



Late presentation and suboptimal treatment of breast cancer among Syrian refugees: a retrospective study

Hikmat Abdel-Razeq^{1,2} , Faris Tamimi¹,
Nayef Abdel-Razeq¹, Maryam El-Atrash¹,
Baha' Sharaf¹ , Rawan Mustafa¹,
Razan Mansour¹ and Rayan Bater¹

Abstract

Objectives: The crisis in Syria has had a profound impact on the entire region. In this study, we report the patterns of presentation and management of Syrian patients with breast cancer treated at our institution.

Methods: We retrospectively collected data on Syrian refugees treated for breast cancer over the past 10 years at our center. Management was compared against our approved clinical practice guidelines.

Results: A total of 113 patients were eligible and included. The median age (range) at diagnosis was 47 (21–84) years and most women presented with locally advanced or metastatic disease ($n = 74$, 65.5%). Breast-conserving surgery and breast reconstruction were performed in 27 (33.8%) and 11 (35.4%) patients, respectively. Only a few patients received targeted (35.5%) or advanced endocrine therapy (30.0%). In total, 37 (32.7%) patients had considerable deviations from our institutional treatment guidelines and had worse outcomes.

Conclusions: Syrian refugees with breast cancer present late, have more advanced-stage disease, and are more likely to receive delayed and suboptimal therapy. An international systematic approach for cancer care among such vulnerable populations is urgently needed.

Corresponding author:

Hikmat Abdel-Razeq, Department of Internal Medicine,
King Hussein Cancer Center, School of Medicine,
University of Jordan, Queen Rania Al Abdullah Street, P.O.
Box 1269, Amman, 11941 Jordan.
Email: habdelrazeq@khcc.jo

¹Department of Internal Medicine, King Hussein Cancer Center, Amman, Jordan

²School of Medicine, University of Jordan, Amman, Jordan



Keywords

Breast cancer, refugee, Syria, health disparity, patient management, treatment

Date received: 31 October 2020; accepted: 26 April 2021

Introduction

The crisis in Syria has had a profound impact on the entire region. Since its start in 2011, an estimated 5.6 million Syrians have fled their country, largely to Turkey, Jordan, and Lebanon.¹ Jordan hosts over 1 million Syrians; most of them do not reside in refugee camps but rather in host communities, where they have access to existing public health services.² Prior to the Syrian crisis, Jordan hosted hundreds of thousands of Iraqi refugees.^{3,4}

According to the latest national census and estimates, the total population of Jordan is close to 10 million, and 30% of the population are refugees.⁵ Jordan was recently reclassified by the World Bank as an upper-middle-income country.⁶ However, the country continues to experience a lack of natural resources, poor supplies of water, and high rates of inflation and unemployment.⁷ According to official data from the World Bank, Jordan's gross domestic product (GDP) was USD 43.74 billion in 2019.⁸ The GDP per capita was USD 3284 in 2019, which is 13.6% lower than a decade ago and equivalent to only 26% of the world average.⁹

In 2018, cancer affected more than 18 million people worldwide, and more than 9.0 million died from the disease. These figures are expected to double by 2040, with the greatest increase in low- and middle-income countries, accounting for more than two-thirds of the world's cancer burden.¹⁰ Refugees are clearly also susceptible to developing cancer; before arriving in Jordan, many refugees received cancer

treatment in neighboring countries, adding to the cancer burden in those countries.^{11,12}

A lack of sufficient funding from either host countries or international refugee aid organizations results in suboptimal treatment of patients with cancer.¹³ During the period 2011 to 2019, 917 Syrian patients with cancer were registered in the King Hussein Cancer Center (KHCC) hospital-based cancer registry.¹⁴

Cancer is the second leading cause of death in Jordan after cardiovascular diseases.¹⁵ The Jordanian government bears the cost of treating cancer in public hospitals for all Jordanian citizens. However, cancer care among Syrian refugees is fragmented and poorly organized.

Breast cancer is the most common cancer in Jordan as well as in the surrounding region, and it is the third most common cause of cancer death after lung cancer and colorectal cancer.¹⁶ More than 1200 cases were included in the most recent report published by the Jordanian Cancer Registry.¹⁷ Similar to most neighboring countries, breast cancer in Jordan is usually diagnosed at younger ages, with the median age at diagnosis being 51 years; fewer than one-third of patients with cancer are diagnosed over 60 years of age.¹⁸ The disease is associated with a high cure rate if diagnosed at an early stage.¹⁹

In this study, we report the patterns of presentation and management among Syrian refugees with breast cancer who were treated and followed at our institution.

Methods

In this study, we retrospectively collected data of Syrian refugees who presented to our institution with a diagnosis of breast cancer. Data were collected for patients treated from January 2011 to December 2019; however, most of the included patients were treated during the period 2015 to 2019. Data were extracted from our hospital-based cancer registry, which was established in 2006 and includes all patients diagnosed, treated, and followed at our institution since that date. All consecutive Syrian refugee patients with pathologically proven breast cancer who were confirmed, treated, and followed at our institution were included in this analysis. As per our institution's guidelines, all patients signed consent forms prior to all diagnostic or therapeutic interventions.

Eligible patients were age 18 years or older and had more than one medical encounter at our center. We collected data from the electronic medical records and pathology and radiology reports. Management was compared against our approved institutional clinical practice guidelines (CPGs). All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee at KHCC and with the 1964 Declaration of Helsinki and its later amendments. All patient details were de-identified and the requirement for written informed consent was waived by the ethics committee at KHCC. The reporting in this study conforms to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.²⁰

Statistical analysis

Patients' clinical and pathologic characteristics were collected, tabulated, and described using range, median, or

percentage. Vital status at the time of data analysis was obtained from the Department of Civil Status, a governmental agency that issues all death certificates. Primary endpoints were patient's disease-free survival (DFS) and overall survival (OS). Follow-up duration was calculated from the date of diagnosis until the last visit to an oncology clinic. DFS was defined as the time from the date of diagnosis to the date of the first local recurrence, the development of contralateral or ipsilateral breast cancer including ductal carcinoma in situ (DCIS) but not lobular carcinoma in situ, distant metastasis, or death from any cause. Moreover, OS was defined as the time from the date of diagnosis until the date of death from any cause. The median follow-up time was relatively short at 15 (range, 1–103) months. The Kaplan–Meier method was used to estimate OS and DFS. Survival analyses were performed using IBM SPSS version 26 for Mac (IBM Corp., Armonk, NY, USA).

Results

Patient and disease characteristics

During the study period, 147 adult Syrian refugee patients with breast cancer had at least one medical encounter at our institution. All were women, and the median age (range) at diagnosis was 47 (21–84) years. Thirty-four (23.1%) patients did not complete the work-up and missed subsequent visits; these patients were excluded from the analysis. The remaining 113 patients had biopsy-proven invasive ductal carcinoma ($n = 110$) or DCIS ($n = 3$) and continued their treatment and follow-up at our institution; we included all 113 patients in the study. Breast cancer was diagnosed at an early stage in 39 (34.5%) patients whereas 48 (42.5%) and 26 (23.0%) patients had locally advanced or metastatic disease, respectively. Estrogen receptors were

positive in 75 (66.4%) patients and 63 (55.8%) patients had progesterone receptor-positive disease. Human epidermal growth factor receptor 2 (HER2)-positive disease was documented in 31 (27.4%) patients and 18 (15.9%) patients had triple-negative disease (Table 1).

Treatment and outcomes

Eighty (70.8%) patients underwent surgery; among these, 60 (75.0%) were at our institution. The median time (range) from the first medical encounter to surgery for those who underwent upfront surgery was 8 (1–22) weeks. Breast-conserving surgery was performed in 27 (33.8%) women; however, only 11 (35.4%) of the 31 patients eligible for breast reconstruction underwent this procedure (Table 2). Adjuvant radiation therapy was provided to 49 (77.7%) of 63 candidate patients, and some were delayed.

Table 1. Patients' characteristics.

Characteristics	Number	Percentage
Age (years)		
Median	47	
Range	21–84	
Histopathology		
Invasive ductal carcinoma	110	97.3
Ductal carcinoma in situ	3	2.7
Years of first visit		
2011–2013	22	19.5
2014–2016	26	23.0
2017–2019	65	57.5
Disease stage		
Early	39	34.5
Locally advanced	48	42.5
Metastatic	26	23.0
Positive hormone/HER2 receptors		
Estrogen receptor	75	67.0
Progesterone receptor	63	56.3
HER2/neu	31	27.4
Triple negative	18	15.9

HER2, human epidermal growth factor receptor 2.

As shown in Table 2, systemic treatment with chemotherapy was provided to 103 (91.2%) patients, as neoadjuvant ($n=37$, 35.9%), adjuvant ($n=45$, 43.7%), and palliative ($n=21$, 20.4%) therapy. However, only 11 (35.5%) of 31 patients with HER2-positive disease received anti-HER2 therapy. Additionally, only 3 (30.0%) of 10 patients who were candidates for cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors received treatment. Genetic testing and counseling were also suboptimal; only 8 (12.3%) of 65 candidate patients, as judged by the National Comprehensive Cancer Network,²¹ underwent genetic testing. Across all needed treatments, 37 (32.7%) patients had considerable deviations when judged against our institutional CPGs, Figure 1.

After a median (range) follow-up of 15 (1–103) months, 14 (12.4%) patients died. The median OS in patients treated with no deviation from our standard guidelines was 71.5 months compared with 45.3 months for those whose treatment deviated from the guidelines ($p=0.096$), Figure 2a. Similarly, the median DFS for patients treated according to our guidelines was 62.7 months, compared with 28.6 months for those whose treatment deviated from the guidelines ($p=0.011$), shown in Figure 2b.

Table 2. Surgery and chemotherapy.

Treatment	Number of patients	Percentage
Surgery ($n=80$)		
Mastectomy	53	66.3
Breast-conserving surgery	27	33.8
Breast reconstruction*	11	35.4
Chemotherapy ($n=103$)		
Neoadjuvant	37	35.9
Adjuvant	45	43.7
Palliative	21	20.4

*Out of 31 eligible patients.

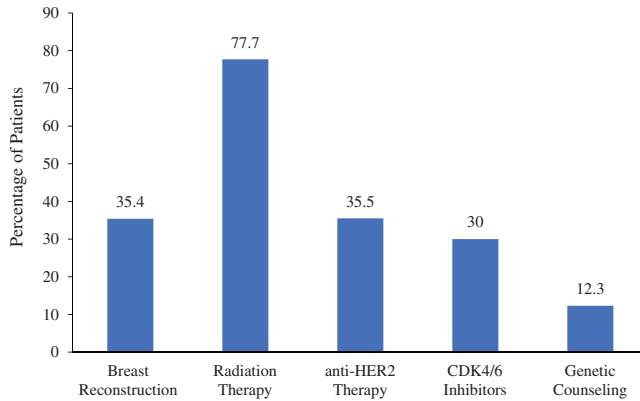


Figure 1. Percentage of patients treated according to local guidelines. HER2, human epidermal growth factor receptor 2; CDK4/6, cyclin-dependent kinase 4 and 6.

Discussion

Cancer, as well as other noncommunicable diseases, are neglected dimensions of refugees' health in many host countries. The complexity and cost of cancer care could be the main contributing factors.²² Breast cancer is a potentially curable disease. Comprehensive cancer control programs that include primary prevention, screening and early detection, multimodality treatment, survivorship, and supportive/palliative care can considerably reduce the cancer burden and improve outcomes. Such dimensions are not addressed in a systematic way for Syrian refugees.

Comprehensive early detection programs directed toward a relatively large number of refugees are difficult to implement in a country with limited resources like Jordan. The geographic distribution of Syrian refugees across most of the northern and central part of the country may complicate efforts to provide access to early-detection facilities.

The silent nature of breast cancer in its early stages, as well as the difficulties most refugee patients may encounter in accessing medical care, may contribute to the late presentation seen among the patients in our study. Nearly two-

thirds of patients had locally-advanced (42.5%) or metastatic disease (23.0%) at diagnosis. Previous studies from neighboring host countries have reached similar conclusions.^{11,12}

It is not unusual for patients to spend much time and effort in reaching a tertiary care center. In our study, 34 (23.1%) patients were seen only once at our institution, never completed the work-up, and missed subsequent visits. Quality cancer care requires a multidisciplinary approach, which is not present in smaller hospitals and primary health care clinics made available for refugees. A clear referral system, taking into consideration patient- and disease-related factors, is urgently needed. However, many host countries require a good deal of financial and logistic support to establish such systems.

Because cancer therapy is becoming extremely expensive, cancer care represents a substantial burden for host countries. Many patients with early-stage disease enrolled in our study had no access to breast reconstruction, despite their younger age at presentation. Anti-HER2 therapy, which is the standard of care among patients with early- or advanced-stage disease, is also difficult to provide; only one-

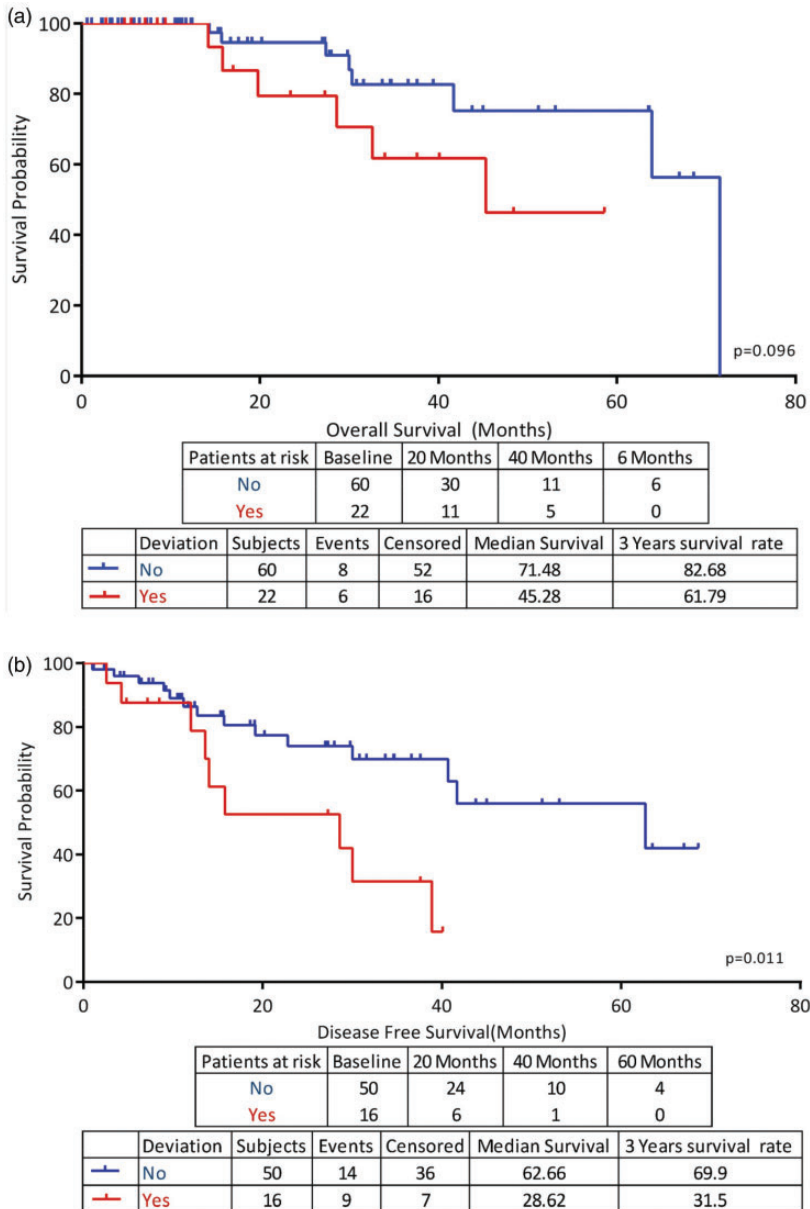


Figure 2. (a) Overall survival, and (b) disease-free survival.

third of our eligible patients were treated with anti-HER2 therapy. Expensive, recently introduced endocrine therapy, such as CDK4/6 inhibitors, is also difficult to obtain.

In a study that modeled the direct cost of cancer care among Syrian refugee populations residing in host countries using the cost per capita approach, the total cancer care cost for all 4.74 million Syrian refugees

in Jordan, Lebanon, and Turkey was estimated to be EUR 140.23 million in 2017.²³

Policy makers should understand that implementing cancer control programs across the continuum, from early detection all the way to survivorship and palliative care programs, is cost effective.²⁴ The 2019 World Health Organization report on cancer found that for every USD 1 invested in cancer, there is a direct productivity return of USD 2.30 and total social return of USD 9.50.²⁵

Our outcome data clearly demonstrate the effect of deviation from standard clinical practice guidelines on treatment outcomes. Such deviations were encountered across all aspects of cancer management in our study, including early detection, diagnosis, and active therapy. Although such differences in outcomes were anticipated, our study confirmed their existence despite the relatively short follow-up and small number of patients included in this study. Such differences can also be expected for other types of cancer.

Cancer therapy does not only involve surgery, chemotherapy, and radiation therapy. Psychosocial support, supportive/palliative care, and survivorship are also key components of therapy. Genetic counseling and genetic testing were performed in only 12% of eligible patients in our study.

A recent policy review study included 733 refugees referred to the United Nations High Commissioner for Refugees in Jordan and Lebanon. Patients were analyzed according to cancer type, risk factors, treatment cost, and coverage status. The study results highlighted the need to increase funding and establish standard operating procedures to ensure equitable access to care across the cancer care continuum from early detection through treatment and including palliative and supportive care.²⁶

Our study addresses the problem of breast cancer among refugees. We believe

that highlighting these problems, particularly among refugee patients with breast cancer, will help with developing solutions within health care systems that are directed toward refugees. Host countries with limited resources, like Jordan, will not be able to cope with the increasing demand for health care. Management of chronic illnesses among refugees, like breast cancer, mandates international partnerships to better improve early detection and prevention, as well as health care service availability and delivery of standard anti-cancer therapy. Additionally, data management systems, including cancer registries linked to treatment outcomes for refugees at national, regional, and international levels, are critically needed.

Our study has several limitations that need to be considered. This was a retrospective study with a limited number of patients from a single institution; thus, the findings might not be generalizable to the entire refugee population in Jordan or throughout the region. Nonetheless, the current study has several strengths; the data were obtained from the largest cancer center in the region and in a country that has previously hosted and currently hosts a large number of refugees.

Conclusions

Syrian refugees with breast cancer present late and with more advanced-stage disease. These patients are more likely to receive delayed and suboptimal treatment that includes surgery, genetic counseling, and systemic anti-cancer therapy. Our findings highlight the urgent need for an international systematic approach to cancer care in such vulnerable populations.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author contributions

Conception and design: Hikmat Abdel-Razeq, Faris Tamimi.

Collection and assembly of data: Faris Tamimi, Maryam El-Atrash, Baha' Sharaf, Rawan Mustafa, Nayef Abdel-Razeq.

Data analysis and interpretation: Hikmat Abdel-Razeq, Faris Tamimi, Nayef Abdel-Razeq, Razan Mansour, Rayan Bater.

Manuscript writing: All authors.

Final approval of the manuscript: All authors.

Accountable for all aspects of the work: All authors.

ORCID iDs

Hikmat Abdel-Razeq  <https://orcid.org/0000-0003-2833-6051>

Baha' Sharaf  <https://orcid.org/0000-0003-4368-1224>

References

1. United Nations High Commissioner for Refugees (UNHCR). Syria Regional Response. Available at: <https://www.unhcr.org/syria-emergency.html> (accessed 25 July 2020).
2. United Nations High Commissioner for Refugees (UNHCR). External Statistical Report on Active Registered Syrians in Jordan. 2015. Available at: <https://data2.unhcr.org/en/documents/download/45699> (accessed 20 July 2020).
3. Mateen FJ, Carone M, Al-Saedy H, et al. Medical conditions among Iraqi refugees in Jordan: data from the United Nations Refugee Assistance Information System. *Bull World Health Organ* 2012; 90: 444–451. doi: 10.2471/BLT.11.097048.
4. Mateen FJ, Carone M, Al-Saedy H, et al. Cancer diagnoses in Iraqi refugees. *Acta Oncol* 2012; 51: 950–951. doi: 10.3109/0284186X.2012.667148
5. Department of Statistics: Jordan Population. Available at: <http://dosweb.dos.gov.jo/population/population-2> (accessed 20 July 2020).
6. World Bank: New country classifications by income level: 2018-2019. Available at: <https://blogs.worldbank.org/opendata/new-country-classifications-income-level-2018-2019> (accessed 20 July 2020).
7. Jordan Department of Statistics: Home page. Available at: <http://dosweb.dos.gov.jo/> (accessed 20 July 2020).
8. Trading Economics. Jordan Gross Domestic Products. Available at: <https://tradingeconomics.com/jordan/gdp> (accessed 26 July 2020).
9. Gross Domestic Product Per Capita. Available at: <https://tradingeconomics.com/jordan/gdp-per-capita> (accessed 26 July 2020).
10. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; 68: 394–424. doi: 10.3322/caac.21492.
11. Bakkal Temi Y, Murat Sedef A, Gokcay S, et al. A study on basic demographic and disease characteristics of cancer-diagnosed Syrian refugees treated in the border city of Turkey, Sanliurfa; a hospital-based retrospective case series study. *J BUON* 2017; 22: 1591–1594.
12. El Saghir NS, Soto Pérez De Celis E, Fares JE, et al. Cancer Care for Refugees and Displaced Populations: Middle East Conflicts and Global Natural Disasters. *Am Soc Clin Oncol Educ Book* 2018; 38: 433–440. doi: 10.1200/EDBK_201365.
13. Spiegel P, Khalifa A and Mateen FJ. Cancer in refugees in Jordan and Syria between 2009 and 2012: challenges and the way forward in humanitarian emergencies. *Lancet Oncol* 2014; 15: e290–e297. doi: 10.1016/S1470-2045(14)70067-1.
14. Mansour A, Al-Omari A and Sultan I. Burden of Cancer among Syrian Refugees in Jordan. *J Glob Oncol* 2018; 4: 1–6. doi: 10.1200/JGO.18.00132.
15. CDC Global Health-Jordan. Available at: <https://www.cdc.gov/globalhealth/countries/jordan/default.htm> (accessed 26 July 2020).

16. Ministry of Health: 2014 Information and Research Report. <http://www.moh.gov.jo/Echobusv3.0/SystemAssets/2d0cc71d-d935-4d6f-a72c-73d60cd0a16c.pdf> (accessed 20 July 2020).
17. Jordan Cancer Registry Annual Report. Available at: <https://www.moh.gov.jo/Pages/viewpage.aspx?pageID = 185> (accessed 26 July 2020).
18. Abdel-Razeq H, Mansour A and Jaddan D. Breast Cancer Care in Jordan. *JCO Glob Oncol* 2020; 6: 260–268. doi: 10.1200/JGO.19.00279.
19. Walsh EM, Smith KL and Stearns V. Management of hormone receptor-positive, HER2-negative early breast cancer. *Semin Oncol* 2020; 47: 187–200. doi: 10.1053/j.seminoncol.2020.05.010.
20. Von Elm E, Altman DG, Egger M, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007; 147: 573–577.
21. National Comprehensive Cancer Network (NCCN). Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic. Available at: https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf (accessed 01 July 2020).
22. United Nations High Commissioner for Refugees. Health sector humanitarian response strategy: Jordan 2019–2020. Health Sector Humanitarian Response Strategy. February, 2019. Available at: <https://data2.unhcr.org/en/documents/download/68348> (accessed 23 July 2020).
23. Abdul-Khalek RA, Guo P, Sharp F, et al. The economic burden of cancer care for Syrian refugees: a population-based modeling study. *Lancet Oncol* 2020; 21: 637–644. doi: 10.1016/S1470-2045(20)30067-X.
24. Marzouk M, Kelley M, Fadhil I, et al. “If I have a cancer, it is not my fault I am a refugee”: A qualitative study with expert stakeholders on cancer care management for Syrian refugees in Jordan. *PLoS One* 2019; 14: e0222496. doi: 10.1371/journal.pone.0222496.
25. World Health Organization. WHO report on cancer: setting priorities, investing wisely and providing care for all. Available at: <https://apps.who.int/iris/handle/10665/330745> (accessed 25 July 2020).
26. Spiegel PB, Cheaib JG, Aziz SA, et al. Cancer in Syrian refugees in Jordan and Lebanon between 2015 and 2017. *Lancet Oncol* 2020; 21: e280–e291.