

Appendix D: Clinical evidence tables

Study	Aarum 2007 ¹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in Sweden; Setting: University Hospital
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Verified diagnosis, age ≥ 50 years, no heredity for hyperparathyroidism or multiple endocrine neoplasia, no concomitant large goitre, no previous thyroid/parathyroid surgery and fitness for day surgery.
Exclusion criteria	Not reported
Recruitment/selection of patients	Recruited from a cohort of patients with an established diagnosis of PHPT referred to our surgical outpatient clinics at Karolinska Hospital and Huddinge University Hospital from October 2000 to March 2004.
Age, gender and ethnicity	Age - Median (range): localisation 64 (46–84); no localisation 62 (50–80). Gender (M:F): localisation 8:41; no localisation 11:39. Ethnicity: not stated
Further population details	n/a
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: preoperative localisation with sestamibi scintigraphy and ultrasonography Treated accordingly (i.e. minimally invasive parathyroidectomy (using an open unilateral approach with a short transverse incision in the middle of the neck under general anaesthesia) was performed in patients in whom both localisation studies were consistent with a single pathological gland, bilateral neck exploration was performed in cases with negative localisation findings, equivocal uptake or positive scintigraphy but negative ultrasonography). Focused surgery performed in 23/50 and bilateral surgery performed in 26/50. All scintigraphic examinations were made according to the double-phase technique using only 99 Tcm-hexakis-2-me-thoxyisobutylisonitrile (99lite®Tcm-MIBI, 99Tcm-sestamibi, Cardio-,DuPont Pharma, Billerica, MA, USA). Three planar and two single photon emission computed tomography (SPECT) images were altogether acquired at 10, 60 and 120 min after IV administration of 500 MBq of the tracer. When

Study	Aarum 2007¹
	scintigraphy showed an uptake indicating a single pathological gland, the patient was investigated by high resolution ultrasonography of the neck. Indirectness: No indirectness (n=50) Intervention 2: no preoperative localisation All patients underwent conventional bilateral neck exploration with the aim to visualise 4 parathyroid glands and to remove the macroscopically pathological gland(s) Indirectness: No indirectness
Funding	Government (financial support was given by Stockholm County Health Authorities).
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Pre-operative localisation with MIBI and US versus no pre-operative localisation</p> <p>Protocol outcome 1: persistent hypercalcaemia - Actual outcome: normocalcaemia at 6months post-operatively; Group 1: 47/49, Group 2: 47/50 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</p> <p>Protocol outcome 2: adverse events - Actual outcome: transient recurrent nerve paralysis; Group 1: 1/49, Group 2: 0/50 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	HRQOL; mortality; success (cure) / failure; 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; reoperation; unnecessary neck exploration.

Reference	Agarwal 2012⁴
Study type	Retrospective cohort study
Countries and setting	India; tertiary care referral institute.
Study	Data source: retrieved from a parathyroid disease database

Reference methodology	Agarwal 2012⁴				
	Recruitment: data retrieved for patients with sporadic symptomatic PHPT undergoing parathyroidectomy for single parathyroid adenoma (diagnosed based on histology)				
Number of patients	n = 59				
Patient characteristics	<p>Age, mean (range): 36.3 years (range 24-78).</p> <p>Gender (male to female ratio): 18:41</p> <p>Ethnicity: not reported</p> <p>Inclusion criteria: sporadic symptomatic PHPT undergoing parathyroidectomy for single parathyroid adenoma (diagnosed based on histology).</p> <p>Exclusion criteria: multigland parathyroid disease, parathyroid cancer, renal failure.</p> <p>Details of imaging tests and surgical intervention: people with concordant localisation on ^{99m}Tc-sestamibi and US were offered MIP, the rest were managed with bilateral neck exploration (36 underwent MIP, 23 underwent bilateral).</p> <p>Prior tests: only included people with solitary adenoma (retrospective inclusion from histology)</p> <p>Patient details: n=59 solitary adenoma.</p>				
Index test(s) and reference standard	<p><u>Index test</u> IOPTH: peripheral blood samples collected pre-operatively, before excision, and 5, 10 and 15 minutes after excision. Serum PTH estimations using an immunoradiometric assay iPTH kit (DSL Inc, Webster, TX, USA). IOPTH results not available to the surgeon intra-operatively so were not used for decision making. Positive = >50% drop in the PTH levels at 10 minutes post-excision compared to the pre-excision value</p> <p><u>Reference standard</u> Normal serum calcium levels and histology (serum calcium measured at 1 and 3 weeks and then every 3 months).</p>				
2x2 table	IOPTH	Reference standard +	Reference standard -	Total	Notes: IOPTH results not available to the surgeon at the time for decision making.
	Index test +	55	0	55	
	Index test -	3	1	4	

Reference	Agarwal 2012⁴			
	Total	58	1	59
Statistical measures	Index test: IOPTH Sensitivity: 94.8% Specificity: 100%			
Source of funding	Not reported			
Limitations	Risk of bias: none Indirectness: none (subselection of people with single gland disease is not a limitation for IOPTH as the index test)			

Reference	Agha 2007⁷
Study type	Retrospective study
Countries and setting	Germany, University Hospital
Study methodology	Data source: not reported Recruitment: patients with PHPT treated in the department between January 2003 and July 2005
Number of patients	n = 58
Patient characteristics	Age, mean (SD): not reported Gender (male to female ratio): not reported Ethnicity: not reported Inclusion criteria: patients with PHPT (PTH>65 ng/l) and increased calcium (>2.6 mmol/l) Exclusion criteria: secondary and tertiary HPT Details of imaging tests and surgical intervention: operative technique based on video-assisted minimal-invasive open approach (MIVAP; n=19) with a 1.5cm incision in the line of Kocher's operation. If per-operative localisation successful, this side opened first. Pre-operative work-up included US and scintigraphy. MRI performed if US and scintigraphy unable to localised pathological tissue. Minimally invasive surgery planned if two out of three methods showed matching results. If lack of corresponding results or inconclusive scintigraphy (n=15), or previous surgery (n=10), or concomitant enlarged goiter (n=14), an open cervical approach was chosen (in which case parathyroid glands explored independent of IOPTH).

Reference	Agha 2007⁷				
	<p>Prior tests: no preselection based on prior imaging</p> <p>Patient details: n=51 solitary; n=7 multiple n=10 previous surgery (but parathyroidectomy not specified). Analyse in 1st surgery group.</p>				
Index test(s) and reference standard	<p><u>Index test</u> IOPTH: performed with a sandwich assay containing two antibodies (Roche). Measured at the start of anaesthesia (before skin incision) and 10 and 15 minutes after excision.</p> <p>Positive = >50% drop in the PTH levels at 10 minutes and >60% drop at 15 minutes post-excision compared to the baseline (start of anaesthesia (before skin incision)).</p> <p><u>Reference standard</u> Histology (immediate frozen section by an experienced pathologist) and all patients showed normal serum calcium at follow-up (serum calcium measured at 2 and 6 weeks and 3 and 6 months).</p>				
2×2 table	IOPTH	Reference standard +	Reference standard -	Total	<p>Notes: includes results after continuing to explore and IOPTH after removal of a second site (7 after removal of second site but all eventually had >50% drop and cure). Unable to calculate for >50% drop at 10 minutes for these 7 people.</p> <p>Study IOPTH criteria also included a >60% drop at 15 minutes, however, no one had a negative IOPTH, so can deduce that that all had the >50% drop at 10 minutes.</p>
	Index test +	58	0	0	
	Index test -	0	0	0	
	Total	58	0	58	
Statistical measures	<p><u>Index text: IOPTH</u> Sensitivity: 100% Specificity: -</p>				
Source of funding	Not reported				
Limitations	<p>Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded. Indirectness: none</p>				

Reference	Barczynski 2007³⁴
Study type	Prospective cohort
Countries and setting	Poland, Department of Endocrine Surgery, University College of Medicine
Study methodology	Data source: prospective recruitment of patients with PHPT referred for first-time surgery Recruitment: Consecutive patients meeting the inclusion criteria between January 2000 and June 2006
Number of patients	n = 177 (only group 2 (n=115) had IOPTH – results presented here for group 2 only)
Patient characteristics	Age, mean (SD): 57.1 (12.2) years Gender (male to female ratio): 18:97 Ethnicity: not reported Inclusion criteria: biochemically documented pHPT (biochemical evaluation included increased serum calcium >2.6mmol/L and plasma iPTH level >65ng/L) and referred for first-time surgery, at least one localisation study suggesting single parathyroid adenoma, no previous neck surgery and absence of nodular goitre requiring one-step thyroid surgery. Exclusion criteria: a familial history of pHPT (MEN1, MEN2, hereditary pHPT), negative localization studies, suspicion of multiglandular disease, extracervical ectopy, or parathyroid cancer, concomitant nodular goitre, pregnancy or lactation, age below 18 years, high-risk patients with ASA 4 grade (American Society of Anaesthesiology), emergency surgery for hypercalcaemic crisis, and inability to comply with the scheduled follow-up. Details of imaging tests and surgical intervention: MIBI subtraction scintigraphy or high resolution Doppler US performed, at least one of these suggesting single parathyroid adenoma. Underwent MIP (either video-assisted (MIVAP n=64) or open (OMIP n=51)) with IOPTH. Patients with a thyroid gland volume of ≤25 ml assessed by preoperative US, and parathyroid adenoma <30 mm in diameter were qualified for MIVAP; all other patients underwent OMIP. The parathyroid adenoma was located, dissected, removed through a small skin incision and sent for frozen-section examination. The remaining ipsilateral parathyroid gland was electively not exposed but instead, IOPTH was used. Prior tests: suggested single adenoma by at least one imaging (MIBI or US). Patient details: N=105 solitary adenoma, n=5 double, n=4 four gland hyperplasia, n=1 uncured (ectopic later found). All first time surgery
Index test(s)	Index test (IOPTH. Also MIBI and US, but unable to calculate 2x2 table values for protocol method)

Reference and reference standard	Barczynski 2007³⁴				
	<p>IOPTH: The STAT-IntraOperative-Intact-PTH chemiluminescence immunoassay semiautomated mobile system (Future Diagnostics, Wijchen, the Netherlands) was used within the surgical suite complex for the intraoperative quantitative determination of iPTH levels in EDTA plasma. The following peripheral venous blood samples were analysed: preoperative baseline (before tracheal intubation), pre-excision (after dissection of the adenoma, but before its removal), and 10 min post-excision.</p> <p>Positive = Miami criterion (an iPTH drop of 50% or more from the highest, either preoperative baseline or the pre-excision level at 10 min after gland excision). In patients with an inadequate iPTH decrease at 10 min post-excision, an additional 20 minute estimation made before exploration continued.</p> <p><u>Reference standard</u> Histology and cure (normal serum calcium values within 6 months of postoperative follow-up). Intraoperative frozen sections were routinely used in both groups to confirm parathyroid tissue origin and to determine the underlying pathology of pHPT (parathyroid adenoma or hyperplasia) according to conventional histopathological criteria.</p>				
2x2 table	IOPTH	Reference standard +	Reference standard -	Total	<p>Note: method includes taking a 20 minute time point in people with a negative IOPTH at 10 minutes (can also calculate for only 10 minute time point – below)</p> <p>Can calculate both, but this is IOPTH results after excision of the first gland in people with MGD (TNs either went on to have further glands found or were not cured).</p> <p>Only including the 10 minute time point result</p>
	Index test +	105	0	105	
	Index test -	0	10	10	
	Total	105	10	115	
2x2 table	IOPTH (10 min)	Reference standard +	Reference standard -	Total	
	Index test +	104	0	104	
	Index test -	1	10	11	
	Total	105	10	115	
Statistical measures	<p><u>Index text: IOPTH (including 20 minute delayed time point in people without a fall at 10 minutes)</u> Sensitivity: 100% Specificity: 100%</p> <p><u>Index text: IOPTH (only including 10 minutes)</u> Sensitivity: 99.0% Specificity: 100%</p>				
Source of funding	Not reported				
Limitations	Risk of bias: none				

Reference	Barczynski 2007³⁴
	Indirectness: none (sub selection of people positive on imaging for single gland disease is not a limitation for IOPTH index test).
Reference	Bobanga 2017⁵⁵
Study type	Retrospective review
Countries and setting	USA, Surgery department, medical centre.
Study methodology	Data source: prospectively maintained parathyroid database Recruitment: all patients operated on for PHPT by a single surgeon at the centre between May 1994 and February 2016.
Number of patients	n = 127
Patient characteristics	Age, mean (SD): 60 (13) years Gender (male to female ratio): 27:100 Ethnicity: not reported Inclusion criteria: patients operated on for PHPT by a single surgeon; patients with a single focus of abnormal radiotracer accumulation on technetium-99m-sestamibi with SPECT that corresponded to a homogenous, hypoechoic, oval or bean-shaped mass on US exam consistent with an abnormal parathyroid gland. Exclusion criteria: non-concordant pre-operative imaging, no glands seen on pre-operative imaging but adenoma found at exploration; incomplete medical records. Details of imaging tests and surgical intervention: all patients underwent pre-operative imaging with either surgeon-preformed or radiologist-performed neck US and sestamibi with SPECT. Focused surgery performed to explore the site identified on imaging. IOPTH performed in all patients. Prior tests: sub selection of people with concordant imaging SPECT and US predicting a single adenoma. Patient details: n=122 solitary adenoma, n=2 double, n=3 hyperplasia First surgery / re-operation not reported
Index test(s) and reference standard	<u>Index test</u> SPECT + US together (concordant for prediction of a single adenoma)

Reference	Bobanga 2017⁵⁵				
	Positive = concordant US and SPECT defined as both studies with radiographic features consistent with a single abnormal parathyroid gland on the same side of the neck and in the same upper or lower location.				
	Reference standard Intraoperative findings. But table 1 states the histopathological findings and text states 'all patients were cured of hyperparathyroidism'.				
2x2 table	SPECT+US				
		'True positives' 120	'False positives' 5	All patients had a single adenoma predicted on imaging: Correct localisation of single n=120 (TPs) Incorrect localisation of single n=2 (FNs) Predicted single but final outcome double n=2 (FPs) Predicted single but final outcome hyperplasia n=3 (FPs)	
		'False negatives' 2	'True negatives' 0		
	Total	122	5		127
Statistical measures	Index text: SPECT + US 'Sensitivity': 98.4% 'Specificity': 0%				
Source of funding	Not reported				
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded. Indirectness: sub selection of people with concordant imaging SPECT and US predicting a single adenoma				

Reference	Bonjer 1997⁵⁷
Study type	Retrospective study
Countries and setting	The Netherlands, University Hospital
Study methodology	Data source: patient records Recruitment: all patients who had operations on the thyroid glands at the University hospital between May 1993 and April 1995.
Number of patients	n = 27 (2/27 had secondary or tertiary HPT, but results reported separately so can exclude from calculations)
Patient characteristics	Age, mean (range): 59 (34-79) years Gender (male to female ratio): 6:21 Ethnicity: not reported

Reference	Bonjer 1997⁵⁷			
	<p>Inclusion criteria: hyperparathyroidism confirmed by the findings of raised concentrations of serum parathyroid hormone by a two-site immunoassay; patients with pre-operative sestamibi scans.</p> <p>Exclusion criteria: patients about to undergo first operation of familial HPT, MEN, and secondary and tertiary HPT.</p> <p>Details of imaging tests and surgical intervention: patients had MIBI, SPECT and US of the neck and chest. All patients about to undergo their first parathyroidectomy had bilateral exploration (and an attempt made to identify all parathyroid glands). Patients being operated on for persistent or recurrent HPT or patients having local anaesthesia had unilateral exploration.</p> <p>Prior tests: no preselection based on prior imaging</p> <p>Patient details: 21 people had primary HPT, 6 people had persistent or recurrent HPT (3 persistent PHPT, 1 recurrent PHPT, and 2 excluded from this analysis due to secondary or tertiary HPT). 16% re-operation, results reported separately for 1st operation (n=21) and re-operation (n=4). n=27 solitary adenoma (n=25 PHPT).</p>			
Index test(s) and reference standard	<p><u>Index test (unable to calculate 2x2 table values for US)</u></p> <p><u>MIBI:</u> ^{99m}Tc-sestamibi scans done 10, 90 and 150 minutes after 370MBq of ^{99m}Tc-sestamibi had been given IV. Anterior and posterior planar images of the neck and chest recorded using a gamma camera with a large field of view and a high resolution parallel-hole collimator.</p> <p>Positive = not reported</p> <p><u>Reference standard</u> The operative and histopathological findings of those explorations that resulted in normocalcaemia post-operatively (and states in results that all people became normocalcaemic).</p>			
2x2 table	MIBI		Total	
		'True positives' 21	'False positives' 0	Correct localisation of single n=17 (TPs) Correct localisation of single in persistent/recurrent PHPT n=4 (TPs) Incorrect localisation of single n=1 (FNs) Imaging negative, missed single n=3 (FNs)
		'False negatives' 4	'True negatives' 0	
	Total	25	0	Analyse separately for 1 st operation (17TPs, 4FNs, n=21) and reoperation (4TPs, n=4).

Reference	Bonjer 1997⁵⁷
Statistical measures	Index text: MIBI 'Sensitivity': 84% 'Specificity': -
Source of funding	Not reported
Limitations	Risk of bias: none Indirectness: none

Reference	Bradley 2016⁶⁰
Study type	Retrospective study
Countries and setting	USA, University Hospital
Study methodology	Data source: not reported Recruitment: meeting criteria between 2007 and 2014
Number of patients	n = 49
Patient characteristics	Age, mean (SD): not reported Gender (male to female ratio): not reported Ethnicity: not reported Inclusion criteria: primary hyperparathyroidism; met consensus criteria for surgical treatment including serum calcium >1mg/dL and elevated PTH levels; studies with 99mTc-sestamibi and US (negative sestamibi scan and a single abnormal gland 0.5cm or greater, suggested on US). Exclusion criteria: Details of imaging tests and surgical intervention: sestamibi and US pre-operatively. IOPTH not used routinely. Forty patients selected for focused neck exploration (involved a unilateral horizontal incision 2-3cm along the anterior border of the sternocleidomastoid). Prior tests: only included people with negative sestamibi scan and US suggesting a single adenoma Patient details:

Reference	Bradley 2016⁶⁰			
	First surgery / re-operation not reported			
Index test(s) and reference standard	<p><u>Index test</u> US: performed 1-2 weeks pre-operatively</p> <p>Positive = not reported</p> <p><u>Reference standard</u> All 49 people had post-operative normocalcaemia and were considered surgical cures (patients with normalised calcium and final pathology consistent with their operative findings considered surgical cures).</p>			
2x2 table	US		Total	All patients had a single adenoma predicted on imaging: Correct localisation of single n=41 (TPs) <i>(note: in 1 person the localisation was correct but the adenoma wasn't found on the first operation)</i> Incorrect localisation of single n=6 (FNs) Predicted single but final outcome hyperplasia n=2 (FPs)
		'True positives' 41	'False positives' 2	
		'False negatives' 6	'True negatives' 0	
	Total	47	2	
Statistical measures	<p><u>Index text:</u> 'Sensitivity': 87.2% 'Specificity': 0%</p>			
Source of funding	Not reported			
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded. Indirectness: only included people with negative sestamibi scan and US suggesting a single adenoma			

Reference	Calo 2013⁶⁹
Study type	Retrospective study
Countries and setting	Italy, surgical department, university hospital
Study methodology	<p>Data source: not reported</p> <p>Recruitment: undergoing surgery for PHPT in the surgical department between May 2003 and December 2012.</p>
Number of patients	n = 188

Reference	Calo 2013⁶⁹				
Patient characteristics	<p>Age, median (range): 58 (19-85) years</p> <p>Gender (male to female ratio): 37:202 (total 239 patients including those not undergoing focused)</p> <p>Ethnicity: not reported</p> <p>Inclusion criteria: operated on for PHPT in the surgical department; undergoing focused parathyroidectomy; normal renal function. Exclusion criteria:</p> <p>Details of imaging tests and surgical intervention: pre-operative tests included MIBI (n=191), US (n=233) and SPECT-CT (n=140). All included patients underwent focused parathyroidectomy. All operations were performed under general anaesthesia with endotracheal intubation and by the same team of surgeons, who were highly experienced in parathyroid surgery.</p> <p>Prior tests: only people undergoing focused parathyroidectomy</p> <p>Patient details: n=150 solitary, n=35 hyperplasia, n=3 carcinoma (1.6%) First surgery / re-operation not reported</p>				
Index test(s) and reference standard	<p><u>Index test</u> IOPTH: the STAT-Intraoperative-Intact-PTH Chemilluminescence immunoassay semiautomated mobile system (Future Diagnostics, Wijchen, Netherlands) was used within the surgical suite complex for the intraoperative quantitative determination of PTH levels in EDTA plasma.</p> <p>Positive = Irvin criterion, an intra-operative PTH drop >50% from the highest either pre-incision or pre-excision level after parathyroid excision after 10 minutes (if this didn't occur within 10 minutes, a PTH drop of >50% from the highest basal value within 20 min after gland excision and/or a residual PTH-20 min level within the reference range)</p> <p><u>Reference standard</u> Post-operative normocalcaemia and PTH, and final histology</p>				
2x2 table	IOPTH	Ref standard +	Ref standard -	Total	<p>Note: method includes taking a 20 minute time point in people with a negative IOPTH at 10 minutes (can't calculate for 10 minute time point only)</p> <p>IOPTH results after excision of the 1st gland only for those who had multiple glands – i.e. for these, was the –ve IOPTH result predictive of either more pathological glands removed, or post-op hypercalcaemia (of</p>
	Index test +	167	1	168	
	Index test -	6	14	20	
	Total	173	15	188	

Reference	Calo 2013⁶⁹
	the people with IOPTH –ve, 10 went on to have more glands removed and 4 remained hypercalcaemic)
Statistical measures	Index text: (including 20 minute delayed timepoint in people without a fall at 10 minutes) Sensitivity: 96.5% Specificity: 93.3%
Source of funding	Not reported
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded. Indirectness: none (sub selection of people positive on imaging for single gland disease is not a limitation for IOPTH index test).

Reference	Casas 1994⁷⁹
Study type	Retrospective study
Countries and setting	Georgia, Department of Surgery, Medical College
Study methodology	Data source: not reported Recruitment: diagnosed with PHPT from January 1989 to September 1992
Number of patients	n = 42 (but only 21 underwent imaging with MIBI and analysed here)
Patient characteristics	Age, mean (range), n=21: 59 (39-87) years Gender (male to female ratio): 5:16 Ethnicity: race (black: white): 9:12 Inclusion criteria: patients diagnostic with PHPT based on intact PTH levels, elevated total and ionised serum calcium levels and accompanying symptoms. Tc-99m-sestamibi group consisted of patients who received pre-operative localisation with Tc-99m-sestamibi and Iodine-123 radionuclide subtraction imaging. Exclusion criteria: Details of imaging tests and surgical intervention: pre-operative localisation with Tc-99m-sestamibi and Iodine-123 radionuclide subtraction imaging. All patients underwent neck exploration in a standardised fashion and attempts made to identify as many

Reference	Casas 1994⁷⁹			
	parathyroid glands as could be located with reasonable effort and as surgically indicated.			
	Prior tests: no preselection based on prior imaging			
	Patient details: n=16 solitary, n=1 double, n=4 hyperplasia First surgery / re-operation not reported			
Index test(s) and reference standard	<p><u>Index test</u> MIBI: technetium-99m-sestamibi and Iodine-123 radionuclide subtraction imaging. Oral dose of 14.8MBq of I-123 administered 4 hours before imaging with Tc-99m-sestamibi (IV injection of 148 MBq of Tc-99m-sestamibi and imaging of the neck and upper part of the thorax using a parallel collimator and wide-field of view gamma camera. Subtraction image generated.</p> <p>Positive = not reported</p> <p><u>Reference standard</u> Histology (biopsies of all glands made) and all 21 patients had normal ionised and total post-operative calcium.</p>			
2x2 table	MIBI (subtraction)		Total	Correct localisation of single n=14 (TPs) Predicted multigland but final outcome single n=2 (FNs) Correct prediction of double n=1 (TNs) Correct prediction of hyperplasia n=4 (TNs)
	'True positives'	'False positives'		
	14	0		
	'False negatives'	'True negatives'		
	2	5		
	Total	16	5	21
Statistical measures	<p><u>Index text: MIBI (subtraction)</u> 'Sensitivity': 87.5% 'Specificity': 100%</p>			
Source of funding	Not reported			
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded. Indirectness: none			

Reference	Cayo 2009⁸⁵
Study type	Prospective
Countries and setting	USA, Department of Surgery, University Hospital

Reference	Cayo 2009⁸⁵				
Study methodology	Data source: n/a Recruitment: between November 2000 and March 2008, data were prospectively collected on 755 patients with PHPT who underwent parathyroidectomy				
Number of patients	n = 161				
Patient characteristics	Age, mean (range): 58 (18–88 years). Gender (male to female ratio): not reported Ethnicity: not reported Inclusion criteria: patients with PHPT who underwent parathyroidectomy; had multiple gland disease on pathology, had IOPTH Exclusion criteria: not reported Details of imaging tests and surgical intervention: not reported Prior tests: sub selection of those found to have multi gland disease on pathology Patient details: All multigland disease (72 double, 89 hyperplasia) First surgery / re-operation not reported				
Index test(s) and reference standard	<p><u>Index test</u> IOPTH: PTH samples were collected pre-incision, and then at 5, 10, and 15 min after excision of suspected abnormal parathyroid gland(s).</p> <p>Positive = drop of greater than 50% at 5, 10 or 15 minutes compared to pre-incision</p> <p><u>Reference standard</u> Clinical cure (normocalcaemic postoperatively and remained so for 6 months). All had pathology as all had multigland disease.</p>				
2×2 table	IOPTH	Reference standard +	Reference standard –	Total	Study states 11 people had TN results (no drop in IOPTH and hypercalcaemic post-operatively), but this included 5 people who had recurrence after 6 months (in other studies, e.g. Chen 2005, this is counted as a cure). Therefore, for this analysis these 5 are counted as FNs (no drop in
	Index test +	146	0	146	
	Index test –	9	6	15	
	Total	155	6	161	

Reference	Cayo 2009⁸⁵
	IOPTH but were normocalcaemic within 6 months).
Statistical measures	Index text: Sensitivity: 94.2% Specificity: 100%
Source of funding	Not reported
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded. Indirectness: none

Reference	Chen 2005⁹⁴
Study type	Unclear
Countries and setting	USA, Department of Surgery, Medical School
Study methodology	Data source: not reported Recruitment: consecutive patients with PHPT with positive localisation for a single adenoma and candidates for MIP from January 1990 to June 2004.
Number of patients	n = 345 (only results for group 2 included here, n=188 who had IOPTH)
Patient characteristics	Age, mean (SD), n=188: 60 (3) years Gender (male to female ratio): not reported Ethnicity: not reported Inclusion criteria: PHPT with positive localisation for a single adenoma and candidates for MIP who underwent neck exploration. Exclusion criteria: not reported Details of imaging tests and surgical intervention: minimally invasive parathyroidectomy Prior tests: sub selection of people with positive localisation studies for a single adenoma and candidates for MIP. Patient details:

Reference	Chen 2005⁹⁴				
	n=170 solitary, n=9 double, n=9 hyperplasia First surgery / re-operation not reported				
Index test(s) and reference standard	<p><u>Index test</u> IOPTH: PTH level drawn from a peripheral vein before operative incision and serves as a baseline. Blood collected in EDTA-containing tubes and loaded on 1 of 2 auto analysers (Elecsys 2010 or the Elecsys 1010 (Roche)).</p> <p>Positive = drop of greater than 50% at 5, 10 or 15 minutes compared to pre-incision</p> <p><u>Reference standard</u> Surgical cure (calcium less than 10.2mg/dL). No mention of histology in the methods, but in the results it states that people with an initial inadequate drop in IOPTH had subsequent resection of additional 'hyper cellular' parathyroid glands.</p>				
2x2 table		Reference standard +	Reference standard -	Total	Can calculate both, but this is IOPTH results after excision of the first gland in people with MGD (TNs either went on to have further glands found or were not cured).
	Index test +	170	0	188	
	Index test -	0	18	0	
	Total	170	18	188	
Statistical measures	<p><u>Index text:</u> Sensitivity: 100% Specificity: 100%</p>				
Source of funding	NR				
Limitations	<p>Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded. Unclear if histology used as part of reference standard.</p> <p>Indirectness: none (sub selection of people positive on imaging for single gland disease is not a limitation for IOPTH index test).</p>				

Reference	Chick 2017⁹⁶				
Study type	Retrospective study				
Countries and setting	Hong Kong, Department of Surgery, Hospital				
Study methodology	<p>Data source: not reported</p> <p>Recruitment: patients who received MIP with selective use of IOPTH for PHPT between March 2006 and June 2015. Historical cohort of patients who received MIP with mandatory IOPTH between March 2002 and February 2006.</p>				
Number of	n = 157 (split into 2 groups, group 1 n=100 with optional IOPTH, only 25 had IOPTH and group 2 n=57 with mandatory IOPTH, only 54				

Reference patients	Chick 2017⁹⁶ had IOPTH. Total having IOPTH n=79 included in this analysis)				
Patient characteristics	<p>Age, mean (SD): selective IOPTH group (n=100) 56.4 (13.9) years, mandatory IOPTH group (n=57) 59.3 (14) years.</p> <p>Gender (male to female ratio): 56:101 (all n=157)</p> <p>Ethnicity: not reported</p> <p>Inclusion criteria: patients with PHPT meeting the inclusion criteria for MIP (at least 1 positive localisation study suggesting a single parathyroid adenoma, and the absence of thyroid nodules or tumours requiring thyroidectomy)</p> <p>Exclusion criteria: presence of a thyroid lesion requiring thyroidectomy, negative localisation, extracervical ectopy, suspicion of multi-gland disease, large sized adenoma, familial history of PHPT (including MEN).</p> <p>Details of imaging tests and surgical intervention: sestamibi and US, other localisation such as CT performed at the discretion of the surgeon. All operations performed under general anaesthesia. MIP was a direct, focused approach using a small cervical incision placed according to the location of the diseased gland from pre-operative US performed by the surgeon.</p> <p>Prior tests: sub selection of people eligible for MIP (at least one localisation study suggesting solitary adenoma) and excluded people with negative imaging or suspicion of multigland disease. For group 2, all people had IOPTH, for group 1 only people with discordant MIBI, US and intraoperative findings received IOPTH).</p> <p>Patient details: First surgery / re-operation not reported</p>				
Index test(s) and reference standard	<p><u>Index test</u> IOPTH: Immulite 1000 Immunoassay system 2002-2004 (Siemens, Germany), Roche Modular analytics E170 system 2004-2013 (Roche, Switzerland), Roche cobas e411 sytem 2014-2015 (Roche). Blood for PTH assay collected by venepuncture into EDTA tubes from the peripheral vein before skin incision (pre-incision), after dissection of the adenoma but before its removal (pre-excision) and at 10 minutes.</p> <p>Positive = Miami: drop of 50% or more from the highest baseline value (pre-incision or pre-excision) at 10 minutes. If this did not occur then a 20 minute sample taken and a drop of 50% or more at 20 minutes.</p> <p><u>Reference standard</u> Normocalcaemia at 6 months. No mention of histology in the methods but the results state 'for the pathology...'</p>				
2x2 table	IOPTH	Reference standard +	Reference standard -	Total	Note: method includes taking a 20 minute timepoint in people with a negative IOPTH at 10 minutes (can also
	Index test +	78	0		

Reference	Chick 2017 ⁹⁶				
	Index test -	0	1		calculate for only 10 minute timepoint – below) Group 1: 25TPs, group 2: 53TPs, 1TN IOPTH results after excision of all glands in people with multigland disease Including 10 minute timepoint only
	Total	78	1	79	
2x2 table	IOPTH (10 mins)	Reference standard +	Reference standard -	Total	
	Index test +	75	0		
	Index test -	3	1		
	Total	78	1	79	
Statistical measures	Index text: (including 20 minute delayed timepoint in people without a fall at 10 minutes) Sensitivity: 100% Specificity: 100% Index text: (10 minutes only) Sensitivity: 96.2% Specificity: 100%				
Source of funding	Not reported				
Limitations	Risk of bias: none Indirectness: none (sub selection of people positive on imaging for single gland disease is not a limitation for IOPTH index test).				

Reference	Garner 1999¹⁵³
Study type	Unclear
Countries and setting	USA, Department of Surgery, University Medical Centre
Study methodology	Data source: not reported Recruitment: consecutive patients
Number of patients	n = 130
Patient	Age, mean (SD): 56.9 (12.3) years

Reference characteristics	Garner 1999¹⁵³				
	<p>Gender (male to female ratio): 29:101</p> <p>Ethnicity: not reported</p> <p>Inclusion criteria: not reported Exclusion criteria: not reported</p> <p>Details of imaging tests and surgical intervention: not reported</p> <p>Prior tests: not reported</p> <p>Patient details: First surgery / re-operation not reported</p>				
Index test(s) and reference standard	<p><u>Index test</u> IOPTH: samples collected from either peripheral or jugular veins or peripheral arteries into EDTA tubes. Plasma samples assayed for PTH by the Nichols Institute Diagnostic QuiCk-IntraOperative Intact PTH Assay, an immunochemiluminometric assay. Pre-incision (after anaesthesia induction), pre-excision (after identification of the gland but before removal) and at 5 and 10 minutes.</p> <p>Positive = >50% drop at around 10 minutes (although one person had a delayed drop at 24 minutes)</p> <p><u>Reference standard</u> Normal calcium level post-operatively. Pathology not mentioned in the methods but mentions pathological examination in the results.</p>				
2x2 table	IOPTH	Reference standard +	Reference standard -	Total	<p>Narrative comment 'of the cases that fell <50% after 10 minutes, one fell after a longer time interval (24 minutes)' (however, methods don't state that the 20 minute time point was routinely assessed if there was no drop at 10 minutes, therefore analysed as a FN (unclear if other people with a negative IOPTH at 10 minutes would have had a 20 minute time point taken).</p> <p>IOPTH results after excision of all glands in people with multigland disease</p>
	Index test +	122	3	126	
	Index test -	3	2	4	
	Total	125	5	130	

Reference	Garner 1999¹⁵³
Statistical measures	Index text: Sensitivity: 98.4% Specificity: 40%
Source of funding	Not reported
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded. Indirectness: none

Reference	Hamilton 1988¹⁸¹
Study type	Prospective
Countries and setting	USA, University Hospital
Study methodology	Data source: n/a Recruitment: not reported
Number of patients	n = 10
Patient characteristics	Age, mean (SD): not reported Gender (male to female ratio): not reported Ethnicity: not reported Inclusion criteria: positive diagnosis required an elevated serum calcium on at least 2 separate occasions and an elevated C-terminal PTH level measured by radioimmunoassay. Exclusion criteria: malignancy, sarcoidosis, vitamin D intoxication and idiopathic hypocalciuric hypercalcaemia. Details of imaging tests and surgical intervention: MRI. Operative approach consisted of a transverse cervical incision. Systematic exploration performed with careful attention devoted to the region containing the suspected enlarged gland. Prior tests: no preselection based on prior imaging Patient details: All had solitary adenoma

Reference	Hamilton 1988¹⁸¹				
	No patient had previous exploration of the neck				
Index test(s) and reference standard	<p><u>Index test</u> MRI: General electric 1.5 tesla superconducting magnet. Spin echo images utilising both short and long repetition times and echo time. Images acquired in the axial plane in all cases. Coronal and sagittal imaging obtained selectively to assist localising.</p> <p>Positive = not reported</p> <p><u>Reference standard</u> Normal post-op calcium levels confirmed successful resection in all cases and no patient required a secondary operation. All glands biopsied.</p>				
2x2 table	MRI			Total	Correct localisation of single n=9 (TPs) Incorrect localisation of single n=1 (FNs)
		'True positives' 9	'False positives' 0		
		'False negatives' 1	'True negatives' 0		
	Total	10	0	10	
Statistical measures	<p><u>Index text:</u> 'Sensitivity': 90% 'Specificity' -</p>				
Source of funding	not reported				
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded. Indirectness: none				

Reference	Hanif 2006¹⁸³
Study type	Unclear
Countries and setting	Ireland, Department of Surgery, University Hospital
Study methodology	Data source: not reported Recruitment: a cohort undergoing surgery for HPT over a 3 year period.
Number of patients	n = 51
Patient	Age, mean (SD): 63 (14) years

Reference characteristics	<p>Hanif 2006¹⁸³</p> <p>Gender (male to female ratio): 14:37</p> <p>Ethnicity: not reported</p> <p>Inclusion criteria: patients suitable for minimally invasive radio-guided parathyroidectomy (MIRP) for PHPT; diagnosis of hyperparathyroidism was based on clinical features and confirmed by the findings of high total and/or ionized calcium levels and levels of intact PTH.</p> <p>Exclusion criteria: patients unsuitable for MIRP due to thyroid disease, suspected bilateral multi glandular disease or syndromes causing hyperparathyroidism.</p> <p>Details of imaging tests and surgical intervention: preoperative Tc sestamibi scanning, in the patients with recurrent disease also performed ultrasonography of the neck to support the diagnosis. Each operation was carried out under general anaesthesia using a skin crease transverse cervical incision measuring ≤ 4 cm (mean, 3.3 – 0.4 cm). A hand-held gamma radiation detecting probe (Navigator RMD Watertown, MA, USA) was used to map the abnormal glands.</p> <p>Prior tests: sub selection of people suitable for MIRP</p> <p>Patient details: 3 re-operation (5.9%) n=46 solitary, n=3 double, n=2 ectopic</p>				
Index test(s) and reference standard	<p><u>Index test</u> IOPTH: a baseline rapid iPTH level was taken prior to the first incision using a chemiluminescence immunoassay. This measurement detects levels of intact parathyroid hormone in plasma (Future Diagnostics BV, Wijchen, The Netherlands). A venous sample was taken from the antecubital vein using an intravenous 14–16-gauge cannula. This intravenous access was used for rapid iPTH sampling during the procedure.</p> <p>Positive = a post-excision drop in iPTH $\geq 50\%$ at 5, 10 or 15 minutes relative to the preoperative value</p> <p><u>Reference standard</u> All the patients that were subsequently followed (with a follow-up range from 3 months to 2 years) were normocalcaemic with normal PTH levels. Histopathology of all glands excised confirmed parathyroid adenomas.</p>				
2x2 table	IOPTH	Reference standard +	Reference standard -	Total	IOPTH results taken after removal of all glands in people with multiple adenomas.
	Index test +	48	0	48	
	Index test -	3	0	3	
	Total	51	0	51	

Reference	Hanif 2006¹⁸³
Statistical measures	<p><u>Index text:</u> Sensitivity: 94.1% Specificity: -</p>
Source of funding	States: No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article
Limitations	Risk of bias: none Indirectness: none (sub selection of people for MIRP is not a limitation for IOPTH index test).

Reference	Harris 2008¹⁸⁶
Study type	Prospective
Countries and setting	Canada, Division of Surgery, Health Sciences centre
Study methodology	<p>Data source: n/a</p> <p>Recruitment: all patients referred to the centre for suspected parathyroid adenoma</p>
Number of patients	n = 23
Patient characteristics	<p>Age, median (range): 66 years (26–80) years</p> <p>Gender (male to female ratio): 9:14</p> <p>Ethnicity: not reported</p> <p>Inclusion criteria: not reported Exclusion criteria: not reported</p> <p>Details of imaging tests and surgical intervention: If SPECT-CT negative then bilateral surgery undertaken with the initial side chosen at random. If SPECT-CT positive, the positive side was explored first.</p> <p>Prior tests: no preselection based on prior imaging</p> <p>Patient details: n=18 solitary, n=2 double, n=3 hyperplasia</p>

Reference	Harris 2008¹⁸⁶			
	First surgery / re-operation not reported			
Index test(s) and reference standard	<p><u>Index test</u> SPECT-CT: Patients received 700 MBq of 99m-Tc-sestamibi by intravenous injection. Immediate and 2-hour anterior planar images of the neck and mediastinum were obtained using a low-energy high resolution (LEHR) large field-of-view gamma camera with a high-resolution parallel hole collimator. SPECT-CT scans spanning from the angle of the mandible to the base of the heart were acquired at 2 hours. Both SPECT and CT images were obtained using the Infinia Hawkeye or the Hawkeye 4 (General Electric Medical Systems). Hybrid SPECT-CT images were obtained in the axial, sagittal, and coronal planes.</p> <p>Positive = If a parathyroid adenoma was present on the SPECT-CT images, the nuclear medicine physician plotted out its location using 3-dimensional Cartesian X, Y, and Z coordinates.</p> <p><u>Reference standard</u> SPECT-CT prediction of the parathyroid pathology had to be correct, and the surgeon had to find the parathyroid pathology in the exact location predicted by the scan. States 'after surgery no patient had persistent hypercalcaemia'.</p>			
2x2 table	SPECT-CT		Total	Correct localisation of single n=16 (TPs) Incorrect localisation of single n=2 (FNs) Correct prediction of double n=1 (TNs) Imaging negative, had double n=1 (TNs) Predicted single but final outcome hyperplasia n=2 (FPs) Imaging negative, had hyperplasia n=1 (TNs)
	'True positives'	'False positives'		
	16	2		
	'False negatives'	'True negatives'		
	2	3		
	Total	18	5	23
Statistical measures	<p><u>Index text:</u> 'Sensitivity': 88.9% 'Specificity': 60.0%</p>			
Source of funding	Not reported			
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none			

Reference	Hathaway 2013¹⁸⁹
Study type	Prospective study
Countries and setting	UK, University Hospital (tertiary centre)

Reference	Hathaway 2013¹⁸⁹				
Study methodology	Data source: n/a Recruitment: patients undergoing parathyroidectomy for single gland disease between January 2004 and March 2011.				
Number of patients	n = 303 (splits into 2 groups subgroups by pre-operative calcium level, but results provided here for both groups together).				
Patient characteristics	Age, median (range): median 64 in both groups, (range 18-89) years. Gender (male to female ratio): 61:242 Ethnicity: not reported Inclusion criteria: patients undergoing parathyroidectomy for single gland disease; had IOPTH Exclusion criteria: parathyroid carcinoma, MEN, missing data, no recorded preoperative or 3 month corrected calcium, no recorded adenoma weight. Details of imaging tests and surgical intervention: pre-operative localisation with MIBI and US. A focused approach was used when either localisation test was positive. A bilateral approach was used when localisation was negative, no tumour was found, or no drop in IOPTH at 10 minutes. Prior tests: sub selection of people with single gland disease, people with more than one gland excised were excluded Patient details: First surgery / re-operation not reported				
Index test(s) and reference standard	<u>Index test</u> IOPTH: samples taken at baseline, pre-excision, and at 5 and 10 minutes using a 2-site chemiluminescent assay (Cambridge Diagnostics Ltd., Ireland). Positive = 50% drop from the highest of either the baseline or pre-excision values (presumably at either 5 or 10 minutes). <u>Reference standard</u> Normocalcaemia at 3 months. No mention of pathology, however only included people who had a single gland removed (therefore normocalcaemia alone can determine whether the gland was responsible or not).				
2x2 table	IOPTH	Reference standard +	Reference standard -	Total	Note: reference standard does not included pathology, but only included people who had a single gland excised so normocalcaemia alone
	Index test +	291	2	293	
	Index test -	9	1	10	

Reference	Hathaway 2013¹⁸⁹				
	Total	300	3	303	as the reference standard is sufficient
Statistical measures	<u>Index text:</u> Sensitivity: 97.0% Specificity: 33.3%				
Source of funding	Not reported				
Limitations	Risk of bias: none Indirectness: none (sub selection of people with single gland disease is not a limitation for IOPTH index test).				

Reference	Hindie 1998¹⁹⁷				
Study type	Prospective study				
Countries and setting	France, University Hospital				
Study methodology	Data source: n/a Recruitment: consecutive patients referred for surgical management of PHPT.				
Number of patients	n = 30				
Patient characteristics	Age, mean (SD): not reported Gender (male to female ratio): not reported Ethnicity: not reported Inclusion criteria: referred for first surgery for PHPT; biochemical confirmation of hyperparathyroidism based on accepted diagnostic criteria Exclusion criteria: not reported Details of imaging tests and surgical intervention: standard bilateral neck exploration (except 1 patient had unilateral neck exposure under local anaesthesia. Some normal glands also biopsied). Prior tests: no preselection based on prior imaging				

Reference	Hindie 1998¹⁹⁷				
	Patient details: n=27 solitary (1 ectopic), n=2 double, n=1 three-gland hyperplasia First surgery reported				
Index test(s) and reference standard	<p><u>Index test</u> intravenous injection of 10 MBq 123-iodide and 2-4hr later, 550 MBq 99mTc-sestamibi. Images of both isotopes were acquired simultaneously using two separate energy windows. Results interpreted by the nuclear physician and surgeon before surgery. <u>Technetium-99m-sestamibi (single tracer, double phase technique)</u>: Images of Tc-99m-sestamibi acquired 15 minutes and 120 minutes after tracer injection were visually compared.</p> <p>Positive = based on visual comparison of the early and late Tc-99m-sestamibi images. A positive double-phase scan for the presence of an enlarged parathyroid was defined as a focal area of increased uptake of 99m-Tc-sestamibi which showed, relative to the surrounding thyroid, either a gradual increase over time or a fixed uptake which persisted on delayed imaging contrary to the uptake in the thyroid tissue which gradually decreases over time.</p> <p><u>Index test</u> <u>Technetium-99m-sestamibi and Iodine-123 (subtraction scanning technique)</u>: Images of Tc-99m-sestamibi and I-123 were recorded simultaneously in non-overlapping windows and then subtracted.</p> <p>Positive = Interpretation of the subtraction scan was based on the early 99m-Tc-sestamibi image, the 123-I image and the computer subtraction image.</p> <p><u>Reference standard</u> None of the patients had persistent or recurrent hypercalcemia after 6-24months of follow-up. Pathology not reported in the methods, but is mentioned in the discussion and also states that some normal glands were biopsied so presume pathology considered in determining final outcome.</p>				
2x2 table	Single tracer			Total	
		'True positives' 21	'False positives' 1		Correct localisation of single n=21 (TPs) Predicted double but final outcome single n=1 (FNs) Imaging negative, had single n=3 (FNs)
		'False negatives' 6	'True negatives' 2		Incorrect localisation of single n=2 (FNs) Correct prediction of double n=2 (TNs)
	Total	27	3	30	Predicted single but final outcome hyperplasia n=1 (FPs)
Statistical measures	<p><u>Index text: single tracer</u> 'Sensitivity': 77.8% 'Specificity': 66.7%</p>				

Reference	Hindie 1998¹⁹⁷				
2x2 table	Subtraction			Total	Correct localisation of single n=25 (TPs) Incorrect localisation of single n=1 (FNs) Imaging negative, had single n=1 (FNs) Correct prediction of double n=2 (TNs) Correct prediction of hyperplasia n=1 (TNs)
		'True positives' 25	'False positives' 0		
		'False negatives' 2	'True negatives' 3		
	Total	27	3	30	
Statistical measures	Index text: subtraction 'Sensitivity': 92.6% 'Specificity': 100%				
Source of funding	not reported				
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded; unclear if all people had pathology as part of the reference standard. Indirectness: none				

Reference	Hughes 2011²⁰⁷
Study type	Retrospective study
Countries and setting	USA, University Medical Centre
Study methodology	Data source: single institution database Recruitment: people who underwent parathyroidectomy for PHPT from September 1999 to September 2009.
Number of patients	n = 228 (when include the 'recognised failures' who had an IOPTH drop of <50%). For some of the data in the study, only the n=207 people who had a positive IOPTH were included, but the 2x2 table values calculated here and the PPV given in the study are for total 228.
Patient characteristics	Age, mean, for the n=207 with a positive IOPTH: mean approx. 60 years Gender (male to female ratio), for the n=207 with a positive IOPTH: 39:168 Ethnicity: not reported Inclusion criteria: patients with PHPT found to have multi-gland disease during the course of focused parathyroidectomy. Multi-gland disease defined as a final histologic diagnosis of more than one excised hyper cellular parathyroid gland

Reference	Hughes 2011²⁰⁷				
	<p>Exclusion criteria: preoperative multiple endocrine neoplasia type 1 (MEN-1) diagnosis, lithium exposure, incomplete IOPTH data, or the presence of recurrent disease. 'Recognised failures' who had an IOPTH drop of <50% (part of the exclusion criteria for some analyses in the study, but the 2x2 table values calculated here and the PPV given in the study include these people).</p> <p>Details of imaging tests and surgical intervention: initially underwent focused parathyroidectomy with IOPTH.</p> <p>Prior tests: sub selection of people with multigland disease from histology</p> <p>Patient details: All multigland disease Recurrent disease excluded</p>				
Index test(s) and reference standard	<p><u>Index test</u> IOPTH: IOPTH data that had been collected from either a cervical or peripheral venous blood draw (sampling site was consistent in individual patients, and the kinetics were determined by comparing the baseline PTH value to the final PTH value). The Immulite Turbo immune chemiluminometric PTH assay (DPC, Los Angeles, CA, USA) was used to determine intact PTH levels.</p> <p>Positive = $\geq 50\%$ drop from baseline (the highest of either the pre-incision (after anaesthesia induction) or the pre-excision (just prior to excision) value) at a median of 13 minutes (5-35 minutes). Note: $\geq 50\%$ drop and into the normal range also reported (not analysed here).</p> <p><u>Reference standard</u> Final histologic diagnosis of more than one excised hyper cellular parathyroid gland. Serum calcium level of ≤ 10.2 mg/dl more than 21 days postoperatively.</p>				
2x2 table	IOPTH	Reference standard +	Reference standard -	Total	<p>Note: results are for a >50% decrease (doesn't matter if falls into the normal range or not).</p> <p>Results are for IOPTH taken after multiple gland excision</p>
	Index test +	193	14	207	
	Index test -	7	14	21	
	Total	200	28	228	
Statistical measures	<p><u>Index text:</u> Sensitivity: 96.5% Specificity: 50.0%</p>				
Source of funding	Not reported				
Limitations	<p>Risk of bias: none Indirectness: none</p>				
Comments					

Reference	Hwang 2010²⁰⁹
Study type	Prospective study
Countries and setting	USA, Department of Surgery, University Hospital
Study methodology	Data source: n/a Recruitment: consecutive patients undergoing surgery for PHPT at a single institution during a 3 year period from 2006 to 2009.
Number of patients	n = 280 (including both MIBI positive and negative)
Patient characteristics	Age, mean (SD not reported): 57 years Gender (male to female ratio): 76% female Ethnicity: not reported Inclusion criteria: undergoing surgery for PHPT Exclusion criteria: known familial syndrome; prior failed parathyroidectomy; need for concomitant thyroid surgery; lithium or radiation exposure; begun as open procedure due to imaging studies all negative or discordant or indicating multi-gland disease, known mediastinal adenoma or clinical suspicion for carcinoma. Details of imaging tests and surgical intervention: all underwent sestamibi and surgeon-performed US. IOPTH results only used for surgical decision making in the MIBI-negative, US-positive patients due to a higher probability of multigland disease (but results for all patients reported). Patients with any positive localisation study were offered MIP. Prior tests: sub selection of people selected for MIP. Excluded people whose surgery was begun as open procedure due to imaging studies all negative or discordant or indicating multi-gland disease, known mediastinal adenoma or clinical suspicion for carcinoma. Patient details: Prior failed parathyroidectomy excluded
Index test(s) and reference standard	<u>Index test</u> IOPTH: PTH samples drawn from a peripheral venous site pre-operatively, immediately pre-excision and 10 minutes post-excision. Samples analysed using the Elecsys PTH-STAT assay (Roche Diagnostics) in 2006-2007 and the STAT Intra-Operative PTH System (Future Diagnostics) in 2008-2009. Positive = Miami criteria - drop of >50% from highest pre-excision value (pre-operative or immediately pre-excision) at 10 minutes

Reference	Hwang 2010²⁰⁹				
	<u>Reference standard</u> Eucalcaemia for at least 6 months. Multigland disease confirmed when more than one histologically abnormal gland removed or when they presented with hypercalcaemia within 6 months following removal of a single.				
2×2 table	IOPTH	Reference standard +	Reference standard -	Total	Note: IOPTH results after removal of the first gland (not after removal of multiple glands) – so a TN result is if they went on to have more abnormal glands removed or hypercalcaemia (can calculate both)
	Index test +	247	1	248	
	Index test -	19	13	32	
	Total	266	14	280	
Statistical measures	<u>Index text:</u> Sensitivity: 92.9% Specificity: 92.9%				
Source of funding	Academic (supported by funds from the UCLA Division of General Surgery)				
Limitations	Risk of bias: none Indirectness: none (sub selection of people with at least 1 positive imaging test is not a limitation for IOPTH index test).				

Reference	Iacobone 2005²¹⁰
Study type	Prospective study
Countries and setting	Italy, University
Study methodology	Data source: n/a Recruitment: undergoing operation for PHPT between January 2000 and December 2003
Number of patients	n = 102
Patient characteristics	Age, mean (range): 62 (26-81) years Gender (male to female ratio): 19:83 Ethnicity: not reported Inclusion criteria: underwent bilateral neck exploration or targeted parathyroidectomy for PHPT Exclusion criteria: unclearly documented PHPT; incomplete follow-up data; parathyroid carcinoma; previous parathyroid operations; family

Reference	Iacobone 2005²¹⁰				
	<p>history of HPT or MEN.</p> <p>Details of imaging tests and surgical intervention: conventional bilateral neck exploration (n=44) or focused surgery (n=58; either unilateral, video assisted, radio guided, or open minimally invasive approach) according to availability of pre-operative localisation.</p> <p>Prior tests: no preselection based on prior imaging tests</p> <p>Patient details: n=88 solitary, n=2 double, n=12 hyperplasia Previous parathyroid operation excluded</p>				
Index test(s) and reference standard	<p><u>Index test</u> IOPTH: peripheral venous blood samples collected before skin incision and 5 and 10 minutes after excision (additional measurements obtained if 10 minutes sample did not drop by 50%). Two-site immune chemiluminometric assay specific for intact PTH (Immulite Turbo Intact PTH, USA)</p> <p>Positive = decline of >50% at the last post-excision value from pre-incision.</p> <p><u>Frozen section:</u></p> <p>Positive = frozen section diagnosis of parathyroid adenoma</p> <p><u>Reference standard</u> IOPTH and frozen section results after excision of first gland and whether it correctly predicted prolonging surgery. Definitive histological diagnosis confirmed by paraffin-embedded sections and if necessary, immune histochemical or special stains were used. States all patients were cured (defined as normalisation of calcium and intact PTH in the early post-operative days and at least 1, 3 and 6 months after operation.</p>				
2x2 table	IOPTH	Reference standard +	Reference standard -	Total	Note: IOPTH and frozen section results after excision of first gland and whether it correctly predicted prolonging surgery
	Index test +	84	0	84	
	Index test -	0	18	18	
	Total	84	18	102	
Statistical measures	<p><u>Index text: IOPTH</u> Sensitivity: 100% Specificity: 100%</p>				
2x2 table	Frozen section	Reference standard +	Reference standard -	Total	

Reference	Iacobone 2005²¹⁰			
	Index test +	79	14	93
	Index test -	5	4	9
	Total	84	18	102
Statistical measures	<u>Index text: frozen section</u> Sensitivity: 94.0% Specificity: 22.2%			
Source of funding	Not reported			
Limitations	Risk of bias: none Indirectness: none			

Reference	Jaskowiak 2002²²⁴
Study type	Prospective study
Countries and setting	USA, University teaching hospital.
Study methodology	Data source: n/a Recruitment: consecutive patients undergoing operations for PHPT from December 1, 1999, to November 30, 2000.
Number of patients	n = 57
Patient characteristics	Age, mean (range): 57 (16-81) years Gender (male to female ratio): 14:43 Ethnicity: not reported Inclusion criteria: undergoing operation for PHPT Exclusion criteria: not reported Details of imaging tests and surgical intervention: bilateral explorations, using a small incision when possible, were performed in first-time operations; most reoperations were unilateral. All operations were performed under general anaesthesia, Preoperative planar dual-phase sestamibi used, and in some cases SPECT.

Reference	Jaskowiak 2002²²⁴				
	<p>Prior tests: no preselection of patients based on prior tests</p> <p>Patient details: n=50 solitary (included the one person not cured, presumed to have a single), n=4 double, n=3 multi 6 people with previous operation for HPT (not reported separately) – 12%</p>				
Index test(s) and reference standard	<p><u>Index test</u> <u>Technetium Tc 99m sestamibi</u>: dual-phase SPS of the neck and chest with planar images and, in some cases, single-photon emission computed tomography. Positive = region of uptake on scan.</p> <p><u>High resolution real-time ultrasonography</u>: no further details provided Positive = not reported</p> <p><u>IOPTH</u>: Peripheral blood samples were collected via an antecubital intravenous line after the induction of anaesthesia but before the incision (baseline 1); after the incision but before resection of the gland (baseline 2); at excision; and at approximately 5 and 10 minutes after the excision. Additional samples were collected when necessary, particularly when multiple excisions were performed or when qPTH levels did not fall as expected.</p> <p>Positive = >50% drop from the highest baseline value at 10 minutes (study also reports the following 2 criteria, but >50% drop from highest baseline alone can be calculated from the Nichols criterion: 1. >50% drop from the pre-incision value and return to normal at 10 minutes; 2. Nichols: >50% drop from the HIGHEST baseline value at 10 minutes and an absolute value lower than the lowest baseline level).</p> <p><u>Reference standard</u> Pathology not reported in methods but is mentioned in results and discussion about the histological confirmation of some adenoma (presume histology used to confirm in all patients). Frozen sections of suspected abnormal parathyroid tissue were routinely obtained intraoperatively. 56/57 people were cured (normocalcaemia). The one person not cured was presumed to have a single adenoma.</p>				
2x2 table	MIBI			Total	<p>Results in study assume that the one person not cured had a single adenoma.</p> <p>Correctly identified single n=38 (TPs) Imaging negative, had single n=7 (FNs) Incorrect localisation of single n=1 (FNs) Predicted multiple but final outcome single n=4 (FNs) Predicted single but final outcome double n=2 (FPs) Predicted single but final outcome hyperplasia n=1 (FPs)</p>
		'True positives' 38	'False positives' 3		
		'False negatives' 12	'True negatives' 4		
	Total	50	7		

Reference	Jaskowiak 2002²²⁴				
				<p>Correctly identifies double adenoma n=1 (TNs) Imaging negative, final outcome double n=1 (TNs) Imaging negative, final outcome hyperplasia n=1 (TNs) Imaging shows multiple glands but not all in hyperplasia n=1 (TNs)</p>	
Statistical measures	<p>Index text: MIBI 'Sensitivity': 76.0% 'Specificity': 57.1%</p>				
2x2 table	US			Total	<p>Results in study assume that the one person not cured had a single adenoma.</p> <p>Correctly identified single n=32 (TPs) Imaging negative, had single n=13 (FNs) Incorrect localisation of single n=3 (FNs) Predicted multiple but final outcome single n=2 (FNs) Predicted single but final outcome double n=1 (FPs) Predicted single but final outcome hyperplasia n=1 (FPs) Correctly identifies double adenoma n=1 (TNs) Imaging negative, final outcome double n=2 (TNs) Imaging negative, final outcome hyperplasia n=2 (TNs)</p>
	'True positives'	'False positives'			
	32	2			
	'False negatives'	'True negatives'			
	18	5			
	Total	50	7		
Statistical measures	<p>Index text: US 'Sensitivity': 64.0% 'Specificity': 71.4%</p>				
2x2 table	IOPTH (50% drop from highest baseline)	Reference standard +	Reference standard -	Total	<p>Criterion (Nichols) is for a 50% drop and into the normal range (but results would be the same for only a 50% drop, regardless of whether into the normal range, i.e. all the people with IOPTH -ve are because it didn't drop by at least 50% at 10 minutes).</p> <p>After excision of 1st gland in people with multiple abnormal glands</p> <p>Narrative comment '3FNs had levels of less than 50% of the highest baseline level documented before leaving the operating room at 20 minutes or longer (however, methods don't state that the 20 minute timepoint was routinely assessed if there was no drop at 10 minutes,</p>
	Index test +	45	2		
	Index test -	4	6		
	Total	49	8	57	

Reference	Jaskowiak 2002 ²²⁴
	therefore analysed these 3 as FNs (unclear if other people with a negative IOPTH at 10 minutes would have had a 20 minute timepoint taken).
Statistical measures	Index text: IOPTH (Nichols) Sensitivity: 91.8% Specificity: 75.0%
Source of funding	This study was supported in part by the Nathan and Frances Goldblatt Society for Cancer Research, Chicago.
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded; unclear if all people had pathology as part of the reference standard. Indirectness: none

Study	Kairaluoma 1994 ²³⁴
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=28)
Countries and setting	Conducted in Finland; Setting: University Hospital
Duration of study	Intervention + follow up: at least 1 year
Method of assessment of guideline condition	Unclear method of assessment/diagnosis.
Stratum	No previous surgery
Subgroup analysis within study	n/a
Inclusion criteria	Primary HPT (reports that laboratory investigations were made on entry to the study, but no details of diagnosis criteria reported).
Exclusion criteria	Secondary or tertiary HPT; MEN; prior thyroidectomy for thyroid disease; simultaneous thyroidectomy; previous US localisation; reoperation for HPT; operated on by another surgeon.
Recruitment/selection of patients	All patients with PHPT referred to the clinic for neck exploration. From July 1989 to January 1993.
Age, gender and ethnicity	Age - Mean (SD): group 1: 54 (12) years; group 2: 65 (16) years. Gender (M:F): group 1 5:9; group 2: 4:10. Ethnicity: not reported
Further population details	Proportion of single and multigland disease the same in both groups. Proportion of ectopic disease higher in group 2 (4/14 and 6/14).
Indirectness of population	No indirectness

Study	Kairaluoma 1994²³⁴
Interventions	<p>(n=14) Intervention 1: results of pre-operative US reported to the surgeon before exploration All patients underwent bilateral exploration performed by the same surgeon. Neck exploration started on the side where US found an enlarged gland. Indirectness: No indirectness</p> <p>(n=14) Intervention 2: exploration without knowledge of pre-operative US localisation results All patients underwent bilateral exploration performed by the same surgeon. Exploration always started on the left hand side. Indirectness: No indirectness</p>
Funding	Not reported
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Pre-operative localisation US versus no pre-operative localisation (not reported to surgeon)</p> <p>Protocol outcome 1: success (cure) - Actual outcome: cure (the failures had missed glands and hypercalcaemia); Group 1: 14/14, Group 2: 12/14 Risk of bias: All domain – Very high, Selection – Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover – n/a; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: length of hospital stay - Actual outcome: length of hospital stay; Group 1: 6.2 (2.2) days, Group 2: 5.8 (2.2) days Risk of bias: All domain – Very high, Selection – Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover – n/a; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	HRQOL; mortality; BMD of the distal radius or the lumbar spine; deterioration in renal function; fractures (vertebral or long bone); persistent hypercalcaemia; occurrence of kidney stones; reoperation; adverse events; unnecessary neck exploration.

Reference	Kim 2015²⁵⁰
Study type	Retrospective study
Countries and setting	Korea, University Hospital
Study	Data source: database

Reference methodology	Kim 2015²⁵⁰			
	Recruitment: all patients who underwent parathyroidectomy by a single surgeon for PHPT from 2004 to 2013			
Number of patients	n = 53			
Patient characteristics	<p>Age, mean (SD): 52.8 (15.5) years</p> <p>Gender (male to female ratio): 19:34</p> <p>Ethnicity: not reported</p> <p>Inclusion criteria: sporadic PHPT Exclusion criteria: familial disease and secondary hyperparathyroidism</p> <p>Details of imaging tests and surgical intervention: preoperative localization was done by both sestamibi scan and ultrasonography. Patients underwent the MIP or the BNE, both using IOPTH. Results of IOPTH only available during surgery if MIBI or US localization studies failed to find the parathyroid adenoma or absence of concordance, otherwise IOPTH results only available post-operatively.</p> <p>Prior tests: no preselection based on prior tests</p> <p>Patient details: First surgery / re-operation not reported</p>			
Index test(s) and reference standard	<p><u>Index test</u> IOPTH: the baseline of IOPTH level was measured before parathyroid resection and at 5 and 10 minutes after excision. The IOPTH level was determined with an Elecsys 2010 apparatus (Roche Diagnostics Co., Indianapolis, IN, USA).</p> <p>Positive = drop of >50% at 10 minutes</p> <p><u>Reference standard</u> Normocalcaemia for at least 6 months after operation. Also reports number of single and multiple from pathological examination.</p>			
2×2 table	IOPTH	Reference standard +	Reference standard -	Total
	Index test +	51	0	51
	Index test -	0	2	2
	Total	51	2	53

Reference	Kim 2015²⁵⁰
Statistical measures	<u>Index text: IOPTH</u> Sensitivity: 100% Specificity: 100%
Source of funding	Not reported
Limitations	Risk of bias: none Indirectness: none

Reference	Krausz 2006²⁶⁴
Study type	Retrospective study
Countries and setting	Israel, Medical Centre
Study methodology	Data source: not reported Recruitment: not reported
Number of patients	n = 36
Patient characteristics	Age, mean (SD): 53 (16) years, (range 18-81 years) Gender (male to female ratio): 11:25 Ethnicity: not reported Inclusion criteria: biochemical evidence of PHPT scheduled for surgery based on National Institutes of Health (NIH) criteria Exclusion criteria: not reported Details of imaging tests and surgical intervention: patients with positive MIBI studies underwent focused exploration at the presumed site of the parathyroid adenoma, as determined by scintigraphy; the abnormal parathyroid gland was excised and sent for frozen section examination. In one of the three centers, an intra-operative PTH assay was used to confirm the completion of surgery, sparing the surgeon and patient the need for a frozen section. Bilateral exploration was pursued only in patients with negative imaging results. Prior tests: no preselection of patients based on prior tests Patient details:

Reference	Krausz 2006²⁶⁴			
	n=6 re-exploration for persistent HPT (16.7%)			
Index test(s) and reference standard	<p><u>Index test</u> ^{99m}Tc-sestamibi (MIBI): anterior planar images of the neck and chest were acquired for 15 minutes at 10 and 120 minutes after intravenous injection of 555 MBq ^{99m}Tc-MIBI using a large field-of-view gamma camera equipped with a parallel-hole collimator. A planar thyroid scan, used for visual subtraction of the early MIBI image, was obtained following injection of 74 MBq ^{99m}Tc-pertechnetate in patients showing MIBI uptake in the parathyroid adenoma of intensity similar to that seen in the thyroid gland or in the absence of differential washout on the delayed MIBI scan.</p> <p>Positive = evaluated independently by a team of three nuclear medicine physicians, with differences of opinion solved by consensus. A distinct focus of increased or separate MIBI uptake in the neck or focal uptake in the mediastinum was considered positive for a parathyroid adenoma on scintigraphy.</p> <p><u>Reference standard</u> Histopathologic confirmation of the surgically removed abnormal parathyroid tissue, with subsequent normalization of serum calcium and PTH levels.</p>			
2x2 table	MIBI		Total	Correctly localised single n=33 (TPs) Negative imaging, final outcome single n=1 (FNs) Negative imaging, final outcome hyperplasia n=2 (TNs)
		'True positives' 33	'False positives' 0	
		'False negatives' 1	'True negatives' 2	
	Total	34	36	
Statistical measures	<u>Index text: MIBI</u> 'Sensitivity': 97.1% 'Specificity': 100%			
Source of funding	not reported			
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none			

Reference	Kumar 2000²⁶⁸
Study type	Unclear
Countries and setting	UK, Hospital

Reference	Kumar 2000²⁶⁸		
Study methodology	Data source: not reported Recruitment: referred to the unit for surgery for PHPT over a period of 4 years (March 1995 to March 1999)		
Number of patients	n = 30		
Patient characteristics	Age, median (range): 58 (18-73) years Gender (male to female ratio): 11:19 Ethnicity: not reported Inclusion criteria: referred for surgery for PHPT (referral based on symptomatic hypercalcaemia or asymptomatic patients less than 75 years old, with high serum calcium levels). Exclusion criteria: not reported Details of imaging tests and surgical intervention: pre-operative localisation by sestamibi. Unilateral exploration was adopted as indicated by a positive scan. Prior tests: no preselection based on prior tests Patient details:		
Index test(s) and reference standard	<p><u>Index test</u> 99mTc-sestamibi (MIBI; subtraction): each patient injected with 400MBq of 99mTc-sestamibi intravenously. Planar imaging of the head and neck were acquired with a pin hole collimator attached to the gamma camera. Anterior early images were acquired 10 minutes post-injection and late images acquired 3 hours later. A single view of the mediastinum was obtained to exclude the possibility of ectopic mediastinal adenomas. Immediately after the late image was obtained, the patient was injected with 100MBq of 99mTc-pertechnetate and an additional image acquired 5 minutes later. This allowed the background uptake of sestamibi within the thyroid to be digitally subtracted</p> <p>Positive = findings interpreted by a single radiologist.</p> <p><u>Reference standard</u> Histology undertaken on all excised glands. States all patients were normocalcaemic after 6 months follow-up.</p>		
2x2 table	MIBI (subtraction)		Total Correctly localised single n=29 (TPs) Predicted single but final outcome hyperplasia n=1 (FPs)

Reference	Kumar 2000²⁶⁸			
		'True positives' 29	'False positives' 1	
		'False negatives' 0	'True negatives' 0	
	Total	29	1	
Statistical measures	<u>Index text: MIBI (subtraction)</u> 'Sensitivity': 100% 'Specificity': 0%			
Source of funding	Not reported			
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none			

Reference	Lee 2014²⁷⁶
Study type	Retrospective study
Countries and setting	USA, University Medical Centre
Study methodology	Data source: institutional parathyroid surgery database (prospectively maintained surgical endocrinology database that contains data on 1,243 patients who underwent parathyroidectomy from 1998 to 2010). Recruitment: patients diagnosed with sporadic PHPT, underwent MIP from 1998 to 2010 and had a minimum of 6 months follow-up data.
Number of patients	n = 557 (but IOPTH data only used in n=547)
Patient characteristics	Age, mean (SD): operative success (n=538) 60.5 (12.6) years; operative failure (n=19) 64.5 (12.7) years Gender (male to female ratio): 118:439 Ethnicity: not reported Inclusion criteria: diagnosed with sporadic PHPT and undergoing MIP Exclusion criteria: previous parathyroid or thyroid surgery; familial or multiple endocrine neoplasia-related hyperparathyroidism syndrome; secondary or tertiary HPT; initial operation planned bilateral exploration (such as when the disease could not be localised with pre-operative imaging); parathyroid carcinoma; lithium associated hyperparathyroidism.

Reference	Lee 2014²⁷⁶			
	<p>Details of imaging tests and surgical intervention: initial operation planned MIP according to pre-operative localisation (one or a combination of technetium 99mTc sestamibi imaging, ultrasonography, or four-dimensional computed tomographic scanning).</p> <p>Prior tests: intended initial operation was a MIP (excluded people when the disease could not be located using pre-operative imaging)</p> <p>Patient details: Excluded previous parathyroid or thyroid surgery</p>			
Index test(s) and reference standard	<p><u>Index test</u> IOPTH: intact PTH levels from a peripheral blood sample.</p> <p>Positive = a drop of 50 % or more from the pre-incision value at 10 minutes (also provide data for a 60% and 70% drop)</p> <p><u>Reference standard</u> Eucalcaemia 6 months after parathyroidectomy. MGD was defined as present when more than one abnormal gland (hyperplastic or adenoma on final pathology) was removed at the time of the first operation or when excision of single pathologically abnormal parathyroid gland did not result in operative success.</p>			
2×2 table		Reference standard +	Reference standard -	Total
	Index test +	513	8	521
	Index test -	15	11	26
	Total	528	19	547
Statistical measures	<p><u>Index text: IOPTH</u> Sensitivity: 97.2% Specificity: 57.9%</p>			
Source of funding	Supported in part by The MD Anderson Cancer Center Support Grant CA016672.			
Limitations	<p>Risk of bias: none Indirectness: none (sub selection of people for MIP is not a limitation for IOPTH index test).</p>			
Reference	Lo 2003²⁹⁰			
Study type	Unclear			
Countries and setting	Hong Kong; University Medical Centre			

Reference	Lo 2003²⁹⁰				
Study methodology	Data source: not reported Recruitment: eligible patients referred to the department from 1999 to 2002				
Number of patients	n = 66				
Patient characteristics	<p>Age, median (range): 55 (30-81) years</p> <p>Gender (male to female ratio): 19:47</p> <p>Ethnicity: not reported</p> <p>Inclusion criteria: sporadic PHPT (biochemically confirmed) and 1 unequivocally enlarged parathyroid gland on pre-operative imaging (eligible for MIP). Exclusion criteria: negative or multiple localisations on pre-operative imaging; need for concomitant thyroidectomy' presence of nodular goiter; positive history of familial PHPT; history of previous neck surgery.</p> <p>Details of imaging tests and surgical intervention: pre-operative localisation with US and sestamibi. MIP performed under general anaesthesia.</p> <p>Prior tests: only included those suspected of having a single adenoma on imaging and underwent endoscopic assisted surgery.</p> <p>Patient details: All had solitary adenoma History of previous neck surgery excluded</p>				
Index test(s) and reference standard	<p><u>Index test</u> IOPTH: 2ml aliquot of blood drawn from the peripheral vein after induction. The quick PTH assay was done with a two-site antibody immunochemiluminometric system (Diagnostics Quick-Pak system; Nichols Institute, USA).</p> <p>Positive = drop of >50% from pre-incision value at 10 minutes</p> <p><u>Reference standard</u> Cured of hypercalcaemia with a medium follow-up of 9 months. Pathology not reported in methods but is mentioned in results that it was used in two patients undergoing bilateral operation. All 66 people had a single adenoma and were cured of hypercalcaemia, (therefore normocalaemia alone can determine whether the gland was responsible or not).</p>				
2x2 table	IOPTH	Reference standard +	Reference standard -	Total	Delayed decrease seen in 4 people at 30 minutes (analysed as FNs here as 30 minute
	Index test +	62	0	62	

Reference	Lo 2003²⁹⁰				
	Index test –	4	0	4	timepoint not included in review protocol).
	Total	66	0	66	
Statistical measures	Index text: <u>IOPTH</u> Sensitivity: 93.9% Specificity: -				
Source of funding	not reported				
Limitations	Risk of bias: none Indirectness: none (sub selection of people suspected to have a single adenoma is not a limitation for IOPTH index test).				

Reference	Lo 2007²⁹¹
Study type	Unclear
Countries and setting	Hong Kong; University Medical Centre
Study methodology	Data source: not reported Recruitment: consecutive patients with PHPT planned to have MIP during a 40 month period
Number of patients	n = 100
Patient characteristics	Age, median (range): 55.5 (13-93) years. Note- the inclusion of <18s, but they excluded familial disease Gender (male to female ratio): 30:70 Ethnicity: not reported Inclusion criteria: biochemically confirmed PHPT referred for surgery; unequivocal solitary adenoma by either pre-operative localisation study. Exclusion criteria: recurrent PHPT; familial PHPT or MEN; incomplete localisation study results; MIBI scan negative or showed multiple uptake areas; presence of large palpable nodular goiter; history of previous neck surgery; need for concomitant thyroidectomy or major surgical procedures. Details of imaging tests and surgical intervention: pre-operative localisation with US and sestamibi. MIP performed with a 2 to 2.5cm incision followed by focused exploration with or without the assistance of a videoscope.

Reference	Lo 2007²⁹¹				
	<p>Prior tests: only included those suspected of having a single adenoma on imaging and underwent MIP.</p> <p>Patient details: n=98 solitary, n=1 double, n=1 hyperplasia Recurrent PHPT excluded</p>				
Index test(s) and reference standard	<p><u>Index test:</u> IOPTH: quick PTH assay (no other details provided)</p> <p>Positive = decrease >50% at 10 minutes after excision</p> <p><u>Reference standard</u> Normocalcaemia during the immediate post-operative period and during a median follow-up of 15 months (range 6-43 months). Final pathology included 98 solitary and 2 multigland disease.</p>				
2x2 table	IOPTH	Reference standard +	Reference standard -	Total	<p>After excision of first gland only (i.e. in the 2 people with multigland disease, they had a <50% drop after excision of the first gland and went on to have further glands discovered).</p> <p>Delayed decrease seen in 3 people at 30 minutes (analysed as FNs here as 30 minute timepoint not included in review protocol).</p>
	Index test +	93	0	93	
	Index test -	5	2	7	
	Total	98	2	100	
Statistical measures	<p><u>Index text:</u> Sensitivity: 94.9% Specificity: 100%</p>				
Source of funding	Not reported				
Limitations	<p>Risk of bias: none Indirectness: none (sub selection of people suspected to have a single adenoma is not a limitation for IOPTH index test).</p>				

Reference	Lombardi 2008²⁹²
Study type	Retrospective study
Countries and setting	Italy
Study	Data source: medical records

Reference methodology	Lombardi 2008²⁹²			
	Recruitment: eligible patients who were operated on for PHPT between March 2002 and February 2008			
Number of patients	n = 207			
Patient characteristics	<p>Age, mean (SD): 56.9 (14.15) years (range 20-83 years).</p> <p>Gender (male to female ratio): 28:179</p> <p>Ethnicity: not reported</p> <p>Inclusion criteria: sporadic PHPT who underwent focused parathyroidectomy with IOPTH Exclusion criteria: patients with serum creatinine above the normal range (0.7-1.2 mg/dL)</p> <p>Details of imaging tests and surgical intervention: pre-operative localisation with SPECT and high resolution US. Patients either underwent video-assisted parathyroidectomy or minimally invasive conventional focused approach using central access.</p> <p>Prior tests: selected for focused surgery, suspected single adenoma (by concordant results of US and MIBI)</p> <p>Patient details: N=197 solitary, n=10 double First surgery / re-operation not reported</p>			
Index test(s) and reference standard	<p><u>Index test</u> IOPTH: blood samples collected peripherally at the ankle at pre-incision, pre-excision (after dissection and just before clamping the suspected affected gland's blood supply) and at 10 and 20 minutes after excision. A point of care chemiluminescence immunoassay system (Stat-Intraoperative-intact PTH, Future Diagnostics, The Netherlands) was used.</p> <p>Positive = Miami criteria: drop $\geq 50\%$ from the highest basal (pre-incision or pre-excision) at 10 minutes. <i>Study also includes own criteria, not analysed here as includes a fall into the reference range (negative = $< 50\%$ drop from the highest baseline (pre-incision or pre-excision) value at 20 minutes and/or a 20 minute value higher than the reference range and/or an increase ($> 7.5\text{ng/L}$) from T10 to T20.)</i></p> <p><u>Reference standard</u> Normal post-operative serum calcium. Mentions final histology in the results to confirm single or multiple adenoma.</p>			
2x2 table	IOPTH (Miami)	Reference standard +	Reference standard -	Total

Reference	Lombardi 2008 ²⁹²			
	Index test +	187	5	192
	Index test -	10	5	15
	Total	197	10	207
Statistical measures	Index text: IOPTH (Miami) Sensitivity: 94.5% Specificity: 50.0%			
Source of funding	Not reported			
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none (sub selection of people suspected to have a single adenoma is not a limitation for IOPTH index test).			

Study	Miccoli 2008 ³¹³
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Italy; Setting: University Hospital
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Unclear method of assessment
Stratum	Overall
Subgroup analysis within study	n/a
Inclusion criteria	Not reported
Exclusion criteria	Not reported
Recruitment/selection of patients	Undergoing surgery in the department for PHPT between October 2005 and February 2006
Age, gender and ethnicity	Age - Mean (SD): group 1.; group 2:. Gender (M:F): 6:34. Ethnicity: not reported Prior tests: only included patients positive for a single adenoma on pre-operative localisation with US and MIBI
Further population details	Not reported
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: parathyroidectomy using the MIVAP technique plus IOPTH (surgical procedure was

Study	Miccoli 2008 ³¹³
	ended when a decrease greater than or equal to 50% of the highest preoperative value was reported) Indirectness: No indirectness (n=20) Intervention 2: parathyroidectomy using the MIVAP technique plus a bilateral endoscopic neck exploration (performed via the same central neck access as the MIVAP, and the surgery ended when all 4 glands visualised and removal of any macroscopically enlarged glands) Indirectness: No indirectness
Funding	Not reported
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IOPTH to determine termination of surgery vs visualising all glands to determine termination of surgery	
Protocol outcome 1: persistent hypercalcaemia - Actual outcome: normalisation of serum calcium at 6 months; Group 1: 19/20, Group 2: 20/20 Risk of bias: All domain – High, Selection – High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover – n/a; Indirectness of outcome: No indirectness	
Protocol outcome 2: adverse events - Actual outcome: post-operative complications (haemorrhage laryngeal nerve palsy, hypocalcaemia); Group 1: 0/20, Group 2: 0/20 Risk of bias: All domain – High, Selection – High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover – n/a; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	HRQOL; mortality; success/failure; BMD of the distal radius or the lumbar spine; deterioration in renal function; fractures (vertebral or long bone); occurrence of kidney stones; length of hospital stay; reoperation; unnecessary neck exploration.

Reference	Michel 2013 ³¹⁴
Study type	Prospective study
Countries and setting	Belgium, referral centre
Study methodology	Data source: n/a Recruitment: consecutive patients with biochemically confirmed PHPT who underwent pre-operative MRI between June 2005 and June 2011.

Reference	Michel 2013³¹⁴				
Number of patients	n = 58				
Patient characteristics	<p>Age, mean (SD): 60 (14) years</p> <p>Gender (male to female ratio): 17:41</p> <p>Ethnicity: not reported</p> <p>Inclusion criteria: biochemically confirmed PHPT who underwent pre-operative MRI Exclusion criteria: not reported</p> <p>Details of imaging tests and surgical intervention: all patients had MRI (56 also had sestamibi).</p> <p>Prior tests: no pre-selection of patients based on prior tests</p> <p>Patient details: 19 previous neck surgery (but none for previous parathyroidectomy) – analyse in 1st operation</p>				
Index test(s) and reference standard	<p><u>Index test</u> IOPTH: no details given in the methods</p> <p>Positive = drop of >50% and within the normal range at 20 minutes (as all people were IOPTH positive, we can calculate that all fit the review protocol criteria of >50% drop (regardless of whether in the reference range or not).</p> <p><u>Reference standard</u> Eucalcaemia at last follow-up. Histopathological confirmation of abnormal tissue in all patients.</p>				
2x2 table	IOPTH	Reference standard +	Reference standard -	Total	<p>As all people were IOPTH positive, we can calculate that all fit the review protocol criteria of >50% drop (regardless of whether in the reference range or not).</p> <p>All at 20 minute time point</p>
	Index test +	58	0		
	Index test -	0	0		
	Total	58	0		
Statistical measures	<p><u>Index text: IOPTH</u> Sensitivity: 100% Specificity: -</p>				
Source of	Not reported				

Reference	Michel 2013³¹⁴
funding	
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none

Reference	Miura 2002³¹⁷
Study type	Retrospective study
Countries and setting	USA; University Hospital
Study methodology	Data source: not reported Recruitment: eligible patients from a series of 242 patients from January 1998 to May 2000 who underwent parathyroidectomy by one surgeon at the department of surgery.
Number of patients	n = 115
Patient characteristics	Age, mean (SD): not reported Gender (male to female ratio): not reported Ethnicity: not reported Inclusion criteria: people with PHPT who had undergone IOPTH; without a family history or multiple endocrine neoplasia; normal renal function Exclusion criteria: not reported Details of imaging tests and surgical intervention: patients having an initial operation underwent bilateral surgery with visualisation of all parathyroid glands. MIBI and US used for pre-operative localisation Prior tests: no preselection based on MIBI and US Patient details: n=88 solitary, n=13 double, n=1 triple, n=12 hyperplasia, n=1 carcinoma (<1%) 9 had prior parathyroidectomy (7.8%)
Index test(s) and reference	<u>Index test</u> IOPTH: two-site immunochemiluminometric method with the Quick-Intraoperative intact PTH assay (Nichols Institute Diagnostics, USA).

Reference standard	Miura 2002³¹⁷			
	Serum intact PTH values were measured after induction of anaesthesia and again 10 minutes			
	Positive = drop of more than 50% from pre-incision at 10 minutes			
	<u>Reference standard</u> Accuracy for adequate gland excision. States all people had successful operations (defined as cure of hypercalcaemia after operation (mean follow-up 11 months, range 2–28 months)). Abnormal glands confirmed histologically.			
2×2 table	IOPTH	Reference standard +	Reference standard –	Total
	Index test +	92	3	95
	Index test –	20	0	20
	Total	112	3	115
Statistical measures	<u>Index text:</u> Sensitivity: 82.1% Specificity: 0%			
Source of funding	Supported in part by Mt. Zion/Health Systems, Friends of Endocrine Surgery, James Martin Foundation, and Toranomom Hospital, Tokyo, Japan.			
Limitations	Risk of bias: none Indirectness: none			

Reference	Morks 2001³²¹
Study type	Retrospective study (some data collected prospectively)
Countries and setting	The Netherlands, non-academic Hospital
Study methodology	Data source: medical records Recruitment: all patients with biochemically proven and surgically treated PHPT treated at the Reinier de Graaf Hospital from August 2002 to December 2007.
Number of patients	n = 65
Patient characteristics	Age, mean (range): 63 (29-84) years Gender (male to female ratio): 15:50

Reference	Morks 2001³²¹				
	<p>Ethnicity: not reported</p> <p>Inclusion criteria: biochemically proven PHPT (hypercalcaemia with a concomitant increase or inappropriately high level of serum PTH); IOPTH used for first operation for PHPT</p> <p>Exclusion criteria: lithium therapy, no IOPTH measurements performed, previously undergone parathyroid gland surgery</p> <p>Details of imaging tests and surgical intervention: all patients received pre-operative localisation studies consisting of nuclear scintigraphy (99m-Tc-sestamibi scan) and/or ultrasound investigation and/or spiral computed tomography (CT). Conventional neck exploration or MIP performed under general anaesthesia.</p> <p>Prior tests: no preselection based on prior tests</p> <p>Patient details: First time operation for all patients</p>				
Index test(s) and reference standard	<p><u>Index test</u> IOPTH: levels were measured before incision after induction of anaesthesia, directly before extirpation of the targeted gland, and 3, 6, 9 and 12 minutes after gland removal. Blood samples taken from peripheral venous catheter. IOPTH assessment was carried out using the Siemens Immulite 2500 analyser. Ethylenediaminetetra-acetic acid (EDTA) plasma was added to beads coated with affinity-purified polyclonal goat anti-bodies directed against PTH 44-84. After washing, affinity-purified polyclonal goat antibodies directed against PTH 1-34 conjugated to a marker enzyme were added and the amount of bound enzyme was measured.</p> <p>Positive = drop of 50% or more at 12 minutes compared to pre-incision value.</p> <p><u>Reference standard</u> Normocalcaemia for at least 3 months post-operatively. Pathological evaluation done.</p>				
2x2 table	IOPTH	Reference standard +	Reference standard -	Total	<p>Note: includes IOPTH results after excision of the first gland for some people with MGD (e.g. TN could be that IOPTH did not drop and they went on to have further abnormal glands identified or went on to have hypercalcaemia).</p>
	Index test +	55	1	56	
	Index test -	1	8	9	
	Total	56	9	65	
Statistical measures	<p><u>Index text: IOPTH</u> Sensitivity: 98.2% Specificity: 88.9%</p>				
Source of funding	Not reported				

Reference	Morks 2001 ³²¹
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none

Reference	Mozzon 2004 ³²⁵
Study type	Retrospective study
Countries and setting	France, University Surgical Unit
Study methodology	Data source: not reported Recruitment: neck explorations performed for PHPT using intraoperative PTH monitoring from April 2001 to February 2003
Number of patients	n = 268 (but n=263 available for analysis)
Patient characteristics	Age, mean (range): not reported Gender (male to female ratio): not reported Ethnicity: not reported Inclusion criteria: undergoing operation for PHPT Exclusion criteria: inadequate data on IOPTH; diagnosis of idiopathic hypercalciuria Details of imaging tests and surgical intervention: unilateral or bilateral neck exploration performed (unilateral performed when there was concordant localization of preoperative imaging, except in cases of goitre, MEN syndrome, and previous neck irradiation. Prior tests: no preselection of patients based on prior tests Patient details: n=7 reoperation (both their first and second case included in the 268) (2.6% - analysed in 1 st operation stratum) 4.5% had carcinoma or familial HPT; 3.5% presented with PHPT and chronic renal disease. n=207 unigland disease, n=61 multigland disease
Index test(s) and reference standard	<u>Index test</u> <u>IOPTH</u> : intraoperative PTH levels were measured with a rapid two-site IMCA (Nichols Advantage, Nichols Institute Diagnostics, Saint Clement, CA; normal range in our laboratory, 10–65 pg/mL).

Reference	Mozzon 2004³²⁵				
	Positive = drop >50% from baseline (highest of pre-incision or pre-excision) at 10 minutes (also reported 5 minute time point, but not extracted as 10 minute timepoint available; also reported 30 minute but not extracted as does not match review protocol).				
	<p><u>Reference standard</u> Successful parathyroidectomy (normal post-operative serum calcium and phosphorus at follow-up (range 3 days to 22 months)). 'Pathologic diagnosis' reported in methods.</p>				
2x2 table	IOPTH (10 min)	Reference standard +	Reference standard -	Total	Note: IOPTH results after excision of all glands in people with multigland disease
	Index test +	242	1	243	
	Index test -	12	8	20	
	Total	254	9	263	
Statistical measures	<p><u>Index test: IOPTH (10 min)</u> Sensitivity: 95.3% Specificity: 88.9%</p>				
Source of funding	not reported				
Limitations	<p>Risk of bias: none Indirectness: none</p>				

Reference	Nilsen 2006³⁴³
Study type	Prospective study
Countries and setting	Norway, University Hospital
Study methodology	<p>Data source: n/a</p> <p>Recruitment: consecutive patients undergoing surgery for HPT with IOPTH between December 2000 and May 2004.</p>
Number of patients	n = 100
Patient characteristics	Age, mean (range): 55 (22-82) years

Reference	Nilsen 2006³⁴³				
	<p>Gender (male to female ratio): 20:80</p> <p>Ethnicity: not reported</p> <p>Inclusion criteria: undergoing surgery for PHPT with IOPTH. Diagnosis of PHPT confirmed using serum intact PTH and calcium concentrations pre-operatively.</p> <p>Exclusion criteria: not reported</p> <p>Details of imaging tests and surgical intervention: all patients underwent preoperative tumour localization with a 99m-Tc-sestamibi scintigraphy. With convincing preoperative tumour localization, the surgeon directed the dissection to the anatomical location identified.</p> <p>Prior tests: no preselection of patients based on prior test</p> <p>Patient details: n=93 solitary, n=6 double, n=1 hyperplasia No previous neck explorations</p>				
Index test(s) and reference standard	<p><u>Index test</u> IOPTH: PTH was measured using an immunochemiluminometric assay (ICMA) from Diagnostic Products Corporation (Immulite turbo intact PTH assay). This assay, like other intact PTH assays, recognizes only intact PTH and very large amino-terminal truncated PTH fragments. All blood samples were obtained from a foot vein in the operating room at the induction of general anaesthesia (baseline) and 5 and 10 minutes after excision.</p> <p>Positive = drop of >50% of pre-incision at 5 or 10 minutes</p> <p><u>Index test</u> <u>MIBI</u>: details not reported Positive = not reported</p> <p><u>Reference standard</u> Post-operative normocalcaemia (states all patients were normocalcaemic post-operatively). In all patients the excised tissue was sent for pathological analysis.</p>				
2x2 table	IOPTH	Reference standard +	Reference standard -	Total	IOPTH results after excision of the first gland in people with multigland disease (i.e. TNs include people who went on to have another gland removed).
	Index test +	94	0	94	
	Index test -	0	6	6	
	Total	94	6	100	

Reference	Nilsen 2006³⁴³				
Statistical measures	Index text: IOPTH Sensitivity: 100% Specificity: 100%				
2x2 table	MIBI			Total	Correctly localised single n=88 (TPs) Negative imaging, final outcome single n=5 (FNs) Negative imaging, final outcome double n=1 (TNs) Predicted single but final outcome double n=5 (FPs) Predicted single but final outcome hyperplasia n=1 (FPs)
		'True positives' 88	'False positives' 6		
		'False negatives' 5	'True negatives' 1		
	Total	93	7	100	
Statistical measures	Index text: MIBI 'Sensitivity': 94.6% 'Specificity': 14.3%				
Source of funding	Not reported				
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none				

Reference	Nordin 2001³⁴⁷
Study type	Retrospective study
Countries and setting	Australia, Hospital
Study methodology	Data source: records Recruitment: adults who underwent SPECT in the unit for suspected or proven PHPT between 1994 and 1998.
Number of patients	n = 33 (results here for n=32 as 1 person had carcinoma)
Patient characteristics	Age, mean (range): 53 years (29-78 years) Gender (male to female ratio): 19:14 Ethnicity: not reported

Reference	Nordin 2001 ³⁴⁷				
	<p>Inclusion criteria: proven PHPT who underwent SPECT Exclusion criteria: not reported</p> <p>Details of imaging tests and surgical intervention: not reported</p> <p>Prior tests: no preselection based on prior tests</p> <p>Patient details: n=20 solitary, n=10 hyperplasia, n=2 no pathology detected “Newly diagnosed PHPT” (no previous surgery)</p>				
Index test(s) and reference standard	<p><u>Index test</u> SPECT: IV injection of 99m-Tc-sestamibi (600MBq). Planar images of the neck and thorax acquired at 15 minutes and 2 hours after injection. SPECT of the neck was performed at 30 minutes using an ADAC Vertex with 360° orbit and 64 steps of 5.6° per stop. Planar and SPECT images were interpreted by consensus of 2 experienced physicians.</p> <p>Positive = adenoma considered present if there was a focal area exhibiting washout delay posterior, lateral or inferior to the thyroid gland.</p> <p><u>Reference standard</u> Surgical and histopathological results. States there were no patients with persistent hypercalcaemia.</p>				
2×2 table	MIBI (SPECT)			Total	Correctly localised single n=19 (TPs) Incorrectly localised single n=1 (FNs) Negative imaging, final outcome hyperplasia n=7 (TNs) Negative imaging, no pathology found & normocalcaemic n=2 (TNs) Predicted single but final outcome hyperplasia n=1 (FPs) Correct prediction of hyperplasia n=2 (TNs)
		‘True positives’ 19	‘False positives’ 1		
		‘False negatives’ 1	‘True negatives’ 11		
	Total	20	12	32	
Statistical measures	<p><u>Index text: MIBI (SPECT)</u> ‘Sensitivity’: 95.0% ‘Specificity’: 91.7%</p>				
Source of funding	Author supported by the International Atomic Energy Agency.				
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none				

Reference	Orloff 2001³⁵⁵			
Study type	Prospective study			
Countries and setting	USA, Medical Centre			
Study methodology	Data source: n/a Recruitment: consecutive patients undergoing operation for primary HPT			
Number of patients	n = 23			
Patient characteristics	Age, mean range: 33-78 years Gender (male to female ratio): 10:13 Ethnicity: not reported Inclusion criteria: biochemically proven PHPT Exclusion criteria: not reported Details of imaging tests and surgical intervention: all patients underwent pre-operative sestamibi planar scintigraphy, pre-operative administration of methylene blue and surgical neck exploration. Unilateral or bilateral exploration performed. Prior tests: no preselection based on prior tests Patient details: n=18 solitary, n=2 double, n=3 hyperplasia First surgery / re-operation not reported			
Index test(s) and reference standard	<u>Index test</u> MIBI (planar): Tc-99m-sestamibi scan the day before surgery. Positive = not reported <u>Reference standard</u> Histological confirmation with both frozen section and permanent paraffin-embedded tissue examination. States all patients were cured of hypercalcaemia.			
2x2 table	MIBI		Total	Correctly localised single n=17 (TPs) Negative imaging, final outcome single n=1 (FNs)
		'True positives'	'False positives'	

Reference	Orloff 2001³⁵⁵			
	17	1		Negative imaging, final outcome hyperplasia n=1 (TNs) Predicted single but final outcome double n=1 (FPs) Correct prediction of hyperplasia n=1 (TNs) Predicted multiple glands but not all abnormal glands detected n=2 (TNs)
	'False negatives' 1	'True negatives' 4		
	Total 18	5	23	
Statistical measures	Index text: 'Sensitivity': 94.4% 'Specificity': 80.0%			
Source of funding	Not reported			
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none			

Reference	Ozkul 2015³⁵⁸
Study type	Retrospective study
Countries and setting	Turkey, Training and Research Hospital
Study methodology	Data source: not reported Recruitment: patients who had MIP due to PHPT at the unit between January 2013 and December 2013
Number of patients	n = 11
Patient characteristics	Age, mean (range): 49.23 (27-63) years Gender (male to female ratio): 4:9 Ethnicity: not reported Inclusion criteria: had MIP due to PHPT; biochemically proven PHPT with no previous surgery Exclusion criteria: familial disease; persistent recurrent disease; missing data due to lack of documentation; lacking proper work-up. Details of imaging tests and surgical intervention: imaged by at least 2 modalities, US and 99m-Tc-sestamibi with SPECT. If the imaging was not concordant, MRI, IOPH or frozen section analysis were requested. All patients underwent MIP under general anaesthesia.

Reference	Ozkul 2015 ³⁵⁸				
	<p>Prior tests: all underwent MIP but unclear if only selected people with a particular pre-operative imaging result.</p> <p>Patient details: n=10 solitary, n=1 hyperplasia no previous surgery</p>				
Index test(s) and reference standard	<p><u>Index test</u> MIBI (SPECT): 99m-Tc-sestamibi with SPECT (no further details reported)</p> <p>Positive = not reported</p> <p><u>Reference standard</u> Final pathology. 10 people showed normocalcaemia post-operatively, the remaining person had a second operation to confirm final pathology as hyperplasia.</p>				
2×2 table	MIBI (SPECT)			Total	Correctly localised single n=10 (TPs) Predicted double, final outcome hyperplasia n=1 (TNs)
		'True positives' 10	'False positives' 0		
		'False negatives' 0	'True negatives' 1		
	Total	10	1	11	
Statistical measures	<p><u>Index test: MIBI (SPECT)</u> 'Sensitivity': 100% 'Specificity': 100%</p>				
Source of funding	No financial support received				
Limitations	<p>Risk of bias: none Indirectness: none</p>				

Reference	Patel 1998 ³⁶⁵
Study type	Prospective study
Countries and setting	USA, academic tertiary care centre
Study methodology	Data source: n/a

Reference	Patel 1998 ³⁶⁵
	Recruitment: consecutive patients undergoing parathyroid exploration for adenoma or hyperplasia between January 1, 1995, and December 31, 1996.
Number of patients	n = 43 (but n=10 with hyperplasia had either secondary or tertiary HPT, so not included in the results below for IOPTH).
Patient characteristics	<p>Age, mean (SD): not reported</p> <p>Gender (male to female ratio): not reported</p> <p>Ethnicity: not reported</p> <p>Inclusion criteria: undergoing parathyroid exploration for adenoma or hyperplasia (diagnosis of hyperparathyroidism was determined biochemically based on serum values of calcium and PTH and urinary calcium levels as well as on clinical symptomatology).</p> <p>Exclusion criteria: not reported</p> <p>Details of imaging tests and surgical intervention: bilateral neck exploration and IOPTH. All patients with primary hyperparathyroidism who were suspected of having a parathyroid adenoma underwent preoperative localization with a technetium-99m sestamibi scan. All patients with suspected parathyroid adenoma underwent a technetium-99m sestamibi-directed unilateral cervical exploration with IOPTH. A contralateral neck exploration and biopsy of at least 1 normal gland was also performed in all patients with adenoma to assess the validity of the IOPTH. Patients with multiple gland hyperplasia underwent standard bilateral cervical explorations with rapid PTH sampling to confirm removal of all hyper functioning parathyroid tissue.</p> <p>Prior tests: no preselection based on prior tests</p> <p>Patient details: n=33 solitary First surgery / re-operation not reported</p>
Index test(s) and reference standard	<p><u>Index test</u> IOPTH: rapid PTH immunoradiometric assay was developed in the Department of Laboratory Medicine at Geisinger Medical Center through a simple, previously described modification of an intact PTH overnight assay method (Nichols Institute Diagnostics, San Juan Capistrano, Calif). All patients had peripheral venous blood samples obtained at the induction of general anaesthesia and 7 minutes after excision of all suspected hyper functioning parathyroid tissue.</p> <p>Positive = drop of >50% from pre-excision value at 7 minutes</p> <p><u>Reference standard</u> Post-operative normocalcaemia (minimum 9 month follow-up). Histological confirmation.</p>

Reference	Patel 1998³⁶⁵			
2×2 table	IOPTH	Reference standard +	Reference standard –	Total
	Index test +	32	0	
	Index test –	0	1	
	Total	32	1	33
Statistical measures	Index text: IOPTH Sensitivity: 100% Specificity: 100%			
Source of funding	Not reported			
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none			

Reference	Richards 2011³⁹¹
Study type	Retrospective study
Countries and setting	USA; tertiary referral hospital.
Study methodology	Data source: retrospective review of a prospective database Recruitment: patients who underwent an operation for primary HPT from June 1998 to November 2008 at the Mayo Clinic, Rochester, Minnesota, for people having IOPTH during a primary operation
Number of patients	n = 1882 (results available for n=1750 for IOPTH criteria used)
Patient characteristics	Age, mean (range): 61 (10-97) years (unclear how many <18 years) Gender (male to female ratio): 74.7% women Ethnicity: not reported Inclusion criteria: operation for primary HPT; had IOPTH during primary operation Exclusion criteria: not reported Details of imaging tests and surgical intervention: parathyroid subtraction scintigraphy was performed in 1731 patients (92.0%) and neck ultrasonography was obtained in 581 patients (30.9%). Fourteen patients (0.7%) underwent parathyroidectomy without any imaging.

Reference	Richards 2011 ³⁹¹				
	<p>Patients with imaging results that were highly suspicious for bilateral parathyroid disease underwent bilateral exploration. Those with equivocal imaging results on the contralateral side underwent bilateral exploration when the IOPTH level did not meet curative criteria after a focused exploration. Patients who met the curative criteria after a focused exploration did not undergo bilateral exploration.</p> <p>Prior tests: no preselection based on prior tests</p> <p>Patient details: n=1602 single, n=271 multigland disease All primary operation n=28 MEN (1.5%)</p>				
Index test(s) and reference standard	<p><u>Index test</u> IOPTH: Blood samples were obtained from the jugular vein, radial artery, or a peripheral vein. The baseline jugular vein samples were obtained either before dissection or after mobilization of the abnormal gland. Peripheral vein samples were obtained pre-incision. Intraoperative PTH levels were measured using a standard immunoradiometric assay with either the Immulite (Diagnostics Product Corporation, Los Angeles, California) or the Roche Cobas e411 (Roche Diagnostics Corporation, Indianapolis, Indiana) analyser.</p> <p>Positive = ≥50% drop from baseline (either pre-incision or pre-excision) at 10 minutes</p> <p><u>Reference standard</u> Cure (no hypercalcemia at 6 months or longer follow-up confirmed with biochemical results or personal communication of biochemical results via survey or telephone conversation with the patient). Pathology results reported.</p>				
2×2 table	IOPTH	Reference standard +	Reference standard -	Total	Suggests IOPTH results after excision of all glands for people with multigland disease (although if the surgery decided to stop after excision of the first gland, even though the IOPTH result was negative, that result was taken).
	Index test +	1533	50	1583	
	Index test -	62	105	167	
	Total	1595	155	1750	
Statistical measures	<p><u>Index text: IOPTH</u> Sensitivity: 96.1% Specificity: 67.7%</p>				
Source of funding	Not reported				
Limitations	<p>Risk of bias: none Indirectness: none</p>				

Reference	Rossi 2000³⁹⁷
Study type	Unclear
Countries and setting	USA, Medical Centre
Study methodology	Data source: n/a Recruitment: consecutive re-operations for HPT performed by 1 surgeon from February 1999 to February 2000.
Number of patients	n = 11
Patient characteristics	Age, mean (range): 58.3 (35-78 years) Gender (male to female ratio): 5:6 Ethnicity: not reported Inclusion criteria: hypercalcaemia and elevated PTH caused by PHPT; reoperation Exclusion criteria: not reported Details of imaging tests and surgical intervention: pre-operative studies included sestamibi and US in all patients, MRI in 4 patients, CT in 3, parathyroid arteriogram in 1 and selective venous sampling in 1. All patients underwent intraoperative Tc-99m-sestamibi scanning and IOPTH. Prior tests: no preselection based on prior tests Patient details: n=11 All reoperation (but only 8/11 reoperation for PHPT – 73%) – analyse separately for IOPTH (can subgroup for IOPTH as they were all TPs)
Index test(s) and reference standard	<u>Index test</u> IOPTH: intraoperative PTH immunochemiluminescent assay. Plasma from a neck or peripheral vein obtained prior to incision, after the thyroid gland was mobilised, and at 5 and 10 minutes post-excision. Positive = drop of >50% from baseline (unclear if pre-incision or pre-excision) at 5 or 10 minutes. <u>Index test</u>

Reference	Rossi 2000 ³⁹⁷				
	<p><u>MIBI</u>: pre-operatively all patients injected with 15mCi of technetium 99m sestamibi. Early images of the neck and chest were obtained at 3 hours post injection. The distribution of the sestamibi in the early and delayed images were compared. Positive = not reported</p> <p><u>Index test</u> <u>US</u>: high resolution US Positive = not reported</p> <p><u>Index test</u> <u>MRI</u>: not reported</p> <p><u>Index test</u> <u>CT</u>: not reported</p> <p><u>Reference standard</u> Pathology. States all had low or normal post-operative calcium levels.</p>				
2x2 table	IOPTH	Reference standard +	Reference standard -	Total	Analyse separately for 1 st operation (8TPs, n=8) and reoperation (3TPs, n=3).
	Index test +	11	0	11	
	Index test -	0	0	0	
	Total	11	0	11	
Statistical measures	<p><u>Index text</u>: IOPTH Sensitivity: 100% Specificity: -</p>				
2x2 table	MIBI			Total	Correctly localised single n=7 (TPs) Negative imaging, final outcome single n=4 (FNs)
		'True positives' 7	'False positives' 0		
		'False negatives' 4	'True negatives' 0		
	Total	11	0	11	
Statistical measures	<p><u>Index text</u>: MIBI 'Sensitivity': 63.6% 'Specificity': -</p>				
2x2 table	US			Total	Correctly localised single n=7 (TPs)

Reference	Rossi 2000³⁹⁷				
		'True positives' 7	'False positives' 0		Incorrectly localised single n=2 (FNs) Negative imaging, final outcome single n=2 (FNs)
		'False negatives' 4	'True negatives' 0		
	Total	11	0	11	
Statistical measures	<u>Index text: US</u> 'Sensitivity': 63.6% 'Specificity': -				
2x2 table	MRI			Total	Correctly localised single n=2 (TPs) Incorrectly localised single n=1 (FNs) Negative imaging, final outcome single n=1 (FNs)
		'True positives' 2	'False positives' 0		
		'False negatives' 2	'True negatives' 0		
	Total	4	0	4	
Statistical measures	<u>Index text: MRI</u> 'Sensitivity': 50.0% 'Specificity': -				
2x2 table	CT			Total	Correctly localised single n=1 (TPs) Negative imaging, final outcome single n=2 (FNs)
		'True positives' 1	'False positives' 0		
		'False negatives' 2	'True negatives' 0		
	Total	3	0	3	
Statistical measures	<u>Index text: CT</u> 'Sensitivity': 33.3% 'Specificity': -				
Source of funding	Not reported				
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none				

Reference	Rubello 2006⁴⁰¹
Study type	Prospective study
Countries and setting	Italy
Study methodology	Data source: n/a Recruitment: consecutive patients with clinically and biochemically confirmed PHPT were entered in this study between August 2004 and December 2004.
Number of patients	n = 54 (but only n=22 undergone surgery to date, so only 22 included in analysis here).
Patient characteristics	Age, mean (range): 54.8 (46-70) years Gender (male to female ratio): 6:16 Ethnicity: not reported Inclusion criteria: clinically and biochemically confirmed PHPT; eligible for MIRS (evidence at scintigraphy of a solitary adenoma; clear 99mTc-sestamibi uptake in the adenoma measured both at planar and at SPECT imaging) Exclusion criteria: concomitant thyroid nodules; history of familial hyperparathyroidism or multiple endocrine neoplasia; history of neck irradiation; previous thyroid or parathyroid surgery. Details of imaging tests and surgical intervention: all patients underwent the same single-day localisation imaging work-up, consisting of planar 99mTc-pertechnetate/99mTc-sestamibi subtraction scintigraphy as described previously followed by 99mTc-sestamibi SPECT imaging. Ultrasound (US) examination of the neck was also routinely obtained using a high-resolution 10-Mab transducer. Prior tests: only included people with evidence of a solitary adenoma on MIBI Patient details: n=22 solitary adenoma No previous thyroid or parathyroid surgery
Index test(s) and reference standard	<u>Index test</u> <u>IOPTH</u> : intraoperative quick parathyroid hormone (QPTH) assay was routinely measured by immunochemoluminescent assay (Liason, Byk Gulden, Italy). Positive = drop of 50% or more from pre-excision value at 10 minutes.

Reference	Rubello 2006⁴⁰¹				
	<p><u>Index test</u> MIBI (SPECT): SPECT scintigrams were obtained by a dual-head large-field-of-view (LFOV) gamma camera (e-CAM, Siemens, Hoffman Estates, IL) equipped with parallel-hole, low-energy, high-resolution collimators. Patients were injected with 150 MBq (4 mCi) of 99mTc-Per technetate. Twenty minutes later, 400 mg of potassium perchlorate (KClO₄) was administered orally to speed the thyroid wash-out of 99mTc-per technetate. A 10-min time interval is necessary before KClO₄ begins its action on the thyroid. Five minutes later, a 99mTc-per technetate thyroid image was acquired. Immediately afterwards, and without moving the patient, 550 MBq (15 mCi) of 99mTc-sestamibi was injected, followed by a flush of saline. After planar imaging SPECT imaging commenced.</p> <p>Positive = not reported</p> <p><u>Reference standard</u> No persistent PHPT in follow-up (ranging from 6 to 27 months). Definitive histopathology.</p>				
2x2 table	IOPTH	Reference standard +	Reference standard -	Total	IOPTH results after excision of all glands (as all had solitary adenoma)
	Index test +	22	0	22	
	Index test -	0	0	00	
	Total	22	0	22	
Statistical measures	<p><u>Index text: IOPTH</u> Sensitivity: 100% Specificity: -</p>				
2x2 table	MIBI (SPECT)			Total	Correctly localised single n=22 (TPs)
		'True positives' 22	'False positives' 0		
		'False negatives' 0	'True negatives' 0		
	Total	22	0	22	
Statistical measures	<p><u>Index text: IOPTH</u> 'Sensitivity': 100% 'Specificity': -</p>				
Source of funding	Not reported				
Limitations	Risk of bias: none Indirectness: sub selection of people suspected of having solitary adenoma (limitation for imaging but not IOPTH index test)				

Reference	Saaristo 2002⁴⁰⁹		
Study type	Prospective study		
Countries and setting	Finland, University Hospital		
Study methodology	Data source: n/a Recruitment: consecutive patients with PHPT on the waiting list for operation		
Number of patients	n = 20		
Patient characteristics	Age, mean (range): 60 (40-77) years Gender (male to female ratio): 3:17 Ethnicity: not reported Inclusion criteria: PHPT (verified by elevated serum ionised calcium and intact PTH concentrations, and low serum phosphatase level). Exclusion criteria: previous neck exploration Details of imaging tests and surgical intervention: pre-operative imaging with sestamibi and intraoperative localisation with a handheld gamma probe. Full collar exploration under general anaesthesia. Attempt made to visualise all 4 parathyroid glands. Prior tests: no preselection based on prior tests Patient details: n=16 solitary, n=4 hyperplasia All first surgery		
Index test(s) and reference standard	<p><u>Index test</u> MIBI: Tc-99m-sestamibi (740MBq) administered IV. Planar anterior images of the neck and mediastinum obtained using a high resolution parallel hole collimator. Immediate images were obtained 10-15 minutes after injection, and delayed images were taken at 3 hours.</p> <p>Positive = one nuclear medicine physician interpreted all the scans.</p> <p><u>Reference standard</u> Histological confirmation and states hypercalcaemia normalised in each patient (success of operation assessed by serum ionised calcium 2 months after the operation).</p>		
2x2 table	MIBI		Total
			Correctly localised single n=13 (TPs)

Reference	Saaristo 2002⁴⁰⁹				
		'True positives' 13	'False positives' 0		Incorrectly localised single n=2 (FNs) Negative imaging, final outcome single n=1 (FNs) Correctly localisation hyperplasia n=4 (TNs)
		'False negatives' 3	'True negatives' 4		
	Total	16	4	20	
Statistical measures	Index text: MIBI 'Sensitivity': 81.3% 'Specificity': 100%				
Source of funding	Not reported				
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none				

Reference	Sagan 2010⁴¹²
Study type	Retrospective study
Countries and setting	Poland, Thoracic surgery department, Medical University
Study methodology	Data source: not reported Recruitment: patients who underwent surgery for primary mediastinal parathyroid adenoma with IOPTH at the department from January 1999 to December 2008.
Number of patients	n = 33
Patient characteristics	Age, mean (SD): success at targeted PTx 49.45 (9.4) years; failed at targeted 47.86 (11.24) years Gender (male to female ratio): 20:12 Ethnicity: not reported Inclusion criteria: primary sporadic HPT who underwent surgery for primary mediastinal parathyroid adenoma with IOPTH. Diagnosis of HPT verified by elevated serum calcium and PTH levels. Exclusion criteria: not reported Details of imaging tests and surgical intervention: targeted mediastinal parathyroidectomy through either cervical or thoracic approach

Reference	Sagan 2010 ⁴¹²				
	<p>(site of surgery based on pre-operative imaging). US and sestamibi performed in all patients. Mediastinal work-up performed if cervical imaging negative. If difficulties in locating the adenoma were expected, localisation was aided by handheld gamma probe.</p> <p>Prior tests: no preselection based on prior tests</p> <p>Patient details: n=27 solitary, n=2 double, n=3 hyperplasia All had suspected ectopic adenoma First parathyroid operation</p>				
Index test(s) and reference standard	<p><u>Index test</u> IOPTH: measured with the Immulite 1000 TURBO intact PTH system (Diagnostic Products, USA) in blood drawn from a peripheral vein.</p> <p>Positive = drop >50% from pre-incision (immediately before surgical incision) at 10 minutes</p> <p><u>Reference standard</u> Postoperative normalisation of calcium. Pathological examination.</p>				
2x2 table	IOPTH	Reference standard +	Reference standard -	Total	After excision of first gland in people with multiple glands (can calculate both)
	Index test +	26	0		
	Index test -	0	7		
	Total	26	7		
Statistical measures	<p><u>Index text: IOPTH</u> Sensitivity: 100% Specificity: 100%</p>				
Source of funding	Not reported				
Limitations	<p>Risk of bias: none Indirectness: none</p>				

Reference	Sproue 2001 ⁴⁵⁷
Study type	Prospective study
Countries and setting	USA, University Hospital
Study methodology	Data source: n/a

Reference	Sprouse 2001⁴⁵⁷			
	Recruitment: all patients presenting with a biochemical diagnosis of PHPT between January 1997 and November 2000			
Number of patients	n = 56 (only included people with positive MIBI, this included n=9 who chose a bilateral approach but had pre-operative MIBI anyway).			
Patient characteristics	<p>Age, mean (range): in the 47 patients who selected MIP 69.3 (31-89) years</p> <p>Gender (male to female ratio): in the 47 patients who selected MIP 16:31</p> <p>Ethnicity: not reported</p> <p>Inclusion criteria: biochemical diagnosis of PHPT; patients who chose MIP Exclusion criteria: negative MIBI or suspicion of multigland disease; previous thyroid resection; recurrent or persistent HPT</p> <p>Details of imaging tests and surgical intervention: included patients who chose to have MIP (n=9 who chose to have a bilateral approach but had pre-operative MIBI data were also included). Patients selecting MIP whose MIBI suggested single gland disease at a specific location underwent a directed exploration after injection of local anaesthetic (at the site indicated by the MIBI)</p> <p>Prior tests: sub selection of people – excluded people with negative MIBI or suspicion of multigland disease (only included people with positive MIBI suggesting single gland disease)</p> <p>Patient details: n=52 solitary, n=1 double, n=3 hyperplasia All first surgery</p>			
Index test(s) and reference standard	<p><u>Index test</u> MIBI: performed in concordance with the Society for Nuclear Medicine's procedure guideline for parathyroid scintigraphy. Subtraction scanning with 123I was combined with MIBI in some cases at the discretion of the nuclear radiologist.</p> <p>Positive = not reported</p> <p><u>Reference standard</u> Pathology and normocalcaemia (3 people not rendered normocalcaemic by first operation, but on a subsequent operation were found to have hyperplasia by histology and were rendered normocalcaemic (so final outcome known)).</p>			
2×2 table	MIBI		Total	
	'True positives'	'False positives'		Correctly localised single n=51 (TPs)
	51	4		Incorrectly localised single n=1 (FNs)
	'False negatives'	'True negatives'		Predicted single, final outcome double n=1 (FPs)
	1	0		Predicted single, final outcome hyperplasia n=3 (FPs)

Reference	Sproue 2001⁴⁵⁷
	Total 52 4 56
Statistical measures	Index text: 'Sensitivity': 98.1% 'Specificity': 0.0%
Source of funding	Not reported*
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: sub selection of people suspected of having solitary adenoma

Reference	Stalberg 2006⁴⁵⁹
Study type	Retrospective study
Countries and setting	Australia, University Hospital
Study methodology	Data source: University of Sydney Endocrine Surgery Database Recruitment: consecutive patients with sporadic HPT undergoing MIP in the unit from June 2004 to October 2005
Number of patients	n = 100
Patient characteristics	Age, mean (range): 59.7 (22.4-85.8) years Gender (male to female ratio): 1:3 Ethnicity: not reported Inclusion criteria: sporadic PHPT and unequivocally single site of uptake on nuclear scan using Tc-99m-sestamibi on single photon emission tomography, who were undergoing MIP. PHPT defined as an inappropriate level of serum iPTH in the presence of hypercalcaemia without hypocalciuria Exclusion criteria: negative MIBI or MIBI indicating multiple sites of uptake (and undergoing standard bilateral exploration); any known hereditary HPT syndrome; secondary HPT; coincidental thyroid pathology; previous operation; lithium induced HPT. Details of imaging tests and surgical intervention: nuclear scan using Tc-99m-sestamibi on single photon emission tomography and focused US either by the radiologist pre-operatively or by the surgeon at operation, solely to guide incision placement. MIP undertaken using the lateral focused mini-incision technique. IOPTH was not used to guide decision making during the operation.

Reference	Stalberg 2006 ⁴⁵⁹				
	<p>Prior tests: sub selection of people with suspected single gland disease from MIBI results (people with negative MIBI and MIBI suggesting multiple sites excluded)</p> <p>Patient details: Previous operation excluded</p>				
Index test(s) and reference standard	<p><u>Index test</u> IOPTH: Immulite 2000 Intact PTH assay (DPC), a solid-phase, two-site chemiluminescent enzyme-labelled immunometric assay. Blood samples collected in EDTA plasma tubes.</p> <p>Positive = drop of 50% or more from the highest pre-incision or pre-excision value at 10 minutes</p> <p><u>Reference standard</u> Normocalcaemia at 6 months follow-up. Unclear if all had histological confirmation but 98 patients had cure after removal of a single adenoma (so histology not necessary) and for the other 2 patients, histology is mentioned in results.</p>				
2x2 table	IOPTH	Reference standard +	Reference standard -	Total	<p>Delayed decrease seen in come people at 30 minutes (analysed as FNs here as 30 minute time point not included in review protocol).</p> <p>IOPTH results after excision of the first gland</p>
	Index test +	89	0	89	
	Index test -	9	2	11	
	Total	98	2	100	
Statistical measures	<p><u>Index text: IOPTH</u> Sensitivity: 90.8% Specificity: 100%</p>				
Source of funding	Not reported				
Limitations	<p>Risk of bias: none Indirectness: none (sub selection of people suspected of having solitary adenoma not a limitation for IOPTH index test)</p>				

Reference	Stenner 2009 ⁴⁶⁴
Study type	Retrospective study
Countries and setting	Italy, Hospital
Study methodology	Data source:

Reference	Stenner 2009⁴⁶⁴				
	Recruitment: series of patients with PHPT from March 2005 to March 2008 undergoing minimally invasive video-assisted parathyroidectomy (MIVAP)				
Number of patients	n = 13 (but one patient had MEN, excluded from IOPTH results here, n=12 sporadic PHPT)				
Patient characteristics	<p>Age, median (range): 69 (33-86) years</p> <p>Gender (male to female ratio): 10:3</p> <p>Ethnicity: not reported</p> <p>Inclusion criteria: PHPT (diagnosed on the basis of serum calcium, PTH and clinical symptom) undergoing MIVAP with pre-operative US, sestamibi and IOPTH. Eligible for MIVAP if had single adenoma <35mm on pre-operative imaging without associated goiter, suspected carcinoma of the thyroid, secondary or recurrent HPT, previous neck surgery and previous radiation to the neck.</p> <p>Exclusion criteria: not reported</p> <p>Details of imaging tests and surgical intervention: pre-operative US and sestamibi. Surgery was MIVAP with IOPTH.</p> <p>Prior tests: sub selection of people with single adenoma <35mm on pre-operative imaging.</p> <p>Patient details: n=12 solitary Recurrent HPT and previous neck surgery excluded</p>				
Index test(s) and reference standard	<p><u>Index test</u> IOPTH: blood drawn before skin incision, PTH assay used was UniCel DxI 800 (Beckman Coulter, USA).</p> <p>Positive = drop >50% from pre-incision value at 10 minutes</p> <p><u>Reference standard</u> Eucalcaemia for 6 months or longer. Final histology.</p>				
2x2 table	IOPTH	Reference standard +	Reference standard -	Total	Narrative comment that in one person without a >50% drop at 10 minutes, another sample was taken at 20 minutes and a >50% drop found (however, methods don't state that the 20 minute time point was routinely assessed if there was no drop at 10 minutes, therefore analysed as a FN (unclear if other people with a negative IOPTH at 10 minutes would have had a 20 minute time point taken).
	Index test +	11	0	0	
	Index test -	1	0	0	
	Total	12	0	12	

Reference	Stenner 2009⁴⁶⁴
Statistical measures	Index text: IOPTH Sensitivity: 91.7% Specificity: -
Source of funding	Supported by Beckman Coulter grants (manufacturer of PTH assay)
Limitations	Risk of bias: none Indirectness: none (sub selection of people suspected of having solitary adenoma not a limitation for IOPTH index test)

Reference	Tampi 2014⁴⁷⁶
Study type	Prospective
Countries and setting	India, Hospital and research centre
Study methodology	Data source: n/a Recruitment: patients undergoing surgery for PHPT
Number of patients	n = 7
Patient characteristics	Age, range: 41-76 years Gender (male to female ratio): 3:4 Ethnicity: not reported Inclusion criteria: undergoing surgery for PHPT Exclusion criteria: not reported Details of imaging tests and surgical intervention: not reported Prior tests: no preselection based on prior tests Patient details: n=7 solitary First surgery / re-operation not reported

Reference	Tampi 2014⁴⁷⁶			
Index test(s) and reference standard	<p><u>Index test</u> IOPTH: blood sample drawn from a peripheral vein. PTH levels were estimated by the use of a rapid Electrochemiluminescence immunoassay (ECLIA) on the Cobas 6000 combi analyzer.</p> <p>Positive = drop of >50% from baseline (unclear if pre-incision or pre-excision) at 10 minutes</p> <p><u>Index test</u> Frozen Section (n=6): excised gland sent for frozen section examination</p> <p>Positive = not reported</p> <p><u>Reference standard</u> Normalisation of post-operative calcium. Histopathological confirmation.</p>			
2x2 table	IOPTH	Reference standard +	Reference standard -	Total
	Index test +	7	0	7
	Index test -	0	0	0
	Total	7	0	7
Statistical measures	<p><u>Index text: IOPTH</u> Sensitivity: 100% Specificity: -</p>			
2x2 table	Frozen section	Reference standard +	Reference standard -	Total
	Index test +	6	0	6
	Index test -	0	0	0
	Total	6	0	6
Statistical measures	<p><u>Index text: IOPTH</u> Sensitivity: 100% Specificity: -</p>			
Source of funding	Not reported			
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none			

Reference	Timm 2004⁴⁸⁶
Study type	Prospective study
Countries and setting	Germany
Study methodology	Data source: n/a Recruitment: consecutive patients with PHPT referred to the clinic between November 2000 and February 2002
Number of patients	n = 40 (n=35 had IOPTH)
Patient characteristics	Age, median (range): 54 (20-74) years Gender (male to female ratio): 18:22 Ethnicity: not reported Inclusion criteria: biochemically proven PHPT Exclusion criteria: not reported Details of imaging tests and surgical intervention: all patients had high resolution US and assessment of thyroid pathologies (endemic goiter region). Patients then had scintigraphy with SPECT. Open minimally invasive surgery (focusing on the 1 enlarged parathyroid gland) performed if identical localisation results by US and sestamibi and without thyroid pathology. Unilateral parathyroidectomy performed in people with a positive localisation study and concomitant multinodular thyroid pathology. Bilateral surgery performed in people with negative localisation studies, when an enlarged parathyroid could not be found at the described localisation or if IOPTH negative. Prior tests: no preselection based on prior tests Patient details: n=38 solitary, n=1 double, n=1 hyperplasia First surgery / re-operation not reported
Index test(s) and reference standard	<u>Index test</u> IOPTH: commercially available double antibody chemoluminescence quick PTH assay (Quick-Intraoperative Intact-PTH-Assay, Nichols Diagnostic Institute, USA). Pre-operative sample taken after intubation, prior to disinfection of the skin. Pre-excision drawn after identification of the suspected adenoma prior to resection. Positive = drop >50% from pre-operative or pre-excision levels at 10 minutes, if there was no drop at 10 minutes, samples were taken at

Reference	Timm 2004⁴⁸⁶				
	15 and 20 minutes.				
	<u>Reference standard</u> Accuracy for prediction of further glands after excision of first gland (persistent hypercalcaemia or further glands identified). Definite histopathological findings.				
2x2 table	IOPTH	Reference standard +	Reference standard -	Total	IOPTH results after excision of the first gland in people with multigland disease Note: method includes taking a 20 minute time point in people with a negative IOPTH at 10 minutes (can also calculate for only 10 minute time point – below)
	Index test +	33	0	33	
	Index test -	0	2	2	
	Total	33	2	35	
2x2 table	IOPTH	Reference standard +	Reference standard -	Total	10 minute time point only
	Index test +	28	0	28	
	Index test -	5	2	5	
	Total	33	2	35	
Statistical measures	<u>Index text: IOPTH (including 20 minute delayed timepoint in people without a fall at 10 minutes)</u> Sensitivity: 100% Specificity: 100% <u>Index text: IOPTH (10 minutes only)</u> Sensitivity: 84.8% Specificity: 100%				
Source of funding	Not reported				
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none				

Reference	van Ginhoven 2011⁵⁰²
Study type	Retrospective study (also some prospective collection of data)
Countries and setting	The Netherlands, non-academic centre (department of surgery)
Study methodology	Data source: medical records Recruitment: all patients with biochemically proven PHPT scheduled to undergo surgery from August 2004 to September 2008

Reference	van Ginhoven 2011 ⁵⁰²			
Number of patients	n = 50 (n=4 were excluded from the analysis as no definite outcome could be determined (n=2 not operated, n=2 not cured), therefore n=46)			
Patient characteristics	<p>Age, mean (range): 58 (20-82) years</p> <p>Gender (male to female ratio): 17:33</p> <p>Ethnicity: not reported</p> <p>Inclusion criteria: biochemically proven PHPT, a pre-operative surgeon-performed US and scheduled to undergo surgery. Exclusion criteria: not reported</p> <p>Details of imaging tests and surgical intervention: all patients received preoperative localisation studies consisting of MIBI and/or US (radiologist and/or surgery-performed) and/or CT. both conventional exploration and MIP (operation of choice for suspected single gland disease) performed under general anaesthesia. IOPTH performed during MIP.</p> <p>Prior tests: no preselection based on prior tests</p> <p>Patient details: n=44 first operation, n=4 second operation.</p>			
Index test(s) and reference standard	<p><u>Index test</u> <u>Surgeon-performed US</u>: performed by one of the endocrine surgeons at the outpatient clinic (none were performed in the operating room prior to surgery). The linear ray probe with a frequency of 3-12MHz was used. When a possible enlargement of the parathyroid gland was identified, colour Doppler US was used to determine the vascularity of the lesion.</p> <p>Positive = adenomas defined as any oval, elongated or lobulated lesions connected with the thyroid during swallowing without a central hilum.</p> <p><u>Reference standard</u> Perioperative surgical findings combined with an abnormal gland during pathological analysis and cure (normocalcaemic or hypocalcaemic with normal PTH levels). Uncured patients were left out of the analysis.</p>			
2x2 table	Surgeon US		Total	
	'True positives'	'False positives'		Correctly localised single n=37 (TPs)
	37	2		Incorrectly localised single n=1 (FNs)
	'False negatives'	'True negatives'		Imaging negative, final outcome single n=5 (FNs)
				Predicted single, final outcome multigland n=2 (FPs)

Reference	van Ginhoven 2011⁵⁰²			
	6	1		Correctly localised multigland n=1 (TNs)
Total	43	3	46	
Statistical measures	<u>Index text: Surgeon US</u> 'Sensitivity': 86.0% 'Specificity': 33.3%			
Source of funding	Not reported			
Limitations	Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none			

Reference	Vignali 2002⁵⁰⁴
Study type	Retrospective study
Countries and setting	Italy, University Hospital
Study methodology	Data source: not reported Recruitment: consecutive patients with sporadic PHPT undergoing parathyroidectomy in the period from March 1997 to May 2001
Number of patients	n = 206
Patient characteristics	Age, mean (range): males 51, females 58 (21-82) years Gender (male to female ratio): 46:160 Ethnicity: not reported Inclusion criteria: sporadic PHPT (all had hypercalcaemia and elevated PTH) Exclusion criteria: not reported Details of imaging tests and surgical intervention: 130 patients, selected on the basis of preoperative imaging (neck ultrasound and/or 99mTc-sestamibi) indicating the presence of a single adenoma, absence of goitre, and no previous neck surgery, underwent minimally invasive video-assisted parathyroidectomy, and 76 underwent a standard cervical approach. Prior tests: no preselection based on prior tests

Reference	Vignali 2002⁵⁰⁴				
	Patient details: First surgery / re-operation not reported				
Index test(s) and reference standard	<p><u>Index test</u> IOPTH: blood plasma samples drawn from a peripheral vein or occasionally from the internal jugular vein in EDTA tubes. PTH was measured by a quick immunochemiluminescent assay (Nichols Institute Diagnostic, San Juan Capistrano, CA, USA).</p> <p>Positive = drop >50% from the highest pre-incision (after induction of anaesthesia) or pre-excision (during manipulation of suspected adenoma) value at 10 minutes</p> <p><u>Reference standard</u> Normocalcaemia at follow-up. In results, mentions pathological examination to confirm pathology in people whose IOPTH did not fall after excision of the first gland.</p>				
2×2 table	IOPTH	Reference standard +	Reference standard -	Total	<p>Narrative comment in results that one of the people with a FN had a delayed drop >50% at 20 minutes (however, methods don't state that the 20 minute time point was routinely assessed if there was no drop at 10 minutes, therefore analysed as a FN (unclear if other people with a negative IOPTH at 10 minutes would have had a 20 minute time point taken).</p> <p>IOPTH results after excision of first gland in people with multigland disease (those who had a negative IOPTH and went on to either have further glands removed, or hypercalcaemia counted as TNs) (can calculate both).</p>
	Index test +	192	3	195	
	Index test -	2	9	11	
	Total	194	12	206	
Statistical measures	<p><u>Index text:</u> Sensitivity: 99.0% Specificity: 75.0%</p>				
Source of funding	University grants				
Limitations	<p>Risk of bias: none Indirectness: none</p>				

Reference	Wade 2012⁵⁰⁸				
Study type	Retrospective study				
Countries and setting	USA, Medical College				
Study methodology	Data source: chart review of single institution Recruitment: patients with sporadic PHPT who underwent parathyroidectomy between December 1999 and December 2008				
Number of patients	n = 58 (study divides into 2 groups based on pre-operative ionised calcium, but all results combined in analysis here).				
Patient characteristics	Age, mean (range): elevated iCa 58; normal iCa 60 (25-86) years Gender (male to female ratio): 11:47 Ethnicity: not reported Inclusion criteria: sporadic, normocalcaemic PHPT (defined as normocalcaemic if they had no elevated serum calcium values during the 3 months prior to surgery). Exclusion criteria: persistent, recurrent, familial, secondary, or tertiary HPT Details of imaging tests and surgical intervention: Most of the patients underwent preoperative localization imaging (cervical ultrasonography (US), technetium-99m (99mTc)-labelled sestamibi scanning, or both). Prior tests: no preselection based on prior tests Patient details: n=50 single; n=9 multigland disease Persistent and recurrent HPT excluded				
Index test(s) and reference standard	<u>Index test</u> IOPTH: details reported elsewhere ⁵³³ Positive = drop by ≥50% from the highest baseline (either pre-incision or at time of parathyroid removal, time zero) value at 10 minutes (study also reports for a drop of 50% or more and into the normal range, not required by review protocol). <u>Reference standard</u> Normal serum calcium at last follow-up (all but 1 had normal serum calcium at last follow-up, but this person developed recurrent disease after 6 months, therefore none had persistent hypercalcaemia). Pathology.				
2x2 table	IOPTH	Reference standard +	Reference standard -	Total	Results of IOPTH after excision of all glands in

Reference	Wade 2012⁵⁰⁸				
	Index test +	55	0	51	people with multigland disease.
	Index test -	3	0	7	
	Total	58	0	58	
Statistical measures	<u>Index text:</u> Sensitivity: 94.8% Specificity: -				
Source of funding	No financial disclosures				
Limitations	Risk of bias: none Indirectness: none				

Reference	Wei 1997⁵¹⁵
Study type	Prospective study
Countries and setting	Georgia, Medical College of Georgia Hospital
Study methodology	Data source: n/a Recruitment: consecutive patients with hypercalcaemia and a diagnosis of PHPT between December 1992 and January 1996
Number of patients	n = 22
Patient characteristics	Age, mean (range): 50.5 (22-76) years Gender (male to female ratio): 7:15 Ethnicity: not reported Inclusion criteria: hypercalcaemia and a diagnosis of sporadic PHPT (diagnosis confirmed by total and ionised calcium levels and intact PTH) Exclusion criteria: family history of HPT; prior neck surgery Details of imaging tests and surgical intervention: all patients underwent dual-phase Tc-99m-sestamibi scanning and bilateral exploration. The side of the neck where the adenoma was localised was explored first. An attempt was made to identify all parathyroid glands within the surgical field.

Reference	Wei 1997⁵¹⁵			
	<p>Prior tests: no preselection of the basis of prior tests</p> <p>Patient details: n=19 solitary (1 ectopic), n=3 hyperplasia. No prior parathyroid surgery</p>			
Index test(s) and reference standard	<p><u>Index test</u> MIBI: dual-phase Tc-99m-sestamibi scanning using Tc-99m-sestamibi alone. A 1.5 hour delayed image followed by a 3 hour delayed scan and whole mediastinal view. 148MBq of Tc-99m-sestamibi administered intravenously and 15 2-minute images acquired with a gamma camera with a high resolution parallel hole collimator. The 2nd to 15th images were added together and the composite image normalised to the thyroid image</p> <p>Positive = scans interpreted by a single independent observer.</p> <p><u>Reference standard</u> All patients had correction of hypercalcaemia (one required a second operation to confirm an ectopic adenoma) and pathology. Normal parathyroid glands biopsied and confirmed histologically.</p>			
2x2 table	MIBI		Total	Correctly localised single n=16 (TPs) Incorrectly localised single n=2 (FNs) Imaging negative, final outcome single n=1 (FNs) Imaging negative, final outcome hyperplasia n=1 (TNs) Predicted single, final outcome hyperplasia n=2 (FPs)
	'True positives'	'False positives'		
	16	2		
	'False negatives'	'True negatives'		
	3	1		
	Total	19	3	22
Statistical measures	<p><u>Index test: MIBI</u> 'Sensitivity': 84.2% 'Specificity': 33.3%</p>			
Source of funding	Not reported			
Limitations	Risk of bias: none Indirectness: none			

Reference	Witteveen 2011⁵²⁴
Study type	Retrospective study

Reference	Witteveen 2011 ⁵²⁴
Countries and setting	The Netherlands, University Medical Centre
Study methodology	Data source: patients' hospital records Recruitment: control group with sporadic PHPT who had a scan before initial surgery
Number of patients	n = 42 (only able to calculate 2x2 table values for the first surgery subgroup (n=23). Not all patients undergoing re-operative surgery were cured, so final outcome unknown).
Patient characteristics	Age, mean (SD): first surgery (n=23) 59 (12) years Gender (male to female ratio): first surgery 2:21 Ethnicity: not reported Inclusion criteria: patients with persistent PHPT who had a scan before reoperative surgery or patients with sporadic PHPT due to single gland disease who had a scan before initial surgery (only initial surgery subgroup included in analysis in this review, n=23). Exclusion criteria: not reported Details of imaging tests and surgical intervention: SPECT following by bilateral, unilateral or MIP surgery. Bilateral neck exploration consisted of visualization of all four parathyroid glands. Unilateral neck exploration and minimally invasive neck exploration were guided by IOPTH. Prior tests: sub selection of people with single gland disease Patient details: n=19 solitary adenoma, n=4 single hyperplastic gland removed. First surgery n=23
Index test(s) and reference standard	<u>Index test</u> <u>MIBI (SPECT)</u> : technetium 99m sestamibi single emission computed tomography (Tc99m-MIBI-SPECT). After IV injection of 500 MBq of Tc99m MIBI, planar images of the head and neck region and chest were performed. Scintigraphy was performed as a dual-phase single tracer examination. Images were acquired 15 min and 2 h after injection of the radiopharmaceutical. A gamma camera (Toshiba GCA-7200, Tokyo, Japan) equipped with low-energy high-resolution collimators was used for image acquisition. SPECT was performed 90 min after the injection. The filtered back projection was used for image reconstruction, using a Butterworth filter (8 order, subset 12). Positive = All Tc99m-MIBI-SPECT scans were reviewed by an experienced nuclear medicine physician who was blinded to the outcome

Reference	Witteveen 2011⁵²⁴			
	of the surgical procedure.			
	<u>Reference standard</u> Cure (sustained normal serum calcium and PTH concentrations more than 6 months) and histological confirmation			
2x2 table	MIBI (SPECT)		Total	Correctly localised single n=14 (TPs) Incorrectly localised single n=1 (FNs) Imaging negative, final outcome single n=8 (FNs)
		'True positives' 14	'False positives' 0	
		'False negatives' 9	'True negatives' 0	
	Total	23	0	
Statistical measures	<u>Index text: MIBI (SPECT)</u> 'Sensitivity': 60.9% 'Specificity': -			
Source of funding	Not reported			
Limitations	Risk of bias: none Indirectness: sub selection of people with single gland disease			

Reference	Ypsilantis 2010⁵³⁷
Study type	Retrospective review
Countries and setting	UK, district general hospital
Study methodology	Data source: not reported Recruitment: consecutive patients with PHPT who underwent MIP with IOPTH at a district general hospital over 6 months
Number of patients	n = 11
Patient characteristics	Age, mean (range): 61 (46-67) years Gender (male to female ratio): 9:2 Ethnicity: not reported

Reference	Ypsilantis 2010⁵³⁷				
	<p>Inclusion criteria: patients with PHPT who underwent MIP with IOPTH Exclusion criteria: not reported</p> <p>Details of imaging tests and surgical intervention: preoperative assessment with ultrasound and sestamibi scans then underwent MIP with IOPTH. However, 3 patients underwent planned full neck exploration facilitated by IOPTH.</p> <p>Prior tests: no preselection based on prior tests</p> <p>Patient details: n=10 solitary, n=1 double First surgery / re-operation not reported</p>				
Index test(s) and reference standard	<p><u>Index test</u> IOPTH: intact PTH was assayed by a sandwich electrochemiluminescence immunoassay</p> <p>Positive = drop $\geq 50\%$ from baseline (immediately after excision, time zero) within 15 minutes (at 5, 10 or 15 minutes)</p> <p><u>Reference standard</u> Post-operative normocalcaemia and histological confirmation.</p>				
2x2 table	IOPTH	Reference standard +	Reference standard -	Total	IOPTH results after excision of the first gland in people with multigland disease (i.e. TN if the person went on to have more abnormal glands located)
	Index test +	10	0	10	
	Index test -	0	1	1	
	Total	10	1	11	
Statistical measures	<p><u>Index text: IOPTH</u> Sensitivity: 100% Specificity: 100%</p>				
Source of funding	Did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.				
Limitations	<p>Risk of bias: unclear if only people with sporadic PHPT were included and whether people with familial PHPT or MEN were excluded Indirectness: none</p>				