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A multi species evaluation of the radiation dosimetry of [¹¹C]erlotinib, the radiolabeled analog of a clinically utilized tyrosine kinase inhibitor

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Abstract

Introduction—Erlotinib is a tyrosine kinase inhibitor prescribed for non-small cell lung cancer patients bearing epidermal growth factor receptor mutations in the kinase domain. The objectives of this study were to (1) establish a human dosimetry profile of [¹¹C]erlotinib and (2) assess the consistency of calculated equivalent dose across species using the same dosimetry model.

Methods—Subjects examined in this multi-species study included: a stage IIIa NSCLC patient, 3 rhesus macaque monkeys, a landrace pig, and 4 athymic nude-Fox1nu mice. [¹¹C]erlotinib PET data of the whole body were acquired dynamically for up to 120 min. Regions of interest (ROIs) were manually drawn to extract PET time activity curves (TACs) from identifiable organs. TACs were used to calculate time-integrated activity coefficients (residence times) in each ROI, which were then used to calculate the equivalent dose in OLINDA. Subject data were used to predict the equivalent dose to the organs of a 73.7 kg human male.

Results—In three of four species, the liver was identified as the organ receiving the highest equivalent dose (critical organ). The mean equivalent doses per unit of injected activity to the liver based on human, monkey, and mouse data were 29.4 μSv/MBq, 17.4 ± 6.0 μSv/MBq, and 5.27

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$\pm 0.25 \mu\text{Sv/MBq}$, respectively. The critical organ based on the pig data was the gallbladder wall ($20.4 \mu\text{Sv/MBq}$) but the liver received a nearly identical equivalent dose ($19.5 \mu\text{Sv/MBq}$).

Conclusions—(1) When designing PET studies using [^{11}C]erlotinib, the liver should be considered the critical organ. (2) In organs receiving the greatest equivalent dose, mouse data underestimated the dose in comparison to larger species. However, the effective dose of [^{11}C]erlotinib to the whole body of a 73.7 kg man was predicted with good consistency based on mice ($3.14 \pm 0.05 \mu\text{Sv/MBq}$) or the larger species ($3.46 \pm 0.25 \mu\text{Sv/MBq}$).

Keywords

radiation; dosimetry; erlotinib; TKI; OLINDA

Introduction

Erlotinib and other tyrosine kinase inhibitors (TKIs) can have a dramatic impact on the treatment of non-small cell lung cancer (NSCLC). Patients that harbor epidermal growth factor receptor (EGFR) mutations within the kinase domain (notably in-frame deletions in exon 19 and the L858R point mutation in exon 21) are often treated with TKIs. Compared to chemotherapy, TKIs produce a greater response rate (~70% versus 20-30%) and longer progression free survival (8-13 months versus 3-5 months) [1-5]. The PET tracer [^{11}C]erlotinib (*N*-(3-ethynylphenyl)-6-(2-(methoxy- ^{11}C)ethoxy)-7-(2-methoxyethoxy)quinazolin-4-amine) is the radiolabeled version of the TKI erlotinib. It has been shown that the tracer binds specifically in tumors containing mutant EGFR in both patients and animal models [6-10]. PET imaging using [^{11}C]erlotinib could provide valuable insights into the heterogeneity of mutant EGFR, early indicators of TKI resistance, and characterization of NSCLC metastases.

The present study is the result of a multi-institutional effort to merge and compare radiation dosimetry data of [^{11}C]erlotinib across different species. Participating institutions (and their studied species) included: VU University Medical Center (human), Yale University (monkeys), Aarhus Medical Hospital (pig), and Hadassah Medical Center (mice). Unlike most dosimetry analyses performed in a single animal model, the present combining of studies provided a unique opportunity to assess the consistency of calculated equivalent dose to humans based on four different species. We also chose to compare the utility of dosimetry in small species (mice) versus large species (pig, monkey, and human).

Materials and Methods

PET Imaging

VU University Medical Center—A female patient (37 yr; 55 kg) with stage IIIa NSCLC, harboring an exon 19 deletion (delE746-A750), was included within the context of an ongoing clinical study approved by the Medical Ethics Review Committee of the VU University Medical Center. She previously underwent a right middle lobe lobectomy and, approximately one year later, developed a local relapse. At that point she underwent a series of whole body [^{11}C]erlotinib scans for dosimetry purposes. Afterwards, the patient was treated with chemoradiotherapy.

Whole body (9 bed positions) PET scans were performed on a Gemini TF-64 PET/CT scanner (Philips Medical Systems, Best, Netherlands [11]). The scan protocol consisted of a low dose CT (30 mAs) for attenuation correction followed by 5 whole body PET scans after an intravenous bolus injection of 403 MBq of [^{11}C]erlotinib (0.011 μg ; 99% radiochemical purity). Scans started at 7, 18, 35, 56, and 87 minutes post injection (p.i.) and lasted for 30, 60, 90, 120, and 180 s per bed position in each of the successive scans. Data were acquired in list mode and reconstructed using the Blob-OS-TF algorithm in combination with CT-based attenuation correction, providing images with a final voxel size of $4\times 4\times 4\text{ mm}^3$ and a spatial resolution of 5-7 mm full width at half maximum (FWHM). Reconstructions included all usual corrections, such as detector normalization, decay, dead time, attenuation, randoms, and scatter corrections.

Yale University—Three healthy rhesus macaque monkeys (1 female, 2 male; 7.7 - 12.9 kg) were scanned on a Biograph mCT (axial FWHM 4.4 mm, Siemens/CTI, Knoxville, TN [12]) for 120 min. Monkeys were scanned according to a protocol approved by Yale's Institutional Animal Care and Use Committee. Prior to scanning, subjects were anesthetized and fitted with an intravenous line in the lower leg for tracer injection. Monkeys were placed in the center of the field of view before a whole body CT transmission scan (X-ray source) was performed for attenuation correction. Whole body (either 4 or 5 bed positions depending on subject size) dynamic emission scans (13 or 14 passes at $2\times 18\text{s}$, $3\times 36\text{s}$, $3\times 72\text{s}$, $3\times 180\text{s}$, 2 or $3\times 300\text{s}$) were performed following [^{11}C]erlotinib injection ($175 \pm 13\text{ MBq}$; $0.137 \pm 0.026\text{ }\mu\text{g}$; 99% radiochemical purity). PET data were reconstructed using OSEM with 2 iterations and 21 subsets to yield a final voxel size of $2.04\times 2.04\times 2\text{ mm}^3$. Standard corrections for attenuation, scatter, dead time, detector sensitivity, randoms, radionuclide decay, and frame-wise motion were applied.

Aarhus University Hospital—All experiments were approved by the Danish Ministry of Legal Affairs and performed in accordance with European Union, nationally, and institutionally approved guidelines for animal welfare. One healthy female pig underwent PET scans on an ECAT EXACT HR (Siemens/CTI, Knoxville, TN [13]) for 70 min. The 35 kg female Danish Landrace $\times$ Yorkshire pig was premedicated with 50 mg midazolam and 500 mg ketamine IM. After placing of ear vein catheter, anesthesia was induced with 50 mg midazolam and 250 mg ketamine IV. After intubation, the anesthesia was maintained with 2% isoflurane in an oxygen- N_2O air mixture (1:2). The pig was placed head-first, supine in the scanner and a whole body (8 bed positions) transmission scan using ^{68}Ge rod sources was acquired. After an injection of 299 MBq [^{11}C]erlotinib ($\sim 2\text{ }\mu\text{g}$; $>99\%$ radiochemical purity), three consecutive whole-body emission scans were acquired at 0, 18, and 45 min p.i. Each consecutive scan was performed for 2, 3, and 4 min per bed position. Data were reconstructed using attenuation-weighted OSEM with 6 iterations and 16 subsets to produce images with a voxel size of $3.67\times 3.67\times 3.67\text{ mm}^3$. All relevant corrections were applied (attenuation, scatter, dead-time, detector normalization).

Hadassah Medical Center—Four male athymic nude-Fox1nu mice (4 – 5 wk; 27.9 - 33.9 g) were obtained from Harlan (Rehovot, Israel). All animal studies were conducted under a protocol approved by the Animal Research Ethics Committee of the Hebrew

University of Jerusalem, and in accordance with its guidelines. Mice bearing wild-type EGFR tumors (cell line QG56) were anesthetized with isoflurane (1 – 2.5% in O₂) and maintained at normothermic conditions using a heating pad. Following an attenuation scan, PET acquisitions were carried out in list-mode using an Inveon PET-CT dedicated small animal scanner (axial FWHM 1.4 mm, Siemens Medical Solutions, USA [14]). Whole body dynamic PET scans (single bed position) were started at the time of [¹¹C]erlotinib injection via the lateral tail-vein (17.9 ± 3.5 MBq; 0.516 ± 0.252 µg; >97% radiochemical purity), and lasted for 60 min, re-binned into 27 time frames (2×5s, 5×10s, 8×30s, 5×60s, 4×300s, 3×600s). Emission sinograms were normalized and corrected for attenuation, scatter, randoms, dead time, and decay. Image reconstruction was performed using Fourier rebinning and 2D OSEM with 4 iterations and 16 subsets yielding a final voxel size of $0.776 \times 0.776 \times 0.796$ mm³.

Image Analysis

Reconstructed PET images were visually inspected for organ activity concentrations exceeding background level. Regions of interest (ROIs) were manually drawn within the boundaries of identifiable organs using CT images or ⁶⁸Ge transmission µ-maps for anatomical reference. Commonly identifiable ROIs included: gallbladder, heart, kidneys, liver, lungs, and urinary bladder (a complete list of ROIs drawn on each species can be found in Table 1). The localized volume of cancerous lung in the human subject was omitted from the lung ROI. Time activity curves (TACs) were extracted from the defined ROIs as mean radioactivity concentration at each time frame. Decay correction applied during image reconstruction was removed. Time-integrated activity coefficients ($\tilde{a}$; h) in each source organ (r_s), scaled to a 73.7 kg man, were calculated using Equation 1:

$$\tilde{a}_{r_s} = \frac{1}{A_0} C V_{r_s} \int_0^{T_D} A(r_s, t) dt \quad (1)$$

where A_0 is the injected activity (Bq), C is the subject mass scale factor (weight of subject/ 73.7 kg), V is the volume of a representative organ in a 73.7 kg male (mL), T_D is the dose integration period ($T_D = \infty$ to reflect total dose), $A(r_s, t)$ is the TAC of an organ without decay correction (Bq/mL), and t is the time after injection (h). Equation 1 is a standard calculation for $\tilde{a}$ scaled to account for subject size [15]. Formerly identified as residence time (τ), $\tilde{a}$ denotes the total number of nuclear transformations occurring in r_s over the time period 0 to T_D , normalized by injected activity.

Residual radioactivity present post scanning was modeled as mono-exponential radionuclide decay and integrated from scan-end to infinity as part of the integral in Equation 1. Organ volumes were either derived from reference phantoms or CT scans [16-18].

A remainder term ($\tilde{a}_R$) was calculated through standard methods in order to account for nuclear transformations occurring outside of our drawn ROIs:

$$\tilde{a}_R = \tilde{a}_{max} - \sum \tilde{a}_{r_s} \quad (2)$$

where $\tilde{a}_{max}$ represents the maximum time-integrated activity coefficient (no physiological efflux of radiolabeled tracer) defined as the half-life of $^{11}\text{C}/\ln 2$ (h).

Using time-integrated activity coefficients extrapolated from animal to human, OLINDA 1.0 software was used to calculate the equivalent dose per unit injected activity (H/A_0) in 22 different organs of the adult male model [18]. Total body dose, effective dose (ED), and effective dose equivalent (EDE) were also estimated in this manner.

Results

Biodistribution

Representative PET images (approximately 30 min p.i.) from each studied species are shown in Figure 1. The liver, gallbladder, and gastrointestinal tract were identifiable as having higher uptake compared to background. TACs in the liver were comparable among all species, characterized by initial uptake followed by rapid washout (Figure 2a). Human liver kinetics were slower compared to other species. Gallbladder TACs were consistent between human and monkey data, exhibiting gradual uptake until about 60 min p.i. followed by washout (Figure 2b). Pig gallbladder uptake was approximately twice that of the other species but otherwise followed a similar time-course.

Dosimetry

Mean time-integrated activity coefficients were longest in the liver, followed by the lungs in each of the examined species. The range of $\tilde{a}$ in the gallbladder was from $3.20\text{E-}3$ h based on monkeys to $6.77\text{E-}3$ h based on the pig. Remainder $\tilde{a}$ was smallest in the human (0.302 h) and greatest in the mice (0.448 ± 0.003 h). The percent difference between mean $\tilde{a}$ in small and large species was greatest in the stomach and liver (134% and 124%, respectively) and smallest in the urinary bladder (-3.2%). Calculated time-integrated activity coefficients for all ROIs can be found in Table 1.

In monkeys, mice, and human, the liver was found to be the organ with the highest equivalent dose (i.e., the critical organ). Mean equivalent dose to the liver was $29.4 \mu\text{Sv}/\text{MBq}$ in the human subject, $17.4 \pm 6.0 \mu\text{Sv}/\text{MBq}$ in monkeys, and $5.27 \pm 0.25 \mu\text{Sv}/\text{MBq}$ in mice. In the pig, the gallbladder was the critical organ ($20.4 \mu\text{Sv}/\text{MBq}$). Equivalent dose in the pig liver was $19.5 \mu\text{Sv}/\text{MBq}$. Equivalent dose to the liver was $17.9 \pm 9.9 \mu\text{Sv}/\text{MBq}$ in large species and $5.27 \pm 0.25 \mu\text{Sv}/\text{MBq}$ in small species. Difference in equivalent dose between large and small species was greatest in the gallbladder, liver, and kidneys (113%, 109%, and 87%, respectively). The calculated equivalent dose to the liver was positively correlated with the weight of the subject examined ($r^2 = 0.69$; $p < 0.01$).

The mean ED was $3.60 \mu\text{Sv}/\text{MBq}$ based on the human, $3.70 \pm 0.29 \mu\text{Sv}/\text{MBq}$ based on the monkeys, $3.41 \mu\text{Sv}/\text{MBq}$ based on the pig, and $3.14 \pm 0.05 \mu\text{Sv}/\text{MBq}$ based on the mice. The mean EDE was $5.05 \mu\text{Sv}/\text{MBq}$ based on the human, $4.90 \pm 0.50 \mu\text{Sv}/\text{MBq}$ based on the monkeys, $5.50 \mu\text{Sv}/\text{MBq}$ based on the pig, and $3.34 \pm 0.05 \mu\text{Sv}/\text{MBq}$ based on the mice. Table 2 contains the estimated equivalent dose to individual organs in a standard 73.7 kg adult male (based on each species). Equivalent dose estimates of selected organs were generated for a 370 MBq injection of [^{11}C]erlotinib (Figure 3).

Discussion

The present analyses identified the liver as the critical organ in 3 of 4 species. The pig identified the gallbladder as the critical organ but had nearly identical equivalent dose to the liver. The relatively high estimated dose to the liver and gallbladder implies that [^{11}C]erlotinib (and its radioactive metabolites) is cleared through gastrointestinal pathways including the hepatobiliary system. These findings and interpretations are consistent with the known clearance profile of erlotinib primarily through metabolism and excretion via the digestive tract [19].

[^{11}C]erlotinib only binds specifically to EGFR containing a mutant kinase domain. Non-human subjects used in the present study expressed only wild-type EGFR. Therefore, activity observed in source organs was not due to specific binding of erlotinib. Equivalent doses may be greater in regions containing EGFR with kinase domain mutations due to prolonged retention of [^{11}C]erlotinib. Consequently, in patients who are candidates for erlotinib therapy, the equivalent dose could be different compared to the values predicted here. Common sites of metastasis in NSCLC such as bone, brain, and muscle exhibited minimal tracer uptake in healthy organs, but these uptake values may be higher in the presence of TKI-sensitive tumors (dependent on lesion volume and affinity for erlotinib).

In studies operating under the authority of a local Radioactive Drug Research Committee (RDRC), the cumulative annual dose to a critical organ is limited to 150 mSv (50 mSv for sensitive organs, i.e., whole body, active blood-forming organs, lens of the eye, and gonads) [20]. We commonly use the RDRC organ dose limits in our applications to the Food and Drug Administration for Investigational New Drug (IND) approvals. According to our identification of the liver (or gallbladder) as the critical organ, the greatest permissible cumulative activity of [^{11}C]erlotinib to a 73.7 kg male in a year would be: 5100 MBq based on the human, 8640 MBq based on the monkeys, 7350 MBq based on the pig, and 28500 MBq based on the mice. Overall, the greatest estimated EDE for [^{11}C]erlotinib (5.50 $\mu\text{Sv}/\text{MBq}$ based on pig data) is within the lower range of EDE values (3.3 - 17.4 $\mu\text{Sv}/\text{MBq}$) reported in a recent review of carbon-11 radiotracer dosimetry studies [21].

In Europe, the ED and a risk category assigned to a study determines the maximum allowable dose from a tracer. The International Commission on Radiological Protection (ICRP) proposed the currently used risk categories [22, 23]. As the definition of these risk categories is somewhat vague, the Dutch Commission on Radiation Dosimetry (NCS) recently provided a national guideline for radiation exposure to subjects participating in medical research [24], together with a further interpretation of the various risk categories. In most cases, the risk category for adult subjects will be IIb with an associated maximum allowable ED of 10 mSv. Using our data in accordance with the European Commission's guidelines, the largest allowable amount of injected activity of [^{11}C]erlotinib in a year would be 2780 MBq based on the human, 2700 MBq based on the monkeys, 2930 MBq based on the pig, and 3190 MBq based on the mice.

It should be noted that in ICRP Publication 103, new weighting factors used to calculate the ED and EDE were proposed [25]. The ICRP has recommended the use of computational phantoms in place of mathematical models utilized by OLINDA 1.0.

Study Limitations

Mean injected mass of [^{11}C]erlotinib was 0.01 μg in the human, 0.14 μg in monkeys, 2 μg in the pig, and 0.25 μg in the mice. Although these values do not vary significantly, the range of injected mass per body weight is wider: 0.0002 $\mu\text{g}/\text{kg}$ in the human, 0.013 $\mu\text{g}/\text{kg}$ in the monkeys, 0.057 $\mu\text{g}/\text{kg}$ in the pig, and 8 $\mu\text{g}/\text{kg}$ in the mice. If there were sites of specific for erlotinib in our healthy animals, this could be a source of error in the results. However, as none of the animals expressed any kinase domain mutants EGFR, there were no sites of specific binding.

Our observed positive correlation between equivalent dose to the liver and the weight of the subject ($r^2 = 0.69$; $p < 0.01$) could be an artifact of a bias in the subject mass scale factor C (Equation 1). The scale factor is not organ specific. Implicitly, the scale factor assumes that for all species, a given organ occupies the same fraction of whole body volume as it does in the human dosimetry model. Rodent livers occupy a greater proportion of whole body volume compared to humans [26], causing an underestimation of time-integrated activity coefficients in mice. Mouse data predicted an equivalent dose to the liver and gallbladder that was half that of larger species. As data were collected in one human subject, readers should take care when interpreting the reported results. Because data were generally consistent among larger species, guidance for [^{11}C]erlotinib dose administration should be based on results from the human, pig, and monkeys, collectively. In order to overcome underestimation of the equivalent dose to the organs of small animals, more sophisticated methods of allometry than those presented here are needed.

There are two general ways to introduce error into the integral in Equation 1. First, insufficient sampling due to a small number of time frames. Pig emission data were reconstructed into only 3 time frames (the least of any species). Second, a short scan duration which necessitates more estimation. Tracer clearance after the scan-end was modeled as being entirely due to radioactive decay. This method may cause underestimation if the TAC is increasing at the end of the scan or overestimation if the TAC is decreasing faster than radionuclide decay (i.e., significant physiological clearance). In the present study, the second case was operative. Equivalent doses to individual organs based on the pig data (scan duration: ~ 80 min) were generally greater than the human (scan duration: ~ 110 min) and monkeys (scan duration: ~ 130 min) as visualized in Figure 3.

Due to differences in the size and ability to delineate organs, there was a disparity in the number and location of ROIs drawn on the images of the different species. The resolution of most commercial small-animal scanners does not allow for precise delineation of small ROIs in mice. In the present study, the limited anatomical information was insufficient to place ROIs with confidence on the mouse gallbladder, pancreas, and organs of the upper digestive tract (which contained significant [^{11}C]erlotinib activity). The remainder term, $\tilde{a}_R$ (Equation 2), represents the amount of unused information in each subject compared to the total amount available ($\tilde{a}_{max}$). The remainder term was greater in mice data (0.448 ± 0.003 h) in

comparison to large species (0.341 ± 0.033 h). Source organs accounted for approximately 8% of $\tilde{a}_{max}$ in mice in contrast to 30% in larger species. Thus, more of the available information was used when estimating equivalent doses in large species compared to the mice

OLINDA uses $\tilde{a}_R$ to approximate activity that is not accounted for by user-inputted time-integrated activity coefficients in source organs. This is meant to reduce underestimation of equivalent doses, particularly in whole-body metrics: total body, ED, and EDE. Indeed, the total dose and ED vary by less than 10% between small and large species. The use of $\tilde{a}_R$ does not eliminate discrepancies between small and large species in high dose organs. Estimation of equivalent dose to the liver, gallbladder, and kidneys did not vary significantly whether the remainder term was used or not (data not shown). The use of the remainder term within OLINDA is detailed in Cloutier et al. [27].

Conclusion

[^{11}C]erlotinib dosimetry based on human, monkey, and mouse subjects identified the liver as the critical organ. The estimated *effective dose* was consistent whether it was based on data from mice or the larger species. However, mice data did significantly underestimate the equivalent dose per unit injected activity to organs of high equivalent dose, including the critical organ.

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Figure 1.
Representative [^{11}C]erlotinib PET image at approximately 30 min post injection (overlaid on CT when available) in a human subject (a), rhesus monkey (b), landrace pig (c), and nude-Fox1nu mouse (d).

Figure 2.

Representative TACs in the liver (a) and gallbladder (b) in a 55 kg human (◆), 7.7 kg monkey (■), 35 kg pig (▲), and 30.4 g mouse (●). TACs are normalized as standard uptake values ($SUV(r_s, t) = A(r_s, t) \cdot \text{subject mass} / A_0$). Line segments are used for visualization. Based on the adult male model in OLINDA [18], the liver is 2.6% of the total body mass and the gallbladder is 0.01%.

Figure 3. Equivalent dose to selected organs of a 73.7 kg male due to 370 MBq of injected activity of [^{11}C]erlotinib (standard deviation shown as error bars) based on human data (blue), monkey data (red), pig data (green), and mouse data (orange).

Table 1

Mean (standard deviation) time-integrated activity coefficients based on each species. A mean was also calculated between the human, monkey, and pig subjects ("Large Species" column). Time-integrated activity coefficients for each analyzed ROI common to large species and the mice were compared by calculating the percent difference in means. Percent difference in means was calculated as (large species – small species)/average of species.

ROI	Mean Time Integrated Activity Coefficient (hr)								% Difference
	Human	Monkeys		Pig	Large Species		Mice		
Brain		1.42E-03	(6.45E-05)		1.42E-03	(6.45E-05)	1.21E-03	(6.92E-05)	15.7
Gallbladder	3.77E-03	3.20E-03	(2.55E-03)	6.77E-03	4.03E-03	(2.38E-03)			
Heart	4.01E-03	2.81E-03	(3.85E-04)	5.20E-03	3.53E-03	(1.10E-03)	1.21E-03	(7.62E-05)	97.9
Kidney	4.02E-03	6.64E-03	(7.87E-04)	1.43E-02	7.65E-03	(3.93E-03)			
Liver	1.72E-01	9.83E-02	(3.58E-02)	1.11E-01	1.15E-01	(4.07E-02)	2.70E-02	(1.56E-03)	124.3
Lung	3.64E-03	1.17E-02	(2.89E-03)		9.71E-03	(4.69E-03)	1.16E-02	(1.81E-03)	-17.5
Pancreas		1.70E-04	(5.92E-05)		1.70E-04	(5.92E-05)			
Small Intestine		5.89E-03	(2.34E-03)		5.89E-03	(2.34E-03)			
Spleen		3.24E-03	(1.76E-03)		3.24E-03	(1.76E-03)			
Stomach		2.80E-03	(3.34E-03)		2.80E-03	(3.34E-03)	5.56E-04	(1.93E-04)	133.8
Urinary Bladder	2.48E-04	2.34E-03	(7.81E-04)	2.00E-03	1.86E-03	(1.07E-03)	1.92E-03	(1.14E-03)	-3.2
Remainder	3.02E-01	3.50E-01	3.58E-02	3.50E-01	3.41E-01	(3.34E-02)	4.48E-01	(2.85E-03)	-27.2

Table 2

Mean (standard deviation) equivalent dose to the organs of an idealized 73.7 kg male per unit injected activity of [^{11}C]erlotinib based on each species. A mean was also calculated between the human, monkey, and pig subjects (“Large Species” column). Equivalent dose based on large species and the mice were compared by calculating the percent difference in means. Percent difference in means was calculated as (large species – small species)/average of species.

Organ	Mean Equivalent Dose (mSv/MBq)								% Difference
	Human	Monkeys		Pig	Large Species		Mice		
Adrenals	3.96E-03	3.62E-03	(1.62E-04)	3.81E-03	3.65E-03	3.16E-04	3.23E-03	(8.16E-06)	12.3
Brain	1.69E-03	7.32E-04	(5.31E-05)	1.94E-03	1.28E-03	6.23E-04	7.69E-04	(1.35E-05)	50.1
Breasts	1.95E-03	2.12E-03	(1.21E-04)	2.08E-03	2.14E-03	1.94E-04	2.41E-03	(8.16E-06)	-11.9
Gallbladder Wall	1.44E-02	1.19E-02	(6.22E-03)	2.04E-02	1.25E-02	7.01E-03	3.49E-03	(1.71E-05)	112.9
Heart Wall	4.11E-03	3.73E-03	(1.36E-04)	4.45E-03	3.89E-03	5.04E-04	3.28E-03	(2.50E-05)	17.2
Kidneys	5.70E-03	7.72E-03	(5.18E-04)	1.45E-02	7.74E-03	4.89E-03	3.06E-03	(5.77E-06)	86.8
Liver	2.94E-02	1.74E-02	(5.95E-03)	1.95E-02	1.79E-02	9.91E-03	5.27E-03	(2.46E-04)	109.0
LLI Wall	2.19E-03	2.63E-03	(2.11E-04)	2.52E-03	2.63E-03	4.07E-04	3.17E-03	(2.16E-05)	-18.7
Lungs	2.56E-03	4.39E-03	(6.44E-04)	2.69E-03	3.41E-03	9.21E-04	4.00E-03	(4.33E-04)	-15.9
Muscle	2.17E-03	2.38E-03	(1.35E-04)	2.36E-03	2.41E-03	2.35E-04	2.73E-03	(9.57E-06)	-12.5
Osteogenic Cells	2.98E-03	3.34E-03	(2.58E-04)	3.32E-03	3.41E-03	4.30E-04	4.01E-03	(2.06E-05)	-16.1
Pancreas	3.78E-03	2.89E-03	(4.41E-04)	3.73E-03	3.43E-03	4.14E-04	3.31E-03	(8.16E-06)	3.5
Red Marrow	2.10E-03	2.26E-03	(1.03E-04)	2.26E-03	2.28E-03	1.67E-04	2.51E-03	(5.77E-06)	-9.3
Skin	1.71E-03	1.90E-03	(1.35E-04)	1.89E-03	1.94E-03	2.31E-04	2.26E-03	(1.15E-05)	-15.2
Small Intestine	2.70E-03	4.56E-03	(6.10E-04)	2.93E-03	3.36E-03	8.33E-04	3.25E-03	(1.71E-05)	3.3
Spleen	2.37E-03	6.13E-03	(2.56E-03)	2.74E-03	3.56E-03	1.74E-03	2.98E-03	(1.41E-05)	17.6
Stomach Wall	2.75E-03	4.24E-03	(1.67E-03)	2.90E-03	3.27E-03	6.71E-04	3.20E-03	(1.00E-04)	2.2
Testes	1.82E-03	2.16E-03	(2.21E-04)	2.11E-03	2.20E-03	3.74E-04	2.72E-03	(1.73E-05)	-20.9
Thymus	2.20E-03	2.44E-03	(1.80E-04)	2.42E-03	2.47E-03	2.62E-04	2.83E-03	(8.16E-06)	-13.5
Thyroid	1.94E-03	2.25E-03	(2.18E-04)	2.21E-03	2.30E-03	3.60E-04	2.80E-03	(1.15E-05)	-19.6
ULI Wall	2.98E-03	3.17E-03	(4.51E-05)	3.12E-03	3.12E-03	1.03E-04	3.22E-03	(1.41E-05)	-3.1
Urinary Bladder Wall	2.18E-03	3.96E-03	(7.09E-04)	3.67E-03	3.49E-03	8.98E-04	4.16E-03	(7.25E-04)	-17.4
Total Body	2.92E-03	2.88E-03	(1.15E-05)	2.88E-03	2.88E-03	2.80E-05	2.85E-03	(5.00E-06)	1.0
Effective Dose Equivalent	5.05E-03	4.90E-03	(5.02E-04)	5.50E-03	4.70E-03	9.42E-04	3.34E-03	(5.26E-05)	33.9
Effective Dose	3.60E-03	3.70E-03	(2.86E-04)	3.41E-03	3.46E-03	2.49E-04	3.14E-03	(4.65E-05)	9.9