Biophysical Inputs into the Software "MIRDose"

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Summary

Admistered amount of activity decides on absorbed dose in thyroid gland during therapy of thyroid cancer tumors by ^{131}I. Medical Internal Radiation Dose (MIRD) methodology estimates this dose as well as influence on other organs. MIRDose — the software implementation of MIRD — is permanently improving and has reached a substantial degree of maturity. Thus the reliability of the results depends predominantly on quality of the input data. The residence time and functional volume of the thyroid gland of a particular patient are the key inputs. Here we concentrate on the former one. We found that the traditionally used mono-exponential model, characterized by the effective half-life, introduces non-negligible modelling error. It cannot be improved by any data processing. For this reason, we proposed a novel accumulation model. Now we inspect influences of differences in the guessed residence time on the outputs of MIRDose. We briefly characterize MIRDose software, recall the improved model and present illustrative results of evaluations.

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Souhrn

Množství aplikované aktivity rozhoduje o absorbované dávce ve štítné žláze při terapii karcinomů štítné žlázy pomocí ^{131}I. Odhad této dávky i vlivu na jiné orgány usnadňuje metodologie MIRD (Medical Internal Radiation Dose). Její programová realizace MIRDose je neustále zlepšována a dosáhla značné přesnosti. Spolehlivost získaných výstupů tudíž závisí především na uživatelských vstupních datech popisujících akumulační schopnosti a na hmotnosti štítné žlázy konkrétního pacienta. Zde se soustředíme na první ze vstupů. Zjistili jsme, že tradičně používaný monoexponenciální model vede, přes námi navržené prokazatelné zpřesnění, k významným chybám. Ty plynou z inherentní chyby tohoto modelu charakterizujícího zkoumanou dynamiku klasickým efektivním poločasem. Navrhli proto jsme zlepšený model akumulační dynamiky. Pro jeho využití zkoumáme, nakolik jsou výstupy systému MIRDose citlivé na zadávanou kumulovanou aktivitu. V textu krátce charakterizujeme MIRDose software, připomeneme podstatu zlepšeného modelu a uvedeme ilustrativní kvantitativní výsledky zmiňované citlivostní studie.

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1 Introduction

The amount of the activity administered for therapy has to be large enough to reach the administration aims. On the other hand it should be as low as possible in order to minimize a damage of healthy tissues. It calls for a reliable estimation of the dose absorbed in the human body ([1]–[9]). The well established MIRD (Medical Internal Radiation Dose) methodology [10] provides the necessary physical and experimental background. Knowledge of the residence time in the inspected tissues is its main user's input. The residence time is the integral under the time trajectory of the instantaneous activities divided by the admistered activity. This trajectory has to be reconstructed from a few measurements. It means that a sort of interpolation is needed: a curve from a pre-specified class has to be fitted to the noisy measurements.

The quality of the resulting estimate of the cumulated activity is significantly influenced by the class of the fitted curves which results from the deterministic modelling.

This paper inspects to which extent the model improvements proposed in [11] influence the results provided by the software MIRDose — a software implementation of the MIRD methodology.

2 MIRD Method

In nuclear medicine applications, the absorbed dose quantifies the amount of the energy transferred to an inspected (target) tissue from internal sources (source organs) of ionizing radiation. This complex transfer process depends on

- the type of emitted radiations,
- the amount of energy emitted by the source organs, expressed usually as the product of the number of transmutations per time unit and the (mean) energy emitted per transmutation,
- the mutual target-source organs geometry,
- the type (mass, size) of organs.

MIRD method can be interpreted as an application of the law of the energy conservation. The method takes of the burden from practitioners by tabulating adequate conversion factors (so called S-factors) from user's data to doses. Factors are available for a wide set of radionuclides and for various combinations of source and target organs. With this support, the following inputs are needed for the evaluation of the absorbed doses:

- radionuclides present in the human body,
- masses of the inspected target organs,
- cumulated activities in the source organs.

This paper addresses sensitivity of the MIRDose results of estimation of the cummulated activity.

3 Mirdose Software

MIRDose software (now version 3) is developed in Oak Ridge Institute for Sciences and Education, Oak Ridge, Tennessee [12]. It is distributed as free-ware when signing a standard disclaimer. It is written in Visual Basic and contains well structured input-output forms as well as on-line helps. It relies on interactive processing but supports a simple file management that allows the user to feed the data in by modifying a previously stored input form. Among others, it contains

- extensive tables of S-values allowing to estimate doses for all major organs and a wide list of radionuclides,
- ten phantoms including a new one for average western female,
- nodule module that provides estimate of absorbed fraction dose in dependence on size (it is prepared for soft tissues that can be approximately taken as spheres within the weight range 0.01–6 000 g).

4 Accumulation Model

When treating thyroid cancers by ^{131}I, a diagnostic amount of the radionuclide is administered with the aim to estimate abilities of various lesions to accumulate the (radioactive) iodine. The same accumulation ability is supposed during the therapeutic phase. Then, the dose absorbed during the therapeutic phase can be estimated and the adequate activity administration determined.

Knowledge of the instantaneous and cumulated activities in the therapeutic phase is also required in order to

- control the radiohygienic regime of patients,
- check the similarity of accumulation abilities in both phases.

The residence time T_r required as the input for MIRDose is defined as a time integral of the instantaneous activities $A(t)$ for time $t > t_0 = \text{application\_time} = 0$ divided by the administered activity. Because of medical/technical reasons, the induced counts $a(t)$ corresponding to activity values $A(t)$ are measured in several time instants t_i only (maximum 2–18). In order to provide the needed reliable estimate of the residence time T_r, these data have to be used for estimating the whole curve $A(t)$, $t > 0$.

The registered counts $a(t)$ are related to the activity by

$$a(t) = c \cdot A(t) \cdot \text{noise} \tag{1}$$

where c denotes the calibration factor which can safely be estimated using an appropriate calibration procedure [13]. Under the given measurement conditions, the desired characterization of the whole curve can be obtained only when

- the trajectory $A(t)$, $t > 0$, is parametrized by a smooth function containing a few time invariant parameters only;
- the adequate probabilistic noise description is selected.

For algorithmic reasons, the probabilistic modelling is simplified and logarithmic-normal noise model is considered,

$$\ln a(t) = \ln(cA(t)) + \text{white normal noise}. \tag{2}$$

We concentrate on the inspection how the novel model

$$f(t) = \ln(cA(t)) \tag{3}$$

proposed in [11] suits as a generator of input data into MIRDose.

5 Tested Model

Usually, the affine model of the inspected trajectory is used:

$$f(t) = \ln(cA(t_1)) - \frac{t - t_1}{T_{ef}} \ln 2, \qquad t > t_1. \tag{4}$$

Here, $t_1 > 0$ is the time instant after which fast transients of the activity distribution can be neglected. The effective half-life T_{ef} parametrizes this model together with t_1, $cA(t_1)$.

The parameters $cA(t_1)$, T_{ef} can be simply estimated by least squares. The cumulated activity for $t > t_0$ is taken as the area under the mono-exponential with amplitude $A(t_1)$ and exponent $-\frac{t}{T_{ef}} \ln 2$. It gives the residence time

$$T_r = \frac{A(t_1)}{A(t_0)} \cdot \frac{T_{ef}}{\ln 2}. \tag{5}$$

This model was found as too crude in a significant portion of the inspected cases [11], [14], [16], [17]. Generic activity trajectories resulting from the compartmental models suggest $f(t)$ as a sum of several exponentials. Such a form is, however, unfeasible with a few measurements available. Thus, a slight deviation from the affine form is only acceptable when searching for a better model.

Shapes of the time trajectories of activities for the reference man [14], [15] led us to the following potential candidates:

$$f(t) = k_1 \, + \, k_2 \ln t \, + \, k_3 t^{k_4} \ln(k_5 t) \, - \, \frac{t}{T_p} \ln 2, \tag{6}$$

where T_p is the known physical half-life of the ^{131}I.

The proposed model has also triple of unknown parameters (k_1, k_2, k_3) which can be estimated by least squares. The parameters k_4, k_5 have to be fixed as they are built in non-linearly. In [11] $k_4 = 0$ and $k_5 = 2$ were proposed. This choice was further improved. Here we confine ourselves to the best choice found with $k_4 = 2/3$, $k_5 = 1$. Notice that the sensitive choice of t_1 is avoided. The model can be used immediately after the administration. Consequently, no data are lost and no part of the cumulated activity ($t < t_1$) is neglected.

The trajectory $f(t) = cA(t)$ modelled in this way has the following desirable qualitative properties:

- starts at zero if $k_2 > 0$ (no activity is cumulated at administration time yet),
- vanishes faster than by the physical decay if $k_3 < 0$,
- possess a single extreme for $t > 0$ if $k_3 < 0$,
- models explicitly the physical decay so that the individual biological elimination is to be estimated only.

On the other hand, the transition time T_r cannot be found analytically; numerical integration is needed. Due to the smoothness of $f(t)$ it is simple task solvable by standard routines.

6 Experiments

6.1 Material Available

The raw material used consists of records related to patients treated for thyroid diseases at the Clinic of Nuclear Medicine, Motol Hospital, 2^{nd} Medical School, Charles University, Prague. The data have been gained as a by-product of routine evaluations made by the software system called JOD [13]. Specifically, data files `welch91.dat` – `welch99.dat` were randomly chosen among 150 available files describing several thousands of patients.

Among the data, the records with at least three measurements (the dimension of the estimated parameter) were processed. The data containing other lesions then thyroid were omitted as well as those that led to physically unjustifiable estimates of effective half-life. In order to keep similar conditions and get sufficient measurements, just data related therapies are compared. In this way, more than 90 patient records was obtained.

6.2 Compared models

The studied model M_1 (cf. (6))

M_1:

$$f(t) \; = \; \ln(cA(t)) \; = \; k_1 \, + \, k_2 \ln t \, + \, k_3 t^{\frac{2}{3}} \ln t \, - \, \frac{t}{T_p} \ln 2, \qquad t > 0,$$

is compared with the standard affine model M_2 (cf. (4)),

M_2:

$$f(t) \; = \; \ln(cA(t)) \; = \; \ln(cA(t_1)) - \frac{t - t_1}{T_{ef}} \ln 2, \qquad t > t_1 = 1.$$

6.3 Inputs into MIRDose

For each model, an estimate of the residence time is computed. For both models, free parameters were estimated by least squares working on logarithm of $f(t)$. The residence time (the integral under the activity curve divided by the applied activity) was computed numerically for the model M_1. The same quantity for the classical model M_2 is $A(t_1)/A(t_0) \cdot T_{ef}/\ln 2$. It serves as the input for MIRDose for computing the dose caused by ^{131}I in thyroid gland on itself (S-factor is $5.64\,\mathrm{mGy}/(\mathrm{s}^{-1}\mathrm{MBq})$).

6.4 Results

First we provide global characteristics of the results.

$$\text{The ratios: } \frac{\text{estimate of radiation dose by model } M_1}{\text{estimate of radiation dose by model } M_2}$$

evaluated for all data are characterized by: Mean=1.362, Standard deviation=0.9309, Median=1.126, Minimum=0.1423, Maximum=4.836.

These results are obtained from individual results summarized in the Table 1.

Estimates of radiation dose provided by MIRDose using a new accumulation model M_1 (a non-traditionally parametrized curve) and M_2 (classical characterized by the effective half-life)

6.5 Discussion

The presented results are almost self-explanatory:

- reliability of the MIRDose outcomes is predominantly determined by the quality of input data
- classical model sometimes provide results that differs from the new by the factor 10 (in spite of the fact that the obviously wrong estimates of effective half-life are not considered);

The previous study shown that the novel model has much better predictive abilities. Thus, we blame for these differences mismodelling caused by the classical model.

7 Conclusions

A recently proposed novel model describing the time evolution of the activity is used for estimating residence time as one of the main inputs into MIRDose software. It is compared with classical characterization of the accumulation dynamics through effective half-life. The observed significant differences make the use of effective half-life to this purpose doubtful when taking into account that the predictive capabilities of the novel model M_1 were found much better than those based on the classical model M_2 [18].

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M_1: estimate of radiation dose [mGy/MBq]	M_2: estimate of radiation dose [mGy/MBq]	M_1: estimate of radiation dose [mGy/MBq]	M_2: estimate of radiation dose [mGy/MBq]
0.3021	0.1708	0.3848	0.1427
0.5694	0.1177	0.5649	0.2475
0.6598	0.2562	0.8824	0.228
1.38	2.708	1.7	1.578
2.519	1.236	3.474	1.125
2.186	15.36	1.976	11.85
2.201	9.154	2.386	6.716
2.904	5.727	3.134	5.267
2.692	5.359	0.2138	0.3614
0.261	0.2306	0.3106	0.1814
0.2643	0.2377	0.3188	0.2391
0.3332	0.2364	0.7341	0.4862
0.8276	0.4931	0.9573	0.5487
0.8814	0.6251	0.945	1.148
1.17	0.8157	1.412	0.7655
1.656	0.7655	4.377	6.149
4.71	4.541	4.352	3.916
4.731	3.311	4.731	3.084
4.776	2.97	0.8064	0.8704
0.8893	0.7109	1.101	0.7109
1.376	0.6238	0.1212	0.2428
0.1327	0.319	0.2824	0.5356
0.3172	0.3925	0.3448	0.3127
0.8672	1.96	0.9678	1.487
0.9956	1.195	1.145	1.058
0.6285	0.6014	0.825	0.3998
0.984	0.3561	1.165	0.3595
0.7579	0.9568	0.9851	0.6631
1.06	0.6205	1.248	0.6205
0.1679	0.15	0.1915	0.1431
0.2334	0.1146	0.3426	0.2202
0.4667	0.1679	0.6347	0.1509
0.156	0.09243	0.204	0.06754
0.2592	0.0634	0.7882	1.326
0.8745	0.9628	0.843	0.8893
1.006	0.8331	1.098	0.8024
1.172	0.8075	0.06213	0.07675
0.07207	0.05459	0.2669	0.2447
0.3173	0.2287	0.3635	0.2273
0.6282	1.904	0.6658	1.464
0.8221	1.004	0.9966	0.7715
0.2675	0.2502	0.3354	0.2099
0.1619	0.25	0.1815	0.2196
0.9751	1.827	1.031	1.835
1.201	1.527	1.51	1.357
0.2162	0.4347	0.2185	0.907
0.2257	0.6737	0.2494	0.5998

Table 1: Results of MIRD outputs compared for the models M_1 and M_2

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