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Profile of Radiotherapy Side Effects in Patients Treated for Breast Cancer in Cameroon: Case of the Douala General Hospital

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Abstract

Background: Conventional radiation therapy is a technique that uses ionizing radiation to destroy tumor cells. Along with surgery, chemotherapy, hormonotherapy and target therapy, it plays a crucial role in the management of breast cancer by reducing its overall mortality and recurrences. **Methods:** We conducted a retrospective and descriptive study by using the records of patients treated in the radiotherapy department of the Douala General Hospital from January 2015 to December 2019. Data concerning radiation-induced toxicities were collected using a pre-established and pre-tested survey and transferred to the CTCAE Version 4.0 software. Data analysis was performed using SPSS version 20.0. **Results:** A total of 206 records were selected. The average age was 46.7 ± 8.2 years. The most represented histological type was invasive ductal carcinoma (n = 187, 90.7%). Multimodality treatment was used in every patient in our series with chemotherapy, surgery, and adjuvant radiation therapy (n = 88, 42.7%) been the most represented. More than half of the participants (n = 108, 52.4%) received a total dose >50 grays, only 89 (43.2%) received the classical fractionation of 2 grays/cession, and the average duration of radiation therapy was 36.8 ± 15.4 days. We encountered 155 (75.2%) side effects. There were more acute toxicities than late toxicities, at 115 (74.1%) versus 40 (25.8%). The main acute lesions were radiodermatitis (68.6%), breast pain (16.5%), radiation pneumonitis (12.2%), and acute pericarditis (2.6%). As late lesions, we identified radiodermatitis (52.5%), radiation pneumonitis (32.5%), and lymphoedema (15%). A total dose >50 grays [**p < 0.001**, **OR: 2.7 (1.58 - 4.9)**], and conservative surgery [**p = 0.04**, **OR: 2.3 (1.3 - 4.1)**], seemed to increase the occurrence of early side effects on bivariate analysis. However, after multivariate logistic regression, only a total dose >50 grays [**p = 0.005**,

OR: 2.1 (1.1 - 6.7)] remained a predictive factor associated to early side effects. We found no factors related to late side effect occurrences. **Conclusion:** The frequency of side effects of radiation therapy for breast cancer at the Douala General Hospital remains relatively high. Both early and late lesions remained present with early toxicities been the most common. Meticulous strategies along with an enhancement of both human and materials resources are paramount in order to reduce their frequency and morbidity.

Keywords

Radiation Therapy, Radiation-Induced Lesions, Breast Cancer

1. Introduction

Radiation therapy (RT) is one of the most common therapeutic modalities, along with surgery and systemic treatment, for the treatment of breast cancer [1]. Breast cancer is the leading female cancer in Cameroon in terms of incidence and mortality. According to GLOBOCAN 2022, there were 4207 (21.5%) new cases of breast cancer and 2285 (17.9%) breast cancer related deaths In Cameroon [2]. Both data are relatively high particularly the mortality range, when compared to data from other countries like the US where GLOBOCAN 2022 reported only 7.1% deaths from breast cancer [2] [3]. Numerous treatment modalities are simultaneously used in the management of breast cancer. Along with chemotherapy, surgery and target therapy, radiation therapy is broadly used and is involved in up to 80% of adjuvant care after primary breast cancer surgery [4]. Over the years, radiation therapy techniques have evolved from 2D conventional radiation therapy to modern-day linear accelerators, 3D planning techniques/treatment verification and brachytherapy in order to provide a better target on cancer cells and to minimize its toxicities on surrounding organs [5]. A study published in 2001 found a frequency of more than 50% in early toxicity (skin lesion, fatigue, myelosuppression) and a range of 5% - 25% in late toxicity (lymphoedema, rib fracture, brachial plexopathy) [6]. A meta-analysis from 2023 has shown a 19.1% rate of skin toxicity with the use of more advanced radiotherapy techniques in breast cancer management [7]. In Cameroon, radiotherapy is delivered in a single public center, covering 22 million inhabitants, and treatment is by 2D conventional radiation techniques using gamma radiation from a Cobalt-60 source. Radiation therapy with cobalt-60 is almost no longer used in our modern era, a study conducted by Fehlauer *et al.* in Germany prospectively follow up women with early breast cancer on radiotherapy with cobalt-60 from 1983 to 1995. In their series, they reported 16% skin fibrosis, 9% breast edema, 4% breast atrophy, and 2% breast pain. They also highlighted age <60 years as a predicting factor for skin toxicity after radiation therapy with cobalt-60 [8]. We therefore sought to carry out this study, which aimed to describe the toxicity profile of conventional

radiotherapy in patients treated for breast cancer in Cameroon. The purpose is to advocate for an upgrade in equipment and techniques in radiation oncology in Cameroon.

2. Methods

We conducted a retrospective, descriptive and analytical study over a 5-year period (from January 2015 to December 2019) in the radiation oncology department of the Douala General Hospital. In our series, we included records of patients with non-metastatic breast cancer (NMBC) and locally advance breast cancer (stage III) who underwent radiation therapy with cobalt-60 with detailed information about radiation parameters, and available follow up information. We subsequently excluded patients with advanced disease (stage IV), incomplete record, and limited information about post radiation follow up. Data collection was done using pre-established and pre-tested survey forms. The variables of interest were age, TNM stage, histological type, total dose, fractionation, treatment protocols, and early and late side effects. **Early side effects** happen during or shortly after treatment. These side effects tend to be short-term, mild, and treatable. They usually resolve within a few weeks after treatment ends. **Late side effects** occur, by definition, more than 6 months after the beginning of radiation without any tendency to regress, even if their functional impact may vary over time. We used the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) V5.0 for the description of adverse events in our study population as shown here:

- **Grade 1:** Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2:** Moderate: minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL)*.
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare ADL**.
- **Grade 4:** Life-threatening consequences; urgent intervention indicated.
- **Grade 5:** Death related to adverse events.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Selfcare ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The data collected was entered using CSPRO 7.3 software. SPSS version 20.0 and Microsoft Office Excel 2016 software were used to process the data. The analyses were done in two stages, first a descriptive analysis of the results, followed by a bivariate analysis using the chi-square test and Fisher's exact test to search for factors associated with the occurrence of side effects. The threshold of statistical significance was below 0.05. Our results are presented in tables and graphs.

3. Results

A total of 206 records were included in our study.

3.1. Demographic and Clinical Characteristics

The average age was 46.7 ± 8.2, with extremes of 22 and 78 years.

The 40 to 50-year-old age group was the most represented (37.8%), as shown in Figure 1. Obesity and smoking were the most common comorbidities, found at 22.8% and 10.2 %, respectively. The most represented histological type in our study was invasive ductal carcinoma (90.7%). Lobular invasive carcinoma and other histologic subtypes, respectively represented 2.9% and 6.3%. TNM stage II (53.4%) and III (45.1%) were the most identified. Only 3 participants (1.45%) presented a TNM stage I Figure 2.

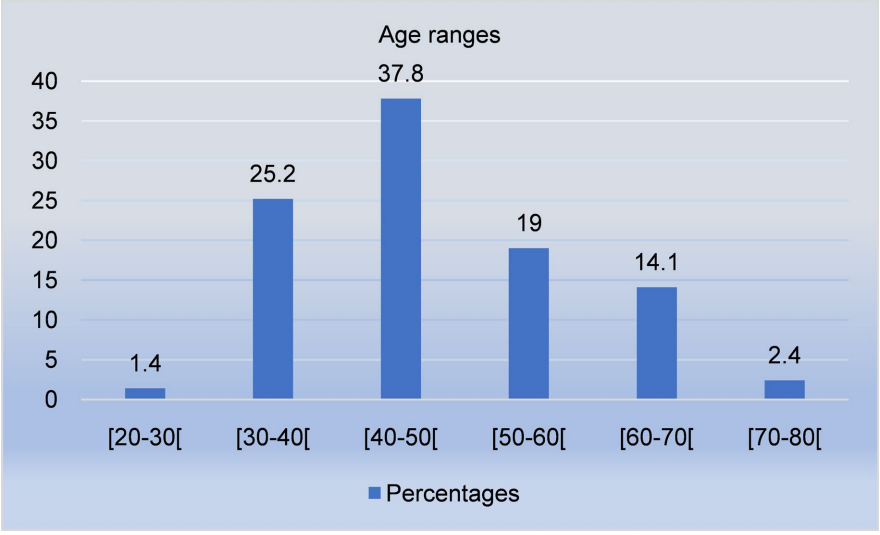

Figure 1. Age distribution of the study participants.

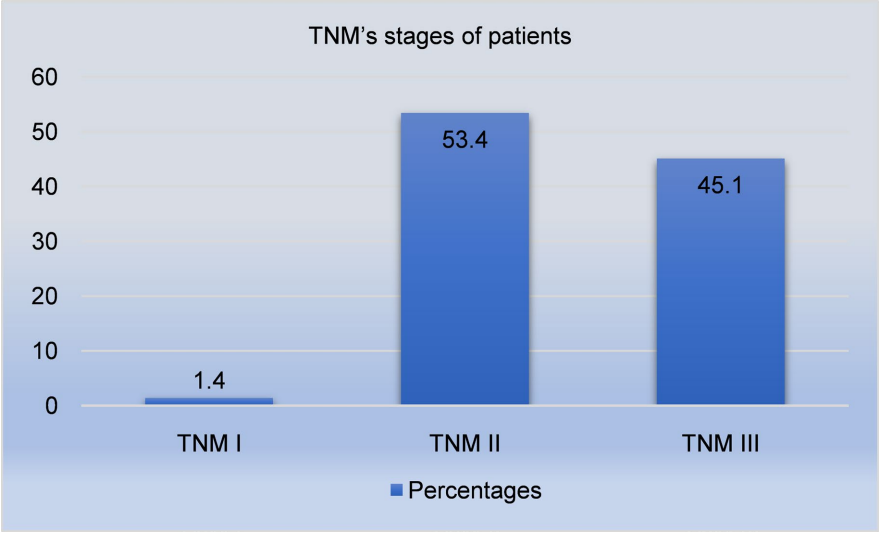

Figure 2. Distribution of the population based on TNM stages.

3.2. Therapeutic Data

All participants in our study were treated in a curative intent. Therapeutic associations were the standard of care, a combination of chemotherapy, surgery, and adjuvant radiation therapy was the most commonly used (42.7%), followed by the aforementioned combination with the addition of hormonotherapy (37.8%). The average total radiation dose delivered was 52.8 ± 6.8 Gy. Among our study population, 52.4% (n = 108) had received a total dose >50 Gy and only 32.5% (n = 67) had received the classical recommend total dose of 50 Gy. Regarding fractionation, a majority of our study population had received the conventional 2 Gy/session (n = 89, 43.2%). Hypofractionation (>2 Gy per session) was used in 78 patients (37.9%) Table 1.

Table 1. Radiation parameters.

Variables	Frequency (206)	Percentage (%)
Total Dose (in Gy)		
<50	31	15.1
50	67	32.5
>50	108	52.4
Schedule (in days)		
<35	51	24.7
35	73	35.4
>35	82	39.8
Fractionation (in Gy)		
<2	39	18.9
2	89	43.2
>2	78	37.9

3.3. Evolution

In our series, we registered a total of 155 radiation-induced lesions. Early and late side effects represented 74.2% and 25.8%, respectively.

3.3.1. Early Side Effects

Early side effects were the most common and accounted for 74.2% (n = 115/155) of all side effects. The skin, breast, lung and heart were the affected organs, represented in order of frequency by radiodermatitis (68.6%, n = 79/115), breast pain (16,5%, n = 19/115), radiation pneumonitis (12.2%, n = 14/115) and pericarditis (2.6%, n = 3/115). There was a predominance of grade II toxicity. Table 2 shows the distribution of patients by type of early side effect and grade.

Table 2. Distribution of patients by type of early side effects and grade.

Variables	Frequency (115)	Percentage (%)
Radiodermatitis	79	68.6
Grade I	18	15.6
Grade II	**46**	**40**
Grade III	15	13.1
Brest pain	19	16.5
Radiation pneumonitis	14	12.2
Grade II	**14**	**12.2**
Pericarditis	3	2.6
Grade II	**3**	**2.6**

3.3.2. Late Side Effects

Late side effects were less common (25.8%, n = 40/155) compared to early side effects and were dominated by radiodermatitis (52.5%, n = 21/40), radiation pneumonitis (32.5%, n = 13/40) and lymphoedema (15%, n = 6/40). Grade II toxicity was also the most predominant in late side effects. Table 3 shows the distribution of patients by type of late side effect and grade.

Table 3. Distribution of patients by type of late side effects and grade.

Variables	Frequency (40)	Percentage (%)
Radiodermatitis	21	52.5
Grade I	4	10
Grade II	**12**	**30**
Grade III	5	12.5
Radiation pneumonitis	13	32.5
Grade I	2	5
Grade II	**11**	**27.5**
Grade III	0	0
Lymphedema	6	15
Grade I	1	2.5
Grade II	**3**	**7.5**
Grade III	2	5

3.4. Factors Associated with the Occurrence of Side Effects

3.4.1. Factors Associated with the Occurrence of Early Side Effects

On bivariate analysis, the occurrence of early side effects was lower in patients treated with a total dose of 50 Gy with a statistically significant difference (p = 0.005), as shown in Table 4. On the other hand, a total dose higher than 50 Gy and conservative breast surgery were associated with more early side effects with a p value < 0.05, as shown in Table 5 and Table 6.

Table 4. Distribution of patients by total dose and occurrence of early side effects.

Variables	Yes (%)	NO (%)	OR (95% CI)	p-value
Less than 50	14 (12.1)	17 (18.7)	0.6 (0.2 - 1.3)	0.2
50	**28 (24.3)**	**39 (42.8)**	**0.4 (0.2 - 0.7)**	**0.005**
More than 50	**73 (63.5)**	**35 (38.5)**	**2.7 (1.58 - 4.9)**	**<0.001**

Table 5. Distribution of patients according to the type of surgery and occurrence of early side effects.

Variables	Yes (%)	No (%)	OR (95% CI)	p-value
Mastectomy	44 (38.3)	54 (59.3)		
Conservative surgery	**71 (61.7)**	**37 (40.7)**	**2.3 (1.3 - 4.1)**	**0.04**

Table 6. Multivariate analysis of predictive factors associated to early side effects.

Variables	OR (95%CI)	p-value
Total dose		
Less than 50	0.7 (1.1 - 3.1)	0.19
50	0.8 (0.6 - 1.8)	0.07
More than 50	**2.1 (1.1 - 6.7)**	**0.005**
Type of surgery		
Conservative surgery	1.7 (1.5 - 3.7)	0.08

3.4.2. Factors Associated with the Occurrence of Late Side Effects

On Bivariable analysis, no factors were identified as predictor of late side effects occurrence.

4. Discussion

Our study aimed to describe the profile of side effects found in breast cancer patients following conventional radiation therapy in Cameroon and also to point out the factors implicated in their occurrence. The average age was 46.7 ± 8.2 years.

The most represented histological type was invasive ductal carcinoma (n = 187, 90.7%). TNM stage II (53.4%) and III (45.1%) were the most common stages found. The most used therapeutic protocols were chemotherapy, surgery, and adjuvant radiation therapy (n = 88, 42.7%) and chemotherapy, surgery, adjuvant radiation therapy and adjuvant hormonotherapy (n = 78, 37.8%). In the study population, 52.4% (n = 108) had received a total dose >50 Gy and 43.2% (n = 89) had received the classical fractionation of 2 Gy/session. Conservative surgery was slightly more represented (n = 108, 52.4%) over mastectomy (n = 98, 47.6%). Acute toxicities were more represented than late toxicities at, 74.1% (n = 115) and 25.8% (n = 40), respectively. The main acute lesions encountered were radiodermatitis (68.6%), breast pain (16.5%), radiation pneumonitis (12.2%), and acute pericarditis (2.6%). As late lesions, we identified radiodermatitis (52.5%), radiation pneumonitis (32.5%), and lymphedema (15%). A total dose >50 Gy, and conservative surgery seemed to increase the occurrence of early side effects.

The average age 46.7 ± 8.2 years found in our study was similar to that found by Engbang *et al.* in 2015 (46 ± 15.87 years) in Cameroon [9].

In our study, TNM stage and histological findings were similar to those found by Kemfang *et al.* in Cameroon in 2011, who found a predominance of nodal positive breast cancer (stage III and IV) and invasive ductal carcinoma [10]. Moreover, a similar finding was reported by a literature review on breast cancer in African countries [11].

A total dose >50 Gy were used in 52.4% of our study population, with 39.8% treated in a spread >35 days. The normal fractionation of 2 Gy/session was commonly used in 43.2% of the patients, but a great proportion of our study population (37.9%) received a hypofractionation >2 Gy/session. This elevation in total dose and spreading time found in our series could be explained by the common use of a 15 Gy booster dose after a conservative surgery in our Cobalt 60 radiotherapy unit [12]. Moreover, the fact that this is the only available service in a country of 22 million inhabitants, availability and economic factors may also justify these findings.

The 74.1% acute side effects found in our series are similar to those of Lecleck *et al.* in 2016, who found 50% acute side effects [13]. A systematic review across sub-Saharan Africa equally reported a 50.6% rate of early side effects [14]. Contrary to our findings, Shapiro and Recht. In 2001 found a varying range of acute effects, with the most common being myelosuppression (>50%), fatigue (>50%), ribs fractures (2%), brachial plexopathies (<1%) and only 6% - 10% range of grade II skin toxicity [6]. The criteria used to diagnose myelosuppression were not assessed in our series, which justifies why it was inexistent. Other factors like fatigue with multifactorial etiology were not recorded and sometimes under report by the assessors. However, rib fractures and brachial plexopathies were not identified in our series and tend to be more prominent with the use of technique like brachytherapy and external radiotherapy with X-ray, which affect more internal organs with less skin exposure.

In our series, we encountered 40 (25.8%) late side effects, contracting the finding of HÖJRIS *et al.* in 2000, who conducted a prospective cohort in a 9-years period. They found a relatively high rate of late toxicities among patients who underwent mastectomy and conventional radiation therapy, with 14% lymphoedema, 50% of shoulder mobility impairment and 60% lung fibrosis. However, they reported no significant late cardiac dysfunction [15]. These differences could first be explained by the retrospective nature of our study with a short follow-up period and secondly by the relatively low number of radiation oncologists in our country, which compels most patients to pursue their follow up with other physicians. In contrast, Leclerc *et al.* in 2016 in France found a relatively similar range of late toxicities with 10% lymphoedema, 50% subcutaneous fibrosis, 1% radiation pneumonitis, and <1% brachial plexitis and heart toxicity even with the use of advance radiation therapy techniques [13]. These unexpected findings stress the need of a prospective cohort study over a more extended period of time in order to record more accurately late radiation-induced toxicities, as our study seems to have minimized them.

Our series identified factors influencing the occurrence of early side effects. Precisely, a total dose >50 Gy [**$p < 0.001$, OR: 2.7 (1.58 - 4.9)**], and conservative surgery [**$p = 0.04$, OR: 2.3 (1.3 - 4.1)**], appeared to have a two-fold increased risk of developing early toxicities. Other studies have had similar findings, Shapiro *et al.* have found and increased risk of hearth toxicity, brachial plexitis in patients who received a total dose >50 Gy [6]. Moreover, an increased breast fat compound and conservative surgery are related to more local skin toxicities [16]. No factors appeared to predict late toxicities occurrence in our series. However, numerous studies like the one conducted by Lilla *et al.* found age as a major factor for the development of skin fibrosis, with more than 10% skin fibrosis and telangiectasia in patients older than 70 years compared to other age groups [17]. A Meta-analysis conducted by Marta *et al.* equally showed more late toxicities in the group of patients who received hypofractionation and a total dose greater than 50 Gy [18]. The above identified predictors of late side effect in other studies should be further appraised in our setting by a study design allowing a lengthy period of patient follow-up over years.

5. Limitations of the Present Study

Our study did not elude the hazards and difficulties of retrospective studies (incomplete medical records and radiotherapy charts, patients lost to follow up). Chronic side effects were not well appraised due to numerous factors related to our study design and insufficient medical resources in Cameroon.

6. Conclusion

Our study aimed to describe the profile of side effects of radiation therapy in patients treated for breast cancer in Cameroun. We observed that 2D conventional radiation therapy with cobalt used in our setting potentially induces toxicity in the

majority of our patients, usually early side effects like radiodermatitis, breast pain, radiation pneumonitis, and pericarditis. However, the relatively low range of late toxicity in our series should be interpreted with caution, as those usually require a lengthy period of time in order to be fully assessed. Conservative surgery and total dose > 50 Gy are the two factors identified as predictors of early side effect occurrence in our study. A study design with a larger sample and lengthy period of observation is required to validate our conclusion and to better appraise late side effects.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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