Presentation and management of female breast cancer in Egypt

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Abstract

Background: There have been system inefficiencies in the profiling and management of female breast cancer in Alexandria, Egypt.

Aims: To identify barriers to full implementation of international guidelines for the management of female breast cancer patients.

Methods: Female breast cancer data were extracted from records of 3 public oncology services in Alexandria, Egypt, from 2007 to 2016 and analysed.

Results: A total of 5236 of the available 7125 records were usable. Median age of the patients was 54 years, and the median duration of pre-diagnosis complaint was 3.1 months. Some 522 (31.5%) of the patients had a family history of cancer. For tumour stage, 2527 (55.2%) were early, 1717 (37.6%) were locally advanced, and 331 (7.2%) were at stage IV. Estrogen receptor, progesterone receptor, and HER2 were positive in 3869 (85%), 3545 (78%), and 461 (15.3%) patients, respectively. Chemotherapy started after a median 1.03 months. Adjuvant chemotherapy was given to 3667 (91.7 %) patients and neoadjuvant chemotherapy to 333 (8.3%); 3686 (92.1%) received anthracycline-based combination chemotherapy, and 3613 (86%) received hormonal treatment. One hundred and eighty of 317 eligible patients received Trastuzumab. Local and/or distant recurrence was seen in 1109 (21.2%) patients. In nonmetastatic cases, median overall and disease-free survival were 149.1 and 77.1 months, respectively. In metastatic cases, median progression-free survival was 19.6 months.

Conclusion: We observed defects in the record system, there was delay in diagnosis and treatment, and nonadherence to targeted therapy in many patients. Strengthening of national and hospital-based registries is needed in Alexandria, Egypt, with a robust patient navigation system and targeted information, education and communication strategies. Continuous outcomes monitoring and adaptation to implementation needs should be sustained.

Keywords: breast cancer, disease management, service delivery, implantation, Egypt

Introduction

Noncommunicable diseases (NCDs) constitute 71% of worldwide mortality, and 80% of them are due to cancer (1). NCD prevention and management is anticipated to reduce mortality, increase productivity gains and enhance achievement of economic Sustainable Development Goals (SDGs) (2). Egypt ranks 114 on the SDG index, with less than average NCD score (3). Breast cancer is the second most common cancer, and it is the most common in women worldwide, with variations in incidence and mortality among regions. In Egypt, it is the most common cause of cancer mortality in women. Egypt has a value of 57/100 on the index of effective coverage in breast cancer treatment (4).

The 25-year mortality trends in the 7 super regions, encompassing 195 countries, have shown an increase, except in rich countries (defined by the Health Metrics and Evaluation: 1) Sub-Saharan Africa; 2) North Africa and Middle East; 3) South Asia; 4) Southeast Asia, East Asia and Oceania; 5) Latin America and Caribbean; 6) Central Europe, Eastern Europe and Central Asia; and 7) High-income). This poses a significant public health risk for low- and middle-income countries (like Egypt) that needs attention and effective intervention (5). With the introduction of modern treatments, survival of metastatic breast cancer has improved, but the mortality figures are still high (6).

Risk factors for breast cancer development and mortality have been investigated to reduce its incidence, to detect it earlier, allowing more successful treatment, and to develop treatment strategies to increase curability (7). Lifestyle modifications have been proposed to reduce breast cancer incidence and morbidity (8). Screening for breast cancer has a well-established role and has resulted in an increase in detection of earlier stage disease and improved survival (at least in rich countries) (9). Awareness of breast cancer screening, management options and correcting misconceptions play a role in using relevant health services at an appropriate time for early diagnosis and management (10). Awareness is especially low among older and less-educated people, resulting in variable degrees of delay (11). Nonmedical university students have lower breast cancer awareness than medical students, except for nonmedical students who have a relative with breast cancer (12).

A breast cancer screening project was inaugurated as a "Women Health Outreach Program" in July 2019. The screening programme has now matured into a full national programme, as a part of the "100 Million Healthy Individuals". Despite full governmental support, economic factors and sustainability are important issues to be addressed (13).

Breast cancer management practice guidelines are based on evidence obtained from efficacy trials or meta-analyses of multiple clinical trials, to homogenize and standardize clinical practice, according to the best available evidence and balancing between several intrinsic and extrinsic factors that prevail in the implementation setting. A comparison of 4 well-known clinical practice guidelines showed that all scored poorly on applicability and 2 scored lower on methodological rigor (14). Clinically efficacious interventions, proved by clinical trials, can result in implementation problems, when applied outside the controlled environment of the study. The problems are more evident when implementing guidelines developed in high-income countries in lower-income countries. The consensus statement from the Breast Health Global Initiative supports cost-effectiveness studies and implementation research to identify system inefficiencies and patient barriers, aiming to develop patient navigation systems, and strengthen functional early detection and treatment programmes (15). Implementation research helps build strategies for successful implementation, to bridge the gaps between clinical trial results, international guidelines and implementation in the local community. Five dimensions need to be explored: actors (who), actions (what), action targets (for whom or for what), temporality (when), and dose (how much) (16).

The objective of this study was to identify barriers to the full implementation of international guidelines in female breast cancer patients from 3 major public oncology centres in Alexandria, Egypt, differing in their administrative and financial systems.

Methods

This was a retrospective, observational cohort study, planned as the exploratory phase of an implementation study, with the objective of identifying gaps in the delivery of services to breast cancer patients. The data for different patient cohorts were retrieved from the records to identify the different clinical pathways of the patients. The clinical records were retrieved from 3 major public oncology services: (1) Alexandria Clinical Oncology Department (ACOD), Main University Hospital: the first established oncology centre that has served Alexandria and Northwest Egypt for several decades and patients are managed under a government sponsored system. There were 1562 records (21.9%). (2) Gamal Abd-elnasser Insurance Hospital (GAN) Clinical Oncology Department: the second oncology centre that was established 3 decades ago and serves patients with employment health insurance. There were 4047

records (56.8%). (3) Alexandria Ayadi Almostakbel Oncology Center (AAAOC): the first nongovernmental-organization-sponsored oncology centre. There were 1516 records (21.2%).

The surveyed records covered the period January 2007 to December 2016. After approval from Alexandria University Institutional Review Board (IRB00012098), the medical records were anonymously reviewed for demographic data: age at presentation, residence, family history of breast cancer, history of contraceptive pills, associated diabetes or hypertension, cancer stage, histological type and grade, hormone receptor status, Ki67, lymphovascular invasion (LVI), extracellular extension (ECE), type of surgery, duration of complaint before presentation, radiotherapy and chemotherapy details, and delay before start of treatment.

Treatment outcome measures were analysed from the data in the records: 1) overall survival (OS): time from presentation to the treatment centre until death from any cause; 2) disease-free survival (DFS): time between diagnosis and detection of local or distant recurrence; 3) progression-free survival (PFS): time between diagnosis of metastatic breast cancer to relapse of tumour at distant site including lungs, liver, bone and brain; and 4) local recurrence rate (LRR): rate of recurrence of completely resected nonmetastatic breast cancer in the breast/chest wall or regional lymph nodes.

Statistical analysis was conducted using SPSS version 20.0 (IBM, Armonk, NY, USA). The findings were reported as numbers and percentages. The median, range and interquartile range (IQR) were used to report central tendency and dispersion, as appropriate. Survival was reported as median survival and percentage of patients alive at 5 years. Kaplan–Meier survival curves were plotted for HER2-positive patients with or without trastuzumab therapy. The log rank test was used to compare the survival curves. The significance of the obtained results was judged at the 5% level.

Results

Patient characteristics

From January 2007 to December 2016, 7125 records were registered at ACOD, GAN and AAAOC, and 5236 (73.4%) contained usable information. Further analysis was conducted based on available data. Most of the patients (73.3%) were from Alexandria, while 12.9% of the patients were from outside Alexandria. Table 1 shows the residence of the patients registered at the 3 centres and the 2019 population estimates of districts in Alexandria. The number of cases from the eastern districts was the largest and the numbers diminished westwards.

The median age was 54 years (range 21–95 years). Patients with positive family history accounted for 522 (31.5%) of the total. Two hundred and eighty-one (30.8%) patients had a history of oral contraceptive use, 355 had hypertension, 216 had diabetes, and 306 had both diabetes and hypertension. The duration of complaint before

Table 1 Residential locations of patients registered at 3 centres over a 10-year period and population density of districts in Alexandria

Residential location		Population estimate[a]	Residential location		Population estimate[a]
Outside of Alexandria	673				
Almontazah	1025	1 629 132			
Sharq	712	1 190 675			
Wasat	786	558 360			
Algomrok	277	161 091			
Gharb	363	366 416	Alexandria	4512	5 325 227
Alagamy	284	485 078			
Alamreya	135	774 014			
Borg El Arab	22	159 831			
Alexandria District not recorded	235				
Total	5185				

[a]Central Agency for Public Mobilization and Statistics (CAPMAS), Egypt.

diagnosis was recorded in 1184 cases, with a median of 3.1 months (range 0.1–105 months, IQR 1.6–7.5 months).

Surgery

Breast surgery was performed in 4835 patients: modified radical mastectomy in 3593 and breast conservative surgery in 1242 (Table 2). Axillary surgery was performed in 4945 patients: axillary lymph node dissection in 4782 and sentinel lymph node dissection in 163. Thirty-one had no axillary surgery.

Tumour stage

Data on tumour stage were recorded in 4566 cases and were missing in 12.8% of cases (Table 2). The majority (55.2%) of patients were diagnosed at early stages (0–II), 37.6% had locally advanced stage III and only 7.2% had stage IV. The most common histological subtype was infiltrating duct carcinoma and most specimens were classified as grade II. Most cases were hormone receptor positive but most were negative for HER2. LVI and ECE were detected in 2829 of 3533 (80%) and 1657 of 3666 (45.2%) cases, respectively. Ki67 was recorded in 775 cases and was low in 28% intermediate in 10% and high in 61.8%.

Treatment

Duration to start of chemotherapy was < 1 month in 1490 (45.6%) of 2734 patients, 1–3 months in 1672 (51.2%) and > 3 months in 102 (3.1%), and the median was 1.03 months (IQR 0.7–1.6 months). Adjuvant chemotherapy was given to 3667 of 4000 (91.7%) patients and neoadjuvant chemotherapy to 333 (8.3%). Some 3686 (92.1%) received anthracycline-based combination chemotherapy. Non-anthracycline-based chemotherapy was used in 206 (5.6%) of patients receiving adjuvant chemotherapy and 45 (13.6%) of those receiving neoadjuvant chemotherapy. Out of 4199 patients, 3613 (86%) received hormonal treatment, either tamoxifen alone 1878 (44.7%), aromatase inhibitor (AI) alone 1111 (26.4%), sequential tamoxifen and AI 570 (13.6%), LHRH agonist with tamoxifen 12 (0.3%) or LHRH agonist with AI 42 (1%). Out of 317 eligible HER2-positive patients, 180 (56.8%) patients received trastuzumab treatment. Trastuzumab improved the long-term overall survival compared with those who could not afford the treatment (Figure 1), although the difference was not significant (log rank test: P = 0.373).

By the end of the survey period, 3144 patients remained disease free and 1109 developed relapse: 155 with local recurrence, 130 with distant metastasis and 794 with both local and distant metastases. Median overall survival was 149.1 months in 3952 of 5236 nonmetastatic cases and 90.7% were alive at 5 years, and median DFS was 77.1 months in 2167 cases and 59.6% were alive at 5 years. Median PFS was 19.6 months in 127 of 329 metastatic cases and 7.9% were alive at 5 years.

Discussion

ACOD, GAN and AAAOC are 3 out of the 6 public oncology centres serving Alexandria Governorate and parts of the population of the adjacent governorates. The patients' names and breast cancer as a diagnosis were the only data reported in 1889 records and those records were excluded from further study. The remaining 5236 records had some missing data and were excluded from reporting of those specific points. Missing records, missing data in available records and nonstandardized input in available data were the first implementation gaps met by the data collection team. This reduced the certainty of the outcome analysis and improvement efforts. Implementation of good health services in oncology, and in healthcare in general, depends on the adequacy of available data, to evaluate the quality of services, monitor bottlenecks in the implementation process, guide better strategic planning for successful implementation, and assess the success of the implementation strategy. National registries and hospital-based registries have both benefits and limitations (15).

The median age of patients at presentation was 54 years (17). This is higher than the median age of 49–52 years of breast cancer patients in Arab countries

Table 2 Surgical management and pathological features

		Number (%)
Breast surgery	Breast conserving surgery	1242/4976 (25)
	Modified radical mastectomy	3593/4976 (72.2)
	Not recorded	141/4976 (2.8)
Axillary surgery	No axillary dissection	31/4976 (0.6)
	Sentinel lymph node dissection	163/4976 (3.3)
	Axillary lymph node dissection	4782/4976 (96.1)
Staging (n = 4566)	Stage 0	39/4566 (0.8)
	Stage I	556/4566 (12.3)
	Stage II	1923/4566 (42.1)
	Stage III	1717/4566 (37.6)
	Stage IV	331/4566 (7.2)
Histological type (n = 4459)	Intraductal carcinoma	3960/4459 (88.8)
	Invasive lobular carcinoma	222/4459 (5.0)
	Mixed	116/4459 (2.6)
	Others	161/4459 (3.6)
Grade (n = 4107)	I	104/4107 (2.5)
	II	3425/4107 (83.4)
	III	578/4107 (14.1)
Presence of LVI (n = 3533)		2829/3533 (80.0)
ECE (n = 3666)		1657/3666 (45.2)
ER (n =4550)	Negative	681/4550 (15.0)
	Positive	3869/4550 (85.0)
PR (n =4550)	Negative	1005/4550 (22.0)
	Positive	3545/4550 (78.0)
HER2 status (n =3066)	Negative	2605/3006 (86.7)
	Positive	461/3006 (15.3)
Ki67(n =775)	Low (<14)	217 (28.0)
	Moderate (≥14 – 20)	79 (10.0)
	High (≥20)	479 (61.8)

ECE = extracapsular extension; ER = estrogen receptor; LVI = lymphovascular invasion; PR = progesterone receptor.

(including Egypt) and lower than 61 years in the United States of America (USA) (9,18). The median age at diagnosis varied by race and ethnicity. The age difference between the USA and Egypt may be partially explained by the younger population in the latter (19) or cultural differences. Egyptian older women are less likely to seek medical advice than younger women, compared to their counterparts in the USA (20).

Patients residing in the east of Alexandria, which is the most populous area with a paucity of oncology services, represent the largest cluster of patients. This finding is in accordance with an earlier report, partially overlapping the current report in regard to the covered duration and the data source (17).

In developing countries, a large proportion of patients with breast cancer present at a late stage (21). In this study, 48% of patients presented with localized disease, 32.8% had locally advanced stage, 6.3% presented with metastases and 12.8% had no recorded stage. The

increase in early stage presentation compared to earlier Egyptian studies is probably a reflection of increased awareness by women, resulting from governmental and nongovernmental efforts for screening and early detection, with a favourable impact on the estimated cost of management (22). According to the Surveillance, Epidemiology, and End Results (SEER) database, 62% of patients presented with localized disease, 30% at an advanced stage, 6% with metastases and only 2% of patients had no recorded stage (23).

In this study, pathological specimens stained positive for estrogen receptor in 73.9% of patients and positive for progesterone in 67.7% of patients, and 12.2% of patients were negative for both receptors. HER2/neu testing was not available in the first 4 years of the study. HER2/neu status was not documented in 41.1% of the studied cases. In the documented records, 15.3% showed HER2/neu strong positivity and 86.7% showed HER2/neu negativity.

Figure 1 Kaplan–Meier survival curve for overall survival in HER2-positive patients, with and without trastuzumab therapy (log rank test: $P = 0.373$).
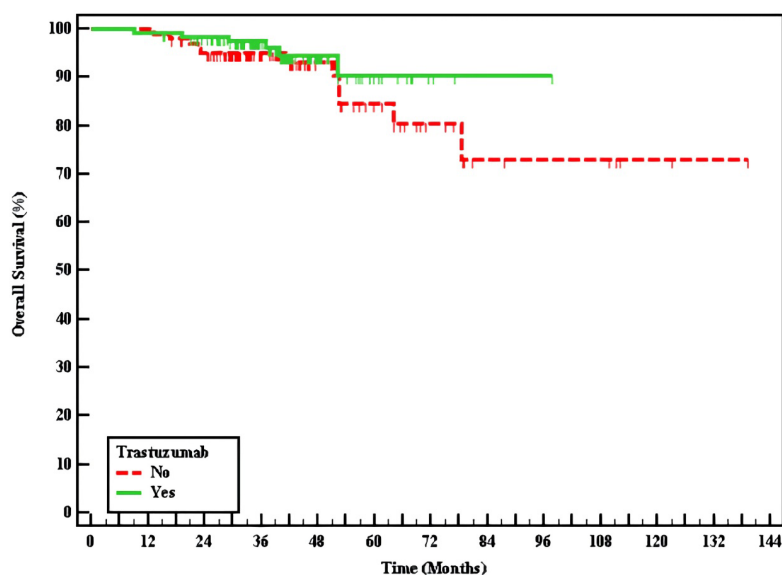
In SEER, 78% of cases were HER2/neu negative, 14% were HER2/neu positive and 8% were unknown (23).

The time between the first symptom and first specialist consultation was < 1 month in 10.7% of cases, 1–6 months in 58.6% and > 6 months in 30.7%, which contradicts the belief that our patients are not aware of breast cancer and always present at advanced stages. More than 75% of patients started chemotherapy within 1.6 months (IQR 0.7–1.6 months). Radiotherapy was started within 6 months in 30% of the patients. In many cases, this was not an actual treatment delay, as early and locally advanced cases were scheduled for adjuvant or neoadjuvant chemotherapy, before radiotherapy, and cases with metastatic disease received systemic treatment upfront and radiotherapy was given when localized symptoms developed.

Care delay has been subdivided into patient delay and healthcare system delay (24). According to Caplan et al., patient delay is a delay in seeking medical attention after self-discovery of a potential breast cancer symptom, whereas system delay is a delay within the healthcare system (25). Patient delay was mainly defined as > 3 months between symptom detection and first medical consultation, and the socioeconomic and cultural background of patients can contribute to patient delay (25). System delay can refer to access barriers, such as long distance to healthcare centres, unavailability of specialized centres, and intrinsic problems of an established healthcare system, such as disease management, problems in obtaining or scheduling diagnostic tests and communication problems between patients and physicians (21,26). To reduce system delay, health services must fit with the socioeconomic and cultural background of patients (27,28). Several groups reported a worse survival rate, regardless of the type of cancer operation, for delays in diagnosis and referral for treatment (29–31).

The 5-year PFS, DFS and overall survival were 7.9%, 59.6% and 90.7%, respectively. The 5-year survival for breast cancer in England, Australia and the USA is 84%, 89.5% and 90.2%, respectively, compared to 66.1% for India (32). Although the overall survival figures in Alexandria are comparable to or exceed those of rich countries, they cannot be taken as an indicator of a perfect healthcare system. This survey included a smaller number of records than the American, English and Australian studies, confounded by gaps in the recording data, which would have reduced the accuracy of survival estimation.

Conclusion

Strategies have been proposed to improve the implementation of an effective programme for prevention, screening, early detection, and treatment of breast cancer that reduces delays and unnecessary expenditure and improves outcomes (15,34,35). The elements of an implementation strategy would include: 1) strengthening of national and/or hospital-based registries and use of centralized electronic health records, indexing patients with their national number; 2) defining subgroups of women at higher risk of developing breast cancer and educating them about health-modifying behaviour to reduce the risk of breast cancer and increase adherence to a healthy lifestyle; 3) educating the public and primary care physicians about screening pathways; 4) establishing a patient navigation system for diagnosis and treatment; 5) expanding the coverage of health insurance to the sectors of the population at risk, guided by cost-efficiency studies; and 6) continuous monitoring of outcomes to see the effect of these strategies and improve the interventions.

Présentation et prise en charge du cancer du sein chez les femmes en Égypte

Résumé

Contexte : Des lacunes dans le système ont été constatées en ce qui concerne le profilage et la prise en charge du cancer du sein chez les femmes à Alexandrie (Égypte).

Objectifs : Identifier les obstacles à la mise en œuvre complète des lignes directrices internationales pour la prise en charge des patientes atteintes d'un cancer du sein.

Méthodes : Des données sur le cancer du sein chez les femmes ont été extraites des dossiers de trois services publics d'oncologie à Alexandrie, en Égypte, de 2007 jusqu'à 2016 et ont fait l'objet d'une analyse.

Résultats : Au total, 5236 des 7125 dossiers disponibles étaient utilisables. L'âge médian des patientes était de 54 ans et la durée médiane des plaintes avant le diagnostic était de 3,1 mois. Près de 522 (31,5 %) des patientes avaient des antécédents familiaux de cancer. En ce qui concerne le stade de la tumeur, 2527 (55,2 %) étaient de stade précoce, 1717 (37,6 %) étaient localement avancés et 331 (7,2 %) étaient au stade IV. Les récepteurs d'œstrogènes, de progestérone et de HER$_2$ étaient respectivement positifs chez 3869 (85 %), 3545 (78 %) et 461 (15,3 %) patientes. Une chimiothérapie a été mise en route après un délai médian de 1,03 mois. Une chimiothérapie adjuvante a été administrée à 3667 patientes (91,7 %) et une chimiothérapie néoadjuvante à 333 patientes (8,3 %) ; 3686 patientes (92,1 %) ont reçu une chimiothérapie combinée à base d'anthracycline et 3613 patientes (86 %) étaient sous traitement hormonal. Cent quatre-vingt des 317 patients éligibles se sont vu administrer le trastuzumab. Une récidive locale et/ou à distance a été observée chez 1109 patientes (21,2 %). Dans les cas non métastatiques, la survie médiane globale et la survie sans maladie étaient de 149,1 et 77,1 mois, respectivement. Dans les cas métastatiques, la survie médiane sans progression était de 19,6 mois.

Conclusion : Nous avons observé des défauts dans le système d'enregistrement, un retard dans le diagnostic et le traitement, et une non-adhésion à la thérapie ciblée chez de nombreuses patientes. Il est nécessaire de renforcer les registres nationaux et hospitaliers à Alexandrie (Égypte), par un système de navigation des patients solide et des stratégies d'information, d'éducation et de communication ciblées. Le suivi continu des résultats et l'adaptation aux besoins de la mise en œuvre doivent être soutenus.

الوقوف على تبدِّيات سرطان الثدي لدى الإناث وعلاجهن في مصر

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الخلاصة

الخلفية: تُوجد أوجه قصور في النظام في تحديد سمات مريضات سرطان الثدي وعلاجهن في الإسكندرية بمصر.

الأهداف: هدفت هذه الدراسة إلى تحديد العقبات التي تحول دون التنفيذ الكامل للمبادئ التوجيهية الدولية بشأن علاج مريضات سرطان الثدي.

طرق البحث: استُخلصت بيانات سرطان الثدي لدى الإناث من سجلات 3 خدمات عامة لعلاج الأورام في الإسكندرية بمصر، في المدة من عام 2007 إلى عام 2016، ثم حُلِّلت تلك البيانات.

النتائج: بلغ عدد السجلات المتاحة 7125، وكان منها 5236 سجلًا قابلًا للاستخدام. وكان متوسط عمر المريضات 54 عامًا، ومتوسط مدة الشكوى قبل التشخيص 3.1 شهرا. ونحو 522 مريضة (31.5٪) لديهن تاريخ عائلي للإصابة بالسرطان. أما مرحلة الورم، فكان يُوجد 2527 حالة ورم مبكرة (55.2٪)، و1717 حالة ورم موضعي متقدم (37.6٪)، و331 حالة في المرحلة الرابعة (7.2٪). وكانت مستقبلات هرمون الإستروجين ومستقبلات البروجسترون ومستقبلات عامل نمو البشرة الثاني إيجابية لدى 3869 مريضة (85٪) و3545 مريضة (78٪) و461 مريضة (15.3٪) على الترتيب. وبدأ العلاج الكيميائي بعد 1.03 شهر في المتوسط. وأعطي علاج كيميائي مساعد إلى 3667 مريضة (91.7٪)، ومعالجة كيميائية داعمة قَبْلية إلى 333 مريضة (8.3٪)، وحصلت 3686 مريضة (92.1٪) على مزيج علاج كيهاوي معتمد على أنثراسيكلين، وحصلت 3613 مريضة (86٪) على علاج هرموني. وتلقَّت مائة وثمانون مريضة دواء تراستوزوماب من أصل 317 مريضة مؤهلة. ورُصدت عودة المرض في الموضع ذاته و/ أو مواضع أخرى في 1109 مريضات (21.2٪). أما في الحالات غير النَّقيليّة فبلغ متوسط إجمالي مدة البقاء على قيد الحياة 149.1 شهرًا ومتوسط مدة البقاء على قيد الحياة مع الخلو من المرض 77.1 شهرًا. وأما في الحالات النَّقيليّة فكان متوسط البقاء على قيد الحياة مع عدم تفاقم المرض 19.6 شهرًا.

الاستنتاجات: لاحظنا وجود عيوب في نظام التسجيل، وتأخُّرًا في التشخيص والعلاج، وعدم الالتزام بالعلاج المُستهدَف في الكثير من حالات المريضات. لذا ثمة حاجة إلى تعزيز السجلات الوطنية والسجلات المستندة إلى بيانات المستشفيات في الإسكندرية بمصر، بالإضافة إلى الحاجة إلى وجود نظام قوي لتقصِّي حالات المريضات، واستراتيجيات تثقيف واتصال، واستراتيجيات موجَّهة لمسائل المعلومات. وينبغي مواصلة رصد النتائج باستمرار والتكيُّف مع احتياجات التنفيذ.

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