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Original article

Breast cancer in octogenarian. Are we doing our best? A population-registry based study

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ABSTRACT

Background: The number of old people with breast cancer is estimated to increase during the next years in developed countries. However, management of breast cancer in octogenarians is not well established. The main objective was to evaluate if patients older than 80 years with breast cancer are receiving the most convenient treatment by using a population registry cancer analysis.

Patients and methods: A retrospective analysis of a population cancer registry was designed. Data were retrieved from the Castellon Cancer Registry (Valencian Community, Spain). Patient records were analyzed from January 1, 1995 to December 31, 2013. Two groups were defined: group A, <80 years; and group B, >= 80 years. Survival analyses were sequentially performed into three phases. First, a non-adjusted Kaplan Meier analysis was conducted. For the second survival analyses, Cox's proportional hazards model of Overall survival was used adjusting for condensed-TNM stage and adjuvant treatments. Finally, the third specific adjustment was carried out adding information of life expectancy by age for Spanish women, corresponding to year 2008 with condensed-TNM stage and Propensity Score variable, as an approximation to relative or disease-specific survival.

Results: The total number of included patients was 1304. Women ≥80 years presented a more extended disease, larger tumors and less in situ carcinomas. A lower proportion of women ≥80 years received adjuvant therapies. In the absence of any adjustment of results, the overall survival in women ≥80 years was poorer than in younger patients (median of 14.1 years for <80y vs. 5.7 years for ≥80y), the crude HR was 4.6 (95% CI: 2.9–7.5) $p < 0.001$. For second survival analysis, the HR was 2.5 (95% CI: 1.8–3.5) $p < 0.001$. After the third adjustment the HR was 1.7 (95% CI: 1.2–2.4) $p = 0.004$.

Conclusions: Octogenarians with operable breast cancer are receiving suboptimal treatments, which can have repercussions on survival. New studies are required to identify a subgroup of women age ≥80 years who may benefit from more aggressive treatment and a population of older women on the basis of tumor characteristics, comorbidities and life expectancy who may not need as aggressive treatment.

1. Introduction

Life expectancy has strikingly increased in the developed countries in recent years. In Spain (Europe), between 1994 and 2016, live expectancy has increased from 74.4 to 80.4 years in men and from 81.6 to 85.9 years in women [1]. With the aging of population and having into account that age is one of the biggest risk factors for the development of breast cancer, the number of old people with breast cancer is estimated to increase during the next years.

Moreover, older patients (usually > 65 years, and even more > 80 years) are usually excluded of clinical trials and, consequently, the clinical trial population is quite different from the population that physicians manage in everyday practice. Although several studies have been conducted to analyze results in old women with breast cancer, the age cut-off has been usually 65 years. Probably, biological differences exist between 65 and 80-years-old women. Furthermore, 65-year-old women are often included in many screening programs (in our province screening program ranges from 45 to 69 years), whereas 80-year-old women are not. Therefore, conclusions of these analyses could not be

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applicable to octogenarians.

Women older than 80 years with breast cancer represent a special group of patients since they are not included in trials and usually have much comorbidity that can modify adjuvant therapies. Age 80 years and older is associated with an increasing risk of chemotherapy-related toxicity. Complications of surgery and chemotherapy may shorten survival and impair quality of life. Modified management strategies are often used for older individuals; however, the evidence for such approaches is poor and resulting undertreatment is well documented. In 2012, the International Society of Geriatric Oncology (SIOG) and the European Society of Breast Cancer Specialists (EUSOMA) published recommendations for management of elderly patients with breast cancer, although these recommendations were not specifically reported for a specific range of age [2].

The main objective of the herein presented study was to evaluate if patients older than 80 years with breast cancer are receiving the most convenient treatment by using a population registry cancer analysis.

2. Patients and methods

A retrospective analysis of a population cancer registry was designed. Data were retrieved from the Castellon Cancer Registry (Valencian Community, Spain). This cancer registry includes data from 4 public and 1 private centers in the Spanish province of Castellon. Only data from Castellon University General Hospital were available to conduct this study.

There were a total of 1304 female patients who fulfilled the inclusion criteria in the database from January 1, 1995 to December 31, 2013. The follow-up period of the present study ended in December 31, 2016. Eligible cases included all invasive female breast cancers, with stage I–III (non-metastatic), who had definitive surgery. Patients with non-curative surgery or non-operative management were excluded. Male patients were also excluded. Data about year of diagnosis, age at the moment of diagnosis, histologic type, tumor grade, multifocality, condensed-TNM classification, surgical treatment, nodal status, estrogen, and progesterone receptor status, Her2/neu expression, chemotherapy, radiotherapy, and hormonotherapy data were obtained from database. Information about HER2/neu expression was only available since year 2000, because it was not done during previous years. HER2/neu was considered as positive for 3+ tumors and FISH was performed on tumors scored 2+. Tumor grade was evaluated according to Elston and Ellis (24). For HER2 assessment, tumors were scored according to the intensity and completeness of cell membrane staining, in a 4-tier scale (0: no immunoreactivity, 1+: weak and incomplete membrane staining, 2+: weak / moderate and complete membrane staining and 3+: strong and complete membrane staining). Tumors scored 3+ were considered as overexpressing HER2. The threshold for estrogen and progestagen receptors positivity was 1%.

We chose the cutoff at 80 years to define two groups of patients: group A, <80 years; and group B, >= 80 years. Descriptive statistics were calculated and compared by group (<80 years and ≥80 years). Mean ± Standard deviation or Median with 25th and 75th percentiles (IQR) for continuous data, and frequencies and percentages for categorical data were calculated. The Mann-Whitney-U test was used to compare <80 years and ≥80 years subjects continuous variables. The Chi-square test or Fihser's exact text as deemed appropriate was used to compare two groups for categorical variables.

Survival analyses were sequentially performed into three phases. First, a non-adjusted Kaplan Meier analysis was conducted: Overall survival was analyzed by applying standard methods of survival analysis, i.e. computing the Kaplan-Meier product limit curves, where the data was stratified by group. Groups were compared using the Log-Rank test. The median rates for each group were obtained from the Kaplan-Meier/Product-limit Estimates and their corresponding 95% confidence intervals were computed using Greenwood's to calculate the Standard error.

For the second survival analyses, Cox's proportional hazards model of Overall survival was used adjusting for condensed-TNM stage and adjuvant treatments. Adjuvant chemotherapy, radiotherapy, and hormonotherapy were poorly balanced in the samples of both groups (Table 1), and so, they were grouped into a single Propensity Score variable (quasi-randomization) by logistic regression for two groups of age.

Finally, the third specific adjustment was carried out adding information of life expectancy by age for Spanish women, corresponding to year 2008 [1] with condensed-TNM stage and Propensity Score (PS) variable, as an approximation to relative or disease-specific survival. Propensitty score is a value of between 0 and 1 indicating the probability that a given patient (with certain biological characteristics) will be allotted to one study branch or another in the absence of randomization. With certain limitations, when results are adjusted using this probability, it can be assumed that the characteristics of patients capable of influencing study results will be distributed in a "quasi-randomized" manner.

A result was considered statistically significant at the $p < 0.05$ level of significance. All Statistical analyses were performed using MedCalc Statistical Software version 15 (MedCalc Software bvba, Ostend, Belgium).

3. Results

The total number of included patients was 1304. The distribution of age of incidence in the registry is shown in Fig. 1. Most cases of breast cancer are diagnosed between 45 and 70 years, the age of population screening program in our province. Clinical and pathologic characteristics of both groups (<80 years and ≥80 years) of patients are shown in Table 1. This analysis showed the factors reaching statistical significance to be method of detection (screening programs in younger women), extension and condensed-pT (consequently, condensed TNM), and adjuvant treatments (chemotherapy, radiotherapy and hormonotherapy). Summarizing these results, older women (>=80 years) presented a more extended disease, larger tumors and less in situ carcinomas. Moreover, a lower proportion of women ≥80 years received adjuvant therapies.

In the absence of any adjustment of results, the overall survival in women ≥80 years was poorer than in younger patients (median of 14.1 years for <80y vs. 5.7 years for ≥80y), the crude HR was 4.6 (95% CI: 2.9–7.5) $p < 0.001$. In other words, in women ≥80y the probability of death was 4.6 times higher than in the group of <80y (Fig. 2).

After adjustment for condensed-TNM and Propensity Score of adjuvant treatments (chemotherapy, radiotherapy and hormonotherapy) the HR was 2.5 (95% CI: 1.8–3.5) $p < 0.001$ (Fig. 3). According to these observations, women ≥80y continued to present a worse prognosis when compared with <80y, but if theoretically they had received the same treatment, the probability of death would declined by nearly half (HR 4.6 vs. HR 2.5).

Finally, another specific adjustment was carried out adding information of life expectancy by age for Spanish women, corresponding to year 2008 [1]. After adjustment, the HR was 1.7 (95% CI: 1.2–2.4) $p = 0.004$ (Fig. 4). Once again, women ≥80y presented a worse particular prognosis, although the adjusted HR by life expectancy declined by about one-third.