

Indications for radioiodine administration in follicular-derived thyroid cancer

Les indications de l'irathérapie dans les cancers thyroïdiens de souche folliculaire

C. Buffet, C. Ghander, E. le Marois, L. Leenhardt*

Unité thyroïde-tumeurs endocrines, Institut d'endocrinologie E3M et Service de médecine nucléaire, Hôpital Pitié-Salpêtrière, Université Pierre-et-Marie-Curie/Institut Universitaire du Cancer, 83, boulevard de L'Hôpital, 75013 Paris, France

Abstract

Indications for radioiodine administration after thyroid cancer surgery have shifted in recent years toward personalized management, adapted to the individual risk of tumor progression. The most recent guidelines and studies favor de-escalation in indications for administration, dosage and means of preparation with exogenous recombinant TSH stimulation as treatment of choice.

Radioiodine administration has 3 possible objectives:

- ablation of normal thyroid tissue remnants in patients with low risk of progression, using low radioiodine activity levels, with the advantage of completing disease staging on whole-body scintigraphy performed after administration of the radioiodine capsule, and of facilitating follow-up by thyroglobulin assay;
- adjuvant treatment for suspected microscopic metastases in patients with intermediate or high risk of progression, using higher activity levels, with the theoretic aim of limiting recurrence and mortality;
- curative treatment in high-risk patients with proven metastases, using exclusively high activity levels, with a view to improving specific survival.

In future, indications for ablation and/or activity prescription may be governed by an algorithm incorporating individual baseline progression risk (essentially founded on pTNM staging) and postoperative data such as thyroglobulin level and neck ultrasound results.

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Résumé

Les indications d'administration d'iode radioactif après une chirurgie pour cancer de la thyroïde se sont modifiées au cours de ces dernières années au profit d'une prise en charge personnalisée, adaptée au risque évolutif tumoral. Les dernières recommandations et les études les plus récentes vont dans le sens d'une désescalade des indications d'administration du radio-iode, des activités prescrites et des modalités de préparation à l'irathérapie au profit de la stimulation par TSH recombinante exogène.

On distingue trois objectifs à l'irathérapie :

- l'ablation de reliquats de tissus thyroïdiens normaux pour les patients à faible risque évolutif, obtenue avec de faibles activités ayant pour avantage de compléter le staging de la maladie grâce à la scintigraphie corps entier faite après prise de gélule d'iode et de faciliter le suivi du patient grâce au dosage de thyroglobuline ;
- un traitement adjuvant d'une maladie métastatique microscopique suspectée chez des patients à risque évolutif intermédiaire ou élevé, obtenu avec de plus fortes activités, dans le but théorique de diminuer le nombre de récurrence et de décès ;
- un traitement curatif chez des patients à haut risque ayant une maladie métastatique prouvée, obtenu uniquement avec de fortes activités, dans le but d'améliorer la survie spécifique.

À l'avenir, les indications d'ablation et/ou les activités prescrites pourraient dépendre d'un algorithme incluant le risque évolutif initial du patient (tenant compte essentiellement de la classification pTNM) et de données post-opératoires comme la valeur de thyroglobuline et le résultat de l'échographie cervicale.

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* Corresponding author.

E-mail Address: laurence.leenhardt@psl.aphp.fr (L. Leenhardt).

1. Introduction

Differentiated thyroid cancer (DTC) treatment usually consists of thyroidectomy, often followed by radioiodine administration. From the 1980s, radioiodine (RAI) was prescribed for virtually all DTC patients. The increase in the incidence of low recurrence-risk DTC patients brought the cost-benefit-risk rationale of this attitude into question. Over recent years, clinicians have, in the light of prospective or large retrospective studies, adopted a risk-adapted management approach. There is a current trend of de-escalation in indications for RAI, activities used and modality of preparation.

2. Initial risk stratification

The most commonly used staging system to predict risk of death in patients with DTC is AJCC/UICC TNM staging (Table 1). Recurrence risk stratification systems have been developed and used in clinical practice for the management of DTC patients, and in particular for the decision to implement postoperative RAI. The most common classifications have been defined in the American [1] and European guidelines [2]. The results of postoperative thyroglobulin assay and post-treatment whole-body RAI scan are included in the assessment of recurrence risk in the American guidelines, which distinguish the following categories:

- low-risk patients: pT1, pT2, intra-thyroidal pT3, N0 or M0 DTC, without aggressive histology and with normal post-treatment whole-body RAI scan if performed;
- intermediate-risk patients: extra-thyroidal pT3 or N1 DTC, or aggressive histology or vascular invasion, or abnormal neck uptake on post-treatment whole-body RAI;
- high-risk patients: pT4 or M1 DTC, or without complete tumor resection, or with thyroglobulin value suggestive of distant metastases.

Risk stratification as defined by the European Thyroid Association (ETA) is as follows:

- very low-risk patients: pT1a(s), N0, M0;
- high-risk patients: N1 or M1 or pT3 or pT4, or without complete tumor resection;
- low-risk patients: all other patients, including those with aggressive histology.

Since the publication of these guidelines, recent data have supported the concept that not all N1 DTC patients are equal [3]. Specific characteristics of lymph-node metastases (pre- or per-operatively diagnosed, size, number, extra-capsular extension) could be used to stratify recurrence risk. Lymph-node metastases that are few in number (≤ 5) and small in size (< 10 mm) and not diagnosed pre- or per-operatively are associated with limited recurrence risk ($< 5\%$). There is a need to reconsider the previous paradigm of equal risk magnitude for all N1 DTCs and to stratify management according to N1 characteristics.

Whether all follicular thyroid cancers should be considered as at high risk of recurrence is controversial. Minimally invasive follicular tumor, especially in young patients (< 45 years old) and without vascular invasion or distant metastasis, appears to have excellent prognosis [4,5].

It is noteworthy that at present none of the mortality or recurrence-risk assessment systems incorporate molecular testing results. Recent publications could lead to this attitude being revised, including molecular alterations such as BRAF or TERT (telomerase reverse transcriptase) promoter mutations in the stratification systems detailed above [6,7].

3. Goals of radioiodine administration

Three situations should be distinguished regarding administration of RAI:

- Remnant ablation, to eliminate the postsurgical normal thyroid remnant in order to achieve an undetectable serum thyroglobulin level. Remnant ablation facilitates follow-up and identification of recurrence by thyroglobulin assay. Systematic whole-body RAI scan, usually performed 3 to 5 days after RAI administration, allows completion of initial staging. Low RAI doses are sufficient for remnant ablation (30-50 mCi).
- Adjuvant therapy, to destroy suspected neoplastic residual tumor in order to improve disease-free, overall and specific survival.
- Treatment to destroy known metastatic locations at diagnosis or during follow-up. The goal of RAI therapy is to improve disease-free, overall and specific survival.

Successful RAI administration in initial management of DTC is defined by an undetectable or very low basal thyroglobulin level (< 0.15 ng/ml or 0.27 ng/ml) in the absence of interfering antibodies or low stimulated thyroglobulin level (< 1 or 2 ng/ml) with normal neck ultrasound [8,9]. Diagnostic whole-body scan is not routinely performed and is mainly reserved for patients with thyroglobulin antibodies. The ultimate goal of RAI administration is to decrease recurrence and mortality rates without impairing quality of life.

4. When radioiodine should be performed and what activities should be used?

There is general agreement that RAI administration improves overall and disease-specific mortality and disease-free survival in high-risk DTC patients. In a systematic review of methodologically acceptable studies examining the effectiveness of postoperative RAI administration, disease-specific mortality was improved in 3 out of 12 eligible studies, including the largest (from Ohio State) and a Turkish study with a high proportion of high-risk individuals [10]. Another study, including about 2,900 patients with a median follow-up of 3 years, demonstrated improved disease-specific and disease-

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