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Triple Negative Breast Cancer: A Single Centre Experience

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Abstract

Purpose: The aim of our study is to evaluate the outcome and prognostic factors of triple negative breast cancers in our own experience and we give a critical analysis and an overview of the current prognostic from other institutions.

Materials and methods: One hundred and forty-two patients were evaluated who presented to National Institute of Oncology of Rabat with triple negative breast cancers between January 2010 and December 2010. They were retrospectively analyzed. All patients had invasive breast carcinoma and distribution of stage was 19%, 49.3%, 11.2% and 20.5% for T1, T2, T3 and T4, respectively. Treatment consisted in a mastectomy or conservative surgery with lymphadenectomy, chemotherapy and adjuvant radiotherapy. Overall survival (OS) and relapse-free survival (DFS) were calculated using Kaplan Meier method.

Results: Median age was 48 years (range: 27-86 years). Postmenopausal women presented 47.2% of cases. With a median follow-up of 24.5 months (10-60 months), the rate of local control was 59.9%. We found 18 (12.7%) local relapses, 26 (18.3%) distant relapses. At 5 years, Overall survival(OS), Relapse free survival (RFS) were 61.7% and 53.2% respectively.

Conclusion: Our results emphasize that triple negative breast cancers have a worse prognosis and tend to relapse early which is consistent with other studies.

Keywords: Triple negative; Breast cancers; Outcome; Prognosis; Invasive carcinoma

Introduction

Approximatively 10% to 15% of breast carcinomas are known to be of the triple receptor negative breast cancers (TNBC) subtype. It is defined as the breast cancer phenotype where the estrogen and progesterone receptor are negative, as assessed by immunohistochemistry (IHC), and there is a lack of overexpression of HER2, as assessed by IHC, or the absence of its gene amplification, as assessed by fluorescence *in situ* hybridization technique [1]. TNBC is more frequently affect younger patients and are more prevalent in African-American woman, generally of a higher grade, and associated with *BRCA* gene mutations [2,3]. Due to the lack of expression of commonly measured receptors present in other breast tumor subtypes, target agents specifically for TNBC are not yet available; this is in contrast to other subtypes of breast cancer. This study focuses on TNBC, analyzing its epidemiology, clinical, therapeutic features and recurrence patterns. Multiples studies have reported a worse prognostic for patients with TNBC. Our goal is to better characterize the TNBC subset so as to aid in clinical decisions and provide prognostic information.

Materials and Methods

Consent and statement of ethical approval

Medical staff of the Centre decided the treatment of each patient; oral consent was obtained from the subjects and was approved by the institutional review boards of the National Institute of Oncology, Cancer Centre, in Rabat. The institutional review boards of National Institute of Oncology, in Rabat, approved this study.

Clinical data

The investigation was a retrospective (the data was collected by chart review), observational, single Centre study. Eligibility requirements included pathologically documented invasive breast carcinoma. We excluded from the study patients who had not followed up after initial diagnosis. Tumors were pathological diagnosed according to the WHO histological classification of breast tumor, graded according to the modified Patley-Scarff scoring system and clinical staged according to the TNM criteria.

Pretreatment evaluation

Initial assessment included the patients history and physical examination. Radiologic evaluation included preoperative mammography, chest and abdomen radiograph. If there were any signs of metastasis to the bone or brain, bone scintigraphy or brain computed tomography (CT) was performed as a standard procedure.

Treatment plan

Local treatment included surgery and radiotherapy. Systemic treatments included chemotherapy. Surgical procedures consisted of mastectomy or breast-conserving surgery with lymphadenectomy. Adjuvant chemotherapy was started within four to six weeks after definitive breast surgery. It consisted of anthracycline and taxane regimen. Radiotherapy consisted of once daily treatment with fraction of 2.8 Gy per day, five fractions per week. The overall schema is to the chest wall for 15 fractions to 42 Gy, followed by a boost on the tumor bed to a total dose of 53.2 Gy (42+11.2 Gy), 2.8 Gy per fraction for patients who underwent breast-conserving surgery.

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Evaluation of response and follow-up

Follow-up examination included manual examination every 3 months for 2 years, every 6 months for 3 more years and yearly thereafter. Mammography was used yearly. Follow up has been maintained by the analysis of medical files and by contacting patients by phone.

Survival

Overall survival (OS) was defined as from the time of diagnosis to last follow up or time of death. Relapse free survival (RFS) was defined as the time of diagnosis to development of local and distant recurrences. SPSS 20 system was used for calculation of OS and RFS using Kaplan Meier survival analysis. Statistical significance is indicated by $p \leq 0.05$. Cox proportional hazards model was used to compare overall survival and relapse free survival between variables including patient age, margin status, nodal status, T stage, menopausal status, tumor size, lymphatic invasion and histologic grade.

Results

Patients characteristics

During one-year study period, we found 142 patients with TNBC treated in our institute, who present 21.6% of all patients treated for breast cancer in the same period. Their pretreatment characteristics as listed in Table 1.

Median age was 48 years (range: 27-86 years). Postmenopausal women presented 47.2% of cases. Distribution of stage T was 19%, 49.3%, 11.2% and 20.5% for T1, T2, T3 and T4, respectively, while the rate ofcN0 and pN0 were 69.7% and 57.7%respectively. Median tumor size was 2 cm (0.3-12 cm); Grade III tumors and lymphovascular invasion represented respectively 58. 3% and 32.4%.

Variable		N (%)
Median age (range)		48 years (27-86 years)
Median tumor size		2 cm (0.3-12)
Stage T	T1	27 (19)
	T2	70 (49.3)
	T3	16 (11 .2)
	T4	29 (20 .5)
Stage N	N0	99 (69.7)
	N1	38 (26 .8)
	N2	5 (3 .5)
Stage M	M0	123 (86.6)
	M1	19 (13 .4)
Surgery	Mastectomy	93 (65.5)
	Conservative surgery	30 (21 .1)
	No surgery	19 (13 .4)
Tumor grade	I	5 (3 .5)
	II	53 (37 .3)
	III	84 (58 .3)
p T	p T1	15 (10 .6)
	P T2	72 (50.7)
	P T3	36 (25.3)
	No surgery	19 (13 .4)
p N	p N0	82 (57 .7)
	p N1	22 (15 .5)
	p N2	21 (14 .8)
	p N 3	17 (12)
Lymphovascular invasion	Present	46 (32.4)
	Absent	96 (67 .6)

Table 1: Patients characteristics.

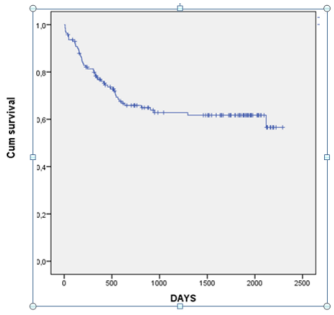

Figure 1: The Kaplan-Meier survival curves of overall survival.

Prognostic factors		Overall survival		Disease free survival	
		5-year OS	p	5-year DFS	P
Age, years (middle)	≤ 35	60%	0.69	60 %	0.97
	>35	61 .9%		52%	
Menopausal status	No	62.1%	0.74	60 %	0.68
	Yes	61.4%		50 .4%	
Tumor size	≤ 5	64.3%	0.061	55.1%	0.10
	>5	26.7%		26.7%	
Lymphatic invasion	Positive	59.8%	0.26	54.1%	0.53
	Negative	66 .2%		52%	
Histologic grade	III	58 .5%	0.55	53 .3%	0.87
	I+II	66.4%		53 .7%	
T stage	T1	77.8%	0.053	73.3 %	0.01
	T2	65.9%		58.4 %	
	T3	42.8%		21.4 %	
	T4	39.9%		26.3%	
N stage	N0	71.2%	0.009	60%	0.04
	N1	44.6%		41.9 %	
	N2	20%		20%	
TNM stage	I+II	69.7%	0.036	64.2%	0.01
	III	59.2%		46.5%	
	IV	26.8%		13.6%	
Margin status	Positive margin	35.4%	0.0001	25%	0.0001
	Negative margin	68.4%		58.7%	

Table 2: 5-year overall survival rate and relapse free survival according to prognostic factors.

Survival

The 5-year overall survival was 61.7% with the median follow-up time was 24.5 months (range, 10-60 months) (Figure 1). Relapse free survival (RFS) was 53.2% and local control was 59.9% at 5 years.

We found 18 (12.7%) local relapses, 26 (18.3%) distant relapses, and 48 deaths. The distribution of the metastatic disease occurred in the TNBC was following like this: 42.4% (11/26) in the lungs, 26.9% (7/26) in the liver, 23% (6/26) in the brain and 7.7% (2/26) in the bones. For the univariate analysis, we study prognostic variables: patient age, margin status, nodal status, T stage, menopausal status, tumor size, lymphatic invasion and histologic grade. Nodal status, T stage, margin status and TNM stage demonstrated a significant influence on overall survival (p=0.009, p=0.053, p=0.0001 and p=0.036 respectively) and disease-free survival:(p=0.04, p=0.01, p=0.0001 and p=0.01 respectively). There was insignificant influence on overall survival and relapse free survival in age, menopausal status, tumor size, lymphatic invasion and histologic grade. Table 2 summarizes the results of univariate analysis. Curves of overall survival according to prognostic variables were presented in Figure 2-4.

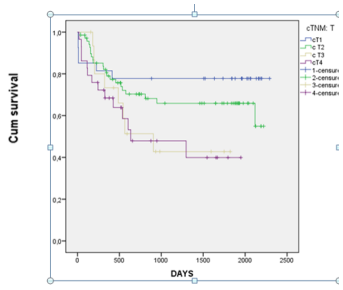

Figure 2: Overall survival curve according to the stage T.

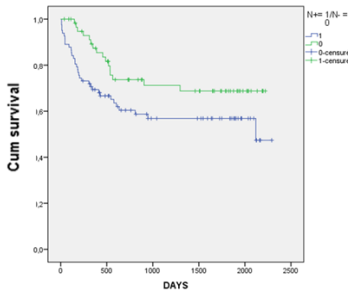

Figure 3: Overall survival curve according to the nodal status.

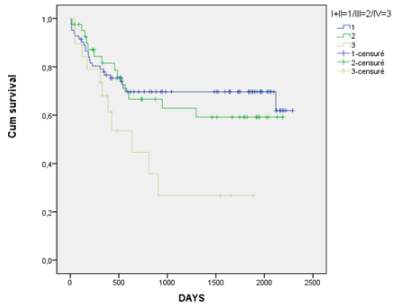

Figure 4: Overall survival curve according to the TNM stage.

Discussion

Triple-negative breast cancers (TNBC) accounts for approximately 10 to 15 percent of breast cancers diagnosed worldwide, which amounts to almost 200,000 cases each year [4]. In our institute, we found a 655 new cases of breast cancer in 2010 which included 142 patients with TNBC. There are multiple limitations to this study. First of all, it is a retrospective study. Second, there was 27 patients lost to follow-up. TNBC is a heterogenous disease with one common feature: a distinctly aggressive nature with higher rates of relapse and shorter overall survival compared to other subtypes of breast cancer. It affected a younger patient. Higher grade and *BRCA* gene mutations were frequently associated [2,3].

In our study, the median age was 48 years and high grade represented 58.3% of cases. TNBC are usually invasive ductal carcinomas of no special type (IDCNST) [4]. Node-negative were more shown in TNBC than other types of breast cancer. In this present study, IDCNST and node-negative represented 85.2% and 57.7% respectively. Radiological features were specific on magnetic resonance imaging, such as rim enhancement and a very high intratumor signal intensity on T2-weighted images [5]. Metastasis to viscera was more frequent to the lung (40%), brain (30%), liver (20%) and bone (10%) [6-8]. In our study, metastasis in the lung, brain, liver and bone represented respectively 33.1%, 23%, 5.6% and 12.7%. The principles for the surgical management and radiation therapy options of breast cancer is applied in a similar way across breast cancer subtypes. Cytotoxic chemotherapy remains the standard treatment. Although there is no standard chemotherapy regimen that specifically applies to women with triple-negative breast cancers, anthracycline and taxane-based chemotherapy remains the most commonly used regimen, especially since taxanes have significant activity in the treatment of triple-negative breast cancers [9-11]. As an example, in the GEICAM 9906 trial of 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) versus FEC followed by paclitaxel, the addition of paclitaxel was associated with a significant improvement in disease-free survival at seven years (74 versus 56 percent, respectively) [11]. Our patients were treated by 3 cycles FEC followed by 3 cycles of decetaxel. Neoadjuvant chemotherapy has been given in 32 patients with locally advanced breast cancer who are not considered operable at presentation or who are not candidates for breast conservation at diagnosis. Many study found that for these patients, pathologic complete response (pCR) is associated with improvement in disease-free survival [8,12]. Liedtke et al found in a largest study involving 1118 patients identified in a prospectively collected clinical database, women with triple-negative breast cancers had a higher pathologic complete response (pCR) rate compared to those with other types of breast cancers (22 versus 11 percent, p=0.034). However, there was a higher risk of recurrence or death among women with residual disease after neoadjuvant chemotherapy (HR 1.5, 95% CI 1.3-1.8) [8] The benefits of targeted therapies have eluded patients with TNBC due to the absence of well-defined molecular targets. Patients with triple-negative breast cancers have a poorer prognosis compared to patients with other breast cancers subtypes [13-15]. In a Canadian study involving a large population by Drent and colleagues, women with TNBC had an increased risk of death (HR3.2; p<0.0001) and distant recurrence (HR 2.6; p<0.0001) compared with non-TNBC [3]. The poorer prognosis may be attributed to biologic characteristics of triple-negative breast cancers, which we are only beginning to understand. In our study, overall survival, relapse free survival at 5 years, were respectively 61.7% and 53.2%.

Conclusion

Triple negative breast cancers are an aggressive disease with limited treatment options and no approved targeted therapies. It has a worse prognosis and tends to relapse early compared with other subtypes of breast cancers.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

KM and AS participated to the acquisition of data; KM and LR draft the Manuscript. HE, TK, SM and NB have revised the manuscript. All authors read and approved the final manuscript.

Informed consent

Written informed consent was obtained from all the patients for publication of this series. A copy of the written consent is available for review by the Editor of this journal.

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