

# Prognostic Value of $^{99m}\text{Tc}$ -Sestamibi Parathyroid Scintigraphy in Predicting Future Surgical Eligibility in Patients With Asymptomatic Primary Hyperparathyroidism

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**Purpose:** Patients with asymptomatic primary hyperparathyroidism might have a positive  $^{99m}\text{Tc}$ -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  $^{99m}\text{Tc}$ -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

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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 levels<sup>1</sup> 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 asymptomatic primary hyperparathyroidism.<sup>2</sup> However, the best way of management for patients with asymptomatic primary hyperparathyroidism remains debatable,<sup>3–6</sup> but surgery is also strongly considered in these asymptomatic patients.<sup>7</sup> Currently, the guidelines<sup>3</sup> 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.

$^{99m}\text{Tc}$ -sestamibi scintigraphy has been widely used as an imaging tool for preoperative localization of primary hyperparathyroidism.<sup>8–12</sup> For asymptomatic primary hyperparathyroidism patients, almost all the clinical parameters have significant correlations with the positivity of  $^{99m}\text{Tc}$ -MIBI scans.<sup>13</sup> We hypothesized that in patients with asymptomatic primary hyperparathyroidism a positive  $^{99m}\text{Tc}$ -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  $^{99m}\text{Tc}$  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,  $59.7 \pm 8.6$  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.<sup>3</sup> 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.

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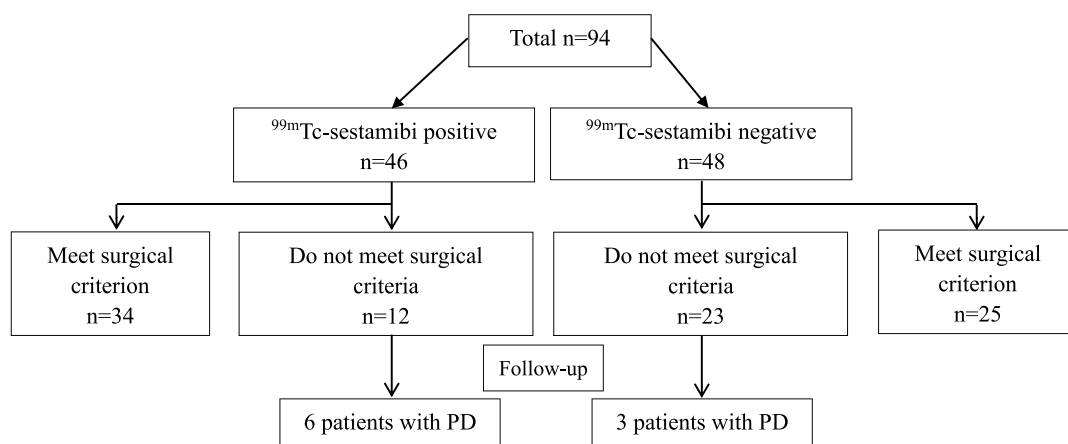
All procedures performed in the studies involving human participants were in accordance with the ethical standards of Tongji Hospital and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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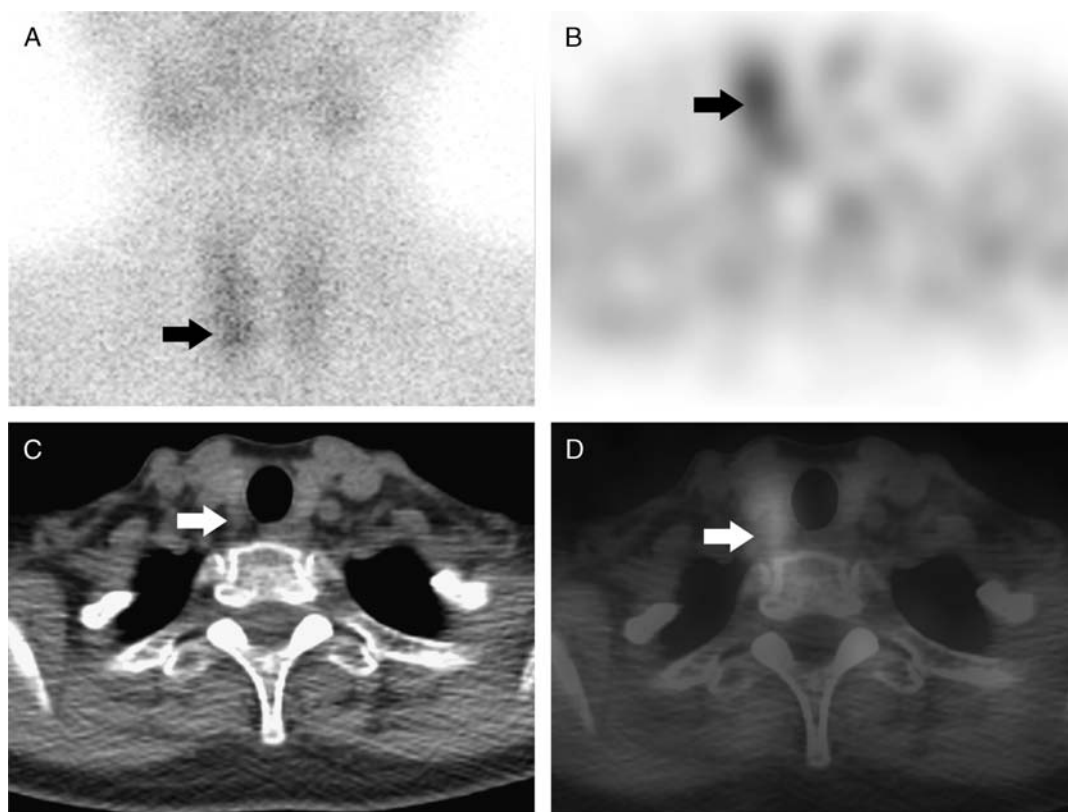
**FIGURE 1.** Flowchart of the 94 patients with asymptomatic primary hyperparathyroidism.

### 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  $^{99m}\text{Tc}$ -sestamibi parathyroid scintigraphy protocol according to the 2009 EANM parathyroid guidelines.<sup>14</sup> 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.  $^{99m}\text{Tc}$ -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	<i>P</i>	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 <sup>2</sup>	88.17 ± 12.40	95.23 ± 11.09	0.005*	80 to 120
BMD <i>T</i> 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 ( $P < 0.05$ ,  $\chi^2$  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,<sup>3</sup> 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.<sup>15</sup> 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	<i>P</i>	Baseline	End of Follow-up	<i>P</i>
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 <sup>2</sup>	91.83 ± 7.18	91.25 ± 6.17	NS	95.52 ± 6.94	92.22 ± 7.87	NS
BMD <i>T</i> 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.

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