



Original article

Incidence and risk factors of lymphedema after breast cancer treatment: 10 years of follow-up

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ABSTRACT

Purpose: To evaluate the incidence and risk factors of lymphedema 10 years after surgical treatment for breast cancer.**Methods:** Prospective observational hospital-based cohort of women undergoing axillary lymph node dissection. Lymphedema was assessed by indirect volume, measured by circumference, and diagnosed if there was a difference of 200 mL between the arms or if the patient was treated for it. Independent variables were patient, tumour and treatment characteristics. Descriptive statistics were conducted as survival analysis using the Kaplan-Meier estimate. Cox regression was performed, considering a 95% confidence interval (95%CI).**Results:** The study evaluated 964 women. The cumulative incidence of lymphedema observed was 13.5% at two years of follow-up, 30.2% at five years and 41.1% at 10 years. Final model showed an increased risk for lymphedema among women that underwent radiotherapy (HR = 2.19; 95%CI 1.63–2.94), were obese (HR = 1.52; 95%CI 1.20–1.92), had seroma formation after surgery (HR = 1.46; 95%CI 1.14–1.87), underwent chemotherapy infusion in the affected limb (HR = 1.45; 95%CI 1.12–1.87) or advanced disease staging (HR = 1.41; 95%CI 1.11–1.80).**Conclusions:** Cumulative incidence of lymphedema was 41.1%. Women undergoing axillary radiotherapy, obese, who developed seroma, underwent chemotherapy infusion in the affected limb and with advanced disease had a higher risk of lymphedema.

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1. Introduction

Breast cancer represents the most common neoplasm among women, and is responsible for 28.2% of all neoplasm cases. In the year 2012, there was an estimated 1.67 million new cases and 522,000 deaths from this cancer worldwide [1]. When detected in the early stages, the disease tends to have a good prognosis. Population-based studies have shown a mean relative survival in five years of 80% in developed countries and of 60% in developing countries [2,3].

Brazil is a developing country which still performs disease diagnosis in advanced stages. A large study conducted in the country reported that 53.5% of the cases diagnosed between the

years 2000 and 2009 were classified as advanced stages ($\geq$ IIb) [4]. Late diagnosis leads to the need of employment of more aggressive treatments, carrying to several complications such as lymphedema [5–7]. Lymphedema is an impairing and chronic condition, which leads to important physical, social and psychological problems [8,9].

Most of the studies published in the current literature report the cumulative incidence of lymphedema in a 5-year follow-up period, which ranges from 3% to 42.2% depending on the assessment of the outcome and characteristics of the sample [10–18]. Considering a 10-year median follow-up, an incidence of 29% of lymphedema, as a self-reported outcome, was found among US multiethnic patients who had undergone breast cancer treatment [19]. In a meta-analysis, the estimated pooled incidence was 16.6%. Among patients who had undergone more aggressive treatment like Brazilian patients (axillary lymph node dissection), pooled incidence estimated was 19.9% [20]. Considering studies with follow-up period $\geq$ 5 years, pooled incidence was 15.6%. A previous analysis of the present cohort was published in 2012 and reported a cumulative

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incidence of 30.3% after a 5-year follow-up, using indirect volumetry (volume >200 ml) as the diagnosis method [21].

Several factors have been associated with the occurrence of lymphedema after breast cancer. Performance of mastectomy, axillary lymph node dissection (ALND), having positive lymph nodes, undergo to regional lymph node irradiation, higher body mass index (BMI), age and the occurrence of post-surgical complications were related to an increase in the risk of lymphedema [10,13–18,20–30].

To date, there are few studies that have assessed the incidence and associated factors of lymphedema in a 10-year follow-up period. As breast cancer has a good prognosis when diagnosed early, and patients will live with the impact of the treatment, it is essential to know the incidence and risk factors of lymphedema in the long term after treatment so that preventive measures can be incorporated into clinical practice.

This study aimed to evaluate the cumulative incidence and risk factors associated with the occurrence of lymphedema after ALND for breast cancer in a hospital-based cohort during 10 years of follow-up.

2. Material and methods

2.1. Study population and follow-up

This was a prospective cohort study, which included women undergoing ALND as surgical treatment for breast cancer from August 2001 to November 2002, in a single reference institution for cancer treatment. The following criteria for exclusion were considered: patients who underwent a sentinel Lymph node mapping; prior oncologic treatment provided at another institution, a previous contralateral or a synchronous bilateral breast cancer, previous lymphedema or functional alteration of one of the upper extremities, a palliative surgery, presence of distant metastasis and inability to answer the study questionnaire. Such women were initially prospectively followed for 60 months with the specific aim of determining the incidence and the predictive factors for lymphedema. The methodologic features of this cohort have been previously published [21].

The initial population of this study was composed of 1243 women, of which 189 did not fulfill eligibility criteria. This resulted in a total of 1054 women that participated in the lymphedema incidence evaluation during a five year follow-up from the surgical procedure [21]. For this study, all women with early lymphedema (developed in the first six months after the surgical procedure) ($n = 70$) and those with a follow-up of less than six months after surgery ($n = 27$) were excluded. Other 7 patients were excluded by mistake in the 5-year follow-up analysis and were reincluded. Thus, a total of 964 women were analyzed.

2.2. Data collection

Medical records from patients without lymphedema at 60 months were reviewed to identify information about the diagnosis of lymphedema after this period, disease progression or death. Women without this information in their medical records were invited for a physical examination at 10 years after surgery.

Demographic data (age, marital status, education level, occupation, race and BMI), treatment characteristics (type of surgery, radiotherapy, chemotherapy, hormonal therapy) and clinical events (recurrence, death) were obtained from medical records. Tumour characteristics (histological type, tumour size, lymph node status, tumour staging, number of axillary lymph nodes surgically removed and number of nodes involved) were abstracted from histopathology reports. Complications related to the healing

process (wound infection, seroma, haematoma) were obtained from reports in medical charts. Post treatment complications (axillary web syndrome, early oedema, paresthesia of the intercostobrachial nerve, winged scapula) were abstracted from the routine physical therapy evaluation for the first six months post-surgery.

The outcome “lymphedema” was assessed at baseline (before surgical procedure) and during the follow-up using a circumference measure that was taken at 14 and 7 cm above, and 6, 14 and 21 cm below, the elbow joint. The volume of each arm was estimated by the formula for the volume of the frustum of a cone [31], and lymphedema was diagnosed if there was a difference of 200 ml between the arms.

2.3. Statistical analysis

Baseline demographics, treatment and clinical characteristics of the cohort were described using measures of central tendency and dispersion for continuous variables and proportions for categorical data.

Survival analysis was conducted by the Kaplan-Meier method, to identify the cumulative incidence and the possible differences in the curves for each exposure group. Censoring was considered for those women who completed 10 years free of lymphedema, those who were lost during follow-up and those who developed local recurrence, distant metastasis or death. The diagnosis of lymphedema was considered the event.

The univariate Cox regression analysis was performed in order to estimate the crude risk factors for the different exposure groups. Variables with $p < 0.20$ were selected for the multivariate model. The multivariate survival analysis was made using Cox regression model. The variables with $p < 0.05$ were retained in the final model.

2.4. Ethical standard

This study was approved by the institutional review board under the protocol 42/02. All patients signed an informed consent before being included in the study.

3. Results

Demographic and clinical characteristics of the 964 analyzed patients at the time of surgery are described in Table 1. The majority of women were married (47.6%), did not complete elementary school (45.1%) and performed housework (61.2%). Considering nutritional status, the mean BMI was 27.72 ($SD = 5.37$) where 36.7% was obese. Regarding treatment, chemotherapy was performed in the majority of patients, and 27.6% had at least one cycle of chemotherapy in the affected upper limb. Adjuvant radiotherapy and hormonal therapy was also performed by the majority of patients. In most of the cases, women had a mastectomy (65.1%), ALND until level III (83.8%), a mean of 17.85 ($SD = 7.52$) lymph nodes removed and 4.46 positive lymph nodes ($SD = 4.84$).

The stages IIA and IIB together represented more than half of the studied sample.

The occurrence of surgical complications is described in Table 2. The suction drain was kept for a mean period of 12.59 ($SD = 2.90$) days. The observed complications, related to the surgical wound, were seroma (62.6%), necrosis (40.7%) and infection (12.9%). Considering functional complications, 81.7% had paresthesia in the intercostobrachial nerve, 33.8% had axillary web syndrome and 66.3% had winged scapula.

The conditional probability of lymphedema occurrence, according to the Kaplan-Meier curve, in a 10-year follow-up is shown in Fig. 1. The cumulative incidence of lymphedema was 13.5% in two

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