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Hypofractionated Radiotherapy for Breast Cancer: Experience of the Radiotherapy Department of the Mali Hospital

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Abstract **Original Research Article**

Aim*:** To evaluate the outcomes of hypofractionated radiotherapy in breast cancer. ***Patients and Methods: It was a retrospective study over a 3-year period, from January 2016 to December 2018, of breast cancer patients treated with hypofractionated radiotherapy at Mali Hospital. All patients with histologically confirmed breast cancer without distant metastases were included. We excluded all patients treated for breast cancer with palliative or normofractionated radiotherapy, patients with metastatic disease on admission and incomplete records. Patients were classified according to the 7th edition TNM classification. Radiotherapy was administered using an Elekta Compact 6MV linear accelerator with the 3D conformal technique, at a total dose of 42 Gy at a rate of 2.8Gy/fraction in 15 sessions, and 5 sessions/week. Data were collected from medical records and treatment sheets, entered into Excel and analysed using SPSS version 23 software. ***Results***: Sixty-four patients out of 129 met our selection criteria (49.61%). The mean age was 44.65+/-11.11 with extremes of 25 and 88 years. Previous hormonal contraception was found in 23.43% of cases, familial breast cancer in 6.25% and nulliparity in 4.68% of cases. Ultramammography was performed in all patients. Assessment of distant extension consisted of a thoraco-abdominal CT scan in 92.18% of cases, and abdominal ultrasound combined with a chest X-ray in 7.82% of cases. Histology of the biopsy specimen showed non-specific carcinoma in 96.87% of cases, Scarf-Bloom and Richardson (SBR) grade II in 64.81% and grade III in 27.78%. Immunohistochemistry was performed in 26 patients, hormone receptor positive in 57.69% (n=15) and triple negative in 42.31% (n=11). Patients were classified as stage T3 or T4 in 82.68% of cases. 95.4% of patients underwent mastectomy and 4.6% lumpectomy; all patients underwent axillary curage. The patients were treated with hypofractionated radiotherapy on the wall and the supra- and sub-clavicular lymph nodes in 98.44% of cases and on the wall alone in 1.56% of cases. The mean duration of treatment was 23.08 days (range 19 to 40 days). 14 patients were treated with tamoxifen 20 mg/day and anastrozole 1 mg/day. Toxicities such as radiodermatitis and oesophagitis were detected in 32.81% (n=21) of cases during radiotherapy. After 5 years, 16 patients (25%) were lost to follow-up, 30 (62.5%) were alive, 1 (2.08%) patient had local recurrence (8 months after treatment), 10 patients (20.83%) had distant metastases, and 19 patients (39.58%) were in complete remission. ***Conclusion*:** Hypofractionated radiotherapy saves a considerable amount of time, enabling a greater number of patients to be treated.

Keywords: Radiotherapy, hypofractionated, breast cancer, Radiotherapy Department, Mali Hospital.

INTRODUCTION

Breast cancer is a major public health problem, ranking first in terms of incidence and mortality in women worldwide, with 2.3 million new cases and 685,000 deaths in 2020 [1-3]. In Africa in 2020, 186,598 cases of breast cancer were recorded, with 85,787 deaths in women [3]. In Mali in 2020, according to the Bamako cancer registry, 1,130 cases of cancer were diagnosed in women, including 336 cases of breast cancer (29.9%) [4]. Radiotherapy is an essential part of breast cancer treatment. Studies [2, 5, 6] have shown that radiotherapy improves local control and survival without increasing toxicity. The indication for external radiotherapy in breast cancer is well codified; if it is systematic after lumpectomy, its indication is linked to the presence of poor prognostic factors after radical surgery [1]. This treatment is administered at a dose of 50 Gy in 25 fractions with a supplement of 10 to 16 Gy in the operating bed depending on the case [5]. Moderately hypofractionated radiotherapy delivering 40 to 42.5 Gy in 15 to 16 fractions over 3 to 3.2 weeks has become the

standard for breast irradiation alone following the START (Standardisation of Breast Radiotherapy) A, B and Ontario trials [7, 8]. To date, no study has been carried out on hypofractionated radiotherapy for breast cancer in Mali. The aim of this study is to evaluate the results of hypofractionated radiotherapy in breast cancer.

PATIENTS AND METHODS

This is a retrospective study over a 3-year period from January 2016 to December 2018, covering patients treated for breast cancer in the radiotherapy department of Mali Hospital. We included in the study all patients treated for histologically confirmed breast cancer who had undergone radical or conservative surgery, with or without chemotherapy, followed by curative dose hypofractionated adjuvant radiotherapy. All patients treated for breast cancer with palliative radiotherapy, patients who had received normofractionated radiotherapy, patients with metastatic disease on admission and incomplete files were excluded.

The parameters studied were: epidemiological, histological, therapeutic and evolutionary data. The seventh edition of the International Union Against Cancer (UICC) TNM classification was used for staging. Data were collected from medical records and treatment records and analysed using SPSS version 23 software.

The treatment was performed using an Elekta Compact monocentric linear accelerator using 6 MeV photons. The treatment technique used was 3D radiotherapy. A dose of 42 Gy at a rate of 2.8 Gy/fraction over 15 sessions was used on the chest wall or in the breast (with a boost of 11.6 Gy over 4 fractions) as well as on the sub/superclavicular lymph nodes.

Patients were simulated lying supine on an inclined surface, with both arms raised above the head, thighs supported by knee rests and ankles on foot rests. The organs at risk included the heart, the right and left lungs and the spinal cord.

We followed the patients until March 2024.

Acute toxicity was defined as all side effects observed during treatment and up to 3 months after the end of treatment, and all those occurring beyond 6 months were late-onset. Early toxicity was assessed at the weekly consultation during treatment and was classified according to the severity of the side effects into five grades.

Late toxicity of the treatment was sought during post-irradiation follow-up consultations beyond 6 months. This toxicity was classified according to the severity of the side effects into five grades using the latest version of the RTOG-EORTC scale.

Response to treatment was assessed at post-treatment follow-up visits by clinical examination, mammography and thoraco-abdominal CT scan.

Overall survival was calculated from the date of diagnosis to the date of death or the date of last news. Recurrence-free survival was calculated from the date of initiation of treatment to the date of local or distant relapse, the date of death or the date of last news.

Patients were seen 1 month after treatment and every 6 months thereafter.

RESULTS

Sixty-four patients out of 129 met our selection criteria, 49.61%. The mean age of the patients was 44.65+/-11.11 with extremes of 25 and 88 years. The most common age group was 41-60 years in 57.81% of cases.

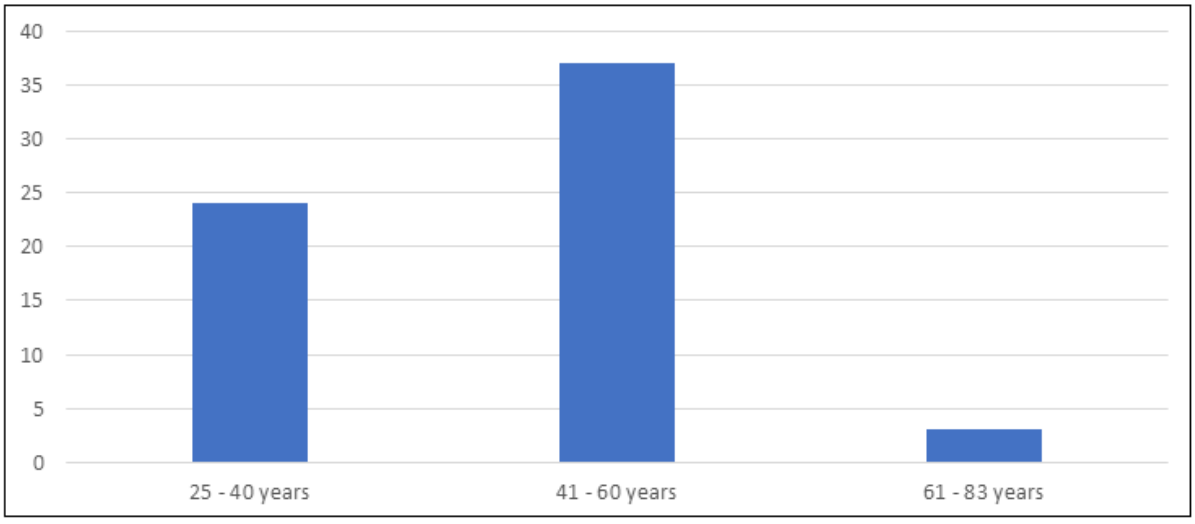

Figure 1: Patients by age group

Hormonal contraception was found in 23.43% of cases, as well as a family history of breast cancer and nulliparity (Table 1).

Table I: Distribution of patients according to risk factors

Risk factors	Frequency	Percentage %
Nulliparity	3	4,68
Family history of breast cancer	4	6,25
Family history of breast cancer + Nulliparity	1	1,56
Notion of taking oestroprogestogen	15	23,43

All patients underwent breast ultrasound and/or mammography.

Biopsy and pathological examination revealed non-specific ductal carcinoma in 96.87% of cases, infiltrating lobular carcinoma in 1.56% and low-grade fibrosarcoma in 1.56%.

Scarf-Bloom and Richardson grade was specified in 54 patients, grade II was found in the majority of cases grade II was found in the majority of cases (35 patients or 64.81%), 27.78% (n=15) had a grade III cancer and 9.25% (n=5) a grade I cancer.

We were able to perform immunohistochemistry on 26 patients (40.62%). Hormone receptors were present in 15 patients (23.43%), the cancer was triple-negative in 11 cases (17.18%), and 2 patients had HER2-positive cancer.

All patients were evaluated for distant extension and underwent thoraco-abdominal CT scans in 92.18% of cases, and abdominal ultrasound combined with a chest X-ray in 7.82% of cases, which made it possible to classify patients according to the TNM classification (see Tables 2, 3 and 4).

Table II: Distribution according to TNM stage T classification of breast cancer

Stage T	Frequency	Percentage %
T1	1	1,92
T2	8	15,38
T3	16	30,76
T4	27	51,92
Total	52	100

Table III: Distribution according to lymph node involvement

Stage N	Frequency	Percentage %
N0	12	23,07
N1	29	55,76
N2	10	19,23
N3	1	1,92
Total	52	100

Table IV: Distribution of patients by cancer stage

Stadification	Frequency	Percentage %
IB	1	1,92
IIA	4	7,69
IIB	9	17,30
IIIA	**11**	**21,15**
IIIB	**25**	**48,07**
IIIC	**2**	**3,84**
Total	52	100

Cerebral CT scans in 3 patients with persistent headaches revealed no lesions. Surgical treatment consisted of mastectomy in 95.4% of patients (n=61) and lumpectomy in 4.6% (n=3). Axillary curage was performed in all patients, with lymph node invasion in the majority of cases (76.93%).

Patients received chemotherapy, which was neoadjuvant in 92.18% of cases (n=59), adjuvant in 56.25% (n=36), and neoadjuvant and adjuvant in 50% of cases (n=32). Chemotherapy was not performed in 1 patient. The most commonly used protocols were: AC protocol combining Cyclophosphamide and anthracycline; Taxane-based protocol; FEC protocol combining 5 Fluoro-Uracil, Cyclophosphamide and

Epirubicin; FAC protocol combining 5 Fluoro-Uracil, Cyclophosphamide and anthracycline.

Hormone therapy was used in 14 patients and consisted of hormone therapy with antioestrogenic treatment such as Tamoxifen 20mg, 1 tablet per day or anti-aromatase (anastrozole 1mg, 1 tablet per day), prescribed for 5 years. None of the patients received Trastuzumab.

All our patients received hypofractionated radiotherapy at a dose of 42Gy in 15 fractions of 2.8 Gy per fraction, 5 days a week. The three patients (4.68%) who underwent conservative surgery (lumpectomy) received a boost of 11.6 Gy in the tumour bed.

Sixty-three patients (98.43%) underwent irradiation of the sub/superclavicular lymph nodes. The axillary region and internal mammary chain were not irradiated in our series. The average spread time was 23.08 days, with extremes of 19 and 40 days.

During treatment and the following 3 months, we recorded 21 cases of acute toxicity (32.81%). These were cutaneous and oesophageal toxicities.

Grade 1 radiodermatitis was found in 15 cases (23.43%), grade 2 in 4 cases (6.25%) and grade 4 in 1 case (1.56%) requiring necrosectomy. Grade 1 oesophagitis was found in 8 patients (12.5%).

The various late toxicities encountered were: a change in skin pigmentation Grade 1 skin pigmentation was found in 12 patients (18.75% of cases) and Grade 1 skin atrophy in 7 patients (10.93% of cases). No cardiac or pulmonary toxicity was detected.

After 5 years, 16 patients (25%) were lost to follow-up. Of the 48 patients of whom we had news, 30 (62.5%) were alive, 19 (39.58%) were in complete remission, 1 patient (2.08%) had presented a local recurrence 8 months after treatment, 10 patients (20.83%) had presented distant metastases: 8.33% in the lung, 4.16% in the bone and 8.33% in the brain, 18 patients (37.5%) had died.

The 5-year recurrence-free survival and overall survival were 39.58% and 62.5% respectively.

DISCUSSION

During the study period, 968 patients were irradiated in our department, including 129 cases of breast cancer (32.25%), we retained 64 files of patients treated for breast cancer.

The mean age of the patients was 44.65 ± 11.11 years, with extremes of 25 and 88 years.

Our data are similar to those found by YEMBA *et al*., [9] in Senegal, BALEKOUZOU *et al*., [10] in the Central African Republic and RANAIVOMANANA *et al*., [11] in Madagascar, who found a mean age of 47, 45.83 ± 13.5 and 52.83 years respectively.

Women with breast cancer in sub-Saharan Africa appear to be younger, with peak incidence ten years earlier (50.2 years) than African-American and Caucasian-American women, whose peak ages are 60.8 and 62.4 years respectively [12]. The average age in Europe at diagnosis ranged from 61 to 63 in 2015 [13].

Although the incidence of breast cancer is low in developing countries, people diagnosed with breast cancer tend to have more advanced disease [12, 14]. In our series, the cancer was stage III in 73.06% of cases. In Bangladesh, more than 87% of breast cancer cases were stage III in 2012 [15], KINGU *et al*., [16] in Kinshasa, SOME *et al*., in Bobo-Dioulasso [17] had 94.4% and 86.8% of breast cancers at an advanced stage (III and IV) respectively. According to a report summarising 83 studies conducted in 17 sub-Saharan African countries, 77% of all staged cases were stage III/IV at the time of diagnosis [18]. This situation could be due to several factors: the absence or inadequacy of mammography screening, limited access to medical care (effective therapies), neglect of certain patients, cultural and social barriers (recourse to traditional medicine) [19, 20].

In developed countries, where screening is widely available and accessible, the vast majority of women (80-85%) will present with early stage disease, while 5% will present with metastatic disease and the remaining 10-15% of women will be diagnosed with more advanced disease [14]. In a Swedish population-based study, the proportion of patients with breast cancer diagnosed at stage III was 12% between 2009 and 2013 [21, 22].

It is now well established that chemotherapy (alone or combined with targeted therapies) and adjuvant hormone therapy improve cure rates for most stages of the disease [23, 24]. Adjuvant hormonal therapy reduces tumour size, thereby improving the quality of surgical excision.

In our study, 63 patients (98.43%) received neoadjuvant and/or adjuvant chemotherapy. Neoadjuvant chemotherapy was given to 59 patients (92.18%), which can be explained by the fact that the majority of our patients (82.68%) were at stage T3 or T4 at the time of diagnosis. None of the patients were treated with trastuzumab (despite the presence of 2 cases of HER2 positivity) because of the rarity and high price of this drug in Mali during the study period.

Surgery consisted of mastectomy associated with axillary curage in the majority of our patients (95.4%), this rate is comparable to those of studies

carried out by other African authors, GUEYE *et al*., [25] in Senegal, BEN AHMED *et al*., [26], in Tunisia, TOGO *et al*., [27] in Mali where the mastectomy rate was respectively 98.6%, 85.5% and 100%. The fact that in these studies the majority of patients had advanced stage cancer (stage III and IV) and difficult access to radiotherapy (which was not always available) could explain these high mastectomy rates.

In high-income countries, the rate of radical surgery is less than 30%. However, in some countries [28, 29], removal of the tumour while preserving the breast has been possible thanks to advances in radiotherapy, imaging, nuclear medicine and medical oncology [29, 30]. Large randomized trials [29, 31] have shown equivalence in terms of overall survival between total mastectomy and conservative surgery, provided that radiotherapy is systematically delivered as an adjunct for tumors smaller than 4 cm. The increase in new cases of breast cancer in a world with limited health resources makes hypofractionation in breast radiotherapy a major public health issue. Radiotherapy will be indicated for the majority of patients with breast cancer [31-33]. Randomised studies have used conventional fractionation with a total dose of 45 to 50 Gy in 25 to 28 daily fractions of 1.8 to 2 Gy, with or without supplementation in the tumour bed [31, 32, 34]. This regimen has several disadvantages: the number of treatment sessions (lasting five weeks), loss of productivity at work (for the company) and at home, and higher transport costs. In theory, a hypofractionated adjuvant radiotherapy regimen could alleviate some of these shortcomings [6]. There is increasing talk of shortening the duration of radiotherapy in the management of breast cancer. Some countries, such as Canada and the UK, have for some years been developing accelerated treatments to shorten treatment times and reduce total treatment time [5]. As a result, there is growing interest in hypofractionated regimens.

Moderately hypofractionated radiotherapy delivering 40 to 42.5Gy in 15 to 16 fractions over 3 to 3.2 weeks has become a standard for breast irradiation alone following the START (Standardisation of Breast Radiotherapy) A, B and Ontario trials [7,8]. In our study we performed hypofractionated radiotherapy at a dose of 42Gy in 15 fractions at a rate of 2.8Gy per fraction over 3 weeks with a mean spread of 23.02 days.

The tolerance of normal tissues to radiotherapy remains the limiting factor in the delivery of a tumour-killing dose, and late morbidity in normal tissues is the most critical factor in the conduct of irradiation. Somatic, functional and structural alterations occur during the treatment itself (acute effects), but late effects may appear months or even years after the acute effects have disappeared and may progress over time [35].

During radiotherapy 32.81% (n=21) of patients showed signs of acute cutaneous toxicity in our study: 23.43% (n=15) had grade 1 toxicity; 6.25% (n=4) grade 2. These rates are lower than those of other authors, AOULAD *et al*., [36] found grade 1 and 2 radiodermatitis rates of 75% and 23%. In the study conducted by FRANCK *et al*., [37], 56% (n=157) presented grade 0 or I acute cutaneous toxicity, 43% (n=102) developed grade 2 toxicity. The overall survival rate at 5 years was 62.41%, which is similar to that of MAPOKO *et al*., [38] at Yaoundé General Hospital, which was 58.60% at 5 years. This low survival rate can be explained by factors such as the long delay between the onset of symptoms and recourse to healthcare, the lack of awareness among women to detect cases of less advanced breast cancer, late treatment, the absence or rarity of advanced therapies and the high cost of treatment [12, 13, 22]. A recent study in five sub-Saharan African countries estimated that 28% to 37% of breast cancer deaths in these countries could be prevented by earlier diagnosis of symptomatic disease and appropriate treatment [12]. Efforts to promote early detection through increased breast cancer awareness and clinical breast examination by trained health care providers, followed by appropriate treatment, are key to improving survival rates. Most countries in sub-Saharan Africa have not implemented and maintained screening programmes due to logistical, socio-cultural and financial constraints.

CONCLUSION

Hypofractionated radiotherapy has become the standard adjuvant treatment for breast cancer in recent years, encouraged by the non-inferiority results of several randomised trials compared with the standard normofractionated regimen, and by a desire to reduce the burden of radiotherapy on an increasing number of patients. Hypofractionation in breast radiotherapy is particularly interesting in developing countries where radiotherapy centres are inadequate.

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