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ONXO RESEARCH

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ONKO RESEARCH

The scientific journal "ONKORESEARCH" is the official journal of the Peruvian Society Medical Oncology (henceforth, PSMO); created on March 14th, 2022. It has an international scope, free access to its full text, arbitrated by peers, quarterly periodicity, printed and electronic publication and also published in English.

The journal scope includes topic and disciplines related to oncological pathologies in adults, teenagers and children alike. Includes; original article , revision article, special article, case reports, letter to the editor, and an editorial.

The journal is composed by an national and international editorial and peer- review team whose are experts in their fields related to Oncology: Medical Oncology, Pathology, Radiotherapy, Surgical Oncology, and Imaging.

Our goal is to publish articles with the highest scientific quality and highly citable to strengthen and stimulate scientific research in Latin America. Also, to utilize this journal as a tool for every Latin American researcher to the improvement of the quality of life and survival of our patients.

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CONTENTS

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EDITORIAL

Current status of scientific publishing in Latam and Peru: challenges and opportunities

Estado actual de las publicaciones científicas en Latam y Perú: desafíos y oportunidades

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By 2020, GLOBOCAN estimated 19.3 million new cases and 10 million cancer deaths worldwide, noting a growing trend in both incidence and prevalence of cancer cases, accompanied by a detrimental impact on life expectancy. The latter, related to several risk factors, most of them connected with socioeconomic development, such as globalization and economic growth [(1)]. Likewise, in Latin America and The Caribbean there are 1.5 million new cancer cases and 700,000 cancer deaths calculated annually [(2)].

Additionally, a better understanding of cancer biology has been demonstrated to help predict therapy responses and outcomes to reduce the cancer burden; however, this cannot entirely explain the differences between populations, especially vulnerable ones like those in Latin American countries. Moreover, there is a scarcity of scientific publications in Latin America, compared with other regions [(3,4)]. Therefore, the growing incidence and mortality, joined by a lack of understanding of cancer biology in vulnerable populations, and the lack of studies in Latin America are the main challenges that we are facing nowadays.

To overcome these challenges, efforts have been made to produce and disseminate the scientific knowledge that is being generated overseas, especially in developing countries, and to make them available to the scientific community around the world. However, to date, most publications on cancer research come from developed countries. Cabral et al. reported that the United States (32.7%) and China (24.5%) were the countries with the highest scientific production, followed by Japan, Germany and Italy [(5)].

According to SCImago Journal & Country Rank (SJR), a platform that provides a series of quality indicators to evaluate scientific journals and publications, no Latin American journal has been ranked within the 50 positions worldwide that generates a high impact, influence, prestige, H index and bibliographic reference [(6)].

Latin America has achieved a growth of 9% in publications between the period 2000-2018, being Brazil the country with the highest scientific production in oncology (41.8%), followed by Mexico (16.6%) and Argentina (12.9%). Meanwhile, the lowest production countries were Cuba (3.79%), Peru (3.22%) and Ecuador (1.9%) (Figure 1). In addition to this, Brazil had the highest number of citations, while Argentina and Uruguay had the highest average number of citations per article [(4)]. Despite this, these numbers are still low compared to North America, Europe and Asian countries [(3)].

Ranking	Country	N. Publications
1	Brazil	3565
2	Mexico	1412
3	Argentina	1100
4	Chile	828
5	Colombia	513
6	Uruguay	385
7	Cuba	323
8	Peru	275
9	Ecuadror	127

Source: Ruiz-Patiño, 2020. Scientific publications in cancer: In Latin-America, strong scientific networks increase productivity (The TENJIN study).

Figure 1. Scientific production in the Oncology field in Latin America between 2000-2018.

In Peru, the lack of an indexed journal specialized in cancer research does not only allow for the dissemination of research worldwide, but the recognition of the authors at a local, regional and global level. Moreover, another important aspect that prevents having a scientific production in our country is that many national authors choose to publish at indexed international journals that have scientific prestige, editorial committee reputation, advisory board, experience and easy access to the published data; thus perpetuating the lack of publications at the local level.

Given the above, the *Onkoresearch Journal* was founded with the impetus of allowing Latin American investigators to publish articles that have the highest standards of quality research, scientific and ethical integrity. We believe the development of such journals will also strengthen and stimulate scientific production in Latin America. Furthermore, this journal will allow the assessment of clinical, pathological and molecular factors, interactions amongst them and their impact on survival. Consequently, this publication aims at improving prognostication and identifying new approaches to enhance outcomes and survivorship in Latin American patients suffering from cancer. Likewise, its use as a tool for scientific discussions will incentivize greater investment and promotion of new directions and public policies in cancer research.

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ORIGINAL ARTICLE

Clinical characteristics and outcomes in cancer patients affected by COVID-19: a study from a Peruvian cancer center

Características clínicas y desenlace en pacientes oncológicos afectados por el COVID-19: estudio de un centro oncológico en el Perú

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ABSTRACT

Objective: To describe the clinical features and outcomes of COVID-19 infection in cancer patients and evaluate the risk factors associated with severe disease. **Materials and methods:** An observational retrospective study was performed in Oncosalud-AUNA. We included patients with diagnosis of invasive cancer with a SARS-CoV-2 confirmed infection by RT-PCR assay. Univariate and multivariate binary logistic regression analysis were performed to evaluate the risk factors associated with severe desease. **Results:** A total of 36 patients were included. Median age was 61 years old; 36.1% males; 58.4% with ≥1 comorbidity. Breast cancer was the most frequent malignancy. 72% of patients were on anticancer treatment. All patients were symptomatic. 16.7% were admitted to the ICU and 27.8% of patients died. The severity of disease was: mild, 27.8%; moderate, 33.3%; severe, 22.2%; and critical – ARDS, 16.7%. Patients with severe or critical disease were frequently >60 years old, male, in ECOG 2-3 and were receiving treatment with palliative intention. **Conclusions:** COVID-19 cancer patients were frequently overweight older adults with at least one comorbidity with active treatment and developed typical COVID-19 symptoms. Severe or critical COVID-19 occurred in more than one third of patients. Male patients and those >60 years old were at greater risk of developing severe or critical COVID-19.

Keywords
Cancer; COVID-19; SARS-CoV-2; Breast neoplasms (source: MeSH NLM).

RESUMEN

Objetivo: Describir las características clínicas y el desenlace clínico de los pacientes con cáncer infectados por COVID-19 y evaluar los factores de riesgo asociados a la enfermedad grave. **Materiales y métodos:** un estudio retrospectivo observacional fue llevado a cabo en Oncosalud-AUNA. Se incluyeron pacientes

con diagnóstico de cáncer invasivo con infección confirmada por SARS-CoV-2 mediante ensayo RT-PCR. Se realizaron análisis de regresión logística binaria univariante y multivariante para evaluar la asociación entre las características clínicas y la gravedad. **Resultados:** Se incluyó un total de 36 pacientes. La mediana de edad fue de 61 años; 36,1% hombres; 58,4% con ≥1 comorbilidad. El cáncer de mama fue la neoplasia más frecuente. El 72% de los pacientes estaban en tratamiento activo contra el cáncer. Todos los pacientes fueron sintomáticos. El 16,7% ingresó en la UCI y el 27,8% de los pacientes fallecieron. La gravedad de la enfermedad fue: leve, 27,8%; moderada, 33,3%; severa, 22,2%; y crítico – SDRA, 16,7%. Los pacientes con enfermedad grave o crítica fueron frecuentemente mayores de 60 años, varones, en ECOG 2-3 y recibían tratamiento con intención paliativa. **Conclusiones:** Los pacientes oncológicos con COVID-19 fueron frecuentemente adultos mayores con sobrepeso y al menos una comorbilidad en tratamiento activo contra el cáncer y desarrollaron síntomas típicos de COVID-19. Se produjo COVID-19 severo o crítico en más de un tercio de los pacientes. Los pacientes varones y los mayores de 60 años tuvieron mayor riesgo de desarrollar COVID-19 severo o crítico.

Palabras clave
Cancer; COVID-19; SARS-CoV-2; Neoplasias de la mama (fuente: DeCS BIREME).

INTRODUCTION

The world is experiencing a global pandemic due to a new coronavirus of zoonotic origin, SARS-CoV-2. In early March 2020, the World Health Organization (WHO) officially announced the COVID-19 pandemic [1] and as of January 6th, 2021, 86,809,552 confirmed cases and 1'876,156 deaths have been reported [2]. During 2020, Latin America emerged as the epicenter of the pandemic.

Cancer patients represent a population susceptible to developing infections and SARS-CoV-2 does not seem to be the exception. Overall, accumulating data indicates that cancer patients have a higher prevalence of COVID-19 infection [3,4] and a greater chance of developing a more severe illness and death when compared with non-cancer patients [3,5,6]. The effect of recent anti-cancer therapy on mortality risk remains uncertain [7-9].

Although there is increasing information on the epidemiological and clinical features of COVID-19 in cancer patients, this information is still scarce and comes mostly from the USA, China, and Europe; with results that are not necessarily applicable to a Latin American setting. The aim of this study was to describe the clinical features and outcomes of COVID-19 infected cancer patients and to evaluate the risk factors associated with severe disease.

MATERIALS AND METHODS

Study design and setting

We conducted a retrospective observational study at Oncosalud-AUNA, the largest specialized private cancer center in Peru.

Subjects

Patients with a previous diagnosis or history of invasive cancer with a SARS-CoV-2 confirmed infection as assessed by RT-PCR assay from nasopharyngeal swabs diagnosed between 13 March 2020 and 22 August 2020 were included.

Study definitions

COVID-19 disease severity was assessed according to the interim guidance of WHO for COVID-19 and classified into mild, moderate (pneumonia), severe (severe pneumonia) and critical disease (acute respiratory distress syndrome, sepsis/septic shock) [10]. Nosocomial transmission was considered definite if a patient developed symptoms at least 14 days after being admitted [11]. As previously described [9], a severe clinical event was defined as a condition requiring admission to an intensive care unit (ICU), the use of mechanical ventilation, or death. Active anticancer therapy was defined as any modality of treatment (surgery, radiotherapy, or systemic treatment) administered within 30 days of the COVID-19 diagnosis.

Instrument and procedure

Our source was the clinical history and the data was collected in a data repository.

Data collection

Clinical data were collected from the electronic medical records, including demographic, epidemiological and clinical information and laboratory and radiological findings. Patients were contacted by phone to retrieve any missing data.

Data analysis

For the descriptive analysis, categorical variables were presented through frequencies and percentages and continuous variables through summary measures (average, median, range as appropriate). Fisher's exact test was used to contrast variables between patients who developed severe or critical disease vs. those who did not. A univariate binary logistic regression was performed to assess relationship between demographic or clinical characteristics and severity with a CI of 95%. A multivariate binary logistic regression was performed with the statistically significant variables found in the univariate analysis.

Statistical analysis was carried out using SPSS Statistics version 26.0 (IBM, New York, NY). A two-sided P-value <0.05 was considered statistically significant.

Ethical approval

This study was approved by the Institutional Review Board (IRB) of Oncosalud-AUNA.An informed consent was waived by the Ethics Committee, according to the statuses of Oncosalud-AUNA.

RESULTS

We included 36 patients. Demographic and clinical characteristics are summarized in Table 1. The median age was 61 years (36- 85); 23 (36.1%) of them were males. In addition to cancer, 21 (58.4%) patients had at least one or more comorbidity, obesity (27.8%) and hypertension (33.3%) were the most frecuent. Patients had an ECOG performance status of 1 or 2 in 91.6% of cases.

Data regarding cancer characteristics and treatment is shown in Table 2. Breast cancer was the most frequent type of malignancy (n=9, 25.0%), followed by hematological cancer (n=7, 19.4%) and colorectal cancer (n=5, 13.8%). While 18.8% of patients were diagnosed with stage IV cancer, 31.8% of patients had metastases at the diagnosis of COVID-19. Seventy two percent (n=26) were on active anticancer therapy at the diagnosis of COVID-19 either with curative (50%) or palliative intent (50%). Systemic treatment (n=22, 84.6%) was the most

Table 1. Demographic and clinical characteristics.

Patients	n=36	%
Age		
Median (range)	61 (36, 85)	
<60	17	47.2
≥60	19	52.8
Sex		
Male	13	36.1
Female	23	63.9
Comorbidities		
None	15	41.7
1	14	38.9
2	5	13.9
≥3	2	5.6
Type of comorbidities		
BMI		
Low weight: <18.5	1	2.8
Normal: 18.5 – 24.99	6	16.7
Overweight: 25 – 29.99	19	52.8
Obese: ≥30	10	27.8
Hypertension		
No	24	66.7
Yes	12	33.3
Hypercholesterolemia		
No	18	78.3
Yes	5	21.7
Unknown	13	-
Other cardiovascular diseases		
No	34	94.4
Yes (CVA, cardiac arrhythmia)	2	5.6
Diabetes		
No	32	88.9
Yes	4	11.1
Asthma/COPD		
No	34	94.4
Yes	2	5.6
Smoking		
No	32	91.4
Yes	3	8.6
Unknown	1	-
Alcohol		
No	27	77.1
Yes	8	22.9
Unknown	1	-
Status performance (ECOG)		
1	17	47.2
2	16	44.4
3	3	8.3

BMI: Body Mass Index; COPD: Chronic obstructive pulmonary disease; ECOG: Eastern Cooperative Oncology Group.

Table 2. Data regarding cancer characteristics and treatment.

Patients	n=36	%
Type of neoplasms		
Breast	9	25
Hematological	7	19.4
Colorectal	5	13.8
Prostate	3	8.3
Stomach	2	5.6
Cervix	2	5.6
Other	8	22.4
Clinical Stage (at diagnosis)		
I	3	9.4
II	12	37.5
III	11	34.4
IV	6	18.8
NA	4	-
Metastasis (at diagnosis of COVID-19)		
No	15	68.2
Yes	7	31.8
Unknown	1	-
Neoplasm status (at diagnosis of COVID-19)		
In follow-up without cancer	7	19.4
In follow-up with cancer	3	8.4
In cancer treatment (during or within 30 days)	26	72.2
Intent of current cancer treatment	(n=26)	
Curative	13	50
Palliative	13	50
Current treatment	(n=26)	
Surgery	3	11.5
Radiotherapy	1	3.9
Systemic Therapy	22	84.6
Current systemic treatment	(n=22)	
Chemotherapy	11	50
Target therapy	4	18.2
Hormonotherapy	4	18.2
Biological Therapy	3	13.6

common modality as follows: chemotherapy (n=11, 50%), target therapy (n=4, 18.2%), hormonal therapy (n=4, 18.2%) and biological treatment (n=3, 13.6%).

COVID-19 characteristics, treatment and outcomes are summarized in Table 3. In 94.4% of patients, COVID-19 was acquired at a community level and in 5.6% a nosocomial transmission was considered definite. The former group came to the ER with symptoms. Median time from the onset of symptoms to the diagnosis was 3 days. All patients were symptomatic. The most commonly presented symptoms were fever (n=26, 72.2%), cough (n=20, 55.6%) and dyspnea (n=18, 50%). The SpO2 at diagnosis were: 55.6% between 94-100%, 33.3% between 90-93% and 4% ≤90%.

Table 3. COVID-19 characteristics, treatment, and outcomes.

Patients	n=36	%
Type of transmission		
Comunitary	33	94.4
Nosocomial	2	5.6
Time from symptom onset to diagnosis	3 (0, 14)	
Symptoms / Signs		
Fever	26	72.2
Difficulty breathing	18	50
Cough	20	55.6
Rhinitis	4	11.1
Myalgia	4	11.1
Anosmia	4	11.1
Asthenia	4	11.1
Diarrhea	4	11.1
Dysgeusia	2	5.6
Headache	1	2.8
O2 saturation at diagnosis of COVID-19 (%)		
94 – 100	20	55.6
90 – 93	12	33.3
<90	4	11.1
Use of supplemental O2		
No	19	52.8
Yes	17	47.2
O2 supplement type		
Nasal cannula	11	64.7
Venturi mask	1	5.9
Reservoir mask	1	5.9
Mechanical ventilation	4	23.5
Medical Treatment		
Azithromycin	11	30.6
Hydroxychloroquine	7	19.4
Antiviral	2	5.6
Tocilizumab	5	13.9
Corticosteroids	8	22.2
Other antibiotics	21	58.3
Severity of COVID-19		
Mild	10	27.8
Moderate	12	33.3
Severe	8	22.2
Crítical	6	16.7
ARDS, sepsis and septic shock	3	-
ARDS, sepsis	1	-
ARDS	2	-
Other complications		
Arrhythmia	3	-
Heart failure	1	-
Encephalitis	1	-
Serious clinical event (MV, ICU or death)		
No	24	66.7
Yes	12	33.3

(Va a la pág. 9)

Table 3. COVID-19 characteristics, treatment, and outcomes. *(Viene de la pág. 8)*

Patients	n=36	%
Clinical Outcome		
Discharged (including 9 outpatient clinics)	26	72.2
Remains hospitalized *	-	
Death	10	27.8
ICU Death	6	66.7
Death cause		
Related to COVID-19	9	90
Related to Cancer	1	10
Patients	36	
Symptoms onset time to diagnosis	3 (0, 14)	-
Patients	24	
Symptoms onset time to hospitalization (range)	3.5 (0, 11)	-
Patients	6	
Time from hospitalization to ICU admission		
Patient 1-3	0 days	-
Patient 4	4 days	-
Patient 5	5 days	-
Patient 6	7 days	-
Patients	10	
Symptoms onset time to death (range)	11.5 (5, 33)	-

A total of 17 patients (47.2%) required oxygen supplementation and 4 of them were put on invasive mechanical ventilation. Thirty percent of cases (n=11) were administered azithromycin; 19.4% (n=7), hydroxychloroquine; 5.6% (n=2), antivirals and 58.4% (n=21), empirical antibiotics. Systemic corticosteroids were given to 22.2% of patients (n=8), 7 of them with severe disease. Tocilizumab was prescribed to 13.9% of patients (n=5).

At the time of writing this report all patients had either been discharged or had died. Seventy five percent of patients (n=27) were admitted as inpatients with a median hospital stay of 12 days (4 – 30) and 16.7% (n=6) were admitted to the ICU with a median stay of 11 days (5- 24).

Overall, the severity of disease was mild, moderate, severe, and critical (ARDS) in 27.8% (n=10), 33.3% (n=12), 22.2% (n=8) and 16.7% (6) of patients, respectively. Among inpatients, the severity of disease was mild, moderate, severe, and critical (ARDS) in 11.1% (n=3), 37.0% (n=10), 29.6% (n=8) and 22.2% (n = 6) of patients, respectively. Thirty-three percent of patients developed a severe clinical event: 11.1% (n=4) were put on mechanical ventilation, 16.7% (n=6) were admitted to ICU and 27.8% (n=10) of the patients died (overall mortality). Among inpatients mortality was 37%, however, the cause of death was related to COVID-19 in 9 cases and related to cancer in 1 (inpatient specific mortality 33.3%). The median time from admission to death was 11.5 days (5-33).

Table 4. Laboratory and radiological findings.

Patients	n=29	%
Leukocytes cel/uL (range)	5500 (1780, 44300)	
≤4500	5	17.2
4500 – 11000	21	72.4
>11000 (use of Colony Stimulating Factor)	3	10.3
Lymphocytes cel/uL (range)	876 (160, 3514)	
≤1300	22	75.9
>1300	7	24.1
Neutrophils cel/uL (range)	4268 (831, 39870)	
≤1500	2	6.9
>1500	27	93.1
Patients	27	
PCR mg/dL (range)	7.54 (0.44, 37.49)	
≤0.5	3	11.1
>0.5	24	88.9
PCR mg/dL		
≤10	18	66.7
>10	9	33.3
Patients	26	
DHL U/L (range)	278 (171, 4119)	
≤225	6	23.1
>225	20	76.9
Dímero-D ug/ml (range)	0.87 (0.11, 4.00)	
≤0.5	9	34.6
>0.5	17	65.4
Patients	24	
Ferritine ng/mL (range)	551 (59, 10088)	
≤400	10	41.7
>400	14	58.3
Patients	11	
IL-6 pg/ml (range)	47.3 (6.0, 928.0)	
≤7	1	-
>7	10	-
Patients	32	
Chest CT	32	
Diffuse opacity in ground glass	20	62.5
Focal opacity in ground glass	5	15.6
Focal nodular and diffuse opacity in ground glass	3	9.3
Focal nodular	1	3.1
Diffuse Nodular	1	3.1
Normal	2	6.3

For patients who were eventually able to continue treatment with either systemic therapy, radiation or surgery, median time from COVID-19 diagnosis to restart was 41 days.

Table 5. COVID-19 infection severity according to clinical characteristics. Univariate logistic regression.

	Mild - Moderate		Severe - critical		
Patients	**n=22**	**%**	**n=14**	**%**	**p**
Age					
<60	14	63.6	3	21.4	
≥60	8	36.4	11	78.6	0.019
Sex					
Female	18	81.8	5	35.7	
Male	4	18.2	9	64.3	0.014
Comorbidities					
No	8	36.4	7	50	
Yes	14	63.6	7	50	0.644
Obesity					
No	15	68.2	11	78.6	
Yes	7	31.8	3	21.4	0.797
HTA					
No	15	68.2	9	64.3	
Yes	7	31.8	5	35.7	1
Type of tumor					
Solid	17	77.3	12	85.7	
Hematological	5	22.7	2	14.3	0.681
Current cancer treatment					
On Follow-up	8	36.4	2	14.3	
On treatment	14	63.6	12	85.7	0.255
Intent of current treatment					
Curative	10	71.4	3	25	
Palliative	4	28.6	9	75	0.049
ECOG					
1	14	63.6	3	21.4	
2- 3	8	36.4	11	78.6	0.033
Laboratory findings					
Leukocytes					
<4500	7	46.7	3	21.4	
>4500	8	53.3	11	78.6	0.245
LDH					
<225	5	41.7	1	7.1	
>225	7	58.3	13	92.9	0.065
CRP					
<0.5	2	15.4	1	7.1	
>0.5	11	84.6	13	92.9	0.596
CRP					
<10	11	84.6	7	50	
>10	2	15.4	7	50	0.103
D-dimer					
<0.5	4	33.3	5	35.7	
>0.5	8	66.7	9	64.3	1

ECOG: Eastern Cooperative Oncology Group; LDH: Lactate dehydrogenase; CRP: C-reactive protein .

Laboratory and radiological findings are found in Table 4. The blood count results showed leukopenia in 17.2% of patients, leukocytosis in 10.3% and lymphopenia in 75.9% patients. High levels of lactate dehydrogenase were found in 76.9% of patients, elevated D-dimer in 65.4% and elevated ferritin in 58.3%. Highly sensitive C-reactive protein levels were observed in 88.9% of patients and in 33.3% it was over 10 mg/dL. All but 2 patients had abnormal findings on chest CT with ground-glass opacities (GGO) being the predominant CT imaging pattern, observed in 78.1% patients (diffuse in 62.5% and focal in 15.6%). GGO associated with patchy consolidation was the second most common finding in 9.3% of patients.

Table 6. Factors associated with the severity of COVID 19 infection. Multivariate logistic regression.

	OR (IC95%)	p
Age		
<60	Reference	
>60	8.6 (1.4, 53.5)	0.021
Sex		
Female	Reference	
Male	9.0 (1.5, 54.7)	0.017
Obesity: No vs. Yes	-	0.647
Hypertension: No vs. Yes	-	0.44
Comorbidities: No vs. Yes	-	0.222
Type of tumor: Solid vs. Hematological	-	0.829
Metastasis: No vs Yes	-	0.522
Actual treatment: Follow-up vs in treatment	-	0.377

Table 5 shows risk factors for severe disease. When comparing mild and moderate vs. severe and critical illness, significant differences were found. Cancer patients with severe or critical disease were more frequently over 60 years old (78.6% vs 36,4%; p=0.019), male (64.3% vs 18.2%; p=0.014) in status performance of ECOG 2-3 (78.6% vs 36.4%; p=0.033) and were receiving treatment with palliative intention (75% vs 28%; p=0.049). In the multivariate logistic regression analysis, patients over 60 years old and male patients were 8.6 and 9 times more likely to develop severe or critical illness, respectively (Table 6). No significant differences were found in the presence of obesity, hypertension or other comorbidities, the type of tumor, the presence of metastases at COVID-19 diagnosis, active antitumor treatment, or laboratory findings.

DISCUSSION

Since December 2019, infection from the SARS-CoV-2 virus has virtually spread worldwide, posing enormous pressure over all healthcare systems.

Even before the pandemic, Latin American health care systems, which are generally overburdened, fragmented

and underfunded were struggling to meet basic needs for their population affected by a high prevalence of endemic infections as well as an increasingly higher rates of non-communicable diseases [12]. The ability to respond to the pandemic has been therefore limited and the large human toll is striking. Containing only 8.2% of the world population, the region had 28% percent of deaths worldwide by the end of December 2020 [13]. The COVID-19 lethality rate in Latin America is 6 times higher than Europe. Peru and Brazil are among the countries with the higher reproductive number (Rt) in the region 2.4 and 2.2, respectively [14]. A recent position paper which compared 2019 and 2020 data from 9 Latin American countries found a major decrease in the number of first-time visits to oncology services and chemotherapy, radiotherapy, surgery, and pathology usage as well as screening in both public and private cancer institutions [15]. ONCOSALUD-AUNA, the biggest private Peruvian cancer center, has maximized efforts in trying to guarantee the continuity of cancer therapy while treating affected patients. Herein we report the characteristics and outcomes of a cohort of 36 cancer patients with COVID-19 treated in our institution, the majority of whom were receiving active treatment.

In agreement with what has been previously reported [13,16-19], mean age of presentation for patients from the present series was 60 years old and the majority had comorbidities [3,5], with hypertension as the most frequent. The high proportion of patients with obesity (27%) reported herein in addition to those overweight (59%), leads to a striking 86% of patients who had a nutritional disorder when diagnosed with COVID-19. A robust case-control study reported an increase in the risk of COVID-19 infection in association with increasing BMI, suggesting that it is not only a risk factor for developing severe COVID-19 disease, but also for acquiring the infection itself [20].

Based on our analysis, the highest incidence of COVID-19 infection was found among breast cancer patients, followed by those with hematological malignancies and colorectal cancer. The largest cohort reported to date, which included 928 oncological patients with COVID-19, found that patients with hematological malignancies, followed by those with breast and prostate cancer were the most affected [7]. Other series reported a predominance of lung cancer, followed by esophageal and breast cancer [9]. In general, the distribution of oncological diagnoses varies among the multiple series, probably due to the epidemiological profile of each individual treating institution. However, according to the UK Coronavirus Cancer Monitoring Project (UKCCMP) report, patients with hematological malignancies appear to be at a significantly increased risk of COVID-19 infection, as they were overrepresented in their setting, but this was not observed in our center [21]. The proportion of patients from our series presenting with metastatic disease at COVID-19 diagnosis was 31.8%, lower than what has been reported by other series ranging from 36 to 60% [8-10,22]. Importantly, 72% percent of patients from our study were on active anticancer therapy at the diagnosis of COVID-19. This contrasts with most series, which have on average 20% of patients in active cancer treatment [6-9]. Our results are unusual, they are only surpassed by Hospital 12 de Octubre's results, where 96% of the patients evaluated were in active treatment [23].

All patients presented COVID symptoms similar to those reported in non-cancer patients. In general, laboratory and radiological findings from our series were alike those previously reported. We observed that 75% of patients presented lymphopenia, a common characteristic in patients receiving anticancer treatment that has also been spotted in COVID-19 patients [24]. Among the inflammation markers, we found increased DHL in 77%, as well as D-dimer in 65% of patients. C-reactive protein (CRP) was increased in almost 90% of patients, with a median of 7.54 (range 0.44 - 37.49) and one third of patients with values over 10mg/dL. Levels of CRP greater than 10 have been found to be related to moderate or critical illness and these patients are at higher risk of developing severe disease from COVID-19 [25]. Regarding radiological findings, 93.7% of the patients presented abnormalities in the chest CT scan; 68% had diffuse-type ground-glass opacities as the only pattern and an additional 13% of patients exhibited this pattern in combination with nodular-type opacities; therefore, in a total of 81% of patients a diffuse ground-glass pattern was present.

In line with the UKCCMP report, in which 45% of patients developed severe or critical disease, we found that 51.8% of the patients from the present series presented the same [8]. Our results also paralleled those reported by the CCC19 [7] in terms of ICU admission (14% vs 16.7% in the current study) and need for mechanical ventilation (12% vs 11.1% in the current study). Even though more than half of the patients developed severe or critical illness, the admission rate to the intensive care unit remained relatively low. While 37% of our patients met the criteria for ICU admission, only 16.7% were admitted. The reason why few patients were considered for this specialized treatment could be related to the low perceived usefulness of intensive support in patients with very advanced or uncontrolled cancer disease. A situation similar to that was reported in the study presented by the Hospital 12 de Octubre, where no cancer patients underwent mechanical ventilation or were admitted to the intensive care unit as the services were reserved for non-comorbid patients [23]. Overall, mortality from the present series was 27.8%, which is consistent with the 25.6% case fatality rate reported by a systematic literature search

that included 52 studies and 18,560 patients with both COVID-19 and cancer [26]. Likewise, in the Latin American setting, the Brazilian National Cancer Institute reported a COVID-19 specific mortality for inpatients of 33.1% [27], which is equal to the inpatient mortality reported by the present series.

Although our analysis is limited by the size and heterogeneity of the analyzed group, well-recognized risk factors for severe COVID-19 in the general population appear to be relevant for cancer patients as well [9,10,22,23]. Men and patients older than 60 years had an 8- and 9-times greater risk of developing severe disease, respectively. These data can help identify patients requiring admission or a closer follow-up and inform treatment decisions. More importantly, we did not find an increased risk of severe COVID-19 nor death in those patients who had received recent anti-cancer treatment. In fact, the effect of recent treatment on COVID-19 severity and outcomes remains controversial. The UKCCMP reported that among 800 patients with cancer, the receipt of any systemic treatment or radiotherapy within the previous 4 weeks did not affect mortality from COVID-19. The authors concluded that mortality from COVID-19 in cancer patients appeared to be mainly driven by gender, age, and comorbidities [8]. Also, the CCC19 study did not find an association between 30-day mortality and recent anticancer therapy [7]. Conversely, a retrospective analysis from nine Chinese hospitals, which included 205 patients, found that those who received chemotherapy within 4 weeks before the symptom onset had a higher risk of death.

Some limitations should be considered when interpreting the findings of this study. First and foremost, the small sample size limits the interpretation of results. Second, patients were naturally restricted to those with symptomatic disease who sought help at our center. Patients who were receiving long term low risk treatments such as hormonotherapy, or those undergoing a longer follow-up, were probably treated with non-cancer insurance outside of our center if they developed COVID-19. Having said this, the group studied is not representative of all patients with cancer and COVID-19, but we think it is representative of cancer patients undergoing active treatment.

In conclusion, COVID-19 cancer patients in our study were frequently overweight older adults with at least one comorbidity, who were receiving active treatment and developed typical COVID-19 symptoms. Severe or critical COVID-19 occurred in more than a third of the patients, with men and those over 60 years of age being a population highly susceptible to developing this form of disease. The mortality rate reported in our study is high and consistent with that reported for other groups of patients. Nevertheless, most cancer patients recovered from COVID-19 despite active anticancer treatment.

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ORIGINAL ARTICLE

Out-of-pocket expenditure in childhood cancer during the COVID-19 pandemic in Peru

Gastos de bolsillo en cáncer infantil durante la pandemia de COVID-19 en Perú

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ABSTRACT

Background: The COVID-19 pandemic has led to unprecedented economic and health vulnerability and inequities globally. **Objective:** This study examines the out-of-pocket expenses assumed by parents of children and adolescents with cancer in Peru during the COVID-19 pandemic and compares them to those corresponding to the pre-COVID era. **Materials and methods:** We conducted a cross-sectional survey of parents and caregivers of pediatric cancer patients who were cared for in public and private institutions between October and November 2020. All of them gave their consent before completing the survey. Respondent parents of children diagnosed before March 2020 were considered the pre-COVID-19 pandemic group, whereas if the definitive diagnosis was made after this date, it was classified as part of the COVID-19 group. **Results:** A total of 222 parents and caregivers of children with cancer responded to the survey. Almost half of the respondents lived in Lima. The average monthly family income was USD 388.4 and USD 314.7 before and during the COVID-19 pandemic. The average expenditure was USD 487.0 (SD, 453.5) and USD 415 (SD, 414.5) before and during the COVID-19 pandemic, before the cancer diagnosis. The average expenditure was USD 454.6 (SD, 406.7) and USD 387.5 (SD, 323.4) before and during the COVID-19 pandemic after a cancer diagnosis. In the COVID-19 group, the rate of catastrophic expenditure on these families was 86% before the definitive diagnosis and 75% after the cancer diagnosis. According to the type of cancer, families with a child diagnosed with a solid tumor had significantly higher out-of-pocket expenses than a leukemia than those with a child with leukemia prior to their diagnosis. **Conclusion:** Our study suggests that high out-of-pocket

health expenses were frequent in families with a child with cancer in Peru during the COVID-19 pandemic. It is possible to infer that this situation was aggravated by the decrease in economic income of most families due to the disruption of formal and informal employment.

Keywords
Covid-19 pandemic; Health insurance; out-of-pocket; universal coverage (source: MeSH NLM).

RESUMEN

Antecedentes: La pandemia de COVID-19 ha generado vulnerabilidad e inequidades económicas y sanitarias sin precedentes en todo el mundo. **Objectivo:** este estudio examina los gastos de bolsillo asumidos por los padres de niños y adolescentes con cáncer en Perú durante la pandemia de COVID-19 y los compara con la era pre-COVID. **Materiales y métodos:** Realizamos una encuesta transversal a padres y cuidadores de pacientes oncológicos pediátricos atendidos en instituciones públicas y privadas entre octubre y noviembre de 2020. Todos dieron su consentimiento antes de contestar la encuesta. Los padres encuestados de niños diagnosticados antes de marzo de 2020 fueron considerados el grupo pre-pandemia de COVID-19, mientras que si el se realizó el diagnóstico definitivo después de esta fecha, se clasificó como parte del grupo COVID-19. **Resultados:** Un total de 222 padres y cuidadores de niños con cáncer respondieron a la encuesta. Casi la mitad de los encuestados vivían en Lima. El ingreso familiar mensual promedio fue de USD 388,4 y USD 314,7 antes y durante la pandemia de COVID-19. El gasto promedio antes del diagnóstico de cáncer fue de USD 487,0 (SD, 453,5) y USD 415 (SD, 414,5) antes y durante la pandemia de COVID-19. El gasto promedio después del diagnóstico de cáncer fue de USD 454,6 (SD, 406,7) y USD 387,5 (SD, 323,4) antes y durante la pandemia de COVID-19. En el grupo de COVID-19, la tasa de gasto catastrófico de estas familias fue del 86% antes del diagnóstico definitivo y del 75% después del diagnóstico de cáncer. Según el tipo de cáncer, las familias con un niño diagnosticado con un tumor sólido tuvieron gastos de bolsillo significativamente más altos que un niño con leucemia antes de su diagnóstico. **Conclusión:** Nuestro estudio sugiere que los altos gastos de bolsillo en salud fueron frecuentes en las familias que tienen un hijo con cáncer en Perú durante la pandemia de COVID-19. Es posible inferir que esta situación se agravó por la disminución de los ingresos económicos de la mayoría de las familias debido a la disrupción del empleo formal e informal.

Palabras clave
Pandemia de COVID-19; Seguro de salud; gasto de bolsillo; Cobertura universal (fuente: DeCS BIREME).

INTRODUCTION

The COVID-19 pandemic is causing a significant social and economic impact in developing countries, as well as increasing health disparities and inequities. Delivering care for cancer patients during this crisis is challenging, given the competing priorities in public health. Pediatric cancer services have been significantly disrupted during the COVID-19 pandemic in many countries of Latin America, which has been more severe in territories with low healthcare expenditure [1]. In Peru, an upper-middle-income country, COVID-19 infection in children with cancer made visible significant income inequalities affecting the access to health services, leading to worse outcomes [2].

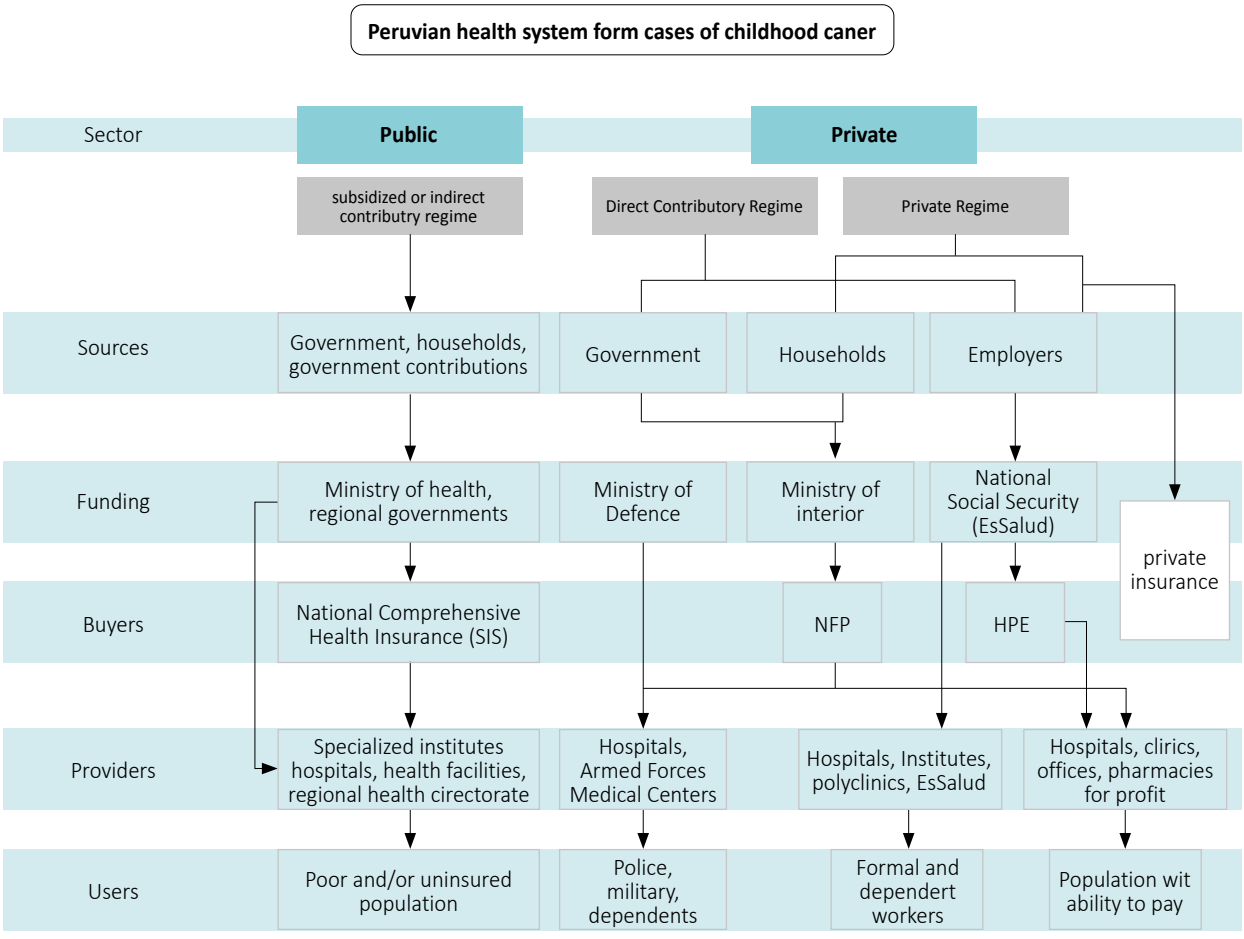
Out-of-pocket (OOP) health expenditure is defined as direct payments made by individuals to health care providers at the time-of-service use, including fees charged for medical consultations and procedures, cost of medicines, supplies, and others [3]. Health and life are at risk whenever the health expenditure is equal to or exceeding 40% of a household's non-subsistence income, defined as catastrophic health expenditure [4]. In Peru, despite increasing the coverage of the national insurance system (*Integral Health Insurance*-SIS), OOP spending remains high among patients without any affiliation to public insurance [5].

A close association of OOP expenditures with health inequalities has been described in developing countries [6], although evidence related to cancer treatment is still scarce. Moreover, there is a lack of evidence of the OOP variations during the COVID-19 pandemic. This study aims to examine the OOP expenses assumed by parents of children and adolescents with cancer in Peru during the COVID-19 pandemic and compare this to the pre-COVID era.

MATERIALS AND METHODS

Study design and setting

The Peruvian health system is divided into public and private facilities (Figure 1). Public centers work as *subsidized or indirect contributory regimes* where the government offers health services to the uninsured population through the National Comprehensive Health Insurance (SIS), being its target population individuals living in conditions of poverty and extreme poverty. This mechanism included the network of facilities of the Ministry of Health (MINSA), hospitals and specialized institutes located nationwide. The *direct contributory regime* includes the national Social Security (EsSalud) and private facilities (EPS). EsSalud offers health services to the employed contributors and their families. The armed forces (FFAA) and the National Police of Peru (PNP) have their separate health subsystem. Private facilities include private insurers, private clinics, medical centers and polyclinics. The resulting system contains multiple providers of services and insurance,



FISSAL: Intangible Solidarity in Health Fund; SIS: Integral Health Insurance; NPP: National Police of Peru; HPE: Health Provider Entities.

Figure 1. Peruvian health system for cases of childhood cancer.

often performing functions with a high degree of overlap and little coordination.

We conducted a cross-sectional survey with parents of pediatric cancer patients who are cared for in the public and private systems (National Institute of Neoplastic Diseases, National Institute of Child Health, Rebagliati National Hospital, Almenara National Hospital, Armed Forces Hospital, Delgado and Anglo-American Clinic) between October and November of 2020. All of them gave their consent before answering the survey.

Subjects

Our study population was composed of parents of children and adolescents (0 to 18 years old) diagnosed with cancer between January 2015 and July 2020 and signed their informed consent as participants. This time frame was chosen due to the economic stability of the local currency during the last five years, which would allow for an adequate analysis. Respondent parents of children diagnosed before March 2020 were considered the pre-COVID-19 pandemic group, whereas for definitive diagnoses made after this date, they were classified as part of the COVID-19 pandemic group.

Study definitions

Catastrophic expenditure was defined according to the World Health Organization (WHO) as the occurrence of expenditure in childhood cancer care equal or greater to 40% of the total non-subsistence household income (capacity to pay). Expenditures were classified as medical (diagnostic tests and medication) and extra-medical (transportation, food, and lodging). The catastrophic expenditure rate will be defined as the proportion of families who experience catastrophic expenditure out of all families included in the study.

Instrument and procedure

Our instrument was a survey. The first part of it consisted of questions about the child's socio-demographic circumstances and clinical information with cancer. The second part of the survey included questions regarding the family income and expenditure before and after the child's definitive diagnosis, along with specific areas of spending. OOP costs included all expenses related to the childhood cancer care paid by the parents and not reimbursed by the hospital. The survey was distributed electronically and in printed format through contacts obtained from hospital records in public and private pediatric oncology outpatient and inpatient settings.

Data collection

The survey was applied online through Google Forms and in person, assisted by the researchers. After that, it was downloaded into a database, which was subsequently tabulated and analyzed.

Data analysis

The analysis included a baseline comparison of parents and caregivers of children with cancer in the pre-COVID-19 group or COVID-19 group. Medians and interquartile ratios (IQR) were calculated for the continuous variables, and percentages were calculated for categorical measures. Statistical differences between the pre and COVID-19 groups were determined with chi-square tests for categorical variables and t-test for continuous variables. The differences between both groups were significant for the two-sided p-value (less than 0.05). All the analyses were carried out using the Stata 16.0 software.

Ethical approval

The survey did not provide identifiable data of the patients; hence, an institutional review board evaluation was not necessary. Regardless of the aforementioned points, an informed consent form was signed by the respondents.

RESULTS

A total of 222 parents and caregivers of children with cancer responded to the survey. The majority of caregivers were mothers (84.3%) and married or cohabiting (69.7%). Almost half of the respondents (47.5%) were originally from Lima and 52.5% lived outside the capital. The most frequent type of cancer in children was leukemia (57%). Ninety-seven percent of respondents had insurance (SIS, 60.4%; Social Security of Peru, 33%, Armed Forces, 1.7%; and private, 2.2%), whereas 3% did not have any type of insurance. Most mothers were unemployed (58.1%), whereas 79.2% of fathers had independent or dependent work (54% and 25.2%, respectively). (Table 1) Age, relationship with the patient, type of cancer diagnosis, marital status, residency type, and home location were not significantly different between the pre-COVID-19 and COVID-19 groups. However, in the COVID-19 group, there was a considerably higher proportion of patients affiliated to the national public insurance and a decrease in the proportion of patients covered by the Social Security of Peru (p=0.006).

Seventy-five percent of the respondents' children had a cancer diagnosis before starting the COVID-19 pandemic in Peru (before March 2020). Responses included cases diagnosed since 2015. The average monthly family income was USD 388.4 (SD, 339.2) and USD 314.7 (SD, 310.3) before and during the COVID-19 pandemic. The average expenditure was USD 487.0 (SD, 453.5) and USD 415 (SD, 414.5) before and during the COVID-19 pandemic, before

Table 1. Baseline characteristics of the survey respondents (parents and caregivers of children with cancer in Peru) according to the time that the child was diagnosed (before March 2020, pre COVID-19 or after March 2020, COVID-19 era) (N=222).

Variables[a]	Pre COVID-19 (n=166)	COVID-19 (n=56)	p-value
Age, median (range)	35 (17,52)	37 (19,61)	0.45
Family member	Mother (84.3%) Father (12.7%) Other (3%)	Mother (83.9%) Father (7.2%) Other (8.9%)	0.32
Type of cancer diagnosis	Leukemia (60.6%) Solid tumors (39.4%)	Leukemia (56.9%) Solid tumors (43.1%)	0.62
Stage at diagnosis	I-II (31.3%) III- IV (68.7%)	I-II (37.5%) III- IV (62.5%)	
Marital status	Married (67.7%) Divorced (30.5%) Widow (1.8%)	Married (75.9%) Divorced (22.4%) Widow (1.7%)	0.49
Residency type	Rural (36.7%) Urban (63.3%)	Rural (31.1%) Urban (68.9%)	0.44
Home location	Lima (46.3%) Regions (53.7)	Lima (50.9%) Regions (49.1)	0.55
Type of insurance	Public, Seguro Integral de Salud (SIS) (56.2%) Public, Social Security of Peru (Essalud) (39.1%) Armed Forces (1.2%) Private (2.3%) No insurance (1.2%)	Public, Seguro Integral de Salud (SIS) (70.7%) Public, Social Security of Peru (Essalud) (17.3%) Armed Forces (3.5%) Private (1.7%) No insurance (6.9%)	0.006
Employment, mother	Formal job (21.4%) Independent or informal (25%) Not working (53.6%)	Formal job (12.1%) Independent or informal (19%) Not working (68.9%)	0.10
Employment, father	Formal job (27.3%) Independent or informal (55.8%) Not working (16.9%)	Formal job (20.7%) Independent or informal (51.7%) Not working (27.6%)	0.19
Monthly family income, average (SD)	388.4 (±339.2)	314.7 (±310.3)	0.17
OOP expenses, average (SD), before the diagnosis	487.0 (±453.5)	415 (±414,5)	0.35
OOP expenses, average (SD), after the diagnosis	454.6 (±406.7)	387.5 (±323.4)	0.26

[a] were missing in marital status, residency type and location in 3 cases, employment in 5 cases for mother and 7 cases in fathers, family income in 11 cases and OOP in 13 and 12 cases, before and after diagnosis, respectively.

OOP: out-of-pocket; SD: standard deviation

the cancer diagnosis. The average expenditure was USD 454.6 (SD, 406.7) and USD 387.5 (SD, 323.4) before and during the COVID-19 pandemic after a cancer diagnosis. There were no significant differences between the pre-COVID-19 and COVID-19 groups in the OOP costs.

In the COVID-19 group, the rate of catastrophic expenditure on these families was 86% before the definitive diagnosis and 75% after the cancer diagnosis. OOP expenses before the cancer diagnosis were allocated to medical and laboratory consultations, medicines, food, transportation, and accommodation. (Figure 2) According to the type of cancer, families of a child diagnosed with a solid tumor had significantly higher OOP expenses than a leukemia diagnosis before the diagnosis. (p=0.0007) (Figure 3).

DISCUSSION

Our study reveals the high burden of OOP expenditure in families of children with cancer in Peru, despite having free

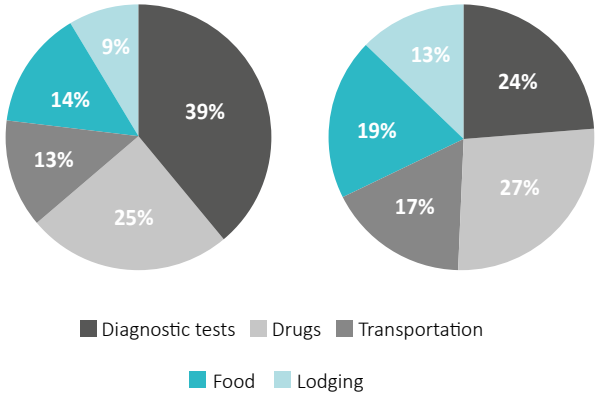


Figure 2. Concepts of out-of-pocket health expenses before and after diagnosis.

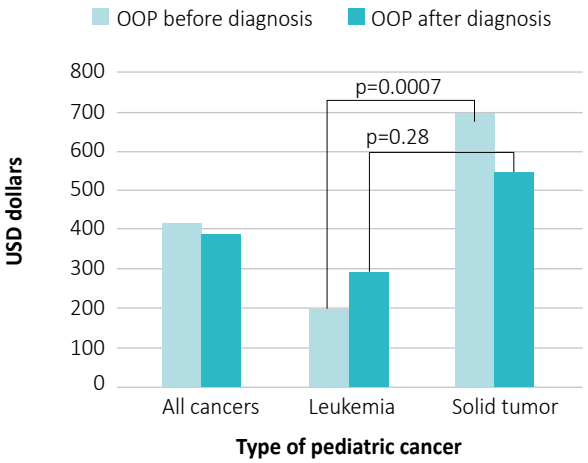


Figure 3. OOP according to the type of pediatric cancer.

treatment insurance. As a result of the economic impact of the COVID-19 pandemic, the average income of Peruvian families was reduced, mainly due to unemployment or informal jobs. This crisis led to a significant reduction in the proportion of families covered by the Social Security of Peru, as employers are obligated to make monthly health contributions. The OOP expenditures of the families of children with cancer remained high before and during the COVID-19 pandemic, above the expected family income leading to catastrophic spending.

Several studies address OOP spending on health in Peru [7-9]; however, there is no specific data for children with cancer. In 2016, OOP spending in Peru was 28% as a percentage of total health spending, considerably higher than the WHO standard (between 15% and 20%) [10]. In 2018, the OOP health expenditure of Peruvians was 11,000 million soles (nearly 3000 million dollars) per year, of which 39% was spent on medicines, according to the National Household Survey [11]. OOP spending was positively associated with a lack of affiliation to public insurance in poor households [5]. Although a national health policy named Intangible Solidarity in Health Fund (Fissal) covers the high cost of cancer treatment for seven types of cancer (leukemia, lymphomas, breast, cervical, colon, stomach, and prostate cancer), the expenses of having a child with cancer in Peru is still leading to catastrophic costs in Peruvian families.

Some causes of the high burden of OOP expenditure in families of children with cancer include that the insurance is activated once the cancer diagnosis is confirmed, leading to families incurring in OOP expenses to establish the diagnosis. Additionally, 90% of children with cancer are treated in Lima, the capital of Peru. Centralizing the institutions that provide childhood cancer care in Peru causes most parents and caregivers to cover the high cost of transferring patients from the regions to Lima. Finally, patients might require diagnostic studies or high-cost drugs that are not covered by public insurance. A specific national policy for the protection of this vulnerable population has been recently developed with the approval of the Childhood Cancer Law in Peru, which guarantees the universal coverage of cancer care from the moment in which a diagnosis of childhood cancer is suspected, provides social protection for parents of children with cancer and favor the improvement of health services aiming at a timely and quality care of these children [12].

Among the areas of OOP expenses found in our study, this could be compared with the study by Ahuja et al., which suggests that families incur direct medical and non-medical costs (food, lodging, and transportation) leading to substantial, imposing a catastrophic burden and affecting employment, education, and housing [13]. These differ in other studies from high-income countries such as Canada. The highest costs of families of children with cancer are transportation and time allocated to unpaid activities [14]. Parents of children diagnosed with a solid malignant tumor had higher OOP expenses when compared to leukemia. This finding could be likely explained by the high cost of medical laboratory and imaging tests needed before diagnosing most causes of solid tumors (Wilms tumors, neuroblastoma, and sarcomas). Interestingly, the median health expenditure of the families was higher than the median family income. This could be explained by the fact that many of the families in our country had to gain extra income from other activities, through external support (such as foundations), bank loans, among others. This phenomenon has been previously described in other contexts of low- and middle-income countries, especially related to cancer treatments [15,16].

A limitation of this study is that, due to the cross-sectional nature of the survey, causal relationships cannot be established and the possible memory bias on the part

of the respondent, typical of suis survey-based studies. We could not establish a comparison of the expenditures between the pre-pandemic and pandemic groups after the diagnosis as OOP is likely to be very different related to a different stage of progression and treatment. Additionally, out-of-pocket spending on medicines and supplies can present individual, family, or a combination of both levels not collected by the survey. An important limitation is the lack of details related to the expenses according to the types of drugs, whether innovative new cancer drugs or traditional chemotherapies. This could impact OOP in a significant manner as there is a huge cost difference between the types of drugs received by patients. Finally, this study does not have the approval of the ethics committee, since it does not collect direct information from the patient.

As a strength, this study provides evidence of the high burden of OOP on families of children with cancer in low- and middle-income countries, especially during such a relevant era of COVID-19. Interestingly, we observed a highly inequitable distribution of employment among parents according to gender, suggesting that most mothers did not work or probably resigned from their jobs to attend to their children during their children's difficult diagnosis and treatment.

In conclusion, our study observes that high OOP health expenditures were frequent in families who have a child with cancer in Peru during the COVID-19 pandemic. It is possible to infer that this situation was aggravated by the decrease in economic income of most families due to the disruption of formal and informal employment. Further studies are needed to confirm these findings.

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ORIGINAL ARTICLE

Survival in adolescents and young adults with B-cell non-Hodgkin's lymphoma in a referral hospital in Peru

Supervivencia en adolescentes y adultos jóvenes con linfoma no Hodgkin de células B en un hospital de referencia en Perú

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ABSTRACT

Objective: Compare the survival rates between pediatric and adult regimens for adolescents and young adults with B-cell non-Hodgkin lymphoma in Peru. **Materials and methods:** This retrospective study included patients aged 10-39 years with B-cell non-Hodgkin lymphoma (2010-2016). Characteristics were analyzed using Fisher's exact test, and survival differences were compared. **Results:** Thirty-one adolescents and young adult patients (6 with pediatric regimens, and 25 with adult regimens) were included. The 3-year overall survival rate was 100% for the pediatric group and 64% for the adult group (p=0.13). The only patient in the pediatric regimen who relapsed, achieved a second complete remission with Rituximab plus ifosfamide, carboplatin, etoposide and autologous stem cell transplantation, while all patients of the adult regimen group died of progressive disease. **Conclusions:** our findings suggest that adolescents and young adults with the diagnosis of B-cell Non-Hodgkin's lymphoma have better survival rates in comparison to those who are treated with adult regimens. Multicenter studies with a larger number of patients are required to confirm these results.

Keywords

Survival; Lymphoma, B-Cell; Lymphoma, non-Hodgkin; Adolescent, Young adult; Cancer (source: MeSH NLM).

RESUMEN

Objetivo: Comparar las tasas de supervivencia entre los regímenes pediátrico y adulto para adolescentes y adultos jóvenes con linfoma no Hodgkin de células B en Perú. **Materiales y métodos:** Este estudio retrospectivo incluyó pacientes de 10 a 39 años con linfoma no Hodgkin de células B (2010-2016). Las características se analizaron mediante la prueba exacta de Fisher y se compararon las diferencias de supervivencia. **Resultados:** Se incluyeron 31 pacientes adolescentes y adultos jóvenes (6 con regímenes pediátricos, 25 con regímenes para adultos). La tasa de supervivencia global a los 3 años fue del 100% para el grupo pediátrico y del

64% para el grupo de adultos (p=0,13). El único paciente del régimen pediátrico que recayó logró una segunda remisión completa con rituximab más ifosfamida, carboplatino , etopósido y trasplante autólogo de progenitores hematopoyéticos, mientras que todos los pacientes del grupo del régimen de adultos fallecieron por progresión de enfermedad. **Conclusiones:** nuestros resultados sugieren que adolescentes y adultos jóvenes con diagnóstico de linfoma no Hodgkin de células B tienen tasas de supervivencia comparados con aquellos que son tratados con regímenes para adultos. Sin embargo, se necesitan estudios con un mayor número de pacientes.

Palabras clave

Supervivencia; Linfoma de células B; Linfoma no Hodgkin; Adolescente, Adulto joven; Cáncer (fuente: DeCS BIREME).

INTRODUCTION

Adolescents and young adults (AYAs) cancers account for approximately 8% of all Non-Hodgkin's lymphoma (NHL) [1]. Most of the NHLs in AYAs are mature B-cell lymphomas, and the histological subtypes are divided in accordance with age. Burkitt's lymphoma is the most common NHL in children aged <15 years (38%), while diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma (PMBL) are most common after 15 years of age (55-70%) [1,2].

B-cell lymphoma treatment in AYAs depends on whether a pediatric or adult approach is taken. This is the case with BL, DLBCL, and PMBL, which are treated with the same approach in most pediatric trials but not in the adult ones [3]. The Berlin-Frankfurt-Munster (BFM) and the French-American-British/Lymphomes Malins de Burkitt 96 (FAB/LMB96) groups are the most used in pediatric protocols. These regimens achieve event-free survival (EFS) rates of 82% and 87%, respectively [4,5]. In adult patients, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) is the standard first line treatment for DLBCL, which has a 6-year EFS of 60-80% [6]. In BL and PMBL, the standard regimen is DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab), and the EFS is 85% and 93%, respectively [7,8].

AYAs with NHL generally have a lower survival rate than children, suggesting the presence of a different disease [2]. Additionally, although treatment differences between pediatric and adult regimens regarding survival outcomes between B-cell lymphomas in AYAs have been reported separately, little is known about which of these regimens is the best for the AYA population. This study therefore aims at comparing the survival rates between pediatric and adult regimens for AYA patients with B-cell lymphoma in Peru. We hypothesized that the pediatric approach is associated with better survival rates than the adult approach. The main endpoint of this study is, therefore, overall survival (OS) between groups, which was defined as the percentage of AYAs patients belonging to the treatment group who are still alive for a certain period of time after being diagnosed or starting treatment.

MATERIALS AND METHODS

Study design and setting

We conducted a retrospective study, with a cohort of patients with an anatomopathological diagnosis of B-cell NHL were identified and reviewed retrospectively through a search of clinical records at the Department of Oncology and Radiotherapy, Hospital Nacional Edgardo Rebagliati Martins, Peru.

Subjects

Patients were diagnosed between January 2010 and December 2016 and their cases were followed up until June 2018. The anatomopathological diagnosis of B-cell NHL followed the histopathological criteria defined in the World Health Organization Classification [9]. Additional inclusion criteria were as follows: [1] patients aged 10-39 years, [2] anatomopathological diagnosis of B-cell NHL performed by the Department of Pathology at Hospital Nacional Edgardo Rebagliati Martins (or reviewed and confirmed by our pathologist if biopsy was performed outside of our hospital), and [3] patients who completed at least 3 cycles of chemotherapy. We excluded patients with prior treatment in other healthcare centers, lost or destroyed medical records, and incomplete or insufficient data for pathological characterization.

We collected, from medical records, data about the following sociodemographic and clinical covariates: gender, age, place of residence, Eastern Cooperative Oncology Group performance status (ECOG-PS), B symptoms, histology subtype, clinical stage, extranodal disease, and clinical stage, for B-cell NHL, we used the Ann Arbor staging system for adult's patients and Murphy/St Jude for pediatric patients [10].

Data collection

Using a standardized case report form, an oncology resident collected all data related to this study.

Data analysis

We used Fisher's exact test to compare categorical variables. OS and EFS were estimated using Kaplan-Meier curves and the log-rank test, with a significance level of 5%. All statistical procedures were conducted using Stata/SE version 16.1 (StataCorp, College Station, TX) for Windows 10 Pro 64-bit.

Ethical approval

The study was approved by the Ethics Committee of the Hospital Nacional Edgardo Rebagliati Martins (Letter No. 2034-GNHERM-GRPR-ESSALUD-2018) for the use of patient data. The information was drawn exclusively from medical records and no contact was ever made with the patients. Additionally, no information that could identify the patient was collected; hence, informed consent was not requested. We ensured that the data were securely and anonymously stored.

RESULTS

Among patients who were diagnosed with B-cell lymphomas, only 31 met the inclusion criteria. Six patients were treated with pediatric regimens (LMB96 with/without rituximab and BFM95), and 25 patients with adult regimens like R-CHOP (rituximab, prednisone, vincristine, cyclophosphamide, and doxorubicin], and methotrexate at high doses) or R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin], and methotrexate at high doses) (Figure 1).

The median age of the pediatric and adult regimen groups was 13.3 and 33.8 years, respectively (p=0.001). The stage of disease, extranodal disease, B symptoms, and histology subtype were similar between the groups. The proportion of patients with ECOG-PS of ≤1 was significantly higher in the pediatric regimen group than in the adult regimen group (100% vs 64%, p=0.03). Regarding the relapse rate, there is no statistically significant difference (17%, n=1, in the pediatric regimen group, and 32%, n=8, in the adult regimen group; p=0.43). Among relapsed cases, the only patient in the pediatric regimen who relapsed, achieved a second complete remission with R-ICE (rituximab, ifosfamide, carboplatin, and etoposide phosphate) and autologous stem cell transplantation. Meanwhile, all patients from the adult regimen who relapsed died of progressive disease (Table 1).

For the whole cohort, the 3-year EFS was 67% and the OS was 70%. The 3-year EFS was 83% in the pediatric treatment group and 64% in the adult treatment group

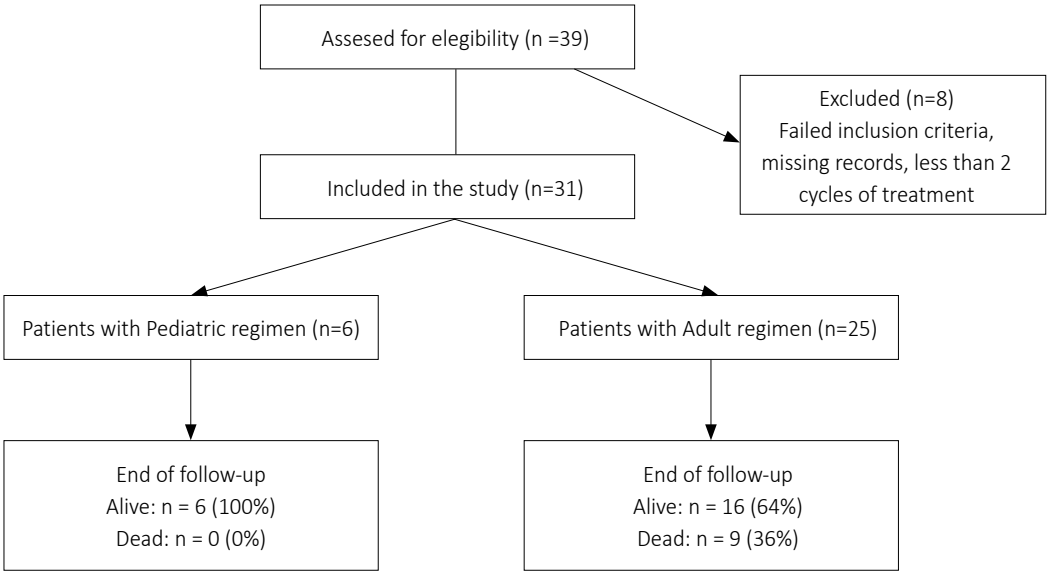

Figure 1. Flow-chart of participation in the study.

Table 1. Characteristics of the total study cohort and according to the regimens.

	Pediatric regimens N=6	Adult regimens N=25	p-value
Gender (male/female)	3/3 (50%/50%)	14/11 (56%/44%)	0.79*
Age, years (median, range)	12.5 (10-15)	33.8 (24-39)	0.0002**
Place of residence (Lima/outside Lima)	2/4 (33%/67%)	16/9 (64%/36%)	0.208*
Stage (I-II/III-IV)	2/4 (33%/67%)	9/16 (36%/64%)	0.902*
Extranodal disease (≤1, ≥2)	6/0 (100%/0%)	19/6 (76%/24%)	0.309*
B symptoms (yes/no)	4/2 (67%/33%)	16/9 (64%/36%)	0.902*
Histology (DBGCL/Burkitt's/other)	5/1/0 (83%/17%/0%)	22/1/2 (88%/4%/8%)	0.598*
ECOG-PS (≤1, ≥2)	6/0 (100%/0%)	16/9 (64%/36%)	0.101*
Follow-up, years (median, range)	2.6 (1.7-3.3)	3.6 (0.5-6.9)	0.201**
Relapse rate	1 (17%)	8 (32%)	0.423*
Death rate	0 (0%)	9 (36%)	0.101*

* By Fisher's exact test

**By Mann-Whitney U test

ECOG-PS: Eastern Cooperative Oncology Group performance status.

(p=0.35). The 3-year OS was 100% in the pediatric treatment group and 64% in the adult treatment group (p=0.13) (Figure 2).

DISCUSSION

Our alternative hypothesis was to prove that the pediatric approach is associated with a better survival than the adult approach. In our preliminary report, we suggested a trend of better survival rates in AYA patients with B-cell NHL when using the pediatric approach. This result could be supported by previous findings showing that the outcome after treatment for children with NHL is superior to that observed in adults [11,12].

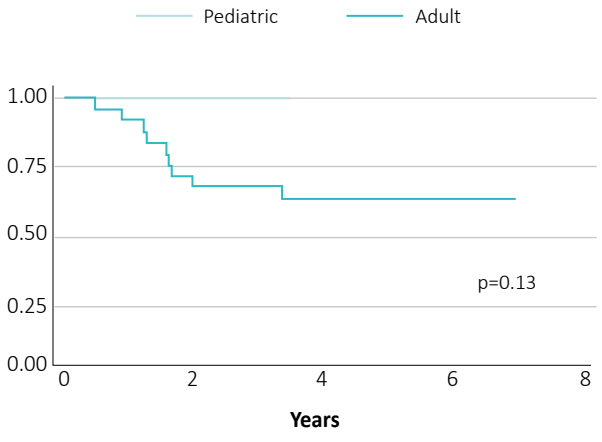

Figure 2. Overall survival by regimen of treatment.

Our result of better survival rates with the pediatric approach could be due to the fact that our patients who were treated with the pediatric approach were younger (10-15 years old) and our patients who were treated with the adult approach were older (24-39 years old). For instance, although the research question of comparing regimens was not directly assessed between AYAs with B-cell lymphoma, a large German trial showed a significant difference between age groups, wherein the younger patients (<15 years old) had better 5-year EFS than the older AYA group (15-18 years old) (85% vs 79%) and both groups were treated with the same pediatric BFM protocol [4]. The rationale could be that a biological factor such as age is an important prognostic factor for survival.

Another theory that could explain our results is that pediatric approaches are intensive regimens characterized by higher doses and broader drug combinations, compared to adult approaches. Even though pediatric treatments do not usually employ protocols that include rituximab use, as adult approaches do [13]. For instance, our results are supported by some retrospective studies showing that AYA lymphoblastic leukemia had a better outcome when treated with pediatric protocols [14,15].

Most pediatric B-cell NHL protocols worldwide treat BL and DLBCL on the same risk-stratified regimens with excellent outcomes. The BFM, for example, consists of 5 days of therapy pulses per course, based on dexamethasone, ifosfamide, cyclophosphamide, methotrexate, cytarabine, doxorubicin, etoposide, and intrathecal chemotherapy. The number of courses is

defined according to the spread of the disease. This treatment achieved a 5-year EFS of 82% for patients with BL, 85% for patients with DLBCL, and 57% for patients with PMLBL [4]. Meanwhile, the FAB/LMB96 consists of pulses of chemotherapy, which start with cyclophosphamide, vincristine, prednisone, and doxorubicin and continue with methotrexate at high doses, cytarabine, etoposide, and intrathecal chemotherapy, according to the risk classification. The 3-year EFS was 88% for the entire cohort [2,5].

Another explanation for our findings is that compared with patients treated with the pediatric approach, those treated with the adult approach had a higher rate of adverse clinical features, such as an ECOG-PS of >1 (36% vs 0%) and extranodal compromise (24% vs. 0%), and a higher relapse rate (32% vs. 17%).

Importantly, previous studies on AYA B-cell lymphomas have made comparisons between the AYA population and adult population, and interestingly, there was a trend to use adult regimens in all of them. Also, it is remarkable that none of these studies compared pediatric protocols with adult protocols. For instance, Coso et al. demonstrated that AYAs aged 15-30 years who had B-cell lymphomas did not show differences in OS or EFS, compared with the adult population (31-65 years old), after receiving adult treatment (CHP [cyclophosphamide, doxorubicin, and prednisone], R-CHOP, or BEAM [carmustine, etoposide, cytarabine, and melphalan]) [16]. In addition, Suzuki et al. found similar OS and PFS in an observational study in AYAs aged 40-60 years, the majority of whom received the CHOP or R-CHOP regimen [17]. The results of these two previous studies were quite similar to our results on the adult regimen.

On the other hand, Beck et al., who evaluated a cohort of patients aged 13-30 years with DLBCL, observed a lower 5-year EFS (52%) and OS (58%) than our results (EFS of 64% and OS of 64%). However, nearly 97% of patients were treated with adult protocols as described in their study [11].

In conclusion, this study revealed that AYA patients who were diagnosed with B-cell NHL treated with pediatric regimens had a trend toward higher survival rates than those treated with adult regimens, although the difference was not statistically significant.

Within the limitations of the study, it is the small sample size that could decrease its power and an observational design that could limit the availability of complete data. Additionally, patients in each age group received only one form of treatment (pediatric or adult, respectively) which prevented the comparison of their effectiveness within each of them. There were also no patients between 16 and 23 years old. It is necessary to annotate that, since this study was carried out in a single center in Peru, generalization cannot be guaranteed. Another important limitation was that the follow-up was only carried out until 2018, and it could not be continued due to the unavailability of the researchers. However, the main strength was that our hospital is a highly specialized cancer referral center concentrating on the majority of NHL cases in the AYA population.

Finally, AYA is a population that deserves to be studied not only in its clinical-biological aspects but also to determine which are the best treatments, since it is, undoubtedly, a special group with a behavior different from that of the pediatric population and, according to our results, this study could be the basis for future experimental studies with a larger population and thus help determine the best approach in patients whose ages are within the AYA group.

This study was presented as an abstract in the Poster Discussion Plenary Session at the 6th International Symposium on Childhood, Adolescent and Young Adult Non-Hodgkin's Lymphoma, held on September 26-29, 2018, in Rotterdam, The Netherlands.

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SPECIAL ARTICLE

Genetic counseling, testing and management of epithelial ovarian carcinoma patients: recommendations from a consensus of experts from the National Institute of Neoplastic Diseases of Peru

Asesoramiento genético, testeo y manejo de pacientes con carcinoma epitelial de ovario: recomendaciones de un consenso de expertos del Instituto Nacional de Enfermedades Neoplásicas del Perú

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ABSTRACT

The objective was to provide tools for the profiling and management of patients with epithelial ovarian cancer through genetic testing. The Consensus was made up of experts in oncology and genetics from the National Institute of Neoplastic Diseases of Peru and followed the guidelines of the Consensus Conference on Standard Operating Procedures of the European Society of Medical Oncology. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology was used to assess the evidence and make recommendations. The clinical practice guidelines were graded following the Appraisal of Guidelines for Research and Evaluation instrument II (AGREE II). Genetic counseling and testing is recommended for all patients with epithelial ovarian cancer. Regardless of the findings in the tumor, germinal testing should be performed. Testing is suggested to include *BRCA1, BRCA2, ATM, BRIP1, MLH1, MSH2, MSH6, PALB2, RAD51C, RAD51D, TP53, PTEN, PMS2, EPCAM* and *NBN*. Test findings can guide pharmacological treatment. In conclusion, patients with epithelial ovarian cancer and their relatives at risk should be identified and provided with genetic counseling. The recommendations given in this consensus will be useful if they are known and implemented. Genetic counseling and testing are expected to be included in daily clinical practice.

Keywords

Carcinoma, ovarian epithelial; Genetic counseling; Genetic profile; Consensus; Poly(ADP-ribose) polymerase inhibitors (source: MeSH NLM).

RESUMEN

El objetivo fue proporcionar herramientas para el perfilamiento y manejo de pacientes con cáncer epitelial de ovario mediante pruebas genéticas. El Consenso estuvo conformado por un grupo multidisciplinario y balanceado de médicos especialistas expertos en oncología y genética pertenecientes al Instituto Nacional de Enfermedades Neoplásicas y se realizó siguiendo los lineamientos de la "Conferencia de consenso de procedimientos operativos estandarizados de la sociedad Europea de Oncología Médica. La aproximación de calificación de recomendaciones, su desarrollo y evaluación (GRADE) se utilizó para evaluar la evidencia y hacer recomendaciones. Las guías de práctica clínica fueron calificadas por dos evaluadores siguiendo el "Instrumento para la apreciación y la evaluación de guías de práctica clínica II (AGREE II). A toda paciente con cáncer epitelial de ovario a quien se le recomiende una evaluación genética, debe ser asesorado genéticamente. Para todas las pacientes con cáncer epitelial de ovario, se recomienda testeo germinal. Por otra parte, el testeo somático puede proporcionar información que sugiera un potencial hallazgo germinal. Se sugiere que a toda paciente con cáncer epitelial de ovario no mucinoso se le realice testeo genético que incluya *BRCA1, BRCA2, ATM, BRIP1, MLH1, MSH2, MSH6, PALB2, RAD51C, RAD51D, TP53, PTEN, PMS2, EPCAM* y *NBN*. El resultado del testeo genético puede guiar el tratamiento farmacológico. En conclusión, las pacientes con cáncer epitelial de ovario y sus familiares deben de ser identificados y deben de recibir el asesoramiento genético correspondiente. Las recomendaciones de esto consenso se consideran de utilidad y deberían ser implementadas. El asesoramiento genético y el testeo deben ser incluidas en la práctica clínica del día a día.

Palabras clave

Carcinoma epitelial de ovario; Asesoramiento genético; Perfil genético; Consenso; Inhibidores de poli(ADP-ribosa) polimerasas (fuente: DeCS BIREME).

INTRODUCTION

Cancer is a type of genetic disease in which not one, but many mutations are required [1]; however, not all these mutations are inherited in families. For example, sporadic mutations occur in tumor/somatic cells only. On the other hand, genetic cancer predisposition syndromes are often characterized by variants associated with an increased risk for certain cancers (i.e., a high penetrance phenotype) and transmission to offspring through the mother and/or father [2]. Scientific and technological advances in genomics are revolutionizing our approach to genetic counseling, genetic testing, and target therapies, fulfilling the promise of personalized medicine [3].

The incidence rate of ovarian cancer in Peru was 6.7 cases per 100,000 inhabitants per year and the standardized adjusted mortality rate was 4.0 per 100,000 inhabitants according to data from Globocan 2020 (Global Cancer Observatory) [4]. Between 85%-90% of all ovarian cancers are epithelial in origin, and approximately 70% of all epithelial ovarian cancers are high-grade serous adenocarcinoma (HGS) [5]. Approximately 25% of all ovarian cancers are caused by genetic conditions. Of these, mutations in the *BRCA*1 and *BRCA*2 genes occur in approximately 18% of epithelial ovarian cancers and approximately 6% of these are caused by genes other than *BRCA*1 and *BRCA*2, including homologous recombination-associated genes (HRR) [6].

The cumulative ovarian cancer risk for *BRCA*1 mutation carriers is approximately 40% and 18% for *BRCA*2 [7]. Approximately 41%-50% of epithelial ovarian cancers exhibit homologous recombination deficiency (HRD) [8] involved in DNA damage repair and replication.

The main clinical practice guidelines (CPG) in the world recommend the use of poly (ADP)-ribose polymerase

inhibitors (PARPi) as maintenance treatment in these patients with advanced disease after first line and at recurrence [9-12].

Medical societies recommend genetic testing for all women diagnosed with ovarian cancer, but only 30% of women undergo genetic testing [13]. Additionally, there is still a lack of resources and strategies on how to best incorporate genetic testing into medical practice.

This consensus aims at providing recommendations and tools for the profiling of patients with epithelial ovarian cancer and seeks to impact prevention, early detection and treatment with targeted therapies. It is important to sensitize the medical staff in the identification and suspicion of genetic alterations in these patients, to reduce clinical variability in treatment and to optimize timely referral to a geneticist. The recommendations given in this consensus are not a substitute for medical judgment, they are only a support for decision making.

METHODS

The Consensus was formed by specialists in oncology and genetics (6 clinical oncologists and 1 geneticist) who work at the National Institute of Neoplastic Diseases (INEN) and was carried out following the guidelines of the "Consensus Conference on Standard Operating Procedures of the European Society of Medical Oncology (ESMO) [14].

In a first virtual meeting with the panel, the questions to be answered in the consensus were drafted and voted on. The definition of the clinical questions took into account the existence of controversy in the management or lack of clear guidelines and valid evidence of the efficacy of interventions. A total of 5 questions were defined. There was total agreement. 7/7 (100%) of the votes agreed with each of the questions.

The outcomes of questions 1, 2, 3, 5 were considered critical and the outcomes of question 4 were considered important but not critical.

A systematic search of the literature was carried out to identify the clinical practice guidelines (CPG) and to evaluate the relevance of adopting or adapting some of their recommendations. Databases consulted: PubMedD/MEDLINE (Public Medical Literature Analysis and Retrieval System Online). Limits: Clinical practice guidelines, published in Spanish or English, in the last 10 years. The search was supplemented in the Guidelines International Network (GIN) database.

Strategy of the search: (("ovarian neoplasms"[mh] OR (("ovarian"[tw] OR "ovary"[tw]) AND ("neoplasm*"[tw] OR "cancer"[tw] OR "carcinoma"[tw]))) AND ("genes, brca1"[mh] OR "BRCA1"[tw] OR "BRCA-2" [tw] OR "genes, brca2"[mh] OR "BRCA2"[tw] OR "BRCA-2"[tw] OR "BRIP1"[tw] OR "BRIP-1"[tw] OR "PALB2"[tw] OR "PALB-2"[tw] OR "BARD1"[tw] OR "BARD-1"[tw] OR "RAD51C"[tw] OR "RAD51D"[tw] OR "SMARCA4"[tw] OR "ARID1A"[tw] OR "CCNE1"[tw] OR "CCNE-1"[tw] OR "WT1"[tw] OR "WT-1"[tw] OR "BRAF"[tw] OR "PIK3CA"[tw] OR "PTEN"[tw] OR "ATM"[tw] OR "TP53"[tw] OR "TP-53"[tw] OR "MLH1"[tw] OR "MLH-1"[tw] OR "MSH2"[tw] OR "MSH-2"[tw] OR "MSH6"[tw] OR "MSH-6"[tw] OR "PMS2"[tw] OR "PMS-2"[tw] OR "CDK12"[tw] OR "CDK-12"[tw] OR "receptor, erbb-2"[MH] OR "ERBB2"[tw] OR "ERBB-2"[tw] OR "EPCAM"[tw] OR "KRAS"[tw])) Filters: Practice Guideline, English, Spanish, from 2011/1/1- 2021/12/31

The systematic search for epithelial ovarian cancer yielded a total of 13,466 references, 7,844 published in the last 10 years in any language. Filtering by clinical practice guidelines, articles in Spanish or English, yielded 22 results for full-text review. These searches were extended to GIN, a site that compiles CPGs. Fourteen CPGs were identified that met the selection criteria for review and evaluation. The searches were conducted by a bioinformatics expert. Search update date: January 2022.

The CPGs were scored by two raters following the Assessment of Guidelines for Research and Evaluation Instrument II (AGREE II) [15]. Most of the evaluated guidelines could be recommended (n=9) or recommended with modifications (n=5) for use in clinical practice. The overall evaluation score of the guidelines was between 100% and 80% (for 9 guidelines), between 79 - 60% (for 3 guidelines) and between 50% and 59% (for 2 guidelines). (Details about the evaluation of the selected CPGs in the Supplementary Appendix available at onkoresearch.com).

All the questions posed are answered in more than one of the CPGs reviewed. Therefore, no *de novo* searches were performed. The CPGs that cover the questions of interest meet the desired thoroughness. The recommendations given by the CPGs and answering each of the consensus questions were put to the panel for consideration and voting.

The titles and abstracts of the searches were reviewed by two reviewers who applied the selection criteria defined for each question independently. Once the selection was completed, it was compared for disagreement. The generic inclusion criteria taken into account were: Include the target population, the intervention and the comparator of interest for each question. And the following exclusion criteria: To be written in a language other than English or Spanish.

For each question, a protocol was prepared that included: the search strategy and results, a brief review of the literature identified and its methodological quality, and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) [16] summary of findings table to support the panel in formulating recommendations.

The quality of evidence, also referred to as confidence, reflects the degree of confidence we have that the estimate of an effect is adequate to support a recommendation. Although the quality of evidence is a continuous spectrum, GRADE [17] proposes a classification into four categories (high, moderate, low and very low). (Details about of quality of evidence in the Supplementary Appendix, available at onkoresearch.com).

The GRADE [17] methodology was also used to grade the strength and direction of the recommendations. Based on the judgment obtained on each of the aspects presented and the balance between risks and benefits, the panel formulated the recommendations according to the criteria proposed by the GRADE. (Details about GRADE can be found in the Supplementary Appendix, available at onkoresearch.com).

To generate the recommendations, two virtual meetings of four hours each were held via the Zoom® platform. The meetings were led by a methodological expert. All panel members received the information to be discussed prior to each meeting. The methodological group presented the evidence in summary. An open discussion was held with the participation of all attendees. After drafting and adjusting the recommendation, it was put to a vote through the Google forms® electronic voting system, which keeps the vote anonymous. The margin for accepting the recommendation after discussion was established as a vote of ≥ 80% of the total number of persons eligible to vote on each of the questions (Table 1).

Subsequently, a draft of the final consensus document was generated, incorporating adjustments according to the additional contributions of the panelists, socialized and submitted for peer review. The meetings were audio and video recorded for later reference.

Update of the Consensus:

This consensus will be updated every three years from its publication date in the event of new evidence that sways in or against the direction of any of the recommendations.

Table 1. Level of agreement by voting on consensus recommendations.

Question and Recommendation	Level of panel agreement	
	(%)	n/N
What profile of a patient with epithelial ovarian cancer would be suitable for genetic counseling? Genetic counseling is recommended for any patient with epithelial ovarian cancer who is ordered to undergo genetic testing.	85.7	6/7
Which criteria must a patient with epithelial ovarian cancer meet for a genetic testing to be indicated? It is recommended that all patients with non-mucinous epithelial ovarian cancer undergo genetic testing.	100	7/7
What are the genes to be evaluated in patients with epithelial ovarian cancer? It is suggested that all patients with non-mucinous epithelial ovarian cancer undergo genetic testing that includes the genes (*BRCA1, BRCA2, ATM, BRIP1, MLH1, MSH2, MSH6, PALB2, RAD51C, RAD51D, TP53, PTEN, PMS2, EPCAM, NBN*). In any case, it is suggested that the type of genes contained in the genetic testing panel should depend on the best available evidence at the time of sampling.	100	7/7
What recommendations do clinical practice guidelines give about somatic testing in patients with epithelial ovarian cancer? Regardless of the findings in the tumor, germline testing should be performed if clinically indicated (and for epithelial ovarian cancer, testing is clinically indicated), and tumor testing may provide information suggestive of a potential germline finding. Pathogenic or probably pathogenic variables reported in the tumor may be of somatic or germline origin	85.7	6/7
What is the multidisciplinary team's recommendation for the therapeutic (pharmacological) management of patients with epithelial ovarian cancer who are negative, positive or inconclusive for a variant of unknown significance (VUS) for the BRCA1/2 genes of the homologous recombination repair (HRR) pathway at either the somatic or germline level? For positive, negative or unknown results, see Table N°4. VUS result: Clinical decisions should not be based on a VUS result. Reclassification of the VUS result is an ongoing process and eventually it is possible to determine definitively whether the variant is deleterious or benign. Until that time, the patient's clinical features and family history should guide clinical decision making.	100	7/7

If there is no new evidence, it will be reviewed again in three years.

In the event of new evidence that modifies any of the recommendations of the consensus, it will be updated every three years after its publication. If there is no new evidence, it will be reviewed every three years.

Recommendations

Question 1. *What profile of patient with epithelial ovarian cancer would be suitable for genetic counseling?*

Recommendation: Genetic counseling is recommended for all patients with epithelial ovarian cancer who are ordered to undergo genetic testing. Strong recommendation in favor. Moderate certainty of evidence. Seven CPGs support this recommendation [9,10,18-22].

Good Practice Point: The decision to offer genetic counseling/testing involves three steps: 1) Pretest genetic counseling. 2) Consideration of the most appropriate test. 3) Post-test genetic counseling, when the result is given to the patient [6]. A medical geneticist, oncologist or surgeon with experience and expertise in cancer genetics should be involved in each step of the process. Counseling/testing should be considered when it is likely to impact the risk management and/or treatment of the patient and/or family members who are at risk.

Question 2. *Which criteria must a patient with epithelial ovarian cancer meet for a genetic testing to be indicated?*

Recommendation: It is recommended that all patients with non-mucinous epithelial ovarian cancer undergo genetic testing. Strong recommendation in favor. Moderate certainty of evidence. Nine GPC support this recommendation [9-11,18-23].

Good practice point: All women diagnosed with non-mucinous epithelial ovarian cancer should be offered germline genetic testing for *BRCA*1/2 and other ovarian cancer susceptibility genes, regardless of clinical features of the disease or family history of cancer (strong recommendation in favor). First- and second-degree blood relatives of an ovarian cancer patient with a germline pathogenic or probably pathogenic variant in a cancer susceptibility gene should be offered individualized genetic risk assessment, counseling, and genetic testing (strong recommendation in favor).

Question 3. *What are the genes to be evaluated in patients with epithelial ovarian cancer?*

Recommendation: It is suggested that all patients with non-mucinous epithelial ovarian cancer undergo genetic testing that includes the genes BRCA1, BRCA2, ATM, BRIP1, MLH1, MSH2 MSH6, PALB2, RAD51C, RAD51D, TP53, PTEN, PMS2 ,EPCAM and NBN (Details about risk and definition in the Supplementary Appendix, available at onkoresearch.com). In any case, it is suggested that the type of genes contained in the genetic testing panel should depend on the best available evidence at the time of sampling. Conditional (weak) recommendation in favor. Moderate certainty of evidence, five CPGs support this recommendation [9-11,18,21].

Question 4. *What recommendations do clinical practice guidelines give about somatic testing in patients with epithelial ovarian cancer?*

Recommendation: Regardless of the findings in the tumor, germline testing should be performed if clinically indicated (and for epithelial ovarian cancer, testing is clinically indicated), and tumor testing may provide information suggestive of a potential germline finding. Pathogenic or probably pathogenic variables reported in the tumor may be of somatic or germline origin. Conditional (weak) recommendation in favor. Low certainty of evidence. Three CPGs support this recommendation [9,18,21].

Question 5. *What is the multidisciplinary team's recommendation for the therapeutic (pharmacological) management of patients with epithelial ovarian cancer who are negative, positive or inconclusive for a variant of unknown significance (VUS) for the BRCA1/2 genes of the homologous recombination repair (HRR) pathway at either the somatic or germline level?*

Recommendation: For positive, negative or unknown results, see more in the Supplementary Appendix, available at onkoresearch.com

VUS result: Clinical decisions should not be based on a VUS result. Reclassification of the VUS result is an ongoing process and it is possible to eventually determine definitively whether the variant is deleterious or benign. Until that time, the patient's clinical features and family history should guide clinical decision making. Strong recommendation in favor. Certainty of evidence is high. Eight CPGs support this recommendation [9,11,12,21,24-27].

DISCUSSION AND CONCLUSIONS

Genetic risk assessment for epithelial ovarian cancer is a multistage process that involves identifying and counseling individuals at risk for familial or hereditary cancer. Its purpose is to educate individuals on genetic, biological and environmental factors related to cancer diagnosis and/or risk. Testing should be considered in patients with a personal or family history suggestive of genetic susceptibility and for whom the result will help with risk management and treatment.

Genetic testing strategies are greatly facilitated when a pathogenic or probably pathogenic variant has already been identified in a family member. In such a case genetic testing can be limited to searching for pathogenic or probably pathogenic variants in other family members at the same location in the gene. However, if there is reason to suspect more than one pathogenic or probably pathogenic variant in the family, then more extensive testing should be considered. Upon the finding of a variant of unknown significance (VUS), a genetic alteration that may at the time represent a benign polymorphism unrelated to an increased risk of cancer or may indicate an increased risk of cancer, the patient should be considered for inclusion in a clinical trial that allows the variant to be followed over time. Advances in sequencing technologies have resulted in the increasing availability of multigene panels for genetic analysis. Given the small number of patients carrying some of these mutations, the level of evidence is basically expert opinion. A disadvantage of multigene panels is that they are most often reporting VUS.

Performing germline or tumor testing sequentially or in combination will depend on national health regulations and existing guidelines for each country. In any case, the identification of deleterious *BRCA*1 and *BRCA*2 mutations in tumor tissue requires subsequent germline testing to assess the heritability of such variation after appropriate genetic counseling. Patients with ovarian cancer without deleterious germline *BRCA*1and *BRCA*2 mutations will require tumor testing to identify an additional percentage of patients who may benefit from iPARP. Most women with advanced stage epithelial ovarian cancer will have a relapse of their disease and will require additional treatment despite initial therapy. The introduction of poly (ADP-ribose) polymerase inhibitors (PARPi) has resulted in a major change in the approach to epithelial ovarian cancer throughout the treatment life cycle.

Translating recommendations into decisions made in clinical settings involves processes aimed at modifying the behavior of users of consensus recommendations. Health care institutions and patients will follow the recommendations contained therein if they are adequately aware of them and could apply them. In the context of consensus implementation, the following are identified as the main barriers to the application of the recommendations of restrictions on patients' access to health care services, whether due to lack of timely care, delays in authorizations, failure to enroll, economic restrictions or inability to pay, denial of authorizations or refusal to provide services and medicines, lack of knowledge about genetic profiling of patients with epithelial ovarian carcinoma by the first level of care and barriers during the referral and counter-referral process between related specialties.

Interventions aimed at overcoming barriers include distribution of printed and/or digital educational materials;academic training activities with the participation of local opinion leaders;socialization activities with patient participation, dissemination in mass media and written materials in scientific journals and national academic publications and coordination with national health authorities to define actions to implement the consensus recommendations.

Finally, we will seek to define a follow-up and evaluation plan for the process of implementing the recommendations, which will make it possible to evaluate the impact on the outcomes of patients with epithelial ovarian carcinoma in the country by generalizing genetic profiling.

Limitations of this Consensus

The accelerated appearance of new markers of clinical interest in the pathologies treated by this consensus could in the short to medium term modify some of the recommendations and the appearance of new target therapies could change the recommendations in one direction or another. The literature search was limited to PubMed and GIN (Guidelines International Network). The primary evidence on which the CPGs are based was not used, although the CPGs were graded using the AGREE II instrument. Since this is an expert consensus, the risk of subjectivity in the opinions is always implicit.

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Supplentary Appendix

Additional information about this article is available in the Supplementary Appendix.

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SPECIAL ARTICLE

Genetic counseling, testing and management of prostate adenocarcinoma patients: recommendations from a consensus of experts from the National Institute of Neoplastic Diseases of Peru

Asesoramiento genético, testeo y manejo de pacientes con adenocarcinoma de próstata: recomendaciones de un consenso de expertos del Instituto Nacional de Enfermedades Neoplásicas del Perú

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ABSTRACT

The objective was to provide tools for genetic profiling and treatment of patients with prostate adenocarcinoma. The Consensus was made up of oncologists and geneticists from the National Institute of Neoplastic Diseases of Peru and followed the guidelines of the "Consensus Conference on Standard Operating Procedures of the European Society of Medical Oncology". The GRADE methodology was applied to assess the evidence and make recommendations. The clinical practice guidelines were graded following the "AGREE II". All patients with prostate adenocarcinoma and risk factors should be ordered genetic testing and counseling. Testing should include *BRCA1/2, ATM, CHECK2 PALB2, MLH1, MSH2/6,* and *PMS2*. Additional genes may be requested based on the clinical condition. In patients with metastatic castration-resistant or regional prostate cancer, somatic testing may be considered. The result of the test can guide treatment. In conclusion, there are many unmet needs in the approach and management of prostate cancer. Cancer genetic risk assessment and genetic counseling involve the identification and counseling of individuals at risk for hereditary cancer. Genetic counseling and testing are expected to be included in daily clinical practice.

Keywords

Prostate, adenocarcinoma; Genetic Counseling; Genetic Profile; Germline; Consensus; Poly(ADP-Ribose) Polymerase Inhibitors (source: MeSH NLM).

RESUMEN

El objetivo fue proporcionar herramientas para el perfilamiento genético y manejo de pacientes con adenocarcinoma de próstata. El Consenso lo conformaron oncólogos y genetistas del Instituto Nacional de Enfermedades Neoplásicas y siguió los lineamientos de la Conferencia de consenso de procedimientos operativos estandarizados de la Sociedad Europea de Oncología Médica. La metodología GRADE se utilizó para evaluar la evidencia y hacer recomendaciones. Las guías de práctica clínica fueron calificadas siguiendo el "AGREE II". A todo paciente con adenocarcinoma de próstata y factores de riesgo se le debería ordenar testeo y asesoramiento genético; el testeo debería incluir *BRCA1/2, ATM, CHECK2 PALB2, MLH1, MSH2/6,* y *PMS2*. Genes adicionales pueden solicitarse dependiendo del contexto clínico. En pacientes con cáncer de próstata metastásico resistente a la castración o regional, puede ser considerado el testeo somático. El resultado del testeo puede guiar el tratamiento. En conclusión, existen muchas necesidades insatisfechas en el enfoque y manejo del cáncer de próstata. La evaluación del riesgo genético del cáncer y el asesoramiento genético involucra la identificación y el asesoramiento de individuos con riesgo de cáncer hereditario. Se espera que el asesoramiento y el testeo genético sean incluidos en la práctica clínica diaria.

Palabras clave

Adenocarcinoma, próstata; Asesoramiento Genético; Perfil Genético; germinal; Consenso; Inhibidores de Poli(ADP-Ribosa) Polimerasas (fuente: DeCS BIREME).

INTRODUCTION

Cancer is a genetic disease in which many mutations are involved [1]; however, not all of these mutations are inherited in families. For example, sporadic mutations occur in tumor/somatic cells only. On the other hand, genetic cancer predisposition syndromes are often characterized by variants associated with an increased risk for certain cancers (i.e., a high penetrance phenotype) and transmission to offspring through the mother and/or father [2]. Scientific and technological advances in genomics are revolutionizing our approach to genetic counseling, genetic testing, and target therapies, fulfilling the promise of personalized medicine [3,4].

Growing evidence suggests that prostate cancer (PC) has a significant inherited predisposition [5], with high risk conferred by the breast cancer susceptibility gene 1 and 2 (BRCA1/2), (associated with the breast and ovarian cancer genetic predisposition syndrome [HBOC]) and the homebox B13 (HOXB13) (associated with hereditary prostate cancer [HPC]) [6]. Inherited genetic mutations have been discovered in up to 11.8% of men with metastatic prostate cancer (mPC), primarily in deoxyribonucleic acid (DNA) repair genes such as BRCA2 and ataxia telangiectasia mutated (ATM) [7]. Identifying the genetic mutations of the genetic predisposition syndrome for PC therefore has implications for the patient and their family, allowing for accuracy in the patient's treatment, family genetic counseling and is being incorporated into clinical practice guidelines.

Prostate tumors associated with germline BRCA2 mutations often have Gleason scores greater than 8 and nodal or distant metastases at diagnosis, but these genetic variants cannot be excluded in patients without such clinicopathologic features. Germline mutations in BRCA2 are associated with poor clinical outcomes, while the prognostic implications of heritable mutations in other DNA damage response (DDR) genes are less well established. Thirty percent of patients with metastatic prostate cancer who carry a pathogenic/likely pathogenic germline DDR variant had no previous family history of cancer. Some somatic and germline mutations in genes involved in the homologous recombination pathway are potential predictors of response to platinum-based chemotherapy and poly (ADP)-ribose polymerase inhibitors (PARPi) [8].

Most patients with hormone-sensitive PC treated with the standard of care (androgen deprivation therapy) will progress to metastatic castration-resistant prostate cancer

(mCRPC) within 2 to 3 years of diagnosis. With no curative therapies available, mCRPC remains an aggressive disease with a poor prognosis and for which better therapeutic options are needed. Two PARP inhibitors, olaparib and rucaparib, were approved by the US Food and Drug Administration (FDA) as target therapy for mCRPC [9,10]. Olaparib was approved by the FDA for patients with mCRPC with a pathogenic/likely pathogenic variant germline or somatic homologous recombination repair (HRR) gene mutations that had progressed to enzalutamide or abiraterone, based on the results of the PROfound study [10].

Accelerated approval was granted to rucaparib in BRCA1/2 mutated mCRPC (germline or somatic) that had previously received androgen receptor-targeted therapy and taxane-based chemotherapy based on the results of the TRITON2 study [9]. Therefore, germline testing has substantial implications when deciding on treatment [11].

This consensus aims at providing tools for the profiling of patients with prostate adenocarcinoma and seeks to impact prevention, early detection and treatment with targeted therapies. It is important to sensitize the medical profession in the identification and suspicion of genetic alterations in these patients, reduce clinical variability in treatment and optimize timely referrals to a geneticist. The recommendations given in this consensus are not a substitute for medical judgment, they are only a support for decision making.

METHODS

The Consensus was formed by specialists in oncology and genetics (6 clinical oncologists and 1 geneticist), who work at the National Institute of Neoplastic Diseases (INEN), and was carried out following the guidelines of the "Consensus Conference on Standard Operating Procedures of the European Society of Medical Oncology (ESMO) [12].

In a first virtual meeting with the panel, the questions to be answered in the consensus were drafted and voted on. The definition of the clinical questions took into account the existence of controversy in the management or lack of clear guidelines and valid evidence of the efficacy of the interventions. A total of 5 questions were defined. There was total agreement. 7/7 (100%) of the votes agreed with each of the questions.

The outcomes of questions 1, 2, 3, 5 were considered critical and the outcomes of question 4 were considered important but not critical.

A systematic search of the literature was carried out to identify the clinical practice guidelines (CPG) and evaluate the relevance of adopting or adapting some of their recommendations. Databases consulted: PubMedD/MEDLINE (Public Medical Literature Analysis and Retrieval System Online). These searches were extended to GIN, a site that compiles CPGs. Limits: Clinical practice guidelines, published in Spanish or English, in the last 10 years. The search was supplemented in the Guidelines International Network (GIN) database.

Search strategy: Search: ("prostate neoplasms"[mh] OR ("prostate"[tw]) AND ("neoplasm*"[tw] OR "cancer"[tw] OR "carcinoma"[tw])) Filters: Practice Guideline, English, Spanish, from 2012/1/1 - 2021/12/31. The systematic search yielded a total of 179,371 references, 88,035 published in the last 10 years in any language. When filtering by clinical practice guidelines, articles in Spanish or English, 134 results were obtained. The abstracts were reviewed and 14 references were obtained for full-text review. Finally, 9 CPGs were identified that met the selection criteria for review and evaluation. The searches were performed by a bioinformatics expert. Search update date: January 2022."

The CPGs were rated by two evaluators following the Assessment of Guidelines for Research and Evaluation Instrument II (AGREE II) [13]. Most of the evaluated guidelines could be recommended (n=8) or recommended with modifications (n=1) for use in clinical practice. The overall assessment score of the guidelines was between 100% and 80% (for 7 guidelines), between 79- 60% (for 1 guideline) and between 50% and 59% (for 1 guideline). (Details about the evaluation of the selected CPGs in the Supplementary Appendix are available at onkoresearch.com).

All the questions posed were answered in more than one of the CPGs reviewed. Therefore, no de novo searches were performed. The CPGs that cover the questions of interest meet the desired rigor.

The titles and abstracts of the searches were reviewed by two reviewers who applied the selection criteria defined for each question independently. Once the selection was completed, it was compared for disagreement. The generic inclusion criteria taken into account were: include the target population, the intervention and the comparator of interest for each question. And the following exclusion criteria: to be written in a language other than English or Spanish.

For each question, a protocol was prepared that included: the search strategy and results, a brief review of the literature identified and its methodological quality, and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) [14] summary table of findings to support the panel in formulating recommendations.

The quality of evidence, also referred to as confidence, reflects the degree of confidence we have that the estimate of an effect is adequate to support a recommendation. Although the quality of evidence is a continuous spectrum, GRADE [15] proposes a classification into four categories (High, Moderate, Low and Very Low). (Details about quality of evidence can be found in the Supplementary Appendix, available at onkoresearch.com).

The GRADE [15] methodology was also used to assess the strength and direction of the recommendations. Based on the judgment obtained on each of the aspects presented and the balance between risks and benefits, the panel formulated the recommendations according to the criteria proposed by the GRADE. (Details about GRADE can be found in the Supplementary Appendix, available at onkoresearch.com).

To generate the recommendations, two virtual meetings of four hours each were held through the Zoom® platform. The meetings were led by a methodological expert. All panel members received the information to be discussed in advance of each meeting. The methodological group presented a summary of the evidence. An open discussion was established with the participation of all attendees. After drafting and adjusting the recommendation, it was submitted to a vote through the electronic voting system Google forms®, which keeps votes anonymous. The margin to accept the recommendation after discussion was established as a vote ≥ 80% of the votes of the total number of people eligible to vote in each of the questions (Table 1).

Recommendations

Question 1. *What profile of patient with prostate adenocarcinoma would be suitable for genetic counseling?*

Recommendation: Genetic counseling is recommended for any patient with prostate adenocarcinoma who is ordered to undergo genetic testing. Strong recommendation in favor. Moderate quality of evidence. Five CPGs support this recommendation [16-20].

Table 1. Level of agreement, by voting, of the consensus recommendations.

Question and Recommendation	Panel agreement level	
	(%)	n/N
What profile of patient with prostate adenocarcinoma would be suitable for genetic counseling? Genetic counseling is recommended for any patient with prostate adenocarcinoma who is ordered to undergo genetic testing.	83.3	5/6
What are the criteria that a patient with prostate adenocarcinoma must meet for genetic testing to be indicated? Germline testing is recommended for patients with PC and any of the following: High or very high regional or metastatic risk PC, regardless of family history; Askenazi Jewish ancestry; Family history of high-risk germline mutations; Intraductal/cribbiform histology; Strong family history of PC.	100	6/6
What are the genes to be evaluated in patients with prostate adenocarcinoma? It is suggested that all patients with prostate adenocarcinoma undergo genetic testing that includes the genes shown in table 2.	100	6/6
What recommendations do clinical practice guidelines give about doing somatic testing in patients with prostate adenocarcinoma? In patients with mCRPC, somatic testing for alterations in HRR pathway genes and testing for "high levels of microsatellite instability" (MSI-H) or discrepancy repair deficiency (dMMR) is recommended. In patients with mCRPC or regional PC, somatic testing for alterations in HRR pathway genes and testing for MSI-H or dMMR can be considered.	100	6/6
What is the multidisciplinary team's recommendation for the therapeutic (pharmacological) management of patients with prostate adenocarcinoma who are negative, positive or inconclusive for a variant of unknown significance (VUS) for the pathway genes at either the somatic or germline level?		
Olaparib is a treatment option for patients with mCRPC and a pathogenic/likely pathogenic variant (germline or somatic) in one of the HRR genes in: second line after a first line with abiraterone or enzalutamide independently of prior docetaxel therapy; Second line after docetaxel; In subsequent lines		
Rucaparib* is a treatment option in mCRPC with pathogenic/probably pathogenic BRCA1/2 variant (germline or somatic): Second line after a first line with abiraterone or enzalutamide; in second line after docetaxel; in subsequent lines.	83.3	6/6
Rucaparib* can be given in patients who have not received prior taxane-based chemotherapy because they are unsuitable.		
*Rucaparib is not yet registered for use in prostate cancer patients in Peru.		
VUS result: Clinical decisions should not be based on a VUS result.		

Subsequently, a draft of the final consensus document was generated, incorporating adjustments based on additional input from the panelists, socialized and sent for peer review. The meetings were audio and video recorded for later reference.

In the event of new evidence that modifies any of the recommendations of the consensus, it will be updated every three years after its publication. If there is no new evidence, it will be reviewed every three years.

Question 2. *What are the criteria that a patient with prostate adenocarcinoma must meet for genetic testing to be recommended?*

Recommendation: Germline testing is recommended for patients with PC and any of the following: High or very high regional or metastatic risk PC, regardless of family history; Ashkenazi Jewish ancestry; family history of high-risk germline mutations; intraductal/cribriform histology; strong family history of PC consisting of sibling or parent or multiple family members diagnosed with PC (non-localized) under age 60 or who died of PC.

Strong recommendation in favor. Moderate quality of evidence. Six CPGs support this recommendation [16-19,21,22].

Question 3. *What are the genes to be evaluated in patients with prostate adenocarcinoma?*

Recommendation: It is suggested that all patients with prostate adenocarcinoma undergo genetic testing that includes the genes listed in Table 2. In any case, it is suggested that the type of genes contained in the genetic testing panel should depend on the best available evidence at the time of sampling. Conditional (weak) recommendation in favor. Quality of evidence: moderate. Four CPGs support this recommendation [16,17,19,23].

Question 4. *What recommendations do clinical practice guidelines give about doing somatic testing in patients with prostate adenocarcinoma?*

Recommendation: In patients with mCRPC, somatic testing for alterations in HRR pathway genes and testing for "high levels of microsatellite instability" (MSI-H) or discrepancy repair deficiency (dMMR) is recommended. In patients with mCRPC or regional PC, somatic testing for alterations in HRR pathway genes and testing for MSI-H or dMMR may be considered. Conditional recommendation in favor. Quality of evidence: moderate. Four CPGs support this recommendation [16,18,21,22].

Good practice point: Tumor testing may provide information suggestive of a potential germline finding. Regardless of tumor findings, germline testing should be performed if clinically indicated (Conditional recommendation in favor. Quality of evidence: moderate). MSI-H (microsatellite instability) describes cancer cells that have a large number of mutations (in 30% or more of the microsatellites). Microsatellites are short, repeated sequences of DNA. Cancer cells with MSI-H may have a defect in the ability to correct errors when copying DNA. The dMMR (discrepancy repair deficiency) and its characteristic genetic signature, genome-wide MSI-H, define a unique biological subset of cancers characterized by a high mutational tumor burden and potential responsiveness to immunotherapy.

Table 2. Genes to be evaluated in patients with prostate adenocarcinoma

Genes to evaluate	Definition
BRCA1	Breast cancer susceptibility gene 1
BRCA2	Breast cancer susceptibility gene 2
ATM	Ataxia telangiectasia mutated
CHECK2	Checkpoint kinase 2
PALB2	Partner and localizer of BRCA2
MLH1	MutL homolog 1
MSH2	MutS homolog 2
MSH6	MutS homolog 6
PMS2	Post-meiotic segregation increased 2
Additional genes to consider depending on the clinical context	
RAD51B	RAD51 paralog B
RAD51C	RAD51 paralog C
RAD51D	RAD51 paralog D
RAD54L	RAD54 paralog L
BARD1	BRCA1 Associated RING Domain 1
CDK12	Cyclin Dependent Kinase 12
CHECK1	Checkpoint kinase 1
FANCL	FA Complementation Group L
ATR	Ataxia telangiectasia and Rad3-related protein
NBN	Nibrin
GEN1	Flap endonuclease GEN homolog 1
EPCAM	Epithelial cellular adhesion molecule
MRE11A	MRE11 homolog A, double-strand break repair nuclease
BRIP1	BRCA1 Interacting Helicase 1
FAM175A	FAM175A protein

Question 5. *What is the multidisciplinary team's recommendation for the therapeutic (pharmacological) management of patients with prostate adenocarcinoma who are negative, positive or inconclusive for a variant of unknown significance (VUS) for the pathway genes at either the somatic or germline level?*

Recommendation: Olaparib is a treatment option for patients with mCRPC and a pathogenic/likely pathogenic variant (germline or somatic) in one of the HRR genes in: second line after a first line with abiraterone or enzalutamide independently of prior therapy with Docetaxel; second line after Docetaxel. In subsequent lines Rucaparib* is a treatment option in mCRPC with pathogenic/likely pathogenic BRCA1/2 variant (germline or somatic) in: second line after first line with abiraterone or enzalutamide; in second line after docetaxel; in subsequent lines.

Rucaparib* can be given in patients who have not received prior taxane-based chemotherapy because they are unsuitable.

*Rucaparib is not yet registered for use in prostate cancer patients in Peru.

VUS outcome: Clinical decisions should not be based on a VUS outcome.

Strong recommendation in favor. High to moderate quality of evidence. Five CPGs support this recommendation [16,21-24].

DISCUSSION AND CONCLUSIONS

Guidelines are limited with respect to genetic counseling and genetic testing for prostate adenocarcinoma and focus only on BRCA1/2 testing. In most advanced prostate tumors, actionable targets are identified. In very low-risk and low-risk PC patients, germline testing is recommended if there is a positive family history. For intermediate-risk patients, germline testing is recommended if there is a positive family history or intraductal/cribriform histology. Germline testing is always recommended in high and very high risk patients. Much progress has been made in the discovery of genes and their mutations related to the risk of genetic predisposition to cancer syndrome. This is an exponentially growing field and not all the information currently received from commercial testing panels correlates with the possibility of therapeutic intervention. However, it proves to be useful information, to assess familial cancer risk and to be able to take preventive measures. While substantial recent advances have been made, there are many unmet needs in the approach and management of prostate cancer. Somatic and germline mutations in homologous recombination repair (HRR) genes may predict the clinical benefit of PARPi.

Translating recommendations into decisions made in clinical settings involves processes aimed at modifying the behavior of users of consensus recommendations. Healthcare providers and patients will follow the recommendations contained therein if they are adequately aware of them and have the ability to apply them. In the context of the implementation of the consensus, the main barriers to the application of the recommendations have been identified as follows: restrictions for patients in access to health services, either due to lack of timely care, delays in authorizations, failures in affiliation, economic restrictions or ability to pay, denial of authorizations or refusals to provide services and medicines; lack of knowledge about genetic profiling of patients with prostate adenocarcinoma by the first level of care and little agility for the process of referral and counter-referral between related specialties.

Among the interventions aimed at overcoming barriers, the following are proposed: distribution of printed and/or digital educational materials; academic training activities with the participation of local opinion leaders; socialization activities with the participation of patients; dissemination in the mass media; written materials in national scientific journals; and coordination with national health authorities to implement the consensus recommendations.

Finally, we will seek to define a follow-up and evaluation plan for the process of implementing the recommendations, which will make it possible to evaluate the impact on the outcomes of patients with prostate adenocarcinoma in the country by generalizing genetic profiling.

Limitations of this consensus

The accelerated appearance of new markers of clinical interest in the pathologies treated by this consensus could in the short to medium term modify some of the recommendations and the appearance of new target therapies could change the recommendations in one direction or another. The literature search was limited to PubMed and supplemented in GIN. The primary evidence on which the CPGs are based was not used, although the CPGs were graded using the AGREE II instrument. Since this is an expert consensus, and despite being based on evidence, the risk of subjectivity in the opinions is always implicit.

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Supplementary Appendix

Additional information about this article is available in the Supplementary Appendix.

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CASE REPORT

Cervical embryonal rhabdomyosarcoma: a case series from a single-institution

Rabdomiosarcoma embrionario de cuello uterino: serie de casos de una sola institución

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ABSTRACT

Rhabdomyosarcoma is an aggressive malignant neoplasm that originates in the mesenchyme. It is the most frequent type of sarcoma in infants and children. Its localization in the uterus is extremely rare, and its incidence increase from 20 years-old onwards. Prognosis typically depends on the histological type, age, and the absence of metastasis. We present 5 cases of young females with a history of bleeding, a cervical tumor, whose biopsy was positive for embryonal rhabdomyosarcoma, botryoid variant. All patients received chemotherapy and surgery. Since rhabdomyosarcoma has a high rate of incidence in young women and its diagnosis in the cervix is less aggressive, conservative management of these cases is recommended fertility preservation. Post-surgical management should always consist of chemotherapy, as advances in this type of therapy have been shown to improve general survival rates. Hence, it is essential to report on rare tumors, as it helps in acquiring experience and appropriate knowledge for their clinical management and raises the need for further studies on this disease.

Keywords
Rhabdomyosarcoma; Adolescent, Young adult; Cervix (source: MeSH NLM).

RESUMEN

El rabdomiosarcoma es un neoplasma maligno agresivo que se origina en el tejido mesenquimal. Es el tipo más frecuente de sarcoma en la edad pediátrica. Su localización en el útero es extremadamente rara y su incidencia incrementa desde los veinte años de edad en adelante. El pronóstico generalmente depende del tipo histológico, la edad y la ausencia de metástasis. Presentamos 5 casos de mujeres jóvenes con antecedente de sangrado, tumor uterino, cuya biopsia fue positiva para rabdomiosarcoma embrionario, variante botrioide. Todas las pacientes recibieron quimioterapia y cirugía. Dado que el rabdomiosarcoma tiene una alta tasa de incidencia en mujeres jóvenes y su diagnóstico en el cuello uterino es menos agresivo, se recomienda un manejo conservador de estos casos para asegurar la preservación de la fertilidad. El manejo posquirúrgico siempre debe consistir en quimioterapia, ya que se ha demostrado que los avances en este tipo de terapia mejoran las tasas generales de supervivencia.

Es fundamental reportar los tumores raros, ya que ayuda a adquirir experiencia y conocimientos adecuados para su manejo clínico y plantea la necesidad de realizar más estudios sobre esta enfermedad.

Palabras clave

Rabdomiosarcoma; Adolescente, Adulto joven; Cervix (fuente: DeCS BIREME).

INTRODUCTION

Rhabdomyosarcoma (RMS) is an aggressive malignant neoplasm that originates in the mesenchyme. It is the third most frequent solid tumor in the pediatric population and the most common type affecting infants and children [1]. It is usually located in the head and neck areas; however, the second most commonly affected location for this type of cancer is the genitourinary tract (bladder and prostate in men and the vagina for women). Cervical RMS is extremely rare, but its incidence increases towards the second decade of life. Prognosis typically depends on the histological type, patients' age and the absence of metastasis [2].

Due to its low incidence and prevalence, there is a scarcity of global epidemiological data on this disease. Based on the information available in the SEER (Surveillance, Epidemiology, and End Results) repository, 144 RMS patients with lower female reproductive tract origin (cervix, vagina and vulva) were detected between 1973 and 2013. The median age in patients was sixteen years old. Only around 10 patients had distant metastases and 76% were embryonal RMS [3].

Five young females diagnosed with cervical RMS are presented in this report. These female patients had a history of vaginal bleeding, discharge of vaginal tissue, and a cervix tumor, whose biopsy was positive for embryonal RMS–botryoid variant. All patients received chemotherapy and surgery. In this case series, we discuss the challenges of multidisciplinary management of this disease.

CASES REPORT

Our report includes five cases of RMS. All patients presented a history of bleeding with no significant clinical symptoms before the first physician consultation. In 2 of the cases, an endocervical polyp was found during clinical examination, and one patient expelled a small piece of tumor through the vaginal conduct. There were no signs of fever, pain, palpable mass, or systemic symptoms. Patients' clinical features are presented in Table 1. The overall median age was 16.5 years (range, 5-21) and the median tumor size was 5 cm (range, 4-10) (Figure 1). Represents an endocervical polypoid tumor similar to a bunch of grapes. All patients underwent a biopsy of the

Table 1. Clinical characteristics of patients diagnosed with cervical rhabdomyosarcoma

ID (year of diagnosis)	Age (years)	Clinical presentation	Location (size in cm)	Type of surgery	Therapy	Status (follow-up in years)
1 (2010)	18	Bleeding and tumor	Cervix (3x2)	Conization, polypectomy TAH	CT (IMEV) RT	NED (9)
2 (2016)	21	Postcoital bleeding and tumor	Cervix (6x5)	RH	Delayed CT (IVA)	DOD (1)
3 (2017)	14	Bleeding, tissue discharge and tumor	Cervix (6x5) uterus Pelvic recurrence (7x6)	Polypectomy TAH Pelvic tumor removal	Delayed CT (IMEV), RT CT	NED (2)
4 (2018)	13	Bleeding, tissue discharge	Cervix (4x3)	Vaginoscopy Trachelectomy	CT (VAC) + RT	NED (1)
5 (2018)	6	Bleeding, tissue discharge	Cervix (1.5x1.5)	Vaginoscopy Microcone	CT (VAC)	NED (2)

RH: radical hysterectomy; PLD: pelvic lymphatic dissection; TAH: total abdominal hysterectomy; SOB, salpingo oophorectomy bilateral; NED: no evidence of disease; DOD: dead of disease; CT: chemotherapy; VAC: Ifosfamide-Vincristine-Dactinomicin; IMEV: ifosfamide-mesna-vincristine and etoposide; VAC: vincristine-dactinomycin- cyclophosphamide; RT: radiotherapy.

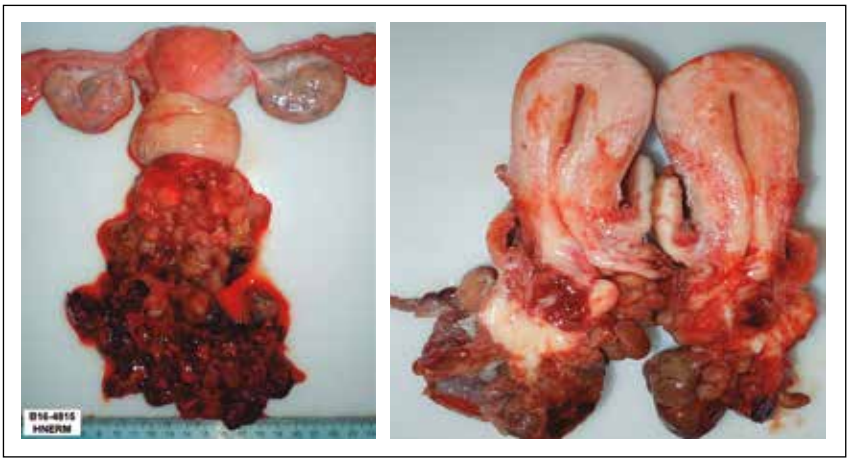

Figure 1. Hysterectomy specimens with endocervical polypoid tumor resembling a bunch of grapes.

lesion, and the pathology report was coherent with the botryoid variant of embryonal RMS (Figure 2).

Regarding the diagnosis of the 5 patients studied, two of them had an initial diagnosis different from that of RMS and were treated in other hospitals; however, the evaluation of the surgical specimens by pathologists at the Rebagliati Hospital in Lima, Peru confirmed the diagnosis of RMS. All patients underwent surgery. In case 2, type III radical hysterectomy was performed in addition to pelvic lymphadenectomy with appendectomy. Case 3 presented with an exophytic polyp, thereby polypectomy was performed with cervical conization, followed by a total abdominal hysterectomy with bilateral salpingectomy. Myomectomy was performed by considering the tumor as a uterine fibroid in case 4. Subsequently, case 4 underwent surgery twice for the resection of the tumor. Case 5 was misdiagnosed with an ovarian tumor, but after the confirmation of an RMS diagnosis, a primary cytoreduction was performed with a pelvic tumor resection. Chemotherapy was the treatment of choice in all cases (vincristine, D-actinomycin and cyclophosphamide) for high-risk RMS. Only one patient received second-line chemotherapy, but her prognosis was dismal.

With a median of 15 months of follow-up, there were distinct signs of relapse in 3 patients, leading to performing a radical hysterectomy and pelvic lymphadenectomy. One patient died of the disease and 4 remained alive with no evidence of the disease.

Ethical considerations

Informed consent and assent were obtained from the patients and parents. The confidentiality of the data obtained from the medical records was maintained.

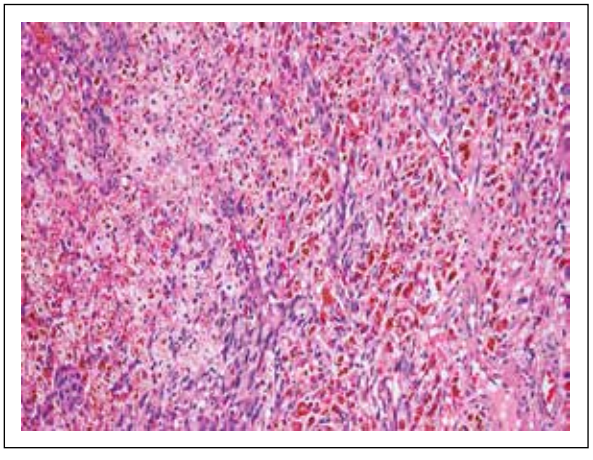

Figure 2. Haematoxylin and eosin stain shows embryonal RMS of the uterine cervix.

DISCUSSION

This report describes five cases of young women with cervical embryonal RMS (cERMS) of lower reproductive tract. RMS is a rare malignant neoplasia, primarily diagnosed in areas without striated muscle [4]. It is a soft-tissue tumor, relatively frequent during the second decade of life, and its incidence radically decreases with age until it becomes a rare entity among the adult population (less than 1%) [5]. The vagina is the most commonly affected organ by an embryonal RMS affecting the urogenital tract. The cervical uterine compromise is only found in 0.5% of RMS female cases [6] and are often presented with early signs of vaginal bleeding.

In this age group, most cases present occasional genital bleeding and some present tumor growth infiltrating the vagina and protruding from the introitus. The tumor is presented as a polyploid morphology in the

shape of a bleeding bunch of grapes. The most distinct histological findings include hypercellularity around epithelial components and nuclear atypia. The skeletal muscle antibodies staining positivity enables the accurate confirmation of the diagnosis [2]. Differential diagnoses of this entity comprehend benign and malignant conditions, such as a prolapsed endometrial polyp, fibroepithelial polyp, endometriosis, leiomyoma, endometrial stromal neoplasm, fibroadenoma, and adenosarcoma [7].

Most cases occur sporadically without any recognizable predisposed risk factors; however, a low percentage is linked to genetic factors. Most common RMS cases are linked to specific genetic variations, such as those involved in K-ras activation or p53 inactivation. Particularly, the embryonal variant is accompanied by a mutation in exon 6 of the Tp53 gene, located in chromosome 17, whereas links of cervical embryonal RMS with DICER1 germline mutations were first established in three families by Foulkes in 2011 [8]. These mutations were later reported by Dehner et al., who found a connection between RMS and pleuropulmonary blastoma familial syndrome with confirmed DICER1 mutations [9,10].

In 2013, the World Health Organization classified RMS into four histologic subtypes: embryonal RMS (including botryoid subtype), solid anaplastic alveolar RMS, pleomorphic RMS and spindle cell/sclerosing RMS [11]. Previously published research has shown adult cases of botryoid RMS, which have demonstrated a slower growth rate, higher chemosensitivity, and lower metastatic capacity [12].

This pathology is rare in adulthood, with universal literature limited to only 115 cases [2], posing constraints onto physicians in terms of planning for appropriate treatments according to protocols used to treat infants with this disorder, or based on experiences accumulated by centers where the number of patients over 40 years old. Since the beginning of the 1980s, combined chemotherapy (Vincristine, Ifosfamide, Actinomycin, Adriamycin, cyclophosphamide, and doxorubicin in prolonged treatment regimens) had become the predominant treatment for patients of all ages. Higher progression-free survival (PFS) rates are associated with optimal surgery and radiotherapy. Globally observed 5-year PFS is 70% and about 90% for non-metastatic diseases in high-income countries. These rates were more variable and less optimistic among adult women, ranging approximately from 60 to 70% in patients with Group 1 and embryonal subtype, and slightly lower, about 30%, in bulky, disseminated, or histologically more aggressive disease [13].

The following subtypes have been identified to have a poor prognosis: alveolar and pleomorphic RMS, tumor size larger than 5 cm, age older than 20, tumor location in the body and cervix, myometrial infiltration, disease progression during chemotherapy, presence of metastasis and macroscopic residual disease (≥ group III) [14]. According to the data published in the literature, the progression of this disease in cases with poor prognosis occurs between 9 and 15 months.

The conventional treatment for cERMS has been a fertility-compromising surgery [14]. Nevertheless, considering that the highest incidence of this neoplasm occurs among young women, patients usually wish for fertility preservation. Current literature suggests that botryoid cERMS has a less aggressive behavior than botryoid sarcoma of the vagina and the uterus, enabling the evolution of cERMS management towards the preservation of genitourinary organs (oncofertility) [14]. A specific chemotherapy regimen is chosen based on risk stratification, which often requires a more conservative surgical approach, enabling complete tumor resection. Nowadays, radiotherapy is reserved as salvage therapy for unfit patients that would not be able to stand intensive chemotherapy regimens [10].

According to the RMS study group, fertility-preserving surgery followed by chemotherapy is an adequate treatment for patients with localized disease. Nonetheless, cases with unfavorable results have been reported despite adequate surgical treatment and chemotherapy, emphasizing the necessity of consistent and close clinical follow-up. Fertility-preserving surgery must be contemplated in cases of extensive uterine compromise and/or metastasis, deep myometrial invasion, and lymphovascular invasion. Alveolar subtype foci should receive aggressive surgical treatment [15].

Prognosis depends on tumor localization, type (better prognosis for embryonal RMS and worst prognosis for pleomorphic RMS), and age, with younger patients experiencing the highest mortality rates. Yet, it is important to note that RMS located in the genital region have a better prognosis than those located in other areas. Nowadays, physicians prefer the approach of surgery and adjuvant therapy, combined with chemotherapy and radiotherapy in selected patients, which has led to a significant increase in survival rates [1].

Since RMS has a high rate of incidence in young women and its diagnosis in the cervix is less aggressive, conservative management of these cases is recommended to ensure the preservation of fertility. Post-surgical management should always consist of chemotherapy, as advances in this type of therapy have been shown to improve general survival rates. Hence, it is essential to report on rare tumors, as it helps in acquiring experience

and appropriate knowledge for their clinical management and raises the need for further studies on this disease.

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