The development of immune checkpoint inhibitors has revolutionized the field of cancer therapeutics, but it has also brought to forefront the issue of optimal assessment of clinical benefit during treatment with these agents. The use of these immune-activating drugs often can be associated with atypical patterns of therapeutic response, ranging from hyperprogression, pseudoprogression, and dissociated or mixed response to durable clinical responses long after discontinuation of therapy. Hyperprogression, which reflects unexpectedly rapid progression of disease in patients receiving immunotherapy (with clinically deleterious implications), has been a topic of intense discussion among oncologists. With publication of multiple clinical reports of different cancer types worldwide, hyperprogression is now accepted by most oncologists to be a true phenomenon rather than natural progression of disease. However, major limitations remain in the literature, particularly with regard to heterogeneity in assessment criteria used to define hyperprogression, the retrospective nature of analyses, and the lack of a comparator group in most studies of this phenomenon.

Park and colleagues present the results of a systematic review of hyperprogression and a meta-analysis of its incidence in patients with solid malignant neoplasms receiving immune checkpoint inhibitors, while summarizing the current challenges with regard to assessment of hyperprogressive disease. The authors have analyzed data from 24 studies, including 16 retrospective studies, 5 studies with retrospective analysis of clinical trials, and 2 prospective cohort studies, to report a 13.3% (95% CI, 10.1%-16.5%) pooled incidence of hyperprogression. Of note, the range of this incidence was wide (5.9% to 43.1%), reflecting the heterogeneity of the patient population studied and the definitions used for assessment. Those studies that reported survival outcomes found an association between hyperprogression and poor prognosis. More importantly, shorter overall survival was reported in most studies of patients with hyperprogressive disease compared with those with natural disease progression without hyperprogression, further underscoring the clinical importance of hyperprogression.

Definitions for hyperprogression vary substantially in the literature. Park and colleagues used common definitions of hyperprogression to divide the studies in their analysis into 4 broad assessment criterion categories: (1) tumor growth rate ratio, (2) tumor growth kinetics ratio, (3) early tumor burden increase, and (4) a combination of the other categories. The reported pooled incidence of hyperprogression in these 4 subgroups range from 9.4% to 20.6%. Furthermore, the authors highlighted various challenges in accurately detecting hyperprogressive disease with these nonuniform criteria, including the lack of consideration of development of new lesions or changes in nontarget lesions; lack of consensus regarding optimal time for imaging assessment; discrepancy with the commonly used Response Evaluation Criteria in Solid Tumors; and reliance on prebaseline imaging for measurement of tumor growth acceleration, which is often not available (especially in the treatment naïve settings). These challenges are reinforced by the results of a recent retrospective study of patients with advanced non-small cell lung cancer, which was not included in the current study, in which different rates of hyperprogression were detected in the same population treated with PD-1 (programmed cell death 1) or PD-L1 (programmed cell death 1 ligand 1) inhibitors according to application of various definitions used in the literature. With respect to survival outcomes, these
definitions failed to adequately discriminate between those with disease progression with vs without hyperprogression.\(^7\)

The biological underpinnings of hyperprogression and whether it has implications for survival exclusively for treatment with immune checkpoint inhibitors vs chemotherapy or molecularly targeted therapy remain unknown. Proposed contributing pathological mechanisms include modulation of tumor immune microenvironment through macrophages and regulatory T cells as well as activation of oncogenic signaling pathways.\(^3\)\(^,\)\(^8\) Risk factors for hyperprogression during immunotherapy have not been clearly validated, although some studies have reported associations between hyperprogression and \(\text{MDM2}\) or \(\text{MDM4}\) amplifications and \(\text{EGFR}\) alterations in tumor cells as well as older age, female sex, and the presence of more than 2 pretreatment sites of metastases.\(^1\)\(^,\)\(^5\)\(^,\)\(^9\) Similarly, guidance is lacking for optimal treatment of patients who experience hyperprogressive disease during immune checkpoint inhibitor therapy. As the use of immune checkpoint inhibitors is accepted in frontline settings across tumor types, including as first-line therapy for metastatic disease and adjuvant therapy for earlier stage disease, it is paramount to study hyperprogression in well-designed prospective studies.

The major barrier to development of a robust evidence-based knowledge base on risk factors, pathophysiology, early detection, and management of hyperprogressive disease remains the lack of concise and simple-to-use assessment criteria that can be used without the requirements of prebaseline imaging studies and complicated calculations. As these objective consensus criteria are being developed, incorporation of dynamic measures of patients' functional status as well as next-generation technologies, such as immunoimaging and circulating tumor DNA analysis, could be useful for further evaluation in prospective studies and real-world large data sets.

**ARTICLE INFORMATION**


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