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ORIGINAL ARTICLE

The Use of EPID-based *in vivo* Dosimetry for Small Animal Radiation Research

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OBJECTIVE

To validate the feasibility of electronic portal imaging device (EPID)- based in vivo dosimetry system for the verification of small animal radiation research

METHODS

The workflow can be divided into three steps. In the first part, external body of the rat phantom was modeled based on the computed tomography (CT) dataset of a real rat previously scanned for another radiobiological experiment and the structure set was exported to 3D Slicer program to convert DICOM file to. stl file format. Tissue-equivalent rat phantom was, then, printed using Makerbot Replicator Z18 3D-printer. In the second part, treatment plans were created for different anatomical sites including whole brain and total lung irradiation using Elekta Versa HD linear accelerator. In the last part, measurements were performed with EPID-based 3D *in vivo* dosimetry system. During the analysis, 3D γ analysis method was used and γ evaluation criteria were set to 3 mm distance-to-agreement and 3% dose differences for local dose.

RESULTS

According to our analysis, EPID measurement for each modality and anatomical site met the protocol value except for % $\gamma \leq 1$ and γ mean values for total lung irradiation, but both of these parameters met the proposed minor variation criteria.

CONCLUSION

Implementation of EPID-based 3D *in vivo* dosimetry for preclinical radiation research with small animals seems to be feasible.

Keywords: Electronic portal imaging device; *in vivo* dosimetry; preclinical radiotherapy.
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INTRODUCTION

Preclinical radiation research with small animal models is an indispensable step between *in vitro* experiment and clinical implementation.[1–4] In the past two decades, radiotherapy (RT) machines have undergone huge technical development for the targeted RT modalities such as intensity-modulated radiation therapy, volumetric-modulated arc therapy (VMAT), and stereotactic radiosurgery/RT with sophisticated treatment platforms (robotic, gyroscopic, ring gantry system, etc.). Although, delivery of RT with targeted beams led to a paradigm shift in cancer treatment, there is no standardization to validate the feasibility of highly conformal treatment modalities for radiobiological experiment with small animal models.[5–8]

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In fact, in many studies, conventional irradiation techniques like whole body irradiation or using simple partial treatment field have been still preferred as a standard approach.[3,9,10] Therefore, the data collected from the radiobiological experiment for combination therapies such as RT plus novel drugs or molecular targeted agents does not accurately represent the effects of highly non-uniform and conformal dose distribution typically delivered to real patients. To overcome this problem, recently, many studies have focused on the dedicated methods for small animal radiation research (e.g., the use of microcomputed tomography (CT), dedicated treatment planning system (TPS), and microirradiator).[3] As an alternatively, although, dose delivery in small animal scale is not generally verified as a part of a quality assurance (QA) program in clinical linear accelerator, these systems are routinely used in many clinics to avoid large capital investments to the dedicated small animal irradiation platforms. However, preclinical radiation research with clinical linear accelerator presents some challenges such as the use of very small field size, wider penumbra, and build-up region due to the higher beam energy. Therefore, the accuracy of the delivered dose in small animal scale needs to be verified with dedicated phantoms and detectors before conducting radiobiological experiment in clinically available treatment platforms.

3D-printed small animal phantoms have emerged as one of the promising and cost-effective solution for the dosimetric verification of the radiobiological experiment in clinical linear accelerator.[11–16] In the literature, mouse or rat phantoms were generally modified to accommodate film dosimetry and small volume detectors such as microionization chamber, SRS diode, thermoluminescance or optically stimulated dosimetry for commissioning or pretreatment verification of the linear accelerator.[3,12] Although electronic portal imaging device (EPID)-based *in vivo* dosimetry is defined as one of the promising solution in clinical practice,[17] to the date, there is no study evaluating the feasibility of EPID dosimetry for the verification of delivered dose during radiobiological experiment. Therefore, in the present study, it was focused to validate the feasibility of clinically available EPID-based 3D *in vivo* dosimetry system for small animal radiation research.

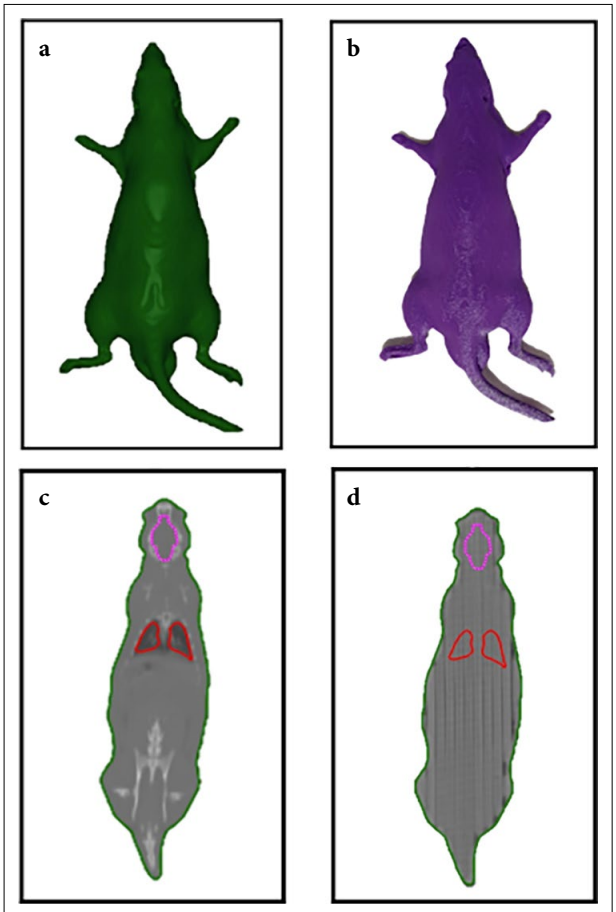

Fig. 1. A representative view of (a) modelled and (b) 3D printed rat phantom and coronal view of the CT image for (c) real rat and (d) phantom model with defined target volumes (whole brain and total lung).

MATERIALS AND METHODS

Modeling and 3D Printing

CT dataset of a real rat previously scanned for another radiobiological experiment were transferred to RayStation TPS version 8.0 (RaySearch Lab., Stockholm, Sweden) to create 3D model of external body (Fig. 1a). This structure set was exported to 3DSlicer software version 4.3 (The Slicer Community, Harvard, MA, United States of America [USA]) with SlicerRT extension in DICOM format and external body was saved as. stl file format for 3D printing. Rat phantom was printed in Makerbot Replicator Z18 3D-printer (MakerBot Industries, Brooklyn, NY) using polylactic acid filament, a thermoplastic polyester with a density of 1.25 g/cm^3, and printing parameters were set as 95% infill percentage, diamond infill pattern, and vertical printing direction to create tissue-equivalent phantom, as illustrated in Figure 1b.

Analysis of Printing Accuracy and Uniformity

Printing accuracy of the phantom was evaluated through physical measurements at multiple position along the phantom using a Vernier caliper with a res-

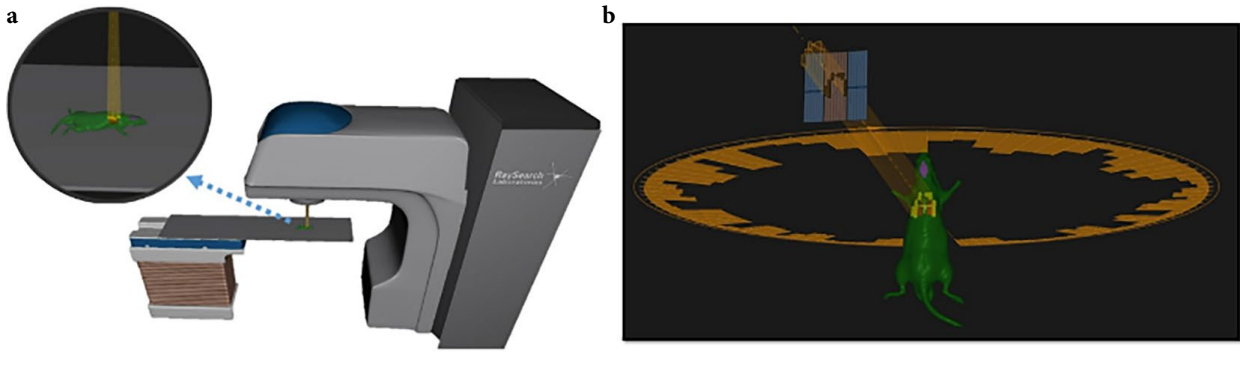

Fig. 2. A typical view of (a) phantom setup in treatment machine and (b) beam angle arrangement for VMAT technique in total lung irradiation.
VMAT: Volumetric-modulated arc therapy.

olution of 0.1 mm. In addition, the mean Hounsfield unit (HU) value and line profile for HU in both superior-inferior and left-right direction were analyzed in TPS to evaluate the uniformity of the phantom.

Treatment Planning and Measurements

Target volumes for various anatomical sites including whole brain and total lung were delineated on the CT dataset of rat phantom using fused real CT dataset, as illustrated in Figure 1c and d. After that, four different treatment plans; three-dimensional conformal RT (3D-CRT) with lateral opposed fields and VMAT technique with single arc (arc angle: From 175° to 185°) for whole brain, AP-PA treatment fields, and VMAT technique with single arc (Arc angle: From 175° to 185°) for total lung irradiation, as shown in Figure 2, were created using 6 MV photon energy in Elekta Versa HD linear accelerator (Elekta AB, Stockholm, Sweden) and dose was prescribed as 2 Gy/fr for all scenarios. All measurements were performed with EPID-based iViewDose v.1.0.1 software (Elekta AB, Stockholm, Sweden) working in conjunction with the existing EPID panel. Since the back-projection algorithm used in the clinical version of iViewDose software underestimate the dose values in field sizes smaller than 3.0×3.0 cm. EPID was re-commissioned for only small fields between the sizes of 1.0×1.0 cm and 4.0×4.0 cm using the correction factor for the cross calibration of the measured dose with respect to calculated dose in TPS. The model created in the present study was saved only for non-clinical use.

γ Evaluation

EPID-reconstructed and calculated dose distribution in TPS was analyzed using 3D γ analysis method. As an evaluation criterion, 3 mm distance-to-agreement (DTA) and 3% dose differences (DD) were used. Pass-fail criteria of the treatment planning are based on the differences in mean γ value (γ mean), the maximum 1% γ value (γ 1%), and the percentage of points with γ≤1 within the 50% isodose surface of the planned maximum dose or γ passing rate (% γ≤1) and dose to reference point (ΔDRP). The protocol (minor variation) values for passing criteria used as a clinical protocol were 0.5 (minor variation: 0.7), 3 (minor variation: 3.5), 90% (minor variation: 85%), and 3% (minor variation: 5% at high dose gradient region) for γ mean, γ 1%, % γ ≤ 1, and ΔDRP values, respectively.

RESULTS

Analysis of Printing Accuracy and Uniformity

The measured differences between the modeled and the printed dimensions of the rat phantom were within 0.5 mm (±0.1 mm resolution of the Vernier caliper). Printed dimension of the external body was on average 0.3 mm (range: 0.1–0.5 mm) greater than modeled. In addition, 3D-printed rat phantom had a uniformity over the external body and there was no any region containing unwanted air cavities or high-density areas over than 1 mm in diameter. The mean HU value of the phantom was found as −20.77 HU.

EPID-based Measurements

Reconstructed dose with re-commissioned beam model for small field sizes was found to be compatible with TPS data. As illustrated in Figure 3, in-plane beam profiles measured at 1.5 cm depth for defined field sizes were well matched with the calculated dose profiles in TPS. In percentage depth dose (PDD) measurement, the relative DD increased with depth, as shown in Figure 4. How-

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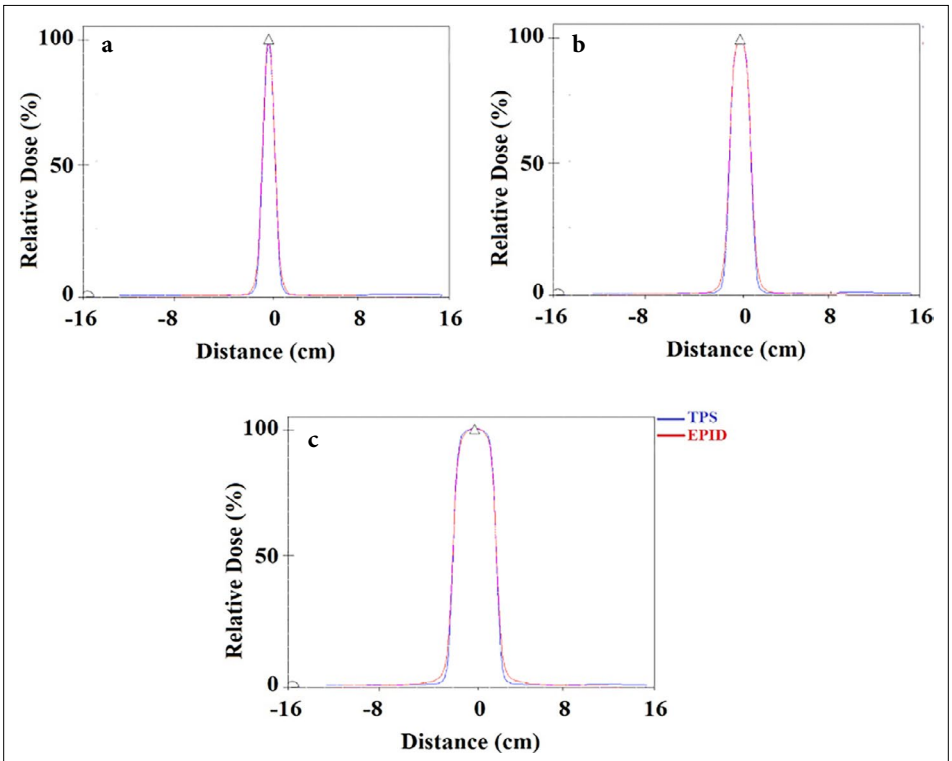

Fig. 3. Measured (red) and calculated (blue) beam profile (in-plane direction) at 1.5 cm depth for defined field sizes; (a) 1×1 cm, (b) 2×2 cm and (c) 4×4 cm using 6 MV photon energy.

ever, the maximum ΔDRPs at 5 cm and 10 cm were <3% and 5% for all commissioned field sizes, respectively (protocol: 3% and minor variation: 5% at high-dose gradient region). In 3D γ analysis, % γ≤1 value (γ passing rate for evaluation criteria: 3 mm DTA/3% DD) for all field size were >85% in defined phantom geometry.

According to measurement with rat phantom, the results of 3D *in vivo* dosimetry for each technique and treatment region met the protocol value except for % γ≤1 and γ mean values of lung treatment, as presented in Table 1. Nevertheless, % γ≤1 and γ mean values for lung treatment met the proposed minor variation criteria for both techniques. Dose line graphics for measured and calculated dose distribution are illustrated in Figure 5 for whole brain irradiation and in Figure 6 for total lung irradiation. In point dose comparison, ΔDRP between TPS and measured with EPID was 3.54% (3D-CRT), 2.50% (VMAT) for whole brain irradiation and 1.19% (3D-CRT), 2.85% (VMAT) for total lung irradiation.

DISCUSSION

In the present study, EPID-based *in vivo* dosimetry system which is already mounted to clinical linear accelerator was proved as a promising solution for independent verification of the delivered dose in small animal radiation research. According to our analysis, all measurements for all defined scenarios including whole brain and total lung irradiation with 3D-CRT and VMAT techniques were within the clinically acceptable tolerance levels in terms of 3D γ analysis. In point dose comparison at beam isocenter, the maximum point DD was found as 3.54% for whole brain irradiation with 3D-CRT. Similarly, Perks et al.[18] also reported the accuracy of the measured point dose as within 5% for different scenarios including lung tumors (measurement with ionization chamber) and primary subcutaneous or orthotopic tumors (measurement with MOSFET detectors) irradiated in clinical linear accelerator using small animal phantom. Recently, several dedicated software (e.g., EPIgray (Dosisoft, Paris, France), DISO (Università Cattolica S. Cuore, Rome, Italy), Dosimetry Check (Math Resolutions, Columbia, MD, USA), iViewDose (recently is not avaliable) (Elekta AB, Stockholm, Sweden), etc., also provide a 3D γ analysis of calculated dose distribution in TPS and measured transit EPID dose during treatment. In this way, DD can be evaluated slice by slice on CT

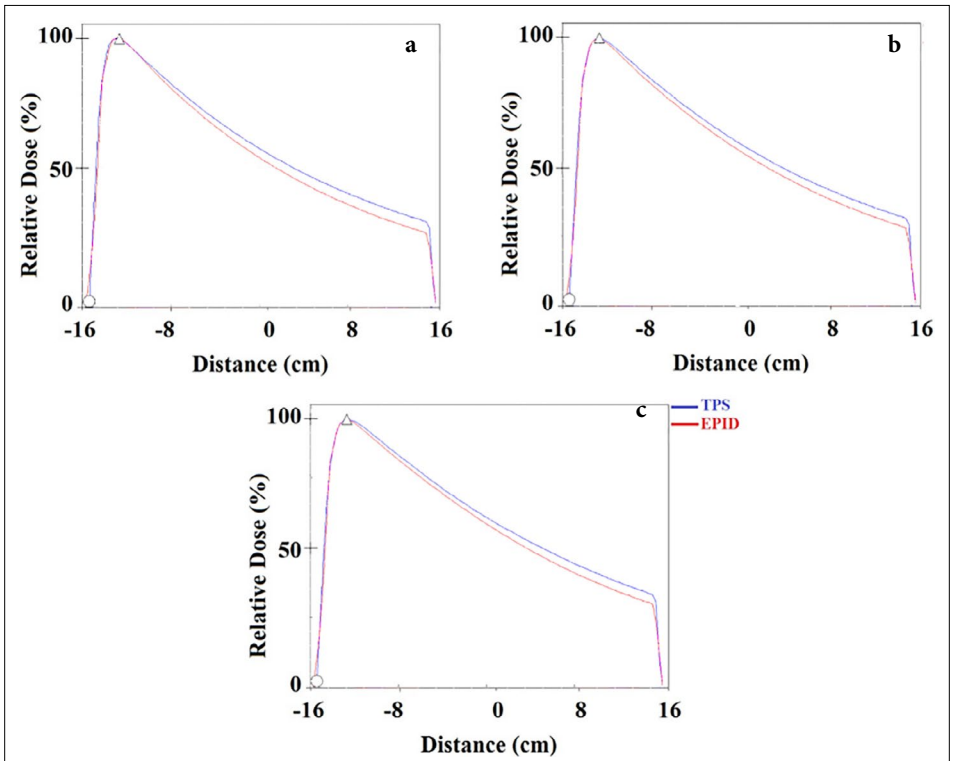

Fig. 4. Measured (red) and calculated (blue) percentage depth dose graphics at defined field sizes; (a) 1×1 cm, (b) 2×2 cm and (c) 4×4 cm using 6 MV photon energy.

data and dose profile of the irradiated beam can also be analyzed in any desired depth and axis.

The advance in 3D printing technology makes it easy to create dedicated small animal phantoms or QA tools with high precision and uniformity.[11–16] In the present study, the maximum (mean) measured differences at multiple points between the modeled and the printed dimensions of the rat phantom were found as 0.5 (0.3) mm and the phantom had good homogeneity and uniformity over the external body. Similar to our findings, Esplen et al.[12] and Price et al.[15] reported that 3D-printed rat phantom revealed an excellent uniformity over the printed product and well matched with the designed model. In addition, Price et al.[15] provided their 3D-printed phantom design and printing methodology as an open source to encourage the pre-clinical researcher about QA and to adopt a common QA standard using the dedicated phantom geometry.

This study has still some limitations that have to be pointed out. The first one is that since the back-projection algorithm used in the clinical version of iViewDose software underestimates the dose values in field sizes smaller than 3.0×3.0 cm, we could not use the clinically commissioned model in the present study. Therefore, we created new models for only commissioned between the field sizes of 1.0×1.0 cm and 4.0×4.0 cm and additional correction factor was used to equalize calculated dose in TPS and measured dose with EPID. Nevertheless, the differences between the calculated and reconstructed dose for PDD measurement were <3% and 5% at 5 cm and 10 cm depth, respectively. The second limitation is that reconstruction algorithm used in iViewDose software is commissioned in homogeneous conditions and inhomogeneity correction is not applied during the reconstruction of the dose distribution, and so measurement was only performed with ho-

Table 1 The results of 3D γ analysis

Treatment plans	γ mean	γ 1%	% γ ≤1
3D-CRT Brain	0.46	1,11	97.39
VMAT Brain	0.50	1,06	97.83
3D-CRT Lung	0.63	2,39	87,78
VMAT Lung	0.66	1,67	86.04

* Passing criteria: γ mean: protocol ≤0.5; minor variation ≤0.7; γ 1%: protocol ≤3; minor variation ≤3.5; % γ ≤1: protocol ≥90; minor variation ≥85

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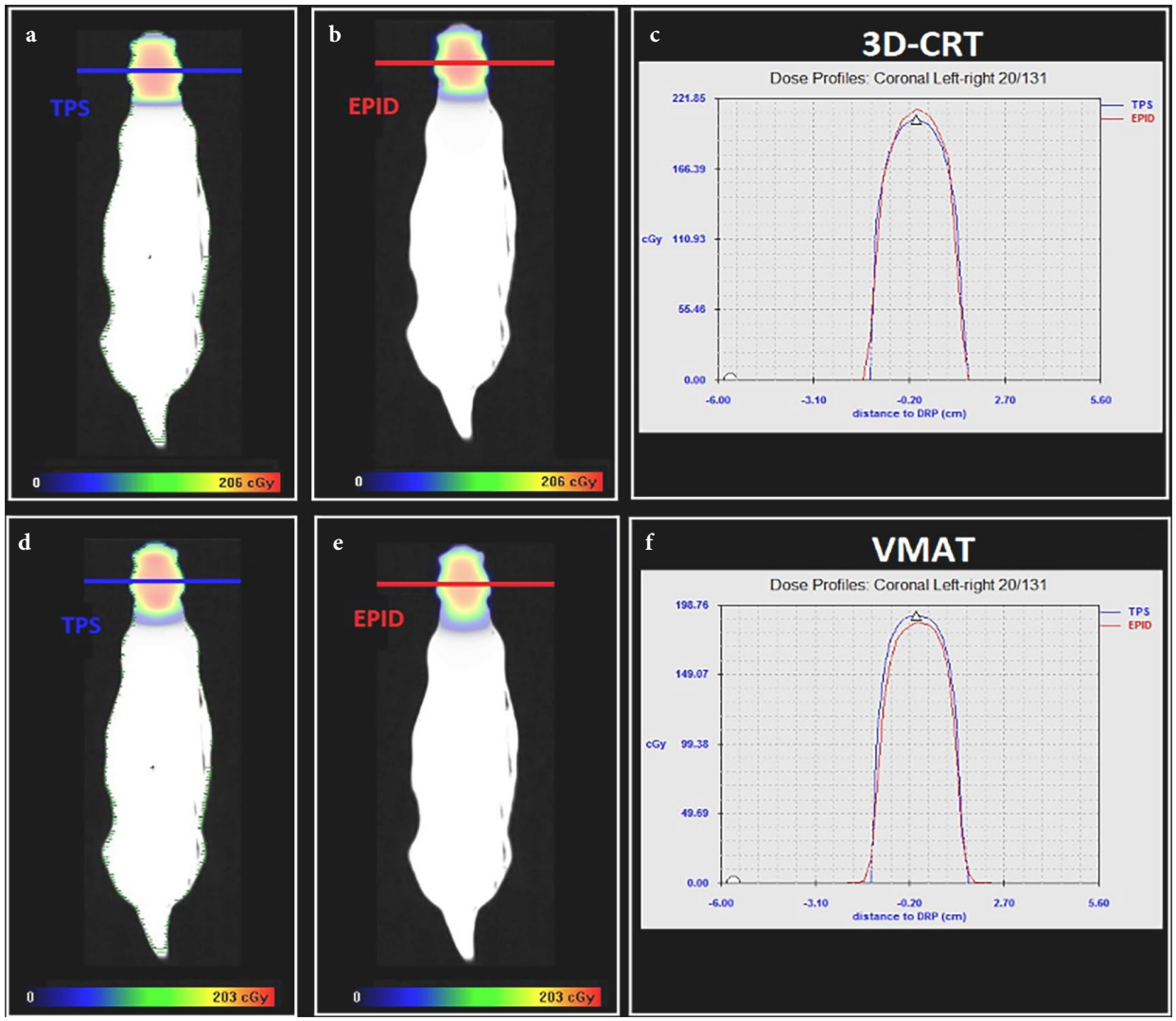

Fig. 5. A coronal view of the calculated (left), EPID reconstructed dose distribution (middle) and comparison of central dose line profile (right) for whole brain irradiation using 3D-CRT (a-c) and VMAT (d-f) techniques.
EPID: Electronic portal imaging device; VMAT: Volumetric-modulated arc therapy.

mogeneous rat phantom. Therefore, in real rat irradiation, especially with heterogeneous medium like lung irradiation, in-aqua *vivo* method can be used to minimize the dose reconstruction errors during calculation, but this approach was not validated for small animal irradiation in the present study. Therefore, this need to be further investigated with the scope of another dosimetric study. The last one is that despite the obvious advantages of EPID *in vivo* dosimetry in preclinical studies, the use of0 EPID as an *in vivo* tool is still limited over worldwide due to the necessity of dedicated software and, recently, this approach does not also seem as a useful tool for the verification of electron beams for both in clinical practice and preclinical studies.

CONCLUSION

As an easily accessible *in vivo* dosimetry tool, EPID system can provide standardization for the verification of delivered dose in small animal radiation research. The extension of this study would be the check of feasibility of EPID dosimetry in real radiobiological experiment for different irradiation scenarios. Nevertheless, there is still need for the whole international community to

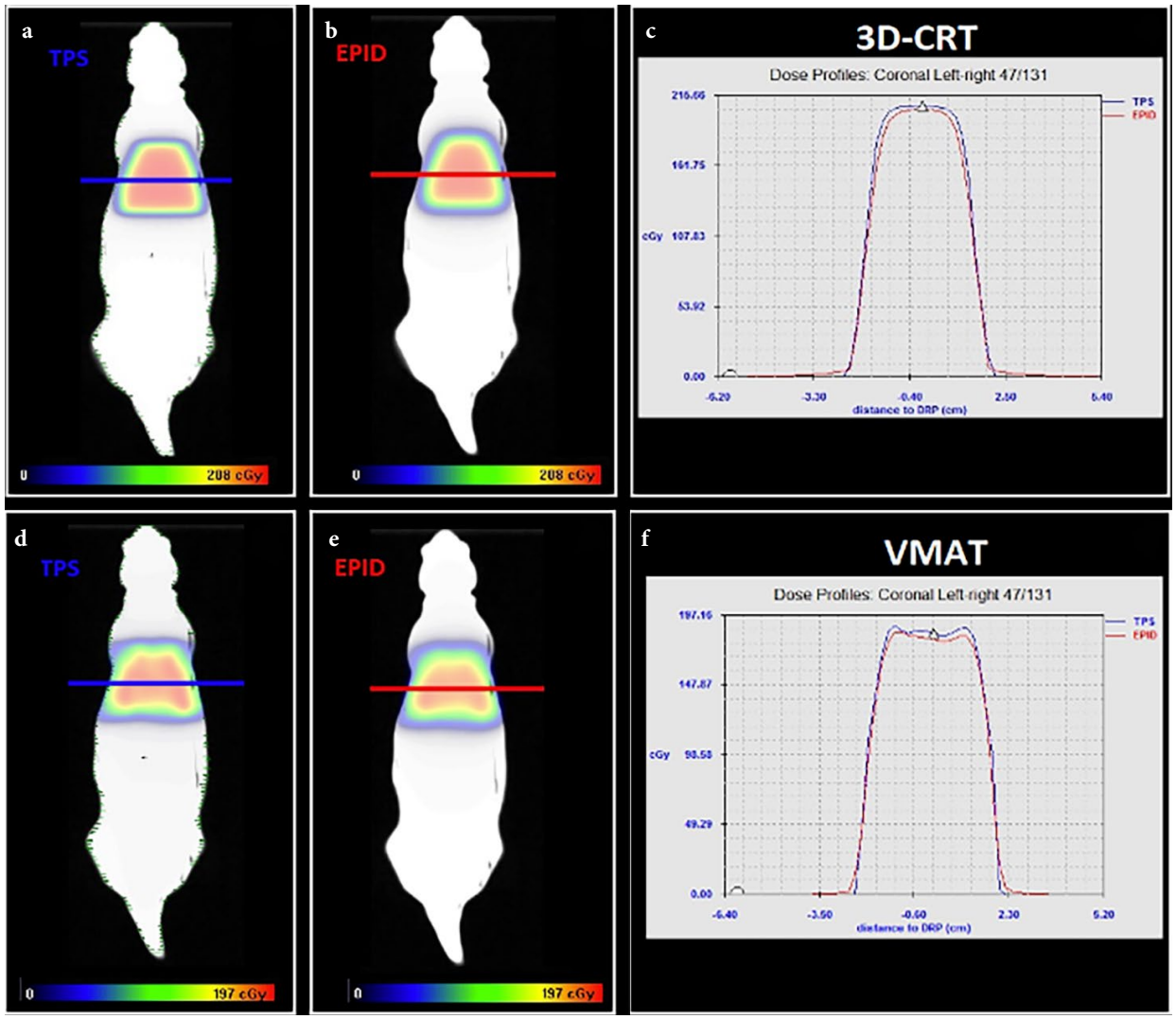

Fig. 6. A coronal view of the calculated (left), EPID reconstructed dose distribution (middle) and comparison of central dose line profile (right) for total lung irradiation using 3D-CRT (a-c) and VMAT (d-f) techniques.
EPID: Electronic portal imaging device; VMAT: Volumetric-modulated arc therapy.

come to a consensus about the standardization of QA protocols for EPID dosimetry in small animal RT with clinical linear accelerator before implementing this approach in routine practice.

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Authorship contributions: Concept – F.B.; Design – F.B., G.Ö.; Supervision – G.Ö.; Materials – F.B.; Data collection and/or processing – F.B.; Data analysis and/or interpretation – F.B., G.Ö.; Literature search – F.B.; Writing – F.B.; Critical review – G.Ö.

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