Spatiotemporal evolution of lesion response heterogeneity to ^{177}Lu-DOTATATE therapy in advanced gastroenteropancreatic neuroendocrine tumors

Timothy G Perk[1,2], Stephen SF Yip[1,2], Robert Jeraj[1,2,3], Scott B Perlman[4]

1 University of Wisconsin, Department of Medical Physics, Madison, Wisconsin **2** AIQ Solutions, Inc – Madison, Wisconsin
3 University of Ljubljana, Ljubljana, Slovenia **4** University of Wisconsin, Department of Radiology, Madison, Wisconsin

School of Medicine and Public Health
UNIVERSITY OF WISCONSIN–MADISON

WONIX Wisconsin Oncology Network of Imaging eXcellence

INTRODUCTION

Patients treated with ^{177}Lu-DOTATATE (Lutathera) therapy often have a mixed response to therapy, with some metastases responding better than others[1,2]. In patients with many lesions, it would be helpful to determine which lesions are responding, as alternate treatments could be attempted for the non-responding metastases.

The purpose of this investigation was to understand and quantify the inter-lesion heterogeneity in treatment response seen on ^{68}Ga-DOTATATE PET/CT imaging over the course of Lutathera therapy.

METHODS

- This was a retrospective study, approved under an IRB-approved umbrella protocol, of 14 patients receiving ^{68}Ga-DOTATATE PET/CT imaging during Lutathera therapy
  - 14/14 received at least two PET/CT scans
  - 8/14 patients also had an additional third PET/CT scan
- Images were analyzed using a modified version of the AIQ Solutions technology platform.

The AIQ technology platform performed the following steps:

1) **Organ Segmentation:** Organs were segmented using a previously-trained 3D convolutional neural network[3].
2) **Lesion Detection:** Lesions were detected using organ-specific thresholds method on all PET images, SUV>10 for liver and lung, SUV>2.5 for bone, and SUV>15 in other regions.
3) **Lesion Quantification:** For lesion quantification, maximum (SUV_{max}) and total (SUV_{total}) standardized uptake value were computed within each detected lesion.
4) **Lesion Matching:** Corresponding lesions were matched between longitudinal images based on articulated registration.
5) **Response Assessment:** Lesions were classified into five different categories based on response of either SUV metric: complete response, partial response (ΔSUV<-30%), stable disease (ΔSUV ≤|30%|), progressive disease (ΔSUV>30%), or new lesions. Heterogeneous response was defined as patients with both favorable and unfavorable lesion response using either SUV_{max} or SUV_{total}.
6) **Quality Check:** The accuracy of step 1 to 5 was carefully reviewed by a nuclear medicine physician or medical physicist.

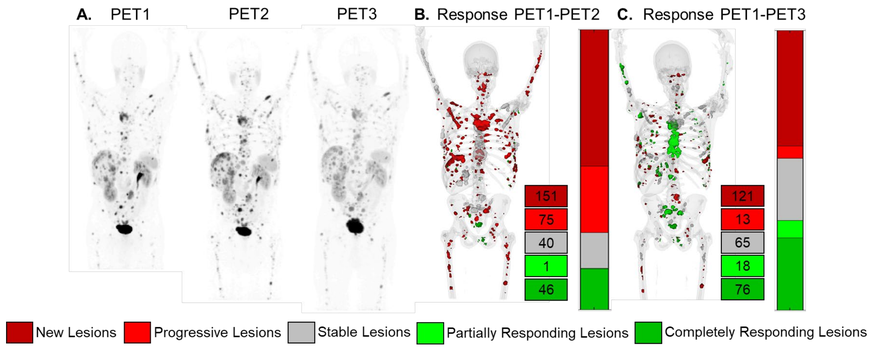

Figure 1. Example analyzed patient. A) 3 sequential PET images B) Response from PET1 to PET2 is used to determine the number of lesions per category, which are normalized into a bar plot. C) Response from PET1 to PET3.

RESULTS

- **Heterogenous response of lesions was identified in all patients (Figure 2)**
  - From PET1 to PET2, 93% (13/14) of patients exhibited both responding and progressing lesions
    - The exception was in a patient with two responding lesions at PET2 but developed three new lesions by PET3.
  - Between PET1 and PET3, lesion response heterogeneity was present in 100% (8/8) of patients.
  - The proportion of favorably responding lesions increased at PET1 to PET3 in 50% (4/8) of the patients as compared to the proportions at PET1 to PET2.
- **Different levels of heterogeneity could alter treatment decisions (Figure 3)**
- **Varied levels of patient level response were identified**
  - Patient level response from PET1 to PET2 based on total disease burden indicated that 29% (4/14) patients had responded to treatment, 50% (7/14) remained stable, and 21% (3/14) progressed
  - Patient level response from PET1 to PET3 indicated more changes with 50% (4/8) of patients responding to treatment, 13% (1/8) remaining stable, and 38% (3/8) progressing
- Review revealed high accuracy of lesion detection, matching, and quantification

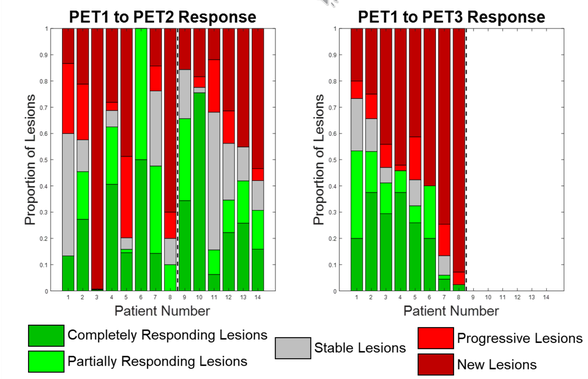

Figure 2. Inter-lesion heterogeneity plots where the proportion of lesions in different response category are plotted for each patient (gray=<30% change in SUV_{total}, green=complete response or partial responding lesions, red = progressing or new lesions). The dashed line separates patients that did not receive the PET3 image (Patients number 9-14). Patients are sorted by increased proportion of unfavorable response, based on PET1 to PET3 response (right figure). **All patients have both red and green, implying a heterogeneous response.**

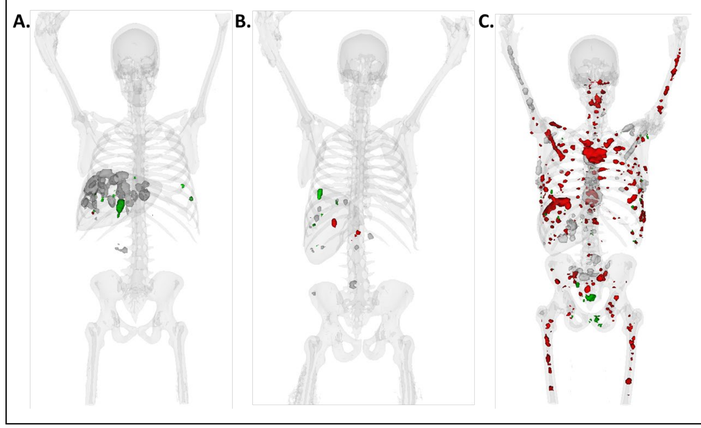

Figure 3. Example of 3 patients with lesions colored by response of SUVmax. In patient A most of the disease is responding or stable. In patient B the disease is more heterogeneous with two progressing lesions in the liver and might be a **suitable candidate for a targeted ablation**. In patient C disease is mostly progressive lesions and a **change in treatment strategy would be recommended**.

CONCLUSIONS

- **All patients exhibited a heterogeneous response to Lutathera as reflected by ^{68}Ga-DOTATATE PET/CT imaging**
- **This heterogeneity increased throughout treatment**
- **Early quantification of heterogeneity of response provides valuable information for patient management**
  - **For example: local ablation of resistant lesions might be helpful to alleviate symptoms and possibly improve patient outcome**

ACKNOWLEDGEMENTS

This project was supported in part by AIQ Solutions, the University of Wisconsin Carbone Cancer Center Support Grant P30 CA014520 and the Wisconsin Oncology Network for Imaging eXcellence (WONIX). We would like to thank the UW Radiopharmaceutical Production Facility (RPF) for providing tracers for this study.

REFERENCES

1. Frilling, A., Modlin, I.M., Kidd, M., Russell, C., Breitenstein, S., Salem, R., Kwekkeboom, D., Lau, W.Y., Klersy, C., Vilgrain, V., Davidson, B., Siegler, M., Caplin, M., Solcia, E. and Schilsky, R. Recommendations for Management of Patients with Neuroendocrine Liver Metastases. Lancet Oncol **15**(1), e8-21 (2014). (http://www.ncbi.nlm.nih.gov/pubmed/24384494).

2. van der Zwan, W.A., Bodei, L., Mueller-Brand, J., de Herder, W.W., Kvols, L.K. and Kwekkeboom, D.J. Gepnets Update: Radionuclide Therapy in Neuroendocrine Tumors. Eur J Endocrinol 172(1), R1-8 (2015). (http://www.ncbi.nlm.nih.gov/pubmed/25117465).

3. Kamnitsas K, Ledig C, Newcomb, V.F.J., Simpson J.P., Kane, A.D., Menon, D.K., Rueckert, D., Glocker, B. Efficient multi-scale 3D CNN with fully connected CRF for accurate brain lesion segmentation. Med Image Anal **36**, 61-78 (2017). (https://www.sciencedirect.com/science/article/pii/S1361841516301839)

CONTACT INFORMATION

Timothy G Perk
tim.perk@aiq-solutions.com