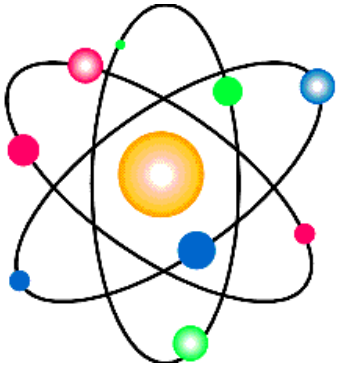
SIG RADIONUCLIDE INTERNAL DOSIMETRY
2nd Symposium on Molecular Radiotherapy Dosimetry:
The future of theragnostics 2025
EFOMP

A European clinician's perspective on the application of internal dosimetry



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Characteristics of RPT and historical reasons for resistance to internal dosimetry

- Historical roots of RPT are in medicine, not in radiology nor in radiotherapy!
- First use of radionuclides for therapy dates back to the ‘30
- ^{32}P Sodium phosphate for chronic leukemia
- Initial applications only radiopharmaceuticals in salt forms ($^{89}SrCl_2$, $^{224}RaCl_2$, $Na^{131}I$)
- ***Focus on the physiology and on the mechanism of uptake***, rather than on radiation dose

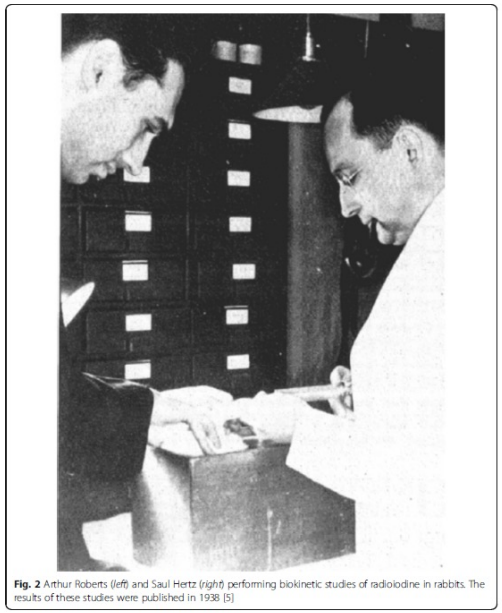

Fig. 2 Arthur Roberts (*left*) and Saul Hertz (*right*) performing biokinetic studies of radioiodine in rabbits. The results of these studies were published in 1938 [5]

Fahey FH et al. EJNMMI Physics 2017

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Moreover….

The putative systemic natu
administration make it mo
EBRT

In chemotherapy, treatmen
but on cohorts of patients

While in EBRT the relevance of dosimetry for therapy optimization is not a matter of discussion, NM lacks a clear path to include radiation dose calculations in therapy

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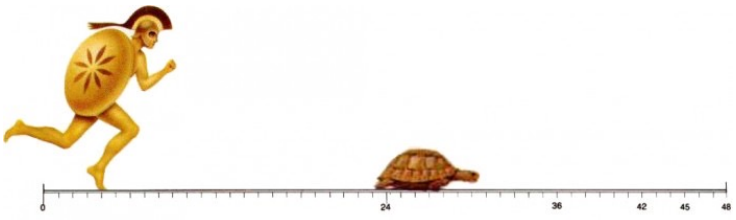
journal homepage: www.elsevier.com/locate/ejmp

Review paper

The contest between internal and external-beam dosimetry: The Zeno's paradox of Achilles and the tortoise

Francesco Cicone [a,b,*], Katarina Sjögreen Gleisner [c], Anna Sarnelli [d], Luca Indovina [e], Jonathan Gear [f], Silvano Gnesin [g,h], Françoise Kraeber-Bodéré [i], Angelika Bischof Delaloye [h], Vincenzo Valentini [e,j], Marta Cremonesi [k]



The arguments against dosimetry….

Because it is complicated

Because it is resource intensive / not enough medical physicists

Because it is impractical for the patient and for NM department

Because it is inaccurate

Because radiobiology of radionuclide therapy is unclear

Because it has no proven effect on survival

Because radiopharmaceutical companies do not appreciate

So….better not to do it!!!

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My opinion is that….

However, the field has significantly expanded over the past 15-20 years

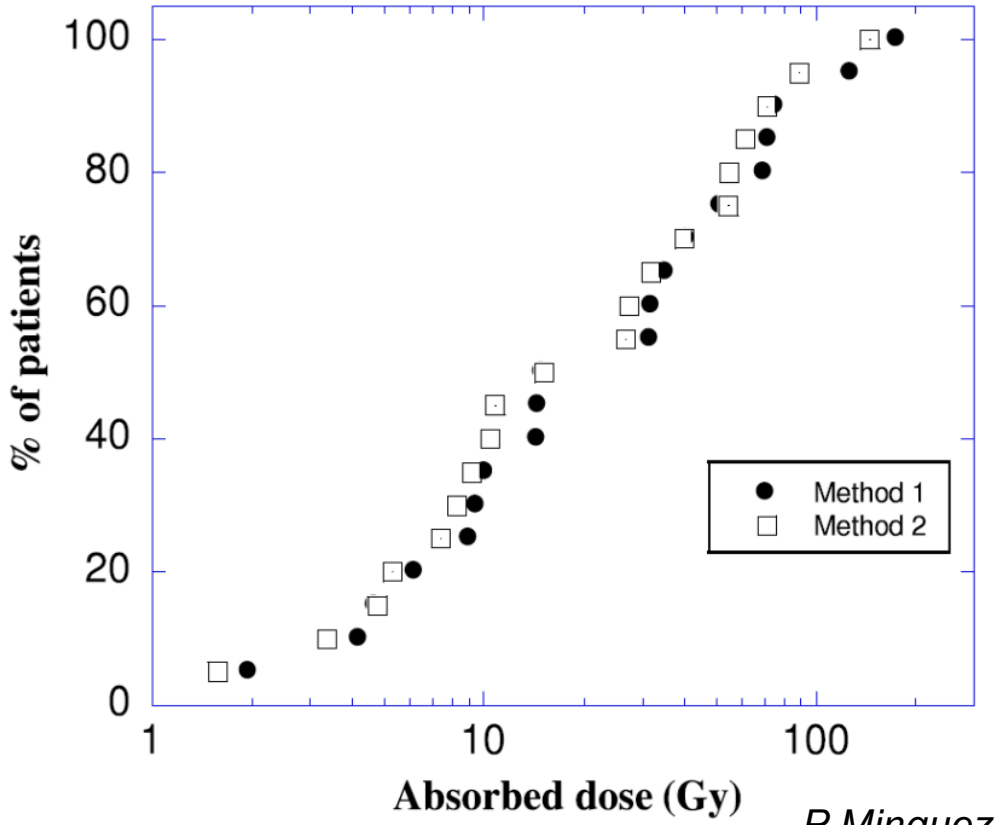
Internal dosimetry has gained cultural, commercial and legal recognition (e.g. reimboursement, software development etc)

Yet several challenges remain to be addressed

Same activity does not mean same dose

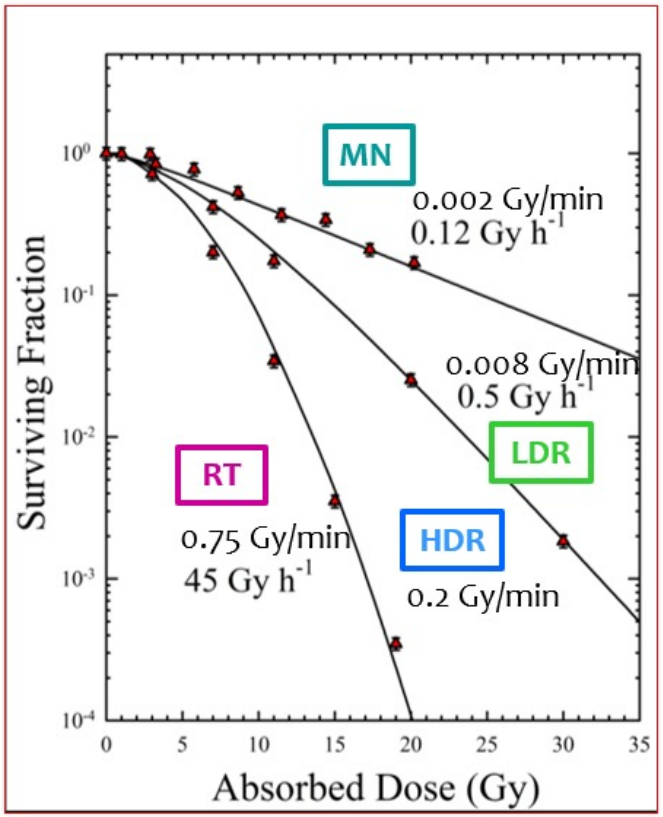
Same injected activity gives doses to remnant of **2-200 Gy**

Thyroid remnant ablation $Na^{131}I$



P Minguez et al, Med Phys, 2016

Same DOSE does not mean same ***biological effect!***



BED = biological effective dose

EBRT = no repair of subletal damage during irradiation + full repair between fractions

$$BED = n \cdot d \cdot \left(1 + \frac{d}{\alpha/\beta}\right)$$

RPT = the subletal damage is repaired during irradiation

$$BED = D + \frac{G(\infty)}{\alpha/\beta} D^2$$

$$BED_i = D_i + \beta/\alpha \cdot \frac{T_{1/2rep}}{T_{1/2rep} + T_{1/2eff}} \cdot D_i^2$$

Accuracy of $T_{1/2eff}$ calculation depends on time sampling

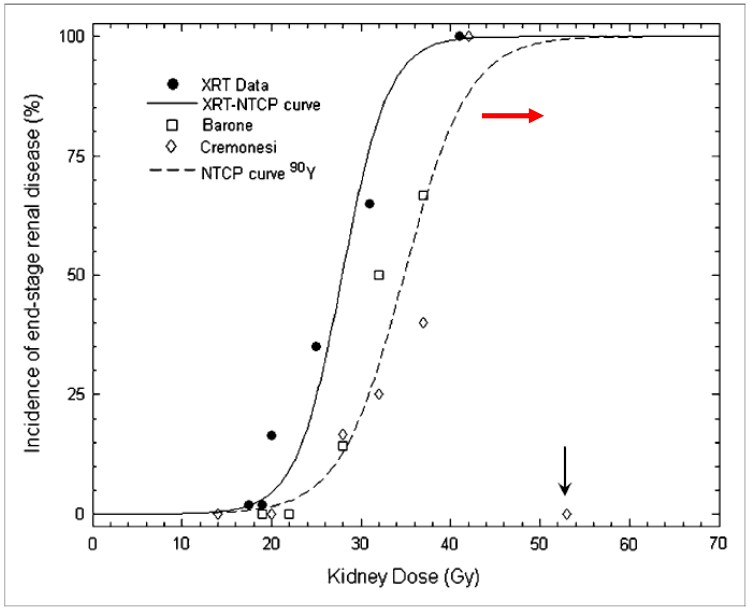
EBRT vs. RPT

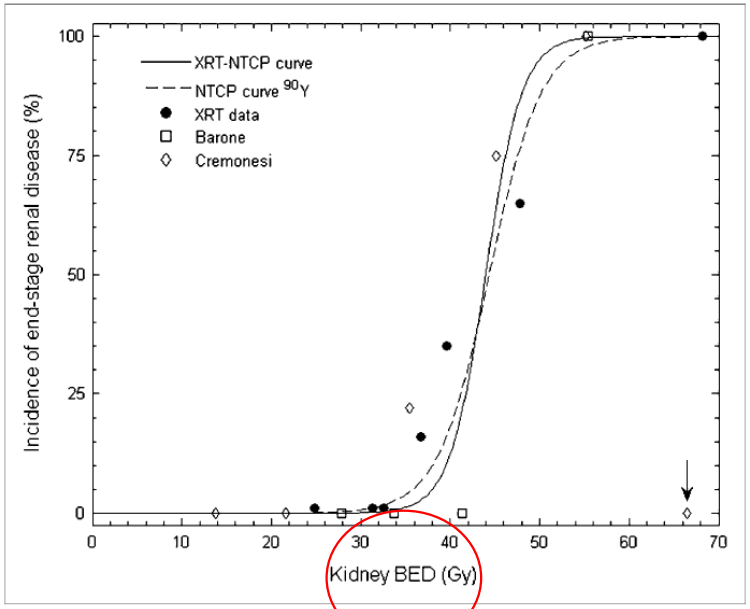
SPECIAL CONTRIBUTION

MIRD Pamphlet No. 20: The Effect of Model Assumptions on Kidney Dosimetry and Response—Implications for Radionuclide Therapy*

Barry W. Wessels[1], Mark W. Konijnenberg[2], Roger G. Dale[3], Hazel B. Breitz[4], Marta Cremonesi[5], Ruby F. Meredith[6], Alan J. Green[7], Lionel G. Bouchet[8], A. Bertrand Brill[9], Wesley E. Bolch[10], George Sgouros[11], and Stephen R. Thomas[12]

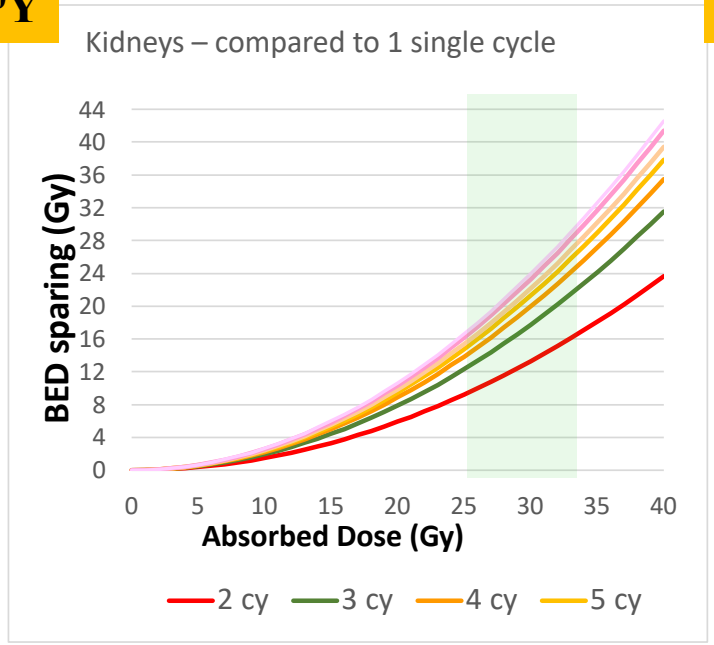
*In collaboration with the MIRD Committee of the SNM: Stephen R. Thomas (Chair), Wesley E. Bolch, A. Bertrand Brill, Darrell R. Fisher, Ruby F. Meredith, George Sgouros, Barry W. Wessels (Task Group Leader), and Pat B. Zanzonico



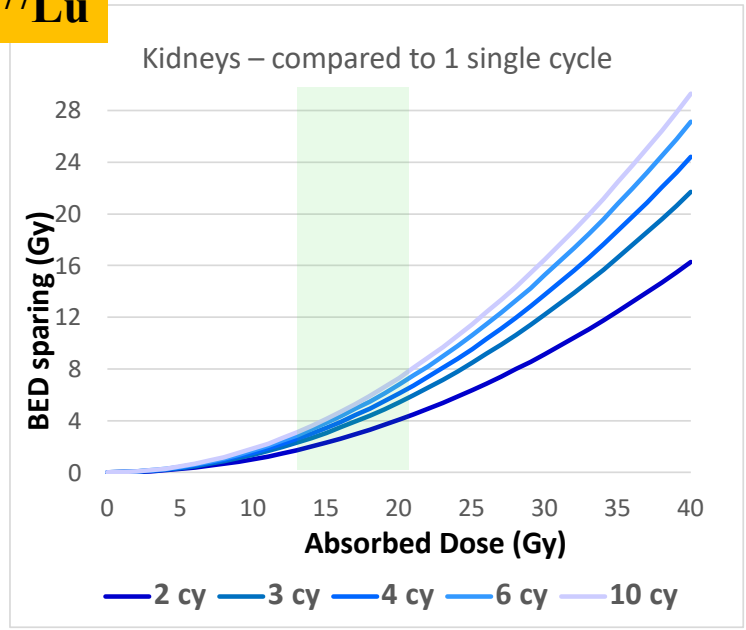


Potential impact of Radiobiology on treatment optimization
Activity fractionation

^{90}Y



^{177}Lu



Adapted from Sarnelli A et al. QJNMMI 2017, Courtesy of Marta Cremonesi

BED sparing vs. Cumulative Absorbed Dose to the kidney if therapy is splitted in several cycles as compared to one single cycle

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Activity fractionation: effects on tumor BED

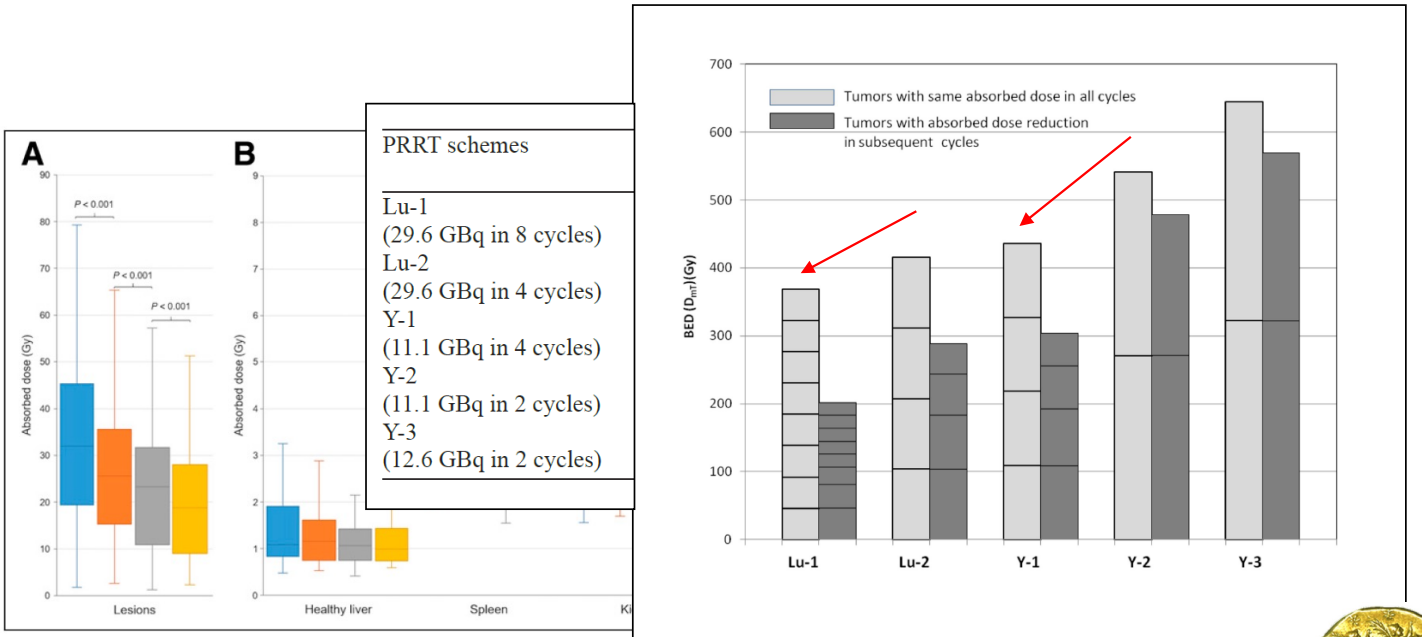


FIGURE 1. Distribution of ADs by lesions (A) and selected healthy organs (B) in 4 PPRT cycles.

Hebert et al. JNM 2024

Sarnelli A et al. QJNMMI 2017

Radiobiology for RPT Optimization

European Journal of Nuclear Medicine and Molecular Imaging (2022) 49:3830–3840
https://doi.org/10.1007/s00259-022-05786-w

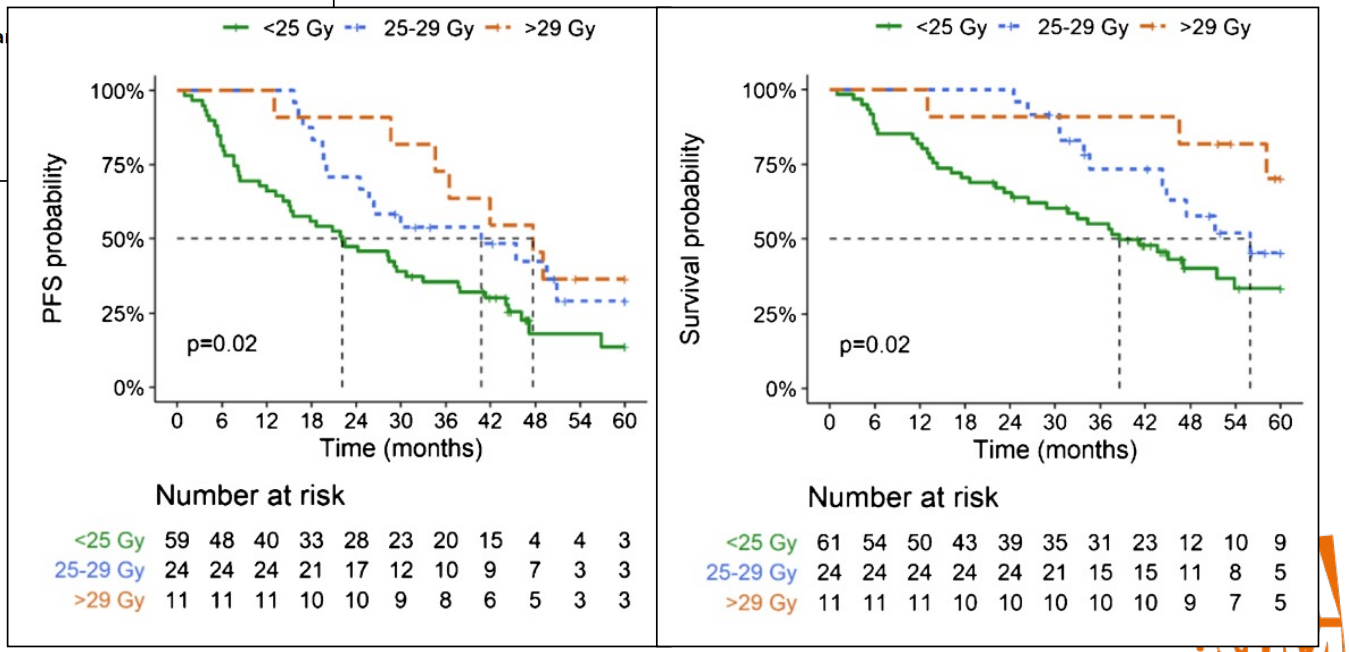
ORIGINAL ARTICLE

Phase II trial demonstrates the efficacy and safety of individualized, dosimetry-based ^{177}Lu-DOTATATE treatment of NET patients

Anna Sundlöv[1] · Katarina Sjögreen Gleisner[2] · Jan Tennvall[1] · Michael Ljungberg[2] · Ca
Kajsa Holgersson[3] · Andreas Hallqvist[3,4] · Peter Bernhardt[5,6] · Johanna Svensson[3,4]

Received: 13 October 2021 / Accepted: 28 March 2022 / Published online: 22 April 2022

All patients were planned for treatment up to a cumulative renal BED of 27 ± 2 Gy (step 1). Thereafter, patients complying with the inclusion and exclusion criteria for step 2 were offered further treatment up to a renal BED of 40 ± 2 Gy



European Journal of Nuclear Medicine and Molecular Imaging (2019) 46:728–742
https://doi.org/10.1007/s00259-018-4209-7

ORIGINAL ARTICLE

Personalized ^{177}Lu-octreotate peptide receptor radionuclide therapy of neuroendocrine tumours: initial results from the P-PRRT trial

Michela Del Prete[1,2,3,4] · François-Alexandre Buteau[1,2] · Frédéric Arsenault[1,2,3,4] · Nassim Saighi[1,2,3,4] · Louis-Olivier Bouchard[1,5] · Alexis Beaulieu[1,2] · Jean-Mathieu Beauregard[1,2,3,4]

Median IA of 36.1 (range, 6.3–78.6) GBq

The Uppsala and the Lund groups have suggested varying the number of fixed-IA induction cycles to deliver 23 Gy or 27 Gy to the kidney. In such a protocol, the length of the induction course can vary from as little as 2 months (two 2-monthly onthly cycles).
Another approach : personalizing IA to deliver a prescribed renal absorbed dose of 23 Gy to the kidney over a fixed number of cycles. While both personalized PRRT approaches can increase the cumulative absorbed dose to the tumour to a similar extent as compared to empiric PRRT, our protocol is the only one that can also increase the tumour absorbed dose per cycle, which has the potential to accelerate and amplify the therapeutic response.

A Phase II Trial of a Personalized, Dose-Intense Administration Schedule of ^{177}Lutetium-DOTATATE in Children With Primary Refractory or Relapsed High-Risk Neuroblastoma–LuDO-N

Fredrik Sundquist[1], Kleopatra Georgantzi[1,2], Kirsten Brunsvig Jarvis[3], Jesper Brok[4], Minna Koskenvuo[5], Jelena Rascon[6], Max van Noesel[7], Per Grybäck[8], Joachim Nilsson[8], Arthur Braat[9], Mikael Sundin[10], Sandra Wessman[11], Nikolas Herold[1,2], Lars Hjorth[12], Per Kogner[1], Dan Granberg[13], Mark Gaze[14] and Jakob Stenman[1,15]

[1] Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden, [2] Pediatric Oncology, Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden, [3] Department of Paediatric Haematology and Oncology, Oslo University Hospital, Rikshospitalet, Oslo, Norway, [4] Department of Paediatrics and Adolescent Medicine, Rigshospitalet, Copenhagen, Denmark, [5] Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland, [6] Center for Pediatric Oncology and Hematology, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania, [7] Solid Tumor Department, Princess Máxima Center for Pediatric Oncology, Utrecht, Netherlands, [8] Department of Medical Radiation Physics and Nuclear Medicine, Karolinska University Hospital, Stockholm, Sweden, [9] Department of Nuclear Medicine, Princess Máxima Center for Pediatric Oncology, Utrecht, Netherlands, [10] Division of Pediatrics, Department of Pediatric Hematology, Immunology and HCT, Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [11] Department of Pathology, Department of Oncology-Pathology, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [12] Department of Clinical Sciences Lund, Paediatrics, Lund University, Skane University Hospital, Lund, Sweden, [13] Department of Breast, Endocrine Tumors and Sarcomas, Department of Molecular Medicine and Surgery, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [14] Department of Oncology, University College London Hospitals NHS Foundation Trust, London, United Kingdom, [15] Department of Pediatric Surgery, Karolinska University Hospital, Stockholm, Sweden

Background: Half the children with high-risk neuroblastoma die with widespread metastases. Molecular radiotherapy is an attractive systemic treatment for this relatively radiosensitive tumor. ^{131}I-mIBG is the most widely used form in current use, but is not universally effective. Clinical trials of ^{177}Lutetium DOTATATE have so far had disappointing results, possibly because the administered activity was too low, and the courses were spread over too long a period of time, for a rapidly proliferating tumor. We have devised an alternative administration schedule to overcome these limitations. This involves two high-activity administrations of single agent ^{177}Lu-DOTATATE given 2 weeks apart, prescribed as a personalized whole body radiation absorbed dose, rather than a fixed administered activity. "A phase II trial of ^{177}Lutetium-DOTATATE in children with primary refractory or relapsed high-risk neuroblastoma - LuDO-N" (EudraCT No: 2020-004445-36, ClinicalTrials.gov Identifier: NCT04903899) evaluates this new dosing schedule.

Study Interventions

A baseline ^{68}Ga-DOTATOC PET/CT is performed within 2 weeks, prior to ^{177}Lu-DOTATATE treatment. A total of two doses of ^{177}Lu-DOTATATE are administered intravenously 2–4 weeks apart. A weight-based activity of 200 MBq kg^{-1} is used for the first dose. The activity of the second dose is calculated based on whole body activity scans as well as SPECT CT scans to determine the absorbed kidney dose. The aim is to administer ^{177}Lu-DOTATATE corresponding to a whole-body dose of 1,2 Gy, with a cumulative whole-body dose of about 2,4 Gy over two courses, and not exceeding a cumulative renal dose of 23 Gy, in order to avoid renal toxicity (41).

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However, clinical data are still being reported without dosimetry

Long-Term Nephrotoxicity of ^{177}Lu-PSMA Radioligand Therapy

Lisa Steinhelfer*[1,2], Lukas Lunger*[3], Lisena Cala[1], Christian H. Pfob[4], Constantin Lapa[4], Philipp E. Hartrampf[5], Andreas K. Buck[5], Hannah Schäfer[6], Christoph Schmaderer[6], Robert Tauber[3], Julia Brosch-Lenz[1], Bernhard Haller[7], Valentin H. Meissner[3], Karina Knorr[1], Wolfgang A. Weber[1], and Matthias Eiber[1]

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β-emitting ^{177}Lu targeting prostate-specific membrane antigen (PSMA) is an approved treatment option for metastatic castration-resistant prostate cancer. Data on its long-term nephrotoxicity are sparse. This study aimed to retrospectively evaluate post–^{177}Lu-PSMA estimated glomerular filtration rate (eGFR) dynamics for at least 12 mo in a cohort of metastatic castration-resistant prostate cancer patients. **Methods:** The institutional databases of 3 German tertiary referral centers identified 106 patients who underwent at least 4 cycles of ^{177}Lu-PSMA and had at least 12 mo of eGFR follow-up data. eGFR (by the Chronic Kidney Disease Epidemiology Collaboration formula) at 3, 6, and 12 mo after ^{177}Lu-PSMA radioligand therapy was estimated using monoexponentially fitted curves through available eGFR data. eGFR changes were grouped (≥15%–<30%, moderate; ≥30%–<40%, severe; and ≥40%, very severe). Associations between eGFR changes (%) and nephrotoxic risk factors, prior treatment lines, and number of ^{177}Lu-PSMA cycles were analyzed using multivariable linear regression. **Results:** At least moderate eGFR decreases were present in 45% (48/106) of patients; of those, nearly half (23/48) had a severe or very severe eGFR decrease. A higher number of risk factors at baseline (−4.51, P − 0.03) was associated with a greater eGFR decrease. Limitations of the study were the retrospective design, lack of a control group, and limited number of patients with a follow-up longer than 1 y. **Conclusion:** A considerable proportion of patients may experience moderate or severe decreases in eGFR 1 y from initiation of ^{177}Lu-PSMA. A higher number of risk factors at baseline seems to aggravate loss of renal function. Further prospective trials are warranted to estimate the nephrotoxic potential of ^{177}Lu-PSMA.

Key Words: nephrotoxicity; PSMA; radioligand therapy; lutetium; mCRPC

J Nucl Med 2024; 65:79–84
DOI: 10.2967/jnumed.123.265986

Prostate-specific membrane antigen (PSMA)–targeted radioligand therapy (RLT) with ^{177}Lu-PSMA-617 was recently approved for the treatment of metastatic castration-resistant prostate cancer (mCRPC) after taxane-based chemotherapy (*1*,*2*). Despite its overall favorable side effect profile, primary safety concerns during ^{177}Lu-PSMA RLT are critical radiation doses to cancer-unaffected sites due to physiologic expression of PSMA (e.g., in the salivary glands and kidneys).

A recent systematic review and metaanalysis reported nephrotoxicity of any stage in 9.5% of 744 patients treated with ^{177}Lu-PSMA (*3*). Consistently, the phase III VISION trial on ^{177}Lu-PSMA (^{177}Lu-PSMA-RLT plus the standard of care versus the standard of care alone) reported renal toxicity of any stage in 8.7% of patients in the intervention arm versus 5.9% in the control arm. Of note, severe renal toxicity (stages 3–5) was observed in 3.4% of patients in the ^{177}Lu-PSMA group and in 2.9% in the group receiving the standard of care alone (*2*).

However, these data may underestimate the long-term incidence of renal toxicity, as it is known from external-beam radiotherapy (EBRT) and other radionuclide therapies that toxicity may develop over a longer period (>1 y) and median survival in the VISION study was only 15.3 mo. We recently reported 3 patients who developed severe radiation nephropathy with a histologically proven renal thrombotic microangiopathylike picture after extensive treatment with ^{177}Lu-PSMA RLT (*4*).

Nephropathy after ^{177}Lu-PSMA RLT is attributed mainly to the renal tubular PSMA expression and the renal excretion of ^{177}Lu-PSMA, resulting in a prolonged retention of the β^- emitter in the kidneys (*5*). Definitive dose limits for RLT are not established, and current thresholds are based on observations with EBRT. Here, homogeneous irradiation of the whole kidneys with 23 and 28 Gy was associated with a 5% and 50% risk of severe radiation nephritis, respectively, within 5 y after treatment (*6*). However, compared with EBRT, the radiation to the kidneys by ^{177}Lu-PSMA is of lower energy, is delivered over a longer period, and is not homogeneously distributed within the kidney tissue (*7*).

Several, mainly retrospective, studies investigated the renal absorbed dose from ^{177}Lu-labeled PSMA ligands. For ^{177}Lu-PSMA 617 and ^{177}Lu-PSMA I&T, mean renal absorbed doses of 0.5 Gy/GBq (SD, 0.2) and 0.7 Gy/GBq (SD, 0.2) have been reported (*8*).

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For correspondence or reprints, contact Lukas Lunger (lukas.lunger@tum.de).
*Contributed equally to this work.
Published online Oct. 19, 2023.

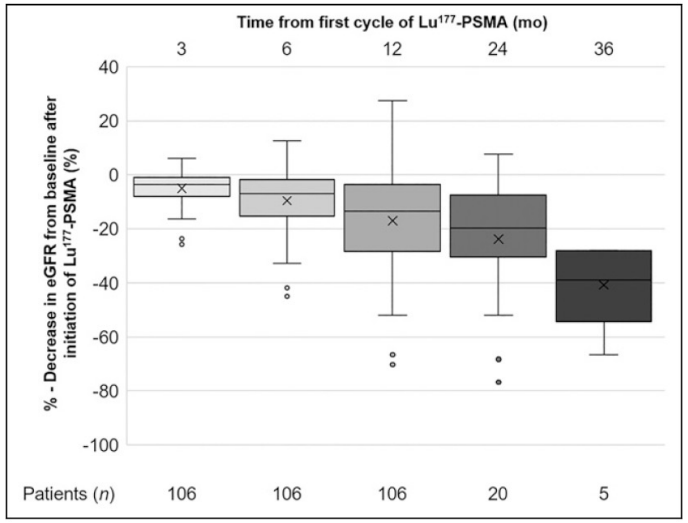


FIGURE 1. Box plots illustrating percentage eGFR decrease from baseline after initiation of ^{177}Lu-PSMA. × within box plots = mean.

No dosimetry !

No dose/response correlations!

Methods for therapy optimization (excluding dosimetry)

Withdrawal interfering therapies (e.g. beta blockers for MIBG)

Acceleration of RPT excretion (diuretics, laxatives, lemon candies)

Administration of «cold» analogues

“Renal protection” by amino acid co-infusion

Thyroid blocking (e.g. potassium perclorate, potassium iodide)

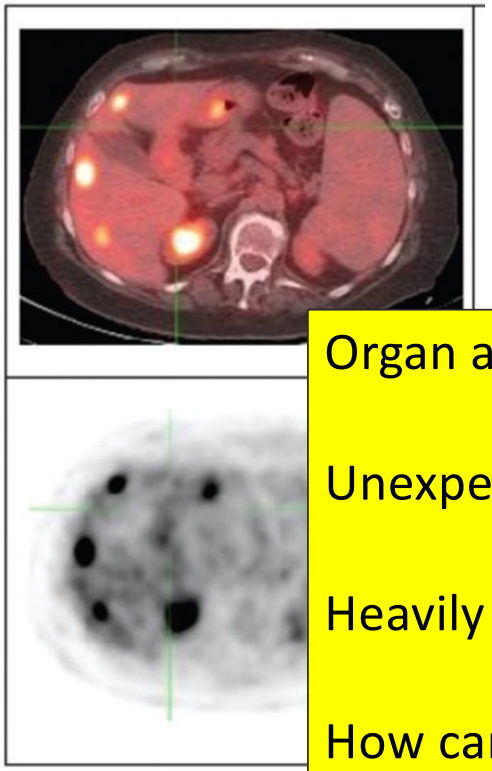
Enhancement of thyroid uptake by hormone withdrawal (increse of TSH levels)

Embolization of aberrant vessels before TARE

Radiobiological models have limitations (and are underused in RPT !)

- **BED** is a useful model to compare doses delivered homogeneously, however it does not take into account the dose heterogeneity.
- **EU-BED** suffers from limitations of resolution and of missing information on micro-dosimetry
- Models need ***experimental data*** for correctly interpreting reality

Reality is complex…..

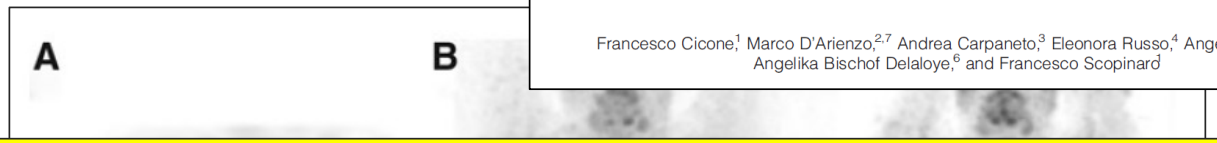


CANCER BIOTHERAPY AND RADIOPHARMACEUTICALS
Volume 28, Number 2, 2013
© Mary Ann Liebert, Inc.
DOI: 10.1089/cbr.2012.1299

Original Articles

Quantification of Dose Nonuniformities by Voxel-Based Dosimetry in Patients Receiving ^{90}Y-Ibritumomab-Tiuxetan

Francesco Cicone,[1] Marco D'Arienzo,[2,7] Andrea Carpaneto,[3] Eleonora Russo,[4] Angela Coniglio,[5] Angelika Bischof Delaloye,[6] and Francesco Scopinaro[1]



Organ absorbed doses well below safety limits

Unexpected severe toxicities

Heavily pretreated patients (including history of drug abuse for Pt 2)

How can this be justified ? Types of liver involvement (focal vs. diffuse), radiobiological parameters?

Patient 1, F 62 y, D
Death 60 days after RIT of hematological toxicity, normal liver function tests until death

Patient 2, M 32 y, DLBCL
Death 100 days after RIT, liver toxicity unexplained by disease progression, hepatic necrosis at autopsy

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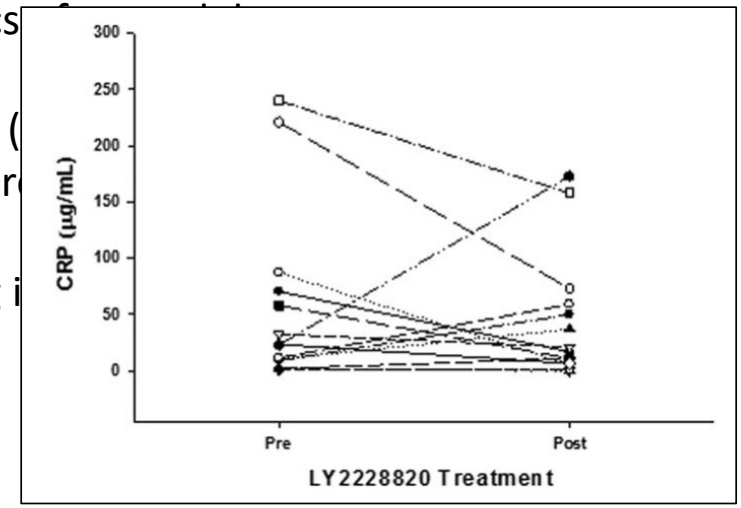
Challenges of predicting pharmacokinetic in oncological patients

If we handle radiopharmaceuticals like chem

The disease status (i.e. inflammation) is known to alter enzymes and transporters activity >> which can significantly affect pharmacokinetic and pharmacodinamics

Cytochrome P450 (reduced drug clear

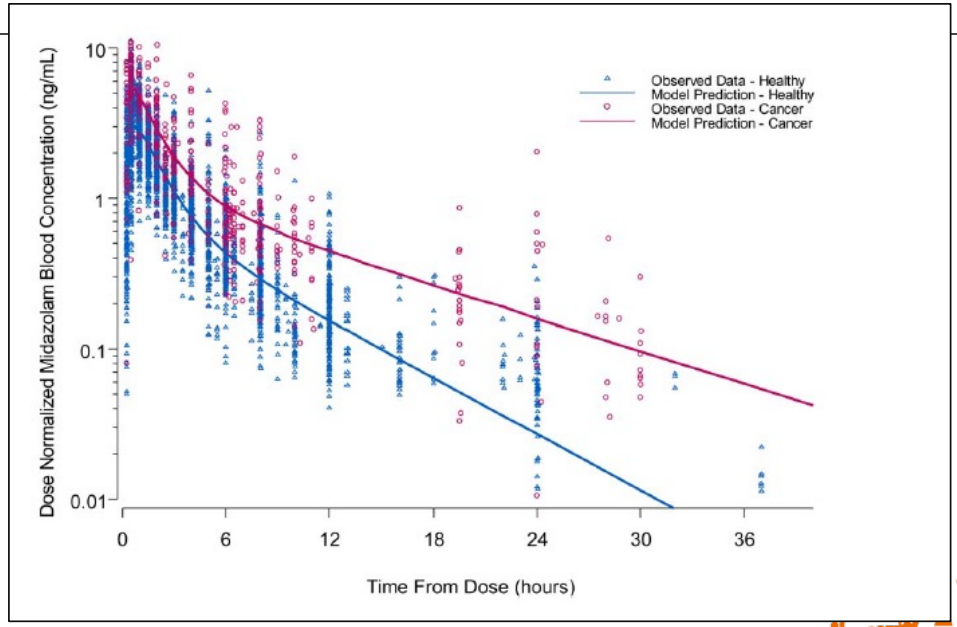
Concomitant drug i



REVIEW

Understanding Disease–Drug Interactions in Cancer Patients: Implications for Dosing Within the Therapeutic Window

DE Coutant[1], P Kulanthaivel[1], PK Turner[2], RL Bell[2], J Baldwin[2], SR Wijayawardana[3], C Pitou[2] and SD Hall[1]



De Coutant et al. 2015;98 (1) Clin Pharmacol & Therapeutics

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Clinical and Translational Science

POSITION PAPER OPEN ACCESS

Challenges in Extrapolating Healthy Volunteer Pharmacokinetics to Oncology Populations: Advocating for a Holistic Perspective

Yan Ji[1] | Romain Sechaud[2] | Abhijit Chakraborty[1]

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Keywords: cancer | clinical pharmacology | clinical trial | healthy volunteer | oncology | pharmacokinetics

We illustrate situations where conclusions drawn from HV PK studies did not align with the outcomes from clinical trials in patients with cancer

TABLE 2 | Comparison of healthy volunteer clinical pharmacology studies and pivotal patient clinical trials for oncology drugs.

		Healthy volunteer clinical pharmacology studies	Pivotal patient clinical trials
Study population	Population type	Healthy volunteers or non-cancer subjects with standardized demographics	Cancer patients of the target indication
	Health condition	Clean medical history (except liver and renal impairment for dedicated organ impairment studies)	Heavily pretreated, presence of comorbidities, chronic inflammation due to tumor burden, and potential impairment of renal and hepatic functions
	Concomitant medications	Prohibited	Not prohibited except those predefined in the protocol, concomitant medication profiles (including comedication types, dose regimens and treatment duration) vary between patients
Study design	Phase and primary objective	Phase I study to evaluate the effect of a single intrinsic or extrinsic covariate factor on drug PK in HVs or non-cancer subjects	Phase II or Phase III study to evaluate the efficacy and safety of a drug in the target cancer patient population
	Design	Cross-over, or randomized parallel in subjects matched by demographic factors to study the covariate effect	Patients randomized to treatment arms to study efficacy and safety
	Dose and duration of treatment	Dose level may be lower than therapeutic dose; Single-dose or short-term treatment with multiple doses	Therapeutical dose level; Chronic dosing until disease progression, death or censoring
	Enrollment criteria	Strict restrictions and exclusions	Less restriction for covariate factors, representative of real-world setting
	Sample size	Small, powered to assess the covariate effect	Large, powered to assess efficacy and safety
	PK collection	Intensive PK sampling	Sparse PK sampling
Data analysis	Dataset	Single-study data	Single-trial data or pooled data from multiple trials
	Methodology	Dense PK data analyzed using NCA to generate PK parameters and statistical assessment of covariate effects, aligning with the study objectives	Population PK analysis of mostly sparse PK data to determine significance of covariate effect; if available, intensive PK data from a subset of patients analyzed by NCA to assess covariate effect

Abbreviations: HV: healthy volunteer; NCA: non-compartmental analysis; PK, pharmacokinetics.

The «holistic» framework

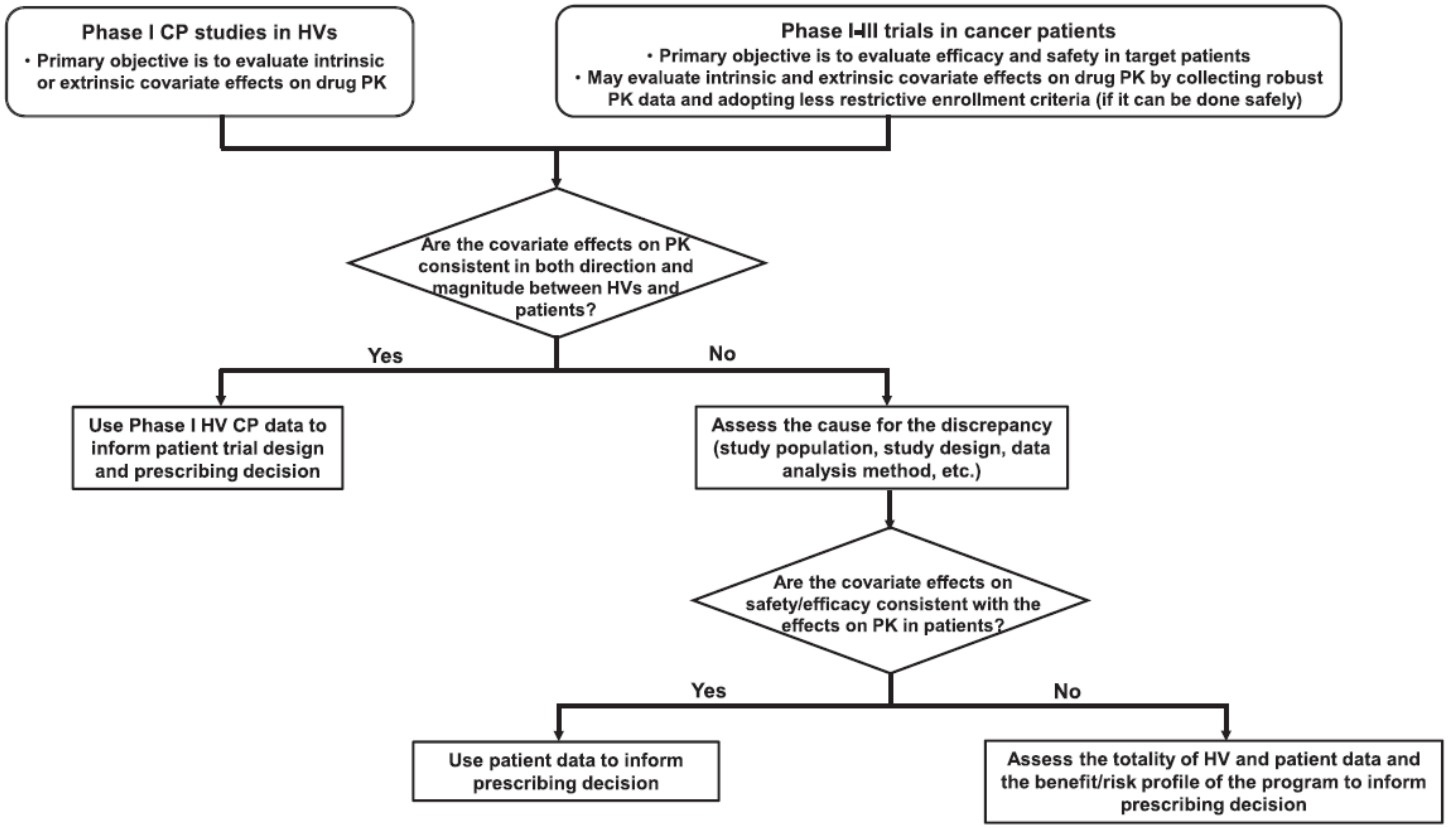


FIGURE 1 | A Holistic Framework for Evaluating Intrinsic and Extrinsic Covariate Effects on Drug PK in Oncology Drug Development.

How these concepts apply to dosimetry in RPT

The «holistic» framework proposed by Ji et al (from Novartis) is applied to systemic anticancer treatments and to the comparison between healthy volunteers and cancer patients

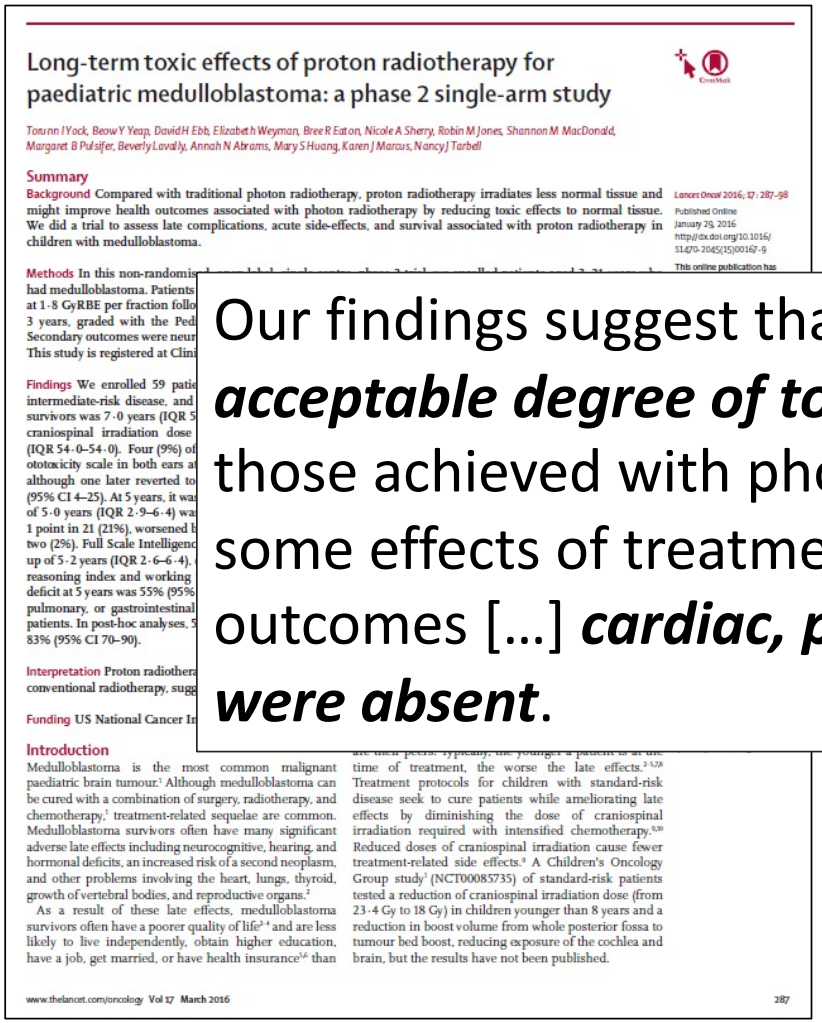
However, a similar framework may be (in my opinion!) used to assess interpatient variability for optimized RPT «dosing» (ex. High vs. low tumor burden or prior vs. no prior treatment)

The need for extensive dosimetry studies in early phase trials is undisputed (same as PK studies for «cold» drugs)

The relevance of symplified dosimetry models relies on the assessment/control of the covariate effects between historical cohorts and case studies.

Lack of randomised trials as an argument against the systematic implementation of dosimetry

In 2016, following the publication of a prospective phase II trial[15] the NHS decided it would pay for children with medulloblastoma to travel abroad to receive proton therapy.[16][10]



Long-term toxic effects of proton radiotherapy for paediatric medulloblastoma: a phase 2 single-arm study

Torunn I Yock, Beow Y Yeap, David H Ebb, Elizabeth Weyman, Bree R Eaton, Nicole A Sherry, Robin M Jones, Shannon M MacDonald, Margaret B Pulsifer, Beverly Lavally, Annah N Abrams, Mary S Huang, Karen J Marcus, Nancy J Tarbell

Summary

Background Compared with traditional photon radiotherapy, proton radiotherapy irradiates less normal tissue and might improve health outcomes associated with photon radiotherapy by reducing toxic effects to normal tissue. We did a trial to assess late complications, acute side-effects, and survival associated with proton radiotherapy in children with medulloblastoma.

Methods In this non-randomis… had medulloblastoma. Patients … at 1·8 GyRBE per fraction follo… 3 years, graded with the Ped… Secondary outcomes were neur… This study is registered at Clini…

Findings We enrolled 59 patie… intermediate-risk disease, and … survivors was 7·0 years (IQR 5… craniospinal irradiation dose … (IQR 54·0–54·0). Four (9%) of… ototoxicity scale in both ears at… although one later reverted to… (95% CI 4–25). At 5 years, it was… of 5·0 years (IQR 2·9–6·4) was… 1 point in 21 (21%), worsened b… two (2%). Full Scale Intelligenc… up of 5·2 years (IQR 2·6–6·4), … reasoning index and working … deficit at 5 years was 55% (95%… pulmonary, or gastrointestinal … patients. In post-hoc analyses, 5… 83% (95% CI 70–90).

Interpretation Proton radiothera… conventional radiotherapy, sugg…

Funding US National Cancer In…

Lancet Oncol 2016; 17: 287–98
Published Online January 29, 2016
http://dx.doi.org/10.1016/S1470-2045(15)00167-9
This online publication has

Introduction

Medulloblastoma is the most common malignant paediatric brain tumour.[1] Although medulloblastoma can be cured with a combination of surgery, radiotherapy, and chemotherapy,[1] treatment-related sequelae are common. Medulloblastoma survivors often have many significant adverse late effects including neurocognitive, hearing, and hormonal deficits, an increased risk of a second neoplasm, and other problems involving the heart, lungs, thyroid, growth of vertebral bodies, and reproductive organs.[2]

As a result of these late effects, medulloblastoma survivors often have a poorer quality of life[3,4] and are less likely to live independently, obtain higher education, have a job, get married, or have health insurance[5,6] than … time of treatment, the worse the late effects.[2,3,7,8] Treatment protocols for children with standard-risk disease seek to cure patients while ameliorating late effects by diminishing the dose of craniospinal irradiation required with intensified chemotherapy.[9,10] Reduced doses of craniospinal irradiation cause fewer treatment-related side effects.[8] A Children's Oncology Group study[1] (NCT00085735) of standard-risk patients tested a reduction of craniospinal irradiation dose (from 23·4 Gy to 18 Gy) in children younger than 8 years and a reduction in boost volume from whole posterior fossa to tumour bed boost, reducing exposure of the cochlea and brain, but the results have not been published.

Our findings suggest that proton radiotherapy ***seems to result in an acceptable degree of toxicity and had similar survival outcomes*** to those achieved with photon-based radiotherapy. Although there remain some effects of treatment on hearing, endocrine, and neurocognitive outcomes […] ***cardiac, pulmonary, and gastrointestinal toxic effects, were absent***.

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Radiotherapy and Oncology 95 (2010) 23–31

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Review

Trials and tribulations in charged particle radiotherapy ☆

Michael Goitein *

Harvard Medical School, Boston, USA

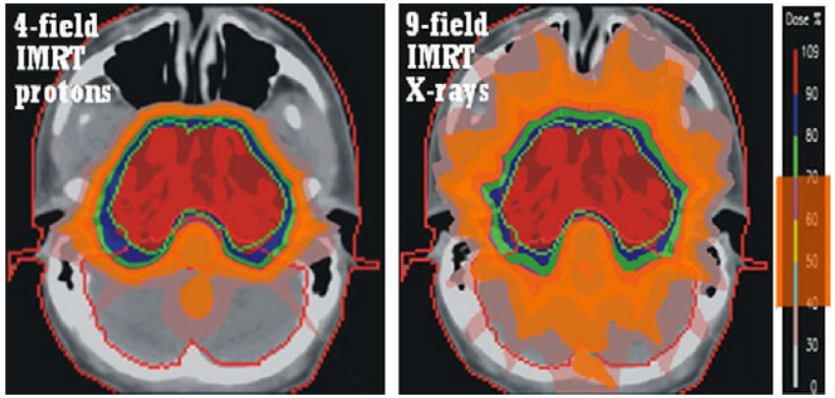

Fig. 2. IMRT plans for protons (left) and X-rays (right). The area receiving between 40% and 70% of the prescribed dose (approximately 30–50 Gy) is shaded in orange. (Figure courtesy of A. Lomax, PSI.)

Randomized trials in CPRT are ethical or unethical ?

Viewpoint

Position statement on ethics, equipoise and research on charged particle radiation therapy

Ethical considerations >> randomization performed to demonstrate cost-effectiveness is unhetical

Clinical and Scientific considerations >> dose distribution is only a surrogate end point for more pertinent clinical outcomes, which may fail to occur ; the already available clinical results may influence the judgment of individual clinicians and of patients

Methodological and evidential considerations >> Where (1) the dose distribution with CPRT suggests substantial superiority to conventional treatments and (2) existing clinical results suggest significant superiority, a randomised controlled trial (RCT) would be neither necessary nor appropriate. However, where predicted differences are small, such as if the same target dose is used and where sparing of normal tissue is unlikely to confer a useful clinical benefit, a RCT may be clinically unrewarding and a poor use of resources.

Sheehan M, et al. J Med Ethics 2014;40:572–575. doi:10.1136/medethics-2012-101290

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How to make progress in the field with limited use of clinical trials ?

Engage in the production of data,

Development of high quality shared infrastructure,

International/global collaborations

ESTRO – EORTC Registry

5-year report of the E²-RADIatE Platform: Executive summary

The **E²-RADIatE Platform** (EORTC-ESTRO RADiotherapy InfrAstrucTure for Europe) is a collaborative initiative launched in 2019 by EORTC and ESTRO to enhance radiotherapy res
related questions through prospective real-world data coll
treatment, focusing on survival, toxicity, quality of life, a
generate new hypotheses to be investigated in future clini
such as Trials within Cohorts (TwiCs).

The platform is structured as an observational multi-coho
across Europe. It uses a unified protocol for data capture,
various radiation oncology centers.

- **ReCare (EORTC-2011)**: Initiated in May 2023, this cohort focuses on high-dose reirradiation for various primary tumors. It has already surpassed recruitment projections with over 350 patients enrolled by the end of 2024. The ReCare study prospectively generates a multimodal real-world dataset – including clinical data, imaging, and radiotherapy plans – curated by the EORTC and its RTQA team to ensure the highest data fidelity. Doing so, ReCare will allow analysing pivotal uncertainties on dose constraints in the context of reirradiation, thus minimizing the risk of toxicity, guiding treatment decisions for an ever-growing patient population, and ultimately supporting the design of the next generation of randomized trials in reirradiation.
- **AlphaCare (EORTC-2352)**: This upcoming cohort aims to assess the safety of combining metastasis-directed radiotherapy with novel anti-cancer drugs. In this prospective non-interventional registry, initial evidence will be generated on severe toxicity associated with the concomitant use of stereotactic body radiotherapy and selected, newly approved, systemic therapies in patients with (oligo)metastatic cancer. In case of a positive safety profile, AlphaCare will provide reassurance for the clinical use of combined modality approach, yet help design future efficacy trials if any safety concerns would arise. As such, it will ultimately lead to improved treatment strategies for metastatic cancer patients requiring combined modality treatment.

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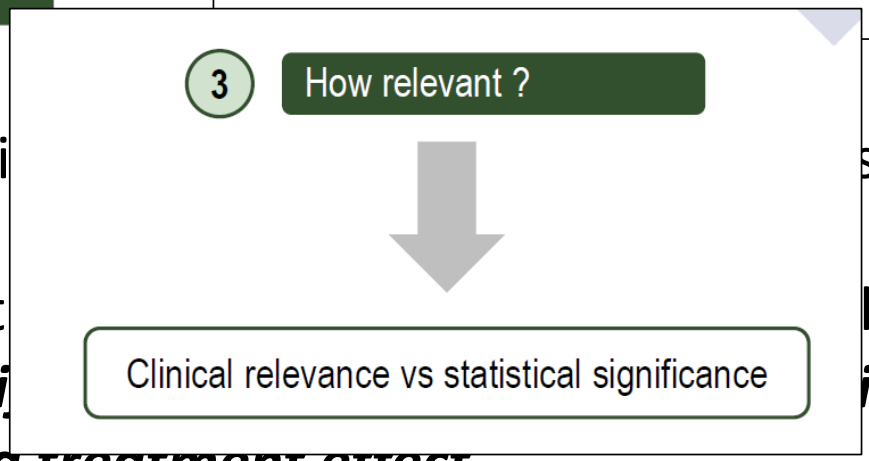
How to interpret a clinical trial ?

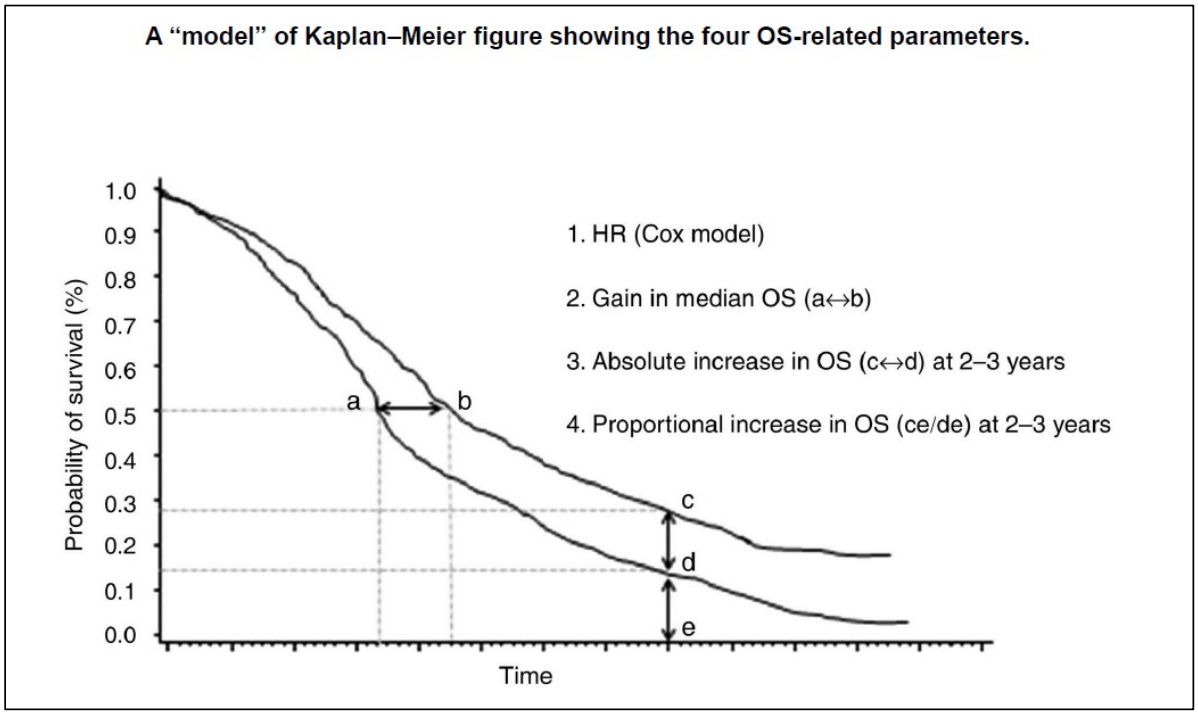
1. How true ?
2. How generalizable ?
3. How relevant ?



Two problems wi size and high price

Modern clinical t larger, ***resulting in statistically signi ith smaller and smaller observed treatment effect***

Minimum clinically meaningful outcome (mCMO)



Revision of 43 registration trials :
Only **2** met their criteria for high benefit using the metric of HR for OS and improvement in median OS;
none of these studies demonstrated large benefit using increase in both absolute and proportional OS.

Sobrero et al. Clin Cancer Res 2015

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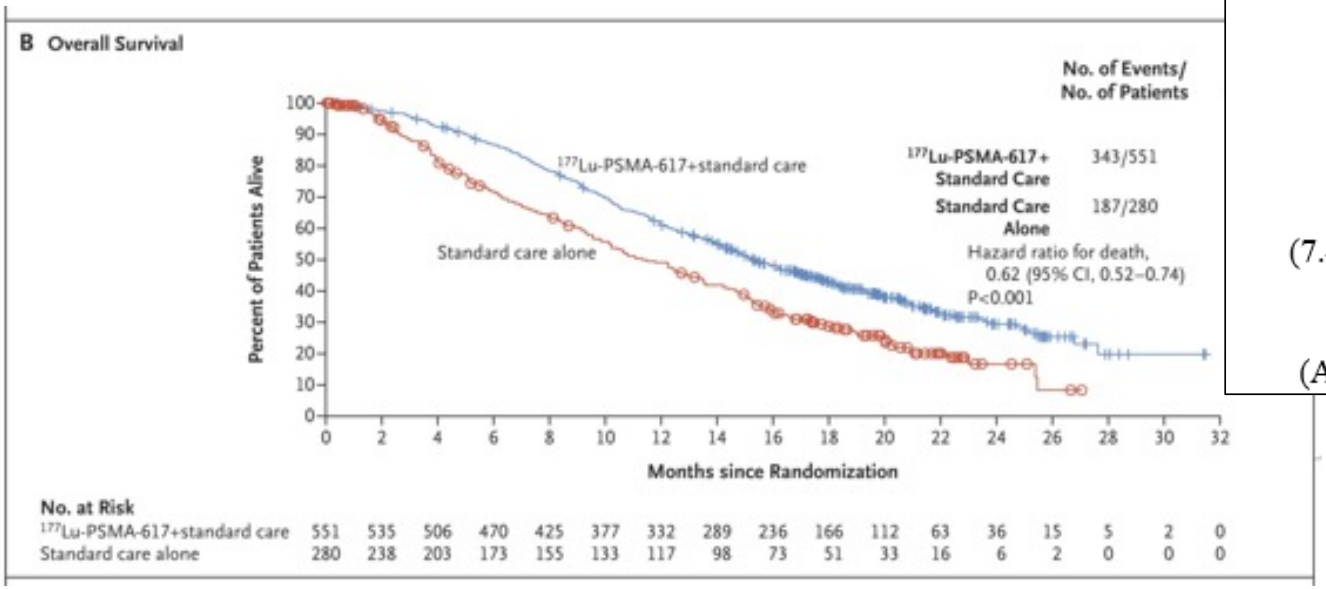
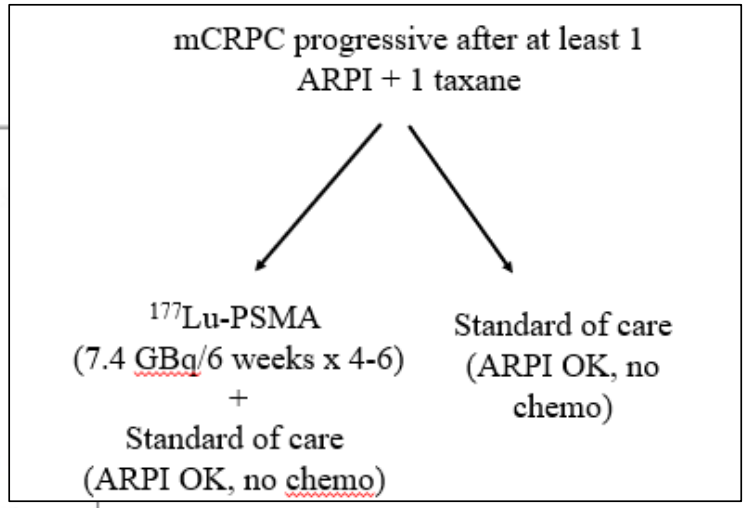
VISION trial





Original Article

Ribociclib plus Endocrine Therapy in Early Breast Cancer

Dennis Slamon, M.D., Ph.D., Oleg Lipatov, M.D., Zbigniew Nowecki, M.D., Nicholas McAndrew, M.D., Bozena Kukielka-Budny, M.D., Daniil Stroyakovskiy, M.D., Ph.D., Denise A. Yardley, M.D., Chiun-Sheng Huang, M.D., Ph.D., Peter A. Fasching, M.D., John Crown, M.D., Aditya Bardia, M.D., Stephen Chia, M.D., Seock-Ah Im, M.D., Ph.D., Manuel Ruiz-Borrego, M.D., Sherene Loi, M.D., Ph.D., Binghe Xu, M.D., Ph.D., Sara Hurvitz, M.D., Carlos Barrios, M.D., Michael Untch, M.D., Ph.D., Rebecca Moroose, M.D., Frances Visco, J.D., Karen Afenjar, M.S., Rodrigo Fresco, M.D., Irene Severin, B.Sc., Yan Ji, Ph.D., Farhat Ghaznawi, M.D., Zheng Li, Ph.D., Juan P. Zarate, M.D., Arunava Chakravartty, Ph.D., Tetiana Taran, M.D., and Gabriel Hortobagyi, M.D.

N Engl J Med
Volume 390(12):1080-1091
March 21, 2024

The NEW ENGLAND JOURNAL of MEDICINE

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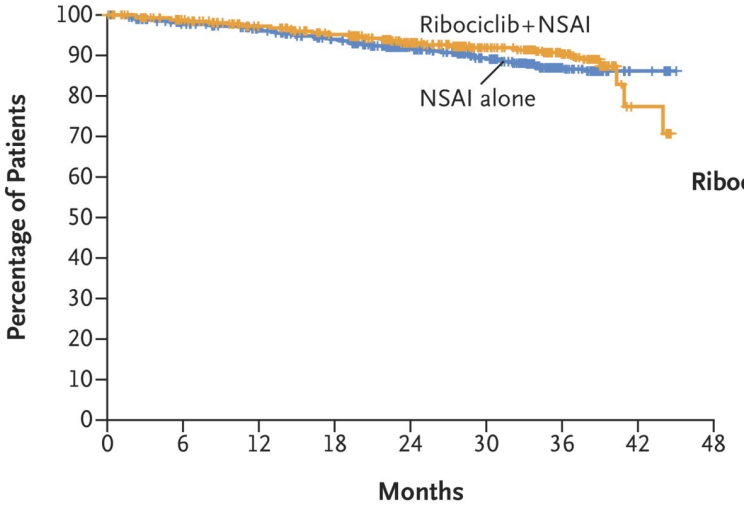
Study Overview

- In patients with stage II or III early breast cancer, the addition of ribociclib to adjuvant hormonal therapy resulted in a significant improvement in 3-year invasive disease–free survival.

Kaplan–Meier Estimates of Invasive Disease–free Survival.



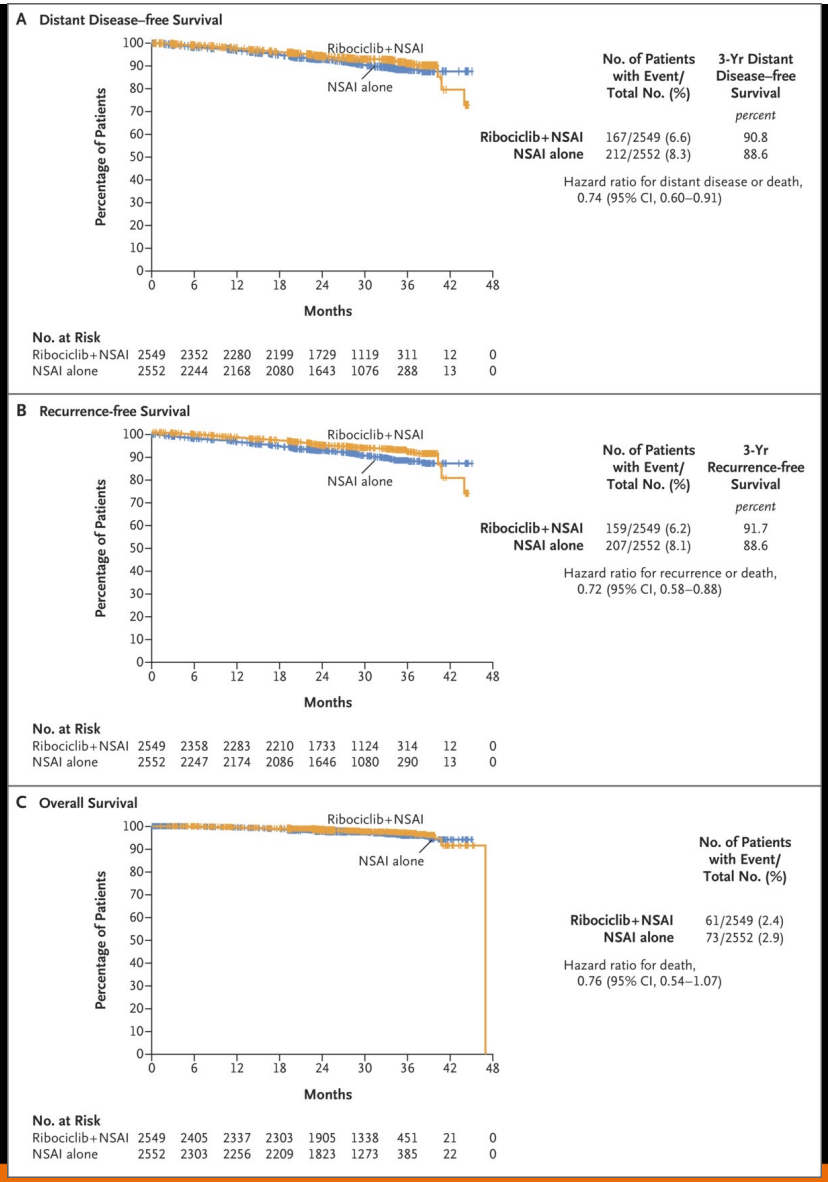
	No. of Patients with Event/ Total No. (%)	3-Yr Invasive Disease–free Survival
		percent
Ribociclib+NSAI	189/2549 (7.4)	90.4
NSAI alone	237/2552 (9.3)	87.1

Hazard ratio for invasive disease, recurrence, or death, 0.75 (95% CI, 0.62–0.91)
Two-sided P=0.003

Median follow-up for invasive disease–free survival, 27.7 mo

No. at Risk

Ribociclib+NSAI	2549	2350	2274	2193	1718	1111	311	12	0
NSAI alone	2552	2240	2166	2071	1631	1067	286	13	0



Kaplan–Meier Estimates of Secondary Efficacy End Points.

Slamon D et al. N Engl J Med2024;390:1080-1091

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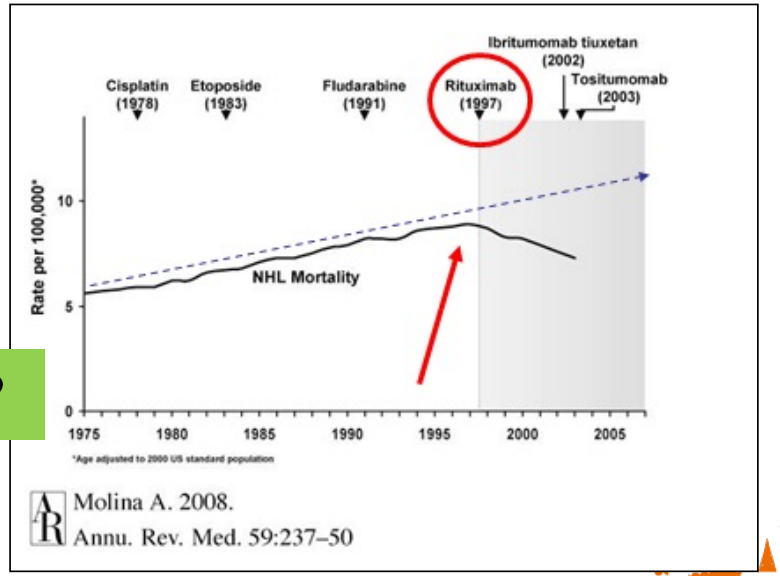
«Is dosimetry effective?» is probably not the right question to ask….

Dosimetry is a ***tool*** to explain/predict the results of NM treatments

Without information on dosimetry, no dose/effect correlations can be established

Dosimetry can be used to optimize NM treatments

…is the treatment effective?



Molina A. 2008.
Annu. Rev. Med. 59:237–50

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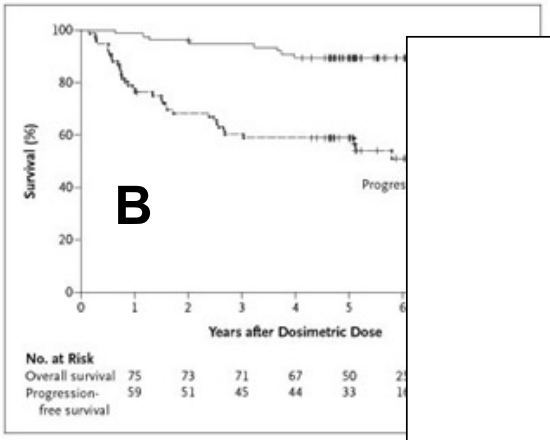
Having the magic bullet does not mean **Success**



Kaminski MS et al. N Engl J Med 2005;3

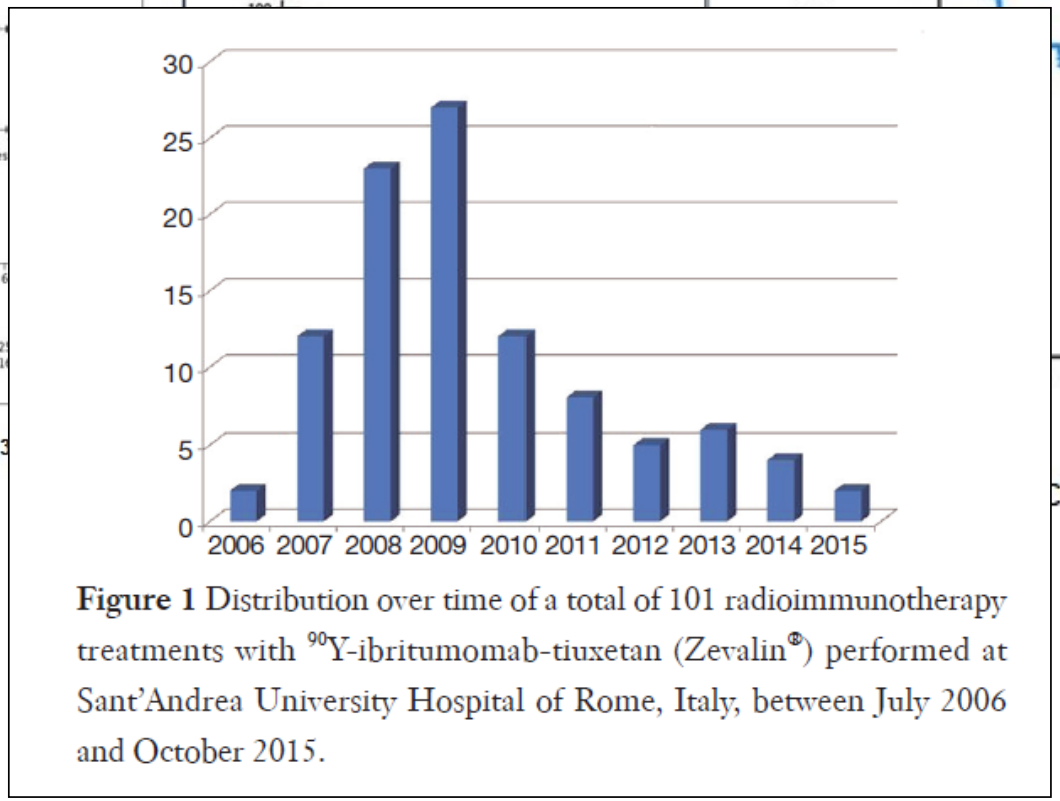
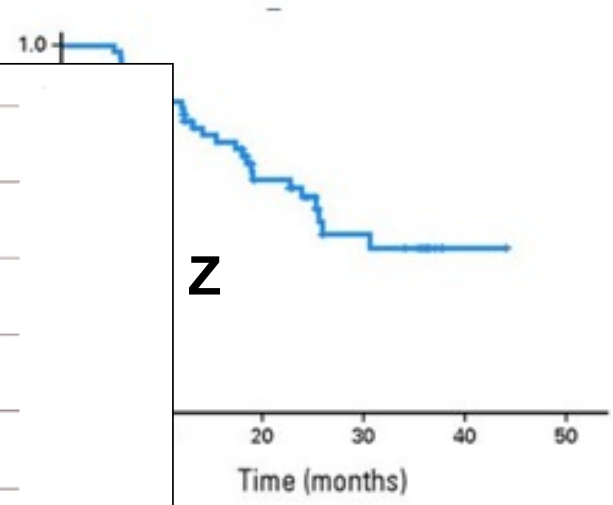


Figure 1 Distribution over time of a total of 101 radioimmunotherapy treatments with ^{90}Y-ibritumomab-tiuxetan (Zevalin®) performed at Sant'Andrea University Hospital of Rome, Italy, between July 2006 and October 2015.



CO 2013;31:308-313

Cicone F et al. Trans Canc Res 2016

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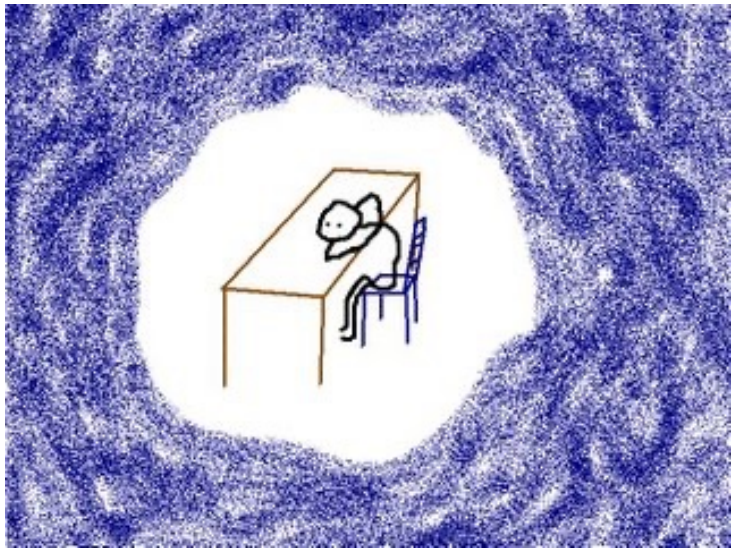
Thanks for your attention



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