Optimal extent of parathyroid resection in patients with Multiple Endocrine Neoplasia syndrome type 1: a meta-analysis

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Running Title: Comparison between Total, Subtotal and Less than Subtotal Parathyroidectomy outcomes in MEN 1 patients.

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ABSTRACT

Background: Hyperparathyroidism is an almost universal feature of Multiple Endocrine Neoplasia type 1 syndrome. We present a systematic review and meta-analysis of the postoperative outcomes of patients undergoing surgical treatment of MEN 1 hyperparhyroidism.

Methods: A comprehensive literature search was performed with apriori defined exclusion criteria, for studies comparing Total (TPT) or Less than Subtotal Parathyroidectomy (LSPT) to Subtotal Parathyroidectomy (SPT).

Results: Twenty-one studies incorporating 1131 patients (272 undergoing TPT, 510 SPT and 349 LSPT) were identified. Pooled results revealed significantly increased risk for long-term hypoparathyroidism in TPT patients (RR 1.61, 95% C.I. 1.12 to 2.31, p=0.009) versus those undergoing SPT. In the LSPT-SPT comparison group, a significantly higher risk for hyperparathyroidism recurrence (RR 1.37, 95% C.I. 1.05 to 1.79, p=0.02), persistence (RR 2.26, 95% C.I. 1.49 to 3.41, p=0.0001) and reoperation (RR 2.48, 95% C.I. 1.65 to 3.73, $p<0.0001$) was noted for LSPT patients, albeit with lower risk for long-term parathyroidism (RR 0.47, 95% C.I. 0.29 to 0.75, p=0.002).

Conclusion: SPT compares favorably to TPT, exhibiting similar recurrence and persistence rates with a reduced propensity for long-term postoperative hypoparathyroidism. The benefit of reduced hypoparathyroidism risk in LSPT is negated by the increase in the risk for recurrence, persistence and reoperation.

INTRODUCTION

Primary hyperparathyroidism (pHPT) is an almost universal feature of Multiple Endocrine Neoplasia type 1 (MEN 1) syndrome, and is usually the first biochemical manifestation in patients with the mutated MEN 1 gene [1]. Hyperparathyroidism in MEN 1 presents usually during the second and third decades of life, a significantly earlier age than sporadic hyperparathyroidism [2, 3]. The patients may present with the classic manifestations of nephrolithiasis, bone demineralization and dyspepsia or more frequently with a non specific systemic malaise that loosely falls under the umbrella of neurocognitive disturbance. Given the early onset of pHPT in MEN1 patients the long term effects may lead to significant sequelae and surgical treatment remains the only solution [4].

In MEN 1 syndrome the pHPT is characterized by metachronous multiglandular disease [1, 5]. The disease progression and severity varies widely and it is not always the case that pHPT of early onset indicates a more aggressive disease variant[3] although prolonged disease exposure is more likely to result in more deleterious effects. The optimal timing for the parathyroidectomy in MEN1 syndrome is debated with the options being an early intervention based on the biochemical evidence of disease or surgery based on symptoms, end organ damage or biochemical severity[6].

The optimal surgical strategy is also still debated with the most popular solutions being a total parathyroidectomy (TPT) with autologous grafting usually in the forearm or alternatively a subtotal or 3.5 gland pararathyroidectomy (SPT). This latter procedure consists in leaving a normal parathyroid or a parathyroid fragment equal in size to a normal gland in situ coupled ideally with a bilateral cervical thymic horn excision [4]. TPT is a more radical procedure, which should lead to a lower rate of postoperative persistence and a lower rate of recurrence or [5, 7]. These apparent advantages or by a higher rate of permanent hypoparathyroidism, despite parathyroid tissue autotransplantation, when compared to SPT [8, 9].

More recently a third surgical option has been proposed that aims in selected cases to minimize the operative risks relating to open neck exploration (i.e. laryngeal nerve injury or long term hypoparathyroidism) and facilitate subsequent neck explorations. This is described as *less than subtotal parathyroidectomy* (LSPT)[7, 10] that encompasses a variety of strategies including minimally invasive, single, two or three gland excisions [7, 8]. The LSPT overall has failed to gain traction due to poor recurrence rates and disease persistence outcomes [9, 11].

We present a systematic review and meta-analysis of the surgical management of pHPT in MEN 1 syndrome with a focus on the postoperative outcomes of patients undergoing the various surgical approaches.

MATERIALS AND METHODS

Search Strategy

A comprehensive literature search of the MedLine, Scopus, Google Scholar and Web of Knowledge databases was performed in order to identify articles published until March 2020. The search terms were; "Multiple Endocrine Neoplasia Type 1", "MEN 1", "MEN I", "parathyroidectomy", "parathyroid surgery", "parathyroid excision". The Boolean operators AND/OR were used in conjunction with the listed search terms in the search protocol employed. Reference lists of screened articles were manually checked for further potentially relevant studies.

Two authors (DP, EK) independently conducted the search and screening of the titles and abstracts of the articles generated by the above search protocol. Following the removal of duplicate studies encountered during the initial screening process, potentially eligible papers were reviewed in full-text. Studies extracted for inclusion in the quantitative analysis were selected by common consensus by two authors (DP, EK). Any discrepancies were resolved by a third author (CN). The present study was conducted according to PRISMA guidelines [12].

Criteria for inclusion/exclusion

The predefined inclusion criteria were: (1) studies with patients diagnosed with Multiple Endocrine Neoplasia 1 (MEN 1) syndrome and hyperparathyroidism, including patients undergoing parathyroid surgery and (2) studies comparing outcomes of subtotal parathyroidectomy with total or less than subtotal parathyroidectomy.

Exclusion criteria were: (1) reviews, case reports and case series, (2) articles published in non-English language, (3) studies including patients without MEN 1 syndrome, (4) non-human studies, (5) studies without comparative data between different types of parathyroid surgery, (6) studies with incomplete or not explicitly reported data, (7) studies including patients undergoing total parathyroidectomy without autotransplantation, (8) studies reporting only outcomes of patients undergoing reoperation.

Data and outcomes of interest

The primary outcomes of interest were the post-operative rates of persistent and recurrent hyperparathyroidism, the rate of long-term hypoparathyroidism and the number of patients requiring reoperative parathyroidectomy.

Secondary data of interest were, the year of publication, the time of data collection, patient demographics, the percentage of patients undergoing transcervical thymectomy and the length of follow-up in months.

Definitions

The term Total Parathyroidectomy (TPT): Excision of all parathyroid glands upon cervical exploration with autotransplantation of a parathyroid fragment in the neck or the arm.

Subtotal Parathyroidectomy (SPT): A parathyroidectomy that intentionally leaves a whole or part of a parathyroid gland in situ on its normal vasculature.

Quality assessment

The Newcastle-Ottawa scale (NOS) is a tool used to assess the methodological quality of cohort studies. The scale is divided in three components; (i) the selection of study groups, (ii) the comparability of the study groups with regards to baseline confounding factors (i.e. patient demographics, preoperative levels of PTH and the percentage of patients undergoing thymectomy in each group, (iii) assessment of the reported outcomes. The scale contains 8 total items, on which each study is individually judged by two reviewers (MP) and awards a maximum score of 9 stars for the highest quality studies. Visual assessment of NOS is available as supplementary material.

Data extraction and statistical analysis

After the initial extraction process, data from eligible studies were entered in standardized excel spreadsheets (Microsoft, Redmond, Washington, USA) and were subsequently cross-validated by three reviewers (AP, EK, DP). Any ensuing disagreements were resolved by common consensus.

All analyses involved in the current review were performed using the Review Manager version 5.3 *(*Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The Relative Risk (RR) and its corresponding 95% confidence intervals were calculated for dichotomous variables. Due to expected methodological heterogeneity regarding the utilized diagnostic criteria for MEN 1, the use of adjunct thymectomy during index parathyroidectomy and differing definitions of subtotal and less than subtotal parathyroidectomy, a random-effects statistical model (DerSimonian and Laird) was selected a priori. Statistical heterogeneity was assessed with the Higgin's I^2 statistic. As per convention, values below 25% represent low heterogeneity, values between 25 and 75% represent medium heterogeneity, while values above 75% represent high heterogeneity.

Assessment of publication bias was performed visually, judging the symmetry of produced funnel plots (available as supplementary material) as well as with Egger's and Begg's tests (calculated using the "Meta-Essentials" excel workbook [13]) for all outcomes involving ten or more studies. A p-value below 0.05 was considered statistically significant. If testing for publication bias was positive, the trim-and-fill method was used to assess the impact of potentially missing studies, causing the encountered funnel plot asymmetry, in the overall statistical significance of the effect size [14].

RESULTS

Overall, 21 studies [7-11, 15-30] incorporating 1131 patients (272 undergoing TPT, 510 SPT and 349 LSPT) were identified through systematic database search. Fourteen studies involved retrospective observational cohorts [5, 8, 9, 15-19, 22-26, 28, 30], three were retrospective database cohorts [10, 26, 29], two were databases with prospective data collection [7, 29], one was a mixed prospective and retrospective database cohort [21] and one was a prospective randomized trial [20]. The years of data collection ranged from 1970 to 2019, with thirteen studies being of European origin [5, 7-10, 15, 17, 18, 21, 24, 26, 29,

[30], six from USA [11, 16, 19, 20, 22, 25], one from Taiwan [23] and one from Australia [28]. Study and patient characteristics are available for review on Tables 1 and 2.

Critical appraisal

Assessment of studies included in the quantitative analysis with the Newcastle-Ottawa Scale suggests methodological adequacy, as is underlined by a median and mean score of 7 stars and a range of 5 to 9 stars. The vast majority of included studies were of high quality regarding the cohort selection and outcome reporting criteria, however adequate control for baseline patient factors (namely; sex, age, preoperative PTH levels and thymectomy) was often either lacking or incomplete. A loss to follow-up greater than 10% of the entire cohort was encountered in 5 studies [16, 21, 22, 24, 25] leading to the subtraction of 1 star from the total score, hence explaining the median score of 7 stars across all included studies. Total Parathyroidectomy (TPT) was defined as the excision of all parathyroid glands upon cervical exploration with autotransplantation of a parathyroid fragment in the neck or the arm. The definitions used for Subtotal Parathyroidectomy (SPT) and Less than Subtotal Parathyroidectomy (LSPT) were variable depending on study, as can be reviewed on Table 1.

The primary outcomes of interest were uniformly defined across the included studies; however, some studies were missing a clearly stated definition. Specifically, a definition for hyperparathyroidism recurrence is provided in 14 studies [5, 7, 9, 11, 15, 16, 18-22, 26, 28, 29] as an increase in calcium and/or PTH levels after 6 months after surgery, preceded by a normocalcemic interval. Lee et al. [23] defined recurrence as biochemical derangements occurring after 6 months. Persistence is defined in 10 studies [7, 9, 17, 19, 20, 22, 26-29] as an increased calcium and/or PTH levels more than 6 months after surgery or as immediately postoperatively increased calcium and/or PTH levels in two studies [11, 25]. A definition for long-term postoperative hypoparathyroidism is stated in 11 studies

[7, 9, 16, 17, 19, 21, 22, 26-29], as the presence of low calcium/PTH levels with a concurrent need for calcium and vitamin D analogue supplements for at least 6 months after surgery.

The rationale for selecting TPT or LSPT over SPT was variable across studies. Eight studies [10, 11, 16, 23, 26-29] state that TPT or SPT was performed after neck exploration depending on surgeon's preference, while two studies [15, 19] report SPT being the standard procedure performed. LSPT was carried out after preoperative localization of hyperfunctioning parathyroids in five studies [7, 9, 19, 26, 28]. Selective removal of marcoscopically enlarged glands, after neck exploration, was noted as a reason for LSPT in two studies [15, 23], whereas unintentional (either when identification of all parathyroid glands was not possible or not accurate) LSPT was performed in another two studies [10, 16].

Recurrent Hyperparathyroidism

Sixteen studies [5, 7-11, 16-18, 20, 22-24, 26, 28, 29] compare recurrence rates in patients undergoing TPT versus SPT, revealing no statistically significant difference (RR 0.69, 95% C.I. 0.45 to 1.07, p=0.09; Figure 2) with medium interstudy heterogeneity (I^2=29%, p=0.13). No publication bias was encountered (Begg's test: p=0.58; Egger's test: p=0.5).

Eighteen studies [7-11, 15-19, 22-26, 28-30] report comparative recurrence rates between LSPT and SPT. A significantly increased risk for recurrence was encountered in patients undergoing LSPT (RR 1.37, 95% C.I. 1.05 to 1.79, p=0.02; Figure 2) with medium intestudy heterogeneity (I^2=27%, p=0.14). No publication bias was encountered (Begg's test: p=0.85; Egger's test: p=0.71).

Persistent Hyperparathyroidism

Twelve studies [5, 7-11, 17, 20, 21, 24, 26, 29] report persistence rates for patients operated on with either TPT or SPT. No statistical difference was encountered (RR 0.65, 95% C.I. 0.34 to 1.25, p=0.2; Figure 3) with no interstudy heterogeneity (I^2=0%, p=0.68). No publication bias was present (Begg's test: p=1; Egger's test: p=0.46).

In regards to hyperpathyroidism persistence (as reported in twelve studies [7-11, 17, 19, 21, 24-26, 29]) in patients undergoing LSPT versus SPT, a statistically significant increase in risk was noted (RR 2.26, 95% C.I. 1.49 to 3.41, p=0.0001; Figure 3) with no intestudy heterogeneity (I^2=0%, p=0.49). No publication bias was encountered (Begg's test: p=0.58; Egger's test: p=0.61).

Long-term Hypoparathyroidism

Overall, fifteen studies [5, 7-11, 16, 18, 20, 21, 23, 24, 26, 28, 29] compare TPT versus SPT regarding long-term postoperative hypoparathyroidism, revealing a statistically significant increased risk of hypoparathyroidism in patients undergoing TPT (RR 1.61, 95% C.I. 1.12 to 2.31, p=0.009; Figure 4) with medium interstudy heterogeneity (I^2=36%, p=0.08). No publication bias was encountered (Begg's test: p=0.88; Egger's test: p=0.83).

Pooled data from fifteen studies [7-11, 16, 18, 19, 21, 23, 24, 26, 28-30] show that LSPT was associated with significantly decreased long-term hypoparathyroidism rates when compared to SPT (RR 0.47, 95% C.I. 0.29 to 0.75, p=0.002; Figure 4) with no interstudy heterogeneity (I^2=0%, p=0.7). Following visual assessment of the relevant funnel plot, possible publication bias was found and was subsequently confirmed by Egger's test (p=0.04). Application of the trim-and-fill analysis revealed that the adjusted long-term hypoparathyroidism rates were still significantly lower in patients undergoing LSPT (RR 0.53, 95% C.I. 0.30 to 0.93, I^2=0%), suggesting little impact of the possible publication bias on the calculated pooled risk ratio.

Reoperative parathyroidectomy

The need for reoperation was evaluated in eight studies [5, 7, 8, 18, 21-23, 29] comparing TPT versus SPT and eight studies [7, 8, 15, 18, 21-23, 29] comparing LSPT versus SPT. No significant difference in the risk for reoperation was encountered for patients undergoing TPT versus those undergoing SPT (RR 0.81, 95% C.I. 0.47 to 1.37, p=0.43; Figure 5) with no interstudy heterogeneity being noted (I^2=0%, p=0.48). On the contrary, LSPT was associated with significantly higher risk for reoperation (RR 2.48, 95% C.I. 1.65 to 3.73, p<0.0001; Figure 5) with low encountered interstudy heterogeneity (I^2=18%, p=0.29).

DISCUSSION

MEN 1 syndrome is associated with a 100% penetrance of pHPT by the age of 65 years[31]. Whilst parathyroidectomy is universally accepted as the mainstay of treatment, there is an ongoing debate as to which surgical approach offers the best results. SPT has been previously proposed as the procedure of choice in hereditary PHPT [32] yet concrete data do not exist, to date, on how it compares to TPT or LSPT in regards to postoperative outcomes.

Total parathyroidectomy with autotransplantation presents an appealing approach for MEN 1 related PHTP, taking into account the multiglandular phenotype it exhibits. In theory, total parathyroidectomy radically addresses the underlying disease by removing all hyperfunctioning parathyroid glands, as well as those susceptible for developing hyperplastic or adenomatous changes in the future and it is rational to assume that TPT achieves lower persistence and long-term recurrence rates when compared to SPT. Our results, however, indicate that there is no statistically significant difference between the approaches, with at most a trend towards lower recurrence (RR 0.69, 95% C.I. 0.45 to 1.07) and persistence (RR 0.65, 95% C.I. 0.34 to 1.25) after a TPT. This finding is in accordance with the results put forward by Lairemore et al. [20] in their prospective randomized trial comparing TPT with SPT which did not demonstrate any significant difference in the recurrence rates between the two surgical methods after a long follow-up.

Autotransplantation of parathyroid tissue during TPT is thought to safeguard against the permanent hypoparathyroidism. The choice of the forearm for autotransplantation is to allow for easier resection in case of recurrence as compared to neck re-exploration of the neck in SPT. Our cumulative results reveal a significantly increased rate of long-term hypoparathyroidism after TPT compared to SPT (RR 1.61, 95% C.I. 1.12 to 2.31). Conversely, LSPT was associated with a 53% reduction of the risk for developing long-term postoperative hypoparathyroidism when compared to SPT. The calculated hypoparathyroidism incidence rates in the pooled patient cohort were 35.5% for TPT, 21.4% for SPT and 7.1% for LSPT, indicating a clear association of long-term hypoparathyroidism with the extent of gland resection as has been previously suggested [26].

Although LSPT compares favorably to SPT in regards to development of long-term hypocalcemia, disease control outcomes are apparently inferior to those achieved by SPT. Specifically our analysis shows that LSPT is associated with a 37% increase in the risk of recurrent hyperparathyroidism and a 126% increase in disease persistence. These treatment failures are attributable to occult disease not localized on preoperative workup[10] and partly to metachronous disease recurrence in the remaining glands [28]. Moreover, the inability to perform cervical thymectomy in minimally invasive approaches [7, 18, 29] may confer and additional risk, given that ectopic parathyroid glands are present in up to 23% of patients [33, 34]. Intraoperative PTH monitoring may be used to supplement localization studies [32], however, its efficacy in reducing persistence and recurrence rates remains arguable [10, 15, 22].

A major concern in the management of patients with MEN 1 related hyperparathyroidism is the need for reintervention and the associated risks for complications such as laryngeal nerve injury during dissection in a previously operated and therefore scarred neck. Our results suggest that TPT and SPT share a similar risk for reoperation, however, LSPT leads to a 148% increase in the need for reoperation when compared to SPT. This finding is reasonable considering the increased propensity for recurrence after LSPT and thus should be taken into account when formulating a treatment strategy.

The novel concept of genotype-phenotype correlation for patients with MEN 1 holds promise for identifying patients at risk for disease recurrence and persistence. Pieterman et al. [9] in their study of 73 patients concluded that nonsense and frameshift mutations in the exons 2, 9 and 10 of the menin gene sequence are related to a lesser risk for recurrence following LSPT, although no such difference was noted after TPT and SPT. These findings imply that the surgical approach selection process could be optimized by incorporating a genetic component to the preoperative patient workup, although more concrete data from prospective cohort studies are required.

The present study is the most comprehensive to date on the topic of surgical strategy in MEN1 related pHPT and has expanded on the results of the previous meta-analysis carried out by Schreinemakers et al. [26] by further adding 9 well designed cohort studies. However, notable limitations were encountered. First of all, the majority of included studies were retrospective cohort studies subject to selection bias. Additionally, considerable heterogeneity was evident in the definitions of SPT and LSPT, the number of patients undergoing concurrent thymectomy and the reported indication for reoperation. All the above are confounding factors that affect our results and plausibly attenuate or overestimate the impact of surgical treatment on disease outcomes. Finally, the low methodologic quality of some of the included studies may negatively impact the robustness of the obtained results.

In conclusion, SPT remains the gold standard procedure for the treatment of MEN 1 pHPT since it is overall superior to TPT: it exhibits similar disease recurrence and persistence rates concurrently with a reduced propensity for long-term postoperative hypoparathyroidism. LSPT when compared to SPT demonstrates a reduced risk for hypoparathyroidism albeit with a significantly increased rate of recurrence, persistence and reoperation. Future cohort studies evaluating the genotype-phenotype correlation of patients with MEN 1 and hyperparathyroidism should be pursued, in an effort to optimally identify candidates for LSPT.

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Study	Year	Country	Type of Study	Interval of data collection	Definition of SPT	Definition of LSPT	Bilateral thymectomy (n, %)
Manoharan	2019	Germany	Prospective database	1997-2019	Removal of 3 or 3.5 glands with bilateral thymectomy	Removal of a single or two glands	n=64, 71.9%
Lamas	2019	Spain	Prospective and retrospective database	N/a	Removal of 3 or more glands leaving one or a remnant behind	Any resection removing less glands than SPT	n=19, 76%
Montenegro	2019	Italy	Retrospective database	1987-2018	Remainder equivalent to one or two normal glands, with routine thymectomy	Removal of less than 3.5 glands	N/a
Tonelli	2018	Italy	Retrospective cohort	1991-2017	Remainder equivalent to an entire or a part of a gland	N/a	N/a
Kluijfhout	2016	USA	Retrospective cohort	1995-2015	Removal of 3 glands with bilateral thymectomy	Unilateral gland removal and ipsilateral thymectomy	n=16 (66.6%)
Fyrsten	2015	Sweden	Retrospective cohort	N/a	Removal of 3 or 3.5 glands	Removal of less than 3 glands	N/a
Lairemore	2014	USA	Prospective randomized cohort	1996-2014	Removal of 3.5 glands	N/a	n=32, 100%
Versnick	2013	Australia	Retrospective cohort	1988-2011	Remainder equivalent to an entire or a part of a gland, with routine thymectomy	Unilateral gland removal and ipsilateral thymectomy	n=26, 100%
Pieterman	2012	Netherlands	Retrospective cohort	1990-2012	Removal of 3 glands or more glands leaving one or less behind	Any resection removing less glands than SPT	N/a
Schreinemakers	2011	Netherlands	Retrospective database	N/a	Removal of 3 or 3.5 glands	Removal of less than 3 glands	N/a
Waldman	2010	UK	Prospective database	1987-2009	Removal of 3 or 3.5 glands, with routine thymectomy	Single gland excision	n=34, 72.3%

Norton	2008	USA	Prospective cohort	1980-2005	Removal of 3 or 3.5 glands	Removal of less than 3 glands	n=24, 28.5%
Hubbard	2006	France	Retrospective cohort	1974-2002	Removal of 3 or more glands leaving one or a remnant behind, with routine thymectomy	Single or double gland excision without thymectomy	n=25, 86.2%
Lee	2006	Taiwan	Retrospective cohort	1982-2002	Removal of 3 glands or more glands leaving one or less behind, with routine thymectomy	Selective enlarged gland excision	n=11, 50%
Lambert	2005	USA	Retrospective cohort	1973-2004	Removal of at least 3 and less than 4 glands	Removal of less than 3 glands	n=12, 38.7%
Elaraj	2003	USA	Retrospective cohort	1960-2002	Removal of 3 or 3.5 glands	Removal of 3, 2.5 or 2 glands	n=79, 86%
Arnalsteen	2002	France	Retrospective cohort	1991-2001	N/a	Removal of macroscopically enlarged glands	n=55, 66.2%
Dotzenrath	2001	Germany	Retrospective cohort	1986-1998	N/a	N/a	n=25, 65.7%
Hellman	1998	Sweden	Retrospective cohort	N/a	Removal of 3 or more glands	Removal of less than 3 glands	N/a
O'riordain	1993	USA	Retrospective cohort	1970-1991	Removal of 3 or 3.5 glands	Any resection removing less glands than SPT	n=11, 13%
Malmaeus	1986	Sweden	Retrospective cohort	1981-1985	Removal of 3 or 3.5 glands	Removal of 1 to 2.5 glands	N/a

Table 1. Characteristics of included studies. SPT = Subtotal Parahtyroidectomy, LSPT = Less than Subtotal Parathyroidectomy, N/a = Not available.

Study	Age (mean, years)	Sex (Male/Female)	Total Patients	TPT N (%)	SPT N (%)	LSPT N (%)	Overall Follow-up (mean, months)
Manoharan	35 (18-70) *	44 / 45	89	38 (42.6%)	23 (25.9%)	28 (31.5%)	112 [a]
Lamas	35.5	30 / 32	62	13 (20.9%)	34 (54.9%)	15 (24.2%)	116
Montenegro	43.5	35 / 58	84	39 (46.4%)	22 (26.2%)	23 (27.4%)	N/a
Tonelli	23.5	11 / 26	37	28 (75.6%)	9 (24.4%)	N/a	11.8
Kluijfhout	42	7 / 17	24	N/a	16 (66.6%)	8 (33.4%)	61
Fyrsten	41	28 / 41	69	8 (11.6%)	30 (43.5%)	31 (44.9%)	197 *
Lairemore	32.5	15 / 17	32	15 (46.8%)	17 (53.1%)	N/a	90
Versnick	42.7	8 / 18	26	10 (38.4%)	10 (38.4%)	6 (23%)	96.3
Pieterman	N/a	N/a	72	32 (44.5%)	23 (31.9%)	17 (23.6%)	51.6 *
Schreinemakers	N/a	N/a	52	6 (11.5%)	17 (32.5%)	29 (56%)	121 *
Waldman	N/a	N/a	47	23 (48.9%)	11 (23.5%)	13 (27.6%)	95
Norton	36	35 / 49	84	9 (10.8%)	40 (47.6%)	35 (41.6%)	86.4
Hubbard	42.4	7 / 22	29	4 (13.8%)	21 (72.4%)	4 (13.8%)	88.5
Lee	43	7 / 15	22	6 (27.3%)	5 (22.7%)	11 (50%)	86.4
Lambert	N/a	N/a	31	4 (12.9%)	14 (45.1%)	13 (42%)	N/a
Elaraj	37	47 / 45	84	13 (15.5%)	58 (69%)	13 (15.5%)	68.4 *
Arnalsteen	40	N/a	79	N/a	66 (83.5%)	13 (16.5%)	48
Dotzenrath	N/a	N/a	38	N/a	25 (65.8)	13 (34.2%)	54
Hellman	44	26 / 24	50	15 (30%)	9 (18%)	26 (52%)	159.6
O’riordain	35 (13-76) *	31 / 53	84	N/a	54 (64%)	30 (36%)	80.4
Malmaeus	N/a	N/a	36	9 (25%)	6 (16.6%)	21 (58.3%)	78 *

Table 2. Patient demographics and characteristics of included studies. TPT = Total Parathyroidectomy, SPT = Subtotal Parahtyroidectomy, LSPT = Less than Subtotal Parathyroidectomy, N/a = Not available. * Presented as median value (range in brackets, where available).

Study	Recurrence N (%)	Persistence N (%)	Permanent Hypoparathyroidism N (%)	Reoperation N (%)
Total Parathyroidectomy versus Subtotal Parathyroidectomy				
Manoharan	4 (4.4%) vs 9 (10.1%)	1 (2.5%) vs 0	12 (32%) vs 4 (17%)	3 (11%) vs 4 (17%)
Lamas	N/a	1 (25%) vs 9 (9%)	1 (20%) vs 9 (39.1%)	0 vs 3 (13%)
Montenegro	2 (5.1%) vs 1 (4.5%)	2 (5.1%) vs 3 (13.6%)	11 (28.2%) vs 3 (13.6%)	N/a
Tonelli	4 (14.2%) vs 4 (44.4%)	0 vs 0	5 (17.8%) vs 2 (22.2%)	3 (10.7%) vs 2 (22.2%)
Fyrsten	0 vs 8 (26.6%)	1 (12.5%) vs 2 (6.6%)	6 (75%) vs 5 (16.6%)	3 (37.5%) vs 10 (33.3%)
Lairemore	2 (13.3%) vs 4 (23.5%)	0 vs 1 (5.8%)	1 (6.6%) vs 2 (11.7%)	N/a
Versnick	3 (30%) vs 3 (30%)	N/a	6 (60%) vs 4 (40%)	N/a
Pieterman	6 (18.7%) vs 4 (17.3%)	6 (18.7%) vs 4 (17.3%)	21 (65.6%) vs 9 (39.1%)	N/a
Schreinemakers	0 vs 11 (64.7%)	1 (16.6%) vs 1 (5.8%)	4 (66.6%) vs 4 (23.5%)	N/a
Waldman	1 (4.3%) vs 0	1 (4.3%) vs 2 (18%)	5 (21.7%) vs 5 (45.4%)	4 (17.4%) vs 4 (36.3%)
Norton	5 (55.5%) vs 18 (45%)	0 vs 5 (12.5%)	2 (22.2%) vs 4 (10%)	N/a
Hubbard	2 (50%) vs 1 (4.7%)	N/a	1 (25%) vs 2 (9.4%)	1 (25%) vs 1 (4.7%)
Lee	0 vs 1 (20%)	N/a	3 (50%) vs 3 (60%)	0 vs 1 (20%)
Lambert	2 (50%) vs 6 (42.8%)	N/a	N/a	2 (50%) vs 4 (28.5%)
Elaraj	3 (23%) vs 19 (32.7%)	N/a	6 (46.1%) vs 15 (25.8%)	N/a
Hellman	3 (20%) vs 4 (44.4%)	0 vs 2 (22.2%)	N/a	N/a
Malmaeus	0 vs 2 (33.3%)	0 vs 0	5 (55.5%) vs 0	N/a

Table 3. Outcomes of patients undergoing Total Parathyroidectomy versus Subtotal Parathyroidectomy.

Study	**Recurrence N (%)**	**Persistence N (%)**	**Permanent Hypoparathyroidism N (%)**	**Reoperation N (%)**
Less than Subtotal Parathyroidectomy versus Subtotal Parathyroidectomy				
Manoharan	19 (21.3%) vs 9 (10.1%)	4 (14.2%) vs 0	0 vs 4 (17%)	24 (27%) vs 4 (17%)
Lamas	N/a	5 (41.6%) vs 9 (9%)	0 vs 9 (39.1%)	4 (36.3%) vs 3 (13%)
Montenegro	0 vs 1 (4.5%)	1 (4.3%) vs 3 (13.6%)	4 (17.4%) vs 3 (13.6%)	N/a
Kluijfhout	1 (12.5%) vs 5 (31.2%)	1 (12.5%) vs 1 (6.2%)	0 vs 2 (12.5%)	N/a
Fyrsten	7 (22.5%) vs 8 (26.6%)	7 (22.5%) vs 2 (6.6%)	2 (6.4%) vs 5 (16.6%)	17 (54.8%) vs 10 (33.3%)
Versnick	0 vs 3 (30%)	N/a	0 vs 4 (40%)	N/a
Pieterman	9 (52.9%) vs 4 (17.3%)	9 (52.9%) vs 4 (17.3%)	4 (23.5%) vs 9 (39.1%)	N/a
Schreinemakers	17 (58.6%) vs 11 (64.7%)	1 (3.4%) vs 1 (5.8%)	2 (6.8%) vs 4 (23.5%)	N/a
Waldman	3 (23%) vs 0	6 (46%) vs 2 (18%)	0 vs 5 (45.4%)	9 (69.2%) vs 4 (36.3%)
Norton	16 (45.7%) vs 18 (45%)	15 (42.8%) vs 5 (12.5%)	1 (2.8%) vs 4 (10%)	N/a
Hubbard	1 (25%) vs 1 (4.7%)	N/a	0 vs 2 (9.4%)	1 (25%) vs 1 (4.7%)
Lee	0 vs 1 (20%)	N/a	1 (9.1%) vs 3 (60%)	0 vs 1 (20%)
Lambert	12 (92.3%) vs 6 (42.8%)	N/a	N/a	10 (76.9%) vs 4 (28.5%)
Elaraj	6 (46.1%) vs 19 (32.7%)	N/a	2 (15.3%) vs 15 (25.8%)	N/a
Arnalsteen	4 (30.7%) vs 5 (7.5%)	N/a	N/a	4 (30.7%) vs 5 (7.5%)
Dotzenrath	3 (23.1%) vs 3 (12%)	N/a	2 (15.4%) vs 3 (12%)	N/a
Hellman	16 (61.5%) vs 4 (44.4%)	9 (34.6%) vs 2 (22.2%)	N/a	N/a

O'riordain	4 (13.5%) vs 9 (16.4%)	5 (16.6%) vs 0	N/a	N/a
Malmaeus	13 (61.9%) vs 2 (33.3%)	5 (23.8%) vs 0	1 (4.7%) vs 0	N/a

Table 4. Outcomes of patients undergoing Less than Subtotal Parathyroidectomy versus Subtotal Parathyroidectomy.

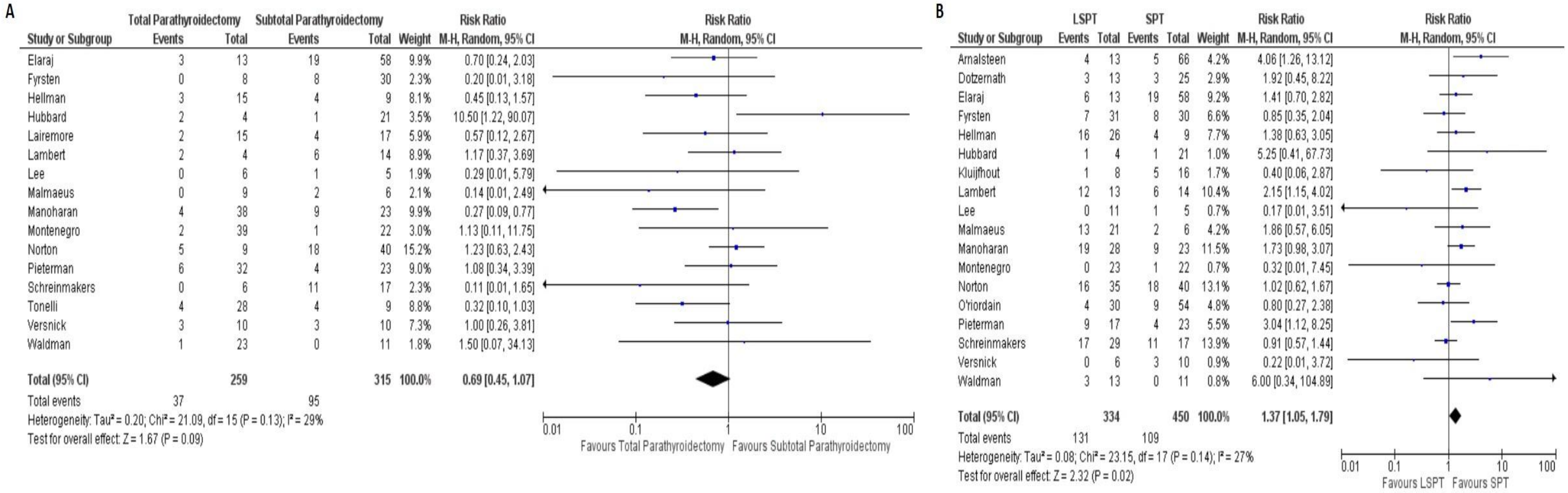

Figure 2. Forest plots for postoperative hypercalcemia recurrence. (A) Total Parathyroidectomy versus Subtotal Parathyroidectomy, (B) Less than Subtotal Parathyroidectomy versus Subtotal Parathyroidectomy. TPT = Total Parathyroidectomy, SPT = Subtotal Parahtyroidectomy, LSPT = Less than Subtotal Parathyroidectomy.

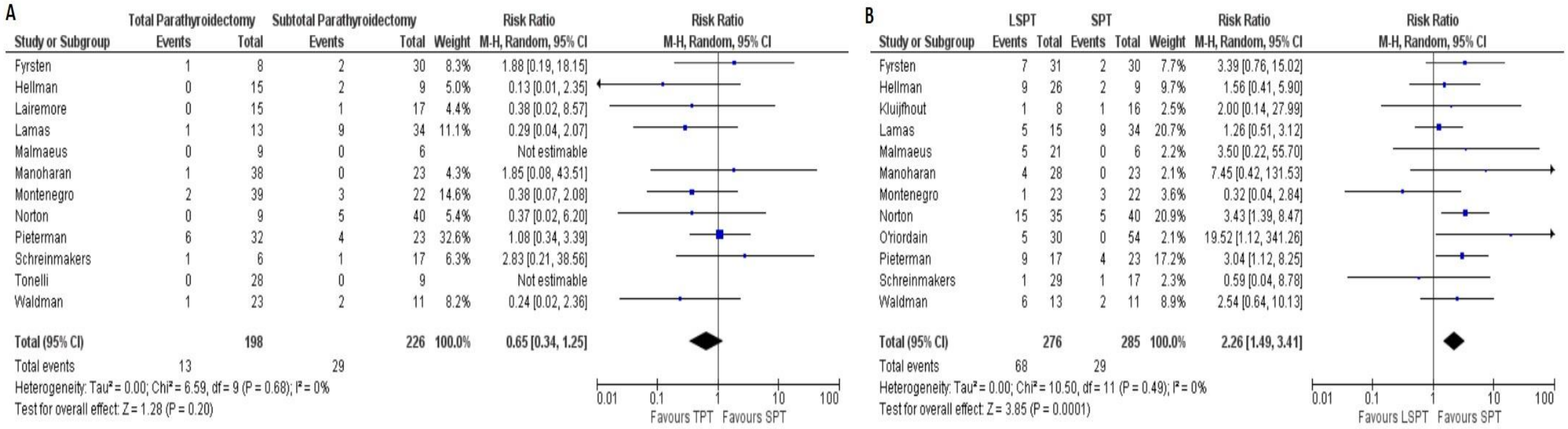

Figure 3. Forest plots for postoperative hypercalcemia persistence. (A) Total Parathyroidectomy versus Subtotal Parathyroidectomy, (B) Less than Subtotal Parathyroidectomy versus Subtotal Parathyroidectomy. TPT = Total Parathyroidectomy, SPT = Subtotal Parahtyroidectomy, LSPT = Less than Subtotal Parathyroidectomy.

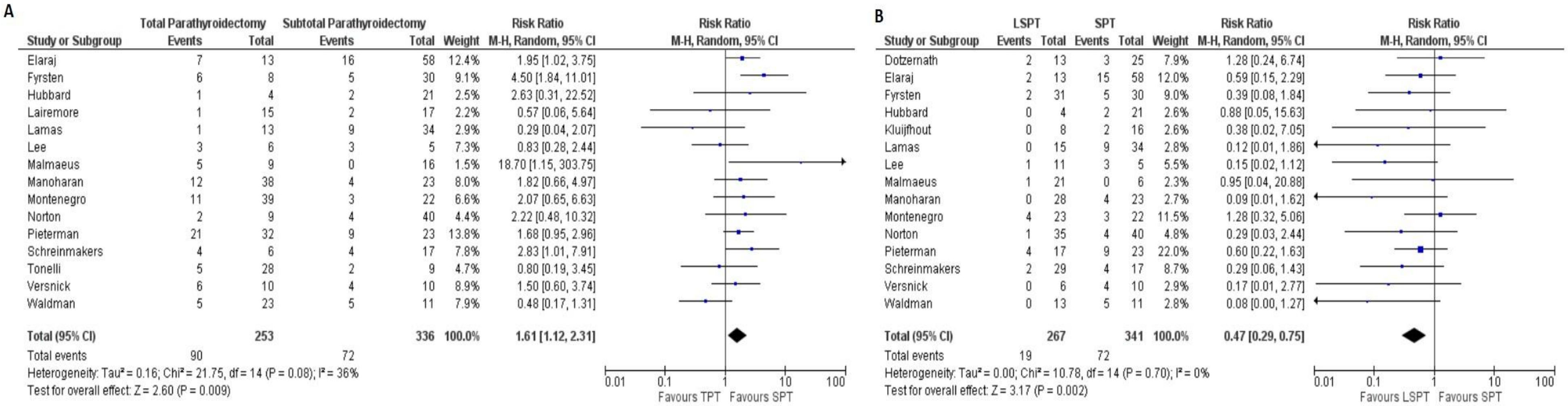

Figure 4. Forest plots for postoperative long-term hypoparathyroidism. (A) Total Parathyroidectomy versus Subtotal Parathyroidectomy, (B) Less than Subtotal Parathyroidectomy versus Subtotal Parathyroidectomy. TPT = Total Parathyroidectomy, SPT = Subtotal Parahtyroidectomy, LSPT = Less than Subtotal Parathyroidectomy.

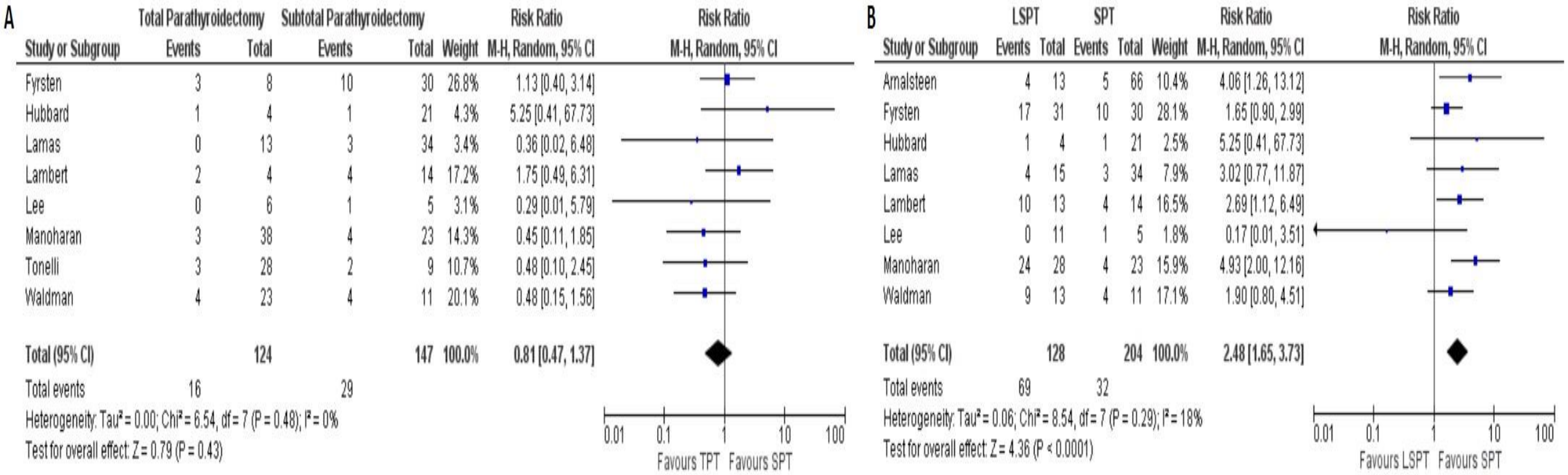

Figure 5. Forest plots summarizing eventual reoperations after the initial parathyroid surgery. (A) Total Parathyroidectomy versus Subtotal Parathyroidectomy, (B) Less than Subtotal Parathyroidectomy versus Subtotal Parathyroidectomy. TPT = Total Parathyroidectomy, SPT = Subtotal Parahtyroidectomy, LSPT = Less than Subtotal Parathyroidectomy.