The Cost-effectiveness of Additional Preoperative Ultrasonography or Sestamibi–SPECT in Patients With Primary Hyperparathyroidism and Negative Findings on Sestamibi Scans

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Objective: To determine whether the use of additional preoperative imaging was cost-effective compared with bilateral neck exploration (BNE) for the treatment of primary hyperparathyroidism in patients with negative findings on scans with technetium Tc 99m sestamibi.

Design: We performed a cost-effectiveness analysis. The decision whether to proceed to BNE or obtain additional preoperative imaging using ultrasonography (US) or single-photon emission computed tomography with technetium Tc 99m sestamibi (SPECT) was modeled using decision analysis. We obtained probabilities of cure, detection of pathologic glands, and the correct side of the neck from recent literature.

Main Outcome Measures: Expected cost, cure rate, and the incremental cost per cured case using the preoperative imaging strategies compared with BNE.

Results: The US strategy dominated the SPECT and BNE strategies, with a lower expected cost ($6030 vs $7131 and $8384, respectively) and a greater expected cure rate (99.42% vs 99.26% and 97.69%, respectively). Threshold analysis suggests that the preoperative imaging strategies continued to dominate unless the cost of BNE was less than $5400 or the cost of unilateral neck exploration exceeded $6500. The US strategy dominated SPECT as a preoperative imaging strategy if the cost of SPECT exceeded $12 or the cost of a US test was less than $1300.

Conclusions: For the treatment of primary hyperparathyroidism in the patient with negative findings on technetium Tc 99m sestamibi scans, a strategy that uses additional preoperative US imaging appears to be cost-effective compared with SPECT or BNE.
Not all treatment of cases of pHPT using a less invasive approach is successful. Cases where an MIP fails to produce normocalcemia involve a double adenoma located in the ipsilateral or contralateral neck or multiple hyperplastic glands. Because the sensitivity of sestamibi scans and US typically range from only 15% to 30% for the detection of both double adenoma glands and less than 20% to 30% for all multiple gland disease (MGD), often not all pathologic glands are detected preoperatively.33-37 In these instances, extension of the surgical excision or conversion to a BNE with thyroid gland palpation and possible thymectomy may be necessary to locate and remove any additional hyperfunctioning glands.

When presented with a scan that fails to localize any parathyroid lesion or one that localizes multiple lesions, the surgeon can seek additional confirmatory radiographic imaging or resort to a BNE. Should preoperative sestamibi scans localize 2 or more lesions, it is questionable whether this finding suggests multigland parathyroid disease or a radiographic artifact that is most often concomitant with thyroid disease. In these instances, should preoperative US be used subsequently, it might enable the identification of 1 of these lesions as being of nonparathyroid origin. In this case, a limited exploration of only 1 side of the neck may be pursued38 (Kirt S. Beus, MD, J.M.R., C.S.H., and B.C.S., unpublished data, June 2005).

Likewise, use of single-photon emission computed tomography with technetium Tc 99m sestamibi (SPECT), with its 3-dimensional tomographic imaging, high rate of glandular detection, and sensitivity for solitary gland disease (SD) and MGD, could also be used to direct an MIP.39-42 Both modalities have been reported to incrementally contribute to the ultimate localization of previously undetected, normally situated, and ectopic parathyroid tissue, as well as the clarification of ambiguous imaging.40-43 Thus, in the patient with pHPT and negative sestamibi scan findings, additional preoperative imaging might be advantageous in allowing for a less-invasive parathyroidectomy. The purpose of this study was to determine the cost-effectiveness of additional preoperative imaging compared with BNE for the treatment of pHPT in patients with negative dual-phase sestamibi scan results.

**METHODS**

**DECISION ANALYSIS MODEL**

Our decision analysis was based on a choice between performing an unguided BNE or seeking additional preoperative imaging with SPECT or high-resolution US to direct a limited neck exploration for the treatment of pHPT. For this model, we assumed that the results of preoperative US were independent of the initial nondiagnostic dual-phase sestamibi scan findings. The results of SPECT, however, were not considered independent of the initial nondiagnostic sestamibi scan findings, because both procedures were often performed sequentially after injection of only 1 dose of technetium Tc 99m sestamibi. Therefore, only publications reporting incremental differences between simultaneous dual-phase planar sestamibi scans and SPECT were used. The decision tree is presented in **Figure 1**.

At the first node, a patient with pHPT presents with a nondiagnostic dual-phase sestamibi scan finding. At this point, the clinician chooses whether to perform an unguided BNE or seek additional preoperative imaging with US or SPECT. If either scan is pursued, then US or SPECT will localize 1 or more glands or prove inconclusive. If either scan localizes a solitary focus, then the clinician may choose to proceed with a minimally invasive surgery in the affected side of the neck. For this study, we assumed that because the patient initially presented with an inconclusive or equivocal dual-phase sestamibi scan, this preoperative result precluded a subsequent radioguided MIP approach. Instead, unilateral neck exploration (UNE)/MIP in conjunction with intraoperative parathyroid hormone assay was always attempted, where possible. Furthermore, for this model, we assumed that surgical success using UNE, BNE, or conversion surgery from UNE/MIP to BNE (BNEC) was defined as the postoperative resolution of hypercalcemia. With a solitary adenoma that is correctly localized or an ipsilateral double adenoma, UNE/MIP will achieve normocalcemia. In the event that UNE/MIP fails intraoperatively because of an inadequate decline in the serum parathyroid hormone assay level, the procedure is immediately converted to a BNE (BNEC). This occurs because the preoperative scan failed to localize the actual parathyroid pathway (false-negative result) or additional undetected pathology existed in the contralateral neck or mediastinum. In this instance, we assumed that only BNEC was attempted. Should an additional median sternotomy to access pathologic glands in the mediastinum have been required, this was considered a surgical failure for BNEC.

Should US or SPECT localize 2 or more foci in the neck, then the choice of surgical procedures is directed by whether the lesions are ipsilateral or contralateral. If the 2 lesions are contralateral, the patient is treated by BNE. However, if 2 foci are detected in the ipsilateral neck, a UNE/MIP is attempted. For this study, we assumed that parathyroid glands preoperatively detected in the ipsilateral neck did not represent 3- or 4-gland hyperplasia, which would necessitate BNE. Instead, our model assumes that 2 glands detected ipsilaterally are initially treated by a UNE/MIP in conjunction with an intraoperative parathyroid hormone assay. In the event that only 2 pathologic glands actually exist and are contained within the ipsilateral neck, then surgical success is achieved. Should contralateral or ectopic parathyroid disease exist, UNE/MIP was assumed to fail by virtue of an inadequate decline in the intraoperative parathyroid hormone assay level. Hence, the patient was treated with BNEC to achieve normocalcemia.

In the event that SPECT or US findings are equivocal or fail to localize any mass/locus, BNE is performed to inspect both sides of the neck. Likewise, at the first-choice node, the clinician may decide not to pursue any further preoperative imaging with SPECT or US and instead proceed directly to surgery. In this instance, it is assumed that an unguided BNE is performed.

**MODEL VARIABLES**

We performed the decision analysis using DATA software (version 4.0; TreeAge Software Inc, Williamstown, Mass). The variables of the decision tree model were expressed by synthesizing data from the literature. Details of this process and all numeric values used for this analysis are contained in Ruda et al.32 Relevant articles published between 1995 and 2004 were selected from a MEDLINE search of combinations of the following search terms: primary hyperparathyroidism, radionuclide imaging, parathyroidectomy, ultrasonography, minimally invasive radioguided parathyroidectomy, unilateral neck exploration, Tc 99m-estamibi, Tc 99m-sestamibi-SPECT, minimally invasive surgery, costs, bilateral neck exploration, minimally invasive parathyroidectomy, adenoma, and ultrasonography. As this study focused exclusively on the detection and treatment of sporadic pHPT, articles that reported data dealing with any other...
form of HPT (e.g., secondary or tertiary) or using any preoperative modality other than SPECT or high-resolution US were excluded.

**PROBABILITIES**

Probabilities used in this model included the probability of SPECT or US localizing SD or MGD, or proving inconclusive, as well as the probability of encountering SD or MGD associated with sporadic pHPT. Diagnostically, the probability of SPECT or US localizing 0, 1, 2, or more glands was calculated using the Bayes theorem. We estimated the probabilities of achieving curative normocalcemia using UNE, BNE, or BNEC from our synthesis of the literature and present them in **Table 1**. In cases in which UNE was converted to a BNE, they were considered surgical failures and included in the overall estimate of UNE success. Surgical success rates associated with BNE, UNE, and BNEC were estimated by taking a weighted average across studies, where the weights were proportional to the sample size of each study.
Table 1. Baseline Values and Ranges Used in Sensitivity Analyses for Decision Tree Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Range for Threshold Analysis</th>
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<tbody>
<tr>
<td>Costs, $</td>
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<tr>
<td>UNE</td>
<td>4766.00</td>
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<td>BNE</td>
<td>8364.00</td>
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<td>BNEC</td>
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<td>US</td>
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<td>0-8000</td>
</tr>
<tr>
<td>SPECT</td>
<td>1073.00</td>
<td>0-8000</td>
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<tr>
<td>Probability of cure, %</td>
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<td></td>
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<tr>
<td>UNE</td>
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</tr>
<tr>
<td>BNEC</td>
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<tr>
<td>Sensitivity, %*</td>
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<tr>
<td>Prevalence, %</td>
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<tr>
<td>Solitary gland disease</td>
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<td>Cases contained in contralateral neck, %</td>
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</tr>
<tr>
<td>Cases contained in ipsilateral neck, %</td>
<td>25.00</td>
<td>0-100</td>
</tr>
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</table>

Abbreviations: BNE, bilateral neck exploration; BNEC, conversion from unilateral neck exploration (UNE)/minimally invasive parathyroidectomy to BNE; SPECT, single-photon emission computed tomography with technetium Tc 99m sestamibi; US, ultrasonography.

*The numerator represents the number of detected parathyroids; denominator, total number of diseased parathyroids.

COSTS

For all cost analyses, we assumed the perspective of the health care provider in a hospital setting. Costs for SPECT, US, BNE, and UNE were obtained from the literature. They are presented in Table 1. The cost of BNEC was assumed to be the incremental difference in the cost between UNE and BNE. Using the medical care component of the consumer price index, all dollar amounts were adjusted to reflect 2004 price levels. The cost used at each terminal node in the decision tree was the sum of the costs assumed in the treatment pathway. For example, the cost at the first terminal node located at the top of the tree is the sum of the costs for US and BNE that are incurred when US is nonlocalizing and necessitates a conversion to BNE to achieve curative normocalcemia.

EFFECTIVENESS

Effectiveness was defined as postoperative normocalcemia for all modes of treatment (BNE, UNE, and BNEC). Results are presented in Table 1. As with the other model variables, effectiveness was estimated from the relevant recent literature.

COST-EFFECTIVENESS ANALYSIS

The incremental cost-effectiveness ratio for the use of SPECT and US in the treatment of pHPT is defined as follows:

\[ \text{ICER} = \frac{C_{\text{US}} - C_{\text{BNE}}}{E_{\text{US}} - E_{\text{BNE}}} \]

where \( C_{\text{US}} \) and \( E_{\text{US}} \) are the expected cost and effectiveness, respectively, of the preoperative imaging strategies and \( C_{\text{BNE}} \) and \( E_{\text{BNE}} \) are the expected cost and effectiveness, respectively, of the BNE strategy. Thus, the incremental cost-effectiveness ratio tells how much in additional costs must be incurred to achieve 1 additional cure if the SPECT or the US strategy is pursued instead of the BNE strategy.

SENSITIVITY ANALYSIS

Our baseline cost-effectiveness results depended on the parameterization of the decision tree model. It was of interest to know whether the US or the SPECT strategy remained dominant as the model variables were changed across reasonable ranges. To study the robustness of our results, we undertook several 1-way sensitivity analyses by changing 1 model variable at a time to determine whether the results were sensitive to our estimated values for the cost of SPECT, US, BNE, BNEC, and UNE. We also determined the threshold values for the probability of cure using UNE, BNE, and BNEC, as well as any values at which the US and SPECT strategies lost their dominance over the BNE strategy.

RESULTS

Table 2 presents the baseline results for the cost-effectiveness analysis. The preoperative US and SPECT strategies were less costly than BNE, with expected costs of $6030 for the US strategy, $7131 for the SPECT strategy, and $8384 for the BNE strategy. This resulted from the avoidance of more invasive surgery secondary to preoperative guidance. Among preoperative strategies, differences in cumulative strategy costs resulted from numerous variables, including the overall strategy effectiveness and the associated cost for each scan, with the cost of US being substantially cheaper than that of SPECT. In addition, the US strategy was more effective than the SPECT strategy, with an expected cure rate of
result of the lower expected overall cost and higher with technetium Tc 99m sestamibi; US, ultrasonography. SPECT indicates single-photon emission computed tomography ultrasonography (US) strategy.

exploration (BNE) strategies are more costly and less effective than the SPECT strategy. As shown in Figure 3, this was as a result of the lower expected overall cost and higher expected cure rate achieved with the US strategy than with the SPECT strategy. This finding translated into an expected cost savings of $688 125 per patient successfully treated with the US strategy than if performed with the SPECT strategy in patients with negative findings of sestamibi scans.

99.42% compared with 99.26% for the SPECT strategy or 97.69% for the BNE strategy. Because the US strategy was more effective than the SPECT strategy, the overall cost of the US strategy was lower than the cost of the SPECT strategy because it avoided the incurred cost of BNEC more frequently. Ultimately, because the US and SPECT strategies were less costly and more effective than BNE, they were not only cost-effective compared with the BNE strategy but also dominated it.

If 1000 patients were treated with the SPECT strategy, one could expect to cure 993 at a total cost of $7 081 381. If the same patients were instead treated with BNE and no additional imaging, one could expect to cure 977 patients at a total cost of $8 191 168. Thus, the SPECT strategy yields 16 additional cures and a cost savings of $1 109 787, or a cost savings of $79 790 per additional successfully treated patient. Moreover, the US strategy was cost-effective compared with the SPECT strategy. As shown in Figure 2, this was as a result of the lower expected overall cost and higher

SENSITIVITY ANALYSES

As seen in Figure 3 and Figure 4, the US and SPECT strategies were cost-effective compared with the BNE strategy. When overall reasonable costs for BNE, BNEC, and UNE were compared, the US strategy was dominant compared with the SPECT strategy. Compared with the BNE strategy, the US strategy was additionally dominant if the cost of BNE exceeded $5400 or the cost of UNE was less than $7750. However, should the cost of BNE decrease to less than $5400 or the cost of UNE exceed $7750, the US strategy was no longer dominant. At this point, the US strategy became less cost-effective relative to the BNE strategy, with the overall cost-effectiveness of the BNE strategy conditional on one’s willingness to pay for 1 additional correct diagnosis. Similarly, the SPECT strategy dominated the BNE strategy if the cost of the BNE exceeded $6600 or the cost of UNE was less than $6500. However, should the cost of BNE decrease to less than $6600 or the cost of UNE exceed $6500, the SPECT strategy was no longer dominant. At that point, the cost-effectiveness of the BNE strategy was again conditional on one’s willingness to pay for 1 additional correct diagnosis.

As seen in Figure 5 and Figure 6, the US and SPECT strategies were individually dominant compared with the BNE strategy if the cost of US or SPECT decreased to less than $2500 or $2400, respectively. When we compared the US strategy with the SPECT strategy, US was dominant if the cost of SPECT exceeded $12 or the cost of US was less than $1300. On threshold analysis, US also dominated SPECT and BNE for all reasonable expected cure rates achieved with BNE and BNEC. Furthermore, US continued to be cost-effective for UNE unless the probability of cure achieved with UNE decreased to less than 7.0%. Below this threshold, SPECT was cost-effective (Table 3).
Since the early 1990s, treatment of sporadic pHPT has been increasingly attempted using less invasive surgical approaches. This has been largely driven by the high sensitivity of preoperative dual-phase sestamibi scans for the detection of diseased parathyroid glands. Guided by technetium Tc 99m sestamibi, a focused, minimally invasive UNE has begun to replace BNE in patients with pHPT. Because sporadic pHPT has been shown to involve SD in approximately 85% to 90% of cases, this less invasive approach has been successful in more than 93% to 98% of cases.\(^4\)\(^5\)\(^2\) However, in the rare case in which preoperative sestamibi scan findings are nondiagnostic or suggestive of possible MGD, the question becomes, what is the optimal strategy to subsequently pursue?

In patients with an initially nondiagnostic dual-phase sestamibi scan result, obtaining additional preoperative imaging with US or SPECT was found to be cost-effective compared with proceeding directly to an unguided BNE. Moreover, when we compared the US, SPECT, and BNE strategies, US was not merely cost-effective compared with the latter strategies, it was dominant. Besides the financial benefits, other additional benefits include the possibility of an improved quality of life, a more favorable cosmetic appearance, and the avoidance of the potential risks and complications of BNE surgery should the contralateral neck be spared.

Because high-resolution US is a reasonably cheap preoperative modality, it is a relatively accessible, affordable, and noninvasive tool used to diagnose pHPT. However, compared with US, SPECT typically requires a much greater degree of patient cooperation during scanning to avoid any radiographic artifact produced from unintentional movement.\(^5\) In addition, SPECT requires a significantly greater amount of time for scan acquisition and image computation, an experienced radiologist skilled in its interpretation, and a sufficient volume of patients to justify the dedicated equipment and staff. Unlike US, SPECT also involves additional patient exposure to a second dose of radiotracer if it is performed separately from the initial dual-phase sestamibi scan. In light of these issues, high-resolution US may offer even more clinical utility and economic advantage in the diagnosis and treatment of sporadic pHPT.

We recognize that this study had several limitations, primarily derived from the fact that results are conditional on the variables of the decision model. Because our model variables were expressed by publications included in our previous systematic review,\(^3\) any limitations inherent to that study were also carried into this decision model. Although our estimates of costs and cure rates for BNE, UNE, BNEC, SPECT, and US were based on published, peer-reviewed studies where available, some of these variables were not well reported in the literature.
For the probability of success using MIP/UNE, we assumed in this model that all minimally invasive approaches used a quick intraoperative parathyroid hormone assay. However, in clinical practice, not all surgeons rely on this modality to confirm successful excision of all offending glands. A recognized objection to this assay is that intraoperative parathyroid hormone levels have been reported to falsely suggest the presence of still unresected parathyroid pathologic tissue. In those cases, an unresolved level of parathyroid hormone has prompted unnecessary BNEC surgery. Furthermore, it has been argued that the successful detection of falsely negative parathyroid glands that were not detected on preoperative imaging is almost proportionally balanced by the number of cases where unnecessary exploration is pursued on account of a falsely elevated intraoperative parathyroid hormone assay. Despite reports that surgical success with MIP/UNE is not significantly improved by use of the intraoperative parathyroid hormone assay, we chose to model that all UNE/MIPs were guided intraoperatively by parathyroid hormone level as is the most common practice.

Our decision model was also hindered by a paucity of articles reporting incremental benefits in the detection of parathyroid disease using SPECT compared with dual-phase sestamibi scanning. No articles were found that directly addressed the value of an additional SPECT scan in a patient with a previously nondiagnostic sestamibi scan finding. However, the use of high-resolution US in this subset of patients was frequently reported. In addition, our model assumed that the preoperative sensitivity of SPECT was not independent of the sensitivity of dual-phase planar sestamibi scans. Thus, SPECT could offer only an incremental advantage over dual-phase sestamibi scans, because SPECT images in clinical practice are usually obtained simultaneously with those of planar sestamibi scans. However, because our model also assumed that additional SPECT was performed separately from the initial dual-phase sestamibi scan, the dependence of SPECT on planar sestamibi scanning might not be absolute.

SPECT has been reported to detect parathyroid lesions as small as 120 to 300 mg, to detect atypically located parathyroid tissue with great success, and to be minimally affected by synchronous thyroid disease. Routine use of SPECT might permit more than just an incremental contribution to planar sestamibi scanning. With its increased image contrast, resolution, and a more precise 3-dimensional detection of hyperfunctioning parathyroid tissue, SPECT may be more cost-effective than our analysis suggests, especially in the reoperative neck or patients with secondary HPT.

Our research supports a role for additional preoperative imaging with US or SPECT in the treatment of patients with an initially nondiagnostic finding on a dual-phase sestamibi scan. Compared with SPECT and BNE, preoperative US was found to possess a higher expected cure rate and a lower expected cost. Preoperative US was cost-effective and dominant compared with additional preoperative SPECT or direct unguided BNE. It will be important to validate these findings in a prospective clinical study.

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10. Saaristo RA, Salmi JJ, Koobi T, Turjanmaa V, Sand JA, Nordback IH. SPECT and a more precise 3-dimensional detection of hyperfunctioning parathyroid tissue, SPECT may be more cost-effective and dominant compared with additional preoperative SPECT or direct unguided BNE. It will be important to validate these findings in a prospective clinical study.


