



Discrepancies of current recommendations in breast cancer follow-up: a systematic review

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Abstract

Introduction Management and optimal follow-up of early breast cancer survivors remain up to this day a challenge due to the lack of well-established guidelines. Multiple medical societies, organizations and working groups have provided recommendations for follow-up but there is no uniform, globally approved algorithm to guide clinical practice.

Methods A systematic review was performed to identify and evaluate discrepancies between available guidelines for the follow-up of breast cancer survivors.

Results Differences in the follow-up schedule, laboratory and imaging investigations were noted. In the clinical practice setting, the situation is complicated further by clinicians who often request unnecessary tests not currently incorporated in any of the existing guidelines.

Conclusions Follow-up of patients with early breast cancer needs to become standardized and prospective clinical trials focusing on optimal follow-up are more than mandatory.

Keywords Follow-up · Breast cancer · Guidelines · Clinical practice · Discrepancies

Introduction

Breast cancer is a common malignancy amongst women, with an overall survival rate of approximately 78% during the first decade following diagnosis [1]. There are 3.3 million breast cancer survivors in the US, a number which is continuously growing worldwide [1]. The need for optimal follow up in these patients is reflected in the number of available algorithms and recommendations published by

national and international societies, organizations and working groups [2–9].

Time points of follow-up visits and recommended laboratory and imaging investigations at each follow-up vary among current guidelines. The discrepancy between available guidelines is partly explained by the complexity of the disease; the multiple potential sites of metastasis and the plethora of the early and late disease manifestations that a clinician must be aware of [10]. Optimal post-treatment management is further complicated by the potential side effects of adjuvant systemic chemotherapy and radiotherapy. Consequently, a standardized follow-up approach which can become patient-specific is necessary for early diagnosis and proper management of disease progression and therapy-related complications. Currently, given the lack of consensus, implementation of current recommendations on follow-up of early breast cancer patients in clinical practice is particularly problematic [11].

We aimed to conduct a systematic review of the literature synthesizing all available data on current clinical guidelines and recommendations for the follow-up of early breast cancer survivors (or patients).

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Materials and methods

Search strategy and data abstraction

This study was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [12]. The protocol of this systematic review was approved by the Institutional Review Board of Alexandra Hospital, Medical University of Athens, Greece. Studies which met the inclusion criteria were identified by a search of MEDLINE bibliographical database for the period of January 1, 2012 up to December 31, 2017. The search strategy included the following keywords: breast [ti] AND (neoplasm [ti] OR cancer [ti] OR carcinoma [ti]) AND (guidelines [ti] OR consensus [ti] OR practice [ti] OR recommendation [ti]) AND (follow up [ti] OR surveillance [ti] OR management [ti]).

Language restrictions were applied (only articles in English, French and German were considered eligible). Two investigators (FZ and AK) performed the literature search and data extraction working independently. Reviews, experts' opinion, prospective and retrospective studies were included in the analysis whilst case reports were excluded for this systematic review. Manuscripts that did not state the name of the authors were excluded. Additional articles were identified from the reference lists of retrieved articles.

All studies that examined clinical practice guidelines for the follow up of patients with early breast cancer were included in the systematic review. The following data were collected from each study: frequency of visits, physical examination, self-examination, mammography, breast ultrasound, breast magnetic resonance imaging (MRI), Xrays, CT scans, pelvic examination, blood tests, tumor markers, bone densitometry, abdomen ultrasound, bone scan, positron emission tomography-computed tomography (PET-CT), and whole-body MRI. In the case of multiple (overlapping) publications stemming from the same study, the most recent publication was included, unless the reported outcomes were mutually exclusive.

Results

Our search identified initially 48 records. Forty-one remained post duplicate entry removal and exclusion of non-eligible articles based on the title and abstract screening. Inclusion criteria were applied by reviewing the articles in full-text and 7 publications were eligible for inclusion in the qualitative analysis. The reference search of the reviews and articles identified 5 additional publications

which met the inclusion criteria. Overall, 12 articles were eligible for inclusion in the systematic review. The study design and article selection process are depicted in Fig. 1.

The differences in the timing of follow-up visits among major guidelines are summarized in Table 1. Great variance was observed in the schedule of follow-up visits. Follow-up was more frequent during the first 2–3 years post-treatment completion (2–4 times/year) becoming less regular during the following years. The most prominent exception were the Canadian guidelines which recommend following a patient-specific follow-up plan [4].

All guidelines are in agreement regarding the need for obtaining a detailed medical history and performing a clinical examination in every visit. Self-examination is not recommended by any medical society apart from the Arbeitsgemeinschaft Gynakologische Onkologie (AGO) and the Canadian guidelines [4, 5]. More specifically, in the AGO guidelines self-examination is a prerequisite, whereas the Canadian guidelines include it according to the patient's wish.

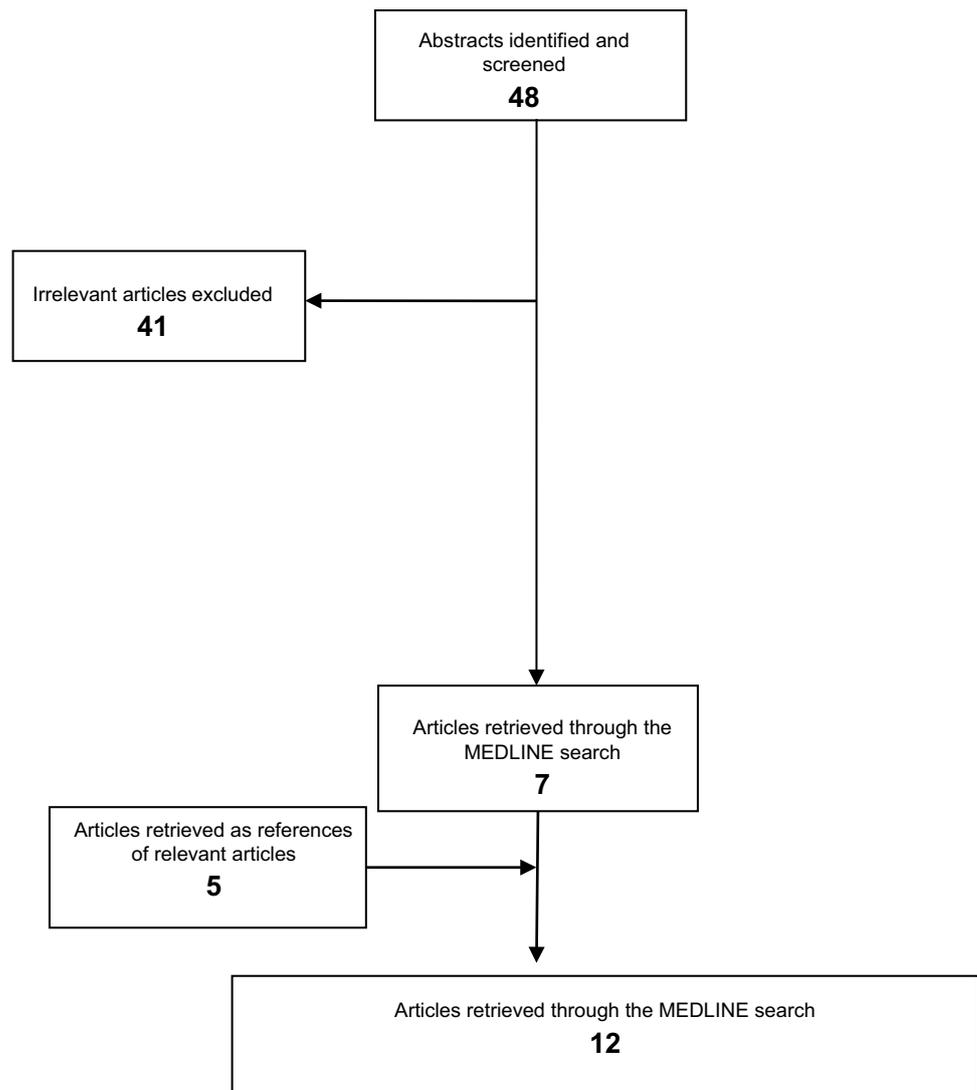
Chest X-ray, CT scans, mammography, breast ultrasound, breast MRI, bone scans, PET-CT, whole body MRI, abdomen ultrasound and bone density scans are the imaging modalities of choice in everyday clinical practice at the follow-up setting [13]. Most guidelines however due to include these examinations leading to discordance between common clinical practice and available recommendations. More specifically, mammography was included in all guidelines, while breast ultrasound is a prerequisite only in ESMO, AGO and Australian guidelines [3, 5, 9]. Breast MRI, is not required in NCCN, Canada and UK guidelines [2, 4, 6], but ASCO, ESMO, AGO and Australian guidelines recommend it in specific groups, i.e. in patients with increased breast cancer risk, with familial and genetic predisposition, or in cases of inconclusive conventional imaging (AGO) [3, 5, 8, 9, 14]. Abdominal ultrasound, PET-CT, whole body MRI and bone scan are not included in any of the major guidelines. Bone density measurement is recommended for post-menopausal women who receive aromatase inhibitors and in pre-menopausal women receiving tamoxifen at high risk of osteoporosis [15].

Blood tests and cancer biomarkers are not included in most of the scheduled laboratory screening recommendations, with the exception of the ESMO guidelines that include blood tests for patients on hormonal therapy [3]. Pelvic examination is included in ESMO and NCCN guidelines for women on tamoxifen [2, 3] while AGO guidelines require a pelvic examination for every patient [5].

Discussion

The optimal follow-up of early breast cancer survivors is challenging and not well established. The current metanalysis demonstrates the extent of discordance amongst available

Fig. 1 Schematic chart with the study design and the selection of articles included



guidelines implicating the potential adverse effect of this discordance on the management and survival of these patients.

Medical history and physical examination remain fundamental elements of the follow-up process according to all reported guidelines [2–9, 14]. Major disparities exist however with regards to the modalities recommended for the imaging and biochemical follow-up of women. Redundant and non-informative laboratory (blood tests and cancer biomarkers) and radiographic investigations are often requested by clinicians [16]. Such clinical practice results in increased health-care costs and adverse psychological effects on patients [11]. Furthermore, the data collected are of uncertain utility for patients' prognosis and the disease natural history. Imaging modalities such as Xrays, CT scans, bone scan, whole body MRI are not included in any of the current follow-up guidelines for the asymptomatic breast cancer patients. This decision stems from the lack of clinical indications as well as financial restrictions [13].

Adjuvant hormonal therapy for the duration of more than 10 years is associated with multiple toxicities and consequently affects the quality of life of women with HR positive breast cancer [17]. Arthralgia, hyperlipidemia, hypertension, hot flashes, fatigue, depression, endometrial hyperplasia, cardiac failure are some of the most common toxicities that might influence quality of life for these patients [17, 18]. Most guidelines include bone density measurement for the prevention of pathologic and osteoporotic bone fractures associated with long-term hormonal therapy. Pelvic examination in the context of screening for secondary malignancies (endometrial carcinoma) is not a well-defined process and is included in the guidelines published by a small number of medical societies (ESMO, NCCN, AGO) [2, 3, 5]. Sexual disorders due to vaginal dryness are common adverse effects commonly underestimated by both clinicians and patients [19]. Management of toxicities requires a close and careful examination of several systems and a detailed

Table 1 Comparison of the guidelines of follow-up for early breast cancer survivors

Timetable	ASCO	ESMO	NCCN	AGO	UK	Canada	Spain	Australia
	3–6 months (1–3 years), 6 months (4–5 years)	3–4 months (1–2 years), 6 months (3–5 years)	3–12 months (1–5 years)	3 month (1–3 years), 6 months (4–5 years)	12 months (1–3 years)	Individually	According to risk groups	3–6 months (1–2 years), 6–12 months (3–5 years)
History	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Phys. exam	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Self exam	No	No	No	Yes	No	Yes if the patient wants to	No	No
Mammography	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
US breast	No	Yes	No	Yes	No	No	No	If indicated
MRI breast	Only for increased breast cancer risk	Only in young patients, with dense breast tissues, familial and genetic predisposition	No	In case of inconclusive conventional imaging	No	No	No	In specific high risk groups
X rays	No	No	No	No	No	No	No	No
CTIs	No	No	No	No	No	No	No	No
Pelvic exam	No	Women in tamoxifen	Women in tamoxifen	Yes	No	No	No	No
Blood test	No	In endocrine therapy patients	No	No	No	No	No	No
Markers	No	No	No	No	No	No	No	No
DXA	Post menopausal patients in Ais, premenopausal in tamoxifen and women with chemo induced premature menopause	Patients in Ais	Women in Ais or with secondary ovarian failure	Women in Ais or with premature menopause	Patients on Ais	Postmenopausal, premenopausal with high risk for osteoporosis and patients on Ais	No	No
US abdominal	No	No	No	No	No	No	No	No
Bone scan	No	No	No	No	No	No	No	No
PET CT	No	No	No	No	No	No	No	No
MRI whole body	No	No	No	No	No	No	No	No

medical history, highlighting the importance of follow-up visits [20].

Overall survival during the first decade following diagnosis reaches 78% [1]. Breast cancer is a complex disease that requires meticulous follow-up. There are multiple potential metastatic sites and a wide range the symptoms and signs that the clinician must be aware of and look out for [20]. At the same time, patient education is crucial to allow early identification of treatment-related side-effects and signs of disease progression and recurrence [21]. This illustrates further the need of a patient-specific follow-up which will allow diagnosis of recurrence and treatment administration in a timely manner and prior to the deterioration of the patient's performance status [20].

Depending on the health care system follow-up of breast cancer survivors is performed either in the hospital setting by medical oncologists or by general practitioners in the community [22]. Studies have not demonstrated differences in the rates of disease recurrence detection and overall survival between different physicians and follow-up settings. Furthermore, there are data showing that breast cancer patients' satisfaction depends on the way they are being treated and followed up rather than where [23]. It has been also demonstrated in the context of other medical specialties such as Emergency Medicine that process standardization (ALS, ACLS) leads to homogenization of the provision of medical services worldwide and decreased medical error [24].

Guidelines represent key tools in medical oncology. For breast cancer specifically, diagnosis and treatment recommendations are relatively homogenous amongst major available guidelines. On the other hand, guidelines on follow-up of women with breast cancer are heterogeneous and, in some cases, vague. To answer this question, a phase III clinical trial (INSPIRE), conducted from the Japan Clinical Oncology Group Study JCOG1204 is still running. This study is comparing intensive follow-up to standard follow-up in terms of overall survival to high risk patients [25]. The American Cancer Society in collaboration with the American Society of Clinical Oncology have published the Practice Guidelines Update. This report includes expert recommendations on optimal follow-up and management after primary treatment [14]. A more recent publication of the Spanish Society of Medical Oncology has summarized the guidelines in agreement with members of scientific societies whose members are involved in the management of these patients, depicting the complexity of the medical management and the need for collaboration of several medical specialties for the ideal follow-up of breast cancer survivors [7]. Moschetti et al., have assessed the effectiveness of several follow-up strategies for the detection of distant metastasis on mortality, morbidity and quality of life in women who received treatment for stages I, II and III breast cancer. They

concluded that physical examination and yearly mammography alone are adequate to detect recurrence without compromising overall survival and affecting the quality of life. The addition of detailed laboratory and radiologic tests did not have an impact on recurrence detection, overall survival or quality of life [26].

As far as the strengths of this study it should be underlined that it has been conducted according to PRISMA principles including the most recent guidelines and recommendations of the major medical societies. As a result, it clearly highlights the heterogeneity of the follow-up approach amongst several health systems. Moreover, one of the assets of this study is its novelty per se: this is the first effort to compare guidelines and recommendations regarding the follow-up of early breast cancer survivors. Regarding the limitations of this manuscript, it should be recognized that common clinical practice is not well documented to the literature. This is a caveat of our research method because it cannot clearly depict the differences between real-world practice and current recommended guidelines.

In conclusion, there is no conformant schedule of follow-up visits and clinical/imaging examinations for the follow-up of early breast cancer patients. More specifically there are inconsistencies amongst major guidelines in the recommended: (a) visit frequency (b) physical examination and medical history and (c) blood tests and imaging examinations. Effective and efficient follow-up of patients with early breast cancer is of prime importance and needs to be optimally standardized. Prospective clinical trials, as data from the Japanese ongoing study, focusing on the definition of optimal follow-up are, therefore, more than necessary.

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Compliance with ethical standards

Ethical standards The authors declare that this systematic review was conducted according to the laws of Greece.

Conflict of interest The authors declare that they have no conflict of interest.

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