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## **Discussion on Radioactive Iodine Treatment of Hyperthyroidism and The Risk of Induced cancer**

### **Traitement par iode-131 des hyperthyroïdies et risque de cancer : mythe ou réalité**

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## **Abstract**

Iodine-131 ( $^{131}\text{I}$ , radioiodine) has been used for over eight decades for the treatment of Graves' disease, either as initial therapy or following failure of thionamides, as well as for the treatment of autonomous thyroid nodules.  $^{131}\text{I}$  treatment is simple to administer, effective, and relatively inexpensive. Recently, there has been some turmoil after a study published in JAMA Internal Medicine reported an increased risk of cancer from  $^{131}\text{I}$  treatment. The impact was of short duration however, as the paper received severe criticisms from many nuclear medicine physicians as well as from endocrinologists. Here we explain why that paper's conclusions are doubtful. We also review the major data on the topic of  $^{131}\text{I}$  therapy of hyperthyroidism and the risk of cancer.

***Hyperthyroidism,  $^{131}\text{I}$ , radioactive iodine, cancer, secondary cancer, radioiodine therapy***

## Résumé

L'iode-131 est utilisé depuis presque huit décennies dans le traitement de l'hyperthyroïdie liée à une maladie Basedow ou à une pathologie nodulaire toxique. Le traitement par  $^{131}\text{I}$  est simple à administrer, efficace, et relativement peu onéreux par rapport aux autres alternatives thérapeutiques. Récemment, il y a eu une certaine turbulence suite à une publication dans « JAMA Internal Medicine » signalant un excès de cancer lié au traitement par  $^{131}\text{I}$ . L'impact a toutefois été de courte durée, cette étude ayant essuyé un grand nombre de critiques méthodologiques de médecins nucléaires à travers le monde mais aussi d'endocrinologues. Dans ce papier nous expliquons les faiblesses de cette étude et résumons les données de diverses autres études sur le sujet.

*Hyperthyroïdie,  $^{131}\text{I}$ , « irathérapie », cancer, cancer radio-induit*

Concerns on whether iodine-131 ( $^{131}\text{I}$ , radioactive iodine, RAI) treatment for hyperthyroidism confers an increased risk of cancer have always been a subject of high interest. Recently there has been a transient decline in the number of patients referred for  $^{131}\text{I}$  after a paper published in a major journal “JAMA Internal Medicine” reported an increased risk of cancer [1]. This trend was of short duration, however; here we explain why that paper’s conclusions are doubtful.

The study by Kitahara et al. was a new analysis of the Cooperative Thyrotoxicosis Therapy Follow-up Study (CTTFS) which was last updated in 1998 [2]. In this new analysis, Kitahara et al introduced a biokinetic model of multi-organ dosimetry to retrospectively estimate patient-specific radiation doses at organ level and projected that  $^{131}\text{I}$  therapy was responsible for 14% of the breast cancer deaths and 7% of deaths from other solid cancers [1]. Their analysis included 18805 patients (mean study entry age 49 years; 78% women; 93.7% had Graves’ disease; 34.1% had multiple  $^{131}\text{I}$  treatments). The mean total administered  $^{131}\text{I}$  activity was 391 MBq (~10.6 mCi) (tertiles: 160, 289, and 724 MBq). In a projection of their findings, considering patients receiving 370-555 MBq  $^{131}\text{I}$  for Graves’ disease, the authors concluded that for every 1000 patients treated with  $^{131}\text{I}$  at the age of 50, an estimated lifetime excess of 18 to 31 solid cancer deaths would occur (including 4 to 6 breast cancers) and that the majority of them (~80%) would occur more than 20 years after treatment [1].

Although the publication received extreme attention from the media, with an Altmetric score exceeding 300, many nuclear physicians around the world, having scrutinized the data, raised skepticism as to the method and conclusions, with many letters and editorials rapidly appearing in the main nuclear medicine journals [3-6].

In an Invited Commentary published in the Journal of Endocrinology and Metabolism we called attention to significant design flaws in the Kitahara et al. study highlighting the following points [7].

- The analysis assessed whether greater absorbed radiation doses to specific organs were associated with increased mortality risk from specific cancers; however, because this analysis was negative for haematological cancers and for the 16 analyzed solid cancers (except borderline significance for breast cancer), the authors decided to sum-up all solid cancers, while arbitrarily using the dose to stomach as the reference [1]. The rationale for this additional analysis, which is not based on the initially planned analysis of absorbed organ dose, is unclear and unjustified [7].
- CTTFS included patients treated between 1946 and 1964 with clinical follow-up to 1968, and many patients were lost to follow-up, with no information available for a large percentage of patients in this last analysis [1,7].
- The CTTFS study was initially designed to compare cancer risk between RAI-treated patients and those treated differently. The last report of the CTTFS data by Ron et al. [2], with 21 years mean follow-up, concluded that RAI was not linked to cancer deaths (except thyroid cancer, with the underlying thyroid disease appearing to play a role). In 1998 Ron et al. found increased risk of breast and lung cancer in patients treated with surgery (most of them had also received thionamides), but not in those treated with RAI [2]. Surprisingly, Kitahara et al. decided not to report data on patients who were not treated with  $^{131}\text{I}$ , which constituted the control groups of the CTTFS study [1,7].
- The CTTFS study used data collected in the 1960s, when even smoking was not a known confounder of cancer risk and severity of Graves' disease. When studying cancer incidence, the risk of confounding factors in Graves' disease and

hyperthyroidism in general is now well recognized [8]. Establishing dose-response relationships does not fully protect against this risk. Confounding factors can be associated with the severity of hyperthyroidism and also with the total administered  $^{131}\text{I}$  activity [7].

- In addition to CTTFS, there are other major studies that also concluded that RAI does not contribute to increased cancer risk [8,9]. We also raise concern on the absence of analysis or discussion of the increased morbidity that would be caused by alternative therapies for hyperthyroidism [7].

Interestingly, two of the co-authors of the study by Kitahara et al., later published data showing that the increase in standardized mortality ratio (SMR) for breast cancer was higher for patients treated only with anti-thyroid drugs (SMR 1.86; CI 1.29-2.58) than in patients treated with  $^{131}\text{I}$  (SMR 1.11; CI 0.94-1.3) [10]. This finding of higher mortality with the use of thionamides was also reported in the previous report by Ron et al. [2].

Concomitant with our Commentary in JCEM, the British Thyroid Association and the Society for Endocrinology published a joint statement in the journal “Clinical Endocrinology”, where they expressed concerns that the article by Kitahara et al may lead patients to reject the use of RAI therapy to manage hyperthyroidism [11]. They stated: “Recent observations have shown the importance of achieving good control of hyperthyroidism in a timely fashion to improve long-term cardiovascular and mortality outcomes. In this context, it would be unfortunate if patients were deprived of the option of rapid, effective control of their hyperthyroidism with radioiodine, due to concerns of cancer risk” [11].

When considering diverse confounding factors, it is important to recognize that hyperthyroidism itself increases the risk of several solid malignancies, including breast cancer [12-15].

Because thyroid cancer patients receive higher radioiodine activities as adjuvant therapy than those used for the treatment of hyperthyroidism, it would be helpful to also point out that results of a recent systematic review were also reassuring concerning risks of second cancers after radioiodine therapy [16]. We need to be careful, however, because the comparison between hyperthyroidism and thyroid cancer is not straightforward, requiring consideration of, not only the administered activities, but also the effective half-life of  $^{131}\text{I}$ , the area under the activity curve in the whole body and specific organs, and additional other parameters. Furthermore, thyroid cancer patients can have increased underlying genetic risk for developing other cancers. The timely publication of the systematic review by Yu et al. dispelled the conclusions of two papers from one team that tried to cast doubt on the risk-benefit from adjuvant  $^{131}\text{I}$  therapy in low and intermediate-risk thyroid cancer [17,18]; again based on biased data and incomplete analysis [15,19].

Attesting to the safety and effectiveness of RAI treatment in patients with hyperthyroidism, the UK National Institute for Health and Care Excellence (NICE) published new guidelines recommending  $^{131}\text{I}$  for first line therapy “Radioactive iodine is recommended as first line treatment for thyrotoxicosis with hyperthyroidism unless antithyroid drugs are likely to achieve remission or it is unsuitable” [20]. At present, the use of RAI for a first episode of hyperthyroidism varies widely from one country to another; being somewhat higher in the United States than in many European countries and rather low in Asian countries, as summarized in one recent report [21].



Importantly, a novel study by Gronich et al., reported on 16,637 patients treated for hyperthyroidism with  $^{131}\text{I}$  or thionamides (propylthiouracil, thiamazole), with 123,166 person-years of follow-up [22]. While the Kitahara et al. findings were based on a hypothetical model and derived cancer mortality, Gronich reported on actual observed cancer rates. With long-term follow-up, there was no association between radioiodine treatment and increased risk of overall cancer in univariate analysis ( $\text{HR} = 0.99$ ,  $p = 0.91$ ) or in multivariate analysis ( $\text{HR} = 1.01$ ,  $p = 0.95$ ) [22]. In an analysis of specific cancer types, an association with non-Hodgkin lymphoma was noted on univariate analysis, but not in multivariate analysis. The univariate analysis finding was not significant as a statistical (Bonferroni) correction was not performed for analysis of 20 cancer types (requiring a P value of  $< 0.0025$  to gain statistical significance).

In summary,  $^{131}\text{I}$  has been used for over eight decades for the treatment of Graves' disease, either as initial therapy or following failure of thionamides, as well as for the treatment of autonomous thyroid nodules.  $^{131}\text{I}$  treatment is simple to administer, effective, and relatively inexpensive [20,23]. Besides classical contraindications (i.e., pregnancy, breastfeeding), it is important to identify patients at risk for exacerbating Graves' orbitopathy and to use appropriate preventive measures [23,24]. Major studies have concluded that  $^{131}\text{I}$  therapy does not contribute to increased cancer risk [2,8,9,22]. Also, when discussing potential risks from  $^{131}\text{I}$  therapy, it is important to take into account risks from alternative treatments, including: cardiac and neurological consequences from uncontrolled thyrotoxicosis [25-28], surgical complications from increased use of thyroidectomies, marrow suppression (agranulocytosis) or hepatotoxicity from increased use of thionamides as well as small risks of thionamide-associated vasculitis and pancreatitis [29]. A study by Boelaert et al. on hyperthyroid patients

aged  $\geq 40$  yrs showed that mortality was increased during periods of thionamide treatment and after radioiodine not resulting in hypothyroidism, but not during follow-up after radioiodine-induced hypothyroidism [25]. It is only in understanding specific and related risks that clinicians can formulate the best therapeutic choices [7,30,31]. It is also important that we deliver valid information, for the patient to have a fully informed role in the choice of therapy [7]. This can be organized at an international level through a multidisciplinary work involving representatives of various medical specialties and patients' associations.

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