DOSIMETRY IN RADIONUCLIDE THERAPY

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Abstract. While it is known that therapeutic effects of radionuclides are due to absorbed radiation dose and to radiosensitivity, individual dosimetry in "Gy" is practiced rarely in clinical Nuclear Medicine but "doses" are described in "mCi" or "MBq", which is only indirectly related to "Gy" in the target. To estimate "Gy", the volume of the target, maximum concentration of the radiopharmaceutical in it and residence time should be assessed individually. These parameters can be obtained usually only with difficulty, involving possibly also quantitative SPET or PET, modern imaging techniques (sonography, CT, MRT), substitution of y- or positron emitting radiotracers for ß⁻-emitting radiopharmaceuticals as well as whole-body distribution studies. Residence time can be estimated by obtaining data on biological half-life of a comparable tracer and transfer of these data in the physical characteristics of the therapeutic agent. With all these possibilities for gross dosimetry the establishment of a dose-response-relation should be possible. As distribution of the radiopharmaceutical in lesions is frequently inhomogenous and microdosimetric conditions are difficult to assess in vivo as yet, it could be observed since decades that empirically set, sometimes "fixed" doses (mCi or MBq) can also be successful in many diseases. Detailed dosimetric studies, however, are work- and cost-intensive. Nevertheless, one should be aware at a time when more sophisticated therapeutic possibilities in Nuclear Medicine arise, that we should try to estimate radiation dose (Gy) in our new methods even as differences in individual radiosensitivity cannot be assessed yet and studies to define individual radiosensitivity in lesions should be encouraged.

1. INTRODUCTION

The Radionuclide Therapy Committee of the European Association of Nuclear Medicine states correctly in the introduction to it's protocols that therapeutic effects of radionuclides in the management of disease are due to the amount of absorbed radiation energy and to the radiosensitivity of the irradiated tissue [1]. Absorbed radiation dose (=Gy), however, is frequently replaced in practical Nuclear Medicine by "mCi" or "MBq" as dose units, even as the amount of activity applied is certainly not the only factor in delivery of an absorbed radiation dose. Radiation dose to an organ or tumour is defined by the simple equation [2]:

$$\text{Gy} = \frac{\text{activity}}{\text{volume}} \times \text{residence time (t)} \times \text{S (mGy/MBq/sec)}$$

The specific S-value of a radionuclide refers to linear energy transfer of it's radiation including also relative biological weighting factors. It would seem logical to establish a clear dose response relationship for Nuclear Medicine therapy (Table I), so that adequate clinical results could be expected. Specific modalities especially of systemic radionuclide therapy, however, make dosimetry and, therefore, an estimate of the dose response relationship quite difficult.

In Nuclear Medicine there is only one therapeutic method which allows a dosimetric calculation as in other forms of radiotherapy: This is radioembolization of hepatoma with ^{90}Y-particles [3]: The tumour (=target) volume is known from CT-scans, 100% of the selectively intraarterially applied activity are in the tumour, no metabolic break-down of the labelled particles occurs for several physical half-lives of ^{90}Y so that "residence time" is derived from physical half-life only. Even intratumoural application of radioactive colloids which should stay in the tumour does not fit in this model, as intratumoural distribution is variable.

TABLE I. DOSE RESPONSE RELATIONS FOR ^{131}I-THERAPY OF THYROID DISEASE

Radiation dose	Radiation effect	Clinical effect
80–100 Gy	moderate atrophy	metabolic activity significantly reduced, growth potential impaired, moderate volume reduction of irradiated tissue
100–150 Gy	significant atrophy	metabolic activity severely reduced growth potential blocked significant volume reduction of irradiated tissue
200–300 Gy	severe atrophy	metabolic activity and growth potential blocked, volume of irradiated tissue: almost gone
500 Gy	necrosis	tissue dead and gone

In all other therapeutic methods (systemic, intracavitary therapy) using unsealed radionuclides dose estimates are much more difficult. In systemic therapy the amount of radioactivity accumulating in the target tissue can basically be measured for radionuclides which emit also y-radiation (e.g. ^{131}I, ^{153}Sm, ^{186}Re) by uptake measurements or quantitative SPET [4]. When therapeutic agents, however, emit only ß$^-$-radiation registration of maximum local concentration of the radionuclide is impossible. It is also not always easy to assess the volume of the target even with modern imaging techniques [5]. Finally "residence time" remains another essential parameter, which can be influenced by metabolic activity and can directly be measured only when y-emitting radiopharmaceuticals are used. When dosimetry should include also dose estimates to bone marrow or critical organs without consideration of the target the same parameters should be obtained to predict and possibly avoid side effects [6].

2. METHODS TO IMPROVE DOSIMETRY

2.1. Assessment of target volume

Without consideration of the specific volume of target tissue with accumulation of the radiopharmaceutical ("functional volume"), anatomic volume of target organs or lesions can today be estimated quite well with modern imaging methods [7] (Table II) in many diseases (e.g. thyroid volume, volume of metastases in lymph nodes, lungs, brain, liver).

TABLE II. ASSESSMENT OF TARGET VOLUME BY

Sonography
CT
MRI
SPECT
PET

In other disorders, however, even these techniques cannot define "target volume": This occurs in intracavitary therapy and in diseases with diffuse bone marrow involvement (Fig. 1). Moreover appropriate diagnostic radionuclide studies can show abnormal uptake in metastases, which could not be localised by other imaging techniques [8]. In such cases emission tomography (ET) can be helpful [9] as it can estimate volume of tissue with uptake of the tracer (or radiopharmaceutical) by now with

sufficient accuracy. Of course such ET-methods are impossible when the radiopharmaceutical emits only ß⁻-radiation. As discussed later, the substitution of the ß⁻-emitter by a gamma- or positron emitter can help, so that it might even be possible to estimate target volume in radiosynovectomy [10] by using identical colloids labelled with ^{86}Y for PET! One could also suggest that e.g. ^{124}I-MIBG could be used to define target volume by PET in patients with diffuse bone marrow metastases of neuroblastoma, ^{124}I for cases with negative conventional imaging and positive ^{131}I-scans in thyroid cancer [11] or ^{124}I labelled tumour antibodies. Essentially all ET-studies for volume estimates use basically the same approach:

$$\text{Volume (mL)} = \frac{\text{pixel vol (ml)} \times \Sigma \text{ n pixels / ROI / slice} \times \text{n(sl)}}{\text{CF}}$$

n	=	number of labelled pixels
n(sl)	=	number of slices with labelled pixels
CF	=	correction factor determined for system using appropriate phantom.

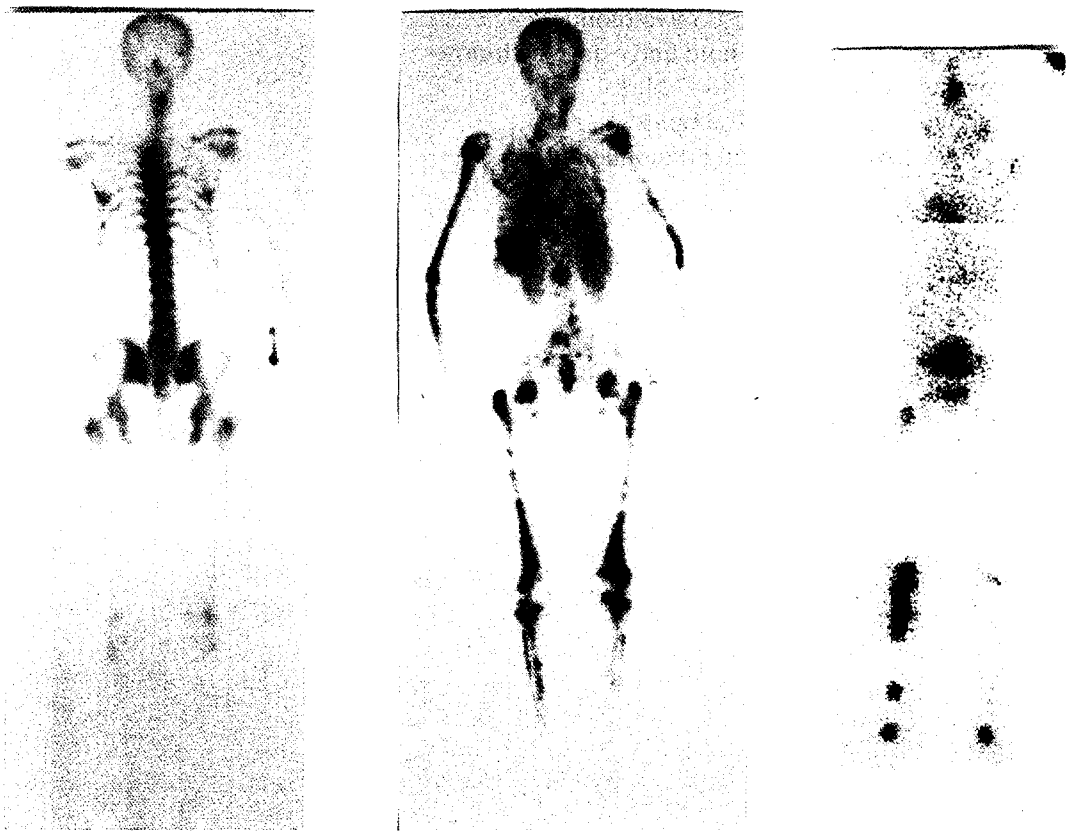

FIG. 1. ***Left****: Bone scan of patient after breast Ca.: diffuse ^{99m}Tc-DPD-uptake in skeleton, kidneys and bladder not visible, renal function normal: "Superscan", suggesting diffuse bone marrow metastases.* ***Middle****: Bone marrow scan of same patient after ^{99m}Tc-granulocyte antibody showing large "cold" areas in axial skeleton as evidence of metastases and displacement of red marrow to long bones in limbs.* ***Right****: Whole body scan after ^{131}I-MIBG in patient with diffuse bone marrow involvement in neuroblastoma.*

2.2. Assessment of maximum local amount of radioactivity in target (Table III)

This again is easy in intracavitary, intraarterial or intratumoural therapy as almost 100% of the applied radiopharmaceutical is localised in the target volume initially. It is more difficult in systemic therapy. But even here, the relative maximum uptake of the radiopharmaceutical (% of administered activity) can well be registered if there is also y-emission by external counting considering also geometry factors, attenuation, scatter and partial volume effects using simple y-counters or quantitative SPECT when appropriate phantoms are studied under comparable conditions.

TABLE III. ASSESSMENT OF UPTAKE OF RADIOPHARMACEUTICAL

(A) Local uptake

1) Radiopharmaceutical emits y- and ß⁻-radiation
   (e.g. ^{131}I, ^{153}Sm, ^{186}Re)
2) Radiopharmaceutical emits only ß⁻-radiation

ad 1) Use SPECT (perhaps ^{123}I instead of ^{131}I) or PET e.g. with ^{124}I

ad 2) a) Use radiotracer with identical chemical composition and y-emission
   (e.g. ^{111}In-DOTA-Octreotide, ^{111}In-DOTA-Lanreotide)
   b) Use PET-radiotracer (e.g. ^{86}Y-Octreotide)

(B) Whole body retention and whole body dose estimate

1) Urinary activity excretion over 48–72 hrs.
2) Blood clearance in serial blood samples
3) Whole body ROI when y-emitting radionuclide

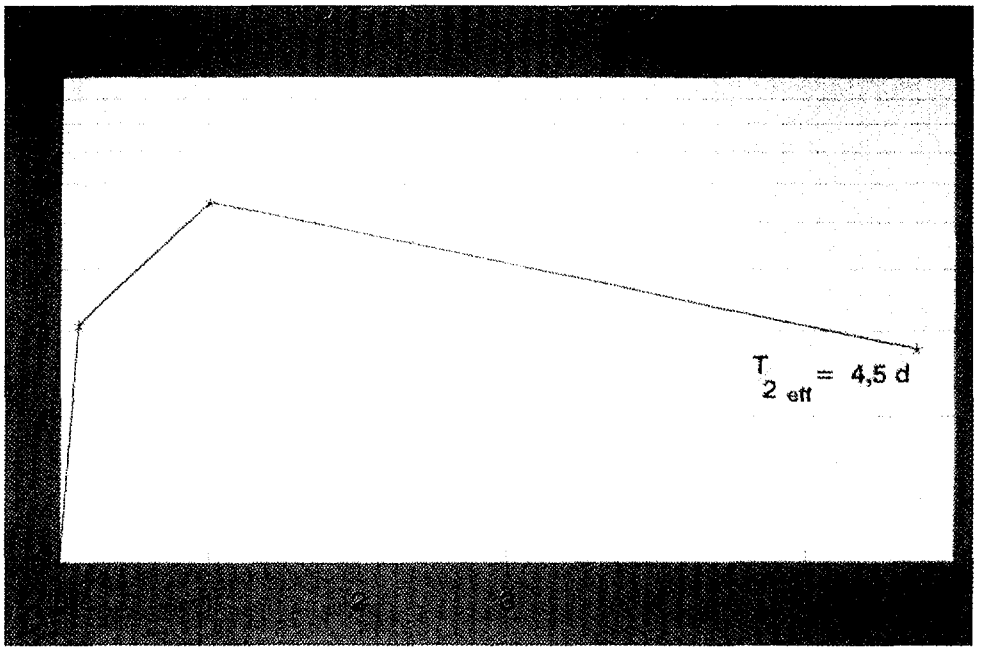

FIG. 2. Direct assessment of effective half-life before ^{131}I-therapy of hyperthyroidism by following thyroidal ^{131}I-activity over several days.

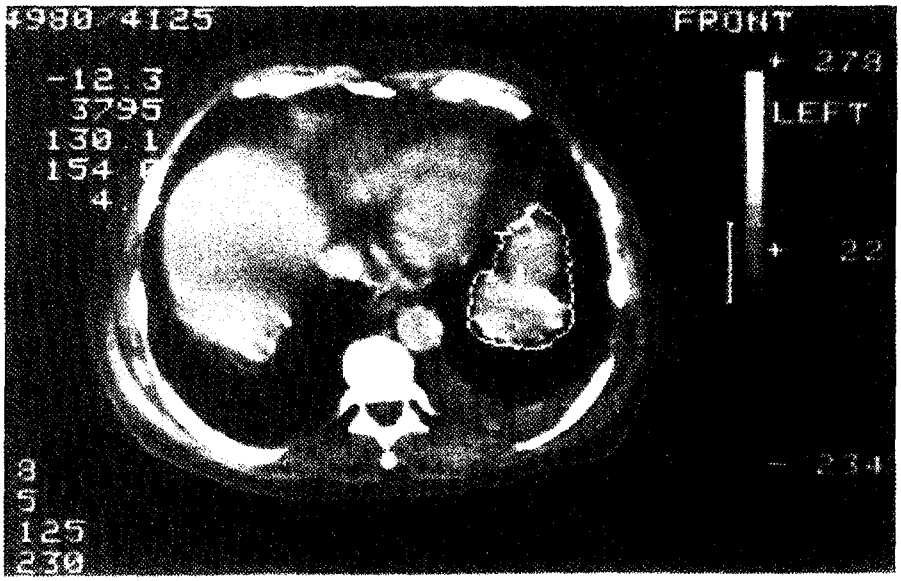

FIG. 3. CT-scan of lung metastases after thyroid cancer: ROI placed over tumour on one slice, similarly relevant ROI's in other slices give tumour volume, when pixel size is known.

FIG. 4. SPECT of disseminated bone metastases with ^{99m}Tc-DPD allowing estimates of lesion volumes in similar manner as described for CT in Fig. 3.

In some applications, even an analogue ^{99m}Tc-tracer can be used for such proposes [12]. When the radiopharmaceutical, however, emits only ß$^-$-radiation these estimates become possible only, when chemically identical radiotracers with y-emission (e.g. ^{111}In-Octreotide for ^{90}Y-Octreotide, ^{85}Sr for ^{89}Sr) or positron emitters (e.g. ^{86}Y for ^{90}Y) are used [13]. When y-emission is present, specific uptake of the radiopharmaceutical in lesions can also be estimated by comparing count-rates in lesion and normal surrounding tissue on conjugate whole body scans [14].

2.3. Assessment of residence time

Serial blood and urine samples of tracer amounts of the radiopharmaceutical or it's substitute (see above) can help to evaluate radiation doses to blood, marrow, kidney and bladder. For residence time estimates in the target, however, similar considerations as for assessment of local radioactivity concentration become important (Fig. 2). There are certainly no problems, when y-emitters are used for therapy but there are considerable difficulties if pure ß$^-$-emitters are applied. Again, y-emitting substitutes can be used as mentioned above, data must be corrected for decay to biological half-life,

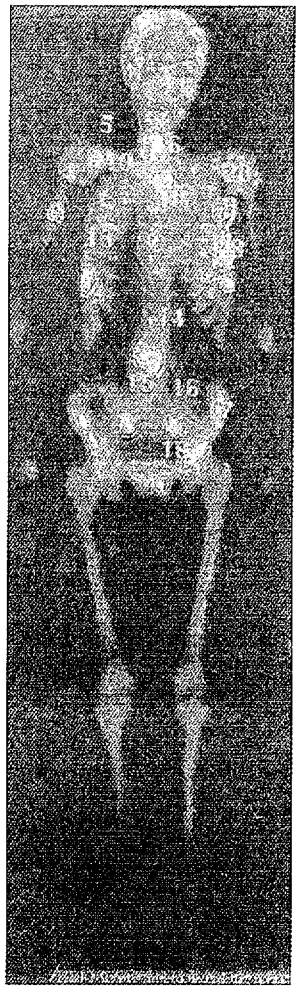

FIG. 5. Whole body bone scan after 555 MBq ^{99m}Tc-DPD. ROI over whole body: 4,134 kcts. = 100%, ROI's over metastases: 544 kcts. = 13,2%. Therefore, maximum uptake 13,2% of administered dose in lesions using ^{153}Sm-EDTMP.

which then gives appropriate information on residence time, as residence time can be derived from effective half-life using

$$\text{(Residence time) } \tau = \frac{T1/2\ \text{eff}}{\ln 2} \qquad (15).$$

2.4. Results of dosimetric radionuclide therapy

Fig. 3 shows an example of tumour volume assessment by CT in metastatic thyroid cancer, Table IV, the conventional formula to assess thyroid volume by sonography [16]. Fig. 4 shows, how volumes of bone metastases can be estimated by SPET. Estimates of local uptake in the target by conjugated view scans with ROI-technique are shown in Fig. 5. Fig. 6 shows an example for the substitution of the ß$^-$-emitter ^{90}Y by ^{111}In. Overall therapeutic strategies using a dosimetric approach seem justified (Table V) as — at least in some diseases — results seem to be better than without dosimetry [17] and dosimetry certainly helped to avoid complications of radionuclide therapy in many applications [18].

FIG. 6. Whole body scan after ^{111}In-DOTA-Octreotide applied together with therapeutic ^{90}Y-DOTA-Octreotide in patient with disseminated metastases of a carcinoid tumour.

TABLE IV. ESTIMATE OF THYROID VOLUME BY SONOGRAPHY

Lobe Volume (mL)	=	max. depth (cm)	×	breadth (cm)	×	length (cm)	× 0,479

TABLE V. FORMULA FOR DOSIMETRY IN ^{131}I-THERAPY OF THYROID DISEASE

Activity (Ci) $\dfrac{\text{cGy} \times \text{W} \times 6{,}67}{\text{T/2 eff.} \times \%\ \text{uptake 24 hrs.}}$

or

Activity (MBq) $\dfrac{\text{cGy} \times \text{W} \times 25}{\text{T/2 eff.} \times \%\ \text{uptake/24 hrs.}}$

W = thyroid weight (g)

3. DISCUSSION

It is obvious that a fairly precise macrodosimetry for radionuclide therapy has become possible today. Several problems in dosimetry for Nuclear Medicine therapy persist: one is the acknowledged fact, that frequently concentration of the radiopharmaceutical is not homogenous in a lesion [19], so that parts of the target will receive a higher dose (Gy/MBq) than others and the second is

microdosimetry, which has provided important insights in microscopic radiation biology in recent years, considering also the effects of Auger electrons and (-particles [20]. It is also obvious that the application of all the mentioned techniques necessary for individual dosimetry require intensive work and high costs as possibly also SPET or PET can be essential. On the other hand it is known, that even without such efforts for dosimetry radionuclide therapy is successful in many diseases [21, 22], even when only "fixed doses" (e.g. ^{131}I, ^{89}Sr, ^{32}P, ^{186}Re-HEDP, intracavitary therapy) are applied. This discrepancy between clinical outcome without dosimetry and scientifically predictable radiation effects in the target can partly be explained by the mentioned unsolved problems of in vivo dosimetry but also by differences in radiosensitivity within targets. This assessment of specific radiosensitivity of a lesion is still an unsolved problem. Studies using Palladium-islets or well plates were done [23] but results so far show, that it still is almost impossible to register e.g. radiosensitivity of a certain tumour in an individual patient. While the efforts to improve registration of specific radiosensitivity by ex-vivo assays should be encouraged in the future one should also try to overcome the old habit of using only amounts of radioactivity as "doses" especially as new and exciting therapeutic applications of radionuclides are being developed. In this situation one should try at least to estimate absorbed radiation dose (= Gy) in therapy, which could improve results of our therapeutic approaches significantly.

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