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Is there an association between lymph node size and hyperprogression in immunotherapy-treated patients?

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Abstract

Background: Hyperprogressive disease (HPD) can be described as an accelerated increase in the growth rate of tumors combined with rapid clinical deterioration observed in a subset of cancer patients undergoing immunotherapy, specifically with immune checkpoint inhibitors (ICIs). The reported incidence of HPD ranges from 5.9% to 43.1% in patients receiving ICIs. In this context, identifying reliable predictive risk factors for HPD is crucial as it may allow for earlier intervention and ultimately improve patient outcomes.

Methods: This study retrospectively analyzed ten metastatic renal cell carcinoma (mRCC) patients. The identification of HPD was based on the diagnostic criteria proposed by Ferrara R *et al.* This study aimed to investigate whether there is an association between LN size and HPD using a cutoff value of 3 cm for LN size. Given the limited sample size, Fisher's exact test was used to test this association. We conducted a Kaplan-Meier (KM) analysis to estimate the median overall survival (OS) of patients with HPD and compared it to those without HPD.

Results: Three patients (30%) developed HPD, while seven (70%) did not. Fisher's exact test revealed a statistically significant association between the HPD and LN size ≥ 3 cm (p=0.008). In the HPD group, the median OS was significantly shorter, with a median OS of 3 months, whereas in the non-HPD group, the median OS was not reached (P =0.001).

Conclusion: The present study found a significant association between LN size ≥ 3 cm in the pretreatment period and HPD development.

Keywords: Hyperprogressive Disease, Immunotherapy, Lymph Nodes, Renal Cell Carcinoma, Risk Factors.

What is new? What is important?

1. Hyperprogressive disease (HPD) has garnered the attention of clinical oncologists and is now widely recognized as a significant challenge in the era of immunotherapy with a high mortality rate.
2. There is a need for reliable predictive biomarkers that can help identify patients at risk for HPD before it occurs.
3. The presence of lymph nodes measuring three centimeters or more in patients with renal cell carcinoma who have undergone treatment with immune checkpoint inhibitors is associated with HPD.

INTRODUCTION

Renal cell carcinoma (RCC) is the sixth-most prevalent cancer in males and the ninth-most prevalent in females, representing 3.7% of all new cancer cases [1][2]. The most prevalent subtype is clear-cell RCC (ccRCC), which accounts for approximately 70% of cases [2]. RCC is an immunogenic tumor; it is known to elicit immune dysfunction by infiltrating immune-inhibitory cells, such as regulatory T cells (Treg) and myeloid-derived suppressor cells, into the tumor microenvironment (TME) [3].

Several mechanisms have been proposed to explain how these tumor-infiltrating cell types block the development of an effective anti-tumor immune response, including the upregulation of suppressive factors like checkpoint molecules, which inhibit the activity of effector T cells and antigen-presenting cells [3]. The use of immune checkpoint inhibition as a way to target immune suppression elicited by tumor cells has revolutionized cancer therapeutics and is considered to be the mainstay treatment of advanced RCC (aRCC) [4]. ICIs are a type of immunotherapy used to treat

cancer by blocking the inhibitory signals cancer cells use to evade the immune system. They target specific proteins, called checkpoint proteins, that are found on the surface of cancer cells and immune cells. These checkpoint proteins act as a "brake" on the immune system, preventing it from attacking and eliminating cancer cells [5][6].

Recent years have seen promising and remarkable responses in numerous cancer patients through the use of ICIs that act against cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), programmed death -1 (PD-1), and programmed death-ligand 1 (PD-L1) [7]. Currently, there are seven FDA-approved ICIs categorized into three groups, including PD-1 inhibitors (pembrolizumab, nivolumab, and cemiplimab), PD-L1 inhibitors (durvalumab, atezolizumab, and avelumab), and CTLA-4 inhibitors (ipilimumab) [8]. However, using ICIs is ineffective in all patients, and in some cases, it can be complicated by hyperprogression.

HPD is a phenomenon in which the disease rapidly progresses in patients receiving ICIs, which has raised significant concern among oncologists due to its harmful effects [9]. The definition of hyperprogression varies across studies, with some using radiological criteria such as measuring tumor growth rate (TGR) or tumor growth kinetics (TGK), while others rely on clinical measures such as time to treatment failure, the appearance of new lesions and performance status and others use combinations of these categories. This lack of consensus makes it challenging to compare results across studies and could lead to confusion in clinical practice [10]. However, despite the growing recognition of hyperprogression as a phenomenon associated with ICIs, many unanswered questions remain about its underlying mechanisms and risk factors [11].

Finally, there is a need for reliable predictive biomarkers that can help identify patients at risk of hyperprogression before it occurs. While some studies have suggested potential genomic markers using next-generation sequencing (NGS), looking for MDM2/4 and EGFR gene alterations as potential HPD predictive biomarkers [12], there still needs to be validated biomarkers that are less expensive, widely accessible, and can be easily used in clinical practice. Identifying such biomarkers could help improve patient selection for ICIs and potentially reduce the risk of hyperprogression in a subset of patients. Therefore, there is a pressing need for more research efforts to identify and validate predictive biomarkers for hyperprogression in different cancer types.

MATERIALS AND METHODS

STUDY DESIGN

This retrospective single-center study included 10 mRCC patients diagnosed between 1 January 2018 and 1 January 2022 and followed up until 1 December 2022 at our Oncology Department at MCAC in Jordan.

PATIENT SELECTION

The study enrolled ten mRCC patients. The patients were selected based on their medical records from the hospital's electronic database. The inclusion criteria were: (1) 18 years old and above; (2) patients with metastatic renal cancer; (3) patients who received previous lines of targeted therapy (TT); (4) patients who received ICIs as part of their treatment regimen; (5) patients with pathological LN metastasis; (6) patients who did not respond to ICIs were required to have at least three radiologic examinations (pre-baseline, baseline, and postbaseline); a minimum of two CT scans (pre-baseline and baseline) before initiating ICIs therapy and one CT scan during treatment (postbaseline). Patients who did not meet these criteria were excluded from the study.

DATA COLLECTION

Data was collected from the patient's medical records, including age, sex, histological subtype, presence or absence of sarcomatoid features, size of LN before ICIs treatment, number of metastatic sites, Eastern Cooperative Oncology Group (ECOG) performance status, nephrectomy status, and tumor response. Tumor response during the first posttreatment CT evaluation was classified based on the Response Evaluation Criteria in Solid Tumors (RECIST) criteria 1.1 as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). HPD was diagnosed according to Ferrara R *et al.* criteria (percentage change of TGR >50%) (table 1). HPD is not part of the RECIST criteria (1.1).

Table 1

Tumor response evaluation after ICIs treatment

Ferrara R *et al.* [18]	
HPD	The percentage change of TGR during ICIs treatment should be 50% higher than the expected increase before treatment
RECIST 1.1	
PD	≥20% increase in SLD compared to smallest SLD in study or progression of non-target lesions or new lesions
SD	No PR, no PD
PR	≥ 30% decrease in SLD, no new lesions, no progression of non-target lesions
CR	The disappearance of all lesions and pathological lymph nodes

HPD: hyperprogressive disease. PD: progressive disease. SD: stable disease. PR: partial response. CR: complete response. TGR: tumor growth rate. SLD: sum of the longest diameters of target lesions.

HPD DEFINITION, CRITERIA, INCIDENCE, AND KEY CONTROVERSIES

DEFINITION

In general, HPD can be defined as an accelerated increase in the growth rate of tumors over a relatively brief period. It suggests that treatment with ICIs is ineffective, leading to rapid clinical deterioration and poor survival outcomes, necessitating the immediate discontinuation of ICIs and transitioning to appropriate alternative treatment [13].

CRITERIA AND KEY CONTROVERSIES

Several criteria have been proposed in different studies; We will explain these criteria and highlight the main controversies associated with each method employed. The first published work was by Sâada-Bouzid et al. focused on identifying hyperprogressors using "tumor growth kinetics" (TGK). TGK is determined by calculating the difference in the sum of target lesion diameters, based on RECIST criteria, per time unit between two radiological tests. The authors considered a case of HPD when the ratio of TGK during immunotherapy to pretreatment TGK exceeded 2. However, it should be noted that this model assumes a linear tumor growth pattern, which may not accurately represent tumor behavior in many types of cancer. To address this limitation, Champiat S et al. investigated HPD using "tumor growth rate" (TGR), which assumes an exponential growth mechanism. HPD was diagnosed when the TGR during treatment (TGR post) had increased at least twofold compared to before treatment (TGR pre) (TGR post/TGR pre ≥2). Another slightly different criterion was employed by Ferrara R *et al*., who proposed that HPD should be characterized by the percentage change of TGR exceeding 50% (rather than a ratio). This suggests that the monthly increase in volume during ICIs treatment should be 50% higher than the expected increase before treatment [15].

To diagnose HPD using any of the above criteria you need at least three radiologic examinations (pre-baseline, baseline, and postbaseline) are required; a minimum of two CT scans (pre-baseline and baseline) before initiating ICIs therapy and one CT scan during treatment (postbaseline). The question follows, what is the optimal time frame to capture HPD? Five studies reported the date of HPD onset/ survival data for each patient with HPD. The earliest onset of HPD was 0.3 months, and the latest onset was 2.7 months; most HPD occurred within 2 months (average, 1.6 months). Most patients with HPD died within 3.5 months. Hence, it is important to clearly define the posttreatment evaluation period within a short timeframe (≤ 2 months) in order to promptly detect HPD [16].

There were slight differences in the timing requirements for obtaining the required imaging between Champiat S *et al.* and Ferrara R *et al.* According to Champiat S *et al.* The baseline CT scan had to be performed within 3 months before the start of ICIs treatment, and there should be a minimum of two weeks between each CT evaluation [17]. Ferrara R *et al.*, on the other hand, used a shorter time frame of (1.5 months) instead of 3 months and maintained a minimum of two weeks between each CT evaluation [18].

As obtaining the necessary CT images can be challenging, other research groups have explored alternative methods by combining clinical and radiological variables to identify HPD. However, these approaches may introduce elements influenced by patient characteristics, thus compromising the objectivity of the criteria. In the studies conducted by Kato S *et al.*, HPD was defined based on the simultaneous consideration of time to treatment failure (TTF) < 2 months, > 50% in tumor burden, and > 2-fold increase in TGR [19]. In the study by Lo Russo G, patients needed to meet at least three out of five criteria to be diagnosed with HPD, which included TTF of less than two months, an increase of 50% in the total diameter of the target lesions, development of at least two new lesions in an affected organ, distribution to a new organ, and clinical deterioration to performance status (PS) of ≥ 2 [20]. In contrast, Matos I *et al.* proposed an HPD definition that eliminated the requirement for a pre-baseline CT scan requiring either the development of HPD in the first eight weeks of starting ICIs with an increase of 40% in the total diameters of the target lesions or the appearance of new lesions in at least two distinct organs [21].

Moreover, authors who wish to use more precise objective criteria should plan in advance to make sure they have met the required imaging studies; eight studies that used the TGR or TGK to define HPD showed that up to 39.1% of patients were excluded because they did not have the required imaging studies (mainly the pre-baseline) [16]. Therefore, clinicians should be aware that HPD definitions using TGR or TGK could not be applied to many patients during ICIs treatment. One of the main disadvantages of criteria based on radiological evaluations is that pre-baseline CT scans are not always available, especially in the case of first-line therapy.

In summary, while there are slight variations, most authors view HPD as a rapid acceleration of tumor growth, with the threshold potentially influenced by the specific type of tumor. Criteria that necessitate a pre-baseline CT scan will likely provide more precise results since they enable differentiation between genuine HPD and fast-growing tumors as it uses each patient as their own control. Conversely, the assumption of exponential tumor growth is a more accurate representation of tumor behavior. Lastly, including complementary clinical criteria could prove advantageous in identifying patients with HPD who may not meet the radiological criteria. However, this approach runs the risk of losing objectivity [17].

INCIDENCE

Due to the novelty of the concept of HPD and the lack of consistent criteria, the reported incidence rate of HPD can vary significantly. A systematic review and meta-analysis conducted by Park HJ in 2021 analyzed twenty-four studies involving 3109 patients. The study found that the occurrence of HPD ranged from 5.9% to 43.1%. This variation is due to the differences in the diagnostic criteria used to identify HPD across the various studies [16].

Tumor Growth Rate

TGR is a measure of the monthly percentage increase in tumor volume, calculated using the following formula where TG is the tumor growth and exp is the exponential function [22]:

$$TGR=100[\exp(TG)-1$$

TG is derived from the following equation, where Ln is the natural logarithm, St and S0 represent the tumor sizes at times t and t0, respectively, defined as the sum of the longest diameters of the target lesions as per the RECIST 1.1 criteria [22].

$$TG=3Ln(St/S0)$$

To calculate the percentage change of TGR:

Step 1: Calculate the TGR before treatment (TGR pre) where St is tumor size at baseline and S0 is tumor size at pre-baseline.

Step 2: Calculate TGR after treatment (TGR post) where St is tumor size at postbaseline and S0 is the tumor size at baseline

Step 3: Calculate the ΔTGR

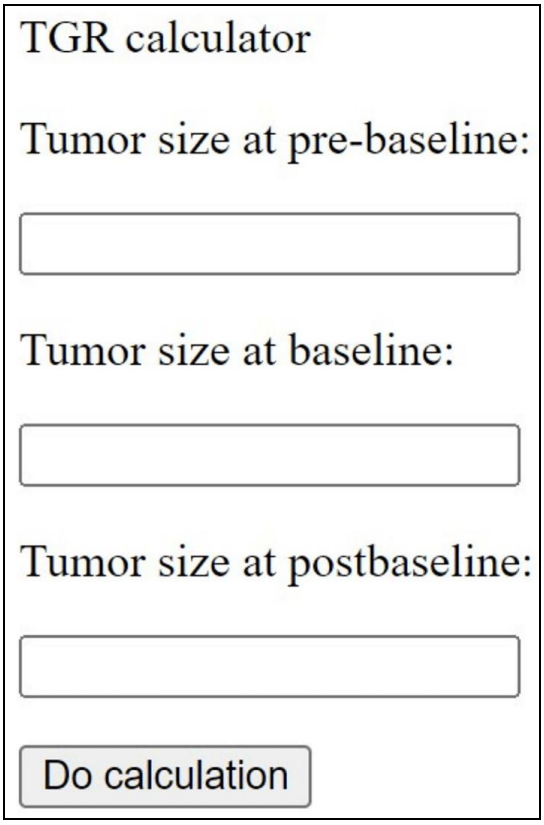
$$\Delta TGR=TGRpost-TGRpre$$

Step 4: Calculate the percentage change of TGR

$$\text{Percentage change of TGR}=\Delta TGR/TGRpre*100$$

We recognize that calculating TGR during clinical practice can be burdensome. Therefore, we have created an online interactive calculator to simplify TGR calculations for doctors in their daily routines. By inputting the tumor size at different

stages (pre-baseline, baseline, and post-baseline) and clicking the "calculate" button, the calculator automatically provides the TGR values before and after treatment and the percentage change in TGR. For authors who prefer a TGR ratio of ≥2 as the criteria for diagnosing HPD, we have also included the TGR ratio. The link to access the calculator can be found in the caption of Figure 1.



TGR: tumor growth rate
Link: http://rashedaltaha.pythonanywhere.com/

Figure 1. TGR calculator.

Case presentation of HPD

Here we showcase how HPD can be presented in a real-life scenario using the medical records of one of our patients included in the study.

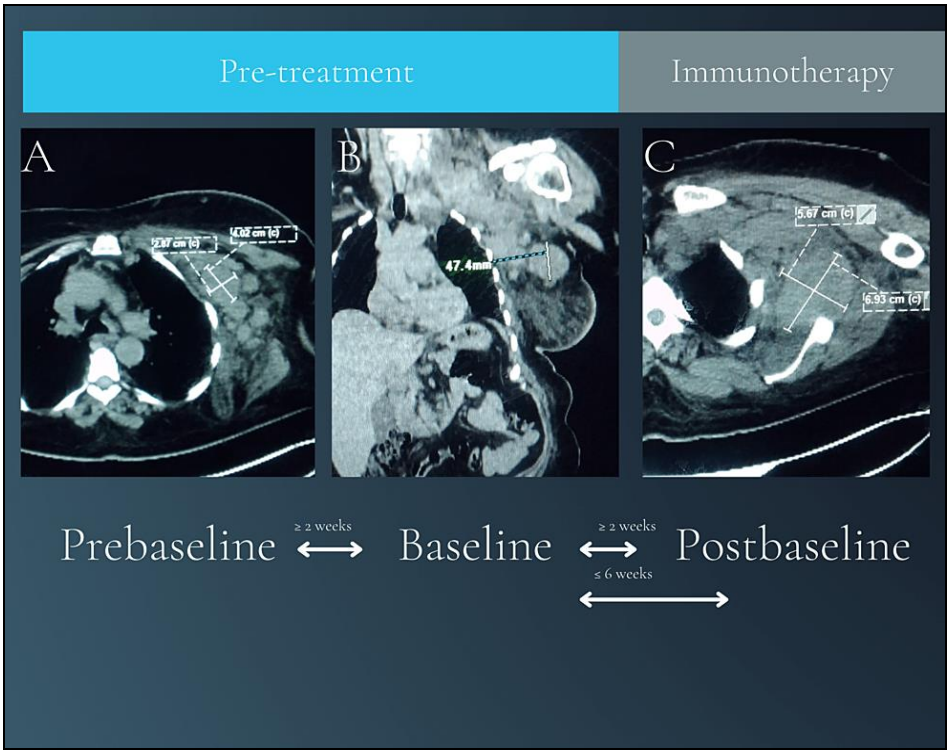
A 57-year-old female patient was diagnosed with RCC with non-regional LN metastasis. Based on the Memorial Sloan-Kettering Cancer Center (MSKCC) model and International Metastatic RCC Database Consortium (IMDC) prognostic criteria, she was considered an intermediate-risk patient with an intermediate prognosis. Her ECOG performance was (1). She was planned to start on ICIs nivolumab/ipilimumab q 3 weeks. Within six weeks of ICIs treatment, she presented with bilateral pleural effusion more prominent on the left. She became completely disabled with an ECOG performance of (4). Based on these symptoms, HPD was suspected as the cause of her rapid clinical deterioration.

To confirm the diagnosis of HPD, we obtained three different CT scan images: a pre-baseline scan, a baseline scan, and a post-baseline scan. The baseline CT scan was conducted within six weeks of immunotherapy initiation, and there was a minimum of two weeks between each CT scan evaluation.

Figures 2A and 2B show the tumor sizes during the pretreatment period, while Figure 2C represents the tumor size after the initiation of immunotherapy. There was a 238.87% percentage increase in TGR after immunotherapy treatment. Therefore, she was diagnosed with HPD, prompting the discontinuation of ICIs and a switch to cabozantinib. Unfortunately, the patient's condition rapidly deteriorated, and she passed away one week later.

PSP is another clinical entity observed during ICIs treatment; it is a transient type of

progression that begins with a visible rise in tumor size or the emergence of new lesions, followed by a decrease in tumor burden and shrinkage. It indicates that the treatment is effective due to an inflammatory cell infiltration in the tumor bed rather than tumor cell proliferation. It does not necessitate the cessation of ICIs therapy [23][24].



A: CT scan at prebaseline. B: CT scan at baseline. C: CT scan at postbaseline
Pseudoprogression (PSP)

Figure 2. Target lesion measurement.

ETHICAL STATEMENT

This is an observational retrospective study. All patients were managed under routine clinical practice. The Institutional Review Board (IRB) at the Jordanian Royal Medical Services in Amman, Jordan, approved the current study.

STATISTICAL ANALYSIS

Descriptive statistics were used to summarize the patient's characteristics. Categorical data were expressed using frequencies and percentages. Numerical data were described as the mean and standard deviation or the median and range, as appropriate. The fisher's exact test was used to assess the association between lymph node size and HPD. Kaplan-Meier (KM) survival curves and log-rank assessment were used to calculate the median OS. Overall Survival (OS) was defined as the time between the initiation of the ICIs and the death of the patient from any cause. All statistical analyses were analyzed using Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Corp., Armonk, NY). A p-value of <0.05 was considered statistically significant.

RESULTS

DESCRIPTIVE STATISTICS

The study included ten mRCC patients. The cohort was divided into two groups: patients who developed HPD and patients who did not. Of those, three patients (30%) were classified as hyperprogressors, while seven patients (70%) were classified as non-hyperprogressors. In terms of LN size, seven patients (70%) had a size less than 3cm, and three patients (30%) had LN size $\geq$ 3 cm. The majority of the patients were female (70%), while 30% were male. The median age was 50.5 years, with the youngest patient being 20 and the oldest patient 69 years old (range: 20–69 years). Out of the sample, 80% of the patients underwent nephrectomy, while 20% did not. The most common histological subtype was clear cell RCC

(80%), while the remaining 20% had non-clear cell RCC. 60% of patients had a metastasis involving < 2 organs involved and 40% with ≥ 2 organs involved (Table 2).

Given the small sample size, we used fisher's exact test to investigate the association between HPD and various patient-tumor characteristics, including age, sex, LN size, histological subtype, presence or absence of nephrectomy, metastatic site, and presence or absence of sarcomatoid features. The results showed that there was a statistically significant association between HPD and LN size (P =0.008). However, no significant association was found between HPD and age (P =0.500), sex (P =1.000), histological subtype (P =0.67), nephrectomy (P =1.000), sarcomatoid features (P =0.500), or metastatic site (P =1.000) (Table 3).

Table 2

Descriptive statistics

Characteristics	**Value**
Number of mRCC Patients	**10**
Patients with HPD	3 (30%)
Patients without HPD	7 (70%)
LN Size	
< 3cm	7 (70%)
≥ 3 cm	3 (30%)
Sex	
Female	7 (70%)
Male	3 (30%)
Median Age	50.5 years
Age Range	20–69 years
Nephrectomy	
Yes	8 (80%)
No	2 (20%)
Histological Subtype	
Clear Cell RCC	8 (80%)
Non-clear Cell RCC	2 (20%)
Sites of Metastasis	
≥ 2 organs involved	4 (40%)
< 2 organs involved	6 (60%)

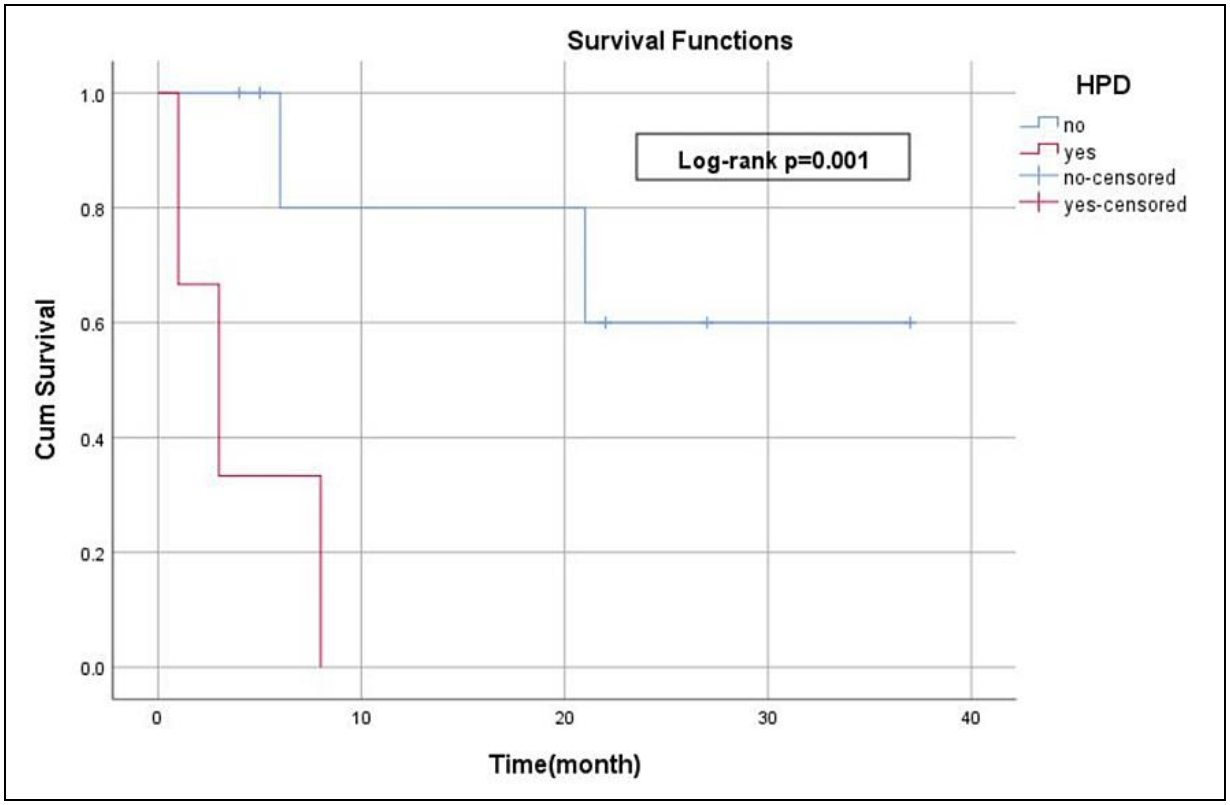
mRCC: metastatic renal cell carcinoma, HPD: hyperprogressive disease, RCC: renal cell carcinoma. LN: lymph node

Table 3

Fisher's exact test

Patient's tumor characteristics		**HPD**	**No HPD**	**Total**	**p-value**
Age	≥ 50	1(16.7%)	5(83.3%)	6	0.500
	<50	2(50%)	2(50%)	4	
Sex	Female	2(28.6%)	5(71.4%)	7	1.000
	Male	1(33.3%)	2(66.7%)	3	
LN Size	≥ 3 cm	3(100%)	0(0%)	3	0.008
	< 3 cm	0(0%)	7(100%)	7	
Histological subtype	Clear Cell Carcinoma	1(12.5%)	7(87.5%)	8	0.067
	Non-Clear Cell Carcinoma	2(100%)	0(0%)	2	
Nephrectomy	Yes	2(25%)	6(75%)	8	1.000
	No	1(50%)	1(50%)	2	
Sarcomatoid Features	Yes	2(50%	2(50%)	4	0.500
	No	1(16.7%)	5(83.3%)	6	
Metastatic Site	≥ 2 Organs Involved	1(25%)	3(75%)	4	1.000
	< 2 Organs Involved	2(33.3%)	4(66.7%)	6	

HPD: hyperprogressive disease. LN: lymph node. A p-value <0.05 was considered statistically significant.



Cum Survival: Cumulative survival. HPD: hyperprogressive disease

Figure 3. Difference in overall survival between HPD and non-HPD patients using KM's method.

SURVIVAL ANALYSIS

A KM analysis compared the median OS between patients with HPD and those without. Of 10 patients, three had HPD; all died, with a median OS of 3 months. On the other hand, seven patients did not have HPD, of whom two died, and the median OS was not reached (P = 0.001) (Figure 3).

DISCUSSION

The recognition of HPD among clinical oncologists is increasing, and it is now widely acknowledged as a significant challenge in the era of immunotherapy [25]. HPD refers to the accelerated growth of tumors recently observed in a subgroup of cancer patients receiving ICIs [26]. This phenomenon is characterized by a rapid progression of the disease, accompanied by rapid clinical deterioration, often resulting in the death of affected patients [27]. The reported incidence of HPD varies between 5.9% and 43.1% among patients receiving ICIs [18]. Consequently, it is vital to identify reliable predictive risk factors for HPD, as doing so may enable earlier intervention and ultimately enhance patient outcomes.

Keeping that in mind, during the current study's early phases, we noticed that a significant proportion of study participants had undergone nephrectomy before commencing ICIs treatment. Hence, including patients with measurable target lesions was necessary to accurately diagnose HPD or the lack thereof. Our clinical and radiological assessments indicated that LN involvement was the best reliable target lesion for measurement in pre and post ICIs treatment; we observed that patients with at least 3 cm in the pretreatment imaging developed a 50% increase in TGR after ICIs treatment. This simple observation during routine clinical practice has prompted an investigation of whether LN size is a risk factor for developing HPD. Several studies have established that LN metastasis is an independent risk factor for poor prognosis and reduced patient survival time in mRCC [28][29]. However, none have linked the possibility of poor prognosis (partly) due to HPD.

Our premise is that a larger LN size during the pretreatment period is a potential risk factor for HPD. However, before establishing this link, we must understand the role of regulatory T-cells (Tregs) and tumor-associated macrophages (TAMs) as the underlying mechanism behind HPD [30]. As more

data becomes available, the underlying reasons for this phenomenon are expected to become more evident, enabling proactive measures to reduce the risk of HPD. While MDM2 and EGFR mutations are regarded as potential risk factors rather than direct causes of HPD, these gene alterations are known to promote the oncogenic nature of tumors and contribute to disease progression [31]. As such, current research efforts are focused on identifying the precise mechanisms behind HPD. Two potential mechanisms have been proposed to date. The first involves the Fc region of anti-PD-1 antibodies inducing M2-like differentiation of tumor-associated macrophages (TAMs), which creates an immunosuppressive environment within the tumor [32]. The second mechanism relates to regulatory T-cells (Tregs) [33].

Tregs are a subset of T-cells that suppress immune responses, including antitumor immune responses, and promote immune tolerance. In cancer, Tregs have been shown to accumulate in tumors and suppress immune responses against cancer cells, which can contribute to tumor progression and metastasis [34]. TAMs, on the other hand, are a type of immune cell that infiltrate the tumor microenvironment (TME) and can either promote or inhibit tumor growth depending on their polarization state. In the context of PD-1 blocking, TAMs are thought to be polarized towards an M2-like phenotype, which promotes tumor growth and progression [35]. We believe that a larger LN size signifies an increased infiltration of Tregs and TAMs into the TME, leading to a greater state of immunosuppression and, on the flip side, a higher risk of HPD; this may appear counterintuitive as the basic idea of immune checkpoint inhibition through PD-1 blocking effects is to reconstitute a durable antitumoral response which does occur in some patients; however, in others, we see exactly the opposite; a phenomenon surprisingly similar to what we see in immune reconstitution inflammatory syndrome (IRIS) in immunodeficient patients infected with the Human Immunodeficiency Virus (HIV) receiving Highly Active Antiretroviral Therapy (HAART).

To date, the exact mechanisms underlying HPD are yet to be fully understood, and the link between HPD and LN size does not come without grave challenges. Furthermore, HPD is a serious complication of ICIs, and the short time in which clinical deterioration occurs is alarming; therefore, informing patients about the potential of HPD before initiating ICIs treatment is essential. Since there is currently no biomarker available to predict HPD, educating patients to promptly report any changes in their clinical condition or new symptoms during treatment visits becomes crucial. Once HPD is confirmed, discontinuing immunotherapy and transitioning to an appropriate alternative treatment is recommended [36].

LIMITATIONS

Due to the infrequent use of preoperative LN dissection as a gold standard modality to confirm pathological LN metastasis [37], another challenge in the current study was the suboptimal sensitivity and specificity of CT and MRI in selecting and labeling patients with true pathological LN metastasis. False negatives may occur due to the inability to detect small foci of metastatic disease, while false positives may occur due to LN hyperplasia caused by inflammation. Among a group of 2954 patients with RCC, 14% had LN size $\geqslant$1 cm identified on preoperative contrast-enhanced CT, but only 29% of these were confirmed to have LN metastases after undergoing LN dissection [37]. Therefore, a novel predictive model of pathological LN metastasis constructed with preoperative independent predictors in patients with RCC is urgently needed. Luckily, a recent study by Sun JX et al. concluded that Low age, large LN size in preoperative imaging, and high clinical T stage could be used as independent predictive factors of pathological LN metastasis in patients with RCC [38].

CONCLUSIONS

Following its discovery in 2016, HPD emerged as a recent concept, and the first challenge was establishing uniform criteria for its definition, which still needs to be solved. The subsequent challenge is to fully understand its underlying mechanisms, followed by identifying patients who are at risk. Unraveling this mystery presents a daunting challenge in the future. However, considerable efforts have been made, and gradual progress through various methods, including case reports all the way to large randomized clinical trials, is still needed. It is of utmost importance to raise awareness among clinicians and motivate them to invest time and effort, as patients and their families expect.

Introducere: Boala hiperprogresivă (HPD) poate fi descrisă ca o creștere accelerată a ratei de accelerare a tumorilor combinată cu o deteriorare clinică rapidă observată la un subgrup de pacienți cu cancer supuși imunoterapiei, în special cu inhibitori ai transducției celulare imune (ICI). Incidența raportată a HPD variază de la 5,9% la 43,1% la pacienții cărora li se administrează ICI. În acest context, identificarea factorilor de risc predictivi fiabili pentru HPD este crucială, deoarece poate permite o intervenție mai devreme și, în cele din urmă, poate îmbunătăți prognosticul pacientului.

Metode: Acest studiu a analizat retrospectiv zece pacienți cu carcinom renal metastatic (RCC). Identificarea HPD s-a bazat pe criteriile de diagnostic propuse de Ferrara R. et al. Acest studiu și-a propus să investigheze dacă există o asociere între dimensiunea LN și HPD folosind o valoare limită de 3 cm pentru dimensiunea LN. Având în vedere dimensiunea limitată a eșantionului, testul exact al lui Fisher a fost utilizat pentru a testa această asociere. Am efectuat o analiză Kaplan-Meier (KM) pentru a estima supraviețuirea globală (SG) mediană a pacienților cu HPD și am comparat-o cu cei fără HPD.

Rezultate: Trei pacienți (30%) au dezvoltat HPD, în timp ce șapte (70%) nu. Testul exact al lui Fisher a relevat o asociere semnificativă statistic între dimensiunea HPD și LN ≥ 3 cm (p=0,008). În grupul HPD, mediana supraviețuirii a fost semnificativ mai scurtă, cu o mediană de 3 luni, în timp ce în grupul non-HPD, mediana OS nu a fost atinsă (P = 0,001).

Concluzie: Studiul de față a găsit o asociere semnificativă între dimensiunea LN ≥ 3 cm în perioada de pretratament și dezvoltarea HPD.

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