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SCIENTIFIC REVIEW

Less Than Subtotal Parathyroidectomy for Multiple Endocrine Neoplasia Type 1 Primary Hyperparathyroidism: A Systematic Review and Meta-Analysis

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Abstract

Background Multiple endocrine neoplasia type 1 (MEN1)-associated primary hyperparathyroidism (pHPT) is classically associated with an asymmetric and asynchronous parathyroid involvement. Subtotal parathyroidectomy (STP), which is currently the recommended surgical treatment, carries a high risk of permanent hypoparathyroidism. The results of less than subtotal parathyroidectomy (LSTP) are conflicting, and its place in this setting is still a matter of debate. The aim of this study was to identify the place of LSTP in the surgical management of patients with MEN-associated pHPT.

Methods A systematic literature review was conducted in accordance with PRISMA and MOOSE guidelines, for studies comparing STP and LSTP for MEN1-associated pHPT. The results of the two techniques, regarding permanent hypoparathyroidism, persistent hyperparathyroidism and recurrent hyperparathyroidism were computed using pairwise random-effect meta-analysis.

Results Twenty-five studies comparing STP and LSTP qualified for inclusion in the quantitative synthesis. In total, 947 patients with MEN1-associated pHPT were allocated to STP (n = 569) or LSTP (n = 378). LSTP reduces the risk of permanent hypoparathyroidism [odds ratio (OR) 0.29, confidence interval (CI) 95% 0.17–0.49)], but exposes to higher rates of persistent hyperparathyroidism [OR 4.60, 95% CI 2.66–7.97]. Rates of recurrent hyperparathyroidism were not significantly different between the two groups [OR 1.26, CI 95% 0.83–1.91].

Conclusions LSTP should not be abandoned and should be considered as a suitable surgical option for selected patients with MEN1-associated pHPT. The increased risk of persistent hyperparathyroidism could improve with the emergence of more efficient preoperative localization imaging techniques and a more adequate patients selection.

Introduction

Multiple endocrine neoplasia type 1 (MEN1) is the most common cause of familial primary hyperparathyroidism, which accounts for 1–5% of all primary hyperparathyroidism (pHPT) cases. It is a rare autosomal dominant inherited disease caused by a germline mutation in the *MEN1* tumor suppressor gene on chromosome 11q13, with a prevalence of 2–3 per 100,000 [1]. PHPT is the most prevalent MEN1 manifestation, affecting more than 90% of MEN1 patients and is often the first manifestation of the disease, appearing at the second or third decade of life [2].

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Other manifestations of this syndrome are pancreatic endocrine tumors, pituitary adenomas and more rarely various tumors such as adrenocortical tumors, neuroendocrine tumors of the stomach, thymus or bronchus [3].

Whether sporadic or genetic, the treatment of pHPT is primarily surgical. As far as MEN1-associated pHPT is concerned, the main goal of surgery is to achieve eucalcemia for as long as possible, avoiding postoperative hypoparathyroidism and facilitating potential subsequent operation for recurrence. Moreover, surgical remission of HPT in MEN1patients has been shown to reduce the risk of kidney stones, fractures, and potentially cardiovascular disease [4, 5].

Unlike sporadic pHPT, whose treatment is well-defined, the optimal surgical strategy toward MEN1-associated pHPT patients is still debatable. Trends are evolving from very invasive procedures such as total parathyroidectomy with auto-transplantation, which is currently almost abandoned due to the very high risk of permanent hypoparathyroidism, toward lesser invasive techniques such as subtotal parathyroidectomy (STP), and more recently less than subtotal parathyroidectomy (LSTP).

However, since all the parathyroid cells of MEN1 patients have the germline mutation, any parathyroid tissue left is a candidate for loss of heterozygosity and, consequently, at risk of growing and developing into a hyperfunctioning gland. This argument is the rationale for the current guidelines that strongly recommend performing STP at initial operation. STP still carries an important risk of permanent hypoparathyroidism, requiring a lifelong calcium and vitamin D intake. It is well-acknowledged that the treatment of hypoparathyroidism may be complex and might result in complications such as soft tissue calcifications, kidney stones, and nephrocalcinosis, and strongly impairs patients' quality of life [6–8]. New therapeutic options for hypoparathyroidism such as recombinant PTH are cumbersome and associated with a high daily cost. Moreover, STP, which involves necessarily a bilateral neck exploration, carries the risk of the other parathyroid surgery complications such as recurrent laryngeal nerve (RLN) injury, neck hematoma or wound infection.

In order to lower the risk of permanent hypoparathyroidism, an increasing number of teams have begun to perform LSTP, which is defined by the resection of less than three parathyroids, for patients with MEN1-associated pHPT. The increasing ability to preoperatively localize large and hyper-functioning parathyroid glands and to intraoperatively monitor PTH levels are other arguments which support the LSTP strategy.

In fact, the parathyroid disease in MEN1 patients is classically multi-glandular, asymmetric, and asynchronous resulting of a mono- or oligo-clonal cellular proliferation arising independently and randomly in each of the parathyroid glands of a same patient [9]. LSTP can therefore be regarded as an attractive surgical option in this setting, especially for young patients that may have not yet developed hyperplasia/adenomas at the four parathyroid glands. It decreases the risk of postoperative hypoparathyroidism but carries, however, a higher risk of persistent or recurrent disease [10, 11].

Evidently, none of the two surgical strategies is free from drawbacks, and which strategy best combines long-term cure while preventing permanent postoperative hypoparathyroidism is still a matter of debate. We believe that there is a need to evaluate and pool the relevant data together in a systematic review and meta-analysis in order to provide more robust evidence regarding the outcomes of LSTP versus STP for patients with MEN1-associated pHPT.

The aim of this study was to perform a thorough analysis of the currently available literature in order to help identify the place of LSTP in the surgical management of patients with MEN1-associated pHPT and to determine whether LSTP could prevent permanent hypoparathyroidism with a reasonable rate of persistent and recurrent hyperparathyroidism.

Material and methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12] and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist [13]. All stages of study identification, selection, quality assessment, and data extraction were carried out independently by two authors (D.B. and H.N.). Any discrepancies were resolved by discussion and consensus or appeal to a third author (C.G.).

Search strategy and selection criteria

We searched electronically the PubMed, EMBASE, Scopus, Google scholar, and the Cochrane databases for randomized controlled trials (RCTs) and prospective and retrospective cohort studies (PCS and RCS) without language restriction from inception to December 2020. The search strategy combined Medical Subject Headings (MeSH) terms and free-text non-MeSH terms related to MEN1-associated pHPT surgery. The MeSH terms identified and used were "Multiple Endocrine Neoplasia Type 1" and "Hyperparathyroidism/surgery." The non-MeSH terms-based research used all the possible synonyms of these terms and allowed a much more comprehensive research.

Screened studies were firstly selected by title, then by abstract and finally by full text reading independently by two authors (D.B. and H.N.). They included all the studies comparing the outcomes of LSTP and STP in adult patients (>18 years old) with MEN1-associated pHPT. Non-human studies, narrative reviews, editorial letters, studies that did not compare LSTP to STP, and studies with less than two patients in LSTP group were excluded. Disagreement in study inclusion was resolved by discussion and consensus or appeal to a third author (C.G.). We did not restrict the language of the manuscripts to English, and non-English studies were also screened. German or Spanish-speaking authors analyzed the results of these studies. All the efforts were done in order to obtain the full texts of the included studies, including contacting study's authors by email and via academic social media.

Quality assessment

The methodological quality of the included studies was assessed independently by the two authors (D.B. and H.N.) using the Newcastle–Ottawa scale [14]. In the case of score discrepancy, discussions took place between the two authors and consensus was reached.

Data extraction

The two reviewers independently reviewed each included article, and any discrepancies were resolved by discussion and consensus. A predefined paper-based sheet was used for data extraction. Data collected for each article comprised the following predefined items:

1. Study identifier (first author, title, year of publication, journal, country);
2. Study design (RCT, PCS, RCS);
3. General characteristics of the eligible studies (inclusion and exclusion criteria, sample size calculation, type of operations performed, number of parathyroids removed, and definition of the three investigated outcomes: permanent hypoparathyroidism, persistent pHPT and recurrent pHPT). Depending on the year of publication, MEN1 diagnosis was either made on familial screening in old series or genetic testing on more recent studies. STP, considered as the conventional treatment of MEN1-associated pHPT, was defined by the removal of 3 or 3.5 parathyroids (leaving the volume of one normal parathyroid gland). LSTP was defined by the removal of less than three parathyroids.
4. Treatment arms and number of enrolled subjects in each arm;
5. Duration of follow-up;
6. Treatment outcomes:
   - Persistent pHPT is defined by the persistence of hypercalcemia with non-suppressed or high parathormone (PTH) level within 6 months after surgery.
   - Permanent hypoparathyroidism is defined by serum calcium levels below the normal range, and requirement for supplemental calcium and vitamin D after 6 months following operation.
   - Recurrent pHPT is defined by a hypercalcemia with non-suppressed or high PTH level appearing after a period of normocalcemia of at least 6 months. In case of recurrent pHPT, the recurrence-free survival (RFS), that is the time elapsed between surgery and recurrence, was also recorded.

Statistical analysis

Statistical analysis was performed using MetaXL software with "Maimputable" function on Odds ratio with the "Random Effect" model parameter. It was verified that the statistical analysis method used (Random Effect) was compatible with the type of results requested (OR) in the MetaXL user guide. The Welch two-sample t test was used to compare the RFS in the two groups.

Results

A total of 708 unique study titles were identified through database searching (Fig. 1). Forty-nine full-text publications were finally assessed for eligibility, of which 25 comparing STP and LSTP in MEN1-associated pHPT patients were included for quantitative synthesis.

Of these, 24 were RCS and one PCS. There was no RCT. In total, 947 patients with MEN1-associated pHPT were allocated to STP (n = 569) or LSTP (n = 378). The follow-up period ranged from 6 to 247 months, mean follow-up was 85.2 months. Some characteristics of the included studies are given in Table 1. The quality scores according to the Newcastle–Ottawa scale varied between 3 and 7, with a median value of 6.

Persistent hyperparathyroidism

Nineteen studies [4, 10, 11, 15–30] involving 696 patients evaluated the persistence of pHPT after LSTP and STP. Seventy-two out of 312 patients (23.1%) had persistent HPT in the LSTP group versus 17 out of 384 (4.4%) in the STP group. Random effect analysis demonstrated that LSTP was associated with significantly more persistent HPT than STP (OR 4.60, 95% CI 2.66–7.97) (Fig. 2).

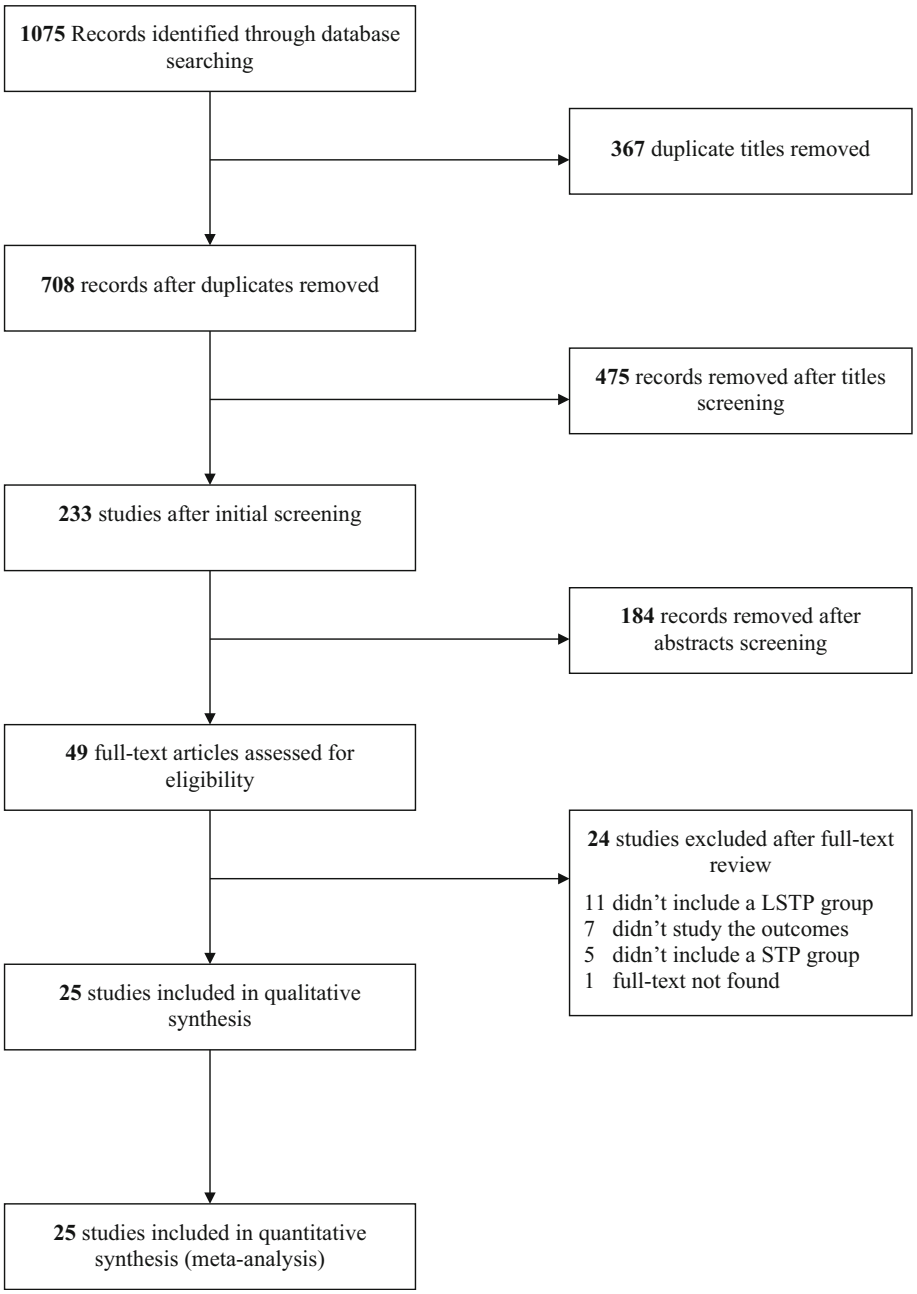

Fig. 1 PRISMA flow diagram for search and selection of articles included in the systematic review and meta-analysis

Recurrent hyperparathyroidism

Twenty-two studies [4, 10, 11, 15–17, 19–29, 31–35] involving 814 patients evaluated the recurrence of hyperparathyroidism after LSTP and STP. A total of 127 patients out of 342 patients (37.1%) had recurrent hyperparathyroidism, appearing after a period of normocalcemia of at least 6 months, in the LSTP group versus 124 out of 472 patients (26.3%) in the STP group. Although there was a trend in favor of STP with less recurrent hyperparathyroidism, no statistically significant difference was shown after random effect analysis (OR 1.26, CI 95% 0.83–1.91) (Fig. 3).

Permanent hypoparathyroidism

Twenty-one studies [4, 10, 11, 15–20, 22–29, 31, 32, 34, 36] involving 748 patients evaluated the occurrence of permanent hypoparathyroidism after LSTP and STP. Fifteen patients out of 338 (4.4%) had permanent hypoparathyroidism in the LSTP group, while 82 patients out of 410 (20%) had permanent hypoparathyroidism in the STP group. Random effect analysis demonstrated that LSTP results in significantly less permanent hypoparathyroidism than STP (OR 0.29, CI 95% 0.17–0.49) (Fig. 4).

Table 1 Characteristics of 25 studies included in the systematic review

Author	Journal, Year	Type of study	Country	Number of patients			Follow up	Newcastle–Ottawa Score
				Exposure Group (LSTP)	Control Group (STP)	Total		
Arnalsteen et al. [21]	Surgery, 2002	RCS	France	13	66	79	48	6
Balsalobre Salmeron et al. [33]	Cir Esp, 2018	RCS	Spain	9	62	71	103	6
Cetani et al. [19]	Clin Endocrinol, 2006	RCS	Italia	3	3	6	19	3
Choi et al. [17]	Sci Rep, 2020	RCS	Korea	12	4	16	58	6
Dotzenrath et al. [31]	Eur J Surg, 2001	RCS	Germany	13	25	38	54	5
Elaraj et al. [36]	Surgery,2003	RCS	USA	13	63	76	68	7
Fyrsten et al. [29]	World J Surg, 2016	RCS	Sweden	31	30	61	247	7
Horiuchi et al. [20]	World J Surg, 2018	RCS		12	21	33	135	7
Hubbard et al. [26]	Arch Surg, 2006	RCS	France	4	21	25	88	7
Kluijfhout et al. [16]	World J Surg, 2016	RCS	USA	8	16	24	68	5
Kraimps et al. [35]	Surgery, 1992	RCS	France	14	22	36	96	5
Lamas et al. [22]	Endocr Connect, 2019	RCS	Spain	15	34	49	116	5
Lambert et al. [28]	Arch Surg, 2005	RCS	USA	16	16	32	52	6
Langer et al. [23]	Chirurg, 2004	RCS	Germany	14	5	19	93	7
Lee et al. [34]	Ann Surg Oncol, 2006	RCS	Taiwan	11	5	16	86	6
Malmaeus et al. [24]	World J Surg, 1986	RCS	Sweden	21	6	27	78	4
Manoharan et al. [25]	Clin Endocrinol (Oxf), 2020	RCS	Germany	28	23	51	112	7
Montenegro et al. [10]	Front Endocrinol, 2019	RCS	Italy	10	22	32	6	5
Norton et al. [4]	Ann Surg, 2008	PCS	USA	35	40	75	204	7
Obara et al. [30]	Henry Ford Hosp Med J, 1992	RCS	Japan	5	9	14	65	6
Pieterman et al. [15]	Ann Surg, 2012	RCS	Netherlands	17	23	40	52	5
Schreinemakers et al. [11]	World J Surg, 2011	RCS	Netherlands	29	17	46	80	7
Twigt et al. [18]	Orphanet J Rare Dis, 2013	RCS	Netherlands	26	17	43	24	6
Versnick et al. [32]	Surgery, 2013	RCS	Australia	6	8	14	76	7
Waldmann et al. [27]	Br J Surg, 2010	RCS	UK	13	11	24	101	7
Total				**378**	**569**	**947**		
Mean							**85.2**	**5.96**

Recurrence-free survival

Recurrence-free survival (RFS) data were available for 14 studies in the LSTP group and 16 studies in STP group. The mean RFS was 85.8 months in LSTP group and 101.8 in STP groups ($p = 0.36$).

Discussion

This systematic review and meta-analysis of 25 studies including 947 patients with MEN1-associated pHPT undergoing either STP or LSTP, indicates than LSTP is associated with a lower risk of permanent hypoparathyroidism and a higher risk of persistent hyperparathyroidism. The occurrence of recurrent hyperparathyroidism was, however, not different between the two groups.

	LSTP		STP				
Study	Events	Total	Events	Total	weight (%)	OR	CI95%
Arnalsteen LC	1	13	1	66	3,7	5,42	[0,32-92,65]
Cetani F	1	3	0	3	2,3	4,20	[0,12-151,97]
Choi HR	0	12	0	4	1,8	0,36	[0,01-20,98]
Fyrsten E	7	31	2	30	10,9	4,08	[0,77-21,55]
Horiuchi K	0	12	0	21	1,9	1,72	[0,03-92,18]
Hubbard JGH	0	4	0	21	1,8	4,78	[0,08-274,09]
Kluijfhout WP	1	8	1	16	3,5	2,14	[0,12-39,47]
Lamas C	5	15	2	34	9,4	8,00	[1,34-47,77]
Lambert LA	2	16	1	16	4,8	2,14	[0,17-26,33]
Langer P	4	14	0	5	3,1	4,71	[0,21-104,49]
Malmaeus J	5	21	0	6	3,3	4,33	[0,21-90,05]
Manoharan J	4	28	0	23	3,4	8,63	[0,44-169,29]
Montenegro FL	1	10	3	22	5,2	0,70	[0,06-7,74]
Norton JA,	15	35	5	40	22,7	5,25	[1,66-16,61]
Obara T	1	5	0	9	2,6	6,33	[0,21-188,16]
Pieterman CRC	4	17	0	23	3,4	15,67	[0,78-313,87]
Schreinemakers JMJ	9	29	1	17	6,4	7,20	[0,82-62,94]
Twigt BA	9	26	1	17	6,4	8,47	[0,96-74,62]
Waldmann J	3	13	0	11	3,2	7,67	[0,35-166,65]
Total	**72**	**312**	**17**	**384**	**100**	**4,60**	**[2,66-7,97]**

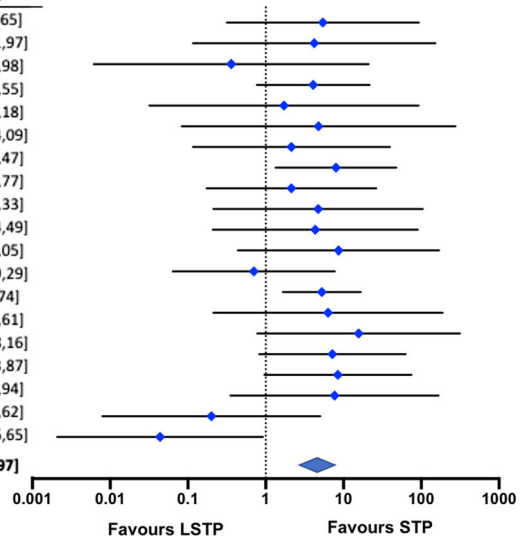

Fig. 2 Forest plot of odds ratios of persistent HPT after LSTP versus STP

	LSTP		STP				
study	Events	Total	Events	Total	weight (%)	OR	CI95%
Arnalsteen LC	3	13	4	66	4,9	4,65	[0,90-23,95]
Balsalobre Salmeron M	5	9	16	62	6,0	3,59	[0,86-15,06]
Cetani F	0	3	1	3	1,3	0,24	[0,01-8,62]
Choi HR	3	12	2	4	2,7	0,33	[0,03-3,51]
Dotzenrath C	3	13	3	25	4,4	2,20	[0,38-12,87]
Fyrsten E	10	31	8	30	8,3	1,31	[0,43-3,96]
Horiuchi K	4	12	11	21	5,7	0,45	[0,10-1,99]
Hubbard JGH	1	4	1	21	1,7	6,67	[0,32-137,40]
Kluijfhout WP	1	8	5	16	2,7	0,31	[0,03-3,29]
Kraimps JI	4	22	4	14	5,1	0,56	[0,11-2,72]
Lamas C	2	15	10	34	4,8	0,37	[0,07-1,94]
Lambert LA	10	16	5	16	5,8	3,67	[0,85-15,84]
Langer P	5	14	3	5	3,3	0,37	[0,05-3,01]
Lee C-H	0	11	1	5	1,4	0,13	[0-3,84]
Malmaeus J	13	21	2	6	3,8	3,25	[0,48-22]
Manoharan J	19	28	9	23	7,9	3,28	[1,04-10,41]
Montenegro FL	0	10	1	22	1,5	0,68	[0,03-18,22]
Norton JA,	16	35	18	40	10,2	1,03	[0,41-2,56]
Pieterman CRC	5	17	4	23	5,6	1,98	[0,44-8,87]
Schreinemakers JMJ	17	29	11	17	7,2	0,77	[0,22-2,67]
Versnick M	0	6	3	8	1,6	0,12	[0,01-2,89]
Waldmann J	6	13	2	11	4,0	3,86	[0,59-25,29]
Total	**127**	**342**	**124**	**472**	**100**	**1,26**	**[0,83-1,91]**

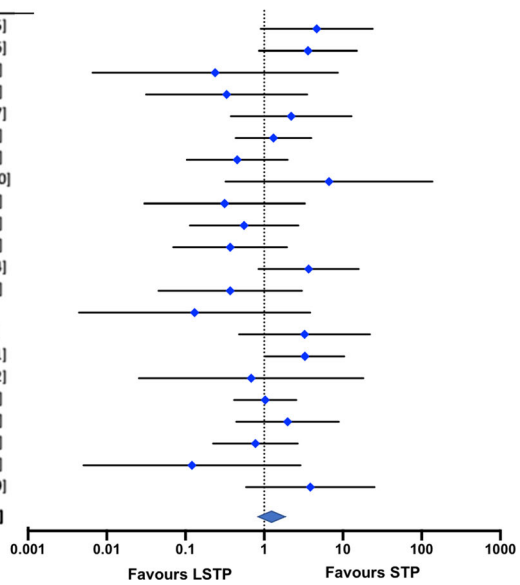

Fig. 3 Forest plot of odds ratios of recurrent HPT after LSTP versus STP

The surgical management of MEN1-associated pHPT is challenging, and contradictory findings on surgical outcomes, depending on the type of surgical intervention, have been reported. Classically, two surgical procedures have been employed in this setting, either total parathyroidectomy with heterotopic auto-transplantation of parathyroid tissue grafts into skeletal muscle, usually of the forearm (TP-AT), or STP leaving a remnant of one parathyroid gland in the neck. In line with the opinion of an increasing number of surgical teams, we believe that total parathyroidectomy with auto-transplantation (TP-AT) is a radical surgical option that carries an extremely high risk of permanent hypoparathyroidism, ranging from 13 to 67% in the literature [11], and should therefore be avoided, at least at initial operation. Albeit the equivalent outcomes of TP-AT and STP, regarding persistent and recurrent hyperparathyroidism [37], STP is currently considered as the treatment of choice as initial operation for MEN1-associated pHPT

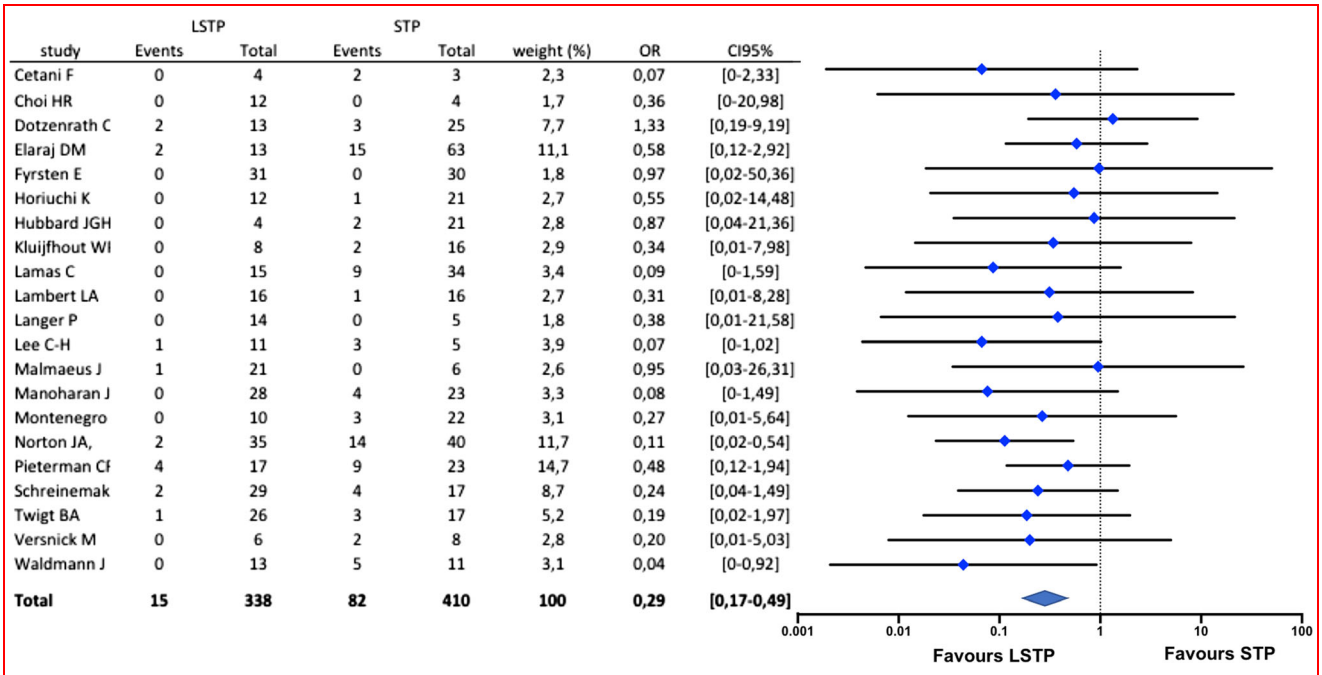

Fig. 4 Forest plot of odds ratios of permanent hypoparathyroidism after LSTP versus STP

[38]. In fact STP is less invasive, it obviates the need of a second surgical incision, and avoids the inherent risk of graft failure, thereby decreasing the rates of transient and permanent hypoparathyroidism to the lowest achievable levels. The aim of our study was to identify the place of LSTP in the surgical management of patients with MEN1-associated pHPT. Therefore, we decided, in this meta-analysis, to compare LSTP to the standard surgical treatment, which is STP.

The prevalence of permanent hypoparathyroidism after STP is not irrelevant; a rate of 20% was determined in this meta-analysis. This high rate could probably be in part explained by the fact that our meta-analysis included many old studies, and the surgical techniques were not always well-detailed. We could assume that there are probably some technical issues that could be improved. In fact, today's modern surgery, with improvement and standardization of surgical techniques, a cautious dissection and preservation of the vascularization of the remnant parathyroid stamp could lead to the improvement of the outcomes of STP.

Nevertheless, as expected, we found that after LSTP, patients have a significantly lower risk of developing permanent hypoparathyroidism than after STP (OR 0.29, CI 95% 0.17–0.49). Permanent hypoparathyroidism implies a heavy follow-up and a lifelong calcium and vitamin D intake, resulting in an increased risk of nephrolithiasis, nephrocalcinosis and impaired renal function [39]. The absence of PTH results in inability of renal tubules to reabsorb calcium, thus resulting in hypercalciuria and nephrocalcinosis. In a large cohort study, Mitchell et al. found rates of chronic kidney disease Stage 3 or higher twofold to 17-fold higher in patients with hypoparathyroidism than in normal individuals followed for 7 years [40]. Two patients in this same cohort required renal transplant due to nephrocalcinosis. Moreover, it have been reported that patients with permanent hypoparathyroidism have increased risks of cardiac arrhythmias and cardiovascular diseases [41]. In addition, this condition is associated with cognitive dysfunction in particular, brain fog, fatigue, and easy fatigability [42]. Finally, higher incidence of anxiety, depression, and overall reduced quality of life occur in patients with hypoparathyroidism compared to normal control groups [6, 43]. For all these reasons, we believe that the significant reduction in the rates of permanent hypoparathyroidism obtained with LSTP is a result of major importance.

However, as expected, LSTP exposes to a significantly higher risk of persistent hyperparathyroidism compared to STP (OR 4.60, 95% CI 2.66–7.97). Owing to this high rate of failure that may actually be considered as unacceptable, that some authors consider that LSTP should not be performed for patients with MEN1-associated pHPT [11, 44].

Nonetheless, most of the studies included in this meta-analysis did not mention which preoperative imaging explorations were performed, and nearly half of them are old studies published more than 10 years ago. In fact, unlike sporadic pHPT, the role of preoperative imaging in

MEN1-associated pHPT has not been well-established. Up till the early 2010s, some teams had been considering that the majority of patients with MEN1-associated pHPT do not require a preoperative localizing study [45]. We believe, however, that with the recent advancements of parathyroid gland imaging, and the emergence of new morphological techniques such as radiolabeled choline positron emission tomography (PET) [46], a preoperative localizing study may improve preoperative identification of hyperfunctioning parathyroid glands and select the best candidates for LSPT. A recent study analyzing a small cohort of patients with MEN1-associated pHPT showed that the combination of three imaging modalities including neck ultrasonography, methoxyisobutylisonitrile labeled with technetium-99 m (sestaMIBI) scintigraphy, and radiolabeled choline PET has a sensitivity of 90% in detecting hyperfunctioning parathyroid glands [47]. Future prospective studies are needed in order to evaluate if systematic preoperative imaging study, using recently developed tools, can help identify the hyperfunctioning parathyroid tissue and select the best candidates for LSTP and consequently improve its results. The idea here is to assign the right intervention, either LSTP or STP, to the right patient, depending on the number and the localization of the hyperfunctioning glands. An extensive surgery would be performed only if multiple gland disease is detected. By selecting the best candidates for LSTP, we would reduce the rates of persistent hyperparathyroidism while maintaining the advantage of a lower risk of hypoparathyroidism.

Nevertheless, it is necessary to consider that a less radical treatment such as LSTP may require a close follow-up including regular imaging examinations that are not without economic consequences. Additional costs are estimated to $1414 for PET Cholin [48], $570 for Sestamibi scanning [49], and $838 for a 4D CT scanner [50]. Moreover, the risk of cumulative exposer to radiation should also be taken into account in these young patients nearly always under the age of 40 and often much younger still. Thus, the quality of life of these young patients with MEN1 can be strongly impaired by repeated screening examinations, as shown in the study of Stromsvik et al. [51].

The last finding of this meta-analysis is the absence of statistically significant difference between the two techniques in terms of recurrence of hyperparathyroidism (OR 1.26, CI 95% 0.83–1.91). As mentioned previously, every single parathyroid cell has the *MEN1* gene germline mutation and is therefore capable of developing into a hyperfunctioning cell following a "second hit." Therefore, the aim of surgery in this setting is not to avoid the recurrence of hyperparathyroidism, which is theoretically inevitable, but rather to provide the longest possible duration of eucalcemia. Nonetheless, it is worth to notice here that logically the more parathyroid tissue is left, the greater is the risk of developing a recurrence of the disease. However, that difference did not reach significance in this meta-analysis. Interestingly, we also found out that there was not a difference in the recurrence-free survival between the two techniques.

In a recently published meta-analysis, including 21 studies, Nastos et al. studied the optimal extent of the initial parathyroid resection in patients with MEN1-associated pHPT and compared the three techniques: TP-AT, STP, and LSTP [52]. It showed, as we did, that LSTP induced less postoperative permanent hypoparathyroidism (RR 0.47, CI 95% 0.29–0.75) and more persistent hyperparathyroidism (RR 2.26, CI 95% 1.49–3.41) compared to STP. However, this study was less specific and less comprehensive than ours. In fact, in our study, we opted for a more specific research and we only focused on the comparison between LSTP and the "gold standard" technique that is STP, considering that TP-AT is a procedure that should no longer be performed due to the high rate of postoperative hypoparathyroidism. Among the 25 studies included in our review, only 17 have been included in Nastos et al.'s review. Therefore, our review is more comprehensive with eight more studies included [17–20, 23, 30, 33, 35], thus 238 more patients included in the quantitative synthesis. The four studies included in Nastos et al. meta-analysis and not in ours [37, 53–55] are studies that compared only TP-AT and STP, and did not include a LSTP group.

This meta-analysis has several limitations because of the retrospective design of all the studies included, and the small number of patients of most of them. Another major limitation is the great heterogeneity in the duration of the follow-up, which logically affects the rates of recurrent hyperparathyroidism. Moreover, the criteria of choice of the surgical strategy are often imprecise. Although it is acknowledged that each strategy has pros and cons according to the specific nature of the disease, this meta-analysis strongly suggests that there is a place for LSPT in the surgical strategy of MEN1-associated HPT. Future studies aiming at sectioning the best candidates for LSPT are needed.

Conclusion

The results of this systematic review and meta-analysis support the fact that LSTP should not be totally abandoned and should be considered as a suitable surgical option for patients with MEN1-associated pHPT. Compared with the recommended surgical operation that is STP, LSTP exposes to less permanent hypoparathyroidism without increasing the risk of recurrence of hyperparathyroidism. Even though

the risk of persistent hyperparathyroidism is greater with LSTP, we believe that with the improvement of preoperative imaging, and with better patient selection, LSTP could provide, for a selected group of patients, a durable cure while preventing postoperative hypoparathyroidism.

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Declarations

Conflict of interest The authors, Damien Bouriez, Caroline Gronnier, Magalie Haissaguerre, Antoine Tabarin, and Haythem Najah, declare that they have no conflicts of interest to disclose.

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