Technology in Cancer Research & Treatment
Volume 22: 1-9

DOI: 10.1177/15330338231209129
journals.sagepub.com/home/tct

Hyperprogressive Disease (HPD) in Solid Tumours Receiving Immune Checkpoint Inhibitors in a Real-World Setting

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Abstract

Introduction: Hyperprogressive disease (HPD) is a state of accelerated tumor growth from cancer immunotherapy, associated with poor outcome. The reported incidence is 6% to 29% among studies using varying definitions of HPD, with no predictive biomarkers. Tumor infiltrating lymphocytes (TILs) are prognostic and predictive for immunotherapy benefit in various tumor types, but have only been tested for correlation with HPD in one study. **Objectives:** The objective of the study was to determine the prevalence of HPD in solid tumor patients treated with immune checkpoint inhibitor therapy in a real-world setting, and to assess clinicopathological features as potential biomarkers for HPD. **Methods:** We conducted a retrospective analysis of solid tumor patients treated with immune checkpoint inhibitors at a single institution. Imaging pre-immunotherapy and postimmunotherapy were assessed for HPD, and correlated against clinicopathological factors, including TILs and programmed death-ligand 1 (PD-L1) status through archival tumor assessment. HPD was defined per Matos et al as response evaluation criteria in solid tumors (RECIST) progressive disease, minimum increase in measurable lesions of 10 mm, plus increase of $\geq$40% in sum of target lesions compared with baseline and/or increase of $\geq$20% in sum of target lesions compared with baseline plus new lesions in at least 2 different organs. **Results:** HPD occurred in 11 of 87 patients (13%), and associated with inferior overall survival (median 5.5 months vs 18.3 months, $P = .002$). However, on multivariate analysis, only liver metastases (hazard ratio [HR] 4.66, 95% confidence interval [CI] 2.27-9.56, $P < .001$) and PD-L1 status (HR 0.53, 95% CI 0.30-0.95, $P = .03$) were significantly associated with survival. Presence of liver metastases correlated with occurence of HPD ($P = .01$). Age, sex, and monotherapy versus combination immunotherapy were not predictive for HPD. PD-L1 status and TILs were not associated with HPD. **Conclusions:** We found 13% HPD among solid tumor patients treated with immunotherapy, consistent with the range reported in prior series. Assessment for HPD is feasible outside of a clinical trials setting, using modified criteria that require comparison of 2 imaging studies. Liver metastases were associated with risk of HPD, while TILs and PD-L1 status were not predictive for HPD.

Keywords

hyperprogressive disease, hyperprogression, immunotherapy, checkpoint inhibitor, PD-1, PD-L1, tumor infiltrating lymphocytes

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Abbreviations

CI, confidence interval; CT, computed tomography; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; HPD, hyperprogressive disease; HR, hazard ratio; OS, overall survival; NLR, neutrophil-to -lymphocyte ratio; PET, positron emission tomography; PD, progressive disease; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; RECIST, response evaluation criteria in solid tumors; TGR, tumor growth rate; TILs, tumor infiltrating lymphocytes; TPS, tumor proportion score; TTF, time to treatment failure

Received: June 15, 2023; Revised: September 15, 2023; Accepted: October 4, 2023.

Introduction

Immune checkpoint inhibitor therapy has revolutionized the field of oncology, and utilized in numerous tumor types including melanoma, lung, renal cell, urothelial, and head and neck squamous cell carcinoma.[1] An advantage from immunotherapy is the durability of treatment response, in contrast to chemotherapy and targeted treatment where resistance ultimately develops in the majority of patients. In line with their unique mechanism of action of immune stimulation, immune checkpoint inhibitor response may display atypical patterns as compared to conventional cytotoxic therapies.[2] Pseudoprogression is a phenomenon where an initial scan suggests disease progression, but is not confirmed on a followup scan at least 4 weeks later; and a subsequent tumour response can be seen.[3] In order to account for the possibility of pseudoprogression, immune-related response evaluation criteria in solid tumors (RECIST), or irRECIST has been developed where progressive disease needs to be demonstrated on a confirmatory scan 4 to 12 weeks later.[4]

Recently, hyperprogression, defined as an accelerated rate of tumor growth, has been reported in 4% to 29% of solid tumor patients treated with immune checkpoint inhibitor therapy.[2,5] Hyperprogressive disease (HPD) has been associated with poor outcome and survival. The ability to predict for HPD would avoid ineffective and potentially harmful therapy in patients. No biomarker has been consistently shown to predict for HPD.[6,7,8] Despite being highly prognostic for outcome to immunotherapy in a variety of tumor types, tumor infiltrating lymphocytes (TILs) have only been assessed for correlation with HPD in one other study.[9] Having reliable biomarkers for HPD is important to avoid harm from immunotherapy in patients but without denying effective treatment from patients who may benefit.

Distinguishing HPD from tumor growth as part of natural history of cancer progression is problematic. To overcome this, the original definition of HPD compares the assessment of tumor growth rate (TGR) prior to and after commencement of immune checkpoint inhibitor therapy.[5] However, in routine clinical practice outside of a clinical trial, having a "reference scan" 2 weeks to 3 months prior immunotherapy commencement, in order to calculate the TGR prior to immune checkpoint therapy is not always possible. Consequently, alternative definitions of HPD were derived including study by Matos et al[10] which only require assessment of 2 (pretreatment and post-treatment) scans.

Use of immune checkpoint inhibitors are now prevalent in oncology with a substantial proportion of treatment taking place in the community, outside of a clinical trial setting. The objective of the study was to determine the prevalence of HPD in solid tumor patients treated with immune checkpoint inhibitor therapy in a real-world setting, and to assess clinicopathological features as potential biomarkers for HPD. We adopted a pragmatic approach by using the definition for HPD by Matos et al,[10] requiring only 2 radiological scans, and focused on pathological factors readily available in most community centers (PD-L1 staining and TILs) in the assessment of potential biomarkers.

Materials and Methods

This is an observational study with retrospective analysis on consecutive patients treated with immune checkpoint inhibitors for solid tumors between March 2014 and March 2019, at The Canberra Hospital, Canberra, Australia. Eligible patients had a histologically confirmed diagnosis of solid organ malignancy and received at least 1 dose of immune checkpoint inhibitor therapy, with either an anti-PD-1 (programmed death-1), anti-PD-L1, anti-CTLA (cytotoxic T-lymphocyte-associated protein) or their combination. The study was approved by the local institutional ethics committee (Australian Capital Territory Health Human Research Ethics Committee, 2019.LRE.00213/2019/ETH13289). The reporting of this study confirms to the STROBE guidelines.[11] Immunotherapy drugs have a long half-life, and durable response beyond discontinuation of the agent has been observed.[2] Consequently, for the present study, where a patient received 2 courses of immunotherapy in their lifetime, the earlier immunotherapy treatment regimen was selected for analysis to avoid any potential confounding impact of the prior immunotherapy regimen on response to subsequent courses of treatment.

Hyperprogressive Disease Definition

The TGR and HPD were assessed using the method published by Matos et al[10] described as follows. Target lesions were assessed between imaging at baseline pretreatment and within 8 weeks post-treatment. Computed tomography (CT) was used for assessment and if not unavailable, the CT portion of the fluorodeoxyglucose positron emission tomography (FDG PET)/CT study was utilized. HPD was defined as RECIST

1.1 progressive disease, minimum increase in the measurable lesions of 10 mm, plus increase of ≥40% in sum of the target lesions compared with baseline and/or increase of ≥20% in sum of the target lesions compared with baseline plus new lesions in at least 2 different organs.[10] Clinicopathological, treatment and survival data were derived from institutional electronic health records.

PD-L1 and TILs Analysis

Archival tumor samples were analyzed for PD-L1 status using immunohistochemistry via the Ventana SP142 PD-L1 clone. The archival samples included formalin-fixed paraffin-embedded blocks of tumor as well as cell blocks from cytology specimens. The tumor proportion score (TPS) was used to assess the PD-L1 expression in tumor. PD-L1 TPS was expressed as a percentage between 0 and 100. PD-L1 expression was classified as positive (≥1%) or negative (0%); and also into 3 subgroups of PD-L1 negative, moderate or high, defined as 0%, 1% to 59%, or ≥60%, respectively. Presence of TIL was assessed peripherally and centrally, each as 0, 1+, 2 + or 3 + to derive a total TILs score. TILs were classified as either present or absent, and also into 3 subgroups of negative, 1, 2+, and 3 + . Assessment was performed by one pathologist and equivocal cases reviewed by a second pathologist to resolve any queries.

Statistical Analysis

Due to the retrospective nature of the study, no power calculation has been performed. Association between HPD and clinicopathological factors were tested. Assessment of HPD status against categorical factors was performed using Fisher's exact or chi-square test. Assessment of HPD status against continuous variable (such as age) was performed using generalized linear models (univariate regression) or Mann-Whitney's test. These factors were also assessed against percentage change in tumor size to test for any association using linear models (analysis of variance, ANOVA). Survival was estimated by the Kaplan-Meier method and compared between groups using log-rank test.

Results

Patient Demographics

There were 87 cases satisfying criteria for analysis (after exclusion of 88 cases due to inadequate imaging and 28 cases due to inadequate archival tumor sample). Demographic features of the analyzable cases are shown in Table 1; with median age at the start of immune checkpoint inhibitor therapy was 69 years, with 59% being male. The commonest tumor type was lung cancer (51%), followed by melanoma (37%), with others being genitourinary (9%), head and neck (2%), and gynaecological cancers (1%). The majority (87%) of patients in the cohort received single agent immunotherapy [anti-PD(L)1 in 78% and anti-CTLA4 in 9%], with 13% treated with combination immunotherapy. The treatment responses were stable disease in 43 (49%), partial response in 20 (23%), progressive disease (PD) without satisfying HPD criteria in 13 (15%) and HPD in 11 (13%).

HPD Cases

Among the 11 hyperprogressive cases, percentage change in tumor growth was between 30% and 105%. The majority (9, 82%) of the HPD cases had tumor growth above 40% on immunotherapy. Two cases, with 30% and 37% tumor growth, respectively, were classified as HPD given each had new lesions developed in at least 2 organs in their experimental scans. Examples of imaging for HPD are shown in Figure 1.

Survival and Hyperprogression

Patients who had HPD had a significantly inferior median overall survival (OS) of 5.5 months, compared with 18.3 months among patients without HPD (hazard ratio [HR] 2.93, 95% confidence interval [CI] 1.45-5.93, $P = .002$; Figure 2). Comparing HPD with the subgroup with non-HPD PD, the median OS was 5.5 months among HPD and 5.8 months among non-HPD PD patients (HR 1.93, 95% CI 0.75-4.97, $P = .12$; Figure 3); with a total of 24 patients in this comparison.

Given lung cancer and melanoma patients represent the largest subgroups in the study population (51% and 37% respectively), univariate analyses for survival outcome by HPD status were analyzed separately within these subgroups. The relationship between HPD and survival for lung cancer and melanoma patients were consistent with that for the study population. Among patients with lung cancer, median OS was 2.2 months among those with HPD and 15.1 months among those without HPD (HR 2.97, 95% CI 1.44-6.12, $P = .003$). Among patients with melanoma, median OS was 5.5 months among those with HPD and 26.9 months among those without HPD (HR 3.33, 95% CI 1.53-7.21, $P = .002$).

On multivariate Cox proportional hazards model, HPD was no longer significantly associated with OS. However, liver metastases (HR 4.66, 95% CI 2.27-9.56, $P < .001$) and positive PD-L1 staining (HR 0.53, 95% CI 0.30-0.95, $P = .03$) were associated with OS (Table 2). When lung cancer and melanoma were incorporated in the multivariate model, there was a non-significant association between lung cancer compared with other diagnoses for poorer overall survival (HR 1.76, 95% CI 0.93-3.3, $P = .08$, Supplemental Table 3), while diagnosis of melanoma was associated with improved survival (HR 0.53, 95% CI 0.27-1.01, $P = .53$, Supplemental Table 4). However, liver metastases remained the strongest predictive factor for poorer survival across all multivariate analyses, while PD-L1 staining had a moderate predictive power for better survival.

PD-L1 and HPD

Overall, in this cohort PD-L1 positivity was present in 39 of 78 (50%) cases among a range of tumor types (Supplemental Table 1). Within the PD-L1 positive cases, there were similar proportions of high (18 of 39) and moderate (21 of 39) expression

Table 1. Patient Characteristics.

Characteristic (n)	HPD (11)	Non-HPD (76)	Total (87)	*P*-value
Sex				.51
– Male	5	46	51 (59%)	
– Female	6	30	36 (41%)	
Age (median, years)	67.9	72.0	68.9	
Tumor type				
– Lung	5	39	44 (51%)	
– Melanoma	6	26	32 (37%)	
– Genitourinary	-	8	8 (9%)	
– Head and neck	-	2	2 (2%)	
– Gynaecological	-	1	1 (1%)	
Liver metastases				.01
– Present	7	17	24 (28%)	
– Absent	4	59	63 (72%)	
Metastatic sites				.20
– ≤2	5	50	55 (63%)	
– >2	6	26	32 (37%)	
Immunotherapy				1.00
– PD(L)1	8	60	68 (78%)	
– CTLA4	2	6	8 (9%)	
– PD(L)1 and CTLA4	1	10	11 (13%)	
Number of cycles (median, range)	4 (2-11)	6.5 (1-62)	6 (1-62)	
PD-L1				.31
– Positive	3	36	39 (45%)	
– Negative	7	32	39 (45%)	
– Unknown	1	9	10 (11%)	
TILs				.74
– Positive	5	39	44 (51%)	
– Negative	5	29	34 (39%)	
– Unknown	1	8	9 (10%)	
NLR (median)	3.33	3.59	3.53	.70
Neutrophil count (median, $\times 10^9$/L)	4.67	4.89	4.77	.53
CRP (median, mg/dL)	47.25	50.6	50.6	1.00
LDH (median, U/L)	413	289	292	.09

Abbreviations: CRP, C-reactive protein; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PD-L1, programmed death-ligand 1; TIL, tumor infiltrating lymphocyte.

cases. PD-L1 status was not known for 9 cases. The majority (70%) of HPD cases had tumors staining negative for PD-L1, compared to non-HPD cases (47%). Among the 3 HPD cases which were PD-L1 positive, only 1 of 3 had high-intensity PD-L1 staining; the remaining 2 of 3 had moderate PD-L1 level. However, no statistically significant correlation between PD-L1 staining and HPD status could be demonstrated ($P = .558$).

TILs and HPD

There were similar distributions of cases with and without TILs among HPD and non-HPD cases. TILs were present in 39 (57%) of non-HPD cases and 5 (50%) of HPD cases (Supplemental Table 2).

Clinical Factors and HPD

HPD was significantly associated with liver metastases, which were present in 7 of 11 (64%) patients in the HPD versus 17 of 76 (22%) in the non-HPD group ($P = .01$). We did not observe an association between HPD and age, whether expressed as continuous variable or stratified between ≤65 and >65 years cutoff. Similarly, there was no correlation observed between HPD and sex or type of immunotherapy (monotherapy or combination) (Table 1). Other potential laboratory and clinical biomarkers examined include neutrophil-to-lymphocyte ratio (NLR), absolute neutrophil count, C-reactive protein, lactase dehydrogenase, and presence of greater than 2 metastatic sites; which were not associated with HPD in this dataset.

Percentage Change in Tumor Size

In assessing percentage change in tumor size; there was no significant association with presence or absence of TILs, or positive or negative with PD-L1 status. Similarly, there was no correlation observed between percentage change in tumor size and clinical variables (age or sex). An association was observed

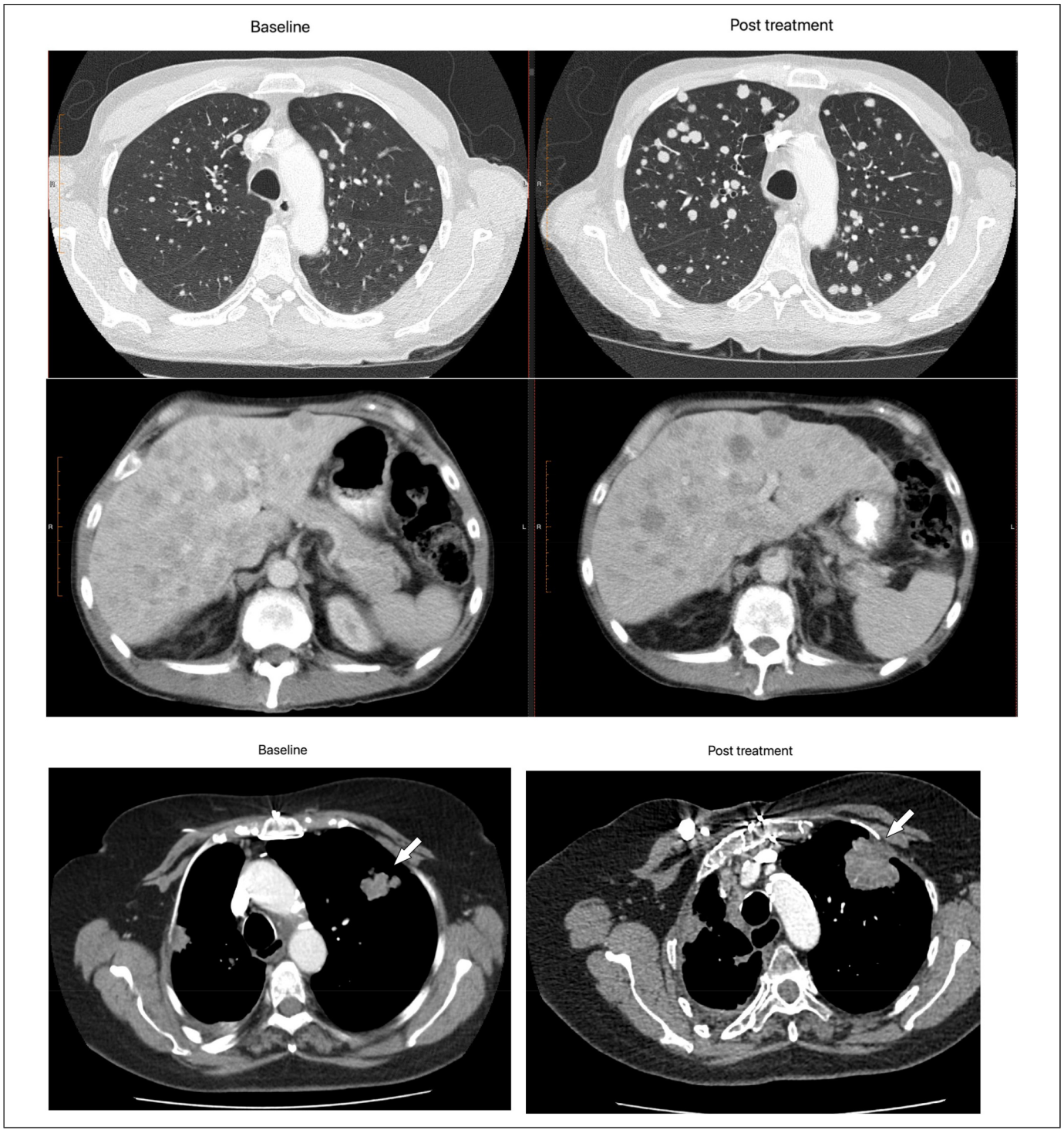

Figure 1. The top row demonstrates pulmonary metastases in a melanoma patient at baseline (left) and progression after treatment with 5 cycles of pembrolizumab immunotherapy (right). The middle row shows concurrent liver metastases in the same patient at baseline (left) and progression following immunotherapy (right). The bottom row shows another patient where the left upper lobe lung primary at baseline (left) demonstrates increase in size by 71% (right) following 6 cycles of nivolumab immunotherapy.

between the type of immunotherapy and the percentage change in tumor size, with mean of 6% increase in tumor size with monotherapy versus 35% decrease with combination immunotherapy ($P = .02$).

Discussion

Our cohort was able to confirm an inferior outcome among patients with HPD on cancer immunotherapy, as shown in multiple series.[5,9,10,12–19] Many series focused on single tumor

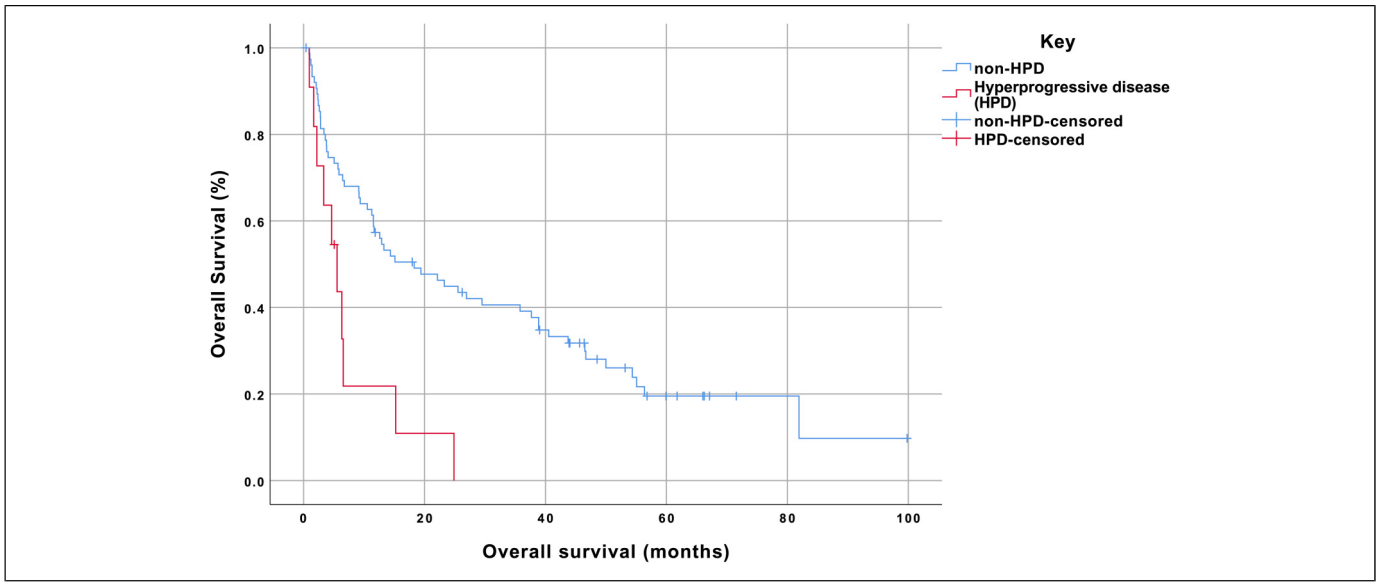

Figure 2. Overall survival of patients with HPD compared with the rest of the cohort. Abbreviation: HPD, hyperprogressive disease.

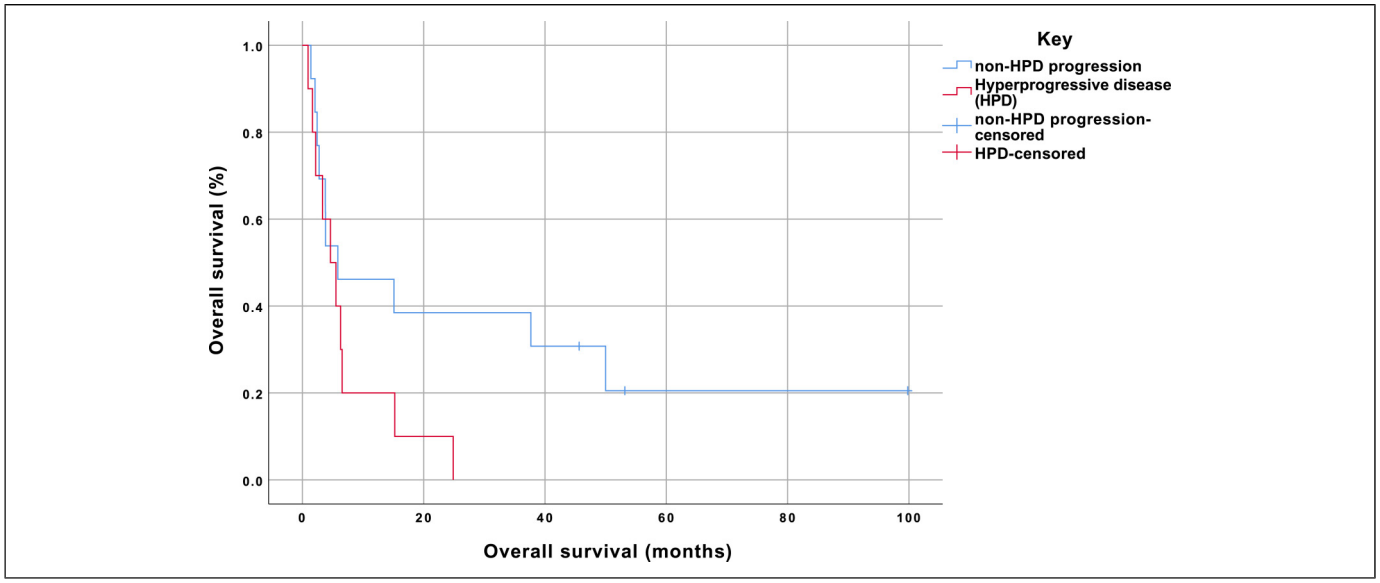

Figure 3. Overall survival of patients with HPD compared with non-HPD progression. Abbreviation: HPD, hyperprogressive disease.

populations, such as lung,[9,13,16,18] gastric,[12] and head and neck cancers;[19] while others included mixed tumor populations.[5,10,14,15,17] We observed a median OS of 5.5 months in patients with HPD compared with 18.3 months for the rest of the study population ($P = .002$). However, we were unable to demonstrate a difference in OS between patients with HPD and non-HPD progression (median OS 5.5 vs 5.8 months, respectively, $P = .12$). Other larger series have shown those with HPD had worse survival outcome than with "conventional" non-HPD progression.[9,10,13,16,18]

Furthermore, we observed that on multivariate analysis, the impact of HPD status on survival no longer reached statistical significance. The presence of liver metastases was significantly associated with reduced survival (HR 4.66, $P < .001$) and positive PD-L1 staining associated with increased survival (HR 0.53, $P = .03$). These findings are as expected, given metastatic disease to the liver is a known poor prognostic factor in many solid tumors.[20] Additionally, positive PD-L1 staining correlates with improved response to immune checkpoint inhibitors in nonsmall-cell lung[21] and triple negative breast cancers,[22] which can account for the improved survival of PD-L1 positive cases in this cohort of solid tumor patients treated with immunotherapy.

We utilized the HPD definition by Matos et al, being RECIST progressive disease in the first 8 weeks after treatment initiation, minimum increase in the measurable lesions of 10 mm, plus

Table 2. Multivariate Cox Regression Analysis for Overall Survival.

Factor	Hazard ratio (95% confidence interval)	*P*-value
HPD	1.29 (0.54-3.06)	.56
Liver metastasis	4.66 (2.27-9.56)	<.001
NLR	1.00 (0.99-1.02)	.75
TILs	1.14 (0.64-2.01)	.66
PD-L1	0.53 (0.30-0.95)	.03

Abbreviations: HPD, hyperprogressive disease; NLR, neutrophil-to-lymphocyte ratio; PD-L1, programmed death-ligand 1; TIL, tumor infiltrating lymphocyte.

increase of ≥40% in sum of the target lesions compared with baseline and/or increase of ≥20% in sum of the target lesions compared with baseline plus new lesions in at least 2 different organs.[10] The reason for selecting this definition was the lack of requirement of a reference scan, which was not always available in our cohort of patients predominantly treated within a standard of care setting. Another definition which does not require a reference scan (in order to calculate tumor growth rate or kinetic in the immediate, pre-immunotherapy period) is one by Kato et al, defining HPD as time to treatment failure (TTF)< 2 months, RECIST >50%, and progression pace >2-fold.[17] A strength in Katos' definition is the incorporation of TTF, which will exclude rare instances of pseudoprogression, where an initial tumor "flare" is followed by response.[2] Patients experiencing pseudoprogression are expected to continue on immunotherapy, as opposed to patients with HPD who will be ceasing treatment early due to lack of clinical benefit.[6]

Comparison between different definitions found the rate of HPD varied between 8.4% and 32.4% among a cohort of 182 patients with advanced cancer in early-phase clinical trials.[14] An analysis focused on 406 non-small cell lung cancer (NSCLC) patients assessed for HPD with 5 definitions (including TGR and tumor growth kinetic [TGK]) found the occurrence of HPD ranging between 5.4% and 18.4%, with only 4.7% of patients classified as HPD by all definitions.[16] Furthermore, the setting in which the immune checkpoint therapy was used may affect the incidence, with HPD occurring in 0.7% versus 8.8% when the atezolizumab (anti-PD-L1 antibody) was used in the first versus subsequent line setting for NSCLC.[23] Our rate of 13% HPD is within the range reported by most prior series, although a wide range (6-29%) in HPD incidence has been previously reported.[24,25] HPD has also been described with chemotherapy, although at lower frequency than with immune checkpoint inhibitors.[12,13] However, HPD has stronger prognostic significance when occurring due to nivolumab than due to irinotecan in a cohort of patients with gastric cancer[12]; implying that the hyperprogression phenomenon is most relevant for cancer immunotherapy. Furthermore, a pooled analysis of NSCLC patients treated with atezolizumab with/without chemotherapy found HPD occurred in 0.7% of patients treated in the first line, compared with 8.8% in the second/later-line setting.[23]

There are a number of putative mechanisms for development of HPD.[26] One hypothesis is the interaction between the Fc fragment of anti-PD-1 antibodies, with Fcγ receptors of M2-like macrophages, which were enriched in tumors of patients who experience hyperprogression.[9] An alternative explanation proposed for HPD was through anti-PD-1 antibodies activating increased proliferation of PD-1 + regulatory T cells (Tregs), in turn inhibiting antitumor immunity.[27] Recently, preclinical work has shown elevated tumoral fibroblast growth factor 2 and beta-catenin signaling to drive hyperprogression during immune checkpoint therapy, and targeting this pathway can prevent HPD.[28]

Our observation of HPD cases being more likely PD-L1 negative (70%) compared to non-HPD cases (47%) is intriguing, pending validation in a larger cohort. Others have not found an association between PD-L1 status and HPD.[5,13,18,23,29] However, in a meta-analysis of studies examining HPD,[24] PD-L1 expression was inversely associated with HPD (odds ratio 0.6, $P = .044$), although the small study effect was present. Tumor PD-L1 staining has been shown to be a predictive biomarker for immunotherapy response in metastatic NSCLC and triple negative breast cancer.[22,30] However, this is not a universal observation, such as in melanoma where immunotherapy benefit if regardless of PD-L1 expression; and other factors are likely at play.

Presence of TILs has been shown to be both a prognostic and predictive marker for triple negative breast cancer and immunotherapy.[31] We therefore hypothesized whether an inverse relationship may exist between degree of TILs and occurrence of HPD on immunotherapy. No association was determined in our study, with approximately equal proportions of TILs rich and poor tumors among HPD and non-HPD cohorts. Our findings are consistent with Lo Russo et al,[9] who also found no differences in subsets of TILs among the HPD compared to non-HPD patients. However, it may be one particular subset of TILs which is relevant. Kamada et al[27] reported that actively proliferating PD-1 + effector Treg cells presence was a marker for HPD in a cohort of patients with gastric cancer treated with anti-PD-1 antibody, although this remains to be demonstrated for other tumor types. Another approach taken was immunophenotyping of peripheral blood CD8+ T lymphocytes, with finding of a lower frequency effector/memory subsets (CCR7-CD45RA- CD8 T cells) and higher exhausted TIGIT + PD-1 + CD8+ T cell among patient with HPD.[18] Interestingly, direct assessment of tumor reactive T lymphocytes (PD-1 + CD8+) did not reveal a correlation with HPD.

Other potential biomarkers for HPD[8] reported in other series include increased age,[5] lower age,[23] elevated lactate dehydrogenase level,[24] platelet count,[23,29] more than 2 metastatic sites,[23,24] liver metastases,[24] Royal Marsden Hospital prognostic score of 2 or higher,[24] tumor-associated M2 macrophages,[9] MSM2/MDM4 amplifications, and epidermal growth factor receptor alterations.[17] An association between HPD and NLR was shown in a series of 50 NSCLC patients,[29] and in a pooled analysis of 3129 NSCLC patients treated with atezolizumab (although 57% of patients received immunotherapy combined with chemotherapy).[23] In contrast, a study of 263 NSCLC patients as well as ours, did not support a correlation with NLR.[18] 18F-FDG PET/CT is an emerging tool for

assessment of HPD, with significant correlation shown between HPD and baseline tumor burden, represented through metabolic tumor volume (MTV) and total lesion glycolysis (TLG).[29] Increased MTV and TLG were predictive for HPD, whereas calculation of maximum standardized uptake value or mean standardized uptake value alone were not.[29] As PET/CTs are increasingly utilized as routine baseline imaging, there is a potential practical applicability of this for HPD assessment.

Recognizing differences exists between HPD definitions, we sought to examine the relationship between percentage change in tumor size with clinicopathological factors. The analysis of percentage change in tumor size as a continuous variable, has a potential advantage in detecting possible associations with putative biomarkers which maybe missed through assessment of a binary definition (HPD vs non-HPD) in a small cohort. However, no relationship was found between percentage change in tumor growth with the clinicopathological factors (age, sex, PD-L1, and TILs) examined in our cohort. While there was an apparent statistically significant association between percentage change in tumor growth with the type of immunotherapy, this is likely a reflection of high response rate related to combination compared with single-agent immunotherapy in general.

To date, HPD has been reported in series derived from clinical trial patients and/or large academic centers. We were able to demonstrate that (i) assessment of HPD is feasible and (ii) the rate of HPD is comparable in a community "real–world" setting. In contrast, other published studies for HPD have predominantly been performed in clinical trial patients where timing for radiological assessment is more strictly defined. Additionally, we focused on assessment of potential biomarkers (PD-L1 and TILs) that are readily available in the majority of pathology laboratories that could be applied in routine daily practice if validated.

We acknowledge the limitations of our retrospective analysis and inherent bias that may influence assessment of biomarkers associated with HPD. Additionally, due to the sample size our findings will need to be validated in larger series. There was no sample size calculation for this study due to its retrospective nature. We were unable to assess for TGR due to absence of a reference scan, therefore unable to apply alternate definitions of HPD to our cohort. Further assessment of our cohort including genomic analysis of HPD cases and assessment of additional clinicopathological factors is planned.

Conclusions

Our cohort demonstrated the occurrence of HPD in 13% of solid tumor patients treated with immune checkpoint inhibitors, predominantly outside of a clinical trial setting. We validated the inferior survival outcome with HPD, consistent with prior studies. The clinical implication of our study findings is that HPD occurs uncommonly, and is associated with significant inferior patient outcome. Awareness and early recognition of this phenomenon has practical implications for the treating clinician, who should apply caution in treatment beyond radiological progression in a clinically deteriorating patient who maybe expressing hyperprogression. In this scenario, prompt cessation of immunotherapy and switching to alternate treatment should be instigated. We have demonstrated the feasibility of assessing for hyperprogression in the community practice setting, using modified criteria that require comparison of 2 imaging studies. Presence of liver metastases was the only predictor for HPD. A potential inverse relationship between PD-L1 status and HPD could be further explored in larger series.

Declaration of Conflicting Interests

YK has received consulting fees from Novartis. DY has received consulting fees from AstraZeneca.

Ethics Approval

The study was approved by the Australian Capital Territory (ACT) Health Research Ethics Committee (2019.LRE.00213/2019/ETH13289). A waiver of consent was granted.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The study received a grant from The Canberra Hospital Private Practice Association Fund.

Informed Consent

Not applicable, because this article does not contain any studies with human or animal subjects.

Trial Registration

Not applicable, because this article does not contain any clinical trials.

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Supplemental Material

Supplemental material for this article is available online.

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