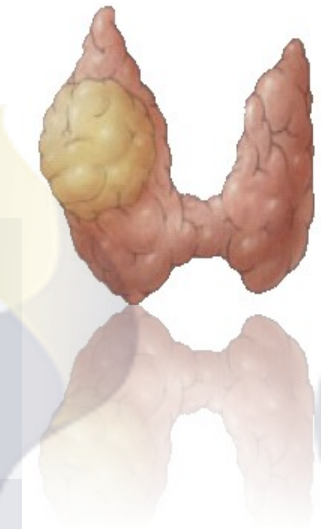
Philipps Universität Marburg

Radiobiology of I-131

Safety of RAI Treatment

markus.luster@med.uni-marburg.de



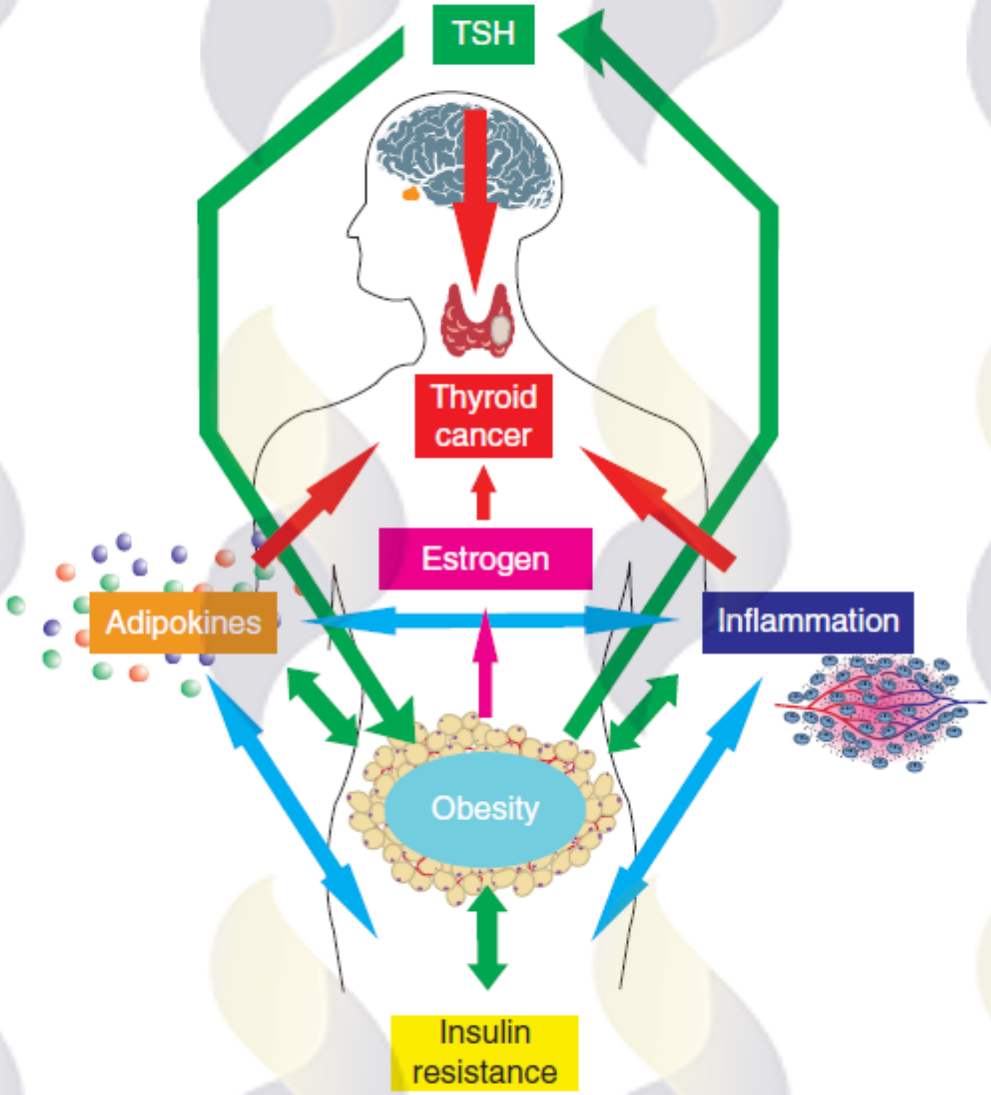
Disclosures

Consultant/ speaker for:

- AstraZeneca
- Bayer Healthcare
- Eisai
- GE Healthcare
- Ipsen
- Novartis
- Sanofi
- Takeda

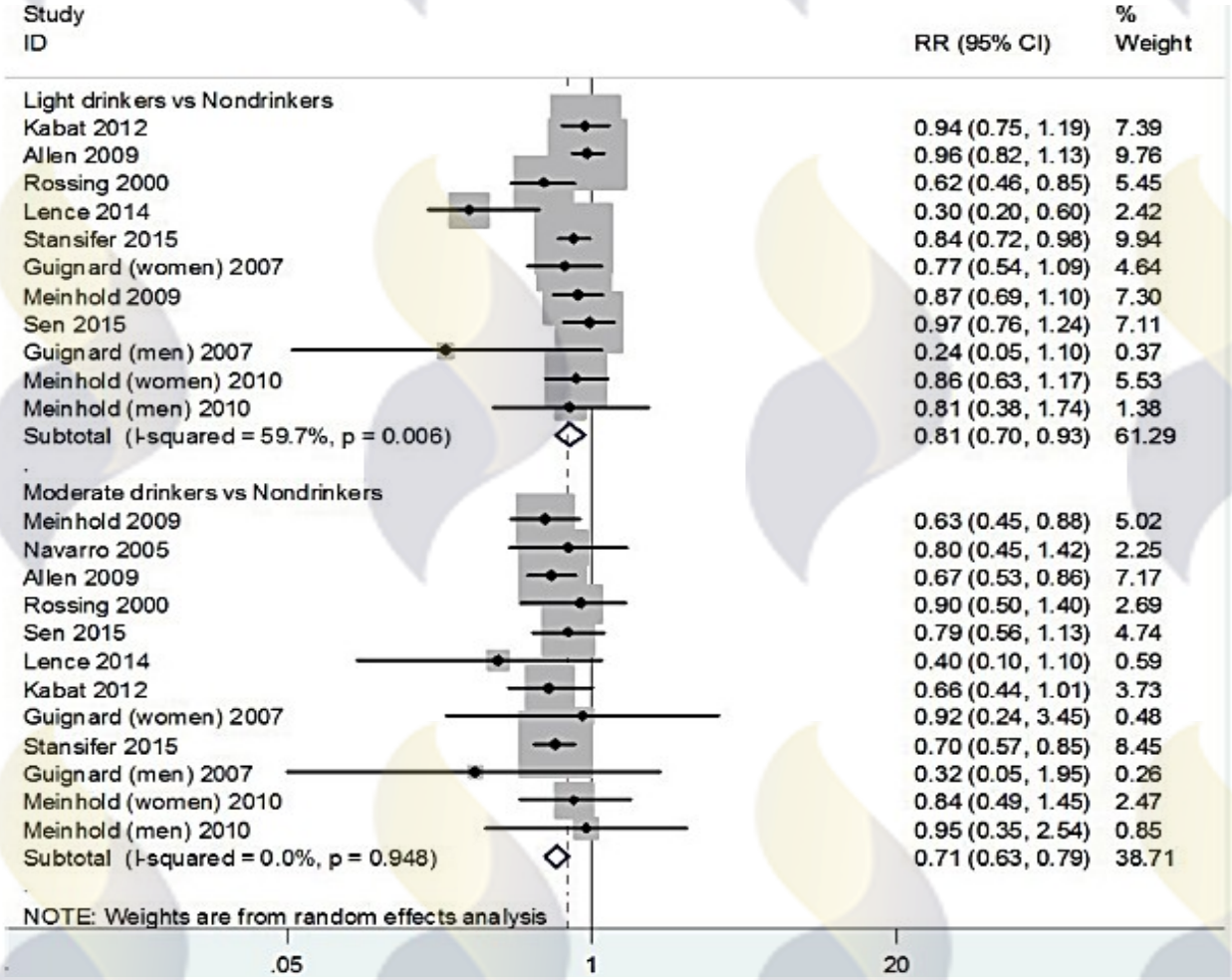
and for:

- Ohne Schilddrüse leben
- Thyroid Cancer Alliance
- Butterfly Thyroid Cancer Trust

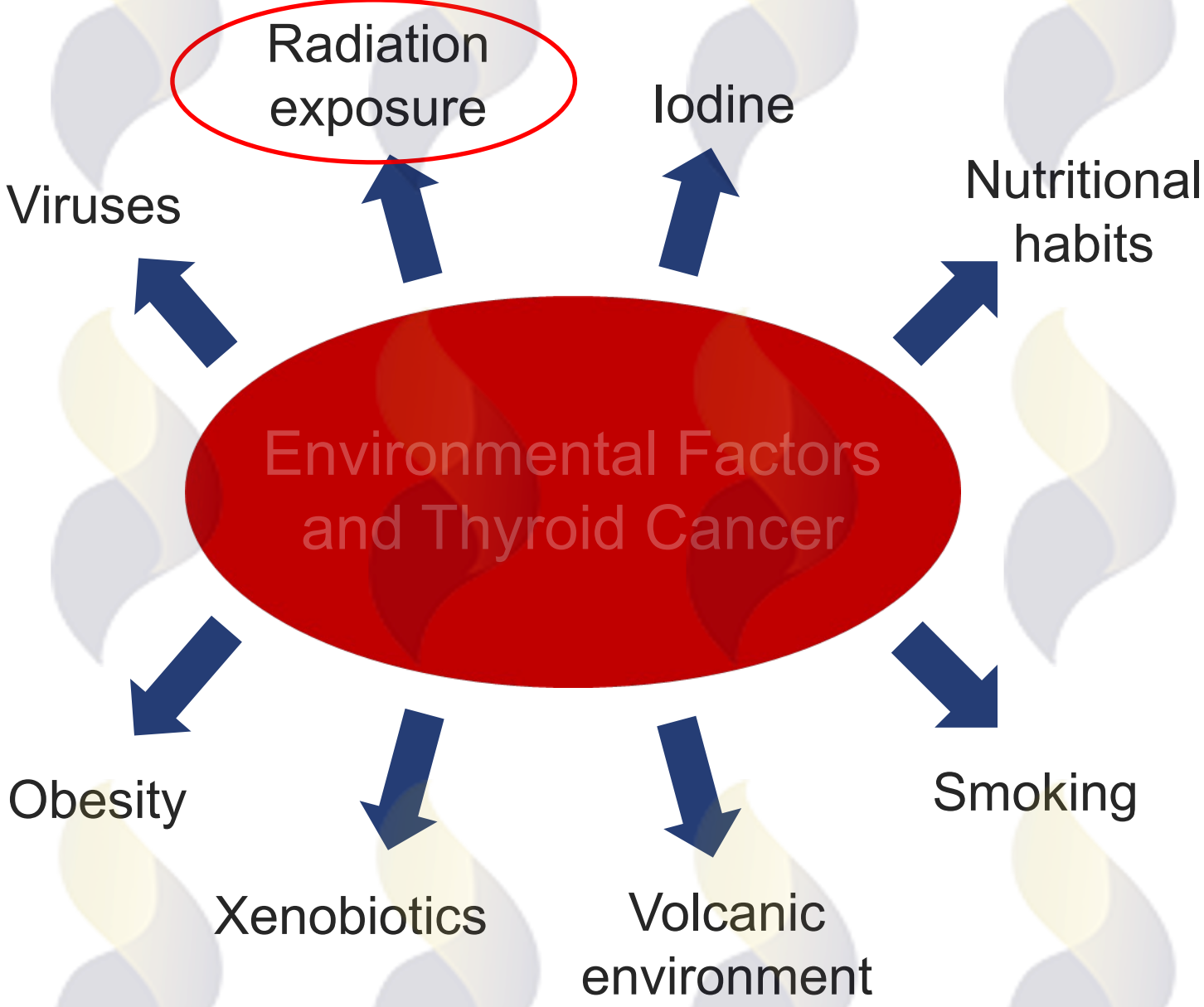


Marcello Endocrine Related Cancer 2014

Risk estimates of alcohol for thyroid cancer risk (light/moderate drinkers *vs* nondrinkers)

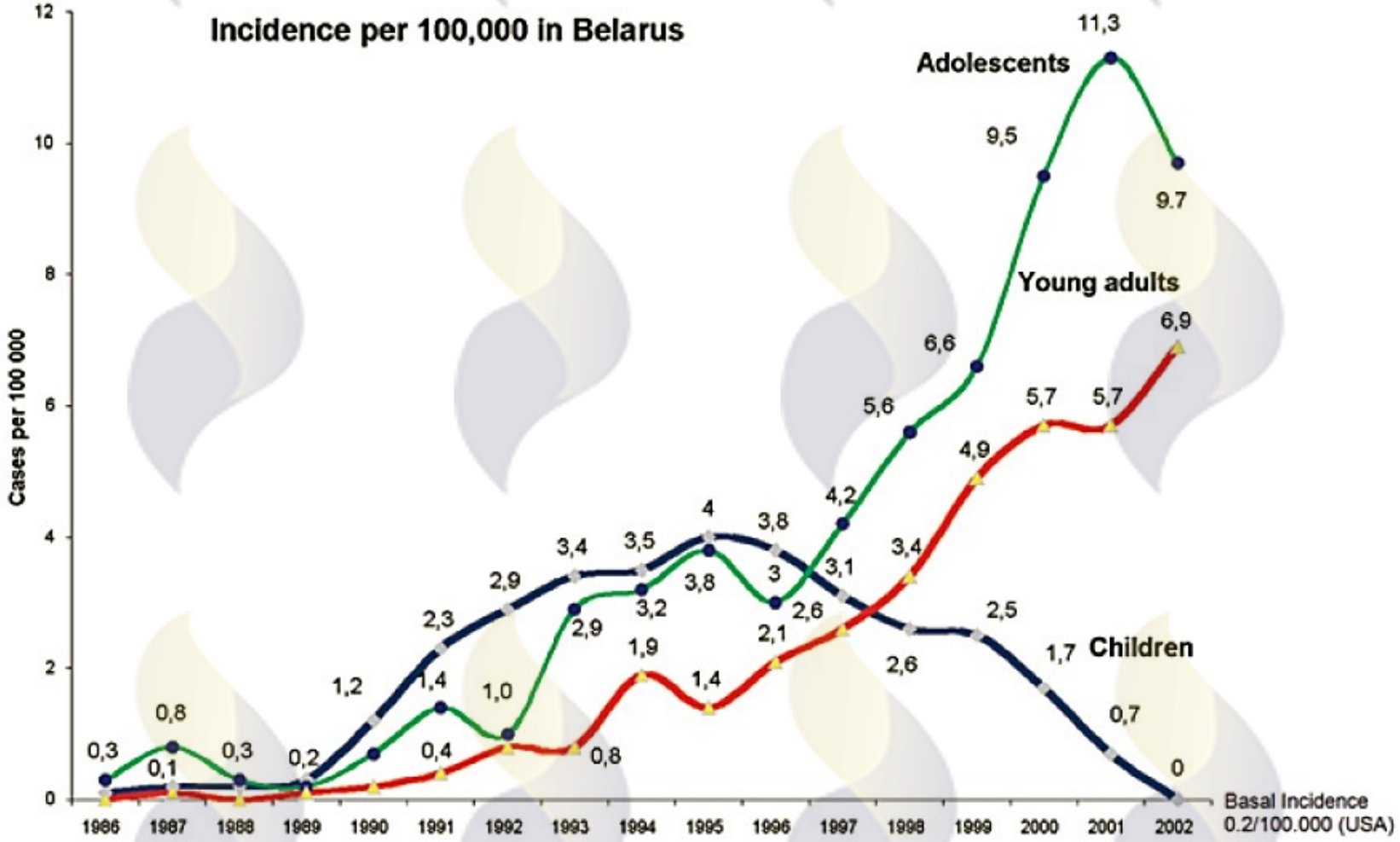


Wang Oncotarget 2016



Courtesy of Leonidas Duntas, Evgenideion Hospital, Athens, Greece

Thyroid cancer and radiation exposure



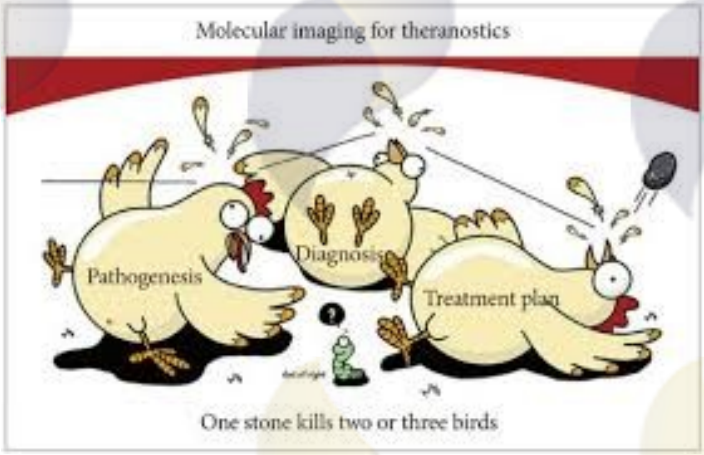
Reiners Hormones 2009

Recommendation for iodine thyroid blocking

Recommendation for iodine thyroid blocking

- To prevent radiation-induced thyroid cancer in highly vulnerable groups: foetuses, children, pregnant and breastfeeding women
- Intake of high doses of stable iodine at levels 100 to 1000 times higher than the daily dietary intake (mg)
- Based on prior radioactive fall-out scenarios
- Most effective (95%) if stable iodine is present shortly before the radioactive iodine exposure

Theragnostics: a “modern” concept



Keywords in personalised medicine:

- diagnostic test in combination with a therapy
- individual patient
  - optimal therapy
  - right dosage
  - targeted

“-Gnostic” = insight of:

- Diagnosis
- Therapy (using the same/similar molecule)
- Prognosis

Fundamental principle

- Test patients for possible response to undergoing a new form of treatment and to tailor a therapy for them based on the test results

- Pharmacogenetics, proteomics and biomarker profiling and functional imaging forms the backbone of theranostics

- In nuclear medicine, theranostics is easy to apply

- Know which sites require treatment (diagnostic scan) and confirm that those sites have been treated (posttherapy scan) > **Radiotheranostics**

Modified after: Jeelani J Pharm Bioallied Sci 2014, Jadvar Radiology 2018

Eur J Nucl Med Mol Imaging (2014) 41:199–201
DOI 10.1007/s00259-013-2609-2

EDITORIAL

Nothing new under the nuclear sun: towards 80 years of theranostics in nuclear medicine

Frederik A. Verburg · Alexander Heinzel · Heribert Hänscheid · Felix M. Mottaghy · Markus Luster · Luca Giovanella

Some time in the early 2000s, the word "theranostics" (or "theragnostics") started surfacing in the medical literature. Theranostics (from the Greek *therapeuein* "to treat medically" and *gnosis* "knowledge") is the use of individual patient-level biological information in choosing the optimal therapy for that individual

In the broader sense, the use of ^{18}F-fluorodeoxyglucose (FDG) PET/CT in oncology is a form of theranostics, especially when linked to a decision on therapy. This is especially evident in, for example, modern protocols for the treatment of lymphoma

In addition, a third aspect of nuclear medicine that is hidden that is in the word "theranostics" as much as therapeutics and diagnostics is prognostics. Many diagnostic tests in nuclear medicine are associated with a clear prognostic stratification.

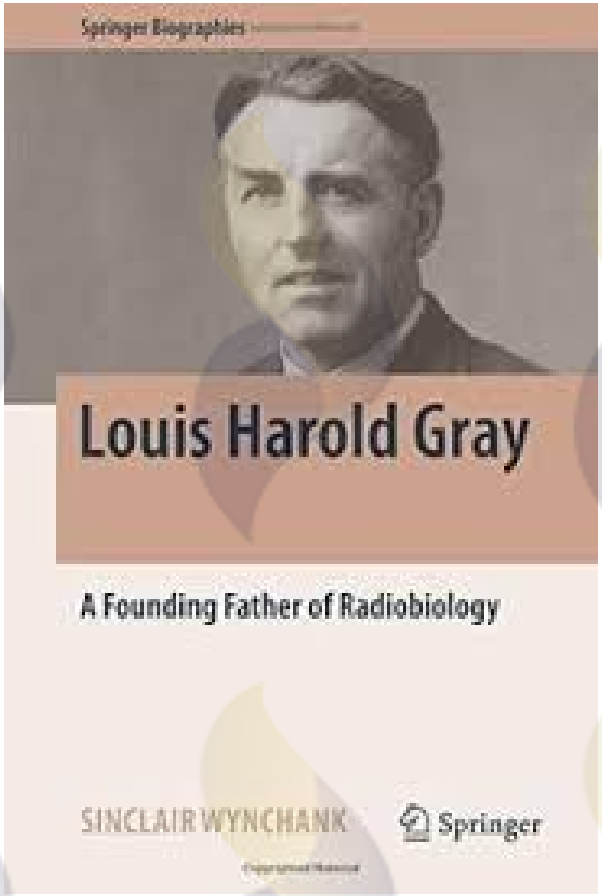
Radiobiology definition

Interactions of ionizing radiation on

molecular structures and

their induced effects on cells, tissues,

and organs, both normal and diseased



Pouget Frontiers in Medicine 2015

Seza´s pick

THYROID
Volume 00, Number 00, 2022

DOI: 10.1089/thy.2021.0522

Radioiodine Is Molecular Radiotherapy Governed by Predictable Deterministic Radiobiology Expressed in Gray, not Millicuries

Yung Hsiang Kao[i]

Dear Editor:

SYSTEMIC RADIONUCLIDE THERAPY such as radioiodine (^{131}I) have much to learn from the rapid scientific progtime integral of fractional uptake in target tissue, now known as Time Integrated Activity Coefficient, formerly known as Residence Time.

Parameters $\bar{E}$ and M are inherent to the metastases and

Radiobiology of radioiodine as molecular radiotherapy

Internal radionuclide therapy is fundamentally a form of low dose rate radiotherapy governed by biophysical laws with predictable dose-response effects

Critical parameter is the absorbed dose expressed in gray (Gy), not activity expressed in Curie (Ci) or Bequerel (Bq)

Without effort to calculate tumor absorbed doses patients cannot be appropriately stratified for meaningful outcomes

1 mCi (37 MBq) of radioiodine may result in tumor absorbed doses ranging from <1 Gy to >100 Gy

Biology

- Absorbed dose rates and absorbed dose distributions in space and time are very different between external irradiation and systemic radionuclide exposure and are likely to be the critical parameters in the radiobiological response

- Distinct radiation-induced biological responses are expected

Pouget Frontiers in Medicine 2015, Aerts EJNMMI 2021

Biology

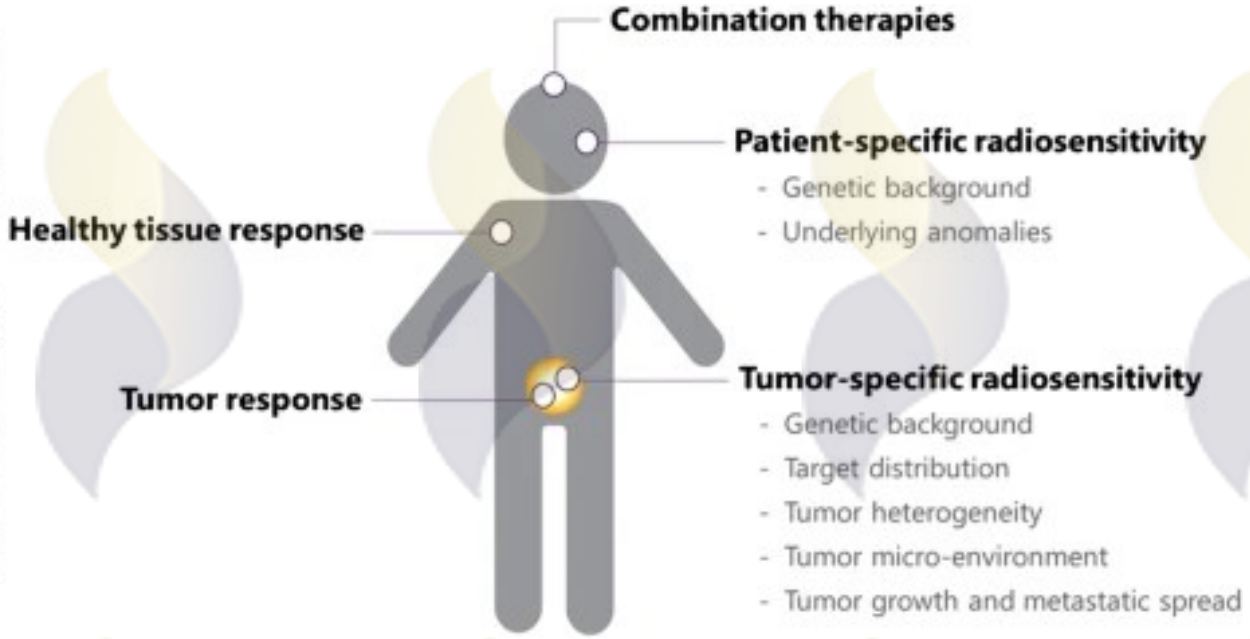
- Relative contribution of targeted and non-targeted effects in the organ and tissue responses to TRT needs to be determined
- Radiobiology findings and absorbed dose measurements will improve estimation and prediction of efficacy and adverse effects
- Basis for the development of radiosensitizing strategies and radioprotectant agents

Pouget Frontiers in Medicine 2015, Aerts EJNMMI 2021

Contributions of radiobiology to nuclear medicine

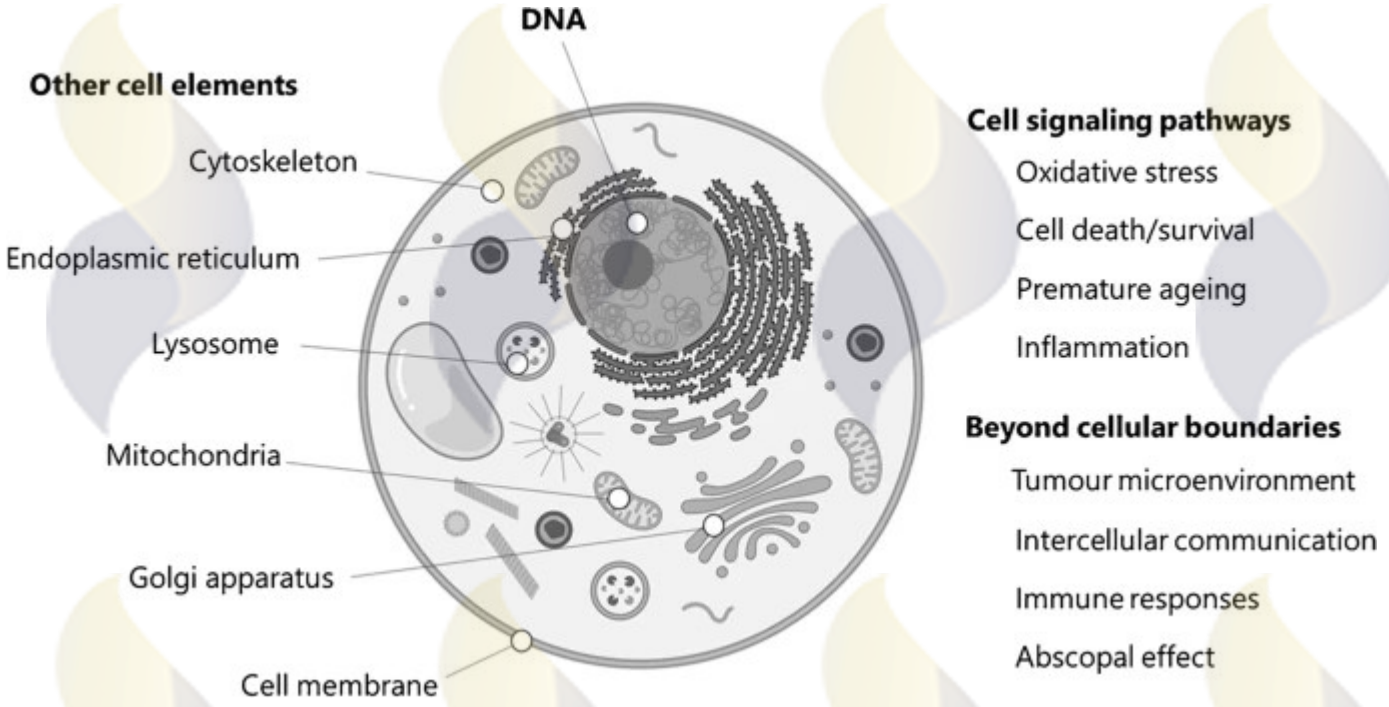
Physical parameters to be examined
- Radiation qualities
- Absorbed dose (rate)
- Spatio-temporal dose (rate) distributions

Endpoints to be assessed
- DNA damage and repair
- Damage to other cell elements
- Death/survival pathways
- Senescence/oxidative stress/inflammation
- Effect on the immune/systemic reactions
- Repair capacities



Aerts EJNMMI 2021

Interaction of ionizing radiation with cellular matter



Aerts EJNMMI 2021

Comparison of external beam and radionuclide therapy

Conventional External Beam Radiotherapy

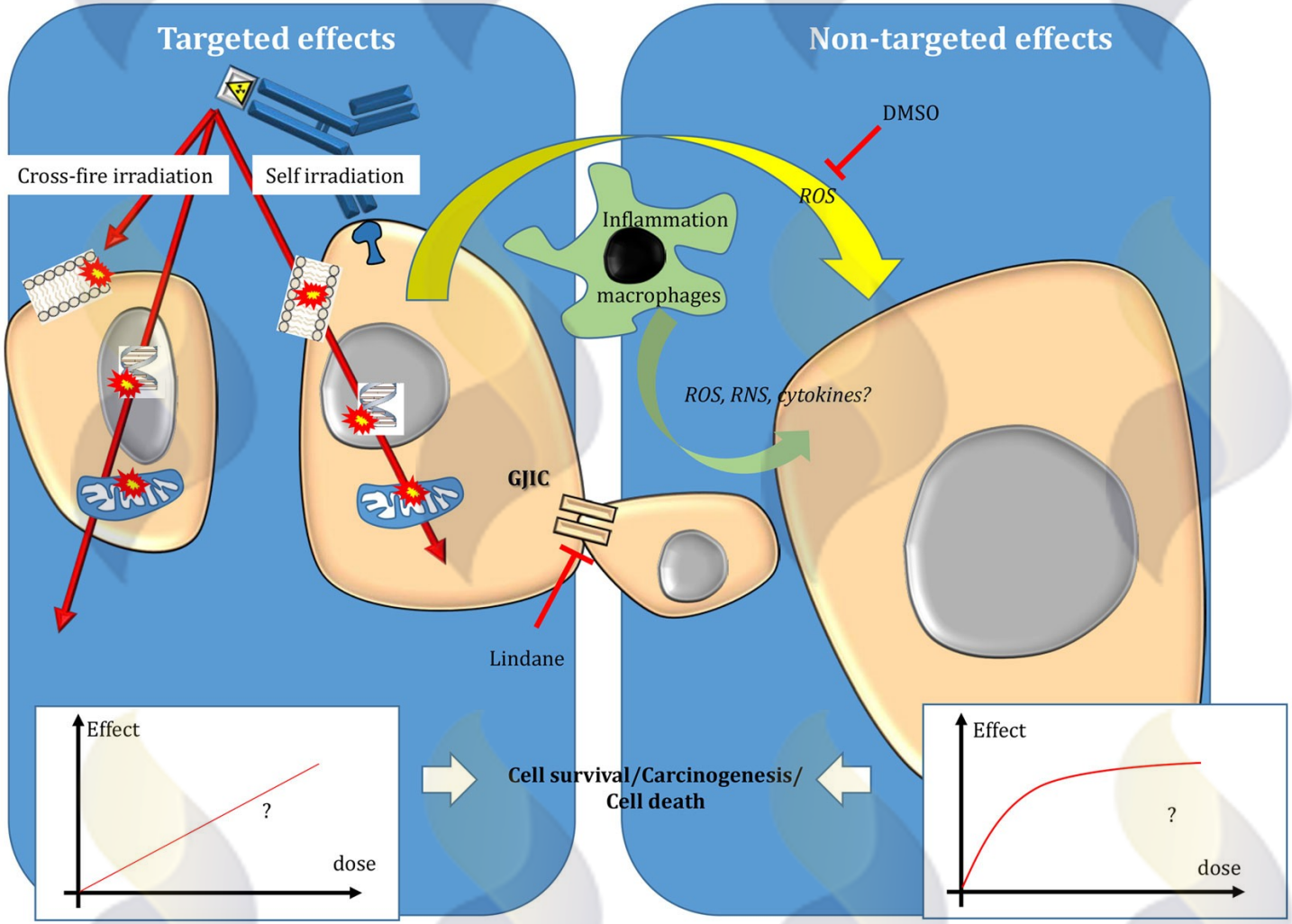
- ❑ Photons and electrons (6, 12, 18, 25 MeV)
- ❑ Low LET radiation : 0.2 keV/µm
- ❑Tumor (radiation sensitivity, microenvironment)
- ❑ Homogeneous irradiation field
- ❑ 2 Gy/fraction, multiple fractions
- ❑ Dose rate (60-120 Gy/h)
- ❑ Well defined dosimetry (50 Gy—80 Gy)

Targeted Radionuclide Therapy

- ❑ Antibody, peptides etc. (Pharmacokinetic/ Pharmacodynamic)
- ❑ Isotope ($T_{1/2Phys}$, specific activity decay spectrum)
  - Alpha particles: 40µm-92µm (e.g. Bi212)
  - Beta particles: µm- 1.2mm (e.g. Y90)
  - Auger electrons: nm-µm (e.g. Pt195m)
- ❑ Tumor (size, antigen density, radiation sensitivity, microenvironment)
- ❑ Heterogeneous dose distribution
- ❑ Protracted exposure (hours→ days)
- ❑ Low absorbed dose rate irradiation (<0.1—1.0 Gy/h)
- ❑ Mixed irradiation (low and high- LET radiation)
  - Alpha particles: 50-230keV/µm
  - Beta particles, γ, x-rays: 0.2 keV/µm
  - Auger electrons: 4-25 keV/µm
- ❑ MIRD Dosimetry (15— 30 Gy)

Pouget Frontiers in Medicine 2015

Targeted and non-targeted effects in radionuclide therapy



Pouget Frontiers in Medicine 2015

Risk/benefit - evaluation

Radioactive Iodine Therapy for Differentiated Thyroid Cancer: Lessons from Confronting Controversial Literature on Risks for Secondary Malignancy

Mark Tulchinsky[1], Ina Binse[2], Alfredo Campennì[3], Sabina Dizdarevic[4], Luca Giovanella[5], Ian Jong[6], Kalevi Kairemo[7], and Chun K. Kim[8]

„Overtreatment“ vs. „Undertreatment“

Literature analysis and search terms

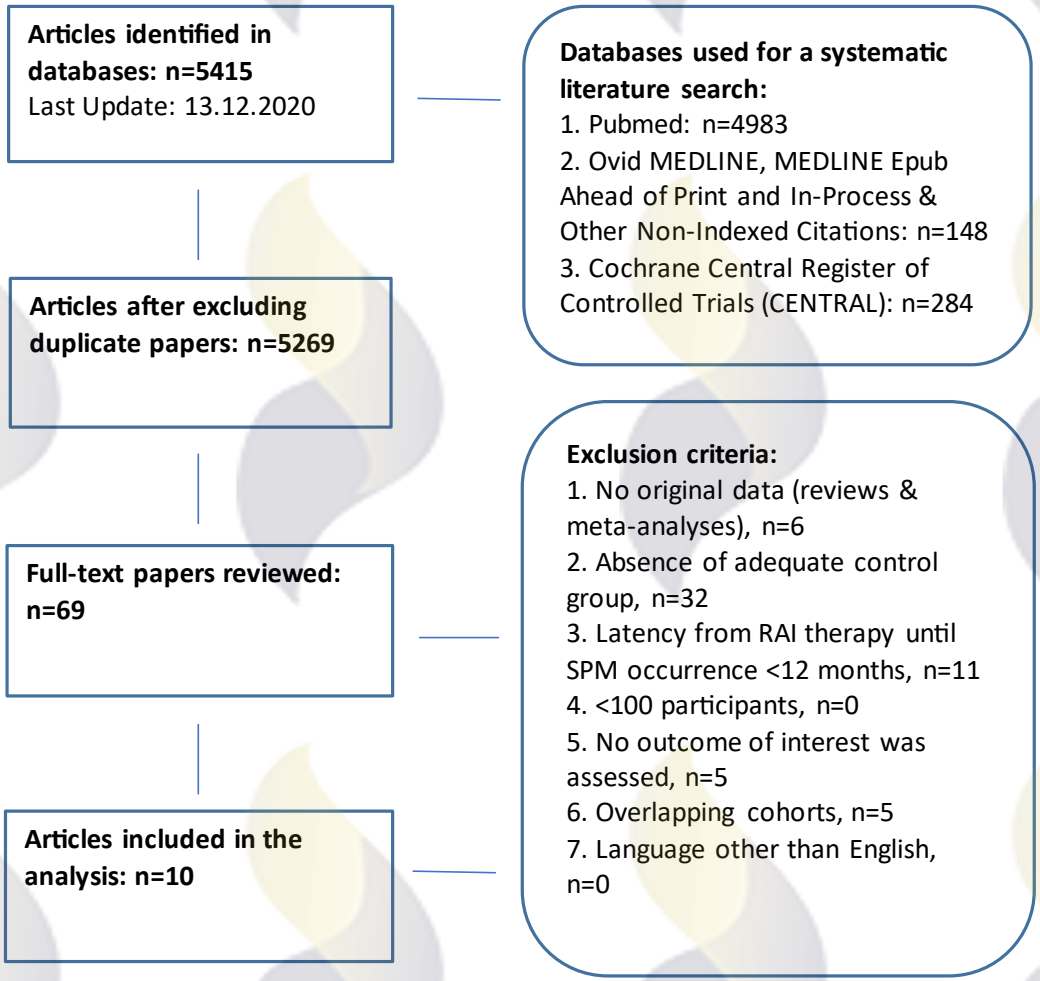
Databases: Pubmed (main source)
Ovid
Cochrane

SPM

Search terms: (second primary cancer[MeSH Terms]) OR (second primary cancer) OR second primary carcinoma) OR second primary malignancy) OR second primary neoplasm) OR second primary cancers) OR second primary carcinomas) OR second primary malignancies) OR second primary neoplasms) OR subsequent cancer) OR subsequent carcinoma) OR subsequent malignoma) OR second primary malignoma) OR subsequent neoplasms) AND (thyroid cancer) OR thyroid neoplasm) OR thyroid carcinoma) OR thyroid malignancy) OR thyroid malignancies) OR thyroid cancers) OR thyroid carcinomas) OR thyroid neoplasms)) OR thyroid cancer[MeSH Terms])

Reinecke, …, Luster EJNMMI 2022 accepted

Literature search strategy



Reinecke, …, Luster EJNMMI 2022 accepted

Study formats

- Interval assessed 1973 - 2020
- Publications included n = 10/69
- Meta-analyses and systematic reviews
- Retrospective cohort analysis or uncertainty of design
- Sample size n = 184 - 211.360

Reinecke, …, Luster EJNMMI 2022 accepted

Parameters considered (1)

- Title
- Author
- Year of publishing
- Journal (including impact factor)
- Number of study participants
- Number of study participants with radioiodine therapy
- Number of individuals in control cohort
- Description of the cohort (type, country, period)
- Follow up interval
- Study design

Reinecke, …, Luster EJNMMI 2022 accepted

Parameters considered (2)

- Cumulative I-131 activity
- Fractionation of radioiodination
- Activity administered per radioiodine therapy
- Latency to Second Malignancy (SPM)
- At what point in time after DTC is a malignancy considered an SPM?
- Include SPMs before DTC?
- Initial histology of thyroid cancer
- Thyroid carcinoma histology in the presence of SPM
- Histology of the SPMs secured?
- Proportion of women, children (age!) → subanalysis

Reinecke, …, Luster EJNMMI 2022 accepted

Additional potential influencing factors

- Prior or subsequent treatments: chemotherapy/external radiation?
- Statistical methods used
- Number of participants "lost to follow up"
- Unrecognized confounders

Special limitations; sources of bias; remarks

Reinecke, …, Luster EJNMMI 2022 accepted

Causality?

At what point in time of occurrence, "metachronic" or "synchronic" after the initial diagnosis of thyroid carcinoma, is a malignancy considered to be a SPM?

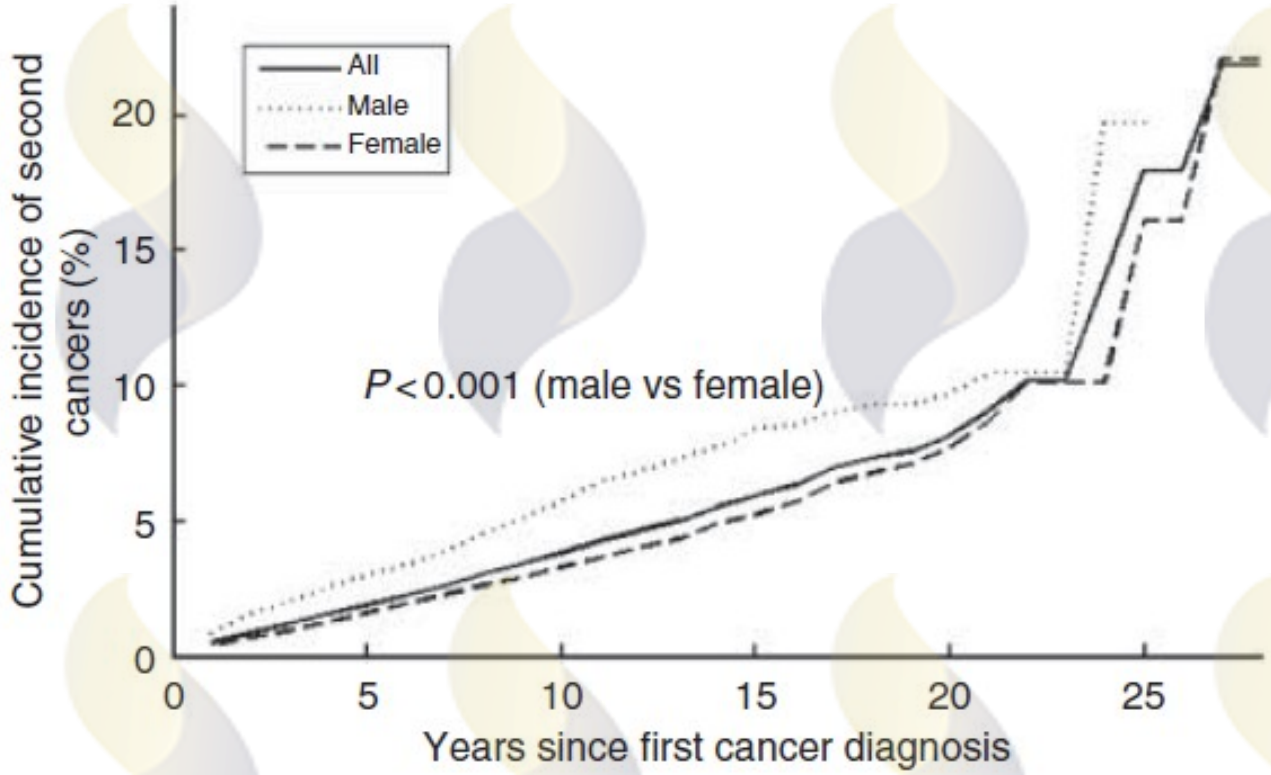
Reinecke, …, Luster EJNMMI 2022 accepted

Organs at risk

- Breast
- Bone marrow (leukemia)
- Lung
- Kidney / urinary tract
- Prostate
- Female reproductive organs
- Stomach
- Colorectal
- Salivary glands
- Central nervous system
- Soft tissue

Reinecke, …, Luster EJNMMI 2022 accepted

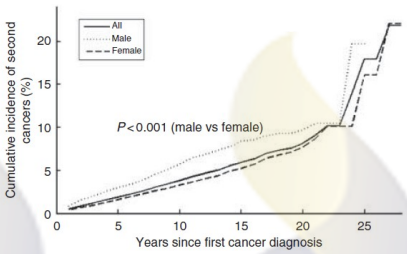
Cumulative incidence of SPM



n = 19.874

Lu European Journal of Endocrinology 2013

Cumulative incidence of SPM



n = 19.874

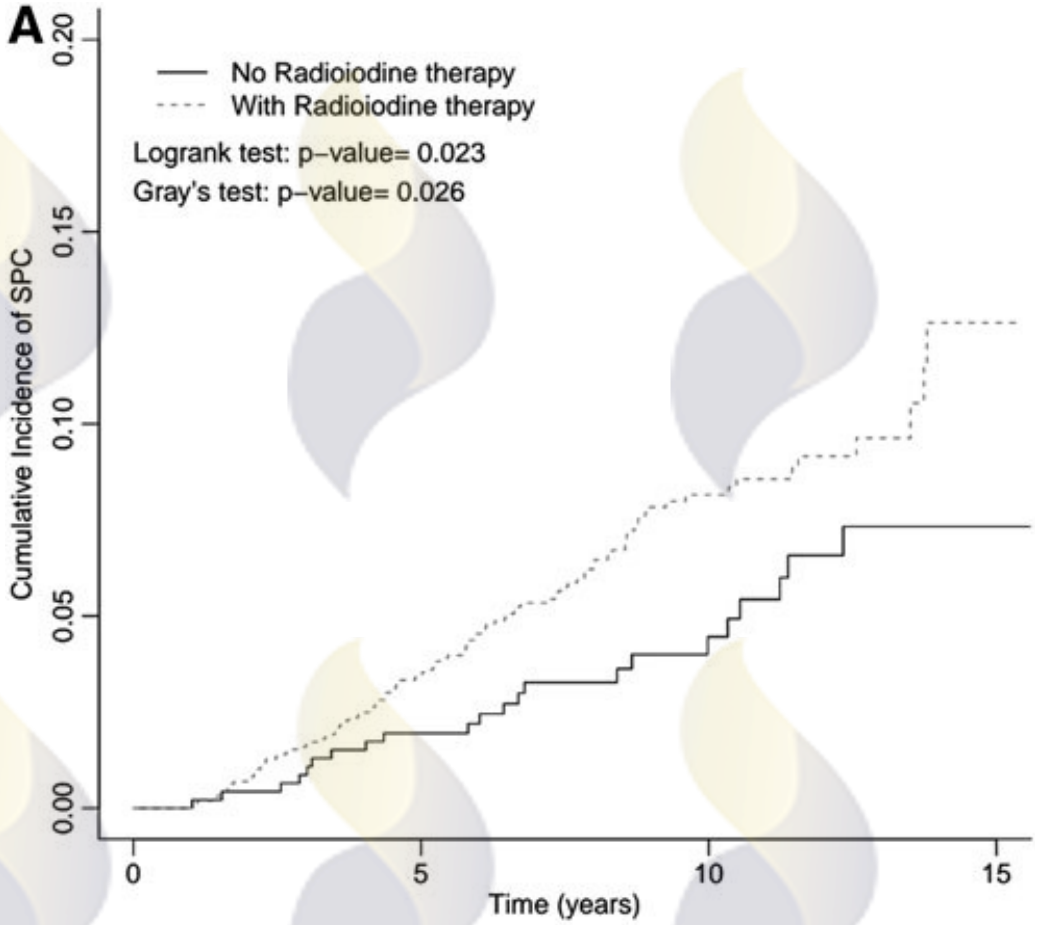
Thyroid cancer is associated with a 33% increased risk of developing second malignancies

However, the results do not allow a causal relationship to be established

SPMs differ from those in the western population, other genetic disposition or environmental/risk factors could play a role

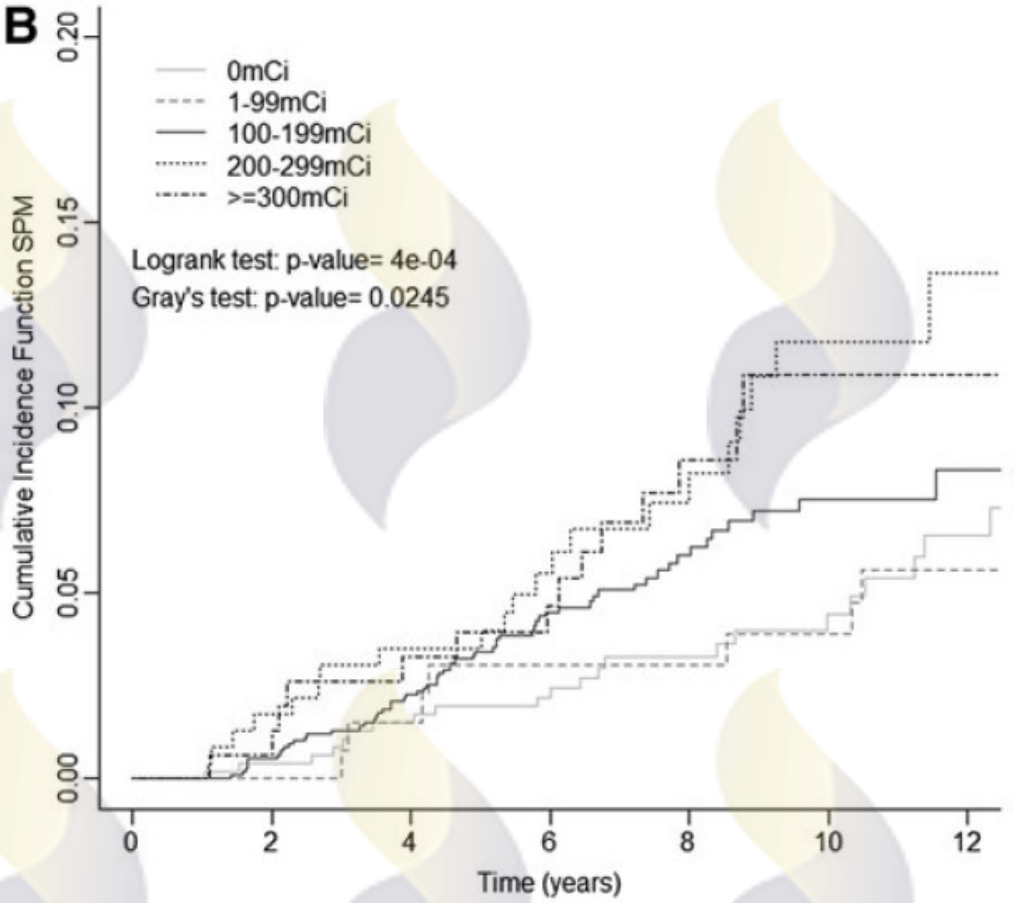
Lu European Journal of Endocrinology 2013

Cumulative incidence of SPM with and w/o I-131



Silva-Vieira Thyroid 2017

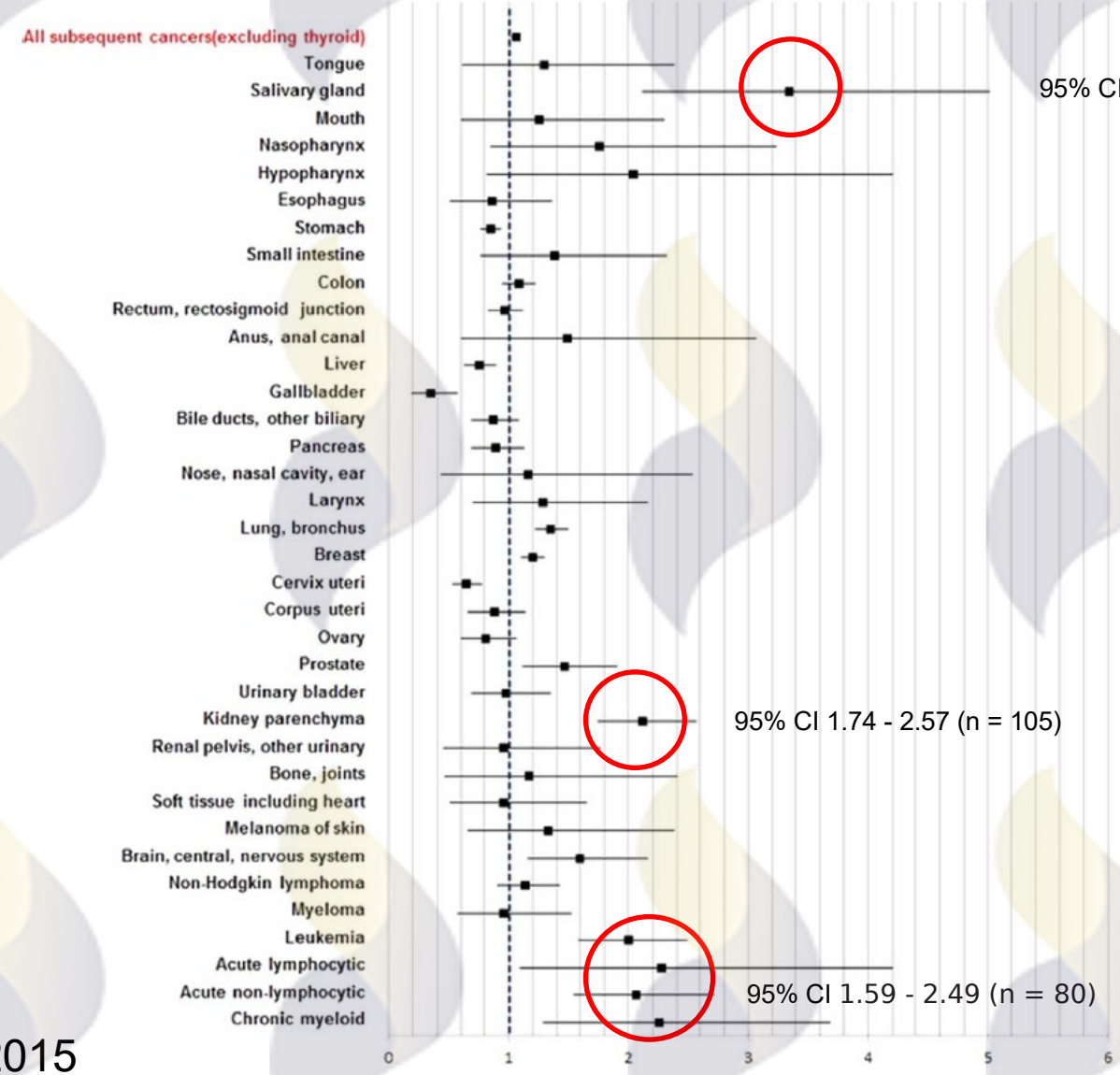
Cumulative incidence of SPM versus amount of I-131



Silva-Vieira Thyroid 2017

Standardized incidence ratios for SPM

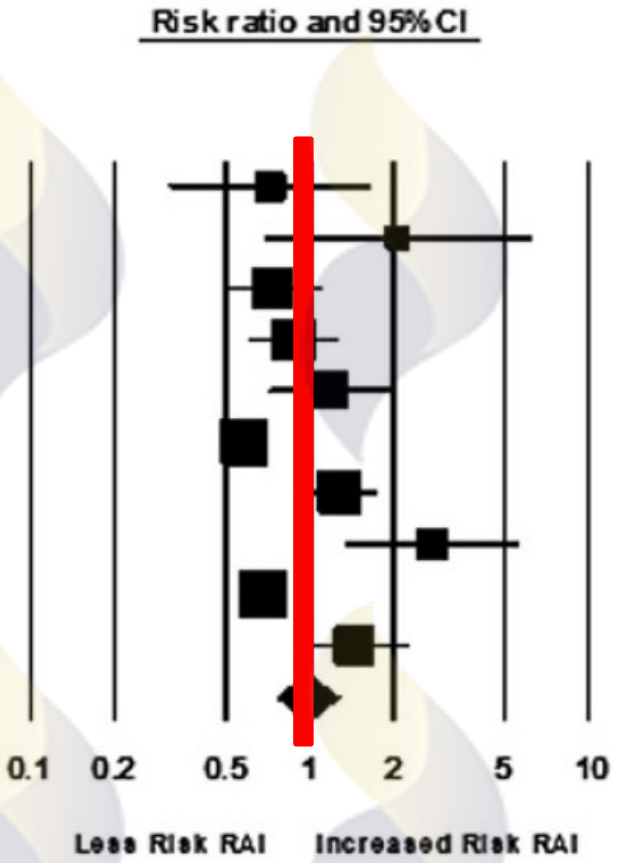
n = 178.844



Cho Cancer 2015

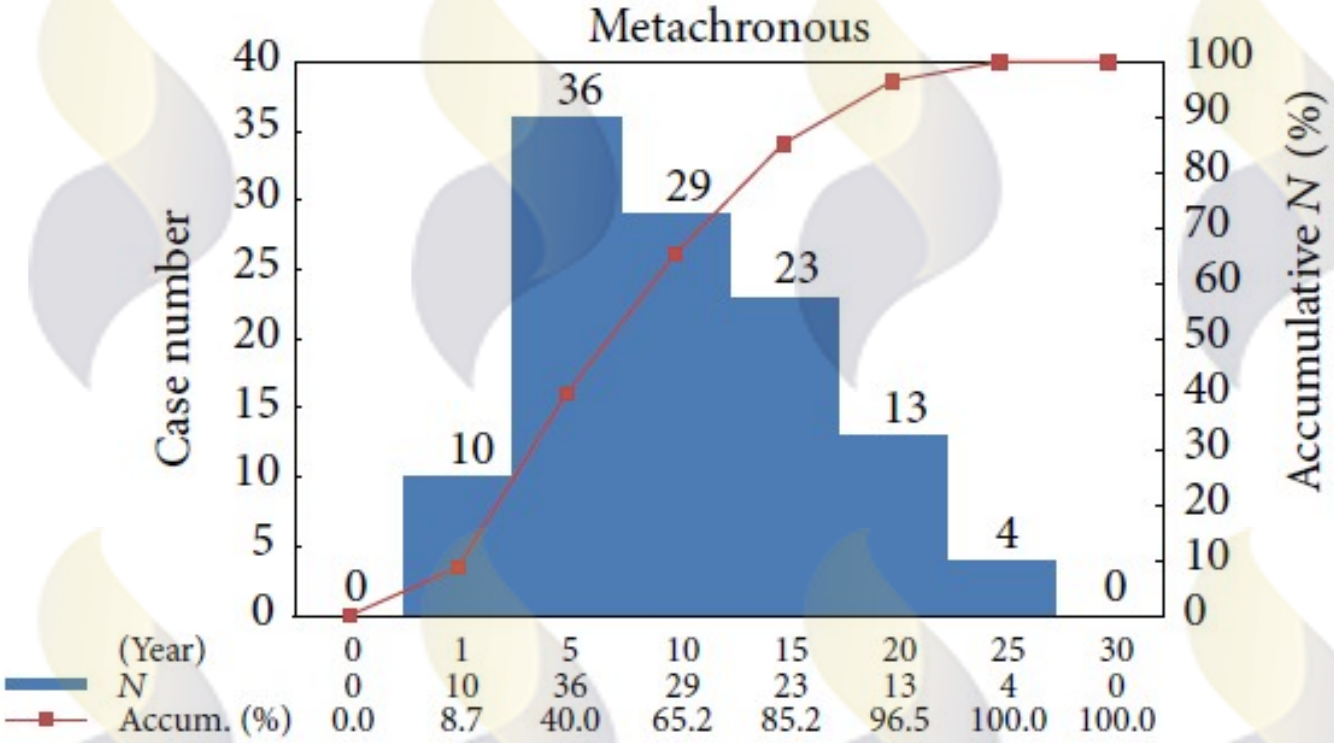
Random effects in meta-analysis

Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Al-Qahtani 2015	0.725	0.314	1.677	-0.751	0.452
De Souza 2016	2.076	0.689	6.257	1.298	0.194
Hakala 2016	0.733	0.488	1.103	-1.491	0.136
Hirsch 2016	0.878	0.612	1.262	-0.701	0.483
Khang 2015	1.184	0.713	1.967	0.652	0.515
Kim 2013	0.587	0.547	0.631	-14.584	0.000
Ko 2015	1.279	0.920	1.776	1.466	0.143
Lang 2012	2.743	1.327	5.672	2.723	0.006
Rubino 2003	0.678	0.580	0.792	-4.886	0.000
Silva-Vieira 2017	1.441	0.922	2.253	1.605	0.109
	0.980	0.758	1.268	-0.153	0.878



Yu Thyroid 2018

Number of metachronic SPM after thyroidectomy



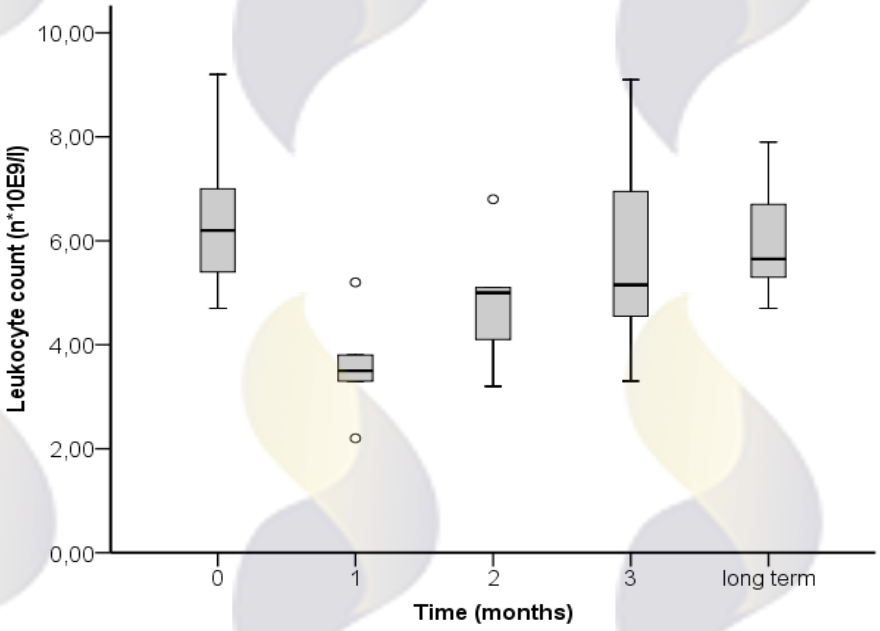
Liou International Journal of Endocrinology 2016

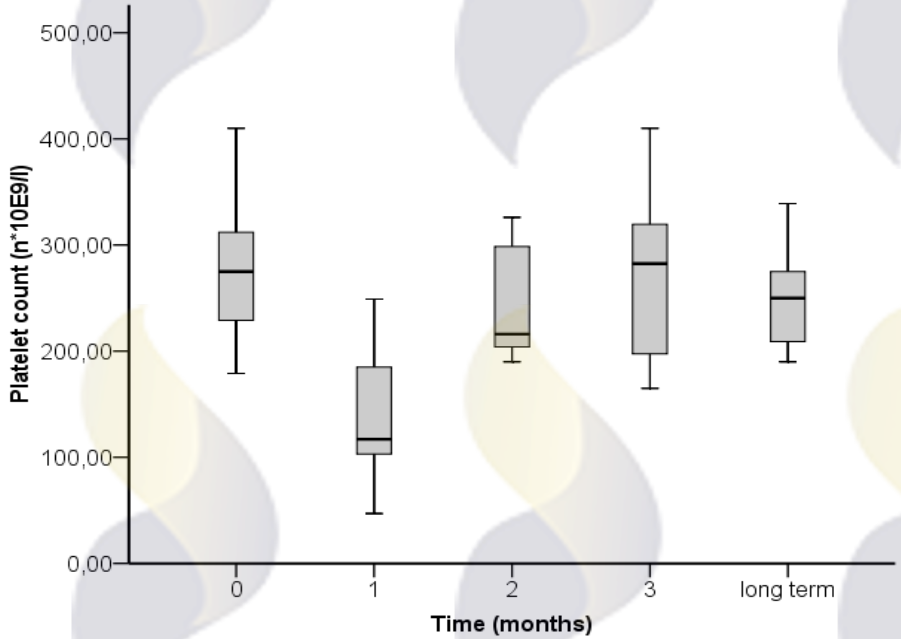
Immediate haematological effects

Eur J Nucl Med Mol Imaging. 2010 May;37(5):896-903. Epub 2009 Dec 24.

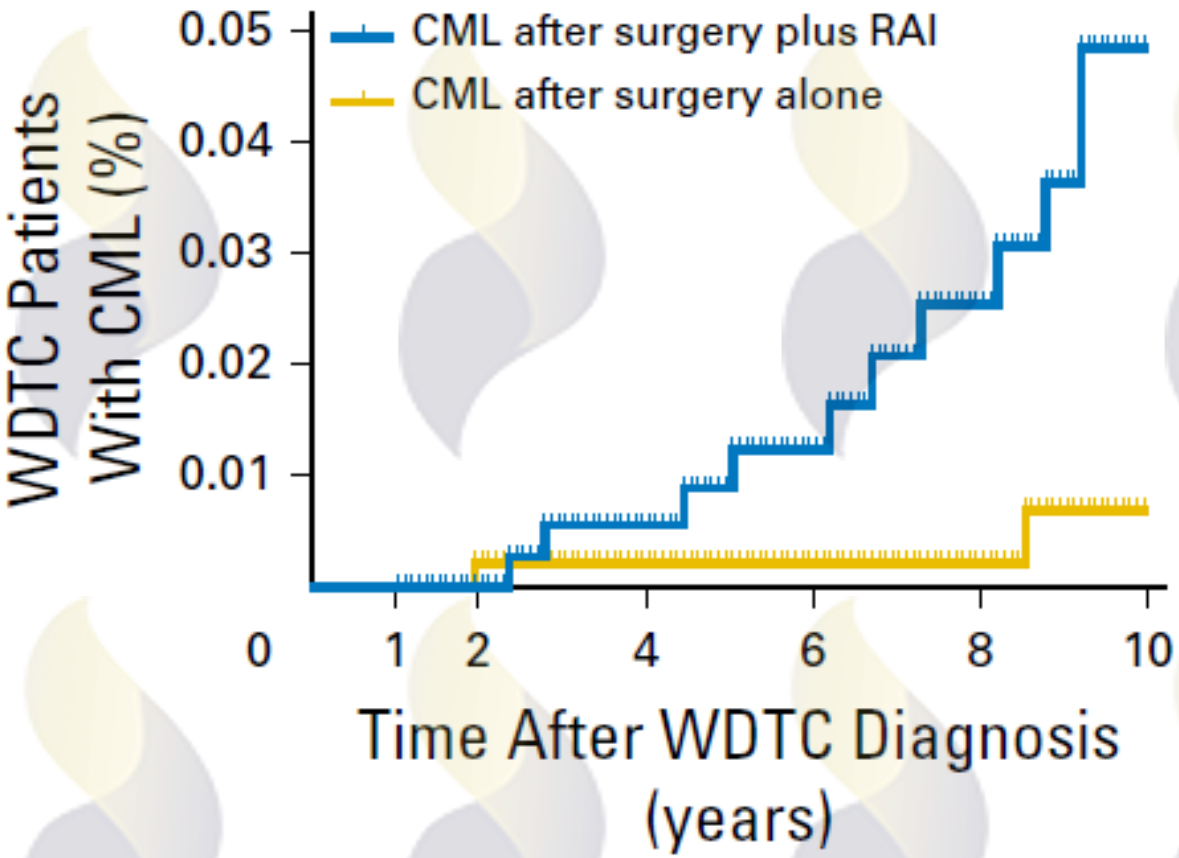
Dosimetry-guided high-activity (131)I therapy in patients with advanced differentiated thyroid carcinoma: initial experience.

Verburg FA, Hänscheid H, Biko J, Hategan MC, Lassmann M, Kreissl MC, Reiners C, Luster M.





Occurrence of systemic haematological diseases



n = 148.215

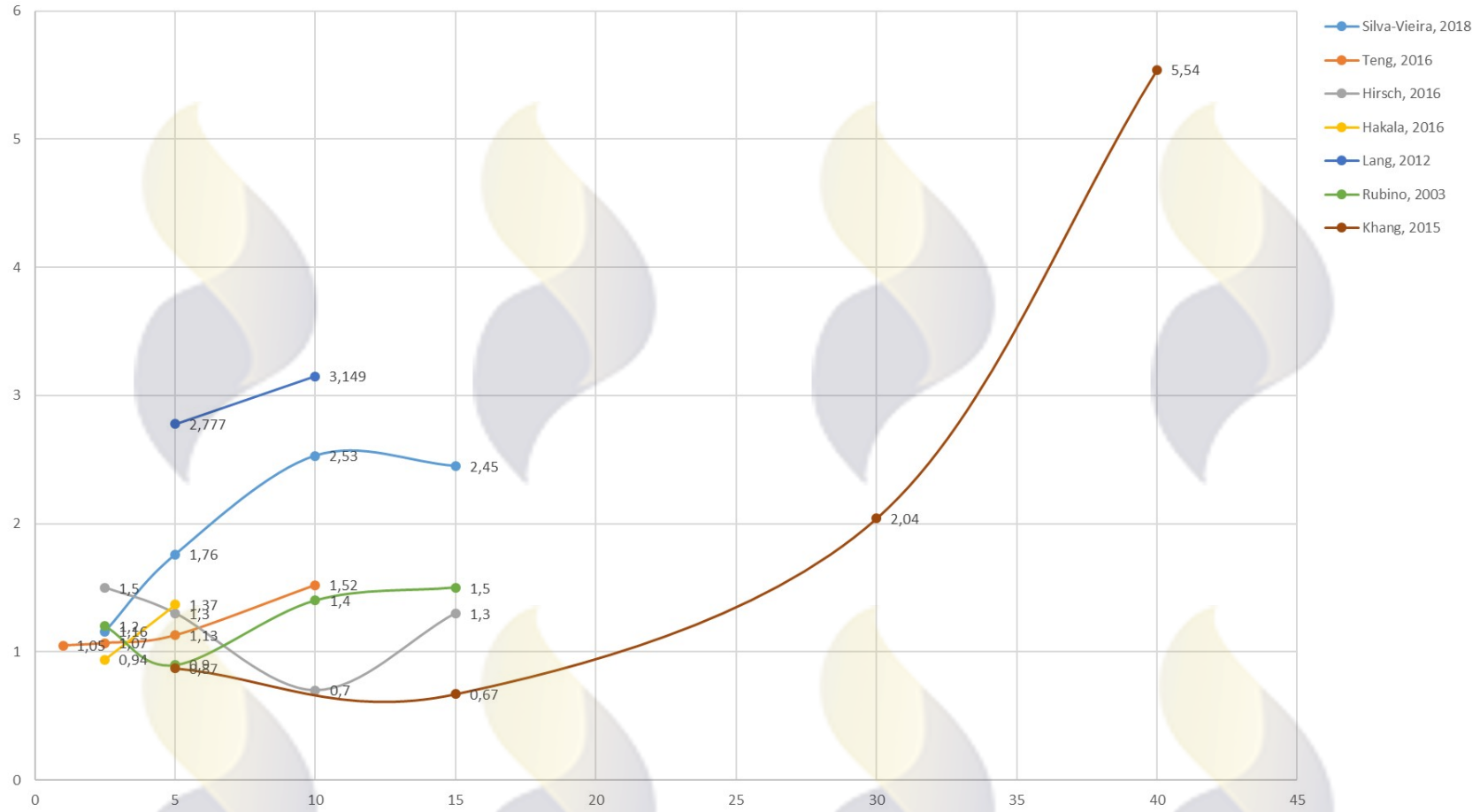
Molenaar Journal of Clinical Oncology 2017

Occurrence of systemic haematological diseases

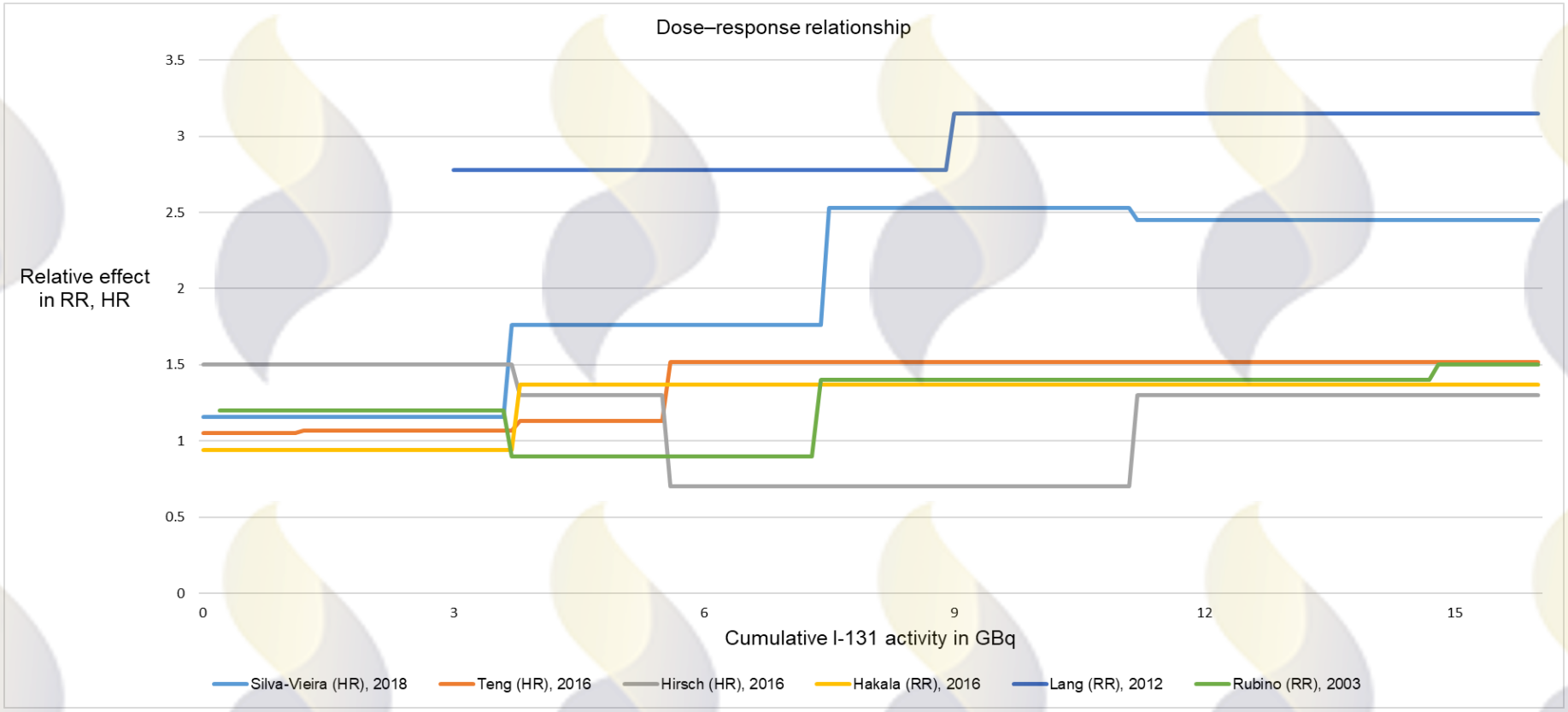
	Leukemia	Multiple Myeloma
Absolute frequency	2 / 210	2 / 210
Relative frequency	0,95%	0,95%
Mean cumulative activity	59,7 GBq	6,3 GBq
Range of cumulative activity	56,5 - 62,9 GBq	4,8 - 7,8 GBq

Kneer in preparation

Dose dependent risk of subsequent malignant neoplasms after RAI



Dose dependent risk of subsequent malignant neoplasms after RAI

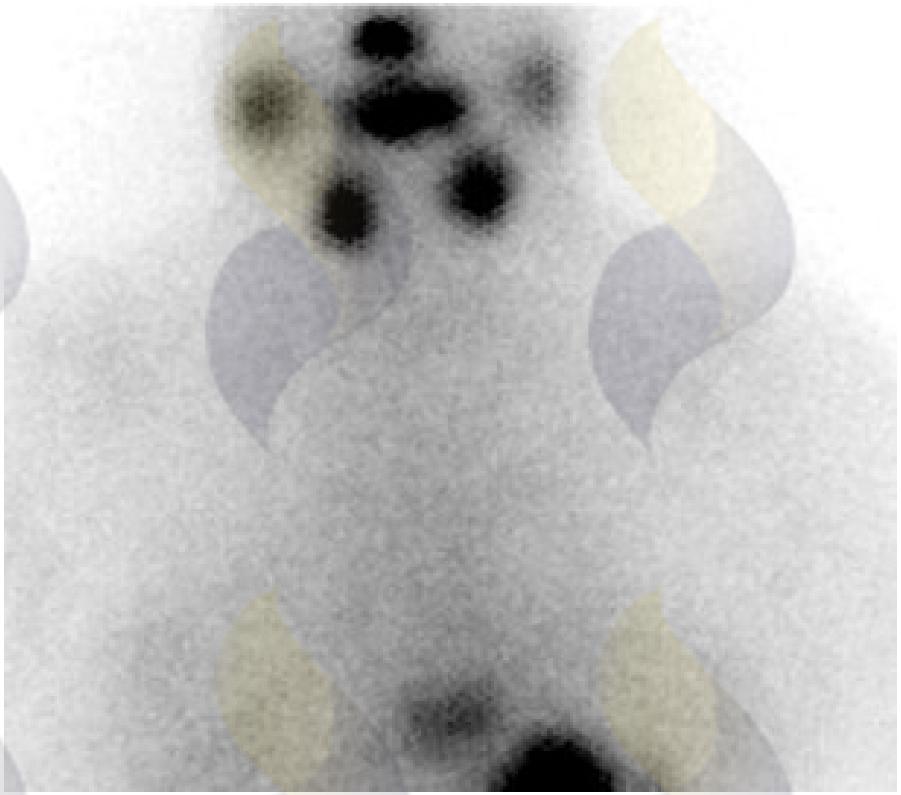


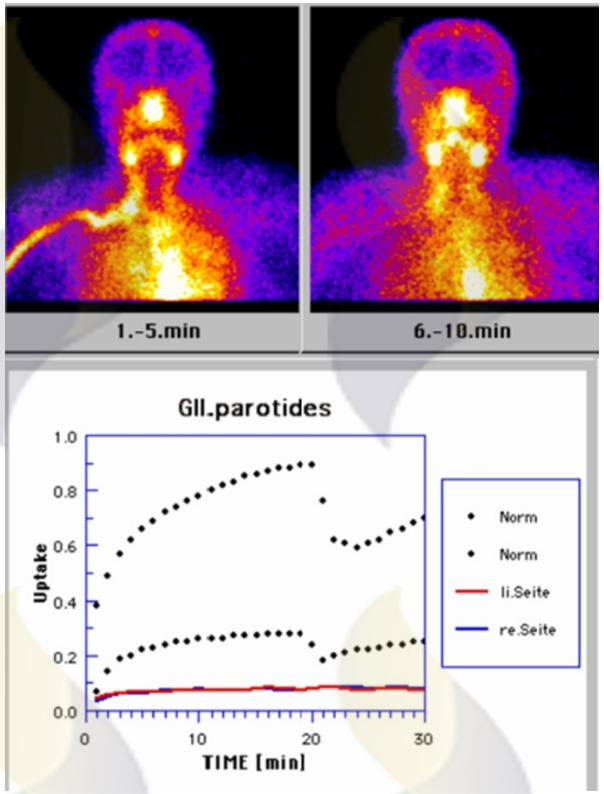
Non-malignant I-131 related adverse effects

Outcome	Group A (rhTSH)	Group B (hypothyroidism)	*P*
Elevated FSH 6 mo after ^{131}I			
Men	4/9 (44.4%)	16/18 (89%)	0.03
Women	1/13 (7.7%)	6/30 (20%)	0.4
Mean increase of FSH			
Men	105%	236%	<0.001
Women	65%	125%	<0.001
Hyperamylasemia 48 h after ^{131}I*	11/30 (36.6%)	48/60 (80%)	<0.001
Symptoms of acute sialoadenitis up to 7 d after ^{131}I*	9/30 (30%)	35/60 (58.3%)	0.01
Thrombocytopenia (<100,000/mm^3) or neutropenia (<1,500/mm^3) (lowest count) up to 60 d after ^{131}I†	2/28 (7%)	12/56 (21.4%)	0.1
Mean decrease of neutrophils (considering lowest count)‡	20%	45%	<0.01
Mean decrease of platelets (considering lowest count)‡	25%	52%	<0.01
Increased 8-epi-$PGF_{2\alpha}$ 96 h after ^{131}I	14/25 (56%)	45/45 (100%)	<0.001
Mean increase of 8-epi-$PGF_{2\alpha}$	60%	125%	<0.001

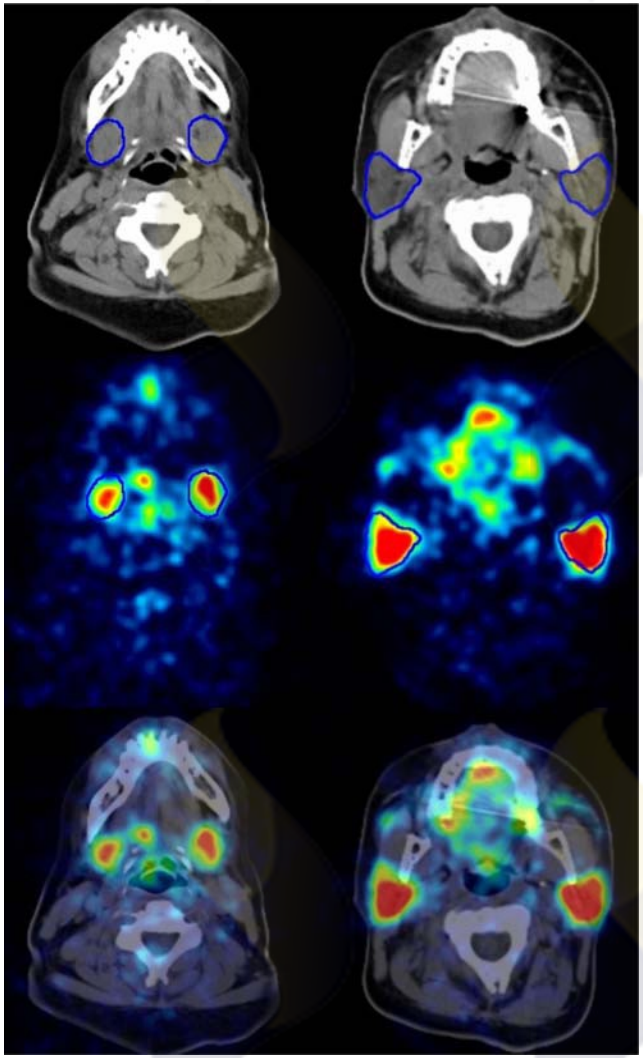
Rosario Journal of Nuclear Medicine 2008

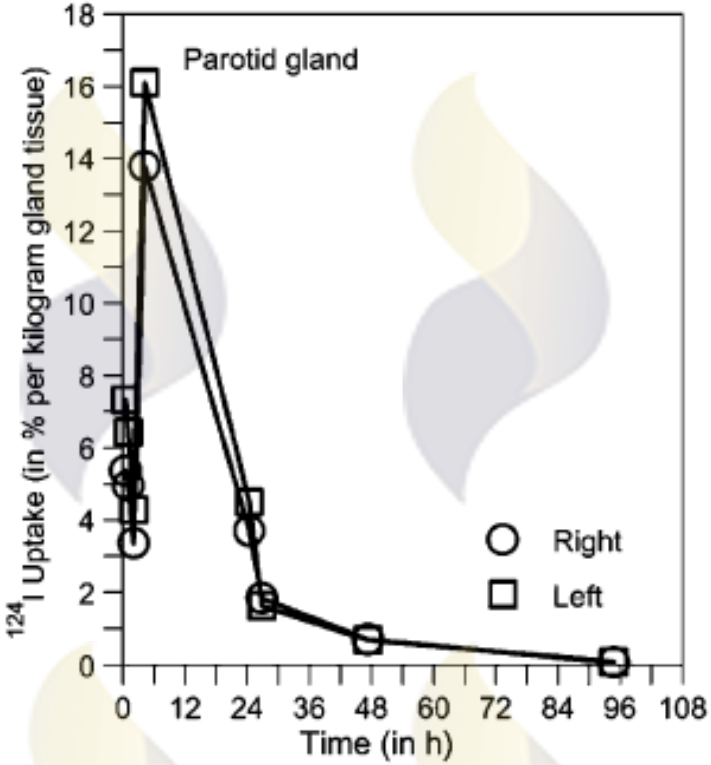
Radiogenic salivary gland damage





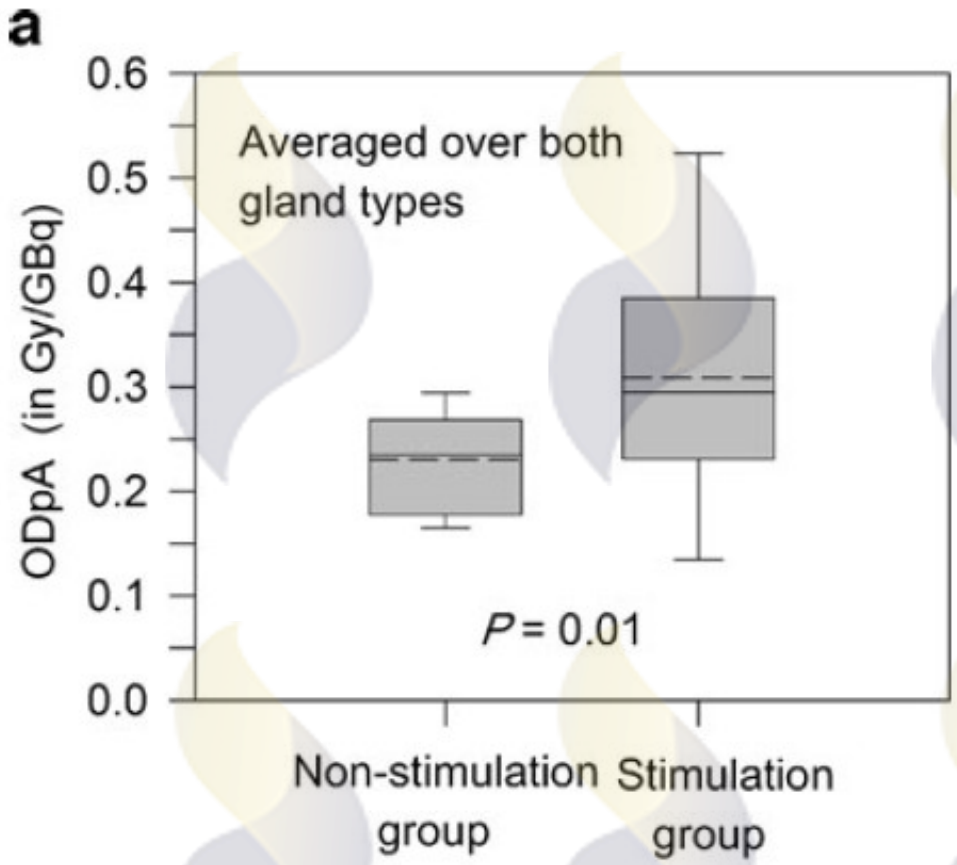
Salivary gland assessment I-124-PET/CT

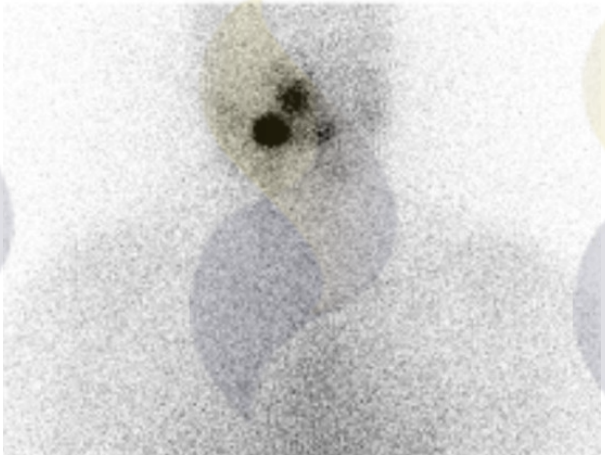




Jentzen Eur J Nucl Med Mol Imaging 2010

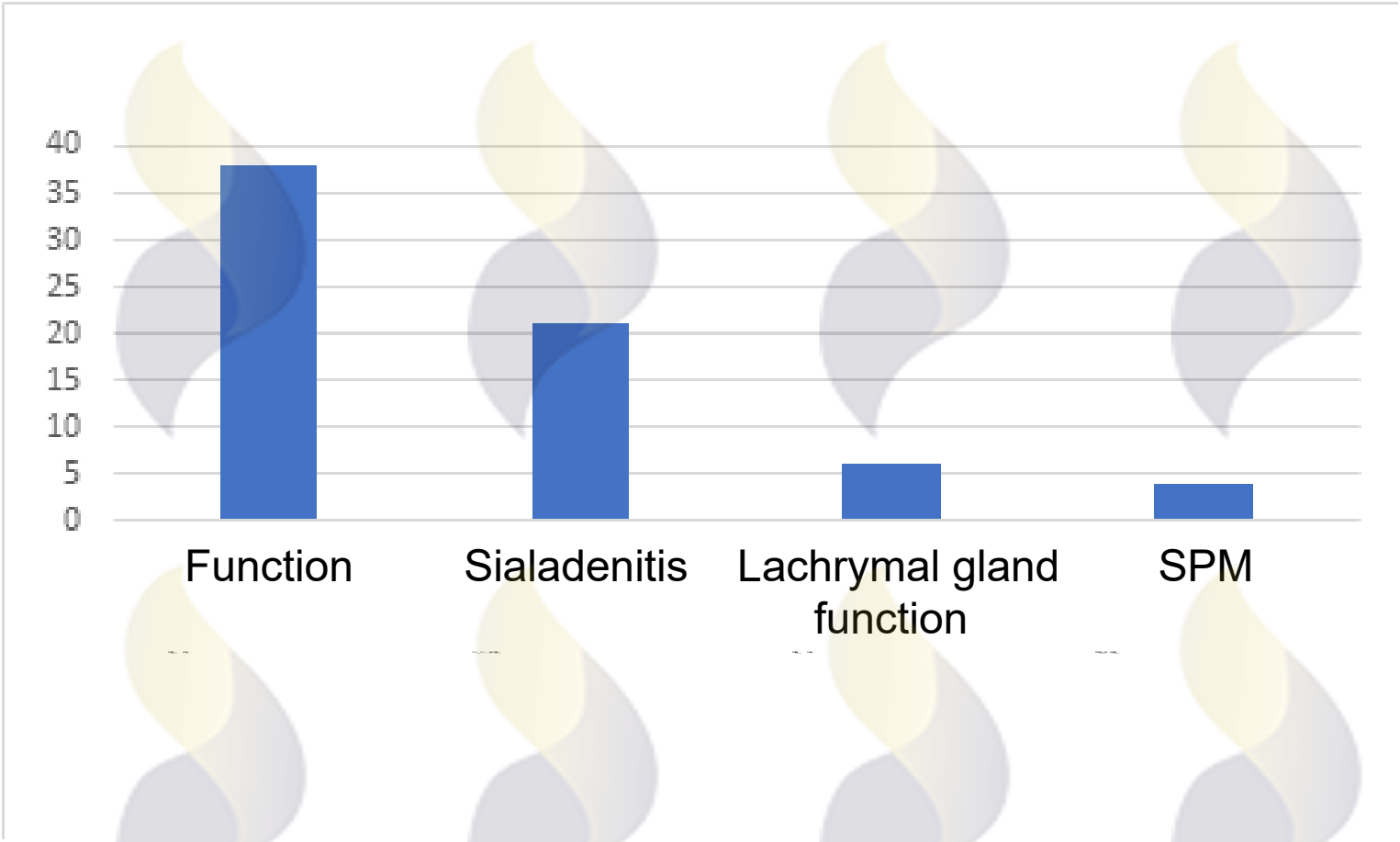
Salivary gland stimulation?



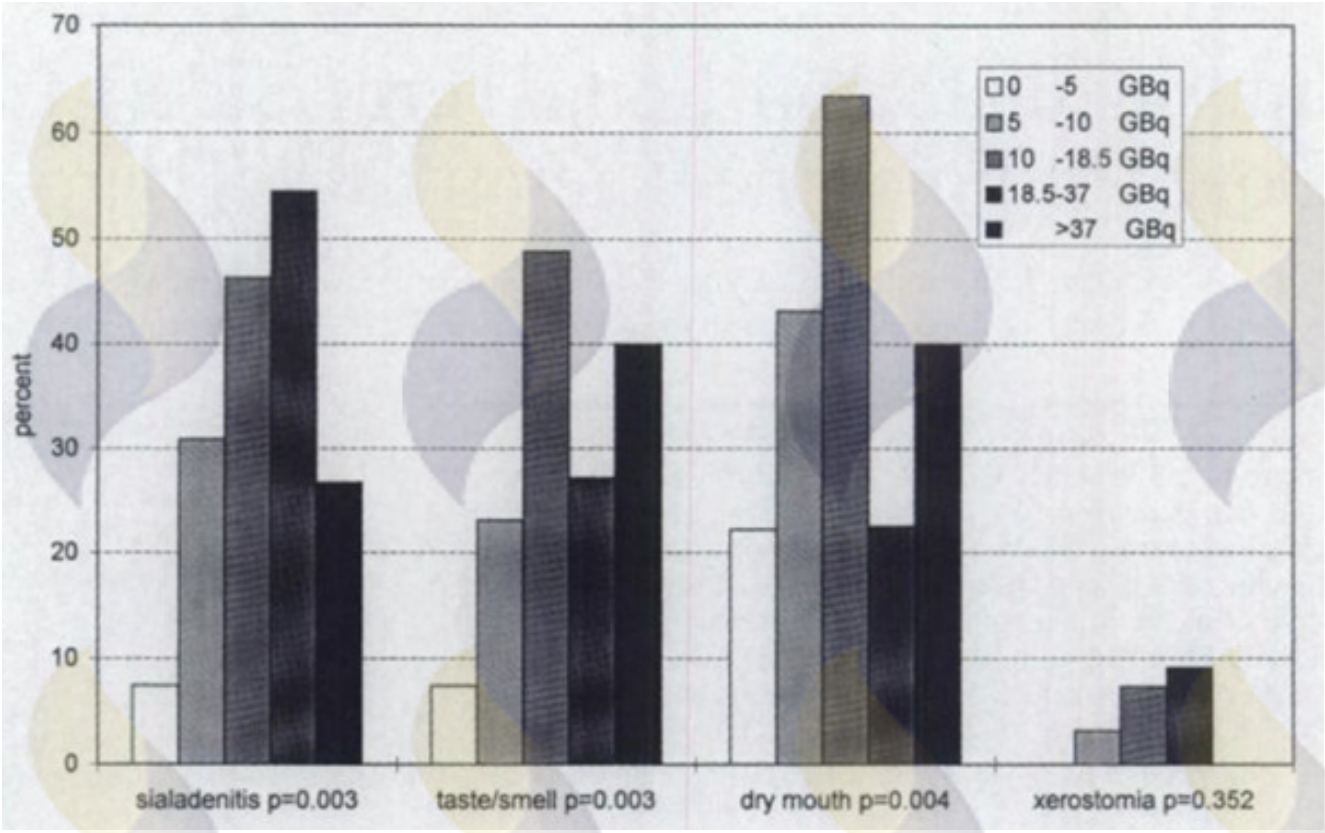


Jentzen Eur J Nucl Med Mol Imaging 2010

Documented salivary gland pathologies



Dose/response relation?



Alexander Journal of Nuclear Medicine 1998

Suggested reading

European Journal of Nuclear Medicine and Molecular Imaging

Second primary malignancies induced by radioactive iodine treatment of differentiated thyroid carcinoma – a critical review and evaluation of the existing evidence

--Manuscript Draft--

Manuscript Number:	EJNM-D-22-00214R1
Full Title:	Second primary malignancies induced by radioactive iodine treatment of differentiated thyroid carcinoma – a critical review and evaluation of the existing evidence
Article Type:	Review Article
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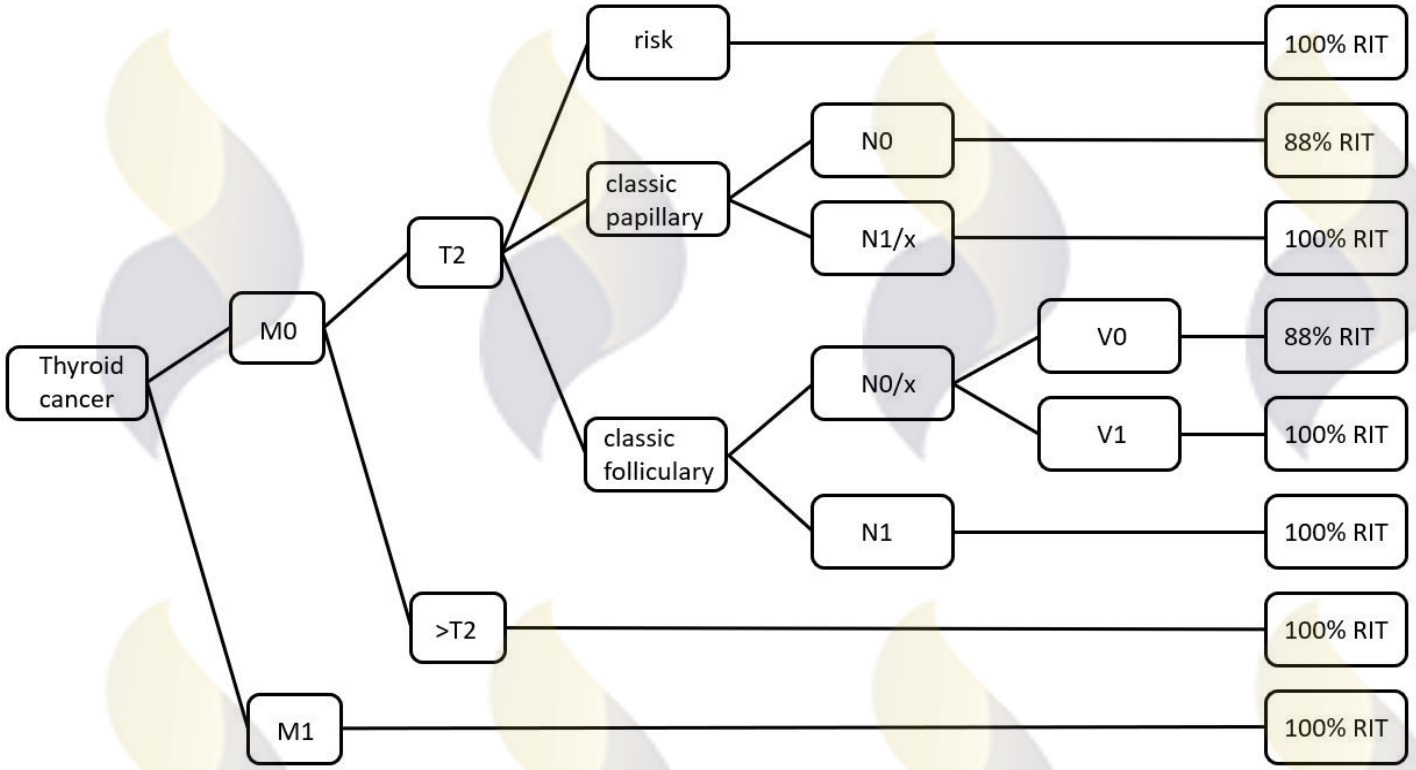
Protective measures after radioiodine therapy

- Avoid pregnancy for 6-12 months in females of childbearing potential
- Avoid conception in male patients within 4 months (spermatozoa life cycle)
- In case of high accumulated therapy activities (i.e. > 15 GBq I-131) address cryopreservation of sperm
- Encourage of increased caries prophylaxis

Relative contraindications

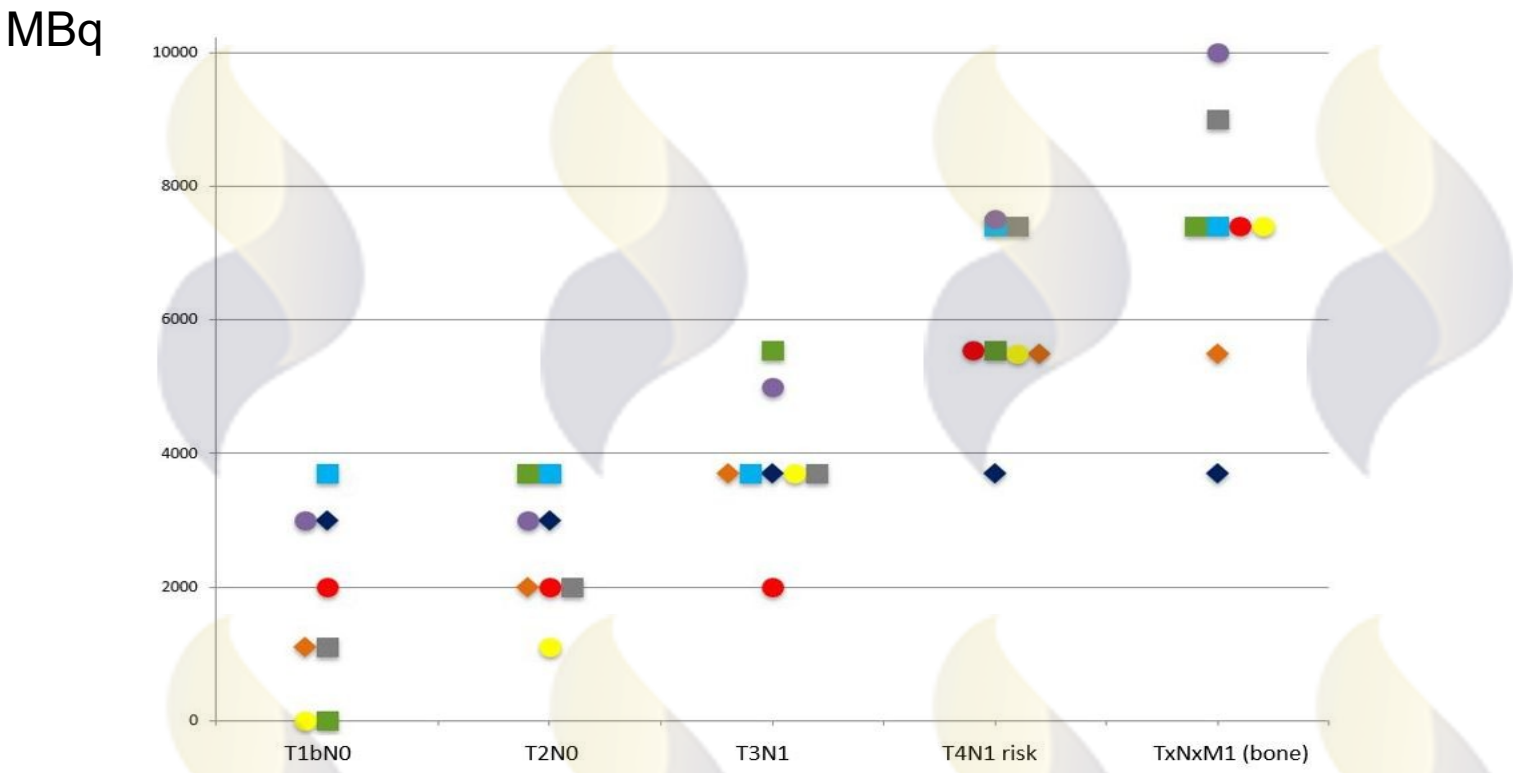
- High-grade bone marrow depression in case of planned high dose therapy
- Significant impairment of lung function if relevant pulmonary I-131 storage is to be expected
- Significant xerostomia with proven function, especially with questionable I-131 storage

Variations in radioiodine therapy in Europe – decision-making



Forrer Oncology 2022

Sample tumour stages and recommended I-131 activities



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Role of dosimetry

… in this context, the increasing role of dosimetry should be considered ... delivered absorbed doses to target differ due to differences in bioavailaibility, receptor expression, vasculature, heterogeneity of uptake and individual variations in radiosensitivity …

… dramatic improvements in imaging and dosimetry methodologies now make this possible …

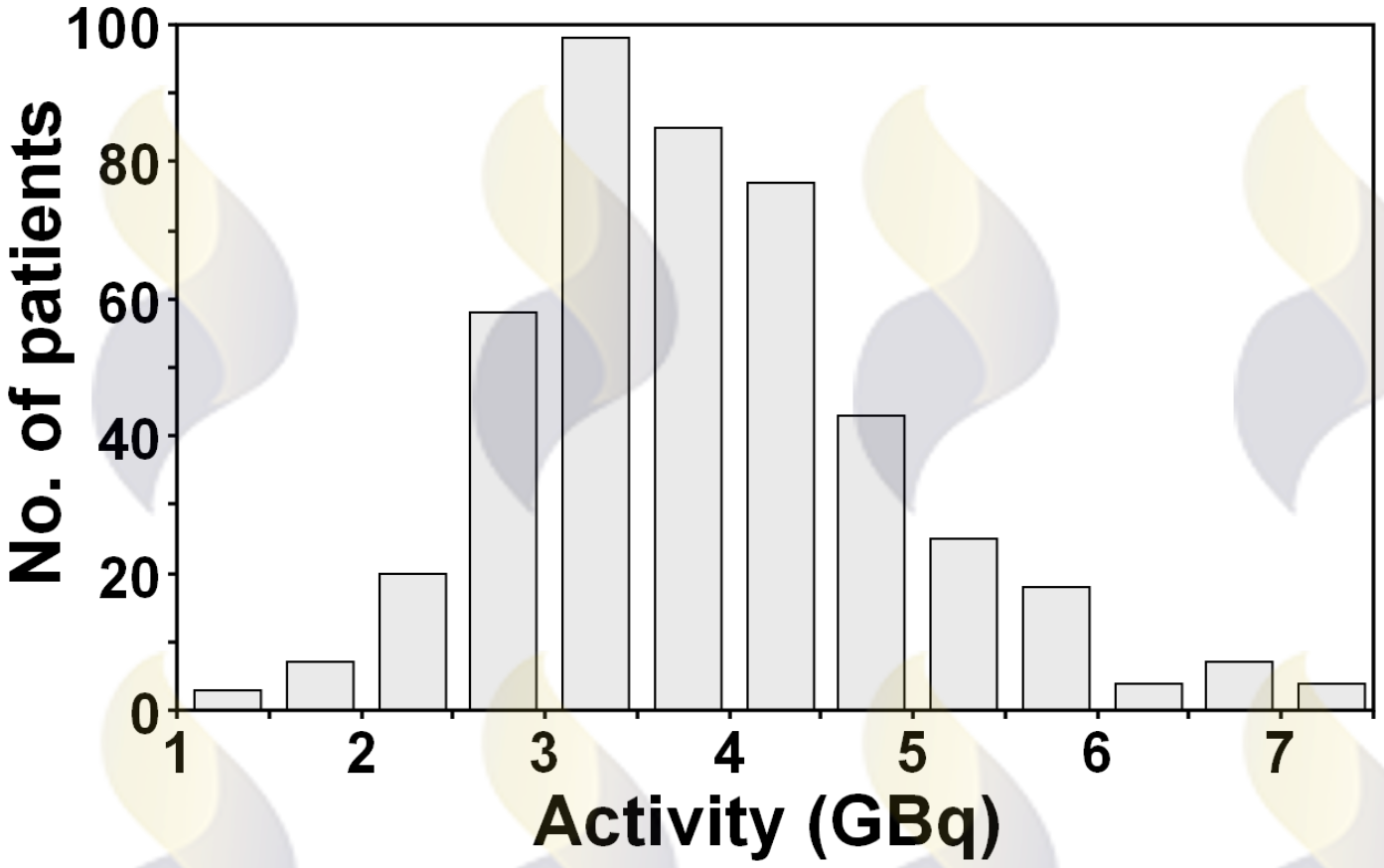
Tuttle Thyroid 2019

I-131 dosimetry

- Large interindividual differences in I-131 kinetics
- Hypothesis: The amount of I-131 in the blood that is available for adjuvant therapy is a better predictor of success than the activity administered
- Blood dose is an indicator of the total amount of I-131 available for absorption in residual thyroid gland

Verburg Eur J Nucl Med Mol Imaging 2010

Activity of I-131 needed for 350 mGy blood dose



Verburg Eur J Nucl Med Mol Imaging 2010

Why dosimetry?

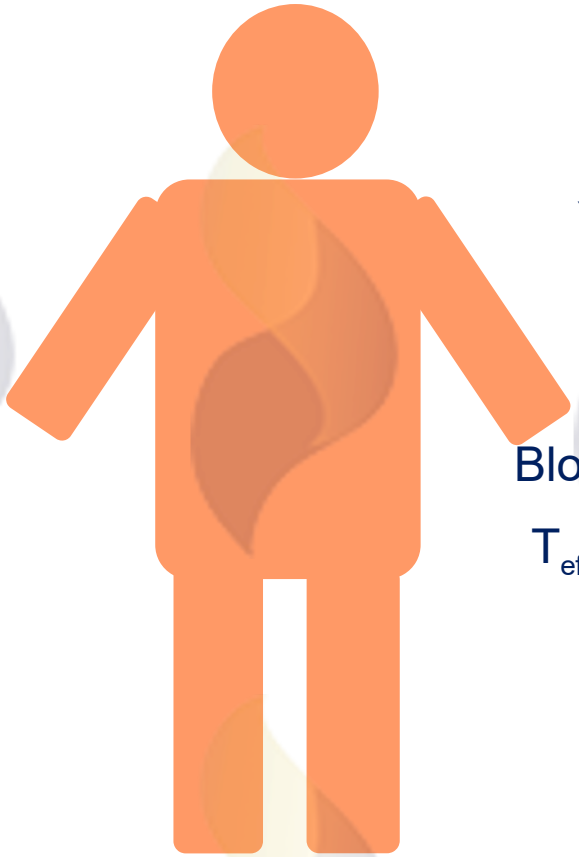
Old lady

155 cm

49 kg

Blood volume 3,5 l

T_{eff} in Blood: 36 h



Young man

210 cm

200 kg

Blood volume 8 l

T_{eff} in blood: 8 h

Variations in administrations currently based on nationality rather than radioiodine kinetics or even weight

Wishful thinking?

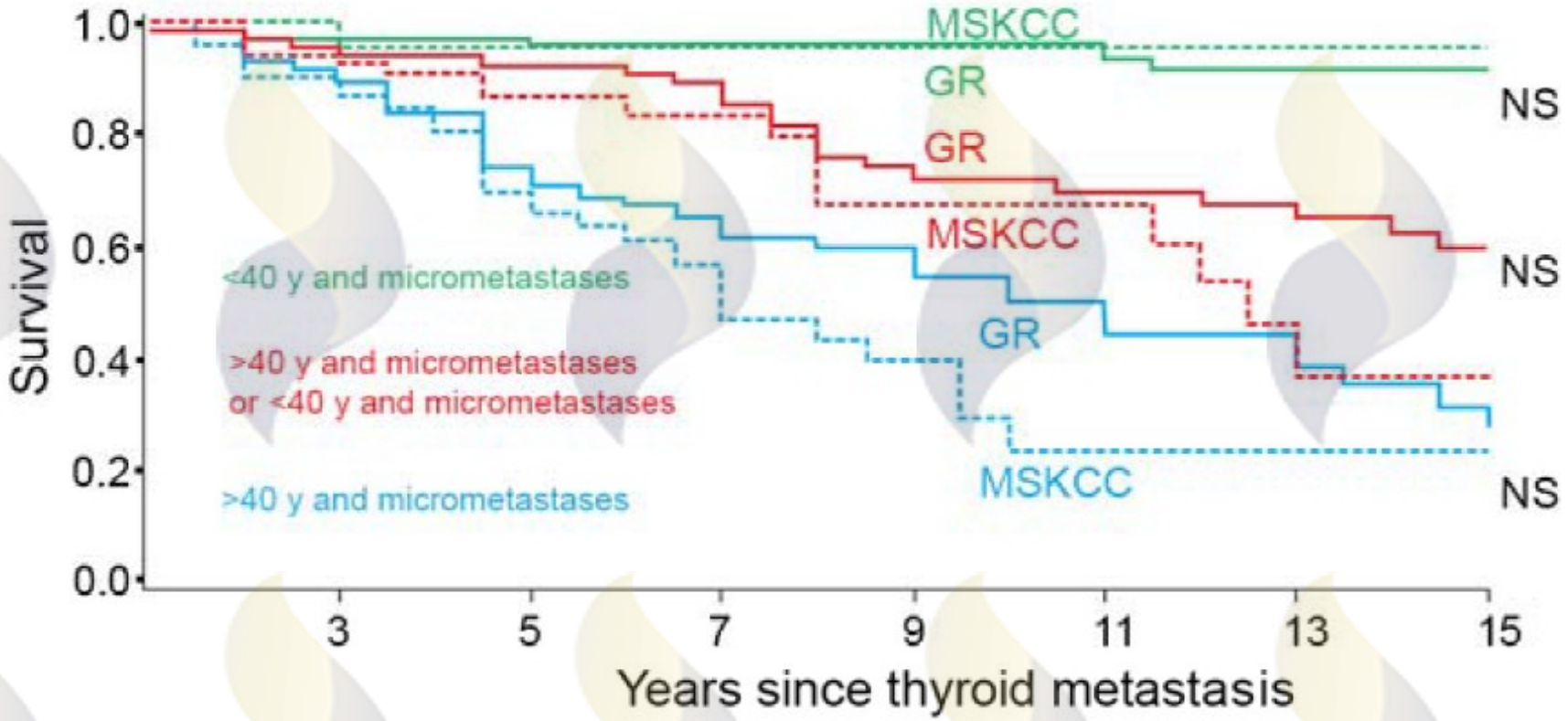
It is now **widely accepted** that nuclear medicine therapy (molecular radiotherapy) would be **more effective** if treatments were routinely planned on the basis of individual normal tissue and target tissue dosimetry

Strigari Eur J Nucl Med Mol Imaging 2014

The physicist´s universe

The battle for dosimetry

Outcome: dosimetry vs. non-dosimetry in thyroid cancer



Deandreis J Nucl Med 2016

Challenges

- Issues of **acceptable measuring error** in thyroid cancer dosimetry and the role in RAI therapy of tumor heterogeneity, tumor hypoxia, and kinetics must be overcome

- Long-term outcome studies following I-131 given **based on this new dosimetry** must be completed before the nuclear medicine community will be able to **predictably cure** our thyroid cancer patients with this technology

Silberstein Sem Nucl Med 2011

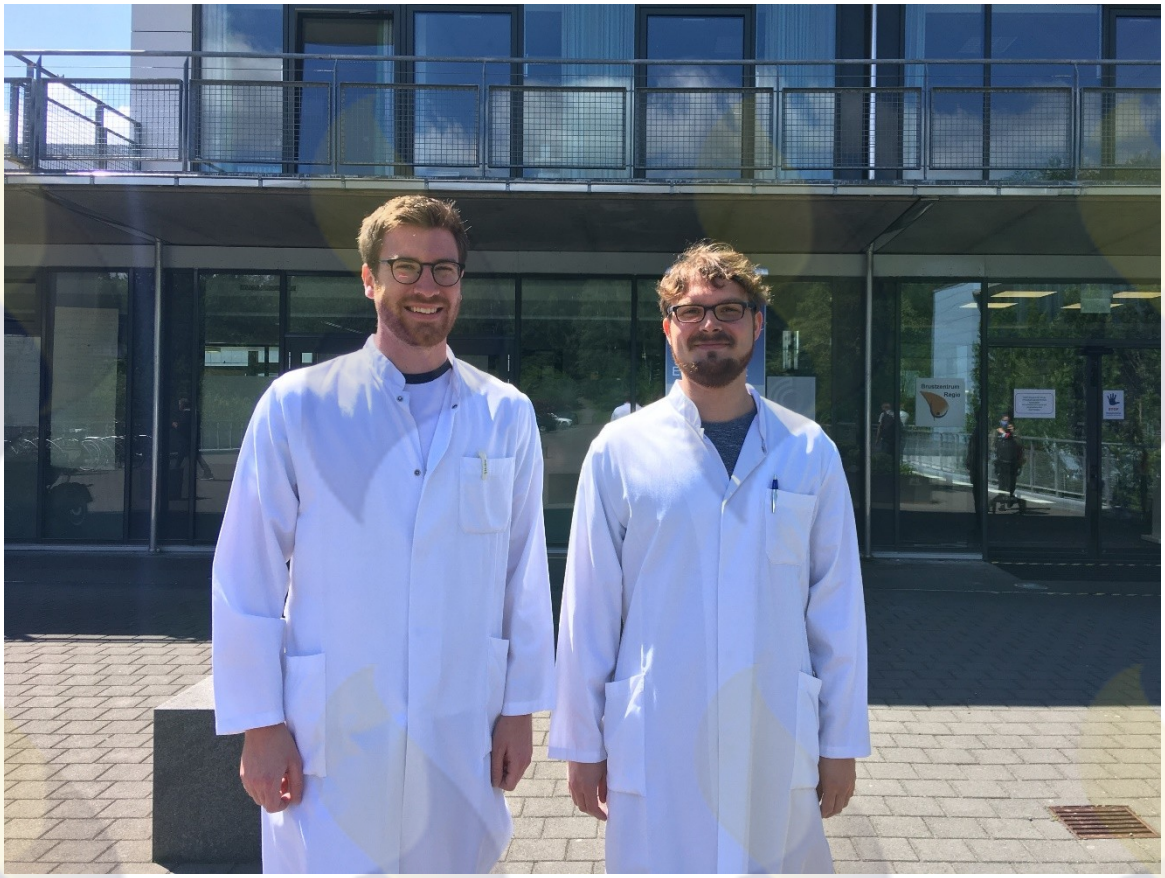
Outlook and dilemma

- Prospective, randomized studies
- Search for confounders
- Tumor registries versus evaluation of individual institutions
- Scoring systems for salivary gland evaluation
- Preventive measures
- Activity determination
- Patient selection

Conclusions

- Published evidence suggests increased risk of SPM after RAI therapy
- Given the low QOE provided by most published studies, further research is required to verify this impression
- Lack of comparability between studies
- Cohorts present vast heterogeneity based on exposure to lifestyle factors (e.g., diet, overweight)
- Problems that future studies should address:
    1) risk of bias due to discussed limitations
    2) imprecision of the presented results
    3) inappropriate control groups

Acknowledgements



Max Reinecke and Gerrit Ahlers

Thank you