progressive increase. Additionally, these patients had undergone comprehensive diagnostic examinations, including thyroid and cervical lymph node ultrasound, chest CT, and bone scintigraphy, which indicated suspected recurrence or metastatic lesions.

Exclusion criteria included: (1) A history of other malignant tumors, (2) Unwillingness to undergo ^{99m}Tc -MIBI imaging, and (3) Inability to provide complete medical records. Prior to ^{131}I treatment, all patients adhered to a low-iodine diet and discontinued levothyroxine (L-T4) for 2-3 weeks to elevate serum thyrotropin (TSH) levels above 30 mU/L. Upon admission, routine tests were conducted, including blood routine, thyroid function, liver and kidney function, and bone imaging.

The diagnostic criteria for radioactive iodine-refractory differentiated thyroid carcinoma (RAIR-DTC) were meticulously defined to ensure precise identification: (1) 3-6 months post-ablation, imaging tests suggested recurrence or metastasis, but no iodine uptake was observed on ^{131}I whole-body scan (WBS); (2) Initial metastases showed iodine uptake, which diminished or disappeared after ^{131}I treatments; (3) Discrepant iodine uptake among lesions, all detectable through other imaging methods; (4) Despite iodine uptake in metastatic lesions after multiple ^{131}I treatments, disease progression within one year, marked by lesion enlargement, new lesion appearance, and rising serum Tg levels.

The study maintained high ethical standards, with approval from the hospital's ethics committee, ensuring confidentiality and ethical handling of all patient data. These comprehensive criteria and preparatory steps provided a robust foundation for evaluating the efficacy of ^{99m}Tc -MIBI SPECT-CT fusion tomography combined with therapeutic iodine scans in assessing RAIR-DTC.^[1]

2.2 Methods

Upon admission, all patients underwent ^{99m}Tc -MIBI SPECT/CT imaging using a Symbia T6 (SIEMENS, Germany). The imaging agent, ^{99m}Tc -MIBI, with a dosage of 555-1110 MBq (15-30 mCi), was intravenously administered, followed by imaging after a 2-hour interval. The ^{99m}Tc was supplied by Atomic High-Tech Co., Ltd., while the MIBI was provided by the Beijing Shihong Pharmaceutical Research Center. The radiopharmaceuticals were synthesized in-house, achieving a purity of over 95%.

For imaging, a low-energy high-resolution parallel-hole collimator was utilized, set to a peak energy of 140 keV, with a window width of 15%. The matrix was configured at 1024×256 , and the acquisition speed ranged between 15-20 cm/min. Patients were positioned supine, and anterior and posterior images were captured, each with a preset count of approximately 1000 K. The ZOOM factor was set to 2.0, ensuring the collimator was close to but not in direct contact with the patient's body surface.

Given the prevalence of neck and chest metastases in thyroid cancer, all patients underwent SPECT/CT fusion imaging specifically targeting these regions. If planar imaging revealed abnormal uptake in other areas, additional SPECT/CT fusion imaging was performed for those specific regions.

Following the SPECT/CT imaging, all patients received an oral therapeutic dose of ^{131}I , sourced from Chengdu Huayi Isotope Co., Ltd., with doses ranging from 1110 MBq to 7400 MBq (30-200 mCi). Whole-body imaging was then conducted 2-5 days post-administration to evaluate the distribution and uptake of the radioactive iodine, aiding in the comprehensive assessment of potential metastatic sites and treatment efficacy. This thorough imaging and treatment protocol ensured a detailed and accurate evaluation of RAIR-DTC.

2.3 Image Analysis and Diagnostic Criteria

The images were interpreted independently by two or more experienced nuclear medicine physicians, who were blinded to the patients' clinical information to ensure objectivity. The criteria for interpretation included the exclusion of physiological sites of radioactive iodine uptake, such as the nasopharynx, salivary glands, gastrointestinal tract, and bladder, as well as any external radioactive contamination. Residual thyroid tissue was identified as iodine uptake foci in the thyroid bed area post-thyroidectomy, confirmed through fusion imaging or other relevant diagnostic methods. Metastases in the neck or lung were defined as iodine uptake foci located outside the thyroid bed area in the neck or lung regions.

The diagnostic criteria for residual thyroid tissue, DTC recurrence or metastasis, and RAIR-DTC were based on a comprehensive evaluation involving pathological results, therapeutic whole-body iodine scans, thyroid and cervical lymph node ultrasound, chest CT, whole-body bone scintigraphy, and thyroid function biochemical tests (including FT3, FT4, TSH, and Tg). Lesions were classified as iodine-refractory differentiated thyroid carcinoma (RAIR-DTC) if they showed no iodine uptake or exhibited progressive growth despite iodine uptake.

The interpretation process involved a detailed analysis of the imaging data, with the goal of identifying any areas of abnormal iodine uptake indicative of residual thyroid tissue, recurrent, or metastatic disease. The combination of multiple diagnostic modalities ensured a thorough and accurate assessment, allowing for the precise differentiation between physiological uptake, residual thyroid tissue, and metastatic lesions. This rigorous approach to image analysis and diagnostic criteria was essential for the effective management and treatment planning of patients with differentiated thyroid carcinoma, particularly those with iodine-refractory disease.

2.4 Statistical Methods

Data analysis and statistical processing were conducted using SPSS 24.0 and GraphPad Prism software. Descriptive statistics were calculated for all relevant data, with measurement data presented as mean \pm standard deviation. For comparisons of continuous variables, such as serum thyroglobulin (Tg) levels, the independent sample t-test was used to determine differences between groups, ensuring the comparison of means from two independent groups.

To assess the diagnostic efficacy of ^{99m}Tc -MIBI SPECT/CT and ^{131}I -WBS, the chi-square test and Fisher's exact test were employed to evaluate categorical data and compare the detection rates of residual thyroid tissue, recurrence, or metastases between the two imaging modalities. These tests provided insights into the effectiveness of each imaging technique in diagnosing RAIR-DTC.

Binary logistic regression analysis was applied to investigate the relationship between elevated Tg levels and the presence of RAIR-DTC, as well as to explore the correlation between MIBI imaging results and disease status. This analysis adjusted for potential confounding variables and provided a multivariate assessment of factors affecting RAIR-DTC diagnosis.

Statistical significance was determined using a significance level of $P < 0.05$, with all tests being two-tailed. The 95% confidence interval for estimates was used to quantify the precision of the results. Additionally, sensitivity and specificity analyses were performed to evaluate the performance of ^{99m}Tc -MIBI SPECT/CT in comparison to ^{131}I -WBS. These statistical approaches ensured a thorough evaluation of the diagnostic capabilities of the imaging techniques and contributed to a comprehensive understanding of their roles in the management of differentiated thyroid carcinoma.

3. Results

3.1 General Information

Since March 2019 to December 2022, a total of 182 patients underwent therapeutic iodine scans. After excluding 156 cases, 26 suspected patients were initially considered, of which 1 was lost to follow-up. Ultimately, 25 patients were included, comprising 23 cases of papillary carcinoma and 2 cases of follicular carcinoma (see Table 1). Among these, 5 cases were confirmed by pathology and 13 cases by comprehensive analysis as RAIR-DTC, including 16 cases of papillary carcinoma and 2 cases of follicular carcinoma, as shown in Table 1.

Table 1: General Information of Patients Included in the Study

Patient Characteristics	Value
Gender	
Male (M)/Cases	8
Female (F)/Cases	17
Age (Y)	56(47-62)
Body Mass Index (BMI) (Kg/(m ²))	24.42(23.4-28.1)
Pathology	
Papillary Carcinoma	23
Follicular Carcinoma	2
Laboratory Tests	
FT3(pg/ml)	1.5(1.2-1.8)
FT4(ng/dl)	0.41(0.30-0.52)
TSH(uIU/ml)	51.4(30.10-91.40)
sTg(ng/ml)	3.70(1.55-100.50)

3.2 Correlation between ^{99m}Tc-MIBI and ¹³¹I-WBS Imaging Results and Tg Levels

Among the 25 suspected RAIR-DTC patients, 15 patients had positive ^{99m}Tc-MIBI imaging and 10 patients had negative ^{99m}Tc-MIBI imaging. The patients were divided into the MIBI (+) group and the MIBI (-) group, with Tg levels of 89.00 ng/ml (3.19-268.00) and 1.60 ng/ml (0.64-3.10), respectively, showing a statistically significant difference (P = 0.002).

Among the 25 suspected RAIR-DTC patients, 15 patients had no ¹³¹I uptake, and 10 patients had partial ¹³¹I uptake. The patients were divided into the ¹³¹I-WBS (+) group and the ¹³¹I-WBS (-) group, with Tg levels of 55.60 (3.04-229.00) and 0.80 (0.17-1.80), respectively, showing a statistically significant difference (P < 0.01). Binary logistic regression analysis showed that stimulated Tg level can be used as a predictive factor for RAIR-DTC. When the cut-off value was set at 2.55 ng/ml, the sensitivity and specificity of stimulated Tg in diagnosing RAIR-DTC were 83.3% and 100%, respectively, with an area under the curve of 0.93, as shown in Figure 1.^[4]

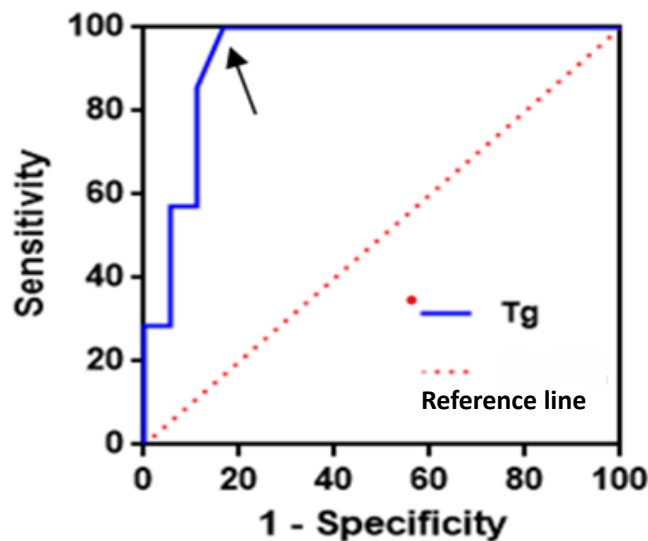


Figure 1: Receiver operating characteristic curve showing the diagnostic performance of stimulated Tg at a cutoff value of 2.55 ng/ml for diagnosing RAIR-DTC.

3.3 Evaluation of Lymph Node Metastasis by ^{99m}Tc-MIBI and ¹³¹I-WBS Imaging

A total of 37 lymph node metastases were found in 18 confirmed RAIR-DTC patients, with 30 lymph nodes showing positive ^{99m}Tc-MIBI imaging and 14 lymph nodes showing positive ¹³¹I-WBS imaging. There was a statistically significant difference (P < 0.001), as shown in Table 2.

Table 2: Imaging Results of ^{99m}Tc -MIBI and ^{131}I -WBS for Metastatic Lymph Node Lesions

	Positive	Negative
^{99m}Tc -MIBI	30	7
^{131}I -WBS	14	23

4. Discussion

DTC (differentiated thyroid cancer) is a common endocrine system tumor with increasing incidence annually, but relatively stable mortality rates. DTC cells retain partial expression of thyrotropin receptors (TSHR) and sodium-iodine symporters (NIS) on their surface, providing a basis for ^{131}I therapy. However, as the disease progresses, DTC cells may dedifferentiate, leading to downregulation or dysfunction of TSHR and NIS expression, resulting in decreased iodine uptake and development into RAIR-DTC (radioactive iodine-refractory differentiated thyroid cancer), which has a poor prognosis. Researchers have suggested that mechanisms contributing to RAIR-DTC may involve mutations in BRAF and TERT genes, angiogenesis, and gene rearrangements [3-4].

Reasons for the gradual loss of iodine uptake capacity in tumor cells include: 1) mutations induced by iodine-131 therapy in some DTC cells, and 2) clearance of iodine-avid tumor cells by iodine-131 treatment. Currently, the diagnosis and follow-up of RAIR-DTC typically involve pathological and comprehensive diagnostic approaches, including serum thyroglobulin (Tg) level testing, chest CT scans, thyroid and cervical lymph node ultrasound, bone scintigraphy, FDG PET/CT, etc.

^{99m}Tc -MIBI is a broad-spectrum tumor-seeking imaging agent widely used in various cancers. Current research on ^{99m}Tc -MIBI imaging in DTC mainly focuses on differentiation, identification of residual thyroid tissue post-surgery, and detection of metastatic lesions. However, there is relatively limited research specifically evaluating patients who develop RAIR-DTC after iodine ablation therapy.

This study found that ^{99m}Tc -MIBI imaging has higher sensitivity and accuracy in diagnosing RAIR-DTC compared to therapeutic ^{131}I whole-body scanning (^{131}I -WBS), which is consistent with the findings of Ji Yanhui et al. [5]. Regarding the detection of cervical lymph node lesions, ^{99m}Tc -MIBI imaging detects more lesions compared to ^{131}I -WBS, which aligns with the results of Wang Ping et al. [6]. However, some patients with metastatic lymph nodes show negative findings on ^{99m}Tc -MIBI imaging, possibly due to small lesion diameter and lower SPECT resolution.

Research indicates that serum thyroglobulin (Tg) levels have predictive value for assessing the efficacy of iodine ablation therapy in DTC, follow-up after ablation, and patient prognosis [7]. However, due to factors influencing Tg levels such as tumor differentiation, number of lesions, ability to synthesize and secrete Tg, and interference from Tg antibodies (TgAb), current studies typically combine Tg testing with other imaging modalities such as ultrasound, CT, therapeutic and diagnostic dose ^{131}I imaging, bone scintigraphy, PET/CT, PET/MR, etc. [8].

This study shows differential Tg levels between RAIR-DTC and non-RAIR-DTC patients. The ROC curve suggests that stimulated Tg levels have predictive value with a sensitivity of 83.3% and specificity of 100%, yielding an approximate area under the curve of 0.83. The cut-off value is determined to be 2.55 ng/ml. In contrast, Hou Fei et al. [9] identified a cut-off value of 13.66 $\mu\text{g/L}$ for predicting RAIR-DTC, indicating a significant difference compared to this study. Possible reasons include: 1) differences in patient inclusion criteria—where the latter study assessed pre- ^{131}I treatment Tg levels while this study focused on post-ablation patients, and 2) variations in sample size, with the latter study having a larger cohort.

Limitations of this study include: 1) a relatively small sample size, which may mask differences in diagnostic performance among different imaging methods, 2) a relatively short follow-up period, limiting further analysis of patient survival and prognosis, and 3) lack of pathological tissue acquisition as the "gold standard" in some patients.

In conclusion, ^{99m}Tc -MIBI imaging combined with therapeutic ^{131}I -WBS, and combined with stimulated Tg, can improve the diagnostic efficacy of RAIR-DTC, and ^{99m}Tc -MIBI imaging has a high diagnostic value for identifying cervical lymph node metastasis in RAIR-DTC patients.

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