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# Radiation dose estimation of human organs for $^{177}$Lu-anti-EGFR-PAMAM complex

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► ***Original article***

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## ABSTRACT

***Background***: Nowadays, radiolabeled monoclonal antibodies (mAbs) are satisfactorily used for the diagnosis and therapy of different types of cancers. In this study, the human absorbed dose of $^{177}$Lu-Cetuximab-PAMAM was estimated based on the biodistribution data in tumor-bearing mice. ***Materials and Methods:*** $^{177}$Lu-DTPA-CHX-Cetuximab-PAMAM was prepared after the conjugation of cetuximab to PAMAM nanoparticles and DTPA-CHX to mAb-PAMAM. The biodistribution of the labeled nano-system was studied in the tumor-bearing nude mice up to 72 h after injection. The absorbed dose of human organs was calculated according to the animals' data utilizing the radiation absorbed dose assessment resource (RADAR) and the relative mass extrapolation methods. ***Results:*** The radiolabeled compound, prepared at the optimized conditions, had a radiochemical purity (RCP) of 99.6% ± 0.4% ($P < 0.05$). Most of the activity was accumulated in the tumor site (10.14 ± 0.89; $P < 0.05$). The liver and the kidneys received the highest absorbed dose with 0.561 and 0.207 mSv/MBq, respectively, which is lesser than the other monoclonal antibodies labeled with $^{177}$Lu. ***Conclusion:*** Considering the special characteristics of $^{177}$Lu-DTPA-CHX-Cetuximab -PAMAM, this radiolabeled nano-system can be considered as a safe and effective radiolabeled compound for treatment of EGFR-expressing tumors.

## INTRODUCTION

Nowadays, the monoclonal antibodies (mAbs) are satisfactorily used for the diagnosis and treatment of different types of cancers [1,2]. The receptors for insulin-like growth factor, (IL)-2 and IL-1, transferrin, Her2/Neu, interleukin, and epidermal growth factor receptor (EGFR) are currently being targeted by a series of mAbs [3]. EGFR, a glycosylated transmembrane protein, is a 170-kD polypeptide member of receptor tyrosine kinases [1, 4], which overexpressed in multiple cancers, including prostate, ovary, head and neck, pancreas, breast, lung, kidney, colon, bladder, and brain [5]. EGFR is known as an attractive candidate for targeted therapies.

Cetuximab, a G1 immunoglobulin G1 human chimeric murine mAb, binds to the extracellular domain of EGFR with a great affinity [6]. Proliferation of cancer cells is inhibited by blocking the intracellular signal transduction using cetuximab [7]. This mAb has gained Food and Drug Administration approval for colorectal cancer, metastatic, Kirsten rat sarcoma viral oncogene (KRAS) head and neck cancer (squamous cell) [8]. The significant improvement of objective response rate (ORR), and overall survival (OS) after cetuximab treatment in the patients with metastatic colorectal cancer was reported in several studies. Nevertheless, about 30% of patients have failed [9].

Multiple radiolabeled cetuximab compounds using different diagnostic and therapeutic radionuclides have been prepared in recent years [10-13]. Among the therapeutic radionuclides used for this purpose, $^{177}$Lu with suitable decay characteristics has received particular attention for the treatment of small tumors []. Radiolabeled cetuximab derivatives seem to be a promising theranostic approach for the treatment of epithelial tumors when combined with external radiotherapy or chemotherapy [9]. However, since the clearance of mAbs is done through the reticuloendothelial system [15], considerable accumulation is seen in the liver. This issue can lead to a significant absorbed dose in the liver and limit the amount of injectable activity.

Targeted nano-drug delivery (utilizing nanoparticles as carriers, antibodies for targeted delivery, and radionuclides as theranostic agents) is recognized as one of the most up-to-date and critical targeted therapies in treating cancer. The application of nanoparticles in the drug delivery systems leads to the production of drugs with higher in-vivo stability, bioavailability, solubility, and also much higher



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uptake in the cells [16]. Among the nanomaterials, dendrimers are unique due to their well-defined and monodisperse structures. Several therapeutic and diagnostic radiolabeled compounds have been introduced using Polyamidoamine (PAMAM) dendrimers.

However, $^{177}$Lu-Cetuximab-PAMAM was recently introduced as a high-potential agent for the treatment of EGFR-expressing tumors [17], but the radiation absorbed dose of this radiolabeled compound has not been reported. The optimal amount of administrated activity for new radiopharmaceuticals strongly depends on the dose received by different organs after the injection of the new agent. Estimation of human absorbed dose using animal data is a common first step and a prerequisite that largely satisfies the (International Commission on Radiological Protection) ICRP 62 recommendations [18, 19]. This study aimed to calculate the human organ absorbed dose of $^{177}$Lu-Cetuximab-PAMAM to evaluate the risk associated with administering this complex. For this purpose, the biodistribution of this new radiolabeled compound was assessed in the tumor-bearing nude mice. The absorbed dose was estimated based on the biodistribution data in the mice like in the previous studies [20-22]. The cumulated activity in human organs was calculated by the relative organ mass method [23]. The equivalent absorbed dose was obtained using RADAR formalism.

## MATERIALS AND METHODS

### *Conjugation of cetuximab to nanoparticles*

The radiolabeled compound was prepared according to the previously reported literature [17]. First, an Amicon filter (Merck Co., Germany) was used to purify cetuximab (Merck Co., Germany) mAb. Then, the conjugation of mAb to nanoparticles was performed according to the following procedure:

A certain amount of purified mAb in 1 mg/mL phosphate-buffered saline (PBS) buffer (Sigma-Aldrich) was added to the vial containing 25 mg of 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) (Sigma-Aldrich) and 15 mg of N-Hydroxysuccinimide (NHS) (Sigma-Aldrich) in 7 mL of PBS buffer. The reaction vial was stirred for 4 h under $N_2$ atmosphere. 300 µl of PAMAM G4 solution (Alborz Nonpharmaceutical Technology Co., Iran) added to the reaction vial and stirred for up to 24 h again under $N_2$ atmosphere. A dialysis membrane with a cut-off of 12K Daltons was utilized to remove excess reagents.

### *Conjugation of DTPA-CHX to mAb-PAMAM*

Five mg of mAb-PAMAM was added to the solution containing 150 mM NaCl (Sigma-Aldrich), 48 mM $NaHCO_3$ (Sigma-Aldrich), 2 mM $Na_2HCO_2$ (Sigma-Aldrich) and 2 mM Ethylenediaminetetraacetic acid (EDTA) (Sigma-Aldrich) while the pH was set to 8.8. 1mg of Diethylenetriamine pentaacetate-CHX (DTPA-CHX; Macrocyclics Co., USA) chelator was then subjoined to the final solution, and the reaction was continued overnight at 37 ° C. A dialysis bag with cut-off 12 k Dalton was used to isolate the chelators that did not participate in the reaction.

### *Preparation of $^{177}$Lu-DTPA-CHX-Cetuximab-PAMAM*

For the preparation of the radiolabeled compound, 300 µl of $^{177}$Lu (185 MBq) was added to 1 mg of DTPA-CHX-Cetuximab-PAMAM (dissolved in 0.1 mL of 0.1 M ammonium acetate buffer) and stirred at 37 °C. PD-10 filter was then used to remove the impurities. The RCP of the final compound was assessed by radio thin layer chromatography (RTLC). For this purpose, Whatman No. 1 paper (Whatman, UK) and 0.1 M citrate buffer (Sigma-Aldrich) (pH 5) were used as the stationary and mobile phases, respectively. Papers were read by a Bioscan AR-2000 radio TLC scanner instrument (Europe Ltd Co., France).

### *Cytotoxicity assay*

Cytotoxicity of PAMAM, PAMAM-Cetuximab, 177Lu-Cetuximab-PAMAM was assessed using 3-[4,5-Dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide (MTT) assay on SW480 cells according to the previously explained method [17]. Briefly, different concentrations of precursors (0-500 nM) were added to each well-containing culture medium (200 µL). After 4 h incubation, the medium was removed, and ethanol-dimethyl sulfoxide solution (150 µL) was added. Finally, the absorbance was read (570 nm) after 20 min more incubation.

### *Biodistribution study*

100 µL of $^{177}$Lu-DTPA-CHX-Cetuximab-PAMAM containing about 150 µCi was intravenously injected into the male tumor-bearing nude mice aged 4-6 weeks with mean weight = 21.3 ± 2.0 purchased from Pasteur Institute (Iran). For tumor induction, $1 \times 10^6$ of human colon cancer cell lines (SW480), obtained from Pasteur Institute (Iran), was subcutaneously injected into the male nude mice. The biodistribution studies were carried out after the tumor had grown up to 7-8 mm. Mice were dissected according to the animal care protocols. The blood samples were taken from the aorta. The tissues were weighed, and their specific activities were determined with the p-type coaxial high-purity germanium (HPGe) detector (model: EGPC 80-200R), and the injected dose per gram (% ID/g) for each organ was calculated. All animals were kept on a routine day/night standard diet, and the United Kingdom Biological Council's Guidelines were used to conduct animal studies [24].



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***Accumulated activity calculation for animal organs***

The non-decay corrected percentage of the injected activity versus time for different animal organs was plotted, and the accumulated activity for animal organs was calculated according to equation 1.

$$\tilde{A} = \int_{t_1}^{\infty} A\ (t)\ dt \qquad (1)$$

Where, A(t) is the activity of each organ at time t.

The curves were extrapolated to infinity by fitting the tail of each curve to a monoexponential curve with the exponential coefficient equal to the physical decay constant of $^{177}$Lu. Whereas the activity of blood at t = 0 was considered the total amount of the injected activity, the activity of all other organs was assumed to be zero at that time.

***Estimation of accumulated activity for human organs***

The cumulated activity for human organs was computed from the extrapolation of the accumulated activity for animal organs using Sparks *et al*. method (equation 2) [21].

$$\tilde{A}_{Human\ organ} = \tilde{A}_{Animal\ organ} \times \frac{Organ\ mass_{human}/Body\ mass_{human}}{Organ\ mass_{animal}/Body\ mass_{animal}} \qquad (2)$$

***Equivalent absorbed dose calculation***

The absorbed dose of human organs was calculated by RADAR formalism (equation 3)

$$D = \tilde{A} \times DF \qquad (3)$$

Where $\tilde{A}$ is the accumulated activity for each human organ, and DF is the factor considering the physical decay characteristics of the radioisotope, the organ size, and the range of the emitted radiations. In this study, the DFs presented in OLINDA/EXM software (Vanderbilt University, USA) were employed [25].

***Statistical analysis***

The biodistribution of $^{177}$Lu-DTPA-CHX-Cetuximab-PAMAM was studied in four varied intervals (4, 24, 48 and 72 h), and the experiment was repeated three times (n = 3). The values were represented as mean ± standard deviation (mean ± SD). The data were contrasted with Student's t-test. *P* values of < 0.05 were regarded statistically significant.

## RESULTS

***Quality control of the radiolabeled compound***

The RCP of $^{177}$Lu-DTPA-CHX-Cetuximab-PAMAM was assessed by the RTLC method (figure 1). While, the free $^{177}$Lu moved to the higher $R_f$ with the mobile phase of 0.1 M citrate buffer (pH 5), and the radiolabeled compound stay at the origin. The results indicated a purity of 99.6% ± 0.4% at about 60 min after preparation.

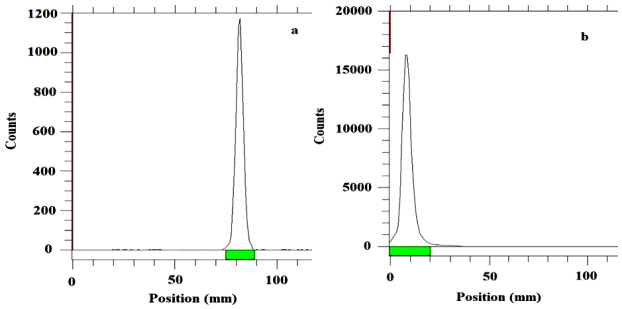


**Figure 1.** RTLC chromatogram of 177Lu **(a)** and 177Lu-DTPA-CHX-Cetuximab-PAMAM **(b)** at 60 min after preparation using the mobile phase of 0.1 M citrate buffer (pH 5), and the stationary phase of Whatman No. 1 paper.

***Cell Cytotoxicity***

The cytotoxicity of nano-systems was studied on the SW480 cell line by MTT assay. As expected, the viability of tumor cells was decreased by increasing the concentration of the nano-systems. Also, cell viability was greater for PAMAM, PAMAM-Cetuximab, and $^{177}$Lu-Cetuximab-PAMAM, respectively. The most cytotoxicity of the tumor cells was observed for $^{177}$Lu-Cetuximab-PAMAM at the concentration of 500 nM, in which the cell viability was reached to about 20%.

***Biodistribution study***

The biodistribution of $^{177}$Lu-Cetuximab-PAMAM was studied in male tumor-bearing nude mice at different intervals. The non-decay corrected percentage of injected activity per gram after injection of the complex into the tumor-bearing nude mice is demonstrated in figure 2. $^{177}$Lu-Cetuximab-PAMAM is mainly accumulated in the spleen and liver. While the most activity of the radiolabeled nano-system is approximately removed from the blood after 24 h, the maximum accumulation of the remained activity was seen in the tumor site 24 h post-injection.

***Calculation of equivalent absorbed dose***

Human organ absorbed dose was estimated according to the biodistribution data in the tumor-bearing nude mice. Table 1 shows the amounts of absorbed dose of various human organs.

The highest absorbed dose amounts after injection of $^{177}$Lu-Cetuximab-PAMAM complex were observed in the liver, spleen, and kidney with 0.516, 0.207 and 0.070 mSv/MBq, respectively.



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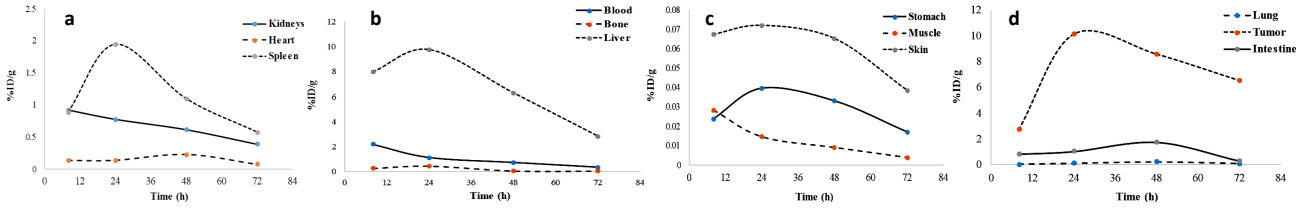


**Figure 2.** Non-decay corrected clearance curves after injection of 177Lu-Cetuximab-PAMAM complex for kidneys, heart, spleen **(a)**, blood, bone, liver **(b)**, stomach, muscle, skin **(c)**, lung, tumor, and intestine of the animals **(d)**.

**Table 1.** Equivalent and effective absorbed dose of human organs after injection of 177Lu-DTPA-CHX-Cetuximab-PAMAM (P-value < 0.05). GW: Gallbladder Wall; LLI: lower large intestine; Int: Intestine; ULI: upper large intestine.

| Target Organs | Absorbed dose (mSv/MBq) |
|---|---|
| **GB Wall** | 0.009 ± 0.000 |
| **LLI Wall** | 0.038 ± 0.002 |
| **Small Int** | 0.001 ± 0.000 |
| **ULI Wall** | 0.002 ± 0.000 |
| **Heart Wall** | 0.017 ± 0.001 |
| **Kidneys** | 0.070 ± 0.004 |
| **Liver** | 0.516 ± 0.025 |
| **Lungs** | 0.006 ± 0.000 |
| **Muscle** | 0.002 ± 0.000 |
| **Red Marrow** | 0.003 ± 0.000 |
| **Bone Surface** | 0.007 ± 0.000 |
| **Spleen** | 0.207 ± 0.008 |
| **Total Body** | 0.017 ± 0.001 |

## DISCUSSION

In this research study, $^{177}$Lu-DTPA-CHX-Cetuximab-PAMAM was prepared only in 60 min with RCP of higher than 80% similar to the previously reported research [17]. The biodistribution of the complex was assessed in the tumor-bearing nude mice (figure 2). The biodistribution results showed that the complex was mainly accumulated in the tumor site with more than 10% accumulation of activity at 24 h post-injection. As expected, some uptake was observed in the liver and spleen (figure 2) as the reticuloendothelial system.

The high uptake of the complex in these organs is in accordance with the biodistribution of the other radiolabeled mAbs [.]. Liver accumulation is a general problem in mAb-based immunoimaging and immunotherapy [9]. Recently, multiple studies have been performed on the radiolabeled compounds of cetuximab with different diagnostic and therapeutic radionuclides, including $^{90}$Y, $^{64}$Cu, $^{111}$In, $^{125}$I, and $^{177}$Lu in animals, all indicated considerable accumulation in the liver [4,9].

In 2014, Liu and his colleagues investigated the biodistribution of $^{177}$Lu-DOTA-cetuximab in UM-SCC-22B tumor-bearing mice after preparing the radiolabeled compound [28]. This group reported the high absorption in the liver and spleen, which first increases with time till 72 h and then decreases. In another research by Yavari and Ghannadi, the highest %ID/g after injection of $^{177}$Lu-cetuximab was seen in the blood (13.2 ± 1.3% at 24 h) and the liver (9.1 ± 1.3% at 24 h) [29].

The biodistribution of $^{177}$Lu-Cetuximab-PAMAM in the SW480 tumor-bearing nude mice (figure 2), indicated the maximum accumulation in the liver and spleen. These findings as well as rapid blood clearance compatible with the Liu and his colleague's work [28]. The highest uptake was indicated in the liver at 24 h compatible with Yavari and Ghannadi research [29]. However, Yavari reported considerable accumulation in blood after 24 h which is contrary to the results of Lee's work and the present study.

Despite the promising results of $^{177}$Lu-cetuximab for targeted therapy of EGFR-positive tumors [28,29], the human organ absorbed dose after injection of this radiolabeled compound has not been reported until now. Regarding the importance of the absorbed dose in determining injected activity, the present study was performed to evaluate the human organ absorbed dose of $^{177}$Lu-Cetuximab-PAMAM for the first time.

However, the biodistribution data can be different not only between humans and animals but also between animals; this method is recognized as the first step for the development of radiopharmaceuticals before human use [30-32], and is recommended by the international commission on radiological protection (ICRP) [19]. The estimated absorbed dose values could helpfully be utilized to determine the maximum injectable activity.

The maximum absorbed dose was observed in the liver and spleen as 0.516 and 0.207 mSv/MBq, respectively (table 1). Bahrami-Samani et al. in 2016 calculated the absorbed dose of $^{177}$Lu-DOTA-trastuzumab based on the biodistribution data in rats []. This group reported the maximum absorbed dose in the liver and spleen with 0.95 and 0.89 mSv/MBq, respectively. Comparing the results indicated that the human organ absorbed dose after injection of $^{177}$Lu-Cetuximab-PAMAM is in the same order and somewhat lesser than the absorbed dose of $^{177}$Lu-DOTA-trastuzumab.

According to these data, the liver can be considered as the dose-limiting organ compatible the presented research on $^{90}$Y-DOTA-Cetuximab [34]. Generally, regarding the high tumor accumulation and lesser absorbed dose in critical organs compared to the other monoclonal antibody based of $^{177}$Lu radiolabeled compounds, this agent can be considered a potential therapeutic agent for EGFR-expressing tumors.



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## CONCLUSION

$^{177}$Lu - DTPA - CHX - Cetuximab - PAMAM was prepared with RCP > 99% and high accumulation in tumors expressing EGFR receptors. The other non-target organs did not show a high accumulation of the radiolabeled compound. The liver and the kidneys received the highest amounts of the absorbed dose with 0.561and 0.207 mSv/MBq, respectively, and should be considered as dose- limiting organs in therapeutic plans. Considering the particular characteristics of this radioimmunoconjugate, it can be regarded an effective and safe agent for treatment of EGFR-expressing tumors.

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***Conflict of interest:*** The authors declare that they have no conflict of interests.

***Author contributions statement:*** S.Z., wrote the main manuscript text and analyzed the dosimetric and biological data, M.R., and A.K., calculated the dosimetric data, and prepared the figures and table, S.M.H., calculated the biological data. All authors reviewed and approved the manuscript.

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