

Appendix D: Clinical evidence tables

Reference	Bonjer 1997⁸⁴
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 Inclusion criteria: hyperparathyroidism confirmed by the findings of raised concentrations of serum parathyroid hormone by a two-site immunoassay; patients with pre-operative sestamibi scan. Exclusion criteria: patients about to undergo first operation of familial HPT, MEN, and secondary and tertiary HPT. 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. Prior tests: no preselection based on prior imaging 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 1 st operation (n=21) and re-operation (n=4). n=27 solitary adenoma (n=25 PHPT).
Index test(s)	Index test (unable to calculate 2x2 table values for US)

Reference and reference standard	Bonjer 1997⁸⁴				
	<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	25	Analyse separately for 1 st operation (17TPs, 4FNs, n=21) and reoperation (4TPs, n=4).
Statistical measures	<p><u>Index text: MIBI</u> 'Sensitivity': 84% 'Specificity': -</p>				
Source of funding	Not reported				
Limitations	Risk of bias: none Indirectness: none				

Study	Peacock 2005⁴⁸²
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	N/A (n=18 patients who had re-operation) [n=78 all participants]
Countries and setting	Conducted in USA
Line of therapy	Mixed line
Duration of study	Intervention time: 52 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: See inclusion criteria

Study	Peacock 2005 ⁴⁸²
Stratum	Patients with failed primary surgery for primary hyperparathyroidism
Subgroup analysis within study	Not applicable
Inclusion criteria	Serum calcium concentration between 10.3 mg/dL (2.57 mmol/L) and 12.5 mg/dL (3.12 mmol/L), and plasma PTH concentration >45 pg/mL. Parathyroid hormone was measured on ≥2 occasions ≥7 days apart during the 12-month before baseline.
Exclusion criteria	Pregnancy; creatinine clearance < 50 ml/min; treatment with bisphosphonates/fluoride within 90 days before baseline; familial hypocalciuric hypercalcaemia; fasting urine calcium/creatinine in mg (molar) ratio less than 0.05 (0.14); requirement for drugs which are metabolised by P450 2D6 (CYP2D6) and have a narrow therapeutic index (e.g. flecainide, thioridazine, tricyclic antidepressants).
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age (overall sample) - Mean (range): 62 (27 - 83). Gender (M:F): 21:57. Ethnicity: Not reported
Further population details	1. Adjusted serum calcium: Not stated / Unclear (See inclusion criteria). 2. Presence of end-organ effects (end organ effects defined as kidney stones, history of fragility fractures or osteoporosis [BMD T-score <-2.5 at any site]): Not stated / Unclear
Extra comments	Adults with PHPT. Women on stable doses of selective oestrogen receptor modulators or oestrogen replacement therapy were eligible. Usually, similar studies exclude people who are on hormone replacement therapy.
Indirectness of population	No indirectness
Interventions	(n=9) Intervention 1: Calcimimetics - Cinacalcet. 30 mg twice daily, but if patients were still hypercalcaemic (serum calcium > 10.3 mg/dL) then the dose was increased to 40 mg twice daily at Week 4 and increased to 50 mg twice daily at Week 8. Duration 52 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=9) Intervention 2: Placebo. 30 mg twice daily, but if the patients were still hypercalcaemic the dose was increased to 40 mg twice daily at Week 4 and 50 mg twice daily at Week 8. Duration 52 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Study funded by industry (Amgen Inc.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CINACALCET versus PLACEBO	
Protocol outcome 1: Persistent hypercalcaemia - Actual outcome: Proportion of participants who achieved a mean serum calcium of ≤10.3 mg/dL (2.57 mmol/L) and a reduction from baseline of	

Study	Peacock 2005 ⁴⁸²
≥0.5 mg/dL (0.12 mmol/L) at 24/52 weeks; Group 1: 7/9, Group 2: 1/9; Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: Some difference in baseline mean plasma parathyroid hormone (SD) was observed: Cinacalcet 105 (36) vs. Placebo 120 (54) pg/mL.	
Protocol outcomes not reported by the study	Health related quality of life; Mortality; Preservation of end organ functions (bone mineral density, fractures, renal stones and renal function); Deterioration in renal function; Cardiovascular events; Adverse events; Cancer incidence

Reference	Rossi 2000 ⁵²⁶
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

Reference	Rossi 2000 ⁵²⁶				
	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	<p><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.</p> <p>Positive = drop of >50% from baseline (unclear if pre-incision or pre-excision) at 5 or 10 minutes.</p> <p><u>Index test</u> MIBI: 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 sestamibi in the early and delayed images was compared. Positive = not reported</p> <p><u>Index test</u> US: high resolution US Positive = not reported</p> <p><u>Index test</u> MRI: not reported</p> <p><u>Index test</u> CT: 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: IOPTH</u> Sensitivity: 100% Specificity: -</p>				
2x2 table	MIBI			Total	Correctly localised single n=7 (TPs) Negative imaging, final outcome single n=4 (FNs)
		'True positives'	'False positives'		

Reference	Rossi 2000 ⁵²⁶			
	7	0		
	'False negatives' 4	'True negatives' 0		
Total	11	0	11	
Statistical measures	<u>Index text: MIBI</u> 'Sensitivity': 63.6% 'Specificity': -			
2x2 table	US		Total	Correctly localised single n=7 (TPs) Incorrectly localised single n=2 (FNs) Negative imaging, final outcome single n=2 (FNs)
	'True positives' 7	'False positives' 0		
	'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	

Reference	Rossi 2000 ⁵²⁶
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