



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

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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.

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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

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