ORIGINAL ARTICLE

Recurrent goiter: risk factors, patient quality of life, and efficacy of radioiodine therapy

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KEY WORDS

levothyroxine, lobectomy, quality of life, radioiodine, thyroid nodule

ABSTRACT

INTRODUCTION Goiter reoccurs in a substantial number of patients after thyroid resection.

OBJECTIVES We aimed to investigate the prevalence and risk factors of recurrent goiters, influence of goiter recurrence on patient quality of life, and the efficacy of therapy with radioiodine (RAI).

PATIENTS AND METHODS This was a case-control study. A total of 481 thyroidectomized patients admitted to the outpatient department within the past year were included in the study and their medical records were analyzed. Also, 30 healthy controls were recruited for comparison. Recurrence was defined as nodular lesions present within the remnant tissue or enlargement of the remaining thyroid tissue that required therapy (reoperation or RAI therapy). Clinical and biochemical data were collected. Randomly selected patients were asked to answer the Polish version of Thyroid-Related Quality-of-Life Patient-Reported Outcome measure (ThyPROpl).

RESULTS A total of 68 patients had recurrent goiter and in 413 patients the recurrence did not occur. Higher thyroid-stimulating hormone at follow-up and lobectomy were the strongest risk factors for goiter recurrence, followed by a longer follow-up. Postoperative levothyroxine therapy was associated with a lower risk of recurrence. Efficacy of RAI was similar to secondary thyroidectomy. Scores in all comparable scales for patients with recurrent goiters were significantly worse than those in the general population sample.

CONCLUSIONS Lobectomies should be avoided as a primary surgical treatment for patients with benign thyroid diseases, and levothyroxine therapy should be considered individually in each patient. RAI therapy seems to be a safe and effective treatment option for patients with recurrent goiters. Recurrent goiters, even if successfully treated, have a negative impact on the quality of life.

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INTRODUCTION In general, the incidence of permanent complications after thyroid surgery is low, although the recurrence rate after thyroid resection is substantial in a number of patients.[1,2] Studies in rats after hemithyroidectomy demonstrated that hypertrophy of thyroid tissue without hyperplasia causes thyroid growth after surgical resection.[3,4] Subsequently, compensatory thyroid growth in patients with thyroid hemiagenesis or after hemithyroidectomy was confirmed.[5-7] A minority of patients with recurrent goiter require secondary therapy.[8] Surgical resection is a therapeutic option. Radioiodine (RAI) is widely used as a therapy of hyperthyroidism.[9,10] However, some patients with recurrent goiter may also benefit from RAI therapy as an alternative therapeutic option when malignancy is not suspected.

We aimed to investigate the prevalence of recurrent goiter and risk factors of its development. In addition, we investigated the influence of recurrent goiter on patient quality of life (QOL) and we analyzed the efficacy of RAI therapy in patients with recurrent goiters.

PATIENTS AND METHODS **Study design and patient recruitment** This was a case-control study. We analyzed the medical records of all patients who were admitted to the outpatient clinic of the Department of Endocrinology, Metabolism and Internal Medicine in Poznań, Poland between June

2017 and May 2018. All patients who had a thyroid gland resected because of benign thyroid disease were included for further analysis. Recurrence was defined as a nodular lesion present in the remnant tissue or enlargement of the remaining thyroid tissue that required therapy (either reoperation or RAI therapy) and was identified on postoperative ultrasound imaging. We excluded patients who were diagnosed with recurrent goiter but did not undergo any therapy. Clinical and biochemical data were collected prior to the primary surgery and during the last visit. In addition, thyroid-stimulating hormone (TSH) levels were analyzed in patients with recurrent goiter prior to the second surgery or before RAI administration and in patients without recurrent goiter at follow-up. The following clinical characteristics of patients were analyzed to determine potential risk factors of recurrent goiter development: age, sex, thyroid volume, presence of nodules, histopathological diagnosis, presence of autoimmune thyroiditis, levothyroxine (LT_4) therapy advised after the operation, type of surgery (total thyroidectomy, subtotal thyroidectomy, or obectomy with or without isthmectomy), and RAI therapy before surgery. Thyroid gland volume was calculated with the ellipsoid formula: width (cm) × depth (cm) × length (cm) × 0.52 = volume (ml). All patients were referred for a thyroidectomy because of suspicion of malignancy, compressive symptoms, or failure of therapy with antithyroid medications.[11] Data on adverse events after surgery were also collected.

The study was approved by the Bioethical Committee of the Poznan University of Medical Sciences.

Health-related quality of life assessment Thirty randomly selected patients treated for a recurrent goiter and 50 thyroidectomized patients without recurrent goiter were asked to answer the Polish version of Thyroid-Related Quality-of-Life Patient-Reported Outcome measure (ThyPROpl). Thirty healthy controls were recruited for comparison. Exclusion criteria included: cancer, pregnancy, and other comorbidities with substantial impact on QOL. ThyPROpl is a linguistically validated version of the original ThyPRO questionnaire.[12] ThyPRO consists of 85 questions summarized in 13 multi-item scales.[12] Each scale ranges from 0 to 100.[13-15] The higher the score, the worse QOL. Five of the ThyPRO scales (Impaired Social Life, Impaired Daily Life, Impaired Sex Life, Cosmetic Complaints, Overall Quality of Life) are specific to thyroid diseases, therefore they cannot be answered by the general population.

Statistical analysis All calculations were performed with the MedCalc Statistical Software, version 18.10 (MedCalc Software bvba, Ostend, Belgium). Normality was analyzed by the D'Agostino–Pearson test. Since data did not follow normal distribution, comparison of the analyzed parameters between the groups was performed with the Mann–Whitney test. The Fisher exact test was used to compare discrete variables.

Simple logistic regression was used to search for factors associated with goiter recurrence. Multiple logistic regression with stepwise selection was used for multivariate comparisons.

A one-way analysis of covariance was conducted to determine a statistically significant difference in ThyPROpl scale scores between subgroups with a control for age, sex, comorbidity, and educational status. Effect size was used to assess the magnitude of differences (mean difference divided by SD at baseline) in accordance with Cohen[16] and was reported as a small effect from 0.2 to 0.5, moderate effect from 0.5 to 0.8, or large effect more than 0.8.

A *P* value of less than 0.05 was considered statistically significant.

RESULTS Clinical and biochemical characteristics In total, 538 patients were eligible for the study. Information about the date or extent of primary surgery was missing in 31 patient records and 26 patients fulfilled exclusion criteria; therefore 481 patients were included in the study. The study group consisted of 68 patients (59 women and 9 men) with a recurrent goiter, while 413 (359 females and 54 men) served as a control group as they did not require a secondary operation nor RAI therapy. A recurrent goiter was diagnosed in 14% of patients and was more frequent in patients who underwent lobectomy or subtotal thyroidectomy.

In the study group the preoperative diagnoses included nontoxic nodular goiter (n = 53), toxic nodular goiter (n = 11), and Graves disease (n = 4), while in the control group the perioperative diagnoses were nontoxic nodular goiter (n = 307), toxic nodular goiter (n = 65), Graves disease (n = 22), and Hashimoto thyroiditis (n = 17) ($P > 0.05$). One patient from the study group and 9 patients from the control group had been treated with RAI before the primary thyroidectomy (because of hyperthyroidism or an enlarged goiter).

Patients with recurrent goiters were younger at the time of surgery than patients without recurrent goiters. Preoperative thyroid volume, nodularity, and number of patients with autoimmune thyroiditis did not differ between groups. After the first surgery, more patients without recurrence had been treated with LT_4, and their TSH levels at follow-up were significantly lower. Clinical and laboratory characteristics of both groups are provided in TABLES 1 and 2.

Univariate logistic regression revealed that higher TSH levels at follow-up and lobectomy were the strongest risk factors for goiter recurrence, followed by a longer follow-up and younger age of patients at the time of surgery. LT_4 therapy advised after the first surgery was associated with a lower risk of recurrence. Other potential

TABLE 1 Clinical characteristics of the study groups

		Patients with recurrent goiter (n = 68)	Patients after thyroidectomy without recurrent goiter (n = 413)	*P* value
Sex, female/male, n (%)		59 (86.8) / 9 (13.2)	359 (86.9) / 54 (13.1)	1.0
Age at the time of surgery, y, median (IQR)		38 (28–48.75)	44 (33–54)	0.006
Preoperative thyroid volume, ml, median (IQR)		21.8 (14.3–35.4); n = 14	21.9 (13.2–37.8); n = 260	0.95
Preoperative thyroid nodules, n (%)	Present	67 (98.5)	402 (97.3)	1.0
	Absent	1 (1.5)	11 (2.7)	
Preoperative radioiodine therapy, n (%)	Yes	1 (1.5)	9 (2.2)	1.0
	No	67 (98.5)	404 (97.8)	
Type of surgery, n (%)	TT	45 (66.2)	269 (65.1)	1.0
	ST	12 (17.6)	114 (27.6)	0.1
	L	11 (16.3)	30 (7.3)	0.03
Follow-up (from the first surgery to the last visit), y, median (IQR)		13.9 (7.7–26.3)	10 (7–16)	0.01
Autoimmune thyroiditis on histopathological examination, n (%)	Present	5 (7.4)	43 (10.4)	0.52
	Absent	63 (92.6)	370 (89.6)	
Levothyroxine therapy advised after the first surgery, n (%)	Yes	45 (66.2)	380 (92)	<0.001
	No	23 (33.8)	33 (8)	

Abbreviations: IQR, interquartile range; L, lobectomy; ST, subtotal thyroidectomy; TT, total thyroidectomy

TABLE 2 Concentration of thyroid-stimulating hormone in patients before the recurrence of goiter or during the follow-up in patients without recurrence, and thyroid-related hormones at the last visit

	Patients with recurrent goiter (n = 63)	Patients after thyroidectomy without recurrent goiter (n = 418)	*P* value
TSH at follow-up, mIU/l	2.35 (1.56–2.98)	1.11 (0.56–1.67)	<0.001
TSH at the last visit, mIU/l	0.67 (0.46–1.55)	0.8 (0.44–1.43)	0.99
FT_4 at the last visit, pmol/l	16.5 (15.20–18.75); n = 56	16.7 (15.32–21.46); n = 229	0.42
FT_3 at the last visit, pmol/l	4.47 (3.89–4.93); n = 55	4.51 (3.91–5.11); n = 314	0.79

Data are presented as median (interquartile range).

Abbreviations: FT_3, free triiodothyronine; FT_4, free thyroxine; TSH, thyroid-stimulating hormone

risk factors were not associated with goiter recurrence. The results of the univariate logistic regression analysis are presented in TABLE 3. The association between age at the time of surgery and recurrent goiter was no longer significant after adjustment for the follow-up.

Radioiodine versus secondary surgery Thirty-nine patients with recurrent goiter were treated with RAI, while the remaining 29 patients were referred for a secondary thyroidectomy. Single administered activity of ^{131}I was 740 MBq (20 μCi), which was repeated twice in 14 patients, and three times in 2 patients. Median follow-up (period from the secondary therapy [RAI or surgery] to the last visit) was similar for both subgroups: for patients who underwent RAI ablation it was approximately 10 years, and for patients who underwent reoperation it was approximately 7.6 years. Thyroid volume reduction was similar for both groups. Recurrence after secondary treatment was not observed in RAI-treated patients, nor in patients who underwent reoperation. Therefore, efficacy of the treatment assessed as thyroid volume reduction and goiter recurrence did not differ between RAI therapy and secondary surgery. Five out of 29 patients who underwent reoperation experienced serious side effects: permanent hypoparathyroidism (n = 4) and damage of recurrent laryngeal nerve (n = 1). No adverse events were observed in patients treated with RAI. The results are shown in TABLE 4.

Quality of life Patients with recurrent goiter had similar age and gender as patients after thyroidectomy without recurrence and the general population sample. TSH concentrations also did not differ between the subgroups (data not shown). Patients with a recurrent goiter experienced a worse QOL for goiter symptoms compared with thyroidectomized patients without recurrence, and the difference was moderate (TABLE 5). Scores in all comparable scales for patients with recurrent goiter were significantly worse than those for the general population sample, and all differences were large (effect size ≥0.8) (TABLE 5).

DISCUSSION

Occurrence of recurrent goiter We found that approximately 14% of operated patients developed recurrent goiter during the follow-up. The recurrence rates varied from 2% to 42% between the previous studies, and was mainly influenced by the definition of recurrence and the follow-up with a peak of recurrence between 10 and 20 years after primary surgery.[8] In our study asymptomatic ultrasound-detectable nodular lesions that did not require therapeutic intervention were not defined as a recurrence, in contrast to some previous studies.[17,18] By applying these criteria we aimed to estimate the prevalence of recurrent goiters that are clinically significant, similarly to other authors.[19]

Risk factors We have analyzed several potential risk factors for recurrent goiter after primary thyroid surgery, that is, extent of primary surgical resection, LT_4 therapy after surgery, initial thyroid volume, presence of autoimmune thyroiditis, TSH levels at follow-up, and preoperative RAI therapy. We confirmed that lobectomy and a longer observation period are associated with a higher risk of recurrent goiter. Recently, in a randomized controlled trial, the prevalence of

TABLE 3 Univariate analysis of predictors for the development of recurrent goiter

Potential risk factors of goiter recurrence	Crude OR	95% CI	*P* value
TSH at follow-up[a]	3.84	2.78–5.29	<0.001
Lobectomy, yes – 1; no – 0	2.35	1.09–5.07	0.04
Observation period, y	1.07	1.04–1.1	<0.001
Age at the time of surgery, y	0.97	0.95–0.99	0.004
Levothyroxine therapy advised after the first surgery, yes – 1; no – 0	0.15	0.08–0.28	<0.001

a TSH after the first surgery in patients with recurrent goiter

Abbreviations: CI, confidence interval; OR, odds ratio; others, see **TABLE 2**

TABLE 4 Comparison of radioiodine therapy and surgical reoperation for recurrent goiter

Parameter	Radioiodine therapy	Secondary surgery	*P* value
Sex, female/male, n	33 / 6	26 / 3	0.73
Age at the secondary therapy, y	40 (30–50)	35 (24–48)	0.37
Follow-up duration[a], y	10.2 (5.8–18.8)	7.6 (2.9–19.2)	0.53
Thyroid volume reduction, %	73 (55–92)	57 (49–90)	0.34
Patients with serious side effects, n	0	5[b]	0.004

Data are presented as median (interquartile range) unless otherwise stated.

a Period from the secondary therapy (RAI or surgery) to the last visit

b Four patients with permanent hypoparathyroidism, 1 patient with damage of recurrent laryngeal nerve

recurrent goiter increased almost 2-fold 10 years after primary surgery, in comparison with 5 years following surgical procedures that were more limited than total thyroidectomy (8.2% vs 15.5%).[17] Similarly to other authors, we found that postoperative therapy with LT_4 was associated with lower risk of goiter recurrence.[20,21] This effect may not be significant among iodine-sufficient patients.[22,23] Interestingly, we observed that lower TSH levels at follow-up also limit the risk of recurrence, and this association needs further investigation. We might speculate that LT_4 therapy prescribed after the operation decreases TSH concentration, which limits the stimulation of thyroid remnants for growth. It would be of high clinical importance to estimate the optimal cut-off value of postoperative TSH levels preventing regrowth of thyroid remnants.

Radioiodine effectiveness We found that RAI ablation is safe and effective for recurrent goiter during long-term observation, with a lower risk of complications, as compared to a surgical approach. As we mentioned above, little is known about the therapeutic outcome of ^{131}I therapy for recurrent goiters. Previous studies have confirmed similar ^{131}I efficacy for reducing thyroid volume in patients with toxic and nontoxic goiters.[24] A decrease in goiter size in nontoxic goiters was directly related to the dose of ^{131}I, but if the initial goiter was large, the reduction was smaller.[25] We have observed a relatively high percentage of reductions in thyroid tissue remnants after RAI therapy, which may be an effect of administered doses of ^{131}I. In general, symptoms improved after RAI therapy, but improvement of goiter-related symptoms or QOL was not correlated with an increase in thyroid volume reduction.[26-29] Administration of recombinant human thyroid-stimulating hormone (rhTSH) before ^{131}I administration (off-label use) might enhance the reduction of nontoxic goiters.[27-30]

Health-related quality of life in patients with recurrent goiter We found that patients treated for recurrent goiter experienced impairment of QOL on all comparable ThyPRO scales compared with the general population sample. Patients with recurrent goiter had more severe impairment connected with goiter symptoms than patients post-thyroidectomy without recurrence. Since there were no differences in thyroid function between the analyzed groups, we cannot explain our findings with biochemical alterations. Also, one can suggest that the follow-up time after a thyroidectomy or even after secondary therapy is relatively long and sufficient for patients to adapt physically and mentally. However, our results suggest that previous invasive therapy (thyroidectomy and/or RAI) and chronic thyroid disease significantly affect mental well-being and cause long-term health-related quality of life (HRQOL) deficits despite biochemical euthyroidism.

As we have mentioned, this is the first study evaluating HRQOL in patients with recurrent goiter. Our findings are in line with other studies that report only partial improvement of HRQOL after therapy in patients with benign thyroid diseases.[31-35] Previous studies investigating patients after thyroidectomy with nontoxic multinodular goiter reported significant relief of goiter symptoms after surgery in short-term observation.[36-38] However, patients after surgery presented some deficits in HRQOL in comparison to the general population sample.[39] We observed much higher goiter symptom scores in patients many years following surgery. We might speculate that this phenomenon is caused by relapse of goiter symptoms in long-term observation periods. Less pronounced relief of symptoms in patients may also be explained by cross-cultural differences. New techniques used to preserve laryngeal nerves may improve the outcome of surgical treatment resulting in better HRQOL in patients.[40]

Strengths and limitation of the study The main limitation of the study was the retrospective data acquisition. However, this was a large study and numerous clinical and biochemical parameters were analyzed. To the best of our knowledge, this is the first study investigating QOL in patients

TABLE 5 Scale scores from the Thyroid-Related Quality-of-Life Patient-Reported Outcome measure of patients who had been treated for recurrent goiter, patients after thyroidectomy without recurrent goiter, and the general population sample

ThyPRO scales	General population sample (n = 30)	Patients with recurrent goiter (n = 30)	Difference between controls and patients with recurrent goiter	Patients after thyroid surgery without recurrent goiter (n = 50)	Difference between patients with recurrent goiter and patients after thyroid surgery
Goiter symptoms	5.2 (10.5)	32.3 (20.5)	1.75	20.3 (16.4)	0.66
Hyperthyroid symptoms	11.8 (12)	25.3 (20.1)	0.84	24.6 (17.4)	NS
Hypothyroid symptoms	15.4 (16.6)	34.8 (28.6)	0.86	29.8 (19.4)	NS
Eye symptoms	10 (14)	23.0 (17.9)	0.82	19.2 (17.8)	NS
Tiredness	0.3 (0.5)	40.4 (9.3)	8.18	45.7 (12.4)	NS
Cognitive complaints	0.5 (0.9)	27.8 (20.1)	2.6	23.3 (21.2)	NS
Anxiety	0.5 (0.5)	37.2 (24.9)	3.0	36.2 (25.2)	NS
Depressive symptoms	1 (1)	37.5 (15.3)	5.1	36.3 (18.6)	NS
Emotional susceptibility	0.4 (0.5)	38.1 (16.3)	4.2	36.1 (15.3)	NS
Impaired social life	–	16.4 (19.8)	–	11.5 (17.8)	NS
Impaired daily life	–	15.7 (17.2)	–	19.5 (20.9)	NS
Impaired sex life	–	25.9 (34)	–	31.6 (33)	NS
Cosmetic complaints	–	18.9 (21.6)	–	14.9 (16.5)	NS
Overall QOL	–	25.8 (26.7)	–	29.1 (29.3)	NS

Data are presented as mean (SD).

Abbreviations: NS, nonsignificant; QOL, quality of life; ThyPRO, Thyroid-Related Quality-of-Life Patient-Reported Outcome

treated for recurrent goiters and the first one assessing RAI efficacy for recurrent goiter therapy.

Conclusion Our results suggest that lobectomies should be avoided as the primary surgery for benign thyroid diseases, and LT_4 therapy should be considered individually in each patient after surgical removal of thyroid gland in order to avoid recurrence. RAI therapy seems to be a safe and effective option for recurrent goiter and should be considered as an alternative treatment option instead of secondary surgery when malignancy is not suspected. Recurrent goiters, even if successfully treated, have a negative impact on QOL.

CONTRIBUTION STATEMENT NS-G designed the study, was involved in data collection, analyzed data, wrote and revised the manuscript. PZ, KM, ACz, PG collected data and were involved in data analysis. JS conceived the study and was involved in data analysis. MR revised the paper. All authors edited and approved the final version of the manuscript.

REFERENCES

1 Cappellani A, Zanghì A, Cardì F, et al. Total Thyroidectomy: the first, the best. The recurrent goiter issue. Clin Ter. 2017; 168: e194-e8.

2 Mauriello C, Marte G, Canfora A, et al. Bilateral benign multinodular goiter: What is the adequate surgical therapy? A review of literature. Int J Surg. 2016; 28: S7-S12.

3 Logothetopoulos J, Doniach I. Compensatory hypertrophy of the rat thyroid after partial thyroidectomy. Br J Exp Pathol. 1955; 36: 617.

4 Clark OH, Lambert WR, Cavalieri RR, et al. Compensatory thyroid hypertrophy after hemithyroidectomy in rats. Endocrinology. 1976; 99: 988-995.

5 Berglund J, Aspelin P, Bondeson AG, et al. Rapid increase in volume of the remnant after hemithyroidectomy does not correlate with serum concentration of thyroid stimulating hormone: a randomised evaluation by ultrasound. Eur J Sur. 1998; 164: 257-262.

6 Pustelnik FS, Gronbek C, Døssing H, et al. The compensatory enlargement of the remaining thyroid lobe following hemithyroidectomy is small and without impact on symptom relief. Eur Archives Otorhinolaryngol. 2018; 275: 161-167.

7 Ruchala M, Szczepanek E, Szaflarski W, et al. Increased risk of thyroid pathology in patients with thyroid hemiagenesis: results of a large cohort case-control study. Eur J Endocrinol. 2010; 162: 153-160.

8 Moalem J, Suh I, Duh QY. Treatment and prevention of recurrence of multinodular goiter: an evidence-based review of the literature. World J Surg. 2008; 32: 1301-1312.

9 Czarnywojtek A, Komar-Rychlicka K, Zgorzalewicz-Stachowiak M, et al. Efficacy and safety of radioiodine therapy for mild Graves ophthalmopathy depending on cigarette consumption: a 6-month follow-up. Pol Arch Med Wewn. 2016; 126: 746-753.

10 Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid. 2016; 26: 1343-13421.

11 Wolinski K, Szkudlarek M, Szczepanek-Parulska E, et al. Usefulness of different ultrasound features of malignancy in predicting the type of thyroid lesions: a meta-analysis of prospective studies. Pol Arch Med Wewn. 2014; 124: 97-104.

12 Sawicka-Gutaj N, Watt T, Sowiński J, et al. ThyPROpl—The Polish version of the thyroid-specific quality of life questionnaire ThyPRO. Endokrynol Pol. 2015; 66: 367-80.

13 Watt T, Hegedüs L, Groenvold M, et al. Validity and reliability of the novel thyroid-specific quality of life questionnaire, ThyPRO. Eur J Endocrinol. 2010; 162: 161-167.

14 Watt T, Cramon P, Hegedüs L, et al. The thyroid-related quality of life measure ThyPRO has good responsiveness and ability to detect relevant treatment effects. J Clin Endocrinol Metab. 2014; 99: 3708-3717.

15 Watt T, Bjorner JB, Groenvold M, et al. Development of a short version of the thyroid-related patient-reported outcome ThyPRO. Thyroid. 2015; 25: 1069-1079.

16 Cohen J. Statistical power analysis for the behavioral sciences. 1988, Hillsdale, NJ: L. Lawrence Earlbaum Associates. 1988; 2.

17 Barczyński M, Konturek A, Hubalewska-Dydejczyk A, et al. Ten-year follow-up of a randomized clinical trial of total thyroidectomy versus dunhill operation versus bilateral subtotal thyroidectomy for multinodular non-toxic goiter. World J Surg. 2018; 42: 384-392.

18 Miccoli P, Antonelli A, Iacconi P, et al. Prospective, randomized, double-blind study about effectiveness of levothyroxine suppressive therapy in prevention of recurrence after operation: result at the third year of follow-up. Surgery. 1993; 114: 1097-102.

19 Delbridge L, Guinea AI, Reeve TS. Total thyroidectomy for bilateral benign multinodular goiter: effect of changing practice. Arch Surg. 1999; 134: 1389-1393.

20 Barczyński M, Konturek A, Gołkowski F, et al. Five-year follow-up of a randomized clinical trial of unilateral thyroid lobectomy with or without postoperative levothyroxine treatment. World J Surg. 2010; 34: 1232-1238.

21 Lytrivi M, Kyrilli A, Burniat A, et al. Thyroid lobectomy is an effective option for unilateral benign nodular disease. Clin Endocrinol (Oxf). 2016; 85: 602-608.

22 Hegedüs L, Nygaard B, Hansen JM. Is routine thyroxine treatment to hinder postoperative recurrence of nontoxic goiter justified? J Clin Endocrinol Metab. 1999; 84: 756-760.

23 Carella C, Mazziotti G, Rotondi M, et al. Iodized salt improves the effectiveness of l-thyroxine therapy after surgery for nontoxic goitre: a prospective and randomized study. Clin Endocrinol. 2002; 57: 507-513.

24 Bonnema SJ, Fast S, Hegedüs L. The role of radioiodine therapy in benign nodular goitre. Best Pract Res Clin Endocrinol Metab. 2014; 28: 619-631.

25 Moli L. Determinants of longterm outcome of radioiodine therapy of sporadic non-toxic goitre. Clin Endocrinol (Oxf). 1999; 50: 783-789.

26 Graf H, Fast S, Pacini F, et al. Modified-release recombinant human TSH (MRrhTSH) augments the effect of 131I therapy in benign multinodular goiter: results from a multicenter international, randomized, placebo-controlled study. J Clin Endocrinol Metab. 2011; 96: 1368-1376.

27 Nielsen VE, Bonnema SJ, Boel-Jørgensen H, et al. Stimulation with 0.3-mg recombinant human thyrotropin prior to iodine 131 therapy to improve the size reduction of benign nontoxic nodular goiter: a prospective randomized double-blind trial. Arch Intern Med. 2006; 166: 1476-1482.

28 Bonnema SJ, Nielsen VE, Boel-Jørgensen H, et al. Improvement of goiter volume reduction after 0.3 mg recombinant human thyrotropin-stimulated radioiodine therapy in patients with a very large goiter: a double-blinded, randomized trial. J Clin Endocrinol Metab. 2007; 92: 3424-3428.

29 Silva MN, Rubió IG, Romão R, et al. Administration of a single dose of recombinant human thyrotrophin enhances the efficacy of radioiodine treatment of large compressive multinodular goitres. Clin Endocrinol (Oxf). 2004; 60: 300-308.

30 Fast S, Hegedüs L, Pacini F, et al. Long-term efficacy of modified-release recombinant human thyrotropin augmented radioiodine therapy for benign multinodular goiter: results from a multicenter, international, randomized, placebo-controlled, dose-selection study. Thyroid. 2014; 24: 727-735.

31 Cramon P, Winther KH, Watt T, et al. Quality-of-life impairments persist six months after treatment of Graves' hyperthyroidism and toxic nodular goiter: a prospective cohort study. Thyroid. 2016; 26: 1010-1018.

32 Sawicka-Gutaj N, Ruchala M, Feldt-Rasmussen U, et al. Patients with Benign Thyroid Diseases Experience and Impaired Sex Life. Thyroid. 2018.

33 Elberling T, Rasmussen A, Feldt-Rasmussen U, et al. Impaired health-related quality of life in Graves' disease. A prospective study. Eur J Endocrinol. 2004; 151: 549-555.

34 Al-Adhami A, Craig W, Krukowski ZH. Quality of life after surgery for Graves' disease: comparison of those having surgery intended to preserve thyroid function with those having ablative surgery. Thyroid. 2012; 22: 494-500.

35 Sowiński J, Sawicka-Gutaj N, Ziółkowska P, et al. Effect of free triiodothyronine concentration on the quality of life of patients treated with levothyroxine. Pol Arch Med Wewn. 2016; 29: 293-296.

36 Mishra A, Sabaretnam M, Chand G, et al. Quality of life (QoL) in patients with benign thyroid goiters (pre-and post-thyroidectomy): a prospective study. World J Surg. 2013; 37: 2322-2329.

37 Sorensen JR, Watt T, Cramon P, et al. Quality of life after thyroidectomy in patients with nontoxic nodular goiter: a prospective cohort study. Head Neck. 2017; 39: 2232-2240.

38 Bukvic BR, Zivaljevic VR, Sipetic SB, et al. Improvement of quality of life in patients with benign goiter after surgical treatment. Langenbecks Arch Surg. 2014; 399: 755-764.

39 Cramon P, Bonnema SJ, Bjorner JB, et al. Quality of life in patients with benign nontoxic goiter: impact of disease and treatment response, and comparison with the general population. Thyroid. 2015; 25: 284-291.

40 Wojtczak B, Sutkowski K, Kaliszewski K, et al. Thyroid reoperation using intraoperative neuromonitoring. Endocrine. 2017; 58: 458-466.