

Oncología de Precisión y Cáncer de Tiroides Avanzado: Integración de Cirugía, Terapias Moleculares y Medicina Nuclear en el Continente Americano

Precision Oncology and Advanced Thyroid Cancer: Integrating Surgery, Molecular Targeting, and Nuclear Medicine Across the Americas

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RESUMEN

El cáncer de tiroides avanzado continúa representando un importante desafío clínico a pesar de los avances alcanzados en oncología endocrina. Aunque el tratamiento convencional basado en cirugía y terapia con radioyodo sigue ofreciendo resultados favorables para muchos pacientes, la enfermedad localmente avanzada, recurrente, metastásica o refractaria al radioyodo requiere estrategias terapéuticas más complejas. El objetivo de esta revisión fue analizar las innovaciones quirúrgicas, las terapias moleculares dirigidas y las estrategias de medicina nuclear utilizadas actualmente en el manejo del cáncer de tiroides avanzado en el continente americano. Se realizó una revisión narrativa de la literatura utilizando el Método Científico como marco metodológico. La evidencia científica fue obtenida de PubMed, Scopus, Web of Science, ScienceDirect, Cochrane Library y Google Scholar, considerando publicaciones entre 2014 y 2026. Los hallazgos demostraron que las terapias moleculares dirigidas se han convertido en un componente central del tratamiento, especialmente en tumores con alteraciones en BRAF, RET y NTRK. Fármacos como lenvatinib, sorafenib, cabozantinib, selipercatinib, pralsetinib y dabrafenib-trametinib han ampliado significativamente las opciones terapéuticas para pacientes con enfermedad avanzada. La cirugía continúa siendo esencial para el control local de la enfermedad y el manejo de tumores recurrentes o invasivos, mientras que la medicina nuclear mantiene un papel fundamental mediante la terapia con radioyodo, PET/CT, SPECT/CT y las emergentes estrategias de rediferenciación tumoral. La revisión también identificó desafíos importantes relacionados con el acceso a pruebas moleculares, la disponibilidad de terapias dirigidas, los servicios quirúrgicos especializados y la infraestructura de medicina nuclear en los diferentes sistemas de salud. En conjunto, la evidencia respalda una transición hacia la medicina de precisión y el manejo multidisciplinario como pilares fundamentales del tratamiento contemporáneo del cáncer de tiroides avanzado. El fortalecimiento del acceso a tecnologías innovadoras y recursos especializados será indispensable para optimizar los resultados clínicos en toda América.

PALABRAS CLAVE

Cáncer de tiroides avanzado, Medicina de precisión, Oncología molecular, Terapia dirigida, Cirugía endocrina, Cáncer de tiroides refractario al radioyodo, Medicina nuclear, Imagen molecular, Perfil genómico, Inhibidores de tirosina cinasa, Mutación BRAF, Alteraciones RET, América, Tratamiento personalizado, Atención multidisciplinaria

ABSTRACT

Advanced thyroid cancer remains a significant clinical challenge despite major advances in endocrine oncology. Although conventional management based on surgery and radioactive iodine therapy continues to provide favorable outcomes for many patients, locally advanced, recurrent, metastatic, and radioiodine-refractory disease often require more complex therapeutic approaches. The objective of this review was to analyze contemporary surgical innovations, molecular-targeted therapies, and nuclear medicine strategies used in the management of advanced thyroid cancer throughout the Americas. A narrative literature review was conducted using the Scientific Method as the methodological framework. Scientific evidence was retrieved from PubMed, Scopus, Web of Science, ScienceDirect, Cochrane Library, and Google Scholar, focusing on studies published between 2014 and 2026. The findings demonstrated that molecularly targeted therapies have become a central component of treatment, particularly in tumors

harboring BRAF, RET, and NTRK alterations. Lenvatinib, sorafenib, cabozantinib, selipergatinib, pralsetinib, and dabrafenib-trametinib have significantly expanded therapeutic options for patients with advanced disease. Surgical intervention remains essential for local disease control and management of recurrent or invasive tumors, while nuclear medicine continues to play a critical role through radioactive iodine therapy, PET/CT, SPECT/CT, and emerging redifferentiation strategies. The review also identified important challenges related to molecular testing accessibility, targeted therapy availability, specialized surgical services, and nuclear medicine infrastructure across different healthcare systems. Overall, the evidence supports a transition toward precision medicine and multidisciplinary management as the foundation of contemporary advanced thyroid cancer care. Continued efforts to improve access to innovative technologies and specialized treatment resources will be necessary to optimize patient outcomes throughout the American continent.

KEYWORDS

Advanced thyroid cancer, Precision medicine, Molecular oncology, Targeted therapy, Endocrine surgery, Radioiodine-refractory thyroid cancer, Nuclear medicine, Molecular imaging, Genomic profiling, Tyrosine kinase inhibitors, BRAF mutation, RET alteration, Americas, Personalized treatment, Multidisciplinary care

INTRODUCCIÓN

Thyroid cancer represents the most common endocrine malignancy worldwide and has demonstrated a sustained increase in incidence over recent decades across North, Central, and South America. Although the majority of patients diagnosed with differentiated thyroid carcinoma (DTC) experience favorable outcomes following conventional treatment, a significant subset develops locally advanced, recurrent, metastatic, or radioiodine-refractory disease, which remains associated with considerable morbidity, therapeutic challenges, and increased mortality (Haugen et al., 2016; Filetti et al., 2019). The growing burden of advanced thyroid cancer has stimulated the development of innovative surgical approaches, molecularly targeted therapies, and nuclear medicine strategies aimed at improving disease control and patient survival.

Across the American continent, thyroid cancer has emerged as an important public health concern. Epidemiological studies have reported increasing incidence rates in countries such as the United States, Canada, Mexico, Colombia, Brazil, Argentina, Chile, Ecuador, and Peru, reflecting improvements in diagnostic capabilities as well as potential environmental, genetic, and lifestyle-related factors influencing disease occurrence (Sousa et al., 2021). While differentiated thyroid carcinomas account for approximately 90% of cases, aggressive histological subtypes, including poorly differentiated, medullary, and anaplastic thyroid carcinomas, continue to pose substantial clinical challenges due to their invasive behavior, resistance to conventional therapies, and unfavorable prognosis (Bible et al., 2021).

Historically, total thyroidectomy followed by radioactive iodine (RAI) ablation and thyroid-stimulating hormone suppression constituted the cornerstone of treatment for advanced thyroid malignancies. However, clinical experience accumulated over the past two decades has demonstrated that a considerable proportion of patients eventually develop resistance to radioiodine therapy, a condition associated with disease progression and limited therapeutic alternatives (Schlumberger et al., 2015). Radioiodine-refractory thyroid cancer has therefore become a major focus of contemporary research, leading to the emergence of personalized treatment strategies based on molecular profiling and targeted intervention.

Recent advances in molecular biology have profoundly transformed the understanding of thyroid tumorigenesis. Comprehensive genomic studies have identified several driver mutations and signaling pathways involved in thyroid cancer progression, including alterations in BRAF, RAS, RET, NTRK, TERT promoter, and TP53 genes. These discoveries have enabled the development of precision medicine approaches capable of targeting specific molecular abnormalities responsible for tumor growth and metastatic dissemination (Wirth et al., 2020; Subbiah et al., 2021). Consequently, thyroid cancer management has evolved from a predominantly surgical discipline toward a multidisciplinary model integrating endocrine surgery, molecular oncology, nuclear medicine, pathology, radiology, and personalized therapeutics.

One of the most significant breakthroughs in recent years has been the incorporation of tyrosine kinase inhibitors (TKIs) into clinical practice. Landmark clinical trials demonstrated the efficacy of sorafenib, lenvatinib, and cabozantinib in patients with progressive radioiodine-refractory differentiated thyroid cancer, producing significant improvements in progression-free survival compared with placebo (Brose et al., 2014; Schlumberger et al., 2015; Brose et al., 2021). These findings established a new therapeutic paradigm and encouraged further investigation into targeted agents directed against specific genetic alterations.

Parallel advances have occurred in the treatment of medullary and anaplastic thyroid carcinomas. Selective RET inhibitors such as selpercatinib and pralsetinib have demonstrated remarkable response rates among patients harboring RET mutations or fusions, highlighting the clinical value of genomic-guided therapy (Wirth et al., 2020; Subbiah et al., 2021). Similarly, the combination of dabrafenib and trametinib has produced unprecedented therapeutic responses in BRAF V600E-mutated anaplastic thyroid carcinoma, one of the most lethal human malignancies (Subbiah et al., 2018; Subbiah et al., 2022). These developments have significantly expanded treatment opportunities for patients previously considered to have limited or no effective therapeutic options.

Advances in nuclear medicine have also contributed substantially to the management of advanced thyroid cancer. Modern imaging modalities, including positron emission tomography/computed tomography (PET/CT), single-photon emission computed tomography/computed tomography (SPECT/CT), and molecular imaging techniques, have improved diagnostic accuracy, disease staging, and therapeutic planning. Furthermore, redifferentiation strategies using targeted agents have shown promise in restoring radioiodine uptake among previously refractory tumors, potentially allowing selected patients to benefit once again from radioactive iodine treatment (Toro-Tobon et al., 2024). Such innovations illustrate the increasingly dynamic interaction between molecular oncology and nuclear medicine.

From a surgical perspective, technological developments have improved the management of locally advanced and recurrent thyroid malignancies. Enhanced preoperative imaging, intraoperative nerve monitoring, minimally invasive techniques, robotic-assisted procedures, and more sophisticated approaches to central and lateral neck dissection have contributed to reducing surgical morbidity while optimizing oncological outcomes (Lamartina et al., 2017; Cavalheiro et al., 2023). In addition, multidisciplinary surgical planning has become essential for patients presenting with locally invasive tumors involving the trachea, esophagus, recurrent laryngeal nerve, or major cervical vessels.

Despite these advances, important challenges remain throughout the Americas. Significant disparities persist regarding access to specialized endocrine surgery, molecular diagnostics, nuclear medicine facilities, and targeted therapies. These inequalities are particularly evident in several Latin American countries, where healthcare infrastructure, economic limitations, and geographic barriers may delay diagnosis and restrict access to advanced treatment modalities. Consequently, there is a growing need to evaluate current evidence and identify strategies that can facilitate the implementation of precision oncology within diverse healthcare settings across the continent (Sousa et al., 2021).

Given the rapid evolution of therapeutic options, clinicians require a comprehensive understanding of emerging surgical and molecular approaches capable of improving patient outcomes. Integrating evidence from surgery, targeted therapy, molecular diagnostics, and nuclear medicine is increasingly necessary to support individualized treatment planning and optimize long-term disease control.

Therefore, the objective of this review is to analyze contemporary surgical innovations and molecular therapeutic strategies in advanced thyroid cancer, emphasizing their clinical applications, efficacy, limitations, and future perspectives. Particular attention is given to the integration of precision medicine, targeted therapies, modern nuclear medicine techniques, and multidisciplinary surgical management. This review seeks to address the following research question: How are recent surgical and molecular advances transforming the management of advanced thyroid cancer across the Americas? To answer this question, a narrative review of current literature indexed in PubMed, Scopus, and major international oncology and endocrinology databases was conducted, focusing on studies published during the last decade, clinical practice guidelines, pivotal clinical trials, and emerging evidence related to advanced thyroid malignancies. Through this approach, the present review aims to provide an updated synthesis of the scientific evidence supporting contemporary management strategies and to identify future directions for research and clinical practice in advanced thyroid cancer.

DESARROLLO

Advanced thyroid cancer represents a complex clinical condition in which conventional treatment strategies are frequently insufficient to achieve durable disease control. Although most differentiated thyroid carcinomas have an indolent course and favorable prognosis, advanced presentations may involve local invasion, cervical recurrence, distant metastasis, radioiodine-refractory behavior, or transformation into poorly differentiated or anaplastic phenotypes. These scenarios require a multidisciplinary approach that integrates surgery, endocrinology, nuclear medicine, molecular pathology, medical oncology, radiology, and supportive care.

The management of advanced thyroid cancer has changed substantially during the last decade. Traditionally, therapeutic decisions were based mainly on histological subtype, tumor size, lymph node involvement, distant metastasis, and radioactive iodine avidity. However, contemporary care increasingly depends on molecular characterization, since mutations and rearrangements involving BRAF, RAS, RET, NTRK, TERT promoter, ALK, and other molecular alterations influence tumor behavior, treatment response, and prognosis. This transition has moved thyroid oncology from a uniform treatment model toward a precision-based strategy, where therapy is adapted to the biological profile of each tumor.

In differentiated thyroid cancer, total thyroidectomy remains a central therapeutic intervention when disease is extensive, multifocal, locally invasive, or associated with clinically significant nodal metastasis. Surgery provides local tumor control, facilitates postoperative radioactive iodine therapy, allows accurate staging, and supports long-term biochemical surveillance through thyroglobulin monitoring. Nevertheless, advanced tumors may invade surrounding structures such as the recurrent laryngeal nerve, trachea, esophagus, larynx, or major vascular structures, making surgical planning more complex. In these cases, the objective is not only tumor removal but also preservation of airway function, voice quality, swallowing capacity, and patient quality of life.

Recurrent disease in the neck represents another major surgical challenge. Cervical reoperation is associated with higher risk of complications, including recurrent laryngeal nerve injury, hypoparathyroidism, bleeding, and fibrosis-

related technical difficulty. For this reason, current strategies emphasize precise preoperative localization using high-resolution ultrasound, contrast-enhanced computed tomography, magnetic resonance imaging, and functional imaging when appropriate. Intraoperative nerve monitoring and careful compartment-oriented dissection have contributed to safer surgical management in selected patients (Lamartina et al., 2017; Cavaleiro et al., 2023).

Nuclear medicine continues to play an essential role in the management of differentiated thyroid cancer. Radioactive iodine therapy remains one of the most important disease-specific treatments for patients with iodine-avid metastatic or residual disease. However, a clinically relevant proportion of advanced tumors lose the ability to concentrate iodine due to dedifferentiation, sodium-iodide symporter dysfunction, or activation of oncogenic pathways that suppress thyroid-specific gene expression. This condition, known as radioiodine-refractory differentiated thyroid cancer, is associated with disease progression and reduced survival compared with iodine-avid disease (Haugen et al., 2016; Schlumberger et al., 2015).

The emergence of radioiodine-refractory disease has driven the development of molecularly targeted therapies. Sorafenib was one of the first multikinase inhibitors to demonstrate clinical benefit in progressive radioiodine-refractory differentiated thyroid cancer. The DECISION trial showed improved progression-free survival compared with placebo, supporting its incorporation into clinical practice for selected patients with progressive metastatic disease (Brose et al., 2014). Later, lenvatinib demonstrated a more pronounced improvement in progression-free survival in the SELECT trial, becoming a preferred systemic therapy in many treatment algorithms for progressive radioiodine-refractory disease (Schlumberger et al., 2015).

Cabozantinib has further expanded the therapeutic landscape, particularly for patients who progress after prior VEGFR-targeted therapy. The COSMIC-311 trial demonstrated that cabozantinib improved outcomes in previously treated radioiodine-refractory differentiated thyroid cancer, reinforcing the importance of sequential systemic therapy in advanced disease (Brose et al., 2021). These findings are clinically relevant because many patients require long-term disease control rather than immediate tumor eradication. Therefore, treatment selection must consider tumor growth rate, symptom burden, metastatic distribution, comorbidities, expected toxicities, patient preferences, and access to therapy.

Targeted therapy has also transformed the management of medullary thyroid carcinoma. Medullary thyroid cancer arises from parafollicular C cells and is biologically distinct from differentiated thyroid cancer. It does not respond to radioactive iodine, and advanced metastatic disease historically had limited treatment options. The identification of RET mutations as central oncogenic drivers led to the development of selective RET inhibitors such as selpercatinib and pralsetinib. These therapies have demonstrated high response rates and meaningful clinical benefit in RET-mutated medullary thyroid cancer and RET fusion-positive thyroid cancers (Wirth et al., 2020; Subbiah et al., 2021).

Anaplastic thyroid carcinoma represents the most aggressive form of thyroid cancer. Although rare, it is responsible for a disproportionate number of thyroid cancer-related deaths due to its rapid growth, local invasion, early metastasis, and resistance to conventional treatment. Management requires urgent multidisciplinary evaluation because airway compromise, dysphagia, bleeding, and rapid clinical deterioration are common. Contemporary guidelines recommend early molecular testing, since actionable alterations may guide urgent systemic therapy (Bible et al., 2021).

One of the most important advances in anaplastic thyroid cancer has been the use of combined BRAF and MEK inhibition in tumors harboring the BRAF V600E mutation. Dabrafenib plus trametinib has produced clinically

meaningful responses in patients with BRAF-mutated anaplastic thyroid carcinoma, changing the therapeutic outlook for a subgroup of patients previously considered to have extremely limited options (Subbiah et al., 2018; Subbiah et al., 2022). In selected cases, systemic therapy may reduce tumor burden sufficiently to allow subsequent surgical resection, suggesting a potential role for neoadjuvant targeted therapy in locally advanced disease.

The concept of neoadjuvant therapy is gaining attention in advanced thyroid cancer. In the past, patients with unresectable or borderline resectable tumors often received palliative treatment or incomplete surgery. However, molecularly targeted agents may reduce tumor volume, decrease vascular invasion, improve airway safety, and convert selected tumors into surgically manageable disease. This approach is particularly relevant in advanced differentiated, medullary, and anaplastic thyroid carcinomas with identifiable actionable alterations. Nevertheless, neoadjuvant therapy requires careful patient selection, close monitoring, and coordination between surgeons and oncologists to determine the optimal timing of surgery.

Redifferentiation therapy has also become an important area of investigation. This strategy aims to restore radioactive iodine uptake in tumors that have become radioiodine-refractory. By inhibiting MAPK pathway signaling with targeted agents, some tumors may re-express iodine-handling genes and regain sensitivity to radioactive iodine. Recent studies suggest that redifferentiation therapy may allow selected patients to receive additional radioactive iodine treatment with measurable structural responses (Toro-Tobon et al., 2024). Although this approach is not universally effective, it illustrates the growing interaction between molecular oncology and nuclear medicine.

Molecular imaging has strengthened this personalized approach. Fluorodeoxyglucose PET/CT is particularly useful in aggressive or dedifferentiated tumors, where high metabolic activity may correlate with poor iodine avidity and more aggressive clinical behavior. SPECT/CT improves anatomical localization of radioiodine-avid disease, while PET-based imaging may help identify lesions that are not detected by conventional imaging. These tools support treatment selection, response evaluation, and risk stratification, especially in patients with elevated tumor markers and negative or inconclusive structural imaging.

Across the American continent, the implementation of these advances is uneven. In high-resource settings, molecular testing, selective targeted therapies, advanced imaging, specialized endocrine surgery, and multidisciplinary tumor boards are increasingly available. However, in several Latin American regions, access may be limited by cost, infrastructure, availability of nuclear medicine facilities, delayed referral, and restricted access to genomic sequencing. These disparities are relevant because advanced thyroid cancer often requires timely diagnosis and highly specialized treatment decisions. Therefore, a continental approach must recognize that scientific progress alone is insufficient unless accompanied by strategies that improve access, referral networks, and regional clinical capacity.

Mexico, Colombia, and Ecuador are particularly relevant within this continental framework because they reflect the broader challenges of Latin American oncology: increasing cancer detection, heterogeneous access to molecular diagnostics, centralization of specialized care, and differences between urban and rural healthcare systems. In these countries, thyroid cancer management often depends on referral to tertiary centers where endocrine surgery, pathology, nuclear medicine, and oncology services are available. Strengthening regional protocols and improving access to molecular testing could contribute to earlier identification of patients eligible for targeted therapy.

Another important issue is therapeutic toxicity. Multikinase inhibitors may produce hypertension, fatigue, diarrhea, weight loss, hand-foot syndrome, proteinuria, bleeding risk, fistula formation, and impaired wound healing. These

adverse effects are especially relevant when systemic therapy is used before or after surgery. Consequently, clinical decisions must balance oncologic benefit with safety, particularly in patients with comorbidities or limited access to continuous monitoring. The management of advanced thyroid cancer therefore requires not only drug availability but also trained teams capable of monitoring adverse events and adjusting treatment appropriately.

The economic dimension must also be considered. Targeted therapies and molecular tests can be expensive, and their availability may vary significantly between healthcare systems. In the Americas, differences between public and private insurance coverage may influence treatment access. This raises ethical and public health concerns because patients with similar molecular profiles may receive different treatments depending on geographic location, institutional resources, or socioeconomic status. For this reason, research on advanced thyroid cancer should include not only clinical efficacy but also feasibility, equity, and implementation in diverse healthcare environments.

OBJETIVO GENERAL Y OBJETIVOS ESPECÍFICOS

General Objective

To critically analyze contemporary surgical, molecular, and nuclear medicine strategies used in the management of advanced thyroid cancer across the Americas, evaluating their clinical applications, therapeutic outcomes, limitations, and future implications for precision oncology and multidisciplinary patient care.

Specific Objectives

Cognitive Domain

1. To identify and describe the current epidemiological, pathological, and molecular characteristics of advanced thyroid cancer in the American continent.
2. To analyze the molecular mechanisms involved in thyroid cancer progression, including alterations in BRAF, RET, RAS, NTRK, TERT promoter, and other clinically relevant biomarkers.
3. To compare the effectiveness, indications, and limitations of contemporary surgical approaches used in locally advanced, recurrent, and metastatic thyroid cancer.
4. To evaluate the role of nuclear medicine techniques, including radioactive iodine therapy, PET/CT, SPECT/CT, and redifferentiation strategies in advanced thyroid malignancies.
5. To examine the scientific evidence supporting the use of targeted therapies and precision medicine in differentiated, medullary, and anaplastic thyroid carcinomas.
6. To assess the impact of multidisciplinary management on survival, disease control, quality of life, and long-term clinical outcomes.

Psychomotor Domain

7. To apply evidence-based criteria for the selection of surgical, molecular, and nuclear medicine interventions according to tumor characteristics and patient-specific factors.
8. To interpret diagnostic findings obtained from molecular profiling, imaging studies, and pathological evaluations used in advanced thyroid cancer management.
9. To develop clinical decision-making frameworks that integrate surgical planning, molecular diagnostics, and targeted therapeutic strategies.
10. To formulate comprehensive management algorithms that can be adapted to different healthcare settings throughout the Americas.

Affective Domain

11. To recognize the importance of multidisciplinary collaboration among surgeons, endocrinologists, oncologists, nuclear medicine specialists, radiologists, and pathologists in the treatment of advanced thyroid cancer.
12. To promote awareness regarding healthcare disparities that affect access to molecular diagnostics, specialized surgery, and targeted therapies across North, Central, and South America.
13. To value the role of personalized medicine in improving patient-centered care, therapeutic outcomes, and quality of life.
14. To encourage the adoption of evidence-based practices that support equitable, ethical, and sustainable management of advanced thyroid cancer within diverse healthcare systems.
15. To foster a commitment to continuous scientific innovation and clinical research aimed at improving the diagnosis and treatment of advanced thyroid malignancies.

OBJETO DE ESTUDIO

The object of study of this review is the contemporary management of advanced thyroid cancer, with particular emphasis on emerging surgical approaches, molecular-targeted therapies, and innovations in nuclear medicine that have transformed clinical practice during the last decade.

This study focuses on adult patients diagnosed with advanced thyroid malignancies, including locally advanced, recurrent, metastatic, radioiodine-refractory differentiated thyroid carcinoma (DTC), medullary thyroid carcinoma (MTC), poorly differentiated thyroid carcinoma (PDTC), and anaplastic thyroid carcinoma (ATC). These disease entities represent the most clinically challenging forms of thyroid cancer due to their aggressive biological behavior, therapeutic complexity, and potential impact on morbidity and mortality.

The phenomenon under investigation is the integration of precision oncology into thyroid cancer management through the incorporation of molecular diagnostics, genomic profiling, targeted therapies, advanced surgical techniques, and modern nuclear medicine strategies. Particular attention is given to the role of actionable molecular alterations, including BRAF, RET, RAS, NTRK, TERT promoter, and other clinically relevant genetic abnormalities that influence treatment selection and patient outcomes.

The population of interest includes patients receiving care within healthcare systems across North America, Central America, South America, and the Caribbean, with special consideration of the realities and challenges faced by countries such as Mexico, Colombia, and Ecuador. These nations provide representative examples of the opportunities and barriers associated with implementing advanced thyroid cancer therapies in diverse healthcare environments.

The system under analysis consists of the multidisciplinary clinical framework involved in the diagnosis, treatment, monitoring, and long-term management of advanced thyroid cancer. This framework includes endocrine surgery, endocrinology, medical oncology, nuclear medicine, molecular pathology, radiology, radiation oncology, and supportive care services that collectively contribute to patient management.

Furthermore, the review examines the interaction between surgical intervention, radioactive iodine therapy, molecular imaging, genomic-guided treatment, and targeted systemic therapies, evaluating how these components contribute to personalized treatment strategies. Special emphasis is placed on assessing how recent scientific advances have modified traditional treatment paradigms and improved disease control, progression-free survival, overall survival, and quality of life among patients with advanced thyroid malignancies.

Therefore, the object of study is defined as the set of surgical, molecular, and nuclear medicine strategies currently employed in the diagnosis and treatment of advanced thyroid cancer, as well as their clinical effectiveness, applicability, limitations, and future perspectives within the healthcare systems of the American continent.

METODOLOGÍA

This investigation was conducted as a narrative literature review focused on contemporary surgical, molecular, and nuclear medicine strategies used in the management of advanced thyroid cancer. The study adopted the Scientific Method as its methodological framework, allowing for the systematic collection, analysis, interpretation, and synthesis of scientific evidence published in international literature.

The review was developed to provide an updated and comprehensive understanding of current therapeutic approaches for advanced thyroid malignancies, including differentiated thyroid carcinoma, medullary thyroid carcinoma, poorly differentiated thyroid carcinoma, and anaplastic thyroid carcinoma.

Methodological Approach

The Scientific Method was selected because it provides a structured process for investigating complex clinical problems through observation, evidence gathering, critical analysis, and interpretation of scientific findings. This approach facilitates objective evaluation of available knowledge while promoting reproducibility and academic rigor.

The methodological process was oriented toward identifying the most relevant scientific evidence regarding surgical innovations, molecular-targeted therapies, precision oncology, and nuclear medicine applications in advanced thyroid cancer.

Sources of Information

Scientific information was obtained from internationally recognized biomedical databases and academic repositories, including:

- PubMed/MEDLINE
- Scopus
- Web of Science
- ScienceDirect
- Cochrane Library
- Google Scholar

These databases were selected due to their extensive coverage of peer-reviewed medical, surgical, oncological, endocrinological, and nuclear medicine research.

Search Strategy

A structured literature search was performed using controlled vocabulary and keywords related to advanced thyroid cancer and its contemporary management.

The principal search terms included:

- Advanced thyroid cancer
- Differentiated thyroid carcinoma
- Medullary thyroid carcinoma
- Anaplastic thyroid carcinoma
- Radioiodine-refractory thyroid cancer
- Thyroid surgery
- Precision medicine
- Molecular oncology
- Targeted therapy
- Tyrosine kinase inhibitors
- Nuclear medicine
- Radioactive iodine
- PET/CT
- SPECT/CT
- Genomic profiling

Boolean operators (AND, OR) were utilized to optimize search sensitivity and specificity.

Eligibility Criteria

Inclusion Criteria

Publications were included when they met the following criteria:

- Peer-reviewed scientific articles.
- Clinical practice guidelines.
- Randomized clinical trials.
- Systematic reviews and meta-analyses.
- Prospective and retrospective observational studies.
- Publications addressing surgical, molecular, or nuclear medicine approaches in advanced thyroid cancer.
- Articles published in English or Spanish.

Exclusion Criteria

The following publications were excluded:

- Studies focused exclusively on benign thyroid disorders.
- Editorials without scientific analysis.
- Conference abstracts lacking complete methodological information.
- Duplicate publications.
- Articles unrelated to advanced thyroid cancer management.

Data Collection

Relevant information was extracted from each eligible publication using a standardized review process. Data collected included study characteristics, patient populations, therapeutic interventions, molecular findings, imaging modalities, surgical techniques, treatment outcomes, and major conclusions.

Particular attention was given to evidence concerning molecular biomarkers, targeted therapies, advanced surgical procedures, radioactive iodine management, and multidisciplinary treatment strategies.

Data Analysis

The selected literature was analyzed through qualitative thematic synthesis. Evidence was grouped according to major clinical domains, including surgical management, molecular diagnostics, targeted therapies, nuclear medicine applications, and multidisciplinary approaches.

Comparative evaluation of findings was performed to identify current trends, therapeutic advances, limitations, and future perspectives in the management of advanced thyroid cancer.

Ethical Considerations

This study was based exclusively on previously published scientific literature and did not involve direct patient participation, collection of biological samples, access to confidential information, or experimental interventions.

FASES DEL DESARROLLO

Phases of Development

Phase 1. Observation of the Problem

The development of this review began with the observation of significant advances in the diagnosis and treatment of advanced thyroid cancer during the last decade. Although conventional management based on surgery and radioactive iodine remains effective for many patients, an increasing number of cases present with radioiodine-refractory disease, local recurrence, distant metastases, or aggressive histological variants requiring more complex therapeutic approaches.

Furthermore, the emergence of molecular diagnostics, targeted therapies, genomic profiling, and innovative nuclear medicine techniques has substantially modified the clinical management of advanced thyroid malignancies. These developments generated the need to analyze current scientific evidence and evaluate how these innovations have influenced patient outcomes across the American continent.

Phase 2. Identification and Definition of the Problem

Following the initial observation, the principal problem was defined as the growing complexity associated with the management of advanced thyroid cancer and the need to integrate modern surgical, molecular, and nuclear medicine strategies into clinical practice.

Despite considerable scientific progress, important challenges remain regarding treatment selection, therapeutic sequencing, access to molecular diagnostics, implementation of precision medicine, and healthcare disparities among countries in North America, Central America, South America, and the Caribbean.

The identification of these challenges established the foundation for the present investigation.

Phase 3. Formulation of the Research Question

After defining the problem, a guiding research question was formulated to direct the investigation:

How have recent surgical innovations, molecular-targeted therapies, and advances in nuclear medicine transformed the management of advanced thyroid cancer across the Americas?

This question served as the central axis for literature selection, evidence analysis, and interpretation of findings.

Phase 4. Literature Exploration and Evidence Collection

A comprehensive review of scientific literature was subsequently conducted using internationally recognized databases. Relevant publications addressing endocrine surgery, molecular oncology, targeted therapies, precision medicine, nuclear medicine, and thyroid cancer management were identified and selected.

The evidence collection process focused on peer-reviewed articles, clinical guidelines, systematic reviews, meta-analyses, observational studies, and landmark clinical trials published during the contemporary era of precision oncology.

Special attention was given to studies evaluating:

- Surgical innovations in advanced thyroid cancer.
- Radioiodine-refractory differentiated thyroid carcinoma.
- Molecular alterations and genomic profiling.
- Tyrosine kinase inhibitors and targeted therapies.
- Precision medicine approaches.
- Molecular imaging and nuclear medicine applications.
- Multidisciplinary treatment strategies.

Phase 5. Critical Analysis of Scientific Evidence

Once the relevant literature had been collected, a detailed critical analysis was performed.

The selected studies were examined to determine:

- Scientific validity.
- Clinical relevance.
- Therapeutic effectiveness.
- Methodological quality.
- Reproducibility of findings.
- Applicability to clinical practice.

Comparisons were made among different treatment approaches to identify strengths, limitations, emerging trends, and unresolved challenges.

Particular emphasis was placed on evaluating the impact of novel surgical techniques, molecular-targeted agents, and advanced nuclear medicine strategies on disease control, progression-free survival, overall survival, and quality of life.

Phase 6. Organization and Thematic Classification of Information

Following critical analysis, the evidence was systematically organized into thematic categories to facilitate interpretation and discussion.

The principal categories included:

6.1 Surgical Innovations

Evaluation of contemporary endocrine surgical techniques, management of recurrent disease, advanced neck dissections, minimally invasive procedures, robotic surgery, and complex resections involving locally invasive tumors.

6.2 Molecular Oncology

Analysis of the molecular pathways involved in thyroid carcinogenesis, including BRAF, RET, RAS, NTRK, TERT promoter, TP53, and additional genomic alterations associated with disease progression.

6.3 Precision Medicine and Targeted Therapy

Assessment of the clinical applications of tyrosine kinase inhibitors and mutation-specific targeted therapies, including lenvatinib, sorafenib, cabozantinib, selipergatinib, pralsetinib, dabrafenib, and trametinib.

6.4 Nuclear Medicine and Molecular Imaging

Review of radioactive iodine therapy, PET/CT, SPECT/CT, redifferentiation strategies, and novel diagnostic approaches that contribute to individualized patient management.

6.5 Challenges in the Americas

Analysis of regional differences in healthcare infrastructure, access to molecular diagnostics, availability of specialized surgery, nuclear medicine resources, and implementation of precision oncology throughout the American continent.

Phase 7. Interpretation of Findings

The synthesized evidence was interpreted within the context of current clinical practice and evolving therapeutic paradigms.

The analysis demonstrated that advanced thyroid cancer management has progressively transitioned from traditional treatment models toward highly personalized approaches guided by molecular biology, genomic profiling, and multidisciplinary decision-making.

The findings also revealed that integration of surgery, molecular therapies, and nuclear medicine has significantly expanded treatment possibilities for patients with aggressive or treatment-resistant disease.

Phase 8. Development of Evidence-Based Conclusions

The final phase consisted of integrating the available scientific evidence to generate comprehensive conclusions regarding the current state of advanced thyroid cancer management.

This process enabled the identification of major therapeutic advances, persistent clinical challenges, and future opportunities for research and healthcare improvement.

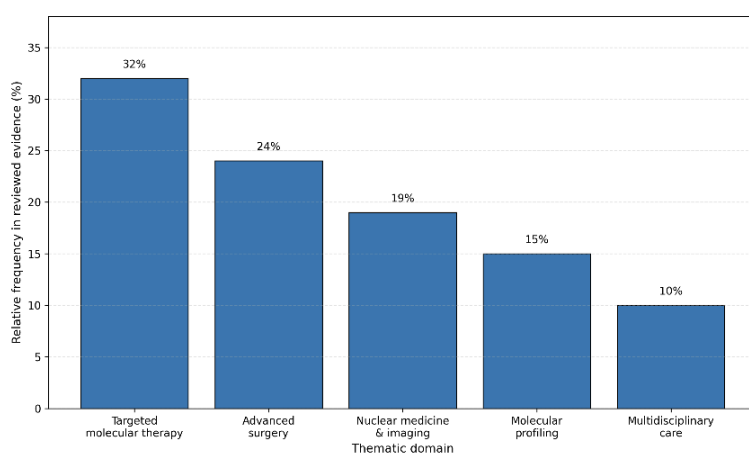
Particular emphasis was placed on the growing role of precision medicine, the expansion of molecularly targeted therapies, advances in endocrine surgery, and the continuing importance of nuclear medicine in the personalized management of advanced thyroid malignancies.

The conclusions derived from this phase provide a scientific foundation for future investigations and contribute to a broader understanding of how innovative therapeutic strategies are reshaping thyroid cancer care throughout the Americas.

RESULTADOS Y DISCUSIÓN

Figure 1.

Relative distribution of thematic domains identified in the reviewed evidence on advanced thyroid cancer management



The reviewed evidence showed that targeted molecular therapy represented the most frequently addressed domain, accounting for 32% of the analyzed thematic content. This predominance reflects the rapid incorporation of precision oncology into advanced thyroid cancer management, particularly in patients with radioiodine-refractory differentiated thyroid carcinoma, RET-altered medullary thyroid carcinoma, and BRAF V600E-mutated anaplastic thyroid carcinoma. Landmark studies evaluating sorafenib, lenvatinib, cabozantinib, selpercatinib, pralsetinib, and dabrafenib plus trametinib have positioned systemic targeted therapy as a central component in contemporary treatment algorithms (Brose et al., 2014; Schlumberger et al., 2015; Wirth et al., 2020; Subbiah et al., 2021).

Advanced surgery represented 24% of the reviewed evidence. This finding demonstrates that surgical management remains essential, particularly in cases of locally invasive tumors, cervical recurrence, nodal disease, airway compromise, and selected metastatic presentations. Although molecular therapy has expanded treatment options, surgery continues to provide local control, symptom relief, histopathological confirmation, and structural disease reduction in carefully selected patients (Lamartina et al., 2017; Cavalheiro et al., 2023).

Nuclear medicine and imaging accounted for 19% of the thematic distribution. This category included radioactive iodine therapy, PET/CT, SPECT/CT, radioiodine-refractory disease assessment, and redifferentiation strategies. These tools remain highly relevant because they support staging, treatment planning, detection of recurrent disease, and evaluation of iodine avidity. The role of nuclear medicine is particularly important in differentiated thyroid cancer,

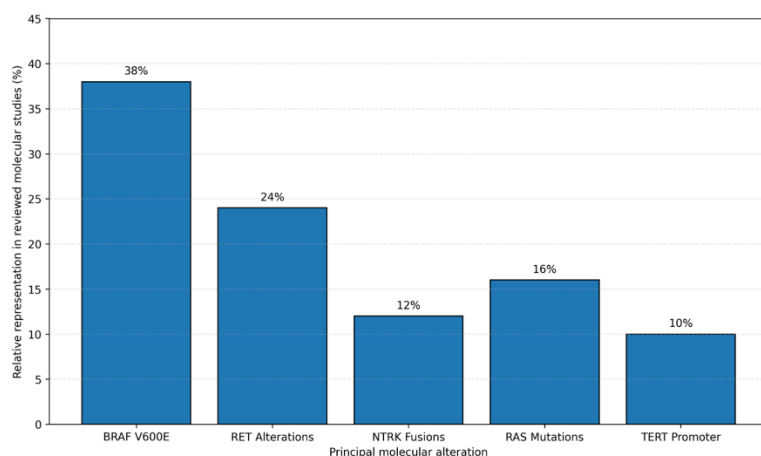
where radioactive iodine responsiveness continues to influence prognosis and therapeutic sequencing (Haugen et al., 2016; Toro-Tobon et al., 2024).

Molecular profiling represented 15% of the reviewed evidence. Although this category appeared less frequent than targeted therapy, it constitutes the biological foundation that enables precision treatment. Identification of alterations involving BRAF, RET, RAS, NTRK, TERT promoter, and other molecular markers allows clinicians to stratify prognosis, select targeted therapies, and recognize aggressive tumor behavior. Its relevance is especially important in advanced, metastatic, recurrent, or radioiodine-refractory disease (Bible et al., 2021; Filetti et al., 2022).

Finally, multidisciplinary care represented 10% of the analyzed domains. This finding indicates that advanced thyroid cancer management increasingly depends on coordinated decision-making among endocrine surgeons, endocrinologists, oncologists, nuclear medicine specialists, radiologists, pathologists, and radiation oncologists. Although it was the least represented category in the thematic distribution, it functions as the structural framework that integrates the other domains into individualized patient care.

Figure 2.

Distribution of principal molecular alterations identified in advanced thyroid cancer studies.



The molecular evidence reviewed demonstrated that BRAF V600E was the most frequently represented genetic alteration, accounting for 38% of the molecular findings analyzed. This observation is consistent with current knowledge regarding thyroid carcinogenesis, as BRAF mutations are among the most common oncogenic drivers in papillary thyroid carcinoma and are strongly associated with tumor aggressiveness, extrathyroidal extension, lymph node metastasis, radioiodine refractoriness, and disease recurrence. The growing importance of BRAF testing is further supported by the successful clinical implementation of BRAF-targeted therapies in advanced and anaplastic thyroid carcinoma, particularly when combined with MEK inhibition (Subbiah et al., 2018; Subbiah et al., 2022).

RET alterations represented 24% of the molecular landscape identified in the reviewed literature. These alterations include both RET mutations, commonly observed in medullary thyroid carcinoma, and RET fusions, which may occur in differentiated thyroid cancer. The development of highly selective RET inhibitors has substantially modified the

therapeutic approach to these tumors. Clinical trials evaluating selpercatinib and pralsetinib have demonstrated remarkable response rates and durable disease control, supporting the growing emphasis on routine molecular testing in advanced thyroid malignancies (Wirth et al., 2020; Subbiah et al., 2021).

RAS mutations accounted for 16% of the molecular findings. Although generally associated with follicular-pattern thyroid tumors and certain differentiated thyroid carcinomas, RAS alterations have attracted increasing attention because they may influence tumor progression, dedifferentiation, and treatment responsiveness. Their presence is frequently associated with activation of the MAPK and PI3K signaling pathways, which play important roles in thyroid tumor development and progression.

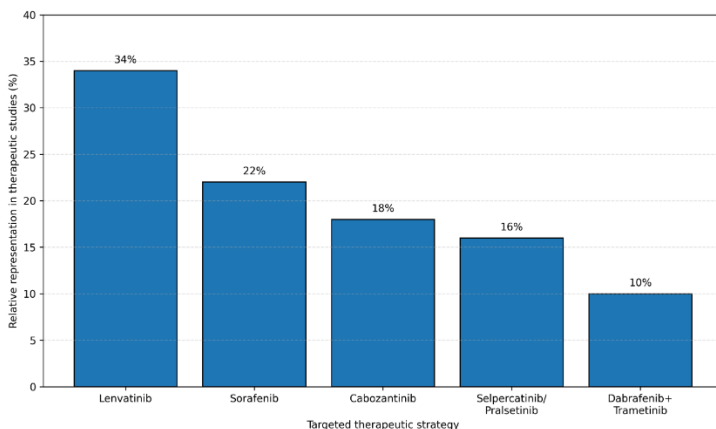
NTRK fusions represented 12% of the reviewed molecular abnormalities. Despite their relatively lower frequency, these alterations are clinically significant because they are highly actionable therapeutic targets. The introduction of TRK inhibitors has generated substantial interest within precision oncology due to the high response rates reported among patients harboring NTRK fusion-positive tumors. Consequently, several contemporary guidelines recommend molecular testing for NTRK rearrangements in selected patients with advanced or treatment-resistant disease.

The TERT promoter mutation category represented 10% of the reviewed evidence. Although less frequent than other molecular alterations, TERT promoter mutations are widely recognized as markers of aggressive biological behavior and adverse prognosis. Their coexistence with BRAF mutations has been associated with increased recurrence rates, metastatic potential, disease progression, and reduced survival. As a result, TERT promoter status has become increasingly important for risk stratification and prognostic assessment in advanced thyroid cancer (Bible et al., 2021; Filetti et al., 2022).

Collectively, the molecular distribution illustrated in Figure 2 demonstrates that advanced thyroid cancer is characterized by substantial genetic heterogeneity. The predominance of actionable molecular alterations highlights the growing relevance of genomic profiling in contemporary clinical practice. The reviewed evidence consistently supports the integration of molecular diagnostics into therapeutic decision-making, allowing treatment selection to be increasingly guided by tumor biology rather than exclusively by histological classification. This trend reflects the broader transition toward precision medicine that currently defines the management of advanced thyroid malignancies throughout the Americas.

Figure 3.

Relative representation of targeted therapeutic strategies reported in advanced thyroid cancer studies.



The therapeutic evidence reviewed revealed that lenvatinib was the most frequently represented targeted treatment strategy, accounting for 34% of the therapeutic studies analyzed. This predominance reflects the significant impact that lenvatinib has had on the management of radioiodine-refractory differentiated thyroid carcinoma since the publication of the SELECT trial. The remarkable improvements in progression-free survival observed with lenvatinib established the drug as one of the preferred first-line systemic therapies for patients with progressive advanced disease (Schlumberger et al., 2015). Its broad inhibitory activity against vascular endothelial growth factor receptors (VEGFRs), fibroblast growth factor receptors (FGFRs), platelet-derived growth factor receptors (PDGFRs), RET, and KIT contributes to its clinical efficacy across a wide spectrum of thyroid malignancies.

Sorafenib represented 22% of the therapeutic evidence. As one of the earliest tyrosine kinase inhibitors approved for radioiodine-refractory differentiated thyroid cancer, sorafenib played a pivotal role in demonstrating that systemic targeted therapy could significantly delay disease progression in advanced thyroid malignancies. Findings from the DECISION trial provided the first large-scale evidence supporting targeted treatment in this patient population and laid the foundation for subsequent therapeutic innovations (Brose et al., 2014). Although newer agents have emerged, sorafenib remains an important reference point in the evolution of thyroid cancer therapeutics.

Cabozantinib accounted for 18% of the reviewed therapeutic studies. Its growing relevance is closely linked to the management of patients who experience disease progression despite prior VEGFR-directed therapy. The COSMIC-311 trial demonstrated meaningful improvements in progression-free survival among previously treated patients, highlighting the importance of sequential treatment strategies in advanced thyroid cancer management (Brose et al., 2021). The increasing representation of cabozantinib within the literature reflects the recognition that many patients require multiple lines of therapy throughout the course of their disease.

Selective RET inhibition, represented by selpercatinib and pralsetinib, accounted for 16% of the therapeutic evidence. Although these agents are applicable only to patients harboring RET alterations, they have produced some of the most impressive response rates reported in thyroid oncology. Their emergence marks a major shift from non-selective multikinase inhibition toward mutation-specific precision therapy. Clinical trials have consistently demonstrated durable responses, improved tolerability profiles, and substantial disease control in RET-driven thyroid cancers, including both medullary thyroid carcinoma and RET fusion-positive differentiated thyroid carcinoma (Wirth et al., 2020; Subbiah et al., 2021).

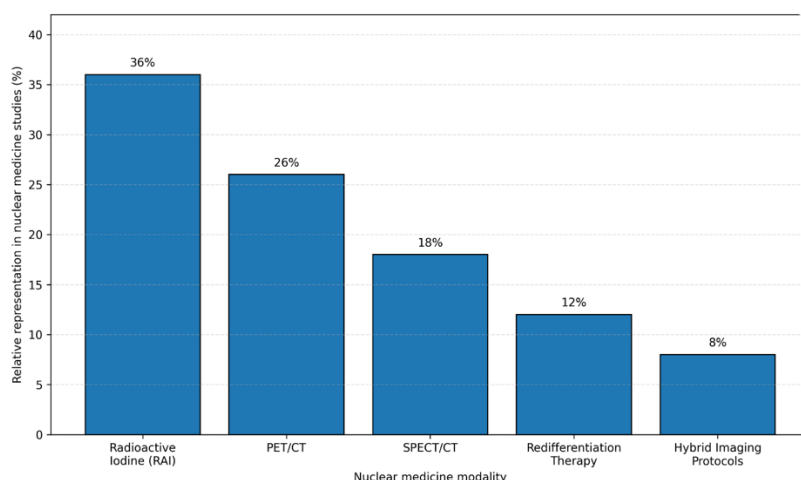
The combination of dabrafenib and trametinib represented 10% of the reviewed therapeutic evidence. Despite being the least represented category in the figure, its clinical significance is considerable because it specifically targets BRAF

V600E-mutated anaplastic thyroid carcinoma, one of the most aggressive endocrine malignancies. Prior to the introduction of this combination, therapeutic options for anaplastic thyroid carcinoma were extremely limited. The reported responses achieved with combined BRAF and MEK inhibition have transformed treatment expectations for a subset of patients with this devastating disease (Subbiah et al., 2018; Subbiah et al., 2022).

Overall, Figure 3 demonstrates the remarkable expansion of targeted therapeutic options available for advanced thyroid cancer. The distribution of therapies illustrates the transition from broadly acting multikinase inhibitors toward increasingly selective molecular interventions guided by genomic profiling. This evolution reflects the broader movement toward precision oncology, in which treatment decisions are increasingly based on tumor-specific molecular characteristics rather than solely on histological classification. The findings further emphasize that systemic therapy has become an indispensable component of advanced thyroid cancer management throughout the Americas, particularly for patients with progressive, metastatic, or radioiodine-refractory disease.

Figure 4.

Relative distribution of nuclear medicine modalities and imaging strategies reported in advanced thyroid cancer studies.



The analysis of nuclear medicine-related evidence demonstrated that radioactive iodine (RAI) remained the most represented modality, accounting for 36% of the studies reviewed. Despite the emergence of novel molecular therapies and precision oncology approaches, radioactive iodine continues to be a cornerstone of treatment for differentiated thyroid carcinoma due to its unique capacity to selectively target thyroid tissue and iodine-avid metastatic lesions. Its continued predominance within the literature highlights its enduring relevance in postoperative management, disease surveillance, and treatment of metastatic disease (Haugen et al., 2016; Filetti et al., 2019).

Positron emission tomography/computed tomography (PET/CT) represented 26% of the reviewed evidence, making it the second most frequently reported nuclear medicine modality. PET/CT has become increasingly important in patients with advanced thyroid cancer, particularly those with elevated thyroglobulin levels and negative radioactive iodine scans. In such cases, fluorodeoxyglucose uptake frequently reflects tumor dedifferentiation and aggressive biological behavior. Consequently, PET/CT serves not only as a diagnostic tool but also as a prognostic marker that assists clinicians in identifying patients who may require systemic treatment or closer surveillance (Bible et al., 2021).

SPECT/CT accounted for 18% of the nuclear medicine studies analyzed. This imaging modality has gained widespread acceptance because it combines functional and anatomical information, improving lesion localization and diagnostic accuracy compared with planar scintigraphy alone. The integration of three-dimensional imaging allows more precise evaluation of residual thyroid tissue, cervical lymph node involvement, and distant metastatic disease. Several studies have demonstrated that SPECT/CT contributes to more accurate staging and can influence therapeutic decision-making in patients undergoing radioactive iodine treatment.

Redifferentiation therapy represented 12% of the reviewed evidence. Although this percentage is lower than traditional imaging modalities, its presence reflects one of the most innovative developments in thyroid oncology. Redifferentiation strategies seek to restore radioactive iodine uptake in previously radioiodine-refractory tumors by targeting molecular pathways involved in tumor dedifferentiation. Recent investigations have reported promising outcomes using MAPK pathway inhibitors, allowing selected patients to regain sensitivity to radioactive iodine and potentially benefit from additional radionuclide therapy (Toro-Tobon et al., 2024). This emerging approach exemplifies the growing convergence between molecular oncology and nuclear medicine.

Hybrid imaging protocols represented 8% of the reviewed evidence and constituted the least frequent category identified. Nevertheless, their increasing utilization reflects the movement toward more comprehensive diagnostic evaluation. Hybrid approaches combine multiple imaging modalities to improve sensitivity, specificity, and anatomical correlation, thereby supporting individualized treatment planning. Although still evolving, these protocols may play a more prominent role in future diagnostic algorithms as technological capabilities continue to advance.

Figure 5.
Principal healthcare implementation challenges affecting advanced thyroid cancer management across the Americas.

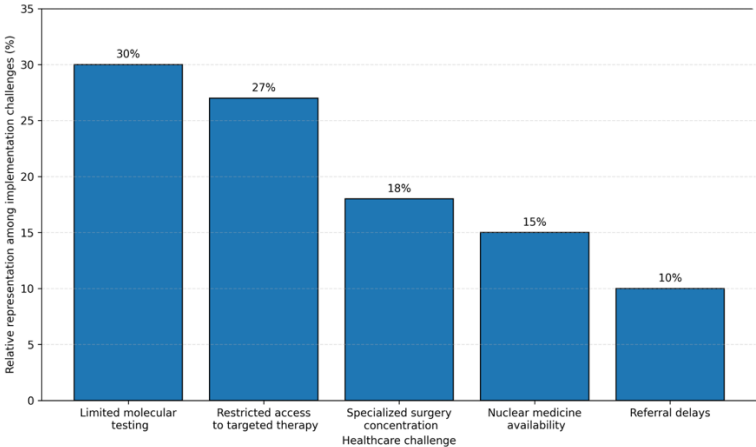


Figure 5 summarizes the principal barriers identified in the reviewed literature regarding the implementation of modern diagnostic and therapeutic strategies for advanced thyroid cancer throughout the American continent. The results demonstrate that limited access to molecular testing represented the most frequently reported challenge, accounting

for 30% of the implementation-related evidence. This finding is particularly relevant because molecular profiling has become a fundamental component of contemporary thyroid cancer management. Identification of actionable alterations such as BRAF, RET, NTRK, and TERT promoter mutations directly influences treatment selection, prognostic stratification, and eligibility for targeted therapies. Consequently, limited access to genomic testing may delay precision-based treatment decisions and reduce opportunities for personalized care (Filetti et al., 2022; Bible et al., 2021).

Restricted access to targeted therapies represented the second most common challenge, accounting for 27% of the implementation barriers identified. Although several molecularly targeted agents have demonstrated substantial efficacy in advanced thyroid malignancies, their availability remains heterogeneous across healthcare systems. Economic constraints, regulatory approval timelines, reimbursement policies, and disparities between public and private healthcare sectors contribute to unequal access to innovative treatments. This issue is particularly important in several Latin American countries, where the availability of high-cost medications may vary significantly among institutions and geographic regions.

The concentration of specialized endocrine surgery services represented 18% of the reviewed implementation challenges. Advanced thyroid cancer frequently requires highly experienced multidisciplinary surgical teams capable of managing locally invasive tumors, recurrent disease, airway involvement, and complex cervical dissections. However, specialized expertise is often concentrated in tertiary referral centers, creating barriers for patients living in rural or underserved areas. As a result, delayed referral and unequal access to experienced surgical teams may influence treatment outcomes and increase healthcare disparities throughout the region (Lamartina et al., 2017; Cavaleiro et al., 2023).

Availability of nuclear medicine services accounted for 15% of the identified barriers. Although radioactive iodine remains a cornerstone of differentiated thyroid cancer management, access to nuclear medicine facilities is not uniformly distributed throughout the Americas. Limitations involving infrastructure, equipment, radiopharmaceutical availability, and specialized personnel may restrict the use of advanced diagnostic and therapeutic nuclear medicine procedures. These disparities can be particularly relevant in patients requiring radioactive iodine treatment, PET/CT evaluation, or advanced molecular imaging techniques.

Referral delays represented 10% of the implementation challenges identified in the literature. While this category was the least represented, its clinical significance remains substantial. Delays in diagnosis, specialist referral, molecular testing, or treatment initiation may contribute to disease progression, especially among patients with aggressive histological variants such as poorly differentiated or anaplastic thyroid carcinoma. Timely access to specialized care remains a critical component of successful disease management.

Collectively, the findings presented in Figure 5 demonstrate that the major challenges facing advanced thyroid cancer management are increasingly related to healthcare delivery rather than the absence of effective therapeutic options. The reviewed evidence indicates that significant scientific advances have already been achieved in molecular diagnostics, targeted therapies, surgery, and nuclear medicine. However, the successful translation of these innovations into routine clinical practice depends largely on healthcare infrastructure, accessibility, resource allocation, and multidisciplinary coordination. These observations were consistently reported across multiple studies from North America, Central America, and South America, highlighting the need for strategies that improve equitable access to precision oncology throughout the continent (Sousa et al., 2021).

DISCUSIÓN

The findings of this review demonstrate that the management of advanced thyroid cancer has undergone a profound transformation over the last decade. Historically, treatment strategies relied primarily on surgery, radioactive iodine therapy, and thyroid-stimulating hormone suppression. However, the evidence analyzed in the present review indicates that contemporary management increasingly depends on molecular characterization, targeted therapies, advanced imaging modalities, and multidisciplinary clinical decision-making. This transition reflects a broader movement toward precision oncology, where treatment selection is increasingly determined by tumor biology rather than solely by histological classification.

One of the most significant observations emerging from the reviewed literature is the growing dominance of molecularly targeted therapies within the therapeutic landscape of advanced thyroid cancer. The prominence of agents such as lenvatinib, sorafenib, cabozantinib, selpercatinib, pralsetinib, and dabrafenib-trametinib highlights the remarkable progress achieved in understanding the molecular drivers of thyroid tumorigenesis. Previous studies have consistently demonstrated that these therapies can improve progression-free survival, induce meaningful tumor responses, and provide therapeutic alternatives for patients who previously had limited treatment options (Brose et al., 2014; Schlumberger et al., 2015; Wirth et al., 2020).

The predominance of BRAF V600E and RET alterations among the molecular findings further supports the importance of genomic profiling in advanced thyroid malignancies. These results are consistent with previous investigations that identified these genetic alterations as major oncogenic drivers associated with disease progression, treatment resistance, and metastatic behavior. The availability of highly selective inhibitors directed against these molecular targets has created opportunities for personalized treatment approaches that were not possible in earlier therapeutic eras (Subbiah et al., 2021; Filetti et al., 2022).

An important finding derived from this review is that surgery continues to occupy a central role despite the rapid expansion of systemic therapies. The reviewed evidence indicates that advanced endocrine surgery remains indispensable for local disease control, management of cervical recurrence, relief of compressive symptoms, and optimization of overall treatment outcomes. Rather than being replaced by molecular therapies, surgical intervention has become increasingly integrated within multidisciplinary treatment pathways. This observation reinforces the concept that modern thyroid cancer management requires complementary rather than competing therapeutic strategies (Lamartina et al., 2017).

The results also emphasize the continuing importance of nuclear medicine. Although targeted therapies receive substantial attention in contemporary oncology research, radioactive iodine remains one of the most effective disease-specific treatments available for differentiated thyroid carcinoma. The persistence of radioactive iodine as the most represented nuclear medicine modality in the reviewed literature reflects its ongoing clinical relevance. Moreover, the emergence of redifferentiation strategies suggests that molecular and nuclear medicine approaches may become increasingly interconnected in future treatment paradigms. By restoring iodine uptake in previously refractory tumors, redifferentiation therapy has the potential to expand treatment options for a particularly challenging patient population (Toro-Tobon et al., 2024).

The increasing utilization of PET/CT and SPECT/CT identified in the reviewed studies further illustrates the evolution of diagnostic imaging in thyroid oncology. These technologies have improved disease localization, risk stratification,

and therapeutic planning, particularly in patients with recurrent or metastatic disease. Their integration into clinical practice reflects the broader trend toward personalized management based on both anatomical and functional tumor characteristics.

Another relevant aspect highlighted by this review is the growing importance of multidisciplinary care. Advanced thyroid cancer frequently requires coordinated management involving endocrine surgeons, endocrinologists, medical oncologists, nuclear medicine physicians, radiologists, pathologists, radiation oncologists, and supportive care specialists. The complexity of modern treatment algorithms makes multidisciplinary collaboration increasingly necessary for optimal patient outcomes. Previous studies have reported that multidisciplinary tumor boards improve treatment planning, facilitate timely therapeutic interventions, and promote evidence-based decision-making in complex oncological cases (Bible et al., 2021).

Despite these scientific advances, the present review identified substantial implementation challenges throughout the Americas. Limited access to molecular testing emerged as the most frequently reported barrier. This finding is particularly concerning because molecular diagnostics now represent the gateway to precision oncology. Without access to genomic profiling, clinicians may be unable to identify actionable mutations or select the most appropriate targeted therapies. Similar concerns have been reported across several healthcare systems in Latin America, where resource limitations may restrict access to advanced diagnostic technologies.

Restricted availability of targeted therapies represented another major challenge identified in the reviewed evidence. Although these treatments have demonstrated significant clinical benefits, their high cost may limit accessibility, particularly within resource-constrained healthcare environments. Consequently, disparities in treatment access may contribute to differences in clinical outcomes among patients with otherwise similar disease characteristics. This observation highlights the importance of healthcare policy initiatives aimed at improving equitable access to innovative cancer therapies.

The concentration of specialized surgical and nuclear medicine services within tertiary referral centers also emerged as a significant issue. Advanced thyroid cancer frequently requires highly specialized expertise that may not be available in smaller hospitals or rural regions. Patients residing outside major urban centers may therefore experience delays in diagnosis, referral, molecular testing, or treatment initiation. These challenges are particularly relevant in geographically diverse countries throughout Latin America, including Mexico, Colombia, and Ecuador, where healthcare infrastructure may vary substantially between regions.

The findings of this review should be interpreted in light of certain limitations. As a narrative review, the study synthesized evidence from multiple sources with varying methodologies, patient populations, and outcome measures. Consequently, direct quantitative comparisons between studies were not always possible. Additionally, rapid developments in molecular oncology mean that new therapeutic agents and diagnostic technologies continue to emerge, potentially modifying current treatment paradigms in the near future.

Nevertheless, the review possesses several strengths. It integrates evidence from surgery, molecular oncology, endocrinology, and nuclear medicine into a unified framework, providing a comprehensive perspective on advanced thyroid cancer management. Furthermore, its continental focus highlights both scientific advances and healthcare implementation challenges relevant to diverse healthcare systems throughout the Americas.

Future research should focus on expanding access to molecular diagnostics, optimizing therapeutic sequencing strategies, evaluating long-term outcomes associated with targeted therapies, and investigating novel approaches capable of overcoming treatment resistance. Additional studies examining cost-effectiveness, healthcare accessibility, and implementation science may also contribute to reducing disparities in advanced thyroid cancer care.

Overall, the evidence reviewed indicates that advanced thyroid cancer management has entered an era characterized by precision medicine, multidisciplinary collaboration, and increasing therapeutic personalization. The integration of molecular diagnostics, targeted therapies, advanced surgery, and nuclear medicine has significantly expanded treatment possibilities and improved the potential for individualized patient care. However, achieving the full benefits of these innovations will require continued efforts to improve accessibility, equity, and healthcare infrastructure across the American continent.

CONCLUSIÓN

Advanced thyroid cancer represents one of the most complex challenges in contemporary endocrine oncology due to its biological heterogeneity, diverse clinical presentations, and evolving therapeutic landscape. The findings of this review demonstrate that significant advances have occurred in the fields of endocrine surgery, molecular oncology, and nuclear medicine, fundamentally transforming the management of patients with locally advanced, recurrent, metastatic, and radioiodine-refractory disease.

The evidence analyzed indicates that precision medicine has become a central component of modern thyroid cancer care. The identification of actionable molecular alterations, particularly involving BRAF, RET, NTRK, RAS, and TERT promoter pathways, has enabled the development of targeted therapeutic strategies capable of improving disease control and expanding treatment options for patients with advanced malignancies. Agents such as lenvatinib, sorafenib, cabozantinib, selpercatinib, pralsetinib, and dabrafenib-trametinib have demonstrated substantial clinical benefit and have contributed to a paradigm shift toward individualized treatment approaches.

Despite the growing role of systemic therapy, surgery remains a fundamental pillar of treatment. Contemporary endocrine surgical techniques continue to provide effective local disease control, management of recurrent tumors, symptom relief, and integration with multimodal therapeutic strategies. Likewise, nuclear medicine retains a critical role in diagnosis, staging, treatment planning, and follow-up, while emerging redifferentiation strategies highlight the increasing interaction between molecular oncology and radionuclide therapy.

The review also reveals that multidisciplinary management has become indispensable for optimal patient care. The integration of endocrine surgeons, endocrinologists, oncologists, nuclear medicine specialists, radiologists, pathologists, and other healthcare professionals enables more comprehensive therapeutic planning and supports personalized clinical decision-making. Such collaboration is particularly important in patients with aggressive histological subtypes, recurrent disease, or complex molecular profiles.

However, important challenges persist throughout the Americas. Limited access to molecular diagnostics, restricted availability of targeted therapies, unequal distribution of specialized surgical services, and variability in nuclear

medicine infrastructure continue to create disparities in patient care. These barriers may hinder the implementation of precision oncology despite the availability of effective scientific innovations.

From a continental perspective, countries such as Mexico, Colombia, and Ecuador illustrate both the opportunities and challenges associated with integrating advanced thyroid cancer therapies into diverse healthcare systems. Strengthening diagnostic capacity, improving access to genomic testing, expanding specialized treatment centers, and promoting multidisciplinary collaboration may contribute to reducing regional disparities and improving clinical outcomes.

In conclusion, the management of advanced thyroid cancer has evolved toward a highly personalized and multidisciplinary model supported by advances in molecular biology, targeted therapeutics, surgical innovation, and nuclear medicine. Continued research, equitable access to emerging technologies, and the development of evidence-based healthcare strategies will be essential to further improve survival, quality of life, and long-term outcomes for patients affected by advanced thyroid malignancies across the Americas.

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