

Interndosimetri ved Lutathera

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Innhold

Introduksjon

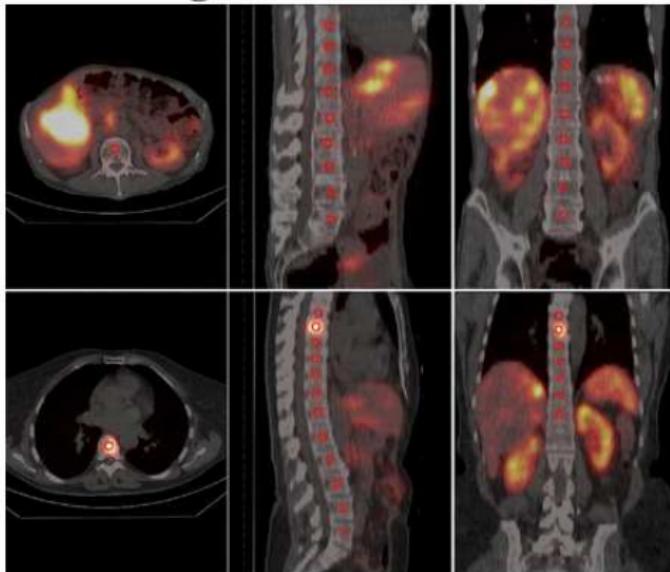
Dosimetri - et forslag

Introduksjon

Hvem er jeg?

- Jeg heter Johan Blakkisrud
- Nylig ansatt på OUS i en stilling tilknyttet dosimetri ved PRRT-behandling
- I siste fase av en avhandling om interndosimetri med et radionuklide-antistoff-konjugat der nukliden er ^{177}Lu
- Interessert i dosimetri og er tvilling (stjernetegnet, jeg har ingen tvilling [som jeg vet om])

Cover image



FEATURED ARTICLE

Bone Marrow Absorbed Doses and Correlations with Hematologic Response During ^{177}Lu -DOTATATE Treatments Are Influenced by Image-Based Dosimetry Method and Presence of Skeletal Metastases. Linn Hagmarker et al. See page 1406.



NYTT I NORGE: – Det er spennende for meg, men også for de som jobber siden her siden dette er såpass nytt, sier kreftpasient Marianne Sustad. Fysiker Kristine Fasmer, seksjonsoverlege Torjan Haslerud, avdelingsradiograf Jostien Frid og nuklearmedisiner Ankush Gulati har hver sine arbeidsoppgaver. **Foto:** Silje Katrine Robinson

KREFT

Haukeland først ute med ny radioaktiv kreftmedisin

177-Lu-DOTATATE (Lutathera^(R))

- Behandling for GEP-NET (GastroEnterPancreatic
NeuroEndocrine Tumours)
- Tumorene må uttrykke somatostatin
- Gis i en fast dose på 7.4 GBq (opptil) fire ganger med åtte ukers mellomrom
- Benmarg og nyrer er dosebegrensende organer

Dosebegrensende organer

- Nyrer: Ansett som hoveddosebegrensende organ
- Benmarg: 10 % opplever alvorlig hematologisk toksitet, 1-2 % utvikler myelodysplastisk syndrom og akutt leukemi

Hvorfor gjøre dosimetri?

- Ansvar for å vite hvor høy strålebelastning det er til pasienten (EU-direktiv 2013/59 - Euratom)
- Grunnlag for å kunne vurdere ytterligere behandling forbi de fire første
- (Bygge kompetanse)

Hvorfor gjøre dosimetri?

ORIGINAL RESEARCH

Open Access



Feasibility of simplifying renal dosimetry in ^{177}Lu peptide receptor radionuclide therapy

Anna Sundlov^{1,2}, Johan Gustafsson², Gustav Biolin², Nadja Mortensen¹, Rebecca Hermann⁴, Peter Bernhardt^{4,5}, Johanna Svensson³, Michael Ljungberg¹, Jan Tennvall¹ and Katarina Sjögren Gleisner²

In the Iluminet trial, the hypothesis was that by using individualized treatment planning, the balance between treatment effect and toxicity is optimized. Patients with advanced, progressive NET were treated with 7400 MBq ^{177}Lu -dotatate at 8–12-week intervals, and detailed post-therapeutic imaging and dosimetry were performed in all patients after every cycle. The number of cycles each patient received was determined by a combined evaluation of dosimetry, treatment effect and toxicity. Patients with risk factors for nephrotoxicity received treatment up to a cumulative renal biologically effective dose (BED) of (27 ± 2) Gy, and patients without such risk factors were offered to continue up to (40 ± 2) Gy. This individualized approach led to a wide range in the number of cycles per patient, differing substantially from the standard four treatment cycles [18].

Hva gjør dette vanskelig?

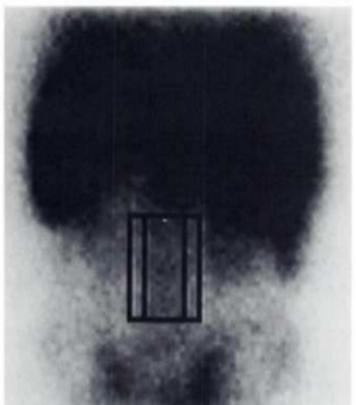
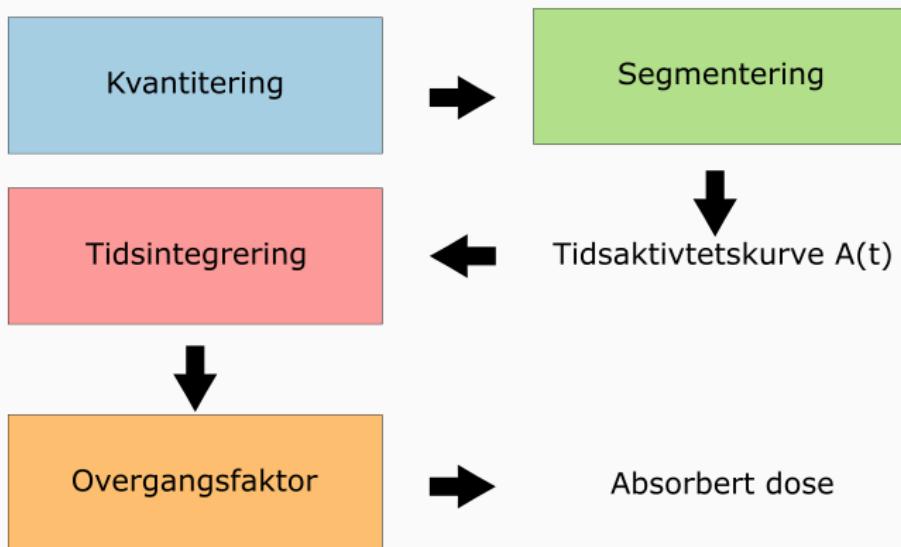


FIGURE 1. Standard marrow and background ROIs superimposed on posterior abdominal image. Based on CT analysis, a standard marrow ROI (L2, L3, L4) width of 5 cm was used. Background ROI width was 1 cm on each side of the marrow ROI and was the same height as the marrow ROI. Height of the ROIs varied based on CT measurements. Liver, spleen, kidneys and pelvis (acetiliac joints) serve as landmarks. Targeted abdominal mass (above ROI) was excluded from the ROI.

- Interndosimetri i seg selv er ikke vanskelig
- Krevende for pasient (og skanner)
- Modeller kan (potensielt) skape mye usikkerhet/uskarphet
- Det har skjedd en utvikling de siste årene på teknologisiden

Flertrinnsprosess



Flertrinnsprosess

- Flere trinn medfører fare for feil i hvert ledd som forplanter seg
 - feilforplantning
- Før var det vanskelig - nå har det blitt litt mer formalisert i retningslinjer (hurra!)

Flertrinnsprosess - hviskeleken



EANM practical guidance on uncertainty analysis for molecular radiotherapy absorbed dose calculations

Jonathan I. Gear¹ • Maurice G. Cox² • Johan Gustafsson³ • Katarina Sjögreen Gleisner³ • Iain Murray¹ •
Gerhard Glatting⁴ • Mark Konijnenberg⁵ • Glenn D. Flux¹

Flertrinnsprosess - nå matematisk

After substituting the covariance expressions of Eqs. 47 and 49 into Eqs. 43 and 44 it can be seen that:

$$\begin{aligned} \left[\frac{u(A_i)}{A_j} \right]^2 &= \frac{u(A_i, A_j)}{A_i A_j} = \left[\frac{u(Q)}{Q} \right]^2 + \left[\frac{u(R)}{R} \right]^2 \\ &\quad + \left[\frac{u(C_i)}{C_i} \right]^2 - \frac{\varphi}{R^2 v} \frac{\partial R}{\partial v} u^2(v) \end{aligned} \quad (50)$$

Given the equal fractional uncertainties for all the A_i and with perfect covariance between the A_i and A_j , it is appropriate to treat these uncertainties in a manner similar to a systematic error. Hence the fractional uncertainties in activity can be propagated into a systematic component of uncertainty for cumulated activity $u_s(\bar{A})$, where

$$\left[\frac{u(A_i)}{A_i} \right]^2 = \left[\frac{u_s(\bar{A})}{\bar{A}} \right]^2, \quad (51)$$

$$V_p = \frac{\chi^2}{n-q} \left[J_p^\top J_p \right]^{-1} \quad (53)$$

where J_p is the matrix of first-order partial derivatives of the TAC model with respect to p , evaluated at A . The TAC is generally represented as a sum of exponential functions. For the purpose of presentation, only the case of a single exponential function is described:

$$f(t) = A(t) = A_0 e^{-\lambda t}, \quad (54)$$

where A_0 is the activity at time zero and λ is the effective decay constant, for which

$$J_p = \begin{bmatrix} \frac{\partial A_1}{\partial A_0} & \frac{\partial A_1}{\partial \lambda} \\ \vdots & \vdots \\ \frac{\partial \bar{A}_n}{\partial A_0} & \frac{\partial \bar{A}_n}{\partial \lambda} \end{bmatrix} = \begin{bmatrix} e^{-\lambda t_1} & -A_0 t_1 e^{-\lambda t_1} \\ \vdots & \vdots \\ e^{-\lambda t_n} & -A_0 t_n e^{-\lambda t_n} \end{bmatrix} \quad (55)$$

and

$$V_p = \begin{bmatrix} u^2(A_0) & u(A_0, \lambda) \\ u(A_0, \lambda) & u^2(\lambda) \end{bmatrix}. \quad (56)$$

Time–activity curve parameters

Cumulated activity

Flertrinnsprosess - nå matematisk

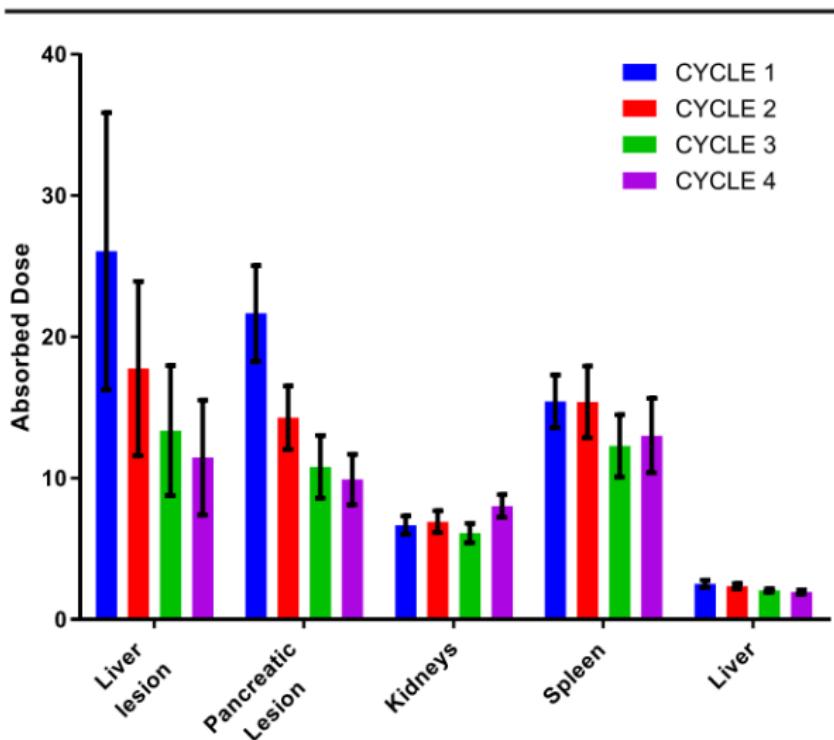


Fig. 12 Absorbed doses to lesions and normal organs over four treatment cycles. *Error bars* represent standard uncertainties in the dose values





Gertrude Stein Eksilamerikaner i Paris. Kjent for bla. frasen "En rose er en rose er en rose"



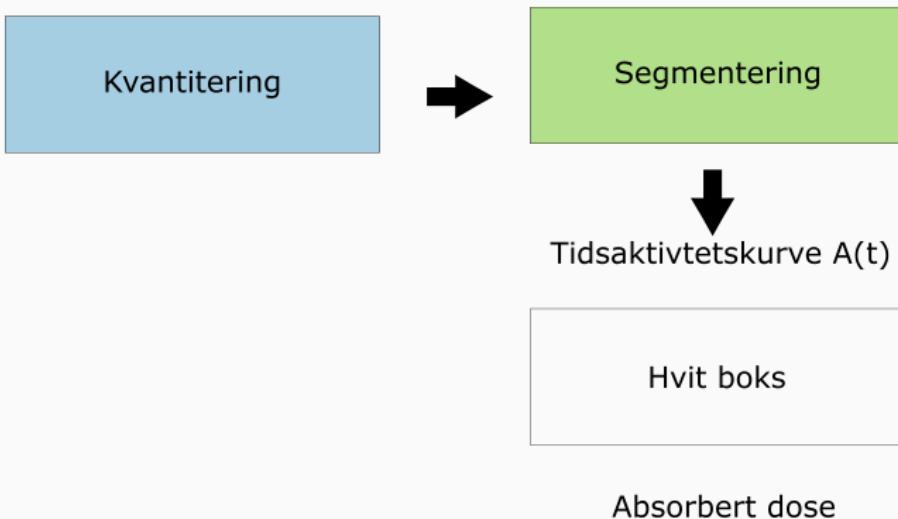


Ernest Hemingway Eksilamerikaner i Paris. Kjent for mye (min personlige favoritt er Den gamle mannen og havet) - svarte Stein med "a stone is a stein is a rock is a boulder is a pebble"

Noen påstander

- En gray er en gray er en gray?
- En Bq er en Bq er en Bq er en Bq?
- En fysisk halveringstid er en fysisk halveringstid er en fysisk halveringstid?

Flertrinnsprosess - med en snarvei



Hva bør vi gjøre?

- Enes om noe
- Noen ting er skanner-uavhengig
- Gjøre det enkelt, men ikke for enkelt
- Forsøke å unngå dyr programvare
- Alle kan gjøre hva de vil, men har vi en felles parallel beregning kan vi sammenligne data
- (Standarisere samtykke fra pasienter?)

Litteraturvitenskap re-visited





William Shakespeare Europeer
bosatt i Europa - Kjent for mange ting
- finner en positivistisk løsning i Romeo
og Julie "... a rose by any other name
would smell as sweet"

Hva bør vi gjøre?

- OUS kan legge endel ressurser i dette - vi har en hel fysikerstilling (hei, hei!) knyttet til dosimetri og PRRT
- Vi har også arbeidet med dosimetri med ^{131}I -behandling og ^{90}Y -SIRT-kuler siden... Lars Tore?

- Relativt stort organ - kvantitering enklere
- (Tilsynelatende) enkel kinetikk - godt beskrevet av en monoexp etter første døgnet
- Mulig opptaket er homogent ute i parenchymet (i det minste i rotter)
- Mye (god) litteratur tilgjengelig

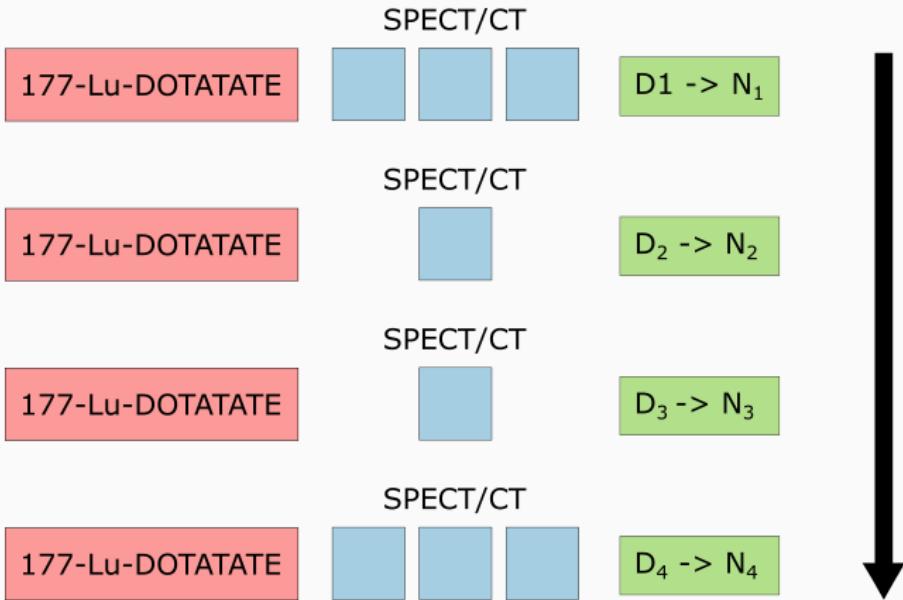
Benmargsdosimetri

- Distribuert organ med individuell variasjon - vanskelig å måle
- Avhengig av et modellområde for å gjøre en aktivitetsmåling mulig
- Blod som surrogat sannsynligvis utilstrekkelig
- Heterogen struktur i størrelsesordenen β -partikkelrekkevidde - energiavsetning mer kompleks

Nyrer og benmarg

Begge er løsbare!

Bildetagning på OUS



Dosimetri - et forslag

Dosimetri - et forslag

Fu█ you.
I won't do what you tell me.

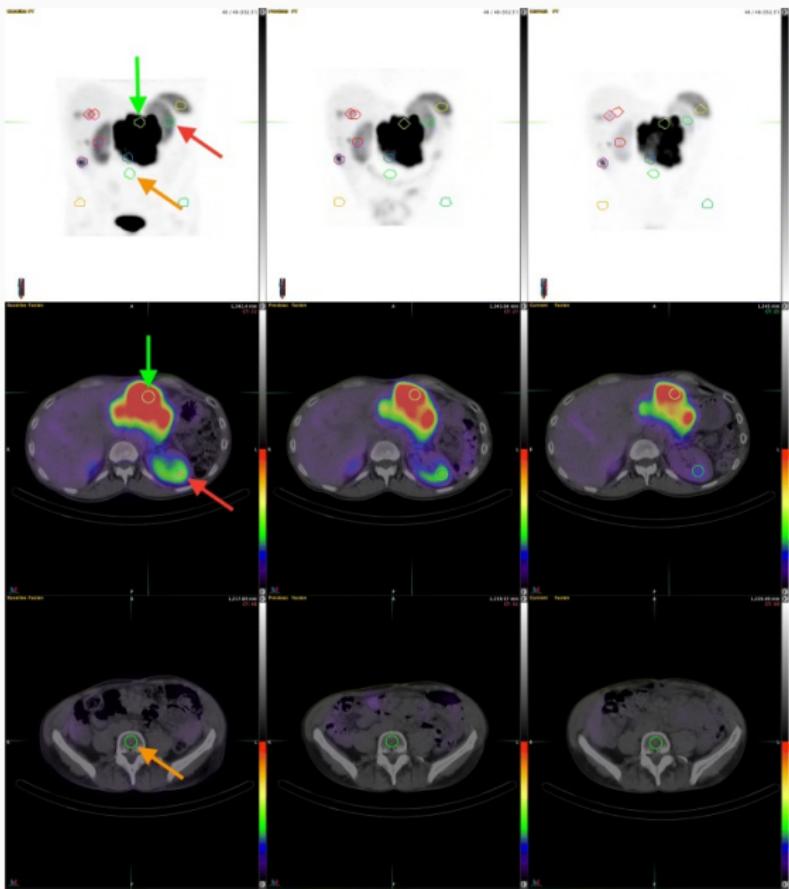


someecards
user card

Segmentering

Its complicated!

Segmentering



Eur J Nucl Med Mol Imaging (2010) 37:212–225
DOI 10.1007/s00259-009-2166-8

ORIGINAL ARTICLE

Individualized dosimetry in patients undergoing therapy with ^{177}Lu -DOTA-D-Phe 1 -Tyr 3 -octreotate

Mattias Sandström · Ulrike Garske · Dan Granberg ·
Anders Sundin · Hans Lundqvist

ORIGINAL RESEARCH

Open Access



Method dependence, observer variability and kidney volumes in radiation dosimetry of ^{177}Lu -DOTATATE therapy in patients with neuroendocrine tumours

Mattias Sandström^{1,2*}, Ezgi Ilan^{1,2}, Anna Karlberg³, Silvia Johansson³, Nanette Freedman⁴ and Ulrike Garske-Román¹

ORIGINAL RESEARCH

Open Access



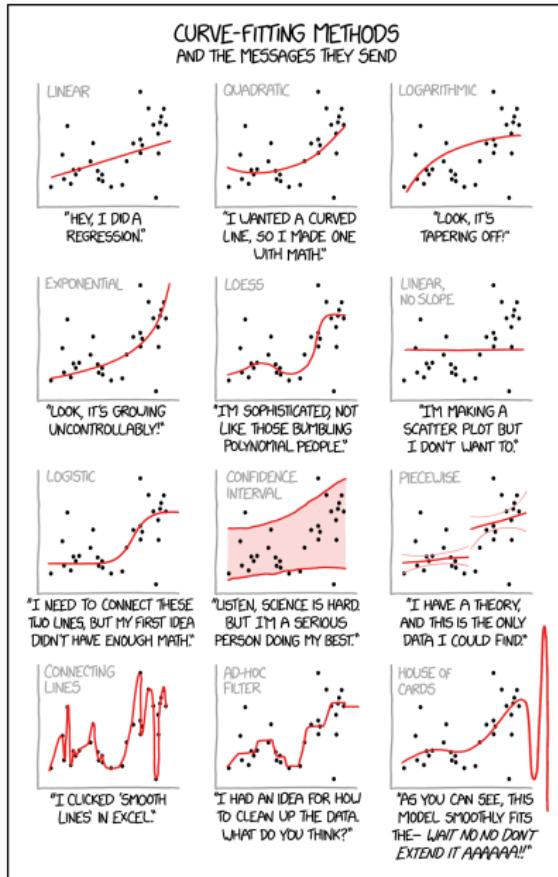
Accuracy and reproducibility of simplified QSPECT dosimetry for personalized ^{177}Lu -octreotate PRRT

Michela Del Prete^{1,2}, Frédéric Arseneault^{1,2}, Nassim Saighi^{1,2}, Wei Zhao^{3,4}, François-Alexandre Buteau^{1,2},
Anna Celler^{3,4} and Jean-Mathieu Beauregard^{1,2*}

Segmentering

- Plassere en liten sfærisk VOI (4 cm^3)
- For nyrene, plassere den i det homogene opptaket utenfor nyrebekkenet
- For benmargen, plassere den i en lumbalvirvel
- Regn gjennomsnittlig aktivitet i VOlen

Kurvetilpasning



Kurvetilpasning

Det viktigste er at vi blir enige om noe

Kumulativ aktivitet til absorbert dose

Now what?

Enkle overgangsfaktorer

Kan være komplisert, men man trenger bare å tenke én gang

Faktorer for nyrene - pass på enheter

$$D_{\text{Organ}} = \xi * t_{\text{residence}} * A_{\text{admin}}$$

(Sandstrøm, 2010)

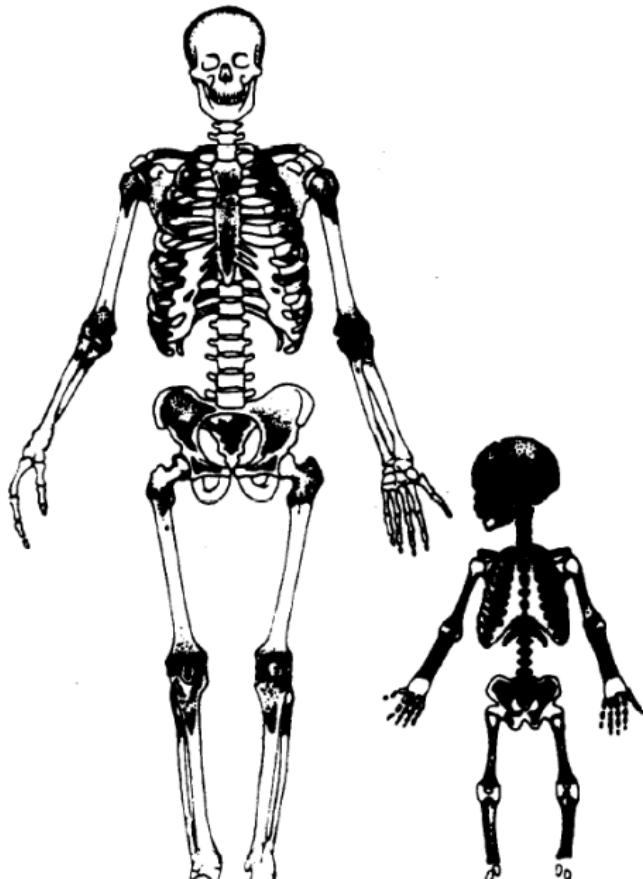
$$D_0 = \text{DCF} \times C_{cum0}$$

(Sandstrøm, 2013)

$$D = \xi \cdot \frac{1}{M_{\text{VOI}}} \tilde{A}_{\text{VOI}}$$

$$\xi = 0.0236 \text{ [mGy*g]/[MBq*s]}$$

Faktorer for benmargen - its complicated!



Benmargsdosimetri

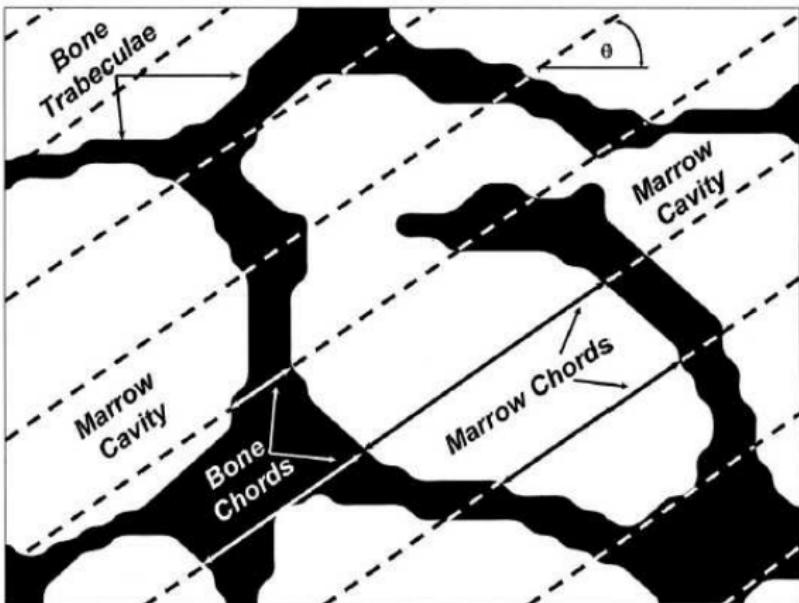


Fig. 1. Schematic demonstrating the acquisition of chord-lengths across bone trabeculae and marrow cavities at scanning angle θ . Two chord-lengths are shown for the bone trabeculae (white arrows) and the marrow cavities (black arrows).

Benmargsdosimetri

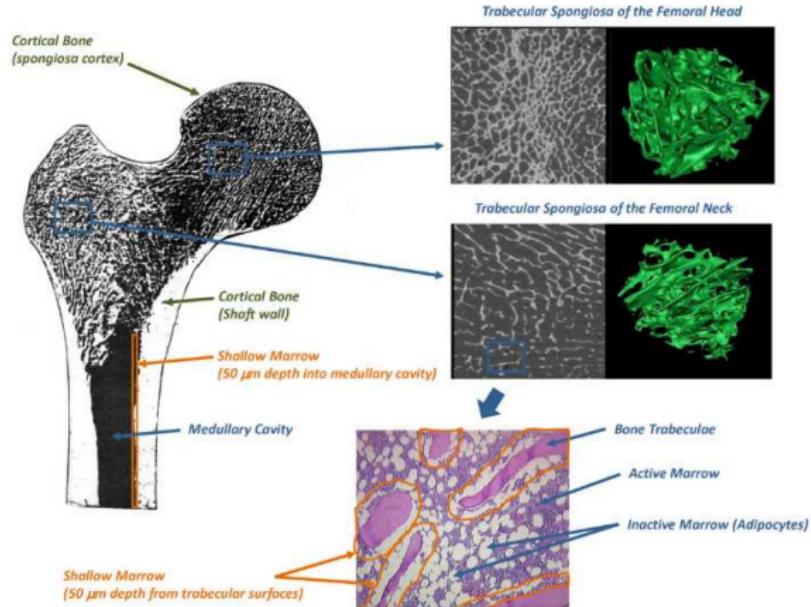


Figure 4. Graphical illustration of the spatial location of shallow marrow within both the trabecular spongiosa regions of the femoral head and neck, as well as along the inner cortical surfaces of the medullary cavity of the diaphysis (shaft).

Benmargsdosimetri

0111

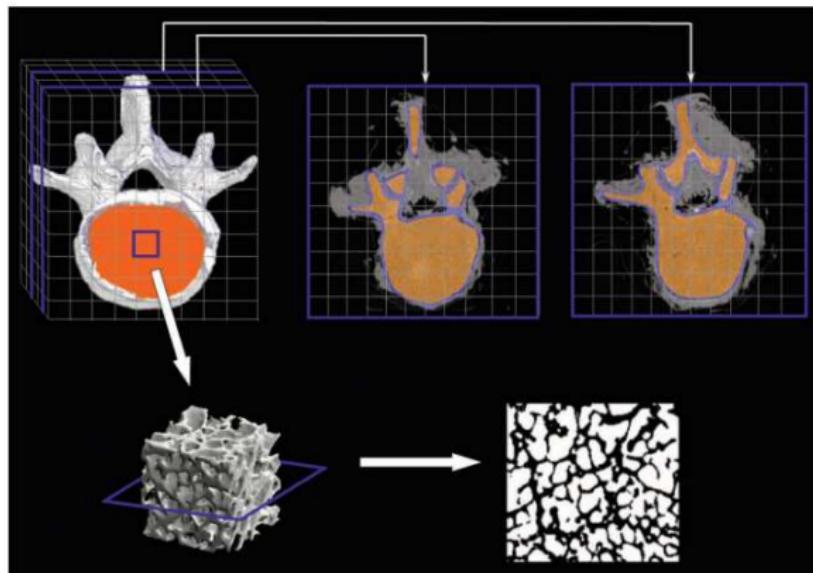


FIGURE 1. Schematic of PIRT model constructed for L4 vertebra.

S-faktorer for benmarg

Considerations of Marrow Cellularity in 3-Dimensional Dosimetric Models of the Trabecular Skeleton

Wesley E. Reich, PhD¹; Phillip W. Putten, PhD²; Dader A. Rajan, MS³; and Wesley E. Reich, PhD²; Derek W. Jokich, PhD²; and Benjamin A. Segal, PhD²

Adipocyte Spatial Distributions Implications for Skeletal Dosimetry

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Nevada-Las Vegas, Las Vegas, Nevada; and ³Department of Nuclear & Radiological Engineering

Gainesville, Florida

Accounting for beta-particle energy loss to cortical bone via paired-image radiation transport (PIRT)

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An image-based skeletal dosimetry model for the ICRP reference adult female—internal electron sources

Shannon E O'Reilly¹, Lindsay S DeWeese^{2,3},

Quantitative impact of changes in marrow cellularity, skeletal size, and bone mineral density on active marrow dosimetry based upon a reference model

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Considerations of anthropometric, tissue volume, and tissue mass scaling for improved patient specificity of skeletal S values

SLI-6131, USA

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Faktor for benmarg - hvilken gresk bokstav?

$$D = \chi \cdot \frac{1}{M_{VOI}} \tilde{A}_{VOI}$$

$$\chi = WIP$$

Fordeler

- Alle kan tegne sfærer i bildedata
- Alle kan integrere en kurve
- Alle kan utføre produkter
- Alle kan gjøre dosimetri uten fancy programvare (not that you should not)

Noen uavklarte spørsmål

- Absorbert dose eller BED? Løsning nå: Regne begge?
- Hvilke dosegrenser er gode?

Avslutning

Tusen takk for oppmerksomheten deres! (email: johbla@ous-hf.no)

