

Prognostic factors for relapse in young breast cancer patients

Oana SAPTEFRATI¹, Xenia BACINSCHI², Dumitru Cristinel BADIU³, Gabriel Cristian POPESCU³, Anca ZGURA², Laurentia GALES², Dragos SERBAN⁴, Rodica ANGHEL²

¹ “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

² Department of Oncology - Radiotherapy, “Prof. Dr. Alexandru Trestioreanu” Institute of Oncology, “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

³ General Surgery Department, “Bagdasar Arseni” Clinical Emergency Hospital, “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

⁴ Department of General Surgery, Emergency University Bucharest Romania

ABSTRACT

Objective. Breast cancer is the leading cause of cancer mortality in women. Most deaths from breast cancer are due to recurrences or metastatic disease. The purpose of this study is to determine the impact of age in treatment strategy correlated with clinicopathological features. **Methodology:** In this retrospective study, 60 female patients with histologically-confirmed primary breast cancer were included. The women were treated in the Oncofort Hospital Bucharest, Romania between 2018 and 2020. The estrogen receptor (ER), progesterone receptor (PR) and HER2 status were determined using immunohistochemistry.

Results. The mean age was 34.14 years (range = 24 – 40 years). Invasive ductal carcinoma of no specific type was seen in 84.1% of patients. The rates of grade I, II and III carcinomas were 6.7%, 28.3% and 65%, respectively. Among all patients, 33.3% had estrogen receptor, progesterone receptor positive tumors and 66.66% had estrogen receptor, progesterone receptor negative tumors. The proportion of patients over-expressing oncoprotein HER2 was 13.3%.

Conclusion. Prognostic value of proliferation index (Ki-67) and hormonal receptors, may vary depending on age.

Keywords: breast cancer, young woman, hormonal receptors, clinicopathological features, relapse

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer in women. In the European Union, the gross incidence of breast cancer is 109.9 cases/100,000 women/year, and mortality is 38.4 deaths/100,000 women/year, with important geographical variations. In Europe, the incidence of breast cancer is the highest since 2012, with a rate of 13.45%. The leading causes of cancer deaths are breast, lung, and colorectal cancer in fe-

males [1]. Seemingly, 15 years ago, breast cancer mortality was declining in most western countries, as a consequence of education, intensive screening programs, and more effective therapy. However, in most recent years, the incidence of breast cancer continues to increase incrementally each year, and mortality has not changed significantly in the last 20 years, remaining extremely high [2]. Breast cancer mortality is often associated with relapse and/or changes in breast cancer

Corresponding authors:

Anca Zgura

E-mail: medicanca@gmail.com

Article History:

Received: 20 June 2022

Accepted: 28 June 2022

disease that cannot be completely eradicated by treatments. Relapse rates are higher in the case of more aggressive subtypes and cancers with poor prognostic factors, such as breast cancer in young women with anatomopathological characteristics of aggression, increased proliferation rate, triple-negative subtype, HER overexpression, and lack of hormone receptors [3-6]. In young women, in addition to the usual adverse reactions related to chemotherapy (alopecia, hematologic toxicities *etc.*), age-specific side effects can also be observed; this is particularly the case for chemotherapy-induced menopause (MCI), which has a significant impact on quality of life [7]. Triple negative breast cancer (TNBC), diagnosed more and more frequently in young patients, is known for its aggressiveness and lack of targeted therapies. Indeed, relapse and metastasis are more common in this tumor subtype and its heterogeneity represents a real challenge in oncology. In fact, our team has highlighted this heterogeneity of TNBCs and has performed studies to identify prognostic and treatment response biomarkers [8]. The aim of this study is to determine the impact of age in treatment strategy correlated with clinicopathological features.

METHODOLOGY

In this retrospective study, 60 female patients with primary breast cancer who were followed-up for long time were included. All patients were diagnosed with stage I to III cancer. Following consent to participate in the study, patients were divided in subgroups according to the stage of the disease. The estrogen receptor (ER), progesterone receptor (PR), and HER2 status was determined using immunohistochemistry. The women were treated in the Oncofort Hospital Bucharest, Romania between 2018 and 2020.

STATISTICAL ANALYSES

Statistical analyses were performed using the IBM SPSS version

Association between two qualitative variables was determined using the Chi² test, and in the presence of small numbers, the Fisher's exact test was used.). The value $P < 0.05$ was considered significant.

RESULTS

Characteristics of patients

The mean age was 34 years (extremes: 24-40 years). Invasive ductal carcinoma of no specific type was found in 84.1% of cases. The rates of grade I, II and III carcinomas were 6.7%, 28,3% and 65%, respectively.

Of the 60 women, 33.3% had ER and PR positive tumors; and 66.66% had ER and PR negative tumors. The proportion of patients over-expressing HER2 was 13.3%. Mean value of Ki-67 was 36.68% (range 1 - 80%).

Relationship between HER2 status and clinicopathological factors

In breast cancer diagnosed in young patients, it is very important to determine the characteristics of the tumor and correlate them with age, in order to establish the best treatment and determine the prognosis.

From the analysis of patients' age in relation to HER 2 oncogenic status no statistical correlation was observed ($p=0.568$), histologic grade ($p=0.666$), and ER status ($p=0.137$) (Figure 1).

The higher proliferative index has a direct significant correlation HER2-positive

The higher Ki-67 and age didn't show significant association in HER2-negative ($p > 0.05$) or TNBC ($p > 0.05$) patients (Figure 2).

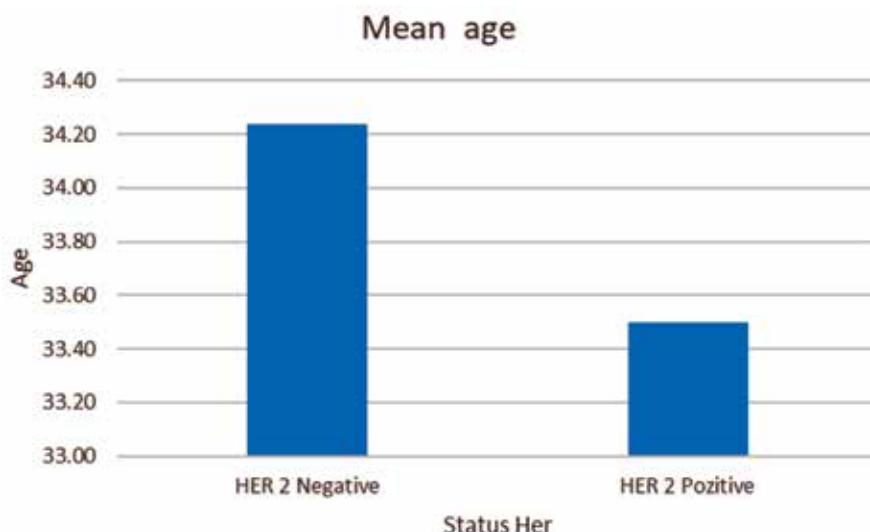


FIGURE 1. Association between age and HER 2 status

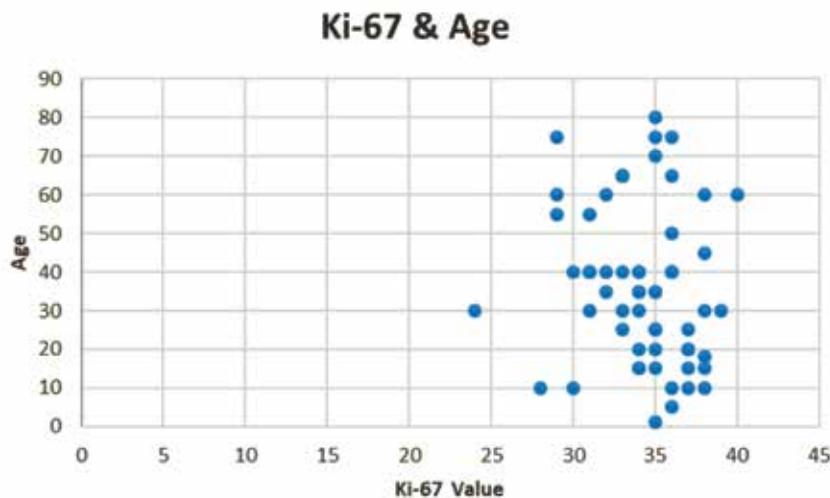


FIGURE 2. Association between age, Ki67 in HER 2 negative patients

Ki-67 expression level and age didn't show significant association in HER2-positive ($p > 0.05$) or TNBC ($p > 0.05$) patients (Figure 3).

In the case of patients diagnosed with TNBC, a higher value of the proliferative index was observed compared to the rest of the patients. HER-2 positive patients had a lower mean age than HER-2 negative patients

The majority of HER 2 positive patients corresponded to high grade tumors (86.2%)

DISCUSSION

Breast cancer is a great public health problem; the number of new cases is constantly increasing in Romania. Clinical outcomes of breast cancer in young woman are different and for this reason the aim of this study is to determine the impact of age in treatment strategy. It is a cancer that is often linked to unfavourable prognostic factors, and several investigators consider age alone as an independent prognostic factor. Thus, young age is

often associated with specific anatomical-clinical parameters and poor prognosis, including delay in diagnosis, increased frequency of advanced forms with increased tumor size, more frequent histological lymph node involvement, higher histological grade, more frequent local and distant recurrences, and lower overall survival.

The vast majority of young patients opt for conservative treatment. This conservative treatment carries an increased risk of local recurrence, especially in young women [9,10]. This risk gradually increases with younger age [11]. Nevertheless, many investigators [12,13] have confirmed that conservative treatment is a therapy perfectly suited to young patients, who meet certain indications. Furthermore, a family history of breast cancer in a young patient is not a contraindication for conservative treatment [12].

Following the analysis, we observed that the risk to determine the impact of age in treatment strategy correlated with clinicopathological features of relapse or progression may be predicted. This conclusion is also

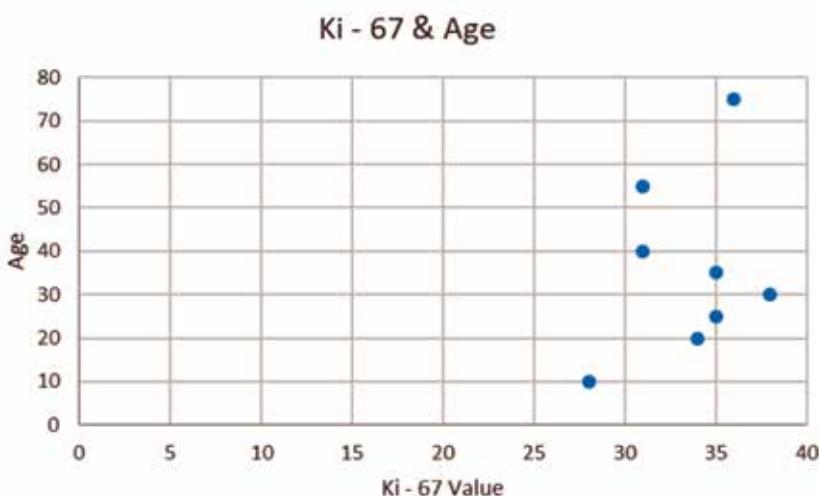


FIGURE 3. Association between age, Ki67 in HER 2 positive patients

supported by data from the literature [13-15]. Therefore, our study concluded that this observation is also valid for non-metastatic patients with triple-negative breast cancer with a risk of death within 10 years, twice as high in relapsed patients compared to patients in remission or not in relapse [16].

For non-metastatic patients (stages I-III), the relapse rate of 31.7% at a median follow-up of 61 months is comparable to the literature data, which list recurrence rates ranging from 10.5% to 39.7% [16] [17-18]. Similar rates were found in numerous studies, 10.5% at a median follow-up of 79 months; 26.6% at a median follow-up of 68 months, 29.5% at a median follow-up of 27 months, 27% at a median follow-up of 67 months, 39.7% at a median follow-up of 83 months [19].

For non-metastatic patients (stages I-III), the relapse rate of 31.7% at a median follow-up of 61 months is comparable to the literature data [20]. Therefore, to improve prognosis, it is necessary to adopt multidisciplinary care, diagnose the disease at an earlier stage, encourage genetic counselling in women at risk, and implement treatments adapted to prognostic factors in young women.

A study reported that the patients treated with neoadjuvant chemotherapy, the prognostic parameters of relapse in univariate analysis are the size of residual tumor, lymph node invasion, Scarff-Bloom-Richardson (SBR) grade, which is an important prognostic factor in breast cancer and the response to chemotherapy. In multivariate analysis, the parameters which remained independent prognostic factors were the number of tumor-containing lymph nodes, and residual tumor size, as it has also been demonstrated in an analysis of more than 10,000 patients in the SEER 18 database [21].

If lymph node invasion and residual tumor size are analyzed independently, our study reaches the same conclusions as those in published literature: a high number of invaded lymph nodes is synonymous with poor prognosis [21-23]. Concomitantly, it has been observed that the relapse rates are much higher in cases where the residual tumour size is high, more specifically over 2 cm [23]. Despite the good chemosensitivity of TNBC, there are tumors that do not appear to respond to chemotherapy and these are the ones where the risk of relapse is higher. The ancillary study of the Phase III EORTC trial10994/BIG 1-00 (Clinicaltrials.gov NCT00017095) demonstrated that, in patients presenting a complete response, only tumor size was predictive of relapse regardless of the tumor subtype. In our case, it appears that tumor size (>2 cm) is important

and especially residual tumors >2 cm were those who exhibited primary resistance to treatment; they can therefore be described as chemo-resistant [24].

Several studies have looked at the prognostic and predictive role of T lymphocytes infiltrating tumor stroma (TILs). They have been shown to be predictors of relapse-free survival and overall survival after adjuvant chemotherapy in triple negative breast cancer (TNBC) [25].

Cancer patients when diagnosed at a young age are in high risk for developing psychiatric disorders such as depression and anxiety [26].

In the treatment of young woman diagnosed with breast cancer and overexpressing hormonal receptor the LH-RH analog play an important role. Oestrogen is produced by the ovaries in response to LH stimulation, itself produced by the pituitary gland in response to LH-RH stimulation by the hypothalamus. Thus, the purpose of LH-RH analogues to attach to LH-RH receptors and cause hyperstimulation.

The pituitary gland will then initially increase its LH secretion, resulting in increased secretion of oestrogen (and progesterone). As a response, the pituitary gland will be hyperstimulated, leading to a decrease or even complete inhibition of oestrogen secretion by the ovaries. It is, therefore, a matter of inducing inhibition of ovarian function, in order to stop the stimulation of tumor growth by oestrogens. The most commonly used molecules are goserelin and leuprorelin, and because of their mechanism of action, they are exclusively indicated for pre-menopausal patients. They will induce reversible amenorrhea if patients are not perimenopausal, hence the preferred indication is for patients under 35 years of age [27].

CONCLUSION

Prognostic value of Ki-67 and hormonal receptors, may vary depending on age and is an important factor for prognosis and treatment decisions in young patients with breast cancer.

Notably, the incidence of breast cancer in women below 40 years of age has increased recently due to screening policies and efficient diagnostic methods.

Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

Financial Disclosure / Grant Approval: There was no funding agency

Conflict of interest: none declared

Financial support: none declared

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