Appendix D: Clinical evidence tables

Study	Ambrogini 2007[7]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Italy; Setting: Referral centre
Line of therapy	Mixed line
Duration of study	Intervention + follow up: Patients followed up to 1 year post-surgery (6 month intervals)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: The PHPT diagnosis was based on increased ionised (>132 mmol/L) or albumin-corrected serum calcium (>10.2 mg/dL [2.55 mmol/L]), with increased (>65 pg/mL [65 ng/L]) or inappropriately normal intact parathyroid hormone.
Stratum	Overall
Subgroup analysis within study	Post-hoc subgroup analysis: Presence/absence of osteoporosis
Inclusion criteria	Patients with mild PHPT who did not meet any of the National Institutes of Health (NIH) criteria for surgery. Asymptomatic PHPT; albumin-corrected serum calcium of <1 mg/dL above the upper limit of normal (11.2 mg/dL [2.8 mmol/L]) on ≥3 occasions; 24-hour urine calcium excretion <400 mg (10 mmol); creatinine clearance in the normal range or reduce by ≤30% compared with age-matched normal people; age- and sex-matched BMD at the distal third of radius to be Z>-2.0; age between 50 and 75 years
Exclusion criteria	Symptomatic disease (nephrolithiasis, osteitis fibrosa cystica, prevalent fragility fractures); familial PHPT; menopause <3 years; disease/therapies affecting the skeleton; current thyroid disease requiring surgery; contraindications to surgery; previous neck surgery
Recruitment/selection of patients	Between January 2002 and September 2005, 412 consecutive patients with PHPT were referred to the Department of Endocrinology at the University Hospital of Pisa. Of these individuals, 198 already met the National Institutes of Health (NIH) criteria for surgery. Of the 214 potentially eligible patients, 161 were excluded for several reasons, and the remaining 53 were asked to participate in the study
Age, gender and ethnicity	Age - Mean (SD): Intervention = 64 (6) vs. Control = 65 (6). Gender (M:F): 4:46. Ethnicity: Not reported
Further population details	1. Adjusted serum calcium: <2.85 mmol/L 2. Age: ≥50 years old 3. Creatinine clearance: ≥ 60 mL/min (study reports as not less than 30% age-matched value). 4. 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]): mixed (people with kidney stones and fractures excluded, some people had osteoporosis but subgroups analysis done within study) (Based on guidelines prior to 2002 so does not exclude people with osteoporosis

Study	Ambrogini 2007[7]
	[subgroup analysis done of people with osteoporosis]. Does not exclude people with osteoporosis based on the T score but does exclude people with low BMD Z score <-2).
Extra comments	[The study began before the 2002 Workshop on Asymptomatic PHPT, therefore, the older guidelines formed the basis for the inclusion criteria. Had the criteria of the 2002 Workshop on Asymptomatic PHPT been adopted, 29 of the 50 participants would have met these criteria for surgery]
Indirectness of population	No indirectness
Interventions	(n=24) Intervention 1: Surgery (parathyroidectomy) – minimally invasive surgery. Two experienced parathyroid surgeons performed all surgery, using the minimally invasive approach when the abnormal gland was identified by pre-operative imaging. Four of the 24 subjects who underwent surgery required standard neck exploration because of equivocal or negative pre-operative imaging studies. Duration: Single surgery. Concurrent medication/care: No patient was given oral calcium supplements. Indirectness: No indirectness (n=26) Intervention 2: Conservative management. Not described. Duration N/A. Concurrent medication/care: Not described. Indirectness: No indirectness Comments: Details about care have not been provided for this control group.
Funding	Academic or government funding (Ministero dell'Istruzione, dell'Universita e della Ricerca Scientifica Rome and the University of Pisa)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MINIMALLY INVASIVE SURGERY versus NO SURGERY

Protocol outcome 1: Quality of life
- Actual outcome: Quality of life (SF-36) at 6 months post-surgery; 0 - 100 Top=High is good outcome; The results were reported as graphs and not as numerical values. Significant beneficial effect of surgery on QOL for the following domains: bodily pain (P=0.001), general health (P=0.008), vitality (P=0.003), mental health (P=0.017);
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 1, Reason: One patient developed chronic myeloid leukaemia 4 months after randomisation.
- Actual outcome: Psychosocial well-being (SCL-90R) at 6 months post-surgery; 0 - 100 Top=High is good outcome; The results were reported as statements about whether there were any differences between the two groups (and p values for some of the domains), and no numerical values were reported.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - It is indicated that no difference was found between the two groups but this is neither supported by numbers nor charts. Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 1, Reason: One patient developed chronic myeloid leukaemia 4 months after randomisation.

Study	Ambrogini 2007[7]

Protocol outcome 2: Fractures (vertebral or long bone)
- Actual outcome: Clinical vertebral fragility fracture at During 1 year post-surgery; Group 1: 0/24, Group 2: 1/25
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 1, Reason: One patient developed chronic myeloid leukaemia 4 months after randomisation.

Protocol outcome 3: Occurrence of kidney stones
- Actual outcome: Kidney stones at During 1 year post-surgery; Group 1: 0/24, Group 2: 1/25
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 1, Reason: One patient developed chronic myeloid leukaemia 4 months after randomisation.

Protocol outcome 4: Bone mineral density (BMD; distal radius or lumbar spine)
- Actual outcome: Lumbar spine (L1-L4) BMD at 1 year post-surgery (change score – described as % change from baseline [% change of g/cm^2 presumed]); Group 1: mean 4.16 % (SD 1.1); n=24, Group 2: mean -1.12 % (SD 0.71); n=25; Comments: p=0.0002
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 1, Reason: One patient developed chronic myeloid leukaemia 4 months after randomisation.
- Actual outcome: Distal radius BMD at 1 year post-surgery (change score - described as % change from baseline [% change of g/cm^2 presumed]); Group 1: mean -0.34 % (SD 0.59); n=24, Group 2: mean -0.55 % (SD 0.53); n=25; Comments: p=0.68
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 1, Reason: One patient developed chronic myeloid leukaemia 4 months after randomisation.

Protocol outcome 5: Adverse events (including voice change and hypoparathyroidism)
- Actual outcome: Surgical complications (such as laryngeal nerve dysfunction) at During 1 year post-surgery; Group 1: 0/24, Group 2: 0/25
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 1, Reason: One patient developed chronic myeloid leukaemia 4 months after randomisation and not analysed due to chemotherapy

Protocol outcome 6: Cancer
- Actual outcome: chronic myeloid leukaemia at During 1 year post-surgery; Group 1: 0/24, Group 2: 1/25
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 1, Reason: One patient developed chronic myeloid leukaemia 4 months after randomisation.

Study	Ambrogini 2007[7]
Protocol outcomes not reported by the study	Mortality; Deterioration in renal function; Persistent hypercalcaemia; Cardiovascular events

Study	Clifton-Bligh 2015[27]
Study type	Non-randomised comparative study
Number of studies (number of participants)	1 (n=561)
Countries and setting	Conducted in Australia; Setting: Hospital
Line of therapy	1st line
Duration of study	Follow up (post intervention): average follow-up not reported
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Before 1972 the diagnosis of PHPT was made if surgical removal of a parathyroid tumour restored eucalcaemia, or if full investigation failed to find another cause of hypercalcaemia; after 1972 the diagnosis of PHPT was made if the serum calcium and serum PTH were above the upper limit of the reference range.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosed with PHPT (before 1972 the diagnosis of PHPT was made if surgical removal of a parathyroid tumour restored eucalcaemia, or if full investigation failed to find another cause of hypercalcaemia; after 1972 the diagnosis of PHPT was made if the serum calcium and serum PTH were above the upper limit of the reference range).
Exclusion criteria	Not reported
Recruitment/selection of patients	All patients diagnosed with PHPT between 1961 and 1994. Medical records were obtained and death registers checked.
Age, gender and ethnicity	Age - Mean (SD): Surgery: 52.9 (14.7); non-surgery: 55.5 (15.9). Gender (M:F): Not reported. Ethnicity: not reported
Further population details	1. Adjusted serum calcium: Not stated / Unclear 2. Age: Not stated / Unclear 3. Creatinine clearance: Not stated / Unclear 4. 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
Indirectness of population	No indirectness
Interventions	(n=448) Intervention 1: Surgery (parathyroidectomy) - 4-gland or bilateral exploration: not reported. Duration: one off surgery (average follow-up not reported). Concurrent medication/care: not reported. Indirectness: No indirectness

Study	Clifton-Bligh 2015[27]
	(n=113) Intervention 2: Conservative management. Duration: average follow-up not reported. Concurrent medication/care: not reported. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARATHYROIDECTOMY versus CONSERVATIVE MANAGEMENT Protocol outcome 1: Mortality - Actual outcome: Death register record at not reported; Group 1: n=448 ; Group 2: n=113; HR 0.67; Lower CI 0.38 to Upper CI 1.18; Comments: Compared with the non-surgically treated group, the hazard ratio of death for the surgically treated group adjusted for age sex and time of diagnosis was 0.67 (0.38-1.18; P=0.167) (Cox proportional hazard multivariate analysis) Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: There was no significant difference in age between groups but the serum calcium and the serum PTH were significantly lower in the non-surgically treated group; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life; Deterioration in renal function; Fractures (vertebral or long bone); Occurrence of kidney stones; Persistent hypercalcaemia; Bone mineral density (BMD; distal radius or lumbar spine); Cardiovascular events; Adverse events (including voice change and hypoparathyroidism); Cancer

Study	Elvius 1995[34]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=48)
Countries and setting	Conducted in Sweden; Setting: Health screening programme
Line of therapy	1st line
Duration of study	Intervention + follow up: Single surgery then 3 years of follow-up
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: No detail given on how hyperparathyroidism was diagnosed, except to report that female patients with moderately raised serum calcium concentrations who were free of symptoms of the disease were randomised.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Not provided
Exclusion criteria	Not provided

Study	Elvius 1995[34]
Recruitment/selection of patients	Between 1971 and 1973, 15,903 employees of the City and County of Stockholm took part in a health screening survey. Hyperparathyroidism was diagnosed in 68 of the subjects. Twenty of these underwent elective operations and the remaining 48 female patients who were free of symptoms were randomised to two treatment groups.
Age, gender and ethnicity	Age - Mean (SD): 58 (3). Gender (M:F): All women. Ethnicity: Not reported
Further population details	1. Adjusted serum calcium: Not stated / Unclear 2. Age: Not stated / Unclear 3. Creatinine clearance: Not stated / Unclear 4. 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	Female patients with moderately raised serum calcium concentrations who were free of symptoms of the disease. No details given for subgroups except that women were diagnosed with asymptomatic HPT
Indirectness of population	Serious indirectness: Not specified whether the participants had 'primary' HPT or other types of HPT
Interventions	(n=26) Intervention 1: Surgery (parathyroidectomy) - 4-gland or bilateral exploration. No detail given. Duration Single surgery. Concurrent medication/care: Not reported. Indirectness: No indirectness Comments: In each surgery case, a parathyroid adenoma was removed. (n=22) Intervention 2: Conservative management. Non-operative conservative management. Duration: Up to 3 years. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Academic or government funding (Serafimer Hospital Research Fund)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARATHYROIDECTOMY versus CONSERVATIVE MANAGEMENT

Protocol outcome 1: Deterioration in renal function

- Actual outcome: Narrative comment that kidney function remained within normal limits during the study period at 17 years; Group 1: 0/12, Group 2: 0/8

Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: For baseline characteristics (age, BMI, postmenopausal age), comparison was only made between the two intervention groups combined and the selected, healthy control population. The baseline characteristics between the two intervention arms were not compared; Group 1 Number missing: 14, Reason: Oestriol taken by one patient. Other reasons not reported. Group 2 Number missing: 14, Reason: Eight had undergone parathyroidectomy during the follow-up (in the absence of evidence of aggregated hypercalcaemia or development of symptomatic disease). Oestriol taken by two patients. Other reasons not reported.

Protocol outcome 2: Bone mineral density (BMD; distal radius or lumbar spine)

- Actual outcome: Bone mineral content (described in paper as g/cm but g/cm^2 presumed) at 17 years; Group 1: mean 0.98 g/cm (SD 0.21); n=12, Group

Study	Elvius 1995[34]
2: mean 1.03 g/cm (SD 0.18); n=8 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: For baseline characteristics (age, BMI, postmenopausal age), comparison was only made between the two intervention groups combined and the selected, healthy control population. The baseline characteristics between the two intervention arms were not compared.; Group 1 Number missing: 14, Reason: Oestriol taken by one patient. Other reasons not reported. ; Group 2 Number missing: 14, Reason: Eight had undergone parathyroidectomy during the follow-up (in the absence of evidence of aggregated hypercalcaemia or development of symptomatic disease). Oestriol taken by two patients. Other reasons not reported	
Protocol outcomes not reported by the study	Quality of life; Mortality; Fractures (vertebral or long bone); Occurrence of kidney stones; Persistent hypercalcaemia; Cardiovascular events; Adverse events (including voice change and hypoparathyroidism); Cancer

Study	Rao 2004[64]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=53)
Countries and setting	Conducted in USA; Setting: hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: Single surgery + Minimum of 24 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Hypercalcaemia was defined as serum Ca>10.1 mg/dL or >2.52 mmol/L. See inclusion criteria for more detail.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 50–75 years; mean of ≥3 albumin-adjusted serum calcium levels 10.1–11.5 mg/dL (2.52–2.87 mmol/L); intact parathyroid hormone level >20 pg/mL (>20 ng/L); normal renal function (serum creatinine <1.5 mg/dL); forearm bone mineral density within 2 S.D. adjusted for age, sex and race (Z-scores); absence of relevant symptoms and complications directly attributable to either hypercalcaemia or excess parathyroid hormone secretion; willingness to participate and ability to give informed consent for a randomised trial of parathyroidectomy; living within a 150-mile radius of the Henry Ford Hospital.
Exclusion criteria	Familial hyperparathyroidism; previous neck surgery or current thyroid disease requiring surgical intervention; non-traumatic vertebral/hip fractures; nephrolithiasis in past 2 years; women within 5 years of menopause; taking medications known to affect bone and mineral metabolism (e.g. glucocorticoids, anticonvulsants, bisphosphonates); unexpected echocardiographic findings that precluded surgery

Study	Rao 2004[64]
Recruitment/selection of patients	Patients were recruited between June 1994 and March 1997 from within the Henry Ford Health System by either physician referral or centralised laboratory computer tracking of all patients with hypercalcaemia.
Age, gender and ethnicity	Age - Mean (SD): Surgery = 67 (7) vs. Observation = 63 (7). Gender (M:F): 11:42. Ethnicity: Black:White = 25:28
Further population details	1. Adjusted serum calcium: <2.85 mmol/L 2. Age: ≥50 years old 3. Creatinine clearance: ≥ 60 mL/min (study states serum creatinine <1.5 mg/dL (<133 umol/L)). 4. 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]): Absence of end-organ effects (excluded people with non-traumatic vertebral or hip fractures and nephrolithiasis. Forearm bone mineral density within 2 S.D. adjusted for age, sex and race [Z-scores]).
Extra comments	Patients with mild asymptomatic PHPT generally representative of the vast majority of patients with contemporary PHPT.
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Surgery (parathyroidectomy) - 4-gland or bilateral exploration. The surgery was performed by an experienced parathyroid surgeon, who attempted to identify 4 parathyroid glands in each patient and resected only the grossly abnormal parathyroid gland(s). No localising imaging study was performed. Duration: One-off surgery. Concurrent medication/care: No detail given. Indirectness: No indirectness Comments: Majority of the participants (23/25) underwent parathyroidectomy within 3 months of randomisation. One participant refused surgery after randomisation but had successful parathyroidectomy a year later, and the other participant did not have surgery in the end. At least one abnormal parathyroid gland was found in each patient. (n=28) Intervention 2: Conservative management. No surgery. The participants were followed up every 6 months for at least 24 months. Duration: Minimum of 24 months. Concurrent medication/care: No detail given. Indirectness: No indirectness Comments: Ultimately, 3 of the 28 participants in the observation group had parathyroidectomy during the follow-up period because one patient developed a small kidney stone 2 years after randomisation; another patient developed pancreatitis; and a third patient developed fatigue, irritability and depression.
Funding	Academic or government funding (NIH Grant DK 43858)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARATHYROIDECTOMY versus OBSERVATION

Protocol outcome 1: Quality of life
- Actual outcome: Quality of life at Minimum of 24 months; SF-36 assessed the following nine domains: [1] physical functioning, [2] social functioning, [3]

Study	Rao 2004[64]
	physical problem, [4] emotional problem, [5] mental health, [6] energy/fatigue, [7] pain, [8] health perception, [9] health change. In comparison with the patients who did not have surgery a statistically significant beneficial effect of parathyroidectomy was seen in 2/9 domains: social function (group difference: p=0.007) and emotional role function. A small decline was seen in 6/9 domains but only that of physical function was significant (p=0.022). In the observation group, a significant worsening occurred in 5/9 domains: social functioning, physical problem, emotional problem, energy, and health perception (p=0.013 to <0.0001). Apart from nine graphs (i.e. nine domains) charting annual changes over 36 months in the two groups and the earlier descriptive text, no other data (e.g. numerical values) were provided in relation to SF-36. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: The mean age of the parathyroidectomy group was older than that of the observation group (p=0.03). All other demographic and biochemical features were similar between the two groups; Group 1 Number missing; Group 2 Number missing Protocol outcome 2: Deterioration in renal function - Actual outcome: Renal dysfunction at Minimum of 24 months; Group 1: 0/25, Group 2: 0/28 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: The mean age of the parathyroidectomy group was older than that of the observation group (p=0.03). All other demographic and biochemical features were similar between the two groups; Group 1 Number missing; Group 2 Number missing Protocol outcome 3: Fractures (vertebral or long bone) - Actual outcome: Skeletal fractures (X-ray performed to assess vertebral fractures) at Minimum of 24 months; Group 1: 0/25, Group 2: 0/28 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: The mean age of the parathyroidectomy group was older than that of the observation group (p=0.03). All other demographic and biochemical features were similar between the two groups; Group 1 Number missing; Group 2 Number missing Protocol outcome 4: Occurrence of kidney stones - Actual outcome: Development of kidney stones at Minimum of 24 months; Group 1: 0/25, Group 2: 1/28 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: The mean age of the parathyroidectomy group was older than that of the observation group (p=0.03). All other demographic and biochemical features were similar between the two groups; Group 1 Number missing; Group 2 Number missing Protocol outcome 5: Bone mineral density (BMD; distal radius or lumbar spine) - Actual outcome: Annual change in lumbar spine BMD at Minimum of 24 months; mean values given but without measure of variance (1.2% and 0.5%, respectively). BMD increase significance: parathyroidectomy p<0.001 vs. observation p=0.087 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: The mean age of the parathyroidectomy group was older than that of the

Study	Rao 2004[64]
observation group (p=0.03). All other demographic and biochemical features were similar between the two groups; Group 1 Number missing; Group 2 Number missing - Actual outcome: Annual change in forearm BMD at Minimum of 24 months; mean values given but without measure of variance (0.4% and 0.2%, respectively). BMD increase significance: parathyroidectomy p<0.001 vs. observation p=0.047 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: The mean age of the parathyroidectomy group was older than that of the observation group (p=0.03). All other demographic and biochemical features were similar between the two groups; Group 1 Number missing; Group 2 Number missing Protocol outcome 6: Adverse events (including voice change and hypoparathyroidism) - Actual outcome: Number of participants developing any adverse events at Minimum of 24 months; Group 1: 2/25, Group 2: 3/28; Comments: p=0.67 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: The mean age of the parathyroidectomy group was older than that of the observation group (p=0.03). All other demographic and biochemical features were similar between the two groups; Group 1 Number missing; Group 2 Number missing	
Protocol outcomes not reported by the study	Mortality; Persistent hypercalcaemia; Cardiovascular events; Cancer

Study (subsidiary papers)	Scandinavian Investigation on Primary Hyperparathyroidism (SIPH) trial: Bollerslev 2007[13] (Lundstam 2015[51 50])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=191)
Countries and setting	Conducted in Denmark, Norway, Sweden; Setting: hospital
Line of therapy	Mixed line
Duration of study	Intervention + follow up: Single surgery then follow-up at 2, 5 and 10 years (end of study)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: The diagnosis of PHPT was based on elevated fasting serum calcium values on 3 occasional days corrected for variation in albumin levels, and ≥2 serum measurements of intact parathyroid hormone to be above the mean of the reference interval at the local laboratory.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Untreated & asymptomatic PHPT; 2.60 ≤ serum calcium ≤ 2.85 mmol/L; age between 50 and 80 years; no

Study (subsidiary papers)	Scandinavian Investigation on Primary Hyperparathyroidism (SIPH) trial: Bollerslev 2007[13] (Lundstam 2015[51] [50])
	medications interfering with calcium metabolism; informed consent
Exclusion criteria	Hyperparathyroid bone disease; previous neck operation; impaired kidney function (creatinine level > 130 µmol/L); kidney stones; complicating medical conditions; psychiatric disorders; multiple endocrine neoplasia / familial hypocalciuric hypercalcaemia / familial hyperparathyroidism
Recruitment/selection of patients	The participants were recruited between 1999 and 2005 in Sweden (n=126), Norway (n=55) and Denmark (n=10).
Age, gender and ethnicity	Age - Mean (SD): 64.2 (7.4). Gender (M:F): 26:165. Ethnicity: Not reported
Further population details	1. Adjusted serum calcium: <2.85 mmol/L 2. Age: ≥50 years old 3. Creatinine clearance: Not stated / Unclear (excluded impaired kidney function [creatinine level > 130umol/l]). 4. 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]): Absence of end-organ effects
Extra comments	Adults with mild asymptomatic PHPT.
Indirectness of population	No indirectness
Interventions	(n=96) Intervention 1: Surgery (parathyroidectomy) - minimally invasive surgery. Parathyroidectomy by an experienced parathyroid surgeon. Duration N/A. Concurrent medication/care: In the surgery group, 14 were on oestrogens and 2 on bisphosphonates. Indirectness: No indirectness Comments: Participants in the surgery group were seen 3 months after surgery for safety reasons and then once yearly. Complications of surgery (e.g. hypocalcaemia), were treated according to local traditions. In the case of unsuccessful primary operation, a secondary operation was offered according to the protocol. However, no patients were operated on more than once. (n=95) Intervention 2: Conservative management. No details given. Duration N/A. Concurrent medication/care: In the medical observation group, 9 patients received oestrogens and 3 bisphosphonates. Indirectness: No indirectness Comments: Participants in the medical observation group were seen 3 months after randomisation for safety reasons and then yearly. If conservatively followed patients developed symptoms or indications for surgery or demanded surgery, they were offered surgery. By the end of the inclusion period, a total of 10 patients randomised to medical observation were surgically treated. In the statistical analyses, they were regarded as medical observation patients (Intention-to-Treat).
Funding	Academic or government funding (The study was supported by the Norwegian Research Council. Several of the authors had received lecture fees from industry [Amgen, Biovitrum, Novartis, Novo Nordisk, Pfizer, Nycomed])

Study (subsidiary papers)	Scandinavian Investigation on Primary Hyperparathyroidism (SIPH) trial: Bollerslev 2007[13] (Lundstam 2015[51] [50])

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARATHYROIDECTOMY versus OBSERVATION

Protocol outcome 1: Quality of life
- Actual outcome: Quality of life at 1 year and 2 years; 0 - 100 Top=High is good outcome; The quality of life results based on SF-36 scores are reported as charts and not as numerical values. Statistical significance was provided for selected domains and time points only.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - The quality of life results are reported as charts and specific numerical values are not given; Indirectness of outcome: No indirectness; Group 1 Number missing; Group 2 Number missing

Protocol outcome 2: Mortality
- Actual outcome: Number of deaths in 5 years at 5 years; Group 1: 2/96, Group 2: 1/95
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - After 5 years, a total of 145 participants were still included in the protocol. For various reasons, 32 participants withdrew from the study (Surgery = 15 vs. Observation = 17), data were missing from 11 participants (Surgery = 7 vs. Observation = 4), and 3 participants died (Surgery = 2 vs. Observation = 1). Over the 5 years, 12 participants in the observation group underwent parathyroidectomy (5 due to increasing calcium levels and 7 for personal reasons). As the intention-to-treat analysis was applied, these 12 participants remained in the observation group.
Indirectness of outcome: No indirectness; Group 1 Number missing: 22, Reason: 15 withdrew from the study and 7 are missing; Group 2 Number missing: 21, Reason: 17 withdrew from the study and 4 are missing

Protocol outcome 3: Fractures (vertebral or long bone)
- Actual outcome: Number of new vertebral fractures in 5 years (assessed by radiograph) at 5 years; Group 1: 0/51, Group 2: 5/55; Comments: Group difference: p=0.058. 5 new vertebral fractures in 5 patients, all females in the OBS group. Four of the new vertebral fractures occurred in patients with no previous history of vertebral fractures. One of the new fractures was a progression of a fracture present already at baseline, in a vertebra containing a hemangioma, with an increase in score from 1 to 2.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - After 5 years, a total of 145 participants were still included in the protocol. For various reasons, 32 participants withdrew from the study (Surgery = 15 vs. Observation = 17), data were missing from 11 participants (Surgery = 7 vs. Observation = 4), and 3 participants died (Surgery = 2 vs. Observation = 1). Over the 5 years, 12 participants in the observation group underwent parathyroidectomy (5 due to increasing calcium levels and 7 for personal reasons). As the intention-to-treat analysis was applied, these 12 participants remained in the observation group.
Indirectness of outcome: No indirectness; Group 1 Number missing: 43, Reason: 15 withdrew from the study, 7 are missing, 21 did not have a follow-up X-ray; Group 2 Number missing: 39, Reason: 17 withdrew from the study, 4 are missing, 18 did not have a follow-up X-ray
- Actual outcome: Number of patients experiencing minor traumatic peripheral skeletal fractures in 5 years at 5 years; Group 1: 3/51, Group 2: 4/55
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - After 5 years, a total of 145 participants were still included in the protocol. For various reasons, 32 participants withdrew from the study (Surgery = 15 vs. Observation = 17), data were missing from 11 participants (Surgery = 7 vs. Observation = 4), and 3 participants died

Study (subsidiary papers)	Scandinavian Investigation on Primary Hyperparathyroidism (SIPH) trial: Bollerslev 2007[13] (Lundstam 2015[51] [50])
(Surgery = 2 vs. Observation = 1). Over the 5 years, 12 participants in the observation group underwent parathyroidectomy (5 due to increasing calcium levels and 7 for personal reasons). As the intention-to-treat analysis was applied, these 12 participants remained in the observation group. Indirectness of outcome: No indirectness; Group 1 Number missing: 43, Reason: 15 withdrew from the study, 7 are missing, 21 did not have a follow-up X-ray; Group 2 Number missing: 39, Reason: 17 withdrew from the study, 4 are missing, 18 did not have a follow-up X-ray Protocol outcome 4: Occurrence of kidney stones - Actual outcome: Number of patients developing radiological signs of new kidney stones in 5 years at 5 years; Group 1: 1/51, Group 2: 1/55; Comments: These were radiological signs of new stones in the urinary tract. No patients experienced clinical symptoms of renal calculi during the study period. Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - After 5 years, a total of 145 participants were still included in the protocol. For various reasons, 32 participants withdrew from the study (Surgery = 15 vs. Observation = 17), data were missing from 11 participants (Surgery = 7 vs. Observation = 4), and 3 participants died (Surgery = 2 vs. Observation = 1). Over the 5 years, 12 participants in the observation group underwent parathyroidectomy (5 due to increasing calcium levels and 7 for personal reasons). As the intention-to-treat analysis was applied, these 12 participants remained in the observation group. ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 43, Reason: 15 withdrew from the study, 7 are missing, 21 did not have a follow-up X-ray; Group 2 Number missing: 39, Reason: 17 withdrew from the study, 4 are missing, 18 did not have a follow-up X-ray Protocol outcome 5: Bone mineral density (BMD; distal radius or lumbar spine) - Actual outcome: Lumbar spine BMD Z-score at 5 years at 5 years; Group 1: mean 0.39 (SD 1.4); n=58, Group 2: mean -0.09 (SD 1.35); n=53; Comments: Validated DXA scans were only available for 111 participants. Difference in change between groups after 5 years: p=0.024. Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - After 5 years, a total of 145 participants were still included in the protocol. For various reasons, 32 participants withdrew from the study (Surgery = 15 vs. Observation = 17), data were missing from 11 participants (Surgery = 7 vs. Observation = 4), and 3 participants died (Surgery = 2 vs. Observation = 1). Over the 5 years, 12 participants in the observation group underwent parathyroidectomy (5 due to increasing calcium levels and 7 for personal reasons). As the intention-to-treat analysis was applied, these 12 participants remained in the observation group. Indirectness of outcome: No indirectness; Group 1 Number missing: 35, Reason: 15 withdrew from the study, 7 are missing, 2 died and 14 were missing DXA scans at follow-up; Group 2 Number missing: 42, Reason: 17 withdrew from the study, 4 are missing, 1 died and 20 were missing DXA scans at follow-up Actual outcome: Radius 33% (BMD, g/cm^2) at 5 years; Group 1: mean 0.614 (SD 0.11); n=40, Group 2: mean 0.584 (SD 0.11); n=46 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Reasons for withdrawals during the inclusion period are explained, however, reasons for cases lost to follow-ups are not provided. There are discrepancies between the numbers provided in the text and those provided on the patient flow chart (Appendix 1, Supplemental Data); Indirectness of outcome: No indirectness; Group 1 Number missing: 40; Group 2 Number missing: 36 - Actual outcome: Ultra-distal radius (BMD, g/cm^2) at 5 years; Group 1: mean 0.304 (SD 0.08); n=39, Group 2: mean 0.297 (SD 0.08); n=46 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Reasons for withdrawals during the inclusion period are explained, however, reasons for cases lost to follow-ups are not provided. There are discrepancies between the numbers provided in the text and those provided on the patient flow chart (Appendix 1, Supplemental

Study (subsidiary papers)	Scandinavian Investigation on Primary Hyperparathyroidism (SIPH) trial: Bollerslev 2007[13] (Lundstam 2015[51] [50])
Data); Indirectness of outcome: No indirectness; Group 1 Number missing: 40; Group 2 Number missing: 36 Protocol outcome 6: Cardiovascular events - Actual outcome: Number of patients with cardiovascular complications in 5 years at 5 years; Group 1: 5/72, Group 2: 8/73 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - After 5 years, a total of 145 participants were still included in the protocol. For various reasons, 32 participants withdrew from the study (Surgery = 15 vs. Observation = 17), data were missing from 11 participants (Surgery = 7 vs. Observation = 4), and 3 participants died (Surgery = 2 vs. Observation = 1). Over the 5 years, 12 participants in the observation group underwent parathyroidectomy (5 due to increasing calcium levels and 7 for personal reasons). As the intention-to-treat analysis was applied, these 12 participants remained in the observation group; Indirectness of outcome: No indirectness; Group 1 Number missing: 24, Reason: 15 withdrew from the study, 7 are missing and 2 died; Group 2 Number missing: 22, Reason: 17 withdrew from the study, 4 are missing and 1 died Protocol outcome 7: Cancer - Actual outcome: Number of patients developing malignancies in 5 years at 5 years; Group 1: 3/72, Group 2: 1/73 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - After 5 years, a total of 145 participants were still included in the protocol. For various reasons, 32 participants withdrew from the study (Surgery = 15 vs. Observation = 17), data were missing from 11 participants (Surgery = 7 vs. Observation = 4), and 3 participants died (Surgery = 2 vs. Observation = 1). Over the 5 years, 12 participants in the observation group underwent parathyroidectomy (5 due to increasing calcium levels and 7 for personal reasons). As the intention-to-treat analysis was applied, these 12 participants remained in the observation group; Indirectness of outcome: No indirectness; Group 1 Number missing: 24, Reason: 15 withdrew from the study, 7 are missing and 2 died; Group 2 Number missing: 22, Reason: 17 withdrew from the study, 4 are missing and 1 died	
Protocol outcomes not reported by the study	Deterioration in renal function; Persistent hypercalcaemia; Adverse events

Study	Talpos 2000[83]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=53)
Countries and setting	Conducted in USA; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: Single surgery + Up to 2 years of follow-up
Method of assessment of guideline	Adequate method of assessment/diagnosis: See inclusion criteria

Study	Talpos 2000[83]
condition	
Stratum	Overall
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	Age 50–75 years; persistent albumin-adjusted serum calcium level 10.1–11.5 mg/dL (2.52–2.87 mmol/L) (normal level < 10.1 mg/dL) from at least 3 measurements over a period of at least 3 months; intact parathyroid hormone level > 20 pg/mL; no other cause for hypercalcaemia; women at least 5 years after menopause; willingness to participate and ability to give consent to a RCT; living within 150-mile radius of downtown Detroit; not currently enrolled in any other clinical trial.
Exclusion criteria	Polyuria/Polydipsia/Anorexia/Nausea/Vomiting; pancreatitis in the past 1 year; symptomatic peptic ulcer disease; objective muscle weakness; history of non-traumatic vertebral/hip fractures; nephrolithiasis in the past 2 years; history of glucocorticoid/anticonvulsant drug therapy; thiazide diuretic therapy for hypertension cannot be changed; family history of PHPT / multiple endocrine neoplasia / benign hypocalciuric hypercalcaemia; evidence of thyroid disease requiring surgery; history of childhood irradiation to head/neck; presence of any of the following abnormalities (mean of 3 corrected serum calcium > 11.5 mg/dL, mean of 3 serum creatinine determinations > 1.5 mg/dL, creatinine clearance level < 70%, forearm BMD >2 SD below the expected value, phalangeal sub periosteal resorption on hand radiographs, vertebral compression fractures, urolithiasis on kidneys/ureter/bladder, unexpected findings on echocardiogram that preclude surgery)
Recruitment/selection of patients	All patients who were referred to the Division of Bone and Mineral Metabolism or the Department of Surgery between April 1994 and March 1997, who met the criteria were invited to participate in the study.
Age, gender and ethnicity	Age - Other: Mean age for operative group = 66.7 vs. observation group = 62.6; p<0.03. Gender (M: F): 11:42. Ethnicity: White = 28; Black = 25
Further population details	1. Adjusted serum calcium: <2.85 mmol/L 2. Age: ≥50 years old 3. Creatinine clearance: ≥ 60 mL/min (study reports an exclusion criteria of having a creatinine clearance level < 70%). 4. 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]): Absence of end-organ effects (exclusion criteria were forearm BMD >2 SD below the expected value, vertebral compression fractures, urolithiasis on kidneys/ureter/bladder, history of non-traumatic vertebral/hip fractures; nephrolithiasis in the past 2 years).
Extra comments	Asymptomatic patients with confirmed PHPT.
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Surgery (parathyroidectomy) - 4-gland or bilateral exploration. All patients randomised to surgery underwent standard parathyroidectomy with a bilateral approach by a single experienced surgeon who had performed >600 parathyroid procedures before the start of the study. Duration: Single surgery. Concurrent medication/care: Routine postoperative care was provided which included frequent calcium

Study	Talpos 2000[83]
	determinations during the average 2-day hospitalisation. Calcium carbonate and magnesium supplements were administered as needed before and after discharge. Indirectness: No indirectness (n=28) Intervention 2: Conservative management. No detail given. Duration: Up to 2 years. Concurrent medication/care: No detail given. Indirectness: No indirectness
Funding	Academic or government funding (National Institutes of Health grant)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARATHYROIDECTOMY versus OBSERVATION

Protocol outcome 1: Quality of life

- Actual outcome: Annual change estimate for SF-36 physical functioning at 2 years; MD; -2.103 (SE: 1.70), Comments: SE calculated from P value of the mean difference;

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: 2 people refused surgery but were analysed in the intervention group on an ITT basis; Group 2 Number missing: 0

- Actual outcome: Annual change estimate for SF-36 social functioning at 2 years; MD; 3.918 (SE: 1.39), Comments: SE calculated from P value of the mean difference;

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: 2 people refused surgery but were analysed in the intervention group on an ITT basis; Group 2 Number missing: 0

- Actual outcome: Annual change estimate for SF-36 physical role functioning at 2 years; MD; 0.392 (SE: 3.17), Comments: SE calculated from P value of the mean difference;

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: 2 people refused surgery but were analysed in the intervention group on an ITT basis; Group 2 Number missing: 0

- Actual outcome: Annual change estimate for SF-36 emotional role functioning at 2 years; MD; 5.955 (SE: 2.29), Comments: SE calculated from P value of the mean difference ;

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: 2 people refused surgery but were analysed in the intervention group on an ITT basis; Group 2 Number missing: 0

- Actual outcome: Annual change estimate for SF-36 mental health at 2 years; MD; 0.225 (SE: 0.92), Comments: SE calculated from P value of the mean difference;

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Study	Talpos 2000[83]
Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: 2 people refused surgery but were analysed in the intervention group on an ITT basis; Group 2 Number missing: 0 - Actual outcome: Annual change estimate for SF-36 vitality at 2 years; MD; 0.970 (SE: 1.10), Comments: SE calculated from P value of the mean difference; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: 2 people refused surgery but were analysed in the intervention group on an ITT basis; Group 2 Number missing: 0 - Actual outcome: Annual change estimate for SF-36 bodily pain at 2 years; MD; 0.649 (SE: 1.63), Comments: SE calculated from P value of the mean difference; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: 2 people refused surgery but were analysed in the intervention group on an ITT basis; Group 2 Number missing: 0 - Actual outcome: Annual change estimate for SF-36 general health at 2 years; MD; 1.815 (SE: 1.12), Comments: SE calculated from P value of the mean difference; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: 2 people refused surgery but were analysed in the intervention group on an ITT basis; Group 2 Number missing: 0 - Actual outcome: Annual change estimate for SF-36 health transition at 2 years; MD; 0.116 (SE: 1.64), Comments: SE calculated from P value of the mean difference; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2, Reason: 2 people refused surgery but were analysed in the intervention group on an ITT basis; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Mortality; Deterioration in renal function; Fractures (vertebral or long bone); Occurrence of kidney stones; Persistent hypercalcaemia; Bone mineral density (BMD; distal radius or lumbar spine); Cardiovascular events; Adverse events (including voice change and hypoparathyroidism); Cancer

Study (subsidiary papers)	Vanderwalde 2006[87] (Vanderwalde 2009[88])
Study type	Non-randomised comparative study
Number of studies (number of participants)	1 (n=1569)
Countries and setting	Conducted in USA; Setting: Hospital
Line of therapy	1st line

Study (subsidiary papers)	Vanderwalde 2006[87] (Vanderwalde 2009[88])
Duration of study	Follow up (post intervention): Retrospective cohort study with a follow-up of 7.4 years (range: 13 days to 10 years).
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: People on the database defined as having PHPT if they had an intact parathyroid hormone (PTH) level greater than 65 pg/mL, a calcium level greater than 10.5 mg/dL (>2.6 mmol/L), and a creatinine level less than 2.5 mg/dL (<221.0 µmol/L). Excluded patients likely to have tertiary HPT or with a history of chronic renal failure requiring dialysis (see exclusion criteria).
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with an intact parathyroid hormone (PTH) level greater than 65 pg/mL, a calcium level greater than 10.5 mg/dL (>2.6 mmol/L), and a creatinine level less than 2.5 mg/dL (<221.0 µmol/L)
Exclusion criteria	<20 years old. To ensure that no patient was included who had tertiary HPT, any patient who had at least 2 separate blood samples drawn for measurement of cyclosporine (laboratory procedure code 8718671), tacrolimus (FK 506;laboratory procedure code 8203004), or sirolimus (laboratory procedure code 8718652) levels was considered to be a probable kidney transplant recipient and excluded. A second database, the Southern California Kaiser Permanente Discharge Abstract Database, was used to exclude patients with any history of chronic renal failure requiring dialysis (International Classification of Diseases, Ninth Revision [ICD-9] code 585.6).
Recruitment/selection of patients	Retrospective cohort study. Screened the Southern California Kaiser Permanente Laboratory Management System database to identify all southern California Kaiser Permanente members eligible for inclusion between January 1, 1995, and December 31, 2000.
Age, gender and ethnicity	Age - Other: Age ≥50 years: parathyroidectomy 138 (87%); conservative management 334 (89%). Gender (M:F): 72/461. Ethnicity:not specified; Race: 65% Caucasian, 17% black, 4% Asian/Pacific Islander, 14% other/unknown
Further population details	1. Adjusted serum calcium: Not stated / Unclear 2. Age: ≥50 years old (89% ≥ 50 years old). 3. Creatinine clearance: Not stated / Unclear 4. 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 (22% had osteoporosis at baseline; kidney stones or history of fragility fractures not reported).
Extra comments	. 2006 paper is the primary study reporting the overall cohort of 1569 people. 2009 paper reports data for N=533 who had BMD data available (hazard ratio also adjusted for BMD).
Indirectness of population	No indirectness
Interventions	(n=159) Intervention 1: Surgery (parathyroidectomy) - 4-gland or bilateral exploration: not reported. Duration average follow-up of 7.4 years (range:13 days to 10 years). Concurrent medication/care: not reported. Indirectness: No indirectness

Study (subsidiary papers)	Vanderwalde 2006[87] (Vanderwalde 2009[88])
	(n=374) Intervention 2: Conservative management. Duration average follow-up of 7.4 years (range: 13 days to 10 years). Concurrent medication/care: not reported. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PARATHYROIDECTOMY versus CONSERVATIVE MANAGEMENT Protocol outcome 1: Fractures (vertebral or long bone) - Actual outcome: Hospitalised fracture at average follow-up of 7.4 years; Group 1: n=159; Group 2: n=374; HR 0.41; Lower CI 0.18 to Upper CI 0.93; Comments: Multivariate analysis confirmed that parathyroidectomy was independently associated with a decreased fracture risk (HR = 0.41; 95% CI 0.18,0.93; p = 0.03) after accounting for all other variables (age, sex, Charlson comorbidity index [CCI]; levels of calcium, PTH, and creatinine; BMD [femurT-score]). Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - Outcome of fracture taken from records of hospitalised fractures (so would not pick up all vertebral fractures on radiograph or outpatient fractures of the extremities); Indirectness of outcome: No indirectness; Baseline details: Patients who were treated operatively were similar with regard to age, gender, and race, but were more likely to have higher calcium (p= 0.001) and PTH levels (p = 0.001) than patients who were observed. Furthermore, those who were observed were more likely to have osteoporosis (p =0.018); Key confounders: Age, sex, Charlson comorbidity index (CCI); levels of calcium, PTH, and creatinine; BMD (T score femur); Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life; Mortality; Deterioration in renal function; Occurrence of kidney stones; Persistent hypercalcaemia; Bone mineral density (BMD; distal radius or lumbar spine); Cardiovascular events; Adverse events (including voice change and hypoparathyroidism); Cancer

Study (subsidiary papers)	Vestergaard 2003[90]
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n=3213)
Countries and setting	Conducted in Denmark; Setting: Nationwide Danish cohort.
Line of therapy	1st line
Duration of study	Intervention + follow up: Data collected from 1 January 1980 to 31 December 1999. 6.1 years (median follow up after diagnosis)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall

Study (subsidiary papers)	Vestergaard 2003[90]
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with a first time diagnosis of primary hyperparathyroidism for the period 1 January 1980 to 31 December 1999.
Exclusion criteria	Not stated
Recruitment/selection of patients	Patients were identified through the Danish National Hospital Discharge Register, which is a nationwide computer-based register of all contacts to Danish hospitals
Age, gender and ethnicity	Age - Mean (SD): surgery - 58.3 (15.2); no surgery 64.2 (17.4). Gender (M:F): Men - surgery 500 (26%); no surgery 293 (23%); Women - surgery 1434 (74%); no surgery 986 (77%). Ethnicity: not stated
Further population details	1. Adjusted serum calcium: Not stated / Unclear 2. Age: Not stated / Unclear 3. Creatinine clearance: Not stated / Unclear 4. 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	--
Indirectness of population	No indirectness
Interventions	(n=1934) Intervention 1: Surgery (parathyroidectomy) - 4-gland or bilateral exploration. Median time to surgery was 31 days from diagnosis (range 0–14 years). Duration 6.1 years (median follow up after diagnosis). Concurrent medication/care: No further details. Indirectness: No indirectness (n=1279) Intervention 2: Conservative management. Conservative management, no further details. Duration 6.1 years (median follow up after diagnosis). Concurrent medication/care: No details. Indirectness: No indirectness
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SURGERY versus CONSERVATIVE MANAGEMENT

Protocol outcome 1: Mortality
- Actual outcome: Mortality at 6.1 years (estimated); Group 1: n=1934; Group 2: n=1279; HR 0.65; Lower CI 0.57 to Upper CI 0.93
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Very high, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: Matched for age and gender; Key confounders: Only adjusted for age key confounder; Group 1 Number missing; Group 2 Number missing

Protocol outcome 2: Kidney stones at 6.1 years (estimated); Group 1: n=1934; Group 2: n=1279; HR 1.87; Lower CI 1.3 to Upper CI 2.69
- Actual outcome: Kidney stones at 6.1 years (estimated)
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Very high, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: Matched for age and gender; Key confounders: Only

Study (subsidiary papers)	Vestergaard 2003[90]
adjusted for age key confounder; Group 1 Number missing; Group 2 Number missing: Protocol outcome 3: Fractures (vertebral or long bone) at 6.1 years (estimated); Group 1: n=1934; Group 2: n=1279; HR 0.69; Lower CI 0.56 to Upper CI 0.82 - Actual outcome: Fractures at 6.1 years (estimated); Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Very high, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Matched for age and gender; Key confounders: Only adjusted for age key confounder; Group 1 Number missing; Group 2 Number missing Protocol outcome 4: Cancer at 6.1 years (estimated) - Actual outcome: Cancer at 6.1 years (estimated); Group 1: n=1934; Group 2: n=1279; HR 1.11; Lower CI 0.9 to Upper CI 1.37 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Very high, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: Matched for age and gender; Key confounders: Only adjusted for age key confounder; Group 1 Number missing; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life; Occurrence of kidney stones; Persistent hypercalcaemia; Bone mineral density (BMD; distal radius or lumbar spine); Cardiovascular events; Adverse events (including voice change and hypoparathyroidism)