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# Histopathological evaluation of recurrent goiter

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**Abstract:** The recurrent goiter is the regrowth of thyroid tissue after thyroidectomy. An inadequate surgical removal of the thyroid gland, lack of substitution therapy and pathological stimulation of the thyroid growth can all promote the recurrence. The aim of this study was to find the connection between the histopathological findings during the first and second operation and the recurrence of goiter. The study group consisted of 29 women and 1 man. The mean time to recurrence was 15 years. The most frequent histopathological finding during the first and second operation was struma nodosa. According to our observations different histopathological findings were found in 63.4% cases after primary and secondary thyroidectomy. Some genetic investigations showed that nodules in recurrent goiters did not derive from nodules left during the first operation but from a group of cells which had high growth potential. Thus, not only the operation technique and substitution after operation are key factors of successful therapy of goiter, but also other factors which stimulate the re-growth of thyroid tissue.

**Key words**: thyroid nodules, goiter, thyroidectomy, recurrent goiter, growth factors

## Introduction

The recurrence rate of multinodular goiter (a thyroid gland that is enlarged and contains multiple thyroid nodules) varies between 8.9% and 40% [1-4]. The main cause of recurrence is the insufficient extent of thyroidectomy (excision of thyroid gland) during the primary operation, which should consist of excision of both lobes together with the isthmus and pyramidal lobe [5-8]. The second factor which can lead to recurrence is the lack of substitution therapy with L-thyroxine (levothyroxine) after primary operation [13,15-18]. But the recurrences occur even if total thyroidectomy is performed, with subsequent therapy with L-thyroxine. Some thyroid cells which were left during the first operation are no longer subject to control within the classical hypothalamic-pituitary-thyroid axis and their growth depends on individual expression of goitrogenic insulin-like growth factors (IGFs) and their binding proteins (IGFBPs) [22]. Nodules in recurrent goiters are mainly polyclonal, with a higher than usual growth potential accelerated by unknown factors, so the recurrence occurs not only from nodules left during the primary operation [23-25].

It has been scientifically proven that thyroid follicular cells replicate only five times [26]. In response to appropriate stimulus, which is usually iodine deficiency, the thyroid cells replicate very fast and it leads to hyperplasia of thyroid gland. The hyperplastic goiter grows and it can then change into colloid and cystic goiter or become neoplastic. Apart from iodine deficiency and action of TSH, other mitogenic agents responsible for hyperplasia produced by fibroblasts, endothelial cells, macrophages and lymphocytes have been proposed. In every case the other factors are responsible for specific changes. In colloid goiter the nodules are produced as a defect of intraluminal thyroglobulin reabsorption. Cystic nodules are the result of imbalance between angiogenesis and cell growth leading to cell damage, necrosis and colliquation. Also lymphatic thyroiditis may be rarely found as a nodular thyroid disease. In thyroid malignancies several activated oncogenes have been found [27]. There are also other factors like positive family history, young age at presentation, bilateral disease and multinodular *vs.* single nodules which have been accepted risk factors for

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**Table 1.** Studied group characteristics

| Parameters | The number of patients and the percentage |
|---|---|
| Number of operations performed in the years of 2003-2009 | |
| Total number of operations | 2630 (100%) |
| Operations on recurrent goiter | 30 (1.4%) |
| Type of primary operation | |
| Total thyroidectomy | 11 (36.6%) |
| Subtotal thyroidectomy | 15 (50%) |
| Excision of only one lobe | 4 (13.4%) |
| Histopathological findings after primary and secondary thyroidectomy | |
| The same histopathological finding | 11 (36.6%) |
| Different histopathological finding | 19 (63.4%) |
| Number of actual and pseudo recurrences | |
| Actual recurrence | 25 (83.4%) |
| Pseudo recurrence | 5 (16.6%) |

goiter recurrence [28]. We should not forget about the environmental chemicals and drugs which are goitrogenic in humans *e.g.* iodine, lithium, thionamides, aniline and phenol derivates, polyhydroxyphenols, flavonoids [27].

## Material and methods

**Tissue samples.** The study group consisted of 30 patients operated due to a recurrent goiter between 2003 and 2009 in the Department of Minimally Invasive Surgery and Proctology and in the Department of General and Oncological Surgery, Medical University in Wroclaw. During this period we performed 2630 thyroidectomies (Table 1). The primary operations were performed between the years of 1980 and 2005. Types of primary operations are presented in Table 1. During the secondary operation all the thyroid tissue was totally removed. The mean age of patients with recurrent goiter was 57 years. The group included only one man. Standard histological examination consisted of macroscopic investigation, fixation in formalin and microscopic examination of slides prepared with HE-staining on a glass slide. Three examples of histological specimens are presented below (Figs. 1, 2, 3).

## Results

The mean time to recurrence was 15 years. The most frequent histopathological finding upon the first and second operation was struma nodosa. According to our observations the same histopathological findings were found in 36.6% cases after primary and secondary thyroidectomy (Table 1). Pseudo recurrence (the recurrence in previously non-operated lobe) occurred in 5 patients (Table 1). All the histopathological findings and mean time to recurrence are presented in Table 2.

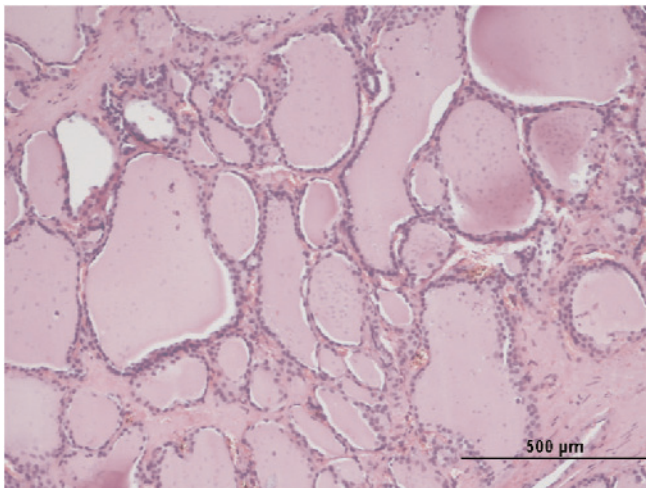


**Fig. 1.** Struma nodosa, H+E (original magnification ×100).

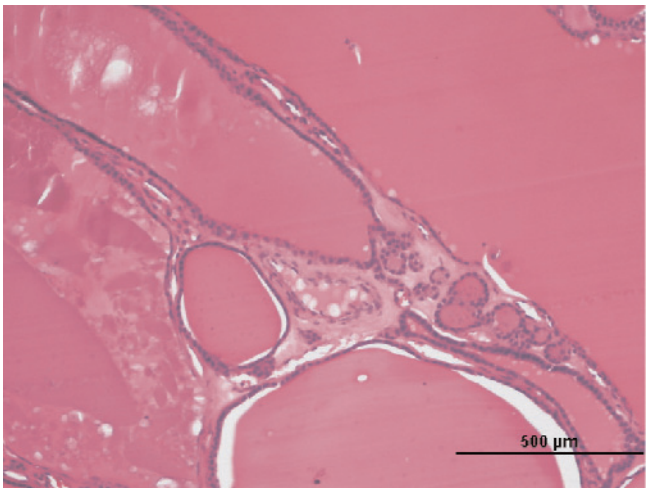


**Fig. 2.** Struma colloides et cystic, H+E (original magnification ×100).

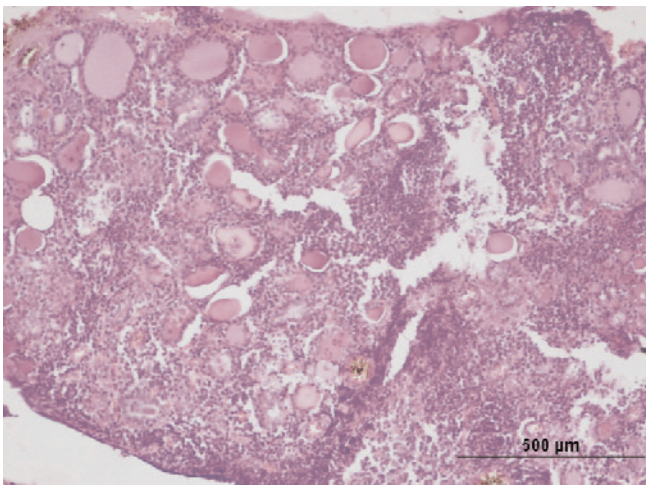


**Fig. 3.** Thyroiditis chronica lymphomatosa, H+E (original magnification ×100).


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**Table 2..** The prevalence of different types of configuration of the histopatological findings during the first and second operation

| Histopathological finding during the first operation | Histopathological finding during the second operation | Number of patients | Mean time to recurrence (years) |
|---|---|---|---|
| Struma nodosa | Struma nodosa | 10 | 19 |
| Struma nodosa | Struma colloides et cystica | 4 | 9 |
| Struma nodosa | Struma nodosa et cystica | 4 | 14 |
| Struma nodosa | Struma colloides | 2 | 9 |
| Struma colloides | Struma nodosa | 5 | 24 |
| Struma nodosa et cystica | Struma nodosa | 4 | 13 |
| Thyroiditis chronica lymphomatosa | Thyroiditis chronica lymphomatosa | 1 | 17 |

## Discussion

Thyroidectomy was performed in 2630 patients (30 patients with recurrent goiter) between the years of 2003 and 2009 in the Department of Minimally Invasive Surgery and Proctology and in the Department of General and Oncological Surgery, Medical University in Wroclaw. Operations on recurrent goiter comprised 1.14% of all thyroidectomies. Our study group was not homogeneous because patients underwent the primary surgery not necessarily in our departments.

In country's leading centers which specialize in goiter surgery the percentage of recurrences does not exceed 1%. Barczyński noted 0.6% and Stajgis 0.8% of recurrences in their material [2,4]. According to some authors, evaluation of patients with recurrent goiter may be imprecise and mistakes can occur. It is not always known where the primary operation was performed and how long did the patient with recurrent goiter wait for the secondary operation.

In our material the mean time to recurrence was 15 years, the shortest one was 1 year and the longest one was 24 years. In the material of Stajgis the time to recurrence ranged between 0.5 and 48 years [10]. In the whole material of Barczyński the time to recurrence was between 1 and 48 years and the mean time to recurrence was 17 years. In his own material it was between 2 and 35 years and 14 years, respectively. He stated that it would be very inaccurate to define the mean time to recurrence because patients can change the hospital for the secondary operation [11].

According to many authors, the strategy of surgical treatment has a considerable impact on the prevention of recurrences; significance of the range and completeness of thyroidectomy is emphasized. It is believed that even 80% of recurrences may result from inadequate surgical treatment. In many cases the limited completeness of surgery may result in the complications [9-12]. The excision of only one lobe with macroscopic changes can lead to quite often observed recurrence of goiter in non-operated lobe (pseudo recurrence). In their own large clinical material (602 patients operated for recurrent goiter between 1955 and 1992), Skrzypek *et al.* found 86.6% of actual recurrences and 13.4% of pseudo recurrences. The mean time to actual recurrence was 12.2 years and the mean time to pseudo recurrence was 5.8 years [12]. Because of the high proportion of pseudo recurrences after thyroidectomy and short time of their formation, the primary operation should be based on dissection of isthmus, removal of pyramidal lobe and bilateral, sufficiently complete excision of both lobes even if one of the lobes does not show macroscopic lesions.

The recurrence after thyroidectomy performed for benign multinodular goiter is always possible. All the thyroid tissue which has macroscopic changes should be removed because even small nodules or cysts can lead to recurrence. Bononi *et al.* regard total thyroidectomy as the most effective method to prevent recurrences. When it is performed by an experienced surgeon the rate of complications is not higher in comparison to subtotal thyroidectomy and especially to excision of recurrent goiter. The postoperative hypothyroidism can be effectively treated with L-thyroxin [29].

The proponents of suppressive therapy with L-thyroxin argue that its dose should be high enough to prevent recurrences. According to some authors in regions where iodine intake is high the substitution therapy is not needed [20]. Some surgeons prescribe L-thyroxin only after total thyroidectomy [29]. Aagaard et al. found that subtotal thyroidectomy reduces only the thyroid mass but not the real cause of recurrence. The remnants of tissue after thyroidectomy have the structural and functional features of pathologic tissue, which is no longer subject to control within the classical hypothalamic-pituitary-thyroid axis, thus substitution therapy may be ineffective [14]. There is a group of opponents of substitution therapy because in their hands it fails to reduce the rate of recurrence [28,30]. They did not find higher recurrence rate in post-thyroidectomy patients without substitution therapy [1]. According to some surgeons recurrence of benign multinodular goiter is unavoidable no matter what form of prophylaxis is used, with the exception of the situation when total thyroidectomy was performed [19].


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Thus, we should think about other factors which may induce the re-growth of thyroid tissue after primary operation. It is an action and regulation at the cellular level: the cells in recurrent goiter do not necessarily derive from nodules left or missed during the primary operation [27]. The histopathological findings after primary and secondary thyroidectomy in our material have been different in 66.6% cases and it suggests that the mechanism of recurrence has not been similar to this, which lead to the primary disease. When a surgeon is not able to remove all the thyroid cells during the primary operation it is very important to develop therapies which will act on cellular level.

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