Lesion-based Response to PSMA Radioligand Therapy: Impact of Absorbed Dose

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Introduction

- Prostate-specific membrane antigen (PSMA) targeting RLT using 177Lu-PSMA-617 has demonstrated favorable PSA response rates and longer progression-free survival and overall survival in patients with metastatic castration resistant prostate cancer (mCRPC) (1,2).
- Understanding the relationship between lesion absorbed dose and tumor response in 177Lu-PSMA-617 Radioligand therapies (RLT) remains complex (3,4,5).
- We aimed to investigate if baseline lesion absorbed dose can predict lesion-based responses and explore the connection between lesion absorbed dose and PSA response..

Material and methods

- In this retrospective study, we evaluated 50 patients with 335 index lesions undergoing 177Lu-PSMA-617 RLT, who had dosimetry analysis performed on SPECT/CT at 24 hours after Cycle 1 and 2.
- First, we identified the index lesions for each patient and measured the lesion-based absorbed doses. Lesion-based response was calculated after Cycle 2.
- We utilized segmentation based on 42% of the maximum lesion dose (6,7), which yielded the mean absorbed dose in Gray (Gy), maximum absorbed dose (Gy), and tumor volumes (mL). Additionally, similar to tumor lesion glycolysis and volumetric intensity product (VIP) used previously (8,9); we calculated the VIP_{PSMA} by multiplying the tumor volume and mean absorbed dose of the index lesions, excluding the least avid lesion
- Additionally, PSA50 response after Cycle 2 was also calculated.
- Lesion level data was averaged for each patient to obtain a patient level data.). A Student's t-test was conducted to assess the relationship between the lesion-based responses and PSA response between the responders and non-responders.

$$\text{Lesion-based } Response = 1 - \frac{Absorbed\ dose\ (Cycle\ 1) - Absorbed\ dose\ (Cycle\ 2)}{Absorbed\ dose\ (Cycle\ 1)}$$

Results

- Of the 50 patients reviewed, 46% achieved a PSA50 response after Cycle 2.
- Of the 335 index lesions, 58% were osseous, 32% were lymph nodes and 10% were soft tissue metastatic lesions.
- The SPECT lesion-based responses were higher in PSA responders versus non-responders ($SPECT_{mean}$ response of 46.8□26.1% versus 26.2 ±24.5%, p=0.007; $SPECT_{maximum}$ response of 45 ±25.1% versus 19 ±27.0%, p=0.001; $SPECT_{VIP\text{-}PSMA}$ response of 49.2 ±30.3% versus 14 ±34.7%, p=0.0005).
- An association was observed between PSA response and $SPECT_{VIP\text{-}PSMA}$ response ($R^2 = 0.40$ and $p < 0.0001$).
- A limited relationship was found between baseline absorbed dose and SPECT lesion-based response (R^2 =0.05, p=0.001 and R^2 =0.03, p=0.007 for mean and maximum absorbed doses respectively).

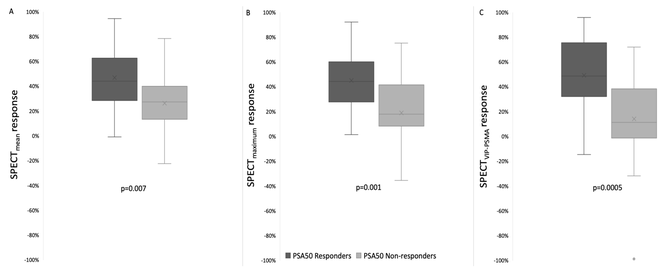


Figure 1: $SPECT_{mean}$ response (A), $SPECT_{maximum}$ response (B) and $SPECT_{VIP\text{-}PSMA}$ response in PSA50 responders and non-responders. Box plots display median, first and third quartiles.

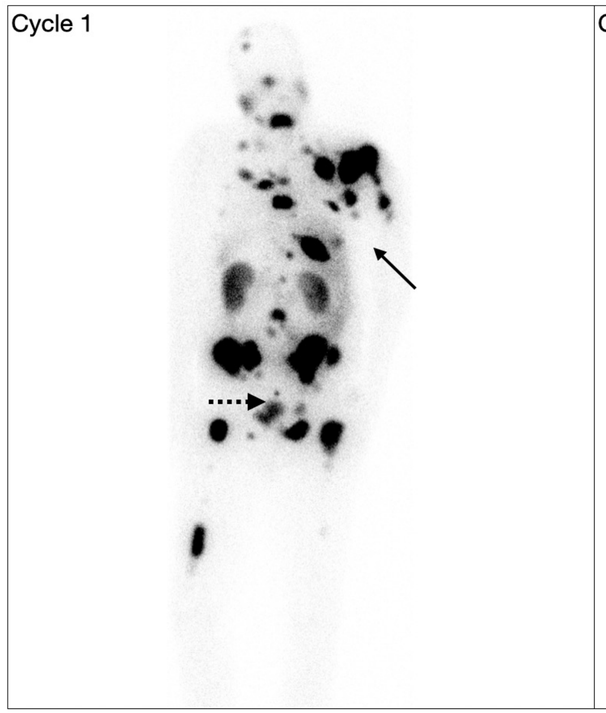
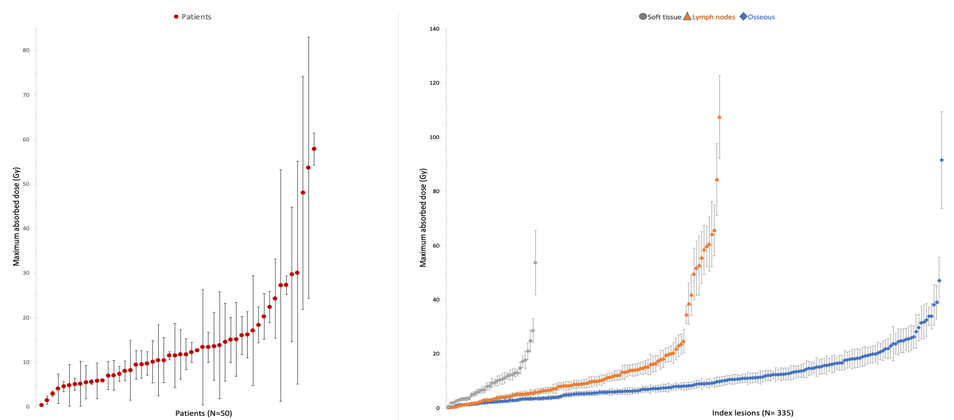


FIGURE 3: A 62-year-old man with mCRPC (Gleason 4+3, baseline PSA - 6.47) treated with two cycles of ^{177}Lu-PSMA-617, demonstrating high baseline absorbed dose in the setting of increased PSA after Cycle 2. Post-cycle 1 planar imaging demonstrates uptake in osseous and nodal disease (black arrowheads). Post-cycle 2 planar imaging demonstrates no significant change in the previously visualized disease (black arrowhead) along with increased uptake in some lesions (black dotted arrowheads). The average of maximum absorbed dose for the index lesions was 15.3 ± 8.3 Gy in Cycle 1 which decreased to 12.7 ± 7.3 Gy in Cycle 2 with a $SPECT_{maximum}$ response of 14 ± 17 %. Serum PSA levels increased by 113 (95.729 to 202.956 ng/ml). The patient was PSA50 non-responder albeit high absorbed dose and further cycles were abandoned.

Figure 2: Scatter plot showing the distribution of the maximum absorbed dose (Gy) for Cycle 1 within each patient (left) and within each index lesion (right). In the patient graph, the marker is the average of the maximum absorbed dose to all the lesions within the patients and the whiskers are the standard deviation. In the lesion graphA, the marker is the maximum absorbed dose within the lesion and the whiskers are the standard deviation of the activity within each lesion..



Conclusion

Scan for references

- In this retrospective study, quantitative lesion-based response correlated with patient level PSA response.
- Our results re-iterate the fact that response to RLT is influenced by factors extending beyond the absorbed dose and is contingent upon the intricate interplay between the cellular and extracellular environments influencing intrinsic radiation sensitivity (10-14) .
- While we observed a limited relationship between baseline absorbed dose and lesion-based responses, most of the variance in response remains unexplained solely by baseline absorbed dose, rendering the establishment of dose-response relationship in RLT a challenging endeavor.