

Breast Cancer in Young Women



BBSG – Brazilian Breast Study Group and Márcia Cristina Santos Pedrosa

Introduction

Although there is no consensus in the literature, breast cancer in young women usually is defined when it occurs before 40 years old.

This is a rare event in such an age group, representing about 10% of cases of breast cancer diagnosed between the ages of 35 and 44, 2.0% between 20 and 34 year-olds, and only 0.1% of cases below 20 years of age.

In developing countries, there is a higher prevalence of cases in younger women when compared to developed countries. As these patients are outside the screening group and also because they present biologically more aggressive tumors (34% triple-negative and 22% Her2+, Azim and Pattridge [1]), they generally present a more advanced clinical stage when compared to the group of patients above 40 years old.

Figure 1 shows the staging of 9278 women with breast cancer under the age of 39, collected by FOSP (*Fundação Oncocentro São Paulo*) and INCA from 2000 to 2009. It is noted that most of the diagnosed cases were between the IIA and IIIB stages, with more than 60% in stage IIB or higher.

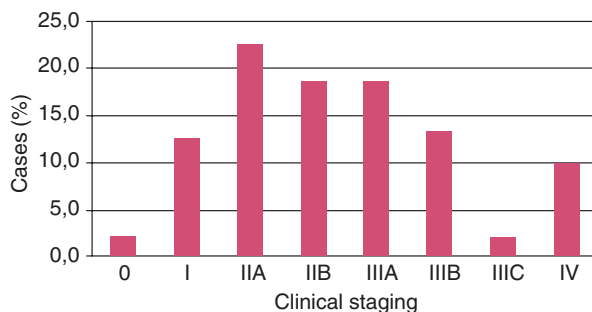
Characteristics of Breast Cancer in Young Women

There are several peculiarities in this age group that differ from the others and that impact on the therapeutic approach:

BBSG – Brazilian Breast Study Group (✉)
BBSG, Sao Paulo, SP, Brazil

M. C. S. Pedrosa
Breast Surgery, IMIP Hospital, Recife, PE, Brazil

Fig. 1 Clinical staging in women below 40 years old. (Source: Pinheiro, Lauter, Medeiros et al. RBC 2013)



- More aggressive disease, with higher frequency of high-grade tumors, negative hormonal receptors and lymphovascular invasion (LVI), and lower rates of carcinoma in situ;
- Many studies relate earlier age with worse prognosis – which may be due to the factors mentioned above associated with the greater clinical staging at diagnosis;
- Higher deleterious mutations prevalence, mainly BRCA 1 and 2;
- Higher multicentricity and multifocality rates;
- Predominance of dense breasts and consequently greater use of MRI in the initial evaluation, which is associated with higher rates of mastectomies;
- Higher rates of risk reducing contralateral mastectomies;
- Desire of fertility preservation;
- Higher impact of hormone therapy on quality of life when compared to older women.

Clinical Condition and Propedeutics

The diagnosis often is made by a patient's palpable nodule or other clinical changes, since this group is outside the routine of the screening.

Multicentricity, multifocality, and dense breasts are common characteristics among women under 40 years old, and the use of magnetic resonance imaging becomes more frequent. This leads a change in the therapeutic planning up to 30% of cases and with a surgical conversion rate conservative treatment for mastectomy between 15% and 35%. However, some studies show that in up to 1/4 of the cases, mastectomy was considered unnecessary after definitive anatomopathological results. Up until now, no data have been found associating routine magnetic resonance imaging in this age group, with an increase in disease-free survival or overall survival.

Percutaneous biopsy is the best choice for histological diagnosis, and the immunohistochemical study is mandatory in this age group, where there is a greater predominance of triple-negative tumors and Her2+. This may be a decisive factor in the choice of initial therapy.

Although there are no differences in the recommendation for initial staging according to age, there are studies that show a higher prevalence of synchronic metastasis in cases of triple-negative tumors, despite the initial clinical stage, suggesting that in these cases imaging should be instituted, even when there is no symptomatology.

Treatment

Historically, it is known that rates of local recurrence after conservative treatment (CT) are higher in younger women. However, when evaluating overall survival rates, there are no differences between CT and mastectomy. On the other hand, in randomized clinical studies on CT versus mastectomies, subgroup analyzes in women younger than 40 years were generally hampered by small sampling.

In a large Danish premenopausal and breast cancer women series, Kroman et al. showed local recurrence rates after CT of 15% in women under 35 years and only 3% in those between 40 and 49 years. From the evaluation of the risk of metastasis and death versus type of treatment (CT or mastectomy) there were no significant differences between the groups studied (<35 years, 35–39 years, 40–44 years and 45–49 years).

In a retrospective analysis of Data collected from the Surveillance epidemiology and Results (SEER), showed in population of 14.764 women, aged between 20 and 39 years old with breast cancer, that conservative surgery was performed in 45 %, while mastectomy in 55% of cases. No significant differences were observed in relation to overall survival (OS) and specific mortality when compared both types of treatment. About one -third of patients had negative hormone receptor (HR) tumors. In the multivariate analysis, factors associated with poor prognosis were: Age at diagnosis, race, histologic grade, lymph node status, and progesterone receptor.

Few studies have evaluated molecular subtype and type of surgery in young women. In a series with 1930 women with triple-negative breast cancer, 289 (15%) are less than 40 years old, Rodosa et al. showed that the younger group presented more advanced stage in the initial diagnosis and higher rates of mastectomy, axillary lymph node dissection and chemotherapy.

However, no significant differences were observed regarding disease-free survival at 5 years and local recurrence during the mean follow-up right over 6 years. Age and type of surgery were not associated with a higher risk of metastases. Therefore, despite higher rates of local recurrences, CT is considered equivalent to mastectomy in young women.

Contralateral mastectomy indication is more frequently among young women with breast cancer, mainly because of a higher percentage of them can be allocated in the high family / genetic risk group. There are several recommendations for indication of genetic testing in this population, especially when the cancer presents basal-like phenotype. It is estimated that up to 30% of women with breast cancer before the age of 35 may be carriers of known deleterious mutations.

Some retrospective studies have shown benefit from the risk-reducing contralateral mastectomy in young women, but age alone should not be a determining factor for this surgery. Other factors should be taken into account, such as BRCA mutation and high family risk. There are no prospective studies evaluating the impact of contralateral mastectomy on disease-free survival and overall survival, and the strongest evidence to date is restricted to BRCA mutation group.

Systemic Treatment and Radiotherapy

Systemic treatment should not be different from the group of women over 40 years. The drug choice of chemotherapy and target therapy is based on staging and immunohistochemical profile. Differently, hormone therapy may be influenced by the age range among younger women. Data from the TEXT and SOFT studies showed that the benefit of ovarian suppression associated with the aromatase inhibitor was markedly higher in women younger than 35 years and at high risk for recurrence (GH3, N +, mainly 4 or more lymph nodes, T > 2 cm), reaching a 15% survival gain when compared to the group that only underwent tamoxifen hormone therapy.

Radiotherapy in the young patients follows the same principles and indications of that in patients over 40 years, whether for conservative surgery or mastectomy. However, age may be considered a risk factor for recurrence when associated with lymphovascular or positive axilla invasion after mastectomy, and it's an indication criterion.

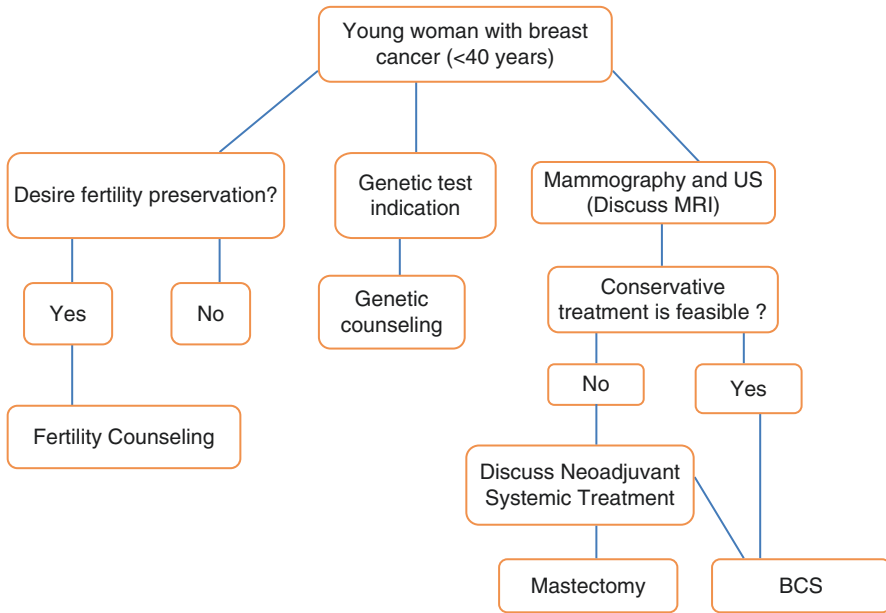
Boost should always be performed in patients under 40 years of age, as demonstrated in the EORTC randomized clinical trial published in 2007 by Bartelink H et al. The group that received the boost had a 50% reduction in local recurrence in 10 years.

Breast partial radiotherapy is contraindicated for this group of patients. Criteria of ASTRO and ESTRO place these patients in the high-risk group for local recurrence with this method of treatment, so it should be avoided.

Preservation of Fertility

About 15% of breast cancers occur in women in the reproductive range, and chemotherapy has a cytotoxic effect on ovaries, which can irreversibly impair fertility. Currently the strategies for preservation of fertility include the use of GnRh analog during chemotherapy (POEMS study), with cryopreservation of ovarian tissue and ova being valid options. The best option would be the preservation of embryos, as long as the patient has a partner who agrees with the fertilization.

Flowchart



Flowchart 1 Management of Breast Cancer in young women

Recommended Reading

1. Azim HA Jr, Partridge AH. Biology of breast cancer in young women. *Breast Cancer Res.* 2014;16:427–36. *Review on the biological characteristics of breast cancer in young women and the impact on the treatment and outcome of the disease.*
2. Boughey J, Attai DJ, Chen SL, et al. Contralateral Prophylactic Mastectomy (CPM) Consensus statement from the American Society of Breast Surgeons: data on CPM outcomes and risks. *Ann Surg Oncol.* 2016;23(10):3100–5. *Publication of a review compiling the results of the main studies on risk-reducing contralateral mastectomy.*
3. Hwang ES, Lichtensztajn DY, Gomez SL. Survival after lumpectomy and mastectomy for early stage invasive breast cancer. *Cancer.* 2013;119:1402–11. *Analysis of the California-US database between 1999 and 2014 showing that conservative treatment was associated with better disease-free survival rate, regardless of age and hormonal status.*
4. Mahmood U, Morris C, Neuner G, et al. Similar survival with breast conservation therapy or mastectomy in the management of young women with early-stage breast cancer. *Int Radiat Oncol Biol Phys.* 2012;83(5):1387–93. *SSER analysis shows no benefit from mastectomy in young women below 39 years of age and with initial breast cancer*
5. Rodosa JC, Eaton A, Stempel M, et al. Evaluation of local and distant recurrence patterns in patients with triple-negative breast cancer according to age. *Ann Surg Oncol.* 2017;24(3):698–704. *A study that evaluated the impact of age on outcome (free survival and disease and metastasis) of patients with triple-negative tumors. Age and type of surgery were not associated with risk of metastasis, but with classic factors such as lymph node staging and lymphovascular invasion.*