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EDITORIAL

I-131 as adjuvant treatment for differentiated thyroid carcinoma may cause an increase in the incidence of secondary haematological malignancies: an "inconvenient" truth?

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Over the past 75 years [1], I-131 therapy (RAI) has played an important role in the treatment of differentiated thyroid cancer (DTC). Originally hailed in the popular press as a form of magic, it quite soon became evident that even this very specific, targeted drug is not without its long-term side-effects and complications. First reports of acute myeloid leukaemia in DTC patients treated with RAI were already published in the 1950s [2] by the group who first introduced I-131 for DTC. In the ensuing decades, many more scientific publications which examined the role of RAI in inducing secondary malignancies, emerged with differing results: some reports allege that RAI does induce not only haematological, but also possibly solid malignancies, whereas others could show that excess non-thyroid malignancy rates are observed before as well as after RAI, making a causal relationship unlikely.

Nonetheless, the suggestion that exposure to radioactive iodine might cause an increase in the rate of secondary haematological malignancies is not implausible. I-131 will, after oral or i.v. application, first circulate systemically before being taken up in DTC cells. Well-perfused organs such as the bone marrow are therefore exposed to similar radiation-absorbed doses as the blood itself — as was already shown in the 1960s [3]. As the red bone marrow is a highly proliferative tissue, it is also highly sensitive to any DNA-damaging agents or interventions (this is not just limited to radiation, but may also include cytotoxic chemotherapy), which may cause a short-term depression in complete blood cell counts (CBCs) [4, 5]. Furthermore, at least in theory, DNA damage to this highly proliferative tissue may in the long term contribute to the induction of malignant neoplasms. However, although only based on a few patients, there is also some evidence that the DNA damage to the blood is effectively repaired after RAI [6].

In the light of the above history, previously established data, and theoretical considerations, any prudent nuclear medicine physician should have informed patients of a potential risk of haematological malignancies after RAI.

Hence it is all the more puzzling why a recent larger, retrospective database study by Molenaar et al. [7, 8] caused considerable commotion for reporting that the rate of secondary haematological malignancies was elevated after RAI. This article was followed by a flurry of letters by a number of individual groups, detailing not only the possible methodological shortcomings of the paper, but also almost conveying a sense of outrage at the wording used for conclusions.

Certainly, it cannot be denied that the work by Molenaar et al. [7, 8] has methodological flaws which make the data difficult to interpret or, for that matter, accept. Whereas the total number of secondary haematological malignancies is sufficient for a reliable statistical analysis, the various subgroups by diagnosis each are comprised of such a small number of patients that an analysis by specific diagnosis may be

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unjustified. Also the paradigm of treatment with ionizing radiation, namely the causal relationship between absorbed dose (or even simpler, as used in many epidemiological studies, administered activity) and effect is completely neglected.

The attempt by Molenaar et al. to show values of bone marrow absorbed doses in their supplementary figure 5 [7] neglects many years of successful research on dose–effect relationships for bone marrow toxicity after RAIs. Further potential shortcomings have been described in sufficient detail in the various responses to the paper by Molenaar et al. that they need not be repeated here in detail.

Still, the reaction to this paper may not just be driven by mere methodological concerns alone. Unfortunately, in most parts of the world the need for post-operative RAI is increasingly called into question, especially for low- and intermediate-risk patients. This trend is driven mainly by endocrinologists practicing in expert reference centres, where most patients are optimally diagnosed and treated before possible RAI. Whether RAI in such patients may or may not be beneficial is a whole different topic in itself; suffice it to say that the aggressive promotion of a RAI-free DTC treatment has caused many in the nuclear medicine community to worry about the quality of patient care. The strong reaction to the work by Molenaar et al. may therefore also have been driven in part by this existential concern.

Certainly, it cannot be denied that so far nuclear medicine at large has failed to adequately respond to the territorial onslaught brought upon RAI in DTC treatment. Instead of acting on and promoting decades of positive patient responses, extremely favourable outcome and a normal life expectancy observed in > 85% of DTC patients after RAI [9], nuclear medicine has thus far allowed itself to be driven into a position of reacting to largely non-data-driven suppositions and merely hypothetical scaremongering by colleagues either driven by an unjust fear of radionuclides or, even worse, a possibly merely territorially driven interest in retaining control of the patient. In this respect, the papers by Molenaar et al., and the reactions to the same, should be regarded as a wake-up call — nuclear medicine should be *acting* instead of *re-acting*.

What has gone largely unremarked, however, is that the data presented by Molenaar et al. can also be explained as strong evidence *in support of* radioiodine therapy in DTC. As was detailed in one letter to the editor, the data presented by Molenaar et al. allow the calculation of the absolute excess risk of haematological malignancies in DTC patients treated with RAI. This risk amounts to approximately one case per 10 million patient years [10]. Even assuming that all these cases will result in a fatality — which is hardly likely the case — RAI may still compare favourably to not giving RAI, e.g., by missing the diagnosis of and thereby timely treatment of distant metastases when this treatment modality is omitted [11].

Therefore, with benefit of some reflection, it appears prudent to recognize some possible truths with regard to RAI and secondary haematological malignancies. Firstly, both from historical and present data as well as from theoretical considerations it is not unlikely that RAI may induce an increase in the rate of secondary haematological malignancies. Secondly, while statistically significant, the effect appears to be small — so small as likely to be unnoticed in the individual physicians' life-long practice. So small in fact, that it may be less risky in terms of risk of mortality to perform RAI than to make a patient drive to the attending physicians' office more often - as would be necessary without RAI -, than taking an aspirin [12], or many other environmental risks from daily life.

Hence, until evidence from randomized trials has assessed the long-term prognostic impact of RAI, we are convinced and still believe that, as stated before [13], post-operative RAI remains an eminently sensible idea for most DTC patients.

Compliance with ethical standards

Conflict of interest None of the authors have any conflict of interest to report pertaining to this text.

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