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Surgery versus Imaging in Non-Localizing Primary Hyperparathyroidism: A Cost-Effectiveness Model

Ethan Frank, MD; WayAnne Watson, BS; Shannon Fujimoto, MD; Pedro De Andrade Filho, MD; Jared Inman, MD; Alfred Simental, MD

Objective: To determine whether advanced imaging is cost-effective compared to primary bilateral neck exploration in the management of non-localizing primary hyperparathyroidism.

Study Design: Cost-effectiveness analysis.

Methods: Cost-effectiveness analysis based on decision tree model and available Medicare financial data using data from 347 consecutive patients having parathyroidectomy for primary hyperparathyroidism with either 1) positive, concordant ultrasound and sestamibi or 2) negative sestamibi and negative ultrasound.

Results: Bilateral neck exploration (BNE) costs $9578 and has a success rate of 97.3%. Single photon emission computed tomography (SPECT) + minimally invasive parathyroidectomy (MIP) was modeled to have a total cost of $8197 with a success rate of 98.9% and a 98.6% success rate. Four-dimensional (4D)–CT + MIP was modeled to cost $8146 with a success rate of 99%. Incremental cost-effectiveness ratios (ICER) (as compared to BNE) were $536.1, $605.5, and $701.6 ($/percent cure rate) for SPECT, SPECT/CT, and 4D-CT respectively. One-way sensitivity analyses demonstrate the change in IECR and cut-off points (IECR = 0) for four major variables.

Conclusions: In patients with non-localizing primary hyperparathyroidism, advanced imaging is associated with cost-savings compared to routine bilateral neck exploration. Increased cost-savings were predicted with increased imaging accuracy and decreased imaging costs. Increasing time for BNE or decreasing time for MIP were associated with increased cost savings.

Key Words: Hyperparathyroidism, cost-effectiveness, bilateral neck exploration, non-localizing, minimally invasive parathyroidectomy.

Level of Evidence: III

Laryngoscope, 130:E963–E969, 2020

INTRODUCTION

Hyperparathyroidism remains a common pathology for the endocrine surgeon. Most cases are caused by hypersecretion of parathyroid hormone-producing adenomas or hyperplastic glands. In appropriate surgical candidates, bilateral or unilateral neck exploration offers a ≥95% chance of durable cure and is standard of care. In asymptomatic patients, parathyroidectomy has been shown to be a cost-effective option compared to observation. Current surgical management of hyperparathyroidism begins with localizing studies to determine if the patient is a candidate for minimally invasive parathyroidectomy (MIP) or bilateral neck exploration (BNE). Intraoperative parathyroid hormone (PTH) monitoring is commonly used—either in addition to or in lieu of preoperative imaging—to guide the extent of surgery and confirm removal of the appropriate gland(s).

Most pathologic glands localize with Te-99 m sestamibi scans or ultrasound, but 12% to 18% of patients will have non-localizing disease. Non-localization is thought to be related to multiglandular disease as well as parathyroid size and histology and has been shown to not simply represent inadequate radiographic evaluation. Failed localization creates significant issues in patient care, causing delays in surgical referrals and ultimately reducing the percentage of patients having surgery. Ultimately, these patients will require either BNE with guidance by intraoperative PTH levels or advanced imaging in hopes of identifying pathologic gland(s) and proceeding with MIP.

Previous studies have demonstrated the cost-effectiveness, distinct from the utility, of preoperative localizing strategies in all patients with hyperparathyroidism. Our institution has shown that in patients with negative sestamibi and ultrasound, outcomes from BNE and intraoperative PTH without further imaging are comparable to outcomes in surgery for localizing disease. The cost-effectiveness of a BNE-first strategy in patients with non-localizing disease, however, has not been evaluated. We hypothesize that there is a cost savings associated with routine BNE in patients presenting with non-localized hyperparathyroidism when compared to obtaining further imaging with the goal of performing an MIP.
MATERIALS AND METHODS

Decision Tree Modelling

A decision tree was formulated based on the reference case of a patient with hyperparathyroidism having both a preoperative Tc99m-sestamibi scan and neck ultrasound without localization of the involved parathyroid gland. The primary decision node was the choice of surgery first versus advanced imaging first and the secondary decision node constituted the imaging modalities of interest. Chance nodes represented the localization accuracy of the imaging modalities, cure rates for surgery on localized disease, and cure rates for surgery on non-localized disease. The end nodes denoted a final outcome of surgical cure versus persistence of disease. Overall cure rates or each imaging first pathway were calculated as the sum of the products of cure rates for each patient sub-group (localized vs non-localized) and the percentage of patients in each group by imaging modality accuracy (eg, for single positron emission computed tomography [SPECT], overall cure rate = [cure rate for localized disease × percentage of patients localized by SPECT] + [cure rate for non-localized disease × percentage of patients without localization on SPECT]). Per standard decision tree nomenclature, decision nodes were denoted with a square, chance nodes with a circle and end nodes by a triangle. The decision tree model was terminated following the first instance of surgical intervention for each branch of the tree. This model leaves a percentage of reference cases with an end node denoting persistent disease.

Clinical Outcomes Data

Outcomes data was extracted from a cohort of 347 consecutive patients having either BNE for non-localizing hyperparathyroidism (n = 147) or MIP with positive, concordant findings on preoperative sestamibi and ultrasound (n = 200). One hundred seventy-four patients with discordant imaging on sestamibi and ultrasound were excluded from analysis. Data included surgical cure rates, operating room time, number of frozen section specimens sent, and number of intraoperative PTH assays sent. Intraoperative PTH levels were drawn at time of excision and at 10, 15, and 20 minutes post-excision, with criteria of PTH drop ≥50% at 10 minutes post-excision and normalization of PTH by 20 minutes post-excision.15-19 Surgical cure was defined as normalization of calcium (<2.6 m mol/L) and PTH (<65 pg/mL) maintained for 6 months postoperatively. Operating room time was the time from patient entry into the room to patient exit. This definition accounts for anesthesia induction and patient preparation (including placement of an arterial line at our institution) as well as surgeon time and represents the total time considered by institutional cost centers in calculating the billing of operating room time. For the purpose of this analysis, operating time data was divided into two groups, patients with localization disease (defined by concordance of preoperative Tc99m-sestamibi and ultrasound) and patients with non-localizing disease (defined by negative findings on both preoperative Tc99m-sestamibi and ultrasound). Since most parathyroid disease will localize with preoperative imaging and because preoperative imaging is recommended as standard of care by current guidelines, we did not evaluate the cost-effectiveness of upfront BNE without imaging.3 Patients with ectopic disease or discordance between pre-operative imaging modalities were not analyzed in this cohort in order to maximize and best assess the difference between well-localized and non-localized disease. As institutional data was not available for all of the assessed imaging modalities, data regarding accuracy of the included imaging modalities were compiled from a systematic review of all meta-analyses in the past 10 years in which at least one of the three imaging modalities was evaluated in patients with hyperparathyroidism. MEDLINE database searches were performed using search term combinations: “hyperparathyroidism,” “SPECT,” “SPECT/CT,” and “4D CT.” Summary effect data was extracted from the included analyses and an overall weighted average was calculated using the previously validated method for combining results of meta-analyses published by Tang et al.20

Financial Data

All financial calculations were completed from the perspective of the insurance provider, which for this analysis was the Center for Medicare Services (CMS). Financial data was extracted from the 2018 Center for Medicare Services (CMS) Fee Schedule, 2018 OSHPD Chargemaster document for Loma Linda University Medical Center, and internally generated billing documents. The total charge for operative procedures was defined as the sum of the following: charges per minute for operating room time, charges billed by the operating surgeon, charges billed for anesthesia care, and professional and technical charges billed by pathology and laboratory services—including professional charge for the pathology consultation and charges for intraoperative frozen sections and PTH assays. Charges for operating time were determined by averaging the reimbursed charges for all CMS patients having procedure 60500 (removal or exploration of parathyroid glands)—derived from internally generated billing documentation—and dividing the averaged charge by the average operating time for the same group of patients. Professional charges were extracted from the 2018 CMS fee schedule, utilizing the limiting charge reported by CMS for healthcare common procedure coding system (HCPCS) codes 60500 (parathyroidectomy or exploration of parathyroids), 88329 (pathology consultation during surgery), 36620 (arterial catheterization or cannulation for sampling, monitoring, or transfusion), 83970 (assay of parathormone), 88331 (pathology consultation during surgery; first tissue block, with frozen section[s], single specimen), and 88332 (pathology consultation during surgery; each additional tissue block with frozen section[s]). Charges for radiologic studies were also extracted from the 2018 CMS fee schedule, using the limiting charge for HCPCS codes 78071 (parathyroid planar imaging [including subtraction, when performed]; with tomographic [SPECT], 78072 [parathyroid planar imaging [including subtraction, when performed]; with tomographic [SPECT], and concurrently acquired computed tomography [CT] for anatomical localization], 70491 (computed tomographic [SPECT], and concurrently acquired computed tomographic [CT] for anatomical localization), 70491 (computed tomography, soft tissue neck; with contrast material[s]), 77293 (respiratory motion management), and A9500 (tc-99m sestamibi, diagnostic, per study done). Charges for in-hospital stay were taken from recorded per day charges in the 2018 OSHPD chargemaster document for LLUMC for a basic (Med-Surg) bed.

Incremental Cost-Effectiveness Ratios and Sensitivity Analysis

Incremental cost-effectiveness ratios (ICER) were calculated for each imaging-first treatment pathway considering the surgery first (BNE) group as the control in the assessment. ICERs were displayed as dollars spent per each additional percentage point gained in the cure rate relative to BNE ($/percent cure). Negative numbers represented cost savings associated with improved cure rates while positive numbers represented additional spending for improved cure rates. A tornado diagram was constructed to model the relative effects on ICER for advanced imaging produced by changes in the major analysis variables. Cost and time data were varied by ±50% and radiologic sensitivity was varied over a range of 0.5–1.0. As changes in three of five major variables (BNE time, MIP time, and operating room cost) produce the same relative changes in ICER across all imaging modalities, a single tornado diagram was
constructed with averaged changes in IECR for changes in radiology sensitivity and radiology costs. One-way sensitivity analyses were conducted to model the change in the primary input variables of interest: radiologic accuracy, cost for radiologic studies, operating room time, operating room costs, and surgical cure rates. Sensitivity analysis was not carried out for in-hospital length of stay as the cost differential was statistically similar between patients having BNE and MIP and did not impact overall cost differences. Sensitivity analyses were displayed graphically as change in the IECR (y-axis) for each unit of change in the variable of interest (x-axis). The threshold level for cost equivalence (IECR = 0) was marked graphically and calculated for each variable of interest.

RESULTS

Clinical Outcomes

Total operating room time for patients undergoing BNE for non-localizing disease was 145 ± 51 minutes, while

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<th>CMS limiting charges (per unit)</th>
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<th>Table I. Per Unit Charges for Cost Variables.</th>
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<td>Pathology &amp; Laboratory Fees</td>
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<td>Intraoperative PTH assay</td>
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4D-CT = four-dimensional computed tomography; CMS = Center for Medicare Services; SPECT = single photon emission computed tomography; SPECT/CT = single photon emission computed tomography/computed tomography.

Fig. 2. Tornado diagram of effect on IECR for changes in key cost variables. BNE = bilateral neck exploration; MIP = minimally-invasive parathyroidectomy.
total operating time was 106 ± 36 minutes for patients with localizing disease undergoing MIP. The average number of intraoperative PTH's drawn was 4.3 in the non-localizing group and 3.6 in the localizing group. Average number of frozen sections samples sent were 2.5 and 1.2 for non-localizing and localizing disease, respectively. Surgical cure rate was 97.3% for non-localizing disease with BNE and 99.2% for localizing disease with MIP. In-hospital stay duration was 0.5 ± 0.7 days and 0.4 ± 0.6 days for patients with non-localizing and localizing disease, respectively. Weighted averages based on available data for the sensitivity of SPECT, SPECT/CT, and 4D-CT were 71%, 86%, and 89% in all patients with hyperparathyroidism.\(^7,21-23\)

### Decision Tree Analysis

The overall success of BNE as the initial management step in non-localizing pHPT was 97.3% compared to
98.6%, 98.9%, and 99% for SPECT, SPECT/CT, and 4D-CT, respectively (Fig. 1). Individual/unit costs for each factor considered in the analysis are laid out in Table I. The overall cost for BNE was $9,578.45 and an IECR was not calculated for the BNE-first option as this strategy was designed as the reference case. Overall cost for SPECT + MIP was $8,196.79 with an IECR of −536.1. Overall cost for SPECT/CT + MIP was $8,271.19 with an IECR of −605.5. Total cost for 4D-CT + MIP was $8,146.05 with an IECR of −701.6. The total cost savings associated with imaging-first management strategies were $1,381.66, $1,307.26, and $1,432.40 per case for SPECT + MIP, SPECT/CT + MIP, and 4D-CT + MIP, respectively.

Sensitivity Analysis

Construction of a tornado plot revealed that variations in BNE time and MIP time generated the most significant change in IECR, followed by radiology sensitivity, operating room costs, and radiology costs (Fig. 2). One-way sensitivity analysis of radiologic accuracy is displayed in Figure 3. Thresholds for cost-effectiveness equivalence occurred at sensitivities of 0.391, 0.424, and 0.369 for SPECT, SPECT, and 4D-CT, respectively. Increased cost of radiologic studies by +81.4% for SPECT, +120.7% for SPECT/CT, and +142.2% for 4D-CT eliminated the cost-effectiveness of advanced imaging, as shown in Figure 4. Sensitivity analysis for changes in operative times for MIP and BNE are shown in Figures 5 and 6. Cost-effectiveness of advanced imaging prior to surgery decreased expectantly with increased MIP operative times, with cost-effectiveness thresholds at 131.8 minutes for SPECT, 134.9 minutes for SPECT/CT, and 139.2 minutes for 4D-CT. Cost-effectiveness of advanced imaging was inversely associated with BNE time on one-way sensitivity analysis, with cost-effectiveness thresholds (for BNE time) of 125.9 minutes for SPECT, 122.9 minutes for SPECT/CT, and 118.6 minutes for 4D-CT.

DISCUSSION

Despite advances in the preoperative workup of patients with pHPT, the decision to obtain further advanced imaging studies or proceed directly with parathyroid exploration remains a challenge in patients with non-localizing disease. BNE, the traditional gold standard, has demonstrated excellent cure rates and offers the opportunity to directly examine all parathyroid glands; however, operative times are increased compared to MIP. Advances in preoperative imaging have improved identification of glands that may be missed with the standard planar Tc-99 m sestamibi scan and neck ultrasound, offering the potential for MIP to this subset of patients.

Multiple imaging modalities have been studied in patients with non-localizing pHPT, including SPECT, SPECT/CT, and 4D-CT. While several studies demonstrated excellent localization with surgeon-performed ultrasound in patients presenting with negative sestamibi only, the parameters for this cost study assume that both sestamibi and ultrasound were non-localizing.13,14,24 Krishnamurthy et al. found that in patients with negative dual-phase planar sestamibi or iodine subtraction-SPECT, repeat iodine-subtraction SPECT/CT converted 75% and 86% of patients to positive localization respectively.13 Similarly, in a study by Lubitz et al., 4D-CT was found to precisely localize 60% and correctly lateralize 70% of glands that had been missed on planar sestamibi, while Seeliger et al. found that 52% of patients with negative imaging were accurately localized by thin-slice or 4D-CT.24–26 While some authors have reported less impressive conversion rates from negative to positive imaging with further scans—Joon Suh et al. found 4D-CT to localize only 8% of patients with negative sestamibi and ultrasound—reports have been predominantly positive.13,14,25–29

While some have shown improved localization rates with newer imaging modalities in nonlocalizing pHPT, other authors report excellent outcomes for BNE without further imaging.8,16,30,31 Chan et al. reported 97.6% cure...
rate without complications following intraoperative PTH guided neck exploration protocol in 42 patients with non-localizing pHPT. Utilizing a similar protocol, our institution has previously demonstrated equivalent cure and complication rates for BNE patients with non-localizing pHPT compared to MIP patients with localizing disease. Overall, the unique challenges of non-localizing disease suggest a more nuanced consideration of management strategies, assessing factors such as cost, institutional abilities, and various aspects of patient-centered quality.

In patients with pHPT but no imaging, localization studies are cost-effective compared to routine BNE. Both Lubitz et al. and Fahy et al. found limited parathyroid surgery to be cost-effective versus BNE, with cost-savings derived from reductions in operative time and in-hospital length of stay. Similarly, we found overall cost-effectiveness to be highly sensitive to changes in operative times, with only 19–27 minute (13–19%) reductions in BNE time or 26–33 minute (25–31%) increases in MIP time required to reach the threshold of cost-equivalence, compared to the 81% to 142% increases in radiology prices required to ameliorate the cost benefits. Notably, the cost effectiveness of preoperative localization is system dependent, as the United Kingdom's NHS scheme has reported the cost of localizing studies is not completely offset by savings from shorter operative times or inpatient stays.

The most cost-effective management strategy in our analysis was 4D-CT, with an overall cost savings of $1,432 and IECR of $701, due to its excellent sensitivity and resulting increase in the number of patients having MIP. These results are consistent with findings from other groups, including Lubitz et al. who found 4D-CT to be cost-effective compared to BNE in patients without preoperative imaging, patients with negative ultrasound, and patients with negative SPECT. SPECT, which was the second most cost-effective strategy in our analysis has similarly been confirmed by Rudin et al. to reduce costs compared to BNE in patients with previously negative planar sestamibi. With increased use of imaging, however, comes additional radiation exposure. While there is little data explicitly regarding cancer risk following CT scan, epidemiological data from radiation exposure survivors have estimated that up to 0.4% of all cancers in the USA may be attributed to medical imaging-related radiation exposure. Consequently, unnecessary radiation exposure from medical imaging is a significant issue in quality of care discussions. 4D-CT radiation exposure is 10.4 mSv (average annual background radiation exposure is 3 mSv) at some institutions with SPECT exposing patients to 7.8 mSv. Although protocols and radiation exposure vary by institution, with one study reporting only 5.6 mSv exposure for 4D-CT, it is important to consider cumulative radiation doses in patients with non-localizing disease who have already been exposed to elevated radiation levels (3.3 mSv) from standard preoperative sestamibi scans. Thus, it is reasonable to elect for operation without further imaging in order to maximize this facet of patient safety.

We acknowledge the limitations to this study. One notable limitation was the use of a cost-effectiveness study design as opposed to cost-utility analysis. Since clinical outcomes and complication rates following BNE for non-localizing disease are similar compared to those of localizing disease, the differences in post-operative quality of life changes were felt to be minimal. Additionally, there is significant heterogeneity in published quality of life adjustment factors for parathyroidectomy patients, limiting the accuracy and generalizability of a utility analysis. Also notable is the fact that available radiologic data for the imaging modalities assessed included all patients with pHPT and was not specific to patients with previously non-localizing disease, who are known to have increased incidence of multinodular disease and generally smaller pathologic glands. Accordingly, available data may overestimate imaging accuracy in localizing diseased parathyroid glands and potentially skew the results towards an imaging-first management strategy.

The surgical and radiological factors this analysis uses are highly variable. While we previously showed that outcomes are similar for localized and non-localized cases (although operative time is increased by non-localization), these distinctions may be surgeon-dependent. Additionally, the accuracy of radiographic modalities available to the surgeon may vary by institution.

This study also does not consider other patient-related factors that may influence treatment decisions. The costs related to time and inconvenience for patients were not factored into this analysis and may be increased with additional imaging. Particularly at centers with referrals from a large catchment area, the difficulty of repeated travel for imaging and surgical appointments may lead some patients to elect for routine BNE.

CONCLUSION

In patients with pHPT that is non-localizing on ultrasound and sestamibi, further imaging with 4D-CT, SPECT, or SPECT/CT is associated with cost-savings—greatest with 4D-CT—and increased cure rates. However, these imaging modalities are not entirely benign interventions, with risks that must be weighed against moderate potential benefit relative to BNE.

BIBLIOGRAPHY
