Quantitative PET/CT imaging and dosimetry of 89Zr labelled compounds

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Summary and Future perspectives

7.1 Summary

Immuno positron emission tomography (immunoPET) is a new diagnostic tool that combines the specificity of a monoclonal antibody for targeting specific antigens (over-expressed in tumours) and the high sensitivity of a PET scanner. In this thesis, new methods for PET/computed tomography (PET/CT) based *in vivo* quantification of ^{89}Zr labelled monoclonal antibodies (mAbs) are presented, investigating their impact on accurate estimation of organ absorbed and effective radiation doses. In clinical research, first-in-human PET studies of radiolabelled mAbs can provide information on the optimal drug dose for tumour targeting, as well as on uptake in critical (normal) organs to predict toxicity. In addition, pre-therapy PET scans may have added value in patient selection, as they may give insight in receptor expression in tumours and drug accumulation over time. Another important aspect of PET imaging of radiolabelled mAbs is whether the dose deposited to normal tissue and whole body remains within certain limits. According to ICRP (1), an investigation that involves an effective radiation dose of > 10mSv is regarded to have a moderate level of risk. ImmunoPET studies may exceed the latter dose limit, but this can be justified if the benefit of the patient is substantial such as prevention of serious disease or saving of life. In conventional [^{18}F]FDG PET/CT studies an important aspect of quantification in multicentre studies is harmonization of imaging procedures, thereby ensuring comparable quantitative data between institutes. Although the same harmonization procedures can be also applied to ^{89}Zr PET/CT studies, additional radionuclide specific factors (e.g. low count rates, emission of cascade γ rays) need to be considered and adjustments to the harmonization protocol may be required. This thesis also deals with PET/CT based radiation dosimetry for ^{89}Zr-cetuximab with special emphasis on determining the red marrow absorbed dose. In addition, a fast and accurate method for semi-automatic delineation of organs in successive scans was developed, allowing for time-efficient estimation of organ absorbed doses. Finally, an automatic red marrow delineation method based on active contour was developed and its impact on accurate estimation of activity concentration and absorbed dose was investigated against a manual delineation method. This is of particular interest as red marrow can be the dose limiting tissue in immunotherapy applications.

Chapters 2 and **3** describe and validate harmonization strategies for [^{18}F]FDG and ^{89}Zr PET/CT multicentre studies, respectively. The aim of this part of the thesis was to explore whether it is feasible to acquire quantitatively accurate and consistent PET/CT images (for ^{18}F or ^{89}Zr) in

a multicentre setting.

Chapter 2 deals with harmonization strategies for [^{18}F]FDG PET/CT studies in multicentre trials. Phantom and clinical data were reconstructed using various settings (i.e. number of iterations and subsets, time-of-flight kernel width, and blob radius) and were analysed using three different methods to define volumes of interest (VOI: $\text{VOI}_{A50\%}$, VOI_{3Dpeak} and VOI_{max}). This variation in settings allowed for simulating, to a certain extent, differences in PET image characteristics that may be encountered in multicentre trials. The phantom images showed variation in recovery coefficients (RC) for different reconstruction settings and VOI types. It was shown that the modified EANM/NEMA phantom was best suited for harmonizing image quality and quantification, whereas the SNM-CTN phantom was better suited for assessing lesion detectability. For both phantom and clinical data, $\text{VOI}_{A50\%}$ and VOI_{max} showed similar (high) sensitivity of RC and standardized uptake value (SUV) results to variations in reconstruction settings. A substantially lower sensitivity was obtained for VOI_{3Dpeak}. Therefore, VOI_{3Dpeak} appears to be the most suitable VOI for use in multicentre studies.

Extending this harmonization concept to a completely different class of radiopharmaceuticals, **Chapter 3** investigates the feasibility of accurate quantification and harmonized image quality in multicentre ^{89}Zr PET/CT studies. Accurate quantitative data in ^{18}F PET/CT multicentre data require standardization of image acquisition, reconstruction and analysis procedures, as prescribed in the European Association of Nuclear Medicine guidelines for tumour imaging and implemented in the EARL accreditation program. For ^{89}Zr, however, additional factors should be considered, i.e. the emission of non-prompt 900 keV γ rays after each positron emission may affect cross calibration between PET/CT scanner and local dose calibrator. In addition, low count rates due to low injected dose and late imaging time may lead to degradation of image quality. To this end, a method that consists of certain additional steps for EARL accredited scanners, i.e. calibration of the local dose calibrator to a common dose calibrator and post-reconstruction smoothing of images acquired on Gemini or Discovery scanners is implemented. In addition, use of VOI_{3Dpeak} for analysis of activity concentrations in lesions can minimize interscanner differences. This method led to improved accuracy in measuring local activity concentrations and minimized RC variability for each sphere across all PET/CT scanners, enabling quantitatively accurate multicentre ^{89}Zr PET/CT studies with harmonized image quality.

Chapter 4, **5** and **6** focus on quantification and dosimetry of ^{89}Zr-

cetuximab PET/CT studies. The wider purpose of the studies described in this part of the thesis is the development of novel methods for extracting organ VOI, allowing for time-efficient and accurate estimation of both organ time activity curves and dosimetry of ^{89}Zr PET/CT studies.

Chapter 4 reports on PET/CT based whole body dosimetry of ^{89}Zr-cetuximab with special emphasis on determining red marrow absorbed dose. Whole body PET/CT scans as well as blood samples were obtained 1, 24, 48, 94 and 144 h post injection. Red marrow activity concentrations were calculated from manual delineation of the lumbar vertebrae (image based approach) and from blood samples assuming a constant red marrow to plasma activity concentration ratio (plasma based approach). The (self and total) red marrow and organ absorbed doses as well as the effective whole body absorbed dose were obtained using dose conversion factors from OLINDA/EXM 1.1. The plasma based approach deviated by –21% in self dose and –6% in total dose from the image based one. A simplified dosimetry approach with only three time points (1, 48 and 144 h) was also evaluated and the organ dose estimates obtained with this approach deviated by at most 5% from the full dosimetry approach. The highest ^{89}Zr absorbed dose was observed in liver at 2.60 ± 0.78 mGy·MBq^{-1}, followed by kidneys, spleen and lungs, whilst the effective whole body dose was 0.61 ± 0.09 mSv·MBq^{-1}. Although total red marrow dose estimates obtained with image and plasma based approaches only differed by at most 6%, the image based approach is preferred, as it accounts for non-constant red marrow to plasma activity concentration ratios. This may be of particular importance in radio-immunotherapy using mAbs labelled with pure or nearly pure β^- emitters (^{90}Y or ^{177}Lu), where only the self dose component is relevant in red marrow dose estimation. In this case discrepancies in self dose, when using the plasma based approach, may exceed 20% and the image based approach should be used. The simplified approach using only three time-points appeared to be feasible, reducing logistical costs and scanning time required.

The purpose of the study described in **Chapter 5** was to develop and validate simplified VOI delineation methods that would enable accurate and time-efficient absorbed dose estimates for ^{89}Zr PET/CT studies using ^{89}Zr-cetuximab as an example. To this end, simplified manual VOIs were drawn independently on CT scans using various voxel sizes. In addition, rigid and non-rigid registration algorithms were used to enable projection of the VOIs from the first CT scan onto all successive CT scans of the same patient. Dice similarity coefficients and Haussdorf distances were used to assess the performance of the various registration strategies. Organ total activity,

organ absorbed dose and effective dose were calculated for all methods. Semi-automatic delineation based on non-rigid registration showed excellent agreement for lungs and liver (DSC: 0.90 ± 0.04; 0.81 ± 0.06) and good agreement for spleen and kidneys (DSC: 0.71 ± 0.07; 0.66 ± 0.08). Hausdorff distance ranged from 13 mm to 16 mm depending on the organ. Simplified manual delineation methods, in liver and lungs, performed similarly as semi-automatic delineation methods. For kidneys and spleen, however, poorer accuracy in total activity and absorbed dose was observed, as voxel size increased. Organ absorbed dose and total activity based on non-rigid registration were within 10%. The effective dose was within ±3% for all VOI delineation methods. In summary, a fast, semi-automatic and accurate delineation method based on non-rigid registration was developed for determination of organ absorbed and effective dose of ^{89}Zr-cetuximab, which may also be applied to other long-lived radionuclides.

In **Chapter 6**, the impact of manual and automatic VOI delineation methods on accurate estimation of bone marrow activity concentrations and absorbed doses of ^{89}Zr PET/CT studies was investigated. VOIs in the lumbar vertebrae component of the spine were drawn manually on all five CT scans of each patient. In addition, the bone marrow volume of the lumbar vertebrae was delineated using an active contour method based on an iterative optimization scheme applied to the CT scan. The (self and total) red marrow absorbed doses were obtained using dose conversion factors from OLINDA/EXM 1.1. Average percentage differences in red marrow activity concentrations and total absorbed doses between manual and automatic methods were 5% and 3%, respectively. In conclusion, this automatic method can be used for dosimetry purposes, obviating the need for manually defining VOIs in a series of CT scans.

7.2 Future perspectives

Further research can be directed towards the development of an atlas based VOI definition method for whole body studies, as this would enable truly automatic VOI extraction. This will, however, require a large PET/CT database that can serve as basis for the production of different probabilistic templates tailored to patient specific characteristics. VOI probability maps, produced on the basis of a database of MR images, have been used extensively in brain PET studies, providing an objective and reproducible way to assess regional brain values from PET scans (2). Unlike the brain, the other human organs (i.e. liver, lungs, heart) may enlarge, shrink, and/or move

making it more challenging to generate VOI probability maps. Nevertheless, efforts to generate such VOI templates is important, as it will obviate the need for manual VOI delineation and therefore only require minimal observer intervention.

Unlike ^{89}Zr, ^{124}I has a complex decay scheme that poses specific challenges to PET/CT imaging. Prompt emission of γ rays in ~50% of the disintegrations may introduce quantitative bias and degrade image quality. This necessitates the development and validation of prompt γ correction techniques. However, it should be noted that differences in prompt γ correction algorithms between different PET/CT systems will lead to incomparable quantitative parameters. Such issues may be tackled again using a multicentre calibration procedure (3), similar to the approach in the present thesis for ^{89}Zr.

References

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