Editorial

Red flag or red herring

I think everyone in the world knows what a red flag is. Though it is used as the flag of communism and socialism, it is also universally known as a flag of warning. A red flag on a beach means do not go into the water; a red flag on a train means stop the train.

The term red herring, however, may be less familiar to those from a non-English origin. Herrings are fish in the northern oceans which are about 20 cm long and fished for food. If anyone has seen a herring they know they are silver and not red. It appears in the 18th century herrings were smoked till they became red and were used to divert hunting dogs to go in the wrong direction. I expect most of us to meet a red herring in detective programs on television. The first suspect is never the actual criminal and the program's first 30 min is always spent "chasing these red herrings."

What has this to do with nuclear medicine? A recently published paper in the Journal of Clinical Oncology (JCO) has identified that patients with a history of differentiated thyroid cancer in whom radioactive iodine (RAI) was given as well as surgery had an increased risk of developing a secondary hematological malignancy.[1] They looked at an index of a standardized incidence ration (SIR) which compared the study group with aged-matched subjects which did not have the disease. They found the SIR was 155, which means that 55% more patients suffered from a hematological malignancy than their aged-matched controls though the overall incidence remains very small at <1% of patients receiving RAI.

The authors declare this should be a red flag to the use of RAI ablation postsurgery in patients with differentiated thyroid cancer. However, should this paper be taken as a true red flag which should change the standard practice of the last 40 years or is it a red herring.

The first piece of interesting data is that the SIR for hematological malignancies in those patients treated with surgery only is 119 which means even those patients who were never given any RAI had a risk of developing a secondary hematological cancer was 19% higher than aged-matched controls. This is not unexpected as we know that those patients who suffer one malignancy are more likely to get a second cancer. The second problem is that the two groups of patients are not identical. Surgery only is normally offered to patients with small primary tumors without nodal disease and histologically low-risk disease. RAI, however, tends to be given to those patients with more extensive disease at diagnosis or those with high-risk disease on histology. All this is explained in the most recent American guidelines for the treatment of differentiated thyroid cancer.[2] In the study, the authors did note that the patients who had RAI tended to have more advanced disease at diagnosis or had higher risk histology. Therefore, the two groups were not indeed matched.

Could there be another confounding aspect to this story? Again if the American guidelines are to be followed patients postsurgery and ablation tend to be put on doses of thyroxine (T4) replacement which are greater than physiological levels of T4. The theory being that any residual thyroid cancer cells are driven by thyroid stimulating hormone, the levels of which can be suppressed by higher than normal levels of T4. This means that many patients after thyroidectomy and RAI are rendered mildly hyperthyroid. This itself can lead in the long term to issues such as osteoporosis, but in a study published over two decades ago, it was found that patients with hyperthyroidism from any cause was three times more likely to develop leukemia than aged-matched control.[3]

It may appear that the authors of the JCO paper have indeed found a red flag, but the use of RAI has proved to be a red herring. The real culprit may be the supra-physiological doses of T4 used. Maybe the time has come to have a real debate as to what level of supraphysiological thyroxine should be given but more importantly for how long and controversially is it needed at all.

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