

## Scientific Session-2 Thyroid – 2

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### Radioiodine-negative, Somatostatin-Receptor PET-negative Thyroid Cancer: Current Status and Developments

Prof. Roy Moncayo, University of Innsbruck, Austria

No abstract available

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### Paediatric Thyroid Cancer

Prof. Isabel Roca, Servicio Medicina Nuclear, HGU Vall d'Hebron, 08035 Barcelona, Spain

No abstract available

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### rhTSH-stimulated Radioiodine Therapy in Metastatic Differentiated Thyroid Carcinoma: Indian Experience

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**Background:**  $^{131}\text{I}$  to be sufficiently taken up by thyroid cancer cells to deliver enough radiation absorbed dose for ablative therapy, thus requires high level of TSH stimulation not only for uptake of radioiodine but also to retain it for sufficient time to deliver desired radiation absorbed dose. The use of rhTSH is initially approved for  $^{131}\text{I}$  whole body scanning in late 90's, and now EMA and FDA have approved it for  $^{131}\text{I}$  remnant ablation. However, its utility and efficacy has yet to be proven in patients with metastatic disease in differentiated thyroid carcinoma (DTC).

**Patient and Methods:** The off-label use has been scantily reported in literature. We want to share our initial experience in last 8-years. We have used rhTSH in conjunction with  $^{131}\text{I}$  therapy in 46 patients (23 females; age range 26-79 years; 26 PCT and 20 FCT) with residual macroscopic disease in 4, metastatic in 36, recurrent disease in 6 patients on compassionate ground. All patients had undergone total or near-total

thyroidectomy, and all had received prior  $^{131}\text{I}$  therapy after T4 withdrawal, except 4 highly-educated patients who wanted to avoid hypothyroidism due to various reasons, asked for rhTSH stimulated radioiodine therapy (130 total treatments and 54 under rhTSH). Disease burden: bone metastases alone in 16, lungs 9, nodal 2, and 15 had multiple sites. Baseline median thyroglobulin level 452 ng/mL, ranged from 22 to 87540, reflecting the heterogeneity of the patient population.

**Results:** The median  $^{131}\text{I}$  administered activity is 370 mCi (ranged 100-1630; in 1 to 10 divided doses). Thirty patients had received single rhTSH stimulated  $^{131}\text{I}$  therapy, 10 received 2, and one has received 4 therapies by this protocol; serum TSH (just prior to  $^{131}\text{I}$ ) level varied from 95 to 212 IU/L. Clinical examinations, ECOG performance score, structural imaging using US, NCCT and MR when felt clinically appropriate and regular serum Tg and anti-Tg assays performed every 6 monthly. After median follow up of 4.3 years (range 1-9), 16 cases are disease free, 12 deaths: 11 died of disease, 1 due to myocardial infarction, and 18 are surviving with disease: 11 with partial remission (30% decrease in baseline Tg value) and 7 with stable disease (no change to <30% drop in Tg value). In follow-up visits, 7 patients with extensive skeletal metastases showed marked clinical improvement in pain and ECOG score. Those 11 patients died of progressive disease the median survival was 3.2 years ranged from 2-7 years after initial therapy in this protocol. No major rhTSH related adverse events were reported during the therapy, or subsequently in any patient. Twenty percent patients complained of mild headache and 7% had nauseating sensation.

**Conclusions:** From our encouraging initial experience, we conclude that rhTSH offers a promising alternative to conventional T4 withdrawal radioiodine therapy in advanced DTC. This result sets the stage for a large phase III clinical trial before it can be recommended as standard of care in clinical practice.

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**Radioiodine Therapy of Benign Thyroid Disorders**

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No abstracts available

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**Targeted radiotherapy and radiobiology**

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The role of ionizing radiation in cancer therapy is recognized worldwide. The three major approaches to deliver radiation to treat patients are: i) external beam radiotherapy ii) sealed source interstitial and intracavitary brachytherapy and iii) systemic delivery using unsealed sources, also called radionuclide, internal or targeted radiotherapy, including the use of receptor ligands, metabolic precursors or monoclonal antibodies. Radiation therapy is a local treatment, whose goal is to kill all clonogenic cells and to reach complete local tumour remission. It is surprising that to date dosimetry is largely empirical and radiation biology is not usually considered. Although advances in personalized radiation therapy have been achieved, the biological parameters that define individual radiosensitivity remain unclear. In fact, actual radiotherapy planning dosimetry is individualized in the sense that radiation is delivered much as possible to the target tumour avoiding normal tissues, and the radiation dose do not overpass the dose limits to critical organs. Identical purpose is applied to targeted radiotherapy, being the limiting normal tissues usually the red marrow but also lungs, liver, intestinal tract or kidneys. Much of the research in radiotherapy has been driven by technological advances, rather than by underlying biological parameters. The therapy effectiveness, depends on the total absorbed dose delivered to the tumor, the dose rate and the biologic response. The total dose and dose rate depend on the physical properties of the radionuclide, the injected activity, the non-uniform activity distribution, the biokinetics, the uptake, clearance within the tumor, etc. Dosimetric calculations usually are estimated using the MIRD formalism, where the S factor (mean absorbed dose in the target region per unit of activity accumulated) is dependent of geometrical and physical properties as anatomy, composition and

density of tumours. The anatomy, composition and density of tumours do not take into account the intrinsic response to radiation and could not be considered the correct parameters, owing to the recent developments on molecular and cellular biology. The radiobiologic parameters of interest, are intrinsic radiosensitivity, proliferation, hypoxia and the number of clonogenic cells. In fact, the 4Rs of radiobiology were initially described in an attempt to provide a means to understanding the success or failure of localized radiotherapy: i) the differential repair of tumour and normal cells between treatment fractions, ii) the redistribution of cells into more or less radiosensitive phases of the cell cycle, iii) the repopulation of tumour cells between fractions and iv) the re-oxygenation of tumour cells during treatment were all invoked to explain the net outcome of radiotherapy. Later, the system was revised to include intrinsic radiosensitivity into the 5Rs of radiobiology. The radiobiological response to radiation, 20are an important factor for the probability of local control following radiotherapy. In spite of targeted radiotherapy as a form of therapy for which the dose rate is continually varying, the linear quadratic (LQ) formulation may also be applied linking physical and biological factors. The BED - Biologically Effective Dose (Gy) concept is used in conventional radiotherapy and may also be used to quantify targeted radiotherapy. The two principal radiobiological parameters required in such assessments are the  $\alpha/\beta$  ratio, which provide a quantitative indication of the sensitivity of a given tumor and the sublethal damage recovery constant  $\lambda$ . The principal caveats associated with modeling-based assessments of targeted radiotherapy are: (1) lack of knowledge of some radiobiological parameters, (2) difficulties in incorporating exact temporal uptake/clearance profiles into the model, and (3) limitations in the LQ model. Within this model, the concept of biologically effective dose (BED) may be used to quantify the magnitude of the biological effect. The recent MIRD Pamphlet No. 21A (Generalized Schema for Radiopharmaceutical Dosimetry, J Nucl Med 50:477-484, 2009) introduces the concepts of EUD - Equivalent Uniform Dose (Gy), taken in account that the dose delivered to an organ is generally not uniform and BED which accounts for the dose rate variation in the case of radionuclide therapy. The fraction of cells surviving (SF) after irradiation as a function of the dose delivered (D) is often represented as:  $\ln(SF) = -\alpha D - \beta D^2$  where  $\alpha$  and  $\beta$  are parameters related to

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tissue radiosensitivity; the  $\hat{I}_{\pm}/\hat{I}^2$  ratio of these parameters determine the shape of a cell survival curve. Generally the term  $\hat{I}_{\pm}$  is thought to describe cell death from single hits, whereas the  $\hat{I}^2$  term has dose rate dependence. It is therefore thought that the  $\hat{I}^2$  term is of greater importance in targeted radionuclide therapy. The BED is considered to be the product of the total dose and a biological factor designated as the relative effectiveness per unit dose and is expressed by:  $BED = D (1 + D/\hat{I}) (\hat{I}_{\pm}/\hat{I}^2)$ . So, the term absorbed dose should be replaced by biologic effective dose. The clinical introduction of internal dosimetry for targeted radiotherapy has been slow, and is still far from being implemented routinely considering personalized biologic parameters. Recent studies, have shown that the administration of fixed activities result in a wide range of absorbed doses and that patient outcome is more likely to be correlated with biologic effective dose rather than absorbed doses. It is vital for patients' interests that dose assessment for tumor become a routine in clinical practice, aided by improved techniques and a significant improvement in our understanding of radiobiological considerations. Recent examples of targeted radiotherapy dosimetry considering biologic parameters will be outlined.