

## Parathyroid Scintigraphy in Primary and Secondary Hyperparathyroidism: Accuracy of Preoperative Localisation Using Combined Imaging Techniques

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### ABSTRACT

**Objective:** To evaluate the accuracy of preoperative parathyroid scintigraphy for lesion localisation in primary and secondary hyperparathyroidism.

**Methods:** The archives of 3 regional Hong Kong hospitals extending over a 12-month period were retrospectively reviewed for parathyroid scintigraphies in subjects who underwent subsequent first-time parathyroidectomy. Scintigraphic techniques comprised early- and late-phase <sup>99m</sup>Tc-sestamibi planar imaging (100% of studies), emission computed tomography (97%), and supplementary <sup>99m</sup>Tc-pertechnetate thyroid imaging (13%). Images were re-interpreted by applying a scoring scale to different lesional locations. Accuracies were determined by operative and histological findings.

**Results:** This series was based on 19 patients with primary hyperparathyroidism (23 lesions) and 19 with secondary hyperparathyroidism associated with chronic renal failure (70 lesions). The frequencies of primary lesions in left upper, left lower, right upper, right lower, and ectopic positions were 13%, 30%, 9%, 44%, and 4% respectively; corresponding figures for secondary lesions were 24%, 24%, 26%, 23%, and 3%. The sensitivity, specificity, positive predictive, and negative predictive values of scintigraphy for locating primary lesions were 91%, 99%, 96%, and 97% respectively; and for secondary lesions corresponding figures were 74%, 84%, 93%, and 54%. The corresponding overall results for all lesions were 79%, 95%, 94%, and 82%.

**Conclusions:** Preoperative scintigraphy for localising hyperfunctioning parathyroids has a better accuracy in primary than secondary hyperparathyroidism (97% vs. 77%). Primary lesions have a preponderance for lower positions (74%) and may be subjected to scintigraphy-guided minimally invasive parathyroidectomy. The lower sensitivity (74%) and negative predictive value (54%) for secondary lesions render scintigraphy less helpful in secondary hyperparathyroidism, except on rare occasions to locate ectopic lesions.

**Key Words:** Hyperparathyroidism; Parathyroidectomy; Radionuclide Imaging; Sensitivity and Specificity; Technetium Tc 99m Sestamibi

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## 中文摘要

### 原發性及繼發性甲狀旁腺機能亢進症的核素顯像：使用綜合影像技術作術前定位檢查的準確度

譚曉東、黃月紅、張盛基、魏偉達、蔡柏達

**目的：**評估甲狀旁腺核素顯像對原發性及繼發性甲狀旁腺機能亢進症作術前病變定位檢查的準確程度。

**方法：**回顧香港三間地區醫院在12個月的研究期內首次進行甲狀旁腺切除的患者的核素顯像圖。核素顯像包括早期及晚期<sup>99m</sup>Tc-sestamibi平面成像術（100%），發射電腦斷層攝影術（97%），和補充性<sup>99m</sup>Tc-pertechnetate甲狀腺顯像術（13%）。利用評分表再次替不同病變位置的影像重新闡釋，然後對比手術結果及病理學結果來計算攝影術對病變定位的準確度。

**結果：**研究包括19名原發性甲狀旁腺機能亢進症患者（共23個病灶），另有19名並發慢性腎衰竭的繼發性甲狀旁腺機能亢進症患者（共70個病灶）。累及腺體的位置分為左上、左下、右上、右下和異位，原發性病變發生在這些位置的比率分別為13%、30%、9%、44%和4%，而繼發性病變發生在這些位置的比率分別為24%、24%、26%、23%和3%。核素顯像對原發性病變定位的敏感性、特異性、陽性預測率和陰性預測率分別為91%、99%、96%和97%；對於繼發性病變分別為74%、84%、93%和54%；總結果分別為79%、95%、94%和82%。

**結論：**對於甲狀旁腺機能亢進症的病變定位，術前核素顯像對原發性病變的準確度比繼發性的高（97%比77%）。大部分原發性病變出現在腺體下部的位（74%），可由核素顯像引導微創甲狀旁腺切除術進行治療。由於核素顯像對繼發性甲狀旁腺機能亢進症的敏感性（74%）和陰性預測率（54%）都偏低，對定位幫助不如原發性病變，但它偶爾也可對異位病變作定位。

## INTRODUCTION

Hyperparathyroidism is a common endocrine disorder characterised by increased production and secretion of parathyroid hormone. Primary hyperparathyroidism refers to an autonomous overproduction of the hormone; single adenomas are responsible for 80 to 90%, and multiple-gland disease (adenomas or hyperplasia) results in the remaining 10 to 20%, whilst carcinoma is very rarely the cause (about 1%).<sup>1</sup> Secondary hyperparathyroidism is a consequence of chronic hypocalcaemia, with renal failure being the most common cause. The state of hypocalcaemia activates a compensatory mechanism to stimulate all parathyroid tissues, thereby causing multiple-gland hyperplasia. In longstanding cases, one or more of the glands may turn autonomous, resulting in tertiary hyperparathyroidism.<sup>2</sup>

Parathyroid glands are generally 4 in number (range, 2 to 6), and subdivided into 2 upper and 2 lower glands. Their eutopic locations are posterior to the superior and inferior aspects of the 2 thyroid lobes. Based on embryology, ectopic parathyroid glands can be located

anywhere from the angle of mandible down to the mediastinum, and occasionally occur as intra-thymic or intra-thyroidal glands.<sup>3</sup>

Parathyroid surgery is warranted in virtually all symptomatic primary hyperparathyroidism. It is also beneficial in selected subjects with asymptomatic primary hyperparathyroidism and some renal patients with secondary (or tertiary) hyperparathyroidism refractory to medical therapy.<sup>4-6</sup> Conventional surgery entails a routine bilateral neck exploration. Since the great majority of primary hyperparathyroidism presents in patients with a single adenoma, the current trend is towards minimally invasive parathyroidectomy; the success of which relies entirely on precise preoperative localisation by imaging.<sup>7-9</sup> Contrarily, the minimally invasive approach is inappropriate for multiple-gland disease or secondary hyperparathyroidism in which case preoperative imaging becomes less essential, but it may help minimise the failure of conventional surgery after detection of unsuspected ectopic or supernumerary glands.<sup>10,11</sup>

Parathyroid scintigraphy is one of the most commonly employed imaging modalities. It is not useful for diagnosing or confirming hyperparathyroidism; rather, its role is to localise hyperfunctioning glands preoperatively in patients with a biochemically confirmed diagnosis. Although parathyroid scintigraphy has been in clinical use for more than 2 decades, precise imaging techniques and protocols remain diverse across different centres.<sup>12-14</sup> In the 1980s, the very first dual-tracer subtraction technique employed thallium-201 (<sup>201</sup>Tl-thallos chloride) and technetium-99m (<sup>99m</sup>Tc-sodium pertechnetate).<sup>15</sup> Thallium-201 has largely been supplanted by <sup>99m</sup>Tc-sestamibi since 1990s.<sup>16</sup> Nowadays, a dual-tracer protocol often employs <sup>99m</sup>Tc-sestamibi together with either <sup>99m</sup>Tc-pertechnetate or <sup>123</sup>I-iodide. Alternatively, the use of <sup>99m</sup>Tc-sestamibi alone (i.e. as a single-tracer) can adopt a dual-phase imaging protocol.<sup>17</sup> Moreover, there is a plethora of imaging techniques being practised, such as planar imaging in the anterior view, pinhole magnified imaging, additional oblique viewing, single-photon emission computed tomography (SPECT), and hybrid SPECT/computed tomography (CT).<sup>12</sup> These technical variations and various other factors have led to wide discrepancy in the accuracies of parathyroid scintigraphy in both local and international publications, with sensitivities reported to be below 30% to over 90%.<sup>1,12,18-22</sup>

The objective of this study was to evaluate the accuracy of preoperative parathyroid scintigraphy using a combination of imaging techniques, for the purpose of lesion localisation in primary and secondary hyperparathyroidism in a multicentre setting.

## METHODS

This retrospective study retrieved and searched the archival record of 153 <sup>99m</sup>Tc-sestamibi parathyroid scintigraphies from 3 large regional hospitals in Hong Kong (North District, Pamela Youde Nethersole Eastern, and Prince of Wales hospitals) over a 12-month period (1 January to 31 December 2007). All scintigraphies performed for first-time localisation of hyperfunctioning parathyroid glands with subsequent parathyroidectomy (by July 2009) were recruited. Demographic, clinical, and biochemical findings around the time of scintigraphy, and subsequent operative and histopathological findings were analysed. Recruited patients/scintigraphies were separated into 2 groups: primary hyperparathyroidism and secondary hyperparathyroidism.

The imaging protocols and techniques were reviewed. All patients received 555 to 740 MBq (15 to 20 mCi) <sup>99m</sup>Tc-sestamibi intravenously with no specific prior preparation. All scintigraphic images were acquired with either a single-head APEX 4HR, a dual-head Infinia SPECT, or an Infinia Hawkeye SPECT/CT system (GE Healthcare, Milwaukee, WI, USA), equipped with a low-energy high-resolution parallel-hole collimator. Early-phase and late-phase imaging commenced at 15 and 90 minutes, respectively, after the <sup>99m</sup>Tc-sestamibi administration. Each imaging phase comprised one static planar image of the neck and thorax in anterior view, and one magnified (2×) image of the thyroid bed. The image acquisition parameters were 600 seconds per view in 256×256 matrix size. Most patients had SPECT immediately following the early-phase planar imaging. All SPECTs were performed in a step-and-shoot mode, every 3 degrees over 360-degree orbit with body-contour adjustment, and 20 seconds per projection image in 128×128 matrix size. In selected patients, separate supplementary thyroid scintigraphies were performed by administering 74 to 185 MBq (2 to 5 mCi) <sup>99m</sup>Tc-pertechnetate intravenously, followed by similar planar imaging views, thus facilitating direct visual comparison with the set of <sup>99m</sup>Tc-sestamibi images.

All scintigraphies were pooled and uploaded onto Xeleris workstations (GE Healthcare). They were re-interpreted by 2 experienced nuclear medicine specialists blinded to the operative and histopathological results, and by whom consensus scores were given. A 5-point scoring scale was adopted: 1 = definitely negative, 2 = probably negative, 3 = equivocal, 4 = probably positive, 5 = definitely positive. The scale was applied on different anatomical locations of the parathyroid glands, which were categorised into 5 locations: LU = left upper, LL = left lower, RU = right upper, RL = right lower, EC = ectopic sites. This scheme was a simpler modification from other researchers' work using 13 locations for analyses.<sup>23</sup>

The variables in the 2 patient groups — primary hyperparathyroidism and secondary hyperparathyroidism — were statistically compared using chi-squared, Fisher's exact, or Student's *t* tests (SPSS version 15), as appropriate. The accuracy of scintigraphy was calculated on a lesion-by-lesion basis. The scores at each location were classified: 1 to 3 as negative findings, 4 and 5 as positive findings. Operative and histological results were the gold standards for determining the sensitivity, specificity,

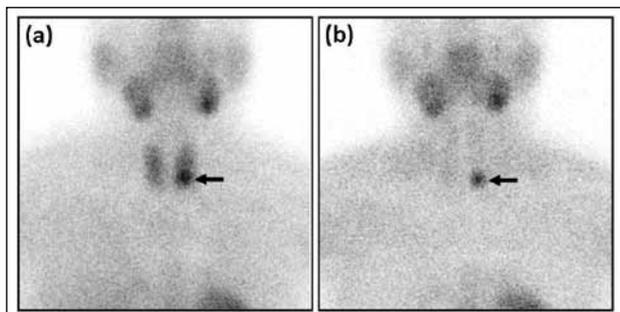
positive predictive value, negative predictive value, and accuracy of parathyroid scintigraphy.

## RESULTS

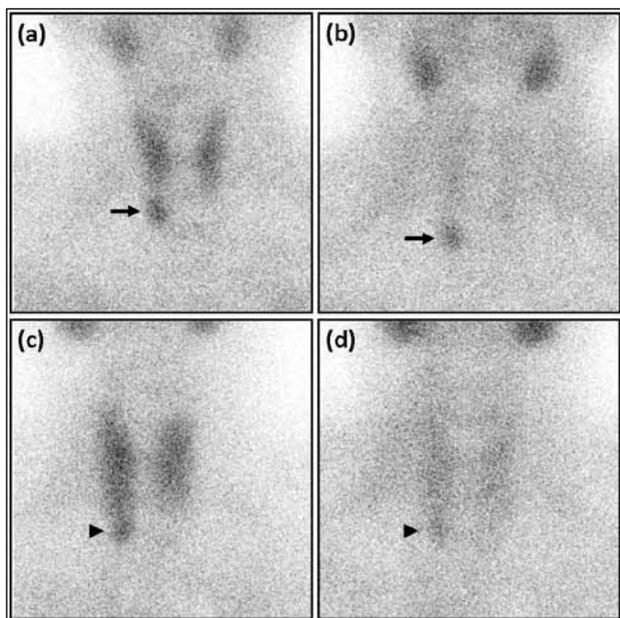
A total of 38 surgical patients, including 19 with primary hyperparathyroidism and 19 with secondary hyperparathyroidism, were recruited. All those with secondary hyperparathyroidism had end-stage renal

failure. There was a female predominance in patients with both primary (74%) and secondary (79%) hyperparathyroidism. The patients in the primary hyperparathyroidism group were older than those in the secondary hyperparathyroidism group (mean  $\pm$  standard deviation [SD]:  $56 \pm 13$  years vs.  $49 \pm 9$  years;  $p = 0.041$ ). Compared with patients with secondary hyperparathyroidism, those with primary hyperparathyroidism had a higher mean serum albumin-adjusted calcium level ( $2.72 \pm 0.15$  mmol/L vs.  $2.37 \pm 0.15$  mmol/L;  $p < 0.0005$ ), a lower mean serum phosphate level ( $0.89 \pm 0.17$  mmol/L vs.  $2.05 \pm 0.45$  mmol/L;  $p < 0.0005$ ), and a lower serum mean parathyroid hormone level ( $55 \pm 54$  pmol/L vs.  $479 \pm 739$  pmol/L;  $p = 0.022$ ).

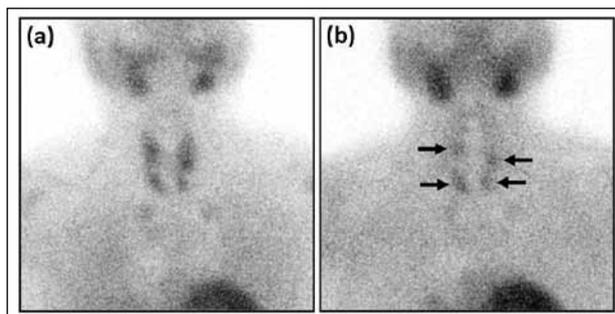
In the primary hyperparathyroidism group (Figures



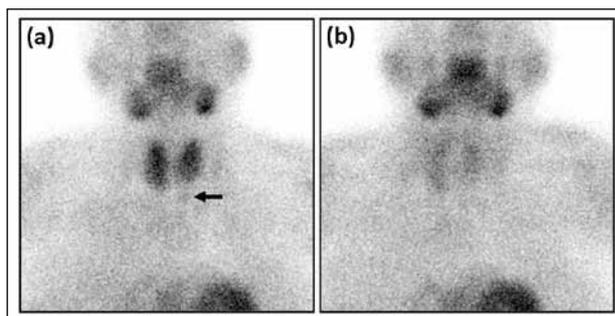
**Figure 1.**  $^{99m}\text{Tc}$ -sestamibi dual-phase images showing a single left lower parathyroid adenoma that turned out to be an ectopic intra-thyroidal gland. (a) Early-phase image shows tracer uptake by the thyroid gland and the parathyroid adenoma (arrow). (b) Late-phase image shows normal tracer washout from the thyroid but delayed washout from the adenoma (arrow).



**Figure 2.**  $^{99m}\text{Tc}$ -sestamibi dual-phase images from 2 different patients, each had a right lower parathyroid adenoma, but with different washout patterns. Patient A: (a) Early-phase image shows tracer uptake by a right lower parathyroid adenoma (arrow), (b) Late-phase image shows a delayed washout from the adenoma (arrow). Patient B: (c) Early-phase image shows uptake by another right lower parathyroid adenoma (arrowhead), (d) Late-phase image shows an early (or minimally delayed) washout from the adenoma (arrowhead).



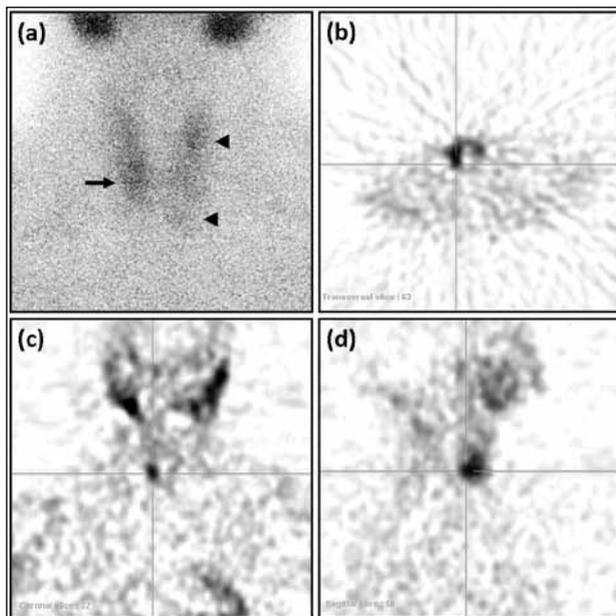
**Figure 3.**  $^{99m}\text{Tc}$ -sestamibi dual-phase images showing a 4-gland parathyroid hyperplasia. (a) Early-phase image shows tracer uptake by the thyroid and the parathyroids. (b) Late-phase image shows delayed tracer washout from all hyperplastic parathyroids (arrows).



**Figure 4.**  $^{99m}\text{Tc}$ -sestamibi scintigraphy from a patient with secondary hyperparathyroidism. (a) Early-phase planar image shows faint uptake by a left lower hyperplastic and ectopic parathyroid gland in the thyrothymic tract (arrow). Another right lower hyperplastic gland in eutopic location was also identified with the aid of single-photon emission computed tomographic images (not shown). (b) Late-phase planar image shows early tracer washout from the hyperplastic glands (thus not well visualised).

1 and 2), 17 patients had single adenoma, 1 had double adenomas, 1 had 4-gland hyperplasia. These 23 hyperfunctioning glands were located in the LU (13%), LL (30%), RU (9%), RL (44%), and in EC (4%) positions; their mean  $\pm$  SD weight was  $1134 \pm 1469$  mg. In the secondary hyperparathyroidism group (Figures 3 and 4), 70 hyperplastic glands were surgically identified and removed. They were distributed in the LU (24%), LL (24%), RU (26%), RL (23%) and in EC (3%) positions, and their mean  $\pm$  SD weight was  $624 \pm 489$  mg. There was a significant preponderance of primary lesions and adenomas in the lower positions (LL or RL, altogether 74%;  $p < 0.0005$ ). The difference in the weights between primary and secondary parathyroid lesions was statistically insignificant.

All patients having scintigraphies had had them for first-time localisation of hyperfunctioning parathyroid glands and underwent subsequent parathyroidectomy. Recourse to combined imaging techniques (dual-phase planar imaging [Figures 1-4], SPECT [Figure 5], supplementary thyroid scintigraphy [Figures 6-7]) was similar in primary and secondary hyperparathyroidism. For the primary group, early- and late-phase planar imaging (100%), SPECT (95%) and supplementary thyroid scintigraphy (16%) were used. For the secondary group, similar dual-phase planar imaging (100%), SPECT (100%), and thyroid scintigraphy (11%) were used. All these parathyroid scintigraphies were interpreted as having at least 1 non-zero score per patient among the 5 possible lesion locations. The accuracies of these imaging findings as analysed and interpreted by our specialists are shown in the Table.



**Figure 5.**  $^{99m}\text{Tc}$ -sestamibi scintigraphy from a patient with secondary hyperparathyroidism. Of the 4 hyperplastic parathyroids, 3 could be localised. (a) Early-phase planar image shows tracer uptake by the thyroid gland, mild uptake by 3 hyperplastic parathyroids (arrow and arrowheads). Single-photon emission computed tomograms of (b) axial, (c) coronal, and (d) sagittal slices corresponding to the right lower hyperplastic gland, which was posterior to the lower pole of right thyroid lobe.

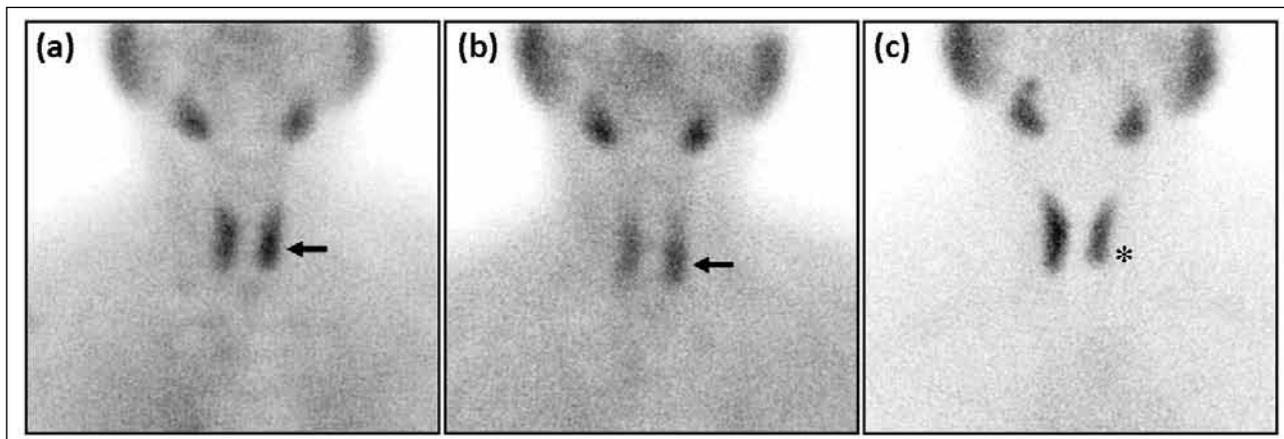
There were 5 false-positive scintigraphic lesions; 1 occurred in the primary hyperparathyroidism group, and 4 in the secondary group. One of these lesions was a metastatic lymph node from a thyroid papillary carcinoma. The remaining 4 sestamibi-avid lesions did not correspond to any specific intra-operative lesion, thus their causes were undetermined. Altogether there were 20 false-negative locations on scintigraphy, 2 in the primary group and 18 in the secondary group. Most of these false negatives (1 primary and all secondary lesions) were related to hyperplastic glands. In this series, 3 ectopic parathyroid glands were resected: 1 intra-thyroidal, 1 intra-thymic (in the lower neck), and 1 intra-thymic in the mediastinum (small lesion). Scintigraphy identified the former 2 lesions.

## DISCUSSION

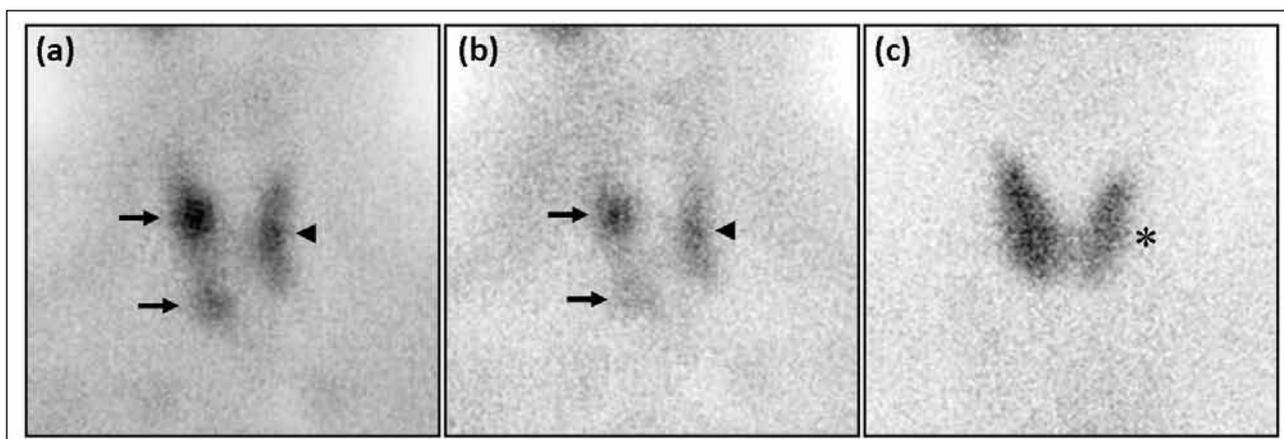
The widespread use of parathyroid scintigraphy for preoperative localisation of hyperfunctioning glands has not met with uniform success. Many factors influence the performance and accuracy of parathyroid scintigraphy, including disease molecular aspects (e.g. oxyphil cell content, P-glycoprotein membrane expression), disease severity, number and position of

**Table.** The sensitivity (SN), specificity (SP), positive predictive value (PPV), negative predictive value (NPV), and accuracy (Acc) of preoperative parathyroid scintigraphy for lesion localisation in hyperparathyroidism.

Hyperparathyroidism	SN (%)	SP (%)	PPV (%)	NPV (%)	Acc (%)
Primary	91	99	96	97	97
Secondary	74	84	93	54	77
Overall	79	95	94	82	87



**Figure 6.**  $^{99m}\text{Tc}$ -sestamibi and  $^{99m}\text{Tc}$ -pertechnetate scintigraphies of primary hyperparathyroidism. (a) Early-phase  $^{99m}\text{Tc}$ -sestamibi image shows tracer uptake by thyroid gland and an inconspicuous lesion (arrow). (b) Late-phase image raises suspicion of a left lower parathyroid adenoma with mildly delayed tracer washout (arrow). (c)  $^{99m}\text{Tc}$ -pertechnetate image shows tracer uptake by the thyroid gland only, the left lower pole of which (asterisk) had lesser uptake as compared with  $^{99m}\text{Tc}$ -sestamibi images, thus confirming the presence of a left lower parathyroid adenoma.



**Figure 7.**  $^{99m}\text{Tc}$ -sestamibi and  $^{99m}\text{Tc}$ -pertechnetate scintigraphies from a patient with secondary hyperparathyroidism. (a to b) Dual-phase  $^{99m}\text{Tc}$ -sestamibi images show 2 definite (arrows) and 1 suspected (arrowhead) hyperplastic parathyroids. (c)  $^{99m}\text{Tc}$ -pertechnetate image shows tracer uptake by thyroid gland. By comparing with  $^{99m}\text{Tc}$ -sestamibi images, the suspected parathyroid near the mid portion of left thyroid lobe (asterisk) could also be confirmed. The 4th hyperplastic gland remained obscured.

lesions, concomitant thyroid state, radiopharmaceutical quality, and scintigraphic imaging techniques.<sup>12,13,23-28</sup> The diversity of imaging techniques is of particular note.

This study evaluated the performance of a combined set of imaging techniques in 3 hospitals. Recruiting cases from multiple centres helped improve sample size and representation. To date, there is no specific radiopharmaceutical that targets only the parathyroid tissue. Therefore, either a dual-tracer, or a single-tracer with dual-phase imaging technique needs to be employed. We used  $^{99m}\text{Tc}$ -sestamibi, which is the

most widely employed radiotracer. It is a monovalent lipophilic cation that diffuses passively through cell membranes and accumulates almost exclusively in mitochondria. The exact mechanism of its selective uptake in abnormal parathyroid glands remains uncertain, but high mitochondrial activity is considered a major factor.<sup>17,29</sup>

The radiotracer distributes into the thyroid and parathyroid tissues. As compared with  $^{201}\text{Tl}$  (thallous chloride), the uptake of sestamibi per gram of parathyroid tissue has been shown to be lower than that of  $^{201}\text{Tl}$ , but the ratio between parathyroid and

thyroid tissue was higher. The biokinetics of  $^{99m}\text{Tc}$ -sestamibi also differ in parathyroid and thyroid tissues, with washout being more rapid from the latter.<sup>17</sup> Such phenomena are the basis of the dual-phase imaging. Together with better imaging characteristics and lower radiation dose,  $^{99m}\text{Tc}$ -sestamibi has rendered the use of  $^{201}\text{Tl}$  largely obsolete.

As clinical experience accumulates, it is now recognised that there are 2 patterns of  $^{99m}\text{Tc}$ -sestamibi washout from the parathyroid glands (Figure 2). The more common pattern is a delayed washout; less common, but not rare, is an early washout. Delayed washout can be defined as parathyroid retention of sestamibi evident on late-phase image, relative to the more rapid washout from normal thyroid tissues. Even this delayed washout pattern is not entirely specific for hyperfunctioning parathyroids, as such a washout pattern can also occur with thyroid nodules (notably adenoma). Early washout can be defined as minimal or no retention of sestamibi in the parathyroids on late-phase images. This means that the washout rate of  $^{99m}\text{Tc}$ -sestamibi from parathyroid and thyroid tissues is similar. The differential retention of  $^{99m}\text{Tc}$ -sestamibi in hyperfunctioning parathyroids is therefore best described as a continuum, ranging from early to delayed washout.<sup>30</sup> Because it is more difficult to identify those parathyroids if there is early washout, the dual-tracer technique is often considered to outperform the single-tracer dual-phase technique.<sup>12,31</sup>

A dual-tracer protocol normally uses  $^{99m}\text{Tc}$ -sestamibi together with either  $^{99m}\text{Tc}$ -pertechnetate or  $^{123}\text{I}$ -iodide. These two are used to reveal normal thyroid tissues for a visual or subtractive comparison with the  $^{99m}\text{Tc}$ -sestamibi image.  $^{123}\text{I}$ -iodide is a better choice because the emission of  $^{123}\text{I}$  has a different energy from  $^{99m}\text{Tc}$ , thus allowing simultaneous image acquisition (i.e. obtaining both  $^{123}\text{I}$ -iodide images and  $^{99m}\text{Tc}$ -sestamibi images at the same time) for a spatially accurate comparison. However, it is much more expensive and not readily available in many regions, including Hong Kong. The alternative tracers,  $^{99m}\text{Tc}$ -sestamibi and  $^{99m}\text{Tc}$ -pertechnetate, emit gamma rays of the same energy, hence the need for separate imaging. Besides, the dual-tracer protocol cannot entirely substitute the dual-phase technique, since the latter sometimes provides other helpful information.<sup>14,31</sup> Having considered these reasons, we did not routinely adopt a dual-tracer protocol. The need and decision to use supplementary  $^{99m}\text{Tc}$ -pertechnetate thyroid scintigraphy rested with the judgement of the attending nuclear medicine physician

or radiologist. Overall, less than one-fifth of our patients underwent the thyroid scintigraphies.

The use of SPECT was almost a routine in our imaging protocol, as it was shown to offer increased sensitivity and provide more precise localisation of abnormal parathyroids as well as better anatomical demarcation of ectopic glands.<sup>32-35</sup> It should be performed immediately following the early-phase planar imaging to avoid false-negative results (due to lesions with rapid early washout). More recently, hybrid SPECT/CT systems combining state-of-the-art multi-detector CT and gamma cameras are commercially available.<sup>36</sup> There are publications extolling their advantages, but clear superiority over SPECT has not been demonstrated using surgical success as the end-point.<sup>23,37,38</sup> While the role of SPECT/CT as a preoperative routine remains investigational, its usefulness in delineating ectopic glands and distorted neck anatomy should be recognised.<sup>39,40</sup>

In this study, all images were re-interpreted in order to calculate the accuracy of scintigraphy on a per-lesion basis. The proficiency of reporting doctor is important. A prospective study found that parathyroid  $^{99m}\text{Tc}$ -sestamibi study interpreted by an endocrine surgeon reading together with a nuclear medicine physician resulted in improved accuracy of gland localisation and lateralisation when compared to reading by a nuclear medicine physician alone.<sup>41</sup> This improvement may be related to increased awareness of clinical factors and head-and-neck anatomy. Another retrospective analysis reported that experienced nuclear medicine physicians reading all images together—including early pinhole, late pinhole, subtraction images, SPECT—could achieve higher sensitivity and accuracy than when reading them separately.<sup>42</sup> This improved reporting approach was adopted in the present study.

Our results (Table) were comparable to the best sensitivity figures compiled in meta-analyses or systematic reviews.<sup>1,12,13,18,28,42</sup> The high sensitivity (91%) and positive predictive value (96%) in primary hyperparathyroidism (mostly single-gland disease) can facilitate a minimally invasive surgical approach. In this study, a preponderance of primary adenomas in the lower parathyroid glands (74%) was noted, which concurred with some, but not all, reports.<sup>2,20</sup> Concerning this study's high specificity for primary hyperparathyroidism (99%), this could have been biased by the methodology. For instance, any of the 5 possible

parathyroid locations not classified as “positive” would have to be classified as “negative”. Thus a patient with correct localisation of a single adenoma by scintigraphy would give 1 true-positive and 4 true-negatives. The high number of true negatives led to a high specificity. Similar methodological biases were also recognised in similar research contributed by others.<sup>23,42</sup> While there are prior studies on a per-patient basis reporting only the sensitivity for detecting a lesion,<sup>1,18</sup> those based on per-lesion studies appear more relevant to current surgical trends towards minimally invasive parathyroidectomy.

Parathyroid scintigraphy is well recognised to have lower accuracy in secondary hyperparathyroidism or multiple-gland disease, irrespective of the imaging technique. The reported sensitivities were in the range of below 30% to above 80%; dual-tracer techniques tended to have better results.<sup>10,18,21,43-49</sup> In this study, we achieved a sensitivity of 74%. However, the relatively low negative predictive value of 54% would not suffice for localising secondary lesions preoperatively.

Apart from being a retrospective study analysing only cases with surgical outcomes, our study has several other limitations. Among 153 scintigraphies, only 38 (25%) patients underwent surgery in the subsequent 19 to 31 months. The rest were managed conservatively or defaulted follow-up. Since we had no retrospective data about the selection criteria for subsequent surgery, the patient population could be regarded as being biased towards those in whom scintigraphies are followed by planned surgery. The overall sample size remains relatively small, which did not allow further subgroup analyses on different degrees of disease severity or approaches to reporting. Further studies with larger sample size could be helpful. The combined imaging techniques in this study had been quite standardised, except for the variable use of supplementary thyroid scintigraphies, for which we could not retrospectively identify any clinical indication. We believe a higher rate of dual-tracer technique usage might have helped improve localisation of secondary lesions.

## CONCLUSION

Parathyroid scintigraphy is widely employed for preoperative lesion localisation. Its role has been established in primary hyperparathyroidism but remains controversial in secondary hyperparathyroidism. The diversity of imaging techniques, reporting approaches, and other factors have resulted in variable performance and discrepant results. This multicentre study adopted

a combined set of imaging techniques, encompassing <sup>99m</sup>Tc-sestamibi dual-phase planar imaging, SPECT and on-need basis, dual-tracer technique (i.e. supplementary <sup>99m</sup>Tc-pertechnetate thyroid scintigraphy) for a visual comparative analysis. It achieved a higher accuracy in primary than secondary hyperparathyroidism (97% vs. 77%). Primary lesions were also found to have a preponderance for lower positions (74%) and could be subjected to scintigraphy-guided minimally invasive parathyroidectomy. Lower sensitivity (74%) and negative predictive value (54%) for secondary lesions rendered scintigraphy less helpful in secondary hyperparathyroidism, except for locating ectopic lesions on rare occasions (3%).

## REFERENCES

1. Ruda JM, Hollenbeak CS, Stack BC Jr. A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003. *Otolaryngol Head Neck Surg.* 2005;132:359-72.
2. Fraser WD. Hyperparathyroidism. *Lancet.* 2009;374:145-58.
3. Phitayakorn R, McHenry CR. Incidence and location of ectopic abnormal parathyroid glands. *Am J Surg.* 2006;191:418-23.
4. Udelsman R, Pasieka JL, Sturgeon C, Young JE, Clark OH. Surgery for asymptomatic primary hyperparathyroidism: proceedings of the third international workshop. *J Clin Endocrinol Metab.* 2009;94:366-72.
5. O’Shea S, Johnson DW. Review article: Addressing risk factors in chronic kidney disease mineral and bone disorder: can we influence patient-level outcomes? *Nephrology (Carlton).* 2009;14:416-27.
6. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis.* 2003;42(4 Suppl 3):S1-201.
7. Mihai R, Barczynski M, Iacobone M, Sitges-Serra A. Surgical strategy for sporadic primary hyperparathyroidism: an evidence-based approach to surgical strategy, patient selection, surgical access, and reoperations. *Langenbecks Arch Surg.* 2009;394:785-98.
8. Moure D, Larrañaga E, Domínguez-Gadea L, et al. <sup>99m</sup>Tc-sestamibi as sole technique in selection of primary hyperparathyroidism patients for unilateral neck exploration. *Surgery.* 2008;144:454-9.
9. Rubello D, Massaro A, Cittadin S, et al. Role of <sup>99m</sup>Tc-sestamibi SPECT in accurate selection of primary hyperparathyroid patients for minimally invasive radio-guided surgery. *Eur J Nucl Med Mol Imaging.* 2006;33:1091-4.
10. Fuster D, Ybarra J, Ortin J, et al. Role of pre-operative imaging using <sup>99m</sup>Tc-MIBI and neck ultrasound in patients with secondary hyperparathyroidism who are candidates for subtotal parathyroidectomy. *Eur J Nucl Med Mol Imaging.* 2006;33:467-73.
11. Alkhalaf K, Bural G, Alavi A. Visualization of five hyperplastic parathyroid glands using <sup>99m</sup>Tc-sestamibi scintigraphy in a patient with chronic renal failure. *Eur J Nucl Med Mol Imaging.* 2007;34:615.
12. Hindié E, Ugur O, Fuster D, et al. 2009 EANM parathyroid guidelines. *Eur J Nucl Med Mol Imaging.* 2009;36:1201-16.
13. Rubello D, Gross MD, Mariani G, AL-Nahhas A. Scintigraphic techniques in primary hyperparathyroidism: from pre-operative localisation to intra-operative imaging. *Eur J Nucl Med Mol Imaging.* 2007;34:926-33.
14. Koranda P, Halenka M, Myslivecek M, Kaminek M. Localization

- of parathyroid enlargement: dual-tracer subtraction technique and double-phase  $^{99m}\text{Tc}$ -MIBI scintigraphy are complementary procedures. *Eur J Nucl Med Mol Imaging*. 2008;35:219-20.
15. Ferlin G, Borsato N, Camerani M, Conte N, Zotti D. New perspectives in localizing enlarged parathyroids by technetium-thallium subtraction scan. *J Nucl Med*. 1983;24:438-41.
  16. Coakley AJ, Kettle AG, Wells CP, O'Doherty MJ, Collins RE.  $^{99m}\text{Tc}$ m sestamibi — a new agent for parathyroid imaging. *Nucl Med Commun*. 1989;10:791-4.
  17. O'Doherty MJ, Kettle AG, Wells P, Collins RE, Coakley AJ. Parathyroid imaging with technetium-99m-sestamibi: preoperative localization and tissue uptake studies. *J Nucl Med*. 1992;33:313-8.
  18. Gotthardt M, Lohmann B, Behr TM, et al. Clinical value of parathyroid scintigraphy with technetium-99m methoxyisobutylisonitrile: discrepancies in clinical data and a systematic metaanalysis of the literature. *World J Surg*. 2004;28:100-7.
  19. Chan FK, Tiu SC, Choi KL, AuYong TK, Tang LF. Primary hyperparathyroidism in Hong Kong: an analysis of 44 cases. *Hong Kong Med J*. 1998;4:229-34.
  20. Lo CY, Lang BH, Chan WF, Kung AW, Lam KS. A prospective evaluation of preoperative localization by technetium-99m sestamibi scintigraphy and ultrasonography in primary hyperparathyroidism. *Am J Surg*. 2007;193:155-9.
  21. Lai EC, Ching AS, Leong HT. Secondary and tertiary hyperparathyroidism: role of preoperative localization. *ANZ J Surg*. 2007;77:880-2.
  22. Wong SW, Chan KW, Paulose NM, Leong HT. Scan-directed unilateral neck exploration for primary hyperparathyroidism: eight-year results from a regional hospital. *Hong Kong Med J*. 2009;15:118-21.
  23. Lavelly WC, Goetze S, Friedman KP, et al. Comparison of SPECT/CT, SPECT, and planar imaging with single- and dual-phase  $^{99m}\text{Tc}$ -sestamibi parathyroid scintigraphy. *J Nucl Med*. 2007;48:1084-9. Erratum in: *J Nucl Med*. 2007;48:1430.
  24. Kao A, Shiao YC, Tsai SC, Wang JJ, Ho ST. Technetium-99m methoxyisobutylisonitrile imaging for parathyroid adenoma: relationship to P-glycoprotein or multidrug resistance-related protein expression. *Eur J Nucl Med Mol Imaging*. 2002;29:1012-5.
  25. Mehta NY, Ruda JM, Kapadia S, Boyer PJ, Hollenbeak CS, Stack BC Jr. Relationship of technetium Tc 99m sestamibi scans to histopathological features of hyperfunctioning parathyroid tissue. *Arch Otolaryngol Head Neck Surg*. 2005;131:493-8.
  26. Rink T, Schroth HJ, Holle LH, Garth H. Limited sensitivity of parathyroid imaging with  $^{99m}\text{Tc}$ -sestamibi/ $^{123}\text{I}$  subtraction in an endemic goiter area. *J Nucl Med*. 2002;43:1175-80.
  27. Stephen AE, Roth SI, Fardo DW, et al. Predictors of an accurate preoperative sestamibi scan for single-gland parathyroid adenomas. *Arch Surg*. 2007;142:381-6.
  28. Mihai R, Simon D, Hellman P. Imaging for primary hyperparathyroidism — an evidence-based analysis. *Langenbecks Arch Surg*. 2009;394:765-84.
  29. Hetrakul N, Civelek AC, Stagg CA, Udelsman R. In vitro accumulation of technetium-99m-sestamibi in human parathyroid mitochondria. *Surgery*. 2001;130:1011-8.
  30. Eslamy HK, Ziessman HA. Parathyroid scintigraphy in patients with primary hyperparathyroidism:  $^{99m}\text{Tc}$  sestamibi SPECT and SPECT/CT. *Radiographics*. 2008;28:1461-76.
  31. Leslie WD, Dupont JO, Bybel B, Riese KT. Parathyroid  $^{99m}\text{Tc}$ -sestamibi scintigraphy: dual-tracer subtraction is superior to double-phase washout. *Eur J Nucl Med Mol Imaging*. 2002;29:1566-70.
  32. Slater A, Gleeson FV. Increased sensitivity and confidence of SPECT over planar imaging in dual-phase sestamibi for parathyroid adenoma detection. *Clin Nucl Med*. 2005;30:1-3.
  33. Lorberboym M, Minski I, Macadziob S, Nikolov G, Schachter P. Incremental diagnostic value of preoperative  $^{99m}\text{Tc}$ -MIBI SPECT in patients with a parathyroid adenoma. *J Nucl Med*. 2003;44:904-8.
  34. Perez-Monte JE, Brown ML, Shah AN, et al. Parathyroid adenomas: accurate detection and localization with Tc-99m sestamibi SPECT. *Radiology*. 1996;201:85-91.
  35. Billotey C, Sarfati E, Aurengo A, et al. Advantages of SPECT in technetium-99m-sestamibi parathyroid scintigraphy. *J Nucl Med*. 1996;37:1773-8.
  36. Seo Y, Mari C, Hasegawa BH. Technological development and advances in single-photon emission computed tomography/computed tomography. *Semin Nucl Med*. 2008;38:177-98.
  37. Harris L, Yoo J, Driedger A, et al. Accuracy of technetium-99m SPECT-CT hybrid images in predicting the precise intraoperative anatomical location of parathyroid adenomas. *Head Neck*. 2008;30:509-17.
  38. Gayed IW, Kim EE, Broussard WF, et al. The value of  $^{99m}\text{Tc}$ -sestamibi SPECT/CT over conventional SPECT in the evaluation of parathyroid adenomas or hyperplasia. *J Nucl Med*. 2005;46:248-52.
  39. Krausz Y, Bettman L, Guralnik L, et al. Technetium-99m-MIBI SPECT/CT in primary hyperparathyroidism. *World J Surg*. 2006;30:76-83.
  40. Akram K, Parker JA, Donohoe K, Kolodny G. Role of single photon emission computed tomography/computed tomography in localization of ectopic parathyroid adenoma: a pictorial case series and review of the current literature. *Clin Nucl Med*. 2009;34:500-2.
  41. Melton GB, Somervell H, Friedman KP, Zeiger MA, Cahid Civelek A. Interpretation of  $^{99m}\text{Tc}$  sestamibi parathyroid SPECT scan is improved when read by the surgeon and nuclear medicine physician together. *Nucl Med Commun*. 2005;26:633-8.
  42. Nichols KJ, Tomas MB, Tronco GG, et al. Preoperative parathyroid scintigraphic lesion localization: accuracy of various types of readings. *Radiology*. 2008;248:221-32.
  43. Martin D, Rosen IB, Ichise M. Evaluation of single isotope technetium 99m-sestamibi in localization efficiency for hyperparathyroidism. *Am J Surg*. 1996;172:633-6.
  44. Pons F, Torregrosa JV, Vidal-Sicart S, et al. Preoperative parathyroid gland localization with technetium-99m sestamibi in secondary hyperparathyroidism. *Eur J Nucl Med*. 1997;24:1494-8.
  45. Neumann DR, Esselstyn CB Jr, Madera A, Wong CO, Lieber M. Parathyroid detection in secondary hyperparathyroidism with  $^{123}\text{I}$ / $^{99m}\text{Tc}$ -sestamibi subtraction single photon emission computed tomography. *J Clin Endocrinol Metab*. 1998;83:3867-71.
  46. Jeanguillaume C, Ureña P, Hindié E, et al. Secondary hyperparathyroidism: detection with I-123-Tc-99m-Sestamibi subtraction scintigraphy versus US. *Radiology*. 1998;207:207-13.
  47. Périé S, Fessi H, Tassart M, et al. Usefulness of combination of high-resolution ultrasonography and dual-phase dual-isotope iodine 123/technetium Tc 99m sestamibi scintigraphy for the preoperative localization of hyperplastic parathyroid glands in renal hyperparathyroidism. *Am J Kidney Dis*. 2005;45:344-52.
  48. Lomonte C, Buonvino N, Selvaggiolo M, et al. Sestamibi scintigraphy, topography, and histopathology of parathyroid glands in secondary hyperparathyroidism. *Am J Kidney Dis*. 2006;48:638-44.
  49. Pham TH, Sterioff S, Mullan BP, Wiseman GA, Sebo TJ, Grant CS. Sensitivity and utility of parathyroid scintigraphy in patients with primary versus secondary and tertiary hyperparathyroidism. *World J Surg*. 2006;30:327-32.