

The recurrent goiter: prevention and management



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AIM OF THE STUDY: *Conservative surgery of thyroid is followed by recurrence in 2 to 70% of cases in an 8 – 20 years period. The surgical treatment of such recurrence is affected by higher morbidity than a primary total thyroidectomy. We wanted verify in our series this difference and discuss motivations for conservative or radical surgery of goiter.*

MATERIALS AND METHODS: *We compared a series of 91 primary total thyroidectomy (A) with 11 cases of total thyroidectomy for recurrence (B) performed between 2001 and 2005.*

RESULTS: *Postoperative complications were: Transient hypocalcemia 7 (7.69%) in A and 3 (27%) in B, Permanent hypocalcemia only 1 (9%) in B, Transient RLN deficit 2 (2.1%) in A and 2 (18.1%) in B.*

CONCLUSIONS: *Due to the need of a lifelong therapy with LT₄ no utility is observed in conservative surgery of thyroid. Further, in primary surgery, differences in incidence of perioperative complications cannot be advocated to justify a conservative approach. Sophisticated technologies are not able to prevent all damages to parathyroid or to recurrent nerves when operating on recurrent goiter.*

Our experience confirms the results of a review of literature on this topic: the best management of recurrent goiter is its prevention by primary total thyroidectomy.

KEY WORDS: Goiter

Introduction

The conservative procedures in thyroid surgery are characterized by high recurrences. In the literature the recurrences of a goiter after less than a total thyroidectomy range from 2 to 39%. The rate then goes up to 70% in the absence of replacement therapy¹⁻⁷.

In the past, the problem of the recurrences has been underestimated. This is probably due to the prolonged lag of time between the surgical intervention and the

recurrence itself (from 8 to 20 years), time when the patient is often already lost in follow-up.

This should not decrease the magnitude of the problem, especially because the treatment of the recurrence is associated with a greater degree of permanent complications compared to the primary total thyroidectomy (Table I). This problematic issue opens the door to several discussion points and important technical controversies.

In order to clarify some of these issues, we retrospectively reviewed our experience on thyroid surgery from January 1980 to March 2006.

Materials and Methods

From January 1980 to March 2001, the procedures of choice for benign thyreopathies were:

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- subtotal thyroidectomy with bilateral residual gland not greater than 5 grams;
- near total thyroidectomy, with a unilateral residual thyroid tissue of 2-3 grams.

These procedures were performed in 480 cases of nodular goiter, and in all cases the recurrent laryngeal nerves and the parathyroid glands were clearly identified and preserved.

In 2000 the indications for total thyroidectomy were extended to the benign thyreopathies, so from March 2001 it became the gold standard. In total we performed 91 total thyroidectomies for primary goiter. An additional 11 cases were done for recurrent goiter. None of these recurrences were initially treated at our institution. The 11 recurrences were 7 women and 4 men with age between 65 and 83 years old. The recurrences were diagnosed between 13 and 26 years after the initial operation (average 22). Four of the recurrences occurred in patients who initially underwent a lobectomy and isthmusectomy. The other 7 patient had a subtotal thyroidectomy. Two patient of the latter group (1 man and 1 woman) had a monolateral permanent deficit of the recurrent laryngeal nerve.

The indications for the surgical procedures were compressive symptoms (N=8), and suspected neoplasia (=3), then histologically confirmed in all cases.

The preoperative evaluation always included the routine laboratory screening, FT3, FT4, TSH levels, Calcemia, PTH level, chest radiograph focusing in particular on the trachea, esophagogram and fiber optic laryngoscopy.

The standard treatment for all recurrences was a total thyroidectomy. In the 3 cases of suspected neoplasia a Berry pick lymph node biopsy was performed, as well. In all cases the lymphnodes were negative for metastasis. The recurrent laryngeal nerves (RLN) and the parathyroid glands were routinely identified. This process was relatively easy for the cases of previous lobectomy and isthmusectomy and more time consuming in the other cases. In the 2 cases of permanent unilateral RLN injury from the previous operation, the nerve was not identified because of absence of thyroid tissue on that side (N=1) or because the nerve was not recognizable (N=1).

During the postoperative course the serum calcium level was checked twice a day for two consecutive days. The following measurements were dictated by the patient's symptoms. The laryngeal nerve function was assessed clinically. Fiberoptic laryngoscopy was only utilized in suspicious cases.

Results

The average operating room time for the recurrent cases was 127 minutes (range 88-255 minutes), as opposed to 98 minutes (range 78-170 minutes) of the primary thyroidectomy.

The length of hospital stay was 2 days for 10 patients and

TABLE I - Hypocalcemia and deficit of Recurrent Laryngeal Nerve after total primary thyroidectomy and after completion thyroidectomy for recurrent goiter.

Outcome	Primary goiter		Recurrent goiter	
Total Thyroidectomy	91		11	
Transient hypocalcemia	7	7.69%	3	27%
Permanent hypocalcemia	0		1	9%
Transient RLN deficit	2	2.1%	2	18.1%
Permanent RLN deficit	0		0	

4 days for one. The latter patient developed symptomatic hypocalcemia in the immediate postoperative period.

Postoperative hypocalcemia was observed in 4 patients. Three of the four experienced temporary (less than 7 days) hypocalcemia and only one became symptomatic. One patient developed permanent hypocalcemia (more than 6 months) and is currently on oral replacement therapy. No hemorrhage or bilateral RLN deficit occurred in the perioperative period, however, two patients developed transient unilateral RLN deficits, which resolved within 2 months.

The postoperative complications (both transient and permanent) after redo operations were significantly higher than those in patients who underwent primary thyroidectomy (Table I).

Discussion

The recurrent goiter could be described as the increase in residual thyroid parenchymal volume due to:

- Development of new nodules after subtotal bilateral thyroidectomy;
- Enlargement of small nodules left behind at the time of the primary operation ¹;
- Compensatory hyperplasia of the residual thyroid parenchyma ⁸.

We will use the term "false" recurrence to describe the cases in which the affected hemi thyroid has never been surgically manipulated (lobectomies or lobectomies+ isthmusectomies). Whereas the term "true" recurrence will be utilized for those arising from residual parenchyma after subtotal or near total thyroidectomies. Nevertheless a recurrence could be originating from an ectopic thyroid tissue or from structures embryologically related to the development and migration of thyroid buds (i.e. thyreoglossal duct, pyramidal lobe, thyreo-thymic remnant, tubercle of Zuckerkandl), and as such, can present even after total thyroidectomy ⁹. In the latter cases the treatment is more complex and requires a more strict absolute indication to the surgical intervention itself.

Some other authors believe that a recurrent goiter should be described only in case of remnant thyroid tissue with an echographic volume greater than 20 cc and/or new nodules of volume greater than 0.5 cc ⁹.

The recurrence rates of a goiter after conservative treatment have been reported between 2.5% to 73% (average 10%)^{1,2,4-7}. In addition, asymptomatic micro or macro nodular alterations have then been described in 60% of the patients who underwent conservative surgical treatment of their goiters, regardless of the post-operative medical treatment³.

Although some correlation between recurrent goiter and genetic factors such as female gender and young age, has been described¹¹, the incidence of recurrent goiters seems to be more strongly associated with euthyroid multinodular goiters and, mostly, with a larger glandular remnant^{5,6,12-16}.

Some authors believe that the recurrences after the apparent removal of the entire affected glandular tissue could be due to the polyclonal origin of the thyroid nodules¹⁷, or to the polyclonal growth potential of morphologically and functionally independent aggregates present in the entire gland¹⁸. These hypotheses suggest that the recurrent lesions are the result of an '*ex-novo*' proliferation of different group of thyrocytes that share a common abnormally elevated growth rate. Alternatively, an unknown stimulating factor might be responsible for the proliferation itself. Ambrosi in 1999 suggested that the growth factors EGF and IGF were involved in the development of a goiter and his recurrences^{19, 20}. Harter et al. postulated a genetic component of the recurrences based on the fact that these are frequently observed in patient who underwent surgical treatment at a young age¹⁷. It seems reasonable to conclude that multinodular goiter, even if apparently limited to only one lobe, it is in reality a disease of the entire gland and, as such, it should be treated with a total thyroidectomy³.

If the first surgical approach is a total thyroidectomy, we should face a recurrence only in case of a non-recognized or ectopic thyroid remnant. The debate on this approach for a benign disease is still open.

The supporters of conservative treatments base their opinion on the following issues^{21,22}:

- Avoidance of lifelong replacement therapy
- Avoidance of injury to the RLN.
- Avoidance of permanent hypoparathyroidism.

The problem of avoiding hypothyroidism was certainly prominent during the era of Kocher. In those days the sequelae of a total thyroidectomy were mixedema and post-thyroidectomy chachessia, which excluded a euthyroid goiter patient to a vegetative state^{23,24}.

Nowadays, the argument of avoidance of lifelong replacement treatment does not stand anymore, since a substitutive pharmacologic therapy is available. Moreover a high rate of these patients will need replacement therapy based on a persistent subclinical hypothyroidism and the difficulty to achieve a good hormonal compensation^{2,5,19,24-26}.

Marchesi et al. in 1998 in his experience of 108 subtotal thyroidectomies and 451 total thyroidectomies for multinodular euthyroid goiter concluded that there is no

"hormonal" benefit in conservative surgeries, and that total thyroidectomy, instead, reduces the recurrences by 26%. Furthermore at least half of the recurrences will develop significant transient complication after the second surgical intervention²⁷.

Whether patients who have had surgery for nodular or multinodular goiter should be treated with suppressive doses of levothyroxine, versus replacement therapy to normalize the serum TSH concentration, is controversial. The results of some but not all trials suggest that levothyroxine therapy does prevent recurrent goiter. In one study with a 10-year follow-up, as example, the recurrence rate was much lower in the patients treated with levothyroxine (5% vs 42% in the untreated group had recurrent goiter)²⁸. In another study from an iodine deficient region of Italy, 58 of 210 patients (28%) following a hemithyroidectomy and given L-T4 postoperatively had recurrence of goiter compared to 33 of 58 patients (57%) who did not receive L-T4.²⁹ So usually the recommendation is to prescribe high doses of levothyroxine in order to suppress the TSH stimulus on the remaining gland³⁰⁻³³.

However, this benefit was not confirmed in a report with 30-year follow-up: the recurrence rates were similar (41% and 45%) in treated and untreated patients³⁴. Other authors^{13, 15} in spite of their support for a subtotal thyroidectomy, do not advocate the use of suppressive therapy, reporting an average recurrence rate of 24%. Randomized trials have found no significant reduction in recurrent goiter in patient receiving L-T4. Because L-T4 suppressive therapy results, by definition, in subclinical hyperthyroidism, treated patients may be at increased risk for atrial fibrillation, other cardiac abnormalities, or reduced bone density. These possibilities, combined with the uncertainty regarding efficacy, has led to recommendations that vary depending upon the age, sex, and menopausal status of the patient³⁵.

In addition, if we consider that the recurrences usually become manifest in 8-10 years after the initial treatment, it is likely that we will encounter higher recurrence rates as the follow-up period extends. Even authors that report a low recurrence rate, note that the results might be underestimated because of lack of an adequate follow-up³³. In fact the asymptomatic patient, operated on for a benign disease, commonly skip follow-up visits.

The great variety of conservative procedures, the lack of uniformity of the studies and the obvious nomenclature discrepancies result in a difficult interpretation of the substantial amount of literature available.

The different surgical procedures described are: thyroid lobectomy; subtotal thyroidectomy with bilateral remnants; near-total thyroidectomy; thyroid lobectomy with contralateral sub-total emythyroidectomy (also known as sub-total thyroidectomy with monolateral remnant); total thyroidectomy.

The ideal amount of residual parenchyma to leave after

a subtotal thyroidectomy varies in the different publications^{1,25}.

Once we established that the partial excisions do not avoid the need for a lifelong therapy, except in selected cases of benign unilateral lesions with a gland otherwise normal, let's analyze the reasons for a conservative treatment. Obviously the fear is of iatrogenic unilateral or bilateral RLN injury or permanent hypothyroidism.

The risk of an iatrogenic injury, today as in the days of Kocher, is such to dissuade surgeons to proceed with an operation potentially more dangerous. Nevertheless, a careful analysis of the published series shows that the incidence of RLN injury and permanent hypoparathyroidism following total thyroidectomies for benign diseases is comparable to the incidence after more conservative interventions³⁷⁻³⁹.

The importance of visualizing the RLN and the parathyroids even in the conservative operations has been proven by Seiler et al¹⁸, who reported a decrease of RLN injuries from 2.7% in partial resections (from 1972 to 1990), to 0.7% in more radical approaches (total ipsilateral hemithyroidectomy and contralateral subtotal thyroidectomy, at a minimum) in the years 1991 to 1996. The incidence of hypoparathyroidism has decreased, as well (from 3.6% to 1%)^{18, 40,41}.

It is important to note as the transient postoperative hypocalcemia it is not necessarily due to a structural damage of the parathyroid glands, except in case of inadvertent removal or damage to the blood supply of the glands. Sturniolo compared 312 patients after total thyroidectomy with a control group of 100 patients who underwent other non thyroid related procedures. The group of patients who had a non-thyroid related operation had a transient (i.e. 5 days or less) hypocalcemia in 62% of the cases compared to 75% of the group who underwent thyroidectomy⁴². In this latter group, 2 patients became severely symptomatic requiring medical treatment with Calcium and Vitamin D for 10 days.

The permanent hypoparathyroidism is directly related to the surgical technique. Thomusch has extensively studied the issue by conducting a multivariate analysis on 5,864 patients. He found that the independent risk factors for hypoparathyroidism were in order of frequency: a total thyroidectomy; the bilateral central ligation of the inferior thyroid arteries; the identification and preservation of only one, or worse no, parathyroids³¹.

With the increased number of total thyroidectomies, we are noticing a reduction of the redo operations for recurrent goiters, occult carcinomas or carcinoma on recurrences (occult carcinomas left in situ?)^{29, 38-39, 44}.

The occurrence of an occult carcinoma after a thyroidectomy for presumed benign disease represents a real problem with a prevalence of 3 to 16% (mean 8%)^{46,47}. This, of course, generates the question whether or not an immediate re-intervention is necessary. Even in the cases where the completion thyroidectomy is not warranted because of a small residual gland or a papillary

tumor, it is always necessary to submit the patient to radio iodine treatments and to keep a much stricter follow-up than if he or she had a total thyroidectomy in the first place.

The conservative approach still advocated by prestigious schools, will continue to generate interesting discussion on the treatment of recurrent goiters.

The surgical debate:

- the first issue to address is if, when, and how to treat the recurrent goiter;
- the surgical indications are more less the same as the primary goiter;
- suspect neoplasia;
- toxic goiter transformation;
- tracheal deviation or compression;
- mediastinal syndrome;
- cosmesis

The indications have to be selected very carefully, in fact the chance of complications from a redo-operation are definitely superior to the ones of the first surgical intervention.

From an accurate review of large series, it appears that the indications for the re-intervention are obvious in 25-75% of the recurrent cases⁸.

The suspicion for neoplasia represents an absolute indication for the surgical treatment. In case of hyperthyroidism or compressive symptoms, some authors advocate the use of radio Iodine for the poor surgical candidates^{48,49}. The radioiodine therapy is usually effective in reducing the volume of the goiter in 2-3 months, but does not give good results in the cases of large goiters (> 60 g), especially if associated with Basedow disease⁵⁰.

It is necessary to specify that advanced age is not in itself a contraindication to thyroid surgery. In fact the large series on patients over 75 years of age have shown a similar incidence of postoperative complications, when compared to younger groups⁵¹.

The incidence of RLN lesions, both unilateral and bilateral, have been reported up to 5 times higher in redo-operation compared to primary operation, even in the hands of the same surgical team⁵².

Also the permanent hypoparathyroidism seems to occur more frequently after redo-operation (0.5-9.5%, average 1.5%) compared to primary surgery⁵²⁻⁵⁶.

Hence, it seems obvious that the recurrent goiter requires a more careful surgical strategy than the primary one. More important than the strategy itself, the experience of the surgeon can make a difference in the final outcome.

First of all the surgical incision has to be wide and not being limited by a previous scar carried out too low for cosmetic reasons. This incision is usually adequate for retrosternal recurrences, as well, and a median sternotomy is rarely required⁵⁵. The lateral-posterior approach, advocated by several northern European schools is not

usually necessary ^{40, 54}. The strap muscles, usually preserved during the first operation, will have to be transected in the reoperative cases.

The use of the operative microscope, for the surgeons that are already familiar with it, or of magnifying loops, definitely helps in the identification of the RLN, which is usually dislodged from his natural course. In fact, the course could be anterior or lateral to the recurrence, based on the tissue of origin of the recurrence itself.

Wahl ⁵⁷ has classified the RLN based upon its position in the recurrences: not identified (X); not in the scar (A); in the scar (B) B1 dorsal, B2 lateral, B3 ventral. He showed a progressive increase in the risk of nerve injury from position A to X to B.

Some German authors ⁵⁸⁻⁶¹ have utilized the electrophysiological monitoring of the RLN.

This monitoring can be accomplished in several ways:

1. By electromyography:

– through preoperative laryngoscopic implant of fixed electrodes;

– through superficial electrodes implanted preoperatively or attached to an endotracheal tube. This method is less sensitive than the one with fixed vocal cords electrodes and requires an outside assistant;

– through electrodes implanted into the cricothyroid membrane. This method can be adopted by the surgeon at anytime of the procedure and so does not require any external collaboration or preoperative planning.

2. By manometry.

This method is based on the pressure evoked by the contraction of the vocal cords.

3. By optical monitoring of the vocal cords motility.

This method is the most reliable, since it directly monitors the movements of the vocal cords, but it is also the one with more potential risks and it also requires an extensive involvement by the anesthesiologist ⁵⁸.

In the electromyographic method, the nerve is identified by an electric stimulation, and an electromyography is recorded by the dedicated apparatus (Nerve Integrity Monitor NIM-2. Xomed Trace).

The preoperative implant of the electrodes has the disadvantage not only of a potential displacement of the electrodes, but also of the inability of intraoperative verification of the correct position. Furthermore, the intraoperative activity does not have any positive or negative predictive value on the postoperative motility of the vocal cords ⁵⁸. It is also true that, although all the RLN monitoring modalities have been successfully implemented during the primary thyroid operations, the failure rates for the redo-operations and for the voluminous goiters have been reported as high as 7.6% ^{59,60}. In light of these latest findings, some authors have advocated that in recurrent goiters the intra-operative monitoring of the RLN does not reduce the incidence of permanent lesions ⁵⁷. In order to assess the efficacy of the intra-operative monitoring of the RLN, Kunath et al. analyzed the results of both the preoperative and postoperative laryn-

goscopic examination in 926 patients undergoing thyroidectomies. The laryngoscopy was conducted by a physician not belonging to the operating team. The transient monolateral and bilateral RLN deficits were present in 6% of the cases and resolved in 68% of them. The permanent deficit was significantly different in the primary interventions (0.51%), the primary intervention for cancer (4.8%) and the re-interventions (6.6%) ⁵⁹.

The availability of newer energy sources (i.e. ultrasonic dissectors) has been successfully implemented in the primary thyroid operations in an effort to decrease the operating time and the blood loss, as demonstrated by randomized prospective trials ^{62,63}.

In conclusion, even in specialized referral centers, the intervention for recurrent goiters is characterized by significantly higher risks for complications than the primary surgical procedure. The total thyroidectomy should be utilized, then, as the first intervention. In fact, it prevents recurrences, it allows for an easier control of the postoperative hypothyroidism and for the removal of microscopic foci of carcinoma.

Riassunto

SCOPO DELLO STUDIO: Il trattamento chirurgico conservativo della tiroide è seguito da una recidiva nel 2-70% dei casi in un lasso di tempo che va dagli 8 ai 20 anni. Il trattamento chirurgico di tali recidive è gravato da una morbidità maggiore di quella che segue una tiroidectomia totale d'emblée. Gli AA. vogliono verificare questo dato nella loro casistica ed esaminare le motivazioni di un trattamento conservativo o radicale.

CASISTICA E METODI: Vengono comparati gli esiti di una serie sottoposta a tiroidectomia totale (91 casi) con una di 11 casi di tiroidectomia totale eseguita per recidiva di gozzo dopo terapia conservativa tra il 2001 ed il 2005.

RISULTATI: Le complicanze post-operatorie furono: ipocalcemia transitoria (7 casi, pari al 7,69%) nella serie A e 3 (27%) nella serie B; ipocalcemia permanente in 1, solo caso (9%) nella serie B; deficit transitorio del nervo ricorrente laringeo in 2 casi (2,1 %) nella serie A ed in 2 (18,1%) nella B.

CONCLUSIONI: In primo luogo considerando la necessità di una terapia con LT4 per tutta la vita, la terapia conservativa del gozzo non sembra consigliabile. Oltre a ciò, nella chirurgia d'emblée, non si osservano differenze nell'incidenza di complicanze perioperatorie, tali da giustificare la terapia conservativa. Anche tecnologie sofisticate non sono in grado di prevenire tutti i danni eventuali alla paratiroide od al ricorrente, in caso di intervento per gozzo recidivo.

L'esperienza degli AA. conferma i risultati della Letteratura su questo argomento: il miglior trattamento di un gozzo recidivo è la sua prevenzione con una tiroidectomia totale

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