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The role of thymectomy during parathyroidectomy in multiple endocrine neoplasia type 1-associated hyperparathyroidism: a systematic review and meta-analysis

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Abstract

Background Current guidelines recommend transcervical thymectomy (TCT) during parathyroidectomy (PTX) for Multiple Endocrine Neoplasia Type 1 (MEN1)-associated primary hyperparathyroidism (PHPT) despite limited evidence substantiating efficacy. We aimed to determine the role of TCT in disease control and safety outcomes.

Methods A systematic review and meta-analysis were conducted on comparative observational studies exploring the efficacy of PTX with or without concomitant TCT for managing PHPT in patients with MEN1. Pooled event proportions were estimated using Freeman-Tukey double arcsine transformation method and converted to relative risk. Six studies ($n=306$ patients) were included.

Results TCT showed significantly reduced rates of persistent (relative risk 0.15; 21.9% vs. 3.1%; $p<0.01$) and recurrent PHPT (RR 0.34, 43.8% vs. 12.9%; $p=0.004$) necessitating re-operation compared to PTX alone, suggesting improved disease control. Interestingly, the addition of TCT reduced rates of transient PHPT (RR 0.07; 9.3% vs. 0%; $p<0.01$) and permanent recurrent laryngeal nerve injury (RR 0.32, 3.9% vs. 1.0%; $p=0.04$), indicating possible benefits in morbidity.

Conclusions Concomitant TCT may improve the safety and efficacy of PTX in MEN1-associated PHPT by synergistically clearing all cervical disease and minimizing adverse sequelae. Our findings provide further evidence to support existing recommendations for TCT and can guide surgical decision-making.

Keywords Hyperparathyroidism, Transcervical thymectomy, MEN1, Morbidity, Endocrine surgery, Relapse, Hypercalcemia

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Introduction

Multiple endocrine neoplasia type 1 (MEN1) is an inherited endocrine disorder characterized by the presence of primary hyperparathyroidism (PHPT), pituitary tumors, and pancreatic neuroendocrine tumors. PHPT is often the earliest and most common manifestation of MEN1 with almost 100% prevalence in all affected patients by the age of 50 years [1]. The signs and symptoms of hypercalcemia secondary to PHPT include bone pain, kidney stones, nausea, vomiting, constipation, and behavioral manifestations such as depression and confusion. The standard treatment for MEN1-associated PHPT is parathyroidectomy (PTX) with the rationale that removing all parathyroid tissue can mediate these symptoms and improve quality of life [2].

Transcervical thymectomy (TCT) is recommended when performing initial PTX in treating MEN1-associated PHPT due to the presence of intrathymic parathyroid tissue contributing to the symptomatic PHPT, prevent any biochemical recurrence, and preempt the incidence of thymic tumors that have shown to be associated with MEN1 [3, 4]. Despite stated recommendations, there is limited data substantiating benefit of TCT regarding curative outcomes, resolution of PHPT-related symptoms, or safety parameters. We aim to examine the role of concomitant TCT with initial PTX in the setting of MEN1 on curative efficacy, post-operative disease control, and adverse events.

Methods

Literature search

We systematically searched PubMed, Web of Science, Scopus, and Science Direct databases from inception through February 8, 2024, using terms related to “multiple endocrine neoplasia”, “parathyroidectomy”, “thymectomy”, and other relevant keywords. Reference lists of included studies were hand-searched for additional citations. No language restrictions were applied.

Eligibility criteria

We included observational studies and randomized trials comparing outcomes of PTX with or without concomitant TCT in patients with PHPT due to MEN syndrome. All studies investigating surgical outcomes in the treatment of MEN1-related PHPT, regardless of the specific surgery performed, were included. Included studies were required to have sample sizes of at least 10 patients per group and to report at least one of the following outcomes: cure rates, persistent/recurrent disease, or post-operative complications.

Quality assessment

The Newcastle-Ottawa scale was used to appraise the quality of included studies. This scale evaluates studies

based on three criteria: selection of study groups, comparability of cohorts, and ascertainment of outcomes, using a star rating system.

Data extraction

Two groups comprised of some of the authors (A.A/M.A.A. and T.B/R.M.E/J.A.J.) independently reviewed titles, abstracts and full texts applying the eligibility criteria. Discrepancies were resolved by consensus after discussion by a senior author (E.T). The following data was extracted into standardized tables: first author, year, country, study design, sample sizes, patient characteristics, surgical details, and rates of outcomes in each group including cure, persistent disease, recurrent disease, reoperation, transient and permanent hypoparathyroidism. Cure was defined as normal serum calcium or PTH levels without supplementation. Persistent disease was defined as elevated serum calcium or PTH levels within six months of surgery. Recurrent disease was defined as elevated serum calcium or PTH levels after six months of surgery.

Statistical analysis

Data analysis was performed using RStudio *meta-R* package. Pooled event rates were estimated using Freeman-Tukey double arcsine transformation with confidence intervals (CI) calculated accordingly. Comparisons between PTX alone and with TCT groups were performed using Chi-squared tests. The relative risk (RR) was computed as the ratio between outcome proportions in each group ($RR = \text{Proportion group 2} / \text{Proportion group 1}$). The 95% CI for the RRs were derived using the formula: $RR (95\% CI) = RR \times (e^{\pm 1.96 \times \text{Standard Error } \ln(RR)})$. The standard error was calculated from the data values. Heterogeneity across studies was quantified using the I^2 statistic. Random-effects meta-analysis models were applied in case of significant heterogeneity defined as $I^2 \geq 50\%$. Evaluation for publication bias included visual assessment of funnel plots and quantitative Egger's regression asymmetry testing where applicable. Sensitivity analyses were conducted via the leave-one-out method to evaluate result consistency.

Results

Study identification and screening

As depicted in Fig. 1, our comprehensive literature search identified six eligible studies published between 2004 and 2018 examining outcomes of PTX with or without concomitant TCT for MEN1 syndrome [4–9]. There were no available articles for MEN2A syndrome.

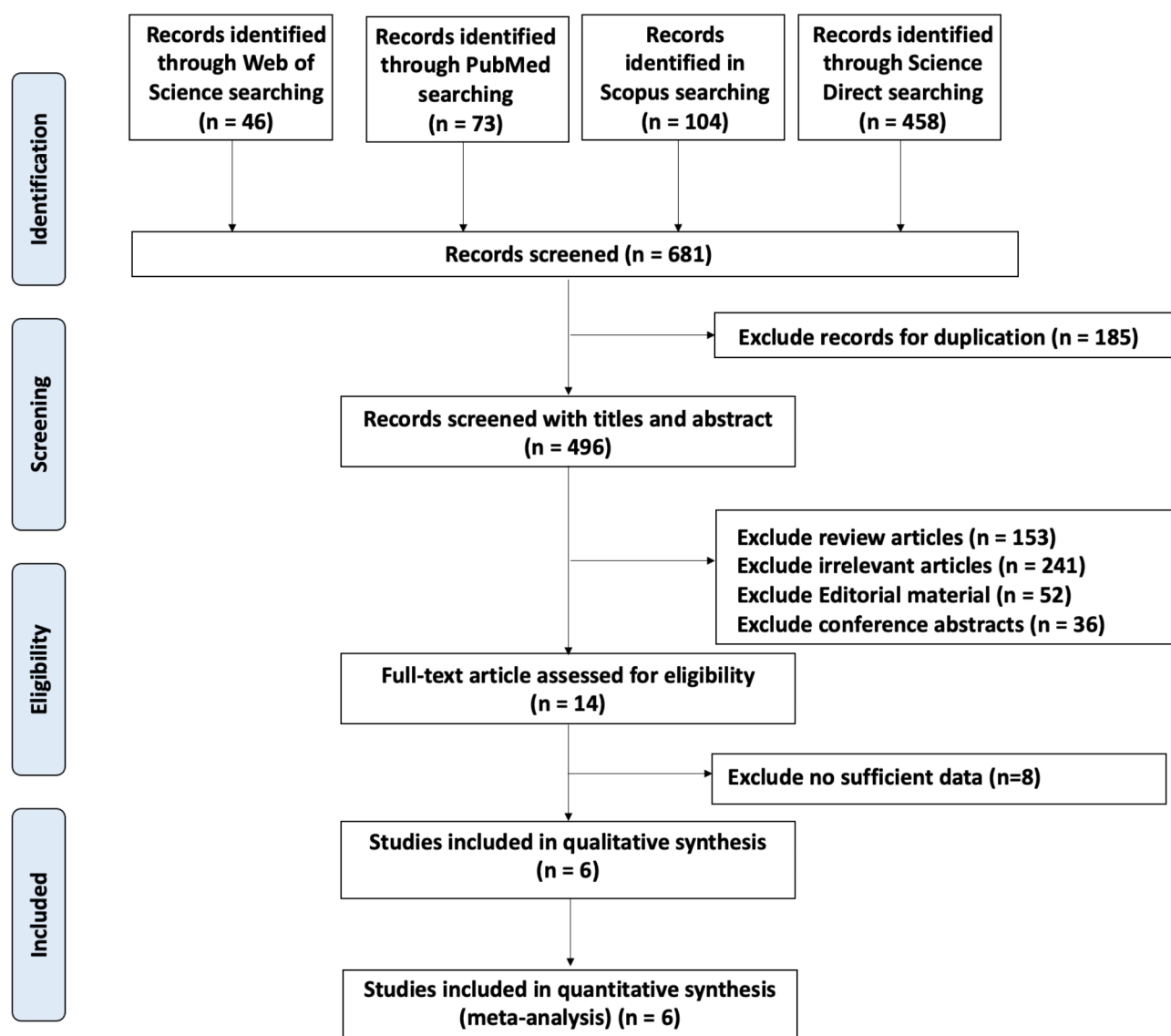


Fig. 1 Article identification and selection. PRISMA flow diagram outlining database search strategy and screening process for identification of eligible studies on outcomes in MEN1 patients who underwent parathyroidectomy with/without transcervical thymectomy

Study characteristics

A total of 306 patients were included across 6 observational studies conducted in several countries: the United States (2 studies), Germany (2 studies), Spain, and Italy. The pooled cohort had slightly more women (171) than men (135). Most patients (239) underwent both PTX and concomitant TCT procedures. PTX alone was performed in 67 cases, Table 1.

Quality assessment

The included studies were appraised for methodology quality using the Newcastle-Ottawa Scale, as detailed in Table 1. Overall, four studies were deemed good quality while two were considered fair. Regarding selection criteria, patient populations appeared sufficiently

representative in most cases. Comparability of cases and controls was moderate given the observational non-randomized nature of data. Outcome ascertainment relied largely on medical chart reviews. Total scores ranged from 6 to 8 stars across all studies.

Patient characteristics

The cohort largely comprised young and middle-aged adults. The pooled mean patient age was 37.3 years (95% CI 34.3–40.6 years). Females made up 55.95% (95% CI 50.27–61.55%) of participants across studies.

Follow-up duration was documented in only 4 of the 6 included studies. Among these, the mean follow-up was 90 months (95% CI 75.2–107.7 months). The reasonably lengthy surveillance of around 7.5 years should allow

Table 1 Characteristics of eligible studies

Author, year	Country	Total sample	PTX	PTX + TCT	Sex (F/M)	Age, years	Follow-up, months	Quality	Ref
Salmeron, 2018	Spain	71	18	53	41/30	38 (14.5)	NA	Good	[5]
Waldmann, 2010	Germany	47	13	34	22/25	41.5 (11.5)	107.1 (76.5)	Good	[4]
Powell, 2009	USA	66	0	66	35/31	33.5 (12.9)	76.7 (5.9)	Good	[6]
Tonelli, 2007	Italy	51	0	51	34/17	40.3 (11.8)	80 (62)	Good	[7]
Lambert, 2005	USA	37	17	20	22/15	32 (10.8)	NA	Fair	[8]
Langer, 2004	Germany	34	19	15	17/17	39.2 (15.3)	105.8 (61.7)	Fair	[9]

USA: United States of America; NA: not applicable. For age and follow up variables, mean (standard deviation) values are shown. PTX: parathyroidectomy; TCT: transcervical thyroidectomy. Quality assessment was assessed using The Newcastle-Ottawa scale

assessing longer term postoperative outcomes. However, there was significant heterogeneity ($I^2=85\%$) and lack of reporting from all studies limit's conclusions about durability.

Summary of outcomes

Outcomes gathered and compared among the included studies include cure, persistent disease, recurrent disease. Cure was considered as post-operative serum calcium level being normal (less than 2.6 mmol/L). Persistent disease was considered as post-operative serum calcium level being above normal (more than 2.6 mmol/L) within six months after surgery. Recurrent disease was considered as raised post-operative serum calcium level after six months of normocalcemia.

Treatment efficacy

Overall analysis showed that nearly three-fourths of patients achieved resolution of hypercalcemia and associated symptom control after surgery. The pooled cure rate following PTX with and without concomitant TCT was 73.02% (95% CI 60.37–84.08%) across studies, Fig. 2A.

Disease control

A small subset of patients (4.93%, 95% CI 0.38–12.91%) had persistent hypercalcemia despite initial PTX, as shown in Fig. 2B. The recurrence rate was 25.56% (95% CI 15.1–37.58%) indicating approximately one-fourth of patients experienced return of hypercalcemia/hyperparathyroidism during follow-up after initial complete cure, Fig. 2C. Based on the pooled data of 3 studies, the average disease-free survival time until recurrence detection was 69.5 months (95% CI 36.7–131.5 months). Nearly one-fifth or 19.39% (95% CI 9.87–31.0%) of the cohort underwent redo PTX due to recurrent disease, as presented in Fig. 2D.

Postoperative complications

Safety outcomes demonstrating potential complications rates. The pooled estimated rate of transient hypoparathyroidism was 1.94% (95% CI 0–6.35%), Fig. 3A. The rate of permanent hypoparathyroidism was 12.97% (95% CI 5.66–22.4%), Fig. 3B. The estimated rate of transient

recurrent laryngeal nerve injury was 1.63 (95% CI 0.06%–4.51%), Fig. 3C. The estimated rate of permanent recurrent laryngeal nerve injury was 0.87% (95% CI 0–3.94%), Fig. 3D. Additionally, in one study, the rate of subsequent thymic carcinoid development following prior PTX with concomitant TCT was reported to be 0.75% (95% CI 0–2.99%).

Subgroup analysis

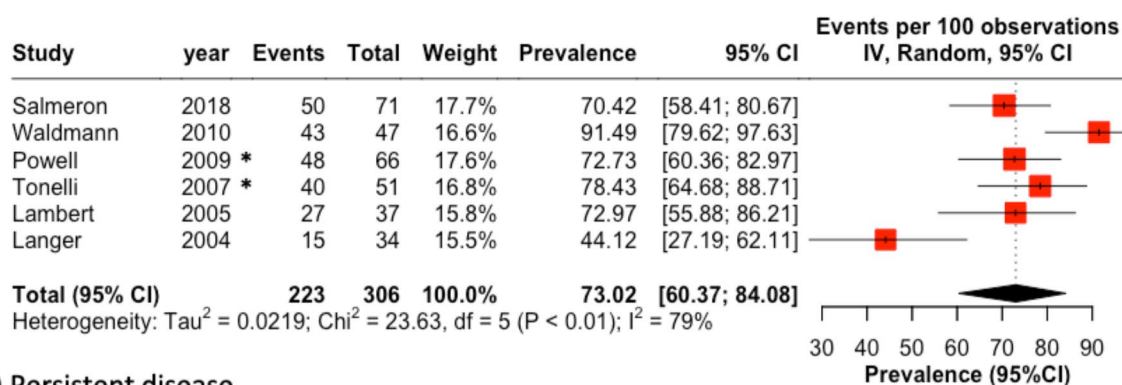
A subgroup analysis stratified by geographical location found largely comparable outcomes between European (4 studies) and North American (2 studies) cohorts, without statistically significant evidence of regional differences across endpoints. Cure rates ($p=0.94$), persistence of disease ($p=0.65$), need for reoperation ($p=0.81$), recurrent disease ($p=0.23$), permanent hypoparathyroidism ($p=0.78$) and nerve injury ($p=0.45$ – 0.76) showed no significant variation by continent, Table 2. While transient hypoparathyroidism was numerically higher in European studies (7.95% vs. 1.76% North America), this only approached statistical significance ($p=0.07$).

Impact of concomitant thymectomy

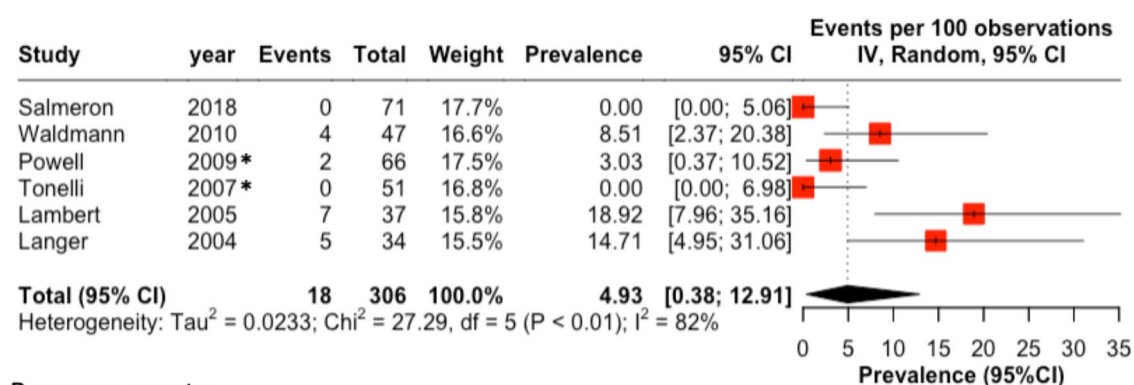
Of 6 total studies, 4 had study arms allowing comparison of outcomes between PTX alone ($n=32$ patients) and PTX with concomitant TCT ($n=166$ patients), Table 3. While cure rates (38.95% vs. 81.37%; RR 2.09, 95% CI 0.90–4.84; $p=0.26$) and need for reoperation (17.1% vs. 9.9%; RR 0.58, 95% CI 0.15–2.20; $p=0.65$) were statistically similar between the groups, the addition of TCT to PTX significantly reduced rates of persistent disease by 85% (RR 0.15; 95% CI 0.05–0.43; 21.9% vs. 3.1%; $p<0.01$) and lowered risks of recurrent disease warranting repeat surgery by 56% (RR 0.34, 95% CI 0.17–0.70; 43.8% vs. 12.9%; $p=0.004$).

Likewise, relative likelihood of developing transient hypoparathyroidism and permanent vocal cord injury were minimized by 93% (RR 0.07, 95% CI 0.01–0.51; 9.3% vs. 0%, $p<0.01$) and 68% (RR 0.32, 95% CI 0.11–0.96; 3.9% vs. 1.0%; $p=0.04$) respectively with the TCT-augmented approach. While no definitive conclusions can be drawn due to between-study heterogeneity, these findings indicate potential optimization of long-term disease control

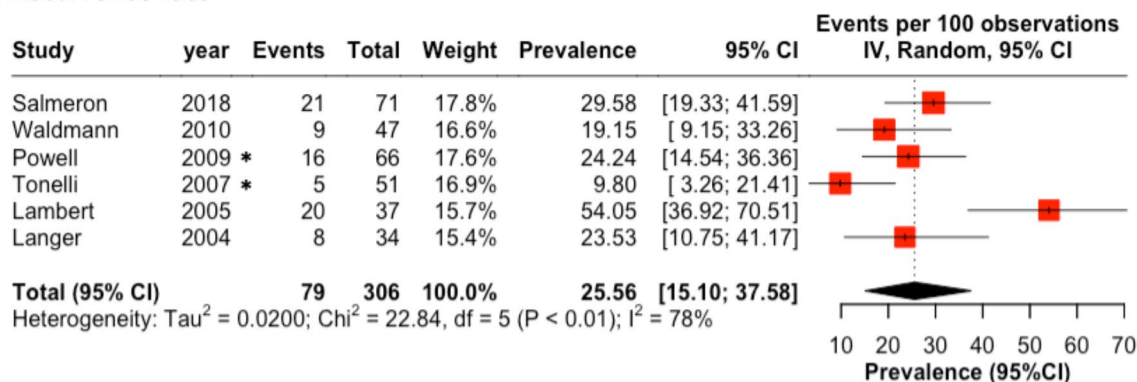
(A) Cure rate



(B) Persistent disease



(C) Recurrence rate



(D) Reoperation

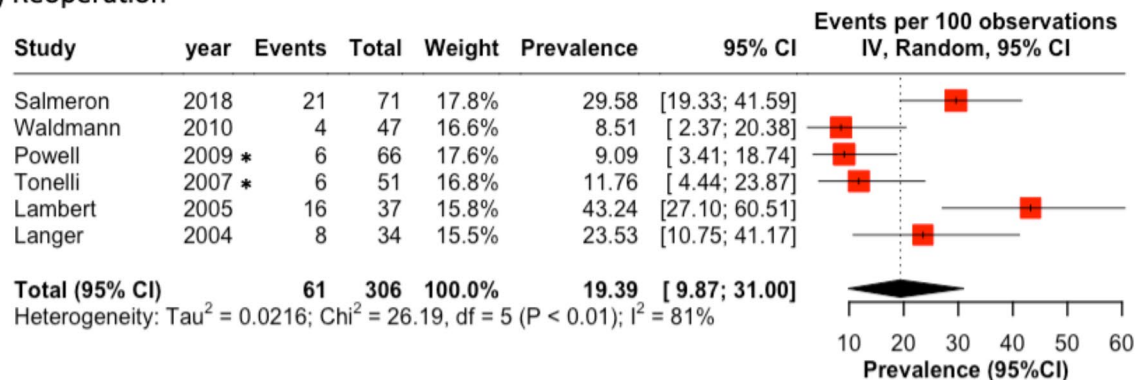


Fig. 2 (See legend on next page.)

(See figure on previous page.)

Fig. 2 Treatment efficacy and disease control outcomes. **(A)** The pooled cure rate following parathyroidectomy with or without transcervical thymectomy in MEN1 patients was 73.02% (95% CI 60.37–84.08%). A random effects model was used, and Freeman-Tukey double arcsine transformation is reported **(B)** Rate of persistent disease was 4.93% (95% CI 0.38–12.91%). **(C)** Pooled recurrence rate was 25.56% (95% CI 15.1–37.58%). **(D)** Rate of reoperation was 19.39% (95% CI 9.87–31.0%). A random effects model was used, and Freeman-Tukey double arcsine transformation is reported. *Studies included only parathyroidectomy with thymectomy

and avoidance of morbidity when PTX is augmented with TCT in MEN1 syndrome.

Discussion

MEN1 is an autosomal dominant disorder caused by loss-of-function germline mutations in *MEN1*, a tumor suppressor gene on chromosome 11q13 [10, 11]. The disorder holds an estimated prevalence of 2 per 100,000, with more than 95% of mutation carriers demonstrating biochemical evidence and increasing penetrance with age [12]. PHPT is the earliest manifestation of MEN1, with an early age diagnosis often influencing clinicians to perform genetic testing on their patients to evaluate MEN1 [13]. Furthermore, MEN1-associated PHPT tends to have greater adverse events when compared to sporadic PHPT such as more severe bone demineralization and increased recovery time after surgery [13]. With the cure for MEN1-associated PHPT depending on the amount of parathyroid tissue removed, PTX has been the standard treatment for this aspect of the disorder [14]. Recommendations have called for performing concomitant TCT in addition to PTX for MEN1-associated PHPT. Indeed, hyperfunctioning parathyroid tissue can be found in an ectopic location in up to 31% of total cases, the thymus being the most common location [15]. As such, a TCT may also be performed to completely address the signs and symptoms of PHPT in MEN1 cases.

We found that PTX with concomitant TCT carries significantly less risks for persistent PHPT and recurrence. This may be attributed to ectopic parathyroid tissue that can be in the thymus, implying that performing TCT can reduce the probability of undetected hyperfunctioning parathyroid tissue. Furthermore, we found that performing concomitant TCT carries a significantly less risk for transient hypoparathyroidism. Although various mechanisms may exist to explain this, one plausible reason is that removing the TCT can allow surgeons to explore the mediastinum and nearby areas for more thorough exploration, allowing them to properly identify all hyperfunctioning parathyroid glands and reduce the probability for aggressively resecting any normal tissue. Such thorough yet careful exploration can also minimize trauma to any nearby normal parathyroid glands, better preserving their function. Indeed, these benefits can also explain the significantly lower rate of reoperation in PTX associated with the addition of TCT.

Our findings agree with recent studies which demonstrated high rates of PHPT and hypercalcemia after

performing PTX alone. Goudet et al. found that supplementing surgery with TCT resulted in serum calcium returning to baseline more often than that without TCT which may be beneficial in patients suffering from severely symptomatic hypercalcemia secondary to MEN1-associated PHPT [16]. Recent studies have recommended TCT under specific conditions. Powell et al. highlighted the importance of initial PTX with concomitant TCT specifically when less than four entopic parathyroid glands are identified with the rationale that additional parathyroid tissue may be found in the thymus [3].

While routine TCT is advised for surgical management of MEN1-associated PHPT, our analysis substantiates a definitive benefit regarding enhancement of disease control, countering prior assumptions of merely theoretical impact [6]. With concomitant TCT mitigating rates of persistent hypercalcemia by 85% and recurrent events necessitating re-operations by 56% compared to PTX alone, it seemingly optimizes the likelihood of durable remission through comprehensive clearance of any occult ectopic parathyroid proliferation. This justification for upfront extended surgery appears stronger considering the substantially higher predisposition for multi-focal disease in MEN1. However, longer follow-up tracking will better elucidate if lower relapse risk persists over time.

Interestingly, we found no major differences in initial postoperative cure proportions between performing PTX alone and with concomitant TCT. This implies any parathyroid remnants harbored in the mediastinal thymus may require time for proliferation and biochemical manifestation, rather than causing immediate surgical failure. Hence, the theoretical rationale likely translates to reality during downstream surveillance. Moreover, potential surgical morbidity seems mitigated with addition of thymectomy, contrary to prior reservations. This comprehensive cervical approach facilitated by visualization from both thyroid and mediastinal sides may enable more meticulous resection avoiding injury to adjoining vascular or nervous structures. Standardization of techniques will further optimize safety.

Unfortunately, we were unable to assess the type of PTX that was performed in our data. The PTX performed were less-than-subtotal, subtotal, or total PTX which are characterized by the removal of enlarged glands only, 3–3.5 glands, and entire parathyroid, respectively. Recent studies have shown that undergoing

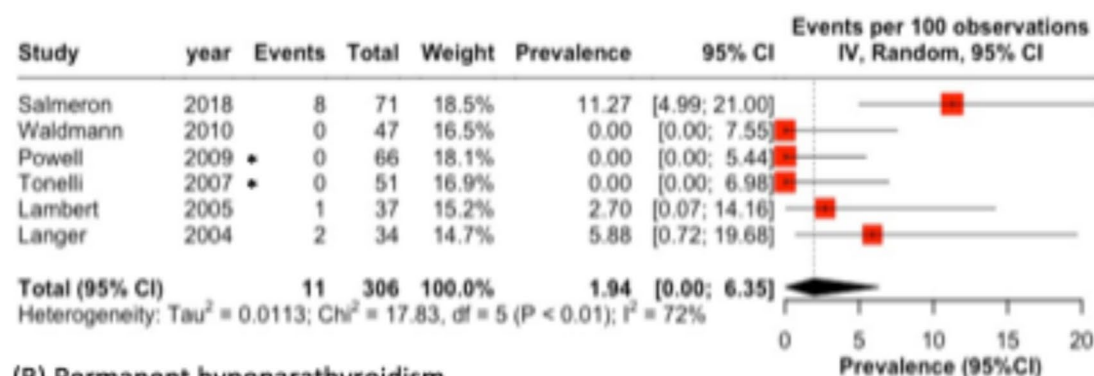
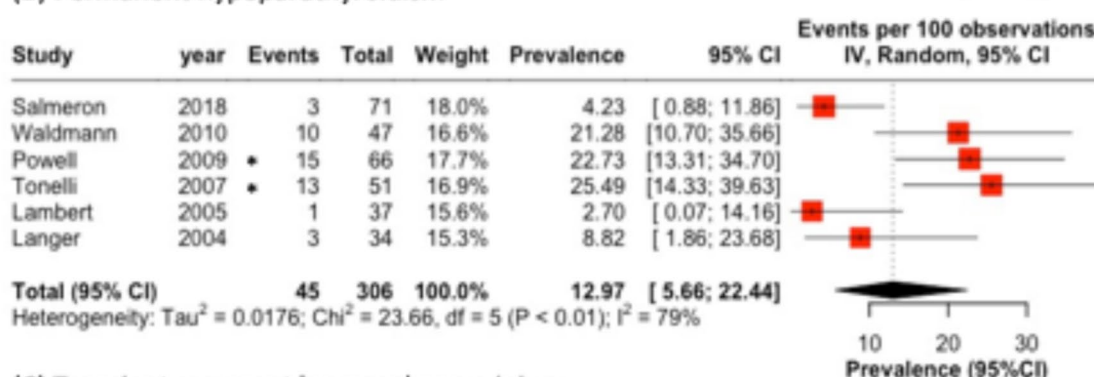
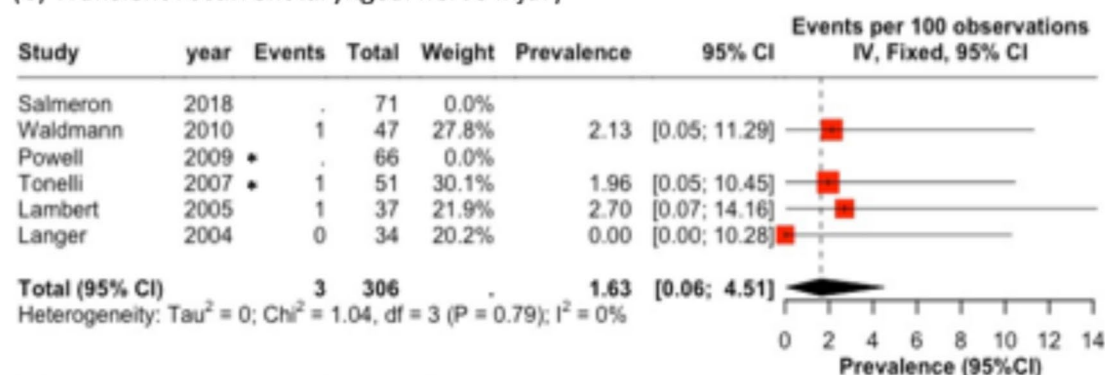
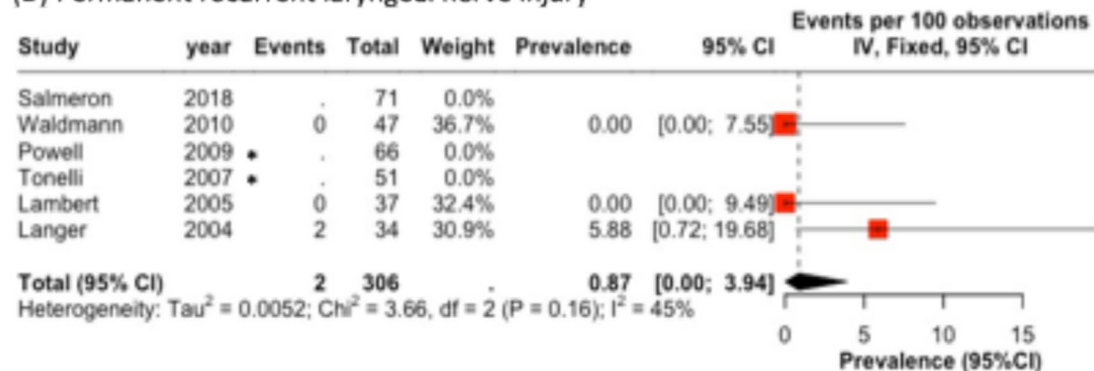
(A) Transient hypoparathyroidism**(B) Permanent hypoparathyroidism****(C) Transient recurrent laryngeal nerve injury****(D) Permanent recurrent laryngeal nerve injury**

Fig. 3 Postoperative complications. Forest plots for **(A)** Transient hypoparathyroidism rate. **(B)** Permanent hypoparathyroidism rate. **(C)** Transient recurrent laryngeal nerve injury rate. **(D)** Permanent recurrent laryngeal nerve injury rate. Pooled proportions calculated using Freeman-Tukey double arcsine transformation method. *Studies included only parathyroidectomy with thymectomy

Table 2 Proportions of pooled surgical outcomes in parathyroidectomy with and without concomitant thymectomy

Outcomes	European studies (n = 203)	American studies (n = 103)	p-value
Cure rate	73.68 (50.44–88.5)	72.82 (63.44–80.52)	0.94
Persistent disease	5.05 (1.27–18.08)	8.50 (1.29–39.82)	0.65
Recurrent disease	20.67 (13.23–30.79)	37.05 (14.5–68.51)	0.23
Reoperation	17.87 (9.83–30.26)	21.94 (3.70–67.27)	0.81
Transient hypoparathyroidism	7.95 (4.44–13.85)	1.76 (0.35–8.36)	0.07
Permanent hypoparathyroidism	13.54 (5.93–28.02)	9.94 (1.12–51.88)	0.78
Transient RLN injury	1.90 (0.55–6.35)	2.70 (0.07–14.16)	0.76
Permanent RLN injury	4.14 (1.20–13.3)	0.0 (0.0–9.49)	0.45

RLN: recurrent laryngeal nerve. Log transformed proportion (95% confidence interval) is presented

less-than-subtotal PTX results in higher rates of persistent PHPT and recurrence. Santucci et al. recently evaluated the largest cohort study of MEN1-associated PHPT and showed significantly higher frequencies of persistent PHPT and recurrence after less-than-subtotal PTX in 517 patients, demonstrating correlation between the amount of parathyroid tissue remaining and PHPT [17]. Interestingly, only 26% of patients with recurrence after receiving less-than-subtotal PTX underwent reoperation since they experienced severely symptomatic hypercalcemia [17]. This may suggest that although persistent PHPT and recurrence may be present after surgery, it may not be clinically significant or overly bothersome. Although these results stem from only a single institution, this may encourage clinicians to perform less-than-subtotal or subtotal PTX to avoid the risk of hypoparathyroidism. However, the disease present in MEN1-associated PHPT involves asymmetric and heterogeneous parathyroid tissue growth that can pose as a surgical challenge. High surgeon experience is needed to localize and excise the abnormal parathyroid gland in a less-extensive PTX and lower the risk of missed glands. A recent retrospective analysis of MEN1-associated PHPT revealed how performing less-than-subtotal PTX resulted in missing

86% of enlarged contralateral parathyroid glands, motivating authors to discourage this type of surgery for MEN1-associated PHPT due to the risk of missing glands [18]. Although there is limited evidence in the literature regarding which type of PTX is more favorable for MEN1-associated PHPT, surgeon experience and thorough neck exploration have been noted to correlate strongly with more favorable rates of persistent PHPT and recurrence, and are essential to treatment [19].

Apart from PHPT, indications to perform TCT in MEN1 also involve tumor prevention. Interestingly, thymic neuroendocrine tumors have been shown to appear in up to 8% of patients with MEN1 [20]. Although they seem to be uncommon, those with such tumors have a mortality risk at least four times greater than unaffected patients [21]. Unfortunately, there is limited evidence regarding risk factors of developing thymic neuroendocrine tumors or the role of prophylactic TCT in patients with MEN1. Further studies are required to assess the efficacy of prophylactic TCT in this context.

Of note, our analysis failed to identify major geographical differences between North American and European cohorts. While clinical practices and trends often naturally vary transnationally, the consistency suggests generalizability of findings across continents. Nevertheless, multi-institutional registries using standardized protocols can facilitate more reliable identification of subtler variations potentially influenced by regional factors.

Overall, this systematic review compiles evidence from six studies and aggregates data on 306 patients who underwent PTX with and without TCT for MEN1-associated PHPT [4–9]. After comparing outcomes within this relatively large cohort, we demonstrated significantly improved disease control outcomes and reduced complication risks with complementing PTX with TCT. Limitations of our analysis include between-study heterogeneity, small sample sizes and low number of available studies, lack of information regarding indications for re-operation, missing data regarding patient follow-up in two studies which limit our evaluation of recurrence, and reliance largely on single center retrospective

Table 3 Comparative surgical outcomes in parathyroidectomy patients

Outcomes	No Thymectomy (n = 32)	Thymectomy (n = 166)	p-value	RR (95%CI)
Cure rate	38.95 (2.35–94.41)	81.37 (68.59–89.73)	0.26	2.09 (0.90–4.84)
Persistent disease	21.89 (10.81–39.33)	3.14 (1.25–7.68)	<0.01	0.15 (0.05–0.43)
Recurrent disease	43.76 (27.89–61.02)	12.87 (6.11–25.11)	<0.01	0.34 (0.17–0.70)
Reoperation	17.05 (1.47–73.85)	9.88 (5.61–16.81)	0.65	0.58 (0.15–2.20)
Transient hypoparathyroidism	9.33 (1.87–21.62)	0.0 (0.0–0.58)	<0.01	0.07 (0.01–0.51)
Permanent hypoparathyroidism	1.65 (0.0–12.03)	15.25 (5.46–28.81)	0.06	9.24 (0.85–100)
Transient RLN injury	0.0 (0.0–2.97)	1.62 (0.26–4.09)	0.19	NA
Permanent RLN injury	3.9 (0.05–13.04)	1.0 (0.0–0.58)	0.04	0.32 (0.11–0.96)

RLN: recurrent laryngeal nerve. Log transformed proportion was pooled and data was reported as percentage and 95% confidence interval (CI) for each group. Pairwise comparison between the two cohorts was performed and relative risk (RR) and 95% confidence interval was reported. Bold values are significant at $p < 0.05$

observations introducing risk of confounders and low power of comparability. The actual quality of evidence remains moderate pending controlled comparisons. However, the rarity of this syndrome poses obvious challenges for accruing large samples. Qualitative synthesis still yields meaningful insights for clinical guidance. Indeed, this study can motivate for future analyses to attempt to collect more specific individual patient details to enable risk factor adjustments and build upon these findings. Finally, longer follow-up tracking recurrence patterns or quality of life impacts will better inform healthcare policy.

Conclusion

Our systematic analysis substantiates existing recommendations for routine TCT in conjunction with parathyroidectomy as appropriate first-line surgery for MEN1-associated PHPT as it facilitates consolidative clearance and enhances long-term disease control. Multi-institutional prospective registries can augment evidence further to develop standardized management algorithms tailored for this complex patient population.

Author contributions

E.A.T., M.A., M.H.H., and E.K. conceptualized the study. A.A., M.A., T.B., R.E., and J.J. curated the data. E.K., Y.B., and M.H.H. analyzed the data. E.A.T., M.A., A.G., and M.H.H. led the methodology. E.A.T. managed the resources. E.A.T. and M.H.H. provided visualization. S.N. and E.K. provided validation. All authors contributed to drafting, editing, and reviewing the manuscript. E.A.T. and E.K. supervised the study.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval

Not applicable.

Consent to participate

Not applicable.

Consent to publish

Not applicable.

Competing interests

The authors declare no competing interests.

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