Value of Dual-Phase $^{99m}$Tc-Sestamibi Scintigraphy With Neck and Thoracic SPECT/CT in Secondary Hyperparathyroidism

OBJECTIVE. Surgical intervention in the form of parathyroidectomy is generally considered only for severe secondary hyperparathyroidism (sHPT). However, correct location of the parathyroid glands before parathyroidectomy is a challenge. The purpose of this study was to compare the diagnostic value of early and delayed phase $^{99m}$Tc-sestamibi SPECT/CT in the detection of parathyroid tissue to guide operative treatment of patients with sHPT.

SUBJECTS AND METHODS. Eighty patients with sHPT who were undergoing hemodialysis were evaluated preoperatively with dual-phase $^{99m}$Tc-sestamibi SPECT/CT parathyroid scintigraphy to locate parathyroid tissue before parathyroidectomy. The scintigraphic results were classified as positive or negative. The accuracy of $^{99m}$Tc sestamibi early and delayed phase SPECT/CT scintigraphy was determined.

RESULTS. Early phase $^{99m}$Tc-sestamibi SPECT/CT depicted 3.57 parathyroid glands (PTGs) and delayed phase $^{99m}$Tc-sestamibi SPECT/CT depicted 3.55 PTGs per study. The specificity of both early and delayed phase $^{99m}$Tc-sestamibi SPECT/CT in detecting PTGs was 100%. The $^{99m}$Tc-sestamibi SPECT/CT images of 7 of 80 patients showed positive findings in the delayed phase and negative findings in the early phase. The $^{99m}$Tc-sestamibi SPECT/CT images of 6 of 80 patients showed positive findings in the early phase and negative findings in the delayed phase.

CONCLUSION. The results of our study indicate that both early and delayed phase $^{99m}$Tc-sestamibi SPECT/CT should be performed in the preoperative evaluation of hemodialysis patients with sHPT due to chronic kidney disease. Performance of both early and delayed phase $^{99m}$Tc-sestamibi SPECT/CT did not increase the radiation dose compared with the use of only the early or the delayed phase.

Secondary hyperparathyroidism (sHPT) is a frequent and challenging issue in the treatment of patients with chronic kidney disease. Dysregulation of calcium and phosphorous homeostasis decreases renal phosphate excretion, increases serum phosphorous concentration, and reduces synthesis of calcitriol, the active form of vitamin D. All of these factors increase synthesis and secretion of parathyroid hormone (PTH) and parathyroid hyperplasia with diffuse polycyclonal hyperplasia followed by monoclonal nodular hyperplasia [1, 2]. SHPT can cause substantial morbidity and mortality consequent to progressive osteodystrophy and vascular and soft-tissue calcification [3]. Current medical interventions have the potential to improve biochemical profiles and other surrogate markers. Surgical intervention in the form of parathyroidectomy is generally only considered in severe sHPT [4]. In suitable candidates, parathyroidectomy dramatically ameliorates sHPT symptoms and signs and increases survival rates and patient quality of life. However, the rate of persistent and recurrent disease after parathyroidectomy is high, ranging between 10% and 30% [5]. Most failures occur when the surgeon does not remove all hyperfunctioning parathyroid tissue [6]. Therefore, it is extremely important to correctly locate all parathyroid tissue preoperatively.

SPECT/CT has a wide range of applications and affords the opportunity to shorten acquisition time, perform accurate attenuation correction, increase specificity, and improve localization of disease. SPECT/CT has been used in the diagnosis of thyroid carcinoma [7, 8], neuroblastoma [9], and bone lesions [10–12]. Dual phase $^{99m}$Tc-sestamibi planar parathyroid scintigraphy has been used in the diagnosis of primary hyperparathyroidism and...
sHPT [13]. Previous studies have shown that SPECT can improve accuracy compared with planar imaging in parathyroid adenoma [14]. The goal of this study was to compare the diagnostic value of early and delayed phase 99mTc-sestamibi SPECT/CT in the detection of parathyroid tissue to guide operative treatment of patients with sHPT. To our knowledge, no study has directly compared early with delayed phase 99mTc-sestamibi SPECT/CT in the detection of parathyroid tissue in sHPT patients.

**Subjects and Methods**

**Patients**

The study population consisted of 80 patients (51 women, 29 men; average age, 66.1 ± 8.2 [SD] years) with chronic kidney disease treated by hemodialysis consecutively registered between January 2006 and December 2012 who also underwent evaluation with both early and delayed phase 99mTc-sestamibi SPECT/CT scintigraphy before parathyroidectomy for sHPT at a major academic medical institution. Preoperatively, all patients underwent dual-phase 99mTc-sestamibi SPECT/CT scintigraphy. According to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative 2003 guideline [4], patients with a parathyroid hormone concentration greater than 600 pg/mL, calcium concentration greater than 10.4 mg/dL, serum phosphate concentration greater than 6.6 mg/dL, calcium-phosphate product greater than 55, or worsening symptoms resistant to medical therapy were candidates for surgical treatment.

**Dual-Phase 99mTc-Sestamibi Scintigraphy With SPECT/CT**

Patients were given an IV injection of 740 MBq (range, 718–763 MBq) of 99mTc-sestamibi. Image acquisition was performed with a 4-MDCT scanner (Symbia T2, Siemens Healthcare) and a dual-head gamma camera equipped with 5/8-inch NaI crystals.

Early phase SPECT/CT images of the neck were obtained 15 minutes and delayed phase SPECT images 120 minutes after injection. Anterior neck images were acquired for 10 minutes in a 128 × 128 matrix with a 20% window centered on the 140-keV photopeak with a pinhole collimator. The SPECT volume included the neck and thorax with an axial FOV of 53.3 × 38.7 cm. A 128 × 128 matrix was used, and 64 40-second projections were acquired over 360°. The SPECT data were reconstructed with a 3D iterative algorithm. Images were smoothed with a 3D spatial gaussian filter. Immediately after early phase SPECT acquisition, a CT topogram was acquired and followed by a helical CT acquisition performed in a volume session similar to that of the SPECT acquisition. CT acquisition parameters were as follows: tube current, 60 mA; collimation, 2 × 2.5 mm; pitch, 2. For CT data reconstruction, a 3-mm section thickness with 2-mm increment and a B70 kernel filter were used. No contrast medium was injected during the procedure. In the delayed phase, only SPECT data were acquired for SPECT/CT because CT acquisition data in the early phase can be used for delayed phase SPECT/CT. Early and delayed phase SPECT/CT data were analyzed at a workstation (e.soft, Siemens Healthcare) that provided transaxial, sagittal, and coronal slices of SPECT/CT, and fused SPECT/CT data. CT data were displayed in the neck or mediastinum window settings.

Interpretation of 99mTc-sestamibi scintigraphy was performed in consensus by two experienced nuclear medicine physicians. The image findings were scored as positive or negative. A scintigraphic finding was recognized as positive if there was a definite focus of increased or separate 99mTc-sestamibi uptake relative to the uptake in the thyroid tissue of the neck or mediastinum on either early or delayed SPECT/CT images. The precise location of each focus was reported. When a corresponding nodular mass was found on an integrated CT scan, its axial diameter was measured. A scintigraphic finding was negative when focal uptake in the neck or mediastinum was absent in both early and delayed phase SPECT/CT studies. Agreement between the two physicians was achieved in all cases [15].

**Surgical Procedures**

Subtotal or total parathyroidectomy with implant was performed on young patients or candidates for kidney transplantation. Total parathyroidectomy was performed on elderly patients without autotransplants. All patients underwent bilateral transcervical thyroidectomy. The surgeon referred to the 99mTc-sestamibi scintigraphic results during preoperative planning. Subtotal parathyroidectomy included ablation of three glands and one half of the fourth gland. The half of the gland with the closest to normal appearance (or determined to be in an anatomic position that facilitated re intervention in the case of recurrence) was left in situ and marked with a nonabsorbable thread or metallic clip to facilitate future detection. The choice of the gland with the lowest chance of recurrence was based on size criteria, vascularization, appearance at gross surgical examination, and when possible, lack of 99mTc-sestamibi uptake. The excised glands were sent for frozen sections, and on the basis of the histologic finding, parathyroid hyperplasia was classified as either diffuse or nodular.

**Statistical Analysis**

Statistical software (SPSS 15.0 for Microsoft Windows XP, SPSS) was used for data analysis. Comparisons of the average longitudinal diameter of PTGs and weight of PTGs were performed with the Student’s test. Comparisons between early and delayed phase 99mTc-sestamibi SPECT/CT scintigraphy in the detection of sHPT were performed with the McNemar test. A nonparametric method was used for comparing paired dichotomous data. A value of p < 0.05 was considered statistically significant.

**Results**

**Surgical Results**

Assuming four PTGs per patient, there should have been a total of 316 PTGs in 80 patients (two patients had undergone previous hemithyroidectomy). In our series, 278 PTGs were identified and surgically resected in the 80 patients. Fifty-two of 80 patients had four PTGs, 10 patients had PTGs located in mediastinum, six patients had five PTGs (three intrathyroidal, two in supernumerary retroesophageal ectopic glands), six patients had three PTGs, six patients had two PTGs (two patients had undergone previous hemithyroidectomy). At pathologic examination, 58 PTGs (20.8%) exhibited diffuse hyperplasia and 220 PTGs (79.2%) exhibited nodular hyperplasia.

**Early and Delayed Phase 99mTc-Sestamibi SPECT/CT Scintigraphic Results**

Evaluation of the early phase 99mTc-sestamibi SPECT/CT images showed that 61 patients had positive results for sHPT: A total of 218 PTGs were detected in these patients. At

**TABLE I: Comparison of Average Number, Longitudinal Diameter, and Weight of Parathyroid Glands Detected at Early and Delayed Phase SPECT/CT**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Average No.</th>
<th>Average Diameter (mm)</th>
<th>Average Weight (mg)</th>
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<tbody>
<tr>
<td>Early phase</td>
<td>3.57</td>
<td>9.3 ± 0.9</td>
<td>1054 ± 96</td>
</tr>
<tr>
<td>Delayed phase</td>
<td>3.55</td>
<td>9.5 ± 0.6</td>
<td>1031 ± 99</td>
</tr>
<tr>
<td>t</td>
<td>1.721</td>
<td>1.162</td>
<td>0.974</td>
</tr>
<tr>
<td>p</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
<td>&gt; 0.05</td>
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the same time, delayed phase images showed 62 patients had positive results for sHPT: a total of 220 PTGs in these patients. On average 3.57 PTGs were detected in each early phase $^{99m}$Tc-sestamibi SPECT/CT study compared with 3.55 PTGs detected in each delayed phase study, indicating that early and delayed phase SPECT/CT can depict similar numbers of PTGs ($t = 1.721$, $p > 0.05$). The average longitudinal diameter of PTGs detected on early phase images was $9.3 \pm 0.9$ mm and on delayed phase images was $9.5 \pm 0.6$ mm, indicating that the diameters of PTGs detected with early and delayed phase SPECT/CT were similar ($t = 1.162$, $p > 0.01$). The average weight of PTGs at pathologic examination that had positive early phase $^{99m}$Tc-sestamibi SPECT/CT results was $1054 \pm 96$ mg (range, 210–4900 mg), whereas the average weight of PTGs with positive results on delayed phase images was $1031 \pm 99$ mg (range, 160–4800 mg), indicating that the weights of PTGs detected with early and delayed phase SPECT/CT were similar ($t = 0.974$, $p > 0.05$) (Table 1).

The specificity of both early and delayed phase $^{99m}$Tc-sestamibi SPECT/CT in detecting PTGs was 100%. The sensitivity of dual-phase $^{99m}$Tc-sestamibi SPECT/CT in detecting PTGs was 85% (68/80). There were no false-positive findings in either early or delayed phase imaging. The images of 7 of the 80 patients showed positive findings in the delayed phase and negative findings in the early phase (Fig. 1). The $^{99m}$Tc-sestamibi SPECT/CT images of 6 of 80 patients showed positive findings in the early phase and negative findings in the delayed phase (Fig. 2). Therefore, the accuracy rates of early and delayed phase $^{99m}$Tc-sestamibi SPECT/CT are similar (chi-square, 1.167; $p > 0.05$) (Table 2).

**Discussion**

A large number of patients with end-stage renal disease experience a severe form of sHPT that necessitates surgical treatment [16]. In light of recent advances in medical therapy for sHPT, elucidation of the specific role of parathyroidectomy is pertinent [16]. Moreover, for the substantial number of dialysis patients with an uncontrollable form of sHPT who cannot afford or otherwise obtain new therapeutics, parathyroidectomy remains the best treatment option [16]. However, surgical results among sHPT patients with uremia are less satisfactory than those among patients with primary hyperparathyroidism, the rates of persistent and recurrent disease...
SPECT/CT of Hyperparathyroidism

TABLE 2: Comparison of Early and Delayed Phase ⁹⁹ᵐTc-Sestamibi SPECT/CT

<table>
<thead>
<tr>
<th>Delayed Phase</th>
<th>Early Phase</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>55</td>
<td>7</td>
</tr>
<tr>
<td>Negative</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>61</td>
<td>19</td>
</tr>
</tbody>
</table>

Note—Values are numbers of findings; chi-square, 1.167; p = 1.000 > 0.05 (McNemar test).

being higher. The main cause of surgical failure is incomplete intraoperative identification of all PTGs [17]. CT, MRI, arteriography, and high-resolution ultrasound have all been used in the diagnosis of shPT [18]. However, the performance of these anatomic techniques is not satisfactory in preoperative identification of shPT [18].

Parathyroid scintigraphy is almost universally regarded as the best preoperative localizing method for patients with primary hyperparathyroidism or shPT [5]. Technetium ⁹⁹ᵐ–sestamibi has been used in parathyroid scintigraphy. This tracer can accumulate early in the parathyroid and thyroid glands and usually washes out of normal thyroid tissue more rapidly than it does out of abnormal parathyroid tissue. This is the principle of the dual-phase method, which was first reported in 1992 [19]. In that study, a dual-phase ⁹⁹ᵐTc-sestamibi protocol was used in the diagnosis of shPT. Hybrid SPECT/CT has since emerged. The SPECT/CT camera can provide more information, including functional and anatomic images, which have been widely used in many diagnostic nuclear medicine scans [9, 20]. Previous studies have evaluated many parathyroid scintigraphic methods, including ⁹⁹ᵐTc-sestamibi SPECT of the parathyroids [14, 21]. However, in these studies only a single set of SPECT images, either early or delayed phase, is acquired. Some investigators [22, 23] have described the application of SPECT/CT to parathyroid scintigraphy. However, the optimal scintigraphic protocol of ⁹⁹ᵐTc-sestamibi parathyroid scanning was not clear for primary hyperparathyroidism or shPT because few studies have directly compared different scintigraphic protocols. Although some studies directly compared the different methods, no consistent conclusion was made. Therefore, different scintigraphic protocols have been used in parathyroid scans. Ciappucini et al. [13] reported the use of dual-phase ⁹⁹ᵐTc-sestamibi SPECT/CT parathyroid scanning in the diagnosis of primary hyperparathyroidism. However, the use of dual-phase ⁹⁹ᵐTc-sestamibi SPECT/CT of the parathyroids in the diagnosis of shPT has not been reported previously, to our knowledge.

In our study, we directly compared early and delayed phase ⁹⁹ᵐTc-sestamibi SPECT/CT. All patients underwent the early and delayed phases of imaging. On average 3.57 PTGs were detected in each early phase and 3.55 PTGs were detected in each delayed phase study, indicating that early and delayed phase SPECT/CT can depict similar numbers of PTGs. PTG diameters and weights were similar on early and delayed phase SPECT/CT images. All of these data showed that the ability to detect parathyroid tissue in shPT patients is the same with early and delayed phase ⁹⁹ᵐTc-sestamibi SPECT/CT.

However, the findings that 7 of 80 patients had positive results in the delayed phase and negative results in the early phase and that 6 of 80 patients had positive results in the early phase and negative results in the delayed phase suggests that either early or delayed phase ⁹⁹ᵐTc-sestamibi SPECT/CT can depict new lesions to the same degree as imaging in the other phase. Early and delayed phase ⁹⁹ᵐTc-sestamibi SPECT/CT together can depict more lesions than with either phase alone. Schachter et al. [24] reported that delayed phase ⁹⁹ᵐTc-sestamibi may be nondiagnostic when similar washout rates between thyroid and parathyroid tissue are found. They reported that only 60% of adenomas exhibited retention of activity on delayed phase images. They concluded that early phase SPECT is useful for localizing parathyroid adenomas and is superior to dual-phase delayed imaging. Delayed phase SPECT is not recommended because it may cause false-negative results due to rapid washout [24].

Perez-Monte et al. [15] also reported that early phase ⁹⁹ᵐTc-sestamibi SPECT is most accurate in the detection and localization of parathyroid adenomas. Carty et al. [25] reported that early phase scanning in dual-phase ⁹⁹ᵐTc-sestamibi SPECT was more sensitive than the delayed phase in the detection of PTGs (sensitivity, 92% and 74%). However, Civelek et al. [21] reported that delayed phase SPECT is a promising protocol in the preoperative detection and localization of parathyroid adenomas in both unexplored and reexplored patients. Although all patients underwent both early and delayed phase scanning in our study, CT data were acquired only once. The CT data can be used in not only the early phase but also in the delayed phase of ⁹⁹ᵐTc-sestamibi SPECT/CT. This method does not entail more radiation dose than early or delayed phase scanning alone.

There were no false-positive results in our study, and the specificity of early and of delayed phase ⁹⁹ᵐTc-sestamibi SPECT/CT was 100%. Although previous studies showed some false-positive findings on static planar ⁹⁹ᵐTc-sestamibi scintigrams related to hyperplastic lymph nodes, lymphomatous lesions, thyroid adenomas, and Hashimoto thyroiditis, none were observed in our study population [26, 27]. The most likely explanation for our lack of false-positive findings is the high initial positive predictive value in our patient population because the parathyroid hormone concentrations were all greater than 600 pg/mL, and all patients were undergoing hemodialysis for chronic kidney disease.

Another advantage of SPECT/CT is the accurate and anatomic depiction of PTG location, size, and adjacent tissues and structures, which facilitates operative planning. Hybrid SPECT/CT systems that combine conventional CT with SPECT have become available for clinical application. SPECT/CT has been found to be more specific and sensitive in the detection and interpretation of small PTGs. This is due to the combination of precise anatomic detail available with high-spatial-resolution CT and the metabolic and functional information acquired through SPECT [28, 29].

Conclusion

Our study results indicate that both early and delayed ⁹⁹ᵐTc-sestamibi SPECT/CT should be performed in the preoperative evaluation of hemodialysis patients with shPT due to chronic kidney disease. The combination of early and delayed ⁹⁹ᵐTc-sestamibi SPECT/CT did not increase the radiation dose compared with early or delayed imaging alone.

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