

Improving diagnostic accuracy in molecular imaging of patients treated with immunologic therapy



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- No relevant disclosures

The Rise of Immunotherapy

- Immunotherapy has taken off in recent years has revolutionized clinical oncology achieving clinical responses and outcomes that were before unthinkable.
- In addition, immunotherapy has brought to light the concept of precision medicine targeting specific disease processes with a common goal—treat the disease while limiting further damage.
- However, a critical issue that has arisen which has gain research traction is the understanding of and monitoring treatment response.

Molecular Imaging and Cancer after Immunotherapy

- Molecular imaging, namely PET/CT, is the standard assessment
- Accurate response assessment is paramount to understand treatment success and failure as early as possible.
- Efficacy of FDG PET/CT may be diminished and misleading secondary to the upregulated immune response
- Immune response is secondary to immunotherapy in cancer treatment with the “Warburg effect” in proliferative neoplastic tissues increasing glucose turnover.

Benefits of PET/CT

- Highly sensitive to hypermetabolic processes
- FDG-PET can provide useful information on the metabolic state of the tumor microenvironment and on the expression of checkpoint inhibitors
- Availability for new PET/CT related biomarkers
- Early detection of immune related side effects prior to clinical manifestation
- Great for staging re-staging and assessing complete response and significant progression

Pitfalls of PET/CT after immunotherapy

- Pseudoprogression
- Imaging immunotherapy-related adverse events
 - Thyroiditis, pneumonitis, hypophysitis, colitis can lead to unusual patterns of tracer uptake. Especially when they are yet to be clinically evident
 - Diagnostician must become familiar with different drugs, their side effects, and their patterns on PET/CT
- Small tumor size, there is no good predictor of response
- PET/CT over and/or underestimates therapeutic effect of ICI using classical imaging response criteria

Pseudoprogression

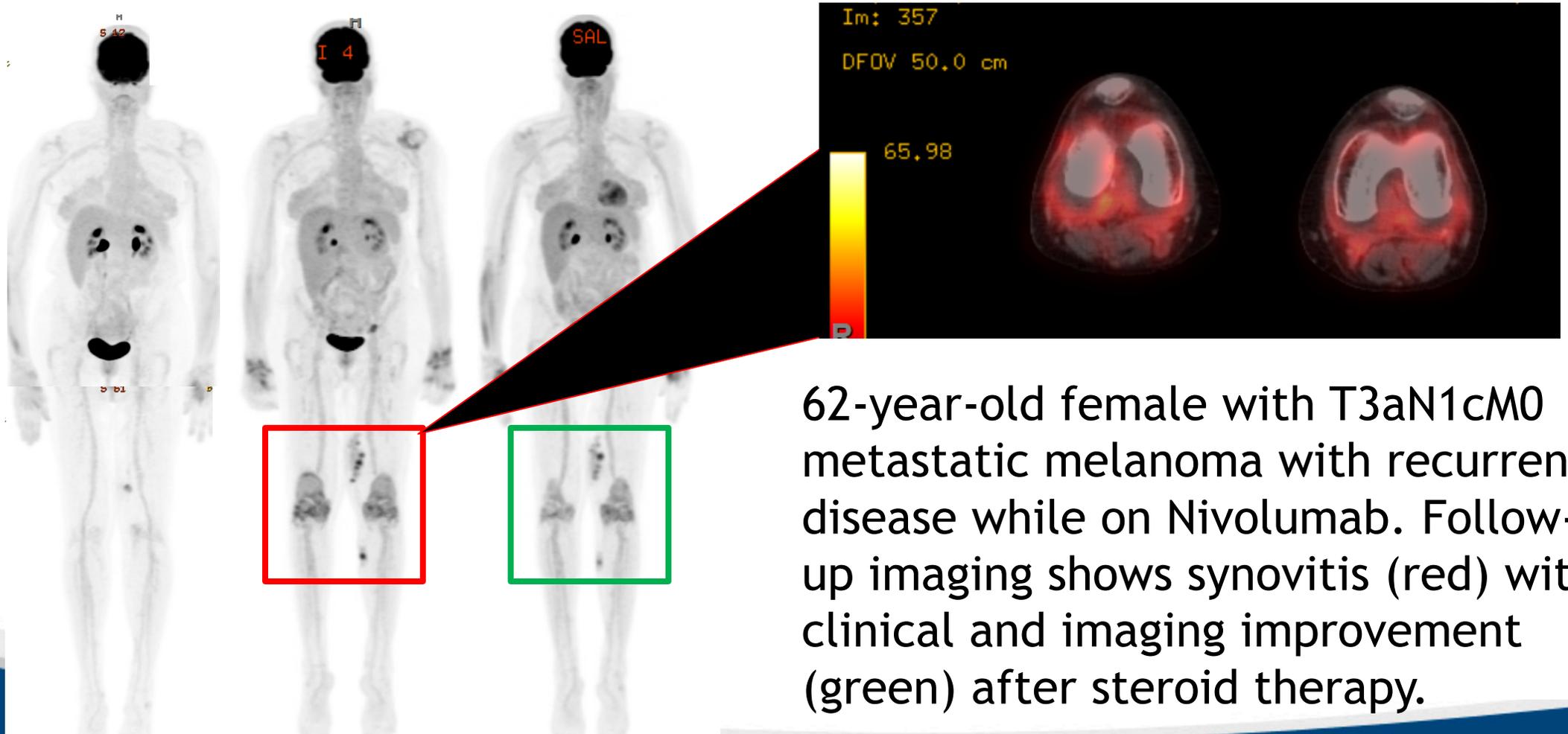
- Hypermetabolic “flare-phenomenon” caused by the initial T-cell tumor infiltration. Although, this is found less frequently than effective disease progression
 - More common with anti-CLTA4 agents, then PD-1 agents
- Should only be considered when clinical condition is concomitantly improving

Why is treatment response after immunotherapy so difficult?

- Patterns differ from those to chemotherapeutic and molecularly targeted agents
 - Hyperprogression
 - denoting accelerated tumor growth rate early after immunotherapy initiation (reported to occur in 7-10% of patients) with worsened overall survival
 - Differing immune response with different therapies
 - Side effects
 - Non-universal response criteria
- Responses are usually early but they can also be delayed

Assessing immune related side effects

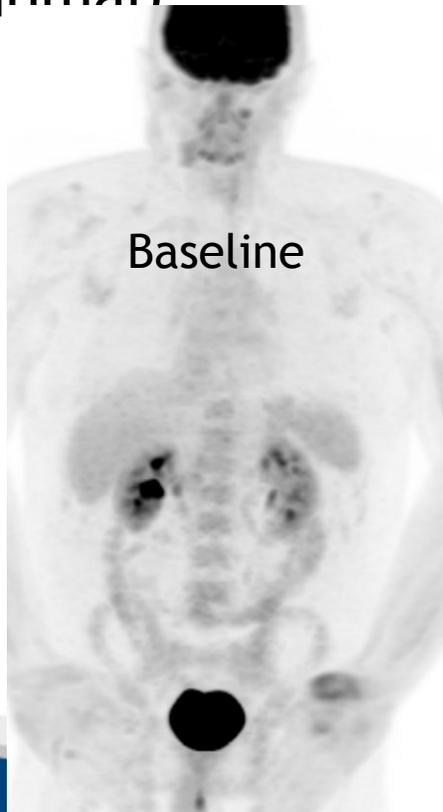
- More common with anti-CTLA agents (ie. Ipilimumab)



62-year-old female with T3aN1cM0 metastatic melanoma with recurrent disease while on Nivolumab. Follow-up imaging shows synovitis (red) with clinical and imaging improvement (green) after steroid therapy.

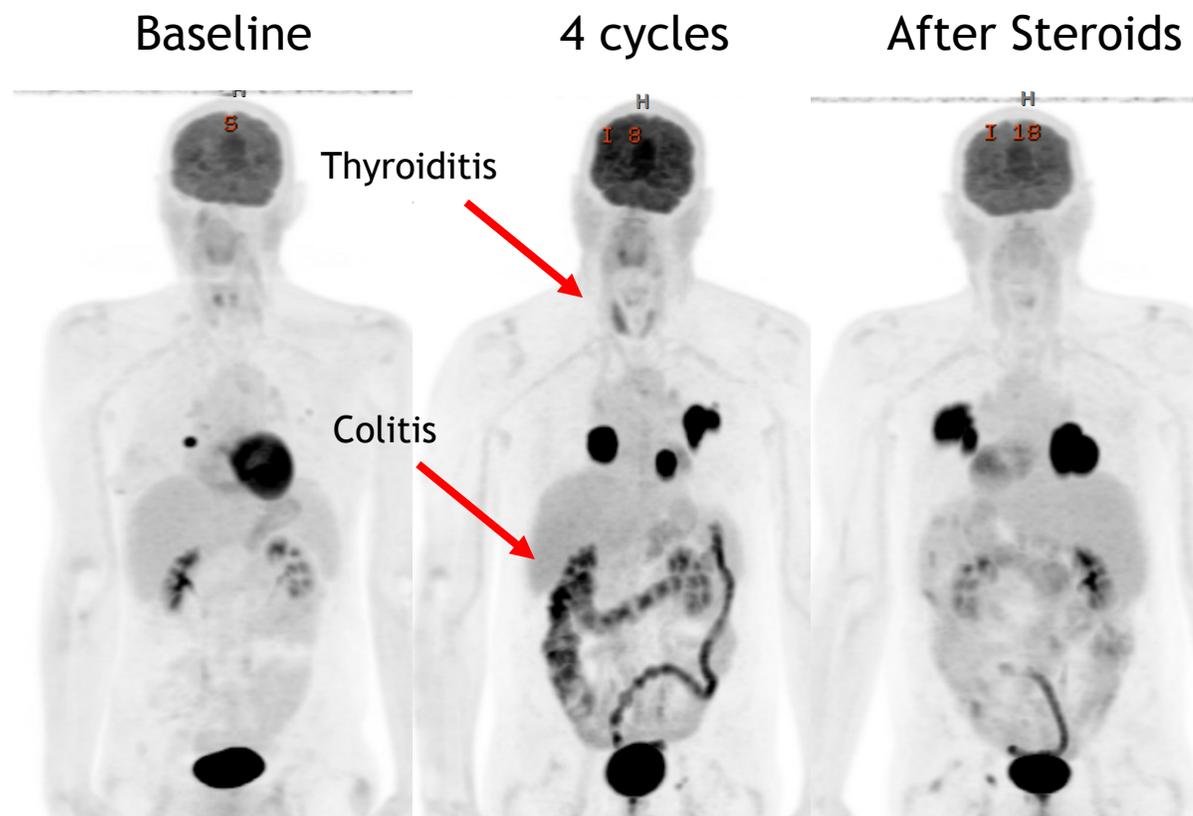
Assessing immune related side effects

- Consider pattern of new nodal and/or organ uptake
 - Here, suggests pancreatitis with or without periportal nodes with resolution at follow-up in a 29-year-old with melanoma s/p nivolumab and ipilimumab



Assessing immune related side effects

- Refer to baseline scan when organ frequently showing increased physiological uptake is thought to be involved by immune-related side effect (thyroid/colon)



65-year-old male with melanoma of the left foot metastatic to the lungs status post 4 cycles of ipilimumab

Assessing immune related side effects

- Pay attention to life-threatening adverse effects or those likely to need treatment withdrawal or corticosteroid treatment (colitis and **pneumonitis**)
- When immune-related side effects are shown on previous PET, check patients recovery



53-year-old female with diffuse large B-cell lymphoma develops pneumonitis s/p 6 cycles of CHOP-R

When do you image?

- General consensus
 - Performed before the start of immunotherapy, together with conventional contrast-enhanced CT
 - Repeated at the first treatment response evaluation, which in most cancer types is 8 or 9 weeks after the start of immunotherapy, which is generally after two or three cycles of treatment
 - Subsequent imaging with FDG-PET is recommended at the end of immunotherapy, before treatment stop.
- Much work is needed to further understand best strategy
- Many studies have tested several methods with variable, unreliable results

Different Cancers, different criteria

- General - PERCIST and EORTC
- Lung Cancer - iPERCIST
- Melanoma - PERCRIT, PERCIMT, and imPERCISTS
- Lymphoma - LYRIC
- EORTC - general response established in 1999

- There is a need for standardization; however, it is difficult given different therapies for different cancers with different responses and side effects

Conclusions

- PET/CT has many advantages in evaluating post-treatment response in cancer
- There is a need for the evaluating diagnostician to be familiar with the drugs used, the possible side effects, and how those adverse reactions may appear on PET/CT
- Familiarity with hyperprogression and pseudoprogression is paramount
- There is no standardized time table for imaging post-immunotherapy and there is a need for standardization