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Comparison of empiric versus whole body/blood clearance dosimetry-based approach to radioactive iodine treatment in patients with metastases from differentiated thyroid cancer.

We read with interest the article by Deandreis *et al* [1] that compared a fixed activity approach to radioiodine treatment of metastatic differentiated thyroid cancer with a method based on whole body/blood clearance dosimetry. Similar survival was seen for both cohorts. This study highlights the continuing uncertainty regarding the lack of an optimal approach to treatment for the highest risk patients, as recognised by both EANM and ATA guidelines [2,3], and demonstrates the difficulty of performing retrospective analyses. It is notable that despite the treatment regimens and patient cohort characteristics at the two centres appearing to differ substantially, a personalised approach was taken in all cases, with patients in both cohorts receiving highly variable levels of cumulated activity, numbers of treatments and intervals between administrations. Patient follow up varied from 5 months to 31 years. The paper shows that a highly personalized approach is, in oncologic terms, extremely successful in considerably extending the lifespan of patients with distant metastases. Likely due to this great success, the comparatively smaller differences that may exist between the different approaches to personalization, if they exist, may have been obfuscated.

This article appears precisely 80 years after the initial development of radioiodine. The ablation of remnant thyroid following thyroidectomy and the treatment of persistent thyroid disease and distant metastases is surely one of the great success stories of cancer management. The pioneering work of clinician Saul Hertz and physicists Karl Compton and Arthur Roberts, following a luncheon talk by Dr Compton on “What Physics Can Do for Biology and Medicine” in November 1936, demonstrated the enormous potential of the fusion of nuclear physics and medicine, and led directly to what is possibly the closest conceivable approach to the ‘magic bullet’ for cancer [4]. Initial studies recognised that the effect of radiation on either healthy or malignant tissue is dependent on the amount of radiation delivered and, over 10 years before the development of the Anger camera, great efforts were made to calculate the *absorbed doses* (in Gy) delivered to thyroid metastases and to healthy organs [5]. The work led to the formation of the Radioactive Isotope Research Institute in Boston, Massachusetts in September 1946 with Dr Saul Hertz as the Director and Dr. S.M. Seidlin as the Associate Director. In the seminal paper by Seidlin *et al* [6] concerning treatment of metastatic thyroid cancer, an empiric activity of 3700 MBq (100 mCi) of I-130 NaI was administered concomitantly with 760 MBq I-131 NaI to deliver 90 Gy to the tumour. I-130 NaI was found to cause depression of leucocytes, and future administrations settled on treatment solely with I-131 NaI, although still with an administered activity of 3700 MBq.

This fortuitous combination of the ‘magic number’ with the ‘magic bullet’ paved the way for the use of radiotherapeutics and the paradigm was applied to the majority of further radiotherapeutics as they were developed. 3700 MBq, or multiples thereof, were subsequently administered for the treatment of adult and paediatric neuroendocrine tumours with I-131 mIBG, Y-90 DOTATOC and Lu-177 DOTATATE, the initial

treatment of liver metastases with Y-90 microspheres and more recently Lu-177 PSMA for bone metastases from prostate cancer.

Highly successful outcomes were reported in the article by Deandreis *et al* [1] without apparent correlations either with the whole body/blood absorbed doses or with the levels of activity administered. These factors are undoubtedly important but may not be sufficient to generate the improved outcomes that must be available with a more scientific approach. In a dawning era of personalised and precision medicine, radioiodine treatment of DTC affords the opportunity to realise the full potential of an individualised approach to treatment that could result in significant patient benefit. This can only be tackled by close collaborations between clinicians and medical physicists, based on the increasing evidence that outcome is dependent on the radiation doses delivered rather than on the activities administered [7]. The birth of nuclear medicine was blessed with a phenomenally successful cancer treatment by the visionary work of Hertz, Compton and Roberts. It is surely time to capitalise on their legacy to further improve the treatment, particularly for high risk and paediatric patients, with the application of imaging and lesion dosimetry in prospective multicentre clinical trials.

References

1. Deandreis D, Rubino C, Tala H *et al* Comparison of empiric versus whole body/blood clearance dosimetry-based approach to radioactive iodine treatment in patients with metastases from differentiated thyroid cancer *J Nucl Med* doi:10.2967/jnumed.116.179606 2016

2. Haugen, Alexander, *et al* American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer*.,* Thyroid. Jan 2016, 26(1): 1-133.

3. Luster M, Clarke SE, Dietlein M *et al*. Guidelines for radioiodine therapy of differentiated thyroid cancer. *Eur J Nucl Med Mol Imaging* 35:1941–59 2008

4. Hertz B Dr. Saul Hertz (1905–1950) Discovers the Medical Uses of Radioactive Iodine: The First Targeted Cancer Therapy Thyroid Cancer - Advances in Diagnosis and Therapy Ed. Ahmadzadehfar H, ISBN 978-953-51-2589-1 2016

5. Hertz S, Roberts A. Radioactive iodine in the study of thyroid physiology: the use of radioactive iodine therapy in hyperthyroidism. *J American Med Assoc* 131: 81–86 1946

6. Seidlin SM, Marinelli LD, Oshry E. Radioactive iodine therapy,effect on functioning metastases of adenocarcinoma of the thyroid *J Am Med Assoc*. 132(14):838–47 1946

7. Strigari L, Konijnenberg M, Chiesa C *et al***.** The evidence base for the use of internal dosimetry in the clinical practice of molecular radiotherapy *Eur J Nucl Med Mol Imaging* Oct;41(10):1976-88 2014

Glenn Flux
Joint Department of Physics
Royal Marsden Hospital
Sutton, UK

Frederik A. Verburg
Department of Nuclear Medicine
University Hospital Marburg
Marburg, Germany

Carlo Chiesa
Nuclear Medicine Division
Foundation IRCCS Istituto Nazionale Tumori
Milan, Italy

Manuel Bardiès
Centre de Recherches en Cancérologie de Toulouse
UMR 1037 INSERM Université Paul Sabatier
Toulouse, France

Katarina Sjögreen Gleisner
Department of Medical Radiation Physics
University of Lund
Sweden

Barbara Hertz
Curator
Saul Hertz, MD Archives

Mark Konijnenberg
Department of Nuclear Medicine
Erasmus MC Rotterdam
The Netherlands

Michael Lassmann
Department of Nuclear Medicine
University of Würzburg
97080 Würzburg, Germany
Germany;

Michael Ljungberg
Department of Medical Radiation Physics

University of Lund
Sweden

Markus Luster
Department of Nuclear Medicine
University Hospital Marburg
Marburg, Germany

Michael Stabin
Department of Radiology and Radiological Sciences
Vanderbilt University
US

Lidia Strigari
Regina Elena
NCI IFO
Rome, Italy