European Journal of Nuclear Medicine and Molecular Imaging (2019) 46:2410–2411
https://doi.org/10.1007/s00259-019-04522-1

LETTER TO THE EDITOR

Regarding the manuscript entitled "Association of Radioactive Iodine Treatment With Cancer Mortality in Patients With Hyperthyroidism"

Xin Zhang[1,2] · Guangliang Shan[3] · Qiang Liu[4] · Yansong Lin[1,2]

Received: 12 August 2019 / Accepted: 30 August 2019 / Published online: 6 September 2019

Dear Sir,

It is well known that as one of the time-tested safe and effective treatment modalities, RAI holds its superiority in hyperthyroidism control, particularly for patients who are not indicated for antithyroid drugs (ATDs) or surgery. We read, with great interest, the recent article by Kitahara and colleagues [1] published in "JAMA Internal Medicine" reporting the results of a "modest" positive association between greater organ-absorbed doses of radioactive iodine (RAI) and the risk of death from solid cancer.

We note that the authors did a great job in the field of low-dose radiation biological effects as a result of a large cohort size, a long-term follow-up, and an innovative method used to estimate organ- and tissue-absorbed doses. However, we are afraid that the conclusion might lead to anxiety and doubt of the value of RAI in hyperthyroidism from a simple glimpse of the conclusion. In fact, some essential issues should be noted for further discussion in case of any misinterpretations, as follows:

Lack of a necessary control cohort

In total, data from 31,332 patients with hyperthyroidism from 4 regional centers in the USA were collected in this study, while only patients treated with RAI therapy were enrolled for further study ($n = 18{,}805$) [1]. It is noteworthy that 11,774 patients treated with modalities other than RAI were excluded, accounting for up to 40% of the total patients. It is reasonable to use the excluded non-RAI patients as a fundamental control group to address the differential influence between treatment modalities (RAI vs. non-RAI) on mortality, thus providing the premise for a subsequent analysis of the radiation effects. Hence, the lack of a necessary control cohort would undoubtedly reduce the stringency of the conclusion and acceptance of this study.

Uncertainties regarding the absorbed dose estimation

It is well known that absorbed doses are more reliable if they are based on real-time measurements; however, this was impossible in this study, which was limited by its retrospective nature. Moreover, we note that the primary data, as well as the organ- and tissue-specific dose estimation, were calculated merely by a biokinetic model derived from the author's previous small sample study ($n = 197$), which is far from well recognized [2]. A small-sized estimation model is not representative enough to be applied to a large cohort ($n = 18{,}805$) with diversity in terms of demographic characteristics, iodine metabolism, disease duration, treatment preference of the doctors, etc. Therefore, dose estimation with a less representative biokinetic estimation model made the results uncertain and less convincing.

Interference of other therapies

If we take a further look at the enrolled cohort, we can see that only 46.1% of patients were treated with RAI alone, while

This article is part of the Topical Collection on Endocrinology

✉ Yansong Lin
linyansong1968@163.com

1 Department of Nuclear Medicine, Peking Union Medical College (PUMC) Hospital, Chinese Academy of Medical Sciences & PUMC, Dongdan Campus, No. 1 Shuaifuyuan Wangfujing Dongcheng District, Beijing 100730, China

2 Beijing Key Laboratory of Molecular Targeted Diagnosis and Therapy in Nuclear Medicine, Beijing, China

3 Department of Epidemiology and Statistics, Institute of Basic Medical Sciences, School of Basic Medicine, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China

4 Tianjin Key Laboratory of Radiation Medicine and Molecular Nuclear Medicine, Institute of Radiation Medicine, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

more than half (53.9%) of the patients were treated with the combination of RAI and ATDs or thyroidectomy, while the duration and sequence between RAI and the combination therapy remain unknown [1]. The effect of RAI on cancer modalities is inevitably interfered with by other treatments (surgery, ATDs, or both), making a subgroup analysis necessary to avoid interference from treatment modalities other than RAI, though the author admitted that "additional studies are needed of the risks and advantages of all major treatment options available to patients with hyperthyroidism."

The potential influence on the incidence and mortality of breast cancer among included patients

The study suggested that in RAI-treated patients with hyperthyroidism, the risk of death from breast cancer showed a modest positive association with greater organ-absorbed doses [1]. We know that breast cancer is the most commonly diagnosed cancer and the second most common cause of cancer-related death in women in the USA [3]. Of note, among the 18,805 patients in the study cohort, nearly 80% were women, and the mean (SD) age at entry was 49 (14) years, which is also a prominent period of the incidence and mortality of female breast cancer (from 35–39 to 45–49 years, with the relative rates jumping from 63.6 per 100,000 to 194.7 per 100,000 and from 6.6 per 100,000 to 19.5 per 100,000, respectively) according to the Surveillance, Epidemiology, and End Results (SEER) database [4]. High endogenous estrogen is also a known risk factor for breast cancer in women. According to the report by Akande and colleagues [5], estrogen levels may be 2- to 3-fold higher in women with hyperthyroidism compared with women with euthyroidism. Therefore, it remains unclear whether the likelihood of the incidence and mortality of breast cancer in this cohort was derived from hyperthyroidism or RAI. Moreover, the White race is also a well-established high-risk factor for breast cancer [6], while race constitution was not illustrated in the population characteristics in this study.

On the basis of the confounding factors mentioned above, the potential influence of both patient demographics and hyperthyroidism on breast cancer mortality cannot be excluded. Thus, a subgroup analysis might be necessary to address the probable effects of confounding factors.

Statistical analysis

Regarding statistical analysis, the lower 95% confidence interval (CI) limit of the RR was almost 1 in all the statistically significant results in this study, including the dose-response relationships for solid cancer mortality (95% CI, 1.02–1.10), female breast cancer (95% CI, 1.003–1.32) and all other solid cancers (95% CI, 1.01–1.10), suggesting no significant dose-response relationship with solid cancer mortality. Moreover, even if the results are statistically significant, they may not have clinical significance; hence, clinical evaluation and studies remain needed for further verification.

Conclusion

In conclusion, considering the profound influence of this study on the analysis of radiation effects, the five aspects we addressed in this letter deserve further attention and should remind our colleagues worldwide to interpret the results more carefully. Necessary control groups and further subgroup analyses are needed to improve the reliability of this study's conclusion before arguing the value of RAI, which is an effective and well-accepted method that has been tested for more than seven decades.

Funding information This study was funded by the National Natural Science Foundation of China (grant numbers 81771875 and 81571714) and the Medicine and Technology Innovation Project of the Chinese Academy of Medical Sciences (grant number 2016-I2M-2-006).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

References

1. Kitahara CM, Berrington de Gonzalez A, Bouville A, et al. Association of radioactive iodine treatment with cancer mortality in patients with hyperthyroidism. JAMA Intern Med. Published online July 1, 2019.
2. Melo DR, Brill AB, Zanzonico P, Vicini P, et al. Organ dose estimates for hyperthyroid patients treated with (131)I: an update of the thyrotoxicosis follow-up study. Radiat Res. 2015;184:595–610.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69:7–34.
4. Howlader N, Noone AM, Krapcho M, Miller D, et al. SEER cancer statistics review, 1975-2016, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2016/, based on November 2018 SEER data submission, posted to the SEER web site, April 2019.
5. Endogenous Hormones and Breast Cancer Collaborative Group, Key TJ, Appleby PN, et al. Sex hormones and risk of breast cancer in premenopausal women: a collaborative reanalysis of individual participant data from seven prospective studies. Lancet Oncol. 2013;14:1009–19.
6. Bradley CJ, Given CW, Roberts C. Race, socioeconomic status, and breast cancer treatment and survival. J Natl Cancer Inst. 2002;94:490–6.