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Risk Factors for Recurrent Nodular Goiter after Thyroidectomy for Benign Disease: Case-control Study of 244 Patients

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Abstract. Surgery for recurrent nodular goiter is associated with a significant risk of parathyroid and recurrent laryngeal nerve (RLN) morbidity. Total thyroidectomy for benign disease is assessed. The aim of this study was to evaluate the risk factors for recurrence and the morbidity associated with reoperation. From 1969 to 1996 a total of 4334 thyroidectomies were performed, of which 122 were for recurrent nodular goiter (group I: 116 women, 6 men). A matched case-control study of 122 patients operated on for nonrecurrent multinodular goiter was performed (group II: 112 women, 10 men). Age, family history, initial surgery, pathology, and morbidity were compared in the two groups by χ^2 test, Fisher's exact test, and the Mantel-Haenszel test. The mean age was 39.88 years in group I and 47.89 years in group II. There was no statistical difference in relation to the extent of thyroidectomy or morbidity after initial surgery. Statistical differences were identified regarding age ($p = 0.000002$) and the multinodular nature of the initial goiter ($p = 0.005$). Bilaterality and family history were less significant ($p = 0.09$ and $p = 0.08$, respectively). Temporary RLN palsy and temporary hypoparathyroidism were higher in group I (12.3% vs. 5.7%, $p = 0.0737$; 10.6% vs. 1.7%, $p = 0.00337$). Permanent RLN palsy was found in 0.8% in group I and in none in group II ($p = 0.5$, NS). Young age and multiple nodules at initial surgery are risk factors for recurrence. A higher rate of temporary morbidity was demonstrated after surgery for recurrent goiter. Total thyroidectomy for multinodular goiter is advisable.

The surgical management of multinodular thyroid disease remains controversial. The use of total thyroidectomy for benign disease is not widely accepted. However, subtotal thyroidectomy has been the gold standard for many years because it was thought to be a safer procedure. This is despite the risk of recurrent nodular goiter, which ranges from 3% to 20% [1]. Recurrences often occur more than 10 years after the initial surgery, when many patients have been lost to follow-up. Suppressive L-thyroxine therapy has been used to reduce the rate of recurrence but with minimal efficiency [2–8]. Thyroid tissue regrowth is attributed to multiple growth factors, including insulin-like or fibroblast growth factor, associated with thyroid-stimulating hormone (TSH). Despite this, some recommend suppressive L-thyroxine therapy when there is an increased postoperative TSH level, in cases of thyroiditis or dysthyroidism, or in subjects with a strong family history of thyroid disease [9–11].

Following subtotal thyroidectomy, further surgery is often required with an associated increased risk of morbidity, specifically parathyroid gland and recurrent laryngeal nerve (RLN) injury. Total thyroidectomy avoids these complications and may be considered the gold standard for treating multinodular goiter [7, 12–14].

The opponents of total thyroidectomy argue for the negative consequence of lifelong thyroid replacement. Despite this, there has been a worldwide trend toward total thyroidectomy for bilateral multinodular goiter. Our approach has changed accordingly, and we now perform total thyroidectomy regularly for bilateral multinodular goiter.

The aim of this retrospective study was to determine the risk factors for recurrence. We also assessed the morbidity rate associated with surgery for benign recurrent nodular goiter.

Materials and Methods

From 1969 to 1996, a total of 4334 patients were operated on for nodular goiter, 122 of whom had a benign recurrent nodular goiter. Patients with Graves' disease or thyroid cancer recurrence were excluded. To avoid biases due to different surgical techniques, we included only patients who had both the primary and second operation done in our institution.

A matched case-control study was designed, with two groups of 122 patients each distributed as follows: group I with 116 females and 6 males who had a recurrence; group II with 112 females and 10 males (control group). Patients in the control group were randomly selected from the 4334 patients who had had their first procedure performed during the same period and matched group I for the

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year they had their operation (primary surgery for group I). Age, sex, and extent of initial surgery were not part of the selection criteria.

Ultrasonography has been available in our institution since 1976. Recurrence was detected by clinical examination and ultrasonography on all patients in group I, except for the few who had their second operation before 1976. All patients in the control group underwent a clinical examination and ultrasonography to detect a recurrence; none was found. The main criteria for reoperation were a palpable nodule, the size and number of nodules at ultrasonography, compression symptoms, suspicion of malignancy, and the patient's motivation.

A standardized surgical technique was performed in all patients. After retracting the strap muscles from the lobes, the gland was palpated (bilaterally) to detect small nodules not seen on ultrasonography. Identification of the RLN and careful preservation of the parathyroid glands were always performed on the side of resection, unilaterally in case of isthmolobectomy, or bilaterally in cases of subtotal or total thyroidectomy. Any parathyroid gland that could not be preserved was autotransplanted in the conventional fashion to the sternocleidomastoid muscle. The extent of resection was performed according to the location of the nodules and the amount of normal residual glandular tissue sufficient to ensure euthyroidism. Intraoperative frozen section examination was performed on all specimens.

Direct laryngoscopy was performed in all patients on postoperative day 2 or 3. Preoperative laryngoscopy was carried only out in patients with a suspicion or history of vocal cord paralysis. RLN palsy was defined as permanent if no proof of recovery was demonstrated by laryngoscopy within 6 months of surgery. The calcium level was assessed on postoperative day 1 and again on postoperative day 2 if necessary. Hypoparathyroidism was defined as symptomatic hypocalcemia (calcemia < 2 mmol/l with extremity tingling or carpopedal spasm). It was considered permanent if calcium replacement was required for longer than 6 months.

Age, gender, family history, initial surgery, uninodular or multinodular goiter, unilateral or bilateral nodules, pathology, and morbidity were analyzed and compared in the two groups.

Logiciel Epi-info 5.01b software (Ecole Nationale de Sante Publique, Rennes, France) was used to archive the data and perform the statistical analysis. The χ^2 test, Fisher's exact test, and the Mantel-Haenszel test were used for statistical analysis. A value of $p < 0.05$ was considered significant.

Results

The mean age at initial surgery was 39.88 years (range 17–86 years) in group I and 47.89 years (range 14–83 years) in group II. The difference is statistically significant ($p = 0.000002$). Altogether, 24 patients in group I (19.67%) and 15 in group II (12.29%) had a family history of thyroid disease. There was no statistical significant difference ($p = 0.08$) on comparison of family history and gender (116 females in group I versus 112 in group II).

Subtotal thyroidectomy was the initial procedure in 64 cases (52%) and an isthmolobectomy in 58 cases (48%) in group I. In group II, there were 51 subtotal thyroidectomies (42%) and 71 isthmolobectomies (58%) performed. There was no significant difference ($p = 0.09$).

In group I, there were 100 benign multinodular goiters (81%) and 22 benign isolated nodules (19%) found during pathologic examination. Seven patients had a toxic or pretoxic goiter (5.38%), and three patients had thyroiditis (2.4%). In group II, a total of 81 multinodular goiters (66%) and 41 isolated nodules (33%) were observed. Four patients had a toxic or pretoxic goiter, and eight patients had thyroiditis (6.56%). There was a significant difference between the groups ($p = 0.005$). The multinodular nature of a goiter was a risk factor for recurrence.

Table 1. Comparison of the two groups for initial surgery.

Parameter	Group I	Group II	*p*
Age (years), mean	39.88	47.89	0.000002
Gender			
Women	116	112	ns
Men	6	10	
Family history	19.67%	12.29%	ns
Initial surgery			
Subtotal	64 (52%)	52 (42%)	ns
Isthmolobectomy	58 (48%)	71 (58%)	
Type of goiter			
Multinodular	100	81	0.005
Uninodular	22	41	
RLN palsy			
Temporary	7 (5.7%)	7 (5.7%)	ns
Permanent	1 (0.81%)	0	
Hypoparathyroidism			
Temporary	1 (0.81%)	2 (1.6%)	ns
Permanent	0	0	

RLN: recurrent laryngeal nerve.

Multinodular goiters were unilateral in 36 cases in group I and 30 cases in group II. The difference was not statistically significant ($p = 0.09$).

After initial surgery, transitory RLN palsy was observed in seven patients in each group (5.7%); one case was permanent (0.8%) in group I. One patient in group I (0.81%) and two patients of group II (1.6%) had transitory hypocalcemia. The difference was not significant ($p = 0.5$). No hematomas or infections occurred in either group. Table 1 presents a comparison between the two groups following initial surgery.

The mean recurrence-free follow-up in group II was 168 months (± 85 months). The average time of recurrence in group I was 121 months (± 62 months).

In all, 85 total thyroidectomies (70%) and 37 subtotal thyroidectomies (30%) were performed at reoperation. residual tissue was left posteriorly in 16 cases because of adhesions to the RLN or technical difficulties with parathyroid gland dissection. In most cases, multiple nodules were found on pathologic examination (83%); a solitary nodule was found in only 17% of patients. One patient had a toxic goiter (0.8%), and eight had thyroiditis (6.56%). A carcinoma was found in six patients (5%) (five papillary tumors and one undifferentiated tumor). One patient also had a parathyroid adenoma, which was removed at the same time.

Fifteen patients had RLN palsy (12.29%), in one of whom it was permanent (0.8%). Thirteen patients had transient hypocalcemia (11%). One patient with papillary cancer who underwent bilateral lymph node dissection had permanent hypocalcemia (0.8%). None of the 16 patients who had residual thyroid tissue intentionally left there suffered RLN or parathyroid gland complications. Table 2 indicates the incidence of permanent and transitory complications in the two groups, with difference being statistically significant.

Table 2. Recurrent laryngeal nerve and parathyroid morbidity, with comparison of reoperation and group II morbidity.

	Initial surgery			
Morbidity	Group I	Group II	Reoperation	*p*
Temporary nerve palsy	7 (5.70%)	7 (5.70%)	15 (12.30%)	0.07
Permanent nerve palsy	1 (0.81%)	0	1 (0.81%)	NS
Temporary hypoparathyroidism	1 (0.81%)	2 (1.60%)	13 (11.00%)	0.003
Permanent hypoparathyroidism	0	0	1 (0.81%)	NS

Discussion

The frequency of recurrent nodular goiter is increasing because subtotal thyroidectomy was the gold standard for many years. The incidence of recurrent goiter is variably reported in the literature and difficult to appreciate [1, 9, 11, 14]. Diagnosis depends on the method of evaluation—clinical examination or ultrasonography [11]—and the length of follow-up [15]. Most recurrences are asymptomatic and are diagnosed on ultrasonography, which has a higher sensitivity than clinical examination [15, 16]. The mean interval until recurrence and reoperation is long, entailing at least 10 years of follow-up for these young patients [9, 17, 18].

The risk of occult carcinoma emphasizes the need for a long follow-up and reoperation. Altogether, 5% of our patients were found to have carcinoma at pathologic examination, concordant with the 6% to 22% reported in the literature [9, 14, 15, 17–20].

Young age at initial surgery is the main risk factor for recurrence, as reported by Visset et al. [7] and Levin et al. [19]. They reported a mean age of less than 40 years for patients who developed a recurrence. Our review supports these results, with the mean age in group I significantly lower than that of the controls (group II) at the time of the primary operation.

The main cause of recurrence is inadequate initial surgery. Early reoperation is rare if the initial surgery is well adapted to the thyroid disease. Reliable preoperative staging is essential. Ultrasonography is an operator-dependent examination. An experienced sonographer can highlight micronodules that must be treated at the same time to avoid earlier recurrence. Barbier et al. reported that 44% of the nodules were seen to be isolated on preoperative ultrasonography [10]. At surgery, however, 36% of these nodules were found to be multiple. Hence an isolated nodule often is found to be multiglandular disease during surgery with a high risk of recurrence [11]. At reoperation, multinodular disease is more frequent, found in 60% to 80% of cases [7, 11, 15, 17].

In our study, the multinodular nature of the goiter, whether bilateral or unilateral, was found to be a risk factor for recurrence. However, in this subgroup of patients with multinodular goiter, the risk of recurrence was equal for those with bilateral or unilateral goiters. Multinodularity seems to define a disease with characteristics different from those of a uninodular goiter in terms of the natural history. The recurrence rate correlated directly with the size of the thyroid remnant [11, 21]. Berghout et al., in 1989, noted an increased recurrence following unilateral lobectomy compared to subtotal thyroidectomy (85% vs. 61%) [22]. Surgical treatment therefore should take the natural history of disease into account and not simply the location of the nodules [6, 7, 10, 13–15, 20]. Today, enucleation of nodules or subtotal unilateral lobectomy has no place in the treatment of multinodular goiter.

Two accepted risk factors for recurrence noted in the literature—family history and bilateral disease—were not significant in this study [22]. However, these criteria are controversial [9]. If twice the number of patients were available, the borderline *p* values (respectively, 0.07 and 0.09) would become statistically significant.

During reoperation, fibrosis after previous thyroidectomy makes RLN dissection more difficult, and it is associated with higher morbidity. RLN palsy rates vary from 0 to 14% in the literature, according to various surgeons' experience [17, 18, 23–25]. Bilateral RLN palsy rarely occurs after reoperation for benign goiter: one bilateral temporary palsy among 949 reoperations was reported by Muller et al. [23]. An RLN palsy rate of 1% to 6% of is noted after initial surgery, with 1% for lobectomy and 2% to 3% for total thyroidectomy [25]. La Gamma et al. [15] and Delbridge et al. [24] noted identical morbidity rates after total thyroidectomy and reoperation. Muller et al. reported a significantly higher rate of permanent RLN palsy after reoperation (3.0% vs. 0.7%, $p < 0.001$) with an identical rate of transitory RLN palsy (3.0% vs. 5.0%, $p = 0.02$) [23]. In the present study, we noted a significant increase in transitory RLN palsy in the recurrence group, with no increase of permanent RLN palsy, as previously reported [17].

Preoperative vocal cord examination seems essential. RLN palsy following previous surgery may be masked by contralateral vocal cord compensation, and the voice may appear normal. If preoperative assessment does detect an RLN injury on the opposite side, remnant thyroid tissue should be left posteriorly at operation to avoid bilateral RLN damage [17].

Before reoperation, it is impossible to assess the location and functional status of the parathyroid glands. Fibrosis after previous surgery can make parathyroid gland preservation difficult, and it is often necessary to autotransplant the gland to avoid permanent hypocalcemia. Autotransplantation should not be performed systematically, however, as has been proposed [14, 17, 26]. As well as temporary RLN palsy, we noted a high rate of temporary hypocalcemia after reoperation. The rates of permanent hypocalcemia were equal in our two groups, similar to that reported by Muller et al. in 2001 [23]. Higher, but quite acceptable, parathyroid morbidity (transient or permanent) rates have been reported [17]. A cautious near-capsule dissection allows parathyroid gland preservation and results in less hypoparathyroidism, a disabling complication in permanent cases.

Conclusion

We identified two risk factors for recurrence: young age and the multinodular nature of the disease. Bilateral nodules and a family history of thyroid disease were also associated with an increased risk of recurrence but did not reach statistical significance. We report a higher rate of temporary complications at reoperation, but there was no difference in permanent RLN or parathyroid gland

injury. Although reoperation can be performed safely by an experienced thyroid surgeon, there is always a higher risk of temporary or permanent parathyroid gland or RLN damage. To avoid these possible future complications, our unit now performs total thyroidectomy in all patients with bilateral multinodular goiter, especially in young patients.

Résumé. La chirurgie pour goiter nodulaire récidivé est classiquement associée à une morbidité parathyroïdienne et récurrentielle plus élevée. Les buts de cette étude étaient d'évaluer les facteurs de récidive et la morbidité des réinterventions. De 1969 à 1996, 4334 thyroïdectomies ont été réalisées dont 122 pour récidive (groupe I: 116 femmes et 6 hommes). Une étude cas témoins a été réalisé en constituant un groupe témoin apparié (groupe II: 112 femmes et 10 hommes). L'âge, les antécédents familiaux, l'exérèse initiale, le caractère uni ou bilatéral, uni ou multinodulaire, et la morbidité ont été analysés. L'âge moyen était de 39.88 ans (17–86 ans) dans le groupe I et de 47.89 ans (14–83 ans) dans le groupe II. Il n'y avait pas de différence significative en ce qui concerne l'étendue de la résection initiale et la morbidité après la première intervention. Le jeune âge ($p = 0.000002$), et le caractère multinodulaire ($p = 0.005$) étaient statistiquement significatifs comme facteur de récidive. Le caractère bilatéral des nodules et les antécédents familiaux ne pouvaient être considérés comme facteurs de risque ($p = 0.09$ et $p = 0.08$). La morbidité récurrentielle et parathyroidienne transitoire était plus fréquente dans le groupe I (12.3% versus 5.7%, $p = 0.0737$; 10.6% versus 1.7%, $p = 0.00337$). Une paralysie récurrentielle et une hypocalcémie définitives (0.08%) étaient notées dans le groupe I, aucune dans le groupe II. L'âge et le caractère multinodulaire sont des facteurs de risque de récidive après thyroïdectomie. La morbidité transitoire plus importante des réinterventions incite à proposer une thyroïdectomie totale pour les goitres multinodulaires.

Resumen. La cirugía para el bocio multinodular recidivante conlleva un riesgo significativo de hipoparatiroidismo y lesión al nervio laríngeo recurrente. La finalidad de este estudio fue la de evaluar las factores de recurrencia y la morbilidad de las reintervenciones por esta patología. Un total de 4334 tiroidectomías fueron realizadas en el servicio entre 1969 y 1996; de las cuales, 122 correspondieron a reoperaciones por bocio multinodular recurrente. Mediante un estudio de casos y controles, se diseñaron dos grupos comparativos (Grupo I: Pacientes reoperados 116 mujeres, 6 hombres) y Grupo II control (112 mujeres y 10 hombres). La edad media fue de 38.88 años (17–86 años) en el grupo I y de 47.89 años (14–83 años) en el grupo II. No hubo diferencia significativa en cuanto a la resección inicial y la morbilidad posterior al procedimiento inicial. La edad temprana ($p = 0.000002$) y el carácter multinodular de las lesiones ($p = 0.005$) demostraron ser estadísticamente significativos como factores de recurrencia. El carácter bilateral de los nódulos y los antecedentes familiares no lograron ser significativos para ser considerados como factores de riesgo ($p = 0.09$ y $p = 0.08$). La lesión al nervio e hipoparatiroidismo transitorios fueron más frecuentes en el Grupo I (12.4% vs. 5.7%, $p = 0.0737$; 10.6% vs. 1.7%, $p = 0.00337$). Un paciente presentó hipoparatiroidismo definitivo y otro mas daño definitivo al nervio laríngeo recurrente en el Grupo I (0.08%), ninguno en el grupo II. La edad y el carácter nodular son factores de riesgo de recurrencia posterior a la tiroidectomía por bocio. La mínima morbilidad de las reoperaciones sugiere que la tiroidectomía total es un abordaje seguro para los pacientes con bocio.

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