IV Geant4 International User Conference at the physics-medicine-biology frontier

Internal dosimetry of salivary glands in PSMA-targeted PET/CT: a Monte Carlo based study

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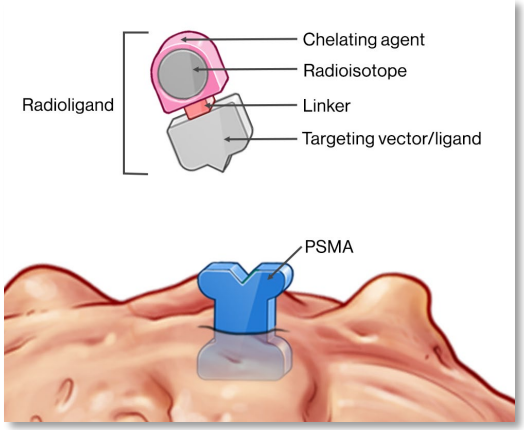
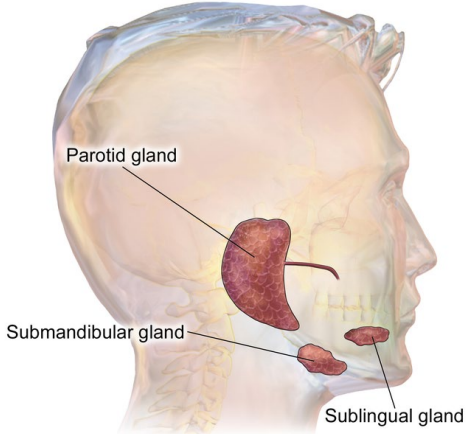
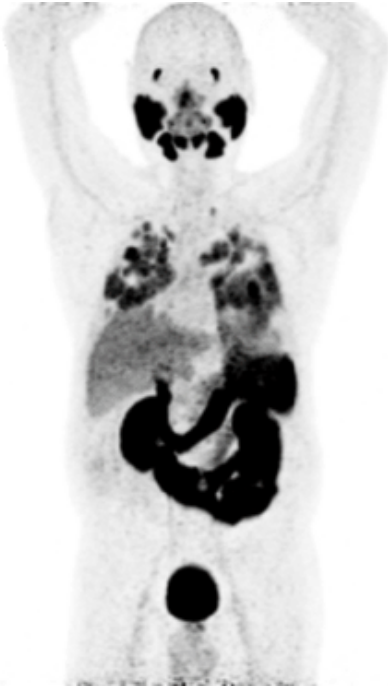
Context

- Prostate-Specific Membrane Antigen (PSMA) radiolabelled ligands are used for diagnosis and therapy of prostate cancer
- Salivary glands (SGs) also exhibit high PSMA-ligands uptake → are the dose-limiting organ in PSMA-targeted therapies
- SG dosimetry is usually performed adopting simplified approaches (e.g. organ-level MIRD) and approximated geometries (e.g. SGs treated as a unique organ)





Salivary Glands



Boxtel et al. 2020
Theranostics **10** 2273-2283

Aim of the study

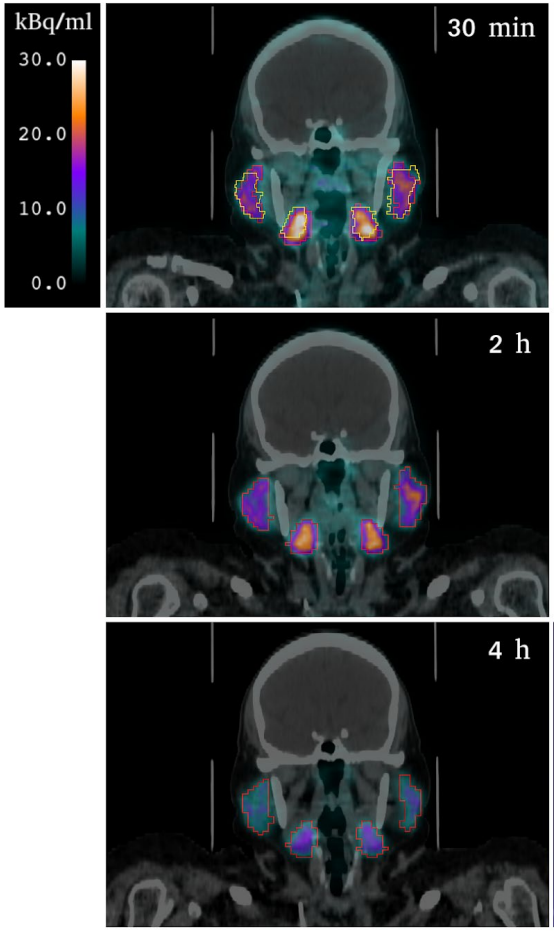
- Perform 3D voxel-level patient-specific dosimetry of salivary glands ^{18}F-PSMA-1007 PET/CT:
  - Separately for left and right parotids and submandibular glands
  - Using GATE/GEANT4 direct Monte Carlo simulations with tomographic imaging as input

- Compare with other simplified dosimetric methods:
  - Spherical method of OLINDA/EXM 2.1
  - Ellipsoidal method by Amato et al. [1]
  - MIRD approach with OLINDA's and OpenDose's organ-level S-factors

[1] Amato et al. 2014 *AAPP* **92**(1) A1, https://doi.org/10.1478/AAPP.921A1

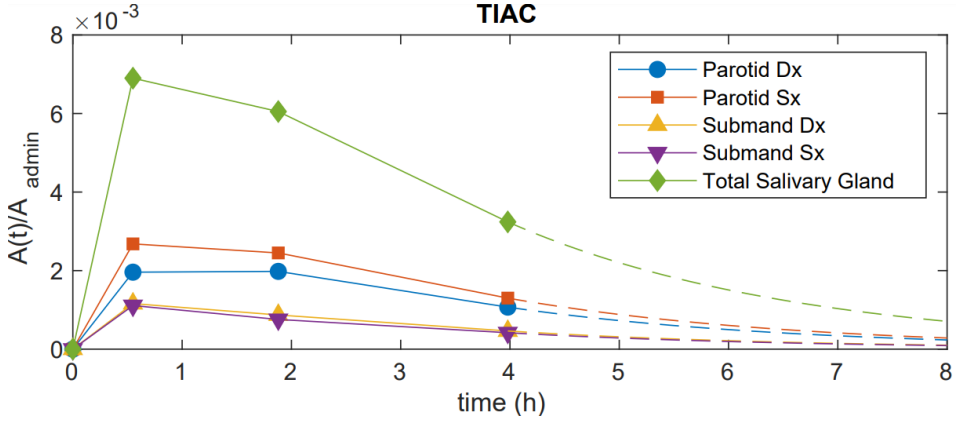
Patient data

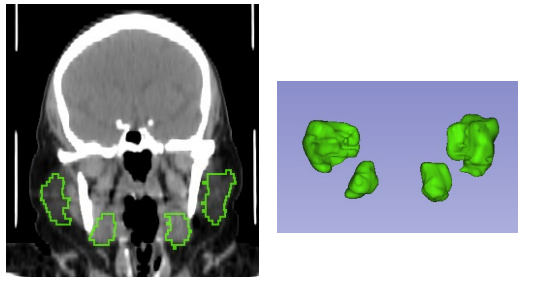
- 5 patients with prostate cancer recurrences enrolled ("Mater Domini" Hospital of Catanzaro, Italy)
- Each one underwent 3 sequential PET/CTs of head-neck at 30 min, 2 h and 4 h after ^{18}F-PSMA-1007 injection

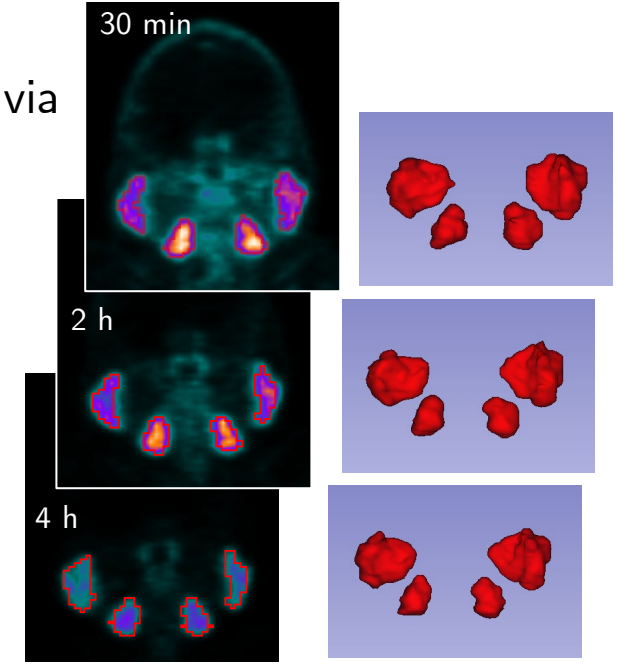


VOIs segmentation and time-activity analysis

- Morphologic VOIs segmentation on 30 min CT (manual)
  - → vol. and mass of SGs (density 1.045 g·cm^{-3} from ICRP 89)
- Functional VOIs segmentation on each ^{18}F-PSMA-1007 PET (thresholding: 25% of the max A(t) in SGs [2])
  - For simplified methods:
    - → total normalized activity ($A(t)/A_{admin}$) in each VOI
    - → Time-Integrated Activity Coefficients (TIACs) via trapezoid + physical decay tail integration







[2] Hobbs et al. 2013 *Q J Nucl Med Mol Imaging* **57**(1) 79–91

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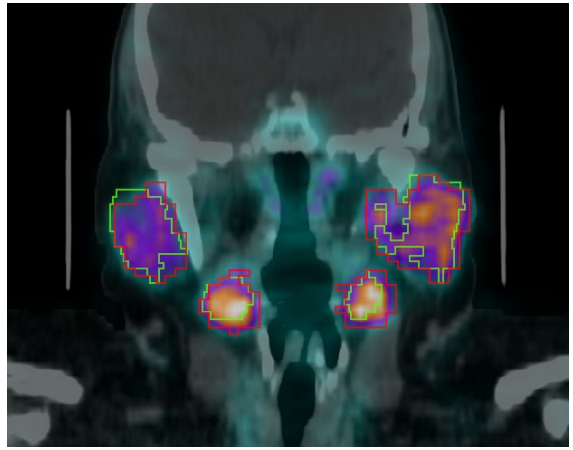
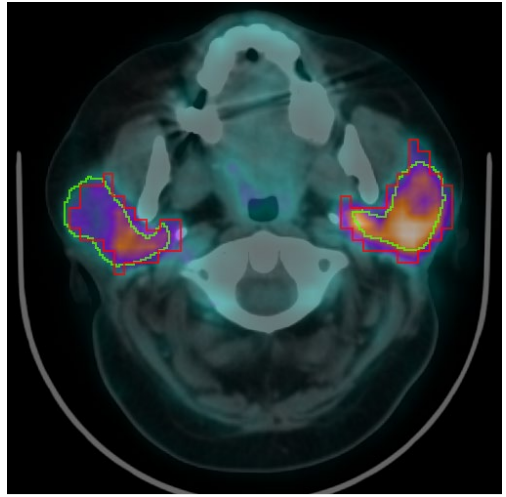




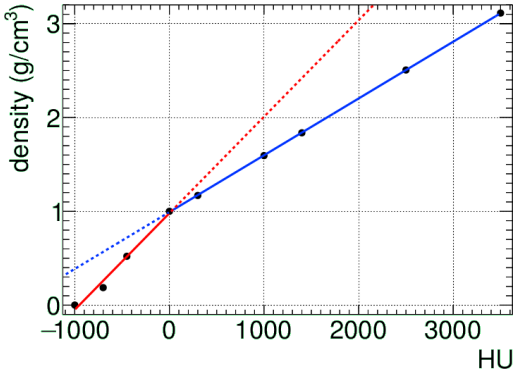
- Purpose:
  - Take into account activity spill-out and non-optimal spatial matching of PET activity distribution with respect to CT morphology

[2] Hobbs et al. 2013 *Q J Nucl Med Mol Imaging* **57**(1) 79–91

GATE/GEANT4 Monte Carlo simulations (1/3)

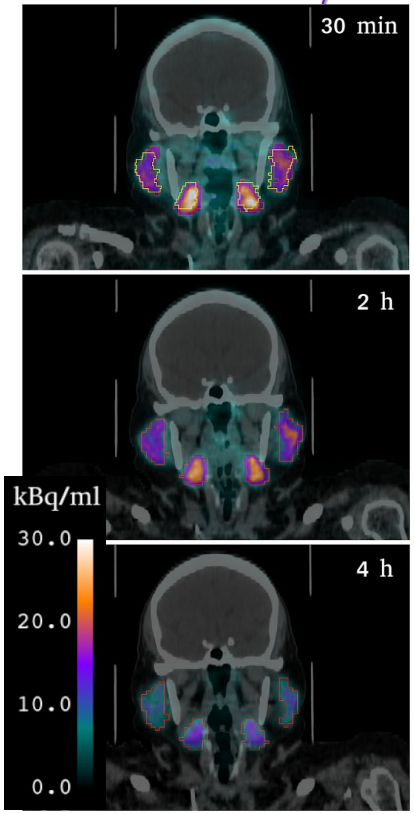
Monte Carlo simulations with GATE 9.1 (GEANT4 10.7) using tomographic imaging as input

- CT → voxelized phantom of patient's body: HU to density conversion via *Automated HU stoichiometric calibration* according to [3], *density tolerance* of 0.01 g/cm^3, materials in Tab.
- PET → radionuclide (^{18}F) spatial decay probability via *linear translator* of *imageReader*



G4 Materials (ICRP)	HU intervals	ρ (g/cm^3)
AIR	HU ≤ -900	ρ ≤ 0.10
LUNG	-900 < HU ≤ -150	0.10 < ρ ≤ 0.85
ADIPOSE_TIS.	-150 < HU ≤ -50	0.85 < ρ ≤ 0.94
SOFT_TIS.	-50 < HU ≤ 290	0.94 < ρ ≤ 1.2
BONE_CORT.	HU > 290	ρ > 1.2

PET/CTs



[3] Schneider et al. 2000 *Phys Med Biol* **45** 459-478

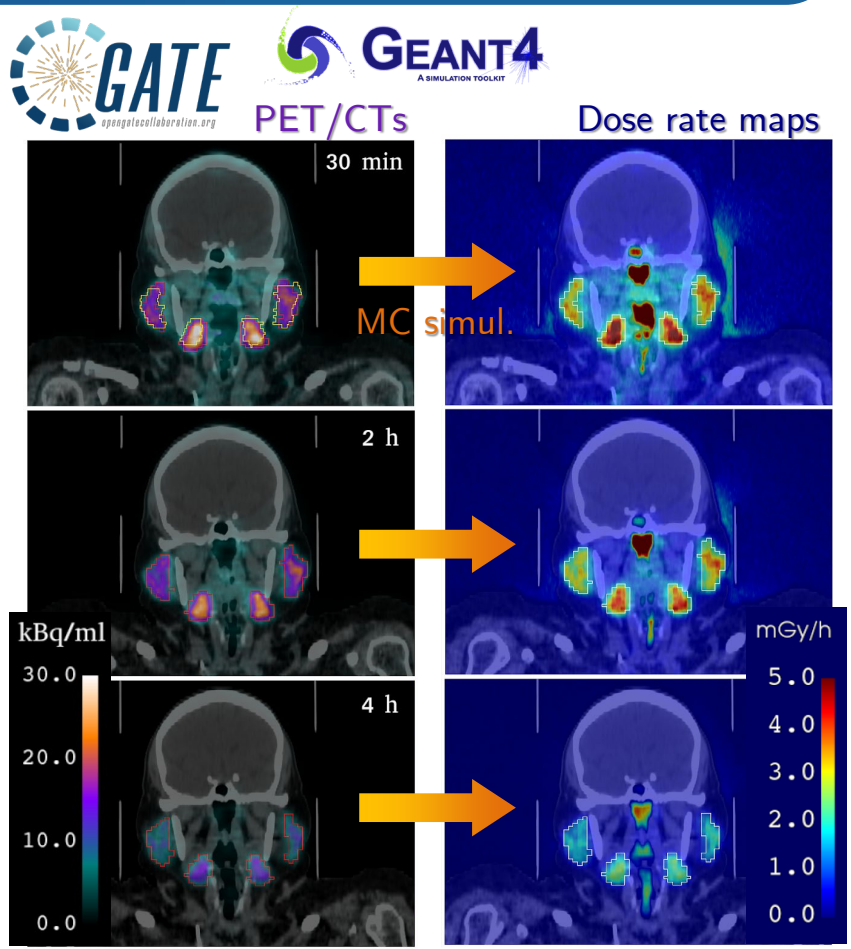
GATE/GEANT4 Monte Carlo simulations (2/3)

Monte Carlo simulations with GATE 9.1 (GEANT4 10.7) using tomographic imaging as input

- Simulations settings:
  - ^{18}F decays: *G4RadioactiveDecay*
  - Physics List: *G4EmStandard_opt4*
  - range cuts: 0.1 mm
  - absorbed dose scoring: *DoseActor* with *MassWeighting* algorithm, CT resolution
  - $N_{evts} = 2{\cdot}10^8$ for each simulation

- For each time-point: absorbed dose rate ($\dot{D}(t)$) map

$$\dot{D}^{ijk}(t) = D_{MC}^{ijk}(t) \cdot A_{FOV\ PET}(t)/N_{evts}$$



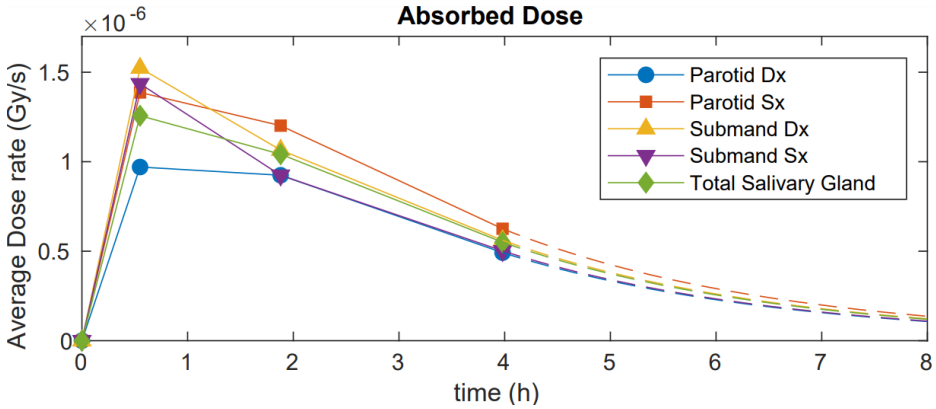
GATE/GEANT4 Monte Carlo simulations (3/3)

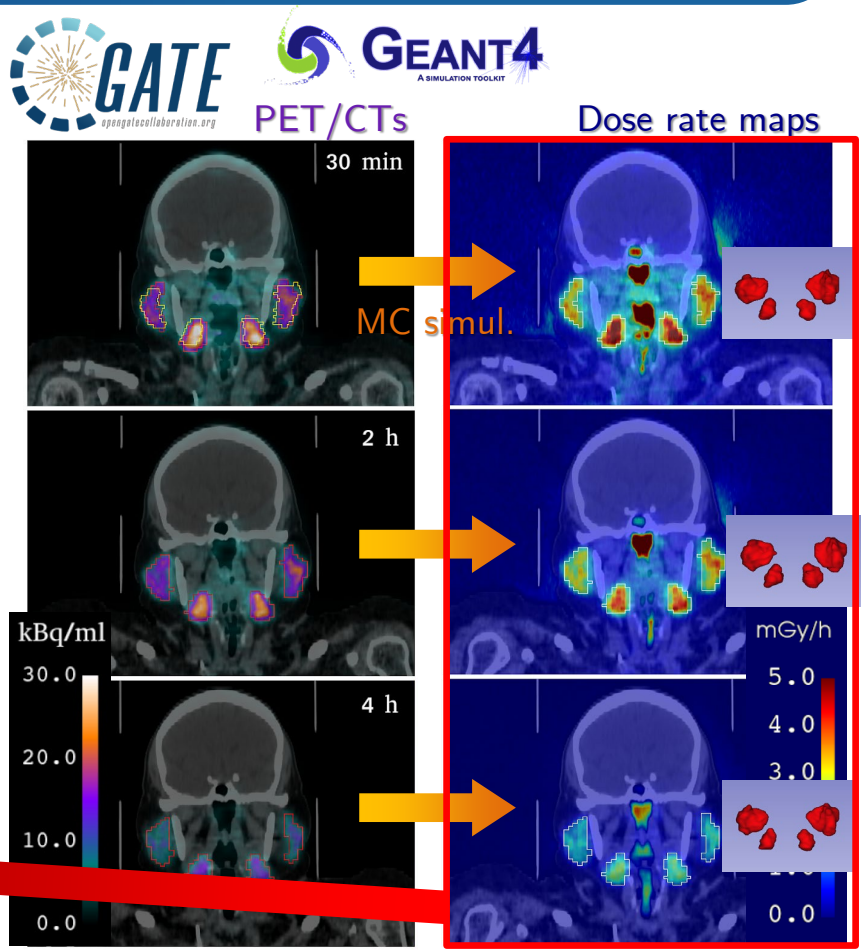
Monte Carlo simulations with GATE 9.1 (GEANT4 10.7) using tomographic imaging as input

- Average $\dot{D}(t)$ calculated in SG functional VOIs (with possible air and bone voxels excluded) + applying corrective factor for mass:

$$\langle \dot{D}(t) \rangle_{gland} = \left\langle \dot{D}^{ijk}(t) \right\rangle_{funct\ VOI} \cdot \left(Vol_{funct\ VOI} / Vol_{morph\ VOI} \right)$$

- Average D via trapezoid + phys. decay tail integr.





Simplified dosimetric methods for comparison (1/2)

- (**SM**) Spherical method of OLINDA/EXM 2.1
  - Calculates average self absorbed dose ($\langle D \rangle$) to sphere of homogeneous material and density and uniform activity
  - Each SG treated as individual sphere of soft tissue
  - Volume and mass adjusted to patient's ones from morphologic segmentations
  - TIACs deduced from ^{18}F-PSMA-1007 PETs entered in the software for each gland
  - → Average absorbed dose to each SG and to union of the four glands (tSG) calculated

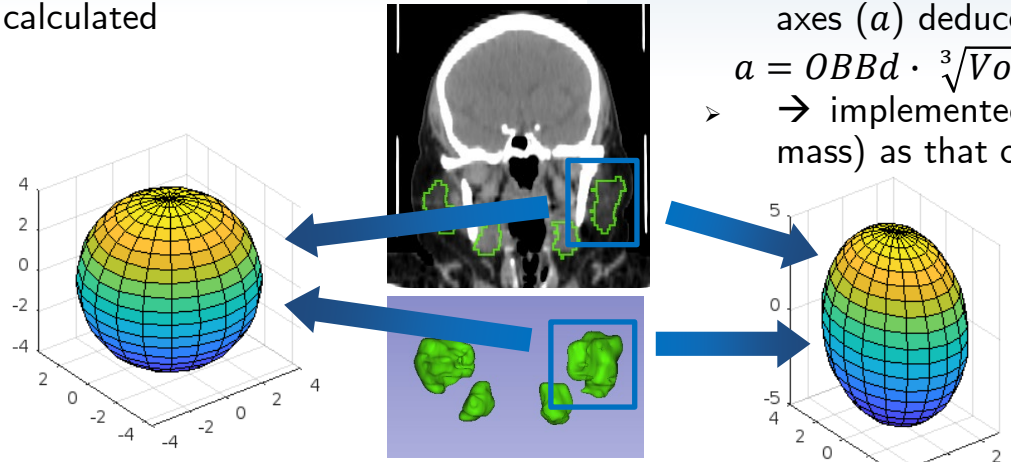
$$\langle D \rangle_{tSG} = \frac{\sum_i m_i \langle D \rangle_i}{\sum_i m_i}$$

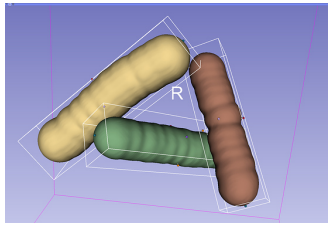
i = individual SG

- (**EM**) Ellipsoidal method by Amato et al. [1]
  - Similar to spherical method but using ellipsoids
  - Analytic model, from GEANT4 simuls., implemented on spreadsheet employing emission spectrum of radionuclide (from http://www.doseinfo-radar.com/)
  - Inputs: ellipsoid axes, density, TIAC, injected activity
  - Ellipsoids' axes deduced exploiting 3D Slicer:
    - *Labelmap statistics* tool → Oriented Bounding Box diameters (*OBBd*) of the SG VOIs → actual axes (a) deduced as:

$$a = OBBd \cdot \sqrt[3]{Vol_{OBB\ ellipsoid}/Vol_{morph\ VOI}}$$

    - → implemented ellipsoid has same volume (and mass) as that of the morphologic gland





OBB = smallest non-axis aligned box encompassing a VOI

[1] Amato et al. 2014 *AAPP* **92**(1) A1, https://doi.org/10.1478/AAPP.921A1

Simplified dosimetric methods for comparison (2/2)

- Organ S-Factors MIRD approach

  - Average absorbed dose to tSG following the organ-level MIRD formalism:
  - $D_{(T \leftarrow S)} = S_{(T \leftarrow S)} \cdot A_{adm} \cdot TIAC_{(S)}$ S = source, T = target
  - $S_{(T \leftarrow S)} = \sum_i y_i \, E_i \, \Phi_{i\,(T \leftarrow S)}$

  where Φ_i = Specific Absorbed Fraction (SAF, kg^{-1}), y_i = yield (Bq^{-1}·s^{-1}) and E_i = energy (J) for radiation type i

  - Using the S-factors provided by:
  - (**S-O**) OLINDA/EXM 2.1: calculated with NURBS voxel-based adult male phantom adjusted to ICRP 89 masses [4]
  - (**S-OD**) OpenDose collaboration: calculated with ICRP 110 voxel-based adult male phantom [5,6]

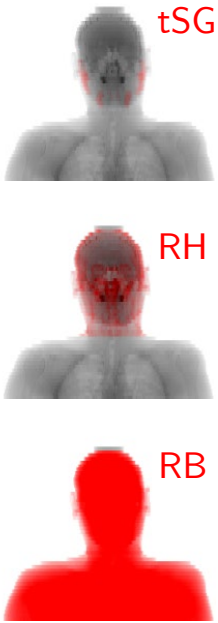
- The following source-target setups were investigated:

OLINDA

- **S-O1**: tSG only source and target
- **S-O2**: S-O1 + additional contrib. of remainder of body (RB) as source, using $TIAC_{RB} = TIAC_{WB} - TIAC_{tSG}$, with $TIAC_{WB}$ = 2.64 h (^{18}F's τ) [7] (in absence of whole-body imaging, assumption of phys. dec. only, no bio. wash-out)

OpenDose

- **S-OD1**: tSG only source and target
- **S-OD2**: same as S-O2 with OpenDose S-fact.
- **S-OD3**: S-O1 + additional contrib. of remainder of head (RH) as source, deducing $TIAC_{RH} = TIAC_{PET\,FOV} - TIAC_{tSG}$ from scans (as in slide 4)
- In all the cases, correction for mass applied $\langle D \rangle_{tSG} = D_{(T \leftarrow S)} \cdot (m_{tSG\,phantom}/m_{tSG\,patient})$



Coronal view of OpenDose source organs adopted

[4] Stabin and Siegel 2018 *J Nucl Med* **59** 154–160 https://doi.org/10.2967/jnumed.117.196261
[5] Chauvin et al 2020 *J Nucl Med* **61**(10) 1514-1519 https://doi.org/10.2967/jnumed.119.240366
[6] https://www.opendose.org/
[7] Giesel et al 2017 *Eur J Nucl Med Mol Imaging* **44**(4) 678-688 https://doi.org/10.1007/s00259-016-3573-4

Results: MC vs simplified methods, total SG VOI

For total salivary gland VOI:

- All methods except S-OD2 underestimate w.r.t MC
- Average relative percent differences (ε) and standard deviation (SD) among patients:

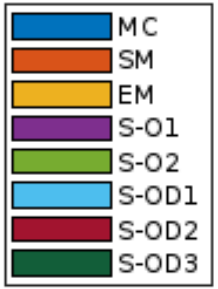
$$\varepsilon_X = 100 \cdot \frac{\langle D \rangle_X - \langle D \rangle_{MC}}{\langle D \rangle_{MC}}$$

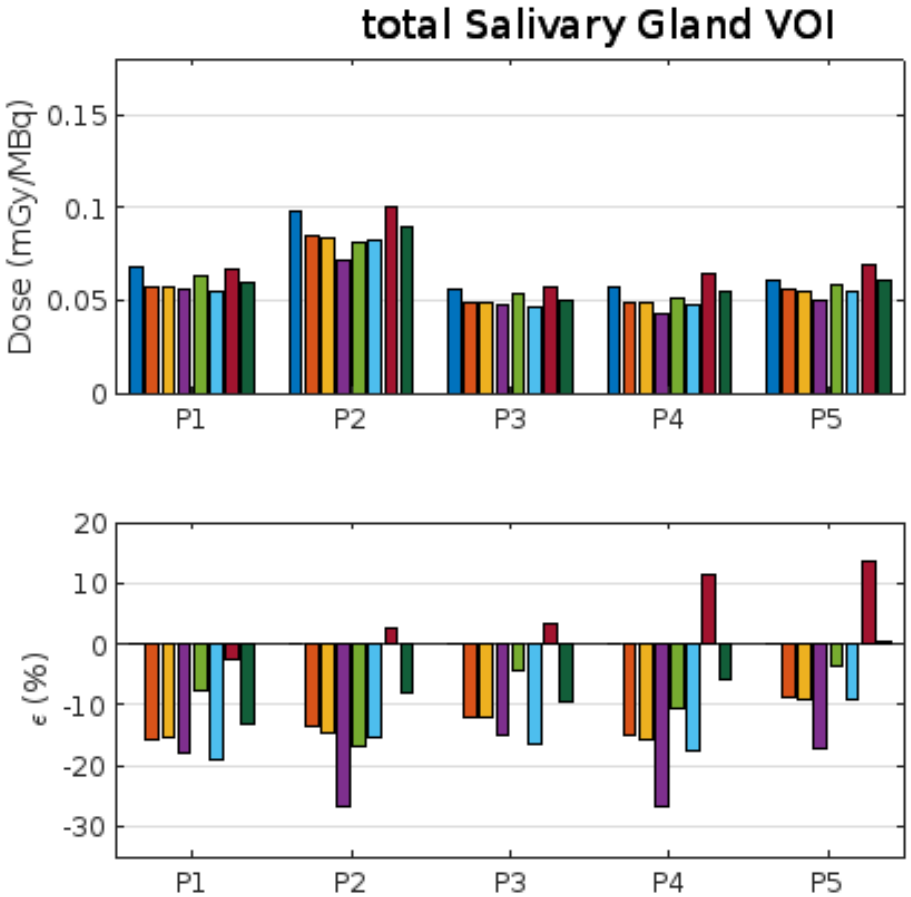
X = simplified *dosimetric method*

method	$\langle \varepsilon \rangle$	SD
SM	-13.0	2.8
EM	-13.4	2.9
S-O1	-20.7	5.4
S-O2	-8.6	5.3
S-OD1	-15.5	3.7
S-OD2	5.7	6.6
S-OD3	-7.2	5.0

Causes of discrepancies w.r.t. MC

- No cross-dose from activity outside glands (SM, EM, S-O1, S-OD1)
- Simplified gland geometry (SM, EM)
- Different voxel geometries in anthropomorphic phantoms w.r.t. patient (S-O and S-OD)
- Uniform activity within the glands (all)





Results: MC vs simplified methods, individual SGs

For individual salivary glands:

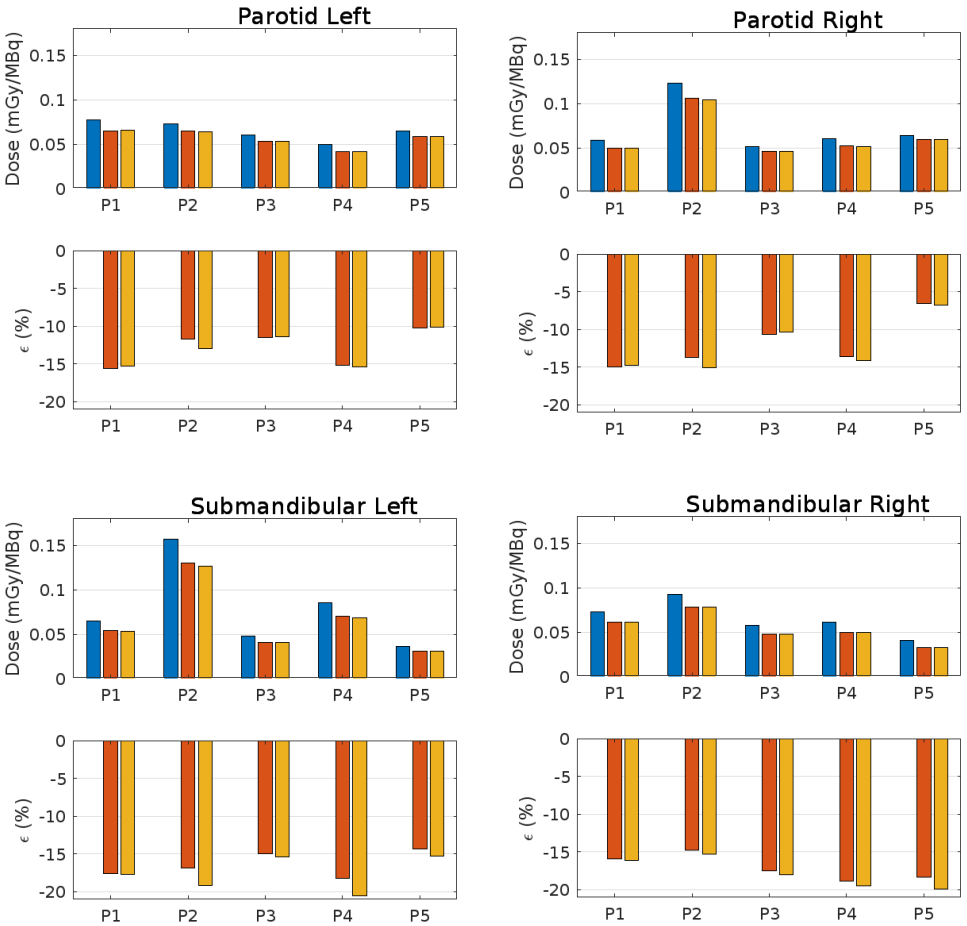
- Both spherical method (SM) and ellipsoidal method (EM) underestimate w.r.t. MC, bewteen -20% and -6%
- Average relative percent differences (ε) and standard deviation (SD) among patients:
  - $\langle\varepsilon\rangle_{SM}$ = -14.5%, SD_{SM} = 3.2
  - $\langle\varepsilon\rangle_{EM}$ = -15.1%, SD_{EM} = 3.6

Causes of discrepancies w.r.t. MC

- no cross-dose from activity outside glands
- simplified geometry of the glands
- uniform activity within the glands

$$\varepsilon_X = 100 \cdot \frac{\langle D\rangle_X - \langle D\rangle_{MC}}{\langle D\rangle_{MC}}$$

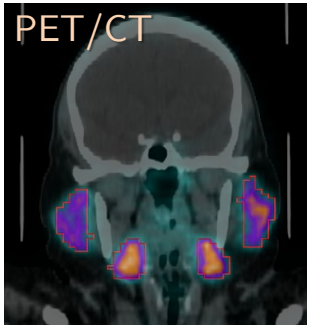
X = simplified *dosimetric method*

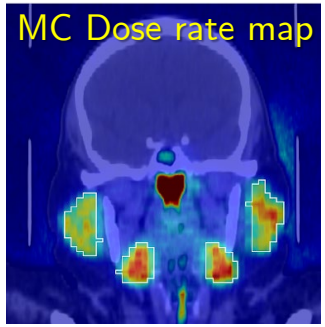


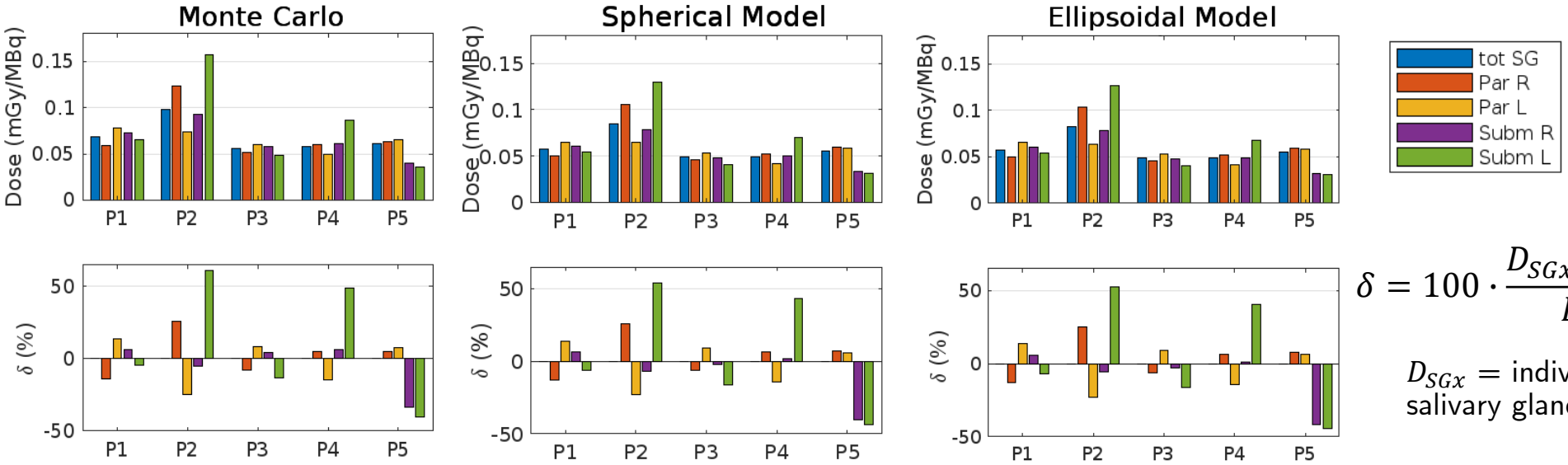
Results: comparison among individual SGs

For each method enabling dose estimation for individual SGs (MC, SM, EM):

- Non-negligible differences of absorbed dose in individual salivary glands
- Differences with respect to tSG between -50% and +65% with high intra- and inter-patient variability







$$\delta = 100 \cdot \frac{D_{SGx} - D_{tSG}}{D_{SGx}}$$

D_{SGx} = individual salivary gland x

Conclusions and perspectives

- General trend: simplified methods underestimate absorbed dose in salivary glands (SGs) with respect to MC for ^{18}F-PSMA PET dosimetry (except for method S-OD2)
- Average discrepancies w.r.t MC within 10% only with methods accounting for cross-dose from activity outside glands (S-O2, S-OD2, S-OD3)
- MC and methods enabling dosimetry for individual SGs (SM, EM) highlight patient-specific heterogeneous dose distribution in the four SGs considered (parotids and submandibular) → considering only ''total SG'' can be a strong approximation (overestimating or underestimating dose to individual SGs)
- Studies continuing on ^{18}F-PSMA-1007 dosimetry, trying to quantify the contribution of the different causes of discrepancies w.r.t. MC:
  - patient's SGs masses w.r.t. standardized masses, cross-dose from activity outside glands, simplified geometry of the glands, uniform activity within the glands
- Future perspectives: extend this kind of study to therapeutic radionuclides and radiopharmaceuticals
- Paper containing the reported study currently under review, provisional version on arXiv: https://doi.org/10.48550/arXiv.2210.01616

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  - University of Catanzaro: Dr. Francesco Cicone, Prof. Giuseppe Lucio Cascini
  - University of Lausanne and CHUV: Dr. Silvano Gnesin

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CHUV

THANK YOU FOR YOUR ATTENTION!

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