Values of $^{99m}$Tc-methoxyisobutylisonitrile imaging after first-time large-dose $^{131}$I therapy in treating differentiated thyroid cancer

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Objective: The aim of this study is to investigate the use of $^{99m}$Tc-methoxyisobutylisonitrile (MIBI) imaging for evaluating the treatment response of differentiated thyroid cancer (DTC) after the first administration of a high dose of $^{131}$I.

Methods: Patients with DTC who received $^{131}$I therapy underwent $^{99m}$Tc-MIBI imaging after successive increases in the therapeutic dose of $^{131}$I, and the serum levels of thyroglobulin (Tg) were measured.

Results: A total of 191 patients were enrolled in the final analysis, including 65 metastases and/or thyroid remnant-positive patients (22 patients with metastases and 43 patients with thyroid remnants). The sensitivity of $^{99m}$Tc-MIBI imaging for detecting positive cases and thyroid remnants was 56.9% and 39.5%, respectively, which was significantly lower than that of $^{131}$I imaging (92.3% and 100%, respectively, $P<0.01$ for both). The sensitivity of $^{99m}$Tc-MIBI imaging for detecting metastases was 90.9%, which was slightly higher than that of $^{131}$I imaging (77.3%, $P>0.05$). The Tg levels in the positive group were significantly higher than that in the negative group ($P<0.01$). In addition, the Tg levels in the $^{99m}$Tc-MIBI/$^{131}$I group were significantly higher than that in the $^{131}$I/$^{99m}$Tc-MIBI group ($P<0.05$).

Conclusion: After the first $^{131}$I therapy, although $^{99m}$Tc-MIBI imaging was able to detect the existence of metastatic lesions in patients with DTC better, its assessment for the removal efficiency of thyroid remnants was unsatisfactory. The results of $^{99m}$Tc-MIBI imaging showed good correlations with the Tg level.

Keywords: differentiated thyroid cancer, $^{99m}$Tc-MIBI imaging, therapeutic dose $^{131}$I imaging, thyroglobulin

Introduction
Thyroid cancer (TC), the most common malignant tumor among endocrine and head–neck tumors, with an increasing incidence in recent years, accounts for ~3% of all malignancies.1 Differentiated thyroid cancer (DTC) accounts for >90% of all TC cases. Currently, the routine treatment for DTC is surgery plus $^{131}$I therapy plus thyroid-stimulating hormone (TSH) suppression therapy.2,3 Total or near-total thyroidectomy is the most commonly used surgical procedure. $^{131}$I therapy includes the ablation of thyroid remnants and local/distant metastases with the postoperative use of different activities of $^{131}$I. The suppression of TSH using supraphysiologic doses of levothyroxine to supplement thyroid hormone and to inhibit the growth of DTC cells is an effort to decrease the risk of recurrence.

After the first (postoperative) application of $^{131}$I therapy, the patient should be evaluated for the presence of remnants or metastases, which is important for
determining the necessity of repeated $^{131}\text{I}$ therapy. Serum thyroglobulin (Tg) level is the most sensitive and specific indicator for monitoring DTC recurrence or metastases, but it cannot be used to locate the lesions or distinguish remnants from metastases; therefore, combining with other imaging methods is needed for evaluation. Ultrasonography and computed tomography are commonly used, but they have certain deficiencies for detecting functional TC recurrent or metastatic lesions, especially for the diagnosis of some minor metastatic lesions. $^{131}\text{I}$ imaging with diagnostic dose might not be able to detect small metastases and might induce a stunning effect (a reduction in the uptake of $^{131}\text{I}$ therapy dose induced by a pretreatment diagnostic activity) of remnants/metastases, which might influence the efficacy of subsequent $^{131}\text{I}$ therapy. $^{99m}\text{TcO}_4^{-}$-imaging$^8$ can provide information about the clearance of thyroid remnants, but it is not a tumor-specific imaging; therefore, it cannot be used to evaluate the clearance of TC metastases. Although $^{18}$F-fluoro-2-deoxy-D-glucose positron emission tomography ($^{18}$FDG-PET) imaging can provide information about remnants and metastases with a high metabolism, it is too expensive for wider use in clinical application; besides, partial metastatic lesions (especially lymph node metastases) show no high intake of fluorodeoxyglucose. $^{99m}\text{Tc}$-methoxyisobutylisonitrile (MIBI) is a nonspecific tumor-philic imaging agent; it has been used for diagnosing and evaluating the efficacy of treatments for lung cancer, breast cancer, bone cancer, gliomas, and other malignant tumors. The present study compared the results of $^{99m}\text{Tc}$-MIBI imaging and therapeutic-dose $^{131}\text{I}$ imaging, aiming to assess the use of $^{99m}\text{Tc}$-MIBI imaging in patients with DTC after surgery and the first (postoperative) application of $^{131}\text{I}$ therapy.

Materials and methods
Clinical data
A total of 192 patients with DTC (38 men and 154 women; aged 7–78 years [mean±SD: 43.2±8.6 years]) who underwent total or near-total thyroidectomy for pathologically diagnosed DTC (including 171 cases of papillary carcinoma and 21 cases of follicular carcinoma) and who were treated in our hospital between February 2010 and March 2014 were enrolled. All patients underwent $^{99m}\text{Tc}$-MIBI imaging and high-dose $^{131}\text{I}$ imaging 6 months after the first (postoperative) application of $^{131}\text{I}$ therapy (the mean dose was 113.5±20.8 mCi) and stopped receiving thyroxin preparation as a medication, 4 weeks before the imaging. This study was conducted in accordance with the Declaration of Helsinki. This study was conducted with the approval from the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. Written informed consent was obtained from all participants.

Laboratory tests
By using the chemiluminescence method, the serum Tg level (reference value, <35 ng/mL) was measured in all patients, both after they stopped the medication of thyroxin preparation 4 weeks prior to imaging and just before the imaging. The radioimmunoassay method was used to detect the levels of TSH (reference range, 0.3–5.0 mIU/L) and Tg antibody (TgAb, reference value, <30%).

$^{99m}\text{Tc}$-MIBI imaging
Patients were intravenously injected with 740–925 MBq $^{99m}\text{Tc}$-MIBI (Beijing Xinke Co., Beijing, People’s Republic of China), and then, neck and chest as well as systemic planar images were obtained after 90 minutes. A single-photon emission computed tomography (SPECT)/computed tomography (CT) instrument (Symbia T2; Siemens, Munich, Germany) was used, which was equipped with a parallel low-energy high-resolution collimator with an energy peak of 140 keV and a window width of 20%. The magnification fold when performing neck and chest scanning was 1.5, with a matrix of 256×256 pixels and an acquisition count of 500 K. The magnification fold when performing systemic scanning was 1.0, with a matrix of 256×1,024 pixels and scanning speed of 15 cm/min.

$^{131}\text{I}$ imaging
Patients were orally administered a mean dose of 5,550–8,140 MBq (150–220 mCi) $^{131}\text{I}$ (provided by Chengdu Gaotong Isotope Co., Ltd.) on the second day after $^{99m}\text{Tc}$-MIBI imaging; they underwent neck–chest scanning and systemic scanning on the fourth day after $^{131}\text{I}$ administration (namely, high-dose $^{131}\text{I}$ imaging). A SPECT/CT instrument (Symbia T2) was used, which was equipped with a parallel low-energy high-resolution collimator with a matrix of 256×1,024 pixels, an energy peak of 364 keV, and a window width of 20%; the magnification fold was 1, with a scanning speed of 15 cm/min and acquisition count of 100–150 K.

Image analysis
The images were evaluated independently by two physicians with SPECT/CT diagnostic experience. The images with consistent evaluation results were then included in the final analysis. Positive cases were defined as the presence of an abnormal radioactive uptake outside the thyroid gland bed area or the thyroid gland – as found on either of the above-mentioned imaging methods – and negative cases were
defined as no imaging agent uptake outside the thyroid gland bed area and the thyroid gland.

**Statistical analysis**

SPSS 13.0 software (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. The data were assessed using the chi-square test. The measurement data were expressed as \( \bar{x} \pm s \). The intergroup data were compared with an independent samples t-test, with \( P<0.05 \) considered statistically significant.

**Results**

**Imaging results of all patients**

The imaging results of a total of 191 patients with DTC were included in the study (the images of one patient were excluded owing to considerable differences between the evaluation results of the two physicians). Among them, 126 (66.0%) patients were negative on both imaging methods, 32 (16.8%) patients were positive on both imaging methods, 28 (14.7%) patients were high-dose \(^{131}\)I whole body scan (Rx-WBS) positive but \(^{99m}\)Tc-MIBI negative, and five (2.6%) patients were \(^{99m}\)Tc-MIBI positive but Rx-WBS negative. The imaging results of some patients are shown in Figures 1-4. A total of 65 patients (34.0%) were found to be positive, including 37 patients found by \(^{99m}\)Tc-MIBI imaging, with a sensitivity, specificity, and accuracy of 56.9%, 100%, and 85.3%, respectively; while 60 patients were found by Rx-WBS, with a sensitivity, specificity, and accuracy of 92.3%, 100%, and 97.4%, respectively. The sensitivity of \(^{99m}\)Tc-MIBI imaging in finding positive cases was significantly lower than that of Rx-WBS (\( \chi^2=14.7, P<0.01 \)) (Table 1).

**Imaging results of \(^{99m}\)Tc-MIBI and Rx-WBS toward residual thyroid tissues and metastases**

Among the 65 positive patients, 43 patients exhibited residual thyroid tissues; \(^{99m}\)Tc-MIBI imaging only detected 17 cases (39.5%) while Rx-WBS detected all 43 cases (100%). Accordingly, the sensitivity of \(^{99m}\)Tc-MIBI imaging for detecting residual thyroid tissues was significantly lower than that of Rx-WBS (\( \chi^2=24.0, P<0.01 \)). Among the 22 patients with DTC metastases, \(^{99m}\)Tc-MIBI imaging was significantly lower than that of Rx-WBS (\( \chi^2=21.4, P<0.01 \)).

*Figure 1* Imaging results from a 61-year-old female patient with FTC who felt right iliacal pain.

**Notes:** Right iliacal tissue has an abnormal uptake of (A) \(^{99m}\)Tc-MIBI on \(^{99m}\)Tc-MIBI imaging, and the liver, spleen, intestinal tract, heart, and bladder tissue have significant physiological uptake and (B) \(^{131}\)I on Rx-WBS imaging, showing the liver also has more \(^{131}\)I uptake, and hence, we cannot exclude that this patient has liver metastases.

**Abbreviations:** FTC, follicular thyroid carcinoma; MIBI, methoxyisobutylisonitrile; Rx-WBS, high-dose \(^{131}\)I whole body scan.
Figure 2 Imaging results from a 78-year-old male patient with PTC.

Notes: Neck and both lungs have (A) an abnormal uptake of 99mTc-MiBi on 99mTc-MiBi imaging and (B) no abnormal uptake of 131I on 131I imaging.

Abbreviations: PTC, papillary thyroid carcinoma; MiBi, methoxyisobutylisonitrile.

Figure 3 Imaging results from a 48-year-old female patient with PTC.

Notes: (A) Neck and whole body have no abnormal uptake of 99mTc-MiBi on 99mTc-MiBi imaging and (B) neck tissue had an abnormal uptake of 131I on Rx-WBS imaging, considered as a normal residual thyroid tissue.

Abbreviations: FTC, papillary thyroid carcinoma; MIBI, methoxyisobutylisonitrile; Rx-WBS, high-dose 131I whole body scan.
detected 20 cases (90.9%), while Rx-WBS detected 17 cases (77.3%). The sensitivity of $^{99m}$Tc-MIBI imaging for detecting TC metastases was higher than that of Rx-WBS, although the difference was not significant ($\chi^2=0.57, P>0.05$). On further analysis, 33 positive patients showed discrepant results between the two imaging methods (only positive on $^{99m}$Tc-MIBI imaging or on Rx-WBS imaging). A total of 28 cases were positive on Rx-WBS but negative on $^{99m}$Tc-MIBI, among whom 26 cases exhibited radioactive $^{131}$I uptake in the thyroid gland bed area and two cases exhibited an abnormal $^{131}$I uptake outside the gland. Five cases were positive on $^{99m}$Tc-MIBI but negative on Rx-WBS, among whom three cases exhibited $^{99m}$Tc-MIBI uptake outside the thyroid gland and two cases exhibited $^{99m}$Tc-MIBI uptake in the thyroid gland bed area (Table 2).

**Results of serum Tg in each group**

According to imaging results, all patients were classified into four groups: group I ($^{99m}$Tc-MIBI negative and $^{131}$I negative), group II ($^{99m}$Tc-MIBI positive and $^{131}$I positive), group III ($^{99m}$Tc-MIBI negative and $^{131}$I positive), and group IV ($^{99m}$Tc-MIBI positive and $^{131}$I negative). The serum Tg levels of the positive groups (namely, groups II, III, and IV) were significantly higher than the negative group (group I), and those of the $^{99m}$Tc-MIBI-positive group (group IV) was significantly higher than the $^{131}$I-positive group (group III). All the groups exhibited TSH levels >30 mIU/L and TgAb levels within the reference range, indicating that the Tg results (Table 3) were not influenced by TgAb.

### Table 1 Imaging results of 191 patients

| Imaging results       | Cases | Percentage (%) |
|-----------------------|-------|----------------|
| $^{99m}$Tc-MIBI/$^{131}$I- | 126   | 66.0           |
| $^{99m}$Tc-MIBI/$^{131}$I+ | 32    | 16.8           |
| $^{99m}$Tc-MIBI/$^{131}$I- | 28    | 14.7           |
| $^{99m}$Tc-MIBI/$^{131}$I+ | 5     | 2.6            |
| $\chi^2$              | 14.6667 |
| P-value               | 0.0001*** |

**Note:** $***P<0.01$.

**Abbreviation:** MIBI, methoxyisobutylisonitrile.
Table 2 Imaging results of two imaging methods toward residual thyroid tissues and metastases

|                          | Positive cases of 99mTc-MIBI imaging (sensitivity) | Positive cases of large-dose 131I imaging (sensitivity) | χ² | P-value |
|--------------------------|-----------------------------------------------------|---------------------------------------------------------|-----|---------|
| Residual thyroid tissues (n=43) | 17 (39.5%)                                          | 43 (100%)                                               | 24.0385 | 0.000001** |
| Metastases (n=22)         | 20 (90.9%)                                          | 17 (77.3%)                                              | 0.57143 | 0.45*    |

Note: *P<0.05; **P<0.01. 
Abbreviation: MIBI, methoxyisobutylisonitrile.

Discussion

The evaluation of whether postoperative TC metastases exist in patients with DTC should be preferably performed after the first (postoperative) application of 131I therapy (namely, ablation of the thyroid gland) because the existence of residual normal thyroid tissue might influence the 131I uptake of metastases, thus leading to false-negative results. The search for an imaging method that can not only sensitively detect TC metastases but also objectively assess whether residual thyroid tissues in the neck are completely resolved is important for the follow-up treatment of patients with DTC.

99mTc-MIBI is a nonspecific tumor-philic imaging agent with good physicochemical properties and a low radiation absorbance dose; therefore, it can be administered in high doses. In recent years, 99mTc-MIBI imaging has been widely used for the diagnosis of TC, breast cancer, lung cancer, bone tumors, and other malignancies. 99mTc-MIBI is absorbed into the cytoplasm by passive diffusion and then goes into mitochondria by active transportation. Tumor cells have a high number of mitochondria, active metabolism, and an increased local blood supply, and thus, they can absorb and temporarily retain more MIBI. This characteristic of fast uptake and relatively slow excretion is significantly different from the uptake and excretion pattern of benign cells. This is the reason why the tumor tissues can be easily identified. Accordingly, as the active ratio of the target tumor tissues to nontarget tissues is higher on delayed 99mTc-MIBI imaging, the delayed imaging is more obvious; therefore, this study only analyzed the results in the delayed phase.

The use of 99mTc-MIBI as a radioactive tracer has the following advantages in evaluating the existence of remnants and metastases in patients with DTC after surgery and the first application of 131I therapy: ideal physical properties of 99mTc-MIBI led to less radiation damage in patients and are suitable for SPECT imaging; is easily prepared and has low production cost; does not get affected by the serum TSH level, no need for long-term withdrawal of levothyroxine before imaging and avoids hypothyroid symptoms; its uptake is related to the contents and metabolism of intracellular mitochondria (both functional and nonfunctional metastases can ingest 99mTc-MIBI, which could overcome the limitation of misdiagnosis of nonfunctional or dedifferentiated TC metastases of 131I imaging); and is without the “stunning” effect and does not affect the efficacy of subsequent 131I therapy.

As the most common metastatic areas of TC are the neck and chest, our department normally acquires neck and chest images (enlarged 1.5 times) and systemic images, which are helpful to discover the neck or lung metastases and provide information about iliac or other metastases. 99mTc-MIBI is excreted through the hepatobiliary system, which leads to obvious accumulation in the liver and intestines. Therefore, plain 99mTc-MIBI scanning has substantial limitations in assessing metastases in the spine, gastrointestinal tract, and other organs. Figure 1 shows that systemic 99mTc-MIBI imaging revealed lesions with an abnormal 99mTc-MIBI uptake in the right iliac region of a patient. 131I imaging also exhibited uptake in this site, so it might be considered an iliac metastasis; furthermore, as more 131I uptake was seen in the liver, we could not exclude the possibility that the lesion was accompanied by liver metastasis. While even 99mTc-MIBI imaging exhibits obvious aggregation in the liver and intestinal tract, it cannot be used to assess the possibility of liver metastasis.

Among the 65 positive cases found in this study, 131I imaging could detect 60 cases (92.3%) and 99mTc-MIBI imaging could detect 37 cases (56.9%). The positive rate on 99mTc-MIBI imaging was significantly lower than that on 131I imaging, while the combination of 99mTc-MIBI imaging with 131I imaging can increase the positive rate of diagnosis. A total of 43 patients were found to have residual thyroid tissues; the sensitivity of 131I imaging was 100% and that of
It is a pity that not one of them had the pathological exami-

dedifferentiation or poor differentiation of TC metastases.

We thought that the possible reasons for this difference might

131

patients with TC metastases were

show negative results on

while because of losing iodine uptake ability, the patients

cells and showing positive results on

thus enhancing
ters (dDTCs) have higher metabolism compared to DTCs,

thyroid cancers (pDTCs) and dedifferentiated thyroid can-

of differentiation degree of DTC;

of

uptake value
during or after

metastatic lesions of patients with DTC gradually lost iodine

difference was not significant (P

). The study found that the uptake value

99mTc-MIBI negative (the result of one patient is shown in Figure 2).

The authors report no conflicts of interest in this work.

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is not clear. For these patients, the efficacy of routine 131I

therapy might be poor and other treatment options should be

Another two patients’ metastatic lesions show a

result of 131I positive but 99mTc-MIBI negative, which might

be due to the lower mitochondria content in tumor cells, but

the exact reason is still not clear.

Tg is synthesized by thyroid follicular cells. The serum

Tg level was a specific marker for monitoring residual tumor
cells, recurrence, and metastasis of DTC and for assessing the
efficacy of treatment. In patients who underwent total thyroi-
dectomy and who had already been treated with 131I ablation
of the thyroid gland, the serum Tg levels should be below
the reference line or undetectable; therefore, an increase in
Tg might suggest a recurrence or metastasis of TC. In this
study, the TgAb levels of all patients were within the refer-
ence range, indicating that antibodies did not interfere with
the Tg results. The serum Tg level of the positive group was
significantly higher than that of the negative group, indicating
that the imaging results had good correlations with the Tg
levels, consistent with previous reports.23 We noted that the
survival rate and the reliability of Tg as a tumor marker during
the follow-up period were directly influenced by whether 131I
could completely clear patients’ residual thyroid tissues.

In summary, after the first (postoperative) application of
131I therapy, 99mTc-MIBI imaging could sensitively detect
metastatic TC lesions in patients with DTC by not only having
a high positive rate for cervical lymph node metastases but
also finding distant metastases. The use of 99mTc-MIBI for
detecting cervical residual thyroid tissues is limited; there-
fore, it cannot be used instead of 131I imaging, but it can be
used as one of the inspection methods for evaluating patients
with DTC, thus providing important information about the
need for subsequent 131I therapy. 99mTc-MIBI imaging and 131I
imaging had good correlations with the serum Tg levels.

Disclosure

The authors report no conflicts of interest in this work.

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