



## CONSENSUS DOCUMENT

# Spanish consensus for the management of patients with advanced radioactive iodine refractory differentiated thyroid cancer



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## KEYWORDS

Differentiated thyroid cancer;  
Radioactive iodine refractory;  
Spanish consensus;  
Clinical management

## Abstract

**Background:** Approximately one third of the patients with differentiated thyroid cancer (DTC) who develop structurally-evident metastatic disease are refractory to radioactive iodine (RAI). Most deaths from thyroid cancer occur in these patients. The main objective of this consensus is to address the most controversial aspects of management of these patients.

**Methods:** On behalf of the Spanish Society of Endocrinology & Nutrition (SEEN) and the Spanish Group for Orphan and Infrequent Tumors (GETHI), the Spanish Task Force for Thyroid Cancer, consisting of endocrinologists and oncologists, reviewed the relevant literature and prepared a series of clinically relevant questions related to management of advanced RAI-refractory DTC.

**Results:** Ten clinically relevant questions were identified by the task force. In answering to these 10 questions, the task force included recommendations regarding the best definition of refractoriness; the best therapeutic options including watchful waiting, local therapies, and systemic therapy (e.g. kinase inhibitors), when sodium iodide symporter (NIS) restoration may be expected; and how recent advances in molecular biology have increased our understanding of the disease.

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**PALABRAS CLAVE**

Cáncer diferenciado de tiroides;  
Refractario al yodo radioactivo;  
Consenso español;  
Manejo clínico

*Conclusions:* In response to our appointment as a task force by the SEEN and GHETI, we developed a consensus to help in clinical management of patients with advanced RAI-refractory DTC. We think that this consensus will provide helpful and current recommendations that will help patients with this disorder to get optimal medical care.

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## Consenso español sobre el tratamiento de los pacientes con cáncer de tiroides diferenciado avanzado resistente al yodo radioactivo

**Resumen**

*Antecedentes:* Alrededor de un tercio de los pacientes con cáncer diferenciado de tiroides (CDT) que desarrollan enfermedad metastásica estructural son refractarios al yodo radioactivo. Desafortunadamente, la mayoría de las muertes debidas al cáncer de tiroides ocurren en pacientes con CDT avanzado refractario al yodo radioactivo. El principal objetivo de este consenso es abordar los aspectos más controvertidos del manejo de estos pacientes.

*Métodos:* En nombre de la Sociedad Española de Endocrinología y Nutrición (SEEN) y del Grupo Español de Tumores Raros e Infrecuentes (GETHI), el grupo de trabajo para el Cáncer de Tiroides, compuesto por endocrinólogos y oncólogos, revisó la literatura más destacada y desarrolló una serie de preguntas clínicamente relevantes concernientes al manejo de los pacientes con CDT refractario.

*Resultados:* Diez preguntas clínicamente relevantes fueron identificadas por el grupo de trabajo. En las respuestas el grupo incluyó recomendaciones sobre la mejor definición de la refractariedad, las mejores opciones terapéuticas, entre las cuales se incluyen la actitud expectante, las terapias locales y la terapia sistémica (por ejemplo inhibidores de tirosín-cinasa), cuándo esperar la recaptación de yodo radioactivo mediada por NIS y cómo los recientes avances en genética molecular han ayudado a comprender mejor la enfermedad.

*Conclusión:* En respuesta a nuestro compromiso como grupo de trabajo de la SEEN y GETHI hemos creado un consenso para asistir al manejo clínico de los pacientes con CDT avanzado refractario al yodo radioactivo. Pensamos que este consenso proporcionará unas recomendaciones útiles y actualizadas que ayuden a los pacientes con esta enfermedad a tener un cuidado óptimo.

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**Introduction**

Thyroid cancer is the most prevalent type of endocrine malignancy and its incidence has been steadily increasing over the last three decades.<sup>1</sup> Due to this rise in its incidence, thyroid cancer is currently the fifth most common new cancer diagnosis in women and the eighth most common new cancer diagnosis overall in the United States of America (USA).<sup>2</sup> It is now more frequently diagnosed than all leukaemias combined, as well as ovarian, uterine, pancreatic, or oesophageal cancers. For the majority of patients with thyroid cancer, treatment with surgery, radioactive iodine (RAI) ablation and TSH suppressive therapy allows an overall survival (OS) rate of 97.7% at five years.<sup>3</sup> Nevertheless, locoregional recurrence occurs in up to 20% of patients, and distant metastases in approximately 10% at 10 years. Some of these patients with locoregional recurrences and/or distant metastases lose the ability for iodine uptake leading to RAI-refractory metastatic disease. Patients with RAI-refractory metastatic disease have an overall survival rate of less than 50% at three years and account for more deaths in the USA at present than Hodgkin's lymphoma, osteosarcoma, or testicular cancer.

Differentiated thyroid cancer (DTC) derive from thyroid follicular cells and accounts for more than 90% of all thyroid cancers. The dominant histotypes are papillary and follicular cancers, while Hürthle cell thyroid cancer (a follicular thyroid cancer subtype) and poorly differentiated thyroid cancer are less common variants. Undifferentiated or anaplastic thyroid carcinomas, always RAI-refractory, are not reviewed in this consensus. Around one third of DTC patients with structurally-evident locoregional and/or metastatic disease becomes RAI-refractory, with inadequate radiation doses to malignant cells and failure to eradicate metastasis. Thus, RAI-refractory DTC is defined more by behavior than specific histopathology. Notably, although anaplastic thyroid cancers have higher mortality rates than DTC, most of the estimated deaths from thyroid cancer will be in patients with RAI-refractory DTC.<sup>2</sup>

Over the last decade, there have been substantial advances in the management of RAI-refractory DTC. Because controversy exists in some areas, the Spanish Task Force for Thyroid Cancer on behalf of Spanish Society of Endocrinology Thyroid Cancer Working Group (GTSEEN) and the Spanish Group for Orphan and Infrequent Tumors (GETHI) have created together a national task force in order

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