Pharmacokinetic of tumor FDG uptake in subcutaneous and orthotopic preclinical models of breast cancer – Influence of administration route

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Introduction

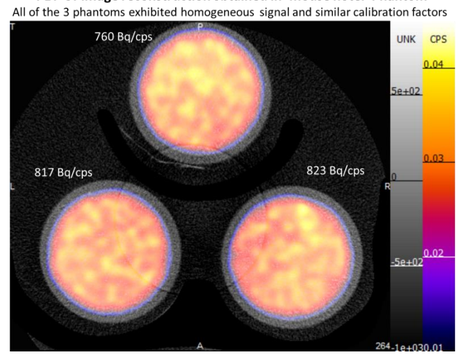
- ✓ Numerous studies evaluated FDG tumor uptake using microPET imaging in preclinical models. However, low attention was paid to the kinetic of FDG uptake that could differ according tumor localization. In the same time, many orthotopic tumor models were developed to better mimic human pathology.
- ✓ Besides, in preclinical studies, repeated intravenous administration of anticancer drugs is common and may cause damages on lateral tail vein and prevent a reliable FDG administration.

- ✓ Therefore, in the present study, our objective were:
  - to better **characterize the kinetic of tumor uptake of FDG in subcutaneous and orthotopic models** of breast cancer xenografts in mice, and
  - **to evaluate alternative routes of administration of FDG** that could be useful in preclinical studies involving repeated treatments via iv route.

Methods

- ✓ **Animal models**: NOD Scid mice were subcutaneously xenografted in the flank with BT-474 cells (HER2+ human breast cancer) and Balb/C mice were engrafted in the mammary fat pad with 4T1 cells (triple negative mouse breast cancer). For each tumor subtype, when tumor volume reached 200mm3, mice were randomized in 3 experimental groups according FDG administration route: subcutaneous (sc, interscapular), intraperitoneal (ip) or intravenous (iv) (n= 5-9 / group).
- ✓ **FDG PET/CT imaging:**
  - A preliminary phantom study validated the use of mouse-hotel imaging bed for accurate BioPET/CT (Bioscan) imaging in 3 mice simultaneously (calibration factor: 800 ± 20 Bq/cps) **(Figure 1)**.
  - Overnight fasted mice were anaesthetized and positioned in the imaging bed and injected with FDG (4-6 MBq) (3 mice injected within the same min)
  - A 90-min emission acquisition was immediately launched after the last injection (dynamic acquisition, list mode, tumor-centered, 250-700 keV) and followed by a CT scan (150µA, 45kV, 240 projections, 2 shots/projection).
- ✓ **PET images reconstructions:**
  - Thirty 180 sec frames were extracted from the 90 min acquisition to construct tumor time activity curves (TAC).
  - A static reconstruction covering the entire unique 90-min acquisition length was performed to determine the contours of the tumor.
- ✓ **PET images analyses:**
  - In the static 90-min reconstruction image, tumor contours were manually traced on each slice and a volume of interest (VOI) was obtained by summing the results. Then, VOIs were superimposed onto the reconstructed dynamic PET images.
  - TAC were built using mean tumor SUV values for each 3-min frame dynamic imaging.
  - Tumor SUV was calculated for 30-min periods after variable uptake times of 20min, 30min, 45min and 60min.

Figure 1
PET-CT image reconstruction obtained in 'mouse hotel' Phantom
All of the 3 phantoms exhibited homogeneous signal and similar calibration factors



Results

- ✓ For all 3 routes of administration, FDG was biodistributed mainly in heart and urinary system (kidneys/bladder) **(Figure 2.)**. After sc administration, FDG was also present in sc region but resorbed progressively during the 90-min acquisition period and did not impact contouring of subcutaneous BT-474 or orthotopic 4T1 tumors. After ip FDG, a significant signal was observed all along the 90-min acquisition period in the peritoneal cavity rendering delineation of tumor contour delicate for 4T1 orthotopic mammary tumors **(Figure 3)**.

Figure 2- Whole body biodistribution of FDG after intravenous, subcutaneous or intraperitoneal administration in subcutaneous BT-474 tumor-bearing mice

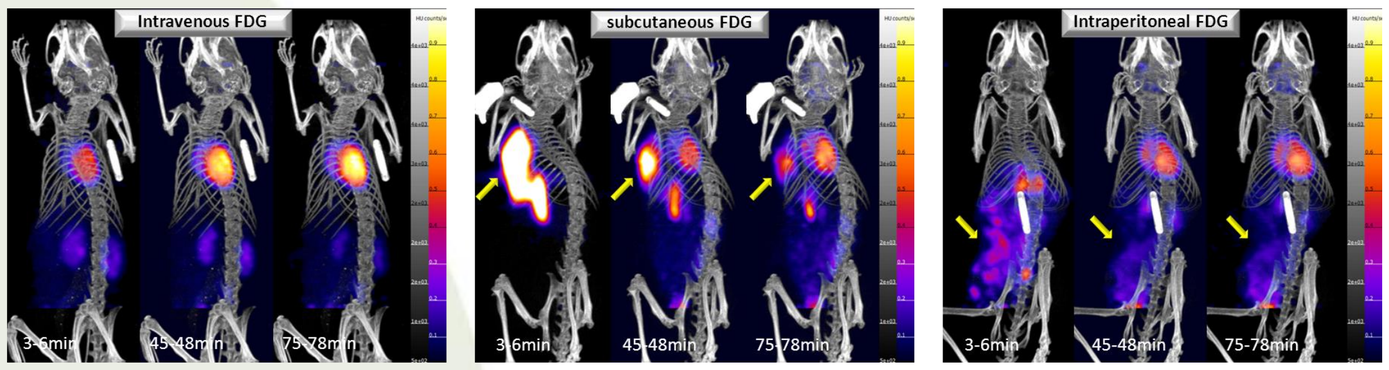
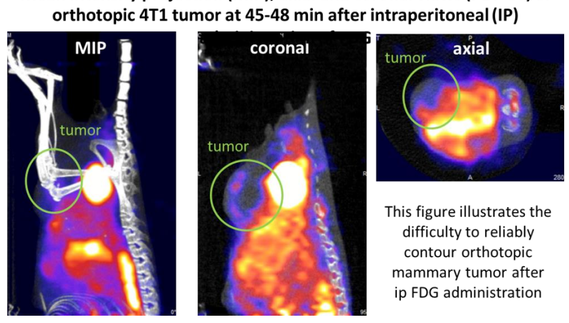


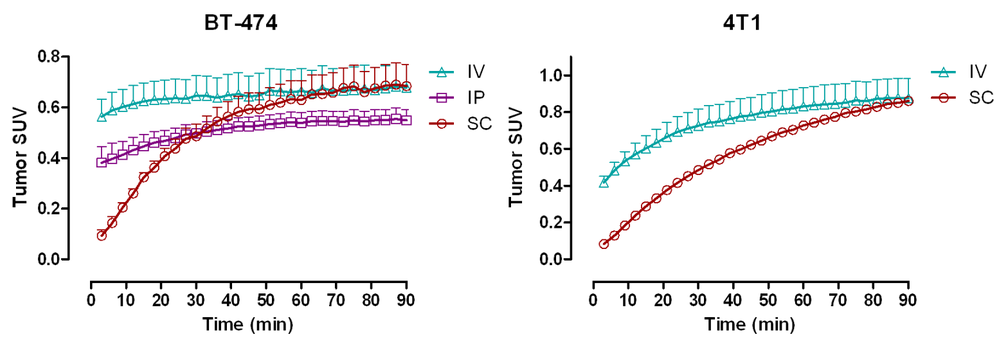
Figure 3
Mean intensity projection (MIP), axial and coronal views (PET-CT) of orthotopic 4T1 tumor at 45-48 min after intraperitoneal (IP)



This figure illustrates the difficulty to reliably contour orthotopic mammary tumor after ip FDG administration

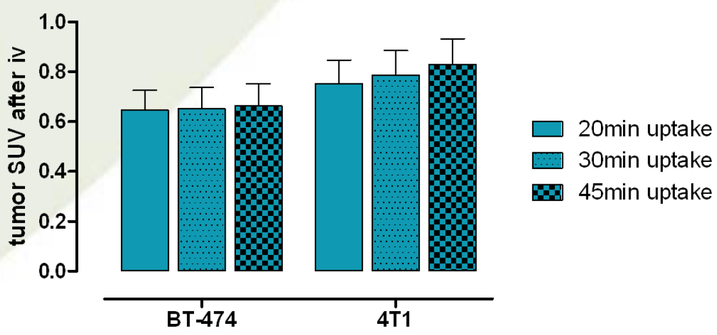
- ✓ In mice bearing subcutaneous BT-474 tumors, FDG tumor uptake plateaued within 15-20 min after iv injection, 30-35 min after ip injection and 50-60 min after sc administration. Tumor FDG uptake at 90 min were similar in iv- (0.68±0.09 SUV units) or sc- (0.69±0.09 SUV units) injected mice but lower in ip-injected mice (0.55±0.04 SUV units) **(Figure 4)**.
- ✓ In orthotopic 4T1 tumors, FDG uptake appeared to be slowed down for both iv and sc groups when compared to BT-474 tumors. In ip group, tumor delineation was not reliable due the vicinity of ip cavity. As for subcutaneous tumors, orthotopic 4T1 tumor FDG content was similar in iv- (0.87±0.11 SUV units) or sc- (0.86±0.07 SUV units) injected mice at 90 min post-administration **(Figure 4)**.

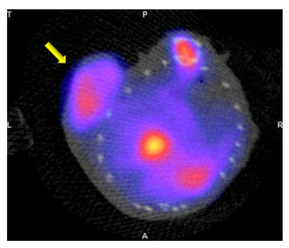
Figure 4
Tumor FDG time-activity curves after intravenous (IV), subcutaneous (SC) or intraperitoneal (IP) administration in subcutaneous BT-474 and orthotopic 4T1 tumor-bearing mice



- ✓ In both tumor models,
  1. similar FDG tumor uptakes were measured in iv groups after 20, 30 or 45 min uptake period **(Figure 5)**
  2. FDG tumor uptake measured 60 min post-sc injection was similar to that measured 30 min post-iv injection **(Figure 6)**.

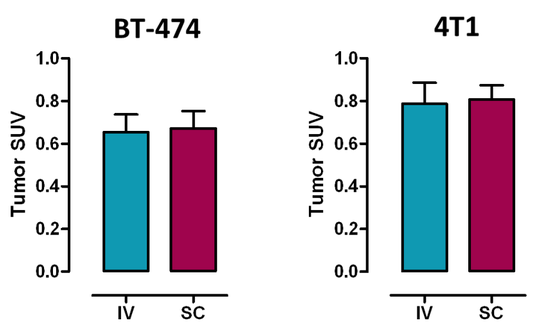
Figure 5
Comparison of different uptake times on SUV evaluation after iv FDG in subcutaneous BT-474 and orthotopic 4T1 tumor-bearing mice





Representative PET-CT image (axial view) in BT-474 tumor bearing mouse

Figure 6
Comparison of tumor SUV in subcutaneous BT-474 (left panel) and orthotopic 4T1 (right panel) tumor, after 30min uptake for iv route and 60min uptake for sc route of FDG administration



Conclusion

- ✓ **The present work showed that the kinetic of FDG tumor uptake was different in subcutaneous and orthotopic mice models of breast cancer.**
- ✓ **In these models, ip FDG administration may not be a relevant option to replace iv FDG injection because of a lower uptake or images that could not be reliably interpreted because of tumor positioning.**
- ✓ **In our experimental setting, subcutaneous administration of FDG can however be considered as an alternative route of administration, provided that the uptake period is extended to ensure that the plateau of FDG tumor uptake is reached.**
- ✓ **It is to be noted that additional studies are needed to validate the possible use of subcutaneous FDG administration in other experimental models, and that a particular care must be taken to the localization of both tumor and injection point.**

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