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RISK ASSESSMENT IN QUALITY ASSURANCE PROGRAM IN NUCLEAR MEDICINE USING RADIOIODINE

PROCENA RIZIKA U PROGRAMU OSIGURANJA KVALITETA U PRIMENI RADIOJODA U NUKLEARNOJ MEDICINI

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Key words
nuclear medicine, radioiodine, risk assessment, Monte Carlo, QA program

Ključne reči
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Abstract

Therapeutic or diagnostic radiopharmaceutical capsule containing $Na^{131}I$ stays in stomach for 15 minutes before the absorption starts, long enough to make possible risky exposure. During the oral application it is reasonable to measure effective dose in stomach. Direct measurements of organ doses are not possible so there is a strong recommendation to estimate them by calculation.
Investigations were performed at Institute of Pathophysiology and Nuclear Medicine, Faculty of Medicine, Ss. Cyril and Methodius University, Skopje, Macedonia. 87 patients were reviewed, age between 21 and 73. Patients were divided in 20 groups receiving average dose per group from 1813 MBq to 6105 MBq. For the purpose of this paper the nominal activity of 2000 MBq has been chosen The main goal is the ^{131}I risk assessment. Monte Carlo code MCNP4b was used to model the transport of gamma and beta particles emitted by radionuclide ^{131}I considered as a point source at the bottom of the stomach. Absorbed energy per unit transformation in stomach and surrounding organs has been calculated. The dose equivalents in these organs have been calculated in aim to determine the effective doses using appropriate tissue weighting factor values. Obtained results (total risk of 373.8×10^{-5}) had significant importance for radiation protection but they were also important for establishment of new calibration procedures as a part of QA and QC programs in radiopharmaceuticals production and control as well as in administration procedures and hospital trials.

INTRODUCTION

Two types of biological effects of ionizing radiation are recognized: deterministic and stochastic effects. Deterministic effects are those caused by the decrease in or loss of organ function due to cell damage or cell death. For these effects threshold doses exist: the function of many organs and tissues is not affected by small reductions in the number of available healthy cells. Only if the decrease is large enough, will a clinically observable pathological dysfunction appear. In the case of treatment of thyroid cancer, metastases, hyperthyroidism and euthyroid goitre, the objective is to bring about the cell-killing effect while not affecting other organs in such a way that deterministic effects occur [1].

Due to the capacity of thyroid cells to take up iodine thyroid diseases can be treated with radioactive iodine. The β-emitting ^{131}I is often the radionuclide of choice for these treatments, although the associated γ- emission gives rise to exposures to other tissues and even to other individuals.

The probability of a radiation-induced fatal cancer for the average population has been estimated at

approximately 5 % per Sievert for low doses and at 1 % per Sievert for serious genetic diseases [2]. For elderly people, older than about 60 years, the probability seems to be 3 to 10 times lower. This is because the future life span of elderly people may not be long enough for the cancer to become apparent and it is also unlikely that genetic damage is passed to offspring. For children up to the age of 10 years, the probability of fatal cancer induction seems to be about 2-3 times higher. For pregnant women the risk is the same as for the average population; however, the unborn child is assumed to have the same risk of developing a fatal cancer as children. [1,2].

The treatment of hyperthyroidism with radioiodine is based on the uptake by hyperactive thyroid cells and the damaging and destruction of these cells by β-radiation. This result in fewer functioning thyroid cells and therefore in normal or even below-normal thyroid function. For this treatment the administered activity is usually under 1000 MBq of ^{131}I [1,3].

Some goiters (strums) are euthyroid, which means that the thyroid is enlarged although function is normal according to clinical and biochemical parameters. However, these goiters may displace other organs or tissues because of the increased volume. One possible therapy is the reduction of the thyroid tissue volume with radioactive iodine. However, due to the large volume of the thyroid, high levels of activity up to 3000 MBq ^{131}I may be necessary [1,3].

In the case of thyroid cancer, the first choice for treatment is surgery. However, it is often impossible to remove all the cancer tissue and metastases may develop. Therefore, even after surgery, a treatment with radioactive iodine usually is applied to kill the remaining cancer cells.

Thyroid cancer cells lose part of their capacity for iodine uptake and also the organification process is disturbed. As a result, the uptake of iodine in thyroid cancer cells is lower than in normal thyroid tissue. After surgical removal of cancerous thyroid tissue, an initial activity of about 3000 MBq is given to ablate the thyroid bed remnants [1,3]. A much higher administration, up to 8000 MBq, is then necessary to treat any metastases [1,3]. If there is no normal tissue left after surgery, but metastases exist, high activities are given immediately. Repeated treatment might be necessary in either case. Normally, the activity is limited for safety reasons to around 7.4 GBq [1,3].

Presently, there are two dosimetry concepts for the treatment of thyroid cancer using radioiodine: a) the bone marrow dose limited approach and b) lesion-based dosimetry. Usually, patients are treated with standard activities reflecting the physician's rating of the highest safe or 'adequate' dosage rather than with an optimized treatment activity based on prior measurement of the patient's individual biokinetic. Such a standard activity poses a risk of either under dosing the patient or of exceeding common safety limits [4].

Biokinetic models intended for estimation of absorbed dose after intake of radioiodine have been published by the ICRP and some other authors, both for occupational and environmental exposure, as well as for nuclear medicine patients. In the models intended for estimating the dose to nuclear medicine patients, the stomach wall is identified as an organ of interest showing an enhanced activity concentration. The uptake is estimated to approximately 10 % of the activity administered [5]. The effective dose from intake of radioiodine is dominated by the absorbed dose to the thyroid. Under certain circumstances, however, the dose caused by uptake of iodide in the stomach may be of interest. In the biokinetic models it is usually assumed that the uptake in the stomach is located to the wall. From the stomach content the activity is transported to the small intestine, and, since the model primarily is designed for oral intake of iodide, it is assumed that activity entering the small intestine is almost immediately transferred to the circulation. In the present study the influence of a minor fraction leading on the colon is studied.

The therapy of the thyroid with radioiodine is usually performed with oral administration of iodide. Normally the effective dose from radioiodine is completely dominated by the absorbed dose to the thyroid. Under certain circumstances, however, the uptake in the thyroid may be very small, and in these cases the absorbed dose due to iodide taken up in the stomach may be of more interest. A diminished thyroid uptake may e.g. be a result of thyroid blocking or surgical removal of the gland. The biokinetic models, which include the stomach, usually assume that the activity seen in the stomach is located in the wall. The evidence for this assumption is, however, weak, with little substantial data behind it, and, since it may significantly influence the absorbed dose a clarification is important. The dose to the stomach wall is a factor of 2 – 3 higher if the source is located entirely within the wall itself compared to when it is found only in the contents [5].

Therefore, the rationale for using a dosimetry-based approach is to replace the conventional fixed activity regimen by a modern setting, which allows the administered therapeutic activity to be increased while avoiding undesired side effects. Using this strategy, the absorbed dose to iodine-avid tissue (remnants/metastases) can be optimized without inducing potential toxicity [4].

The administration of $Na^{131}I$ capsules or solutions is oral. We presume that the absorption in gastrointestinal tract starts immediately if the solution is used while

for the case of capsule therapy we estimate that radioactivity of ^{131}I stay in stomach for 15 minutes in average before the absorption starts. Institute of nuclear sciences VINCA is a manufacturer for $Na^{131}I$ capsules and it is experimentally obtained that the capsule dissolving time is 15 minutes. In this time interval a large amount of radioactivity needlessly expose a part of stomach and several surrounding organs. Comparing to the solution treatment of patients this is the additional risk. The longer remaining of capsule in stomach increase the real risk. These doses are not measurable but could be easily estimated using numerical experiment. Monte Carlo technique, also gives a good and reliable tool for risk assessment. The aim of this paper is to show one of the possible way how the additional risk can be estimated.

2. MATERIAL AND METHODS

2.1. Radiation risk as a quantity

Risk is stochastic variable, corresponding to a probability distribution of observing all significant health effects arising out of exposure to radiation. Risk of radiation induced cancer is represented through effective dose quantity which provides a number proportional to the radiobiological detriment (carcinogenesis, life shortening, hereditary effects) from radiation exposure [2,6,7].

The lifetime risk estimates considered here for exposure to internally deposited radionuclides are subject to uncertainties, arising from the dosimetric assumptions made, from the quality of cancer incidence and mortality data and from aspects of risk modeling; including variations in baseline rates between populations for some cancer types. Doses were calculated using defined biokinetic and dosimetric models, including reference anatomical data for the organs and tissues of the human body. In the case of internal irradiation, short-range charged particle emissions may be the dominant or sole contributors to radiation dose and risk, depending on the emissions of the radionuclide concerned, and its location within tissues and cells [8,9]. ICRP and NCRP gave lifetime fatal cancer probability coefficients for specific organs. This coefficient is the lowest for bone surface ($5x10^{-4}$/Sv), and the highest for stomach ($1.1x10^{-2}$/Sv) and $5x10^{-2}$/Sv in total [2,10,11].

2.2. Absorbed dose concept

The absorbed dose from internally deposited radionuclides is a major factor in assessing the risk. Although direct measurements of absorbed dose and dose distributions in vivo would be preferable, this generally is not feasible for routine clinical studies. Absorbed dose, defined as the energy absorbed per unit mass, is estimated from the localized uptake and retention of administered radiopharmaceuticals, the radiation decay data of the radionuclide and simulations of radiation transport in anthropomorphic models [12]. The mean absorbed dose to tissue is given in the MIRD schema by (1)

$$\bar{D} = \tilde{A}\,S \qquad (1)$$

where D is the mean absorbed dose in Gy, Ã is the cumulated activity expressed by Bqs and S is the mean absorbed dose per unit of cumulated activity in Gy/Bqs [12].

The absorbed dose to target may be expressed in terms of absorbed dose per unit administrated activity A_0 (in Bq) and the source residence time τ defined as ration given by [12]

$$\tau = \frac{\tilde{A}}{A_0} \qquad \ldots\ldots \qquad (2)$$

therefore, the mean dose to the target per unit administered activity is given by (3)

$$\tau = \frac{\tilde{A}}{A_0} \qquad (3)$$

The estimation of the absorbed dose depends on two types of information: time-dependent biokinetic factor incorporated in $\tilde{A},\tau$ and time independent physical factor represented within value S [12].To determine the cumulated activity in the desired source regions, serial measurements of region activity must be made following administration of the radiopharmaceutical. Mathematical models that describe the kinetic processes of a particular agent may be used to predict its behavior in regions where direct measurements are not possible. It is from the particular interest to measure administrated activity with low uncertainty and to improve calibration procedure. The source activity is given by (4):

$$A_j = \left({}^{I_A I_p}/_{e^{-\mu c}}\right)^{\frac{1}{2}} \frac{f_j}{c} \qquad (4)$$

where f_j represents correction for the source region attenuation coefficient and source thickness, while μ_c represents total linear attenuation coefficient obtained by measuring ratio of the count rates with and without patient in the position (I/I_0) [12].

The mean absorbed dose to a target organ (r_k)from its exposure to a source organ (r_h) from a radionuclide distributed uniformly in a source organ has been formulated by MIRD as:

$$\bar{D}\,(r_k \leftarrow r_h) = \frac{\tilde{A}_h}{m_k} \sum_i \Delta_i\, \Phi_i(r_k \leftarrow r_h) \qquad (5)$$

where A is cumulated activity (Bqs) in source organ r_h , m_k is the mass of target organ in grams, Δ_i is equi-

librium dose constant for particles of the particular type and energy indicated by i (expressed in gGy/Bgs), $\Phi_i(r_k \leftarrow r_h)$ is absorbed fraction of energy for target organ for particles- i emitted in source organ [13]. Equation (5) can be expressed as:

$$\bar{D}(r_k \leftarrow r_h) = \tilde{A}_h \bar{S}(r_k \leftarrow r_h) \quad (6)$$

where S is the mean dose in the target organ, usually referred as S-factor tabulated in MIRD Pamphlet 11. [13]

Cumulative source activity in organ rk over the time interval of interest is expressed as :

$$\tilde{A}_h = \int_{t_1}^{t_2} A_h(t)dt \quad (7)$$

When the source and target organs are well separated : $\Phi_i(r_k \leftarrow r_h)=0$ [13]

2.3. Estimation of effective dose for different organs using Monte Carlo simulation

General method for determination of effective dose in different organs and for estimation of additional risks is presented as three steps procedure: (1) *Dose equivalents* in tissues or organs are calculated by appropriate radiation transport codes using a suitable mathematical anthropomorphic phantom; (2) *The effective doses*, E, on the basis of tissue weighting factors, has been calculated and (3) *Additional risks* of lifetime mortality were assessed.

The use of the Monte Carlo method to simulate radiation transport has become the most accurate means of predicting absorbed dose distributions and other quantities of interest in radiation treatments of cancer patients using either external or radionuclide radiotherapy. The general idea of Monte Carlo analysis is to create a model, which is as similar as possible to the real physical system of interest, and to create interactions within that system based on known probabilities of occurrence, with random sampling of the probability density functions (PDFs). As the number of individual events (histories) is increased, the quality of the reported average behavior of the system improves, meaning that the statistical uncertainty decreases. The interactions determine the penetration and motion of particles, but, more importantly, the energy deposited during each interaction gives the radiation absorbed dose, when divided by the appropriate values of mass. With sufficient numbers of interactions the mean absorbed dose at points of interest will be given with acceptable uncertainties. Formalism and data based on Monte Carlo calculations, developed by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine, have been published as pamphlets in a series of supplements to the Journal of Nuclear Medicine.[14]

We used the radiation transport code MCNP4b, a general Monte Carlo N-Particle transport code (MCNP), developed at the Los Alamos National Laboratory [15]. This is a multipurpose computational code appropriate for various complex geometries. MCNP provides seven standard neutron tallies, six standard photon tallies, and four standard electron tallies. These basic tallies can be modifed by the user in many ways. Proper tally specification is very important in MCNP calculations. In the case of dose distribution calculation in different organs for gamma rays the tallies *F8 and F6 are applicable and therefore used. And for beta rays only *F8 tally can be used. These tallies give the absorbed energy in organs in units $MeVg^{-1}$ per disintegration. In the case of calculation of local dose distribution in stomach wall beside F6 and *F8 tallies, just for gamma rays F2 tally has been used to. Because this tally represents flux averaged over a surface, flux-dose rate conversion coefficients have been used [16].

The basic concept of dose estimation using Monte Carlo calculation starts from input data and presumptions introduced into consideration. Input data are: data determining the source (nuclear, radiological and shielding data), geometry and materials.

2.4. Geometry and materials

The source of 131I was considered as a point source placed in the middle of the soft tissue sphere. It was reasonable to presume the point source geometry as the small dried drop was deposited on the capsule holder. Self-absorption in such source should not be significant. The calculations performed during this study used a few various anthropomorphic phantoms. [17, 18] The new MIRD anthropomorphic models are very suitable for presented calculation as they are available for broad population and simple for use in Monte Carlo calculation. These models were developed for calculations of doses absorbed in specific organs due to the presence of the source in some other organ [19]. In this paper we presented our results only for the new MIRD model. The phantom consists of three major sections: (a) an elliptical cylinder representing the trunk and arms; (b) two truncated circular cones representing the legs and feet and (c) a circular cylinder on which sits an elliptical cylinder capped by half an ellipsoid representing the neck and head. The other organs are modeled by appropriate geometrical figures. The stomach wall is represented by the volume between two concentric ellipsoids and the contents within the inner ellipsoid. Average stomach masses in grams are between 150 g for wall and 250 g for contents if it is not empty. The stomach is represented as the mass between two ellipsoids (8) and (9) [19,20]

$$\left(\frac{x-8}{4}\right)^2+\left(\frac{y+4}{3}\right)^2+\left(\frac{z-35}{8}\right)^2\le 1 \quad (8)$$

and

$$\left(\frac{x-8}{3.387}\right)^2+\left(\frac{y+4}{2.387}\right)^2+\left(\frac{z-35}{7.387}\right)^2\le 1 \quad (9)$$

The axes are in cm, stomach volume is 151.9 cm^3 and mass is 150 g. The thickness of the stomach wall is assumed to be about 0.613 cm. Only the case of empty stomach is considered in our case, therefore, we did not put into calculation the stomach contents. This consideration is based upon clinical practice in our hospitals that all therapy procedures are given "at the empty stomach". According to this presumption the iodine capsule is at the bottom of the stomach lying at the stomach wall. The highest doses are delivered to the empty stomach because beta particles are absorbed (neutralized) in stomach content if present. Three phantom tissue types are recognized as skeletal, lung and all other tissue (soft tissue). The densities of those tissues are: 1.4 gcm^{-3}; 0.296 gcm^{-3} and 1.04 gcm^{-3} respectively. The exact compositions of each tissue type are given in ICRP reports 70 and 89 and ICRU 46 [21,22,23]. The soft tissue composition used in this paper is presented as 10.6 % H + 11.5 % C + 2.2 % N + 75.1 % O + 0.1 % Na + 0.1 % P + 0.1 % S + 0.2 % Cl + 0.1 % K.

For organs with walls and with the contents as a source (even the very small one) it can be considered that

$$\Phi_i(r_k \leftarrow r_h)=\frac{1}{2m_h} \quad (10)$$

where m_h is the mass of source organ. Thus the dose to the walls of the sections of the gastrointestinal tract and to the urinary bladder from sources in the corresponding contents represents a surface dose for electrons and beta particles.

2.5. Sampling

The present investigations were performed at Institute of Pathophysiology and Nuclear Medicine, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of Macedonia In the present study a total of 87 patients (17 male and 70 female) were reviewed, age between 21 and 73. Papillary carcinoma was found in 61 patients; 13 of them had follicular carcinoma; in 6 patients mass papillary carcinoma was diagnosed; 2 patients were with medullar carcinoma and 5 with Hurtle cell adenoma. Patient were divided in 20 groups receiving average dose per group from 1813 MBq to 6105 MBq. According to our protocol a first ablation dose for residual thyroid tissue is 3700 MBq. For the purpose of this paper we used the average administrated activity of 2000 MBq, but we performed calculations for all 20 activities.

3. RESULTS

In the very first step of calculation MCNP4b software gave us the absorbed energy in the most exposed organs as a consequence of 2000 MBq 131I capsule staying in stomach for 15 minutes. Using calculated imparted energies per transformation as well as radiation quality factors we have calculated dose equivalent rates in different organs as input parameters for effective dose estimation. By means of tissue weighting factors and dose equivalent in different organs the effective dose has been calculated and presented in Table 1.

Table 1. Effective doses in selected organs

Organ	Tissue weighting factor	E [μSv]
Bladder	0.05	269.2
Bone surface	0.01	300.6 x10^{-5}
Colon	0.12	508.6
Liver	0.05	310.8 x10^{-2}
Lungs	0.12	163.8x10^{-2}
Ovary, gonads	0.20	260.0
Skin	0.01	71.8 x10^{-2}
Stomach	0.12	40162.2

Effective dose at the whole body level is 41.2 mSv. As expected, this value is relatively high. The risk coefficients and calculated risks are presented in Table 2.

Table 2. Calculated values of risk coefficients and risks in selected organs

Organ	Risk coefficient [$10^{-2}Sv^{-1}$]	Risk x 10^{-5}
Bladder	0.30	161.6 x10^{-2}
Bone surface	0.05	150,2 x10^{-7}
Colon	0.80	122.8 x10^{-2}
Liver	0.15	93.6 x10^{-4}
Lungs	0.85	109,0x10^{-4}
Ovary, gonads	0.10	129.4x10^{-3}
Skin	0.02	143.2x10^{-5}
Stomach	1.10	368.2
Total		373.8

The additional total risk of cancer death (373.8 $x10^{-5}$) is relatively high and has to be considered in radiation protection protocols in hospitals performing radioiodine therapy.

The same situation comes from the calculation of Summary of the Lifetime Mortality in the Whole Population from Specific Fatal Cancers after Exposure at Low Radiation Dose and Dose Rates. In the vicinity of the capsules we obtained high dose values in order of two grays. Space dose fractionation has to be taken into account. These results indicate that the concept of average organ or tissue dose must be recruited by additional calculations.

4.CONCLUSION

The investigations and calculations were started with assumption that the values of additional effective doses or risks during the 15 minutes of 131I capsules retaining in the stomach before their absorption are not negligible. Application of solution has some advantages as the absorption in stomach wall is immediate but also has a lot of disadvantages. Capsules containing Na131I are widely used as they are more comfortable for administration and there is less possibility for local contamination of patient and medical staff.

During that time a large amount of radioactivity needlessly expose a part of stomach and several surrounding organs. This fact was the main reason for our prediction about the necessity of additional risk estimation. Obtained results indicate that values of local doses in stomach wall could not be ignored. As it is not possible to measure these doses directly Monte Carlo calculation seems to be good solution for this problem. According to the obtained results we recommended some corrections of the traditional concept of risk estimation in our hospitals and we emphasized the necessity to create the concept which is able to cover higher risks under presented circumstances. We strongly recommend the estimation of additional risks for each type of the procedure as a part of QA programs for Na131I capsules application.

This investigation will become actual and important for the case of high doses administrated during radiotherapy treatments. We expect that estimated risks will be higher and therefore more significant for patient protection as well as for radiation protection in general.

Risk assessments and effective dose estimation for wide range of administrated activities of 131I based radiopharmaceutical will give us a good basis for creation of suitable quality assurance and quality control programs in clinical practice.

It also will enable design of appropriate programs for manufacturers and distributors of radiopharmaceuticals.

Designed quality programs will be useful also for regulatory and accreditation bodies in the process of accreditation and radiation protection strategy.

We hope that the results of our investigation will improve safety culture in our health care system and also among authorities who make regulatory decisions.

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Apstrakt

Kapsule koje sadrže radiofarmaceutik $Na^{131}I$, a koje se koriste u dijagnostici ili terapiji, ostaju u stomaku 15 minuta pre apsorpcije, dovoljno dugo za rizično izlaganje. Stoga je, u toku peroralne administracije potrebno meriti efektivnu dozu u stomaku. Kako direktno merenje doze koju prime unutrašnji organi nemoguće preporučuju se tehnike numeričke simulacije. Naša istraživanja su sprovedena na Institutu za patofiziologiju i nuklearnu medicine Medicinskog fakulteta Univerziteta "Sv.Kiril i Metodije" u Skoplju, Makedonija. Obuhvaćeno je 87 pacijenata starosti od 21 do 73 godine. Pacijenti su podeljeni u 20 grupa I primili su srednje doze po grupi u opsegu od 1813 MBq do 6105 MBq. U ovom radu smo izabrali da prikažemo rezultate za administriranu aktivnost od 2000 MBq. Glavni cilj je bila procena rizika od ^{131}I. Za modelovanje transport agama zračenja i beta čestica emitovanih iz radionuklida ^{131}I je korišćen Monte Carlo code MCNP4b. Radiojod je modelovan kao tačkasti izvor na dnu stomaka. Proračunavana je apsorbovana energija po jedinici transformacije u stomaku i okolnim organima. Ekvivalentna doza u tim organima je izračunata da bi se odredila efektivna doza primenom odgovarajućih tkivnih težinskih faktora. Dobijeni rezultati umaju značaja za zaštitu od zračenja (ukupni rizik od $373.8x10^{-5}$), ali su važni i za ustanovljavanje novih kalibracionih procedura kao deo QA i QC programa u proizvodnji i kontroli radiofarmaceutika kao i procedura administriranja i bolničkih trajala.

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