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Impact of positron emission tomography with fluorodeoxyglucose on the survival of patients with Hodgkin's lymphoma in the Mexican population.

Efecto de la tomografía por emisión de positrones con fluorodeoxiglucosa en la supervivencia de pacientes con linfoma de Hodgkin en la población mexicana

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Abstract

OBJECTIVE: To evaluate interim-positron emission tomography (PET) as a prognostic factor in terms of progression-free survival and overall survival in our population.

MATERIALS AND METHODS: A retrospective, descriptive study of patients with classic Hodgkin's lymphoma treated with the ABVD regimen (adriamycin, bleomycin, vinblastine and dacarbazine) at the National Cancer Institute in Mexico, from January 2012 to December 2015. We evaluated interim-PET, response at the end of treatment, progression-free survival, and overall survival.

RESULTS: We analyzed 94 patients, with a median age of 34.5 years (range 16-87), 84% had advanced disease and 65% had bulky disease; complete response on interim-PET was 84%, and 78% at the end of treatment. The 5-year progression-free survival was 86% *vs* 7% (p = 0.0001) in patients with a negative *vs* a positive interim-PET, respectively. Five-year overall survival was 96% *vs* 76% (p = 0.0006). In multivariate analyses, interim-PET was an independent prognostic factor for progression-free survival.

CONCLUSIONS: Interim-PET was highly prognostic in patients with Hodgkin's lymphoma and it could be more useful when adjusting treatment in our population.

KEYWORDS: Positron emission tomography; Hodgkin disease; Progression-free survival; Prognostic.

Resumen

OBJETIVO: Evaluar la tomografía computada por emisión de positrones (TC-PET) intermedia como factor pronóstico de supervivencia libre de progresión y supervivencia global en nuestra población.

MATERIALES Y MÉTODOS: Estudio descriptivo, retrospectivo de pacientes con linfoma de Hodgkin clásico tratados con el régimen ABVD (adriamicina, bleomicina, vinblastina y dacarbazina) en el Instituto Nacional de Cancerología de México, de enero de 2012 a diciembre de 2015. Evaluamos la TC-PET, respuesta al final del tratamiento, supervivencia libre de progresión y supervivencia global.

RESULTADOS: Se analizaron 94 pacientes, con mediana de edad de 34.5 años (intervalo: 16-87), el 84% tenía enfermedad avanzada y el 65% enfermedad volumi-

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nosa; la respuesta completa en la TC-PET intermedia fue del 84% y del 78% al final del tratamiento. La supervivencia libre de progresión a 5 años fue del 86 *vs* 7% (p = 0.0001) en pacientes con TC-PET intermedia negativa *vs* positiva, respectivamente. La supervivencia global a cinco años fue del 96% *vs* 76% (p = 0.0006). En los análisis multivariados, la TC-PET intermedia fue un factor pronóstico independiente de supervivencia libre de progresión.

CONCLUSIONES: La TC-PET intermedia fue de alto valor pronóstico en pacientes con linfoma de Hodgkin y podría ser más útil al momento de ajustar el tratamiento en nuestra población.

PALABRAS CLAVE: Tomografía computada por emisión de positrones; linfoma de Hodgkin; supervivencia libre de progresión; pronóstico.

INTRODUCTION

Classic Hodgkin's lymphoma represents 15% of all lymphomas, and it is the most common lymphoma in young adults.[1,2] In Mexico, GLOBOCAN 2019 reported 2388 new cases and 543 deaths.[3] The long-term prognosis in early clinical stages is good, with cure rates above 90%, but in advanced clinical stages it is more dire, with cure rates between 65 and 75%. Since the early 1990 decade, the AVBD regimen (adriamycin, belomicin, vinblastine and dacarbazine) has become the standard of care in patients with early-stage disease, with proven efficacy and an acceptable safety profile; however, in several studies, results in advanced disease have not been entirely satisfactory.[4] Two decades ago, the German Hodgkin Study Group introduced BEACOPP regimen (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine and prednisone), a more intensive regimen, to obtain better results in patients with advanced disease. BEACOPP has led to prolonged progression-free survival (PFS), but has not modified overall survival when compared with ABVD, and it has also been associated with an increase in secondary neoplasms and long-term toxicity.[5,6,7] There is, however, a group that requires the intensification regimen.

There are several prognostic indices designed to identify the group of patients with the worst prognosis; nonetheless, these have not been effective in identifying the group that may benefit from a more intensive chemotherapy regimen.[8] The introduction of Positron Emission Tomography with fluorodeoxyglucose (PET) has been fundamental in the decision-making process in the treatment of Hodgkin´s lymphoma in the last decade; currently, it is the gold standard in staging, and has recently been introduced as a treatment adjustment tool.[9] In 2007, Gallamini et al. showed the impact of interim PET on progression-free survival (PFS) after two ABVD treatment cycles, reporting a PFS of 13% *vs* 95%, when comparing positive *vs* negative interim PET.[10] Other studies have confirmed these results using the Deauville evaluation score.[11] This has led to trials designed to evaluate the benefit of intensifying treatment after a positive interim PET.[12-15]

These studies have introduced PET in the decision-making process, but results have not been confirmed other than in a clinical study in the

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daily clinical practice setting in our population. Our study shows the value of PET as a prognostic factor in the interim and the end of treatment in our clinical practice.

PATIENTS AND METHODS

A retrospective and descriptive study. We reviewed the medical records of patients with Hodgkin's lymphoma treated at the National Cancer Institute in Mexico, from January 2012 to December 2015. Patients with a classic Hodgkin's lymphoma diagnosis confirmed by pathology, that received ABVD chemotherapy (adriamycin, belomicin, vinblastine and dacarbazine) with/without radiotherapy, with a PET at diagnosis, in the interim and at the end of treatment, were included. Patients who were human immunodeficiency virus positive or whose medical records were incomplete, were excluded.

The response of all cases was classified according to the Lugano 2014 recommendations.[9] PET studies were reevaluated by the Nuclear Medicine Department and interpreted according to the Deauville criteria. A workstation (Multimodality Workplace, Siemens) providing multiplane reformatted images was also used for image display analysis. The SUVmax of whole body tumors was measured with the isocontour of the TrueD Syngo software (Siemens, Erlangen, Germany). A Deauville score of 1-3 was considered a negative PET and a value of 4-5 was compatible with a positive PET. Therapeutic failure was defined as persistence or progression of the disease at the end of first-line treatment, and requiring rescue therapy. Relapse was defined as the new presence of disease after having obtained a complete response.

This study was approved by the ethics committee of this institution in accordance with the Helsinki declaration. No written consent form was needed since this was a retrospective study, with information gathered in an anonymous format.

Statistical analysis

Descriptive statistics were used to summarize patient characteristics, including medians, ranges, frequencies, and percentages. Overall survival was estimated from the date of diagnosis to the time of death; progression-free survival (PFS) refers to the time from diagnosis to therapeutic failure, relapse, or death, whichever occurred first. Kaplan Meier curves were constructed in accordance with the response category in the PET. Univariate data analysis was used to evaluate covariables and their effect on PFS. A multivariate Cox regression model was created to determine the prognostic value of interim PET in patients with HL, and its relationship with PFS after adjusting for the effect of other variables. In this final model, only covariables with a $p < 0.05$ were included, as well as those with clinical significance. All analyses were performed with the IBM-SPSS software, version 22.

RESULTS

A total of 94 patients were analyzed, their median age was 34.5 years (16-87), most patients 79 (84%) presented with advanced disease (IIB, III, IV), 61 (65%) with bulky disease and 40 (43%) had more than 3 poor prognostic factors according to the IPS score. The general characteristics of the population are shown in **Table 1**. All patients were treated with the ABVD chemotherapy regimen, with the exception of one patient who only received radiotherapy since chemotherapy was not an option due to comorbidities. Sixty-one patients (65%) also received radiotherapy to manage bulky disease. No treatment changes were made after interim PET.

Response to treatment and interim PET

The overall response rate was 86% (n 81), a complete response was obtained in 73 patients (78%), and 13 patients (14%) had stable disease

Table 1. Patient characteristics (n = 94)

	No.	%
Median age, years	34.5	Min-max 16-87
Sex		
Male	51	54
Female	43	46
Histology		
Mixed cellularity	44	47
Nodular sclerosis	38	40
Lymphocyte-rich	5	5
Lymphocyte-depletion	1	1
Not specified	6	7
Advanced disease (IIB/X, III- IV)	79	84
B symptoms	71	76
Bulky disease (≥ 10 cm)	61	65
Extranodal disease	40	43
IPS > 3 (advanced disease)	40	43
Leucocyte x10^3/mm^3, median	9.1	Min-max 1.8-24.5
Hemoglobin g/dL, median	12.4	Min-max 3.4-19.4
Lymphocytes x10^3/mm^3, median	1.4	Min-max 0.2-4.2
Albumin g/dL, median	3.4	Min-max 1-4.8
Lymphocyte/monocyte index, median	3.04	0.3-9.0
Treatment		
CHT alone	32	34
Combined CHT/RT	62	65
Radiotherapy alone	1	1
Responses		
Complete response	73	78
Partial response	8	8
SD/progression	13	14

IPS: international prognostic score Hasenclever; CHT: chemotherapy; RT: radiotherapy; SD: stable disease.

or progression. At the time of interim PET, 79 patients (84%) had a negative PET, of these, 71 (90%) continued with a complete response until the end of treatment. In patients with a positive interim PET, 13 (87%) remained positive until the end of treatment. Sensitivity was 62%, specificity 97%, positive predictive value 87% and negative predictive value 90%.

The median follow-up was 64.5 months (min-max 4-99). During follow-up, 3 patients relapsed and 7 (7%) died. Of the 21 patients with a positive end-of- treatment PET (partial response, stable disease/progression), 14 had received rescue treatment and 6 did not receive further treatment due to several causes (lack of resources or treatment rejection), 6 (42%) of the patients who received rescue therapy progressed to autologous hematopoietic stem cell transplantation.

Survival

The overall survival at 5 years was 91% for the entire group (**Figure 1A**), and the progression-

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free survival was 73% (**Figure 1B**); the medians have not been reached. According to the interim PET, 5-year overall survival was 76% *vs* 96% in patients with positive interim PET *vs* negative, respectively (OR 6.7 [95%CI, 3.81-11.7] p = 0.0001), medians have not been reached (**Figure 2A**). The 5-year progression-free survival (PFS) was 7% *vs* 86% in the positive interim PET group compared to the negative interim PET group (p 0.0001), median PFS in patients with a positive PET was 8.9 months (95%CI, 7.59-10.20). **Figure 2B**

Prognosis factors

Regarding PFS in the univariate analysis, only the interim PET was a prognostic factor, and it remained independent in the multivariate analysis; IPS 3 or more points was not a prognostic factor. In the case of overall survival, due to the number of events, Cox regression was not conducted. **Table 2**

DISCUSSION

Hodgkin's lymphoma is the second most common lymphoma in our institution after diffuse large B Cell Lymphoma. The median age at diagnosis is comparable to that referred in previous publications; however, we found a greater number of patients in advanced clinical stages (84%), a difference with previously reported studies in patients from Australia, Japan and China, where less than 30% of cases are diagnosed in stage III or IV. We believe that a lack of timely detection and referral to a tertiary care institution is one of the main causes,[16-19] and perhaps also explains the high frequency of bulky disease 65%, and extranodal disease 43% that we face, compared to 20% reported in the HD15 German study.[20]

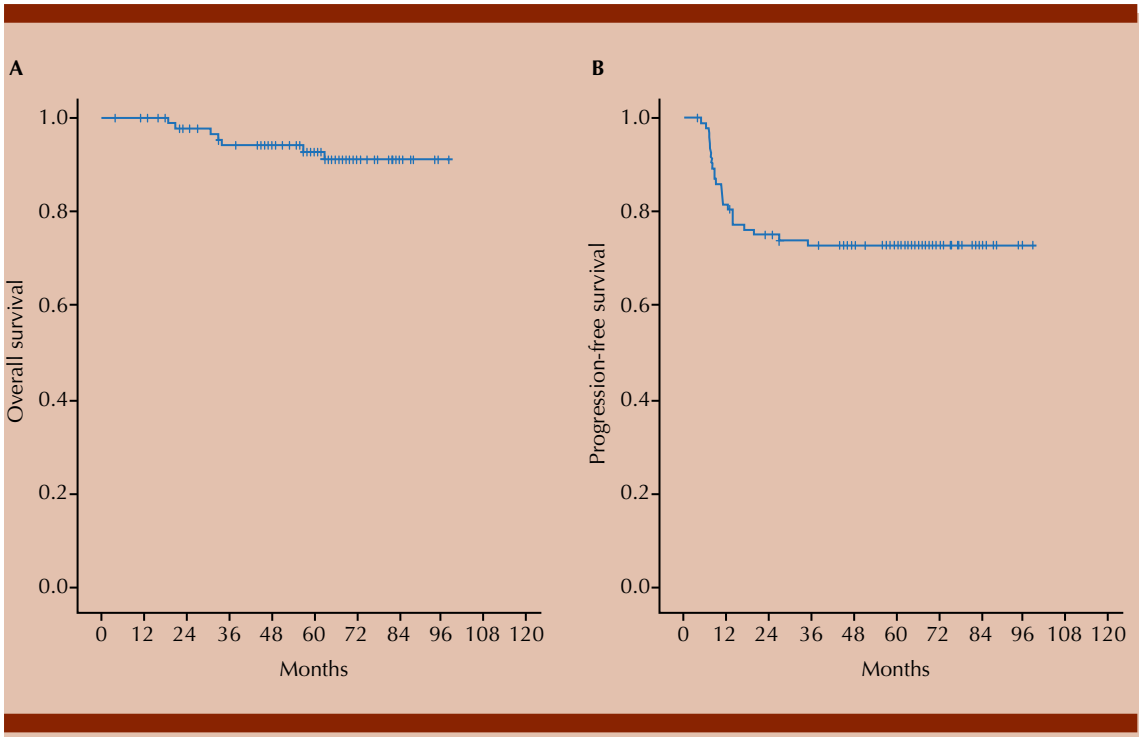

Figure 1. Overall survival **(A)** and progression-free survival **(B)** in patients with Hodgkin's lymphoma.

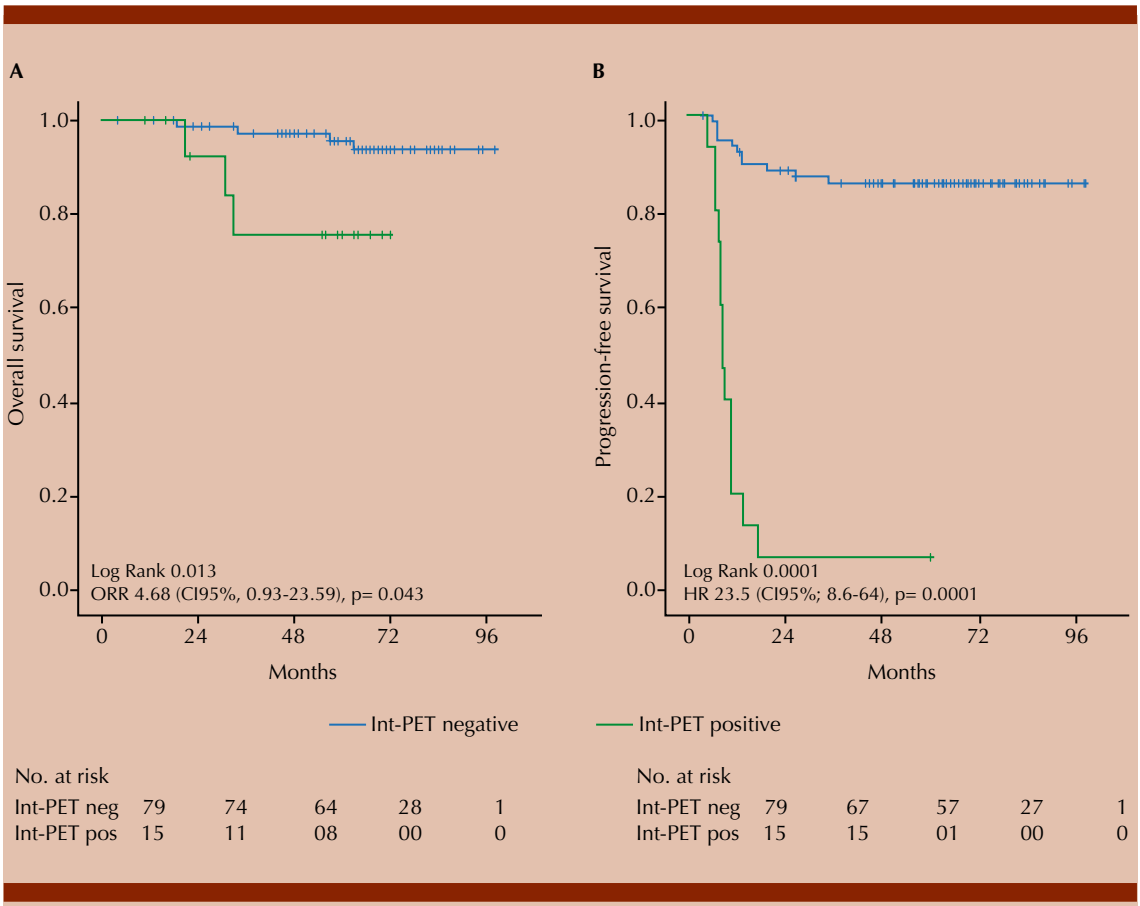

Figure 2. Overall survival according to interim positron emission tomography-computed tomography results: progression-free survival according to interim PET.

The overall 5-year survival was 91%, which is comparable to the value previously reported in other cohorts using the ABVD regimen (adriamycin, belomicin, vinblastine and dacarbazine) in daily clinical practice,[16,17,19,21,22] and progression-free survival (PFS) was 73%. The prognostic value of interim PET was corroborated in our population with PFS of 86% *vs* 7% (HR 23.5 [95%CI, 8.6-64] p = 0.0001), coinciding with the previously reported data by Gallamini et al., who demonstrated the predictive value of a positive interim PET referring a 2- year PFS of 12.8%, using qualitative scales before the description of the Deauville scale.[10]

A second study by the same authors, based on an evaluation with the Deauville scale, confirmed their previous results; the 3-year PFS was 28% in the interim PET positive group *vs* 95% in the group with a negative positron emission tomography-computed tomography (PET-CT).[11,23,24] This study showed that in our population, the interim PET-CT is of prognostic value in terms of overall survival, with 96% in the negative PET group *vs* 76% in the positive group (p = 0.0001). In a previously metanalysis a negative interim PET is associated with an advantage in overall survival (unadjusted HR 5.09, 95% confidence interval [CI] 2.64 to 9.81,

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Table 2. Univariate and multivariate analysis of progression-free survival in patients with Hodgkin's lymphoma (HL) [n = 94]

	Univariate analysis			Multivariate analysis (Cox)		
	OR	CI95%	p	HR	CI95%	p
Male gender	1.07	0.54-2.11	0.83	0.57	0.16-2.01	0.57
B symptoms	1.02	0.46-2.25	0.94	0.46	0.05-4.25	0.49
Bulky disease	0.87	0.42-1.79	0.70	0.74	0.20-2.75	0.21
Advanced disease	0.99	0.39-2.49	0.99	-	-	-
Extranodal disease	1.11	0.55-2.21	0.76	1.10	0.29-4.08	0.88
IPS3 or more	0.72	0.83-1.45	0.35	1.97	0.30-12.83	0.47
Albumin < 3 g/dL	0.70	0.31-1.58	0.38	1.77	0.45-6.97	0.41
Combined treatment	1.09	0.54-2.18	0.80	0.54	0.16-1.82	0.32
Interim positive PET	6.70	3.81-11.7	0.0001	23.59	8.68-64.0	0.0001

OR: Odds ratio; CI: interval confidence; HR: hazard ratio; IPS: international prognostic score (Hasenclever); PET: positron emission tomography.

I^2 = 44%, moderate-certainty evidence); however, the evidence in PFS impact is uncertain (unadjusted HR 4.90, 95%CI 3.47 to 6.90, I^2 = 45%, very low-certainty evidence).[25]

Our study's main limitation is that it is a retrospective study, and to our patients' limited access to rescue therapy, another probable effect on overall survival. Despite our large number of patients with advanced disease, intensification with BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine and prednisone) has not been possible due to the lack of procarbazine in our country; this is why early detection of patients at high-risk of therapeutic failure may allow us to implement new treatment strategies, such as those published by Zinzani et al. that suggest early administration of second-line treatment, consolidation with high-dose chemotherapy and transplant.[14] The introduction of interim PET-CT identifies patients with a poor prognosis, and this will allow us to design new prospective studies in our population that may improve long-term survival.

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