Treatments for MEN1-associated endocrine tumours: three systematic reviews and a meta-analysis

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Summary

Background Multiple endocrine neoplasia type 1 (MEN1) is a rare hereditary disorder characterised by the combined occurrence of parathyroid, pancreatic, and pituitary tumours. Current treatments are based on very low-quality evidence. Our aims were to determine treatment outcomes in patients with MEN1 for: subtotal parathyroidectomy versus less than subtotal parathyroidectomy for primary hyperparathyroidism (Q1); surgery versus active surveillance for non-functioning pancreatic neuroendocrine tumours sized 2 cm or less (Q2); and dopamine agonist responses of prolactinomas in patients with MEN1 versus patients without MEN1 (Q3).

Methods We conducted three systematic reviews and one meta-analysis. Four electronic databases (MEDLINE Ovid, Embase Ovid, The Cochrane Library, and Web of Science) were searched from Dec 1, 2001, to Feb 13, 2023, with no language restrictions. Study designs included randomised controlled trials, prospective and retrospective cohort studies, and case-controlled and case series. Adults and children with MEN1-associated tumours were included in all three systematic reviews. For each clinical question, three pairs of authors independently screened abstracts and assessed the full text for final inclusion, discordant views were resolved by senior authors. Dichotomous outcomes were calculated using risk ratios or hazard ratios for time-to-event analyses, with 95% CIs. Continuous outcomes were ascertained using mean difference with 95% CIs. Where feasible, outcomes from individual studies were analysed through meta-analysis, using a random-effects model. The systematic reviews were prospectively registered (PROSPERO reference numbers CRD42023409912, CRD42023409936, and CRD42023409949).

Findings For primary hyperparathyroidism (Q1), 990 non-duplicate records were screened for title and abstract, of which 23 studies with 1073 patients were eligible for meta-analysis. These studies showed that subtotal parathyroidectomy had a significantly lower risk of persistent primary hyperparathyroidism (RR 0·32, 95% CI 0·20–0·52; I^2=0%) and recurrent primary hyperparathyroidism (RR 0·78, 0·62–0·97; I^2=27%), when compared with less than subtotal parathyroidectomy, although the risk of post-operative hypoparathyroidism was higher (RR 2·64, 1·63–4·29; I^2=0%). For non-functioning pancreatic neuroendocrine tumours sized 2 cm and less (Q2), 1583 non-duplicate records were screened for title and abstract, of which three cohort studies were eligible for analysis. These studies showed that combined metastatic disease and mortality rates were comparable between patients in the surgery group (two [7%] of 27 to three [20%] of 15) and patients in the active surveillance group (one [3%] of 33 to four [8%] of 50]). For prolactinomas (Q3), 475 non-duplicate records were screened for title and abstract, of which ten studies with 505 patients were eligible for analysis. These studies showed that dopamine agonist treatment failure rates to normalise serum prolactin were similar between patients with MEN1 (zero of one to one [33%] of three) and patients without MEN1 (four [6%] of 68 to nine (82%) of 11), n=23 studies). GRADE certainty scores for all were low or very low.

Interpretation In patients with MEN1, subtotal parathyroidectomy achieved greater reductions in persistence and recurrence of primary hyperparathyroidism than less than subtotal parathyroidectomy; for non-functioning pancreatic neuroendocrine tumours sized 2 cm or less, the few available studies suggest that active surveillance might be comparable to surgical resection; and for prolactinomas, dopamine agonist therapy appears to have comparable efficacy as in patients without MEN1.

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Introduction

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant inherited syndrome characterised by two or more endocrine tumours in the same patient. These tumours are usually multifocal and include parathyroid tumours (which cause primary hyperparathyroidism), pancreatic neuroendocrine tumours, and mono-hormonal or pluri-hormonal pituitary adenomas. The vast majority (>95%) of patients with clinical MEN1 will have germline inactivating mutations

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Research in context

Evidence before this study

Tumours of the parathyroids, pancreas, and pituitary are the major lesions of multiple endocrine neoplasia type 1 (MEN1), a rare hereditary disorder. Current treatments for these tumours in patients with MEN1 are based on very low-quality evidence. We therefore searched MEDLINE Ovid, Embase Ovid, The Cochrane Library, and Web of Science for systematic reviews and meta-analyses published between Dec 1, 2001 and Feb 13, 2023, with no language restrictions. For treatment of parathyroid tumours causing primary hyperparathyroidism, there was one meta-analysis (2022) comparing subtotal parathyroidectomy and less than subtotal parathyroidectomy, but this included studies published before the first MEN1 clinical practice recommendations in 2001. There were no systematic reviews for management of non-functioning pancreatic neuroendocrine tumours sized 2 cm or less, or dopamine agonist-resistant prolactinomas. Our search strategy identified 3048 articles for review, including three studies published in 2022; we therefore repeated the systematic review and meta-analysis for these important clinical questions.

Added value of this study

Our systematic reviews and meta-analysis aimed to provide evidence-based recommendations for treatments of parathyroid tumours, pancreatic neuroendocrine tumours, and prolactinomas in patients with MEN1. However, our searches revealed that most (approximately 90%) of the 3048 publications published since 2001 were retrospective series with sparse data that were insufficient to provide high or moderate certainty for evidence, following the GRADE approach. Despite these limitations, we were able to ascertain that 37 (approximately 1·2%) of the 3048 publications met our inclusion criteria. Analysis of these publications provided evidence, albeit at low and very low levels, for some management aspects for each of the three major tumour types associated with MEN1.

Implications of all the available evidence

Our evidenced-based findings will help in the treatment and management of patients with MEN1. Thus, in patients with MEN1: subtotal parathyroidectomy should be considered for treating primary hyperparathyroidism; active surveillance, which might be comparable to surgery, could be considered as an option for non-functional pancreatic neuroendocrine tumours sized 2 cm or less; and dopamine agonist treatment, which is effective, should be used for treating prolactinomas.

or deletions of the *MEN1* gene, which is located on chromosome 11q13 and encodes the tumour suppressor protein menin; the remaining patients (<5%) might have mutations of other genes that lead to a MEN1-like phenotype. MEN1 is rare, with an estimated population prevalence of one per 100 000 individuals to ten per 100 000 individuals, with few published prospective clinical studies. Therefore, clinical practice guidelines are largely based on retrospective studies of varying methodological quality and expert opinion. We performed three systematic reviews centred around three key clinical questions (Q1–3) relating to treatment outcomes for the three major tumours seen in MEN1 (parathyroid tumours, pancreatic neuroendocrine tumours, and pituitary adenomas).

Primary hyperparathyroidism, the most common manifestation of MEN1, is characterised by multiglandular tumours of the parathyroid glands. Parathyroidectomy is the primary treatment, although the optimal timing and extent of initial surgery are debated.[1,2] Subtotal parathyroidectomy is the most frequently used index procedure in MEN1-associated primary hyperparathyroidism. This approach reduces the incidence of long-term post-operative hypoparathyroidism compared with total parathyroidectomy, although some surgeons advocate a more conservative strategy, especially in children, adolescents, and young adults, which includes unilateral clearance of all parathyroid tissue with ipsilateral thymectomy or a single gland parathyroidectomy (collectively termed less than subtotal parathyroidectomy).[3,4] Therefore, Q1 aimed to determine whether less than subtotal parathyroidectomy is associated with a reduced incidence of long-term hypoparathyroidism without increasing the risk of primary hyperparathyroidism persistence or recurrence when compared with subtotal parathyroidectomy.

Non-functioning pancreatic neuroendocrine tumours are characterised by either not secreting hormones or secreting pancreatic polypeptide, which is not associated with any hormonal syndrome or sequelae. Non-functioning pancreatic neuroendocrine tumours are the most frequent duodenopancreatic neuroendocrine tumours in MEN1.[5] The aim of screening for pancreatic neuroendocrine tumours is to identify those patients who might benefit from early surgical resection before the development of metastases, which represents the major cause of disease-related mortality in patients with MEN1.[6–8] Studies have reported that most small MEN1-associated non-functioning pancreatic neuroendocrine tumours are indolent and rarely metastasise before reaching a larger size,[9,10] and tumour size and grade are prognostic factors predictive of distant metastases.[11] There is consensus that non-functioning pancreatic neuroendocrine tumours larger than 2 cm should undergo resection,[12,13] but the approach for tumours sized 2 cm or less is controversial and undefined. Therefore, Q2 aimed to determine the optimal strategy (ie, surgical resection versus active surveillance) for non-functioning pancreatic neuroendocrine tumours sized 2 cm or less.

Prolactinomas, which are the most common hormone-secreting pituitary adenoma in patients with and without MEN1,[14] can present symptomatically with hypogonadism, local mass effect, or both, or can be asymptomatically discovered during screening. Dopamine agonists, such as cabergoline, bromocriptine, and quinagolide, which inhibit prolactin secretion and cellular proliferation, are first-line therapy. Some prolactinomas are resistant to dopamine agonists, defined as either the absence of normalisation of serum prolactin concentrations or a less than 50% reduction in tumour size.[15,16] Such dopamine agonist-resistant prolactinomas are reported to occur more frequently in patients with MEN1.[17] Therefore, Q3 aimed to determine whether dopamine agonist-resistant prolactinomas occurred more frequently in patients with MEN1 than those without MEN1.

Three systematic reviews were therefore conducted to address Q1–3 with the following objectives: Q1 aimed to assess outcomes after subtotal parathyroidectomy versus less than subtotal parathyroidectomy as the index operation for MEN1-associated primary hyperparathyroidism, in terms of disease persistence and recurrence rates, time to recurrence, and incidence of long-term post-operative hypoparathyroidism; Q2 aimed to assess time to surgery, surgical complications, metastasis-free survival, and overall survival following surgical resection compared with active surveillance in patients with MEN1 with non-functioning pancreatic neuroendocrine tumours sized 2 cm or less; and Q3 aimed to assess whether dopamine agonist-resistant prolactinomas (defined by persistent hyperprolactinaemia, <50% reduction in tumour size, and requirement for further treatment by surgery, radiotherapy, or chemotherapy) occurred more frequently in patients with MEN1 than patients without MEN1.

Methods

Search strategy and selection criteria

In these three systemic reviews and meta-analysis, the following electronic bibliographic databases were searched with a combination of free text and MeSH terms without language restriction: MEDLINE Ovid, Embase Ovid, The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials), and Web of Science, from Dec 1, 2001 (ie, after publication of the first MEN1 guidelines),[18] to Feb 13, 2023. The full lists of search terms for all systematic reviews are available in the appendix (pp 3–11). Study designs included were randomised controlled trials, prospective and retrospective cohort studies, and case-controlled and case series (appendix pp 3–12). Adults and children with MEN1-associated tumours were included in all three systematic reviews. Research questions using a population, intervention–exposure, comparator–control, and outcome (ie, PICO/PECO) framework were formulated for Q1–3, together with the inclusion and exclusion criteria for each systematic review (appendix pp 11–12).

An international MEN1 working group, the majority of whom met once in person and thereafter regularly (online) formulated the three clinical questions (Q1–3) with primary and secondary outcomes. Authors were allocated to one of three subgroups to write the study protocols and proposed systematic reviews for submissions to PROSPERO. The Q1 subgroup was comprised of FM, OAS, MLB, and RVT; Q2 was comprised of CRCP, KAE, and GDV; and Q3 was comprised of TC, KAE, KEL, FC, and SGW. SM, RS, and ZM were involved in all three subgroups Q1–Q3. Systematic reviews were conducted according to the PRISMA guidelines (appendix pp 13–14).[19]

For Q1, randomised controlled trials and prospective and retrospective cohort studies that compared subtotal parathyroidectomy with less than subtotal parathyroidectomy were eligible for inclusion. However, no randomised controlled trials were identified. Subtotal parathyroidectomy was defined as any operation that preserved one residual normal-sized functioning source of parathyroid hormone (PTH). This definition included operations involving the removal of three parathyroid glands if the fourth appeared normal or the removal of three glands plus a portion of the fourth if it was enlarged. If supernumerary glands were present, they were also removed to ensure that only a single normal-sized remnant remained. Less than subtotal parathyroidectomy was defined as the removal of less than three parathyroid glands. Primary outcomes were: disease persistence (persistent hypercalcaemia with non-suppressed PTH concentrations <6 months post-operatively); disease recurrence (hypercalcaemia with non-suppressed PTH concentrations after a period of normocalcaemia of ≥6 months); and post-operative chronic hypoparathyroidism (low serum calcium concentrations, with low or normal PTH concentrations requiring supplemental calcium and active vitamin D for ≥6 months after surgery). Secondary outcomes were time to recurrence and post-operative complications.

For Q2, randomised controlled trials, prospective and retrospective cohort studies, and case–control studies that compared outcomes of surgery versus active surveillance for MEN1-associated non-functioning pancreatic neuroendocrine tumours sized 2 cm or less were eligible for inclusion. However, only retrospective cohort studies were identified. Included studies required at least ten participants in each treatment group. Primary outcomes were overall survival and metastasis-free survival. Secondary outcomes were exocrine pancreatic insufficiency, type 3c diabetes, early post-operative complications, and time to surgical intervention for the active surveillance group.

See Online for appendix

For Q3, randomised controlled trials, prospective and retrospective cohort studies, and case series comparing the effect of dopamine agonist therapy on prolactinomas

in patients with and without MEN1, as well as uncontrolled studies assessing therapeutic effects of dopamine agonists either in patients with MEN1 or patients without MEN1 with prolactinomas were eligible for inclusion. One randomised controlled trial, which compared high dose versus low dose dopamine agonist therapy in non-MEN1 prolactinomas,[20] was identified and included as a case series as this study did not compare dopamine agonist response in patients with MEN1 versus patients without MEN1. The remaining studies were retrospective case series and cohort studies. Primary outcomes were the proportion of patients with dopamine agonist resistance and the proportion of patients who had surgery. Secondary outcomes were doses of dopamine agonist required to normalise serum prolactin concentrations, and the proportion of patients undergoing radiotherapy or chemotherapy.

For each clinical question, three pairs of authors (Q1 FM and OAS; Q2 CRCP and KAE; Q3 KAE and KEL for Q3 full text KAE and TC]) independently screened abstracts retrieved via search strategies and assessed the full text for final inclusion. Senior authors adjudicated discordant views (Q1 MLB and RVT; Q2 GDV; Q3 FC and SGW).

Study protocols and planned systematic reviews were prospectively registered on the International Prospective Register of Systematic Reviews (PROSPERO reference numbers CRD42023409912, CRD42023409936, and CRD42023409949).

Data analysis

Two authors (SM and RS) independently extracted relevant data from the selected studies. Any disagreement was resolved by discussion. In cases of insufficient information, authors of the studies were contacted for unpublished data. In cases of multiple publications of the same data, only those data from the most recent and comprehensive report were extracted for inclusion. For studies included for meta-analysis, study identifiers (eg, first author, publication year), study design, country, characteristics of participants (eg, mean age and percentage of male and female individuals), and duration of follow-up were extracted. For Q1, additional data extracted were type of operation, number of parathyroids removed, and post-operative outcomes. Where applicable, information was extracted after the index surgery only. For Q2, additional data extracted were tumour size, Ki-67 labelling index, mitotic rate, WHO grade, presence of lymph node or distant metastases, type of surgery, post-operative complications, treatment groups, number of patients in each treatment group, and outcomes. For Q3, additional data extracted were disease duration, comorbidities, previous treatment or treatments, dose of dopamine agonist, prolactin response, reduction in tumour size, treatment duration, number and types of other treatments received, and outcomes.

Two authors (SM and RS) independently assessed the risk of bias and methodological quality of the included studies. The Cochrane risk of bias tool[21] was used to assess the risk of bias in randomised trials. The Newcastle Ottawa Scale[22] was used for prospective and retrospective cohort studies and case–control studies. The methodological quality of case series was assessed using a tool developed by the Institute of Health Economics,[23] and in order to achieve a picture of the overall quality of the studies, we additionally included for all the checklists the number of "yes" or "good" answers (indicating that the criterion was met) and represented these with the total number of questions for each study, to provide an overall score for quality. Studies were categorised as high quality if they met at least 90% of the quality criteria, medium if they met more than 50% of the quality criteria, low if they had met 50% or fewer of the quality criteria; or uncertain if multiple domains could not be scored.

Dichotomous outcomes were calculated using risk ratios (RR) or hazard ratios (HR) for time-to-event analyses, with 95% CIs. Continuous outcomes were ascertained using mean difference with 95% CIs. Where feasible, outcomes from individual studies were analysed through meta-analysis, using a random-effects model. Treatment effects from observational studies were planned to be analysed using pool-adjusted estimates with the inverse variance approach. The minimum set of variables required for an estimate to be considered adjusted were: age, sex, serum calcium concentration, and PTH concentration at baseline. However, none of the included studies provided adjusted estimates, and therefore crude estimates were pooled. When pooling of data was possible, heterogeneity was assessed using I^2 and χ^2 tests. Statistical analyses were performed using the Mantel–Haenszel (MH) method in RevMan version 5.4 (RevMan MH; Cochrane Collaboration, London, UK).[24] Studies with single-zero events were included in the analysis with a fixed continuity correction, which adds a specific value (usually 0·5) to all cells of the 2×2 table. However, RevMan MH can yield differences in point estimates when compared with MH when studies with low event rates and small sample sizes are included.[24] If meta-analysis was judged not to be feasible due to high clinical or methodological heterogeneity or due to incomplete data in the original publications, then the results were described narratively. Subgroup or sensitivity analyses were not planned. The overall certainty of the evidence for primary and secondary outcomes was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach, by two authors (SM and RS) independently, with rankings of very low, low, moderate, and high.[25] Observational studies started with a low score, but were then further downgraded or upgraded according to GRADE guidance.[21] GRADEpro

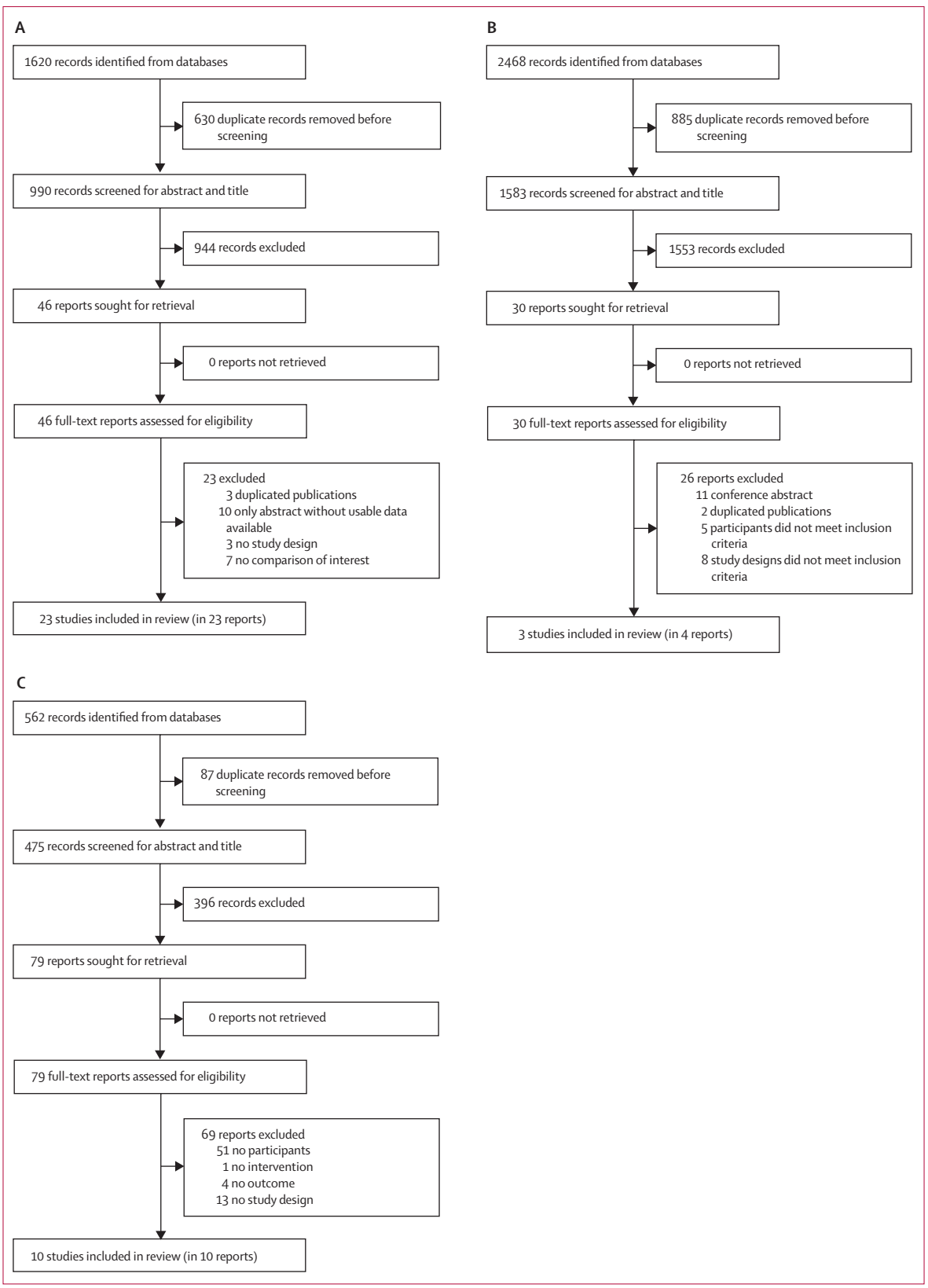


Figure 1: **Study selection for the three questions (Q1–Q3), assessed by the systematic reviews, for MEN1-associated primary hyperparathyroidism (A), MEN1-associated non-functioning pancreatic neuroendocrine tumours (B), and MEN1-associated prolactinoma (C)**
No automation tools were used to exclude records.

	Study design*	Study population	Participant characteristics	
			Subtotal parathyroidectomy	Less than subtotal parathyroidectomy
Arnalsteen et al (2002; France);[27] Balsalobre Salmeron et al (2018; Spain);[28] Choi et al (2020; South Korea);[29] Dotzenrath et al (2001; Germany);[30] Elaraj et al (2003; USA);[31] Fyrsten et al (2016; Sweden);[32] Horiuchi et al (2018; Japan);[33] Hubbard et al (2006; France);[34] Kluijfhout et al (2016; USA);[3] Lamas et al (2019; Spain);[35] Lambert et al (2005; USA);[36] Landry et al (2022; USA);[37] Lee et al (2006; Taiwan);[38] Manoharan et al (2020; Germany);[4] Marini et al (2018; Italy);[2] Montenegro et al (2019; Brazil);[39] Norton et al (2008; USA);[40] Pieterman et al (2012; the Netherlands);[41] Shariq et al (2022; UK, USA, Austria);[42] Twigt et al (2013; the Netherlands);[43] Versnick et al (2013; Australia);[44] Waldmann et al (2010; Germany);[45] Yavropoulou et al (2022; Greece)[46]	Retrospective cohort study (n=22); prospective cohort study (n=1)	MEN1-associated PHPT	Total number of participants (n=649), median number of participants (n=22; IQR 13–36; range 2–95); proportion of male individuals (range 20–50%); proportion of female individuals (range 50–80%); median age 38 years (IQR 36–42; range of mean or median values reported for each study 22–46); median follow-up 54 months (IQR 12–104 months; range of mean or median values reported for each study 4–155)	Total number of participants (n=424), median number of participants (n=13; IQR 12–22; range 4–85); proportion of male individuals (range 0–60%); proportion of female individuals (range 40–100%); median age 39 years (IQR 36–43; range of mean or median values reported for each study 17–52); median follow-up 37 months (IQR 12–80; range of mean or median values reported for each study 4–247 months)

MEN1=Multiple endocrine neoplasia type 1.*No randomised studies were found, none of the included studies provided separate data for children and adults, and none of the included observational studies provided adjusted estimates.

Table 1: **Summary of characteristics of included studies on surgery for primary hyperparathyroidism (Q1)**

	Adjusted absolute effect (95% CI)		RR (95% CI)	Number of patients (number of studies)	Certainty of the evidence (GRADE)
	Risk with less than subtotal parathyroidectomy	Risk with subtotal parathyroidectomy*			
Disease† persistence	228 per 1000	73 per 1000 (46–118)	0·32 (0·20–0·52)	576 (16 observational studies)	Low
Disease† recurrence	453 per 1000	353 per 1000 (281–439)	0·78 (0·62–0·97)	971 (22 observational studies)	Very low
Chronic hypoparathyroidism	38 per 1000	100 per 1000 (62–163)	2·64 (1·63–4·29)	898 (21 observational studies)	Low

Specific details regarding race or ethnicity were not reported in these studies. In GRADE very low certainty, there is very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect. In GRADE low certainty, confidence in the effect estimate is limited; the true effect might be substantially different from the estimate of the effect. GRADE=Grading of Recommendations, Assessment, Development and Evaluations. RR=risk ratio. *Estimates were derived using RevMan (version 5.4) and GRADEPro GDT software. RevMan when used for studies in which no events occur (ie, single-zero event studies), adds a small adjustment (eg, 0.5) to all cells of the 2 × 2 table. Single-zero event studies were included in three (19%) of 16 disease persistence articles, two (9%) of 22 disease recurrence articles, and nine (43%) of 21 chronic hypoparathyroidism articles. Thus, the absolute difference in adjusted rates shown in this table (table 2) when compared with the unadjusted rates shown in figure 2A–C are as follows: 1·1% (73 vs 62 per 1000) for disease persistence; 2·7% (353 vs 326 per 1000) for disease recurrence; and −7·7% (100 vs 177 per 1000) for chronic hypoparathyroidism. †Disease refers to primary hyperparathyroidism.

Table 2: **Summary of outcomes of included studies on surgery for primary hyperparathyroidism (Q1)**

GDT software (McMaster University, Evidence Prime, Hamilton, ON, Canada) was used to prepare the summary of findings tables.[26]

Role of the funding source

There was no funding source for this study.

Results

Figure 1 shows study selection flowcharts for Q1–3.[19] No randomised controlled trials comparing the two treatment groups of each question were identified.

For the systematic review on the surgical approach for MEN1-associated primary hyperparathyroidism (Q1), 990 non-duplicate records were screened for title and abstract, 46 were reviewed in full text, and 23 were excluded (figure 1A; appendix pp 15, 16). 23 studies with 1073 patients were included (tables 1, 2; appendix pp 17–22).[2–4,27–46] Participants in each group were representative of the population of interest, although no adjustment for confounders was performed. Three studies had loss to follow-up of 15–30%,[39,44,46] and participants from two of these studies did not have sufficient follow-up for outcomes to occur.[39,44] For the systematic review on the management of MEN1-associated non-functioning pancreatic neuroendocrine tumours sized 2 cm or less (Q2), 1583 non-duplicate records were screened for title and abstract, 30 were reviewed in full text, 26 were excluded (figure 1B; appendix pp 23, 24). Three cohort studies with 236 patients, reported across four publications,[10,47–49] were included (tables 3, 4; appendix pp 25, 26). However, only one study had a low risk of bias,[47] and the others had a high risk due to confounders not being adjusted for and the outcome of interest (distant metastases) present at baseline.[10,48,49] Participant loss to follow-up was high in one study.[10]

For the systematic review on dopamine agonist resistance in MEN1-associated prolactinomas (Q3), a total of 475 non-duplicate records were screened for title and abstract, 79 were reviewed in full text, and 69 were excluded (figure 1C; appendix pp 27–29). Ten studies, which comprised one cohort study and nine uncontrolled case series, with 505 patients (157 patients with MEN1 and 348 patients without MEN1),[20,50–58] were included (tables 5, 6; appendix

	Study design	Study population	Participant characteristics	
			Surgery	Active surveillance
Nell et al (2018; the Netherlands);*[47] Partelli et al (2016; Italy, UK, Germany);†[48] Triponez et al (2006; France, Belgium);‡[49] Triponez et al (2018; France, Belgium)[10]	Retrospective cohort study (n=3)	MEN1-associated non-functional pancreatic neuroendocrine tumours ≤2 cm (n=2); MEN1-associated non-functional pancreatic neuroendocrine tumours of all size (n=1)	Total number of participants (n=69); median number of participants (n=27; IQR 21–27; range 15–27); proportion male individuals (range 30–60%); proportion female individuals (range 40–70%); median age 36 years (IQR 34–38; range of mean or median values reported for each study 31–40); median follow-up 7 years (IQR 6–9; range of mean or median values 4·5–10·6)	Total number of participants (n=167); median number of participants (n=50; IQR 42–67; range 33–84); proportion male individuals (range 36–67%); proportion female individuals (range 33–64%); median age 36 years (IQR 34–36; range of mean or median values 32–38); median follow-up 9 years (IQR 8–10; range of mean or median values for each study 7·2–10·7)

MEN1=Multiple endocrine neoplasia type 1. *Median tumour size was 1·85 cm in the surgical group and 1·0 cm in the active surveillance group; however, median tumour size was not reported separately for participants with tumours smaller than 2 cm; similarly, the age of the participants at diagnosis of non-functional pancreatic neuroendocrine tumours was not reported separately for those with tumours smaller than <2 cm, only for the total cohort. †Exact tumour size was not reported. ‡In the surgical group versus the active surveillance group, the mean size of the biggest tumour was 1·4 cm × 0·1 cm compared with 1·1 cm × 0·7 cm (p=0·059); the mean number of pancreatic neuroendocrine tumours was 4·8 (SD 2·2) compared with 2·7 (2·1; p=0·048); and the presence of metastasis was four (27%) of 15 participants compared with three (6%) of 50 participants (p=0·044); the age of participants at diagnosis of the tumour was not reported, only age at MEN1 diagnosis.[49]

Table 3: **Summary of characteristics of included studies on surgery versus active surveillance for non-functional pancreatic neuroendocrine tumours ≤2cm (Q2)**

	Outcomes	Number of patients (number of studies)	Certainty of evidence (GRADE)
Mortality, follow-up range 6·7–10·7 years	Surgery 13% (2/15; follow-up 6·7 years [SD 4·0]) versus active surveillance 6% (3/50; mean follow-up 10·7 years [4·2]);[10,49] surgery 4% (1/27; median follow-up 10·6 years [IQR 5·7–14·8]) versus active surveillance 0/33 (median follow-up 9·2 years [IQR 4·6–13·1])[48]	125 (2 observational studies)	Very low*†
New development of metastasis or death, follow-up mean or median range 6·7 (SD 4·0) years to 10·7 (4·2) years (reported as number of participants with new metastasis or death)	Surgery 7% (2/27) versus active surveillance 4% (3/68); adjusted HR 2·04 (95% CI 0·31–13·59);[47] surgery 20% (3/15; mean follow-up 6·7 years [SD 4·0]) versus active surveillance 8% (4/50; mean follow-up 10·7 years [4·2]);[10,49] surgery 7% (2/27; median follow-up 10·6 years [IQR 5·7–14·8]) versus active surveillance 3% (1/33; median follow-up 9·2 years [IQR 4·6–13·1])[48]	236 (3 observational studies)	Low or very low‡
Early post-operative complications, follow-up mean 30 days	Any post-operative complications 50% (20/40); pancreatic fistula (all grades) 45% (18/40); post-operative haemorrhage 3% (1/40); pulmonary embolism 3% (1/40); Clavien–Dindo classification number of complications 50% (20/40), grade I–II 23% (9/40), grade III–IV 25% (10/40), grade V 3% (1/40); post-operative mortality 3% (1/40);[48] post-operative mortality 0/15[10,49]	125 (2 observational studies)	Very low†§
Time to surgery, follow-up range (mean or median range 5·9–10·3 years)	5·9 years (SD 4·7; 14%; 7/50);[10,49] median 10·3 years (IQR not reported; 33%; 9/27)[48]	125 (2 observational studies)	Very low*†

Specific details regarding race/ethnicity were not reported in these studies. The Ki-67 labelling index, mitotic rate, and WHO grade were not reported in the included studies.[10,47–49] In GRADE very low certainty, there is very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect. In GRADE low certainty, confidence in the effect estimate is limited; the true effect might be substantially different from the estimate of the effect. GRADE=Grading of Recommendations, Assessment, Development and Evaluations. MEN1=Multiple endocrine neoplasia type 1. *Downgraded two levels for risk of bias: no adjustment for confounding; >20% lost at follow-up. †Downgraded one level for imprecision: small sample size. ‡Downgraded one level for imprecision: CIs include important benefits and harms. §Downgraded one level for risk of bias: no adjustment for confounding.

Table 4: **Summary of outcomes of included studies on surgery versus active surveillance for non-functional pancreatic neuroendocrine tumours ≤2cm (Q2)**

pp 30–32). The methodological qualities of the included studies for Q1–3 are detailed in the appendix (pp 33–38).

Regarding Q1 primary outcomes, the adjusted risk of primary hyperparathyroidism persistence was significantly lower in patients with subtotal parathyroidectomy (73 [95% CI 46–118] per 1000 patients) than in patients with less than subtotal parathyroidectomy (228 per 1000 patients; RR 0·32 [95% CI 0·20–0·52], I^2=0%; n=16 studies, 576 participants; figure 2A; table 2).[2–4,29,32–36,39–43,45,46] The risk of primary hyperparathyroidism recurrence was also significantly lower in patients with subtotal parathyroidectomy (353 [95% CI 281–439] per 1000 patients) versus less than subtotal parathyroidectomy patients (453 per 1000 patients; RR 0·78 [0·62–0·97], I^2=27%; n=22 studies, 971 participants; figure 2B; table 2).[2–4,27,29,30,32–46] For primary outcomes, GRADE certainty was low or very low (figures 2A, 2B; tables 1, 2; appendix pp 39–40). The risk of post-operative chronic hypoparathyroidism was significantly higher in patients with subtotal parathyroidectomy (100 [95% CI 62–163] per 1000 patients) than patients with less than subtotal parathyroidectomy (38 per 1000; RR 2·64, [1·63–4·29], I^2=0%; n=21 studies, 898 participants; figure 2C; table 2), with low GRADE certainty (figure 2C; tables 1, 2; appendix pp 39, 40).[2–4,28–46]

Regarding Q1 secondary outcomes, there was no difference in time to primary hyperparathyroidism recurrence between subtotal parathyroidectomy (median time-to-recurrence range 4–13 years) and less than subtotal parathyroidectomy groups (median time-to-recurrence range 3–14 years), as reported in nine studies (GRADE certainty very low). Additional post-operative complications were reported in five studies[31,34,44–46] and post-operative outcomes were reported from 23 studies (appendix pp 39, 40).

	Study design	Study population	Participant characteristics	
			Patients with MEN1	Patients without MEN1
Andujar-Plata et al (2017; Spain);*[50] Arya et al (2021; UK);*[51] Breil et al (2018; Germany);*[52] De Castro Moreira et al (2023; Brazil);*[53] De Laat et al (2015; the Netherlands);*[54] Kepenekian et al (2016; France);*[55] Kumar et al (2022; India);*[56] Marini et al (2018; Italy);*[57] Rastogi et al (2013; India);†[20] Verges et al (2002; France)‡[58]	Retrospective case series (n=8); retrospective cohort study (n=1); randomised control trial (n=1)	Non-MEN1 prolactinoma (n=3); MEN1 prolactinoma (n=2); Non-MEN1 and MEN1 prolactinoma (n=5)	Total number of participants (n=180); participants with dopamine agonist as first-line therapy (n=157), median number of participants (n=17; IQR 1–33; range 1–85); proportion of male individuals 28% (range 0–100%); proportion female individuals 72% (range 0–100%); range of mean or median age reported for each study 13·83–38·2 years; range of mean or median follow-up reported for each study 4–14 years	Total number of participants (n=388); participants with dopamine agonist as first-line therapy (n=348), median number of participants (n=38; IQR 11–49; range 10–146); mean proportion of male individuals 31% (range 21–56); mean proportion of female individuals 69% (44–79); range of mean or median age reported for each study 13·8–42·0 years; range of mean or median follow-up reported for each study 1·3-16·0 years

MEN1=Multiple endocrine neoplasia type 1. *Retrospective case series. †Randomised control trial of non-MEN1 prolactinomas, included as a retrospective case series. ‡Retrospective cohort study.

Table 5: **Summary of characteristics of included studies comparing dopamine agonist responses of prolactinomas in patients with and without MEN1 (Q3)**

	Outcome	Number of patients (number of studies)*
Patients who do not normalise prolactin levels; follow-up range 16 months to 16 years	Sporadic prolactinoma (n=348), percent range 6% (4/68) to 82% (9/11); MEN1-associated prolactinoma (n=157), percent range 0/1 to 33% (1/3)	505 (10 observational studies)
Patients who do not have a >50% reduction in tumour size; follow-up range 16 months to 9 years	Sporadic prolactinoma (n=277), percent range 0/10 to 53% (77/146); MEN1-associated prolactinoma (n=123), percent range 0/1 to 47% (17/36)	400 (7 observational studies)
Patients needing surgery at follow-up; follow-up range 4 years to 9 years	Sporadic prolactinoma (n=260), percent range 0/10 to 55% (6/11); MEN1-associated prolactinoma (n=153), percent range 0/30 to 34% (29/85)	413 (8 observational studies)
Patients needing radiotherapy at follow-up; follow-up range 4 years to 14 years	Sporadic prolactinoma (n=246), percent range 1% (1/68) to (3/11) 27%; MEN1-associated prolactinoma (n=152), percent range 0/36 to 12% (10/85)	398 (6 observational studies)
Patients needing chemotherapy at follow-up; follow-up range 4 years to 14 years	Sporadic prolactinoma (n=246), percent range 0/68 to 10% (2/21); MEN1-associated prolactinoma (n=152), percent range 0% (0/1 to 0/85)	398 (6 observational studies)

Specific details regarding race or ethnicity were not reported in these studies. The certainty of evidence (GRADE) for all primary and secondary outcomes were all very low. In GRADE very low certainty, there is very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect. All studies were downgraded one level for risk of bias: indirect comparison between uncontrolled case series or direct comparison from controlled series that did not adjust for prognostic and confounding factors. The breakdown for the primary and secondary outcomes for each study are reported in the appendix (pp 43, 44). GRADE=Grading of Recommendations, Assessment, Development and Evaluations. MEN1=Multiple endocrine neoplasia type 1.

Table 6: **Summary of outcomes of included studies comparing dopamine agonist responses of prolactinomas in patients with and without MEN1 (Q3)**

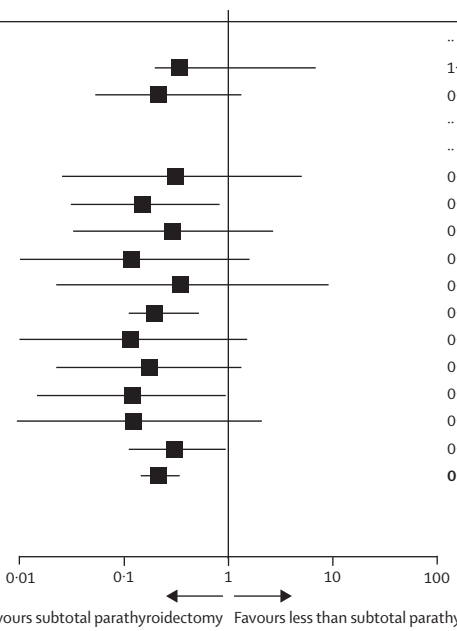
Regarding Q2 primary outcomes, none of the three included studies reported overall survival or metastasis-free survival separately, but instead published combined metastatic and mortality rates for surgical intervention or active surveillance in patients with MEN1 with non-functioning pancreatic neuroendocrine tumours sized 2 cm or less (tables 3, 4; appendix p 41). For these three studies, the combined metastatic and mortality rates were two (7%) of 27 surgery patients versus three (4%) of 68 active surveillance patients;[47] three (20%) of 15 surgery patients versus four (8%) of 50 active surveillance patients;[10,49] and two (7%) of 27 surgery patients versus one (3%) of 33 active surveillance patients;[48] after a mean follow-up range of 6·7 years (SD 4·0) to 10·7 years (4·2).[10,49] These studies had heterogeneity in their design and variability in the reported outcomes, such that a meta-analysis could not be performed for Q2.[10,47–49] However, an examination of these three studies revealed the following: one study (N=95), which used a propensity score to adjust for confounding patient factors between each group, reported that surgery (n=27) for non-functioning pancreatic neuroendocrine tumours smaller than 2 cm, when compared with active surveillance (n=68) was not associated with a significantly lower risk of liver metastases or mortality, adjusted HR 2·04 (95% CI 0·3–13·59; GRADE certainty low).[47] Another study (N=65) reported similar disease progression in patients undergoing surgical resection (five [33%] of 15 patients) versus active surveillance (14 [28%] of 50 patients), and similar mortality in patients undergoing surgical resection (two [13%] of 15 patients) versus active surveillance (three [6%] of 50); with an event-free survival time of 13·9 years (SD 1·1) in the active surveillance group after a mean follow-up of 10·7 years (4·2).[10,49] However, it is important to note that patients who initially underwent surgical resection had a significantly higher number of non-functioning pancreatic neuroendocrine tumours (p=0·048) and metastasis at diagnosis (p=0·044), when compared with the active surveillance group, and that no deaths occurred in seven (14%) of the 50 patients in the initial active surveillance group who subsequently underwent surgery. Finally, in another study (N=60) the whole cohort of patients with non-functioning pancreatic neuroendocrine tumours sized 2 cm or less were reported to have 10-year overall survival of 98% and progression-free survival of 61%, with no difference in progression-free survival between the surgical intervention (n=27) and active surveillance (n=33) groups.[48] However, patients who initially had surgery had a significantly higher number of

A Primary hyperparathyroidism persistence after parathyroidectomy

	Subtotal parathyroidectomy		Less than subtotal parathyroidectomy		Weight	Risk ratio (95% CI)
	Events	Total	Events	Total		
Choi et al (2020)[29]	0	4	0	12	..	..
Montenegro et al (2019)[39]	3	22	2	23	8·1%	1·57 (0·29–8·51)
Fyrsten et al (2016)[32]	2	30	7	31	10·5%	0·30 (0·07–1·31)
Horiuchi et al (2018)[33]	0	21	0	12	..	..
Hubbard et al (2006)[34]	0	21	0	4	..	..
Kluijfhout et al (2016)[3]	1	16	1	8	3·3%	0·50 (0·04–7·00)
Lamas et al (2019)[35]	2	22	5	12	10·6%	0·22 (0·05–0·96)
Lambert et al (2005)[36]	1	14	2	13	4·5%	0·46 (0·05–4·53)
Manoharan et al (2020)[4]	0	23	4	28	2·8%	0·13 (0·01–2·37)
Marini et al (2018)[2]	0	2	1	4	2·8%	0·56 (0·03–9·73)
Norton et al (2008)[40]	5	40	15	35	28·3%	0·29 (0·12– 0·72)
Pieterman et al (2012)[41]	0	16	3	14	2·8%	0·13 (0·01–2·25)
Shariq et al (2022)[42]	1	14	5	16	5·7%	0·23 (0·03–1·73)
Twigt et al (2013)[43]	1	17	9	21	6·0%	0·14 (0·02–0·98)
Waldmann et al (2010)[45]	0	11	3	13	2·8%	0·17 (0·01–2·91)
Yavropoulou et al (2022)[46]	3	35	4	22	11·8%	0·47 (0·12–1·91)
Total	**19**	**308**	**61**	**268**	**100·0%**	**0·32 (0·20–0·52)**

Heterogeneity: τ^2=0·00;χ^2=6·20, df=12 (p=0·91); I^2=0%

Test for overall effect: Z=4·61 (p<0·00001)

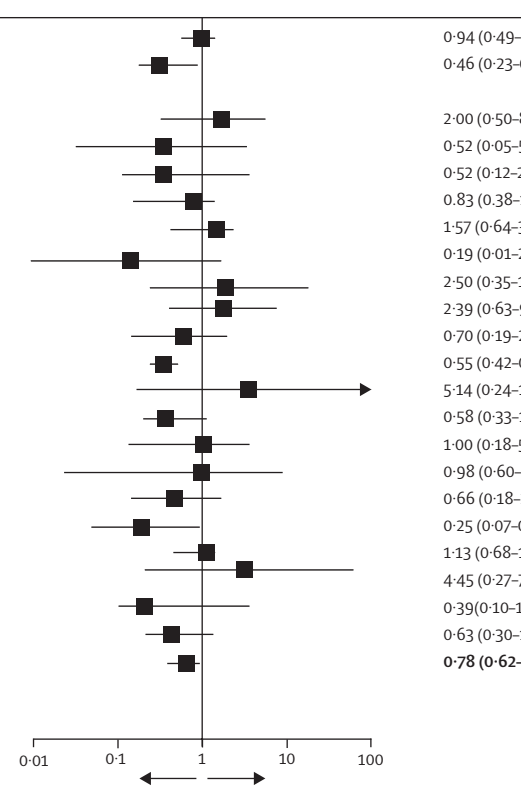


B Primary hyperparathyroidism recurrence after parathyroidectomy

	Subtotal parathyroidectomy		Less than subtotal parathyroidectomy		Weight	Risk ratio (95% CI)
	Events	Total	Events	Total		
Arnalsteen et al (2002)[27]	26	60	6	13	7·6%	0·94 (0·49–1·81)
Balsalobre Salmeron et al (2018)[28]	16	62	5	9	6·7%	0·46 (0·23–0·96)
Choi et al (2020)[29]	2	4	3	12	2·4%	2·00 (0·50–8·00)
Montenegro et al (2019)[39]	1	22	2	23	0·9%	0·52 (0·05–5·36)
Dotzenrath et al (2001)[30]	3	25	3	13	2·2%	0·52 (0·12–2·22)
Fyrsten et al (2016)[32]	8	30	10	31	6·0%	0.83 (0.38–1.81)
Horiuchi et al (2018)[33]	11	21	4	12	4·9%	1·57 (0·64–3·86)
Hubbard et al (2006)[34]	1	21	1	4	0·8%	0·19 (0·01–2·46)
Kluijfhout et al (2016)[3]	5	16	1	8	1·2%	2·50 (0·35–17·97)
Lamas et al (2019)[35]	10	23	2	11	2·5%	2·39 (0·63–9·11)
Lambert et al (2005)[36]	3	14	4	13	2·7%	0·70 (0·19–2·54)
Landry et al (2022)[37]	40	95	65	85	16·4%	0·55 (0·42–0·72)
Lee et al (2006)[38]	1	6	0	11	0·5%	5·14 (0·24–109·89)
Manoharan et al (2020)[4]	9	23	19	28	9·0%	0·58 (0·33–1·02)
Marini et al (2018)[2]	1	2	2	4	1·6%	1·00 (0·18–5·46)
Norton et al (2008)[40]	18	40	16	35	10·4%	0·98 (0·60–1·62)
Pieterman et al (2012)[41]	3	16	4	14	2·6%	0·66 (0·18–2·44)
Shariq et al (2022)[42]	2	14	9	16	2·5%	0·25 (0·07–0·98)
Twigt et al (2013)[43]	11	17	12	21	10·1%	1·13 (0·68–1·89)
Versnick et al (2013)[44]	3	10	0	6	0·6%	4·45 (0·27–73·81)
Waldmann et al (2010)[45]	2	11	6	13	2·4%	0·39(0·10–1·57)
Yavropoulou et al (2022)[46]	9	35	9	22	6·3%	0·63 (0·30–1·34)
Total	**185**	**567**	**183**	**404**	**100·0%**	**0·78 (0·62–0·97)**

Heterogeneity: τ^2=0·06;χ^2=28·83, df=21 (p=0·12); I^2=27%

Test for overall effect: Z=2·19 (p=0·03)



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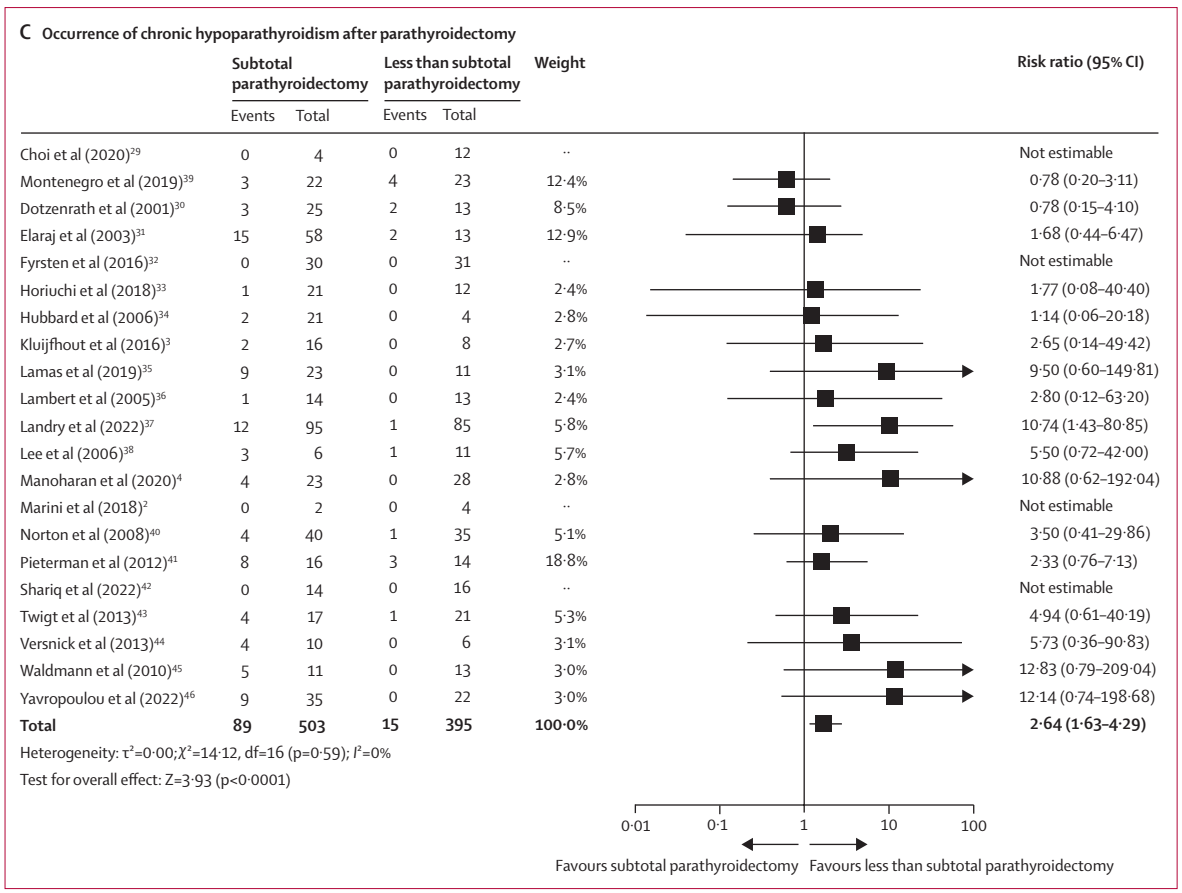

Figure 2: **Forest plots for the MEN1-associated primary hyperparathyroidism meta-analysis (Q1), reporting data about persistent primary hyperparathyroidism (A), recurrent primary hyperparathyroidism (B), and occurrence of post-operative chronic hypoparathyroidism (C)**
Risk ratios are calculated by the Mantel–Haenszel method. 95% CIs are calculated by the Wald-type method. τ^2 values are calculated by the DerSimonian and Laird method. Risk ratios on the left indicate decreased risks and ratios on the right indicate increased risks associated with subtotal parathyroidectomy when compared with less than subtotal parathroidectomy.

non-functioning pancreatic neuroendocrine tumours (p=0·043) and were female (p=0·004), when compared with patients in the active surveillance group, and one patient in the surgery group died from post-operative complications within 30 days of surgery, with no deaths in the surveillance arm (GRADE certainty very low).[48]

Regarding Q2 secondary outcomes, one study reported post-operative complications in 20 (50%) of 40 patients, half of whom were classified as Clavien-Dindo grade III or grade IV (tables 3, 4; appendix p 42).[48] The remaining two studies either did not report post-operative complications[10] or did not report them separately for non-functioning pancreatic neuroendocrine tumours sized 2 cm or less.[47] In the active surveillance groups of two studies, time to surgery was reported in seven (14%) of 50 patients at a mean time of 5·9 years (SD 4·7),[10] and nine (33%) of 27 patients at a median time of 10·3 years (IQR not reported; GRADE certainty very low).[48] No studies reported the incidence of exocrine pancreatic insufficiency or type 3c diabetes separately for patients with non-functioning pancreatic neuroendocrine tumours sized 2 cm or less (appendix p 42).

Regarding Q3 primary outcomes, a meta-analysis was not feasible for Q3 due to a predominance of uncontrolled case series and significant variability in study designs. In ten studies on patients with prolactinomas (157 with MEN1, 348 without MEN1), first-line dopamine agonists did not normalise serum prolactin concentrations in zero of one[51,52,56] to one (33%) of three[55] patients with MEN1; and four (6%) of 68[58] to nine (82%) of 11[56] patients without MEN1 (GRADE certainty very low; tables 5, 6; appendix p 43).[20,50–58] In seven studies on patients with prolactinomas (123 with MEN1, 277 without MEN1), over 50% tumour reduction was not achieved in zero of one[52,56] to 17 (47%) of 36[57] patients with MEN1; and zero of 10[56] to 77 (53%) of 146[53] patients without MEN1 (GRADE certainty very low; table 5; table 6; appendix p 43).[20,50,52,53,56–58] In eight studies on patients with prolactinomas (153 with MEN1, 260 without MEN1) who received first-line dopamine agonist therapy, surgery was required in zero of 30[54] to 29 (34%) of 85[58] of patients with MEN1; and zero of 10[56] to six (55%) of 11[50] patients without MEN1 (GRADE certainty very low; tables 5, 6; appendix p 43).[20,50,51,53–57,58]

Regarding Q3 secondary outcomes, five studies with 227 patients with prolactinomas (39 with MEN1 and 188 without MEN1) reported that the mean or median cabergoline dose needed to achieve normalisation of serum prolactin concentrations was 0·175–4·0 mg/week in patients with MEN1, compared with 0·25–7·5 mg/week in the patients without MEN1 (GRADE certainty very low; appendix p 44).[51–53,56,57] Six studies with 398 patients (152 with MEN1 and 246 without MEN1) reported that radiotherapy was received by zero of 36[57] to ten (12%) of 85[58] patients with MEN1, and one (1%) of 68[58] to three (27%) of 11[50] patients without MEN1 (GRADE certainty very low; tables 5, 6; appendix p 44).[50,51,53,54,57,58] Six studies with 398 patients (152 with MEN1 and 246 without MEN1) reported that chemotherapy was administered to zero of one to zero of 85 patients with MEN1 and zero of 68[58] to two (10%) of 21[51] patients without MEN1 (GRADE certainty very low; tables 5, 6; appendix p 44).[50,53,54,57,58]

Discussion

Our systematic reviews for the three clinical questions relating to the management of patients with MEN1 retrieved a total of 3048 records, although only 37 (1·2%) of these publications met the inclusion criteria. This finding indicates that, although there is substantial research activity and interest in these areas, most studies are retrospective series with sparse data that are insufficient for providing high or moderate certainty for the evidence using the GRADE approach (appendix pp 33–38). Thus, an important message from our study is that there is an unmet need for higher quality clinical studies in MEN1 that would provide evidence-based guidelines and thereby improve health decisions and outcomes for patients with this rare neoplastic disorder. Additionally, it was only possible to perform a meta-analysis for Q1, highlighting the limitations of the available data. Nevertheless, our study provides evidence, albeit at low and very low certainty levels, for some aspects of the management of each of the three major tumours associated with MEN1, namely parathyroid tumours, non-functioning pancreatic neuroendocrine tumours, and prolactinomas.

In patients with MEN1-associated primary hyperparathyroidism, those who had subtotal parathyroidectomy had around a 68% (95% CI 48–80) reduction in the risk of persistent disease and a 22% (3–38) reduction in the risk of primary hyperparathyroidism recurrence compared with those who had less than subtotal parathyroidectomy. However, the median time to disease recurrence was broadly similar between the two groups. Approximately 10% of patients in the subtotal parathyroidectomy group had post-operative hypoparathyroidism (~2·5-fold higher than in the less than subtotal parathyroidectomy group), which is around 1·5 times higher than that reported in subsequent studies in patients who had subtotal parathyroidectomy.[59] This finding might be partly explained by the inclusion of older studies in our meta-analysis, consisting of smaller patient cohorts. Furthermore, variability in study follow-up durations might influence reported rates of post-operative hypoparathyroidism, as some reports suggest that recovery of parathyroid function in patients with MEN1 can occur up to a decade post-operatively,[41] although such recovery of hypoparathyroidism might be due to recurrent parathyroid disease. In a 2024 study that included patients who had reoperation for persistent or recurrent disease, rates of long-term hypoparathyroidism (after final surgery) were comparable between less than subtotal parathyroidectomy and subtotal parathyroidectomy (9% *vs* 7%).[59] Given these considerations, although our analysis indicates a higher risk of long-term hypoparathyroidism with subtotal parathyroidectomy, this must be interpreted in the context of evolving surgical expertise and the risk of future reoperation with less than subtotal parathyroidectomy, which might also contribute to permanent hypoparathyroidism.

Our analyses focused on persistent and recurrent hyperparathyroidism and post-operative hypoparathyroidism because these outcomes have substantial downstream effects on patient morbidity, including nephrolithiasis and bone mineral density (BMD) abnormalities. However, none of the included studies compared the incidence of these other complications by the extent of parathyroidectomy, although these remain important considerations in surgical decision making. Moreover, in patients without MEN1 with primary hyperparathyroidism, some centres have extended the definition of permanent post-operative hypoparathyroidism from 6 months to 12 months post-operatively,[60] and the application of this definition could alter and affect the frequency of hypoparathyroidism following subtotal parathyroidectomy and less than subtotal parathyroidectomy in patients with MEN1. In summary, our analyses indicate that index less than subtotal parathyroidectomy is associated with a decreased risk of long-term hypoparathyroidism, although this benefit is offset by an increased incidence of disease persistence and recurrence. Since our bibliographic search for papers to be included in this systematic review, two further studies have been reported, both of which support the results from our current analyses.[59,61]

For MEN1-associated non-functioning pancreatic neuroendocrine tumours sized 2 cm or less, comparing surgery versus active surveillance, an insufficient number of studies met the inclusion criteria for a meta-analysis. Although there was no clear numerical difference between clinical outcomes in either study group, it is important to note that these results were derived from only three cohort studies.[10,47–49] Confounding factors might also have arisen because of the indication for surgery for non-functioning pancreatic neuroendocrine tumours sized 2 cm or less that exhibit growth on serial imaging, and for which the current MEN1 practice guidelines recommend surgical

resection.[12] Thus, this recommendation might have caused a selection bias for both primary and secondary outcomes, as patients who initially underwent surgical intervention were reported to have a higher number of non-functioning pancreatic neuroendocrine tumours[48,49] and metastases at diagnosis.[49] Therefore, there is likely to be an underestimation of the effects of surgery and, to date, only one study has adjusted for these potential differences between patient groups.[47] Early post-operative complications after pancreatic resection in patients with MEN1 are substantial, with 25% having Clavien-Dindo grade III–IV complications in one study.[48] This risk must be carefully weighed against the benefits of surgery, especially as several well conducted independent cohort studies have reported that these tumours might be indolent.[9,10] Nevertheless, there might be a subset of MEN1-associated non-functioning pancreatic neuroendocrine tumours sized 2 cm or less that could benefit from earlier surgery, especially as distant metastases have been reported to occur in around 3% of cases.[8,62,63] Currently, size, growth, and grade are the only actionable factors associated with a higher risk of metastases.[11]

For prolactinomas, it remains unclear whether dopamine agonist resistance in patients with MEN1 is higher than in patients without MEN1. Although the number of patients (N=505 [157 patients with MEN1 and 348 patients without MEN1]) studied was large, the certainty of evidence was very low. Moreover, a meta-analysis could not be undertaken, because the designs of these ten studies were heterogeneous. Comparisons between prolactinomas in patients with MEN1 versus patients without MEN1 were either in uncontrolled case series, or were direct comparisons from controlled series that did not adjust for prognostic and confounding factors, such as sex, age of the patient, prolactinoma size, dopamine agonist dose titration (ie, dopamine agonist dose required to achieve normoprolactinaemia), and, for non-responders, the maximum dose of the dopamine agonist prescribed. For example, around 20–33% of studies in the non-MEN1 group included patients with giant macroprolactinomas (ie, >4 cm in diameter), compared with 4% in the MEN1 group, although one study did match patients with and without MEN1 with prolactinomas and reported that serum prolactin concentrations in patients with MEN1 were less likely to normalise.[58] However, it should be noted that in this study not all patients had genetic testing for *MEN1* mutations, although patients without MEN1 were reported as not having a hereditary disease.

Our studies and analyses have several limitations. First, despite a comprehensive bibliographic search on several databases without language restriction, we were able to find only a few studies comparing surgery with active surveillance for MEN1-associated non-functioning pancreatic neuroendocrine tumours sized 2 cm or less. Second, we were able to pool results through meta-analysis only for the comparison of subtotal parathyroidectomy versus less than subtotal parathyroidectomy for patients with MEN1-associated primary hyperparathyroidism due to the high clinical and methodological heterogeneity of the reported studies. Third, for this meta-analysis, we had to base our analysis on crude estimates from observational studies, as adjusted estimates were not provided by the study authors, and therefore, our estimates could be biased by the effects of relevant confounders, such as the severity of the disease and age of participants. Fourth, there is the potential influence of surgical expertise on outcomes following parathyroidectomy for MEN1-associated primary hyperparathyroidism, and it is important to note that the studies included in our meta-analysis did not report details on surgeon experience, institutional case volume, or the use of intra-operative PTH monitoring (for patients who underwent less than subtotal parathyroidectomy). These sources of heterogeneity, which we could not control or adjust for in our analyses, might have influenced the observed differences in persistence, recurrence, and hypoparathyroidism rates between subtotal parathyroidectomy and less than subtotal parathyroidectomy. Nevertheless, our findings have the strength to be based on a comprehensive search of the available evidence and on a rigorous methodological approach to evaluate the quality of the studies and the certainty of available evidence.

In conclusion, our findings show that systematic reviews can be effectively conducted in rare diseases to provide an evidence-based framework for guiding clinical management. However, the heterogeneity and variable quality of available data regarding the treatment of MEN1-related endocrine tumours underscore the necessity for well designed, prospective studies to enhance future recommendations and improve outcomes for patients with this rare neoplastic disorder.

Contributors

RVT, GDV, MLB, SGW, FC, and SM contributed to the supervision of the systematic review. RVT, MLB, OAS, and FM contributed to the parathyroid systematic review. GDV, CRCP, and KAE contributed to the pancreatic neuroendocrine tumour systematic review. RVT, SGW, FC, TC, KEL, and KAE contributed to the pituitary section, and SM, ZM, and RS contributed to the methodology and analysis. KAE, CRCP, FM, KEL, TC, OAS, FC, SGW, MLB, RVT, and GDV verified the data; KAE, RS, ZM, and SM had access to the raw data; RVT had final responsibility for decision to submit for publication.

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Data sharing

Study protocols and completed data extraction sheets are available on reasonable request to the corresponding authors (SM and RVT). All data have been published (appendix pp 3–44) and therefore are in the public domain.

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