National Institute for Health and Care Excellence

Draft for consultation

Hyperparathyroidism (primary): diagnosis, assessment and initial management

[E] Evidence review for surgical interventions

NICE guideline

Intervention evidence review

November 2018

Draft for consultation

This evidence review was developed by the National Guideline Centre

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1 Surgical interventions

1.1 Review question: What is the clinical and cost effectiveness of different types of surgical intervention, for example 4-gland exploration, compared with minimally invasive techniques?

1.2 Introduction

In the majority of cases, primary hyperparathyroidism (PHPT) is caused by a benign tumour (adenoma) of one of the parathyroid glands. Less commonly 2 or more glands are involved or all 4 glands can be enlarged due to parathyroid hyperplasia. If pre-operative imaging is able to identify a single adenoma, focused surgery is usually performed. The alternative approach is bilateral neck exploration (also known as 4-gland exploration). Focused surgery can be performed under local or general anaesthesia and involves a slightly smaller incision than bilateral neck exploration, which can only be performed under general anaesthesia. Bilateral neck exploration enables the surgeon to visualise all 4 glands.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Adults (18 years or over) with confirmed primary hyperparathyroidism caused by single adenoma, 4-gland hyperplasia, double adenoma or ectopic adenoma. Strata: • Type of adenoma / hyperplasia (single adenoma, 4-gland hyperplasia or ectopic adenoma): stratify these groups as the accuracy of localisation (and therefore overall effectiveness of surgery will be affected by the type of adenoma) • Previous parathyroidectomy (re-operation): scarring and distortion of tissue planes plus the potential for ectopic gland location leads to lower success rate of pre-op imaging • Pregnant women
Interventions	**Surgical techniques:** • Bilateral neck exploration via direct visualisation of all glands (4-gland exploration) using open traditional incision • Bilateral neck exploration via direct visualisation of all glands (4-gland exploration) using minimally invasive incision • Bilateral neck exploration via direct visualisation of all glands (4-gland exploration) using endoscopic/videoscopic approach • Minimally invasive parathyroidectomy (MIP) guided by IOPTH and preoperative imaging using open unilateral parathyroidectomy • MIP guided by IOPTH and preoperative imaging using open focused parathyroidectomy • MIP guided by IOPTH and preoperative imaging using endoscopic/videoscopic unilateral parathyroidectomy • MIP guided by IOPTH and preoperative imaging using endoscopic/videoscopic focused parathyroidectomy

	Localisation or intra-operative techniques: Pre-operative imaging using one of the following and read by a radiologist or surgeon • US imaging using a high frequency probe, 10-15 MHz. • US imaging using a high frequency probe combined with colour Doppler ultrasound • Technetium 99m- Sestamibi scanning (planar) using single isotope dual phase scan (uses a single isotope and early and delayed phase imaging, usually at about 10-30 minutes and at 90-120 minutes) • Technetium 99m- Sestamibi scanning (planar) using dual isotope subtraction scan (uses isotope, 99 Tc sestamibi to image the parathyroids and either 123 Iodine or 99 Tc pertechnatate to image the thyroid, and then one set of images is subtracted from the other - often performed with early and delayed imaging) • Three-dimensional sestamibi scanning (also known as planar+ or SPECT or SPECT-CT) • MRI • CT • 4DCT • Parathyroid venous sampling **Intra-operative monitoring:** • Methylene blue • intraoperative frozen sections • IOPTH monitoring
Comparisons	Compare targeted/focused surgical techniques versus non-focused/non-targeted techniques/4-gland exploration (with or without any one or combination of the localisation techniques or intra-operative techniques).
Outcomes	• HRQOL (continuous outcome) (critical) • Mortality (dichotomous outcome) (critical) • Success (cure) / failure (dichotomous outcome) (critical) • Adverse events (bleeding (return to theatre), severe hypocalcaemia (as defined in the study),hypercalcemia, laryngeal nerve injury, vocal cord paralysis/laryngeal nerve injury, haematoma, infection) (dichotomous outcome) (important) • BMD of the distal radius or the lumbar spine (continuous) (important) • Deterioration in renal function (dichotomous – study may also report renal replacement) (important) • Fractures (vertebral or long bone) (dichotomous outcome) (important) • Length of hospital stay (continuous outcome) (important) • Occurrence of kidney stones (dichotomous outcome) (important) • Persistent hypercalcaemia (dichotomous outcome) (important) • Reoperation (dichotomous outcome) (important) • Unnecessary neck exploration (dichotomous outcome) (important)
Study design	RCTs and systematic reviews of RCTs

The aim of this review was to investigate the effectiveness of different types of surgical interventions. Hence, this review compares focused/targeted surgical interventions with non-focused/non-targeted interventions/4-gland exploration (with or without any one or combination of the localisation techniques or intra-operative techniques) and does not include studies comparing individual surgical interventions with each other. The committee defined focused/targeted parathyroidectomy to include minimally invasive parathyroidectomy

and all other remaining surgical interventions to be non-focused/non-targeted/4-gland exploration.

1.4 Clinical evidence

1.4.1 Included studies

A search was conducted for randomised controlled trials assessing the effectiveness of different types of surgical interventions for treatment of people with primary hyperparathyroidism caused by single adenoma, 4-gland hyperplasia, double adenoma or ectopic adenoma.

Five studies were included in the review; Bergenfelz 2005[4], Miccoli, 1999[17], Russell 2006[23], Sadik 2011[24], Slepavicius 2008[27] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary tables below (Table 3, Table 4, Table 5 and Table 6). See also the study selection flow chart in appendix C, forest plots in appendix E, study evidence tables in appendix D and GRADE tables in appendix F.

All studies included patients diagnosed with PHPT having indications for surgery, however in 4 studies (Bergenfelz 2005[4], Sadik 2011[24], Russell 2006[23], Micolli 1999 [17]) there was pre-selection of patients with solitary parathyroid adenoma. In the study Slepavicius 2008[27] although there was no pre-selection of patients, if hyperplasia of parathyroid glands was found during the surgery, those patients were excluded from the study (solitary parathyroid adenoma was confirmed by pathological examination in majority of the patients in this study).

All included studies compared focused with non-focused parathyroidectomy/4-gland exploration; however there was a variation in the localisation/intra-operative techniques used in the studies. Pre-operative localisation was used for both the groups in 4 out of 5 studies; and in one study pre-operative localisation was used in the focused group only. Three studies had intra-operative techniques in addition to pre-operative localisation studies. In two studies (Bergenfelz 2005[4], Russell 2006[23]) all patients had pre-surgery sestamibi scintigraphy for localisation of single parathyroid adenomas; in the study Miccoli 1999[17] the focused (MIP) group had intra-operative qPTHa and the classic bilateral neck group had intra-operative frozen section (pre-surgery localisation for both groups); in the study Sadik 2011[24] the focused group had intra-operative surgical sonography and the conventional unilateral open procedure group did not have intra-operative sonography (pre-surgery localisation with imaging using 99mTc-sestamibi for both groups); in the study Slepavicius 2008[27] the focused group had pre-surgery localisation and intact intra-operative parathyroid hormone monitoring (IIPTH) and the conventional parathyroidectomy did not have pre-operative localisation and IIPTH.

Frozen section analysis for tissue confirmation was used in both the groups in Bergenfelz 2005[4] and used only in the bilateral conventional surgery group in Miccoli 1999[17].

Different modes of anaesthesia were used in the studies. Only two studies (Bergenfelz 2005[4] and Miccoli 1999[17]) used local anaesthesia in the focused group, the rest of the studies used general anaesthesia for both the groups. In the study Bergenfelz 2005[4], conventional bilateral surgery was conducted under general anaesthesia and local anaesthesia in focused/MIP group; in the study Miccoli 1999[17], bilateral neck exploration conducted under GA and focused/VAP under general endotracheal anaesthesia or bilateral superficial cervical block in association with laryngeal mask; mode of anaesthesia was not reported in the study Russell 2006[23]; in the study Sadik 2011[24], patients underwent general anaesthesia with endotracheal intubation in both groups; in the study Slepavicius 2008[27] all patients underwent parathyroidectomy under general anaesthesia.

All studies were small with less than 100 patients.

There was a variation in the terminologies for the various types of surgeries conducted in the studies and these have reported as in the papers. Also in some studies, definition of surgical procedures was not clearly defined.

Although all studies compared focused with non-focused parathyroidectomy/4-gland exploration, there was a variation in the use of pre-operative localisation and intra-operative techniques, hence all studies were not pooled together.

The following comparisons have been used for analysis in the review:

1. Focused unilateral parathyroidectomy vs standard bilateral parathyroid exploration [pre-surgery localisation for all patients] – 2 studies for this comparison (Russell 2006[23] and Bergenfelz 2005[4]).

2. Minimally invasive parathyroidectomy with intra-operative surgical sonography (MIPUSS) vs conventional unilateral open procedure (OP) without intra-operative sonography [pre-surgery localisation with imaging for all patients]- 1 study (Sadik 2011[24])

3. Focused parathyroidectomy with pre-operative localisation+ intra-operative intact parathyroid hormone monitoring (IIPTH) vs conventional parathyroidectomy without localisation and IIPTH- 1 study (Slepavicius 2008[27])

4. Video assisted parathyroidectomy (VAP) (type of minimally invasive) + intra-operative qPTHa vs classic bilateral neck exploration + intra-operative frozen section (no qPTHa) [pre-surgery localisation for both groups]– 1 study (Miccoli 1999[17])

All studies were analysed in the stratum single parathyroid adenoma. There was insufficient number of studies to conduct sub-group analysis.

None of the studies reported the critical outcomes mortality and quality of life. The majority of the studies reported the adverse outcomes (temporary/permanent recurrent laryngeal nerve injury, hypocalcaemia, wound infection, drainage of a wound seroma) either at post-operative period or at 1 month and 6 months after surgery. There was evidence from one study each for the outcomes re-operation and length of hospital stay (hours).

There was no clear definition for the outcome success/cure or failure of surgery in the studies; some studies defined success based on serum calcium levels/normocalcaemia/hypercalcemia/ supplementation prescribed/incision used; also, success was defined at different end points in the studies, for example post-operative/6 months after surgery; studies did not report the data in an analysable format. Hence, the results for this outcome have been reported narratively in the review.

1.4.2 Excluded studies

See the excluded studies list in appendix I.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Population	Intervention and comparison	Outcomes	Comments
Bergenfelz 2005[4] RCT Germany	n=50 Patients with a solitary parathyroid adenoma localised before surgery by sestamibi scintigraphy.	Minimally invasive parathyroidectomy versus conventional bilateral exploration All patients had sestamibi scintigraphy for localisation of parathyroid adenomas. Only patients with single enlarged parathyroid gland were eligible for inclusion in the study. Stratum: single parathyroid adenoma	Outcome • Vocal cord palsy (post-operative) • Re-operation • Drainage of a wound seroma (post-operative) • Hypocalcaemia (1 month and 6 months)	Bilateral under general anaesthesia MIP under local anaesthesia. Conversion to BCE was necessary in three patients who had been randomised to undergo MIP under local anaesthesia. Frozen section analysis for both groups.
Miccoli, 1999 [17] RCT Italy	n=38 Patients with PHPT referred for parathyroidectomy. Inclusion criteria: Sporadic form of PHPT, no prior neck surgery, absence of thyroid nodules, and pre-operative ultrasonography suggestive for solitary parathyroid adenoma.	Video assisted parathyroidectomy (VAP) [one of the options of minimal access parathyroidectomy]+ intra-operative qPTHa vs Classic bilateral neck exploration + frozen section Pre-operative localisation done by referring physician. Ultrasound examination of	• Recurrent laryngeal nerve palsy (6 months) • Wound infection (post-operative) • Temporary hypocalcaemia (post-operative)	Bilateral neck exploration (under GA) VAP under general endotracheal anaesthesia or bilateral superficial cervical block in association with laryngeal mask In the classic bilateral exploration - frozen section was used for tissue confirmation. qPTHa was not used in this group.

Study	Population	Intervention and comparison	Outcomes	Comments
		the neck performed by an expert radiologist using a linear transducer with colour Doppler capability. The patients' eligibility for VAP was considered based on clinical history and ultrasound findings. Those considered eligible for VAP were then randomly divided to bilateral or VAP. Stratum: single parathyroid adenoma		In the VAP group - qPTHa used.
Russell 2006[23] RCT UK	n=78 Patients diagnosed with PHPT based on persistent hypercalcemia with a concomitant increased or inappropriate level of serum PTH.	Focused unilateral vs Standard bilateral operation Localisation before randomisation for both groups. All expect 5 patients with proven PHPT underwent dual isotope subtraction scanning using TC and TC labelled sestamibi. Patients with a positive sestamibi scan and pre-operative single tumour identified at the site suggested by the scan were included and pre-operatively randomised to unilateral or bilateral exploration.	• Permanent unilateral vocal cord paralysis • Symptomatic hypocalcaemia (2 days after operation)	Patients randomised at operation to either unilateral or bilateral Mode of anaesthesia not reported

Study	Population	Intervention and comparison	Outcomes	Comments
		Stratum: single parathyroid adenoma		
Sadik 2011 [24] RCT Ireland	n=30 Patients presenting with a bio-chemical diagnosis of primary hyperparathyroidism.	Minimally invasive parathyroidectomy with intra-operative surgical sonography (MIPUSS) vs Conventional unilateral open procedure (OP) without intra-operative sonography All patients underwent pre-admission investigative imaging using 99m Tc-sestamibi. Injection of 20 to 25 mCi 99mTc-sestamibi was performed and views were acquired at 15, 60, and 180 minutes utilising identical acquisition parameters. Stratum: single parathyroid adenoma	• Temporary recurrent laryngeal neuropraxia (30 days post- surgery) • Hospital stay (hours) • Temporary hypocalcaemia (30 days)	Patients underwent general anaesthesia with endotracheal intubation (both groups)
Slepavicius 2008[27] RCT Lithuania	n= 48 Patients with diagnosis of PHPT (determined clinically and with laboratory tests) and having indications for surgery.	Focused parathyroidectomy with pre-operative localisation+ intra-operative intact parathyroid hormone monitoring (IIPTH) vs Conventional parathyroidectomy without pre-operative localisation	• Temporary recurrent laryngeal nerve palsy (post-operative follow-up) • Transient hypocalcaemia (30 days after surgery) • QOL (no data)	All patients underwent parathyroidectomy under GA. All patients discharged 2 days after surgery Solitary parathyroid gland adenoma was confirmed by

Study	Population	Intervention and comparison	Outcomes	Comments
		and IIPTH. Stratum: single parathyroid adenoma		pathological examination in all 21/24 patients in focused group. In 3 focused group patients, IIPTH level 15 min after resection of parathyroid gland did not drop more than 50% from the baseline. Operation was converted to conventional and hyperplasia of all parathyroid glands was found. From 23 patients operated by conventional method, two patients had hyperplasia. The sensitivity of ultrasound examination and sestamibi scintigraphy were 81% vs 82% respectively. And positive predictive value 85% vs 90%. When sestamibi scintigraphy and ultrasound examination did not show the side of adenoma, the blood from both internal jugular veins were investigated.

1 See appendix D for full evidence tables.

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1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Focused unilateral parathyroidectomy compared to standard bilateral parathyroid exploration [pre-surgery localisation for all patients]

Results stratum: single parathyroid adenoma

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard bilateral parathyroid exploration [pre-surgery localisation for all patients]	Risk difference with Focused unilateral parathyroidectomy (95% CI)
Temporary vocal cord palsy	50 (1 study)	VERY LOW[b,c] due to risk of bias, imprecision	Peto OR 7.39 (0.15 to 372.38)	Moderate	
				0 per 1000	4 more per 1000 (from 64 fewer to 144 more)[a]
Drainage of a wound seroma	50 (1 study)	VERY LOW[b,c] due to risk of bias, imprecision	Peto OR 0.14 (0 to 6.82)	Moderate	
				40 per 1000	34 fewer per 1000 (from 40 fewer to 181 more)
Symptomatic hypocalcaemia	150 (2 studies)	VERY LOW[b,c] due to risk of bias, imprecision	Peto OR 0.14 (0 to 6.82)	Moderate	
				20 per 1000	17 fewer per 1000 (from 20 fewer to 102 more)
Re-operation (for missed hyperplasia)	50 (1 study)	VERY LOW[b,c] due to risk of bias, imprecision	Peto OR 0.14 (0 to 6.82)	Moderate	
				40 per 1000	34 fewer per 1000 (from 40 fewer to 181 more)
Permanent unilateral vocal cord paralysis	100 (1 study)	VERY LOW[b,c] due to risk of bias, imprecision	Peto OR 0.11 (0.01 to 1.82)	Moderate	
				44 per 1000	39 fewer per 1000 (from 44 fewer to 33 more)

[a] No events in control group. Manual calculation of absolute risk.
[b] Downgraded by 1 increment if the majority of studies were at high risk of bias, and downgraded by 2 increments if the majority of studies were at very high risk of bias.

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard bilateral parathyroid exploration [pre-surgery localisation for all patients]	Risk difference with Focused unilateral parathyroidectomy (95% CI)

[c] Downgraded by 1 increment if the confidence interval crossed 1 MID, and downgraded by 2 increments if the confidence interval crossed both MIDs.

Table 4: Clinical evidence summary: Minimally invasive parathyroidectomy with intra-operative surgical sonography (MIPUSS) compared to conventional unilateral open procedure (OP) without intra-operative sonography [pre-surgery localisation with imaging for all patients]

Results stratum: single parathyroid adenoma

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Conventional unilateral open procedure (OP) without intra-operative sonography [pre-surgery localisation with imaging for all patients]	Risk difference with Minimally invasive parathyroidectomy with intra-operative surgical sonography (MIPUSS) (95% CI)
Temporary recurrent laryngeal nerve injury	30 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.05 (0 to 3.18)	Moderate	
				100 per 1000	94 fewer per 1000 (from 100 fewer to 161 more)
Temporary hypocalcaemia	30 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.33 (0.07 to 1.68)	Moderate	
				300 per 1000	201 fewer per 1000 (from 279 fewer to 204 more)
Hospital stay (hours)	30 (1 study)	LOW[a] due to risk of bias			The mean hospital stay (hours) in the intervention groups was 24.86 lower (31.2 to 18.52 lower)

[a] Downgraded by 1 increment if the majority of studies were at high risk of bias, and downgraded by 2 increments if the majority of studies were at very high risk of bias.
[b] Downgraded by 1 increment if the confidence interval crossed 1 MID, and downgraded by 2 increments if the confidence interval crossed both MIDs.

Table 5: Clinical evidence summary: Focused parathyroidectomy with pre-operative localisation+ intra-operative intact parathyroid hormone monitoring (IIPTH) compared to conventional parathyroidectomy without localisation and IIPTH

Results stratum: single parathyroid adenoma

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Conventional parathyroidectomy without localisation and IIPTH	Risk difference with Focused parathyroidectomy with localisation+ intra-operative intact parathyroid hormone monitoring (IIPTH) (95% CI)
Transient hypocalcaemia (post-operative)	42 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.5 (0.1 to 2.44)	Moderate	
				191 per 1000	95 fewer per 1000 (from 172 fewer to 275 more)
Temporary vocal cord palsy	42 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 1 (0.07 to 14.95)	Moderate	
				48 per 1000	0 fewer per 1000 (from 45 fewer to 670 more)

[a] Downgraded by 1 increment if the majority of studies were at high risk of bias, and downgraded by 2 increments if the majority of studies were at very high risk of bias.
[b] Downgraded by 1 increment if the confidence interval crossed 1 MID, and downgraded by 2 increments if the confidence interval crossed both MIDs.

Table 6: Clinical evidence summary: Video assisted parathyroidectomy (VAP) (type of minimally invasive) + intra-operative qPTHa compared to classic bilateral neck exploration + intra-operative frozen section (without qPTHa) [pre-surgery localisation for both groups]

Results stratum: single parathyroid adenoma

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Classic bilateral neck exploration + intra-operative frozen section	Risk difference with Video assisted parathyroidectomy (VAP) (type of minimally invasive) + intra-operative qPTHa (95% CI)
Permanent laryngeal nerve palsy (documented with	38 (1 study)	VERY LOW[b,c] due to risk of	Peto OR 6.69	Moderate	
				0 per 1000	50 more per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Classic bilateral neck exploration + intra-operative frozen section	Risk difference with Video assisted parathyroidectomy (VAP) (type of minimally invasive) + intra-operative qPTHa (95% CI)
laryngoscopy 6 months after surgery)		bias, imprecision	(0.13 to 338.79)		(from 82 fewer to 182 more)[a]
Symptomatic transient hypocalcaemia	38 (1 study)	VERY LOW[b,c] due to risk of bias, imprecision	RR 0.3 (0.03 to 2.63)	Moderate	
				167 per 1000	117 fewer per 1000 (from 162 fewer to 272 more)
Wound infection	38 (1 study)	VERY LOW[b,c] due to risk of bias, imprecision	Peto OR 0.12 (0 to 6.14)	Moderate	
				56 per 1000	49 fewer per 1000 (from 56 fewer to 211 more)
Post-operative fever	38 (1 study)	VERY LOW[b,c] due to risk of bias, imprecision	RR 0.22 (0.03 to 1.83)	Moderate	
				222 per 1000	173 fewer per 1000 (from 215 fewer to 184 more)

[a] No events in control group. Manual calculation of absolute risk difference.
[b] Downgraded by 1 increment if the confidence interval crossed 1 MID, and downgraded by 2 increments if the confidence interval crossed both MIDs.
[c] Downgraded by 1 increment if the confidence interval crossed 1 MID, and downgraded by 2 increments if the confidence interval crossed both MIDs.

Narrative data for the outcome success/failure:

Russell 2006 – Success/cure not clearly defined. Study reported that all 100 patients were cured of PHPT as assessed by immediate return of the serum calcium level to normal in the post-operative period and maintenance of normocalcaemia for a mean of 23 (range 3–65) months follow-up.

Bergenfelz 2005 – Success/failure was not reported

Slepavicius 2008 – Study reported that if blood test indicated normocalcaemia or hypocalcaemia 6 months after surgery, a patient is completely recovered. Study reported that 6 months after surgery all patients were eucalcaemic.

Sadik 2011 – Definition of success not reported- study reports that MIPUSS was successful in 18/20 patients; it reported that in 2/20 cases the incision was extended as the adenoma was difficult to localise. At 30 day follow-up, all patients were well and asymptomatic. Calcium levels were returned to normal and no patients required supplementation.

Miccoli 1999 – Success/failure was not an outcome. Study reported that all patients were normocalcaemic 6 months after surgery.

See appendix F for full GRADE tables.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified.

1.5.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

1.5.3 Unit costs

Below are unit costs of surgery for primary hyperparathyroidism, from NHS reference costs.

Table 7: Parathyroid procedures costs (Elective inpatient schedule)

HRG code	Description	Activity	National average unit cost	Average cost of excess bed day	Average Length of Stay - Days	No. Data Submissions
KA03C	Parathyroid Procedures with CC Score 2+	1,444	£3,227	£432	1.47	189
KA03D	Parathyroid Procedures with CC Score 0-1	1,883	£2,851	£578	1.00	186
	Weighted average (including complications and excess bed days)					
KA03C and KA03D	Parathyroid procedures	3,327	£3,154		1.2	

Source: NHS reference costs 2016-17[9]

1.6 Resource costs

The recommendations made by the committee on the type of surgery that is to be used based on this review are not expected to have a substantial impact on resources.

The committee has made a recommendation based on this review that 4-gland exploration should be 'considered' if pre-operative imaging is discordant.

Unlike for stronger recommendations stating that interventions should be adopted, it is not possible to make a judgement about the potential resource impact to the NHS of recommendations regarding interventions that could be used, as uptake is too difficult to predict.

However, the committee noted that where this recommendation is implemented there would be additional costs relating to increased number of surgical parathyroidectomies compared to current practice.

1.7 Evidence statements

1.7.1 Clinical evidence statements

1.7.1.1 Focused unilateral parathyroidectomy vs standard bilateral parathyroid exploration in patients with single parathyroid adenoma [pre-surgery localisation for all patients]

There was no difference between focused unilateral parathyroidectomy and standard bilateral parathyroid exploration for temporary vocal cord palsy (1 study, n=50; Very Low quality); drainage of a wound seroma (1 study, n=50; Very Low quality); symptomatic hypocalcaemia (2 studies, n=150; Very Low quality); re-operation (for missed hyperplasia) (1 study, n=50; Very Low quality); and permanent unilateral vocal cord paralysis (1 study, n=100; Very Low quality).

No evidence was identified for the outcomes HRQOL; mortality; success (cure) / failure; bleeding (return to theatre);hypercalcemia; haematoma; BMD of the distal radius or the lumbar spine; deterioration in renal function ; fractures (vertebral or long bone); length of hospital stay; occurrence of kidney stones; persistent hypercalcaemia; re-operation; unnecessary neck exploration.

1.7.1.2 Minimally invasive parathyroidectomy with intra-operative surgical sonography (MIPUSS) vs conventional unilateral open procedure (OP) without intra-operative sonography in patients with single parathyroid adenoma [pre-surgery localisation with imaging for all patients]

There was clinically important benefit of minimally invasive parathyroidectomy with intra-operative surgical sonography (MIPUSS) compared to conventional unilateral open procedure (OP) without intra-operative sonography for temporary hypocalcaemia (1 study, n=30; Very Low quality); hospital stay (hours) (1 study, n=30; Low quality).

There was no difference between minimally invasive parathyroidectomy with intra-operative surgical sonography (MIPUSS) and conventional unilateral open procedure (OP) without intra-operative sonography for temporary recurrent laryngeal nerve injury (1 study, n=30; very low quality).

No evidence was identified for the outcomes HRQOL; mortality; success (cure) / failure; bleeding (return to theatre); hypercalcemia; haematoma; infection; BMD of the distal radius or the lumbar spine; deterioration in renal function ; fractures (vertebral or long bone); occurrence of kidney stones; persistent hypercalcaemia; re-operation; unnecessary neck exploration.

1.7.1.3 Focused parathyroidectomy with pre-operative localisation + intra-operative intact parathyroid hormone monitoring (IIPTH) compared to conventional parathyroidectomy without localisation and IIPTH in patients with single parathyroid adenoma.

There was no difference between focused parathyroidectomy with pre-operative localisation+ intra-operative intact parathyroid hormone monitoring (IIPTH) and conventional parathyroidectomy without localisation and IIPTH for transient hypocalcaemia (post-operative) (1 study, n=42; Very Low quality); and temporary vocal cord palsy (1 study, n=42; Very Low quality).

No evidence was identified for the outcomes HRQOL; mortality; success (cure) / failure; bleeding (return to theatre, hypercalcemia; haematoma; infection; BMD of the distal radius or the lumbar spine; deterioration in renal function ; fractures (vertebral or long bone); length of hospital stay; occurrence of kidney stones; persistent hypercalcaemia; re-operation; unnecessary neck exploration.

1.7.1.4 Video assisted parathyroidectomy (VAP) (type of minimally invasive) + intra-operative qPTHa vs classic bilateral neck exploration + intra-operative frozen section (without qPTHa) in patients with single parathyroid adenoma [pre-surgery localisation for both groups]

There was a clinically important benefit of video assisted parathyroidectomy (VAP) (type of minimally invasive) + intra-operative qPTHa compared to classic bilateral neck exploration + intra-operative frozen section (without qPTHa) for symptomatic transient hypocalcaemia and for post-operative fever (1 study, n=38; Very Low quality).

There was no difference between Video assisted parathyroidectomy (VAP) (type of minimally invasive) + intra-operative qPTHa and classic bilateral neck exploration + intra-operative frozen section (without qPTHa) for permanent laryngeal nerve palsy (1 study, n=38; Very Low quality); wound infection (1 study, n=38; Very Low quality).

No evidence was identified for the outcomes HRQOL; mortality; success (cure) / failure; bleeding (return to theatre); hypercalcemia; haematoma; BMD of the distal radius or the lumbar spine; deterioration in renal function; fractures (vertebral or long bone); length of hospital stay; occurrence of kidney stones; persistent hypercalcaemia; re-operation; unnecessary neck exploration.

1.7.2 Health economic evidence statements

No relevant economic evaluations were identified.

1.8 Recommendations

Surgical management

Preoperative imaging

E1. If preoperative imaging shows an ectopic adenoma refer the person to a centre with the relevant expertise.

Type of surgery

E2. Offer a choice of focused parathyroidectomy or 4-gland exploration to people who have had preoperative imaging that shows a single adenoma in the neck.

E3. Offer 4-gland exploration to people who have had preoperative imaging that does not identify a single adenoma.

E4. Consider 4-gland exploration for people having surgery for primary hyperparathyroidism whose first-modality and second-modality scans are discordant.

1.9 The committee's discussion of the evidence

1.9.1 Interpreting the evidence

1.9.1.1 The outcomes that matter most

The committee considered the outcomes of health-related quality of life, mortality and success (cure) / failure of surgery as critical outcomes for decision making. Other important outcomes included adverse events (bleeding [return to theatre], severe hypocalcaemia, hypercalcemia, laryngeal nerve injury, vocal cord paralysis/laryngeal nerve injury, haematoma, infection), bone mass density (BMD) of the distal radius or the lumbar spine, deterioration in renal function, fractures (vertebral or long bone), length of hospital stay, occurrence of kidney stones, persistent hypercalcaemia, reoperation and unnecessary neck exploration.

Across comparisons, no evidence was available for the critical outcomes mortality and quality of life. No evidence was identified for important outcomes: hypercalcemia; haematoma; BMD of the distal radius or the lumbar spine; deterioration in renal function ; fractures (vertebral or long bone); occurrence of kidney stones; persistent hypercalcaemia; re-operation; unnecessary neck exploration.

1.9.1.2 The quality of the evidence

There was evidence from 5 randomised controlled trials (RCTs) comparing focused surgery with 4-gland exploration.

All studies included patients diagnosed with primary hyperparathyroidism and having indications for surgery, however in 4 studies there was pre-selection of patients with solitary parathyroid adenoma and in one study, although there was no pre-selection of patients, if hyperplasia of parathyroid glands was found during the surgery, those patients were excluded from the study (solitary parathyroid adenoma was confirmed by pathological examination in majority of the patients in this study).

The committee noted that the evidence did not cover patients with double adenoma, ectopic adenoma and 4-gland hyperplasia.

All of the included studies compared focused surgery with 4-gland exploration; however there was a variation in the localisation/intra-operative techniques used in the studies.

Pre-operative localisation was used for both the groups in 4 out of 5 studies; and in one study pre-operative localisation was used in the focused surgery group only. Three studies used intra-operative techniques (intra-operative qPTHa in one study, intra-operative sonography in one study, and intact intra-operative parathyroid hormone monitoring (IIPTH) in one study) in addition to pre-operative localisation studies.

Different modes of anaesthesia were used in the studies. Only 2 studies used local anaesthesia in the focused surgery group; the rest of the studies used general anaesthesia for both the groups.

The evidence for all outcomes was graded Very Low quality due to risk of bias and imprecision, decreasing our confidence in the estimate of effect of the surgery techniques of interest.

1.9.1.3 Benefits and harms

All studies were analysed in the stratum single parathyroid adenoma. There were an insufficient number of studies to conduct subgroup analysis.

There was no evidence available for the critical outcomes of mortality and quality of life. The majority of the studies reported adverse outcomes (temporary/permanent recurrent laryngeal nerve injury, hypocalcaemia, wound infection, drainage of a wound seroma) either at post-operative period or at 1 month and 6 months after surgery. There was evidence from one study each for the outcomes re-operation and length of hospital stay (hours).

There was no clear definition for the outcome success/cure or failure of surgery in the studies and the studies did not report the data in an analysable format. Hence, the results for this outcome were reported narratively in the review.

Although all studies compared focused surgery with 4-gland exploration, there was a variation in the use of pre-operative localisation and intra-operative techniques; hence all the studies were not pooled together.

The following comparisons were used for analysis in the review: focused unilateral parathyroidectomy versus standard bilateral parathyroid exploration; minimally invasive parathyroidectomy with intra-operative surgical sonography (MIPUSS) versus conventional unilateral open procedure (OP) without intra-operative sonography; focused parathyroidectomy with pre-operative localisation+ intra-operative intact parathyroid hormone monitoring (IIPTH) versus conventional parathyroidectomy without localisation and IIPTH; video assisted parathyroidectomy (VAP) (type of minimally invasive) + quick intraoperative parathyroid hormone assay (qPTHa) vs classic bilateral neck exploration + intra-operative frozen section (no qPTHa).

The evidence for the comparison focused unilateral parathyroidectomy versus standard bilateral parathyroid exploration (2 RCTs) suggested that there was no difference between the groups for the outcomes temporary vocal cord palsy, drainage of a wound seroma, symptomatic hypocalcaemia, re-operation (for missed hyperplasia), and permanent unilateral vocal cord paralysis. The estimates were imprecise for all the above outcomes. The evidence for all outcomes except one (permanent unilateral vocal cord paralysis) was based on one event.

The evidence for the comparison minimally invasive parathyroidectomy with intra-operative surgical sonography (MIPUSS) versus conventional unilateral open procedure (OP) without intra-operative sonography (1 RCT) suggested that there was a clinical benefit of MIPUSS for hospital stay (hours) and temporary hypocalcaemia. Evidence for this comparison suggested there was no difference between the groups for the outcome temporary recurrent laryngeal nerve injury,. he evidence for temporary laryngeal nerve injury was based on one event. The committee highlighted that from their clinical experience, laryngeal nerve injury is a very rare event in first time parathyroid surgery.

The evidence for the comparison focused parathyroidectomy with pre-operative localisation+ intra-operative intact parathyroid hormone monitoring (IIPTH) compared to conventional parathyroidectomy without localisation and IIPTH (1 RCT) suggested that that there was no difference between the groups for the outcomes transient hypocalcaemia (post-operative), and temporary vocal cord palsy. The estimates were imprecise for both the outcomes. The evidence for the outcome temporary vocal cord palsy was based on one event in each group.

The evidence for the comparison video assisted parathyroidectomy (VAP) (type of minimally invasive surgery) + intra-operative qPTHa compared to classic bilateral neck exploration + intra-operative frozen section (without qPTHa) (1 RCT) suggested that that there was a clinically important benefit of VAP + intra-operative qPTHa for symptomatic transient hypocalcaemia and for post-operative fever. The evidence suggested there was no difference between the groups for the outcomes permanent laryngeal nerve palsy

(documented with laryngoscopy 6 months after surgery) and wound infection. The evidence for the outcomes permanent laryngeal nerve palsy and wound infection was based on one event.

Narrative evidence from 4 studies suggested that all patients were cured in both the groups (follow-up at 23 months, 3 months and 6 months after surgery). None of the studies reported the critical outcomes mortality and quality of life.

The evidence for the majority of the outcomes was based on one event from very small studies and was of Very Low quality. Hence, the committee also took their clinical experiences into account when making their recommendations.

The committee from their experience noted that focused surgery was associated with marginal benefits of lower temporary hypocalcaemia, shorter surgery time and cosmesis. The committee however highlighted that the cosmetic benefit with focused surgery was minimal; with the difference in incision for focused surgery and 4-gland exploration being 1 cm. They noted that the incision for focused surgery was 2-2 ½ cm and 3–4 cm for 4-gland exploration except in obese patients. The committee agreed that there was no difference in nerve injury rate between focused surgery and 4-gland exploration.

The committee highlighted that in focused surgery for single parathyroid adenoma there was a slightly higher chance of recurrence (normal calcium after surgery but patients develop adenoma after years) or persistent disease (hypercalcaemia after surgery suggesting disease in other gland/s)

The committee noted that the alternatives to focused surgery for solitary parathyroid adenoma are unilateral exploration and 4-gland exploration. The committee discussed that if 4-gland exploration is performed for single adenoma, the chance of recurrence would be very low.

The committee stated that historically, surgical treatment of primary hyperparathyroidism was by traditional bilateral 4-gland exploration. However, more recently, focused surgery has been preferred because of its cosmetic benefits. The committee discussed that cure rate in 4-gland exploration was marginally higher than in focused surgery and this was attributable to better visualisation of all four glands during 4-gland exploration.

The committee agreed that one of the adverse effects of 4-gland exploration was marginally higher temporary hypocalcaemia and that the surgery time was marginally longer than focused surgery. However, in the experience of the committee there was no difference in hospital stay for focused surgery and 4-gland exploration. The committee therefore based on their experience and low quality evidence agreed that people should be offered a choice of focused parathyroidectomy or 4-gland exploration if the preoperative imaging shows a single adenoma in the neck.The committee agreed on the basis of their clinical experience that for people whose pre-operative imaging (first modality scan with or without a second modality scan) is negative or does not identify a single adenoma, 4-gland exploration should be offered. The committee discussed that in patients with negative imaging, 4-gland exploration is the optimal management because of the increased frequency of multi-glandular disease in such cases. An experienced parathyroid surgeon can identify pathological parathyroid tissue with greater sensitivity than the best current imaging modalities.

The committee discussed that people with pre-operative imaging suggesting hyperplasia or multiple adenoma should have a 4-gland exploration performed by a surgeon with expertise in complex parathyroid surgery.

The committee agreed that if the first and second-modality scans are discordant, 4-gland exploration should be considered. This is because the specific anatomical location of the adenoma cannot be assured.

The committee discussed that in a minority of cases (~1–2%) pre-operative imaging of the parathyroid glands identifies a potential adenoma lying in an ectopic position. The committee discussed that the anatomical location of ectopic parathyroid adenoma is varied and agreed that such cases should be referred to surgeons with expertise at that particular site. The committee noted that for example, an ectopic parathyroid identified in the anterior mediastinum may require additional surgical skills in the use of mediastinoscopy and sternotomy.

The committee discussed that cost saving is not an option when considering focused surgery or 4-gland exploration as all patients get localisation studies, as this makes operation easier. Current practice is that patients with positive imaging can undergo focused surgery; patients with negative scans undergo 4-gland explorations; and those with mixed localisation have focused surgery sometimes with IOPTH or 4-gland exploration.

The committee also noted that irrespective of the technique adopted, there was a strong expertise element attributable to the success of surgery. The committee felt that good outcomes of surgery are also dependent on other factors such as interpretation of imaging by radiologists, high volume centres etc.

1.9.2 Cost effectiveness and resource use

No relevant health economic evaluations were identified for this question.

Unit costs of surgical interventions were presented to the committee for consideration. NHS reference costs do not distinguish between the types of surgical interventions, with the national average cost of parathyroid procedures (consisting of both focused surgery and 4-gland exploration, and includes complications and excess bed days) estimated to be £3,327. Potential differences in cost between focused surgery and 4-gland exploration were therefore discussed with the committee. As mentioned in the benefits and harms section above, the committee noted that 4-gland exploration often requires longer operating times, and as a result 4-gland exploration is likely to be slightly more costly than focused surgery when factoring in the time of the clinicians required during surgery (for example surgeon(s), anaesthetist, nurse(s)). However, the committee discussed that this does not necessarily translate to a material cost saving as these shorter operating times are unlikely to result in more operations being conducted over a set time period. Furthermore, as surgical staff are remunerated at a set salary, the costs incurred in terms of personnel costs are likewise unlikely to change.

However, the committee also considered that 4-gland exploration is more likely to have a marginally higher cure rate than focused surgery as all four glands are explored, thus mitigating the risk of missing additional adenomas. Failure to cure often results in the need for additional treatment – including repeated surgery. Consequently there could be additional resource and cost associated with focused surgery, although this is likely to be small.

The surgeons on the committee suggested that there is no difference in recovery time between focused surgery and 4-gland exploration. For both interventions, the proportion of patients treated as day cases or overnight cases are similar. Hence, it was suggested that the type of surgery does not affect resource use with regards to hospital stay.

Taking all of the above into consideration, overall the committee did not consider that there would be a significant cost difference between the two interventions.

However, the committee expressed concern that currently, people with primary hyperparathyroidism who are eligible for surgery are potentially not being referred to have surgery if their preoperative imaging does not identify a single adenoma. However, it is not certain to what extent this occurs. The committee did not consider this to be best practice,

and therefore made a recommendation that 4 gland exploration should be undertaken if pre-operative imaging does not identify a single adenoma, as this group will more frequently have multigland disease . The committee agreed that 4 gland exploration should be considered if the first and second imaging modalities are discordant. This is because the specific anatomical location of the adenoma cannot be assured. The committee noted that there is uncertainty about how much the recommendation will bring about an increase in the number surgeries carried out. Therefore, there is potential for a substantial resource impact.

The committee noted that an important factor in determining the success of parathyroid surgery is the skill of the surgeon. Hence, focused surgery is not considered to be inherently more effective than 4-gland exploration. As well as this, advances in surgical technique for 4-gland exploration have led to similar outcomes in terms of quality of life – for example, the length of hospital stay and size of surgical scar for people undergoing 4-gland exploration may not be significantly different from those who have focused surgery. Consequently, there is not a notable advantage in terms of quality of life in either type of surgery.

Given that surgery is the only definitive cure for primary hyperparathyroidism, the committee emphasised that the lack of confirmation of a single adenoma in preoperative imaging should not deter clinicians from referring patients to have surgery. With consideration for potential future savings from avoidable costs – for example, use of expensive pharmacological treatments such as calcimimetics or the costs associated with a clinical event resulting from primary hyperparathyroidism – the committee was of the consensus that surgery is a cost effective intervention for people with primary hyperparathyroidism.

1.9.3 Other factors the committee took into account

The committee were aware of data from the Fifth National Audit Report 2017 of The British Association of Endocrine and Thyroid Surgeons [7].The audit reported that mortality after parathyroid surgery was very infrequent. The requirement for calcium ± vitamin D supplementation at 6 months post-operatively was significantly greater after 4-gland exploration (presumed bilateral exploration) than focused surgery for first-time primary hyperparathyroidism. There was an increase in the extent of pre-operative imaging (frequency of usage and number of modalities) prior to parathyroid surgery, even for first-time surgery; however this was not associated with an increase in the rate of focused surgery nor improved cure rates for primary hyperparathyroidism. It also reported that there was a wide variation between surgeons with respect to the proportion of their cases having an initial targeted approach at first-time surgery for primary hyperparathyroidism and this may reflect different philosophies between surgeons regarding the advantages of targeted surgery versus traditional bilateral neck exploration; variation in the accuracy of pre-operative imaging, and in surgeons' confidence in this; differences in local referral practice and variation in surgeons' confidence in performing bilateral neck exploration, with some surgeons referring on cases with negative imaging to colleagues [7].

The report also stated that the overall rate of conversion of planned focused parathyroidectomy to conventional surgery (presumably bilateral neck exploration) for primary hyperparathyroidism is 7.8%. The data suggest that the main reason for conversion is multigland disease (as a significant proportion of converted cases have excision of 2 or more parathyroid glands); or failure to locate the abnormal parathyroid gland during minimal access surgery, or due to a requirement for greater access due to intra-operative difficulties such as large lesion size or bleeding [7].

From clinical experience, the committee stated that 85–90% of patients undergoing parathyroid surgery have a single adenoma, 10–15% have hyperplasia and less than 1% have a parathyroid carcinoma. Ectopic parathyroid glands may occur in any of the above scenarios.

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1 Appendices

2 Appendix A: Review protocols

3 **Table 8: Review protocol: Surgical interventions**

Field	Content
Review question	4.1 What is the clinical and cost effectiveness of different types of surgical intervention, for example 4-gland exploration, compared with minimally invasive techniques? 3.1 What is the clinical and cost effectiveness of using non-invasive imaging techniques (for example parathyroid ultrasound, sestamibi scanning, CT and MRI scanning) prior to surgery? (covered in Evidence report D Surgical localisation) 3.2 What is the clinical and cost effectiveness of using invasive imaging techniques (for example parathyroid venous sampling) prior to surgery? (covered in Evidence report D Surgical localisation) 3.3 What is the clinical and cost effectiveness of using intraoperative second- and third-generation parathyroid hormone assays, methylene blue and intraoperative frozen sections? (covered in Evidence report D Surgical localisation)
Type of review question	Intervention
Objective of the review	To determine the clinical and cost effectiveness of different types of surgical intervention with or without pre-operative localisation procedures and intra-operative parathyroid hormone monitoring.
Eligibility criteria – population	Adults (18 years or over) with confirmed primary hyperparathyroidism caused by single adenoma, 4-gland hyperplasia, double adenoma or ectopic adenoma. Strata: • Type of adenoma / hyperplasia (single adenoma, 4-gland hyperplasia or ectopic adenoma): • Previous parathyroidectomy (re-operation) • Pregnant women Exclude people: • with secondary and tertiary HPT • with multiple endocrine neoplasia • with familial hyperparathyroidism • with parathyroid carcinoma • people on medications interfering with calcium metabolism (for example, lithium). Studies including mixed populations of people with primary and secondary or tertiary hyperparathyroidism will be excluded unless subgroups reported separately by type of hyperparathyroidism. Studies including people with a mix of different types of adenoma (i.e. both people with single adenoma and 4-gland hyperplasia) will be analysed in an

Field	Content
	overall stratum unless the results are reported separately by type of adenoma.
Eligibility criteria – intervention(s)	Surgical techniques: • Bilateral neck exploration via direct visualisation of all glands (4-gland exploration) using open traditional incision • Bilateral neck exploration via direct visualisation of all glands (4-gland exploration) using minimally invasive incision • Bilateral neck exploration via direct visualisation of all glands (4-gland exploration) using endoscopic/videoscopic approach • Minimally invasive parathyroidectomy (MIP) guided by IOPTH and preoperative imaging using open unilateral parathyroidectomy • MIP guided by IOPTH and preoperative imaging using open focused parathyroidectomy • MIP guided by IOPTH and preoperative imaging using endoscopic/videoscopic unilateral parathyroidectomy • MIP guided by IOPTH and preoperative imaging using endoscopic/videoscopic focused parathyroidectomy Compare targeted/focused surgical techniques vs. non-focused/non-targeted techniques (with or without any one or combination of the localisation techniques or intra-operative techniques). Note: Targeted would include minimally invasive parathyroidectomy. Everything else is not targeted. **Localisation or intra-operative techniques:** Pre-operative imaging using one of the following and read by a radiologist or surgeon • US imaging using a high frequency probe, 10-15 MHz. • US imaging using a high frequency probe combined with colour Doppler ultrasound • Technetium 99m- Sestamibi scanning (planar) using single isotope dual phase scan (uses a single isotope and early and delayed phase imaging, usually at about 10-30 minutes and at 90-120 minutes) • Technetium 99m- Sestamibi scanning (planar) using dual isotope subtraction scan (uses isotope, 99 Tc sestamibi to image the parathyroids and either 123 Iodine or 99 Tc pertechnatate to image the thyroid, and then one set of images is subtracted from the other - often performed with early and delayed imaging) • Three-dimensional sestamibi scanning (also known as planar+ or SPECT or SPECT-CT) • MRI • CT • 4DCT • Parathyroid venous sampling (also called selective parathyroid venography and venous sampling): an interventional radiology technique. Involves insertion of a catheter in the femoral vein and selective catheterisation and sampling of PTH in multiple neck and mediastinal veins. Intra-operative monitoring using one of the following • Methylene blue • Intraoperative frozen sections • IOPTH monitoring (peripheral venous measurements, with pre-incision, pre-gland ligation, and 5,10, and 20 minutes post-gland ligation measurements) using second or third generation PTH assay as confirmation of gland resection, as per the Miami criterion, of a fall in serum PTH of 50% at 10 minutes post-

Field	Content
	gland excision from the higher of either a pre-skin incision baseline or a pre-gland excision baseline.
Eligibility criteria – comparator(s)	Targeted/focused versus non-targeted/non-focused /4-gland exploration surgical techniques with or without any one or combination of the localisation or intra-operative techniques.
Outcomes and prioritisation	**Report all outcomes separately for <6 months and ≥6 months** **Critical outcomes:** • HRQOL (continuous outcome) • Mortality (dichotomous outcome) • Success (cure)/failure (dichotomous outcome) **Important outcomes:** • Deterioration in renal function (dichotomous – study may also report renal replacement) • Fractures (vertebral or long bone) (dichotomous outcome) • Occurrence of kidney stones (dichotomous outcome) • Persistent hypercalcaemia (dichotomous outcome) • BMD of the distal radius or the lumbar spine (continuous) • Adverse events (bleeding (return to theatre), severe hypocalcaemia (define), hypercalcemia, laryngeal nerve injury, vocal cord paralysis/laryngeal nerve injury, haematoma, infection) (dichotomous outcome) • Length of hospital stay (continuous outcome) • Reoperation (dichotomous outcome) • Unnecessary neck exploration (dichotomous outcome)
Eligibility criteria – study design	RCTs and systematic reviews of RCTs
Other inclusion exclusion criteria	• Non-English language articles • Conference abstracts
Proposed sensitivity / subgroup analysis, or meta-regression	• Vitamin D replete vs not vitamin D replete prior to surgery
Selection process – duplicate screening / selection / analysis	Studies are sifted by title and abstract. Potentially significant publications obtained in full text are then assessed against the inclusion criteria specified in this protocol.

Data management (software)	• Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5).
	• GRADEpro was used to assess the quality of evidence for each outcome.
	• List software used for
	  ○ Bibliographies / citations, text mining, and study sifting- EndNote
	  ○ Data extraction and quality assessment / critical appraisal- Evibase

Information sources – databases and	Clinical search databases to be used: Medline, Embase, Cochrane Library, CINAHL, PsycINFO

Field	Content
dates	Date: all years Health economics search databases to be used: Medline, Embase, NHSEED, HTA Date: Medline, Embase from 2002 NHSEED, HTA – all years Language: Restrict to English only Supplementary search techniques: backward citation searching Key papers: Not known
Identify if an update	N/A
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10051
Highlight if amendment to previous protocol	N/A
Search strategy – for one database	For details please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details, please see evidence tables in appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale /	For details please see the introduction to the evidence review.

Field	Content
context – what is known	
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Jonathan Mant in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

1

2 **Table 9: Health economic review protocol**

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[19] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the

Review question	All questions – health economic evidence
	health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2002 or later but that depend on unit costs and resource data entirely or predominantly from before 2002 will be rated as 'Not applicable'. • Studies published before 2002 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

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Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017 https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 10: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 06 August 2018	Exclusions
Embase (OVID)	1974 – 06 August 2018	Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2018 Issue 8 of 12 CENTRAL to 2018 Issue 7 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None
CINAHL, Current Nursing and Allied Health Literature (EBSCO)	Inception – 06 August 2018	Exclusions
PsycINFO (ProQuest)	Inception – 06 August 2018	Exclusions

Medline (Ovid) search terms

1.	hyperparathyroidism/ or hyperparathyroidism, primary/
2.	((primary or asymptomatic or symptomatic or mild or familial or maternal) adj6 (HPT or hyperparathyroidis*)).ti,ab.
3.	PHPT.ti,ab.
4.	Parathyroid Neoplasms/
5.	(parathyroid* adj3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14

16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language

1 **Embase (Ovid) search terms**

1.	hyperparathyroidism/ or primary hyperparathyroidism/
2.	((primary or asymptomatic or symptomatic or mild or familial or maternal) adj6 (HPT or hyperparathyroidis*)).ti,ab.
3.	PHPT.ti,ab.
4.	parathyroid tumor/ or parathyroid adenoma/ or parathyroid carcinoma/
5.	(parathyroid* adj3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	Case report/ or Case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	Nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental animal/
19.	Animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language

2 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Hyperparathyroidism] explode all trees
#2.	MeSH descriptor: [Hyperparathyroidism, Primary] explode all trees
#3.	((primary or asymptomatic or symptomatic or mild or familial or maternal) near/6 (HPT or hyperparathyroidis*)):ti,ab
#4.	PHPT:ti,ab
#5.	MeSH descriptor: [Parathyroid Neoplasms] explode all trees

#6.	(parathyroid* near/3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)):ti,ab
#7.	(or #1-#6)

CINAHL (EBSCO) search terms

S1.	(MH "Hyperparathyroidism")
S2.	((primary or asymptomatic or symptomatic or mild or familial or maternal) n6 HPT) OR ((primary or asymptomatic or symptomatic or mild or familial or maternal) n6 hyperparathyroidis*)
S3.	PHPT
S4.	(MH "Parathyroid Neoplasms")
S5.	(parathyroid* n3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumor* or tumour* or cancer* or metasta* or hypercalcemi* or hypercalcaemi*))
S6.	S1 OR S2 OR S3 OR S4 OR S5
S7.	PT anecdote or PT audiovisual or PT bibliography or PT biography or PT book or PT book review or PT brief item or PT cartoon or PT commentary or PT computer program or PT editorial or PT games or PT glossary or PT historical material or PT interview or PT letter or PT listservs or PT masters thesis or PT obituary or PT pamphlet or PT pamphlet chapter or PT pictorial or PT poetry or PT proceedings or PT "questions and answers" or PT response or PT software or PT teaching materials or PT website
S8.	S6 NOT S7

PsycINFO (ProQuest) search terms

1.	su.Exact("parathyroid neoplasms" OR "hyperparathyroidism" OR "hyperparathyroidism, primary")
2.	PHPT
3.	((primary or asymptomatic or symptomatic or mild or familial or maternal) Near/6 (HPT or hyperparathyroidis*))
4.	(parathyroid* near/3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumor* or tumour* or cancer* or metasta* or hypercalcaemi* or hypercalcemi*))
5.	1 or 2 or 3 or 4
6.	(su.exact.explode("rodents") or su.exact.explode("mice") or (su.exact("animals") not (su.exact("human males") or su.exact("human females"))) or ti(rat or rats or mouse or mice))
7.	(s1 or s2 or s3 or s4) NOT (su.exact.explode("rodents") or su.exact.explode("mice") or (su.exact("animals") not (su.exact("human males") or su.exact("human females"))) or ti(rat or rats or mouse or mice))

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to primary hyperparathyroidism population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics papers published since 2002.

Table 11: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2002 – 06 August 2018	Exclusions Health economics studies
Embase	2002 – 06 August 2018	Exclusions Health economics studies

Database	Dates searched	Search filter used
Centre for Research and Dissemination (CRD)	HTA - Inception – 06 August 2018 NHSEED - Inception to March 2015	None

1 **Medline (Ovid) search terms**

1.	hyperparathyroidism/ or hyperparathyroidism, primary/
2.	((primary or asymptomatic or symptomatic or mild or familial or maternal) adj6 (HPT or hyperparathyroidis*)).ti,ab.
3.	PHPT.ti,ab.
4.	Parathyroid Neoplasms/
5.	(parathyroid* adj3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.

38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	26 and 43

1 **Embase (Ovid) search terms**

1.	hyperparathyroidism/ or primary hyperparathyroidism/
2.	((primary or asymptomatic or symptomatic or mild or familial or maternal) adj6 (HPT or hyperparathyroidis*)).ti,ab.
3.	PHPT.ti,ab.
4.	parathyroid tumor/ or parathyroid adenoma/ or parathyroid carcinoma/
5.	(parathyroid* adj3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	Case report/ or Case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	Nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental animal/
19.	Animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.

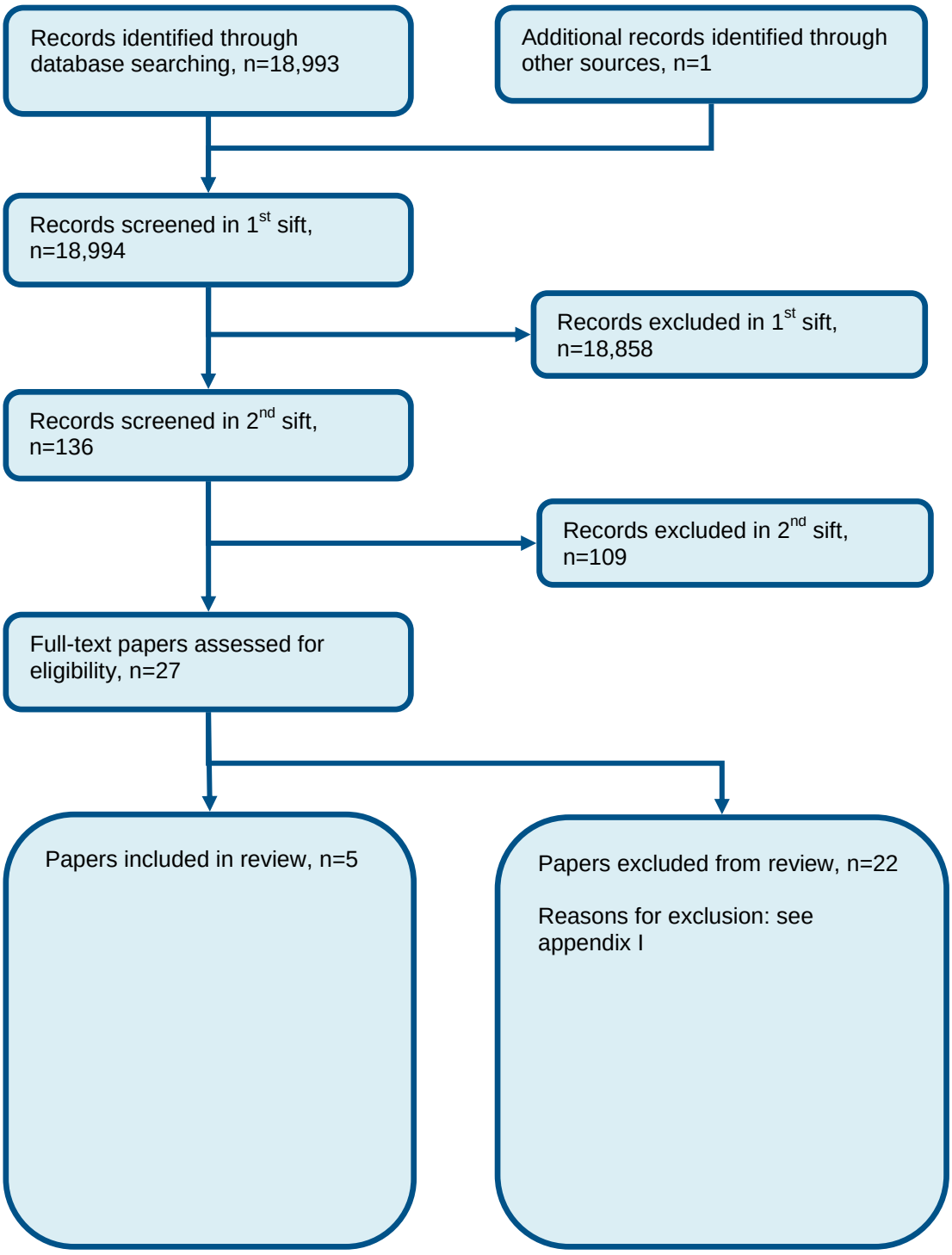
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	24 and 38

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Hyperparathyroidism EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Hyperparathyroidism, Primary EXPLODE ALL TREES
#3.	(((primary or asymptomatic or symptomatic or mild or familial or maternal) adj6 (HPT or hyperparathyroidis*)))
#4.	(PHPT)
#5.	MeSH DESCRIPTOR Parathyroid Neoplasms EXPLODE ALL TREES
#6.	((parathyroid* adj3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)))
#7.	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8.	* IN NHSEED
#9.	* IN HTA
#10.	#7 AND #8
#11.	#7 AND #9

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of surgical interventions



Appendix D: Clinical evidence tables

Study	Bergenfelz 2005[4]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Germany; Setting: University Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: follow-up- 1 and 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Single parathyroid adenoma
Subgroup analysis within study	Not applicable
Inclusion criteria	Only patients with a single enlarged parathyroid gland were eligible for inclusion in the study.
Exclusion criteria	Patients with hereditary HPT (multiple endocrine neoplasia (MEN) 1 and 2, non-MEN-related familial HPT), suspicion of involvement of multiple parathyroid glands on sestamibi scanning, previous neck exploration for thyroid disorders, anticipated or planned simultaneous thyroid operations, and allergy to drugs used for local anaesthesia, as well as those who could not fully comprehend the information given or who rejected confirmation to participate, were excluded. Patients aged less than 18 years, those with a hypercalcaemic crisis and high-risk patients (American Society of Anaesthesiologists grade IV) were also excluded. For the entire group of patients the reasons for exclusion were: negative sestamibi scan, rejected participation, planned simultaneous operation, previous surgery for thyroid disorders, withdrawal of consent and suspicion of involvement of multiple parathyroid glands.
Recruitment/selection of patients	Between February 1999 and September 2002, 233 patients with biochemically proven PHPT and no previous surgery were operated on in the institution. There were 179 women and 54 men of median age 62 (range 16–84) years. The median serum level of calcium was 2·80 (range 2·50–4·80) mmol/l. Once informed consent had been given, patients had sestamibi scintigraphy for localisation of parathyroid adenomas. Only patients with a single enlarged parathyroid gland were eligible for inclusion in the study.
Age, gender and ethnicity	Age - Mean (SD): MIP- 57 (15); BCE- 62 (12). Gender (M:F): MIP- 5:20; BCE- 6:19. Ethnicity: not stated

Study	Bergenfelz 2005[4]
Further population details	Not stated
Extra comments	Patients with a solitary parathyroid adenoma localised before surgery by sestamibi scintigraphy. Patients had sestamibi scintigraphy for localisation of parathyroid adenomas. Only patients with single enlarged parathyroid gland were eligible for inclusion in the study. There was no difference in the symptoms and signs of PHPT between the groups (data not shown).
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Surgical techniques - Targeted/focused with localisation technique/s. Targeted Minimally invasive parathyroidectomy (MIP) via a 2cm incision using LA. The MIP procedure was an open targeted operation for parathyroid adenoma excision. Patients received midazolam 1–5 mg intravenously for sedation. The incision site was anaesthetized locally with 0·5per cent bupivacaine and 1 per cent lignocaine (1: 1v/v).During the procedure additional intravenous analgesics (metamizol, pethricline) and repeated doses of midazolam were permitted. A 2-cm transverse incision was made at the site where the adenoma had been localised by sestamibi scanning. After mobilisation of the thyroid lobe, the parathyroid adenoma was localised, dissected, weighed and sent for frozen-section analysis. The ipsi- lateral parathyroid gland was not explored routinely. Duration not stated. Concurrent medication/care: Oral calcium was administered whenever a patient reported symptoms of hypocalcaemia and/or when the serum calcium was below 1.8 mmol/L. Vitamin D metabolites were given orally only when oral calcium supplementation did not result in complete resolution of hypocalcaemic symptoms. Indirectness: No indirectness Comments: Sestamibi scintigraphy- Scintigraphic evaluations of the neck and mediastinum used 450 MBq 99mTc-labelled sestamibi and a γ probe with a low-energy high-resolution collimator. Planar scans were obtained after 5, 15 and 120 min (128 × 128 matrix) and documented on multi format films. Single-photon emission computed tomography was used routinely. (n=25) Intervention 2: Surgical techniques - Non-targeted/non-focused without localisation technique/s. conventional bilateral cervical exploration (BCE) under GA. After induction of general anaesthesia, patients had a short Kocher incision. The straight muscles were opened in the midline, but not divided. To avoid any bias, the study protocol required the surgeon always to start a BCE on the left side of the neck and to aim to identify all 4 parathyroid glands. Enlarged glands were excised, weighed and sent for frozen-section analysis to confirm their parathyroid origin. The wound was closed, but the patient was kept under anaesthesia until the results of the frozen section examination had been received. Intraoperative PTH levels were not monitored during BCE. Duration not stated. Concurrent medication/care: Oral calcium was administered whenever a patient reported symptoms of hypocalcaemia and/or when the serum calcium was below 1.8 mmol/L. Vitamin D metabolites were given orally only when

Study	Bergenfelz 2005[4]
	oral calcium supplementation did not result in complete resolution of hypocalcaemic symptoms. Indirectness: No indirectness Comments: The study protocol defined conversion from MIP to BCE in the following situations: intraoperative demonstration of two normal parathyroid glands on the side where the scan had suggested the adenoma; inadequate decrease in PTH concentration after adenoma excision; no confirmation of parathyroid tissue by frozen-section analysis; and intraoperative suspicion of multiple gland disease. Conversion was also allowed for safety reasons and the patient's well-being, for example when there was a technical problem or the patient felt uncomfortable during the procedure. Conversion to BCE was necessary in three patients who had been randomised to undergo MIP under local anaesthesia-In two of these patients the parathyroid adenoma was not found through the 2-cm incision in spite of a true-positive preoperative localisation. Another patient felt unable to continue the procedure under local anaesthesia. One patient in the MIP group had raised postoperative levels of serum calcium and PTH despite an adequate decrease in PTH concentration at 5 and 15 min after resection of a parathyroid adenoma. The patient underwent a BCE during the same hospital stay; three hyperplastic glands were found, of which two and a half were resected.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TARGETTED/FOCUSED WITH LOCALISATION TECHNIQUE/S versus NON-TARGETTED/NON-FOCUSED/4-GLAND EXPLORATION WITHOUT LOCALISATION TECHNIQUE/S

Protocol outcome 1: Adverse events (bleeding (return to theatre), severe hypocalcaemia, hypercalcemia, laryngeal nerve injury, vocal cord paralysis/laryngeal nerve injury, haematoma, infection) at end of follow-up
- Actual outcome: vocal cord palsy at post-operative; Group 1: 1/25, Group 2: 0/25
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness
- Actual outcome: Hypocalcaemia at 1 month; Group 1: 0/25, Group 2: 3/25
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness
- Actual outcome: Drainage of wound seroma at post-operative; Group 1: 0/25, Group 2: 1/25
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Reoperation at end of follow-up

Study	Bergenfelz 2005[4]
- Actual outcome: Re-operation at end of follow-up; Group 1: 1/25, Group 2: 0/25 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Deterioration in renal function at end of follow-up; Fractures (vertebral or long bone) at end of follow-up; Occurrence of kidney stones at end of follow-up; Persistent hypercalcaemia at end of follow-up; BMD of the distal radius or the lumbar spine at end of follow-up; Length of hospital stay at end of follow-up; Unnecessary neck exploration at end of follow-up; Mortality at end of follow-up

1

Study	Miccoli 1999[17]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=38)
Countries and setting	Conducted in Italy; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: follow-up- 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Single parathyroid adenoma
Subgroup analysis within study	Not applicable
Inclusion criteria	Sporadic form of PHPT, no prior neck surgery, absence of thyroid nodules, and pre-operative ultrasonography suggestive for solitary parathyroid adenoma.
Exclusion criteria	Not stated
Recruitment/selection of patients	From March to November 1998, 47 patients with PHPT were referred to the unit for parathyroidectomy.
Age, gender and ethnicity	Age - Mean (SD): bilateral- 60 (14); VAP- 48 (13). Gender (M:F): bilateral - 11/6; VAP- 13/7. Ethnicity:
Further population details	not stated
Extra comments	Patients with PHPT. The patients' eligibility for VAP was considered on the basis of clinical history and ultrasound findings. Those considered eligible for VAP were then randomly divided to bilateral or VAP. serum calcium (mg/dL) : bilateral 10.8; VAP 11.1 serum iPTH: bilateral 195; VAP 221

Study	Miccoli 1999[17]
	Pre-operative localisation studies was ordered by the referring physician, ultrasound examination of the neck was performed by an expert radiologist using a linear transducer with colour Doppler capability. The patient's eligibility for VAP was considered on the basis of both clinical history and ultrasound findings.
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Surgical techniques - Targeted/focused with localisation technique/s. Video assisted parathyroidectomy (VAP) (one of the options of minimal access parathyroidectomy). VAP procedures under general endotracheal anaesthesia or bilateral superficial cervical block in association with laryngeal mask. The procedure was carried out through a 15 mm incision at the notch level. The cervical midline was opened, and a conventional 12 mm trocar was inserted between the strap muscles and the thyroid on the side of the suspected lesion. Under endoscopic vision, a 3-4 minute carbon dioxide insufflation allowed a gentle and anatomic dissection of the thyrotraceal groove. The trocar was then removed, and the operative space was maintained with small external retractors. A 30 degree 5 mm endoscope allowed optimal visualisation of the operative field. Needle-scopic instruments (2mm) were used to identify and prepare the parathyroid adenoma. Conventional titanium vascular clips were used for the ligation of the thyroid middle vein and the hylus of the adenoma. Pre-operative localisation for all patients (both groups) was done by referring physician. Ultrasound examination of the neck performed by an expert radiologist using a linear transducer with colour Doppler capability for only VAP group. Duration NS. Concurrent medication/care: not stated. Indirectness: No indirectness (n=18) Intervention 2: Surgical techniques - Non-targeted/non-focused without localisation technique/s. Bilateral neck exploration - Patients underwent a bilateral exploration of the neck under endotracheal GA. Through a traditional cervicotomy, the thyro tracheal groove was exposed; the laryngeal recurrent nerve was identified and carefully preserved, and an attempt was made to identify 4 parathyroid glands. Macroscopically enlarged parathyroid glands were then removed. Frozen section was used for tissue confirmation. No biopsy specimens of normal parathyroid glands were obtained. Intraoperative quick parathyroid hormone assay (qPTHa) was not used. Duration NS. Concurrent medication/care: not stated. Indirectness: No indirectness Extra comment: Two patients had multiglandular disease that was discovered during the surgery and were excluded from the study. In one of these 2 patients (conventional group), a second enlarged gland was found on the same side of the adenoma that was localised before the operation. The other patient underwent VAP (focused) but did not show the expected parathyroid hormone drop after the removal of the adenoma; operation was converted to a traditional approach, and a second cystic adenoma was found in the contralateral side of the neck.
Funding	Funding not stated

Study	Miccoli 1999[17]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TARGETTED/FOCUSED WITH LOCALISATION TECHNIQUE/S versus NON-TARGETTED/NON-FOCUSED/4-GLAND EXPLORATION WITHOUT LOCALISATION TECHNIQUE/S Protocol outcome 1: Adverse events (bleeding (return to theatre), severe hypocalcaemia ,hypercalcemia, laryngeal nerve injury, vocal cord paralysis/laryngeal nerve injury, haematoma, infection) at end of follow-up - Actual outcome: Temporary hypocalcaemia at Post-operative; Group 1: 1/20, Group 2: 3/18 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness - Actual outcome: wound infection at Post-operative; Group 1: 0/20, Group 2: 1/18 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness - Actual outcome: laryngeal nerve palsy at 6 months; Group 1: 3/20, Group 2: 0/18 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Deterioration in renal function at end of follow-up; Fractures (vertebral or long bone) at end of follow-up; Occurrence of kidney stones at end of follow-up; Persistent hypercalcaemia at end of follow-up; BMD of the distal radius or the lumbar spine at end of follow-up; Length of hospital stay at end of follow-up; Reoperation at end of follow-up; Unnecessary neck exploration at end of follow-up; Mortality at end of follow-up

1

Study	Russell 2006[23]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in United Kingdom; Setting: Royal Victoria Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: follow-up- 23 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Single parathyroid adenoma
Subgroup analysis within study	Not applicable

Study	Russell 2006[23]
Inclusion criteria	With the exception of five individuals, all patients with proven HPT during the study interval underwent dual-isotope subtraction scanning using 99mTc and Tc-labelled sestamibi. The decision to advise operation in individual patients was taken on clinical and biochemical grounds, and was not influenced by the outcome of the parathyroid scinti scan. Patients with a positive scan, defined as one residual focus of radioactivity following subtraction, were deemed suitable for scan-directed unilateral neck exploration. In each patient the neck was explored via a short 'collar' incision and the side and site of the parathyroid tumour, as suggested by the isotope scan, was exposed. If the adenoma was identified and considered to be in a position in keeping with the scan report, an attempt was made to identify the ipsilateral normal parathyroid. If there was no evidence of a second enlarged gland on the side initially explored, the patient was randomised to unilateral or bilateral operation by means of a consecutively numbered sealed envelope system. For individuals randomised to unilateral exploration the operation was terminated and the neck closed. The contralateral side of the neck was exposed in those randomised to bilateral operation and an attempt made to identify the two parathyroids on the second side.
Exclusion criteria	Exclusion criteria for unilateral parathyroid exploration Negative isotope scan; more than one focus of activity on isotope scan; tumour not located on side suggested by isotope scan; two enlarged parathyroids found on first side explored; history of familial HPT or multiple endocrine neoplasia.
Recruitment/selection of patients	Between 1 April 1998 and 31 December 2003, a total of 196 patients had cervical exploration for HPT. Six of these were undergoing reoperation for persistent or recurrent hypercalcaemia following initial operation. Thus 190 individuals were submitted to first-time neck exploration for HPT. Of these, 100 patients were deemed suitable for randomisation and the remaining 90 patients were excluded from the study for a variety of reasons.
Age, gender and ethnicity	Age - Mean (range): Focused unilateral: 61·5 (range 35–82) years; Standard bilateral- 62·5 (range 18–81) years) . Gender (M: F): Focused unilateral-12/42; Standard bilateral- 10/36. Ethnicity: not stated
Further population details	Not stated
Extra comments	Patients were diagnosed with HPT on the basis of persistent hypercalcaemia with a concomitant increased or inappropriate level of serum parathyroid hormone (intact molecule assay).
Indirectness of population	No
Interventions	(n=54) Intervention 1: Surgical techniques - Targeted/focused with localisation technique/s. Focused unilateral cervical exploration. No further details. Duration 65.6 mins. Concurrent medication/care: not stated. Indirectness: No indirectness (n=46) Intervention 2: Surgical techniques - Non-targeted/non-focused with localisation technique/s. standard bilateral neck exploration. No further details. Duration 79.7 mins. Concurrent medication/care: not

Study	Russell 2006[23]
	stated. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TARGETTED/FOCUSED WITH LOCALISATION TECHNIQUE/S versus NON-TARGETTED/NON-FOCUSED/4-GLAND EXPLORATION WITH LOCALISATION TECHNIQUE/S Protocol outcome 1: Adverse events (bleeding (return to theatre), severe hypocalcaemia, hypercalcemia, laryngeal nerve injury, vocal cord paralysis/laryngeal nerve injury, haematoma, infection) at end of follow-up - Actual outcome: Permanent unilateral vocal cord paralysis at end of follow-up; Group 1: 0/54, Group 2: 2/46 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Indirectness of outcome: No indirectness - Actual outcome: Symptomatic hypocalcaemia at post-operative period; Group 1: 0/54, Group 2: 0/46 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Deterioration in renal function at end of follow-up; Fractures (vertebral or long bone) at end of follow-up; Occurrence of kidney stones at end of follow-up; Persistent hypercalcaemia at end of follow-up; BMD of the distal radius or the lumbar spine at end of follow-up; Length of hospital stay at end of follow-up; Reoperation at end of follow-up; Unnecessary neck exploration at end of follow-up; Mortality at end of follow-up

1

Study	Sadik 2011[24]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in Irish Republic; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: follow-up- 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Single parathyroid adenoma
Subgroup analysis within study	Not applicable

Study	Sadik 2011[24]
Inclusion criteria	Not stated
Exclusion criteria	Not stated
Recruitment/selection of patients	All patients presenting with a bio-chemical diagnosis of primary hyperparathyroidism between July 2003 and May 2005 were studies. Twenty patients underwent MIPUSS and 10 patients were selected for open procedure (OP). One patient with 4-gland hyperplasia on Sestamibi and ultra-sonographic studies was excluded.
Age, gender and ethnicity	Age - Mean (SD): open procedure- 61.5 +/- 10.46; MIPUSS-65.0 +/-14.59. Gender (M:F): open procedure- 3/7 ; MIPUSS- 5/15. Ethnicity:
Further population details	Not stated
Extra comments	Patients presenting with a bio-chemical diagnosis of primary hyperparathyroidism. Average pre-op serum: OP 2.90 +/- 0.35; MIPUSS 2.96 +/- 0.26
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Surgical techniques - Targeted/focused with localisation technique/s. Minimally invasive parathyroidectomy using surgical sonography (MIPUSS) Pre-operative management: All thirty selected patients underwent pre-admission investigative imaging using 99mTc-sestamibi. Injection of 20 to 25 mCi 99mTc-sestamibi was performed and views were acquired at 15, 60, and 180 minutes utilising identical acquisition parameters. A consultant radiologist and surgeon reviewed all scans. Operative procedure-patients underwent general anaesthesia with endotracheal intubation Once positioned, a surgeon trained in ultrasonography used a 10MHz linear array ultrasound probe (Sonosite, USA) to localise the lesion. The adenoma was identified as a hypoechoic area close to the thyroid. The site was localised percutaneously and the neck marked over the maximum transverse and longitudinal planes. Where these two lines intersected a 3cm transverse mark was placed on the neck. Following skin preparation, the area of incision was infiltrated with 10cc of local anaesthetic (xylocaine 0.5% with 1:10,000 adrenaline) and the incision made. Sub-platysmal planes were created and the strap muscles were mobilised. The thyroid plane was then entered between the strap muscles and the sternocleidomastoid muscle. The plane was then continued down to the adenoma. Once visualised, the adenoma was not immediately mobilised, instead a 14-gauge needle was placed through the wound onto the adenoma. Once the lesion was concordant with ultrasound findings and the recurrent laryngeal nerve identified and avoided, the adenoma was then excised and confirmed on frozen section. The neck was closed with interrupted absorbable sutures and interrupted non-absorbable sutures to the skin which were removed at 48 hours and

Study	Sadik 2011[24]
	replaced with adhesive strips. No drain was used. Duration NS. Concurrent medication/care: not stated. Indirectness: No indirectness (n=10) Intervention 2: Surgical techniques - Non-targeted/non-focused without localisation technique/s. conventional unilateral open procedure (OP) without sonography. All patients underwent pre-admission investigative imaging using 99m Tc-sestamibi. Injection of 20 to 25 mCi 99mTc-sestamibi was performed and views were acquired at 15, 60, and 180 minutes utilising identical acquisition parameters. No ultrasound was used intraoperatively in these cases. After administration of general anaesthesia and intubation the patient was similarly positioned as MIPUSS. A 6cm unilateral incision was made in order to allow exploration of superior and inferior parathyroids on the side localised by preoperative sestamibi scan. The anatomic approach and closure are as same as for MIPUSS. Duration NS. Concurrent medication/care: not stated. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TARGETTED/FOCUSED WITH LOCALISATION TECHNIQUE/S versus NON-TARGETTED/NON-FOCUSED/4-GLAND EXPLORATION WITHOUT LOCALISATION TECHNIQUE/S Protocol outcome 1: Adverse events (bleeding (return to theatre), severe hypocalcaemia, hypercalcemia, laryngeal nerve injury, vocal cord paralysis/laryngeal nerve injury, haematoma, infection) at end of follow-up - Actual outcome: Temporary hypocalcaemia at 30 days; Group 1: 2/20, Group 2: 3/10 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness - Actual outcome: Temporary recurrent laryngeal nerve palsy at 30 days; Group 1: 1/20, Group 2: 0/10 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness Protocol outcome 2: Length of hospital stay at end of follow-up - Actual outcome: Hospital stay at hours; Group 1: mean 22.64 (SD 4.13); n=20, Group 2: mean 47.5 (SD 9.81); n=10 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Deterioration in renal function at end of follow-up; Fractures (vertebral or long bone) at end of follow-up; Occurrence of kidney stones at end of follow-up; Persistent hypercalcaemia at end of follow-up; BMD of the distal radius or the lumbar spine at end of follow-up; Reoperation at end of

Study	Sadik 2011[24]
	follow-up; Unnecessary neck exploration at end of follow-up; Mortality at end of follow-up

1

Study	Slepavicius 2008[27]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=48)
Countries and setting	Conducted in Lithuania; Setting: University hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: follow-up: 1 month, 6 months and 1 year after surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Single parathyroid adenoma
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients from 18 to 90 years of age with diagnosis of primary hyperparathyroidism and having indications for surgical treatment.
Exclusion criteria	Family history of PHPT, relapse of PHPT, previous neck surgery, patients with indications for partial or complete removal of thyroid gland, severe concomitant pathology, making surgical treatment impossible, patients that due to psychical disorders cannot evaluate adequately their health status, pregnancy and breast feeding, patients with symptoms of hypercalcaemic crisis, patients refusing to participate during the study.
Recruitment/selection of patients	Fifty seven patients were referred to the department of abdominal and endocrine surgery of Klaipeda University Hospital and second department of abdominal surgery of Vilnius University Hospital. For the first surgery for PHPT between Feb 2005 and Feb 2008. Before surgery patients with diagnosis of PHPT determined clinically and with lab tests were divided in to 2 groups.
Age, gender and ethnicity	Age - Range: 18-90 years. Gender (M:F): not stated. Ethnicity: not stated
Further population details	Not stated
Extra comments	Patients with diagnosis of primary hyperparathyroidism. All patients were symptomatic.
Indirectness of population	No indirectness
Interventions	(n=24) Intervention 1: Surgical techniques - Targeted/focused with localisation technique/s. Focused parathyroidectomy (FP) group patients were those for which focused parathyroidectomy was performed. For those patients' pre-operative localisation studies before operation as well as intraoperative IPTH monitoring and frozen sections were performed.

Study	Slepavicius 2008[27]
	All patients underwent parathyroidectomy under GA. For FP a2-2.5 cm transverse incision placed on the side of the abnormal gland, medial to the medial margin of the sternocleidomastoid muscle. The incision presumed inferior gland was placed 2 cm above the clavicle, whereas that one for presumed superior gland was placed somewhat higher. The platysma was transected and the sternocleidomastoid muscle was retracted laterally to expose the strap muscles. These were retracted exposing a space of thyroid and parathyroid glands. Parathyroid scintigraphy was performed with 99mTc99m-sestamibi for pre-operative dual-phase sestamibi parathyroid scan of the neck and chest with planar images. A true positive result was defined as a single abnormal focal accumulation or suspected adenoma on sestamibi or ultrasound scanning that corresponded anatomically to a surgically proven parathyroid adenoma. All parathyroidectomies were guided by intact parathyroid hormone (IIPTH) monitoring. Duration surgery (day 1) and discharge (day 2). Concurrent medication/care: Calcium and vitamin D preparations after surgery were administered only in case of occurrence of symptoms of post-surgery hypocalcaemia. Indirectness: No indirectness (n=23) Intervention 2: Surgical techniques - Non-targeted/non-focused without localisation technique/s. Conventional surgery group patients were those for which parathyroidectomy was performed with traditional Kocher incision and revision of all parathyroid glands and frozen section examination. Localisation examination before surgery was not carried. For traditional group of patients surgery was performed through a 6-8 cm standard Kocher incision. Wound drainage was not used for both patient groups. Neither intact parathyroid hormone (IIPTH) monitoring nor pre-operative localisation performed. Duration surgery (day 1) and discharge (day 2). Concurrent medication/care: Calcium and vitamin D preparations after surgery were administered only in case of occurrence of symptoms of post-surgery hypocalcaemia. Indirectness: No indirectness Comments: For patients of both groups, following blood tests were performed: general blood, electrolytes, creatinine, IPTH, alkaline phosphatase. Bone density was determined by DXA method. For all patients kidney echoscopy was performed. If hyperplasia of parathyroid glands was found during the surgery, those patients were excluded from the study. The diagnosis of parathyroid adenoma and hyperplasia was established by conventional histologic criteria supported by gross morphology in both groups and by the intra-operative decrease of IIPTH concentration in the FP group. Solitary parathyroid gland adenoma was confirmed by pathological examination in all 21/24 patients in

Study	Slepavicius 2008[27]
	focused group. In 3 focused group patients, IIPTH level 15 min after resection of parathyroid gland did not drop more than 50% from the baseline. Operation was converted to conventional and hyperplasia of all parathyroid glands was found. From 23 patients operated by conventional method, two patients had hyperplasia.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TARGETTED/FOCUSED WITH LOCALISATION TECHNIQUE/S versus NON-TARGETTED/NON-FOCUSED/4-GLAND EXPLORATION WITHOUT LOCALISATION TECHNIQUE/S Protocol outcome 1: Adverse events (bleeding (return to theatre), severe hypocalcaemia, hypercalcemia, laryngeal nerve injury, vocal cord paralysis/laryngeal nerve injury, haematoma, infection) at end of follow-up - Actual outcome: Temporary recurrent laryngeal nerve palsy at post-operative follow-up; Group 1: 1/21, Group 2: 1/21; Comments: Palsy disappeared in both patients during 1 month after surgery. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness - Actual outcome: Hypocalcaemia at 30 days after surgery; Group 1: 0/21, Group 2: 1/21 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Deterioration in renal function at end of follow-up; Fractures (vertebral or long bone) at end of follow-up; Occurrence of kidney stones at end of follow-up; Persistent hypercalcaemia at end of follow-up; BMD of the distal radius or the lumbar spine at end of follow-up; Length of hospital stay at end of follow-up; Reoperation at end of follow-up; Unnecessary neck exploration at end of follow-up; Mortality at end of follow-up

Appendix E: Forest plots

E.1 Focused unilateral parathyroidectomy versus standard bilateral parathyroid exploration [pre-surgery localisation for all patients]

Figure 2: Temporary vocal cord palsy

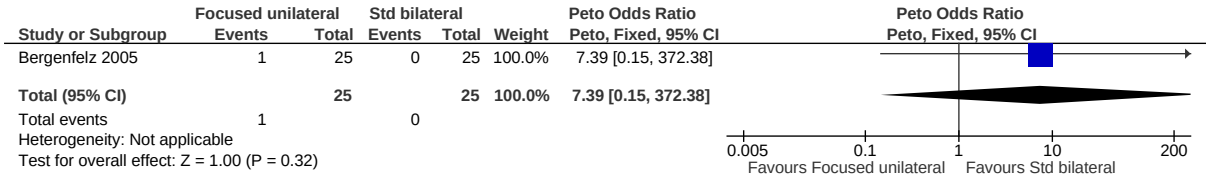


Figure 3: Drainage of a wound seroma

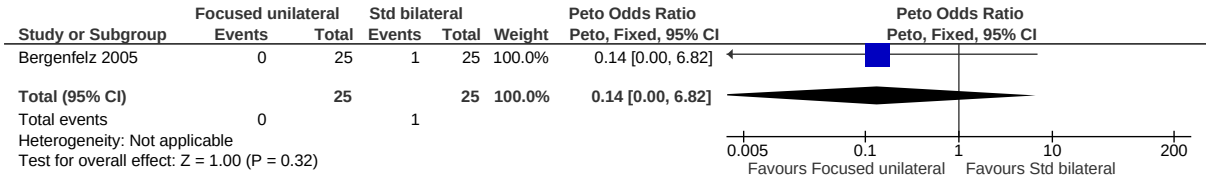


Figure 4: Symptomatic hypocalcaemia

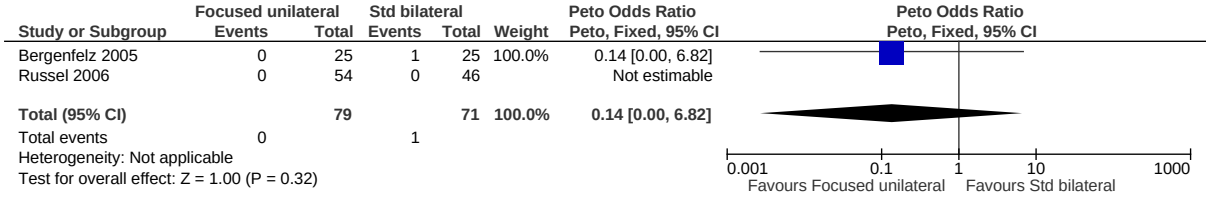


Figure 5: Re-operation (for missed hyperplasia)

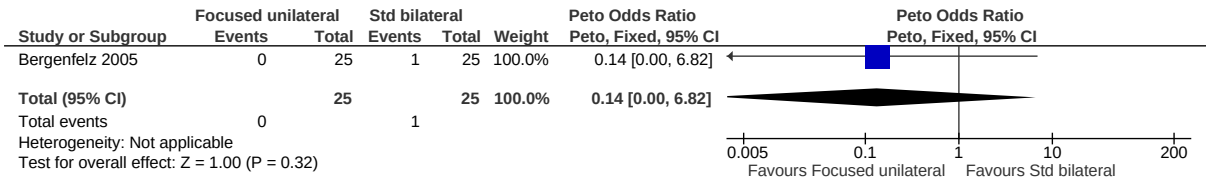
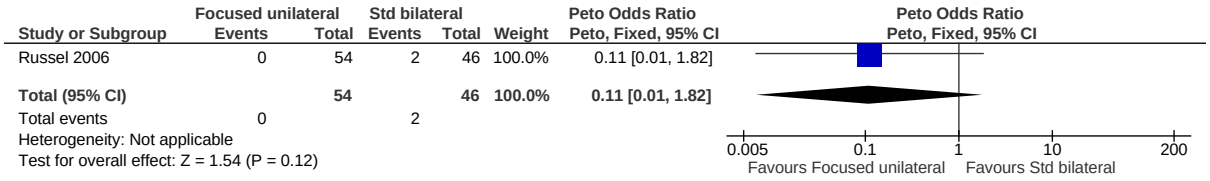


Figure 6: Permanent unilateral vocal cord paralysis



E.2 Minimally invasive parathyroidectomy with intra-operative surgical sonography (MIPUSS) versus conventional unilateral open procedure (OP) without intra-operative sonography [pre-surgery localisation with imaging for all patients]

Figure 7: Temporary recurrent laryngeal nerve injury

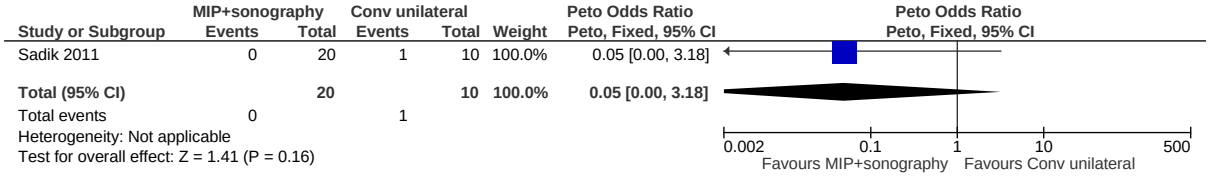
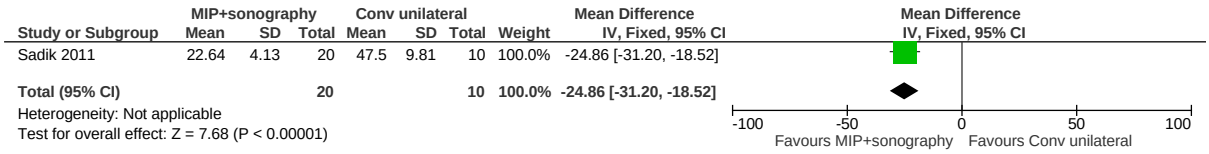


Figure 8: Temporary hypocalcaemia

Figure 9: Hospital stay (hours)



E.3 Focused parathyroidectomy with pre-operative localisation+ intra-operative intact parathyroid hormone monitoring (IIPTH) versus conventional parathyroidectomy without localisation and IIPTH

Figure 10: Transient hypocalcaemia (post-operative)

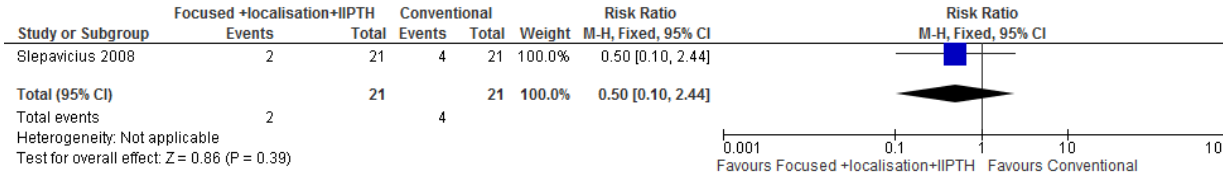
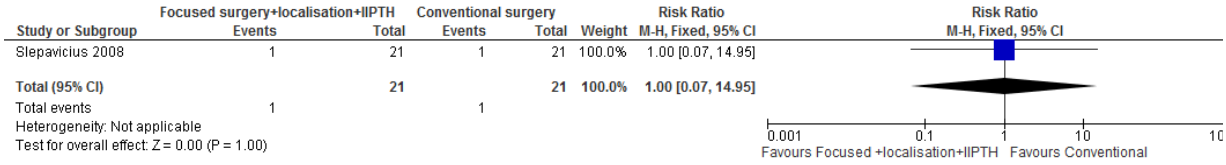


Figure 11: Temporary vocal cord palsy



E.4 Video assisted parathyroidectomy (VAP) (type of minimally invasive) + intra-operative qPTHa versus classic bilateral neck exploration + intra-operative frozen section (without qPTHa) [pre- surgery localisation for both groups]

Figure 12: Permanent laryngeal nerve palsy

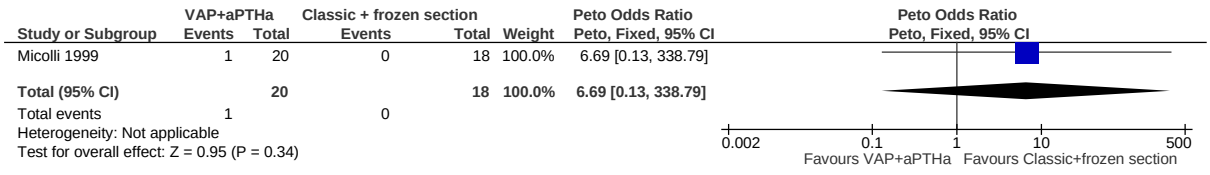


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Figure 13: Symptomatic transient hypocalcaemia

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Figure 14: Wound infection

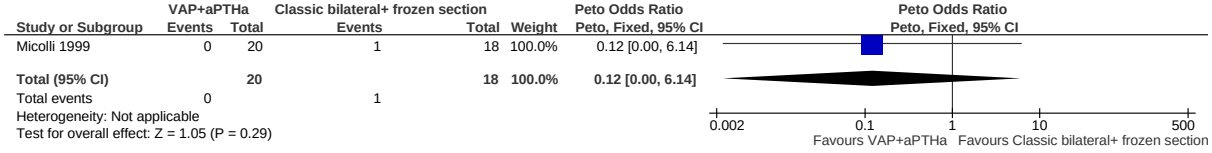

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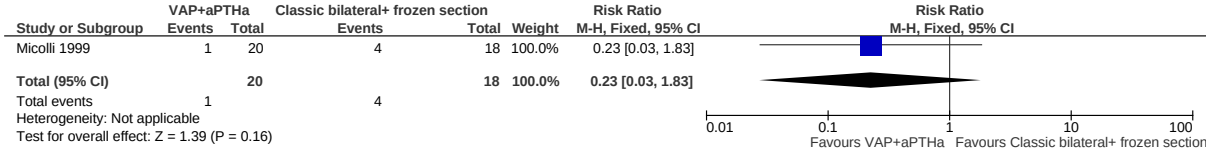
Figure 15: Post-operative fever



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Appendix F: GRADE tables

Table 12: Clinical evidence profile: Focused unilateral parathyroidectomy versus standard bilateral parathyroid exploration [pre-surgery localisation for all patients]

Results stratum: single parathyroid adenoma

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Focused unilateral parathyroidectomy	Standard bilateral parathyroid exploration [pre-surgery localisation for all patients]	Relative (95% CI)	Absolute		
Temporary vocal cord palsy												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/25 (4%)	0%	OR 7.39 (0.15 to 372.38)	4 more per 1000 (from 64 fewer to 144 more)[c]	⊕OOO VERY LOW	IMPORTANT
Drainage of a wound seroma												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	0/25 (0%)	4%	OR 0.14 (0 to 6.82)	34 fewer per 1000 (from 40 fewer to 181 more)	⊕OOO VERY LOW	IMPORTANT
Symptomatic hypocalcaemia												
2	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	0/79 (0%)	2%	OR 0.14 (0 to 6.82)	17 fewer per 1000 (from 20 fewer to 102 more)	⊕OOO VERY LOW	IMPORTANT

Re-operation (for missed hyperplasia)											
1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	0/25 (0%)	4%	OR 0.14 (0 to 6.82)	34 fewer per 1000 (from 40 fewer to 181 more)	⊕OOO VERY LOW	IMPORTANT
Permanent unilateral vocal cord paralysis											
1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	0/54 (0%)	4.4%	OR 0.11 (0.01 to 1.82)	39 fewer per 1000 (from 44 fewer to 33 more)	⊕OOO VERY LOW	IMPORTANT

[a] Downgraded by 1 increment if the majority of studies were at high risk of bias, and downgraded by 2 increments if the majority of studies were at very high risk of bias.
[b] Downgraded by 1 increment if the confidence interval crossed 1 MID, and downgraded by 2 increments if the confidence interval crossed both MIDs.
[c] No events in control group. Manual calculation of absolute risk.

Table 13: Clinical evidence profile: Minimally invasive parathyroidectomy with intra-operative surgical sonography (MIPUSS) versus conventional unilateral open procedure (OP) without intra-operative sonography [pre-surgery localisation with imaging for all patients]

Results stratum: single parathyroid adenoma

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Minimally invasive parathyroidectomy with intra-operative surgical sonography (MIPUSS)**	**Conventional unilateral open procedure (OP) without intra-operative sonography [pre-surgery localisation with imaging for all patients]**	**Relative (95% CI)**	**Absolute**		
Temporary recurrent laryngeal nerve injury												

1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	0/20 (0%)	10%	OR 0.05 (0 to 3.18)	94 fewer per 1000 (from 100 fewer to 161 more)	⊕OOO VERY LOW	IMPORTANT
Temporary hypocalcaemia												
1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	2/20 (10%)	30%	RR 0.33 (0.07 to 1.68)	201 fewer per 1000 (from 279 fewer to 204 more)	⊕OOO VERY LOW	IMPORTANT
Hospital stay (hours) (Better indicated by lower values)												
1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	10	-	MD 24.86 lower (31.2 to 18.52 lower)	⊕⊕OO LOW	IMPORTANT

[a] Downgraded by 1 increment if the majority of studies were at high risk of bias, and downgraded by 2 increments if the majority of studies were at very high risk of bias.
[b] Downgraded by 1 increment if the confidence interval crossed 1 MID, and downgraded by 2 increments if the confidence interval crossed both MIDs.

Table 14: Clinical evidence profile: Focused parathyroidectomy with pre-operative localisation+ intra-operative intact parathyroid hormone monitoring (IIPTH) versus conventional parathyroidectomy without localisation and IIPTH

Results stratum: single parathyroid adenoma

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Focused parathyroidectomy with localisation+ intra-operative intact parathyroid hormone**	**Conventional parathyroidectomy without localisation and IIPTH**	**Relative (95% CI)**	**Absolute**		

							monitoring (IIPTH)					
Transient hypocalcaemia (post-operative)												
1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	2/21 (9.5%)	19.1%	RR 0.5 (0.1 to 2.44)	95 fewer per 1000 (from 172 fewer to 275 more)	⊕OOO VERY LOW	IMPORTANT
Temporary vocal cord palsy												
1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/21 (4.8%)	4.8%	RR 1 (0.07 to 14.95)	0 fewer per 1000 (from 45 fewer to 670 more)	⊕OOO VERY LOW	IMPORTANT

[a] Downgraded by 1 increment if the majority of studies were at high risk of bias, and downgraded by 2 increments if the majority of studies were at very high risk of bias.
[b] Downgraded by 1 increment if the confidence interval crossed 1 MID, and downgraded by 2 increments if the confidence interval crossed both MIDs.

Table 15: Clinical evidence profile: Video assisted parathyroidectomy (VAP) (type of minimally invasive) + intra-operative qPTHa versus classic bilateral neck exploration + intra-operative frozen section (without qPTHa) [pre- surgery localisation for both groups]

Results stratum: single parathyroid adenoma

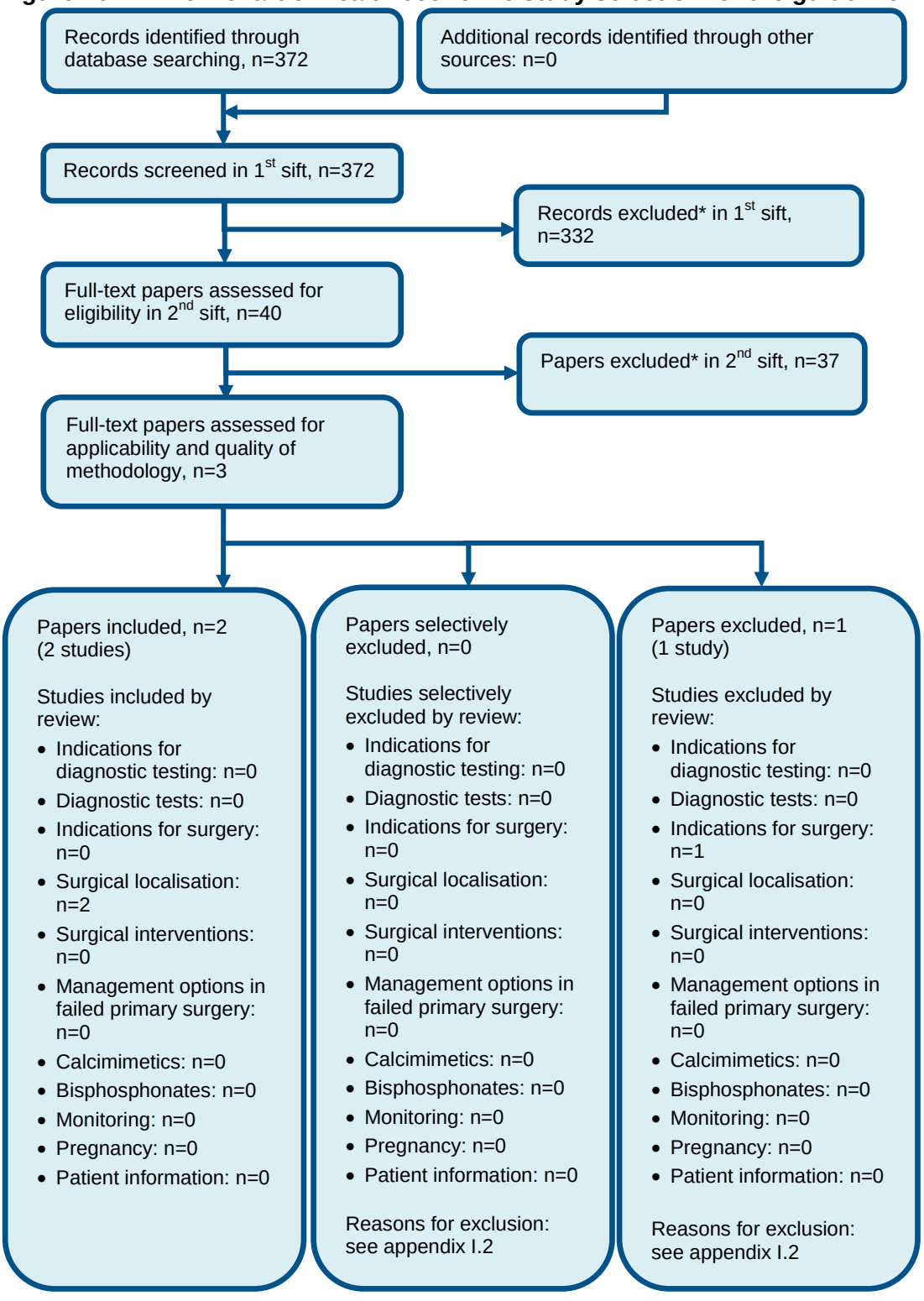
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Video assisted parathyroidectomy (VAP) (type of minimally invasive) + intra-operative qPTHa**	**Classic bilateral neck exploration + intra-operative frozen section**	**Relative (95% CI)**	**Absolute**		
Permanent laryngeal nerve palsy												
1	randomised	Serious[a]	no serious	no serious	very	none	1/20	0%	OR 6.69 (0.13 to	50 more per 1000 (from 82	⊕OOO VERY	IMPORTANT

	trials		inconsistency	indirectness	serious[b]		(5%)		338.79)	fewer to 182 more)[c]	LOW	
Symptomatic transient hypocalcaemia												
1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/20 (5%)	16.7%	RR 0.3 (0.03 to 2.63)	117 fewer per 1000 (from 162 fewer to 272 more)	⊕OOO VERY LOW	IMPORTANT
wound infection												
1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	0/20 (0%)	5.6%	OR 0.12 (0 to 6.14)	49 fewer per 1000 (from 56 fewer to 211 more)	⊕OOO VERY LOW	IMPORTANT
Post-operative fever												
1	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	very serious[b]	none	1/20 (5%)	22.2%	RR 0.22 (0.03 to 1.83)	173 fewer per 1000 (from 215 fewer to 184 more)	⊕OOO VERY LOW	IMPORTANT

[a] Downgraded by 1 increment if the confidence interval crossed 1 MID, and downgraded by 2 increments if the confidence interval crossed both MIDs.
[b] Downgraded by 1 increment if the confidence interval crossed 1 MID, and downgraded by 2 increments if the confidence interval crossed both MIDs.
[c] No events in control group. Manual calculation of absolute risk difference.

Appendix G: Health economic evidence selection

Figure 16: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H: Health economic evidence tables

No economic studies were included in this review.

1 Appendix I: Excluded studies

I.1 2 Excluded clinical studies

3 **Table 16: Studies excluded from the clinical review**

Study	Exclusion reason
Aarum 2007[1]	Inappropriate comparison- patients randomised to pre-operative localisation (group 1) and no pre-operative localisation (group 2). In group 1, minimally invasive parathyroidectomy for positive localisation findings and conventional bilateral neck exploration for negative localisation findings. In group 2 all patients underwent conventional bilateral neck exploration.
Agus 1993[2]	An opinion piece
Barczynski 2006[3]	Inappropriate comparison – minimally invasive video assisted parathyroidectomy versus open minimally invasive parathyroidectomy
Bergenfelz 2002[5]	Inappropriate comparison. Inappropriate comparison. Does not compare focused vs non-focused, compares unilateral vs bilateral.
Bruno 2010[6]	Conference abstract
Chen 1999[8]	Incorrect study design – non randomised study
Gracie 2012[10]	Systematic review. Screened for relevant references.
Hessman 2010[11]	Inappropriate comparison-open minimally invasive parathyroidectomy vs minimally invasive video-assisted parathyroidectomy
Jinih 2016[12]	Conference abstract
Jinih 2017[13]	Systematic review. Screened for relevant references.
Kreidieh 2013[14]	Protocol for a Cochrane review
Laird 2016[15]	Literature review. Screened for relevant references.
Lombardi 2009[16]	Systematic review. Screened for relevant references.
Miccoli 2008[18]	Inappropriate comparison. Both arms compared minimally invasive-study compares focused parathyroidectomy plus quick intra-operative parathormone assay (qPTHa) during minimally invasive video-assisted parathyroidectomy (MIVAP) vs MIVAP with endoscopic bilateral neck exploration.
Nelson 2007[20]	Incorrect study design – cohort study
Norlen 2015[21]	Incorrect study design – retrospective cohort study. Study investigated long term outcomes after focused parathyroidectomy.
Reeve 2000[22]	Systematic review. Screened for relevant references.
Simonella 2005[25]	Paper not in English
Singh Ospina 2016[26]	Systematic review. Screened for relevant references.
Sozio 2005[28]	Paper not in English
Taieb 2013[29]	Article on minimally invasive parathyroidectomy
Westerdahl 2007[30]	Inappropriate comparison. Study compares unilateral vs bilateral; does not compare focused vs non-focused.

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I.21 Excluded health economic studies

2 None.

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