A Conservative Approach Is Reasonable in Patients with Non-Toxic Goitre: Results from an Observational Study during 30 Years

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Key Words

Non-toxic goitre · Goitre epidemiology · Thyroid carcinoma · Thyroid nodules

Abstract

Background: There is a lack of consensus in Europe regarding the management of patients with benign goitre. The object of this study was to find out the long-term results of recommending to patients with clinically and cytologically benign non-toxic goitres not to be operated. **Methods:** 980 patients were initially referred for surgical evaluation due to non-toxic goitre, 508 of whom underwent directly thyroidectomy. The remaining 473 patients (median age 56 years) were not operated and followed prospectively for a median period of 145 months. **Results:** During follow-up, 38% of the 473 patients were re-referred to the surgeon for a new evaluation due to different complaints, mainly growth of the goitre and/or worsening of local symptoms. 102 of the 473 patients (22%) had surgery and 27 (5.7%) developed thyrotoxicosis. 14 patients (3%) were diagnosed with thyroid carcinoma, 4 (0.46%) of whom (all elderly women) died of the disease. **Conclusions:** In patients with non-toxic goitre in whom surgery is not deemed necessary at initial evaluation,

a conservative approach is reasonable. There is, however, a small risk for the development of aggressive carcinomas, and a fourth of the patients are operated at a median follow-up of 12 years.

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Introduction

Palpable goitre has a prevalence of 10–30% in middle-aged women in the Western world [1–5] and, with modern ultrasound, thyroid nodules have been found in 30–70% of the adult population [6, 7]. This implies that a large number of patients with goitre, mainly non-toxic, are referred to surgeons for evaluation every year and the number is increasing since many nodules are detected incidentally in connection with radiological investigations due to non-thyroidal indications. After clinical examination, ultrasound and fine-needle cytology, those with suspicions of malignancy and/or with clear local symptoms will subsequently be candidates for surgery whereas the indications for operative treatment are relative in those with benign findings in combination with no or minimal symptoms.

The natural history of goitre has been studied with palpation [8, 9] or ultrasonography [10–12] with highly variable results. While some studies indicate that many goitres seem to diminish with time [8, 9], other studies claim that most nodules grow slowly but continuously with time [10, 11] or stay stable, at least during a follow-up time of 40 months [12]. Nevertheless, clinical observations suggest that only a minority of goitre patients seek medical advice during a lifetime indicating that the moderately enlarged thyroid gland gives comparatively few symptoms.

The aim of this prospective study was to estimate the risk of future significant thyroid disease in a Swedish population of non-toxic goitre patients recommended expectancy after primary surgical evaluation. Other aims were to find out the frequency of re-referrals and later thyroid surgery in this large group of patients. The study is an extension in material size and follow-up time of a previously published report [13].

Materials and Methods

All patients (n = 980) referred to the Department of Surgery, Höglandssjukhuset, Eksjö, Sweden, for evaluation of non-toxic goitre have been registered prospectively between 1985 and 2009. Höglandssjukhuset is the only district hospital in a geographical area consisting of 110,000 inhabitants. The area is not endemic for goitre. 507 of the patients were operated; in 147 cases malignancy could not be excluded and 360 patients with preoperative benign goitre had local symptoms and/or wished to have their goitre removed.

This study consists of the remaining 473 patients [408 women and 65 men; median age 56 years (range 14–91)] who were diagnosed to have a benign non-toxic goitre and primarily were recommended expectancy (or were themselves reluctant to operation). There were 277 patients with solitary nodules and 196 with multinodular goitre. The diagnosis was made by clinical history and examination, laboratory testing and fine-needle aspiration cytology. Prior to referral, some patients had been investigated with radiolabeled technetium scintigram, computed tomography or ultrasound as well. All patients were seen and examined by one of the authors (J.J.).

All hospital and primary care charts have been reviewed between June 2013 and January 2014. 114 patients had died during the study period and another 13 were not possible to locate at the time for the follow-up. Median follow-up time was 145 months (range 4–338). Follow-up time was calculated as the time between preliminary diagnosis and chart review (n = 347), death (n = 114) or last contact with our regional health service (n = 13). The cause of death was established by reviewing the patient's charts or consulting the Swedish Cause of Death Registry.

Statistical differences between the groups of solitary and multinodular goitres have been evaluated with Fisher's exact test. This study was approved by the Regional Ethical Committee at Linköping University, Sweden.

Table 1. Main indication for 236 re-referrals in 180 patients with benign non-toxic goitre recommended expectancy by the surgeon at first referral

Indication	Time to re-referral, months	Outcome	Patients, n
Growth of goitre (n = 78)	54	surgery expectancy	40 38
Local symptoms (n = 75)	81	surgery expectancy	33 42
Recurrence of thyroid cyst (n = 39)	21	surgery drainage expectancy	16 13 10
Worries about cancer (n = 36)	11	surgery expectancy	7 29
Thyrotoxicosis (n = 8)	112	surgery radioiodine	6 2

Results

During follow-up, 180 patients (38%) were re-referred to the surgical clinic in total 236 times for a new evaluation. The most common indications for re-referral were growth of the goitre and local symptoms (table 1). Table 1 also shows the outcome of the new investigations. Altogether, 102 of the 236 re-examinations resulted in a decision to operate, 13 in a repeated drainage of a thyroid cyst, 2 in radioiodine treatment and 119 consultations resulted in continued expectancy. Thus, 22% of the original 473 patients underwent thyroid surgery during the follow-up period. The predominant operations were lobectomy (53) and total thyroidectomy (41).

Table 2 demonstrates the main indications for thyroid surgery and the histological diagnoses for each indication. Most commonly, the patients themselves requested surgery due to growth of the goitre, worsening of local symptoms, recurrence of a cyst, fear of malignancy or cosmetic problems. Twelve patients were explored since clinical and/or cytological findings could not exclude malignancy (of whom 5 had carcinomas). Six patients had thyroid surgery due to thyrotoxicosis.

The main histological diagnosis was nodular goitre in 83% of the operated patients, follicular adenoma in 10%, thyroid carcinoma in 5% and thyroid cyst in 1%. Altogether, 27 patients (5.7%) developed thyrotoxicosis during the follow-up period (6 treated with surgery and 21 with radioiodine or antithyroid drugs). In addition, an-

Table 2. Main indication for thyroid surgery at re-referral in 102 patients with benign non-toxic goitre managed with expectancy at first visit

Indication for surgery	Histological diagnosis	Patients, n
Patient's own request (growth of goitre, local symptoms, recurrence of cyst, anxiety, cosmetic) (n = 85)	nodular goitre	71
	nodular goitre with occult thyroid cancer	6
	follicular adenoma	4
	Hashimoto's thyroiditis	2
	follicular adenoma with occult cancer	1
	thyroid cyst with occult cancer	1
Suspicion of malignancy (n = 11)	thyroid cancer	5
	follicular adenoma	5
	nodular goitre	1
Thyrotoxicosis (n = 6)	nodular goitre	5
	nodular goitre with occult thyroid cancer	1

other 17 patients were diagnosed with Hashimoto's thyroiditis during the follow-up period.

Fourteen patients (11 women and 3 men; median age 48 (30–87) years at first referral) were diagnosed with thyroid cancer during the follow-up period. Three of them were elderly women who developed anaplastic carcinomas in longstanding multinodular goitres. The carcinomas were diagnosed 8 months, 3 and 12 years after inclusion in the study, respectively. Another 82-year-old woman had an aggressive papillary carcinoma with extensive brain metastases 7 years after being diagnosed with a right-sided benign goitre. These 4 women died from their malignancies shortly after diagnosis. Seven patients had small papillary carcinomas (1–15 mm in diameter) within large nodular goitres (35–250 g), one 93-year-old lady had a 30-mm tumour characterized as minimally invasive follicular carcinoma, one young man had a 10-mm papillary cancer in the wall of a large cyst, and one middle-aged woman had a 5-mm papillary cancer within a 77 g Hashimoto's thyroiditis. All 9 patients were free from disease at follow-up 102 (18–201) months postoperatively and none had undergone reoperative cancer surgery. However, the 93-year-old woman died 2 years after surgery due to pneumonia.

If the data in the material is stratified for solitary and multinodular goitre, there were significant differences between the groups regarding the frequency of thyroid carcinomas in resected specimens and development of thyrotoxicosis during the follow-up period, but not regarding the frequency of re-referrals or thyroid surgery (table 3). Also, the median weight of the resected specimen differed greatly (45 and 99 g in the solitary and multinodular group, respectively).

Table 3. Comparison between outcomes of patients with solitary and multinodular goitre

	Solitary nodule	Multinodular goitre	p
Number of patients	277	196	
Re-referrals	111 (40%)	69 (35%)	0.292
Thyroid surgery	56 (20%)	46 (23%)	0.428
Thyroid carcinomas	2 (0.7%)	12 (6.1%)	0.001
Thyrotoxicosis	9 (3.2%)	18 (9.2%)	0.008

Discussion

There are some scattered reports on the change in functional status and the risk of thyroid cancer in longstanding nodular goitre but the number of patients is small and they are not adequately followed up in some of these studies [8–10, 14–19]. Thus, the true incidence of hormonal dysfunction, cancer development and the need of surgery in the goitre population is not known, nor if generous indications for surgery are more cost-effective than expectancy in the long run. The advantages of expectancy in asymptomatic patients with clinically and cytologically benign non-toxic nodular goitre must be compared with the risk of developing significant thyroid disorders with time – thyrotoxicosis, thyroid cancer and symptomatic thyroid nodules. Similarly, thyroid operations lead to complications and often lifelong medication that must be weighed against the benefit of generous indications for surgery of benign goitres.

In the Whickham Survey Study, with a follow-up of 20 years, the annual incidence of thyrotoxicosis was 0.8 per 1,000 women in the community [9]. This value can be compared with an annual incidence between 4.3 and 18.2 in four relatively small series of goitre populations [8, 10, 17, 18] and the finding of 4.7 new cases per 1,000 patients per year in the present investigation of a large goitre population followed for a long period of time. Evidently, the goitre patient has an increased risk of developing thyrotoxicosis in comparison to the normal population. However, since the treatment of toxic goitre is not hampered by the length of time one has had the disorder, we do not consider the risk for developing this disorder conflicting with a policy of expectancy in asymptomatic goitre patients.

The incidence of thyroid carcinomas in thyroidectomy specimens from patients with benign goitre varies between 4 and 31% [16, 20–32]. The risk of developing thyroid carcinoma in longstanding untreated goitre has been addressed in some previous, rather old studies [10, 15–17, 19] and they report on an annual incidence of 1.3–3.7 new cases per 1,000 goitre patients. This is in the same range as found in the present investigation (annual incidence = 2.5). However, the finding of a differentiated carcinoma in thyroid specimens is difficult to interpret due to the high frequency of occult, subclinical thyroid cancers. In Scandinavia, autopsy studies have revealed that as many as 6–35% of adults harbour small differentiated thyroid cancers [33–35], whereas the number of ‘clinical’ thyroid cancers in Sweden has been consistently 3–400 new cases per year since 1960 [36]. Nine out of the 14 thyroid carcinomas found in this material belonged to the occult type as were the malignancies detected in the previous studies [10, 15–17, 19]. It therefore seems that the absolute majority of patients with clinically benign goitres, simultaneously having occult/differentiated carcinomas found during an operation, are cured by surgery.

However, the risk of developing life-threatening carcinomas in untreated goitres remains to be considered. In our material, 4 elderly women had anaplastic or aggressive papillary carcinomas during the follow-up period; 2 of them almost 10 years after the primary investigation. Anaplastic thyroid carcinoma is said to be preceded by nodular goitre in 25–60% of the cases [37]. On the other hand, only a diminutive percentage of goitre patients will develop aggressive thyroid carcinomas in old age and it has hitherto never been proposed that they should be recommended prophylactic surgery. However, the patient should be informed to seek immediate medical advice if the goitre starts to grow rapidly [20].

It might be argued that this study is hampered by different confounding factors. One of them could be the selection of patients. However, the selection of patients for surgical evaluation in this study was not made by the surgeons but by the different primary care physicians in the region who referred those goitre patients who they thought should benefit from surgical evaluation. The selection of a patient suitable for expectancy was suggested by the surgeon after clinical examination and fine-needle cytology, but the final decision was made by the patient after careful information. Another confounding factor could be that many patients with non-toxic goitre were referred to ENT doctors and thus disappeared from the study. However, in our region, ENT doctors have not handled goitre patients during the study period so any patient with goitre appearing in the ENT clinic has been sent to the surgeon for evaluation.

According to recent investigations, there is lack of consensus in Europe in the management of non-toxic nodular goitre with large discrepancies between centres and countries in terms of preferred approaches to treatment [38, 39]. There are also clinically significant differences between endocrine surgeons and endocrinologists in the management of multinodular goitre [40]. The conservative approach described in this paper is similar to common practice in the UK and there is no evidence available in favour of more surgery in this group of patients. Cost-benefit analyses are also lacking in this field but an expectancy policy seems to save considerable in-hospital costs.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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