Clinical Research Report

99mTcO₄⁻/99mTc-MIBI dual-tracer scintigraphy for preoperative localization of parathyroid adenomas

Zhongke Huang and Cen Lou

Abstract

Objective: To investigate the accuracy of dual-tracer scintigraphy for locating parathyroid adenomas in patients with primary hyperparathyroidism (PHPT).

Methods: We reviewed 268 patients with PHPT. All patients underwent technetium-99m pertechnetate (99mTcO₄⁻) scintigraphy and technetium-99m methoxyisobutylisonitrile (99mTc-MIBI) dual-tracer scintigraphy of the thyroid and parathyroid glands, respectively. 99mTcO₄⁻ planar scintigraphy was carried out initially followed by dual-phase 99mTc-MIBI single-photon emission computed tomography (SPECT)/CT the next day. The findings were combined and interpreted. Individual 99mTc-MIBI and dual-tracer scintigraphy were both analyzed. The sensitivity, specificity, and accuracy were determined in relation to surgical findings. The average interval between scan and surgery was 13 days.

Results: The positive and negative predictive values of 99mTc-MIBI SPECT/CT were 92.0% and 71.3%, respectively, and the sensitivity, specificity, and accuracy were 88.3%, 79.2%, and 85.8%, respectively. The positive and negative predictive values of dual-tracer scintigraphy were 96.3% and 82.3%, respectively, and the sensitivity, specificity, and accuracy were 92.9%, 90.3%, and 92.2%, respectively. Youden’s index for dual-tracer scintigraphy and 99mTc-MIBI SPECT/CT were 0.83 and 0.63, respectively.

Conclusions: These finding suggest that 99mTcO₄⁻ and 99mTc-MIBI dual-tracer scintigraphy is more accurate than other scintigraphy methods for detecting parathyroid adenoma, and may thus be the most suitable imaging technique in patients with PHPT.
Keywords
Dual-tracer, hyperparathyroidism, single-photon emission computed tomography, SPECT/CT, parathyroid adenoma, technetium-99m methoxyisobutylisonitrile, technetium-99m pertechnetate

Date received: 5 August 2018; accepted: 26 October 2018

Introduction
Primary hyperparathyroidism (PHPT) can be caused by parathyroid adenoma, hyperplasia, or parathyroid carcinoma, and is characterized by high serum calcium and parathyroid hormone (PTH) levels. It can lead to multisystem diseases, including skeletal, gastrointestinal, cardiovascular, renal, and central nervous system complications. The only curative treatment for symptomatic PHPT is resection of the hyperfunctioning parathyroid glands. However, preoperative localization of the parathyroid adenoma is crucial for planning effective minimally invasive surgery.

Radioisotope scintigraphy of the parathyroid glands can help the endocrine surgeon to locate the abnormal gland before surgery in patients with PHPT. Thallium-201 (201Tl) and technetium-99m methoxyisobutylisonitrile (99mTc-MIBI) are the most commonly used tracers. The biological features of 201Tl are similar to those of K⁺, but its binding affinity to K⁺ activation sites is 10 times stronger than that of K⁺ during the Na⁺-K⁺ ATPase activation process. 99mTc-MIBI is a lipophilic monovalent cation complex that can diffuse passively into the cell membrane and accumulate in the mitochondria. The metabolic product of 99mTc-MIBI is succinic acid salt, which enhances its ability to combine with mitochondria. Each tracer is taken up simultaneously in both the thyroid and parathyroid glands, but is washed out from the thyroid more rapidly than from a hyperfunctioning parathyroid. However, the adenoma-washout rate is variable and may be rapid, and more effective ways of visualizing and locating the hyperfunctioning parathyroid gland are required. 99mTc-MIBI dual-phase scintigraphy has been used successfully in a number of centers, while, dual-tracer scintigraphy has also been useful for differentiating between thyroid tissue and parathyroid adenomas. In dual-tracer scintigraphy, 99mTc-MIBI displays the thyroid and parathyroid, while 99mTcO₄⁻ delineates the thyroid alone. Subtracting the two resulting sets of images thus reveals the hyperfunctioning parathyroid tissue. 18F-choline positron emission tomography/computed tomography (CT) can also improve the localization of the hyperparathyroid glands, but is not conventionally recommended for PHPT.

We have been carrying out dual-tracer scintigraphy at our institute since 2006. In this study, we carried out a retrospective audit to compare the accuracies of 99mTcO₄⁻/99mTc-MIBI dual-tracer scintigraphy and 99mTc-MIBI single-photon emission CT (SPECT)/CT alone for identifying parathyroid adenomas in patients with PHPT, and to investigate the use of dual-tracer scintigraphy as a preoperative aid for surgical planning.

Patients and methods
Patients
This study was approved by the ethics committee of Sir Run Run Shaw Hospital.
Each patient proved signed informed consent.

A total of 487 patients underwent dual-tracer parathyroid scintigraphy in our center from January 2006 to February 2016, of whom 268 patients diagnosed with PHPT who underwent both dual-tracer parathyroid scintigraphy and surgery were included in the current study.

**Dual-phase and dual-tracer scintigraphy**

All patients were imaged according to our institution’s standard procedures, using a GE Infinia Hawkeye IV SPECT camera (GE Healthcare, Piscataway, NJ, USA) equipped with four-slice CT. $^{99m}$TcO$_4$ planar scintigraphy was carried out first, 20 to 30 minutes after the administration of 185 MBq of $^{99m}$TcO$_4$. Dual-phase $^{99m}$Tc-MIBI scintigraphy was performed and interpreted the next day. Planar imaging was performed 10 minutes and 2 hours after administration of 555 MBq of $^{99m}$Tc-MIBI, respectively. $^{99m}$Tc-MIBI SPECT/CT was carried out 2 hours after administration of the tracer. The average interval between the scan and surgery was 13 days.

**Image interpretation**

All planar and SPECT/CT images were interpreted by two experienced nuclear medicine physicians with 29 and 26 years’ experience of practicing nuclear medicine, respectively. One physician recorded his findings based on $^{99m}$Tc-MIBI planar scintigraphy and SPECT/CT, but blinded to the $^{99m}$TcO$_4$ scintigraphy results. The other physician had access to the $^{99m}$Tc-MIBI planar scintigraphy and SPECT/CT results, and to the corresponding $^{99m}$TcO$_4$ scintigraphy. They evaluated the presence and number of foci compatible with hyperfunctioning parathyroid glands visually and determined their location. A positive test was defined as focal $^{99m}$Tc-MIBI uptake, even if only faint, or no focal $^{99m}$Tc-MIBI uptake but a lesion detected by CT.

**Performance analysis**

The results of each scintigraphy were evaluated for every patient with reference to the surgical and pathological results as the gold standard. The scintigraphy results were classified as true positive when a detected focus corresponded to an abnormal parathyroid gland, false positive if a detected focus did not correspond to an abnormal parathyroid gland, or false negative if an area considered as normal on scintigraphy corresponded to a hyperfunctioning parathyroid gland. We calculated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of each modality on a per-patient basis.

**Statistical analysis**

Data were analyzed using SPSS Statistics for Windows, Version 17.0 (SPSS Inc., Chicago, IL, USA) and 95% confidence intervals (CIs) were calculated. The sensitivity, specificity, PPV, NPV, and Youden’s index were calculated statistically for each scintigraphic method, according to the pathological results. Data were analyzed using $t$-tests and $\chi^2$ tests. A value of $P<0.05$ means indicated a significant difference.

**Results**

The 268 cases included 81 men and 187 women, aged 32 to 73 years (median age, 49 years), with a mean preoperative serum PTH level of 155.4±58.8 pg/mL (range, 85–368 pg/mL; reference level, 16–65 pg/mL) (Table 1). Among these patients, 168 had parathyroid adenomas, 21 had parathyroid hyperplasia, seven had parathyroid carcinoma, and the others had pathologically normal parathyroid glands. The mean
weight of the lesions was 260.5 ± 76.6 mg. Serum PTH levels decreased in all patients at day 1 postoperatively.

The PPV and NPV of $^{99m}$Tc-MIBI SPECT/CT scintigraphy for detecting a hyperfunctioning parathyroid were 92.0% and 71.3%, respectively, and its sensitivity, specificity, and accuracy were 88.3%, 79.2%, and 85.8%, respectively. However, the diagnosis for 35 patients based on these scintigraphy results (35/268, 13.1%) was significantly changed ($P = 0.03$) after accounting for the $^{99m}$TcO$_4^-$ scintigraphy results; the results for 18 patients changed from negative to positive, while the results for the other 17 changed from positive to negative. The PPV and NPV of dual-tracer scintigraphy were thus 96.3% and 82.3%, respectively, and the sensitivity, specificity, and accuracy were 92.9%, 90.3%, and 92.2%, respectively. The specificity of dual-tracer scintigraphy was significantly higher than that of $^{99m}$Tc-MIBI SPECT/CT ($P = 0.03$). Youden’s index (YI) for dual-tracer scintigraphy was 0.83, compared with 0.63 for $^{99m}$Tc-MIBI SPECT/CT (Table 2).

The addition of $^{99m}$TcO$_4^-$ imaging could clearly detect hyperparathyroidism in patients with focally increased $^{99m}$Tc-MIBI uptake on early-phase scans but no retention on delayed imaging, suggesting a negative result, as shown in Figures 1 and 2. Similarly, cases with distinct early-phase focal $^{99m}$Tc-MIBI uptake with early washout, suggestive of thyroid adenomas, were considered to be parathyroid adenomas if clear photopenic areas were detected simultaneously on $^{99m}$TcO$_4^-$ scans. Furthermore, if $^{99m}$Tc-MIBI uptake is focally increased at the periphery of the gland, despite washout or not on delayed imaging, $^{99m}$TcO$_4^-$ imaging may help to confirm or deny the diagnosis if it lacks a contour or peripheral focus (Figures 3 and 4).

We also calculated the 95% CIs for the sensitivity, specificity, and accuracy of each modality, and showed that dual-tracer scintigraphy was superior to dual-phase

---

**Table 1.** Characteristics of patients with PHPT.

| Parameter                              | Value       |
|----------------------------------------|-------------|
| Median age (year)                      | 49          |
| Sex (n=268)                            |             |
| Male                                   | 30.2% (n=81) |
| Female                                 | 69.8% (n=187) |
| Course of disease (month)              | 31.3 ± 27.1 |
| Clinical manifestation                 |             |
| Stone                                  | 45.1% (n=121) |
| Gastrointestinal discomfort            | 34.0% (n=91) |
| Bone pain                              | 33.2% (n=89) |
| Hematuria                              | 32.5% (n=87) |
| Hypertension                           | 20.0% (n=53) |
| Height loss                            | 9.7% (n=26)  |
| Fracture                               | 5.2% (n=14)  |
| Other                                  | 28.4% (n=76) |
| Preoperative PTH serum level (ng/L)    | 155.4 ± 58.8 |

**Table 2.** Accuracies of $^{99m}$Tc-MIBI imaging and dual-tracer imaging.

| Technique                  | Surgical finding | Sensitivity, % | Specificity, % | Accuracy, % | YI |
|----------------------------|------------------|----------------|----------------|-------------|----|
| $^{99m}$Tc-MIBI SPECT/CT    | +                | 173            | 88.3           | 79.2        | 85.8 | 0.68 |
|                            | −                | 23             | 7              | 57          |     |     |
| Dual-tracer scintigraphy   | +                | 182            | 92.9           | 90.3        | 92.2 | 0.83 |
|                            | −                | 14             | 7              | 65          |     |     |
| P value                    |                  | 0.10           | 0.03           | 0.15        |     |     |

YI: Youden’s Index
SPECT/CT, as indicated by higher Wilson’s 95% CI for sensitivity and accuracy, with little overlap (Table 3). Furthermore, dual-tracer scintigraphy detected ectopic parathyroid tissue in 30 patients without the need for further examination.

**Discussion**

Previous studies have reported wide variations of 55% to 90% in the sensitivity of $^{99m}$Tc-MIBI dual-phase scintigraphy for detecting a hyperfunctioning parathyroid,\textsuperscript{3,15–17} while other studies showed that dual-tracer scintigraphy could obviously increase the sensitivity and accuracy. The addition of a second radiopharmaceutical would improve the role of the $^{99m}$Tc-MIBI scintigraphy and enhance the information provided by SPECT/CT. Moreover, dual-tracer parathyroid scintigraphy can play a critical role in the detection and localization of parathyroid adenomas, particularly in cases in which $^{99m}$Tc-MIBI is washed out of the parathyroid rapidly but remains in thyroid adenomas and lymph nodes.\textsuperscript{18}

---

**Figure 1.** (a) $^{99m}$TcO$_4$ imaging showing focal photopenia on left upper thyroid lobe. (b) Dual-phase $^{99m}$Tc-MIBI imaging indicates increased radioactivity in the left upper lobe on early-phase imaging, retained slightly on delayed imaging. Dual-phase $^{99m}$Tc-MIBI imaging alone suggests negative results, but hyperparathyroidism would be considered based on the combined imaging results.
Furthermore, dual-tracer scintigraphy can also be used to exclude ectopic parathyroid tissue, as well as differentiating between parathyroid adenomas and other neck pathologies by second-radiopharmaceutical scintigraphy.

Although dual-tracer scintigraphy may increase radiation exposure, it may also simplify the preoperative evaluation in many patients with PHPT. Furthermore, dual-tracer scintigraphy may provide a precise preoperative localization, thus greatly increasing the confidence of the interpretation and decreasing operation time. The current study showed that dual-tracer scintigraphy was superior to dual-phase SPECT/CT, and the overall accuracy of dual-tracer scintigraphy in this study was 92.2%. Dual-tracer scintigraphy provided immediate and tangible patient benefits, because the additional $^{99m}$TcO$_4^-$ scintigraphy allowed the results to be reinterpreted and any additional pathologies requiring workup to be detected. These results thus provide theoretical support for the importance of dual-tracer scintigraphy of the parathyroid in terms of limiting both false-positive and false-negative results, as indicated by the changed diagnoses in 35 patients after taking account of the results of $^{99m}$TcO$_4^-$ scintigraphy.

From a practical point of view, the fusion of the two radiopharmaceutical-based

Figure 2. $^{99m}$Tc-MIBI SPECT/CT imaging. Radioactivity was slightly increased at the red mark, suggesting a hyperfunctioning parathyroid gland. Postsurgical histology revealed a hyperplastic parathyroid gland (0.15 g) corresponding to the focus. Serum PTH levels decreased from 136 pg/mL preoperatively to 26 pg/mL on the day after surgery.
images can be managed easily by surgeons familiar with multimodal image fusion, such as SPECT/CT and diagnostic CT. Furthermore, the improved accuracy of dual-tracer SPECT/CT imaging provides the clinical team with extra confidence in the diagnostic results, and with the detailed anatomical information necessary to carry out minimally invasive surgery. In addition, this technique allows any unusual anatomy or unusual placement of the parathyroid tissue to be visualized.18

The use of dual-tracer scintigraphy can improve clinical patient management in several situations,19–21 including in cases where $^{99m}$Tc-MIBI uptake is focally increased on early-phase scans but shows no retention on delayed imaging, cases with distinct early-phase focal $^{99m}$Tc-MIBI uptake with early washout, and in the event of focally increased $^{99m}$Tc-MIBI uptake at the periphery of the gland, with or without washout on delayed imaging. In these cases, dual-phase $^{99m}$Tc-MIBI dual-phase imaging alone may suggest a negative result, while the addition of $^{99m}$TcO$_4^-$ could clearly identify hyperparathyroidism. Characteristically increased focal $^{99m}$Tc-MIBI uptake and

Figure 3. (a) $^{99m}$TcO$_4^-$ imaging showing normal radioactivity in both thyroid glands. (b) Dual-phase $^{99m}$Tc-MIBI imaging showing increased radioactivity in the lower extremity of the right lobe, suggesting hyperthyroidism.
delayed retention are generally considered to indicate a typical parathyroid adenoma, but a thyroid lesion, typically a thyroid adenoma, should be considered in the event of corresponding strong $^{99m}$TcO$_4$ uptake. The main factor limiting the specificity of dual-tracer imaging is the presence of an underlying thyroid disease, such as Hashimoto’s thyroid disease or multinodular goiter. However, some true-positive patients also had evidence of underlying thyroid disease, and both thyroid and parathyroid diseases were found in the pathological assessments.

**Figure 4.** $^{99m}$Tc-MIBI SPECT/CT imaging. Uniform density, clear boundary, and increased radioactivity at the red mark suggested a hyperfunctioning parathyroid gland. A parathyroid adenoma (0.34 g) corresponding to the focus was found by pathology. Serum PTH levels decreased from 312 pg/mL preoperatively to 37 pg/mL on the day after surgery.

**Table 3.** Sensitivity, specificity, PPV, NPV, and accuracy for each modality, with Wilson’s 95% confidence intervals.

| Parameter | $^{99m}$Tc-MIBI SPECT/CT | Dual-tracer scintigraphy |
|-----------|--------------------------|--------------------------|
| Sensitivity | 0.883 (0.83–0.92) | 0.929 (0.88–0.96) |
| Specificity | 0.792 (0.68–0.87) | 0.903 (0.81–0.95) |
| PPV | 0.920 (0.87–0.95) | 0.963 (0.93–0.98) |
| NPV | 0.713 (0.61–0.80) | 0.823 (0.72–0.89) |
| Accuracy | 0.858 (0.81–0.89) | 0.922 (0.88–0.95) |

PPV: positive predictive value, NPV: negative predictive value.
of these cases. Moreover, our study suggested that dual-tracer SPECT/CT imaging could significantly reduce the impact of underlying thyroid disease on the diagnostic performance.

In conclusion, dual-phase $^{99m}$Tc-MIBI scintigraphy may produce false-positive results in patients with thyroid disease, while the addition of $^{99m}$TcO$_4$ imaging and CT information can increase awareness of thyroid issues. These findings suggest that $^{99m}$TcO$_4$ and $^{99m}$Tc-MIBI dual-tracer scintigraphy is more accurate for detecting parathyroid adenomas than other scintigraphy methods, and may be the most suitable imaging technique in patients with primary hyperparathyroidism.

**Declaration of conflicting interest**

The authors declare that there is no conflict of interest.

**Funding**

This study was funded by the Health and Family Planning Commission of Zhejiang Province, China (No.: 2015KYB220).

**References**

1. Sandqvist P, Nilsson IL, Grybäck P, et al. SPECT/CT’s advantage for preoperative localization of small parathyroid adenomas in primary hyperparathyroidism. *Clin Nucl Med* 2017; 42: e109–e114.
2. Udelsman R, Lin Z and Donovan P. The superiority of minimally invasive parathyroidectomy based on 1650 consecutive patients with primary hyperparathyroidism. *Am Surg* 2011; 253: 585–591.
3. Erbil Y, Barbaros U, Yanik BT, et al. Impact of gland morphology and concomitant thyroid nodules on preoperative localization of parathyroid adenomas. *Laryngoscope* 2006; 116: 580–585.
4. Bénard F, Lefebvre B, Beuvon F, et al. Rapid washout of technetium-$^{99m}$MIBI from a large parathyroid adenoma. *J Nucl Med* 1995; 36: 241–243.
5. Calendini-Viallet C, Rinaldi JP, Bussy E, et al. Parathyroid adenomas with rapid washout: two case reports. *Med Nucl* 1997; 21: 439–443.
6. Krausz Y, Shiloni E, Bocher M, et al. Diagnostic dilemmas in parathyroid scintigraphy. *Clin Nucl Med* 2001; 26: 997–1001.
7. Taillefer R, Boucher Y, Potvin C, et al. Detection and localization of parathyroid adenomas in patients with hyperparathyroidism using a single radionuclide imaging procedure with technetium-$^{99m}$-sestamibi (double-phase study). *J Nucl Med* 1992; 33: 1801–1807.
8. Rauth JD, Sessions RB, Shupe SC, et al. Comparison of Tc-$^{99m}$ MIBI and Tl-201/Tc-$^{99m}$ pertechnetate for diagnosis of primary parahyperthyroidism. *Clin Nucl Med* 1996; 21: 602–608.
9. Peeler BB, Martin WH, Sandler MP, et al. Sestamibi parathyroid scanning and preoperative localization studies for patients with recurrent/persistent hyperparathyroidism of significant comorbid conditions: development of an optimal localization strategy. *Am Surg* 1997; 63: 37–46.
10. Wakamatsu H, Noguchi S, Yamashita H, et al. Technitium-$^{99m}$ tetrofosmin for parathyroid scintigraphy: a direct comparison with $^{99m}$Tc-MIBI, $^{201}$Tl, MRI and US. *Eur J Nucl Med* 2001; 28: 1817–1827.
11. Ralph V. Clayman. Technetium-$^{99m}$ sestamibi scintigraphy and helical CT together in patients with primary hyperparathyroidism: a prospective clinical study. *Br J Radiol* 2004; 77: 100–103.
12. Huber GF, Hüllner M, Schmid C, et al. Benefit of $^{18}$F-fluorocholine PET imaging in parathyroid surgery. *Eur Radiol* 2018; 28: 2700–2707.
13. Michaud L, Burgess A, Huchet V, et al. Is $^{18}$F-fluorocholine PET/CT a new imaging tool for detecting hyperfunctioning parathyroid glands in primary or secondary hyperparathyroidism? *J Clin Endocrinol Metab* 2014; 99: 4531–4536.
14. Rep S, Hocevar M, Vaupotič J, et al. $^{18}$F-choline PET/CT for parathyroid scintigraphy significantly lower radiation exposure of patients in comparison to conventional
nuclear medicine imaging approaches. *J Radiol Prot* 2018; 38: 343–356.

15. Neumann DR, Esselstyn CB Jr, Kim EY, et al. Preliminary experience with double-phase SPECT using Tc-99m sestamibi in patients with hyperparathyroidism. *Clin Nucl Med* 1997; 22: 217–221.

16. Neumann DR, Esselstyn CB Jr, Go RT, et al. Comparison of double-phase 99mTc-sestamibi with 123I-99mTc-sestamibi subtraction SPECT in hyperparathyroidism. *Am J Roentgenol* 1997; 169: 1671–1674.

17. Hassler S, Ben-Selle D, Hubele F, et al. Dual-isotope 99mTc-MIBI/99mTcO4− parathyroid scintigraphy in primary hyperparathyroidism comparison of subtraction SPECT/CT and pinhole planar scan. *Clin Nucl Med* 2014; 39: 32–36.

18. Korsten A, van Os K, Willie J, et al. The value of parathyroid I-123/Tc-99m subtraction SPECT/CT in primary hyperparathyroidism. *J Nucl Med* 2014; 55: 477.

19. Hindié E, Mellière D, Jeanguillaume C, et al. Parathyroid imaging using simultaneous double-window recording of technetium-99m-sestamibi and iodine-123. *J Nucl Med* 1998; 39: 1100–1105.

20. Leslie WD, Dupont JO, Bybel B, et al. Parathyroid 99mTc-sestamibi scintigraphy: dual-tracer subtraction is superior to double phase washout. *Eur J Nucl Med* 2002; 29: 1566–1570.

21. Wakamatsu H, Noguchi S, Yamashita H, et al. Parathyroid scintigraphy with 99mTc-MIBI and 123I subtraction: a comparison with magnetic resonance imaging and ultrasonography. *Nucl Med Commun* 2003; 24: 755–762.

22. Dennis JL. *The use of single photon emission computed tomography in the investigation of parathyroid and thyroid disorders*. PhD thesis, University of Glasgow, UK, 2011.

23. Sang HH, Rhee Y, Yun M, et al. Usefulness of SPECT/CT in parathyroid lesion detection in patients with thyroid parenchymal 99mTc-sestamibi retention. *Nucl Med Mol Imaging* 2017; 51: 32–39.