Tumor dosimetry for I-131 trastuzumab therapy in a Her2+ NCI N87 xenograft mouse model using the Siemens SYMBIA E gamma camera with a pinhole collimator

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ABSTRACT: We performed imaging and therapy using I-131 trastuzumab and a pinhole collimator attached to a conventional gamma camera for human use in a mouse model. The conventional clinical gamma camera with a 2-mm radius-sized pinhole collimator was used for monitoring the animal model after administration of I-131 trastuzumab. The highest and lowest radiation-received organs were osteogenic cells (0.349 mSv/MBq) and skin (0.137 mSv/MBq), respectively. The mean coefficients of variation (%CV) of the effective dose equivalent and effective dose were 0.091 and 0.093 mSv/MBq respectively. We showed the feasibility of the pinhole-attached conventional gamma camera for human use for the assessment of dosimetry. Mouse dosimetry and prediction of human dosimetry could be used to provide data for the safety and efficacy of newly developed therapeutic schemes.

KEYWORDS: Data processing methods; Computerized Tomography (CT) and Computed Radiography (CR)

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1 Introduction

Trastuzumab, a humanized monoclonal antibody that binds human epidermal growth factor receptor 2 (HER2), has been demonstrated to improve the outcomes for patients with HER2-positive breast cancer. Four phase 3 randomized trials, involving more than 8000 patients, showed that when trastuzumab was administered in combination with or after chemotherapy, the risk of recurrence was decreased by approximately 50%, and the overall survival was improved [1]. Similarly, in preclinical in vitro studies using tumor cell lines, trastuzumab was found to have additive and synergistic effects with some chemotherapeutic agents, and clinical trials investigating combination chemotherapy with trastuzumab and a variety of chemotherapeutic agents have been performed in lung cancer [2]. However, no single standard treatment currently exists for patients with small, node-negative, HER2 expressing breast cancers, because most of these patients have been ineligible for the pivotal trials of adjuvant trastuzumab [3]. Radioimmunotherapy (RIT), such as I-131-labeled tositumomab (bexxar) and Y-90-labeled ibrutinomab tiuxetan (zevalin) [4, 5], is a targeted treatment of cancer using selectively delivered radionuclide-labeled monoclonal antibodies (mAbs) [4], and the monitoring of tumor responses after RIT is known to be important for the treatment.

Dose estimates for nuclear medicine procedures are developed by the Medical Internal Radiation dose Committee of the Society of Nuclear Medicine and a software is available for dosimetry purposes [6]. Biodistribution and radiation dosimetry plays a key role in human studies, and recently, there have been many reports about radiation dosimetry for radiolabeled peptides and...
antibodies [7–9]. However, before considering translation into human use, estimates of human dosimetry are important. For the prediction of human dosimetry, mouse-derived prediction of human dosimetry has been reported using I-124 and Zr-89 [10–12], which are radioisotopes used for diagnostic positron-emission tomography (PET). Moreover, I-131, which emits gamma rays for imaging and beta rays for therapy, is widely used for RIT, for example in the form of I-131 rituximab [13–15]. Monitoring of I-131 rituximab for humans is performed using gamma cameras. In this study, we performed imaging and therapy using I-131 trastuzumab and a pinhole collimator attached to a conventional gamma camera for human use in a mouse model, as there is a need of mouse studies in order to allow for the development of adjuvant-combined therapy. To the best our knowledge, this study is the first report on radiation dosimetry using a mouse model and pinhole collimator attached to a conventional gamma camera.

2 Materials and methods

2.1 SYMBA E scanner

The SYMBA E single-photon emission computed tomography (SPECT) (Siemens, U.S.A.) scanner consisted of 59.1 × 44.5 × 0.95 cm³ NaI(Tl) crystals, with 59 photomultiplier tubes for the readout [16]. The SYMBA E SPECT scanner has interchangeable 2 mm, 4 mm-, 6 mm-, and 8 mm radius sized pinhole collimator. Because 4, 6, and 8 mm radius sized collimator was not suitable for animal imaging, we used 2 mm radius sized collimator for monitoring the animal model after administration of I-131 trastuzumab.

2.2 Mouse model

The animal study was reviewed and approved by the Institutional Animal Care and Use Committee and Institutional review board of the Korea Institute of Radiological and Medical Sciences. All applicable institutional and/or national guidelines for the care and use of animals were followed. The NCI-N87 Her2+ cancer cell line, obtained from the American Type Culture Collection, was maintained in Roswell Park Memorial Institute medium containing 10% fetal bovine serum and antibiotics (Sigma, U.S.A.) at 37°C in a humidified 5% CO₂ incubator. A total of 5 × 10⁶ NCI-N87 cells were subcutaneously injected to flank of the female BALB/nude mice (n = 4) (Shizuoka laboratory center, Japan).

2.3 I-131 Trastuzumab

Trastuzumab is a humanized mAb directed against the extracellular domain of the tyrosine kinase receptor HER2. Trastuzumab has shown clinical activity in HER2-overexpressing breast cancers. Pierce pre-coated iodination tubes (Thermo Scientific, U.S.A.) was used for I-131 radiolabeling with trastuzumab. For radiolabeling, the pierce pre-coated iodination tube was wetted with 1 mL of Tris iodination buffer and decanted. A total of 60 µL (1.0 mCi) of I-131 was added to the pre-coated iodination tube. Iodide was activated for 6 minutes at room temperature. Subsequently, 200 µg of trastuzumab was added and reacted for 6–9 minutes at room temperature. Instant thin layer chromatography (solvent: 100% acetone, C₃H₆O) showed that the I-131 trastuzumab radiochemical purity was > 95%.
2.4 Pinhole gamma camera image

The tumor volume was calculated using the formula \((\text{width}^2 \times \text{length} \times 0.4)\). When the tumor size reached 300 mm\(^3\) I-131 trastuzumab (430–451 \(\mu\)Ci/75 \(\mu\)g) was administered. Tumor targeting of I-131 trastuzumab was monitored using pinhole gamma camera imaging. The mice were anesthetized with 2% isoflurane. Data were acquired for the same amount counts not the same amount time for maintaining image quality. Acquisition scan time was set to different at 1, 24, 48, 72, and 96 hours after administration of I-131 trastuzumab. This was because data counts were reduced when the data was acquired for the same amount time due to decay of I-131 trastuzumab according to effective half life of I-131 trastuzumab in the mouse. In this present study, 300 kcounts of pinhole planar images were acquired at 1, 24, 48, 72, and 96 hours after I-131 trastuzumab administration. The energy window was 364 keV ± 15% the matrix size was 256 × 256 and the pixel size was 2.40 × 2.40 mm\(^2\) The distance from the collimator to the mouse surface was 1 cm.

2.5 Radiation dosimetry

The activity concentrations were determined by the mean pixel intensity within each region of interest (ROI), and were converted to mCi/ml using a crosscalibration factor. Assuming tissue density of 1 g/ml, the ROI activity was converted to mCi/g and normalized as percent injected dose per gram (%ID/g). Human biokinetics was extrapolated from mouse biokinetic data based on linear scaling of the radio-concentration ratio between animals and humans [17–19], as follows:

\[
\left(\frac{\%ID}{\text{organ}}\right)_{\text{human}} = \left(\frac{\%ID}{g}\right)_{\text{animal}} \times \left(\frac{\text{kgTBweight}}{\text{animal}}\right) \times \frac{g_{\text{organ}}}{g_{\text{TBweight}}_{\text{human}}}
\]

The animal whole-body weight (25 g) was converted to a human female (58 kg) phantom using the OLINDA program (OLINDA/EXM Vanderbilt University, U.S.A.; version 1.1) [6, 19]. Inputs to OLINDA|EXM are either residence times themselves (uCi h/uCi, Bq h/Bq) or %IA/organ from which residence times are computed via exponential curve fits. OLINDA|EXM software output is the radiation dose per unit of administered activity (mSv/MBq) in each organ and the total body, as well as effective dose (ED) and effective dose equivalent [11] The absorbed dose was calculated from the time activity curve and fitted to a bi-exponential function using actual mouse planar images.

The sphere model in the OLINDA program provides the absorbed dose for the sphere mass in the range of 0.01–6000 g, and the tumor absorbed dose calculations were performed using this model [10].

2.6 Immunofluorescence imaging

To investigate tumor targeting of trastuzumab, ex vivo immunofluorescence imaging was performed 3 days after administration of Alexa Fluor 488 conjugated trastuzumab. A solution of Alexa Fluor 488 (Invitrogen, U.S.A.) in dimethyl sulfoxide with 1% acetic acid was prepared. This solution was immediately added to 500 \(\mu\)l (10 mg/ml) dissolved 1M sodium bicarbonate solution, pH 8.4. The solution was mixed thoroughly and incubated for 1 h at room temperature. This reaction solution was purified using a size exclusion PD-10 column (GE Healthcare Bio-Sciences AB, Uppsala, Sweden) with phosphate-buffered saline (PBS) as the elution buffer. The purified solution
was measured using a NanoDrop spectrophotometer. The concentration of Alexa-488-trastuzumab was 1.5 mg/ml. When the tumor size reached 200 mm$^3$, 150 µg of Alexa-488-trastuzumab was intravenously injected. Three days later, the mice received a lateral tail vein injection of rhodamine-lectin (Rhodamine labeled Ricinu Communis Agglutinin I, 1 mg in 0.2 ml of PBS) to delineate the blood vessels, and 10 min later, the mice were euthanized by CO$_2$ inhalation and exsanguinated by cardiac puncture before dissection. The tumors were harvested with intact skin and flash-frozen. Subsequently, the tumors were fixed with 4% paraformaldehyde for 1 h at 4°C, and cryopreserved with 30% sucrose in PBS until the tissue sank to the bottom of the tube at 4°C. Next, the tumors were embedded in optimal cutting temperature compound for 1 h at −20°C prior to frozen sectioning on a microtome-cryostat, and stored at −70°C until use. The tumors were sectioned using a Leica CM 1850 cryostat (Leica microsystems, IL, U.S.A.) at 8µm thickness to cover the entire tumor tissue; subsequently, these sections were mounted on SuperFrost Plus slides. Before staining, the slides were warmed at room temperature for 10 min rehydrated with 200 µl PBS for 10 min, and fixed in 4% paraformaldehyde for 10 min. Staining was performed by dropping 4',6-diamidino-2-phenylindole (DAPI) solution onto the slides and covering them with coverslips.

2.7 Microcellular level analysis of trastuzumab accumulation across the tumors

Tissue imaging was performed with a 20× objective using Tissue FAXS (TissueGnostics, Austria). Three different channels were obtained: DAPI for cell nuclei (exposure time: 150 ms), rhodamine for blood vessel (exposure time: 206 ms), and Alexa Fluor 488 for trastuzumab (exposure time: 105 ms). The values obtained from 12 tumor regions for each tumor tissue were summed. Four regions each were measured 25% from the tumor apex, from the central region of the tumor, and 75% from the tumor apex. Each tumor was treated as an independent sample (n = 4). Image analysis was performed using an in-house program written in MATLAB (Mathworks, MA, U.S.A.). Individual image channels were exported as TIFF images for the image analysis. For the measurement of Alexa 488-trastuzumab accumulation across the tumor, an ROI was drawn on the tumor tissue. The total accumulation of Alexa 488-trastuzumab was calculated by the total Alexa 488-trastuzumab intensity in the tumor divided by the total tumor area.

3 Results

Figure 1 shows the representative pinhole planar images at 1, 24, 48, 72 and 96 hours after administration of I-131 trastuzumab. This result showed that I-131 trastuzumab was targeted to the tumor at 24 h after administration.

![Figure 1](image-url)
Figure 2. (a) Mean values of the percent injected dose per gram (%ID/g) of I-131 trastuzumab at 1, 24, 48, 72 and 96 hours after administration for the whole body and (b) at the corresponding time points for humans, based on the biokinetic linear scaling from mouse to human.

Figure 3. The mean percent injected dose per gram (%ID/g) in the tumors after administration of I-131 trastuzumab. The mean values for the percent injected activity per gram are shown without extrapolation to humans.

Figure 2(a) shows the %ID/g of I-131 trastuzumab at 1, 24, 48, 72 and 96 hours after administration of I-131 trastuzumab for the whole body. Figure 2(b) shows the predicted %ID/g of I-131 trastuzumab at the corresponding time points for humans based on the biokinetic linear scaling from mouse to human [17–19]. For 428–451 µCi/75 µg of I-131 trastuzumab administration, the mean effective dose equivalent and effective dose were 0.175 and 0.163 mSv/MBq, respectively. The mean coefficients of variation (%CV) of the effective dose equivalent and effective dose were 0.091 and 0.093 mSv/MBq respectively. The estimated absorbed doses based on the mouse planar image and OLINDA program are shown in table 1. The highest and lowest radiation-received organs were osteogenic cells (0.349 mSv/MBq) and skin (0.137 mSv/MBq), respectively.

Figure 3 and table 2 show the %ID/g and absorbed dose in the tumors after administration of I-131 trastuzumab. The tumor weights ranged from 0.24–0.32 g, and the absorbed doses ranged from 211.79–257.64 mGy/MBq. The amount of I-131 trastuzumab needed to deliver therapeutic 20Gy radiation to the tumor ranged from 77.63–94.43 MBq.

Figure 4 shows representative microcellular tissue level images of Alexa 488trastuzumab accumulation across a tumor. The mean accumulation of Alexa 488-trastuzumab per tissue area was 13.5 ± 1.7 AU/µm².
Table 1. Estimated absorbed doses (mSv/MBq) using actual gamma camera images (CV, coefficient of variation).

| Tissue               | Mean (n=4) | %CV | Minimum       | Maximum       |
|----------------------|------------|-----|---------------|---------------|
| Adrenal              | 1.82E-01   | 9.01E-02 | 1.61E-01     | 1.99E-01     |
| Brain                | 1.53E-01   | 9.26E-02 | 1.35E-01     | 1.68E-01     |
| Breasts              | 1.45E-01   | 8.86E-02 | 1.29E-01     | 1.59E-01     |
| Gallbladder wall     | 1.82E-01   | 9.01E-02 | 1.61E-01     | 1.99E-01     |
| Lower large intestine wall | 1.84E-01 | 9.11E-02 | 1.63E-01     | 2.02E-01     |
| Small intestine      | 1.75E-01   | 9.13E-02 | 1.55E-01     | 1.92E-01     |
| Stomach wall         | 1.78E-01   | 8.91E-02 | 1.58E-01     | 1.95E-01     |
| Upper large intestine wall | 1.84E-01 | 9.11E-02 | 1.63E-01     | 2.02E-01     |
| Heart wall           | 1.79E-01   | 9.17E-02 | 1.58E-01     | 1.96E-01     |
| Kidneys              | 1.74E-01   | 9.11E-02 | 1.54E-01     | 1.91E-01     |
| Liver                | 1.75E-01   | 9.13E-02 | 1.55E-01     | 1.92E-01     |
| Lung                 | 1.67E-01   | 9.03E-02 | 1.48E-01     | 1.83E-01     |
| Muscle               | 1.60E-01   | 8.94E-02 | 1.42E-01     | 1.75E-01     |
| Ovaries              | 1.86E-01   | 9.31E-02 | 1.64E-01     | 2.04E-01     |
| Pancreas             | 1.87E-01   | 8.96E-02 | 1.66E-01     | 2.05E-01     |
| Red marrow           | 1.38E-01   | 9.07E-02 | 1.22E-01     | 1.51E-01     |
| Osteogenic cells     | 3.49E-01   | 9.12E-02 | 3.09E-01     | 3.83E-01     |
| Salivary             | 1.37E-01   | 9.14E-02 | 1.21E-01     | 1.50E-01     |
| Skin                 | 1.75E-01   | 9.06E-02 | 1.55E-01     | 1.92E-01     |
| Spleen               | 1.70E-01   | 9.13E-02 | 1.50E-01     | 1.86E-01     |
| Thymus               | 1.58E-01   | 9.26E-02 | 1.40E-01     | 1.74E-01     |
| Thyroid              | 1.68E-01   | 9.17E-02 | 1.49E-01     | 1.85E-01     |
| Urinary bladder wall | 1.84E-01   | 9.11E-02 | 1.63E-01     | 2.02E-01     |
| Uterus               | 1.61E-01   | 9.09E-02 | 1.43E-01     | 1.77E-01     |
| Total body           | 1.82E-01   | 9.01E-02 | 1.61E-01     | 1.99E-01     |
| Effective dose       | 1.75E-01   | 9.13E-02 | 1.55E-01     | 1.92E-01     |

Table 2. Tumor dosimetry results for I-131 trastuzumab. The I-131 trastuzumab radiation dose estimation in the tumors and the amount of I-131 trastuzumab needed to deliver therapeutic 20 Gy radiation to the tumors are listed.

| Tumor (g) | I-131 trastuzumab dose (mSv/MBq) | I-131 trastuzumab (MBq) to deliver 20 Gy | I-131 trastuzumab (mCi) to deliver 20 Gy |
|-----------|----------------------------------|----------------------------------------|----------------------------------------|
| #1 (0.32) | 2.58E+02                         | 7.76E+01                               | 2.10E+00                               |
| #2 (0.24) | 2.12E+02                         | 9.44E+01                               | 2.56E+00                               |
| #3 (0.25) | 2.13E+02                         | 9.38E+01                               | 2.54E+00                               |
| #4 (0.32) | 2.30E+02                         | 8.69E+01                               | 2.54E+00                               |
4 Discussion

In this study, we reported the radiation dosimetry of I-131 trastuzumab using a mouse model and pinhole collimator attached to a conventional gamma camera.

There are numerous radiation dosimetry studies using I-131; this wide use of I-131 is owing to its capabilities in both imaging and therapy. I-131 emits gamma rays (284 keV [6%], 364 keV [82%], 637 keV [7%], and 723 keV [2%]) for imaging and beta rays (606 keV [90%], 334 keV [7%], and 606 keV [90%]) for therapy. Pretreatment dosimetry prior to I-131 treatment for patients with differentiated thyroid cancer has been shown to optimize the dosing regimen in terms of the effectiveness and safety [20]. Further, patient-specific dosimetry using I-124 mIBG PET/computed tomography (CT) imaging and the Monte Carlo method has been reported for treatment planning [21], and the effective doses per time-integrated activity for pediatric and adult family members exposed to an adult patient released from hospital following I-131 therapy [22], as well as the appropriate guidelines, have also been previously reported [23]. Furthermore, radiation dosimetry and preliminary therapy results using an I-124/I-131 small molecule (MIP-1095) targeting prostate-specific membrane antigen for prostate cancer therapy have also been described [24].

The methodology for I-131 RIT involves using tracer data via a mixed-model fit to time activity, and was developed for the prediction of the therapeutic tumor-absorbed dose [25]. A comparative study of the dose point kernel database using the GATE Monte Carlo simulation toolkit with another Monte Carlo simulation was performed by [26].

Regarding radiation accidents, in utero exposure to I-131 from the Chernobyl fallout and anthropometric characteristics in adolescence have been previously assessed [27].

Although I-131 therapy or I-131 RIT is a conventional therapeutic scheme in nuclear medicine, in the present study, we developed an animal model and performed I-131 RIT using a pinhole col-
limator attached to a gamma camera for human use. The rationale behind this study was that there is an increasing necessity of imaging-based assessments of therapeutic efficacy after combination therapy using mouse models. Anticancer drugs such as paclitaxel enhance the penetration of mAbs into the tumor tissue [28], and pulsed high-intensity focused ultrasound has been shown to increase penetration and therapeutic efficacy of mAbs in murine xenograft tumors [29]. Further, there are some previous reports on combination therapy using trastuzumab and pertuzumab [30], lapatinib [31], or paclitaxel [3]. In addition to combination therapy using anticancer drugs, RIT using radiolabeled antibodies may also represent a possible option for increasing the therapeutic efficacy. Therefore, in the present study, we attempted to perform I-131 trastuzumab therapy using a Her2+ NCI N87 mouse model. Although I-131 imaging was easily obtained using a conventional human-use gamma camera, there is no previous report about I-131 gamma camera imaging for a mouse model using this conventional human-use gamma camera, likely owing to limitations in the spatial resolution. In addition, there is currently no report about I-131 imaging using an animal-dedicated scanner such as the Siemens Inveon PET/SPECT/CT scanner, owing to limitations with the energy window [32]. One of the authors in the present study previously reported modeling an I-131 pinhole collimator for a small animal gamma ray imaging device by Monte Carlo simulation [33]. However, there is no report about actual mouse imaging using a pinhole collimator attached to a conventional human-use gamma camera.

In the present study, we successfully acquired mouse imaging data using a conventional human-use gamma camera with a pinhole collimator. Tumor targeting of I-131 trastuzumab was clearly visible on the gamma camera images, and based on these images for the Her2+ mouse model, we could predict human dosimetry when I-131 trastuzumab was administered (figure 2). In addition, we calculated the tumor dosimetry after administration of I-131 trastuzumab (figure 3), and tumor accumulation of trastuzumab was confirmed by administration of Alexa Fluor 488-conjugated trastuzumab using a microcellular tissue level ex vivo study.

5 Conclusions

In this study, we showed the mouse dosimetry data and prediction of human dosimetry after administration of I-131 trastuzumab. In addition, we showed the feasibility of the pinhole-attached conventional gamma camera for human use for the assessment of dosimetry. Mouse dosimetry and prediction of human dosimetry could be used to provide data for the safety and efficacy of newly developed therapeutic schemes.

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