

Prognostic Value of 99m Tc-Sestamibi Parathyroid Scintigraphy in Predicting Future Surgical Eligibility in Patients With Asymptomatic Primary Hyperparathyroidism

Zhaotong Cheng, MD, Sijuan Zou, MD, Dan Peng, MD,
Guopeng Zhang, MD, PhD, and Xiaohua Zhu, MD, PhD

Purpose: Patients with asymptomatic primary hyperparathyroidism might have a positive 99m Tc-sestamibi parathyroid but do not meet criteria for surgical resection when the disease is diagnosed. However, many of these asymptomatic patients will become symptomatic or meet criteria for surgery later on. The aim of this study was to determine whether a positive sestamibi scan can precede future surgical eligibility in these patients.

Methods: This retrospective study reviewed the records of 94 asymptomatic patients who had hyperparathyroidism and underwent 99m Tc-sestamibi study with SPECT/CT imaging. Among them, 35 patients, including 12 with positive and 23 with negative sestamibi parathyroid scan, did not meet the criteria for surgery at the time of imaging, and follow-up record for at least 1 year was assessed on these patients. The imaging findings and the eligibility for surgery at the end of the follow-up were compared.

Results: With a median follow-up of 2.4 years (range, 1–4 years), among all 35 patients who were initially not eligible for surgery, 6 of 12 patients with a positive sestamibi scan became eligible for surgery, whereas 20 of 23 patients with negative scans remained ineligible for surgery.

Conclusions: Positive parathyroid SPECT/CT predicted a higher possibility of meeting surgical criteria over time in asymptomatic hyperparathyroidism patients who are not surgery eligible at the time of presentation.

Key Words: asymptomatic primary hyperparathyroidism, SPECT/CT, surgical criteria

(*Clin Nucl Med* 2017;00: 00–00)

Different from decades ago when patients with hyperparathyroidism often presented with debilitating symptoms, in recent years, most patients with primary hyperparathyroidism are asymptomatic and are usually discovered by incidental findings of elevated serum parathyroid hormone (PTH) and calcium levels¹ when other diseases are being evaluated. However, the disease has tendency to

become symptomatic over time. Because an overwhelming majority of primary hyperparathyroidism cases are caused by a parathyroid adenoma, surgery is the treatment of choice for all cases of symptomatic primary hyperparathyroidism.² However, the best way of management for patients with asymptomatic primary hyperparathyroidism remains debatable,^{3–6} but surgery is also strongly considered in these asymptomatic patients.⁷ Currently, the guidelines³ for surgical criteria of the asymptomatic hyperparathyroidism include serum calcium greater than 0.25 mmol/L above the upper limit of the normal; bone mineral density (BMD) by dual-energy x-ray absorptiometry *T* score of less than –2.5 or vertebral fracture; creatinine clearance of less than 60 mL/min, 24-hour urine calcium greater than 400 mg/d, and presence of nephrolithiasis or nephrocalcinosis; and age of younger than 50 years. For patients who did not undergo parathyroidectomy, the guidelines for monitoring asymptomatic patients include measurement of serum calcium concentration, and assessment of the skeleton and renal systems annually evaluates whether parathyroidectomy is needed.

99m Tc-sestamibi scintigraphy has been widely used as an imaging tool for preoperative localization of primary hyperparathyroidism.^{8–12} For asymptomatic primary hyperparathyroidism patients, almost all the clinical parameters have significant correlations with the positivity of 99m Tc-MIBI scans.¹³ We hypothesized that in patients with asymptomatic primary hyperparathyroidism a positive 99m Tc-MIBI SPECT/CT might precede the surgical eligibility in some patients.

SUBJECTS AND METHODS

Patients

This retrospective study was approved by our institutional review board with a waiver of patient's consent. From December 2012 to December 2015, we reviewed all patients with asymptomatic primary hyperparathyroidism presented in our department for 99m Tc sestamibi scan. All patients had biochemically confirmed profile of hyperparathyroidism without any related symptoms. Patients were excluded if they had familial hyperparathyroidism, vitamin D insufficiency, or renal or skeleton diseases; were taking calcium-lowering medications; or became menopausal during the follow-up period. A total of 94 patients (66 women and 28 men; mean age, 59.7 ± 8.6 years [range, 36–77 years]) were included in the final analysis (Fig. 1). The surgical criteria of asymptomatic primary hyperparathyroidism were based on previously published guideline.³ Those asymptomatic patients who did not meet surgical criteria were followed up annually (up to 4 years post-sestamibi parathyroid scintigraphy). Those who developed at least 1 surgical criterion during follow-up were designated as being eligible for surgery.

Received for publication November 11, 2017; revision accepted November 17, 2017. From the Department of Nuclear Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

Conflicts of interest and sources of funding: This work was supported by the National Science Foundation of China (no. 81271600 and no. 81671718), the National Science Foundation of Hubei Province in China (no. 2011CDB551 and no. 2016CFB687), the Independent Innovation Foundation of Huazhong University of Science and Technology (no. 2011JC060), and the Clinical Foundation of Tongji Hospital (no. 2201102135). None declared to all authors. All procedures performed in the studies involving human participants were in accordance with the ethical standards of Tongji Hospital and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Correspondence to: Xiaohua Zhu, MD, PhD, Department of Nuclear Medicine, Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China. E-mail: evazhu@vip.sina.com.

Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

ISSN: 0363-9762/17/0000–0000

DOI: 10.1097/RNU.0000000000001941

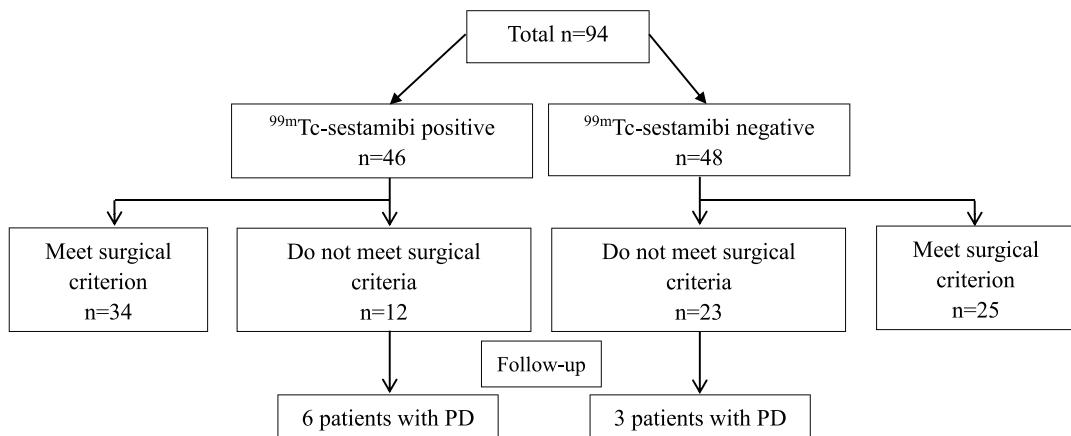


FIGURE 1. Flowchart of the 94 patients with asymptomatic primary hyperparathyroidism.

Laboratory Data Collection

The clinical data of both groups were collected: serum PTH, serum calcium, 24-hour urine calcium, BMD by dual-energy x-ray absorptiometry at lumbar spine, total hip, femoral neck or distal one-third radius (the lowest *T* score was recorded), vertebral fracture by x-ray, estimated glomerular filtration rate (eGFR), and nephrolithiasis by ultrasound.

Image Acquisition and Analysis

All patients underwent dual-phase ^{99m}Tc-sestamibi parathyroid scintigraphy protocol according to the 2009 EANM parathyroid guidelines.¹⁴ A parathyroid SPECT/CT was performed immediately after early-phase planar scintigraphy. If a focally increased uptake in the region of the parathyroid or the mediastinum was shown on

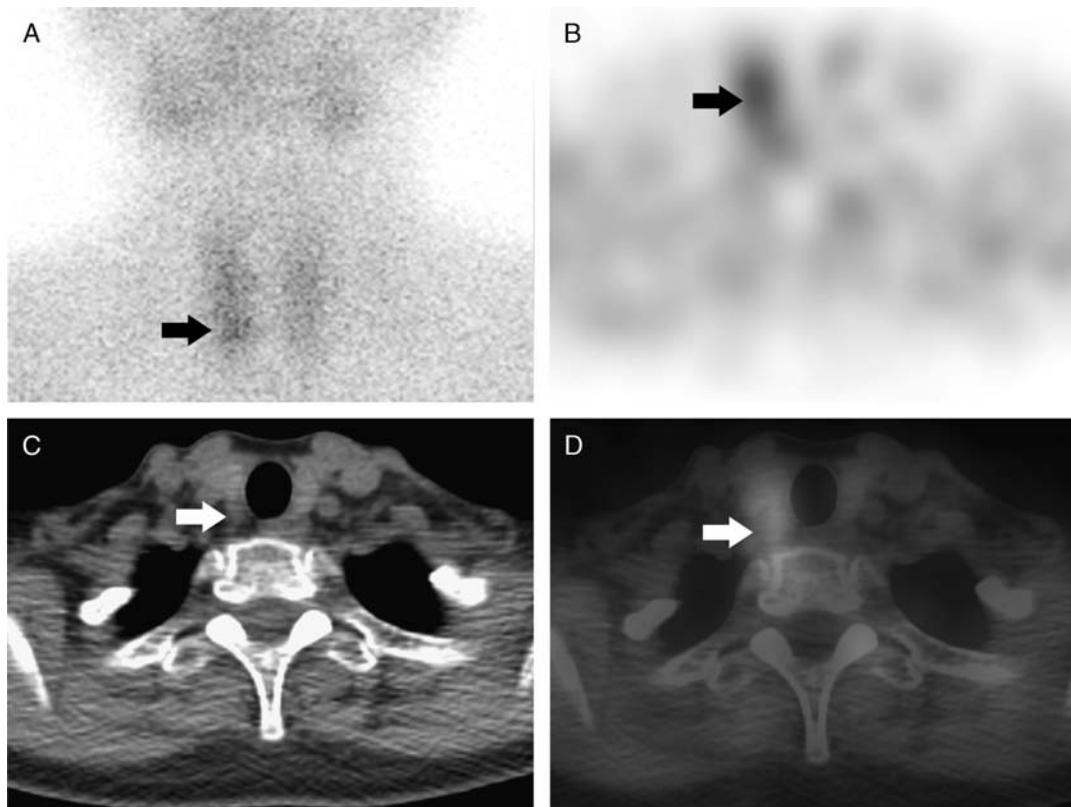


FIGURE 2. A 64-year-old woman with asymptomatic hyperparathyroidism (PTH, 185 pg/mL; serum calcium, 2.69 mmol/L) did not meet any surgical criterion initially. ^{99m}Tc-sestamibi study (A: early-phase planar image; B: axial CT; C: SPECT; D: fusion) showed a mildly increased focal uptake posterior to the right lower pole of the thyroid and a nodule in corresponding area on CT (arrows). Two years after the positive sestamibi study, surgical criterion was met because her serum calcium reached 2.85 mmol/L (>0.25 mmol/L above the upper limit of normal). Pathological examination postparathyroidectomy confirmed parathyroid adenoma.

TABLE 1. Baseline Characteristics of Laboratory Data in Patients With Asymptomatic Hyperparathyroidism

Variables	Sestamibi Scan Positive	Sestamibi Scan Negative	P	Reference Range
No. patients	46	48	—	—
Age, y	60.46 ± 9.34	58.98 ± 7.81	NS	—
Serum calcium, mmol/L	2.75 ± 0.08	2.71 ± 0.08	0.007*	2.25 to 2.55
PTH, pg/mL	259.41 ± 44.29	240.77 ± 50.11	NS	10 to 65
24-h Urine calcium, mmol/24 h	8.46 ± 1.07	7.81 ± 0.91	0.002*	2.5 to 7.5
eGFR, mL/min per 1.73 m ²	88.17 ± 12.40	95.23 ± 11.09	0.005*	80 to 120
BMD T score	-0.98 ± 0.93	-0.48 ± 1.09	0.018*	-1.0 to 1.0
No. patients who met the surgical criteria	34	25	0.029*	—

Values are mean ± SD.

*Statistically significant ($P < 0.05$).

NS indicates not statistically significant.

early-phase SPECT images regardless whether there was persistent uptake on the delayed images, it was reported as positive scan (Fig. 2).

RESULTS

Baseline Characteristics

Figure 1 presents a flowchart of all the 94 patients. Among these patients, there were 46 positive sestamibi parathyroid scans, whereas the other 48 scans were negative. Based on image findings, 45 patients with positive scan result had single orthotopic parathyroid lesion, whereas 2 patients had multiple parathyroid lesions, and 1 patient had single ectopic mediastinal parathyroid lesion. Among all the 94 patients, 59 patients including 34 with positive scan and 25 with negative scan met the surgical criteria, and 57.6% (34/59) of them showed positive scan (Fig. 1). The percentage of patients who were surgery eligible was significantly higher ($P < 0.05$) in those with positive scan (73.9% [34/46]) than in those with negative scan (52.1% [25/48]). The average levels of serum calcium and 24-hour urine calcium in patients with positive scan are higher than in those with negative scan, whereas the patients with positive scan had an average lower eGFR and BMD T scores than did those with a negative scan ($P < 0.05$) (Table 1).

Follow-up Study

The follow-up records (period ranged from 1 to 4 years; median, 2.4 years) in 35 patients who did not meet any surgical criteria initially were available for review. These included 12 patients with positive sestamibi scan and 23 patients with negative

sestamibi scans (Table 2). There was a significantly higher chance ($P < 0.05$, χ^2 test) of becoming surgery eligible (50% [6/12]) in patients who had a positive sestamibi parathyroid scan at the initial evaluation than in those with a negative scan (13% [3/23]). In patients with a positive scan, the average serum PTH and serum calcium levels were significantly higher at the end of follow-up than at baseline ($P < 0.05$), whereas the 24-hour urine calcium levels, eGFR, and BMD T score remained stable. However, in those patients with a negative sestamibi parathyroid scan, all laboratory parameters remained relatively stable during follow-up.

DISCUSSION

According to the 2014 guidelines,³ for patients with asymptomatic hyperparathyroidism but who do not undergo parathyroid surgery, close monitoring is indicated. In a previous study that had a follow-up of 15 years, up to 37% of the previously asymptomatic, non-surgery-eligible patients would meet surgery criteria during the follow-up.¹⁵ In our investigation, 25.7% of patients (9/35) who were initially not surgery candidates became surgery eligible during a median of 2.4 years' follow-up. The difference in the incidence between our result and previous publication is most likely due to much shorter follow-up period in our investigation. Based on our findings, patients with asymptomatic hyperparathyroidism but not eligible for surgery initially are more likely to become eligible for surgery if they have a positive sestamibi parathyroid scintigraphy at the initial evaluation. In contrast, those who had a negative sestamibi parathyroid scintigraphy at the initial presentation will

TABLE 2. Follow-up of Asymptomatic Primary Hyperparathyroid Patients Without Parathyroidectomy (average ± SD)

Variable	Positive Sestamibi Scan (n = 12)			Negative Sestamibi Scan (n = 23)		
	Baseline	End of Follow-up	P	Baseline	End of Follow-up	P
Serum calcium, mmol/L	2.71 ± 0.05	2.74 ± 0.07	0.013*	2.67 ± 0.06	2.67 ± 0.07	NS
PTH, pg/mL	240.00 ± 29.95	265.67 ± 26.06	0.048*	242.09 ± 21.45	243.78 ± 23.73	NS
24-h Urine calcium, mmol/24 h	8.17 ± 0.71	8.31 ± 1.04	NS	7.54 ± 0.78	7.55 ± 0.92	NS
eGFR, mL/min per 1.73 m ²	91.83 ± 7.18	91.25 ± 6.17	NS	95.52 ± 6.94	92.22 ± 7.87	NS
BMD T score	-0.57 ± 0.63	-0.64 ± 0.78	NS	-0.26 ± 0.75	-0.30 ± 0.79	NS
No. patients becoming surgery eligible at the end of follow-up	—	6 (50%)	—	—	3 (13%)	—

*Statistically significant ($P < 0.05$).

NS indicates not statistically significant.

have much smaller chance of becoming surgery eligible during the follow-up.

CONCLUSIONS

Asymptomatic hyperparathyroidism patients with positive sestamibi parathyroid scan but who do not meet surgical criteria initially are much more likely to become surgery eligible over time compared with those with initial negative sestamibi study.

ACKNOWLEDGMENTS

The authors thank Dr Yang Lu (Division of Diagnostic Imaging, Department of Nuclear Medicine, University of Texas MD Anderson Cancer Center, Houston, Tex) for his helpful comments and suggestions on this study.

REFERENCES

1. AACE/AAES Task Force on Primary Hyperparathyroidism. The American Association of Clinical Endocrinologists and the American Association of Endocrine Surgeons position statement on the diagnosis and management of primary hyperparathyroidism. *Endocr Pract.* 2005;11:49–54.
2. Wilhelm SM, Wang TS, Ruan DT, et al. The American Association of Endocrine Surgeons guidelines for definitive management of primary hyperparathyroidism. *JAMA Surg.* 2016;151:959–968.
3. Bilezikian JP, Brandi ML, Eastell R, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. *J Clin Endocrinol Metab.* 2014;99:3561–3569.
4. Udelsman R, Pasieka JL, Sturgeon C, et al. Surgery for asymptomatic primary hyperparathyroidism: proceedings of the third international workshop. *J Clin Endocrinol Metab.* 2009;94:366–372.
5. Udelsman R, Akerstrom G, Biagini C, et al. The surgical management of asymptomatic primary hyperparathyroidism: proceedings of the fourth international workshop. *J Clin Endocrinol Metab.* 2014;99:3595–3606.
6. Minisola S, Cipriani C, Diacinti D, et al. Imaging of the parathyroid glands in primary hyperparathyroidism. *Eur J Endocrinol.* 2016;174:D1–D8.
7. Dowthwaite SA, Young JE, Pasternak JD, et al. Surgical management of primary hyperparathyroidism. *J Clin Densitom.* 2013;16:48–53.
8. Sandqvist P, Nilsson IL, Gryback P, et al. SPECT/CT's advantage for preoperative localization of small parathyroid adenomas in primary hyperparathyroidism. *Clin Nucl Med.* 2017;42:e109–e114.
9. Krakauer M, Wieslander B, Myschetzky PS, et al. A prospective comparative study of parathyroid dual-phase scintigraphy, dual-isotope subtraction scintigraphy, 4D-CT, and ultrasonography in primary hyperparathyroidism. *Clin Nucl Med.* 2016;41:93–100.
10. Thanseer N, Bhadada SK, Sood A, et al. Comparative effectiveness of ultrasound, ^{99m}Tc-sestamibi, and ¹⁸F-fluorocholine PET/CT in detecting parathyroid adenomas in patients with primary hyperparathyroidism. *Clin Nucl Med.* 2017;42:e491–e497.
11. Judson BL, Shahar AR. Nuclear imaging and minimally invasive surgery in the management of hyperparathyroidism. *J Nucl Med.* 2008;49:1813–1818.
12. Yang QS, Wang CY, Wang BC. Dual-phase ^{99m}Tc-MIBI imaging findings in sporadic primary hyperplasia of parathyroid glands. *Clin Nucl Med.* 2015;40:423–426.
13. Ogo A, Sakaki Y, Saito R, et al. A pilot study to examine the management of asymptomatic hyperparathyroidism in Japanese patients in accordance with the guidelines for asymptomatic PHPT proposed at the third international workshop in 2008. *Intern Med.* 2014;53:1749–1754.
14. Hindié E, Ugur O, Fuster D, et al. 2009 EANM parathyroid guidelines. *Eur J Nucl Med Mol Imaging.* 2009;36:1201–1216.
15. Rubin MR, Bilezikian JP, McMahon DJ, et al. The natural history of primary hyperparathyroidism with or without parathyroid surgery after 15 years. *J Clin Endocrinol Metab.* 2008;93:3462–3470.