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Failure event types and prognostic factors after node-positive breast cancer in patients treated by adjuvant chemotherapy: impact on follow-up

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Abstract. Purpose. The role of post-therapeutic follow-up for breast cancer patients (pts) is open to debate. The aim of this study was to identify prognostic factors associated with the type of first event. **Methods.** Data of 2,820 pts included in three adjuvant trials for node-positive breast cancer were used. Competing risk methodology was used to identify prognostic factors associated with time to first failure according to type of event. **Results.** After a median follow-up of 53 months, 732 pts had disease-related events (114 locoregional, 58 contralateral, and 560 distant metastasis). The prognostic factors associated with high locoregional recurrence were young age, number of positive lymph nodes and grade III. In multivariate analysis, the type of first event influenced post-relapse survival. Nottingham Prognostic Index identified three groups of pts at different risk of relapse. **Conclusion.** Early relapse is rare in the first year after surgery and is associated with more aggressive disease. Using the Nottingham Prognostic Index, it is possible to identify pts at lower risks of relapse for whom it seems reasonable to limit the frequency of routine follow-up during the first years. For pts at higher risk of locoregional recurrence, regular follow-up should be maintained in order to detect potential curative events. ▲

Key words: breast cancer, survival analysis, follow-up, competing risks, overall survival post-relapse

Introduction

Breast cancer, with an estimated 1.15 million new cases each year in the world, is the most common cancer in women and it has become a major public health problem. Due to this high incidence and relatively good prognosis related to programs of mass screening and improvements in adjuvant treatments, it is the most prevalent cancer in the world. Consequently, the number of patients attending follow-up visits after curative intent is on the rise.

The main objective of post-therapeutic follow-up is to detect local recurrence or second primary cancer at an early stage [1]. Other objectives are the diagnostic of symptomatic distant metastasis, detecting delayed side effects of treatment, as well as the provision for psychological security and the collection of data for research and quality assurance purposes [2, 3]. Intensive surveillance was a common practice in the 1970s and 1980s, but two large randomized trials have demonstrated that early detection of metastatic disease offers no benefit in terms of long-term survival in comparison to disease, which is discovered by patient symptoms or physical examination [4, 5]. It was important to remark that these two trials were conducted before the recent advances in the treatment of metastatic disease [6, 7]. Based on the results of these two trials, a majority of surveillance programs proposes more frequent examinations during the first three or five first years and annually thereafter. For example, the American Society of Clinical Oncology and the European Society of Medical Oncology

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suggest physical examination three- to six-monthly for three years, then six- to 12-monthly for two years followed by an indefinite period of annual follow-up with recommended annual mammography [8, 9].

Actually, there is no available evidence that early detection and treatment of recurrence has a favorable impact on prognosis. Different studies have investigated the role of routine follow-up to detect locoregional recurrence and the impact on prognosis [3, 10-14]. Only one recent meta-analysis of 13 retrospective studies supports the hypothesis that the detection of isolated locoregional or contralateral breast cancer recurrences in patients without symptoms has a beneficial impact on survival of breast cancer patients when compared to late symptomatic detection [15]. A systematic review was performed whether routine clinical assessment including clinical examination, surveillance mammograms or breast self-examination affects the method of detection of locoregional relapse or contralateral new primaries [16] and does strengthen the argument for the benefit of routine surveillance mammograms. Consequently, in absence of prospective studies, surveillance programs recommend to detect locoregional recurrence.

Concerning distant recurrence, in the absence of data showing improved survival or quality of life with an early detection, recommendations from national oncology societies remain conservative, calling for routine clinic visits but not for any radiologic and/or biological tests for detection of metastases in asymptomatic patients [17].

On the other hand, it has been demonstrated that scheduled clinic visits induce anxiety associated with the risk of detecting tumor relapse [18]. With the cost of complementary investigation and the limited resources of health care systems, the cost-effectiveness of frequent follow-up in terms of survival benefit and quality of life are highly questionable.

Actual post-treatment follow-up does not take into account any prognostics factors. However breast cancer is a heterogeneous disease, whose prognosis and clinical course may be dependent on clinical factors and molecular subtype [19, 20]. Not all patients have the same risk of developing locoregional recurrences, distant metastasis or contralateral breast cancer. Age is one of the most established risk factors for local recurrence after breast conservation [21]. Nodal status does not appear to be associated with an increased risk of local recurrence after either breast conservative surgery or mastectomy, but results from different series are contradictory [21, 22]. Patients who underwent breast conservative surgery in comparison with patients treated by mastectomy and patients with a higher tumor stage were at an increased risk of locoregional recurrence. Concerning distant metastases, the two majors prognostic factors identified in the literature were histologic tumor size and lymph node involvement. Hormonal receptors have been widely analyzed as prognostic factors; their significance has been variable according to different series. More recently, two studies demonstrated important differences in metastatic and locoregional recurrence risk, between breast cancer subtypes as defined by a panel of six-marker immunohistochemical, suggesting different program surveillance according to tumor biology [23]. The main aim of this paper is to identify prognostic factors associated with different types of first events and overall survival post-relapse.

Patients and methods

Study population

Three adjuvant chemotherapy clinical trials sponsored by the Fédération nationale des centres de lutte contre le cancer (FNCLCC) for node-positive breast cancer patients were included in this project: PEGASE-01, PACS-01, and only the over-expressed HER2 subgroup of patients in the PACS-04 trial (i.e., arms C and D). Major inclusion criteria of these three trials were presented in *table 1*. Among the 2,841 patients included in these trials, 21 patients were not analyzed for the following reasons: relapse before end of chemotherapy or radiotherapy, and lost to follow-up after completion of treatment. The remaining 2,820 patients are the subjects of this report. A summary of the three trials is presented below.

The PEGASE-01 protocol was designed to assess the value of one terminal high-dose regimen following conventional chemotherapy in a high risk (>8 involved nodes) population [24]. The standard arm (arm A) used four cycles of FEC100 (500 mg/m^2 of fluorouracil, 100 mg/m^2 of epirubicin [E], and 500 mg/m^2 of cyclophosphamide every three weeks) ($n = 155$). The experimental arm (arm B, $n = 159$) received after four cycles of the same regimen, one cycle of CMA (120 mg/kg of cyclophosphamide, 45 mg/m^2 of mitoxantrone, and 140 mg/m^2 of melphalan). At three years, disease-free survival was significantly better in Arm B (71% *versus* 55%, $P = 0.002$), as was event-free survival (EFS) (68% *versus* 53%, $P = 0.006$). No statistical difference was shown between arms for overall survival at that time.

In the PACS-01 trial, 1,999 patients were randomized to receive six cycles of FEC100 (996 patients) or a sequential regimen of three cycles of FEC100 followed by three cycles of docetaxel (D) (FEC-D) (1,003 patients) [25]. With a median follow-up of 60 months, the results showed that sequential adjuvant chemotherapy significantly improves disease-free and overall survival.

The PACS-04 trial was designed to compare six cycles of concomitant D and E *versus* six FEC100 in the adjuvant