Radiation Dosimetry of Whole-Body Dual Tracer 18F-FDG and 11C-Acetate PET/CT for Hepatocellular Carcinoma

Short Running Title: Radiation Dosimetry of Dual Tracer PET/CT

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ABSTRACT

Combined whole body dual tracer (18F-FDG and 11C-Acetate) positron emission tomography/computed tomography (PET/CT) is increasingly utilized for staging Hepatocellular Carcinoma (HCC) with only limited studies investigating the radiation dosimetry data of these scans. The aim of the study was to characterize the radiation dosimetry of combined whole body dual-tracer PET/CT protocols.

Methods: Consecutive adult patients with HCC who underwent whole-body dual tracer PET/CT scans were retrospectively reviewed with institutional review board approval. OLINDA/EXM 1.1 was used to estimate patient specific internal dose exposure in each organ. Biokinetic models for 18F-FDG and 11C-Acetate as provided by ICRP (International Commission on Radiological Protection) publication 106 were employed. Standard reference phantoms were modified to more closely represent patient-specific organ mass. With patient-specific parameters, organ equivalent doses from each CT series were estimated using VirtualDose. Dosimetry capabilities for tube current modulation protocols were applied by integrating with the latest anatomic realistic models. Effective dose was calculated using ICRP publication 103 tissue weighting coefficients for adult male and female, respectively.

Results: Fourteen scans were evaluated (12 men, 2 women; mean age, 60 years ±19.48). Patient specific effective dose from 18F-FDG and 11C-Acetate was 6.08±1.49 and 1.56±0.47 mSv for male, 6.62±1.38 and 1.79±0.12 mSV for female patients, respectively. Patient specific effective dose of the CT component, which comprised two non-contrast whole body scans, to male and female patients was 21.20±8.94 and 14.79±3.35 mSv respectively. Thus, the total effective dose
of the combined whole body dual tracer PET/CT studies for male and female patients were 28.84±10.18 and 23.19±4.61mSv, respectively.

**Conclusion:** Patient specific parameters allow for more accurate estimation of organ equivalent doses. Considering the substantial radiation dose incurred, judicious medical justification is required with every whole body dual tracer PET/CT referral. Although radiation risks may have less impact for the population with cancer due to their reduced life expectancy, the information is of interest and relevant for both justification, to evaluate risk/benefit, and protocol optimization.

**Key Words:** PET/CT, dual tracer, CT, radiation exposure, effective dose.
INTRODUCTION

Positron emission tomography/Computed Tomography (PET/CT) has become an indispensable imaging modality for the diagnosis, staging and monitoring of therapy response of a broad range of diseases in adult patients (1,2). Despite the significant clinical benefits provided by PET/CT, the relatively high radiation exposure of patients has prompted a heightened concern from the radiology community and regulatory bodies. PET imaging is one of the more challenging areas of radiation protection in medicine as a result of its combination with CT. In this light, quantification of the potential risk from radiation exposure forms a core responsibility for the PET/CT community. As an important aspect in evaluating the use of PET/CT scanning in medical practice, accurate dosimetry can help in the assessment of procedure justification (i.e., benefit greater than risk) (3).

Hepatocellular carcinoma (HCC) is one of the top three causes of cancer death in many Asian countries. The disease is also believed to be showing an upward trend in America because of the increasing frequency of hepatitis C viral infection (4). Accurate staging of HCC is a prerequisite in selecting the optimal treatment and to determine the prognosis. Diagnostic staging prior to treatment relies on imaging evaluation, primarily using either contrast-enhanced CT or Magnetic Resonance Imaging (MRI).

Besides CT and MRI, both 18F-fluorodeoxyglucose (FDG) and 11C-acetate (ACT) PET imaging have demonstrated a certain degree of capacity to detect and stage HCC (5-9). Because of the mutual complementarity based on tumor cellular differentiation, in the past few years, the combined use of these two tracers has been reported to increase the overall sensitivity for the
detection of primary and metastatic HCC (5-7,9), which suggest that dual tracer PET/CT is an improved comprehensive modality compared to single tracer 18F-FDG PET.

However, whole-body dual tracer PET/CT incurs an increased radiation burden to patients compared with a single tracer PET/CT examination. Since these two biochemical probes are widely used in PET/CT studies of malignancy metabolism in humans, estimation of whole body absorbed doses due to the intravenous administration of 18F-FDG or 11C-ACT and radiation exposure from CT have been reported previously (10-12). To our knowledge, there are limited studies investigating the radiation dosimetry data of whole body dual tracer PET/CT scan for HCC, especially combined with a one-stop triple phase contrast-enhanced diagnostic CT of the liver that is performed in our institution. Referral for dual tracer PET/CT studies must be justified in each case as a first general principle of radiological protection (13). Optimization, or ensuring that the diagnostic information is as high as reasonably achievable while maintaining radiation doses as low as reasonably achievable, is the second general principle in radiologic protection according to ICRP (International Commission on Radiological Protection) (14). It was, therefore, the aim of the present study to characterize the radiation dosimetry of whole body dual-tracer PET/CT protocols so as to aid the evaluation of risk/benefit for justification, and protocol optimization in the clinical work-up of HCC patients.

MATERIALS AND METHODS

Study Population

Institutional review board approval with waiver of patient informed consent was obtained to perform a retrospective study of clinically indicated pre-treatment whole body dual-tracer (18F-FDG and 11C-ACT) PET/CT scans performed on HCC patients at Queen Mary Hospital, a
national tertiary referral center in Hong Kong, from November 2014 through February 2015. Consecutive adult patients who had undergone dual tracer PET/CT for HCC were recruited, and patient data including age, gender, weight, height, body mass index (BMI) were reviewed. For each PET series performed, the amount of 18F-FDG and 11C-ACT administered were obtained from the medical records. At our institution, both the FDG and ACT dose administered were adjusted for patient body weight (7.4 MBq/kg for 11C-ACT, 6.3 MBq/kg for 18F-FDG).

The following CT parameters for each series were extracted from the DICOM headers for organ equivalent dose and effective dose calculation: scanner make and model, kVp, mA, beam collimation, rotation time and pitch. The CT scanner used in the PET/CT machine (Discovery PET/CT; GE Healthcare, Milwaukee, Wis) was a 64-detector CT scanner with tube current modulation capabilities that were utilized.

**Dual-Tracer PET/CT and Contrast CT Protocols**

All patients fasted for at least 6 hours, and the blood glucose concentration was determined before the injection of PET radiopharmaceuticals (all had glucose levels of <8 mmol/L). 11C-ACT (440–590 MBq) was administered intravenously; 11 minutes after the administration of 11C-acetate, a non-contrast limited whole body CT (from cerebellum to pubic symphysis) followed by PET data acquisition was performed. About 15 min after the completion of 11C-ACT imaging, 330–520 MBq of 18F-FDG were injected intravenously. Another non-contrast limited whole body CT followed by PET data acquisition began at 60 min after 18F-FDG administration. This comprised a 'typical' dual tracer PET/CT scan (Protocol A). In our clinical practice, we offered two other protocols which we also evaluated; one with additional initial acetate scans at 2 min after administration of 11C-acetate with a standard unenhanced abdomen
CT scan to improve specificity (Protocol B), and another with additional triple-phase contrast-enhanced protocol for dynamic evaluation of the liver (Protocol C) (Supplemental Table 1 for protocol details). CT protocol was 120 kV, auto-mA, pitch 0.98 and rotation time 0.5 sec.

**Internal Radiation-Absorbed Dose Assessment**

The OLINDA\EXM code (version 1.1, Vanderbilt University, Nashville, TN, USA) was used to determine the organ equivalent dose and effective dose from each PET series with patient-specific parameters ([15]). The code allows for the modification of standard reference phantoms to more closely represent patient-specific factors—for the present study, such as patient weight and corresponding organ mass. We used the standard anthropomorphic models as well as models modified to represent patients’ weight and height (i.e., organ sizes of the phantom models used by OLINDA were modified to reflect the patient specific mass of the organ as described by Marine et al and Clark et al ([16-18])). Biokinetic models for 18F-FDG and 11C-ACT as provided by ICRP publication 106 ([19]) were employed. Modified adult male, adult female models in OLINDA’s phantom library were utilized to generate patient specific organ equivalent dose, and then tissue weighting factors from ICRP Publication 103 ([3]) were used to generate patient specific effective dose conversion factor (mSv/MBq). These factors were multiplied by injected activity (MBq) for each PET study to obtain an estimation of effective dose.

Absorbed doses $D_T$ to a tissue or organ $T$ resulting from intravenous administration of an activity $A$ of 18F-FDG and 11C-ACT were also estimated by means of dose coefficients $\Gamma_{FDG_T}$ and $\Gamma_{ACT_T}$ provided by the ICRP Publication 106 ([19]) for a variety of organs and tissues of the
adult hermaphrodite MIRD (Medical Internal Radiation Dose) phantom. The formula for
effective dose estimation is described in ICRP 103 (3).

**External Radiation-Absorbed Dose Assessment**

With patient-specific weight and scan parameters, organ equivalent dose and effective dose
from each CT series was estimated using the VirtualDose (20), which has a comprehensive organ
equivalent dose database derived from Monte Carlo calculations (using the Monte Carlo N
Particle system v2.6 code) involving a suite of modules for CT, cone beam CT and PET/CT
dose reporting, BMI-adjustable anatomically realistic patient phantoms and multi-detector CT
scanners with tube current modulation (TCM) protocols and PET/CT protocols. VirtualDose
allows users to specify the scanner type and scanning parameters. Moreover, dosimetry
capabilities for TCM protocols were applied by integrating a dose information extraction
function module, which could extract dose (e.g., CTDI, DLP, etc.), CT scanner (e.g., kVp, mAs,
scan region, scan protocol, etc.) and patient (weight, age, gender, etc.) information from the
DICOM file headers. These patient-specific parameter information obtained were used as inputs
into VirtualDose, as are start and stop locations of the series, which were interactively selected
using a diagram of the anatomically realistic phantoms provided, to calculate the organ dose and
effective dose for the specific patients. Limited whole-body effective dose in mSv were then
calculated for each CT series for each patient using the latest ICRP publication 103 tissue
weighting coefficients (3), which were consistent with the conversion factors for PET.

For comparison, effective dose from CT examination was also estimated by a generic shortcut
method using DLP and $k$ coefficients from the ICRP publication 110 (21).

**Statistical analysis**
Descriptive and summary statistics were performed with a spreadsheet application (Excel 2007, Microsoft, Redmond, WA).

RESULTS

Study Population Statistics

Of the total 14 dual-tracer PET/CT scans, 12 (85.7%) were performed on male patients and 2 (14.3%) were performed on female patients. Subjects ranged in age from 52 to 86 years (60±19.48 years). The subjects’ weight ranged from 51 to 98 Kg (67.57±27.9Kg), height ranged from 156 to 177 cm (165.57±12.6 cm), and BMI ranged from 17.56 to 36.0 (24.58±8.98) (Supplementary Table 2).

Radiation Doses

18F-FDG and 11C-ACT injected doses were 328.77±89.78 MBq and 481.79±135.37 MBq, respectively. Patient specific effective dose from 18F-FDG and 11C-ACT calculated by OLINDA were 6.08±1.49 and 1.56±0.47 mSv for male, 6.62±1.38 and 1.79±0.12 mSV for female, respectively. Effective dose estimated by the ICRP publication 106 for 18F-FDG and 11C-ACT for adult reference phantoms (18,22) were 6.25±1.71 mSv, and 1.69±0.47 mSv, respectively. Doses from 18F PET scanning to the brain, heart and bladder were appreciably higher than to the other organs and were 12.83, 14.52 and 44.57 mSv for male, and 11.58, 15.16 and 49.62 for female (other organs doses ranges from 2.7 to 7.42 mSv for male, and from 2.48 to 7.99 mSv for female), respectively; doses from 11C PET distributed primarily in kidneys, liver and heart and were higher than the other organs and were 27.64, 7.91 and 6.28 mSv for male, and 29.02, 8.96 and 8.37 mSv for female (other organs doses ranges from 0.44 to 4.45 mSv for male, and from 0.50 to 5.30 mSv for female), respectively. The measured dose coefficients,
organ equivalent doses and effective doses from 18F-FDG and 11C-ACT scans are listed in Supplemental Table 3 and 4.

For the CT component, the patient specific effective dose of a typical dual-tracer PET/CT which comprised two limited whole-body non-contrast CT scans was calculated with VirtualDose. The effective dose to male and female patients was calculated to be 21.20±8.94 mSv and 14.79±3.35 mSv respectively. The CT reference phantom effective doses calculated by k factor from ICRP publication 110 (21) were 30.55±10.58 mSv and 20.73±5.12 mSv for male and female patients, respectively. The CT organ equivalent doses from a typical dual tracer PET/CT (Table 1), with an additional non-contrast abdomen CT (for initial C11-acetate PET scan) or an additional triple-phase contrast-enhanced abdomen CT (Supplemental Table 5 and 6 respectively).

The total effective doses of the typical combined PET/CT studies, calculated by summing the effective doses of CT and dual tracer PET scan, were 28.84±10.18 mSv for male patients and 23.19±4.61mSv for female patients, respectively (Table 1). The total effective doses of dual tracer PET/CT with an additional non-contrast abdomen CT and a triple-phase contrast CT are also listed in Supplemental Table 5 and 6.

**DISCUSSION**

Although risk from radiation exposure to the individual may be of less impact for the population known to have cancer because of their reduced life expectancy (23), the information is still of importance to the evaluation of risk/benefit for justification, and relevant to protocol optimization and personnel protection (24). The use of 18F-FDG and 11C-ACT for the evaluation of patients with HCC are known to provide complementary biochemical sensitivities
to identify tumor cells with various degrees of differentiation. Currently, to our best knowledge, we are not aware of published studies formally assessing radiation-absorbed dose from whole body dual tracer PET/CT to HCC patients. Our study assessed dual tracer PET/CT-based radiation dosimetry of 18F-FDG and 11C-ACT for all organs based on patient specific data and the latest recommendation from ICRP publications; and the derived overall effective dose from dual tracer PET/CT scan with a mean administered FDG and ACT activity of 328 MBq and 481 MBq, respectively, was calculated to be up to about 29 mSv, and up to about 57 mSv if a one-stop triple-phase contrast enhanced abdomen CT was included at the same setting. These results assist in evaluating justification and optimization of protection of the procedure.

For internal absorbed dose assessment, OLINDA\EXM was used to perform dosimetry calculations for the various body organs, which is currently unique in the field of nuclear medicine dosimetry in that it has received approval from the FDA to be distributed after 510(k) premarket notification (15). This code allows calculations for 814 radionuclides and a wide variety of adult, pediatric and pregnant female phantoms; furthermore, it also allows users to modify organ masses in the phantoms for more patient-specific dose calculations when it may be known that an organ is larger or smaller than that assumed in the reference phantom. Moreover, organ doses calculated by OLINDA\EXM based on reference phantoms representing the average patient were found to be in good agreement with patient specific Monte Carlo mean dose estimates (25). We also compared organ equivalent dose and effective dose calculated by OLINDA\EXM with those by the dose coefficients from ICRP publication 106 (19). The dose estimate difference between these two methods may be due to the dose coefficients provided in publication 106 which are computed by age- and gender-averaging, and moreover, ICRP publication 106 still uses tissue weighting factor defined in ICRP publication 60 (26), instead of
the latest ICRP publication 103 (3) applied in the present study. Patient specific organ masses were derived from previous reports on variations in the mass of different body organs in relation to stature and BMI (16-18,27,28). Marine et al, and Clark et al (16,17) described phantoms that model different body types in a series of percentile height phantoms to evaluate how specific absorbed fractions may vary with height and weight differences across the human population. As Stabin stated (29), the biokinetic model used to calculate the dose is one of the major uncertainties in the evaluation of radiation doses for radiopharmaceuticals. If careful patient-specific dosimetry is performed, with attention paid to accurate measurement of individual organ volumes, many of the biokinetic model uncertainties can be minimized, and the total uncertainty in the individual dose estimate can be reduced to perhaps ±10%-20% (29).

With patient specific data, the effective dose from FDG PET scanning was 6.08 mSv for male and 6.62 mSv for female, respectively. These values are consistent with the dose estimates reported in the literature (30-33), and also with the dose estimates from ICRP publication 106 (19). The measured radiation-absorbed doses from ACT PET scanning differ markedly from previously determined estimates of Seltzer et al (11). Because the dosimetry methodologies used by us and by Seltzer et al (11) were different; the difference between the dose estimates obtained is mainly due to the difference in the biokinetic data used to create the kinetic models. Because the kinetic data that we used were from ICRP publication 106 (19) which are more complete, representing all major source organs, more accurate dosimetry estimates are likely possible. We, therefore, believe our estimates of internal doses to be reasonably accurate and represent the best estimates of such internal absorbed doses for our HCC patient population on the basis of the models used.
Currently, a few CT dose calculation tools, including ImPACT Dose (34), CT-Expo (35), CTDOSE (36), and eXposureTM (http://www.radiologysolutions.bayer.com/products/ct-dosemanagement/rep/) report organ doses based on calculations on simplified stylized anatomic models that are anatomically crude but widely used for several decades for practical applications with the standard mathematic representations of the reference man (37) and other representative phantoms in radiation protection, nuclear medicine, and medical imaging (38,39). Recently, more realistic models, developed by Xu et al (40), based on imaging data from human subjects, including updated anatomic information from reference data on adults and children (48) can be used in place of traditional stylized models for more accurate dose estimates (41).

The use of VirtualDose improves upon existing dose calculation tools by considering the latest CT scanners based on the newer realistic models developed by Xu et al (40): 25 available models, including adult male and female models of various body mass, pediatric models from newborn through adolescent and pregnant models of three gestational ages. Standard CT models have been modeled and patient dose calculated using Monte Carlo radiation transport methods, with corrections applied to represent the behavior of most commonly available CT scanners. The Monte Carlo results suggest that the organ equivalent dose estimates can be different by a margin as great as 277% between our calculations and those derived from the use of earlier stylized MIRD-type phantoms (42). VirtualDose enabled us to assess organ equivalent dose under TCM schemes, which has now been frequently implemented in clinical body CT exams for a decade. Quantifying the magnitude of organ dose under TCM, however, is practically challenging. The main challenge relates to the fact that the x-ray radiation is dynamically altered over the patient habitus for TCM examinations. VirtualDose provides accurate estimates of organ equivalent dose, based on modeling change of irradiation condition and integrating it with the anatomical
feature of the patients. Therefore, the use of this dose tool is expected to improve both the accuracy and usability in reporting CT doses.

The limited whole body CT effective dose to reference phantoms determined by $k$ factor (0.0019 for chest-abdomen-pelvis, the publication 110 ICRP) was overestimated in the present study compared with the patient specific effective dose calculated by VirtualDose. This finding is not surprising because $k$ factor is an age and gender averaged parameter, based on data averaged over many scanner makes and models; moreover, effective dose is defined by ICRP as a single parameter to reflect overall risk averaged over all ages and both sexes for a reference patient (3), and is not a physical parameter that can be measured, which is always computed through multiple steps and approximations. It should be noted that OLINDA\EXM and VirtualDose were used in the present study to calculate organ equivalent doses, and then effective doses were calculated using ICRP publication 103 tissue weighting coefficients (3).

The present study is limited because it was performed for a small sample size cohort (n=14) that was recruited consecutively in the first four months of the implementation of such scans for a specific population with HCC in a single center. This limitation should be taken into account in the generalization of the conclusions. However, as noted above, a review of our results against literature values shows general consistency.

CONCLUSION

Patient specific parameters (e.g., weight, and height) identified from patient data allow for more accurate estimate of organ equivalent doses. Considering actual patient specific characteristics resulted in lower organ equivalent dose estimates than traditional reference phantoms and models. We estimated an average patient effective dose from whole-body dual
tracer PET/CT examinations of about 29 mSv. Considering the substantial radiation dose to patient compared with individual PET/CT examinations, a judicious medical justification has to be made with every whole body dual tracer PET/CT referral. This is especially important when its clinical utility is less well established. Although radiation risks may be of less impact for the population with cancer due to their reduced life expectancy, the information is still of importance and relevant for both justification to evaluate risk/benefit and protocol optimization.

DISCLOSURE

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REFERENCES


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*Patient specific average dose calculated by OLINDA; †Two whole body CT dose calculated by VirtualDose; ‡ Effective dose estimated by ICRP publication 103; § Ovaries for female patients/Testes for male patients.
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