JAMA Network Open

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Radioactive Iodine Treatment in Hyperthyroidism and Cancer Mortality—A Still Controversial Issue

Bernadette Biondi, MD

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Hyperthyroidism is a severe condition of thyroid hormone excess.[1] Graves disease (GD), toxic multinodular goiter, and toxic adenoma are the most common causes of hyperthyroidism in younger individuals living in areas with iodine sufficiency and in older individuals in iodine-deficient regions.[1] Hyperthyroidism has been associated with an increased risk of coronary heart disease mortality and incident atrial fibrillation, even in patients with subclinical hyperthyroidism with an undetectable serum thyroid-stimulating hormone level but particularly in older patients and in those with underlying heart diseases.[1] Therefore, fast and effective control of hyperthyroidism is necessary to avoid adverse outcomes.

There are currently 3 main treatment options available for hyperthyroidism: (1) medical treatment with antithyroid drugs (ATDs), (2) radioactive iodine (RAI) therapy, and (3) surgery.[1] Each treatment has specific benefits and risks, which is why international guidelines for the management of hyperthyroidism support the use of personalized treatment according to clinical conditions, a risk-benefit analysis, and patient preferences.[2]

Medical treatment with ATDs is the primary treatment in hyperthyroidism caused by GD. Although associated with rare but serious adverse effects, it gives patients a 40% chance of remission.[1] In Europe, approximately two-thirds of the members of the European Thyroid Association prefer a first approach with ATDs.

RAI therapy or surgery are definitive treatment options that, due to the permanent destruction or removal of the thyroid gland, result in hypothyroidism.[1] RAI is used to cure patients with subclinical and overt hyperthyroidism due to toxic multinodular goiter or toxic adenoma, where remission is not feasible.[1] Approximately one-third of patients with hyperthyroidism require 2 or more I-131 treatments to be cured. RAI is usually the second-line treatment in patients with GD who relapse after initial thionamide treatment, in those who do not tolerate ATDs, and in those with cardiac diseases. However, RAI is the preferred first-line therapy for GD in the United States and the United Kingdom because it is associated with a higher cure rate and lower relapse rate compared with ATDs.[3]

In recent years, conflicting data have been published on the risk of malignant neoplasms in patients with hyperthyroidism following RAI.[4,5] However, hyperthyroidism itself has been associated with an increased risk of cancer, supporting a potential role of thyroid hormone excess on carcinogenicity.[6] In addition, an increased overall risk of cancer and greater cancer mortality has been reported with ATDs therapy when compared with RAI.[7]

The body of evidence on a potential association between RAI treatment and cancer incidence and mortality in patients with hyperthyroidism is still highly heterogeneous because the biological effects of RAI on different tissues are difficult to assess. On the contrary, 2 recent meta-analyses did not find any association between RAI and the risk of incident cancer[4] or cancer mortality[5] in patients with hyperthyroidism. Nevertheless, most studies have some important methodological limits, such as the lack of a control group including patients with hyperthyroidism who are treated with therapies other than RAI and the lack of evaluation of some potential confounding factors, such as smoking, obesity, and alcohol consumption.

In the first analysis of data from a large multicenter trial, the Cooperative Thyrotoxicosis Therapy Follow-up Study, a modest increased risk of solid cancer was reported in patients with

hyperthyroidism treated with RAI, suggesting a dose-dependent association between the total administered RAI dose and solid cancer mortality.[8] In a subsequent cohort of patients with hyperthyroidism treated with RAI, ATDs, surgery, or combination treatment from the United States and the United Kingdom, the authors extended the follow-up (median follow-up, 26 years) to assess the association between the specific treatment received to control hyperthyroidism and the long-term risk of solid cancer death. No statistically increased risk of death or solid cancer mortality was found across treated groups when compared with an external cohort of patients without hyperthyroidism. However, the risk of death from solid cancer increased after the total administered activity of RAI.[9]

Elsewhere in *JAMA Network Open*, Shim and colleagues[10] performed a systematic review and meta-analysis, including 12 observational studies with 479 452 participants, to assess the incidence and mortality of total cancer and site-specific cancer associated with the use of RAI therapy in hyperthyroidism.[10] Most included studies were performed in North America and Europe. Notably, 9 cohort studies were considered of high and moderate quality and only 3 of relatively low or very low quality. This meta-analysis included appropriate control groups for comparison: patients with hyperthyroidism receiving other treatments (surgery, ATD, or both), patients with hyperthyroidism receiving no treatment, and individuals from the general population unexposed to RAI treatment. The results of this meta-analysis showed that RAI therapy was not associated with significant increased risks of total or site-specific cancer incidence or mortality, except for the risk of thyroid cancer (standardized mortality ratio, 2.22; 95% CI, 1.37-3.59). The overall pooled cancer incidence and mortality ratios were 1.02 (95% CI, 0.95-1.09) and 0.98 (95% CI, 0.92-1.04), respectively, for exposure vs nonexposure to RAI therapy. Despite the fact that the overall pooled cancer risk was not significant, a linear dose-response association was found between RAI therapy and solid cancer death. The tumor-specific mortality from solid cancer increased significantly as the RAI administered dose increased, suggesting a linear dose-response association between RAI therapy and solid cancer; however, these findings were provided by only 2 studies that included information on RAI administered activity. The overall results of this important meta-analysis suggest that the risk of radiation-induced cancer following RAI therapy for hyperthyroidism is small and, in observational studies, may only be detectable at higher doses.

The limited quality of the evidence in the literature on the adverse effects of RAI underlines the need for future randomized clinical trials in this area. More research is still needed to determine the risk of developing malignant neoplasms after RAI therapy and to prove a causative role of RAI in the development of cancer.

Future data should include large prospective randomized clinical trials with long-term follow up to clarify the potential adverse effects of RAI therapy vs ATDs. The underlying etiology and severity of hyperthyroidism, cumulative dose of RAI, and important covariates should be considered in future reports to perform subgroup analysis. The evaluation of comorbidities and the genetic background for malignant neoplasms could be helpful for identifying a potential group of patients with hyperthyroidism at a higher risk of adverse effects after RAI.

Despite the limitations, the current analysis from recent literature studies is reassuring on the potential negative effects of RAI. These data can help reduce anxiety in both patients and clinicians as to the risk of cancer after RAI.

ARTICLE INFORMATION

Published: September 17, 2021. doi:10.1001/jamanetworkopen.2021.26361

Corresponding Author: Bernadette Biondi, MD, Department of Clinical Medicine and Surgery, University of Naples Federico II, Via S. Pansini 5, 80131 Naples, Italy (bebiondi@unina.it).

Author Affiliation: Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy.

Conflict of Interest Disclosures: None reported.

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