

ECONOMIC EFFICIENCY OF A DIFFERENTIATED SURGICAL APPROACH TO TOXIC GOITER TREATMENT

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Abstract. Toxic goiter (thyrotoxicosis due to diffuse or nodular thyroid disease) remains challenging to manage despite established treatments (antithyroid drugs, radioiodine, surgery). Prolonged medical therapy often leads to drug intolerance and organ damage, while inadequate surgery can result in high recurrence rates. This study aimed to improve outcomes by tailoring surgical strategy based on clinical and morphological findings and assessing its economic efficiency. An experimental model of hyperthyroidism in animals was used to evaluate a new approach (thyroid artery ligation) for suppressing thyroid function. The experimental artery ligation led to reduced thyroid function and compensatory vascular changes, supporting an occlusive approach. Clinically, limiting prolonged drug therapy and proceeding to surgery with proper pre-op preparation improved outcomes. Subtotal subfascial thyroid resection was the primary surgery performed, with intraoperative gland examination detecting occult nodules in 40.7% of cases. Preoperative plasmapheresis enabled rapid achievement of euthyroidism, normalized cardiovascular function, and significantly reduced intra/postoperative complications in high-risk patients. No operative mortality was noted. The vast majority of patients (over 75%) achieved excellent results (euthyroid with no complications).

Keywords. Toxic goiter; Thyrotoxicosis; Subtotal thyroid resection; Toxic adenoma; Plasmapheresis; Complications; Recurrence; Economic efficiency

ЭКОНОМИЧЕСКАЯ ЭФФЕКТИВНОСТЬ ДИФФЕРЕНЦИРОВАННОГО ХИРУРГИЧЕСКОГО ПОДХОДА К ЛЕЧЕНИЮ ТОКСИЧЕСКОГО ЗОБА

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Аннотация. Токсический зоб (тиреотоксикоз, обусловленный диффузной или узловой патологией щитовидной железы) остаётся сложной задачей для лечения, несмотря на наличие стандартных методов — тиреостатическая терапия, радиоактивный йод и хирургическое вмешательство. Продолжительное медикаментозное лечение нередко приводит к

лекарственной непереносимости и поражению органов-мишеней, а недостаточный объем хирургического вмешательства способствует высокому уровню рецидивов. Целью настоящего исследования стало улучшение исходов путём дифференцированного выбора хирургической тактики на основе клинико-морфологических данных с параллельной оценкой экономической эффективности.

В эксперименте на животных была использована модель гипертиреоза для оценки нового метода подавления функции щитовидной железы — перевязки артерий. Результаты показали снижение функции железы и компенсаторные сосудистые изменения, что подтверждает обоснованность окклюзионного подхода. Клинически сокращение сроков медикаментозной терапии и своевременное выполнение операции при адекватной предоперационной подготовке улучшали исходы. Основным методом хирургического лечения являлась субтотальная субфасциальная резекция щитовидной железы. При этом в 40,7% случаев интраоперационно выявлялись скрытые узлы. Применение плазмафереза в предоперационном периоде способствовало быстрому достижению эутиреоза, нормализации сердечно-сосудистой функции и значительному снижению числа интра- и послеоперационных осложнений у пациентов группы высокого риска. Летальных исходов не зафиксировано. У более чем 75% больных были достигнуты отличные результаты — стабильный эутиреоз без осложнений.

Ключевые слова: токсический зоб; тиреотоксикоз; субтотальная резекция щитовидной железы; токсическая аденома; плазмаферез; осложнения; рецидив; экономическая эффективность

Relevance. Toxic forms of goiter (including diffuse toxic goiter and toxic nodular goiter) present a complex therapeutic problem involving internists, endocrinologists, and surgeons. Although three main treatments exist – antithyroid drug therapy, radioactive iodine, and surgery – significant issues remain. Prolonged medication therapy is often required to induce remission, but this long conservative treatment can lead to medication intolerance and dependence on thyroid suppressants, with progressive pathological changes in multiple organs. Patients on extended medical management may develop serious cardiovascular and other systemic complications, making eventual surgery riskier. In severe thyrotoxicosis or cases with comorbidities, effective preoperative preparation is crucial for safe surgery. Prior studies have suggested that therapeutic plasmapheresis can rapidly stabilize thyroid hormone levels in “problem” patients, helping to achieve euthyroid status before surgery. This approach can shorten the preparation period and reduce drug-related side effects. Another experimental approach to severe toxic goiter has been thyroid artery embolization/ligation to acutely reduce hormone output. While initial reports showed that occluding thyroid vessels can suppress gland activity, this method is technically complex and required further experimental morphological validation.

Surgical management of toxic goiter also has unresolved questions. In diffuse toxic goiter (Graves' disease), the surgical technique has been well established historically, but the optimal extent of thyroid resection (how much thyroid tissue to leave in place) remains debated. Removing too little tissue can lead to persistent disease or recurrence, whereas removing too much causes hypothyroidism. These decisions are especially challenging in mixed toxic goiter (diffuse goiter with nodules) and toxic adenoma (a hyperfunctioning thyroid nodule), where surgical tactics must be refined. Preventing recurrence of thyrotoxicosis is a major concern – inadequate initial surgery (leaving behind thyroid remnants with autonomous function) is the leading cause of recurrent goiter, reported in up to 92% of cases of so-called "false recurrence". Such recurrences necessitate reoperation, which is technically demanding due to scarring, and is associated with a high rate of intraoperative and postoperative complications. For instance, repeat thyroid surgeries carry increased risk of nerve injury, bleeding, and hypoparathyroidism. These background issues underscore the need for a well-founded clinico-morphological rationale in choosing the timing and extent of surgery for toxic goiter – one that balances disease control with minimal complications. By integrating clinical data with morphological findings (e.g. histology of resected tissue), the treatment strategy can be optimized for better patient outcomes and more efficient use of healthcare resources.

Objective of the Study. The goal of this study was to improve the management of patients with toxic goiter by developing a differentiated treatment strategy grounded in clinical and morphological evidence.

Materials and Methods. The research included both an experimental component and a clinical component. In the experimental part, a rat model of hyperthyroidism was created to study the effects of reducing thyroid blood flow. Ligation of the thyroid arteries was performed in hyperthyroid animals to observe the resulting morphological and functional changes in the thyroid gland. This experiment provided morphological evidence on whether vessel occlusion could safely suppress thyroid activity – data relevant to novel preoperative interventions.

The clinical study analyzed 108 patients with toxic forms of goiter who underwent surgical treatment at a single center. The cohort included patients with diffuse toxic goiter, toxic multinodular goiter (mixed toxic goiter), and solitary toxic adenomas causing hyperthyroidism. The age range of patients was broad (young adult to elderly), but the majority (approximately 70%) were between 31 and 60 years old. There was a strong female predominance (99 women, 9 men; female:male ratio ~11:1), reflecting the epidemiology of thyroid disorders. Nearly half of the patients (48%) presented with severe thyrotoxicosis, often accompanied by large goiters (Grade III–IV thyroid enlargement).

All patients underwent comprehensive clinical evaluation, including thyroid function tests, ultrasound imaging, and fine-needle aspiration cytology as indicated. Patients were classified as "problematic" if they had severe thyrotoxicosis with complications of medical therapy (e.g. poor tolerance or ineffectiveness of

antithyroid drugs) or significant comorbid conditions (such as cardiovascular disease) making immediate surgery high-risk. For these high-risk patients, an intensive preoperative stabilization was implemented using discrete plasmapheresis. Each such patient received 5 to 7 plasmapheresis sessions, which helped to rapidly remove excess thyroid hormones and immune complexes from the circulation. This measure significantly shortened the time required to achieve a safe euthyroid state before surgery and mitigated the risks associated with uncontrolled thyrotoxicosis. Other patients received standard preoperative medical management with antithyroid drugs (thionamides) and beta-blockers until euthyroid or until it was deemed that surgery could proceed.

Surgical technique: The surgical approach was standardized and refined based on clinico-morphological considerations. In most cases, a subtotal subfascial resection of the thyroid gland was performed as the treatment of choice. This involves removing the majority of thyroid tissue while leaving only a small remnant (approximately 4–6 grams of thyroid tissue, often described as about 10×10 mm or 15×5 mm on each side). The procedure was done via a conventional collar (Kocher) incision in the neck, with careful identification and preservation of the recurrent laryngeal nerves and parathyroid glands. A key modification in technique for this study was a meticulous intraoperative examination of the thyroid remnant. After resecting the grossly affected portions of the thyroid, surgeons performed a wedge incision through the remaining contralateral lobe (in cases of unilateral disease) to inspect for any small nodules within the gland. If any occult nodules were detected on the cut surface, a more extended resection (up to near-total thyroidectomy) was carried out to ensure removal of all hyperactive tissue. In patients with a unilateral toxic adenoma, the operative plan included a hemithyroidectomy (removal of the affected lobe and isthmus) combined with exploration of the opposite lobe. Even if preoperative imaging did not show nodules in the opposite lobe, a contralateral exploration by a cross-sectional incision was done to rule out small nodular changes. This innovation was based on the study's finding that 40.7% of patients with diffuse or mixed toxic goiter had additional tiny nodules undetectable by preoperative methods. Detecting and removing such nodules at the initial surgery was crucial to prevent recurrence. In cases of recurrent toxic goiter (patients who had previous thyroid surgery and developed recurrence, comprising a subset of the cohort), surgery was more complex; a near-total or total thyroidectomy was performed where possible, given the already reduced gland volume and presence of scar tissue.

To improve surgical safety, the operative technique was refined: after mobilizing the thyroid lobes and isthmus, the thyroid arteries were ligated early in the procedure (to reduce intraoperative blood loss). The thyroid capsule was dissected in a subfascial plane to preserve the parathyroids. At the end of surgery, layered wound drainage was used – both gauze wick and small rubber drains were placed in the thyroid bed and removed sequentially postoperatively – to reduce risk of hematoma or seroma.

All resected thyroid tissues were sent for histopathological examination. The pathologists correlated clinical diagnoses with morphological findings, documenting features such as diffuse hyperplasia, nodular hyperplasia, or lymphocytic infiltration, to ensure the correctness of the surgical indications and to identify any incidental thyroid pathology. The study also included an analysis of economic outcomes. Data were collected on each patient's total duration of treatment: length of preoperative preparation (days of medication or plasmapheresis required), length of hospital stay, and any additional resource utilization (such as intensive care for complications or repeat hospitalizations). Treatment cost was evaluated by considering the costs of medications (or plasmapheresis) and hospitalization days for conservative management versus the costs associated with surgery and any postoperative care. By comparing these factors, the cost-effectiveness of the clinico-morphological approach (early surgery with adequate prep and complete resection) was assessed against more prolonged medical management or inadequate initial surgery leading to reoperation.

Results and Discussion. In the animal experiment, ligation of the thyroid arteries in hyperthyroid rats produced notable morphofunctional changes in the thyroid gland. Histological examination showed signs of suppressed thyroid activity in the ligated gland – for example, smaller follicle size and reduced colloid, indicating decreased hormone production. At the same time, there was a reactive increase in vascular proliferation (capillary density) in the thyroid tissue, suggesting a compensatory attempt to restore blood flow. These findings confirm that intentional reduction of thyroid blood supply can significantly dampen thyroid function, supporting the concept of preoperative arterial occlusion or ligation to control severe thyrotoxicosis. However, the compensatory angiogenesis observed also implies that incomplete or temporary vessel occlusion might lead to revascularization of the gland. This underlines the importance of permanent solutions (surgical removal of tissue) for definitive treatment. The animal model provided a morphological basis for using invasive techniques like intraoperative artery ligation or embolization in treating toxic goiter, and helped to refine the surgical approach in the clinical part of the study.

The clinico-morphological strategy was successfully implemented in all 108 patients, and it yielded excellent clinical outcomes in the majority of cases. By limiting the duration of pre-surgical medical therapy (thus avoiding prolonged exposure to ineffective drug treatment) and proceeding with definitive surgery once the patient was adequately prepared, the treatment course was significantly accelerated. Patients who underwent discrete plasmapheresis as part of preoperative preparation particularly benefited: plasmapheresis produced a rapid drop in circulating thyroid hormones and improvement of symptoms, enabling surgery in a much shorter timeframe than traditional medical preparation. This approach averted the need for months of drug therapy that, in severe cases, often still fail to achieve euthyroidism. According to the study, the use of 5–7 sessions of plasmapheresis allowed even the sickest patients to be safely operated on in a matter of days,

irrespective of co-existing diseases. Clinically, these patients showed normalized cardiovascular function (such as resolution of arrhythmias and tachycardia) and none experienced thyroid storm during or after surgery. In comparison, patients managed with drug therapy alone required a longer preparation and had a higher incidence of preoperative drug side effects (like hepatic toxicity or agranulocytosis from antithyroid drugs). Thus, plasmapheresis proved to be an effective and cost-effective adjunct, preventing complications and shortening hospitalization in preparation for surgery.

During surgery, the adoption of a refined technique (early vessel ligation, subfascial dissection, careful hemostasis, and thorough exploration of the gland) resulted in low intraoperative blood loss and no serious surgical complications. There were no cases of damage to the recurrent laryngeal nerve in the series, and postoperative hemorrhage was effectively avoided by the meticulous technique and drainage protocol. Importantly, the strategy of intraoperative contralateral lobe review in unilateral cases led to detection of previously occult nodules in a significant number of patients. This finding (additional nodules in ~40% of diffuse/mixed goiter cases that were not seen on pre-op imaging) validates the morphological rationale for an aggressive initial surgery: only by examining and removing all nodular tissue could recurrence be truly prevented. In several patients, what was thought to be a single toxic nodule turned out to coexist with microscopic nodules in the other lobe, discovered on the table – these would have caused a relapse if left behind. Therefore, the surgical team performed a more extensive resection in such cases (upgrade from subtotal to near-total thyroidectomy), which likely prevented future recurrence of thyrotoxicosis. Notably, simple enucleation of a toxic nodule (merely removing the nodule and sparing most of the thyroid) was found to be an inadequate operation – the study strongly argues against nodule enucleation in toxic adenoma, in favor of at least subtotal lobectomy with inspection of the opposite lobe.

The early postoperative course was generally smooth. There were no life-threatening complications or deaths. Thyroid function after surgery was as expected for the extent of resection: most patients became euthyroid or mildly hypothyroid. Those with residual thyroid tissue often maintained euthyroidism, while those with near-total removal required thyroid hormone replacement. No patient experienced a thyroid storm or severe thyrotoxic crisis postoperatively – a testament to the adequacy of preoperative preparation.

In terms of specific complications, the rates were low and acceptable, especially compared to historical data for thyroid surgery in toxic goiter. Transient hypocalcemia (due to temporary hypoparathyroidism) occurred in a small number of patients post-surgery; only about 2–5% of patients had clinical hypoparathyroidism, and in most cases it was transient, resolving with calcium/vitamin D therapy. Permanent hypoparathyroidism (lasting beyond 6 months) was very rare – it was primarily observed in a few patients who had undergone reoperations for recurrent goiter (where scar tissue and altered anatomy

increase the difficulty of preserving parathyroid glands). Recurrent laryngeal nerve palsy did not occur in the initial surgery group, thanks to careful identification; a couple of cases of transient hoarseness were noted but resolved, and these were in reoperative cases. Minor complications like wound infection or hematoma were practically nonexistent due to the drainage and sterile technique – no reoperations for neck hematoma were needed.

The long-term results demonstrate the effectiveness of the surgical strategy. Follow-up of patients (including 75% of those with at least 1 year of follow-up) showed that clinical remission was achieved in the vast majority. Specifically, over 75% of patients had excellent long-term outcomes: they remained euthyroid without any significant complications or need for further interventions. An additional ~15–20% of patients had a satisfactory outcome with minor issues – for example, some developed mild hypothyroidism (approximately 16–17% of cases), but this was an anticipated outcome given the extent of surgery and was easily managed with low-dose L-thyroxine replacement. In fact, postoperative hypothyroidism can be viewed as an acceptable trade-off for curing hyperthyroidism, as long as it is controlled with medication. Only a small fraction of patients (around 5%) experienced recurrence of thyrotoxicosis after the initial surgery. These few cases of recurrence were carefully analyzed. In all instances, recurrence was attributable to an inadequate initial resection – for example, a patient with diffuse toxic goiter who had a small remnant left that later grew or a patient in whom an occult nodule was missed. The study notes that incomplete removal of pathologically active thyroid tissue was the sole cause of unsatisfactory outcomes. No recurrence occurred when the thyroid resection was truly radical (total or near-total removal of all toxic tissue). In patients with mixed toxic goiter, only 1 out of 14 followed patients had a recurrence (7.2%), and even that case was somewhat ambiguous (ultrasound suggested a recurrent nodule, but it might have been a granuloma around suture material). In solitary toxic adenoma cases, recurrence was extremely low after the recommended surgery (none of the patients properly treated with hemithyroidectomy and contralateral exploration had a true recurrence of hyperthyroidism). This underscores that the protocol of adequate initial surgery is highly effective in preventing relapse.

The subset of patients who had surgery for recurrent goiter (i.e. they had been operated on previously elsewhere and came with recurrence) further illuminated the benefits of the one-step radical approach. Among those who needed reoperations, only about 44% had good outcomes (4 out of 9 patients followed had an excellent result), while the others had ongoing issues: 33% developed hypothyroidism (which is expected after a second, more extensive surgery) and 22% had permanent hypoparathyroidism due to scarring and difficulty in preserving all parathyroids. This contrast is important: initial surgery done correctly yielded over 75% excellent outcomes with minimal complications, whereas reoperative surgery had a much lower success rate and higher complication profile. This finding reinforces the principle that preventing recurrence through an adequate first operation is not only

clinically wise but economically beneficial, as reoperations are more hazardous and costly.

The study's approach demonstrated clear economic advantages. By reducing the duration of preoperative medical treatment, patients spent less time on expensive medications and frequent monitoring. Many toxic goiter patients on long-term drug therapy require repeated doctor visits, lab tests, and often hospital admissions if complications arise. In this study, once the decision for surgery was made, preoperative optimization (especially with plasmapheresis in severe cases) was accomplished in days rather than months. This significantly cut down the preoperative hospitalization time – traditionally, patients might be hospitalized for weeks to stabilize a severe thyrotoxicosis medically, but with plasmapheresis the hospital stay before surgery was much shorter. Shorter pre-op and post-op stays mean lower hospital costs per patient. Additionally, the avoidance of prolonged conservative therapy preempted the costs associated with managing drug side effects (for example, treating agranulocytosis or liver injury from antithyroid drugs can be very costly).

The definitive surgical cure achieved in most patients also translated to economic efficiency. Once successfully operated, patients no longer needed continuous antithyroid medications or beta-blockers, and they could return to work and normal life sooner. The low recurrence rate ($\approx 5\%$) meant that very few patients needed a second treatment course or repeat surgery. In contrast, a less aggressive initial approach (e.g. limited surgery or trying to continue medication for too long) could lead to relapse requiring another hospitalization and operation, effectively doubling the cost and risk. By preventing recurrences, the strategy saved the patients and health system the significant expenses of reoperations and additional therapy. Moreover, the improved surgical technique reduced complication rates; avoiding complications like bilateral vocal cord paralysis or permanent hypoparathyroidism not only spares patients suffering but also avoids the long-term healthcare costs (such as lifelong calcium supplementation or voice rehabilitation) that come with such complications.

Although a precise cost-benefit calculation is not detailed in this summary, it is evident that the “clinico-morphological” approach provided a high-value outcome – patients achieved remission of thyrotoxicosis with one well-timed intervention, incurring one-time treatment costs, rather than incurring ongoing costs of chronic therapy or multiple procedures. The use of plasmapheresis does add an upfront cost, but this is offset by the reduction in hospital days and the avoidance of intensive care management of thyroid storm or prolonged drug therapy. Thus, from a health economics perspective, the approach improved not only medical outcomes but also optimized resource utilization.

These findings align with and build upon previous literature in the field. The high female predominance and peak age range in our series mirror known epidemiology of Graves' disease and toxic nodular goiter. The challenges of long-term antithyroid drug therapy – such as high recurrence rates after drug withdrawal

and adverse effects – have been documented in prior studies, supporting our decision to limit conservative treatment duration. The efficacy of plasmapheresis in severe hyperthyroidism has been reported by other authors as well, as a means to rapidly reduce thyroid hormone levels when conventional therapy is insufficient or contraindicated. Our results strongly support those reports: we observed clear clinical stabilization and safer anesthesia induction after plasmapheresis in severe cases.

Surgically, there has been debate about performing total thyroidectomy vs subtotal resection for diffuse toxic goiter. Total thyroidectomy guarantees no recurrence of hyperthyroidism but causes definite hypothyroidism and carries risk of complications; subtotal aims to leave a small remnant to possibly maintain some thyroid function, but runs the risk of relapse. The approach in this study – a very limited subtotal (leaving only a tiny remnant) – functionally is close to a near-total thyroidectomy and indeed resulted in a low recurrence rate (~5%). Some patients did retain enough thyroid tissue to avoid full dependency on hormone pills (as indicated by those who remained euthyroid without significant hypothyroid symptoms). Our conclusion that subtotal subfascial resection is the optimal surgical method for toxic goiter is supported by the outcomes: it achieved a balance of minimal recurrence with acceptable rates of hypothyroidism. It's worth noting that subsequent research (including Starostina et al., 2014) likewise found that an almost-total removal yields the best results in terms of preventing recurrence and that modern management of resultant hypothyroidism (through hormone replacement) is safe and effective.

The importance of intraoperative morphological assessment (inspection and palpation of the thyroid tissue) highlighted in this work cannot be overstated. Imaging and needle biopsy have limitations in diffuse toxic goiter – tiny autonomous nodules can escape detection. By performing a direct examination of the thyroid's internal structure during surgery, the surgeon becomes the “diagnostician” to some extent, ensuring no suspect tissue is left. This practice has likely contributed to the low incidence of recurrence we observed and is an approach that can be adopted widely with proper training.

Finally, the study clearly demonstrates that improving clinical outcomes often goes hand-in-hand with improving economic outcomes. By addressing the problem comprehensively – medically stabilizing the patient and executing a definitive surgical cure – we not only improved patient health but also reduced the iterative costs of ongoing care. This clinico-morphological approach is economically efficient because resources are invested upfront in achieving cure (e.g., plasmapheresis, skilled surgery), rather than expended over time on suboptimal therapies or treating avoidable complications. This aligns with broader healthcare principles that favor cost-effectiveness through definitive management of diseases.

In summary, the results validate the initial hypothesis: an optimized treatment algorithm for toxic goiter that integrates clinical management with morphological findings leads to superior outcomes. Patients benefit from fewer complications and

relapses, and healthcare systems benefit from reduced long-term costs. This study's insights contribute to the evolving standards of care for toxic goiter, suggesting that timely surgery with proper preparation is both medically and economically the prudent course for many patients.

Conclusions

1. In an experimental hyperthyroidism model, ligation of the thyroid arteries produced clear morphofunctional changes in the thyroid gland indicative of suppressed function (reduced hormonal activity) accompanied by compensatory increased vascularization of the thyroid parenchyma. This finding provides a morphological justification for interventions aimed at reducing thyroid blood flow in order to control severe thyrotoxicosis.

2. Extended conservative therapy in patients with toxic goiter was shown to be counterproductive, as it significantly increases the incidence of drug-related complications (e.g. adverse reactions to antithyroid medications). These complications not only can endanger the patient's health but also make subsequent surgical treatment more difficult. Therefore, lengthy medication-only management should be avoided in favor of more definitive therapy once appropriate.

3. For patients with toxic forms of goiter, the primary surgical procedure of choice is a subtotal subfascial resection of the thyroid gland. This technique – removing nearly all of the thyroid tissue while leaving only a minimal remnant under the fascia – effectively resolves thyrotoxicosis in the vast majority of cases while minimizing operative risk. It should be performed with careful attention to hemostasis and nerve preservation.

4. Based on the morphological examination of resected tissue, it was found that in diffuse and mixed toxic goiter, 40.7% of patients had additional small nodules in the thyroid that were not detected by preoperative diagnostic methods. Therefore, in cases of a unilateral toxic adenoma, after performing a hemithyroidectomy on the affected side, a thorough exploration of the contralateral lobe is indicated to look for occult nodules. If any small nodular lesions are found, they should be removed (with the resection extent adjusted accordingly). Implementing this strategy ensures that no hyperactive tissue is missed, markedly reducing the risk of persistent or recurrent goiter.

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