Research Article

Advances in Hematology and Oncology Research

Ovarian Metastasis from Breast Cancer over the Last Decade: a Breast Clinical Center Report

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Submitted: 21 Feb 2019; **Accepted:** 28 Feb 2019; **Published:** 15 Mar 2019

Abstract

Background: *A decline in mortality rates in breast cancer patients and an increased probability of developing secondary cancers, namely ovarian metastases, has been widely observed due to diagnostic improvement and treatment advances. The aim of this report is to evaluate the impact of ovarian metastases from breast cancer patients.*

Material and Methods: *A retrospective and descriptive study was performed based on data collected through medical records. Breast cancer patients with ovarian metastases histologically confirmed after surgery in the last decade were included. Statistical analysis was performed using SPSS version 22.*

Results: *Fourteen patients were analyzed, being 71% premenopausal. Primary breast cancer were associated with poor prognostic factors, namely large tumor size (100% >2cm), positive lymph nodes (79%) and differentiation grade 2/3 (50%). Mortality rate was 64%, and a 5-year survival rate after breast cancer diagnosis of 64% while after ovarian metastases diagnosis it was 29%, with a mean survival time of 95 and 38 months, respectively.*

Conclusion: *Screening for distant metastases should become the focus of increased concern in breast cancer patients, mostly premenopausal, and ovarian metastases should stand a warning sign since they rarely occur as an isolated event.*

Keywords: Breast Cancer, Ovarian Metastasis, Premenopausal Women

Introduction

Breast cancer early detection through systematic screening, better access to care, and advances in treatments have been leading to a decline in mortality rates [1-3]. Therefore, the likelihood of developing subsequent cancers becomes higher and breast cancer follow-up becomes of greater concern due to a predictable improvement in breast cancer survivorship in developed countries [4]. A recent meta-analysis states that breast cancer patients have a 17% increase of the risk of developing a new primary non-breast cancer, which is likely to be associated with treatment modalities, shared genetic predisposition or environmental risk factors [5]. About 30% of women with breast cancer will have recurrent metastatic disease, and a range of 3 to 30% will develop breast cancer metastases or micrometastases in the ovaries [4]. Because the primary cancer of ovarian metastases has primarily a gastro-intestinal source (39%), followed by breast cancer (28%) and cancer of the genitourinary tract (20%), the differential diagnosis is challenging [6]. The clinical distinction between recurrent metastatic breast cancer and a new primary malignancy of the ovary is difficult [7]. An adnexal mass detected in a patient with breast cancer history is more likely benign or, if malignant, it originates from a primitive ovarian carcinoma 3 to 7 times as often as it originates from metastatic disease. The correct differential diagnosis is only achieved after a biopsy analysis [4]. Therefore, in addition to the recommended clinical examination and mammography during breast cancer follow-up, in clinical practice it should be also performed a regular gynecologic examination and pelvic ultrasound that enables a diagnosis of ovarian tumor to be suspected as early as possible [6]. Management of these lesions is still controversial, and therapeutic options include ovarian ablation or surgical resection of metastatic pelvic disease, as recent studies point to a possible survival benefit after abdominal and pelvic cytoreductive surgery [4].

The aim of this retrospective study was to determine the clinical and tumoral characteristics of treated breast cancer patients with ovarian metastases, as well as depict their medical and surgical management, follow-up and survival.

Materials and Methods

A retrospective and descriptive study was performed based on data collected through medical records from the Gynecology Department, University Hospital Center of Coimbra, Portugal. Informed consent was obtained from all individual participants included in the study.

The inclusion criteria was breast cancer patients with ovarian metastases histologically confirmed after surgery, during the last decade.

The information included patients' age at diagnosis of breast cancer, menopausal status, personal and family history. Data on primary breast cancer was collected, such as histological type, grading, staging, hormone receptor status, local recurrence and treatment. Regarding ovarian metastases, information on the time of diagnosis, tumor markers, laterality and surgical treatment were recorded.

Statistical analysis was performed using SPSS version 22. Baseline demographic and clinical characteristics were summarized for continuous and categorical variables. Patient survival was calculated using the Kaplan-Meier method. Survival rate was determined since breast cancer diagnosis and ovarian metastases detection, until death. Patients alive at the end-point were censored.

Results

During the last decade at Gynecology Department of University Hospital Center of Coimbra, 2358 patients were diagnosed with breast cancer and 14 patients developed histologically proven ovarian metastases from breast cancer (0.59%).

The mean age of patients at breast cancer diagnosis was 44±7.7 years (range 37-66) and 10 out of 14 (71%) were premenopausal. Just one patient had bilateral breast cancer (7%). Three patients reported family history of breast cancer (21%) and there was no personal or family history of ovarian cancer.

Regarding primary breast cancer, histological types were ductal invasive carcinoma in 7 patients (50%), lobular invasive carcinoma in 6 patients (43%) and mucinous invasive carcinoma in 1 patient (7%). On what concerns tumor differentiation, 21% were classified as G1, 29% moderately differentiated (G2) and 14% were considered undifferentiated (G3). With respect to molecular classification, 9 (64%) tumors were classified as luminal A, 3 (21%) luminal B and 2 (14%) basal like. No triple negative breast tumor metastasized to the ovaries. Hormone receptors status was positive for estrogen in 11 patients (79%) and for progesterone in 9 patients (64%). HER2 overexpression was detected in only 2 cases (14%). All breast tumors were larger than 2 cm, with a mean histological size of 3.63±2.23 cm (range 2-8). Ipsilateral positive axillary lymph nodes at the time of breast cancer surgery occurred in 11 patients (79%). The diagnosis was made in 6 patients at stage IV (43%), 2 stage IIIA (14%), 3 stage IIB (21%) and 3 stage IIA (21%).

All patients underwent breast surgery, consisting in mastectomy in 12 cases (86%) and sentinel node biopsy was performed if axillary node metastases were not detected before surgery. Regarding other therapies, 4 patients (29%) received neoadjuvant chemotherapy, 12 (86%) adjuvant chemotherapy, 11 (79%) adjuvant radiation and 10 (71%) adjuvant hormone therapy. One patient developed local recurrence (7%).

The mean time between primary breast cancer disease and ovarian metastases was 5 years (57.2±60.4 months, range 0-221). Ovarian metastases diagnosis was incidental by routine radiologic check-up in 7 patients (50%), simultaneous with surgical castration in 3 patients (21%), synchronous with breast cancer diagnosis in 2 patients (14%) and suspected due to patient's unspecific symptoms in 2 patients (14%). At the time of ovarian metastases diagnosis, CA 15.3 levels were increased in 11 patients (79%), with a mean value of 88.7±103.6 (range 10-398). At the time of ovarian metastases diagnosis, CA125 mean level was 29065.6 ± 5864.2 (range 15-17,698). Eight patients had different sites of metastases (57%), namely liver, lungs, bones and brain metastases.

Regarding surgical treatment of ovarian metastases, eight patients underwent palliative bilateral oophorectomy/adnexectomy (58%), and remaining patients were submitted to radical and cytoreductive surgery in an attempt to maximize disease free survival. Histopathological analysis revealed bilateral ovarian disease in 12 patients (86%). After surgical treatment, in 7 (50%) patients chemotherapy was administered, 4 (29%) patients received chemotherapy and hormone therapy and 2 (14%) just hormone therapy.

The mean length of follow-up in our study was 130.6±73.2 months (range 52-318) after breast cancer diagnosis and 73.3±39.7 months (range 6-122) after ovarian metastases discovery. During this period, the mortality rate was 64% (9 patients), with a 5-year survival rate after breast cancer diagnosis of 64% and a mean survival time of approximately 95±65 months (range 35-245). After ovarian metastases diagnosis, the 5-year survival rate was 29% and the mean survival time was 38±29 months (range 0-94). Mortality and survival following diagnosis of ovarian metastases did not vary according to menopause status, primary tumor characteristics and treatment, time to recurrence (lower or higher than 5 years) and presence of other site metastases. A significant difference in survival (p=0.05) was observed between patients who received isolated chemotherapy or hormone associated chemotherapy, favoring the last (Figure (1)).

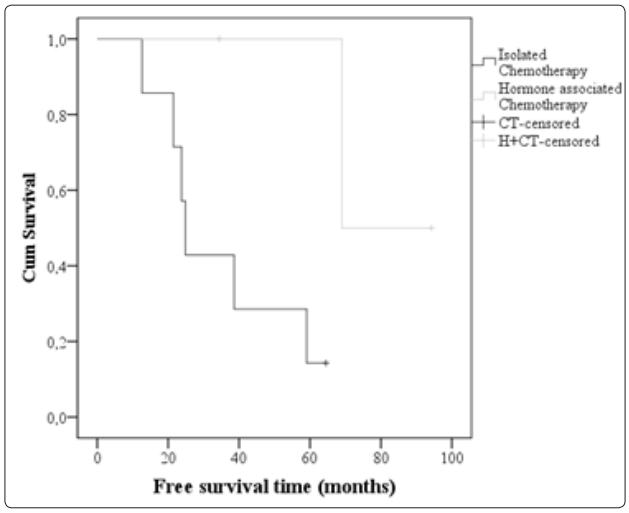

Figure 1: Free survival time after ovarian metastases diagnosis (months) [CT, chemotherapy; H, hormone]

Discussion

In this single center study, we report the third largest published series of breast cancer patients with ovarian metastases histologically confirmed after surgery. Eitan et al. and Ayhan et al. described, also in a single center, a series of 59 patients during 16 years and 35 patients during 22 years, respectively. Recently, Bigorie et al. and Pimentel et al. conducted a multicenter retrospective study, which included 29 patients in a decade time and 28 patients in more than 3 decades, respectively [4,6,8,9].

Ovarian metastases prevalence was 0.59%, however it has been reported a prevalence ranging from 3% to 30% in various series, including autopsies, prophylactic or therapeutic oophorectomies, and incidental findings in routine surgery [7-10].

The mean age of our study population at breast cancer diagnosis was 44 years, slightly younger than in previous reports (47-48 years), and considerably younger than the global population's mean age at breast cancer diagnosis (61 years), according to CDC (Centers for Disease Control and Prevention) [4,6,11]. As previously reported, the majority of breast cancer patients with ovarian metastases were premenopausal [4,6,8,9]. A recent meta-analysis states that women diagnosed with breast cancer at premenopausal ages exhibit a higher risk of second cancers with respect to the general population, when compared to postmenopausal patients at the time of diagnosis, particularly on what concerns ovarian metastases [5]. The authors defend that this association might be related to germline mutations in BRCA1/2 genes, which increase the risk of both types of cancer, or to shared reproductive or environmental risk factors [5].

In our sample, primary breast cancer was associated with poor prognostic factors in the majority of patients, namely larger size tumor (100% tumors > 2 cm) and positive lymph nodes (79%).The frequency of different histopathological subtypes differs from that usually found in general population, showing a greater proportion of lobular invasive carcinoma (43%). This fact corroborates with all previous reports about this subject, namely Pimentel et al. report (2016) that evidences 61% of cases with lobular invasive carcinoma. Bigorie et al. (2010) labeled a sample with 43% lobular invasive carcinoma in 2010, and Eitan et al. (2003) reported a frequency of 22% of the same histological type [4,6,8].

Regarding the tumor's molecular subtype, we observed a high rate of hormone receptor positive breast cancer, which might be associated with the high prevalence of lobular invasive carcinoma and the absence of triple negative tumors. It also suggests that hormone regulation might be involved in the development of ovarian metastases. Basic experimental research is needed to understand the pathophysiology of breast cancer ovarian metastasizing.

The risk of second cancers in women diagnosed with breast cancer is higher during the first 10 years after breast cancer diagnosis [12]. In our population, the mean time between primary breast cancer disease and ovarian metastases was 5 years, as in Bigorie et al. and Pimentel et al. series [4,6].

In two patients, the diagnosis of ovarian metastases was synchronous with breast cancer diagnosis. The remaining patients (71%) presented no abdominal or pelvic symptoms at the time of ovarian metastases diagnosis. Routine incidental radiologic diagnosis of ovarian metastases was performed in 7 patients, despite ultrasound usually revealed normal ovaries, cysts or solid tumors [13].

Concerning tumor markers, increased CA15.3 was frequent, in spite of a prevalent normal CA125 level. However, larger studies should run in order to draw consistent conclusions about CA125 measurement utility. One of the difficulties in diagnosing ovarian metastases from breast cancer is the paucity of symptoms. It has been shown that measurement of CA15.3 allows the diagnosis of nearly 75% of distant metastases 6 to 9 months before clinical or radiological manifestations of secondary lesions development, particularly concerning estrogen positive tumors [6,14]. So, measurement of CA15.3 serum levels might be recommended for monitoring and evaluating response to treatment in primary and metastatic tumors. According to an American Cancer Society publication last year, surveillance of breast cancer after primary treatment continues to be recommended and is largely based on clinical examination and mammography [15]. Screening for distant metastases should become the focus of increased concern because of a predictable improvement in breast cancer survival in developed countries [16]. Sun et al. (2015), concluded that whole-body PET/PET-CT had excellent diagnostic performance for distant metastasis staging in breast cancer patients [17].

Ovarian metastases from breast cancer rarely occur isolated and, in our population, 57% were associated with other metastatic sites, including liver, lungs, bones and brain. However, no differences were observed in survival. Pimentel et al. observed a 14 months survival difference between patients with ovarian metastases alone and multiple metastases, as undoubtedly disseminated disease showed worse prognosis.

Recent studies highlight a possible survival benefit after cytoreductive surgery, and residual tumor volume following surgery seems to be the only predictive factor of survival [7-9,18]. In our study population, the only patient undergoing cytoreductive surgery, died 24 months after ovarian metastases diagnosis.

During follow-up, mortality rate was 64%, three times the overall mortality rate for breast cancer [2]. The average 5-year survival rate is 91%, according to American Cancer Society [19]. In our report, the 5-year survival rate was 64% and the mean time of survival after breast cancer diagnosis was approximately 8 years (95 months). If breast cancer is disseminated, the 5-year survival rate decreases to 26% [20]. Overall prognosis in patients with ovarian metastases looks similar to those with other visceral metastases, providing a median 2 years survival. However, survival of over 10 years has been reported [10,21]. In our population, 5-year survival rate since ovarian metastases diagnosis was 29%, with a mean survival time of 3 years (38 months), similar to that described before [4,6,8]. For the study population, patients who received chemotherapy associated with hormone therapy following surgical treatment of ovarian metastases had a significant higher survival than those who received isolated chemotherapy ($p=0.05$). For other clinical, pathological and treatment variables, no differences were observed regarding mortality and survival following diagnosis of ovarian metastases. Overall prognosis was independent of histological type, contrasting with Pimentel et al. data, whose patients with lobular invasive carcinoma had a significantly shorter survival [6]. A recent study involving more than 1500 patients with breast cancer showed that disease-free and -specific survival were similar in the ductal and lobular invasive carcinoma, after adjustment for tumor size, node status, frequency of recurrence and metastases [22].

In conclusion, metastatic recurrence of breast cancer should not be underestimated, as breast cancer is the most frequent cancer in women worldwide, with a decreasing mortality rate in last decade. A metastatic ovarian tumor is not an unexceptional event in the course of breast cancer, particularly in premenopausal patients with lobular type primary cancer, and usually is associated with poor prognostic factors. Larger series will be needed to conduct a multivariate analysis of prognostic factors. Serum markers could

play a role in monitoring subjects at risk of developing ovarian metastatic tumors.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, et al. (2015) Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 386: E359-E386.
2. Cancer of the Female Breast (Invasive): Age-adjusted U.S. Deatha Rates by Year, Race and Age [2017].
3. Breast Cancer: Estimated Incidence, Mortality and Prevalence Worldwide in 2012. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx.
4. Bigorie V, Morice P, Duvillard P, Antoine M, Cortez A, et al. (2010) Ovarian Metastases From Breast Cancer: Report of 29 Cases. Cancer 116: 799-804.
5. Molina-montes E, Requena M, Sánchez-cantalejo E, Fernández MF, Arroyo-Morales M et al. (2014) Risk of second cancers cancer after a first primary breast cancer: A systematic review and meta-analysis. Gynecol Onco 136: 158-171.
6. Pimentel C, Becquet M, Lavoue V, Henno S, Leveque J, et al. (2016) Ovarian Metastases from Breast Cancer: A Series of 28 Cases 36: 4195-4200.
7. Garg R, Zahurak ML, Trimble EL, Armstrong DK, Bristow RE (2005) Abdominal carcinomatosis in women with a history of breast cancer. Gynecol Oncol 99: 65-70.
8. Eitan R, Gemignani ML, Venkatraman ES, Barakat RR, Abu-rustum NR (2003) Breast cancer metastatic to abdomen and pelvis: role of surgical resection. Gynecol Oncol 90: 397-401.
9. Ayhan A, Guvenal T, Salman MC, Ozyuncu O, Sakinci M, (2005) The role of cytoreductive surgery in nongenital cancers metastatic to the ovaries. Gynecol Oncol 98: 235-241.
10. Perrotin F, Marret H, Bouquin R, Fischer-Perrotin N, Lansac J, et al. (2001) Incidence, diagnosis and prognosis of ovarian metastasis in breast cancer. Gynecol Obs Fertil 29: 308-315.
11. CDC: Basic Information About Breast Cancer. https://www.cdc.gov/cancer/breast/basic_info/index.htm.
12. Molina-montes E, Pollán M, Payer T, Molina E, Dávila-arias C, et al. (2013) Gynecologic Oncology Risk of second primary cancer among women with breast cancer: A population-based study in Granada (Spain). Gynecol Oncol 130: 340-345.
13. Hann LE, Lui DM, Shi W, Bach AM, Selland D (2000) Adnexal Masses in Women with Breast Cancer: US Findings with Clinical and Histopathologic Correlation 1. Radiology 216: 242–247.
14. Stieber P, Nagel D, Blankenburg I, Heinemann V, Untch M, et al. (2015) Diagnostic efficacy of CA 15-3 and CEA in the early detection of metastatic breast cancer – a retrospective analysis of kinetics on 743 breast cancer patients. Clin Chim Acta 448: 228-231.
15. Runowicz CD, Leach CR, Henry NL, Henry KS, Mackey HT, et al. (2016) American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. CA Cancer J Clin 66: 43-73.
16. Ravdin PM, Cronin KA, Howlader N, Berg CD, Chlebowski RT, et al. (2007) The Decrease in Breast-Cancer Incidence in 2003 in the United States. N Engl J Med 356: 1670-1674.
17. Sun Z, Yi YL, Liu Y, Xiong JP, He CZ (2015) Comparison of whole-body PET/PET-CT and conventional imaging procedures for distant metastasis staging in patients with breast cancer: a meta-analysis. Eur J Gynaecol Oncol 36: 672-676.
18. Sal V, Demirkiran F, Topuz S, Kahramanoglu I, Yalcin I, et al. (2016) Surgical Treatment of Metastatic Ovarian Tumors From Extragenital Primary Sites. Int J Gynecol Oncol 26: 688-696.
19. Siegel RL, Miller KD, Jemal A (2016) Cancer Statistics. CA Cancer J Clin 66: 7-30.
20. Breast Cancer: Statistics. http://www.cancer.net/cancer-types/breast-cancer/statistics.
21. Zehetleitner G, Thiel I, Petru E (2002) Long-term disease-free survival after breast cancer metastatic to the ovary. Int J Ginecol Cancer 12: 317-318.
22. Garcia-Fernandez A, Lain JM, Chabrera C, García Font M, Fraile M, et al. (2015) Comparative Long-term Study of a Large Series of Patients with Invasive Ductal Carcinoma and Invasive. Breast J 21: 533-537.