The Breast 31 (2017) 192–196

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

# Is there a role for salvage radiotherapy in locally advanced breast cancer refractory to neoadjuvant chemotherapy?

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ARTICLE INFO

*Article history:*
Received 12 July 2016
Received in revised form
7 September 2016
Accepted 25 October 2016

*Keywords:*
Breast cancer
Locally advanced
Radiotherapy
Neoadjuvant chemotherapy
Retrospective study

ABSTRACT

*Introduction:* Locally advanced breast cancer (LABC) is a major problem, especially in developing countries. The standard treatment for LABC is neoadjuvant chemotherapy, with or without anti-Her2 therapy, followed by surgery, radiotherapy, and adjuvant systemic treatment if appropriate. However, there are few data in the literature addressing alternatives when neoadjuvant chemotherapy fails to reduce the tumour for surgery.

*Materials and methods:* We conducted a retrospective study including all patients who had non-metastatic LABC treated with neoadjuvant chemotherapy and who were not eligible for surgical resection; these patients were submitted to salvage radiotherapy (RTX) between January 2000 and December 2012 at the Brazilian National Cancer Institute.

*Results:* Fifty-seven patients were included, with a median age of 51 (23–72) years. The most frequent clinical stages were IIIA and IIIB, corresponding to 19.3% and 70.2%, respectively; mean tumour size was 8.74 (3–18) cm, and 44 patients (77.2%) had nodal involvement. Chemotherapeutic regimens containing anthracyclines were prescribed to 98.2% of the patients. Fifteen patients (26.3%) received taxanes and anthracyclines. Radiation dose was 50 Gy divided into 25 fractions; 43 patients (75.4%) had their tumours downsized by RTX and underwent mastectomy. Overall survival (OS) was 38 (23–52) months. Patients who were submitted to surgery had an OS of 49 (28–70) months and those who were not eligible for mastectomy after radiotherapy had an OS of 18 (9–27) months.

*Conclusion:* This retrospective study confirms that RTX is an effective treatment to downsize LABC tumours with low or no response to chemotherapy, thereby enabling surgical resection which may improve overall patient outcome.



## 1. Introduction

Breast cancer (BC) is a major global health problem. In Brazil 57,120 new cases are expected in 2016, corresponding to 28.1% of all cancers diagnosed in women [1]. BC has a relatively good prognosis when diagnosed and treated early. Unfortunately, in emergent countries BC mortality rates remain high; this is probably related to late diagnosis and limited access to treatments [2,3]. The survival rates are different around the world, reaching approximately 90% for white women in the United States and less than 40% in low-income countries [4,5].

In Brazil about 30% of patients present with locally advanced tumours [1,2]. The standard treatment for locally advanced breast cancer (LABC) is neoadjuvant chemotherapy with or without anti-Her2 therapy followed by surgery, radiotherapy and adjuvant systemic treatment if appropriate. Some patients with high positive hormonal receptors can be treated with hormone therapy in a neoadjuvant setting [6–10]. However, up to one third of LABCs are resistant to chemotherapy and/or hormone therapy and remain inoperable. It is possible to treat such patients with radiotherapy in order to reduce the tumour burden and allow resection [6–8].

At the Brazilian National Cancer Institute (INCA) many patients have their diagnosis when their disease is locally advanced, and a significant proportion of them have poor responses to neoadjuvant chemotherapy regimens involving anthracyclines ± taxanes ± trastuzumab; thus other therapies are required, such as radiotherapy, to reduce the tumour burden with the aim of surgical resection. There are few data in the literature about this subset of patients.

This retrospective study evaluated the role of neoadjuvant

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http://dx.doi.org/10.1016/j.breast.2016.10.026
0960-9776/

radiotherapy as a salvage treatment in order to allow surgery in a cohort of patients with LABC who remained inoperable after standard neoadjuvant chemotherapy.

## 2. Materials and methods

This was a retrospective cohort study which evaluated non-metastatic LABC patients documented by imaging, treated with at least one standard neoadjuvant chemotherapeutic regimen, and not eligible for surgical resection. These patients were treated with salvage neoadjuvant radiotherapy (RTX), after informed consent, with the objective of reducing the tumour burden to allow surgery. Patients treated between January 2000 and December 2012 were included, aiming for a minimum follow-up of 3 years. All patients included were from INCA (Rio de Janeiro, Brazil). This study was approved by the Ethics in Human Research Committee of INCA and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Clinical data were collected from medical records; demographics, Eastern Cooperative Oncology Group (ECOG) performance status (PS), clinical and imaging stages, tumour characteristics, neoadjuvant treatments before radiotherapy, concurrent treatments with radiotherapy, response, surgery feasibility, surgical complications, and time to recurrence and/or death were all evaluated.

Local response to treatment was assessed through clinical evaluation by surgeons according to the International Union Against Cancer (UICC) criteria as follows: no palpable abnormality at the site indicated a complete response (CR); reduction of $\geq$50% in the product of the two largest perpendicular dimensions of the breast mass and regional adenopathy indicated a partial response (PR); and <50% reduction indicated a minor response. Stable disease was defined as no change in clinical status, and progressive disease was defined as tumour growth or the appearance of new lesions [11].

In general, the first clinical reassessment to evaluate RTX response was performed 4–6 weeks after the end of treatment. Only patients with complete or partial responses were selected for mastectomy and axillary clearance.

If the patient was not eligible for surgery and had HR+ disease, hormonal therapy (HT) was promptly initiated. Thirteen (44.8%) of those patients with HR+ disease who were eligible for resection after RTX received HT before surgery; nine patients (31%) received tamoxifen, and four (13.8%) received anastrozole. To consider the tumour as HR+, oestrogen and/or progesterone receptor expression had to be $\geq$1% of the biopsy sample [12].

We defined standard chemotherapeutic regimens in our institution, at the period evaluated by the study, as the use of anthracyclines and/or taxanes with or without trastuzumab.

Standard radiotherapy included the whole breast by tangential fields and draining nodal chains (three levels of axilla and supraclavicular fossa), and was delivered with anteroposterior (AP)/posteroanterior (PA) fields. All treatment was delivered with three-dimensional conformal radiotherapy employing multileaf collimators and 6 MV photons. Patients received the dose of 50 Gy divided into 25 fractions.

In eight patients, radiosensitisation chemotherapy was prescribed concomitantly with radiotherapy. Seven received capecitabine 850 mg/m$^2$ twice daily for 14 days and repeated every 3 weeks during the radiation therapy, and one had cisplatin 30 mg/m$^2$ weekly during radiotherapy. A separate analysis for these patients was performed, but the result was not different from that for the general population. These data are therefore not described.

During follow-up, patients were evaluated regularly with clinical and physical examinations. Contralateral breast mammography was performed yearly. Other radiological exams and/or biopsies were performed only if there were clinical suspicions of recurrence.

Exclusion criteria included: insufficient records to complete the required data described above; incomplete staging without bone, chest and/or abdominal imaging; another primary neoplasm (except non-melanoma skin cancer); and treatment with neoadjuvant radiotherapy alone or after neoadjuvant hormone therapy without previous chemotherapy. We also excluded patients in which radiotherapy was performed with palliative intention.

Overall survival was estimated from the time of diagnosis (confirmed by biopsy) until death or, for living patients, the last available follow-up; disease-free survival was determined from the date of surgery to either first recurrence or death or the date of last contact for patients who were alive and disease-free. In both cases the Kaplan–Meier method was used. Survival curves were compared by log-rank test. Association between hormone receptor status and outcomes were evaluated by Fisher's exact test. The evaluation of all analyses was performed with the SPSS software, version 18.0.

We did not perform a separate analysis of inflammatory and non-inflammatory breast cancer patients because not all the records specified clearly whether or not the tumours were inflammatory.

## 3. Results

Fifty-seven patients met the inclusion criteria and were selected for this study. Fifty-six patients (98.2%) were women, with a median age of 51 (23–72) years. Tumour characteristics at diagnosis and epidemiological data are described in Table 1.

Tumour characteristics at diagnosis are impressive, reflecting the public health reality in Brazil. Clinical stages IIIA and IIIB, according to TNM system 7th edition [13], were more frequent, corresponding to 19.3% and 70.2% of cases, respectively; the mean tumour size was 8.74 (3–18) cm, and 44 patients (77.2%) had nodal involvement.

Chemotherapeutic regimens containing anthracyclines were prescribed to 98.2% of patients. Fifteen patients (26.3%) received taxanes and anthracyclines, and one was treated with the combination of docetaxel and cyclophosphamide. Trastuzumab was prescribed to only three patients (5%) because we did not have access to trastuzumab in our institution until 2011.

The medium time to surgery after radiotherapy was 20 weeks. In 43 patients (75.4%) tumours were downsized by RTX and the patients underwent mastectomy. If separated according to hormone receptor status, 29 of 32 patients (90.6%) with HR+ and 14 of 24 (58.3%) with negative hormone receptors (HR−) had a response to RTX and were eligible for surgery. One patient was not tested for HR. There were no complete pathological responses. Surgical complications were frequent; nonetheless no patient died because of them. The most common events were chronic pain (12–21.1%), lymphoedema (10–17.5%), wound dehiscence (8–14%) and/or infection (6–10.5%).

Disease-free survival (DFS) was evaluated in patients who underwent surgery. The medium DFS was 20 months. At the second and fifth years, 45.6% and 35.1% were disease-free, respectively. Considering the hormone receptor status, patients who were HR+ had a DFS of 37 months, while those who were HR− had a DFS of 15 months.

Nine patients are being followed without recurrence. Eight are HR+ and one is triple-negative. The last is currently on the fourth year of follow-up. Two patients had a mucinous subtype, and two had HER-2 overexpression and were treated with trastuzumab (HER-2 was tested in five of nine patients).

Overall survival (OS) was 38 (23–52) months, varying according