COMMENTARY

Morphological changes in benign thyroid nodules after radioactive iodine therapy: a focus on ultrasound and FNAC

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ABSTRACT

Radioactive iodine therapy is non-invasive, well-established, and effective treatment for hyperthyroidism. However, there are concerns about its potential to cause thyroid cancer when used for benign thyroid diseases. While studies show mixed results, our observations indicate that the risk of cancer after radioactive iodine therapy for benign conditions is very low, given that pre-therapy nodules have been confirmed as benign either through sonographic examination or fine-needle aspiration cytology. This perspective is grounded because the iodine dose used for benign thyroid diseases is low and causes cell death rather than cancer.

Keywords: Benign thyroid disorders, radioactive iodine therapy, thyroid CA risk, sonographic and cytological evaluation.

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Introduction

Radioactive iodine therapy is a non-invasive, well-established, and effective treatment for hyperthyroidism [1]. Hertz successfully administered the first therapeutic activity of radioiodine-131 (I-131) to a patient with Graves' disease in early 1941 [2]. Since then, radioactive iodine is being successfully used in the treatment of Grave's disease, autonomously functioning solitary thyroid nodules, and toxic multinodular goiter [1]. This commentary delves into the properties of radioactive iodine, its mechanisms of action, and the cytological, histological, and sonographic changes induced, with a focus on the evaluation of malignancy risk in post-radioactive iodine (RAI) therapy for benign thyroid diseases.

Properties of radioactive iodine

Radioactive iodine (I-131) has a physical half life of 8.4 days and undergoes beta-minus decay emitting a principle primary gamma photon of 364 kiloelectron volts (keV) (81% abundance) and beta particles of 0.606 megaelectron volt (89% abundance). Beta particles are responsible for the therapy outcome. The I-131 high-energy beta emissions and long physical half-life of gamma emissions result in a relative high radiation dose to the thyroid [3].

Mechanism of radioactive iodine

The impact of radioactive iodine on tissues is via direct as well as indirect mechanisms. Direct effects target DNA and involve one-electron oxidation reactions, while indirect effects are mediated through water dissociation, leading to the generation of reactive oxygen species, including superoxide radicals and hydrogen peroxide, the precursors of the highly damaging hydroxyl radicals. As a result, there is cellular damage and this damage extends to DNA, inducing genetic mutations, disruptions in normal cellular functions, or cell death. Consequently, these processes can lead to long-term consequences such as diminished thyroid function and structural alterations in the thyroid gland [4]. Understanding these mechanisms is crucial for evaluating the long-term effects of RAI therapy.

Cytological and histological changes induced by radioactive iodine

The existing literature indicates that the alterations brought about by radioactive iodine exhibit heterogeneity across the gland and appear to be unaffected by the administered dose.

Following radioactive iodine treatment, acute post-radioactive iodine cytological changes, include cellular and nuclear enlargement, cytoplasmic vacuolization, coarse chromatin, nuclear atypia, anisonucleosis, and

hyperchromasia. Late cytological changes involve chronic inflammatory cells, histiocytes, oncocytic alterations, abundant cytoplasm, nuclear atypia, and clumped and linear chromatin. It is crucial for pathologists to recognize that these changes signify a benign process in thyroid nodule FNA samples, provided that the relevant patient treatment history is communicated effectively [5-7].

Histological analysis reveals the existence of numerous adenomatous nodules, displaying a range of hyperplasia levels, follicular atrophy, and fibrosclerosis. In addition, there are diffuse and prominent oncocytic alterations, cytoplasmic vacuoles, intraepithelial hemosiderin deposition, nuclear atypia, interstitial lymphocytic infiltrates, and histiocytes. Notably, there is an absence of follicular invasion, and the occurrence of mitoses is rare [5].

Sonographic features of the thyroid gland after radioiodine therapy

Ultrasound is very useful for the identification of suspicious thyroid nodules before RAI therapy. Thyroid imaging reporting and data system (TIRADS) risk score is being used by sonologists to standardize the risk assessment for the ultrasonographic diagnosis of malignant thyroid nodules. The primary benefit of the TIRADS score lies in its notable accuracy in pinpointing suspicious thyroid nodules that merit cytological examination. This capability facilitates early detection while minimizing the need for unnecessary biopsies [5].

USG features suspicious of thyroid malignancy (Figure 1) include solid nodules, hypo echogenicity, micro lobulated or irregular margins, microcalcifications or mixed calcification, and taller-than-wide shape [9,10]. However, sonographic features of thyroid nodules after RAI therapy seem to lose their predictive role for malignancy. Thyroid nodules in individuals with a prior history of RAI treatment are generally associated with a lower likelihood of malignancy, unless the nodule had harbored malignancy before the RAI therapy itself, potentially overlooked or missed during initial assessments.

Risk of malignancy in post-rai therapy patients

The extensive use of RAI therapy raises concerns regarding its malignant potential for thyroid cancer. Conflicting data exists regarding the risk of thyroid malignancy in individuals who have undergone RAI treatment for benign thyroid diseases [11-13]. In our own observations, the risk of malignancy after RAI therapy in benign thyroid diseases appears negligible, given that pre-therapy nodules have been confirmed as benign either through sonographic examination or fine-needle aspiration cytology (FNAC). This perspective is grounded in the low dose of iodine administered and the occurrence of cell death rather than a carcinogenic effect.

Our recommendation is to correlate thyroid ultrasound features post-radioiodine therapy with patient's history. This correlation is crucial to prevent potential misguidance for both the sonologist and the patient, thereby avoiding unnecessary FNAC or surgery as well as psychological trauma to patients.

To avoid misdiagnosis in managing post-RAI therapy patients, a collaborative and comprehensive approach between treating physicians and sonologists is crucial. Here are the key steps:

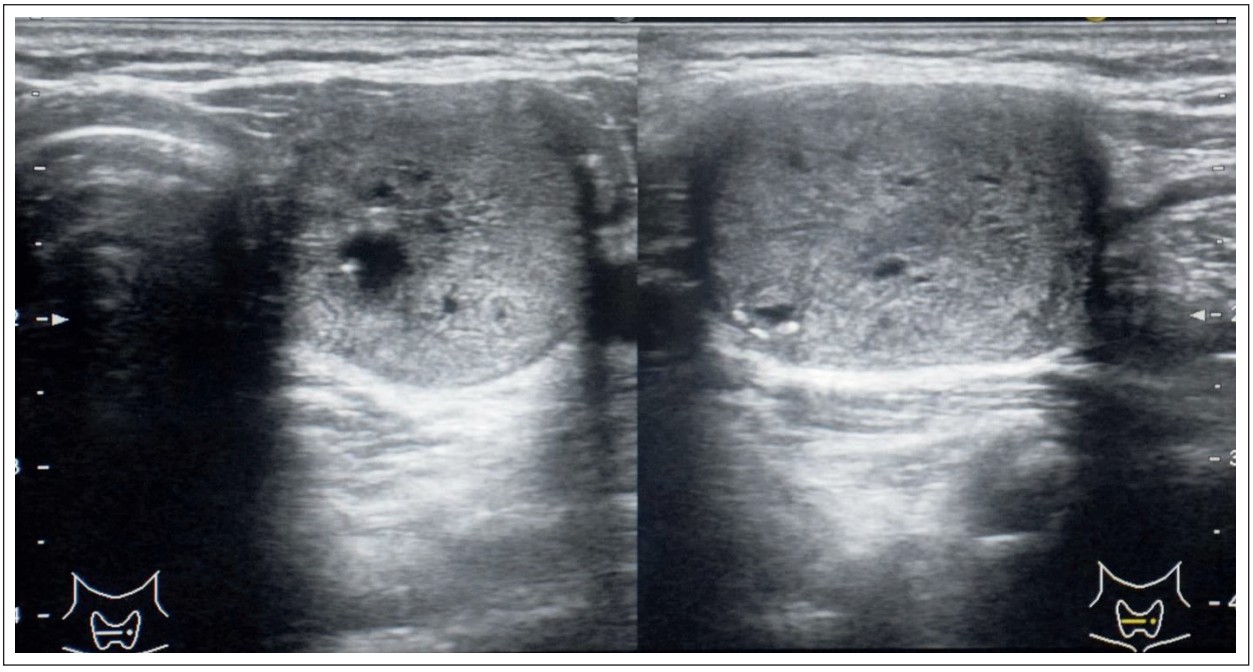

Figure 1. *Ultrasound image of a thyroid nodule with suspicious features, due to post-radioactive iodine ablation changes; displaying a solid nodule, heterogeneous echotexture, and mixed calcifications, commonly seen in post-treatment tissue alterations.*

1. Thorough patient history correlation
   - Treating physicians should provide a detailed patient history, including pre-therapy nodules' confirmation as benign through sonography or FNAC.
   - Sonologists should meticulously correlate post-RAI ultrasound findings with this patient's history to avoid misinterpretation of sonographic features.
2. Cautious interpretation of sonographic features
   - While sonographic features are useful in identifying suspicious nodules before RAI therapy, their predictive role post-therapy may diminish.
   - Sonologists should exercise caution in interpreting sonographic features and recognize that these features alone may not be reliable indicators of malignancy in post-RAI patients.
3. Utilization of thyroid imaging reporting and data system
   - TIRADS can be a valuable tool for sonologists in standardizing risk assessment for ultrasonographic diagnosis of malignant thyroid nodules.
   - However, it is essential to recognize that sonographic features may exhibit variations in post-RAI patients, and clinical judgment should supplement TIRADS scoring.
4. Communication between treating physicians and sonologists
   - Establishing open communication channels between treating physicians and sonologists is critical for sharing relevant patient information and discussing potential diagnostic challenges.
   - Regular interdisciplinary meetings can enhance collaboration and ensure a holistic understanding of each case.
5. Consideration of cytological and histological changes
   - Recognize the unique cytological and histological changes induced by RAI therapy, including distinctive features in FNA smear cytology and histological analysis.
   - Pathologists should be aware of these changes to differentiate benign processes from potential malignancy.
6. Risk-benefit assessment
   - Treating physicians and sonologists should engage in a risk-benefit assessment, considering the potential risks of overdiagnosis leading to unnecessary interventions.
   - Individualized decision-making should factor in patient-specific characteristics and the nature of pre-existing thyroid nodules.
7. Long-term follow-up
   - Establish a systematic long-term follow-up plan for post-RAI patients to monitor any evolving changes in thyroid nodules.
   - Regular imaging and clinical assessments can aid in identifying any concerning developments and guide appropriate interventions.

By implementing these steps, a collaborative and cautious approach can be adopted to minimize the risk of both overdiagnosis in post-RAI therapy patients. Regular communication and a nuanced understanding of the unique challenges presented by RAI therapy contribute to improved patient care and outcomes.

Conclusion

This commentary underscores the multifaceted aspects of radioactive iodine therapy, from its properties and mechanisms to the induced cytological, histological, and sonographic changes. Recognizing the complexities surrounding post-RAI malignancy risk, we advocate for a comprehensive approach, involving a thorough patient history correlation to guide accurate clinical decision-making.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Consent to participate

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Ethical approval

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