Immunotherapy: Imaging Challenges and Advances in Response Assessment

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Evasion of the immune system is the hallmark of carcinogenesis, mediated through specific proteins that avoid or suppress the host's immune response, allowing cancer cells to survive and proliferate.[1] These include cytotoxic T-lymphocytes-associated protein-4 (CTLA-4), programmed cell death-1 protein (PD-1), and PD-1 receptor ligand (PD-L1). These proteins are located on T-cells (CTLA-4 and PD-1) and tumour cells (PD-L1).[2] During the last two decades, various strategies have been attempted to stimulate a cancer-specific immune response in patients' bodies. These include the use of vaccines such as Bacillus Calmette-Guerin (BCG) for superficial urinary bladder tumours, cytokines, and adaptive T-cell such as Chimeric Antigen Receptor (CAR) T-cell therapy (patient's own genetically modified immune cells to fight cancer). However, a breakthrough happened in the last decade with the development and clinical availability of immune checkpoint inhibitors (ICI) as immunotherapy.[3] Immunotherapy has revolutionised the treatment of many malignancies such as melanoma, non-small cell lung cancer, and renal cell carcinoma, and continues to grow at a rapid pace. ICI–induced re-activation of the immune system is initiated by the presentation of tumour antigens to dendritic cells, which is followed by priming, trafficking, and infiltration of T-lymphocytes into the tumour microenvironment.[4] Anti-CTLA-4 (such as ipilimumab) is involved in T-cell priming, while anti-PD1 (such as nivolumab) and anti-PD-L1 (such as atezolizumab) are involved in T-cell proliferation and tumour cell death.

When first introduced, ICI was approved for the treatment of a wide range of metastatic cancers such as melanoma and lung cancers. However, based on promising results of many randomised clinical trials, immunotherapy is now approved for localised disease with the risk of recurrence in the adjuvant and neo-adjuvant settings. Recent clinical evidence also shows greater efficacy of ICI treatment in low burden disease, as it targets tumour cells well before they develop an unfavourable microenvironment.[5] Development of an unfavourable tumour microenvironment leads to resistance against ICI.

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Apart from standard imaging results of a tumour's reaction to treatment—complete and partial, response along with stable disease—ICI has been linked to unusual, atypical response patterns that are infrequently or never seen with standard cytotoxic and targeted anti-cancer therapies.[6] These unconventional patterns are classified as pseudo-progression, hyper-progression, dissociated response, and durable response.

Pseudo-progression is an initial apparent progression in tumour size or the appearance of new lesions on a computerised tomography (CT) or FDG PET/CT (Fluorodeoxyglucose positron emission tomography) scan, with improving clinical status of the patient, followed by a reduction in tumour burden, suggesting a positive response to treatment rather than true progression. It is commonly observed within the first 4–6 weeks of ICI treatment, but may also occur several months later. Proposed mechanisms include T-cells recruitment into the tumour, delayed immune delayed and post-inflammatory oedema.[7] The incidence of tumour pseudo-progression varies with tumour type (melanoma: 10-25%; non-small cell lung cancer: 6-17%)[8] and ICI (anti-CTLA-4: 10-15% anti-PD-1 /PD-L1: <10%).[9] Follow-up imaging at 4-8 weeks is recommended.[10] As no valid biochemical or radiological marker exist, diagnosis relies on discordance between the deteriorating scan and a clinically improving or stable patient. Generally, pseudo-progression is considered a reliable predictor of ICI response.[10]

Hyper-progression is defined as an increase in tumour burden after ICI treatment by a factor of two and is associated with symptomatic deterioration and premature death. It has been attributed to tumour behaviour or ICI–induced accelerated tumour growth. It is more common in elderly patients (>65 years), with MDM2/4 (Murine Double Minute) family amplification or EGFR (epidermal growth factor receptor) aberration.[11] The reported incidence of hyper-progression is 9-29%, with lower frequency of appearance of new lesions as compared to pseudo-progression.[11] It is associated with a worse prognosis, and the discontinuation of ICI is warranted to avoid premature death in patients.

Dissociated response towards immunotherapy is a mixed response where some tumours or lesions show a positive response (shrinking or stabilisation), while others progress or newly appear during treatment. The phenomenon highlights the heterogeneity within metastatic tumours, where different

lesions may have varying sensitivities to immunotherapy. The reported incidence is about 10%,[12] and it may pose a challenge to treatment decisions, as such cases may be mistakenly classified as disease progression according to the Response Evaluation Criteria in Solid Tumours (RECIST) guidelines. Various trials have shown that continuing ICI in patients with a mixed response is linked to a better prognosis than in patients with uniform progression of lesions.[13]

Durable response refers to a long-lasting complete or partial response to treatment, often observed in advanced cancers. Although no universal definition exists, it generally signifies responses that persist even after discontinuation of ICI.[14] Durable responses are thought to be related to ICI induced long-term immune cell activation against cancer cells. The reported incidence is about 10-25% (depending on tumour and ICI type), and such responses are more commonly observed in ICI–treated patients than those treated with chemotherapy or targeted therapies [25% *vs*. 11%].[15]

Response evaluation in patients treated with immunotherapy presents unique challenges due to the potential for delayed responses, atypical response patterns, and the complexity of the immune system. Traditional response criteria—morphological (such as RECIST) and metabolic (such as PERCIST-PET in solid tumours)—may not accurately capture the benefits of immunotherapy, and the potential or treatment resistance remains a concern.[16] Among the response patterns described above, pseudo-progression and hyper-progression are the most challenging to report for nuclear physicians, radiologists, and oncologists. No valid biochemical or imaging marker exists to differentiate pseudo-progression from hyper-progression. During ICI treatment, the use of conventional criteria, such as RECIST and PERCIST, may result in premature discontinuation of treatment in patients who may subsequently achieve prolonged survival.[14] To address this issue, various modified immune-related morphological criteria have been introduced, including immune-related response criteria (irRC), immune-RECIST (iRECIST), and immune-related RECIST (irRECIST). To prevent premature termination of ICI in patients who show increased tumour burden on imaging but without significant clinical deterioration, current criteria propose a wait-and-see strategy, with re-evaluation using a follow-up scan 4–8 weeks later.[14] Pseudo-progression also poses a major challenge to the interpretation of FDG PET/CT using conventional criteria such as PERCIST. Therefore, several modified metabolic criteria for response assessment in patients treated with immunotherapy have been proposed. The PET Response Evaluation Criteria for Immunotherapy (PERCIMT)[14] considers the clinical context and the appearance of more than one new lesion, rather than a more significant increase in standardised uptake value (SUV) and/or appearance of a single new lesion, and may potentially be better at distinguishing between true tumour progression and pseudo-progression. More specifically, progressive disease is defined as the appearance of either ≥4 new lesions <1 cm in functional diameter, ≥3 new lesions >1.0 cm, or ≥2 new lesions >1.5 cm. Otherwise, the patient can be classified as having pseudo-progression.[14]

A joint guideline from several nuclear medicine societies (EANM, SNMMI, and ANZSNM)[14] states that if there is uncertainty about whether a tumour is progressing or represents pseudo-progression, especially during the first post-treatment evaluation, a follow-up FDG PET/CT study should be performed 4 to 8 weeks later, provided the patient remains clinically stable. Therefore, treatment should be continued in clinically stable patients without excessive side effects, helping to prevent premature discontinuation ICI in those who may show a positive response later.[14]

FDG PET/CT is generally considered superior to contrast-enhanced CT, particularly for detecting metabolic changes indicative of response or resistance.[17] FDG PET/CT also shows higher diagnostic accuracy for assessing immune responses after ICI therapy. The initial sign of immune activation is splenomegaly and/or diffusely increased FDG uptake equal to or higher than hepatic uptake (spleen-to-liver ratio; SLR).[14] Other signs include an increased marrow-to-liver ratio and enhanced metabolic activity at the ileocecal valve. Good reproducibility has been reported for spleen and bone marrow measurements.[14] These signs are generally considered to reflect unleashed T-cells activity, with an expected better outcome. Another important role of FDG PET/CT is the detection of immune-related adverse events (irAEs), which can affect almost any organ in the body. The most common areas affected include the skin, colon, liver, lungs, endocrine organs, synovium, and joints. irAEs are considered autoimmune conditions as activated T-cells attack or infiltrate healthy tissues. They are different from chemotherapy-related adverse events, which result from cell destruction by cytotoxic agents. The higher sensitivity of FDG PET/CT compared with CT and MRI allows earlier identification of irAEs. This gives oncologists a chance to intervene before symptoms appear. Alternatively, it can be used to confirm a specific irAE when clinically suspected. While some studies have failed to establish a correlation, others suggest that patients with irAEs may experience better outcomes.[18]

The introduction of immunotherapy has transformed oncology, and ICI has revolutionised cancer treatment paradigms. Since the approval of the first ICI Ipilimumab in 2011, several additional ICI have been approved for wider clinical indications. Unusual tumour response patterns such as pseudo-progression and hyper-progression differ from those seen with cytotoxic chemotherapy because of the unique biologic mechanisms of ICI. Correct and timely identification of these non- conventional response patterns is important either to avoid premature termination of an effective ICI, or timely discontinuation of ICI in hyper-progression, thereby avoiding premature death. To address these diagnostic challenges associated with ICI, modified immune-related morphological and metabolic criteria have been proposed. FDG PET/CT is considered a more reliable and robust modality for response evaluation in immunotherapy. In addition, FDG PET/CT can also exhibit the unleashed T-lymphocytes as a sign of immune

activation. irAEs are autoimmune in nature and are becoming more frequent with the use of dual ICI therapy. FDG PET/CT is a reliable modality, as it can often detect relevant irAEs before the onset of symptoms. In Pakistan, several important immunotherapy agents— such as pembrolizumab, nivolumab, and ipilimumab— have already been approved for cancer treatment, and various clinical trials are underway in major hospitals nationwide.

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REFERENCES

1. Galassi C, Chan TA, Vitale I, Galluzzi L. The hallmarks of cancer immune evasion. *Cancer Cell* 2024; **42(11)**:1825-63. doi: 10.1016/j.ccell.2024.09.010.
2. Buchbinder EI, Desai A. CTLA-4 and PD-1 pathways: Similarities, differences, and implications of their inhibition. *Am J Clin Oncol* 2016; **39(1)**:98-106. doi: 10.1097/COC.0000 000000000239.
3. Rossi S, Toschi L, Castello A, Grizzi F, Mansi L, Lopci E. Clinical characteristics of patient selection and imaging predictors of outcome in solid tumours treated with checkpoint-inhibitors. *Eur J Nucl Med Mol Imaging* 2017; **44(13)**:2310-25. doi: 10. 1007/s00259-017-3802-5.
4. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbe C, *et al*. Guidelines for the evaluation of immune therapy activity in solid tumours: Immune-related response criteria. *Clin Cancer Res* 2009; **15(23)**:7412-20. doi: 10.1158/1078- 0432.CCR -09-1624.
5. Eggermont AMM, Blank CU, Mandala M, Long GV, Atkinson VG, Dalle S, *et al*. Adjuvant Pembrolizumab *versus* placebo in resected stage III melanoma (EORTC 1325-MG/ KEYNOTE-054): Distant metastasis-free survival results from double-blind, randomised, controlled, phase 3 trial. *Lancet Oncol* 2021; **22(5)**:643-54. doi: 10.1016/S1470-2045(21) 00065-6.
6. Borcoman E, Kanjanapan Y, Champiat S, Kato S, Servois V, Kurzrock R, *et al*. Novel patterns of response under immunotherapy. *Ann Oncol* 2019; **30(3)**:385-96. doi: 10. 1093/annonc/mdz003.
7. Gerwing M, Herrmann K, Helfen A, Schliemann C, Berdel WE, Eisenblatter M, *et al*. The beginning of the end for conventional RECIST - novel therapies require novel imaging approaches. *Nat Rev Clin Oncol* 2019; **16(7)**:442-58. doi: 10.1038/s41571-019-0169-5.
8. Waxman ES, Lee Gerber D. Pseudoprogression and Immunotherapy Phenomena. *J Adv Pract Oncol* 2020; **11(7)**: 723-31. doi: 10.6004/jadpro.2020.11.7.6.
9. Mangas Losada M, Romero Robles L, Mendoza Melero A, Garcia Megias I, Villanueva Torres A, Garrastachu Zumaran P, *et al*. [18F] FDG PET/CT in the evaluation of melanoma patients treated with immunotherapy. *Diagnostics (Basel)* 2023; **13(5)**:978. doi: 10.3390/diagnostics13050978.
10. Zhao L, Yang Y, Li W, Li T, Han L, Lin H, *et al*. Pseudo-progression: An indicator for cure in combined immuno-therapy? *Immunotherapy* 2019; **11(13)**:1087-93. doi: 10. 2217/imt-2019-0034.
11. Kato S, Goodman A, Walavalkar V, Barkauskas DA, Sharabi A, Kurzrock R. Hyperprogressors after immunotherapy: Analysis of genomic alterations associated with accelerated growth rate. *Clin Cancer Res* 2017; **23(15)**:4242-50. doi: 10.1158/ 1078-0432.CCR-16-3133.
12. Humbert O, Cadour N, Paquet M, Schiappa R, Poudenx M, Chardin D, *et al*. 18 FDG PET/CT in the early assessment of nonsmall cell lung cancer response to immunotherapy: Frequency and clinical significance of atypical evolutive patterns. *Eur J Nucl Med Mol Imaging* 2020; **47(5)**:1158-67. doi: 10.1007/s00259-019-04573-4.
13. Tozuka T, Kitazono S, Sakamoto H, Yoshida H, Amino Y, Uematsu S, *et al*. Dissociated responses at initial computed tomography evaluation is a good prognostic factor in non-small cell lung cancer patients treated with anti-programmed cell death-1/ligand 1 inhibitors. *BMC Cancer* 2020; **20(1)**: 207. doi: 10.1186/s12885-020-6704-z.
14. Lopci E, Hicks RJ, Dimitrakopoulou-Strauss A, Dercle L, Iravani A, Seban RD, *et al*. Joint EANM/SNMMI/ANZSNM practice guidelines/procedure standards on recommended use of [^{18}F]FDG PET/CT imaging during immunomodulatory treatments in patients with solid tumours version 1.0. *Eur J Nucl Med Mol Imaging* 2022; **49(7)**:2323-41. doi: 10.1007/ s00259-022-05780-2.
15. Pons-Tostivint E, Latouche A, Vaflard P, Ricci F, Loirat D, Hescot S, *et al*. Comparative analysis of durable responses on immune checkpoint inhibitors *versus* other systemic therapies: A pooled analysis of phase III trials. *JCO Precis Oncol* 2019; **3**:1-10. doi: 10.1200/PO.18.00114.
16. Kim HD, Kim BJ, Kim HS, Kim JH. Comparison of the morphologic criteria (RECIST) and metabolic criteria (EORTC and PERCIST) in tumour response assessments: A pooled analysis. *Korean J Intern Med* 2019; **34(3)**:608-17. doi: 10. 3904/kjim.2017.063.
17. Gandy N, Arshad MA, Wallitt KL, Dubash S, Khan S, Barwick TD. Immunotherapy-related adverse effects on ^{18}F-FDG PET/ CT imaging. *Br J Radiol* 2020; **93(1111)**:20190832. doi: 10. 1259/bjr.20190832.
18. Lang N, Dick J, Slynko A, Schulz C, Dimitrakopoulou-Strauss A, Sachpekidis C, Enk AH, Hassel JC. Clinical significance of signs of autoimmune colitis in 18F-fluorodeoxyglucose positron emission tomography-computed tomography of 100 stage-IV melanoma patients. *Immunotherapy* 2019; **11(8)**: 667-76. doi: 10.2217/imt-2018-0146.