

## **FDG and FTT Uptake in Response to PARP Inhibition and DNA Damage**

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Poly-(ADP)-ribose polymerase (PARP) inhibitors are a class of drugs which are commonly used to treat breast and ovarian cancers. PARP inhibitors are especially effective in cancers containing a BRCA mutation, as these cells lack the ability to repair double stranded breaks. Therefore, PARP is heavily relied upon to seal single stranded nicks before lethal double stranded DNA breaks occur. By blocking PARP activity, cancer cells must rely on non-homologous end joining to repair breaks in the DNA, leading to a high level of mutagenicity and eventually cell death. F-18-FluorThanatrace ( $[^{18}\text{F}]\text{FTT}$ ) is a radio-labelled analogue of the PARP inhibitor Rucaparib and  $[^{18}\text{F}]\text{FTT}$  is currently in clinical trials as a tumor imaging agent and a predictive marker of patient response to PARPi therapy. However, some patients have had significant differences in standardized uptake values (SUVs) between coupled  $[^{18}\text{F}]\text{FDG}$  and  $[^{18}\text{F}]\text{FTT}$  scans. By treating breast and ovarian cancers with DNA damaging agents cisplatin and doxorubicin,  $[^{18}\text{F}]\text{FDG}$  uptake of the cells was reduced. Similarly, treatment with rucaparib reduced binding of  $[^{125}\text{I}]\text{KX1}$  (an  $^{125}\text{I}$  labelled rucaparib analogue). Rucaparib treatment also increased FDG uptake in ovarian cancer cells. These findings are important for understanding the clinical results of FDG and FTT scans, allowing physicians to properly diagnose patients and predict or track their responses to chemotherapy. Future studies on the topic should focus on the specific metabolic and cell cycle effects of chemotherapy, as well as clarifying the ability of  $[^{18}\text{F}]\text{FTT}$  to monitor and predict the response of patients with a BRCA mutation to chemotherapy and PARPi therapy, as well as whether patients receiving chemotherapy or PARPi therapy should be imaged with  $[^{18}\text{F}]\text{FTT}$  or  $[^{18}\text{F}]\text{FDG}$ .