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Research Article

Characteristics of Breast Cancers in Brazzaville: About 85 Cases

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Abstract

Objective: To describe the epidemiological, clinical and histological characteristics of breast cancer in Brazzaville

Materials and Method: This was a retrospective study carried out in the Medical Oncology Department of the Brazzaville University Hospital between January 2013 and December 2017. All the patients followed for histological breast cancer were included. Confirmed and having benefited from immunohistochemistry for hormone receptor assay and HER 2 status.

Results: Eighty-five patients were collected. The average age of the patients was 47.4 years with extremes of 22 and 73 years. The average consultation time was 7.9 months. The main reason for consultation was the finding or persistence of a breast nodule. Nonspecific infiltrating carcinoma was the most common histological type, and one case of medullary carcinoma was found. The histopronotic grades SBR I, II and III were respectively in 15.3%, 52.9% and 30.6% of the cases. Tumors of luminal type A and triple negative were the most representative, respectively 42.4% and 38.8%; tumors over expressing HER 2 were found in 10.6% and luminal B in 8.2% of cases. The majority of patients were in stage III (57.6%), 23.5% in stage II and 10.6% in stage IV. The median survival of the patients was 17 months for stage II, 25 months for stage III and 14 months for stage IV. According to the molecular groups, the median survival was 10 months for HER 2 (+) phenotype, 18 months for luminal A and B phenotypes and 28 months for the negative triple phenotype.

Conclusion: In the republic of Congo and more precisely in Brazzaville, breast cancer management remains difficult due to the lack of effective technical facilities and medical treatments.

Keywords: Breast Cancer; Immunohistochemistry; Brazzaville

Introduction

Breast cancer is first in line amongst all cancers affecting women in the developing countries [1-3]. It represents the most frequent cause of death from cancer in women worldwide and mortality rates are at their highest in our countries.

To date, several prognostic and predictive factors enable us to foresee disease evolution and thus orientate therapeutic management. Among these factors, there are classical ones (age, nodal status, tumor size, histology type, histological prognostic grade and hormone receptor status) others are emerging (tumor proliferation markers, HER2 receptor status and topo-isomerase II α expression) [4]. Since year 2000 a molecular or "intrinsic" classification, based on genomic alterations distinguishes 5 subtypes with different progression profiles: luminal A, luminal B, basal like, triple negative, and HER2 positive [3,5]. These subtypes distinguish different categories of Brest cancer with distinct prognosis enabling their individualized management.

It is not always possible to determine the latest prognostic factors for the patients of Brazzaville, on one hand due to their expense and on the other due to insufficient technical services leading us to send our biopsy samples to France.

The aim of this study is to establish a molecular profile in Brest cancer patients of Brazzaville.

Methods

This is a retrospective study based on medical records of patients in the department of medical oncology at the university hospital center of Brazzaville, Republic of Congo, from January 1st, 2013 to December 31th 2017.

We included all patients who were histologically diagnosed with a breast cancer and who benefited from an immunohistochemistry for the dosage of hormonal receptors and HER-2 status. Samples were analysed by CERBA laboratory, France, and the immunohistochemistry performed with Ventana Benchmark® device. The expression of hormonal receptors was evaluated in nuclear labelling percentage of tumoral cells. Ten percent (10%) was considered as being positive. The HER-2/neu expression was evaluated with the Dako tool kit protocol and the results were expressed in accordance with the ASCO recommendations [5].

Tumors with a Ki67 value of more than 14% were considered proliferative. Fluorescence in situ hybridization was indicated in HER 2 2+ patients.

All patients were cared according the same therapeutic approach with distinct aims depending on stage:

- Curative therapy has been prescribed in non-metastatic patients. it was neoadjuvant chemotherapy for locally advanced cases. In the event of a satisfactory tumor response (partial or complete remission), neoadjuvant treatment was followed by adjuvant chemotherapy, hormone therapy in the event of overexpression of hormone receptors and Herceptin if overexpression of the oncoprotein HER2.
- A palliative treatment was prescribed in the case of metastatic cancer, including a chemotherapy associated or not with a hormonotherapy and/or to Trastuzumab according to the hormonal receptors and HER-2 expression.

Combinations of chemotherapy used as neoadjuvant comprised an anthracycline unless contraindication. As adjuvant, taxanes were treatment of choice, except in the case of limited financial resources. In that respect :

- For no metastatic patients, chemotherapy protocols used were the following:
  - As neoadjuvant: 3 to 6 FAC-60 cures (5-fluorouracil: 600 mg/m^2, Doxorubicin: 60 mg/m^2, Cyclophosphamide: 600 mg/m^2 every 3 weeks) or 3 FAC-60 cures followed by 3 Docetaxel cures of 100 mg/m^2 every 3 weeks.
  - As adjuvant, 3 Docetaxel cures of 100 mg/m^2 every 3 weeks. For patients with limited financial resources, FAC-60 protocol was proposed with 3 cures every 3 weeks.
- For metastatic patients, the proposed first line chemotherapy was FAC-60. Continuation of therapy depended on financial resources of patients. This included 100 mg/m^2 of Docetaxel alone every 3 weeks or 175 mg/m^2 of Paclitaxel every 3 weeks associated or not with hormonotherapy or Trastuzumab.

For non-metastatic patients, an adequate treatment was considered in the following cases:

- **Therapeutic pattern 1:** neoadjuvant chemotherapy; surgery (radical or conservative); adjuvant chemotherapy; radiotherapy; more or less hormonotherapy (depending on the hormonal receptors expression); more or less Trastuzumab (depending on the HER2 oncoprotein);
- **Therapeutic pattern 2:** primary surgery (radical or conservative); adjuvant chemotherapy; radiotherapy more or less hormonotherapy (depending on the HER-2 oncoprotein).

Have been considered inadequate:

- Therapeutic sequences not comprising all therapeutic methods needed for non-metastatic patients: chemotherapy, surgery, radiotherapy;
- The lack of hormonotherapy in spite of positive hormonal receptors and the lack of trastuzumab treatment in spite of HER-2 receptor overexpression (metastatic and non-metastatic patients).

Main variables studied were age, time for consultation, parity and gravidity, family history of cancer, tumor size, histological type, SBR grade, molecular profile, AJCC stage and the adequacy of treatment.

Statistical analysis

Survival was calculated using the Kaplan Meier method, taking as time of participation (in months) the time between the date of diagnosis and the date of the latest news. The factors influencing survival were analyzed using a proportional risk model (Cox model).

Statistical analyses were performed with Stata 11 and Epi-Info 3.5.3 softwares. A statistical significance level of 5% was used for all analyses.

Results

We collected data from 85 patients with a mean age of 47.4 years (SD: 12.19; range: 22-73). Patient characteristics are showed in table 1.

Mean time for consultation was 7.9 months (SD: 11.7; range: 1-72). Twenty-nine patients (24.1%) saw a doctor within 3 months, and 30 patients (35.3%) after 6 months. The main reason for consultation was observation or persistence of a mammary nodule (77%). Mean tumoral size was 6.8 cm (range: 2-22).

No specific invasive carcinoma was the most frequent histological type (73%), followed by invasive lobular carcinoma (22%). One case of medullary carcinoma was found. SBR I, II and III histopronostic grades were respectively found in 15.3%, 52.9% and 30.6%.

Variable	Number	Percentage
Age		
≤ 45 ans	37	43,5
> 45 ans	48	56,5
Family history of cancer		
No	72	84,7
Yes	13	15,3
Gravidity		
0-2	21	24,7
3-5	44	51,8
>5	19	22,5
Parity		
0-2	34	40,0
3-5	38	44,7
>5	12	14,1
Consultation time (month)		
0-3	29	34,1
4-6	26	30,6
>6	30	35,3
Histology		
Nospecific invasive carcinoma	62	72,9
LobularCarcinoma	19	22,4
Other	4	4,7
SBR grade		
I	13	15,3
II	45	52,9
III	26	30,6
NR	1	1,2
Molecular profile		
H positive	9	10,6
Luminal A	36	42,4
Luminal B	7	8,2
Triple négative	33	38,8
AJCC stage		
IIA	9	10,6
IIB	11	12,9
IIIA	6	7,1
IIIB	43	50,6
IV	9	10,6
NR	7	8,2

Table 1: Characteristics of the patients.

Luminal A and triple negative tumors were the most frequent: 42.4% and 38.8% respectively. HER-2 was overexpressed in 10.6% of cases and Luminal B cancers represented 8.2%.

Extension work-up enabled to classify patients according to the AJCC stage at diagnostic. Most of patients (57.6%) were at stage III, 23% at stage II and 10% at stage IV. We lacked information on primary tumor for classifying 7 patients.

Therapeutically, treatment sequences were summarized in figures 1, 2 and 3.

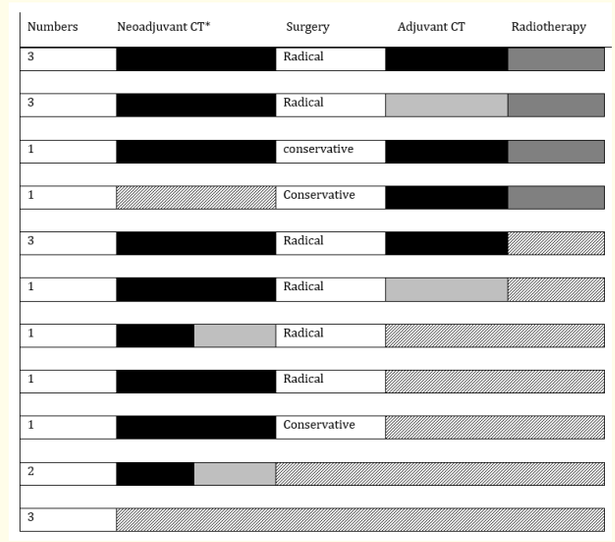


Figure 1: Therapeutic Sequences of AJCC Stage II Patients. *Chemotherapy

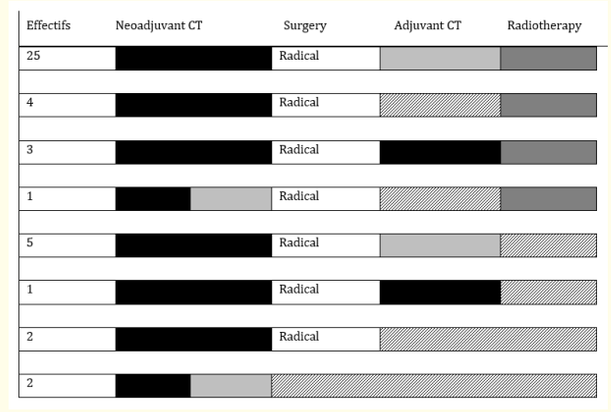


Figure 2: Therapeutic Sequences of AJCC Stage III Patients.

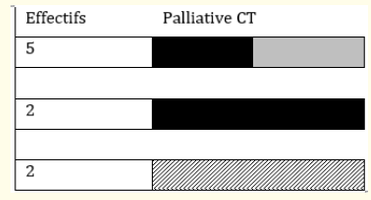
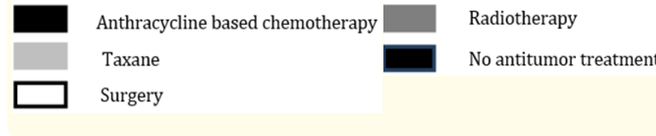


Figure 3: Therapeutic Sequences of AJCC Stage IV Patients



For patients at stage II, chemotherapy was neoadjuvant treatment for 18 patients (90%) and surgery was radical for 12 patients (60%) or conservative for 3 patients (15%); one of which did not receive neoadjuvant treatment. As adjuvant treatment, 12 patients (60%) received chemotherapy and 8 patients (40%) radiotherapy.

For patients with at stage III, 43 patients (87.7%) received neoadjuvant chemotherapy. Radical surgery was applied to all those patients and 34 (69%) received an adjuvant chemotherapy. Radiotherapy was administrated to 33 patients (67%) in that group.

Regardless of staging, trastuzumab was indicated for 16 patients, but only 2 received it. As regards hormonotherapy, initially indicated for 43 patients, only 35 patients could receive it.

Tables 2 and 3 summarize factors related to patients survival in univariate and multivariate analysis.

Variable	Number	Hazard ratio	IC95%	P Value
Age				
≤ 45 ans	37	1		
> 45 ans	48	1,14	[0,70 ; 1,86]	0,60
Consultation time (month)				
0-3	29	1		
4-6	26	0,81	[0,43 ; 1,53]	0,52
>6	30	0,92	[0,52 ; 1,64]	0,78
Histology				
No specific invasive carcinoma	62	1		
Lobular Carcinome	19	0,67	[0,37 ; 1,21]	0,18
Autres	4	1,94	[0,69 ; 5,42]	0,20
SBR garde				
I	4	1		
II	31	0,43	[0,21 ; 0,86]	0,02
III	20	0,52	[0,25 ; 1,11]	0,09
Molecular profile				
HER positive	9	1		
Luminal A and B	43	0,60	[0,26 ; 1,39]	0,23
Triple négative	33	0,49	[0,21 ; 1,14]	0,09
Tumor size (cm)				
]0-5]	41	1		
]5-9]	28	0,94	[0,54 ; 1,64]	0,83
>9	15	0,92	[0,48 ; 1,76]	0,81
Invasive ganglion				
No	19	1		
Yes	33	1,02	[0,56 ; 1,88]	0,93
Not specified	33	1,64	[0,88 ; 3,08]	0,78
AJCC stage				
II	20	1		
III	49	0,96	[0,54 ; 1,73]	0,91
IV	9	2,00	[0,75 ; 5,35]	0,16
Adequate treatment				
No	34	1		
Yes	51	0,44	[0,26 ; 0,73]	0,001

Table 2: Factors related to patient survival in univariate analysis.

Variables	Numbers	Hazard ratio	IC95%	P Value
Molecular profile				
HER positive	9	1		
Luminal A and B	43	0,80	[0,31 ; 2,05]	0,65
Triple négative	33	0,58	[0,22 ; 1,56]	0,09
AJCC stage				
II	20	1		
III	49	1,03	[0,53 ; 2,01]	0,92
IV	9	2,02	[0,72 ; 5,64]	0,18
Adequate treatment				
No	34	1		
Yes	51	0,47	[0,27 ; 0,85]	0,01

Table 3: Factors related to patient survival in multivariate analysis.

Median overall survival was 17 months for patients at stage II, 25 months at stage III and 14 months for stage IV (Figure 4). Under molecular groups, median overall survival was 10 months for HER-2 positive patients, 18 months for Luminal A and B phenotypes and 28 months for triple negative patients (Figure 5). Regarding the adequacy of the treatment, median overall survival was 28 months for patients with adequate therapeutic sequences and 11 months for those with inadequate treatment (Figure 6).

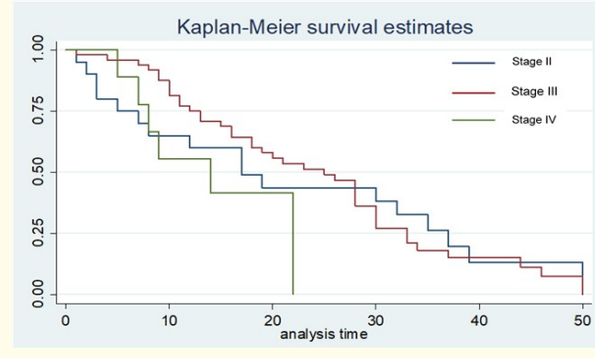
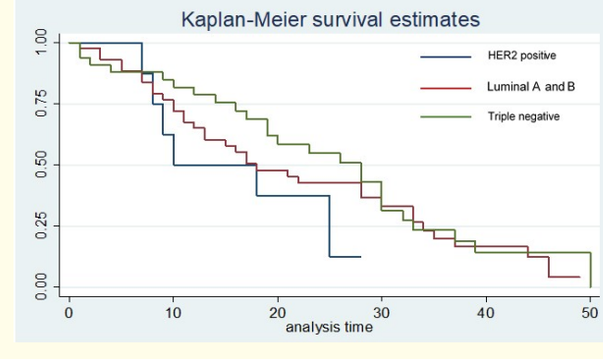


Figure 4: Survival Curves by AJCC Stage.



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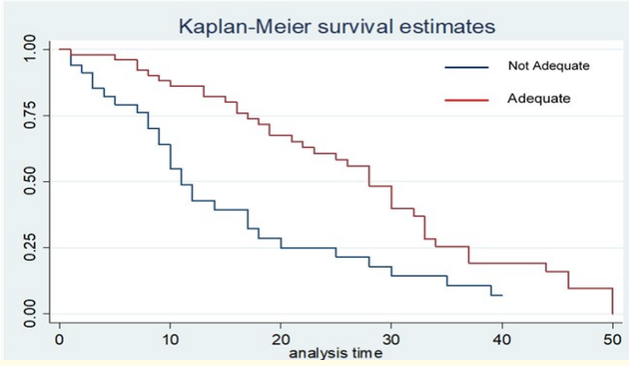

Figure 6: Survival curves according to the adequacy of the therapeutic sequences.

Discussion

Brest cancer is the most common cancer in women worldwide [1] as well as in Brazzaville [6]. In our series the mean age at diagnosis was concordant with those reported by other African series [7,8]. In developed countries the mean age is around 60 years old [9]. Family history of cancer was found in 15% of the study's population; let's keep in mind that mammary tumors that emerge in a hereditary context represent 5 to 10% of all cancers. The combined risk for a woman to develop Brest cancer during her lifetime is 8 to 10%, although if a woman bears a gene of hereditary predisposition, this risk exceeds 80% [10].

In our study as in a majority of African series [3,8,11], consultation delays were long. The average delay for consultation in our patients was 7.9 months. This long delay can be explained by patient's limited financial income, lack of information, illness denial but also their itinerary as revealed by Gombé., *et al*. [12].

The diagnosis of breast cancer was established at advanced stages for our patients. Indeed 58% of our patients were stage III and 10% were stage IV at time of diagnosis. Delay in diagnosis has likewise been observed by Ly Mandani., *et al.* [9]; they reported that in sub-Saharan Africa, Brest cancer was often diagnosed at a late stage, thus stage III and IV in over 50% of cases.

The histological distribution of breast cancer in our series revealed a large majority of non-specific infiltrating carcinomas; other invasive sub-types were rare in accordance with the literature [1,2].

The SBR grade modified by Elston and Ellis [13] represents an important and independent histoprognostic factor for metastases and overall survival. Our study objectified predominance in grade II (53%) in accordance to the results of several studies [14,15]. Grade II gives little information for it is associated to a badly defined (intermediate) recurrence risk. Therefore, in 2006 Sotiriou., *et al.* proposed a DNA microarray molecular grading tool on the basis of 96 genes called GGI (genomic grading index). GGI distinguishes amongst grade II mammary carcinomas, those with high GGI that have high recurrence risk and those with low GGI that have low recurrence risk [15]. In our study this grade did not correlate with survival.

Molecular sub-type analysis of breast cancer in our patients revealed predominance in luminal sub-type (around 51%), that is, tumors expressing oestrogen receptors without over expression of HER 2. These findings were not in accordance to those found in other African series, in which a predominance in triple negative sub-type was observed [17-19]. Nevertheless, we must underline the fact that these were retrospective studies and that they were conducted using blocs of conserved tumors with degraded epitopes such as those of hormone receptors or HER2 so they are badly or not detected with the use of immunohistochemistry. Well-conducted prospective studies are needed in order to validate these findings and to therefore confirm this tendency or not.

Solid cancer management requires several therapeutic modalities: surgery, chemotherapy, hormonotherapy, radiotherapy and innovative therapies. Surgery plays an important part in the management of solid cancers [20]. Radical surgery is performed for the majority of our patients (60% in grade II and 87% in grade III). For our patients, this therapeutic choice can be explained by the fact that diagnosis is established when tumors have reached locally advanced stages with lymph node damage. Conservative surgery concerns only a small amount of patients south of the Sahara [9]. In our series it was performed in 15% cases.

Advanced stages of breast cancer in our patents justified the indication of neoadjuvant chemotherapy. For luminal tumors, neoadjuvant chemotherapy allowed mammary conservation at a rate of 58%, that is, a gain of 10% in a relatively stable manner [21]. However, beyond mammary conservation, histology response has shown to be a factor that evaluates néoadjuvant chemotherapy [21]. A certain amount of studies have shown that triple negative tumors have a higher histological response compared to other mammary tumors but poorer prognosis [22].

HER 2 positive breast cancers, in absence of targeted systemic treatment are associated with a particularly aggressive clinical history, are voluminous and frequently associated with nodal damage [23]. When these tumors are treated by surgery in first intension, they show early local recurrences and/or metastasis [24], hence the need to choose neoadjuvant chemotherapy appropriately.

Radiotherapy is a major treatment for cancer and is almost non-existent in Africa south of the Sahara [9]. For instance in Congo,

their only radiotherapy device has been out of order since 2015, obliging patents to seek care abroad. Consequently in our series, patients who benefited from radiotherapy had received it abroad.

In our patients, median survival for non-metastatic forms was 17 and 25 months. For metastatic forms it was 14 months. These results are in accordance with several studies on the management of breast cancer at metastatic stages, which reported a median survival rate in the black population at 14,3 months compared to 18,7 months in the caucasian population [25]. This observation raises the hypothesis that other factors must influence survival such as the impact of comorbidities [26]. In univariate analysis: age, consultation delay, histology type, SBR grade, molecular profile, tumor size, nodal status and AJCC stage were not significantly related to patient's survival. The adequacy of treatment was the only factor related to survival (p=0,001). In multivariate analysis, after adjustments on the AJCC stage and molecular profile, treatment adequacy was the only independent factor related to survival (p=0,01). Therefore, in our study, the COX model enabled us to reveal only one factor influencing survival: treatment adequacy (p=0,001), even after adjustments on the AJCC stage and molecular profile. Indeed due to the absence of a national policy to fight cancer on one hand and the lack of financial income on the other, a majority of patients did not receive appropriate treatment as previously described.

Conclusion

The access to multiple immunohistochemical methods has profoundly modified the management of breast cancer within developed countries. In the republic of Congo and more precisely in Brazzaville, breast cancer management remains difficult due to the lack of effective technical facilities and medical treatments. The establishment of a national policy to fight cancer is indispensable in order to allow patients to receive the appropriate management though access to chemotherapy, radiotherapy and innovative treatments such as targeted cancer therapies to thus improve their survival.

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Conflicts of Interest

There are no conflicts of interest

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