

# Evaluation of Response to Therapy in Thyroid Carcinoma Patients after Radioactive Iodine Therapy

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## ABSTRACT

Radioactive iodine therapy is an important treatment modality for differentiated thyroid carcinoma patients. Radioactive iodine, similar to elementary iodine, is concentrated in the thyroid follicular cells after oral application, and it can damage the remnant or malignant thyroid cells. Unlike many antineoplastic drugs, radioactive iodine can easily be applied without causing serious side effects.

Radioactive iodine was first used for the treatment of a differentiated thyroid carcinoma patient in 1949. In Turkey, it has been used in many nuclear medicine centers for treatment of both differentiated thyroid carcinoma and hyperthyroid patients since 1954. For evaluation of response to therapy with radioactive iodine, different clinical, biochemical, scintigraphic, and radiological imaging modalities are available. Today, many international guidelines aid the clinicians in the assessment of therapy response after radioiodine application. This review aims to discuss the methods recommended in current guidelines for therapy response assessment in differentiated thyroid carcinoma patients after radioactive iodine therapy.

**Keywords:** Thyroid neoplasms, Iodine radioisotopes, treatment outcome

## ÖZET

Tiroit karsinomlu hastalarda radyoaktif iyotla tedavi sonrası tedaviye yanıtın değerlendirilmesi

Radyoaktif iyot tedavisi dиферансиye tiroit karsinomlu hastalarda önemli bir tedavi yöntemidir. Radyoaktif iyot oral yolla alındıktan sonra, elementer iyotla aynı şekilde tiroit folikül hücrelerinde toplanır ve kalmış olan veya habis tiroit hücrelerine hasar verir. Radyoaktif iyot, birçok kanser ilaçının aksine ciddi yan etkiye yol açmaksızın kolaylıkla uygulanabilir.

Radyoaktif iyot dиферансиye tiroit karsinomlu hastaların tedavisinde ilk kez 1949'da uygulanmıştır. Türkiye'de 1954'ten beri hem dиферансиye tiroit karsinomlarının hem de hipertiroidinin tedavisinde birçok nükleer tip merkezinde kullanılmaktadır. Radyoaktif iyotla tedaviye yanıtın değerlendirilmesi için değişik klinik, biyokimyasal, sintigrafik ve radyolojik yöntemler mevcuttur. Günümüzde radyoaktif iyot uygulanması sonrası tedaviye yanıtın değerlendirilmesinde klinisyene yardımcı olacak birçok uluslararası rehber mevcuttur. Bu derlemede dиферансиye tiroit karsinomu hastalarında radyoaktif iyot tedavisi sonrası tedavi yanıtının değerlendirilmesinde kullanılmakta olan rehberlerin önerdiği yöntemlerin tartışılması amaçlanmıştır.

**Anahtar kelimeler:** Tiroit tümörleri, iyot radyoizotoplari, tedavi son durumu

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## Introduction

Differentiated thyroid carcinomas (DTC), which include papillary thyroid carcinomas, follicular thyroid carcinomas, Hürthle cell carcinomas, and poorly differentiated thyroid carcinomas, originate from thyroid follicular epithelial cells and represent the majority of thyroid carcinomas. They require similar approaches for treatment and follow-up. Most thyroid

cancer patients are diagnosed at an early stage, both due to the slow-growing nature of the disease and as a result of the widespread usage of diagnostic modalities, like ultrasonography and fine needle aspiration biopsy. For this reason, survival rates are generally high in the majority of DTC patients. Nevertheless, disease recurrence is seen in nearly 3% of low-risk group patients, 21% of the medium-risk patients and 68% of the high-risk patients (1). Therefore, appropriate therapy

planning and a proper assessment of therapy response and its adequacy are needed for DTC patients.

Initial staging and risk assessment are recommended for therapy planning and follow-up of patients. The American Thyroid Association (ATA) recommends to divide patients into 3 main groups in terms of risk assessment on the basis of postoperative pathology results (2,3). Accordingly, the low-risk group includes patients without local or distant metastasis, vascular or local invasion, remnant tumor tissue, or aggressive tumor histology. By contrast, high-risk group patients are those with distant metastasis, macroscopic tumor invasion, postoperative remnant tumor tissue, or high thyroglobulin (Tg) values that do not match with imaging, or gross metastatic lymph nodes. Follicular carcinomas with extensive vascular invasion are also in the high-risk group.

Other than initial risk assessment, also the treatment modality applied to the patient should be known. Most patients undergo total or near-total thyroidectomy followed by radioiodine ablation. However, depending on the initial risk assessment, subtotal thyroidectomy or lobectomy may also be preferred. Radioiodine administration is not applied to every DTC patient; it is generally not the treatment of choice in microcarcinomas without invasion or metastasis. In addition, recent ATA guidelines do not routinely recommend radioiodine administration for low-risk group patients, which also includes tumors  $\geq 1$  cm (3).

It is recommended to divide the patients into 4 main groups according to their treatment response (3). Patients with excellent response do not have any clinical, biochemical, or structural sign of disease. Patients with biochemical incomplete response either have abnormally elevated Tg levels or gradually increasing anti-thyroglobulin (anti-Tg) antibody levels. Patients with structural incomplete response have remnant tissue or new emerging local or distant metastasis. Finally, nonspecific imaging or biochemical findings represent an indeterminate response.

Routine response assessment is generally performed 6 months (6-18 months) after radioiodine administration. Serum Tg and anti-Tg antibody measurement under thyroid stimulating hormone (TSH) stimulation and neck ultrasonography should be initially performed, including 2-5 mCi I-123 or I-131 diagnostic whole-body scan if necessary.

There are no certain criteria to define excellent response after radioiodine administration. Many clinicians require Tg

values lower than 1 ng/ml under TSH stimulation in the absence of anti-Tg antibody and in the absence of functional or structural sign of disease (3,4). Nonetheless, current ATA guidelines do not recommend routine I-123 or I-131 diagnostic whole-body scan in low-risk group patients if serum Tg and anti-Tg levels are low and neck ultrasonography is negative [3]. TSH stimulation can be done either with endogenous TSH after thyroid hormone withdrawal for 4-6 weeks or with Thyrogen stimulation. Furthermore, sensitive Tg analysis can be performed without TSH stimulation (5-7).

Therapy response is generally excellent in the majority of low-risk group patients and their recurrence rate is low. Therapy response assessment is especially important to avoid unnecessary aggressive treatment in excellent responders among intermediate and high-risk group patients: The recurrence rate in the intermediate risk group is 36-43%, whereas the recurrence rate in excellent responders among intermediate risk group patients is only 1-2% (3,1,8). Patients with biochemical or structural incomplete response or indeterminate response should therefore be followed up carefully to avoid recurrence.

Biochemical incomplete response is described as high Tg values or increasing anti-Tg antibody values in the absence of localizable disease with scintigraphic or structural imaging. There is no certain Tg threshold value to define biochemical incomplete response, but a Tg value above 10 ng/ml under TSH stimulation is generally accepted as incomplete response in patients treated with total thyroidectomy and RAI ablation (9,1).

Patients with biochemical incomplete response generally have a better prognosis than structural incomplete responders. Vaisman et al. showed that spontaneous remission could be seen in patients with biochemical incomplete response (8). Their progression rate is slower than in patients with structural incomplete response, and 10-year survival rate is 100% under L-thyroxin suppression (9).

Neck ultrasonography is important in response assessment of patients. All patients should have neck ultrasonography 6-12 months after thyroidectomy to evaluate the presence of residual thyroid tissue or lymph node metastasis. If suspicious lymph nodes are detected (especially if  $>8-10$  mm), fine needle aspiration biopsy should be performed under ultrasonography (USG) guidance (3). I-131 or I-123 diagnostic whole-body scan can aid in detecting local or distant metastasis. In patients

whose post-treatment I-131 whole-body scan revealed extra-thyroidal uptake or elevated anti-Tg antibody values, I-123 or I-131 diagnostic whole-body scan is recommended for therapy response assessment (3). Additional spot or SPECT images from neck, mediastinum, or other suspicious sites of uptake could increase the accuracy of the scintigraphic imaging. Increasing usage of integrated hybrid SPECT/CT imaging could give anatomical correlation and diagnostic accuracy of the planar imaging (10).

18F-Fluorodeoxyglucose (FDG) positron emission

tomography (PET) can be used in poorly differentiated thyroid cancer patients, especially when abnormally increased Tg values ( $>10$  ng/ml) are found or when metastases are known. FDG PET is also beneficial in the presence of abnormally elevated Tg values in high-risk group patients with a negative post-therapy I-131 whole body scan to detect sites of metastases. Thorax CT could also be used to detect pulmonary metastases in high-risk group patients with elevated Tg values. Finally, CT or MRI imaging are recommended to detect possible brain or bone metastases.

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