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

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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.

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 hemiagene sis or after hemithyroidectomy was confirmed. ⁵ ⁷ A minority of patients with recurrent goiter require secondary therapy.⁵ Surgical resection is a therapeutic option. Radioiodine (RAI) is widely used as a therapy of hyperthyroidism.⁶ ⁸ 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.
30 healthy controls were recruited without recurrent goiter and 50 thyroidectomized patients randomly selected patients treated for a recurrent goiter because of suspicion of malignancy, compressive symptoms, or failure of therapy with antithyroid medications. 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. ThyPRO consists of 85 questions summarized in 13 multi-item scales. Each scale ranges from 0 to 100. 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 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 LT4, 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. LT4 therapy advised after the first surgery was associated with a lower risk of recurrence. Other potential
TABLE 1  Clinical characteristics of the study groups

<table>
<thead>
<tr>
<th></th>
<th>Patients with recurrent goiter (n = 68)</th>
<th>Patients after thyroidectomy without recurrent goiter (n = 413)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, female/male, n (%)</td>
<td>59 (86.8) / 9 (13.2)</td>
<td>359 (86.9) / 54 (13.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Age at the time of surgery, y, median (IQR)</td>
<td>38 (28–48.75)</td>
<td>44 (33–54)</td>
<td>0.006</td>
</tr>
<tr>
<td>Preoperative thyroid volume, ml, median (IQR)</td>
<td>21.8 (14.3–35.4); n = 14</td>
<td>21.9 (13.2–37.8); n = 260</td>
<td>0.95</td>
</tr>
<tr>
<td>Preoperative thyroid nodules, n (%)</td>
<td>Present 67 (98.5)</td>
<td>402 (97.3)</td>
<td>1.0</td>
</tr>
<tr>
<td>Preoperative radioiodine therapy, n (%)</td>
<td>Yes 1 (1.5)</td>
<td>11 (2.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>Type of surgery, n (%)</td>
<td>TT 45 (66.2)</td>
<td>269 (65.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Follow-up (from the first surgery to the last visit), y, median (IQR)</td>
<td>13.9 (7.7–26.3)</td>
<td>10 (7–16)</td>
<td>0.01</td>
</tr>
<tr>
<td>Autoimmune thyroiditis on histopathological examination, n (%)</td>
<td>Present 5 (7.4)</td>
<td>43 (10.4)</td>
<td>0.52</td>
</tr>
<tr>
<td>Levothyroxine therapy advised after the first surgery, n (%)</td>
<td>Yes 45 (66.2)</td>
<td>380 (92)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Patients with recurrent goiter (n = 63)</th>
<th>Patients after thyroidectomy without recurrent goiter (n = 418)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH at follow-up, mIU/l</td>
<td>2.35 (1.56–2.98)</td>
<td>1.11 (0.56–1.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TSH at the last visit, mIU/l</td>
<td>0.67 (0.46–1.55)</td>
<td>0.8 (0.44–1.43)</td>
<td>0.99</td>
</tr>
<tr>
<td>FT₃ at the last visit, pmol/l</td>
<td>16.5 (15.20–18.75); n = 56</td>
<td>16.7 (15.32–21.46); n = 229</td>
<td>0.42</td>
</tr>
<tr>
<td>FT₄ at the last visit, pmol/l</td>
<td>4.47 (3.89–4.93); n = 55</td>
<td>4.51 (3.91–5.11); n = 314</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range).

Abbreviations: FT₃, free triiodothyronine; FT₄, 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.

Radiiodine 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 ¹³¹I 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.⁴ 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, LT₃ 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...
Radioiodine therapy for recurrent goiter}

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 131I therapy for recurrent goiters. Previous studies have confirmed similar 131I efficacy for reducing thyroid volume in patients with toxic and nontoxic goiters. A decrease in goiter size in nontoxic goiters was directly related to the dose of 131I, but if the initial goiter was large, the reduction was smaller. 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 131I. 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. Administration of recombinant human thyroid-stimulating hormone (rhTSH) before 131I administration (off-label use) might enhance the reduction of nontoxic goiters.

**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. Previous studies investigating patients after thyroidectomy with nontoxic multinodular goiter reported significant relief of goiter symptoms after surgery in short-term observation. However, patients after surgery presented some deficits in HRQOL in comparison to the general population sample. We observed much higher goiter symptom scores in patients many years after therapy in patients with benign thyroid diseases.

**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

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

Data are presented as mean (SD).

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

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**Conclusion**

Our results suggest that lobectomies should be avoided as the primary surgery for benign thyroid diseases, and LT, 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.

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**REFERENCES**

Radioiodine therapy for recurrent goiter