Med Clin (Barc). 2015;144(1):35–41

MEDICINA CLINICA

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Review

Postoperative radioiodine ablation in patients with low risk differentiated thyroid carcinoma☆

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ARTICLE INFO

Article history:
Received 6 January 2014
Accepted 15 January 2014

Keywords:
Radioiodine
Iodine-131
Ablation
Differentiated thyroid cancer
Low risk
Personalised medicine

ABSTRACT

Most patients with newly diagnosed differentiated thyroid carcinoma have tumours with low risk of mortality and recurrence. Standard therapy has been total or near total thyroidectomy followed by postoperative radioiodine remnant ablation (RRA). Although RRA provides benefits, current clinical guidelines do not recommend it universally, since an increase in disease-free survival or a decrease in mortality in low risk patients has not been demonstrated so far. Advancements in our understanding of the biological behaviour of thyroid cancer have been translated into the clinic in a personalised approach to the patients based on their individual risk of recurrence and mortality. Current evidence suggests that RRA is not indicated in most low-risk patients, especially those with papillary carcinomas smaller than 1 cm, without extrathyroidal extension, unfavourable histology, lymph node involvement or distant metastases. Follow-up of these patients with serial measurements of serum thyroglobulin and neck ultrasound is adequate. Careful evaluation of all risk factors of clinical relevance will allow a more realistic assessment of each individual patient.

Ablación posquirúrgica con radioyodo en pacientes con carcinoma diferenciado de tiroides de bajo riesgo

Palabras clave:
Radioyodo
Yodo-131
Ablación
Cáncer diferenciado de tiroides
Bajo riesgo
Medicina personalizada

RESUMEN

La mayoría de los pacientes con carcinoma diferenciado de tiroides presentan tumores de bajo riesgo de mortalidad y recidiva. El tratamiento estándar de estos tumores ha consistido en la tiroidectomía total o casi total, seguida de la ablación de los restos tiroideos con radioyodo (ARI). Aunque la ARI aporta ventajas, las actuales guías clínicas no la recomiendan de forma universal, ya que no se ha demostrado que aumente la supervivencia libre de enfermedad o reduzca la mortalidad en pacientes de bajo riesgo. Los avances en la comprensión del comportamiento biológico del cáncer de tiroides se han traducido en la clínica en una aproximación personalizada al paciente basada en su riesgo particular de recidiva y mortalidad. La evidencia actualmente disponible muestra que la ARI no está indicada en la mayoría de los pacientes de bajo riesgo, especialmente los que presentan carcinomas papilares menores de 1 cm, sin extensión extratiroidea, histología desfavorable, compromiso ganglionar ni metástasis a distancia. El seguimiento de los pacientes de bajo riesgo con determinaciones de tiroglobulina sérica y ecografías seriadas se considera suficiente. La evaluación cuidadosa de todos los factores de riesgo de relevancia clínica nos permitirá una evaluación más realista de cada paciente concreto.

☆ Please cite this article as: Díez JJ, Grande E, Iglesias P. Ablación posquirúrgica con radioyodo en pacientes con carcinoma diferenciado de tiroides de bajo riesgo. Med Clin (Barc). 2015;144:35–41.
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2387-0206/

Introduction

Radioiodine (RI) has been used since the 40s due to the ability of thyroid follicular cells to capture and concentrate this element through the sodium-iodide transporter.[1,2] *RI ablation* (RIA) refers to the first administration of this radio drug in a patient with differentiated thyroid carcinoma (DTC) in order to remove the thyroid tissue remnants left after total thyroidectomy. This procedure is generally used 4–8 weeks after surgery and must not be confused with *RI treatment*, which refers to the administration of therapeutic doses of RI in patients with persistent or recurrent disease after a proper surgical treatment, in order to destroy macroscopic structural disease.[3]

Total thyroidectomy followed by RIA and thyroid hormone suppressive treatment improves the overall survival of patients with medium-to-high risk DTC.[1] However, there is an important group of patients with low-risk DTC that have an excellent prognosis, even without RIA, and represent almost 50% of all the thyroid cancer cases currently.[4]

The selection of patients that need not receive RIA and the dosage required are controversial subjects. Clinical guidelines recognise that there are groups of patients in which the indication is mandatory, others in which its use is selective and, finally, others in which it must not be administrated.[2,5–7] The controversy began when some authors showed that some low-risk patients with theoretically no RIA indication might present lymph node metastases and other characteristics that increase the risk of recurrence during follow-up.[4,8] This article analyses the basics of RIA, its advantages and disadvantages and, finally, the current criteria for the indication or lack of indication for this procedure in patients with low-risk DTC.

Definition of low-risk patient

It is important not to confuse the risk of mortality with the risk of recurrence of the disease. The TNM staging system[9] is given to patients in 4 stages and is used to assess overall and specific mortality (Table 1). Stage I includes patients <45 years without distant metastases and patients ≥45 years with tumours ≤2 cm without lymph node or distant metastases. In patients <45 years, stage II is defined by the presence of distant metastases, while in older patients, stage II includes tumours of up to 4 cm without lymphatic or distant metastases.[9] Low-risk patients are those included in stages I and II of the *American Joint Committee on Cancer* without distant metastases, since they practically have a 100% survival after 5 years.[10]

However, to estimate the risk of persistence or recurrence of the disease, other clinical and histological parameters are used.[5,6] The European Consensus defines very low-risk and low-risk patients pursuant to the characteristics shown in Table 1. These patients have a long-term recurrence rate lower than 2%.[1,5] The *American Thyroid Association* (ATA) classifies the risk of recurrence as low, intermediate and high.[6] The patients from the first group present a risk of recurrence of 3%.[11]

Basics of radioiodine ablation

Objectives

RIA is a form of radioisotope treatment used after a total thyroidectomy, with the objectives included in Table 2. In low-risk patients, the objective of RIA is to remove all the remaining normal thyroid tissue, as well as to destroy possible microscopic tumour remnants not removed during surgery, in order to facilitate the follow-up of the patient with serum thyroglobulin (Tg) determination and full body scans. The Tg is a specific marker of tumour recurrence in patients treated with surgery followed by RIA.[12]

In patients with intermediate or high risk, RIA is a form of adjuvant treatment whose objective is to treat the postoperative or metastatic residual disease, as well as to conduct a full body scan 2–5 days after the RIA for the assessment of the distant disease with a higher sensitivity than scans with diagnostic doses.[5]

Preparation

The preparation of the patient requires a diet low in iodine (<50 μg/day) during the 2–3 weeks prior, no iodine medication, and thyrotropin (TSH) serum levels above 30 mI/U to achieve sufficient RI capture in the healthy or tumour thyroid tissue remnants.[1] An increase in TSH can be achieved by an increase in endogenous TSH through the withdrawal of the treatment with levothyroxine during 4–6 weeks or the administration of recombinant human TSH (rhTSH) (2 injections of 0.9 mg during 2 consecutive days).[1,2] The advantages of using rhTSH include improvements in the quality of life of patients by avoiding the symptoms of hypothyroidism[13,14] and a reduced exposure to radiation of the extrathyroidal tissues, since the clearance of RI is quicker than in the case of hypothyroidism.[15] Pregnancy must be avoided during the administration of RI and during the following 6–12 months.[5,6,16]

Dosage and activity

Ablation is generally achieved when the dose absorbed by the thyroid remnant is equal to or higher than 300 Gy.[2] To estimate the activity of RI required by each patient to achieve this dose, two methods are used: the empirical method and the dosimetric method. The first one is based on the experience and the assessment of several factors, such as the patient's age, the tumour size and histology, the presence of extrathyroidal extension and metastasis. It uses fixed activities ranging from 30 to 200 mCi. The dosimetric method is more complex and involves the calculation, through ^{123}I or ^{131}I, of the radiation absorbed by the various organs, in order to administer the highest tumoricidal dose and avoid undesirable doses in critical organs, such as the lungs and bone marrow.[2]

Two recent randomised clinical trials have compared the RIA success rates after the administration of 30 and 100 mCi, with levothyroxine withdrawal and rhTSH stimulation procedures in low and intermediate risk patients.[13,14] The results, which were very similar, showed that the ablation success rate did not change when using low or high doses of RI, nor when increasing endogenous or exogenous TSH (Table 3). Fewer adverse events were observed after the administration of 30 mCi of RI and after the preparation with rhTSH.[13,14]

As a corroboration of these findings, 2 recent meta-analyses, one with 7 randomised trials including 1772 patients[17] and another one with 9 randomised trials including 2,569 patients,[18] demonstrate that there are no significant differences as to the success of percentages of ablation nor as to the scores of the test on quality of life with activities of 30, 50 and 100 mCi. Moreover, data showed that the lowest dose involved reduced adverse events and admission times.[18]

The rate of long-term recurrence also seems similar when levothyroxine or rhTSH withdrawal is implemented. A recent study examined, during a 10-year follow-up, 159 patients with DTC, most of whom were low or intermediate-risk patients, who received RIA with low activity (30 mCi) and were prepared with rhTSH or withdrawal. The authors found no significant differences among these groups regarding the rates of remission or recurrence.[19]