Parathyroidectomy for asymptomatic primary hyperparathyroidism: A revised cost-effectiveness analysis incorporating fracture risk reduction

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Background. *Recent data demonstrate decreased fracture risk after operation for asymptomatic primary hyperparathyroidism. We performed a revised cost-effectiveness analysis comparing parathyroidectomy versus observation while incorporating fracture risk reduction.*

Methods. *A Markov transition-state model was created comparing parathyroidectomy and guideline-based medical observation for a 60-year-old female patient with mild asymptomatic primary hyperparathyroidism. Costs were estimated using published Medicare reimbursement data. Treatment strategy outcomes, including risk of fracture, were identified by literature review. Quality adjustment factors were used to weight treatment outcomes. A threshold of $100,000/quality-adjusted life year was used to determine cost-effectiveness. Sensitivity analyses and Monte Carlo simulation were performed to examine the effect of uncertainty on the model.*

Results. *Parathyroidectomy was the dominant strategy (less costly and more effective) with an incremental cost savings of $1,721 and an incremental effectiveness of 0.185 quality-adjusted life years. Parathyroidectomy remained dominant when the relative risk reduction of fracture after operation was ≥14%, the cost of fracture was ≥$7,600, or the probability of recurrent laryngeal nerve injury was <12.5%. Monte Carlo simulation showed parathyroidectomy was cost-effective in 995/1,000 hypothetical patients.*

Conclusion. *When fracture risk reduction is considered, parathyroidectomy for mild asymptomatic primary hyperparathyroidism is the dominant strategy when compared to observation. (Surgery 2017;161:16-24.)*

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Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia and occurs in >135,000 patients in the United States each year.[1] Untreated PHPT is associated with bone loss and fracture.[2-6] While parathyroidectomy (PTX) is the only definitive therapy for PHPT, current consensus guidelines continue to identify a subset of asymptomatic PHPT patients with mild biochemical disease and age ≥50 years who are eligible for medical observation as an alternative to operation.[7]

Several recent prospective and retrospective, population-based studies report a 24–31% relative risk reduction and a 4.8–11.34% absolute, 10-year risk reduction of fracture after PTX for PHPT.[2,5,6,8] These data need to be incorporated into the clinical decision-making process for offering an operation versus observation to patients with mild asymptomatic disease. To determine the optimal management strategy for these patients, the potential benefit of future fracture avoidance needs to be weighed against the upfront risks and costs of PTX.

Previous studies have investigated the cost-effectiveness of PTX for observation-eligible

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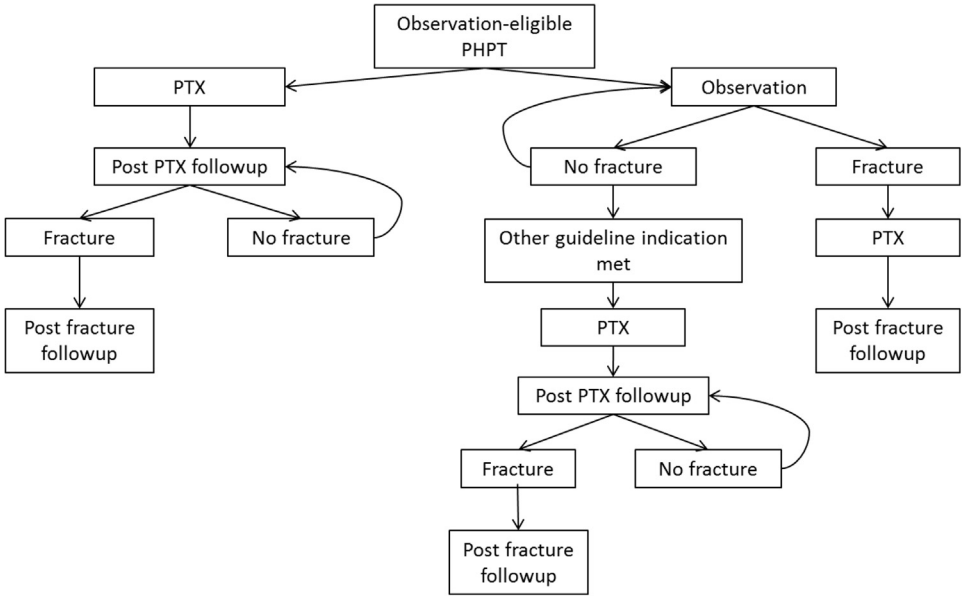

Fig 1. Schematic of the major transition states in the Markov model.

patients with mild, asymptomatic PHPT[9-11]; however, no model has addressed the risk, quality-of-life (QOL) detriment, and cost of fragility fracture during medical observation. We incorporated these outcomes in a revised cost-effectiveness analysis comparing PTX versus observation in asymptomatic PHPT. We hypothesized that PTX is cost-effective for all patients with observation-eligible PHPT.

METHODS

Reference case scenario. The reference case was defined as a 60-year-old female patient with asymptomatic PHPT meeting current consensus guideline criteria for medical observation.[7] The age of 60 years was selected to maintain consistency with the previous model and falls within the reported average age range of observation-eligible PHPT patients.[4,12] This reference patient was a healthy operative candidate for PTX via a cervical incision. The time horizon for the analysis was the patient's remaining life expectancy, as predicted by the current US Social Security System Actuarial Life Table.[13]

Decision model. A previously constructed Markov stochastic cohort transition-state decision model comparing medical observation and PTX was revised to incorporate current cost and outcome data, including fracture risk, for the reference case.[10] The cycle duration was 6 months. All modeling was performed with TreeAge Pro decision analysis software (TreeAge Software, Inc, Williamstown, MA). The major transition states for the medical observation and PTX strategies are shown in Fig 1. The event pathways and probabilities used in the model (Table I) were derived from literature review and current consensus conference recommendations for the medical and surgical management of asymptomatic PHPT.[7]

Patients in the observation arm incurred the annual costs of formal guideline-recommended testing up to 10 years after diagnosis.[10] If an observed patient developed a guideline-based indication for PTX at any time point, PTX was performed. Surgical outcomes, including complications, disease persistence, and recurrence requiring reoperation, were included in the model. The revised model assumed a 30% relative risk of fracture with observation compared to PTX.

PTX was assumed to lower the annual risk of fracture from 3.9% to 3%, which was the annual risk of fracture in an age-matched patient without PHPT.[5,14] These probabilities of fracture were applied to both the PTX and observation strategies, as were the costs and QOL detriment associated with a fracture event. The strategy that produced the greatest quality-adjusted life expectancy (QALE) without exceeding an incremental cost-effectiveness ratio of $100,000 per quality-adjusted life year (QALY) was defined as optimal. A $100,000/QALY willingness-to-pay threshold for cost-effectiveness was selected based on current convention and allocation of heath care resources in the United States.[15,16]

Cost estimation. All costs in the model were reported in 2015 US dollars and are listed in

Table I. Model assumptions

Variable	*Reference case value*	*Range of values used in Monte Carlo simulation distributions*	*Sources*
Probabilities			
Annual risk of fracture in age-matched patient without PHPT	3%	1.5–4.5%	5,14
Annual risk of progression from asymptomatic PHPT to symptomatic PHPT	1.6%	0.8–2.4%	3,10
Annual risk of recurrence after curative PTX	0.05%	0.025–0.075%	26,27
RLN injury after initial PTX	0.5%	0.25–0.75%	10,27
RLN injury after reoperative PTX	4%	2–6%	10,28
Permanent hypoparathyroidism after initial PTX	0.5%	0.25–0.75%	10,27
Permanent hypoparathyroidism after reoperative PTX	1%	0.5–1.5%	10,28
Persistent PHPT after initial PTX	5%	2.5–7.5%	10
Persistent PHPT after reoperative PTX	10%	5–15%	10,28
Costs in US dollars			
Initial parathyroidectomy	$5,702	$2,851–8,553	17
Reoperative parathyroidectomy	$6,114	$3,057–9,171	17
RLN injury treatment	$11,846	$5,923–17,769	10
Cost of fracture	$16,281	$8,140.50–24,421.50	19
Annual cost of permanent hypoparathyroidism	$876	$438–1,314	18
Annual cost to observe asymptomatic PHPT	$278	$139–417	7,17
Annual cost of calcimimetic therapy	$20,192	$10,096–30,288	18
QOL adjustment factors			
Curative PTX	1.00	1.00–1	9,10
Asymptomatic hyperparathyroidism	0.987	0.97–1	10,29,30
Symptomatic hyperparathyroidism	0.897	0.79–1	10,29,30
Long-term hypoparathyroidism	0.894	0.79–1	10,31
Curative PTX with RLN injury	0.891	0.78–1	10,11,29,32
Asymptomatic PHPT with RLN damage	0.878	0.76–1	10,29,30,32
Symptomatic PHPT and permanent RLN damage	0.877	0.75–1	10,29,30,32
Fracture	0.815	0.63–1	22,23
Permanent hypoparathyroidism and RLN injury	0.785	0.57–1	10,11,29,32
Time (y)			
Formal follow-up of asymptomatic disease	10	5–15	10
Reference patient remaining life expectancy	24	12–36	13
Relative risk of fracture in asymptomatic PHPT	30%	0–60%	2,5,6,8
Discount rate	3.0%	0.015–0.045	21
Health care cost inflation rate	3.4%	0.017–0.051	20

RLN, Recurrent laryngeal nerve.

Table I. Direct costs of the medical observation and PTX strategies were estimated using the 2015 Medicare Prospective Payment System, average wholesale drug prices, and previously published cost estimates.[9,10,17-19] A third-party payer perspective was maintained for all costs. Annual observation costs included a physical examination, serum calcium and creatinine

Table II. Threshold conditions for cost-effectiveness and dominance of the PTX strategy during one-way sensitivity analysis

Variable	*$100,000/QALY threshold*	*$150,000/QALY threshold*	*Dominance threshold*
Probabilities			
Annual risk of fracture in age-matched patient without PHPT	None	None	>1.4%
Annual risk of progression from asymptomatic PHPT to symptomatic PHPT	None	None	None
Annual risk of recurrence after curative PTX	<2.8%	<3.4%	<0.6%
RLN injury after initial PTX	<12.0%	<11.9%	<11.7%
RLN injury after reoperative PTX	None	None	None
Permanent hypoparathyroidism after initial PTX	<11.9%	<11.9%	<9.8%
Permanent hypoparathyroidism after reoperative PTX	None	None	None
Persistent PHPT after initial PTX	None	None	<36%
Persistent PHPT after reoperative PTX	None	None	<80%
Costs in US dollars			
Initial parathyroidectomy	<$36,000	<$50,000	<$8,300
Reoperative parathyroidectomy	<$430,000	<$630,000	<$42,000
RLN injury treatment	<$3.8 million	<$5.6 million	<$340,000
Cost of fracture	None	None	>$7,600
Annual cost of permanent hypoparathyroidism	<$170,000	<$245,000	<$15,000
Annual cost to observe asymptomatic PHPT	None	None	>$110
Annual cost of calcimimetic therapy	<$5.7 million	<$8.3 million	<$499,000
QOL adjustment factors			
Asymptomatic hyperparathyroidism	None	None	<0.999
Symptomatic hyperparathyroidism	None	None	None
Long-term hypoparathyroidism	None	None	None
Curative PTX with RLN injury	None	None	None
Asymptomatic PHPT with RLN damage	None	None	None
Symptomatic PHPT and permanent RLN damage	None	None	None
Fracture	None	None	None
Permanent hypoparathyroidism and RLN injury	None	None	None
Time (y)			
Formal follow-up of asymptomatic disease	None	None	>3
Remaining life expectancy	>3	>2.5	>16
Relative risk of fracture in asymptomatic PHPT	None	None	>14%
Discount rate	<33%	<50%	<5%
Health care cost inflation rate	None	None	>1.5%

RLN, Recurrent laryngeal nerve.

measurement, and bone density examination. An average expected, one-time cost of fracture of $16,281 was derived from literature reporting the costs of various types of fracture.[19] A health care inflation rate of 3.4% was calculated from the mean of annual changes in the Consumer Price Index for Medical Care from 2005 to 2015.[20] This inflation rate was applied to the future health care costs of the model and used to adjust older cost estimates to their 2015 values.

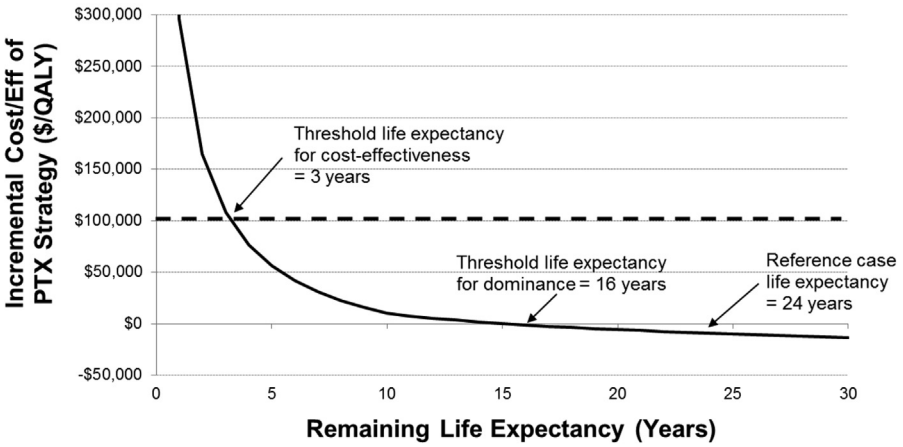

Fig 2. The incremental cost-effectiveness ratio for the parathyroidectomy strategy is displayed as a function of remaining life expectancy. The parathyroidectomy strategy is cost-effective when remaining life expectancy exceeds 3 years and dominant when life expectancy exceeds 16 years.

A discount rate of 3% was applied to all future costs in the model.[21]

Effectiveness. Effectiveness was measured by calculating QALEs for both strategies. Each of the possible treatment outcomes in the model was assigned a quality-adjustment factor based on literature review. The quality adjustment factor for fracture was simplified to an average utility of 0.815, which was derived from literature reporting the quality adjustment for various types of fracture.[22,23] The methods of utility determination used by the primary sources are included in Supplemental Table I. Time elapsed while the reference patient was experiencing a particular outcome was multiplied by the quality adjustment factor of that outcome to yield effectiveness in QALYs. A 3% discount rate was also applied to all accumulated future QALYs.

Sensitivity analysis. Threshold analysis was performed on each variable in the model during 1-way sensitivity analysis to identify values where the PTX strategy became dominant (less costly and more effective) or cost-effective compared to observation. Threshold values for willingness-to-pay levels of $100,000/QALY and $150,000/QALY were calculated. A 3-way sensitivity analysis was performed to examine the combined effects of changes in the quality adjustment factor for asymptomatic PHPT and the cost and quality adjustment factor for fracture.

Probabilistic sensitivity analysis using Monte Carlo simulation was performed, where triangular frequency distributions for each variable were simultaneously sampled during 1,000 consecutive iterations. The distributions were assigned a range of ±50% of the reference case estimate. In the case of utility, risk, or probability estimates, these variables were allowed to vary to the greatest extent, such that the reference case value was at the center of a range containing the boundary 0 or 1.

RESULTS

Reference case. PTX was the less costly and more effective strategy with an expected cost of $6,487 and an effectiveness of 17.54 QALYs. The observation strategy had an expected cost of $8,208 and an effectiveness of 17.35. Observation was $1,721 more costly than PTX and resulted in a loss of 0.19 QALYs. Observation was therefore dominated, because this strategy was both more costly and less effective than PTX. The median expected time to fracture was 17.5 years for the observation strategy and 23 years for the operation strategy.

Sensitivity analysis. The threshold conditions for cost-effectiveness and dominance of the PTX strategy during 1-way sensitivity analysis are shown in Table II. PTX remained the dominant strategy when the relative risk of fracture in observed, asymptomatic PHPT was >14%, the cost of fracture was >$7,600, the health care cost inflation rate was >1.5%, or the remaining life expectancy was >16 years. PTX was cost-effective until the remaining life expectancy was <3 years (Fig 2). Several variables returned no threshold values, because PTX was cost-effective and dominant for all possible values. The model was not sensitive to the rate of disease progression from asymptomatic PHPT to observation ineligibility or the complication rates for reoperative PTX.

The QOL adjustment factor for asymptomatic PHPT was the only quality adjustment variable that produced a threshold for dominance of the PTX

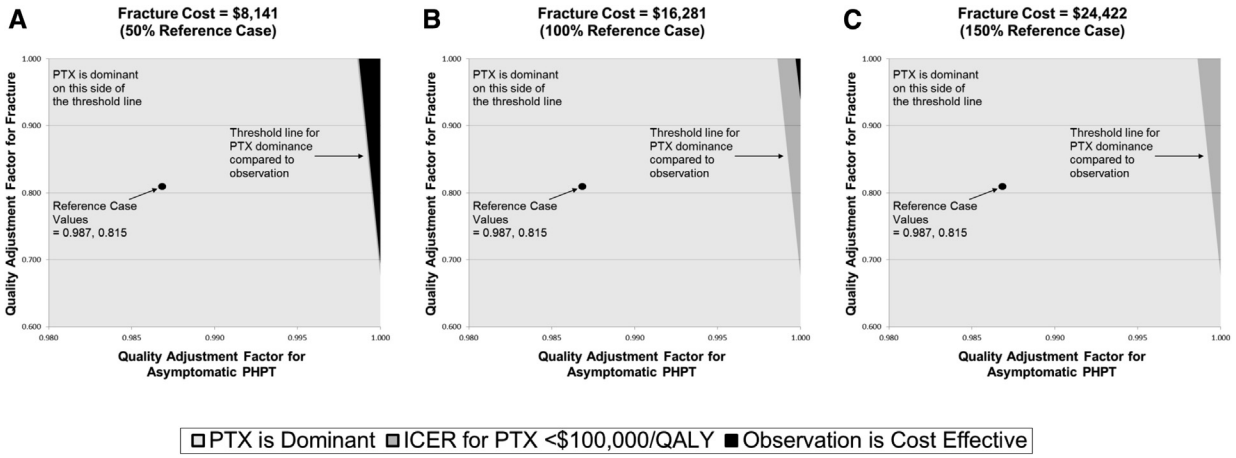

Fig 3. Three-way sensitivity analysis examining the combined effects of the cost of fracture, the quality adjustment factor for fracture, and the quality adjustment factor for mild, asymptomatic PHPT on the cost-effectiveness of the PTX strategy. Intersecting quality-adjustment factors produce results where PTX dominates (*light gray region*), PTX is cost-effective (*dark gray region*), or observation is cost-effective (*black region*). As the cost of fracture increases (*A*–*C*), PTX becomes cost-effective in increasing combinations of quality adjustment factors. When the cost of fracture is 150% of the reference case assumption (*C*), PTX is cost-effective or dominant in all quality-adjustment combinations.

strategy during 1-way sensitivity analysis. PTX was dominant only if the quality adjustment factor for asymptomatic PHPT was <0.999. PTX was cost-effective for all other possible quality adjustment factor values for asymptomatic PHPT.

While the model was not generally sensitive to isolated changes in quality adjustment factors, 3-way sensitivity analysis of the quality adjustment factor for asymptomatic PHPT, quality adjustment factor for fracture, and cost of fracture demonstrated a larger combined effect of these 3 variables on the cost-effectiveness of the PTX strategy. As the cost of fracture increased, PTX was cost-effective in increasing combinations of quality adjustment factors for asymptomatic PHPT and fracture (Fig 3). When the cost of fracture was increased to 150% of the reference case assumption (from $16,281 to $24,422), the PTX strategy was either cost-effective or dominant in all quality adjustment combinations.

Monte Carlo simulation demonstrated PTX to be the optimal strategy in 995 (99.5%) of the iterations. PTX was the dominant strategy (both less costly and more effective) in 749 (74.9%) iterations. In an additional 246 (24.6%) iterations, PTX resulted in gains in QOL or cost savings that produced an incremental cost-effectiveness ratio of <$100,000/QALY. Among the remaining 5 (0.5%) cases in which observation was cost-effective, this strategy was less costly and less effective in 4 (0.4%) and more costly and more effective in 1 (0.1%) compared to PTX. All iterations from this simulation are plotted in Fig 4.

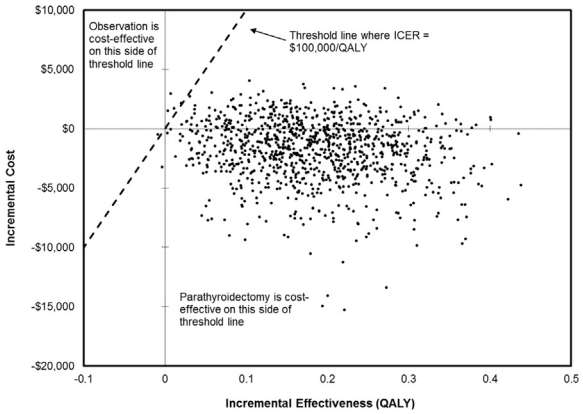

Fig 4. All model assumptions were simultaneously varied across triangular frequency distributions in a 1,000-iteration Monte Carlo simulation. The incremental cost and incremental effectiveness of parathyroidectomy versus observation are plotted for each iteration. Points to the right of the dashed threshold line are iterations where parathyroidectomy was cost-effective (99.5%). Points to the left of the line are iterations where observation was cost-effective (0.5%). Parathyroidectomy was dominant in 74.9% of iterations. Observation was dominant in 0% of iterations. *ICER*, Incremental cost effectiveness ratio.

DISCUSSION

This revised cost-effectiveness analysis demonstrates that PTX is the dominant management strategy for many patients with mild, asymptomatic PHPT, because operative management at the time of diagnosis produced a greater QALE at a lower

cost compared with medical observation. Based on current life expectancy estimates, PTX was dominant for patients <70 years old and remained cost-effective for patients >90 years old.[13]

In previous models of asymptomatic PHPT, PTX was shown to be cost-effective by producing increased QOL with an acceptable additional cost, ranging from $721/QALY to $4,778/QALY.[9-11] When the fracture risk reduction of operation is considered, PTX shifts from being merely cost-effective to a state of dominance with increased QOL and cost savings of $1,721 compared with observation. Similarly, the conclusion of previous models was dependent on the assumption that "asymptomatic" PHPT is in fact symptomatic and produces diminished QOL.

In our previous model, the quality adjustment for asymptomatic PHPT needed to be <0.998 for PTX to be cost-effective.[9] A similar analysis conducted within the French health care system required the quality adjustment factor for asymptomatic disease to be <0.999.[11] Although there is mounting evidence that subjective QOL does in fact improve after operation in seemingly asymptomatic patients, the concept of truly symptom-free PHPT remains part of the current consensus guidelines.[7,24] The present work demonstrates that, once fracture is considered, minor differences in subjective symptoms become insignificant in relation to the objective cost and QOL effects of fracture.

Several limitations are apparent in this study. The known complications of operations deemed to be of low likelihood or significance (wound infection, hematoma requiring operative evacuation, operative mortality, hypertrophic cervical scar, temporary recurrent laryngeal nerve injury, and temporary hypoparathyroidism) were omitted to maintain computational simplicity. More costly and morbid operation to excise ectopic glands was not considered. The absence of these events from the model introduced bias favoring the PTX strategy. Given the strong dominance of PTX compared to observation, these simplifications were unlikely to change the model's conclusions.

The cost and QOL impact of nephrolithiasis during observation of asymptomatic PHPT were omitted due to lack of primary data, introducing bias favoring the observation strategy. The model also favored observation by assuming that patients who progress to symptomatic disease immediately underwent PTX without experiencing the diminished QOL of symptomatic PHPT. Observed patients were followed for 10 years to maintain consistency with our previous analysis. Longer follow-up would have increased the costs of observation. In addition, the model only allowed one lifetime fracture event. In reality, the occurrence of an initial fracture would likely increase the probability of additional future fractures,[25] adding additional costs and QOL detriment to the observation strategy. Removing these biases would have also strengthened the dominance of the operation strategy and would not have changed the model's conclusions.

Other simplifications of the model introduced imprecision without clearly biasing either strategy. The third-party payer perspective was used to maintain consistency with our previous model. A more complete analysis from the societal perspective would have included transportation time and lost patient work productivity associated with medical and operative encounters. These costs would be accumulated through both the PTX and observation strategies, and their inclusion would be unlikely to appreciably change the model's results.

While focused PTX and 4-gland exploration techniques are both performed, no distinction was made between these approaches in the model. This assumption is valid, because operative outcomes are similar and Medicare reimburses identically for the 2 techniques. The occurrence of a fragility fracture and the operative complications of recurrent laryngeal nerve injury and permanent hypoparathyroidism all have a wide spectrum of severity and treatment costs; however, these were all assigned one treatment cost and QOL adjustment. We believe the uncertainty associated with these estimates was adequately addressed with sensitivity analysis.

In conclusion, in our revised model, PTX is less costly and more effective (ie, dominant) compared to medical observation in patients with asymptomatic PHPT who are <70 years old. PTX remains cost-effective for all other surgical candidates with asymptomatic disease. To improve QOL and lower healthcare costs, definitive operative management should be offered to all patients with PHPT.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.surg.2016.06.062.

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DISCUSSION

Dr Jennifer E. Rosen (Washington, DC): Very nicely presented on the expansion of your prior work. I think that some of my endocrinologists are doing the math in their heads in advance and not even referring some of our patients for workups. Have you looked at all at taking these

patients with asymptomatic, mild hyperparathyroidism and taking a step back before they are referred to surgery and look at the cost-effectiveness of even putting them through the workup and the statistical likelihood of success from that? Because that I could take to my endocrinologist to tell them not to do the math in their head.

Dr Kyle A. Zanocco: We have not looked at the initial algorithm for working up a hypercalcemic patient. We always follow a patient that meets guidelines or does not meet guidelines and has the biochemical diagnosis. That would be an interesting study for the future.

Dr Christopher R. McHenry (Cleveland, OH): Why did you pick the age of 70 given that most 70-year-olds have a greater than 3-year life expectancy as a cut-off for recommending parathyroidectomy?

Dr Kyle A. Zanocco: Thank you for your question, Dr McHenry. A few points of clarification about the model. If I could have my slides, it would be helpful. Our reference case patient was a 60-year-old with a life expectancy of 24 years. And this sensitivity analysis shows the threshold for cost-effectiveness. So if the patient had a life expectancy of less than 3 years, theoretically, it would not be cost effective anymore to recommend an operation.

That basically says that any patient who is a surgical candidate should be offered the operation based on the cost-effectiveness analysis. So the reference case was the 60-year-old patient. The 70-year-old patient is actually the threshold for where parathyroidectomy becomes the dominant strategy for both less costly and more effective.

Dr Robert Udelsman (New Haven, CT): I want to challenge you a little bit. First, your assumption that 30% of patients who do not have parathyroidectomy are destined to have fractures. Obviously, that is time dependent depending on how long they plan to live, number one. And based upon the results, I just want to push you, because I think it is so important. I would like to believe you. But in your studies, when I look at your algorithm, you started patients with nonsurgical management and no fracture. And then they also went on to parathyroidectomy. Was there also one that had observation that never had a fracture and lived a normal life and did just fine? And, obviously, it would dramatically change your results. So I would like to push you just a little bit harder.

Dr Kyle A. Zanocco: Could I have my slides back again, please? Again, an opportunity to clarify. I know I went through a lot of this quickly. This is a Markov model. First, to address the 30%, that is the relative risk and it is a time-dependent thing, and these baseline risks for fracture were assumed to be approximately 3%; someone that was being observed with primary hyperparathyroidism had a relative risk of 1.3, so it is 3.9%. So it is a time-dependent relative risk over time, and it is not that 30% of patients ultimately went on to fracture. Over a 10-year period of time, 10% more risk of fracture, I guess, is how to answer that.

And then the algorithm itself, just to clarify, the patients do not all go on to have a parathyroidectomy. There are transition states where you start, and an observation state, and then you may or may not fracture. The probability of fracture is low at any one time. And if you do not fracture, you just go back to observation. So many patients just cycle along here and continue to be observed. However, if they ultimately have an indication for surgery or fracture, then they progress to parathyroidectomy and follow-up.

Dr Scott M. Wilhelm (Cleveland, OH): My question to you is in regard to how you calculated your cost savings in fracture. You came up with this number of 16,000 for a one-time event. I am curious if you looked at just—is this operative management and costs associated with that? Because I think it goes way beyond that when you look at rehab, time lost to patients, and patients with fractures who ultimately do not have just one operation for many orthopedic problems. These are complex fractures in some scenarios. So how did you calculate that?

Just a comment, when you talked about your improvement by slivers, on your slide, it says slivers are small, annoying things that get under your skin or they are very small pieces of dessert. So use a better term that likely makes you look good.

Dr Kyle A. Zanocco: Dr Wilhelm, 16,000 is an aggregate one-time cost for a spectrum of fracture disease which can range from a simple fracture that is dealt with a cast to a debilitating, life-ending hip fracture, and it is very difficult to aggregate that into a one-point estimate, and I agree. So that was a challenge, but we used the best data we have from Medicare to come up with that point estimate.