Application Note:
Theranostic Treatment Response and Toxicity Risk

Introduction

Theranostic therapies combine molecular targeted diagnostics with radionuclides for imaging and therapy in many advanced malignancies. Frequently however, due to heterogeneity of treatment response, complete remission in theranostic treatment is rare; residual lesions often progress and the treatment can induce severe symptoms. Contributing to the problem, are the number of lesions that often metastasize to other areas of the body such as bone and liver. Identifying, measuring and tracking the treatment response of numerous metastatic lesions, using standard medical images, is difficult and challenges the ability to understand the efficacy and safety of a new theranostic treatment expeditiously. This lapse of understanding can cost researchers valuable time and resources.

Theranostic therapies are already in use to treat advanced malignancies such as metastatic prostate cancer or gastroenteropancreatic neuroendocrine tumors (GEP-NETs). There are also additional theranostic therapies in late-stage clinical development for which more informative and timely measurements of treatment response are needed to balance the associated benefits and risks. By assessing patient treatment efficacy and toxicity risk earlier in therapy, investigators will be able to differentiate those patients who are likely to have an optimal vs. sub-optimal response. This information can impact the overall clinical outcome and reduce the number of severe or life-threatening adverse events, resulting in more efficient drug discovery timelines.

Technology Application in Theranostics Assessments

AIQ Solutions (AIQ) has conducted two independent assessments to demonstrate that its medical device technology platform is able to predict theranostic patients' treatment response and toxicity risk.

Assessment 1 - *Predicting Patient Response*

Methods:

This assessment was based on a retrospective study of 14 patients receiving ^{68}Gallium (Ga)-DOTATATE Positron Emission Tomography/ Computerized Tomography (PET/CT) scans during Lutathera® (^{177}Lu DOTATATE) therapy. All patients received at least two PET/ CT scans and some patients received an additional third scan. The images were analyzed using AIQ technology platform to garner Treatment Response Assessments (TRAs) for all lesions. Corresponding lesions were matched between longitudinal images based on articulated registration. Lesions were classified into five different categories based on Standard Uptake Value (SUV). Heterogeneous response was defined as patients with both favorable and unfavorable lesion response using either SUVmax or SUVtotal (See Figure 1). AIQ's technology platform further segmented soft tissue organs. Organ lesions were detected using organ-specific thresholds on all PET/ CT images. All lesions within each patient's liver were then classified into response categories, individually (See Figure 2). The accuracy of each step above was carefully reviewed by a nuclear medicine physician or medical physicist.

Results:

The TRA demonstrated that all patients in this assessment exhibited a heterogeneous response to Lutathera® treatment (See Figure 1), as reflected by Ga-DOTATATE PET/CT imaging. This heterogeneity increased throughout the treatment. Moreover, the TRA demonstrated that each lesion within a patient's liver also responds differently to treatment (See Figure 2). Identification and quantification of the spaciotemporal heterogeneity early in a theranostic therapy could provide valuable information for patient management during later stages of the treatment. Examples include changing the treatment approach or treating the resistance with localized ablation.

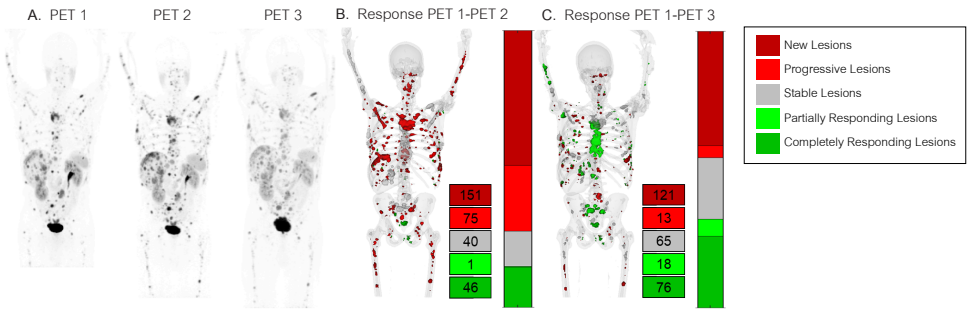


Figure 1

Example patient. A) 3 sequential PET images B) TRA from PET1 to PET2 is used to determine the number of lesions per category, which are normalized into a bar plot. C) TRA from PET1 to PET3.

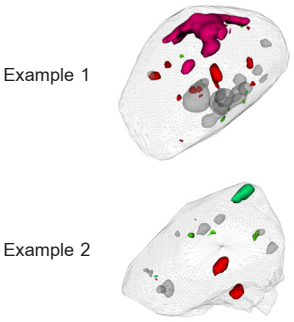


Figure 2

TRA in liver for two example patients receiving Lutathera® therapy normalized into response category for lesions (red is progressing, grey is stable, green is responding).

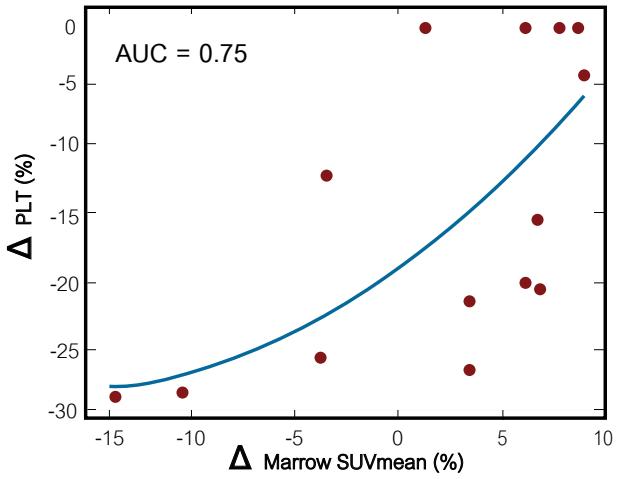
Assessment 2 - *Predicting Patient Toxicity Risk*

Methods:

This assessment was based on a retrospective study of 35 patients receiving Ga-DOTATATE PET/CT scans during Lutathera® therapy. All patients received at least one Ga-DOTATATE PET/CT scan during the course of therapy while 14 received two scans. AIQ Organ Based Assessments (OBAs) were generated with organs segmented. SUV_{mean} and SUV_{hetero} were determined by extracting SUV measures from the bone marrow and kidneys. The SUV measures (SUV for patients with one scan and percent-change in SUV for patients with two scans) were then used to predict patients who would eventually have abnormal lab test values of platelet counts and creatinine levels, which imply treatment induced toxicity. Further correlations were conducted on the 14 patients with multiple PET/CT scans to determine percent-change of SUVs compared to changes in lab tests in the bone marrow and kidneys.

Results:

AIQ demonstrated that an early decrease in bone marrow SUV correlates to a later decrease in platelet count (See Figure 3). Further, AIQ technology accurately predicted those patients who can subsequently receive a reduction in Lutathera® dose due to bone marrow toxicity (toxicity was defined as patient's platelet count - PLT < 100, see Figure 4). Baseline SUV was able to identify patients with later increases in creatinine levels (kidney toxicity was defined as creatine levels >1.5, see Figure 5). AIQ technology provides intelligence earlier in treatment for investigators to identify patients who are likely to experience bone marrow or kidney toxicity. This knowledge would allow subsequent adjustment of the therapy dose to avoid adverse events from theranostic therapies.



Decrease in marrow SUV associated with decrease in PLT

Figure 3:

Correlation between early change in bone marrow SUV (x-axis) and later change in platelet count (y-axis). Patients in bottom left quadrant are those who may be candidates for proactive dose reduction.

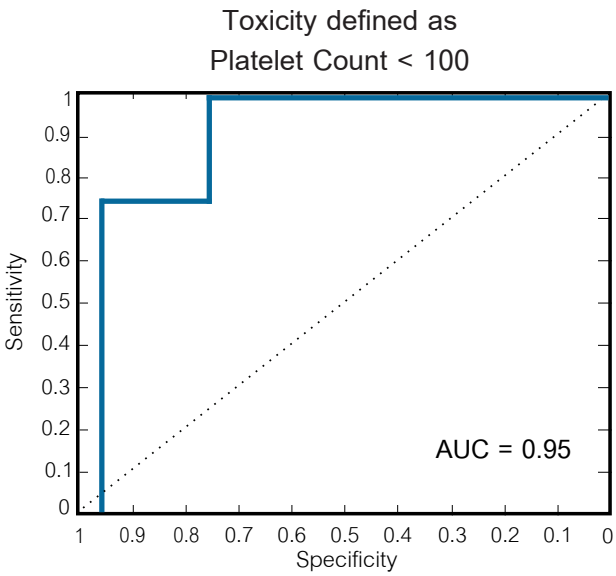


Figure 4:
The change in Ga-DOTATATE uptake is strongly associated with bone marrow toxicity.

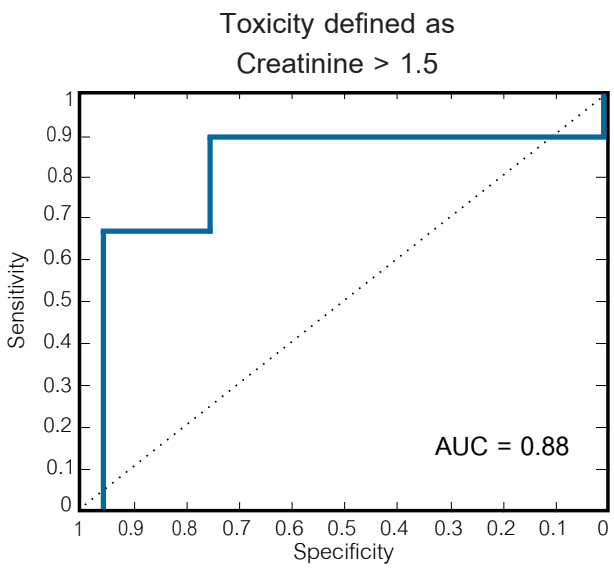


Figure 5:
Prediction and correlation of dose reduction with both high sensitivity and specificity for kidney toxicity. The change in Ga-DOTATATE uptake is strongly associated with kidney toxicity.

Theranostic Technology Application Conclusion

The two assessments discussed above highlight the ability of AIQ technology to generate intelligent data and correlate this data to eventual patient outcome. In the first assessment, the results demonstrated that AIQ technology can identify and classify all lesions in bone and soft tissue. The results also demonstrate both inter- and intra-patient heterogeneity of treatment response in theranostic therapies. In the second assessment, the results demonstrated that early SUV percent-change in bone marrow can predict a later decrease in platelet count. The results also demonstrate that early SUV percent-change in kidney can predict a later increase in Creatinine levels. Together, such information allows AIQ to identify patients who are likely to experience adverse events earlier.

As theranostics research continues to press forward, AIQ has demonstrated that it is well positioned to incorporate its advances in artificial intelligence and machine learning into the early phase clinical study settings. The use of AIQ's algorithms provide insight into patient's response to treatment early in theranostic therapies. This can enable stronger decisions for patient's optimal dose levels while limiting the toxicity risks associated with the radionuclides. Furthermore, the intelligence provided by AIQ ultimately allows investigators pursuing theranostic therapies to accelerate their assets' time to market with greater confidence.

About AIQ Solutions

AIQ has developed a medical device software platform that uses artificial intelligence to automatically quantify treatment response for each individual lesion from longitudinal imaging data. The platform delivers lesion-specific metrics, including spatial information; it also calculates a composite biomarker for each patient that indicates early in the course of treatment whether that patient is likely to exhibit an optimal or sub-optimal response to therapy as well as assess patient's toxicity risk.