Total Versus Near-total Thyroidectomy in Graves Disease

Results of the Randomized Controlled Multicenter TONIG-trial

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Background: Previous data suggest that the incidence of hypoparathyroidism after surgery for Graves disease (GD) is lower after subtotal thyroidectomy compared to total thyroidectomy (TT). The present study evaluated the incidence of postoperative hypoparathyroidism after near-total (NTT) versus TT in GD.

Methods/Design: In a multicenter prospective randomized controlled clinical trial, patients with GD were randomized intraoperatively to NTT or TT. Primary endpoint was the incidence of transient postoperative hypoparathyroidism. Secondary endpoints were permanent hypoparathyroidism, transient recurrent laryngeal nerve palsy (RLNP), reoperations for bleeding, inadvertently removed parathyroid glands, and recurrent hyperthyroidism after 12 months.

Results: Eighteen centers randomized 205 patients to either TT (n = 102) or NTT (n = 103) within 16 months. According to intention-to-treat postoperative transient hypoparathyroidism occurred in 19% (20/103) patients after NTT and in 21% (21 of 102) patients after TT ($P = 0.84$), which persisted >6 months in 2% and 5% of the NTT and TT groups ($P = 0.34$). The rates of parathyroid autotransplantation (NTT 24% vs TT 28%, $P = 0.50$) and transient RLNP (NTT 3% vs TT 4%, $P = 0.35$) was similar in both groups. The rate of reoperations for bleeding tended to be higher in the NTT group (3% vs 0%, $P = 0.07$) and the rate of inadvertently removed parathyroid glands was significantly higher after NTT (13% vs 3%, $P = 0.01$). An existing endocrine orbitopathy improved in 35% and 24% after NTT and TT ($P = 0.61$). Recurrent disease occurred in only 1 patient after TT ($P = 0.34$).

Conclusion: NTT for GD is not superior to TT regarding transient postoperative hypoparathyroidism.

Keywords: Graves disease, near-total thyroidectomy, total thyroidectomy, transient postoperative hypoparathyroidism

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Thyroid resection is one definitive treatment option for Graves' disease (GD). The optimal extent of resection is yet not clearly defined. Nowadays, there are 3 accepted resection strategies for GD, including total thyroidectomy (TT), bilateral near-total thyroidectomy (NTT) with a bilateral remnant of ≤1 g, and hemithyroidectomy with subtotal-total resection (ST) (remnant 2–4 g) of the contralateral site (Hartley-Dunhill procedure). Actual guidelines do not give a definite statement which resection is the procedure of choice. The German S2k-guideline and the American Thyroid Association guideline recommend TT or ST.[1,2] Thus, in daily practice, the extent of resection in GD is still often a matter of the surgeons' preference. Primary goal of the operation should be the definitive control of hyperthyroidism with low complication rates. Three previous randomized trials and 2 metanalyses have demonstrated that TT is associated with a significantly reduced prevalence of recurrent hyperthyroidism compared to ST with remnants around 4 g.[3–7] However, the incidence of temporary hypoparathyroidism was reported to be significantly higher after TT (range 25%–37%) than after ST (range11.4%–13.7%, $P < 0.001$). The rates of permanent hypoparathyroidism were not significantly different, only tended to be higher after TT (range 0.6%–10%) versus ST (range 0%–6%). The underlying causes of postoperative hypoparathyroidism are complex, especially because GD is an independent risk factor for transient postoperative hypoparathyroidism.[8–11] Preparation techniques, particularly the extent of resection, seem to be more influential than inadvertent parathyroidectomy.[8,12] Postoperative hypoparathyroidism, even when only temporary, affects patients' physical health and quality of life.[13]

It was hypothesized that NTT with bilateral remnants of ≤1 g might be a good compromise to TT, as the prevalence of postoperative hypoparathyroidism might be lower because of preservation of the upper parathyroid glands, with a low risk of recurrent disease. The present randomized controlled trial (RCT) was performed to evaluate the rate of temporary hypoparathyroidism after TT versus NTT with defined bilateral remnants ≤1 g as primary endpoint.

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METHODS/DESIGN

Eligibility

Certified reference or competence centers of thyroid and/or endocrine surgery by the German Society of Visceral and General Surgery (DGAV) and selected high-volume centers were offered participation in the trial. Participating centers had to perform at least 150 thyroid resections per year and participating surgeons had to have performed at least 100 thyroidectomies (supplemental table S1, http://links.lww.com/SLA/B731).

Patients with GD scheduled for surgery were eligible for the trial. Indications for surgery followed those of the German S2k-guideline.[1,14] Patients were included in the trial according to the inclusion and exclusion criteria shown in Table 1.

Intervention and Control

The trial was designed as a prospective, randomized, controlled, multicenter trial in a parallel design.[14] Patients and the observer were blinded to the applied surgical intervention throughout the study period. The intervention addressed the surgical procedure. It was defined as NTT with remnants $\leq$1 g on each side in the intervention group. The study protocol described exactly where remnant accounting for $0.5 \times 0.5 \times 0.5 cm^3$ in size at most ($\leq$1 g) should be left at the superior suspensory ligament of Berry. The situs after the resection was photo-documented to monitor the extent of resection. Patients in the control group received TT.

Surgical Methods

The only preparation binding principles in either group were visualization and protection of the recurrent laryngeal nerve (RLN), as well as of parathyroid glands following the German S2K-guideline.[1] If multinodular changes, suspected or frozen-section proven malignancy required TT in the intervention group, or even additional lymphadenectomy in either group, the reason was documented in the case report form.

Definition Of endpoints and Outcome Measures

Primary Endpoint

The primary efficacy endpoint was incidence of postoperative transient hypoparathyroidism. It was defined as an inadequate parathyroid function not exceeding 6 months postoperatively. Calcium (Ca), parathyroid hormone (PTH), levels and substitution medication to achieve normocalcaemia were used to assess hypoparathyroidism. To the best of our knowledge, there is no evidence- or consensus-based definition of postoperative hypoparathyroidism based on calcium and PTH cutoff levels. In line with most experts, the study group defined postoperative hypoparathyroidism as Ca and PTH levels below the locally used normal limit[15–17] because centers had little varying lower limits for Ca (range 2.0–2.1 mmol/L) and PTH (range <11–<15 ng/L) serum levels. Ca and/or vitamin D substitution was only given when postoperative hypocalcemia was diagnosed and/or the hypoparathyroidism was symptomatic. A routine pre- and perioperative substitution of Ca and/or vitamin D was not permitted. Application type, form, and dosage of Ca and vitamin D substitution therapy to achieve normocalcaemia were registered. Ca and PTH levels were recorded before surgery, at the day of discharge, 6 weeks, 6 and 12 months after surgery. The occurrence of the primary endpoint was assessed by 2 physicians (D.K.B., E.M.) after review of these data.

Secondary Endpoints

Secondary endpoints comprised the incidences of permanent hypoparathyroidism, temporary recurrent laryngeal nerve palsy (RLNP), reoperations for bleeding, the number of inadvertently removed parathyroid glands according to the histopathology report, the rate of autotransplantation, recurrent GD, as well as changes of endocrine orbitopathy (EO), and quality of life. Permanent hypoparathyroidism was defined as persisting inadequate parathyroid function exceeding 6 months after surgery.[18,19] The incidence of recurrent GD was assessed by laboratory thyroid function tests at 6 weeks, 6 and 12 months postoperatively with respect to concomitant substitution or thyrostatic medications to achieve euthyrosis.

Reoperations were reported as serious complications. The number of inadvertently removed parathyroid glands were counted from histopathology reports. The incidence of temporary RLNP was assessed through laryngoscopy at discharge. Changes in EO were judged with the validated clinical eyelid, exophthalmos, eye muscle, optic nerve (LEMO) score[20] before and 12 months after surgery. Changes in quality of life were measured before surgery and 6 weeks thereafter using the SF-36 physical and mental health summary score.[21]

Statistical Analysis

Based on published evidence,[4] a reduction in the incidence of transient hypoparathyroidism from 28% after TT to 12% after NTT was assumed. Accounting for 5% drop-out, the planned sample size of 206 patients achieves a power of 80% in a 2-sided chi square test with significance level 0.05.[14]

The primary analysis was performed in the intention-to-treat population, consisting of all randomized patients, evaluated according to the randomly allocated intervention. Confirmatory analysis of the primary endpoint used a logistic regression of transient hypoparathyroidism on randomized allocation adjusted for age. Secondary endpoints were analyzed using appropriate statistical tests. For safety endpoints, such as RLNP and postoperative bleeding, patients were analyzed according to treatment actually received. Analyses of secondary endpoints were descriptive. Statistical analyses were done using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Eighteen centers randomized 207 patients to either TT (n = 104) or NTT (n = 103) between September 2015 and January 2017 (Fig. 1). Baseline characteristics were well balanced between

TABLE 1. Inclusion and Exclusion Criteria for the TONIG-Trial

Inclusion Criteria	Exclusion Criteria
Indication for definite surgery according to the German S2k guideline[1]	Eligibility for conservative treatment according to German guideline
No history of previous thyroid and/or parathyroid surgery	(Suspected) malignancy
Normal vocal cord function	Coincident hyperparathyroidism
Age >18 y	Neurophysiological deficiencies
Expectancy of life >12 mo	
Provision of informed consent	

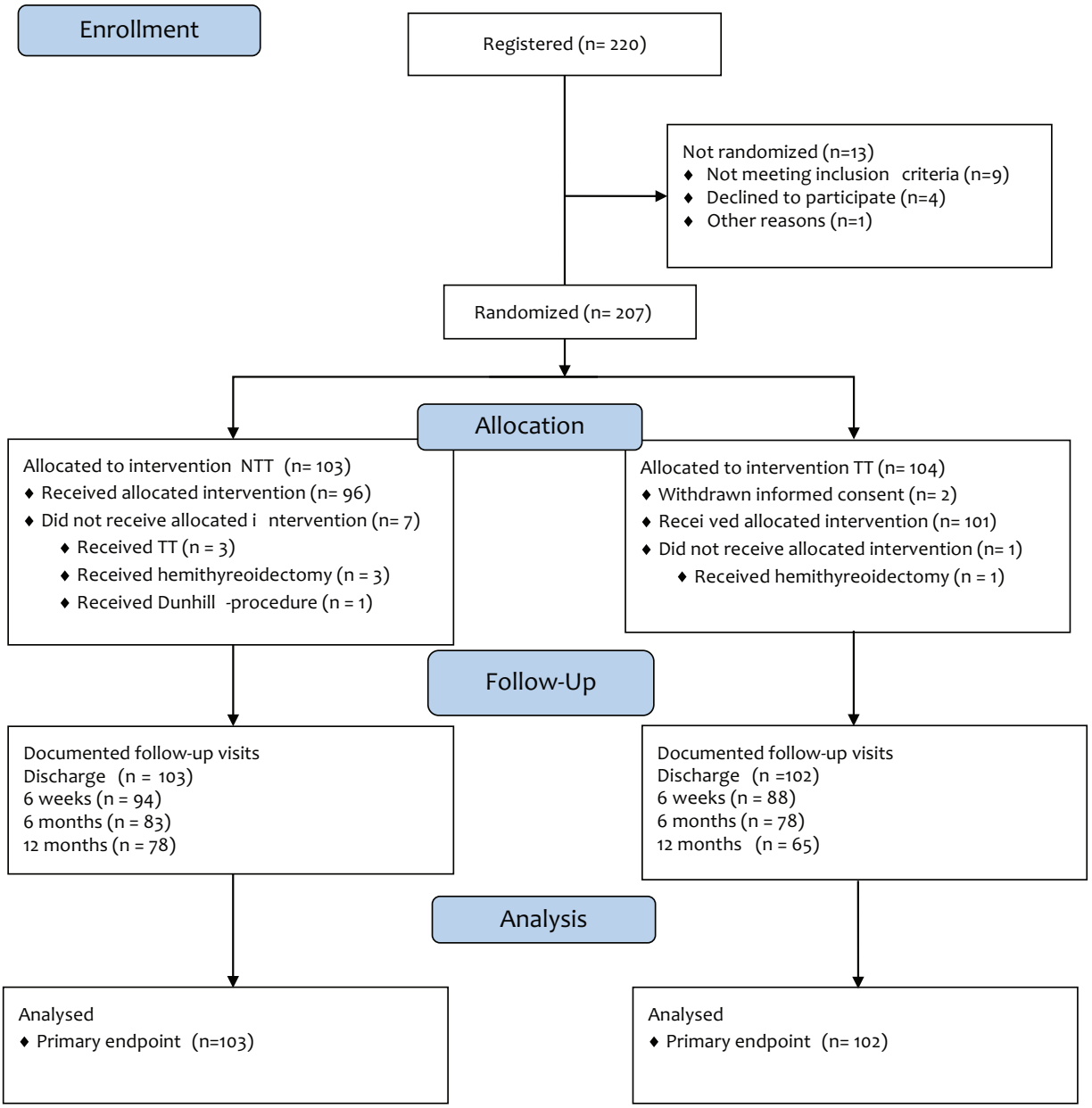

FIGURE 1. CONSORT diagram for the study. Two randomized patients in the TT group withdrew their informed consent after surgery, so that 205 randomized patients remained for analysis.

randomly allocated patients, except weight and body mass index were slightly higher in the TT group (Table 2).

Seven of 103 (7%) patients in the NTT group, and 1 of 102 (1%) patients in the TT group did not receive the randomly allocated intervention because of intraoperative technical problems. The operation was terminated in 3 of 103 in the NTT group and 1 of 102 patients in the TT group after resection of the first site due to suspected RLN damage. In the NTT group, another 4 patients did not receive the allocated procedure because of unfavorably located thyroid nodules or bleeding from the thyroid remnant (Fig. 1).

According to intention-to-treat postoperative transient hypoparathyroidism occurred in 19% (20/103) patients allocated to NTT and in 21% (21/102) patients allocated to TT ($P = 0.84$, Table 3). The rate of transient hypoparathyroidism was also not significantly different between patients with or without inadvertently removed parathyroid glands in either group. Uni- and multivariable logistic regression analysis of transient hypoparathyroidism on randomized treatment inadvertently removed parathyroids and reimplantation of parathyroids showed no significant differences (supplemental table S2, http://links.lww.com/SLA/B731). The hypoparathyroidism persisted $\geq$6 months in 2% (2/84) patients after NTT and 5% (4/76) patients after TT ($P = 0.34$). The 6 of 12 months follow-up was not complete in all patients, as 19 patients of the NTT and 26 patients of the TT group refused to come to the follow-up visits. Five of 19 patients with NTT and 1 of 26 patients with TT and insufficient follow-up had a hypoparathyroidism at discharge and/or 6 weeks

TABLE 2. Patients' Baseline Characteristics

	Overall, n = 205	NTT, n = 103	TT, n = 102	*P*
Sex, n (%)				0.27
Male	40 (20%)	17 (17%)	23 (23%)	
Female	165 (80%)	86 (83%)	79 (77%)	
Age, y, median (range)	43 (18–84)	43 (19–84)	42.5 (18–76)	0.84
Height, cm, median (range)	168 (151–198)	163 (153–185)	168 (151–198)	0.32
Weight, kg, median (range)	72 (43–132)	68 (43–130)	75 (45–132)	0.02
BMI, kg/m^2, median (range)	24.9 (15.1–48.5)	24.2 (17.2–43.4)	25.4 (15.1–48.5)	0.04
Preoperative EO, n (%)	49 (24%)	28 (27%)	21 (21%)	0.27
Preoperative TSH, n (%)				0.91
Normal range	61 (30%)	33 (32%)	28 (27%)	
Below LLN	120 (59%)	58 (56%)	62 (61%)	
Above ULN	22 (11%)	11 (11%)	11 (11%)	
Not done or missing	2 (1%)	1 (1%)	1 (1%)	
Preoperative TRAK level				0.21
n (%)	164 (80%)	86 (83%)	78 (76%)	
Above ULN	61 (20%)	17 (17%)	24 (24%)	

BMI indicates body mass index; LLN, lower limit of normal; TRAK, thyroidea receptor antibody; TSH, thyroid-stimulating hormone; ULN, upper limit of normal.

postoperatively. A last-observation-carried-forward (LOCF)-analysis was performed to determine the significance of the missing follow-up. If one assumes that all these 45 patients had the same condition at the follow-up as at discharge, this would result in a LOCF-NTT: 10 of 103 (9%) and LOCF-TT: 9 of 102 (9%). If one assumes that no one of the 45 patients with missing follow-up had a hypoparathyroidism, it results in a LOCF–NTT: 2 of 103 (2%) and LOCT-TT: 4 of 102 (4%). This is practically the same result as with the formal analysis, thus not changing the outcome of the trial.

The rates of parathyroid autotransplantation were similar in both groups [NTT 24% (25/103) vs TT 28% (29/102), $P = 0.50$]. However, during NTT significantly more parathyroid glands were inadvertently removed than during TT (13% vs 3%, $P = 0.01$, Table 3). Five of 13 NTT patients and none of 3 TT patients with inadvertently removed parathyroid glands had a postoperative transient hypoparathyroidism. Thus, the rate of transient hypoparathyroidism was not significantly different between patients with or without inadvertently removed parathyroid glands in either group.

The rate of transient RLNP with regard to nerves at risk was 3% (5/192) in the NTT and 4% (9/208) in the TT group ($P = 0.35$), if calculated according to treatment actually received. The rate of reoperations for postoperative bleeding tended to be higher after NTT (3% vs 0%, $P = 0.08$).

At the time of operation, 27% (28/103) patients in the NTT group and 20% (21/102) patients in the TT group had an EO ($P = 0.27$). This improved within 12 months postoperatively in 35% (10/28) patients after NTT and 24% (5 of 21) patients after TT ($P = 0.61$). The median SF-36 physical and mental health summary scores 6 weeks after surgery were similar in both groups (52 and 47 with NTT vs 51 and 52 with TT, $P = 0.73$ and $P = 0.96$) with no significant differences between preoperative and early postoperative values. After 12 months, GD recurred in one and none patient of the TT and NTT group, respectively ($P = 0.34$).

DISCUSSION

TT has high cure and negligible recurrence rates for the definitive treatment of GD, but a higher risk of postoperative hypoparathyroidism compared with ST (Table 4).[3–5,12,13,22] It was hypothesized that NTT with a remnant of ≤1 g on each side might be a good compromise to TT. The risk of recurrent disease will remain equally low, but the prevalence of postoperative hypoparathyroidism might be lower because of the reduced risk of intraoperative devascularization of the upper parathyroid glands. The presented study is the first multicenter RCT comparing TT with NTT for surgical treatment of GD. The trial did show no benefit of NTT regarding

TABLE 3. Results of Surgery

	Overall, n = 205	NTT, n = 103	TT, n = 102	*P*
Transient hypoparathyroidism	41 (20%)	20 (19%)	21 (21%)	0.84*
Permanent hypoparathyroidism†	6/160 (3.8%)	2/84 (2%)	4/76 (5%)	0.34
Autotransplantation of PG	54 (26%)	25 (24%)	29 (28%)	0.50
Patients with inadvertently removed PG	16/200	13/96	3/104	0.01
Transient RLNP per NAR‡	14/400 (3.5%)	5/192 (3%)	9/208 (4%)	0.35
Reoperation owing to bleeding	3/200 (1.5%)	3/96 (3%)	0/104 (0%)	0.07
Patients with improvement of EO§	15/49 (31%)	10/28 (36%)	5/21 (24%)	0.61
Recurrent hyperthyroidism	1 (0.5%)	0 (0%)	1 (1%)	0.34

NAR indicates nerves at risk; PG, parathyroid glands. For analyses not based on the randomized treatment, numbers given are enumerator/denominator. No RLNP was observed in the 4 patients who had only hemithyroidectomy owing to suspected intraoperative nerve damage. The median operative time was 103 (range 32–280) minutes in both arms ($P = 0.98$).

*After adjustment for age in a logistic regression model.

†Among patients with a follow-up visit at 6 and/or 12 months after randomization.

‡Analyzed by actually received treatment (excluding 5 patients not receiving NTT or TT) and not by intention-to-treat.

§Among patients with EO at baseline.

TABLE 4. Results of the 4 Existing RCTs Comparing Total Thyroidectomy and Different Types of Subtotal Resection for Surgical Treatment of Graves disease

			Transient Hypoparathyroidism		Permanent Hypoparathyroidism		Transient RLNP		Postoperative Bleeding		Recurrent Hyperthyroidism	
Study	**Design**	**No. of Patients**	**TT**	**ST**	**TT**	**ST**	**TT**	**ST**	**TT**	**ST**	**TT**	**ST**
Braczynski et al 2012[3]	RCT, single center	191	24/96 (25%)	13/95 (13.7%)	1/96 (1%)	0/95 (0%)	9/96 (9.4%)	6/95 (6.3%)	nr	nr	0/96 (0%)	9/95 (9.5%)
Chi et al,* 2005[22]	RCT, single center	340	66/174 (37.9%)	19/166 (11.4%)	1/174 (0.6%)	0/166 (0%)	1/174 (0.6%)	3/166 (1.8%)	0/174 (0%)	6/166 (3.6%)	3/174 (1.7%)	15/166 (9%)
Jarhult et al[5], 2005†	RCT multicenter	43	nr	nr	2/22 (9.1%)	0/21 (0%)	nr	nr	1/22 (4.5%)	2/21 (9.5%)	0/22 (0%)	0/21 (0%)
Witte et al, 2000[4]	RCT single center	150	14/50 (28%)	6/50 (12%)	5/50 (10%)	3/50 (6%)	1/50 (2%)	1/50 (2%)	nr	nr	0/50 (0%)	2/50 (4%)
Current study‡	RCT, multicenter	205	21/102 (21%)	20/103 (19%)	4 (5%)	2 (2%)	9/208 NAR (4%)	5/192 NAR (3%)	0/102 (0%)	3/103 (3%)	1/102 (1%)	0/103 (0%)

Nr indicates not reported.

*Compared bilateral subtotal vs unilateral total and contralateral subtotal thyroidectomy.

†Compared subtotal (remnant 2 g) vs total thyroidectomy in moderate and severe EO.

‡Compared total thyroidectomy with near-total thyroidectomy (remnant <1 g on each side).

the primary endpoint ''incidence of postoperative transient hypoparathyroidism'' compared to TT (19% vs 21%, $P = 0.84$). This result is contrary to the outcome of former 3 RCTs with ST (remnants between 2 and 4 g).[3–5] In these trials TT had rates of transient hypoparathyroidism between 25% and 38%, which is comparably higher than in the present trial. After ST the rates of hypoparathyroidism ranged between 11% to 14% (Table 4). The main reason for this discrepancy might be that the blood supply of the upper parathyroid gland is less impaired during ST with a remnant between 2 and 4 g at the upper gland pole compared to NTT in the present study. Obviously, temporary impairment of the parathyroid blood supply, especially the upper gland, cannot be spared better by NTT compared to TT. It was surprising that the rate of inadvertently removed parathyroid glands was 3 times higher after NTT compared to TT (13% vs 3%, $P = 0.01$), although the rate of autotransplantation was similar. The reasons for this result remain speculative. Uni- and multivariable logistic regression analyses of transient hypoparathyroidism on randomized treatment, inadvertent removal of parathyroids, and reimplantation of parathyroids, however, showed no significant differences, allowing to rule out surgical technique issues as an important bias. Moreover, lack of surgical expertise as major reason is unlikely, as the procedures were performed by experienced thyroid surgeons (supplemental table S1, http://links.lww.com/SLA/B731). In the present study, novel techniques of parathyroid detection such as near-infrared autofluorescence or indocyanine green fluorescence were not used, which might have reduced the number of inadvertently removed parathyroids.[23,24]

The present RCT revealed no difference in the rate of postoperative permanent hypoparathyroidism after NTT compared to TT (2% vs 5%, $P = 0.34$). This result coincides with above-mentioned RCTs and 2 meta-analyses (Table 4).[3–5,12,13] Nevertheless, postoperative hypoparathyroidism is the major complication after surgery for GD as reported in large-scale registry studies.[25,26]

The remnant size seems also responsible for the rate of recurrent hyperthyroidism.[27] Braczynski et al,[3] for example, reported a rate of recurrence of 9.5% after ST and 0% after TT after a follow-up of 5 years. This result was similar to the meta-analysis of Palit et al comprising 7241 patients with GD where a recurrence rate of 0 versus 8% (TT vs ST) was found after a mean follow-up of 5.6 years.[28] The present trial showed no statistically significant difference between TT and NTT regarding the recurrence of GD (0% vs 1%, $P = 0.34$) after a short-term follow-up. NTT seems compared with ST a sufficient surgical procedure to avoid recurrent hyperthyroidism, as the 12 months' recurrence rate was 0% compared to 0% to 9.5% in previous RCTs.[3–5] As long-term follow-up was not the focus of the present trial, the long-term recurrence rate after NTT needs to be awaited to draw definitive conclusions.

In previous RCTs a postoperative improvement of an existing EO was reported in 70% to 85% of patients during a follow-up of 3 to 5 years, both, after TT and ST.[3,4,29] In the present trial, an existing EO postoperatively improved in only 36% of patients in the NTT and 24% of patients in the TT group within 12 months ($P = 0.61$). One reason for this lower improvement rate in the present study might be a different method to define the course of EO, namely the LEMO-score compared to the NOSPECS[3] and a modified ATA score system[4] in the other RCTs, as well as a too short follow-up to reach a final EO improvement. The extent of resection seems not to affect significantly the course of EO.

The rate of transient RLNP was not different between NTT and TT (3 vs 4%, $P = 0.35$) and was in the lower range of previous RCTs and register studies with rates between 2.1% and 7.4%.[3,4,20,22,] In the present trial the rate of reoperations owing to postoperative bleeding tended to be higher in the NTT group ($P = 0.07$). Moreover, 4 of the 103 patients did not receive the randomly allocated intervention NTT because of technical difficulties, for example, anatomical conditions or impossibility of hemostasis at the thyroid remnant. Previous RCTs did not report on technical difficulties with ST.[3–5,22] NTT, however, seems technically more demanding than ST and sometimes even more demanding than TT.

The present study has some limitations. One is the missing serum Ca and PTH levels in 19 patients after NTT and 26 patients after TT after 6 of 12 months to define the rate of permanent hypoparathyroidism. Patients were informed several times about their follow-up appointments. Thirty-nine of these 45 patients had normal Ca and PTH levels at discharge, so one could reasonably exclude permanent hypoparathyroidism. To investigate potential outcomes, we performed analyses with a variety of imputation models, none of which showed a significant difference between NTT and TT group. Moreover, the follow-up of 12 months is too short for a definitive conclusion regarding the recurrence rate of hyperthyroidism and a potential improvement of an existing EO. The prevalence of permanent hypoparathyroidism would have been an even more important clinical outcome. To test this primary endpoint with sufficient statistical power, at least 10 times more patients had to be enrolled. However, the primarily tested condition also significantly impairs the patients' quality of life.

CONCLUSION

NTT for GD is not superior to TT regarding postoperative transient hypoparathyroidism. The risk to inadvertently remove parathyroid glands was higher and the risk of postoperative bleeding tended to be higher after NTT. So, TT should be the preferred procedure as surgical treatment of GD.

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DISCUSSANTS

François Pattou (Lille, France):

First, I would like to thank the ESA for the opportunity to comment on this interesting paper and commend the authors for this large multicenter, randomized trial of the best thyroidectomy procedure for the treatment of Graves disease.

I have 2 questions:

First, the definition of the primary endpoint for hypoparathyroidism, which was ''calcium and PTH levels below the locally used normal range within 6 weeks after surgery", is rather unclear. One would like to know the incidence of clinically significant hypoparathyroidism, that is with symptom or requiring treatment with Ca and/or Vitamin D.

Routine administration of Vitamin D (pre-op) or Ca (post-op) has become common practice in many centers, and may significantly impact the rate of postoperative hypocalcemia. Was it excluded in the protocol?

Second, the paradoxical higher rate of inadvertently removed parathyroids in NTT is difficult to understand. Were these removed glands inferior or superior? Was this finding associated with lower early Ca and/or PTH postoperative levels, with transient and/or permanent hypoparathyroidism? Could this be because of a difference in pathological analysis of the total versus near total thyroid specimen?

Response From Elisabeth Maurer (Marburg, Germany):

Thank you very much for your legitimate questions. Definitions in the literature for postoperative transient or permanent are inconsistent. Within this trial, transient hypoparathyroidism was defined as inadequate parathyroid function not exceeding 6 months after surgery, which is the most often used time interval to differentiate transient from permanent hypoparathyroidism. To the best of our knowledge, there is no evidence- or consensus-based definition of postoperative hypoparathyroidism based on calcium and PTH cutoff levels. As 18 centers participated in the trial, the study group agreed for the definition to be ''below the locally used normal range'' because centers had little varying lower limits for serum levels according to the respective laboratories. However, these ranges were quite narrow.

Ca and/or Vitamin D substitution was only given when postoperative hypocalcemia was measured and/or the hypoparathyroidism was symptomatic with at least one of the following symptoms: carpopedal paresthesia, numbness or spasm, anxiety. Application type and dosage were determined by the treating surgeon. A routine pre- or postoperative substitution of calcium and/or Vitamin D was not permitted according to the protocol.

Regarding your second question, we were also surprised by this high rate of inadvertently removed parathyroid glands. This result cannot be satisfactorily explained. We agree that the exact localization of inadvertently removed parathyroid glands would be of interest, but it could not be determined by pathological analysis, as the upper and/or lower end of the resection specimen had not been marked according to the protocol. Of the patients with inadvertently removed parathyroid glands, 5 and 1 of 13 NTT patients and none of the 3 TT patients developed a postoperative transient or permanent hypoparathyroidism. Thus, the rate of transient hypoparathyroidism was not significantly different between patients with or without inadvertently removed parathyroid glands in either group. Although the pathological work-up was not specified per protocol, it is hard to imagine that the differences are caused by a different pathological analysis of TT and NTT specimens.

In the literature, the rates of inadvertently removed parathyroid glands in thyroid surgery are up to 11% and the few mentioned risk factors do not explain the difference within our trial.

In summary, the reasons for the high rate of inadvertently removed parathyroids in the NTT group remain speculative.

Inne Borel-Rinkes (Utrecht, The Netherlands):

I have to compliment you on a really important and well-conducted study. I was thinking about the complication rate, particularly your reoperation rate, owing to bleeding. Could you please give us a little bit more information regarding the causes of bleeding? Was it at the site of the biopsy of the parathyroid you left in?

Response From Elisabeth Maurer (Marburg, Germany):

Reoperation owing to bleeding only occurred in the NTT group. Participating centers had to document the site and reasons for reoperation. In all 3 cases, the bleeding was localized at the thyroid remnant. There were no reoperations for bleeding necessary when a TT was performed. So, a near-total resection sometimes seems technically more demanding than a total thyroidectomy.