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Follow-up of patients with early breast cancer: Is it time to rewrite the story?

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Contents

Abstract

The guidelines for follow-up in breast cancer survivors support only performance of periodic physical examination and annual mammography. However, medical oncologists and primary care physicians routinely recommend both blood tests and non-mammographic imaging tests in asymptomatic patients, leading to an increased anxiety related to false-positive results and higher medical expenses. Recently, advanced

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imaging technologies have improved sensitivity/specificity to detect metastatic lesions before symptoms arise. Considering the progress made in the treatment of metastatic disease and the rapid evolution of targeted therapy, that requires customization of the strategy according to molecular characteristics of the disease, patients could derive real benefit to early detection of disease recurrence. This hypothesis must be tested in a prospective clinical trial.

Keywords: Early breast cancer; Follow-up; Surveillance; Survivorship care

1. Introduction and terminology

The overall prevalence of women living with a diagnosis of breast cancer (BC) is increasing in the industrialized countries [1], thus management of breast cancer survivors represents a daily practice problem for both oncologists and primary care physicians (PCP).

After a radical primary treatment, patients with early stage cancer enter in a structured surveillance phase usually called "cancer follow-up" [2]. According to the Cochrane Breast Cancer Group, terms such as "routine testing", "follow-up" or "surveillance" indicate the regular use of laboratory or instrumental tests in otherwise asymptomatic patients to detect distant metastases earlier [3]. This definition is primarily focused on early detection of disease recurrence in patients otherwise asymptomatic. However, considering that worldwide population is aging and 50–70% of BC survivors experience persistent impairment or limitations after primary treatment [4,5], physicians also have to deal with co-morbidities and long-term side effects of treatment such as anthracycline-related cardiac damage, anti-estrogen-associated bone disease, chemotherapy-induced infertility, and risk of second malignancies. Supportive and psychological interventions should be an important part of the oncologist role. This more comprehensive activity is usually termed as "survivorship care".

Given the required large amount of resources and the possible important consequences in terms of patients' health and survival, several prospective studies were conducted with the aim of defining the best follow-up strategy in BC survivors [6–11] and clinical guidelines are constantly updated [12,13]. A survival benefit derived from the early detection of disease recurrence was rarely demonstrated in the general population, although several other needs of cancer patients were pointed out, leading to a wider understanding of surveillance and to a shift toward survivorship care. Unfortunately, while oncological research is actively pushed in the field of pharmacological therapy, little has done to solve the many questions that still are open in survivorship care.

2. Surveillance

2.1. Summary of literature review and current guidelines

Data on BC follow-up date back to the 1990, when results from two randomized trials were published: the GIVIO (Gruppo Interdisciplinare Valutazione Interventi in Oncologia, Interdisciplinary Group for Cancer Care Evaluation) trial [6] and the Rosselli del Turco trial [7]. They comparatively evaluated conventional follow-up based on regular physical examinations and annual mammography with more intensive investigations, such as chest X-rays, bone scan, liver ultrasound (US), and laboratory tests for tumor markers in order to search for distant metastases. Both trials showed no overall survival (OS) benefit arising from intensive follow-up as compared with conventional follow-up [8,9]. In particular, the first analysis of the Rosselli Del Turco trial showed an uncertain survival benefit arising from intensive follow-up compared with conventional follow-up, but the data was not confirmed after 10-year follow-up. The 10-year mortality cumulative rates were 31.5% for the conventional follow-up and 34.8% for the intensive ones (hazard ratio 1.05; 95% Confidence Interval (CI) 0.87–1.26) [8]. Similarly, the GIVIO at a median follow-up of 71 months, showed no differences in survival, with 132 deaths (20%) in the intensive group and 122 deaths (18%) in the control group (odds ratio = 1.12; 95% CI = 0.87–1.43). Moreover, the GIVIO trial assessed a decreased health-related Quality-of-life (QoL) in the intensive-screening group [6]. Recently, a Cochrane review involving more than 2500 women, confirmed that intensive follow-up did not improve OS and disease-free survival (DFS). These results were consistent among subgroup analyses according to patient age, tumor size and lymph node status before primary treatment [3].

Other important issues concern frequency and location of follow-up visits. In 1997 a single center trial showed that annual follow-up visits after mammography did not increase the use of local practitioner services or telephone triage compared with visits scheduled every 3–6 months. However, due to the small sample size of this trial, definitive conclusions about effectiveness and cost-effectiveness of routine follow-up with respect to disease outcomes were not assessable [9]. In 1996 and 2006, two multicenter, randomized, controlled trials showed no differences in terms of recurrence-related clinical events rate and health-related QoL between follow-up performed by a medical oncologist or by a PCP [10,11]. However, median follow-up of both trials was short (18 months and 3.5 years, respectively) and studies were underpowered to evaluate the impact on OS.

To date, the ASCO [12] and the NCCN (National Comprehensive Cancer Network) [14] guidelines recommend breast self-examination, annual bilateral mammography and

periodic history and physical examination (every 3–6 months for the first 3 years, then every 6–12 months for 2 years or every 4–6 months for 5 years, respectively, then every 12 months). They also underline the importance of counseling about symptoms of recurrence and active lifestyle. Moreover, they recommend periodic pelvic examinations for every woman, in particular patients taking tamoxifen, who are at increased risk of endometrial cancer, and bone mineral density determination for women undergoing an aromatase inhibitor or who experience ovarian failure secondary to treatment. Physicians should assess and encourage adherence to adjuvant endocrine therapy, and women at high risk for familial breast cancer syndromes should be referred for genetic counseling.

In asymptomatic patients, there are no data to indicate that other laboratory or imaging tests (e.g. blood counts, routine chemistry tests, chest X-rays, bone scans, liver US exams, computed tomography (CT) scans, positron emission tomography (PET) scans or any tumor markers such as CA15-3 or CEA) can produce a survival benefit.

The ESMO guidelines [15] focus attention to survivorship care, highlighting that the purposes of follow-up are also to evaluate and to treat therapy-related complications (such as menopausal symptoms, osteoporosis and second cancers) and to provide psychological support and information in order to enhance returning to normal life after BC. Table 1 summarizes current guidelines on breast cancer follow-up.

Currently, no specific trials were conducted to evaluate the best follow-up strategy in particular population, such as male BC, elderly patients, very young patients, and BRCA1-2 mutation carriers.

2.2. Uses and abuses of resources

In clinical practice intensive follow-up is a widespread reality and it costs 2.2–3.6 times more than guidelines-compliant follow-up [16], as a result of non-mammographic tests performed in the absence of any warning signs or symptoms of recurrence [17]. The ASCO included BC surveillance in the top-five list of oncological practices that could be improved and simplified in order to reduce costs [18].

The higher-than-recommended intensity involves both clinical examinations and imaging. A Canadian population-based analysis showed that the mean number of visits in the first 5 years after primary treatment was usually higher than recommended by the ASCO guidelines. For example, during the second year patients underwent a mean of 11.2 visits by different physicians, including PCP, medical oncologist, radiation oncologist, surgeon and others, compared with 2–4 visits recommended [19]. These numbers are a common result of a widespread duplication of care.

In line with these results, Keating and Colleagues observed that 13.3% of the 37,967 patients collected in the Surveillance, Epidemiology, and End Results (SEER) – Medicare database had at least one bone scan, 29.2% had a tumor antigen test, 10.9% had chest/abdominal imaging, and 58.8% had a chest X-ray in the first year of follow-up, and patients followed by medical and radiation oncologists had the highest chance of undergoing non-recommended tests [20]. Similarly, a National survey conducted among Italian medical oncologists showed an abuse of imaging and tumor markers test in asymptomatic BC survivors [21].

There are multiple possible reasons of overuse of imaging and laboratory testing. The first one is the patient-driven anxiety and the feeling of reassurance induced by examinations. Patients are prone to associate the frequency of clinical examinations and testing with improved outcomes [22] due to the unrealistic belief that more testing could anticipate the diagnosis of recurrence and improve treatment outcomes. A second issue to be taken into account is the dearth of prospective trials with new generation imaging (CT and PET scans) or oriented to special populations (for example women under 40 years old or patients with triple-negative or HER2-positive disease). Finally, an important trigger of unnecessary examinations and visits may be the absence of a clear coordination among all the professionals involved in the survivorship plan [23]. By contrast, uncoordinated care can also be the cause of underuse of appropriate visits and tests: the SEER data [20] showed that in United States only 27% of breast cancer survivors' aged 65 years or older saw their oncologists annually for 3 years after active treatment and a case control study conducted in Ontario [24] highlighted that among BC survivors only a minority underwent colorectal and cervical cancer screening, despite being seen by multiple specialists during the first 5 years after primary treatment. These examples of lower-than-standard practice support the hypothesis that resources may not be equally distributed among surviving patients.

3. Advances in management

3.1. Advances in biology

A huge amount of evidence suggests that the risk of BC recurrence and death is influenced not only by stage at initial presentation but also by the underlying biology of the tumor [25]. Overall, the hazard rate varies over time according to predictive and prognostic factors [25]. A better understanding of patterns of recurrence is an important medical driver for both the treatment and the surveillance clinician decision process.

Currently, BC is classified into five different molecular subtypes [26–28] according to immunohistochemical (IHC) classification:

- Luminal A (characterized by hormone receptors (HR)-positive tumor cells and low Ki-67 expression; human epithelial growth factor receptor 2 (HER2)-negative status)
- Luminal B (HR-positive cells and high Ki-67 expression; HER2-negative status)
- Luminal/HER2 (HR-positive cells and HER2-positive status)

Table 1
Summary of current guidelines on breast cancer follow-up.

Scientific society	History and physical examination	Mammography	Breast self-examination	Intensive follow-up	Bone mineral density	Gynecologic assessment
ESMO 2011 [15]	Not specified	Every 12 months	Not specified	Not recommended	Not specified	Not specified
ASCO Update 2013 [6]	Every 3–6 months for the first 3 years, every 6–12 months for the next 2 years, then annually	Every 12 months	Monthly	Not recommended	Not specified	All women
NCCN Version 3.2013 [14]	Every 4–6 months for 5 years, then annually	Every 12 months	Not specified	Not recommended	Women on aromatase inhibitor or who experience ovarian failure secondary to treatment	Women on tamoxifen: every 12 months
AIOM 2013 [126]	Every 3–6 months for 5 years, then annually	Every 12 months	Not specified	Not recommended	If clinically indicated	Women on tamoxifen: if clinically indicated

- HER2 enriched (HR-negative and HER2-positive status)
- Triple negative (HR-negative and HER2-negative status)

The hazard rates for relapse among HR-negative and/or non-luminal A tumors show a sharp peak soon after initial diagnosis. Conversely, hazard rates for HR-positive and luminal A tumors are persisting low over the time [25]. A recent analysis showed that patients with Luminal B breast cancer had a continuously higher hazard of breast cancer recurrence over time and a shorter OS compared with Luminal A patients [29,30]. Moreover, Luminal B patients had higher rates of bone as first recurrence site than other subtypes. Visceral recurrence as first event was similar among Luminal B, HER2 enriched and triple negative BC.

From a biological point of view, the observation of different patterns of relapse suggests different mechanisms involved in early and late BC events. As a consequence, it is tempting to hypothesize that schedule and intensity of surveillance should vary accordingly.

3.2. Advances in surveillance strategies

3.2.1. Locoregional recurrence

The survival of women suffering locoregional recurrence is markedly different compared to those suffering distant metastases (80% 5-year relative survival rate versus 25% 5-year relative survival rate, respectively) [31] and patients with isolated locoregional or contralateral breast cancer recurrences detected without symptoms have a better survival compared to patients in whom a late symptomatic detection is performed. Over the last two decades, it has been demonstrated that patients with solitary first locoregional recurrence after mastectomy may achieve a 5-year DFS rate of 61–79% if they underwent a radical locoregional treatment combined with systemic adjuvant therapy [32,33].

Unfortunately, the first site of relapse is represented by local recurrence in only one-third of recurrent BC patients [34]. Even if some retrospective analyses suggested that having an inflammatory BC at the primary diagnosis [35] as well as the tumor stage and pathological nodal stage after neoadjuvant treatment [36] may predict for a higher risk of locoregional recurrence, no strategy are current available to identify patients who are more likely to have a local relapse.

The detection of isolated locoregional and contralateral recurrence or new breast primary in asymptomatic patients by mammography leads to an absolute reduction in mortality of 17–28% [37]. Nevertheless, surveillance mammography is affected by both false-negative (approximately 10% of palpable tumors are not clearly visible on mammography) and false-positive results, which require further investigations, especially when deleterious changes in breast tissue have been induced by surgery and radiotherapy [38–40]. In such cases, the reliability of the diagnosis might be improved by the use of US or magnetic resonance imaging (MRI) [41–43]. In particular, MRI of the breast can be used as a problem-solving tool in the evaluation of patients in whom equivocal abnormalities are identified by mammography or physical examination [44,45]. MRI is particularly appealing for surveillance of young women due to its proven higher sensitivity compared to mammography, especially in dense breasts [46–50]. However, due to the relatively low specificity of MRI for BC recurrence (range from 66 to 100%) [51–58] and the current high cost of this technique [59], MRI could not be considered a recommendable tool in BC follow-up. Moreover, a recent study showed that MRI did not reduce the risk of both local and distant disease relapse [60].

For these reasons mammography is the cornerstone of appropriate BC follow-up after primary treatment for all patients [12].

3.2.2. Distant metastases

In the early 1990s it has been reported that a small percentage of metastatic breast cancer (MBC) patients who achieved a complete remission after systemic treatment remained disease-free over 20 years. Overall, these long-survivors represented only 1–3% of all metastatic patients, but they challenged a paradigm: MBC was no longer always a fatal condition [61,62].

Looking into the patient and tumor characteristics of the long-survivors we realized that they shared some important features: they were young, with good performance status and with a limited burden of metastatic disease [63,64]. In particular, having an oligometastatic disease seemed to be the strongest predictor for long survival.

Over the last three decades, several studies confirmed this assumption. The implementation of multidisciplinary aggressive approach in patients with a single metastatic lesion has lead to a disease-free interval longer than 15 years [65–69], and a retrospective analysis of patients with 1 or 2 metastatic sites showed a complete response with systemic treatment of 48% and a 20-year OS rate of 53% [62].

These impressive results can be related with both an improvement in treatment for MBC and an improvement in early detection of metastatic disease limited to 1–2 sites.

However, more than 20% of patients have a multiple sites disease at presentation of metastatic spread [70]. According to a recent retrospective analysis, the most common sites of distant recurrence were bone (41.1%), lung (22.4%), liver (7.3%), and brain (7.3%) [62]. Interestingly, different patient and tumor characteristics underlined different patterns of distant relapse: bone metastases were more likely to be diagnosed in patients with HR-positive disease, lung and liver metastases in patients with a more advanced stage at the time of primary diagnosis, and brain metastases in patients with HR-negative disease [29,62]. The worse survival outcome over the initial years after diagnosis was observed in triple negative BC patients and in patients with HER2-positive disease who did not received any anti-HER2 treatment [29]. Moreover, even if the introduction of drugs targeting the HER2 has led to an impressive improvement in both DFS and OS [71–74], data from the first trial with trastuzumab in metastatic setting showed that patients who received the anti-HER2 treatment upfront had a survival advantage compared with who received it after progression [70]. These findings suggest that an early diagnosis and treatment of HER2-positive disease recurrence may improve outcome of these patients.

Diagnostic tools currently used in the surveillance, such as PET, MRI, and CT, have a wide range of accuracy in the detection of all the sites of relapse [75]; consequently it is not likely to assume a one shot diagnostic examination that can be appropriately used for the surveillance of distant relapse but rather this surveillance is likely to comprise a combination of these technologies. The poor prognosis of patients with distant relapse justify a strong effort to identify a "systemic surveillance strategy" effective in improving outcome.

3.2.2.1. Conventional workup. Conventional imaging tests (CITs) available to detect distant metastases include conventional X-rays, CT scan, US, bone scan and, in a limited number of settings, MRI. Diagnostic accuracy of CITs in surveillance setting of BC survivors is mainly extrapolated from studies comparing conventional workup and PET scan and they are far to be completely assessed [40]. For example, CT scan is widely used in clinical practice but diagnostic accuracy of CT imaging in detecting recurrent and/or MBC, ranges from 40 to 92% in sensitivity and from 41 to 100% in specificity [76–79]. Moreover, abdominal US has the undoubted advantage of minor economical and biological costs but its use in BC is not supported by adequate scientific evidences; most of the studies assessed the diagnostic accuracy of US in the diagnosis of local recurrence and not of liver metastases [41].

A particular mention should be made for the bone involvement. Bone is the most common site of distant metastases from BC [80]; complications resulting from bone metastases include hypercalcemia, bone pain, pathological fractures, and spinal cord compression [81]. Early detection of metastatic disease may prevent skeletal complications, offer a better chance to control the disease process, and improve patients' QoL [82].

From a recent review, emerged that the absence of risk stratification in published data does not adequately evaluate the benefit of intensive surveillance among patients with known high-risk disease, therefore to plan studies for assessing an accurate surveillance strategy in aggressive tumors is a real need [83].

Conventional X-ray has a low sensitivity in detection of bone metastases. It has been estimated that a 30–75% reduction in bone density is required to visualize a metastasis on radiographs. In the same way, a considerable cortical destruction is required for visualization of a metastasis by CT scan; sensitivity and specificity of this modality in detecting early malignant bone involvement [84,85] are relatively low. Bone scan offers a relatively sensitive and reasonably priced evaluation of the whole skeleton in a single imaging examination but it is affected by a poor anatomic resolution [86] that may results in not-detecting lytic lesions or difficulty in distinguishing tumor from degenerative/traumatic events. The detection rate of bone metastases by bone scan in patients with early-stage BC is very low (0.82 and 2.55% in stage I and II, respectively), but it increases to 17% in patients with stage III disease. Therefore, bone scan should be performed in symptomatic patients, when there is a clinical suspicion for metastatic bone involvement [87], and in advanced-stage disease.

Considering that MRI has high soft tissue contrast, and good spatial and contrast resolution, it is an optimal imaging modality for bone marrow assessment. MRI can detect an early intramedullary malignant lesion before there is any cortical destruction or reactive processes. MRI was shown to be better than PET, CT, and bone scan for bone marrow disease [88].

3.2.2.2. PET and PET/CT scanning. The diagnostic potential of whole-body 18-fluoro-2-deoxy-D-glucose (FDG)-PET can be considered in patients with high risk of recurrence [89,90]. Moreover, the advantages of FDG-PET/CT in identifying locoregional recurrence are the high sensitivity and the ability to differentiate post-surgical/radiotherapy changes from true recurrence. An important role of FDG-PET seems to be the detection of distant metastases in patients with suspected recurrence disease, e.g. when biochemical markers (CA15.3 or CEA) increase [91,92].

A recent paper by Parmar et al. [93] reported an increase in use of cross sectional imaging, such as CT and MRI and in particular PET or PET/CT in asymptomatic patients during the surveillance period. From this study appears that there was a significant increase in PET/PET-CT use from 2% to 9% in a 6-year period and a concomitant decrease in bone scan from 21% to 13% in the same period. The rise in PET use and attendant decrease in bone scan implicates a population receiving PET scan in lieu of bone scan for surveillance of asymptomatic metastatic disease. Compared to conventional imaging, FDG PET has been shown to be more sensitive and specific in detecting distant metastatic disease [94]. Most data are derived from the assessment of patients with suspected recurrent or metastatic disease comparing FDG PET with conventional imaging [95–99], although only one study has included asymptomatic patients as well [97]. On the other hand, asymptomatic tumor marker increase was correlated with an elevated sensitivity for the detection of metastases by PET or PET/CT also in comparison with conventional imaging modalities [100].

As recently reported by Groheux et al. [101], the aggressiveness of BC, based on histological features, is directly correlated with the glucose metabolism. Triple negative tumors and non-differentiated cancer (Grade 3) demonstrated a higher uptake of FDG at PET/CT than the other histological type and features.

Isasi et al. [102] performed a meta-analysis to assess FDG-PET for the evaluation of BC recurrences and metastases and reported these results: the sensitivity and specificity were approximately 92% (56–100%) and 82% (0–100%), respectively.

All studies comparing the diagnostic accuracy of PET with PET/CT, consistently showed that PET/CT have improved sensitivity compared with PET but not significant differences in specificity. In these studies, PET/CT was used for the diagnosis of local disease and metastases in different locations and the advantage of PET/CT over PET appears to be true when considered for the detection of disease over a range of locations.

Several studies investigated the diagnostic accuracy of CITs compared with PET or PET/CT on a patient basis [78,97,103–108]; in 2010 Pennant and Colleagues give pooled summary estimates related with the two diagnostic strategies: PET had significantly higher sensitivity [89%, 95% confidence interval (CI) 83%–93% vs 79%, 95% CI 72%–85%, relative sensitivity 1.12, 95% CI 1.04–1.21, $p = 0.005$] and significantly higher specificity (93%, 95% CI 83% to 97% vs 83%, 95% CI 67%–92%, relative specificity 1.12, 95% CI 1.01–1.24, $p = 0.036$) [75].

For bone involvement this gain in diagnostic accuracy obtained with PET is controversial and certainly less evident. In 2011, Houssami and Costelloe [86] reported a systematic review that updates the evidence on comparative test accuracy for imaging of bone involvement in women with BC; the median sensitivity (based on seven studies) for PET was 84% (range 77.7%–95.2%), and for bone scan, it was 80% (67.0%–93.3%). The median specificity (seven studies) for PET was 92% (88.2%–99.0%) and for bone scan 82.4% (9.1%–99.0%).

Overall, PET and PET/CT appear to give improved diagnostic accuracy compared with CIT and in the patient-based analysis, absolute estimates of sensitivity and specificity were around 10% higher for PET compared with CIT. Despite this, the impact of these results on patient management is uncertain. Individual studies emphasize that these technologies do lead to changes in management, but it is difficult to determine to what extent these changes would have taken place with CITs and, more significantly, whether they modified final patient outcome.

Furthermore there are two important limitations of PET and PET/CT: economic cost, and biological cost.

In Europe, a PET and a PET/CT scan range between approximately €600 ($885) and €1000 ($1474), and reimbursement for these examinations varies significantly depending on the respective health care systems [109].

With regards to biological costs, Huang et al. [110] calculated that the effective dose from FDG PET/CT scanning with a diagnostic CT protocol and an administered FDG activity of 370 MBq was up to 32.18 mSv, although the standard employed PET or PET/CT protocol registered an effective dose ranged between 6.24 and 9.38 (low dose CT scan and less FDG administered activity). Moreover, Chinese authors reported that the associated lifetime cancer incidence associated with this dose was estimated to be up to 0.5–14% only for the U.S. population [111].

4. Biomarkers for disease relapse

Since oligometastatic patients have the highest probability to be long-survivor after a multimodality treatment, the early recognition of minimal residual disease should be one of the major goals of BC survivors follow-up.

Depending on the BC subtype, the vast majority of disease recurrences occur within the first 3–5 years after primary treatment [30]. Nevertheless, more than one-half of all recurrences and deaths in women with HR-positive disease occur beyond 5 years from diagnosis [30]. Prognostic biomarkers may allow us to assess the natural history and prognosis of a tumor as well as its potential malignancy over the time. Considering that a good prognostic biomarker should have a high specificity for a given type of tumor and an

appropriate level of sensitivity [112], it is not easy to identify the perfect biomarker for BC relapse. However, a number of different prognostic biomarkers have been evaluated over the last years.

Mutations within the genes whose products participate in DNA repair, such as BRCA1, BRCA2, and P53, predispose the patients to an increased risk of developing BC [113,114]. In particular, it has been demonstrated that p53 accumulation is a strong predictor of both early and late recurrence in HR-positive BC patients treated with aromatase inhibitors as adjuvant endocrine therapy [113]. Therefore, patients with mutations identified within the mentioned genes might be considered for a personalized follow-up strategy.

Circulating tumor cells (CTCs) in peripheral blood of patients with early BC have been shown to be an independent prognostic factor for disease recurrence and death [115]. A recent study provided evidence of a strong correlation between detection of CTCs during the first five years of follow-up and increased risk of late disease relapse and death in patients early BC, regardless from HR status [116]. Moreover, the Authors suggested that the presence of CTCs may indicate chemo- and hormonotherapy-resistance in the microscopic residual disease after primary treatment. These findings may support the role of CTCs monitoring as an adjunct to standard follow-up strategy.

As already mentioned, five different BC subtypes could be detected by IHC and used as a driver for daily clinical practice. However, gene expression analyses may permit a more accurate stratification of patients with more aggressive forms of BC. For example, the MammaPrint Symphony is a 70-gene panel that allowed the stratification of patients into groups of high and low risk of relapse [117]. Similarly, the Oncotype DX is a 21-gene panel developed to assess the probability of relapse of BC within 10 years by the analysis of genes involved in proliferation and invasiveness [118]. Over the years, a number of new gene signatures have been developed and several comparisons between different panel and technique have been published [119–121]. Having a genetic fingerprint of the tumor could be an optimal solution to drive a more aggressive follow-up strategy, but the available data are still inhomogeneous and the best panel has not been identified yet.

MicroRNAs (miRNAs) are a class of small (18–22 nucleotides in length), non-coding RNAs that regulate gene expression on a post-transcriptional level [122]. The identification of a pattern of miRNAs deregulation in BC tissue compared with normal breast tissue was first reported in 2005 [123]. Since then, several studies have been focused on the expression of various miRNAs and their roles in BC development and behavior. The analysis of circulating miRNAs might provide additional individualized information on prognosis and metastatic potential of BC in each patient at the time of primary diagnosis. Several different panel of miRNAs have been evaluated and an association with both disease-free and overall survival has been reported in many cases [124,125], however no validate signature is available yet and the implementation of miRNAs in a follow-up strategy should be further investigated.

5. Rationale to design new studies

Surveillance of BC patients with annual mammography and clinical examination is the current standard of care. Over the last few decades, randomized clinical trials have failed to demonstrate a real benefit of an intensive follow-up strategy. In contrast with patients and physicians perceptions, literature data do not support the introduction of regular blood tests, tumor markers, CT scan, bone scan and other imaging in the surveillance setting. In addition, the abuse of these tools in clinical practice could increase anxiety related to false-positive results and unnecessary expenses.

However, there could be settings in which an instrumental, aggressive follow-up schedule could anticipate the diagnosis of relapse and improve treatment outcomes.

The first possible application of an intensive follow-up program is the MRI surveillance of locoregional recurrence of young and BRCA positive women. As already described, a combined local and systemic treatment can offer real advantages to patients with locoregional relapse. A second field of interest is the search of early systemic relapse in patients with HER2 positive tumors. The recent improvement in screening techniques, combined with the availability of active targeted therapy, may lead to an effective “rescue” treatment in patients with early detection of tumor relapse. Moreover, the increased knowledge in breast cancer biology suggests the need of a subtype-tailored surveillance strategy, focused on the different patterns of relapse intrinsic in every breast cancer molecular subtype. HER2 positive breast cancers seem particularly suitable for an intensive surveillance of distant recurrence: treatment anticipation has shown to confer a significant survival advantage. For testing these hypotheses a new prospective clinical trial should be designed in which conventional surveillance strategy is compared with a CT-PET-based strategy. A further scientific need is the search for diagnostic tools able to anticipate the radiological evidence of recurrence: serum markers and circulating tumor cells are promising and deserve strong investment.

While diagnostic tests in the asymptomatic patients do not confer any benefit, a rapid instrumental assessment must be activated in case of clinical suspect of relapse. Unfortunately these clinical signs are not often straightforward and their presence is usually underestimated both by the patients and by the physicians. Bone pain, nodal lumps, fatigue, unintentional weight loss, bowel dysfunction and dyspnea are example of signs or symptoms whose occurrence should be carefully evaluated in the clinical context and prompt an immediate search of disease recurrence. This process is usually ill-defined and influenced by the subjective skills and expertise of the physician, by the strength of the doctor–patient relationship and by the level of reciprocal trust. The comparative effectiveness of a high-quality,

standardized, symptom-driven diagnostic assessment with the screening of asymptomatic women is another unanswered question.

6. Conclusions

Outside from the experimental setting there is currently no reason to perform any examination in asymptomatic patients other than annual mammography: no single imaging modality has the required characteristics of sensitivity, specificity and cost-effectiveness ratio to be considered suitable for BC follow-up. Intensive surveillance is associated with false-positive findings, induction of anxiety, risk of exposure to radiation, and unjustified costs. Information of patients and education of physicians should be pursued. However, the biological knowledge and the management improvement should be considered the basis for a renewed interest of research in the field of follow-up. Are probably definitively gone the times of a "one size fits all" strategy: BC is a heterogeneous disease and different approaches should be adapted to the different disease subtypes. The combination of the best current diagnostic tools with the best therapies may demonstrate that the anticipation of relapse detection and treatment is worth of value in specific settings. This research is eagerly awaited.

Conflict of interest

The authors declare no conflict of interest.

Authors' contributions

All authors drafted, read and approved the final version of the manuscript.

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