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Impact of perioperative diagnostic tools on clinical outcomes and cost-effectiveness in parathyroid surgery: a decision model-based analysis

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ABSTRACT

Objectives Preoperative and intraoperative diagnostic tools influence the surgical management of primary hyperparathyroidism (PHPT), whereby their performance of classification varies considerably for the two common causes of PHPT: solitary adenomas and multiglandular disease. A consensus on the use of such diagnostic tools for optimal perioperative management of all PHPT patients has not been reached.

Design A decision tree model was constructed to estimate and compare the clinical outcomes and the cost-effectiveness of preoperative imaging modalities and intraoperative parathyroid hormone (ioPTH) monitoring criteria in a 21-year time horizon with a 3% discount rate. The robustness of the model was assessed by conducting a one-way sensitivity analysis and probabilistic uncertainty analysis.

Setting The US healthcare system.

Population A hypothetical population consisting of 5000 patients with sporadic, symptomatic or asymptomatic PHPT.

Interventions Preoperative and intraoperative diagnostic modalities for parathyroidectomy.

Main outcome measures Costs, quality-adjusted life-years (QALYs), net monetary benefits (NMBs) and clinical outcomes.

Results In the base-case analysis, four-dimensional (4D) CT was the least expensive strategy with US\$10 276 and 15.333 QALYs. Ultrasound and ^{99m}Tc-Sestamibi single-photon-emission CT/CT were both dominated strategies while ^{18}F-fluorocholine positron emission tomography was cost-effective with an NMB of US\$416 considering a willingness to pay a threshold of US\$95 958. The application of ioPTH monitoring with the Vienna criterion decreased the rate of reoperations from 10.50 to 0.58 per 1000 patients compared to not using ioPTH monitoring. Due to an increased rate of bilateral neck explorations from 257.45 to 347.45 per 1000 patients, it was not cost-effective.

Conclusions 4D-CT is the most cost-effective modality for the preoperative localisation of solitary parathyroid adenomas and multiglandular disease. The use of ioPTH monitoring is not cost-effective, but to minimise clinical complications, the Miami criterion should be applied for suspected solitary adenomas and the Vienna criterion for multiglandular disease.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Our decision tree model is the most complete for parathyroidectomy; incorporating both solitary adenomas and multiglandular disease and intraoperative parathyroid hormone monitoring.
⇒ In addition to cost-effectiveness, we present the impact of the interventions on the major clinical outcomes.
⇒ Our study is limited to the USA and was conducted from the perspective of the healthcare system.
⇒ The model did not consider the potential institutional variations in the prevalence of multiglandular disease.
⇒ There remains uncertainty for certain parameters of the model as they were derived from a limited number of single-institution studies.

INTRODUCTION

Primary hyperparathyroidism (PHPT) is a common endocrine disorder with a prevalence of 1–7 cases per 1000 adults and is the primary reason for hypercalcaemia.[1] In 70%–90%, 10%–30% and less than 1% of the cases, the underlying cause is a single gland parathyroid adenoma, multiglandular disease (MGD) and parathyroid carcinoma, respectively.[2] Even though PHPT is often diagnosed at an asymptomatic stage, the surgical removal of the diseased tissue is generally recommended due to the long-term deleterious effects of PHPT and remains the only curative treatment.[3]

To optimise surgical cure rates and reduce operative trauma, surgeons often rely on imaging technologies and specialists for the preoperative localisation of the diseased gland(s). If a solitary adenoma is suspected, a focused parathyroidectomy (FP) might be performed with a cure rate that is comparable to the conventional bilateral neck exploration (BNE).[4] FP is associated with reduced operative times, risk of developing postoperative hypoparathyroidism and recurrent laryngeal nerve (RLN) injury compared with BNE.[5] However, the sensitivity of a preoperative localisation varies not only between the different preoperative diagnostic modalities but also between single adenomas (0.55–0.92) and MGD (0.25–0.6).[6–9]

If an FP is performed, an intraoperative parathyroid hormone (ioPTH) monitoring is recommended to exclude MGD and to avoid reoperations.[10] The two most common criteria for defining surgical success, measured as a 50% decline of the ioPTH level 10 min after resection, use different baselines. The Miami criterion uses the highest ioPTH level (preincision or pre-excision) as the baseline, while the Vienna criterion uses the preincision ioPTH level as the baseline.[11]

The overall clinical utility of ioPTH monitoring is under debate as the two criteria possess a differential risk of producing false negative (incorrectly suggesting additional diseased adenomas) and false positive (incorrectly suggesting that all diseased adenomas were removed) results.[12] Furthermore, the application of ioPTH monitoring would require additional resources: increased surgery time and the cost of the procedure.[13] Finally, as pointed out in a recent systematic review, the cure rate for FP without ioPTH monitoring is higher (99.3%) than with ioPTH monitoring (98.1%).[14]

Some recent cost-effectiveness analyses focused only on preoperative imaging modalities without considering the inclusion of patients with MGD and reoperations.[15] Other health economic evaluations only assessed the cost of preoperative localisation and ioPTH monitoring, without addressing the potential health outcomes.[12] The absence of evidence on the clinical benefits and cost-effectiveness of using either criterion for the ioPTH evaluation contributes to the lack of consensus on whether the use of ioPTH monitoring is warranted and what criterion should be for solitary adenomas and MGD.[12]

Thus, this study aims to estimate the clinical outcomes and the cost-effectiveness of common preoperative imaging modalities and ioPTH monitoring criteria for patients with sporadic, symptomatic or asymptomatic PHPT by decision analytical modelling. The major objectives of the study are the (1) assessment of the cost-effectiveness of the four common preoperative modalities, (2) the added value of ioPTH monitoring and (3) the comparison of the clinical utility of ioPTH monitoring with the Miami and the Vienna criterion.

METHODS

Decision analytical model

We structured the clinical decision-making problem using the decision analytical modelling framework, where the architecture of the model is in the form of a decision tree model. We simulated a hypothetical population consisting of 5000 male and female patients aged 58 years with sporadic PHPT (symptomatic or asymptomatic) who met the recently updated National Institutes of Health criteria for parathyroid surgery and were eligible for Medicare reimbursements.[10] Due to differences in their decision tree model structure, we did not include patients with secondary and tertiary HPT in our analysis. The available strategies included four preoperative imaging modalities: ultrasound, ^{99m}Tc-Sestamibi single-photon-emission computed tomography (SPECT)/CT, four-dimensional (4D) CT, ^{18}F-fluorocholine positron emission tomography (FCH-PET/CT). For each preoperative imaging modality, the use of ioPTH monitoring was considered. The baseline value below which a decrease of ioPTH concentration is considered positive was determined by applying either the Miami or Vienna criterion.

For patients with a solitary adenoma, an FP was performed after a successful preoperative localisation and an adequate decrease of ioPTH. A false negative localisation of a solitary adenoma resulted in BNE while a false positive localisation led first to a unilateral neck exploration (UNE) and in cases where the adenoma was located on the contralateral side to a BNE.

For patients with MGD, a true positive localisation and a true positive decrease of ioPTH led to either a UNE or BNE, depending on the localisation of the adenomas, whereas a false negative decrease of ioPTH resulted in a BNE. A false positive localisation of MGD with a false positive decrease of ioPTH leads to a reoperation after UNE or BNE. A false positive localisation of MGD with a true negative decrease of ioPTH leads to a BNE. A false negative localisation leads to a BNE. Figure 1 depicts a simplified version of the decision tree model.

We incorporated the following assumptions into the model. First, an adenoma can always be differentiated macroscopically from a normal parathyroid gland by the surgeon in the absence of ioPTH monitoring. Second, in case of a successful preoperative localisation with an adequate decrease of ioPTH, the surgeon would base his decisions solely on the ioPTH decrease and refrain from further explorations. This assumption implies that, in the case of a false positive localisation of a single adenoma, the surgeon would perform a UNE/BNE irrespective of the ioPTH readout. Therefore, we did not consider false positive and true negative ioPTH readouts for these events. Since a false positive localisation misses an adenoma in MGD, we considered false positive and true negative ioPTH readouts in this case. The time horizon of the analysis was 21 years, which was estimated from the patient demographic data of a recent systematic review.[14] This calculation considered the life expectancy of 58-year-old patients[14] derived from the current US life table[16] assuming a female/male ratio of 3.4:1 (85% and 15%).[14] The time horizon was assumed to be uniform across the different surgeries. To simplify the model, we assumed that the probability of complications, costs and utilities for UNE are identical to those of FP based on a randomised controlled trial.[17] For reoperations, we considered the same model architecture with an increased risk of complications.[18] As PHPT patients with a solitary adenoma and MGD tend to have similar clinical features,[19] we assumed an identical disease model for

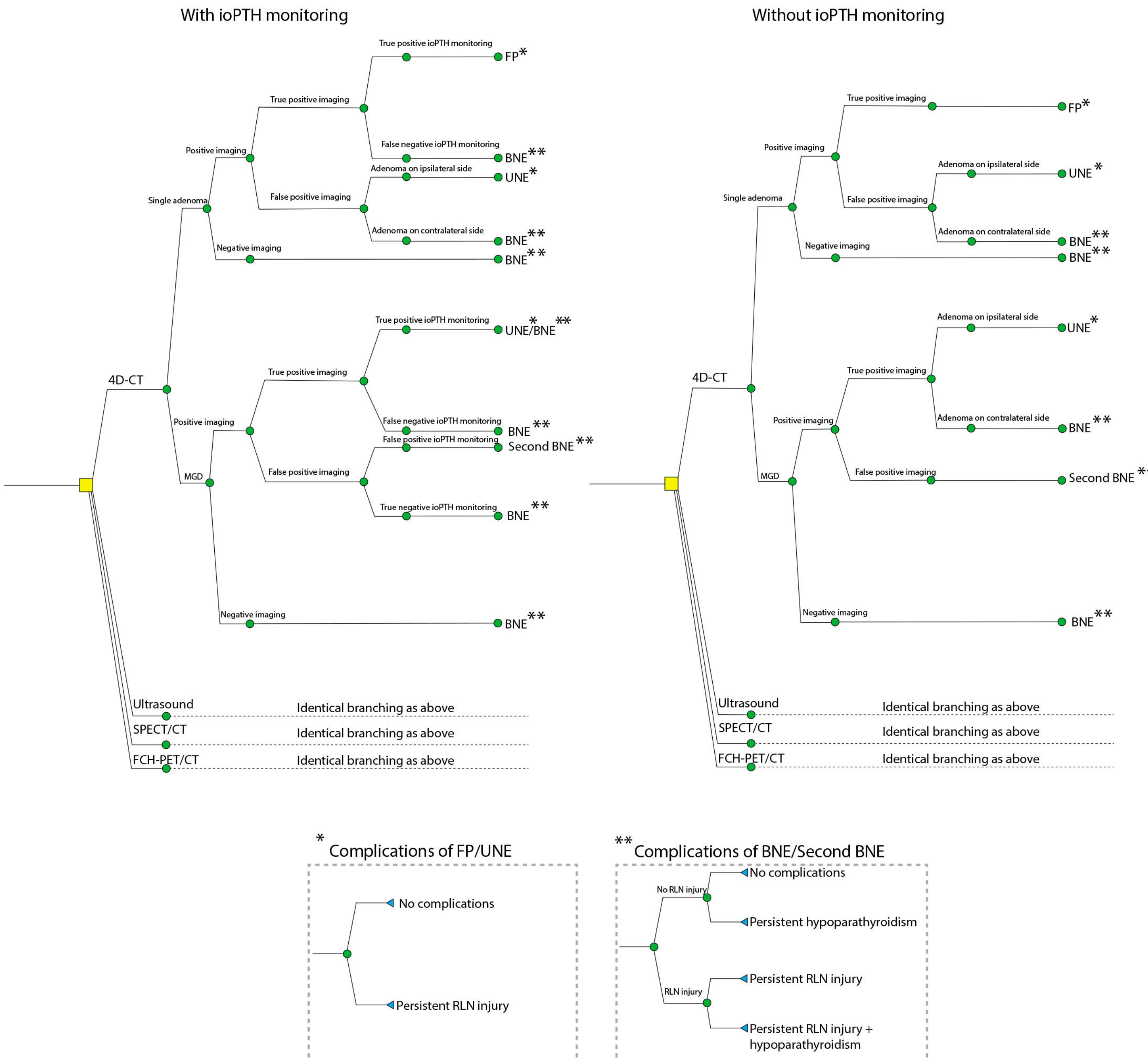

Figure 1 Simplified illustration of the decision tree model. 4D, four dimensional; BNE, bilateral neck exploration; FCH-PET/CT, fluorocholine positron emission tomography; FP, focused parathyroidectomy; RLN, recurrent laryngeal nerve; SPECT/CT, 99mTc- Sestamibi single-photon-emission/CT; UNE, unilateral neck exploration.

both cases. Lastly, we assumed FP and BNE to be carried out in an outpatient and inpatient setting, respectively.

When available, estimates for the probability parameters were derived from the latest systematic reviews. The prevalence of solitary adenomas was taken from the latest surgical guideline by the American Association of Endocrine Surgeons, which was based on a comprehensive review of published papers from 1985 to 2015 by a multidisciplinary panel of experts.[20] The sensitivity and positive predictive value (PPV) of ultrasonography in MGD were obtained from a systematic literature review between 1995 and 2003.[7] The sensitivity and PPV of SPECT/CT, 4D-CT and FCH-PET/CT were retrieved from the latest systematic reviews,[6 8] whereas the sensitivity and PPV for FCH-PET/CT in MGD was taken from a single-institution study.[9] The sensitivity and specificity of the different ioPTH criteria were estimated from two single-institution studies with 570 patients.[11 21] The probabilities of developing persistent postoperative hypoparathyroidism and persistent RLN injury were estimated from a randomised controlled trial with 91 patients.[17] Table 1 lists all the model parameters' estimates and their sources.

The construction of the decision tree model and the analyses were performed using Python V.3.9. The Python codes are publicly available at https://github.com/danielbatora/batora_phpt_cea.

Table 1 Estimated values for each parameter in the decision tree model

Parameter	Base case value	Lower limit	Upper limit	Upper/lower limits presented as	References
Prevalence of single adenomas	0.85	–	–	–	10 20
Prevalence of two ipsilateral adenomas	0.02	–	–	–	20
Sensitivity of SPECT/CT for single adenomas	0.69	0.63	0.75	95% CI	8
Sensitivity of SPECT/CT for MGD	0.25	0.08	0.42	95% CI	8
PPV of SPECT/CT for single adenomas	0.91	0.84	0.96	95% CI	6
PPV of SPECT/CT for MGD	0.91	0.84	0.96	95% CI	6
Sensitivity of ultrasound for single adenomas	0.55	0.47	0.63	95% CI	8
Sensitivity of ultrasound for MGD	0.35	0.30	0.40	95% CI	7
PPV of ultrasound for single adenomas	0.86	0.85	1.00	95% CI	8
PPV of ultrasound for MGD	0.93	0.85	1.00	95% CI	7
Sensitivity of 4D-CT for single adenomas	0.82	0.74	0.89	95% CI	8
Sensitivity of 4D-CT for MGD	0.60	0.53	0.68	95% CI	8
PPV of 4D-CT for single adenomas	0.88	0.84	0.95	95% CI	8
PPV of 4D-CT for MGD	0.88	0.84	0.95	95% CI	8
Sensitivity of FCH-PET/CT for single adenomas	0.92	0.90	0.97	95% CI	6 9
Sensitivity of FCH-PET/CT for MGD	0.52	0.38	0.88	Range	6 9
PPV of FCH-PET/CT for single adenomas	0.92	0.90	1.00	Range	6 9
PPV of FCH-PET/CT for MGD	0.92	0.90	1.00	Range	6 9
Sensitivity of ioPTH monitoring (Miami protocol)	0.98	–	–	–	11 13
Sensitivity of ioPTH monitoring (Vienna protocol)	0.87	–	–	–	11 13
Specificity of ioPTH monitoring (Miami protocol)	0.74	–	–	–	11 13
Specificity of ioPTH monitoring (Vienna protocol)	0.95	–	–	–	11 13
Probability of persistent RLN injury in FP	0.005	0	0.01	Range	17
Probability of persistent RLN injury in BNE	0.01	0	0.08	Range	17
Probability of persistent RLN injury in second BNE	0.04	0.02	0.06	Range	16
Probability of persistent hypoparathyroidism in BNE	0.01	0.01	0.02	Range	17
Probability of persistent hypoparathyroidism in second BNE	0.01	0.01	0.02	Range	16
Probability of persistent RLN injury and persistent hypoparathyroidism in BNE	0.01	0.01	0.02	Range	15 17
Probability of persistent RLN injury and persistent hypoparathyroidism in second BNE	0.01	0.01	0.02	Range	16
Utility weight for BNE without complications	0.99	–	–	–	15
Utility weight for BNE with persistent RLN injury	0.76	–	–	–	15 25 26 35
Utility weight for BNE with persistent hypoparathyroidism	0.84	–	–	–	15 25 26 35
Utility weight for BNE with persistent RLN injury and persistent hypoparathyroidism	0.60	–	–	–	15 25 26 35
Cost for surgery ($) (CPT 60500)	6192	–	–	–	22
Cost for anaesthesia (base unit×CF) ($) (CPT 00320)	129	–	–	–	23 24
Cost for SPECT/CT ($) (CPT 78072)	574	–	–	–	22 36
Cost for ultrasound ($) (CPT 76536)	117	–	–	–	22 36
Cost for 4D-CT ($) (CPT 72127)	244	–	–	–	22 36
Cost for FCH-PET/CT ($) (CPT 78814, CPT A9552)	1974	–	–	–	22 36
Cost for ioPTH monitoring ($) (CPT 83970)	194	–	–	–	15 22
Cost for outpatient hospital stay ($) (CPT 99223)	2270	–	–	–	24
Cost for inpatient hospital stay ($) (CPT 99217)	4804	–	–	–	24

Continued

Table 1 Continued

Parameter	Base case value	Lower limit	Upper limit	Upper/lower limits presented as	References
Operative time for FP (min, time unit)	38, 3	–	–	–	[24]
Operative time for UNE (min, time unit)	38, 3	–	–	–	[24]
Operative time for BNE (min, time unit)	104, 6	–	–	–	[24]
Additional operative time for ioPTH monitoring (min, time unit)	40, 3	–	–	–	[13 21]
Discount rate (%)	3	–	–	–	[28]
Time horizon (years)	21	–	–	–	[14]

BNE, bilateral neck exploration; CPT, Current Procedural Terminology; 4D-CT, four-dimensional-CT; FCH-PET/CT, ^{18}F-fluorocholine positron emission tomography; FP, focused parathyroidectomy; ioPTH, intraoperative parathyroid hormone; MGD, multiglandular disease; PPV, positive predictive value; RLN, recurrent laryngeal nerve; SPECT/CT, ^{99m}Tc-Sestamibi single-photon-emission/CT; UNE, unilateral neck exploration.

Patient and public involvement

As our study modelled a hypothetical cohort of patients, we did not involve patients or the public.

Cost-effectiveness analysis

The cost-effectiveness analysis was conducted from the healthcare payer perspective, focusing on the USA. To calculate the total costs for each strategy, we considered the costs of the preoperative imaging modality, ioPTH assay, hospital stay (depending on the procedures) and the surgery time multiplied by the costs of the operating theatre per minute. Costs were reported in 2022 US dollars. Current Procedural Terminology (CPT)-based physician and facility costs of surgery (CPT 60500), imaging (CPT 78072, CPT 76536, CPT 72127, CPT 78814 and CPT A9552) and ioPTH monitoring (CPT 83970) were derived from the US medical reimbursement schedule.[22] As FCH-PET/CT is currently not authorised in the USA, we combined the cost of a neck PET/CT scan (CPT 78814) with the price of the most commonly used radiotracer, ^{18}F-fluorodeoxyglucose (CPT A9552).

We calculated anaesthesiology fees (CPT 00320) by multiplying the base and time units, and the national average anaesthesia conversion factor (CF) taken from the 2022 Centers for Medicare & Medicaid Services release.[23] The base unit for CPT 00320 was 6, and the time units were expressed in 15 min increments. The national average anaesthesia CF was 21.5623. The length of surgeries was converted into time units. The costs for outpatient (CPT 99223) and inpatient (CPT 99217) hospital services were derived from a previous study,[24] which calculated the costs for the diagnostic-related group 627.

We expressed the effectiveness of each intervention as quality-adjusted life-years (QALYs), which were calculated by multiplying the life expectancy by utility weights. The utility weights for persistent hypoparathyroidism and RLN injury, where a utility value of 1 corresponds to a perfect state of health and 0 corresponds to being dead, were derived from previous studies that used Short Form 36-Item Health Survey and the standard gamble method.[25 26] As metrics for cost-effectiveness, we used incremental cost-effectiveness ratios (ICER) and the net monetary benefit (NMB). The ICER was calculated by dividing the incremental costs with the incremental QALYs both compared with the least expensive strategy as a reference. The NNB was calculated as the difference between two measures: (1) the total effectiveness times the willingness-to-pay (WTP) threshold, which values the effectiveness generated by the intervention in terms of the opportunity cost forgone and (2) the total cost of the intervention.[27] We applied an equal 3.0% discount rate for both costs (reoperations with a mean follow-up of 2 years[14]) and QALYs according to the latest US guidelines extracted from a systematic review.[28] We evaluated the impact of discounting on the outcomes of the base case analysis by applying a 1.5% and 0% discount rate. We evaluated the following clinical outcomes, that is, the probabilities of reoperation due to missed MGDs, BNE, persistent postoperative hypoparathyroidism and persistent RLN injury, by calculating the proportion of people experiencing these events in the simulated cohort. To simplify the model, we did not account for radiation exposure for preoperative imaging modalities (4D-CT, SPECT/CT and FCH-PET/CT). For the base case analysis, we report incremental costs, QALYs, the ICER and NMBs for each modality compared with the least expensive modality.

Sensitivity and uncertainty analyses

To determine the influence of each model parameter on the model outcomes, we conducted a one-way sensitivity analysis by varying the parameter values within ±50% of their base case values and evaluating the resulting effect on the NMBs. The sensitivity analysis was performed on all parameters, and its result was presented as a tornado diagram, which ranks model parameters according to their influences. To account for the effect of uncertainty in the model parameter estimates, we conducted an uncertainty analysis using a Monte Carlo sampling approach. For probabilities and utility weights, we fitted beta distributions, where the parameters were estimated by using the method of moments.[29] For costs, gamma distributions were used, and we followed the same approach for estimating their parameters. When 95% CIs were available, we assumed that the CIs were 1.98×2 SD wide. When only the lower and upper limits were reported, we assumed the limits to be equal to the 95% CIs. We generated 5000 random samples of the parameters' estimates from the corresponding beta and gamma distributions and evaluated our model at each sample. We presented the results of the uncertainty analysis using scatter plots and cost-effectiveness acceptability curves. We calculated the cost-effectiveness threshold for the WTP of US$95 958 depicted in the scatter plots against the mean cost and utility of the least expensive strategy. To identify the values of the influential parameters at which the conclusions of the cost-effectiveness analyses change (from being cost-effective to not cost-effective), we performed threshold analyses. The selection of the influential parameters was based on the results of the sensitivity analyses.

RESULTS

Cost-effectiveness analysis

Base case analysis

The least expensive preoperative localisation modality was 4D-CT with US$10 276 and 15.333 QALYs, which was followed by ultrasound with US$10 732 and 15.297 QALYs and the SPECT/CT with US$10 774 and 15.319 QALYs (table 2). FCH-PET/CT was the most expensive modality with a cost of US$11,619, although it provided 15.352 QALYs (table 2, online supplemental table 1). At a US$95 958 WTP threshold, FCH-PET/CT resulted in an NMB value of US$416 (ICER: US$73 251 per QALY gained). For all imaging modalities, the addition of ioPTH monitoring generated higher costs and fewer QALYs, thereby making them dominated strategies (table 2). The use of the Miami criterion was found to be less expensive and associated with more QALYs in all cases when compared with using the Vienna criterion (table 2). The comparison of the two non-dominated strategies is depicted in online supplemental table 1. We further evaluated the base case analysis of the two non-dominated strategies with 1.5% and 0% discount rate, resulting in an INMB of US$700 (ICER US$63 082) and US$1062 (ICER US$53 414), respectively (online supplemental table 1).

Sensitivity analysis

We conducted two one-way sensitivity analyses focusing on comparing the non-dominated preoperative localisation strategies and ioPTH monitoring. In the comparison between the non-dominated preoperative localisation strategies without ioPTH monitoring, that is, the 4D-CT compared with FCH-PET/CT, the model was most sensitive to the prevalence of single adenomas with NMB ranging from −US$7345 to US$3050, the sensitivity of FCH-PET/CT for single adenomas with NMB ranging from −US$7082 to US$1990, the PPV of FCH-PET/CT

Table 2 Base case analysis for all interventions

Intervention	Total costs ($)	QALYs	Incremental costs ($)	Incremental QALYs	ICER	INMB
4D-CT without ioPTH monitoring	10 276	15.333	0	0	0	0
Ultrasound without ioPTH monitoring	10 732	15.297	456	−0.036	−12667 (D)	−3906
SPECT/CT without ioPTH monitoring	10 774	15.319	498	−0.014	−35571 (D)	−1841
4D-CT with ioPTH monitoring (Miami criterion)	10 804	15.332	528	−0.001	−528000 (D)	−624
4D-CT with ioPTH monitoring (Vienna criterion)	10 971	15.321	695	−0.012	−57917 (D)	−1846
Ultrasound with ioPTH monitoring (Miami criterion)	11 284	15.297	1008	−0.036	−28000 (D)	−4462
SPECT/CT with ioPTH monitoring (Miami criterion)	11 370	15.317	1094	−0.016	−68375 (D)	−2629
Ultrasound with ioPTH monitoring (Vienna criterion)	11 400	15.289	1124	−0.044	−25546 (D)	−5346
SPECT/CT with ioPTH monitoring (Vienna criterion)	11 534	15.307	1258	−0.026	−48385 (D)	−3753
FCH-PET/CT without ioPTH monitoring	11 619	15.352	1343	0.019	73 251	416
FCH-PET/CT with ioPTH monitoring (Miami criterion)	12 226	15.349	1950	0.016	121 875	−415
FCH-PET/CT with ioPTH monitoring (Vienna criterion)	12 449	15.335	2173	0.002	1 086 500	−1981

D, dominated strategy; 4D-CT, four-dimensional CT; FCH-PET/CT, ^{18}F-fluorocholine positron emission tomography; ICER, incremental cost-rffectiveness ratio; INMB, incremental net monetary benefit; ioPTH, intraoperative parathyroid hormone; QALYs, quality-adjusted life-years; SPECT/CT, ^{99m}Tc-Sestamibi single-photon-emission/CT.

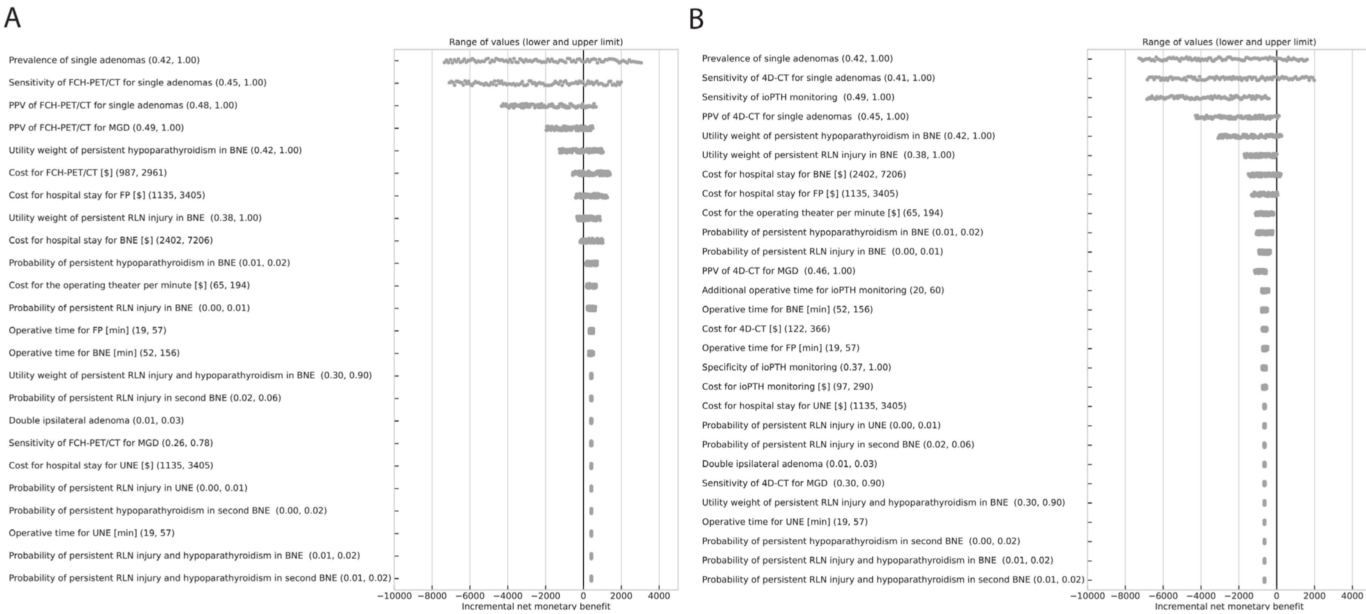

Figure 2 One-way sensitivity analysis. (A) Variation of the parameters of the ^{18}F-fluorocholine positron emission tomography (FCH-PET/CT) without intraoperative parathyroid hormone (ioPTH) monitoring within ±50% of their base case values. Incremental net monetary benefits were calculated in comparison with the base case values of the four-dimensional CT (4D-CT) without ioPTH monitoring, as this was the least expensive intervention in our base case analysis. (B) Incremental net monetary benefits of 4D-CT with ioPTH monitoring were calculated in comparison with the base case values of the 4D-CT without ioPTH monitoring. BNE, bilateral neck exploration; FP, focused parathyroidectomy; MGD, multiglandular disease; PPV, positive predictive value; RLN, recurrent laryngeal nerve; UNE, unilateral neck exploration.

for single adenomas and MGD with NMB ranging from −US$4333 to US$660 and −US$1967 to US$489, and the cost of the FCH-PET/CT with NMB ranging from −US$573 to US$1406, respectively (figure 2A).

In the comparison of the with and without ioPTH monitoring strategies for 4D-CT imaging, the model was most sensitive to the prevalence of solitary adenomas with NMB ranging from −US$7262 to US$1603, followed by the sensitivity of ioPTH monitoring with NMB ranging from −US$6852 to −US$410, the sensitivity of the 4D-CT for single adenomas with NMB ranging from −US$6834 to US$1984, and the PPV of 4D-CT for single adenomas with NMB ranging from −US$4283 to US$120. Furthermore, the results were sensitive to the cost for outpatient and inpatient hospital stay (−US$1492 to $221, −US$1 325 to US$51), the utility weights for complications (persistent hypoparathyroidism (−US$3094 to US$255) and RLN injury (−US$1707 to US$10) and the cost of the operating theatre per minute (−US$1117 to −US$162) (figure 2B).

Uncertainty analysis

When accounting for uncertainties in all parameters, the 4D-CT without ioPTH monitoring was the least expensive strategy with US$10 282 (95% CI US$10 286 to US$10 296) and 15.3333 QALYs (95% CI 15.3331 to 15.3335). The most expensive and the only non-dominated intervention was the FCH-PET/CT with US$11 609 (95% CI US$11 607 to US$11 626) and 15.3520 QALYs (95% CI 15.3519 to 15.3521) (online supplemental table 2). For the rest of the interventions, the point estimates from the uncertainty analysis were similar to the base case analysis with narrow 95% CIs and are depicted in online supplemental table 2. The results of all simulations are shown in online supplemental figure 1A. Varying the WTP thresholds from US$20 000 to US$287 874 revealed that the FCH-PET/CT is unlikely to be cost-effective at WTP thresholds below US$75 000 (online supplemental figure 1B). The influence of the variation within the uncertainty estimates for each parameter is depicted in online supplemental figure 2.

Threshold analysis

For 4D-CT, we identified the values for different parameters that would render the ioPTH monitoring with the Miami criterion cost-effective: an MGD prevalence of more than 50%, a PPV of 4D-CT for detecting MGD of less than 69%, a probability of persistent hypoparathyroidism due to reoperation of more than 37% and a probability of persistent RLN injury due to reoperation of more than 26% (online supplemental figure 3).

Clinical outcomes by using the Miami or Vienna criterion for ioPTH monitoring

By using 4D-CT with the Miami criterion, the rate of reoperations decreased from 10.50 to 2.77 per 1000 patients compared with not using ioPTH monitoring. With the Vienna criterion, which has a higher specificity, the rate of reoperations decreased to 0.58 per 1000 patients compared with not using ioPTH monitoring.

With the Miami criterion, the rate of BNEs increased from 257.45 to 274.34 per 1000 patients while it increased to 347.45 per 1000 patients with the Vienna criterion due

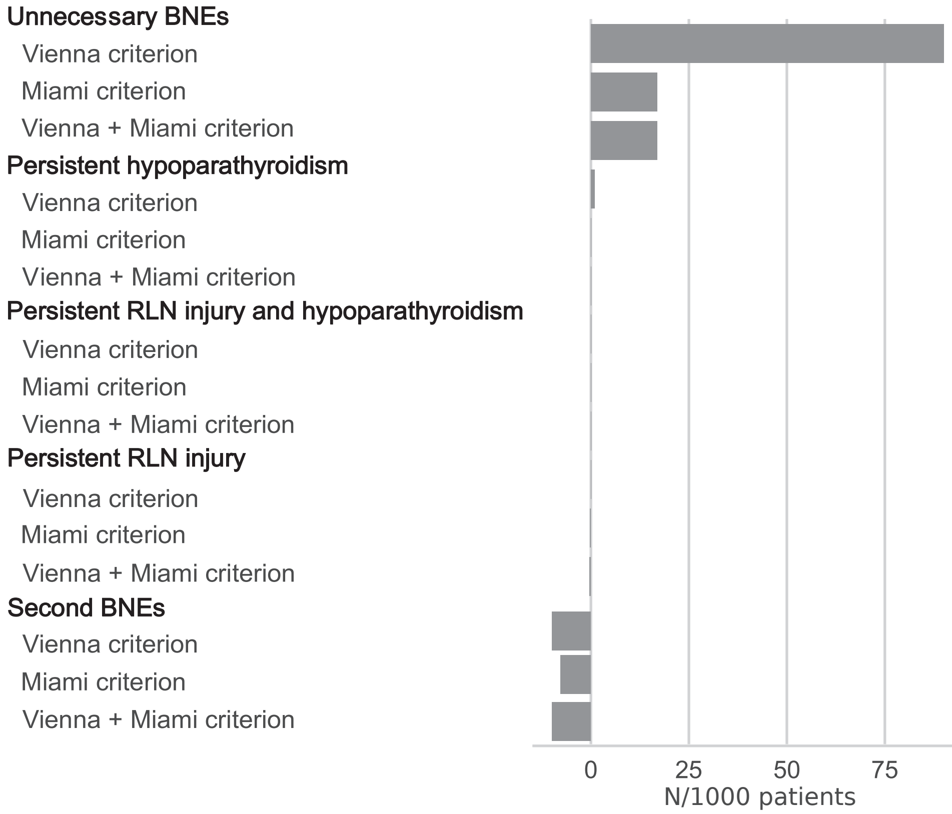

Figure 3 The impact of different intraoperative parathyroid hormone (ioPTH) criteria on the main clinical events using four-dimensional-CT. Differences in clinical events per 1000 parathyroidectomies compared with patients without ioPTH monitoring. BNE, bilateral neck exploration; RLN, recurrent laryngeal nerve.

to its lower sensitivity compared with not using ioPTH monitoring.

The rate of complications associated with the surgery was higher with the Vienna criterion: the overall probability of persistent hypoparathyroidism and persistent RLN injury increased from 2.91 to 3.81 per 1000 patients and from 1.68 to 1.74 per 1000 patients, respectively, compared with not using ioPTH monitoring. With the Miami criterion, the rate of persistent hypoparathyroidism increased to 3.03 per 1000 patients, whereas the rate of persistent RLN injury decreased to 1.45 per 1000 patients compared with not using ioPTH monitoring (figure 3). With all the other preoperative imaging modalities, the trends were generally similar (online supplemental table 3).

DISCUSSION

This study evaluated the clinical impact and cost-effectiveness of preoperative and intraoperative diagnostic tools in the surgical management of PHPT in the USA. The study has three major results. First, 4D-CT alone was found to be the least extensive preoperative localisation strategy and FCH-PET/CT to be cost-effective near the US WTP threshold. Second, the addition of ioPTH monitoring decreased the frequency of reoperations; however, it was not cost-effective due to a higher rate of BNEs, in addition to the assay and anaesthesia costs. Third, the rate of BNEs was considerably higher and the reoperation rate was lower when using the Vienna criterion instead of the Miami criterion.

An accurate localisation of parathyroid adenoma(s) is a vital component of the preoperative planning of parathyroid surgery. Our analysis demonstrated that 4D-CT was the least expensive preoperative imaging modality while both SPECT/CT and ultrasound were more expensive and provided fewer QALYs than 4D-CT. FCH-PET/CT was superior to 4D-CT in terms of the QALYs gained and is likely cost-effective below a US$75 000 WTP threshold. Of note, the use of FCH-PET/CT is reserved for the localisation and staging of cancer cases in the USA, however, it is widely used for the localisation of single adenomas in Europe.[15] Our results were consistent with the most recent cost-effectiveness analysis[15] despite using more conservative estimates for the diagnostic performance parameters of several preoperative localisation strategies (ultrasound, SPECT/CT and 4D-CT) from the latest meta-analyses. A plausible explanation for reaching a comparable conclusion might lie in the inclusion of MGD cases in our study, for which the preoperative localisation is considerably less accurate.[6 7]

Even though our analysis showed 4D-CT imaging to be the least expensive strategy, the use of 4D-CT as the first-in-line preoperative imaging modality in the future could be restricted to centres with a high frequency of PHPT cases, as its operation requires considerable radiological training. Along this line, it will be important to factor in the excess radiation exposure in the evaluation of using 4D-CT as the first-line or second-line imaging modality.[30] Due to limited available data, our model could not evaluate the cost-effectiveness of the sequential application of preoperative imaging modalities, which is commonly applied in clinical practice to reserve the more expensive modalities for cases where the first-line treatment is likely less accurate.

In our analysis, the addition of ioPTH monitoring was not cost-effective, even though it led to a significantly reduced number of reoperations. The clinical benefit of ioPTH monitoring was outweighed by erroneous classifications by the method, resulting in a substantial increase of unnecessary BNEs. Additionally, the sensitivity analysis revealed that the sensitivity of the assay and the occupancy of the operating theatre were key determinants in the cost-effectiveness of ioPTH monitoring. In line with our results, the study of Badii *et al* showed that ioPTH monitoring was not cost saving due to substantially longer operative times.[13] Morris *et al* suggested that the use of ioPTH monitoring would only be beneficial in a relatively small fraction of patients where the accuracy of preoperative localisation was low.[12] This finding is supported by our threshold analysis, which revealed that only a PPV for MGD of less than 69% would render ioPTH monitoring cost-effective (online supplemental figure 3). Recent technological innovations in the field aim to substantially reduce both cost and time expenditure for ioPTH monitoring, such as rapid tests, which suggest the possibility of reaching cost-effectiveness in the future.[31 32] Our threshold analysis indicates that solely reducing the additional operative time of ioPTH monitoring to 5 min (one time unit) would still result in an INMB of −US$301 (online supplemental figure 4). Therefore, to achieve cost-effectiveness for ioPTH monitoring, the combination of (1) using rapid tests with (2) minimising the assay costs and (3) the selection of the optimal criterion tailored to the disease characteristics of patients is necessary.

In addition to the cost-effectiveness, reducing the complications in parathyroid surgery is essential. We found that ioPTH monitoring using the Vienna criterion minimised the risk of reoperations, while the Miami criterion minimised complication rates. The physical manipulation of an adenoma during operation might lead to an increase in ioPTH.[3] This risk could be higher in the case of MGD due to the manipulation of more than one gland. The Miami criterion has a higher risk of false positive results due to using the highest ioPTH level (preincision or pre-excision) as the baseline value. Surgeons should, therefore, consider using the Vienna criterion for patients with suspected MGD to maximise specificity and the Miami criterion for patients with suspected solitary adenoma to maximise sensitivity.

Overall, the interpretation of our model is limited to the USA. However, our uncertainty analysis suggested the decision analytical model is robust and can be adapted to other countries with distinct cost structures.

Limitations of the study

Our study has several limitations. To simplify the model, we assumed the same time horizon for symptomatic and asymptomatic PHPT. Even though the surgical procedure and the associated complications which were the focus of the current study are identical for both cases, differences in the time horizon could arise due to the differences in morbidities. As the use of FCH-PET/CT and 4D-CT imaging has only been recently introduced for the localisation of parathyroid adenomas, there were only a handful of available systematic reviews to inform the estimates of the model parameters related to the imaging modality. Hence, for the sensitivity and PPV values for FCH-PET/CT in MGD, we relied on data from a single institutional report,[9] which limits the generalisability of our results. Data for the sensitivity and PPV values for ultrasound in MGD were retrieved from a systematic review of studies published between 1995 and 2003. Similarly, data for estimating the model parameters related to the ioPTH protocol were derived from a limited number of studies, which showed considerable variations in the estimates. Furthermore, utilities in this study were derived from either the SF-36 health state descriptions or the standard gamble method and might be outdated, despite no apparent updates on these estimates as summarised in a recent systematic review.[33] To overcome these limitations in the evidence base, we conducted sensitivity analyses to determine how robust the conclusions were to variation in the model parameter values. Furthermore, our uncertainty analysis accounted for the effect of uncertainty in the estimates of the model parameters on the cost-effectiveness analysis results. Nevertheless, meta-analyses that stratify solitary adenomas and MGD are warranted to reduce the risk of bias in the performance values of localisation techniques.

Moreover, the true rate of solitary adenomas is also debated, as some institutions report a significantly higher rate of MGD than the consensus value.[2] Accordingly, our threshold analysis reveals that the prevalence of MGD strongly impacts the complication rates which influences the cost-effectiveness of ioPTH monitoring. Therefore, it is critical to consider the existing institutional variations in this parameter during the decision-making process. In addition, as FCH-PET/CT is not yet authorised in the USA, our model likely underestimates the future cost of FCH by inferring from the cost of the most used PET tracer, ^{18}F-fluorodeoxyglucose (CPT A9552); suggesting that the threshold to reach cost-effectiveness for FCH-PET/CT might be higher than estimated. Similarly, as a societal perspective was not incorporated into our evaluation, for example, absence from work due to inpatient hospitalisation, the economic consequences of unnecessary BNEs due to ioPTH monitoring might be underestimated in our model.

Finally, our study applied to patients under Medicare reimbursement, for which the data might have a bias towards the delivery of care in specific patient groups.[34]

Conclusions

In our decision analytical model of parathyroidectomy in PHPT patients which also considered the MGD cases, 4D-CT was found to be the least expensive diagnostic tool for the preoperative localisation of parathyroid adenomas, and FCH-PET/CT is likely a cost-effective modality. In our model, the use of ioPTH monitoring was found not cost-effective in PHPT due to an excessive increase of BNEs but led to a significant reduction in the rate of reoperations. If ioPTH monitoring is used, our model suggests that the Miami criterion should be applied for suspected solitary adenomas and the Vienna criterion for suspected MGD. As our model relied on several assumptions, our findings should be further evaluated in a relevant clinical setting.

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