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Surgical strategies in the management of thyroid cancer: Approach, complications

Estrategias quirúrgicas en el tratamiento del cáncer de tiroides: Abordaje, complicaciones

Estratégias cirúrgicas no tratamento do cancro da tiroide: Abordagem, complicações

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ABSTRACT

Thyroid cancer is a type of cancer that originates in the thyroid gland, a small butterfly-shaped gland located in the front of the neck. 1 The thyroid gland produces hormones that 2 control the body's metabolism. 3 An exhaustive literature review was conducted on surgical strategies in the management of thyroid cancer, covering approach, complications, and long-term outcomes. Databases such as PubMed, Scopus, and Web of Science were consulted, using key terms such as "thyroid cancer", "surgery", "thyroidectomy", "complications", and "long-term outcomes". 4 Original studies, systematic reviews, and meta-analyses published in recent years were selected, prioritizing those with the highest methodological quality and clinical relevance. The treatment and follow-up of thyroid cancer have advanced considerably in recent decades, offering patients safer and more effective treatment options, as well as personalized follow-up strategies to ensure early detection of recurrences and improve long-term outcomes.

Keywords: Thyroid cancer, Surgery, Thyroidectomy, Complications, Long-term outcomes.

RESUMEN

El cáncer de tiroides es un tipo de cáncer que se origina en la glándula tiroides, una glándula pequeña con forma de mariposa ubicada en la parte frontal del cuello. La glándula tiroides produce hormonas que controlan el metabolismo del cuerpo. Se realizó una revisión bibliográfica exhaustiva sobre estrategias quirúrgicas en el manejo del cáncer de tiroides, abarcando abordaje, complicaciones y resultados a largo plazo. Se consultaron bases de datos como PubMed, Scopus y Web of Science, utilizando términos clave como "cáncer de tiroides", "cirugía", "tiroidectomía", "complicaciones" y "resultados a largo plazo". Se seleccionaron estudios originales, revisiones sistemáticas y metaanálisis publicados en los últimos años, priorizando aquellos con mayor calidad metodológica y relevancia clínica. El tratamiento y seguimiento del cáncer de tiroides han avanzado considerablemente en las últimas décadas, ofreciendo a las pacientes opciones de tratamiento más seguras y efectivas, así como estrategias de seguimiento personalizadas para garantizar la detección temprana de recurrencias y mejorar los resultados a largo plazo.

Palabras clave: Cáncer de tiroides, Cirugía, Tiroidectomía, Complicaciones, Resultados a largo plazo.

RESUMO

O cancro da tiroide é um tipo de cancro que tem origem na glândula tiroide, uma pequena glândula em forma de borboleta localizada na parte da frente do pescoço. A glândula tiroide produz hormonas que controlam o metabolismo do corpo. Foi realizada uma revisão exaustiva da literatura sobre estratégias cirúrgicas no tratamento do cancro da tiroide, abrangendo a abordagem, as complicações e os resultados a longo prazo. Foram consultadas bases de dados como PubMed, Scopus e Web of Science, utilizando termos-chave como “thyroid cancer”, “surgery”, “thyroidectomy”, “complications” e “long-term outcomes”. Foram selecionados estudos originais, revisões sistemáticas e meta-análises publicados nos últimos anos, dando prioridade aos que apresentavam maior qualidade metodológica e relevância clínica. O tratamento e o seguimento do cancro da tiroide avançaram consideravelmente nas últimas décadas, oferecendo aos doentes opções de tratamento mais seguras e eficazes, bem como estratégias de seguimento personalizadas para garantir a deteção precoce de recidivas e melhorar os resultados a longo prazo.

Palavras-chave: Cancro da tiroide, Cirurgia, Tireoidectomia, Complicações, Resultados a longo prazo.

Introduction

Thyroid cancer is the most frequent malignancy of the endocrine system and for decades represented the fastest-growing cancer worldwide. In particular, the increase in incidence over the past 30 years has been almost entirely due to the increased diagnosis of well-differentiated thyroid cancer (WDTC). Despite the significant increase in incidence, the associated mortality has remained stable, suggesting that these small tumors do not have relevance for patient survival, considering that there is a true 'epidemic of overdiagnosis' that does not reflect a real increase in the incidence of the disease and does not contribute to reducing mortality. Furthermore, researchers from various countries affirm that this overdiagnosis has led to overtreatment that produces more harm than benefit (1).

According to the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO), thyroid cancer ranks tenth in the list of the most frequent tumors worldwide. In 2020, the age-standardized incidence rate worldwide, according to this registry, was 6.6 cases per 100,000 inhabitants. In Spain, it reached slightly higher values, 7.4 cases per 100,000 (2). In Latin America, it is estimated that 9 out of 100,000 people per year are diagnosed with this pathology, affecting women to a greater degree, although with a low mortality rate, with Ecuador, Brazil, Costa Rica, and Colombia being the countries with the highest rates in the region, obtaining the following figures: in Ecuador 0.016% per 100,000 inhabitants, Brazil (0.014%), Costa Rica (0.012%), and Colombia (0.011%). In Ecuador, according to the Society for the Fight against Cancer (SOLCA), the cities with the highest incidence of cases are Quito, Cuenca, Loja, Guayaquil, Manabí, and El Oro, with differentiated thyroid cancer (DTC), which includes papillary and follicular carcinoma, accounting for more than 90% of cases (3).

In general, differentiated thyroid cancer has a good prognosis, but locoregional recurrences have been found in up to 30% of cases, with involvement of the lateral neck compartment in more than 50% of cases, while relapses in the central compartment are less than 30% (4).

The management of low-risk differentiated thyroid cancer (DTC) continues to be a matter of controversy given its indolent nature and the difficulty in achieving an adequate balance between treatment morbidity and the risk of disease progression. Over the past decades, better understanding of thyroid cancer biology, as well as classification according to recurrence risk, have guided management towards more conservative and personalized therapeutic options (5).

Methods

An exhaustive literature review was conducted on surgical strategies in the management of thyroid cancer, covering approaches, complications, and long-term outcomes. Databases such as PubMed, Scopus, and Web of Science were consulted, using key terms such as 'thyroid cancer,' 'surgery,' 'thyroidectomy,' 'complications,' and 'long-term outcomes.' Original studies, systematic reviews, and meta-analyses published in recent years were selected, prioritizing those with higher methodological quality and clinical relevance. The different surgical techniques employed were analyzed, as well as their impact on disease control and patient quality of life. Complications associated with surgery were evaluated, risk factors and prevention strategies were analyzed. Long-term outcomes in terms of survival, recurrence, and metastasis were examined, and prognostic factors and follow-up strategies were identified

Results

The main histological types of thyroid cancer

Tabla 1. Thyroid Cancer Classification Variants 1953, 1992, and 2004

Classification	1953	1992	2004
Benign	Follicular adenoma Papillary cystadenoma	Follicular adenoma (Conventional and variants)	Follicular adenoma (Multiple variants) Hyalinizing trabecular tumor
Differentiated Malignant	Follicular carcinoma Papillary carcinoma	Follicular carcinoma Papillary carcinoma (Conventional and variants)	Papillary carcinoma (Multiple variants) Follicular carcinoma (Minimally invasive and widely invasive)
Poorly Differentiated Malignant		Insular carcinoma (Others)	Poorly differentiated carcinoma
Undifferentiated Malignant	Anaplastic carcinoma	Anaplastic carcinoma	Anaplastic carcinoma

Fuente: Adapted from Asa (6).

The classification of thyroid cancers has evolved significantly over the last century. Initially, in 1953, benign and malignant tumors were distinguished, each with papillary and follicular variants based on their architecture. However, the discovery of metastases in non-invasive papillary tumors led to questioning the existence of benign papillary adenomas. The classification was further complicated by the presence of follicular areas in papillary carcinomas, giving rise to the category of 'mixed' carcinomas. Subsequently, the importance of nuclear characteristics, such as nuclear enlargement and clearing, in the diagnosis of papillary carcinomas was recognized, leading to the reclassification of follicular tumors as variants of papillary carcinoma. Additionally, new variants of papillary carcinomas with more aggressive behavior, such as tall cell and columnar cell carcinomas, were identified, as well as the concept of progressive dedifferentiation in thyroid carcinoma. In 2004, the WHO classified all tumors with 'distinctive nuclear features' as variants of papillary carcinoma, leaving aside architecture and invasion as the main classification criteria (6).

Surgical Indications and Approach Selection

The management of differentiated thyroid carcinoma (i.e., papillary, follicular, Hürthle cell) can be challenging, as until recently, few prospective randomized treatment trials had been conducted. Most treatment information comes from large patient cohort studies where treatment has not been randomly assigned. This accounts for much of the disagreement regarding differentiated carcinoma management. Nevertheless, most patients can be cured of this disease when treated appropriately by experienced physicians and surgeons. The treatment of choice is surgery, followed by radioiodine ablation (RAI) (iodine-131) in selected patients and thyroxine therapy in most patients. Before surgery, imaging studies are performed to determine the extent of the disease and aid in the surgical decision-making process. A cervical ultrasound, including the thyroid and central and lateral compartments, is recommended as the primary imaging modality (7).

Minimally invasive video-assisted thyroidectomy (MIVAT), originally described by Miccoli et al. in the late 1990s, has proven to

be a safe procedure with potential advantages in aesthetic and postoperative outcomes compared to the conventional procedure, including shorter scar length, better aesthetics, and reduced pain. Although descriptions of this procedure date back more than 20 years, it remains one of the preferred endoscopic techniques for thyroid gland removal. Furthermore, over the past decade, an impressive number of different remote access approaches (Robot-assisted transaxillary thyroidectomy (RATT), Transoral endoscopic thyroidectomy vestibular approach (TOETVA)) have been described as methods to remove the thyroid gland while avoiding a neck scar. These techniques have been developed to potentially provide a more aesthetically pleasing outcome for some patients and have often resulted as an expression of different habits and expectations of patients from different geographical regions and cultures. However, although initially met with skepticism due to technical challenges, the introduction of new complications, and concerns about oncological safety and cost, some of them have been progressively more widely adopted by the endocrine surgeon community (8).

One of the challenges in determining the optimal surgical approach for patients with thyroid cancer is that these patients live for many years and rarely die from their disease. However, recurrences can be a problem for these patients, and due to the indolent nature of their disease, they can occur up to 20 years after the initial diagnosis. Because of these issues, the final effects of changes in our management may not be clinically evident for 10 to 20 years. An additional feature that complicates surgical clinical trials is that permanent complications after thyroid surgery are rare (9).

Minimally Invasive Video-Assisted Thyroidectomy (MIVAT)

Since its introduction in the late 1990s, minimally invasive video-assisted thyroidectomy (MIVAT) has been adopted worldwide due to its reproducibility and results comparable to the conventional open approach. This minimally invasive technique allows surgeons to perform thyroidectomies safely and offers the typical advantages of endoscopic surgery, including magnified vision, better aesthetic outcomes, and reduced postoperative pain. Although initially introduced for small benign thyroid nodules, its use has been extended to the treatment of thyroid cancer, demonstrating its feasibility and safety even in these patients. Ideal candidates for MIVAT are patients with a thyroid volume estimated by ultrasound not exceeding 25 ml and nodules smaller than 35 mm. Absolute contraindications include large multinodular goiters, previous neck surgery or irradiation, locally invasive carcinoma, and lateral compartment lymph node metastases. The presence of enlarged lymph nodes in the central compartment is not necessarily a contraindication, although caution is recommended. Thyroiditis, adverse anatomical aspects, and hypervascularization of the thyroid gland represent relative contraindications (8).

Robot-Assisted Transaxillary Thyroidectomy (RATT)

Robot-assisted transaxillary thyroidectomy (RATT) emerged as an alternative to avoid neck scars after thyroid surgery. Although endoscopic thyroidectomy initially presented limitations, the introduction of surgical robots, such as the da Vinci system, offered technical improvements like magnified 3D vision and increased freedom of movement. RATT, popularized by Chung et al., became widespread in East Asian countries, possibly influenced by cultural factors, although its adoption in Europe and America has been slower due to anthropometric differences, costs, and the need for training. Currently, RATT is considered an option for benign pathologies and low-risk differentiated thyroid carcinomas, with specific indications and contraindications. While potential complications such as brachial plexus injuries have been described, they are rare (8).

Various studies have demonstrated equivalent oncological outcomes between RATT and conventional thyroidectomy in terms of completeness and recurrence rate. RATT has been proven safe and effective even in more advanced cases of thyroid cancer, including those with adjacent muscle invasion or perinodal infiltration, and allows for precise lymph node resection. Although RATT presents aesthetic advantages and is considered a valid alternative to conventional thyroidectomy in selected patients, especially those concerned about scarring, there are limitations such as the lack of haptic feedback, operative time, and costs (8).

Transoral Endoscopic Thyroidectomy Vestibular Approach (TOETVA)

This is the only technique that allows for a scarless thyroidectomy. Although various TOET techniques exist, TOETVA is the most widely used due to its surgical outcomes and low complication rate. This NOTES (natural orifice transluminal endoscopic surgery) procedure is performed through three small incisions in the lower lip vestibule, creating a pre-mandibular space and dissecting under direct vision and CO2 insufflation. Unlike other endoscopic techniques, TOETVA offers an excellent view of the surgical field and access to both sides of the central neck, although the identification and dissection of the recurrent laryngeal nerve, which often divides into multiple branches, requires a top-down approach, which can be risky (8).

Eligibility criteria for TOETVA include a thyroid gland no more than 10 cm in diameter, encompassing benign thyroid nodules, papillary microcarcinoma without evidence of metastasis, follicular neoplasm, or well-controlled Graves' disease. It can be safely performed in patients with previous surgery or radiation in the chin and neck area. Some studies suggest that TOETVA may be safe and effective in cases of low-risk thyroid carcinoma up to 2 cm in diameter, although other authors recommend limiting its use to malignant tumors less than 2 cm. While acceptable oncological outcomes and complication rates comparable to conventional thyroidectomy have been reported, more long-term studies are needed to evaluate the oncological validity and safety of this approach, especially regarding oncological integrity and technical feasibility (8).

Immediate and Long-Term Complications

Complications of thyroidectomy are well-known and consist of transient or permanent hypocalcemia, transient or permanent recurrent laryngeal nerve injury, and neck hematoma. The rate of permanent complications is well-established, and in expert hands, should be less than 2-3%. Probably more important than the extent of surgery, however, is the surgeon's experience. Although many highly experienced surgeons have published very low complication rates after total thyroidectomy, those results should not be extrapolated to most surgeons performing thyroid surgery who do fewer than 20 cases per year. Sosa et al. published the first data on thyroid surgery complications in relation to surgeon case volume. He found that high-volume surgeons (defined as those performing >100 cases/5 years) had 75% fewer complications than low-volume surgeons (4.3% vs. 16.1%). This was confirmed in another study by Stavrakis in 2007, which showed that the complication rate of thyroidectomy, when performed by experienced surgeons (>50 cases/year), was 1.6%, but the complication rate increased to 4.3% if the surgeon did fewer than 10 cases per year and to 7.2% if the surgeon did fewer than 5 cases per year (9).

The most common significant complications of thyroidectomy are hypoparathyroidism and recurrent laryngeal nerve injury, which occur more frequently after total thyroidectomy. Postoperative transient clinical hypoparathyroidism is common in adults and children undergoing total thyroidectomy. One study reported hypocalcemia in 5.4% of patients immediately after total thyroidectomy, which persisted in only 0.5% of

patients 1 year later. Another study reported a 3.4% incidence of long-term recurrent laryngeal nerve injury and a 1.1% incidence of permanent hypocalcemia. Superior laryngeal nerve injury is underreported and negatively impacts voice projection and high-pitch range. When experienced surgeons perform thyroidectomies, complications occur at a lower rate. A study of 5,860 patients found that surgeons performing more than 100 thyroidectomies per year had the lowest overall complication rate (4.3%), while surgeons performing fewer than 10 thyroidectomies per year had 4 times more complications (7).

Follow-up and Long-Term Outcomes

Use of Thyroglobulin and Cervical Ultrasound in Post-Surgical Surveillance

The American Thyroid Association defines disease-free survival as the absence of tumor evidence, either clinically or on imaging, and undetectable thyroglobulin (Tg) levels during thyroid-stimulating hormone (TSH) suppression or stimulation. Guidelines for surveillance include a regular physical examination and serial serum Tg levels, as well as a cervical lymph node mapping (LNM) ultrasound performed 6-12 months after thyroidectomy and subsequently (10).

Although serum Tg monitoring is the cornerstone of surveillance, it is not always straightforward due to variations in different assays and the presence of serum anti-Tg antibodies. High-resolution cervical LNM ultrasound has become an important diagnostic tool for evaluating locoregional recurrence of papillary thyroid cancer (PTC). The reported sensitivity for LNM ultrasound in detecting cervical disease ranges from 70 to 100%. Suspicious characteristics of cervical chain lymph nodes on LNM ultrasound include enlarged nodes, loss of fatty hilum, architectural distortion, the presence of microcalcifications, and peripheral hypervascularity (10).

Radioactive Iodine Therapy: When Is It Indicated

It is particularly useful for differentiated, recurrent, or metastatic thyroid cancer because they represent the majority of thyroid cancers and are associated with a 10-year survival rate of between 90% and 95%. This survival rate suggests the need for long-term surveillance and recurrence testing. Although it has been used primarily as adjuvant therapy (11). Traditionally, RAI treatment has been used in all patients with differentiated thyroid cancer (DTC) to ablate residual thyroid tissue and to eradicate possible residual cancer postoperatively, thereby decreasing the long-term risk of recurrent disease. It should not be used in patients with anaplastic thyroid cancer (ATC), even if they have DTC in addition to ATC in the pathology. It can also be used to identify and treat patients with RAI-sensitive distant metastatic disease (11).

Radioactive iodine (RAI) therapy, specifically with iodine-131 (I-131), is a common treatment for hyperthyroidism and some malignant thyroid neoplasms, such as thyroid cancer. However, radiation exposure, including I-131 therapy, has been associated with the development of primary hyperparathyroidism (PHPT), suggesting a mutagenic effect. I-131 is absorbed by thyroid cells through iodine transporters, where it causes cell destruction through beta decay, the range of which can also affect nearby parathyroid glands, increasing the possibility of adverse effects (12).

Studies have indicated that RAI treatment can lead to an increase in parathyroid hormone (PTH) levels and increase the long-term risk of parathyroid adenomas. However, research on how RAI influences the clinical and laboratory variability of PHPT has shown mixed results. Given the continued use of RAI in thyroid pathologies, understanding its impact on the clinical presentation and treatment outcomes of PHPT is crucial, and this study aims to explore this relationship in depth (12).

Need for Levothyroxine Replacement Therapy

Levothyroxine is currently the most widely used formulation for the treatment of hypothyroidism worldwide. It is a safe and effective drug for restoring euthyroid status in most patients with hypothyroidism, including children with congenital hypothyroidism. However, in adult endocrinology, it has been shown that there is a form of 'resistance' to exogenous thyroid hormone (RHTE, or RETH for its acronym in English) in 5-10% of the hypothyroid population, particularly in patients undergoing thyroidectomy. Despite correct adherence to levothyroxine treatment, affected patients persistently complain of symptoms such as lethargy, concentration deficit, anxiety, and nervousness, which are summarized in a state of physical and psychological malaise (13).

The indicated treatment in DTC includes total thyroidectomy completed with an ablative dose of radioactive iodine. Subsequently, based on the risk of recurrence, a replacement (very low-risk patients) or suppressive dose of oral levothyroxine is administered. The suppressive dose aims to induce hyperthyroxinemia with pituitary suppression of TSH, which could be a potential stimulus for tumor remnants. Depending on the suppression obtained during hormone treatment, the American Thyroid Association (ATA) has established the following risk groups in levothyroxine treatment: 1) Low-risk group >0.5 mIU/L; 2) Intermediate-risk group: 0.1-0.5 mIU/L; and 3) High-risk group: <0.1 mIU/L. Patients with exogenous treatment (for DTC) as well as those with endogenous hyperthyroidism are subjected to prolonged periods of the effect of thyroid hormones on bone. Currently, many aspects related to bone loss that this therapy can cause, either directly or by suppressing the pituitary-thyroid axis, are becoming known. Levothyroxine treatment in DTC is based on giving doses that suppress serum TSH levels below the normal range, causing a state similar to subclinical hyperthyroidism (14).

Recurrence Rates and Prognosis by Histological Type and Treatment Performed

Following the initial treatment of patients with thyroid cancer, it is essential to evaluate all relevant data, including pre- and postoperative information, to stratify the risk of recurrence. The ATA guidelines recommend postoperative ultrasounds, whole-body scans, and serum thyroglobulin (Tg) measurements, along with molecular analyses such as TERT mutation, to classify patients into low, intermediate, or high risk, thus allowing for appropriate follow-up that is modified according to the patient's evolution (11).

Follow-up varies according to the risk level. Low-risk patients have reviews every 6-12 months with a TSH target between 0.5 and 1.5 mIU/L. For those at intermediate risk, follow-ups are performed every 6 months with a TSH target of 0.1 to 0.5 mIU/L and are evaluated with scans if Tg rises. High-risk patients require more intensive follow-up every 3 months, with a TSH target of 0.1 mIU/L and more diagnostic tests. During follow-up, responses are categorized as excellent, incomplete biochemical, incomplete structural, or indeterminate, which determines the next course of action, including possible additional therapies and decisions on localized treatments for progressive disease, always considering the risks and benefits together with the patient (11).

Brassard et al (15) conducted a prospective study that evaluated the recurrence rate in 715 patients with differentiated thyroid cancer who had no evidence of persistent disease after total thyroidectomy and lymph node dissection in 94% of them, followed 1 by radioiodine ablation (30–100 mCi), and assessed the predictive value of initial thyroglobulin (Tg) levels to detect recurrence, both during levothyroxine (LT4) treatment and after TSH stimulation.

Of the 32 recurrences, 17 occurred within the first 2 years and 29 during the first 5 years. Both median Tg1 and Tg2 were lower in patients with neck recurrences than in those

with recurrence in distant sites, and this is probably related to the lower disease burden in patients with neck recurrence. This indicates that even low levels of serum Tg should be taken into account and that a neck ultrasound should be performed in all patients, according to guidelines. The vast majority (84%) of patients had a Tg1 of 0.27 ng/ml or less, and TSH stimulation did not increase the negative predictive value of Tg determination on recurrence risk, which was 99% in both conditions. Therefore, TSH-stimulated Tg determination can be avoided in patients with Tg1 less than 0.27 ng/ml, and this would result in lower follow-up costs (15).

Conclusión

Thyroid cancer has undergone a significant evolution in its classification over time, which has influenced treatment and follow-up strategies. Surgery, followed by radioactive iodine ablation and thyroxine therapy, stands as the treatment of choice for most patients with differentiated thyroid cancer.

Minimally invasive video-assisted thyroidectomy (MIVAT) has gained popularity thanks to its aesthetic advantages and results comparable to conventional surgery. Other techniques such as robot-assisted transaxillary thyroidectomy (RATT) and transoral endoscopic thyroidectomy vestibular approach (TOETVA) offer innovative options to avoid neck scars, although their adoption and study continue to develop.

Post-surgical follow-up of thyroid cancer is essential to detect recurrences and ensure treatment success. Serum thyroglobulin (Tg) measurement and cervical ultrasound have become established as essential tools in this process, allowing for comprehensive and personalized surveillance for each patient.

Radioactive iodine (RAI) therapy is used in specific cases of differentiated thyroid cancer, especially those with a risk of recurrence or metastasis. However, its use must be carefully considered due to possible adverse effects, such as primary hyperparathyroidism.

Levothyroxine replacement therapy is essential for patients with hypothyroidism, including those with thyroid cancer who have undergone thyroidectomy. The levothyroxine dose must be individually adjusted to achieve optimal TSH levels and avoid both hypothyroidism and subclinical hyperthyroidism.

Regarding recurrence rates, studies have shown that most recurrences occur within the first 5 years after initial treatment. Continuous follow-up and evaluation of Tg levels are crucial to detect any signs of recurrence and take timely action.

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