Surgery versus medical follow-up in patients with asymptomatic primary hyperparathyroidism: a decision analysis

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Abstract

Objectives: To examine the cost-effectiveness of strategies for management of primary asymptomatic hyperparathyroidism: surgical strategies and medical follow-up versus surgery.

Design: We used a Markov state-transition decision-analytic model for an hypothetical cohort of 55-year-old women to compare with a lifetime horizon costs and effectiveness of bilateral neck exploration (BNE), unilateral neck exploration (UNE), video-assisted parathyroidectomy (VAP) and lifelong medical follow-up shifting for either BNE or UNE in case of disease progression.

Methods: Data on localization tests, complications and treatment efficacies were derived from a systematic review of the literature. Outcomes were expressed as quality-adjusted life years (QALY). Costs (£2002) discounted at 3% yearly were estimated from the health care system perspective.

Results: In the base-case analysis, VAP strategy (VAPS) was the most effective and BNE strategy (BNES) was the least costly. UNE strategy (UNES) had an incremental cost-effectiveness ratio of £2688/QALY versus BNES and VAPS of £17 250/QALY in comparison with UNES. Surgical management was more effective than medical follow-up with acceptable incremental cost-effectiveness ratios. VAPS became less effective than UNES over 71 years. Differences between UNES and VAPS were sensitive to success and complication rates, quality-of-life weights and procedural costs. Medical follow-up strategies became the most effective if quality-of-life weight for this condition was higher than 0.99.

Conclusions: Surgery is more effective than medical follow-up at a reasonable cost and can be preferred except in patients choosing medical follow-up. Minimally invasive surgery is cost-effective compared to the traditional surgical approach.

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Introduction

Primary hyperparathyroidism is a rather common disorder. Its prevalence and incidence have been estimated to be 0.1–0.5% and 0.03%, respectively (1, 2). Parathyroidectomy is presently the only definitive treatment for primary hyperparathyroidism (3). Some medical therapies have been proposed but none have yet been proved to be both effective and safe in the long term (3). As 49% of patients are asymptomatic, North American guidelines on the management of asymptomatic primary hyperparathyroidism limit indications to surgery to patients with risk factors for complications (3, 4). Patients with a mildly elevated calcemia, no previous episodes of life-threatening hypercalcemia and normal renal and bone status, can be assigned to medical monitoring, shifting to parathyroidectomy only in the case of progression of the disease.

Three main surgical approaches are currently available: traditional bilateral neck exploration (BNE) and two minimally invasive approaches, unilateral neck exploration (UNE) and video-assisted endoscopic parathyroidectomy (VAP) (5). Proponents of BNE argue that it is a safe procedure with the highest cure rate and low morbidity when performed by experienced surgeons because 12–15% of patients with primary hyperparathyroidism may have diffuse hyperplasia and 2% have double or triple adenoma. Both minimally invasive procedures are indicated if preoperative localization studies and intra-operative parathyroid hormone (PTH) monitoring prove a single adenoma. Proponents of minimally invasive surgery argue that these procedures decrease surgical costs and morbidity.
while improving cosmesis. To our knowledge, the outcomes of these surgical approaches had never been evaluated together in randomized clinical trials. UNE has been compared to BNE (6–15) and might be safer and more effective, only one small randomized study has compared the outcomes of VAP with those of BNE (16). Moreover, only three studies (17–19) have explored the efficacy of medical follow-up compared to surgery. Among them, only one (17) concluded that surgery was more effective in asymptomatic patients.

Short-term economic evaluations of various surgical procedures (6, 12, 20–33) have been conducted although are seldom related to outcomes. A recent cost analysis (24) concluded that the use of any preoperative localizing strategy before an initial operation, especially when leading to UNE, is cost-beneficial compared to nondirected BNE. Cost-effectiveness studies (6, 12, 25–33) of UNE versus BNE leading to controversial conclusions did not meet the methodological standards (34–36). Furthermore, the cost-effectiveness of medical monitoring compared to surgery has not yet been established (1, 37).

Thus to our knowledge the effectiveness and costs of the strategies for asymptomatic primary hyperparathyroidism have not been compared until now. Our objective was to answer the following questions for patients with sporadic primary hyperparathyroidism excluding those with multiple endocrine neoplasia or parathyroid cancer. Which is the most effective surgical approach in patients eligible for surgery? Is long-term medical follow-up an effective option compared with immediate surgery in patients not eligible for surgery? Are minimally invasive surgical approaches or long-term follow-up cost-effective options?

The method chosen was a decision-analytic model with base-case analysis and variations of every parameter in sensitivity analyses.

**Methods**

**Literature review**

We reviewed both the English and French language medical literature from 1970 to 2004, using a structured Medline search supplemented by manual searches of bibliographies of selected articles. Studies were excluded if the patient series was less than 30, if they did not report separate results for primary hyperparathyroidism and other hyperparathyroidisms, for primary surgery and reoperation, if results for patients with multiple endocrine neoplasia or parathyroid cancer could not be excluded, or if localization studies had been performed in the series reporting results of BNE. If the same patient series was published more than once, only data from the latest publication were included. Among studies reporting results of parathyroid localization the studies selected were those reporting quantitative data allowing categorization of each patient as a true or false positive. When possible a summary analysis was performed and exact 95% confidence intervals calculated (38).

**Efficacy and complications of the surgical procedures**

Apart from death never reported after UNE or VAP, potential complications (Table 1) were identical for each of the surgical procedures examined (10, 11, 13, 23, 27, 29, 39–79). Surgical failure was ascertained on persistent hypercalcemia immediately after surgery. Short-term complications (<6 months) included hematoma requiring evacuation, transient vocal cord palsy and hypocalcemia. Long-term complications (>6 months) were permanent dysphonia or hypoparathyroidism (10, 13, 27, 40–44, 47, 52, 53, 55–58, 61, 63, 67, 69). Hyperparathyroidism may recur (41, 47, 55, 57, 71, 73, 75) but recurrence rates after VAP are unknown (16, 80–84).

**Localization studies**

For each localization study, positive predictive value and proportion of positive results are summarized in Table 2. Results of localization studies were classified as true positive if a single adenoma was detected in the neck both by imaging and by an initial operation or for reoperation if all glands enlarged (adenomas or hyperplasia) detected during the intervention were found by preoperative localization.

**Medical follow-up**

During a 10-year medical follow-up (85, 86), 24.5% of asymptomatic patients underwent surgery by the following guidelines: increase in calcemia (7.55%), decrease in creatinine clearance (3.77%) or decrease in bone mineral density (3.77%) (87).

**Case definition**

Sporadic primary hyperparathyroidism (cancer excluded) was defined by hypercalcemia in the presence of inappropriately normal or elevated levels of PTH (88, 89). Seventy-five per cent of patients are women with an average age at diagnosis of 55 years (90). Our base-case was therefore a 55-year-old woman with asymptomatic hyperparathyroidism; cases were simulated in which she was eligible for surgery without previous neck surgery and also in which she was not eligible for surgery (3).
Table 1 Rates, probabilities and utilities used in the baseline and sensitivity analyses for cost-effectiveness analysis of primary hyperparathyroidism.

<table>
<thead>
<tr>
<th>Health state</th>
<th>Rates and probabilities</th>
<th>95% CIs or extreme values*</th>
<th>QOL adjustment factor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Short term†</td>
<td>Long term‡</td>
</tr>
<tr>
<td><strong>BNE</strong></td>
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<tr>
<td><strong>First operation</strong></td>
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<tr>
<td><strong>Short-term events</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Surgery</td>
<td>0.21% (40, 42, 43, 46, 47, 49, 52)</td>
<td>0.01–0.48%</td>
<td>3.88</td>
</tr>
<tr>
<td>Death</td>
<td>0.37% (40, 43, 56, 57)</td>
<td>0.02–2.38%</td>
<td>2</td>
</tr>
<tr>
<td>Transient dysphonia</td>
<td>1.87% (23, 27, 40, 42–44, 46, 48, 50, 52–54, 56, 57, 59)</td>
<td>1.26–2.75%</td>
<td>1.54</td>
</tr>
<tr>
<td>Transient hypocalcemia</td>
<td>9.98% (23, 40, 42–44, 46–51, 53–57, 59)</td>
<td>8.82–11.27%</td>
<td></td>
</tr>
<tr>
<td>Persistent hyperparathyroidism</td>
<td>5.28% (23, 27, 39–49, 51–60)</td>
<td>4.49–6.20%</td>
<td>0.9047</td>
</tr>
<tr>
<td><strong>Long-term events</strong></td>
<td></td>
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<tr>
<td>Permanent dysphonia</td>
<td>0.00% (43, 44, 47, 52, 58)</td>
<td>0.00–0.48%</td>
<td>0.8913</td>
</tr>
<tr>
<td>Permanent hypoparathyroidism</td>
<td>1.75% (27, 42–44, 52, 53, 55–57)</td>
<td>1.12–2.71%</td>
<td>0.8914</td>
</tr>
<tr>
<td>Recurrent hyperparathyroidism</td>
<td>0.06%/year (41, 47, 55)</td>
<td>0.02–0.16%</td>
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</tr>
<tr>
<td>Scar</td>
<td>100%</td>
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<tr>
<td><strong>Reoperation</strong></td>
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<tr>
<td><strong>Short-term events</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Surgery</td>
<td>11.10</td>
<td></td>
<td>0.9924</td>
</tr>
<tr>
<td>Death</td>
<td>0.29% (71–76)</td>
<td>0.02–1.87%</td>
<td>2</td>
</tr>
<tr>
<td>Transient dysphonia</td>
<td>3.92% (109)</td>
<td>0.68–14.59%</td>
<td>1.54</td>
</tr>
<tr>
<td>Transient hypocalcemia</td>
<td>10.40% (73–76)</td>
<td>7.03–15.03%</td>
<td></td>
</tr>
<tr>
<td>Persistent hyperparathyroidism</td>
<td>10.17% (71–76)</td>
<td>7.28–13.98%</td>
<td>0.9047</td>
</tr>
<tr>
<td><strong>Long-term events</strong></td>
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<tr>
<td>Permanent dysphonia</td>
<td>0.47% (71, 74, 75)</td>
<td>0.02–2.98%</td>
<td>0.8913</td>
</tr>
<tr>
<td>Permanent hypoparathyroidism</td>
<td>5.61% (71, 74, 75)</td>
<td>3.06–9.83%</td>
<td>0.8941</td>
</tr>
<tr>
<td>Recurrent hyperparathyroidism</td>
<td>0.70%/year (71, 73, 75)</td>
<td>0.31–1.51%</td>
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<tr>
<td>Scar</td>
<td>100%</td>
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<tr>
<td><strong>UNE</strong></td>
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<tr>
<td><strong>Short-term events</strong></td>
<td></td>
<td></td>
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<tr>
<td>Surgery</td>
<td>0.59% (10, 57, 62–64, 66, 68, 70)</td>
<td>0.23–1.50%</td>
<td>3.36</td>
</tr>
<tr>
<td>Transient dysphonia</td>
<td>1.09% (10, 11, 57, 62–64, 66–70)</td>
<td>0.59–2.00%</td>
<td>2</td>
</tr>
<tr>
<td>Transient hypocalcemia</td>
<td>6.28% (10, 11, 13, 57, 61, 63–67, 69)</td>
<td>4.66–8.37%</td>
<td></td>
</tr>
<tr>
<td>Persistent hyperparathyroidism §</td>
<td>6.43% (60, 61, 63–65, 69)</td>
<td>4.17–9.72%</td>
<td>0.9047</td>
</tr>
<tr>
<td>Sestamibi scintigraphy</td>
<td>5.62% (10, 13, 68, 98)</td>
<td>3.84–8.12%</td>
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<tr>
<td>Ultrasonography</td>
<td>5.35% (11, 57, 70)</td>
<td>1.54–7.37%</td>
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<tr>
<td>Long-term events</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Permanent dysphonia</td>
<td>0.00% (63)</td>
<td>0.00–6.76%</td>
<td>0.8913</td>
</tr>
<tr>
<td>Permanent hypoparathyroidism</td>
<td>0.00% (10, 63, 67)</td>
<td>0.00–2.42%</td>
<td>0.8941</td>
</tr>
<tr>
<td>Recurrent hyperparathyroidism</td>
<td>0.34%/year (57)</td>
<td>0.06–1.36%</td>
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<tr>
<td>Scar</td>
<td>100%</td>
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<tr>
<td><strong>VAP</strong></td>
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<tr>
<td><strong>Short-term events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td>7.44</td>
</tr>
<tr>
<td>Anesthesia-related death</td>
<td>0.0054% (100)</td>
<td>9.68–14.26%</td>
<td></td>
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<tr>
<td>Conversion into bilateral neck exploration</td>
<td>11.75% (80–82, 84)</td>
<td>9.68–14.26%</td>
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<tr>
<td>Hematoma</td>
<td>0.36% (80–82, 84)</td>
<td>0.13–1.63%</td>
<td>2</td>
</tr>
<tr>
<td>Transient dysphonia</td>
<td>0.64% (80–82, 84)</td>
<td>0.24–1.57%</td>
<td>1.54</td>
</tr>
<tr>
<td>Transient hypocalcemia</td>
<td>1.66% (80–82, 84)</td>
<td>0.93–2.90%</td>
<td></td>
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<tr>
<td>Persistent hyperparathyroidism§</td>
<td>1.40% (80–82, 84)</td>
<td>0.74–2.58%</td>
<td>0.9047</td>
</tr>
<tr>
<td><strong>Long-term events</strong></td>
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<tr>
<td>Permanent dysphonia</td>
<td>0.38% (80–82, 84)</td>
<td>0.10–1.21%</td>
<td>0.8913</td>
</tr>
<tr>
<td>Permanent hypoparathyroidism</td>
<td>0.00% (80–82, 84)</td>
<td>0.00–0.61%</td>
<td>0.8941</td>
</tr>
<tr>
<td>Recurrent hyperparathyroidism ¶</td>
<td>0.34%/year (80–82, 84)</td>
<td>0.06–1.36%</td>
<td></td>
</tr>
<tr>
<td>Scar</td>
<td>100%</td>
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</tbody>
</table>

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We examined the cost-effectiveness of five strategies for managing patients with primary hyperparathyroidism. The following strategies were compared first: (1) surgical BNE strategy (BNES); (2) UNE strategy (UNES); (3) VAP strategy (VAPS). These strategies were compared next with (4) lifelong medical follow-up followed by either BNES (Follow-up/BNES) or (5) UNES (Follow-up/UNES) in the event of a change in the value of the parameters monitored leading to a surgical indication (3). We used Decision Maker (Decision Maker Software, Beta version 2002) (91, 92), a decision-analysis software package, to model these strategies as a Markov state-transition decision-analytic model (93, 94) and to perform base-case and sensitivity analyses. We used a 1-month cycle length and a lifetime horizon (the decision model is available upon request from G M V-T). Rates and probabilities of complications used in the model for the base-case appear in Table 1.

**Table 1. Continued**

<table>
<thead>
<tr>
<th>Health state</th>
<th>Rates and probabilities</th>
<th>95% CIs or extreme values*</th>
<th>QOL adjustment factor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cervicosternotomy</strong></td>
<td></td>
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<tr>
<td><strong>Short-term events</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Surgery</td>
<td>12.37</td>
<td>0.9827</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1.89% (77–79)</td>
<td>0.33–7.32%</td>
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<tr>
<td>Hematoma</td>
<td>2.74% (78, 79)</td>
<td>0.48–10.44%</td>
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</tr>
<tr>
<td>Transient dysphonia</td>
<td>6.85% (78, 79)</td>
<td>2.55–15.93%</td>
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<tr>
<td>Transient hypocalcemia</td>
<td>33.96% (77–79)</td>
<td>25.22–43.88%</td>
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<tr>
<td>Persistent hyperparathyroidism</td>
<td>16.18% (77, 79)</td>
<td>8.73–25.53%</td>
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<tr>
<td><strong>Long-term events</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Permanent dysphonia</td>
<td>12.68% (77, 78)</td>
<td>6.31–23.20%</td>
<td></td>
</tr>
<tr>
<td>Permanent hypoparathyroidism</td>
<td>2.63% (78)</td>
<td>0.14–15.43%</td>
<td></td>
</tr>
<tr>
<td>Recurrent hyperparathyroidism</td>
<td>0.00%/year (77)</td>
<td>0.00–3.08%</td>
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<tr>
<td>Scar</td>
<td>100%</td>
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<tr>
<td><strong>Medical follow-up</strong></td>
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<tr>
<td>Indication for surgical treatment</td>
<td>0.78%/year (85, 86)</td>
<td>0.38%/year – 2.81%/year</td>
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</tr>
</tbody>
</table>

* 95% confidence intervals (CIs) or extreme values indicate the range of rates examined in the sensitivity analyses. When possible, exact 95% confidence intervals were estimated (38).
† For short-term outcomes quality-adjustment factor is expressed in days and subtracted from life expectancy.
‡ For long-term outcomes quality-adjustment factor is multiplied by life expectancy.
§ The risk of persistent hyperparathyroidism varies according to the localization studies performed and to other factors.
¶ Not yet available in the literature and assumed in the base-case to be similar to values estimated for limited neck exploration.

**Decision-analytic model**

We examined the cost-effectiveness of five strategies for managing patients with primary hyperparathyroidism. The following strategies were compared first: (1) surgical BNE strategy (BNES); (2) UNE strategy (UNES); (3) VAP strategy (VAPS). These strategies were compared next with (4) lifelong medical follow-up followed by either BNES (Follow-up/BNES) or (5) UNES (Follow-up/UNES) in the event of a change in the value of the parameters monitored leading to a surgical indication (3). We used Decision Maker (Decision Maker Software, Beta version 2002) (91, 92), a decision-analysis software package, to model these strategies as a Markov state-transition decision-analytic model (93, 94) and to perform base-case and sensitivity analyses. We used a 1-month cycle length and a lifetime horizon (the decision model is available upon request from G M V-T). Rates and probabilities of complications used in the model for the base-case appear in Table 1.

In the BNES (Table 1), patients were hospitalized and explored under general anesthesia without any previous localization study. Short-term complications included hematoma, transient vocal-cord paralysis and death. Hematoma resulted in a reoperation with its risk of death from general anesthesia. Every patient visited a specialist 1 and 6 months after surgery and received calcium and alfacalcidol for 15 days to prevent post-surgical hypocalcemia. This treatment was extended for 6 months in patients with transient hypoparathyroidism. Patients with persistent hypercalcemia were reoperated 6 months later after ultrasonography, sestamibi scintigraphy, venous catheterization with PTH assessment, computed tomography (CT) and magnetic resonance imaging (MRI). According to the results of these localization studies, a BNE or a cervicosternotomy (Table 1)

**Table 2** Positive predictive values (PPVs) and rates of positive results of localization studies performed before UNE or VAP.

<table>
<thead>
<tr>
<th>Preoperative localization</th>
<th>PPV (95% CI)</th>
<th>Positive rates (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First operation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sestamibi scintigraphy (29, 33, 60, 65, 110–116)</td>
<td>94% (91–96%)</td>
<td>77% (75–79%)</td>
</tr>
<tr>
<td>Ultrasonography (11, 53, 54, 112, 117)</td>
<td>97% (93–99%)</td>
<td>73% (69–76%)</td>
</tr>
<tr>
<td>Reoperation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sestamibi scintigraphy (109, 118, 119)</td>
<td>91% (83–96%)</td>
<td>83% (79–87%)</td>
</tr>
<tr>
<td>Ultrasonography (119)</td>
<td>86% (73–94%)</td>
<td>71% (65–77%)</td>
</tr>
<tr>
<td>Computed tomography (120–122)</td>
<td>74% (60–84%)</td>
<td>58% (53–64%)</td>
</tr>
<tr>
<td>Magnetic resonance imaging (118, 121, 122)</td>
<td>82% (72–90%)</td>
<td>80% (76–84%)</td>
</tr>
<tr>
<td>Venous catheterization with intact parathormone dosage (118, 123–128)</td>
<td>91% (87–94%)</td>
<td>78% (76–81%)</td>
</tr>
</tbody>
</table>

CI, confidence interval.
was performed. Permanent dysphonia or hypoparathyroidism were assumed to occur after each of these surgical procedures only in patients who experienced transient dysphonia or hypoparathyroidism. Patients without any complication underwent a lifelong medical follow-up including a visit each year to the general practitioner and calcemia measurement. In case of recurrence, patients underwent reoperation (BNE or cervicosternotomy; Table 1) after ultrasonography, sestamibi scintigraphy, venous catheterization with PTH assessment, CT scanning and MRI.

In the UNES (Table 1), patients underwent in preoperative cervical ultrasonography and sestamibi scintigraphy in a day-care setting. If both were positive (localization of a single adenoma in the neck), patients underwent UNE under local anesthesia; if not, they underwent BNE. Rapid intraoperative assays of PTH confirmed the resection of a single adenoma by an adequate reduction in PTH levels (5). Surgical failure was assumed to depend on both the positive predictive values of localization studies and other factors such as the surgeon’s skills. Short- and long-term complications of UNE were the same as those of BNE except for death. Post-operative monitoring was identical. Patients with persistent hypercalcemia or recurrent hyperparathyroidism were reoperated on 6 months later or when detected, respectively. They underwent BNE or cervicosternotomy (Table 1) according to the results of ultrasonography, sestamibi scintigraphy, venous catheterization with PTH assessment, CT scanning and MRI.

In the VAPS (Table 1), ultrasonography and sestamibi scintigraphy were performed in day-care settings: if both were positive, patients underwent VAP under general anesthesia; if not, they underwent BNE. PTH was measured using intraoperative assays. When VAP failed to find the adenoma, a BNE was performed immediately. Short-term complications included death related to general anesthesia. Other complications were the same as those for BNE. The rate of recurrence was assumed to be the same as after UNE.

In the medical follow-up strategies (Table 1), patients were monitored according to the guidelines and may have experienced nonspecific symptoms (3). We assumed no incremental risk of death. Either BNE or UNE was performed when patients met at least one criterion for surgery thus avoiding complications of hyperparathyroidism such as fractures or renal colic attacks.

**Effectiveness**

Outcomes were expressed as quality-adjusted life expectancy. Population-based mortality rates were derived from French tables of vital statistics.

**Quality of life (QOL)**

We adjusted life expectancy for both short-term (for example complications such as hematoma, hospitalization or recovery) and long-term (complications such as dysphonia or hypoparathyroidism, persistent hyperparathyroidism or scarring) morbidity. Mean QOL weights for each health state (short-term and long-term morbidities) identified as potentially reducing QOL (Table 1) were drawn from a survey in an opportunistic sample of 109 volunteers without the disease. Utilities of health states were elicited using the time trade-off method (95) by one trained interviewer.

**Costs**

Costs (Table 3) were computed from the healthcare delivery system perspective and were expressed in € for the year 2002. Average total inpatient costs were derived from the cost accounting system of the Assistance Publique – Hôpitaux de Paris, a hospital network of 50 non-profit university hospitals in the Paris region. Non-healthcare costs were not considered. Hospital costs included all personnel costs, supplies, drugs and blood products, tests, housekeeping and hospital overheads. Ambulatory costs were estimated using the national reimbursement schedule provided by the Social Security, prices for drugs were derived from the French Red Book (Dictionnaire Vidal). Guidelines (3) were used to estimate the periodicity of clinic visits and tests during medical follow-up. Experts’ opinions were used for recovery lengths. Costs and health benefits were discounted at 3% yearly (95, 96).

**Sensitivity analyses**

Sensitivity analyses (one- or two-way) were performed on every variable included in the model. The extreme values of reported data or the estimated 95% confidence intervals were used (Table 2). We varied major cost components (for example length of hospitalization and frequency of ambulatory follow-up) and QOL adjustments. All sensitivity analyses used a discount rate of 3% unless otherwise noted.

**Results**

**Base-case analysis**

In a 55-year-old woman with sporadic asymptomatic hyperparathyroidism eligible for surgery (Table 4a), the VAPS was marginally the most effective strategy, resulting in a gain of 0.004 QALY (1.46 days) compared with UNES (0.0892 QALY; 32.49 days) compared with BNES. UNES resulted in a gain of 0.0852 QALY (31.03 days) compared with BNES and its incremental cost-effectiveness ratio was €2688/QALY. The incremental cost-effectiveness ratio of VAPS was €17 250/QALY compared with UNES (€3341/QALY) and BNES (less than €20 000/QALY).
### Table 3  
Average costs of (a) management for hyperparathyroidism and (b) complications of therapy for primary hyperparathyroidism.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>First-month cost (€)</th>
<th>Subsequent patient cost for first year (€)</th>
<th>Subsequent outpatient costs, following years (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(a)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BNE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First operation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient visits†</td>
<td>69 (3)</td>
<td>46 (2)</td>
<td>20 (1)</td>
</tr>
<tr>
<td>Biological and hormonal measurements‡</td>
<td>116</td>
<td>164</td>
<td>8</td>
</tr>
<tr>
<td>Surgery§</td>
<td>2100</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Post-surgical preventive therapy of hypocalcemia¶</td>
<td>88</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2373</td>
<td>210</td>
<td>28</td>
</tr>
<tr>
<td>Re operation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient visits†</td>
<td>69 (3)</td>
<td>46 (2)</td>
<td>20 (1)</td>
</tr>
<tr>
<td>Biological, hormonal measurements and localization studies**</td>
<td>1982</td>
<td>164</td>
<td>8</td>
</tr>
<tr>
<td>Surgery§</td>
<td>2100</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Post-surgical preventive therapy of hypocalcemia¶</td>
<td>88</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>4239</td>
<td>210</td>
<td>28</td>
</tr>
<tr>
<td><strong>UNE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient visits†</td>
<td>69 (3)</td>
<td>46 (2)</td>
<td>20 (1)</td>
</tr>
<tr>
<td>Biological, hormonal measurements and localization studies††</td>
<td>733</td>
<td>164</td>
<td>8</td>
</tr>
<tr>
<td>Surgery††</td>
<td>1890</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Post-surgical preventive therapy of hypocalcemia¶</td>
<td>88</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2780</td>
<td>210</td>
<td>28</td>
</tr>
<tr>
<td><strong>VAP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient visits†</td>
<td>69 (3)</td>
<td>46 (2)</td>
<td>20 (1)</td>
</tr>
<tr>
<td>Biological, hormonal measurements and localization studies††</td>
<td>754</td>
<td>164</td>
<td>8</td>
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<tr>
<td>Surgery††</td>
<td>2189</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Post-surgical preventive therapy of hypocalcemia¶</td>
<td>88</td>
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<td>NA</td>
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<tr>
<td><strong>Total</strong></td>
<td>3100</td>
<td>210</td>
<td>28</td>
</tr>
<tr>
<td><strong>Exploration by cervicosternotomy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient visits†</td>
<td>69 (3)</td>
<td>46 (2)</td>
<td>20 (1)</td>
</tr>
<tr>
<td>Biological, hormonal measurements and localization studies**</td>
<td>1982</td>
<td>164</td>
<td>8</td>
</tr>
<tr>
<td>Surgery§§</td>
<td>3910</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Post-surgical preventive therapy of hypocalcemia¶</td>
<td>88</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>6049</td>
<td>210</td>
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</tr>
<tr>
<td><strong>Medical follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient visits (specialist visits)</td>
<td>23 (1)</td>
<td>23 (1)</td>
<td>46 (1)</td>
</tr>
<tr>
<td>Biological measurements, abdominal ultrasounds and dual X-ray absorptiometry†††</td>
<td>145</td>
<td>8</td>
<td>89</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>168</td>
<td>31</td>
<td>135</td>
</tr>
<tr>
<td><strong>(b)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hematoma</strong>*</td>
<td>328</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Dysphonia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical evaluation of a speech problem†††</td>
<td>46 (2)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Laryngoscopy†††</td>
<td>29 (1)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Vocal-cord re-education sessions†††</td>
<td>220 (20)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>295</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Hyppoparathyroidism</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient specialist visits†††</td>
<td>NA</td>
<td>69 (3)</td>
<td>46 (2)</td>
</tr>
<tr>
<td>Biological measurements</td>
<td>NA</td>
<td>96 (6)</td>
<td>32 (2)</td>
</tr>
<tr>
<td>Alfacalcidol</td>
<td>31</td>
<td>344</td>
<td>375</td>
</tr>
<tr>
<td>Calcium</td>
<td>9</td>
<td>102</td>
<td>111</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>40</td>
<td>611</td>
<td>564</td>
</tr>
</tbody>
</table>

All costs are in € for 2002; NA indicates not applicable. The number of visits, examinations or sessions is indicated in parentheses.
† Outpatients visits denote specialist visits for the first year and general practitioner visits for the subsequent years.
‡ Denotes the costs in an ambulatory setting of measurements of PTH, vitamin D, calcemia, protidemia, 24-h urinary calcium, creatininemia, complete blood count, prothrombin time, ECG and CAT in the first month; of measurements of calcemia, protidemia, 24-h urinary calcium, 24-h creatininuria and creatininemia 2-fold in subsequent months of the first year and calcemia annually in the subsequent years.

K Sejean and others  
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Sensitivity analyses

Comparisons between BNES and UNES Varying rates of complication and QOL weights did not significantly change the effectiveness of BNES compared to UNES. BNES became more effective than and dominated (was more effective and less expensive than) UNES when the risk of mortality associated with UNE exceeded 0.88% (base-case, 0.00%) or when the QOL weight for UNE scarring was less than 0.9885 (base-case, 0.9979).

The incremental cost-effectiveness ratio of UNES versus BNES remained inferior to€6000 until 80 years of age (Fig. 1). UNES became less costly than and dominated BNES when the cost of UNE was less than €1483 (base-case, €1890; −22%).

Comparisons between UNES and VAPS VAPS was the most effective surgical strategy for otherwise healthy women from 40 to 71 years of age (Fig. 1). UNES became the most effective strategy and dominated VAPS over 71 years, when the risk of mortality associated with VAPS exceeded 0.05% (base-case, 0.0054%), the risks of transient or permanent dysphonia associated with VAP exceeded 1.30 or 0.60%, respectively (base-case, 0.64 and 0.38%, respectively), the risk of immediate failure (conversion into BNES excluded) or the annual rate of recurrence after VAP exceeded 3.71 or 0.49%, respectively (base-case, 1.40 and 0.34%, respectively). Lowering the risk of immediate failure or the annual rate of recurrence after UNE under 1.91 or 0.19%, respectively (base-case, 3.30 and 0.34%, respectively) also made UNES the most effective strategy. Also, UNES dominated if QOL weights for permanent dysphonia or for VAP scarring were less than 0.7766 and 0.9984, respectively (base-case, 0.8913 and 0.9988, respectively) or if QOL weights for UNE scarring exceeded 0.9984 (base-case, 0.9979). VAPS was less expensive than and dominated UNES if the cost of VAP was less than €2068 (base-case, €2189; −6%). We also studied the effect of varying the discount rate from 0 to 5%. If the discount rate was 0%, UNES dominated VAPS.

Consequences of the selection among preoperative localization studies The most effective strategy was VAPS when VAP and UNE were performed after sestamibi scintigraphy only, on an outpatient basis (Table 5). UNES became the least costly when UNE was performed after ultrasonography only and was even less costly if UNE was performed during day-care hospitalization. The model was insensitive to the selection among preoperative localization studies before reoperation.

Patients not eligible for surgery The follow-up strategies were less effective but less costly than the surgical strategies in a 55-year-old woman not eligible for surgery (Table 4b).

Every surgical strategy was more effective than these strategies for women between 40 and 80 years of age, but they remained the least costly (Fig. 1). The incremental cost-effectiveness ratio of UNES compared with Follow-up/UNES increased in older women but remained less than €6000/QALY for women at all ages studied. If no decrement in QOL was associated with lifelong monitoring, Follow-up/UNES became more effective than and dominated UNES: the threshold for the QOL weight of medical monitoring between UNES and Follow-up/UNES was 0.9914 (base-case, 0.9047). No other reasonable changes in the values of the variables led to make Follow-up/UNES more effective than UNES. Follow-up/UNES only dominated UNES when the mortality risk associated with UNE exceeded 15.48% (base-case, 0.00%).

Follow-up/UNES was more expensive than if the annual cost of medical follow-up was more than €216 (base-case, €132).

Discussion

To identify the best choice for managing patients with sporadic asymptomatic primary hyperparathyroidism in the absence of a randomized clinical trial comparing all the therapeutic strategies currently used, we used a decision-analytic model. We compared, in a cost-effec-

---

§ Includes professional fees, anesthesia, surgery, and an average 4-day hospitalization.
¶ Includes a 15-day treatment with calcium and alfacalcidol.
** Biological, hormonal measurements and localization studies (sestamibi scintigraphy, ultrasonography, CT, MRI, venous catheterization with PTH measurements) are performed in a day-care setting before surgery; include also biological tests performed before general anesthesia; calcemia, protidemia, 24-h urinary calcium, 24-h creatinuria and creatininemia are measured in an ambulatory setting twice in the subsequent months of the first year and calcemia annually in the subsequent years.
†† Biological, hormonal measurements and localization studies (sestamibi scintigraphy and ultrasonography) are performed in a day-care setting before surgery; include also biological tests performed before anesthesia; calcemia, protidemia, 24-h urinary calcium, 24-h creatinuria and creatininemia are measured in an ambulatory setting twice in the subsequent months of the first year and calcemia annually in the subsequent years.
††† Includes professional fees, anesthesia, surgery, and an average 2-day hospitalization.
‡‡ Denotes the costs of measurements in an ambulatory setting of calcemia, 24-h urinary calcium, creatininemia, creatinine clearance, abdominal ultrasonography and dual-energy X-ray bone absorptiometry (three sites) in the first month; of the measurements of calcemia twice in the subsequent months of the first year and of calcemia biannually, 24-h urinary calcium, creatininemia and dual-energy X-ray bone absorptiometry (three sites) annually in the subsequent years.
*** Denotes the cost of an average 2 days in a hospital and of biological tests. The number of visits, examinations or sessions is indicated between parentheses; two numbers between parentheses denote number during the first year and the following years.
**** Denotes the costs of biological measurements (calcemia, protidemia, 24-h urinary calcium); the number of measurements is indicated in parentheses.

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tiveness analysis, the surgical strategies recommended in patients with risk factors for developing complications of hyperparathyroidism and then we compared these strategies with medical monitoring in patients not eligible for surgery (3, 97). We found both minimally invasive surgical strategies (UNES and VAPS) to be more effective than the traditional BNES with an acceptable incremental cost-effectiveness ratio (less than €20,000/QALY). VAPS was slightly more effective than UNES in a 55-year-old women and UNES became the least expensive surgical strategy if only one preoperative localization study – ultrasonography – was performed. Moreover, every surgical strategy was more effective than the medical follow-up strategies except in patients feeling no decrement in QOL. UNES had a very reasonable incremental cost-effectiveness ratio compared with follow-up, even in the elderly.

We estimated the risk of surgical mortality of BNE at 0.21% between the 0.04 and 0.73% extreme mortality rates assessed in surgical series (20). The higher surgical risk and the larger decrement in QOL due to the cervicotomy scarring participated in the lower effectiveness of BNES compared with VAPS and UNES. Despite shorter hospital stays and lower reoperation rates, UNES and VAPS had higher average lifetime costs than BNES partly due to the cost of localization studies. However, the incremental cost-effectiveness of UNES makes it a very 'reasonable' choice for patients of all the ages studied (<€6000/QALY). Performing only one localization study instead of two (sestamibi scintigraphy and ultrasonography) before minimally invasive surgery lead to higher efficiency of these strategies. In addition, UNES became the least-costly surgical strategy when ambulatory ultrasonography was performed. In our base-case, both explorations had to localize a single adenoma at the same place for a minimally invasive procedure to be performed, which occurred only in 56% of cases instead of 77% and 73% for sestamibi scintigraphy and ultrasound, respectively. However, if both localization studies were performed at the same time and considered positive if only one of them was positive, the rate of positive localization studies may be higher than that supplied by only one localization study (98). The gain of VAPS compared with UNES was 1.46 days of quality-adjusted life expectancy in our base-case due to a higher QOL weight for scarring and to a lower failure rate of VAPS apart from immediate conversion into BNE. Less persistent hyperparathyroidism lead to fewer reoperations and therefore a lower perioperative mortality or morbidity. However, there were a large variety of conditions where VAPS became less effective than UNES. If the failure rate of VAP exceeded 3.71%, VAPS became less effective than

![Figure 1](https://www.eje-online.org)

**Figure 1** Incremental cost-effectiveness ratios (CERs) of the minimally surgical strategies (VAPS and UNES) versus BNES and UNES versus medical follow-up as a function of patient age. The figure portrays a one-way sensitivity analysis examining the incremental cost-effectiveness ratio of VAPS or UNES compared with BNES and medical follow-up (Follow-up/BNE) as a function of patient age. Incremental cost-effectiveness ratios are shown of: ♦, UNES versus BNES; ▲, UNES versus medical follow-up; ◼, VAPS versus UNES. The incremental cost-effectiveness ratio of VAPS increases with age. VAPS is no longer the most effective strategy over 69 years. The incremental cost-effectiveness ratio of UNES compared with both BNES and Follow-up/BNE but did not exceed €6000 until 80 years.

---

**Table 4** Base-case analysis of discounted cost and effectiveness of management strategies for sporadic asymptomatic primary hyperparathyroidism with criteria for (a) surgery and medical follow-up.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost (€)</th>
<th>QALE (QALY)</th>
<th>ΔCost (€)</th>
<th>ΔEffectiveness (QALY)</th>
<th>ΔCost-effectiveness ratio (€/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNE</td>
<td>3537</td>
<td>17.0329</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UNE</td>
<td>3766</td>
<td>17.1181</td>
<td>229</td>
<td>0.0852</td>
<td>2688</td>
</tr>
<tr>
<td>VAP</td>
<td>3835</td>
<td>17.1221</td>
<td>69</td>
<td>0.0004</td>
<td>17.250</td>
</tr>
<tr>
<td>(b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical follow-up/BNES</td>
<td>2538</td>
<td>15.7469</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical follow-up/UNES</td>
<td>2563</td>
<td>15.7543</td>
<td>25</td>
<td>0.0074</td>
<td>*Extended dominance</td>
</tr>
<tr>
<td>BNE</td>
<td>3537</td>
<td>17.0329</td>
<td>974</td>
<td>1.2786</td>
<td>762</td>
</tr>
<tr>
<td>UNE</td>
<td>3766</td>
<td>17.1181</td>
<td>229</td>
<td>0.0852</td>
<td>2688</td>
</tr>
<tr>
<td>VAP</td>
<td>3835</td>
<td>17.1221</td>
<td>69</td>
<td>0.0004</td>
<td>17.250</td>
</tr>
</tbody>
</table>

QALE, quality-adjusted life expectancy (discounted at 3% per year). *This is denoted as extended dominance because the incremental cost-effectiveness ratio of medical follow-up/UNES compared with medical follow-up/BNES is larger than the incremental cost-effectiveness ratio of BNE compared with medical follow-up/BNES.
UNES. The first study reporting outcomes of V AP was published in 1998 (99) but the hyperparathyroidism recurrence rate after this procedure is still unknown. Thus we assumed a similar recurrence rate for V AP and UNE (0.34%). However, V APS was no longer the most effective strategy if the annual recurrence rate after V AP increased above 0.49%. We also found that the cost-effectiveness ratio of V APS versus UNES increased with age until 71 years, and then V APS became less effective than UNES. Further, V AP is usually performed under general anesthesia. Though none of the V AP series that we analyzed (80–82, 84) reported perioperative deaths, the literature (100) reports an extremely low risk of anesthesia-related mortality (0.0054%), which we included in our base-case. When this risk was higher (0.05%), especially in the elderly with comorbidities, UNES became the preferred strategy over V APS.

Finally, in our study, the strategies of medical monitoring were less effective than surgery. The decrement in QOL found from our population study was reported previously in patients who were minimally hypercalcemic using the SF-36 Health Survey (17, 101, 102) or a specific tool (58, 103). However, some patients may feel no decrement in QOL due to monitoring or non-specific symptoms making the medical follow-up strategies dominant over surgery (the most effective and the least costly). Therefore, patient preferences must be factored into the decision. Surgery became less expensive than follow-up if the annual cost of follow-up exceeded 64% of the base-case estimate. This could occur if medical therapies were added to this monitoring.

Our study has some limitations. We assumed no increment in mortality due to lifelong medical follow-up. This could have biased the results against the surgical strategy. Controversial results were reported: some studies (104–107) demonstrated a higher risk of mortality in patients with hyperparathyroidism than in the general population, another (18) showed a lower risk of mortality for patients with hyperparathyroidism surgically treated than for others whereas other authors found no increment in mortality of asymptomatic patients (108). Thus further randomized studies involving placement of asymptomatic patients not eligible for surgery into surgical and non-surgical groups, such as the one by Talpos et al. (17), are expected. Because of lack of perspective, we also had to assume that recurrence rate after VAP was similar to that after UNE. Furthermore, practice preferences of surgeons regarding anesthesia or hospitalization length vary. However, our sensitivity analyses examined the consequences of our choices in the base-case. In addition, most of the data analyzed in our literature review were drawn from cohort or

Table 5 Analysis of discounted cost and effectiveness of management strategies for sporadic asymptomatic primary hyperparathyroidism with criteria for surgery according to the localization studies performed and to the care setting.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost (£)*</th>
<th>QALE (QALY)</th>
<th>ΔCost (£)</th>
<th>ΔEffectiveness (QALY)</th>
<th>ΔCost–effectiveness ratio (£/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasonography only*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UNE</td>
<td>3458</td>
<td>17.1367</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAP</td>
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<td>17.1394</td>
<td>59</td>
<td>0.0027</td>
<td>21 852</td>
</tr>
<tr>
<td>BNE</td>
<td>3537</td>
<td>17.0329</td>
<td>20</td>
<td></td>
<td>S.D.</td>
</tr>
<tr>
<td>Sestamibi scintigraphy only*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNE</td>
<td>3537</td>
<td>17.0329</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UNE</td>
<td>3707</td>
<td>17.1397</td>
<td>170</td>
<td>0.1068</td>
<td>1592</td>
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<td>VAP</td>
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<td>17.1433</td>
<td>35</td>
<td>0.0036</td>
<td>9722</td>
</tr>
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<td>Ultrasonography only and UNE (outpatient basis)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>3427</td>
<td>17.1376</td>
<td></td>
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</tr>
<tr>
<td>VAP</td>
<td>3517</td>
<td>17.1394</td>
<td>90</td>
<td>0.0018</td>
<td>50 000</td>
</tr>
<tr>
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<td>3537</td>
<td>17.0329</td>
<td>20</td>
<td></td>
<td>S.D.</td>
</tr>
<tr>
<td>Sestamibi scintigraphy only and UNE (outpatient basis)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNE</td>
<td>3537</td>
<td>17.0329</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UNE</td>
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<td>VAP</td>
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<tr>
<td>Ultrasonography, scintigraphy and UNE (outpatient basis)*</td>
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<tr>
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<td>111</td>
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QALE, quality-adjusted life expectancy; S.D., standard deviation.
* Indicates changes in selection of localization studies and in the setting of care compared to the base-case. Ultrasonography or sestamibi scintigraphy when performed as the unique procedure is performed on an outpatient basis.
case-series studies and not from randomized clinical trials. Finally, QOL weights were obtained from a population without the disease instead of a patient population for feasibility reasons.

In most cases, the decision for the management of asymptomatic hyperparathyroidism is driven by a number of individual factors, such as age, general health, individual perception and patient preference. However, the minimally invasive surgical strategies (UNES and VAPS) are the most effective strategies at a reasonable cost except in patients without surgical indication, who prefer medical monitoring. Locally available facilities and expertise should also guide the choice between minimally invasive surgical strategies.

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