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Original research article

Clinicopathological features and prognosis of triple negative breast cancer in Kuwait: A comparative/perspective analysis☆

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ABSTRACT

Aim: The aim of this study was to determine the incidence of TNBC in Kuwait, to analyze the clinicopathologic features and prognosis of this type of breast cancer, and compare it with reports from other regions of the world.

Background: Triple negative breast cancer (TNBC) is defined as a subtype that is negative for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2). There is a growing evidence of the heterogeneity of such entity on the molecular level that may cause discrete outcomes.

Methods: We analyzed the clinicopathologic features of 363 TNBC cases which were diagnosed in Kuwait from July 1999 to June 2009. The disease-free survival (DFS) and overall survival (OS) were analyzed by Kaplan–Meier method. Comparison was done with reports from USA, Europe, Middle and Far East.

Results: Among 2986 patients diagnosed with breast cancer in Kuwait, 363 patients (12.2%) were TNBC. The median age was 48 years, 57.2% had lymph nodes (LN) metastasis, 56.9% were of grade III tumor and 41.9% had stage II disease. 81% developed recurrences and 75% of deaths occurred by 2.5 years after treatment. There is marked variation of clinicopathologic features according to country of patients' cohort.

Conclusion: The incidence of TNBC in our study is similar to other studies. TNBC patients showed an early major recurrence surge peaking at approximately year 2.5. Regional variation of clinicopathologic features indicates a need for molecular studies to define underlying molecular features and its impact on survival.

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1. Background

Breast cancer (BC) is increasingly recognized as a heterogeneous disease exhibiting substantial differences with regard to biological behavior and requiring distinct therapeutic interventions. Steroid hormone receptors (HR) such as estrogen receptor (ER) and progesterone receptor (PR) in concert with the oncogene ErbB-2/human epidermal growth factor receptor 2(HER-2) are critical determinants of these BC subtypes.[1–6] Triple-negative breast cancer (TNBC) is characterized by a lack of expression of both ER and PR as well as HER-2. A recent analysis indicates that TNBC carries a distinct molecular profile when compared with HR-positive BC.

A breast cancer classification emerged in the scientific scene based on gene expression profiles. The subgroups (luminal, HER2, normal breast and basal-like; BLBC) have distinct gene expression patterns and phenotypical characteristics. TNBC shares phenotypical features with basal-like breast cancer, which is in turn the most aggressive and with worse outcome.[7–11] However, the molecular classification of breast cancer has not led to changes in treatment recommendations and should yet be considered investigational, as the clinicopathological entities defined by the use of common immunohistochemistry (IHC) methods still represent the base for such recommendations.[12]

In Kuwait, a trend of presentation of breast cancer at earlier age was documented.[13] This carries a risk of having more patients with TNBC (that is known to be more common at young ages). Many reports from different countries across the world documented different clinicopathological features that may be different by ethnicity.

2. Aim

The aim of this study was to determine the incidence of TNBC in Kuwait. In addition, analysis of the clinical and pathologic features of TNBC patients in Kuwait as well as the prognosis of this type of breast cancer was documented. Third, these findings were compared with reports representing different ethnic and demographic populations over the world.

3. Patients and methods

This is a retrospective analysis of the patients who attended the Kuwait Cancer Control Center (KCCC) for treatment or follow-up of breast cancer. Based on the Hospital cancer registry, medical files of all patients diagnosed with breast cancer in the period from July 1999 to June 2009 were reviewed. For all patients, the pathology was reviewed to confirm the diagnosis and the hormonal receptor and Her-2-neu status. Pathological diagnosis was based on biopsy from the primary breast lesion even in the context of cases presented with metastasis. We analyzed the clinicopathologic features of 363 triple negative cases which were diagnosed in this period. The TNM staging was based on pathologic findings in patients who had undergone upfront surgical treatment, while it was clinical and radiologic staging in patients who had received neoadjuvant chemotherapy. The disease-free survival (DFS) and overall survival (OS) were analyzed by the Kaplan–Meier method.

ER and PR were assessed using immunohistochemical staining for quantitative and qualitative assessment. Negativity was defined as absent IHC stain in all the examined tissue, i.e. 0%. Her-2-neu scores of 0 and 1 were considered negative, and a score of 3 was considered positive.[14] Score of 2 was considered equivocal and FISH was considered. Ki67 was considered positive if it was more than 10%.

Follow up of patients was scheduled to be every 4 months for the first 2 years post-treatment, every 6 months for the next 3 years then annually. Follow up was by clinical examination and annual mammography. Follow up duration was 41.9 months in average (range 1–131 months). Studies from the USA, Europe, Lebanon, Korea and Japan were reviewed.[23–30]

4. Results

4.1. *Clinical features*

During the period from July 1999 to June 2009, 2980 patients were documented to have breast cancer in KCCC. Out of them, 363 patients (12.2%) were confirmed to have a triple negative disease. Patient characteristics are summarized in Table 1. The mean age was 48 ± 11.7 years for the study population. Median age at the first birth was 23 ± 5.3 years.

4.2. *Pathological features*

Tumor characteristics are summarized in Table 1. Sixty two percent had T1-2 tumor and the mean tumor volume was 3 cm. Majority of cases had node negative (42.8%) and 24.1% had N1 disease. N2-3 disease was the rule in 33.1%. Her-2-neu was negative by IHC staining in 87.6% while FISH was needed to confirm diagnosis in 45 patients.

Treatment modalities are summarized in Table 2. It should be mentioned that, in our patient cohort, 51 patients had not received chemotherapy at all during their treatment course.

4.3. *Pattern of failure Table 3*

There were 100 documented recurrences in our study population. The most common site of recurrence was local recurrence in 10.7% of cases (39% of all recurrences) followed by bone and lung metastasis that occurred in 7.7% of cases each (28% of all recurrences each). Liver metastasis was documented in 5.2%, brain metastasis in 3.8%, and contra-lateral breast recurrence in 2.2%, (19%, 14%, 8% of all recurrences, respectively) (Table 3).

4.4. *DFS and OS (Fig. 1)*

Excluding patients presented with metastatic disease, most of recurrences happened in the first 2–3 years i.e. 81% of recurrences occurred by 2.5 years after treatment. DFS was 76.6%

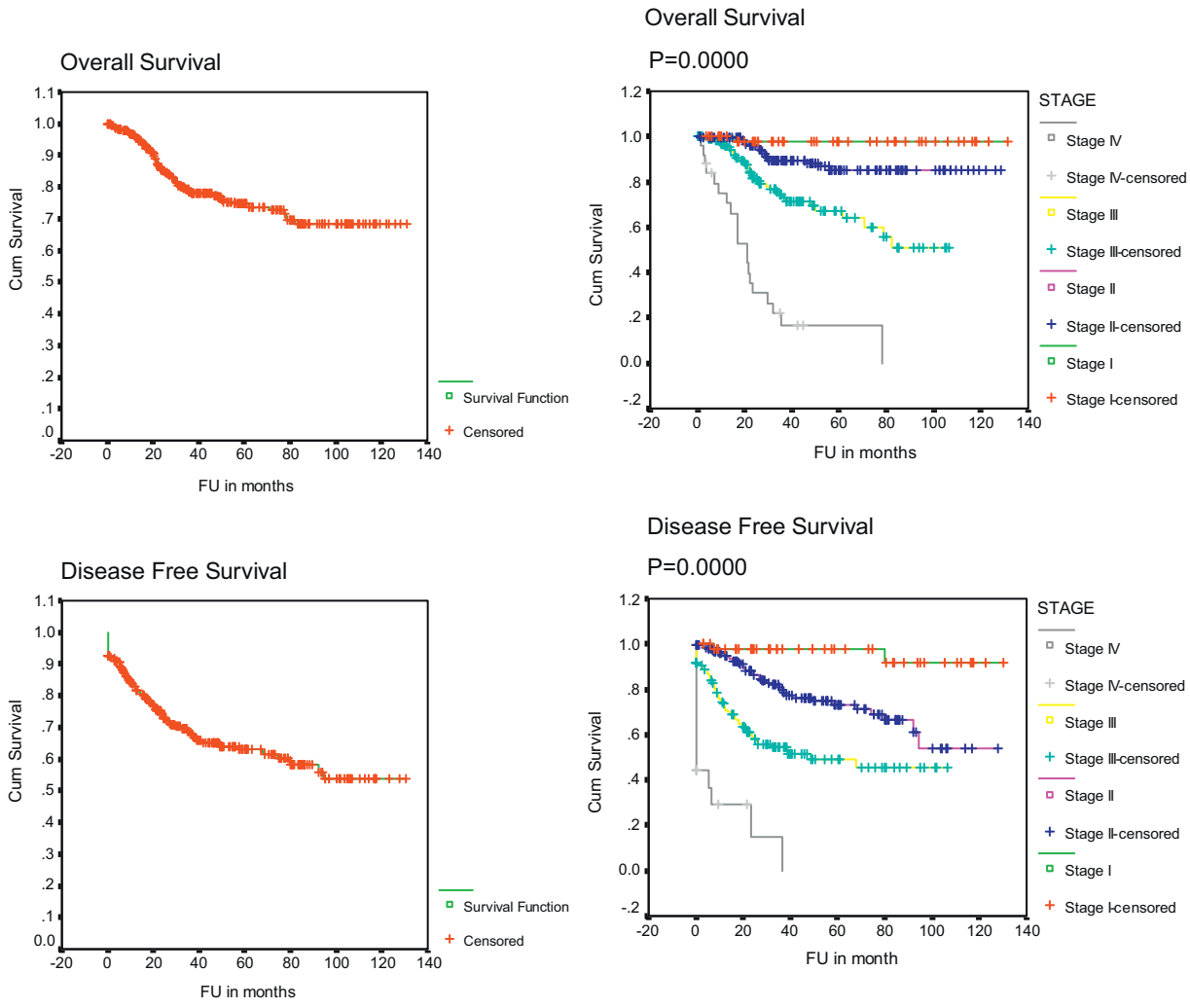

Fig. 1 – DFS and OS of all study cohor (cumulative and by stage).

and 74.4% at 3 and 5 years of follow-up, respectively. OS was 83.2% and 81.5% at 3 and 5 years of diagnosis, respectively.

5. Comparison to other reports from different regions of the world

5.1. *Epidemiology and risk factors (Table 4)*

There have been no prospective studies specifically designed to examine the risk factors associated with specific molecular subtypes of breast cancer. However, several retrospective studies of large population-based cohorts have attempted to answer this question. The epidemiological risk factors for TNBC compared with non-TNBC appear to differ significantly.[15–22] Also, it was observed that the epidemiological and clinicopathologic features of breast cancer vary across the globe. Based on our results analysis, we can confirm that variation also applies to TNBC. We compared our results with results from published peer-reviewed results from the USA, Europe, Turkey, Lebanon, Singapore, Korea and Japan.[23–30] Table 4.

5.2. *Prevalence*

Overall, the prevalence of TNBC in large unselected breast cancer patient cohorts is 11–20%.[10,17,18,20,29,31–35] In the compared studies, Korea seems to have the highest and Lebanon the lowest[27,28] prevalence. In our study, the prevalence of TNBC was 12.2%.

5.3. *Age and reproductive history*

Compared to other breast cancer subtypes, TNBC develops earlier in life, and consequently more often in pre-menopausal women.[18,29,36]

As documented, 63% of patients with triple-negative tumors were diagnosed before the age of 60 compared with fewer than half among those with other tumor types.[17] High average age was noticed in a study from MayoClinic (59.7 years).[35] In a meta-analysis of 1997 patients by Yang et al., the mean age was 56.[26]

However, many studies documented 50 years as the mean age at diagnosis of TNBC.[17,23,29,37] In our study, the mean age was 48 years, younger than the mean age of breast

Table 1 – Patient and tumor characteristics.

	n	%
Ethnicity (n = 363)		
Caucasian	298	82
Asian	65	18
Age (n = 363)		
Bellow 40	88	24
40–60	220	61
Above 60	55	15
Menopausal status (n = 363)		
Premenopausal	221	61
Postmenopausal	142	39
Family history of cancer (n = 349)[a]		
Breast	75	21
Other gynecologic	14	4
Others	7	2
History of breast cancer (n = 344)[a]		
Positive	12	3
Negative	332	97
Smoking (n = 298)[a]		
Yes	23	8
No	275	92
Parity (n = 299)[a]		
More than 3	146	49
History of hormone therapy (n = 210)[a]		
Yes	92	44
No	118	56
Breast feeding (n = 208)[a]		
Yes	132	63
No	76	37
Laterality of breast cancer (n = 363)		
Right	191	53
Left	169	46
Bilateral	3	1
Localization (n = 363)		
UOQ	167	46
Multicentric	38	10
Histological type (n = 363)		
IDC	291	80
ILC	13	4
Medullary	35	10
Mucinous and tubular	9	2
Others	12	4
Grade (n = 320)[a]		
I	33	10
II	105	33
III	182	57
T stage (n = 353)[a]		
T1	63	18
T2	156	44
T3	43	12
T4	91	26
N stage (n = 353)[a]		
N0	151	43
N1	85	24
N2	94	27
N3	23	6
Metastatic at diagnosis (n = 25)[b]		
Bone	15	60
Lung	10	40
Liver	8	32
Stage (n = 353)[a]		
I	49	14
II	148	42
III	131	37
IV	25	7
Ki67 (n = 198)[a]		
Positive	128	65
Negative	70	35
LVI (n = 315)[a]		
Present	90	29
Absent	225	71
DCIS (n = 301)		
Present	77	26
Absent	224	74

[a] Only available data in cohort cases could be analyzed.
[b] Some patients were presented with two or more sites of metastasis.

Table 2 – Treatment modality (n = 363).

	N	%
Surgery (n = 315)		
MRM	201	64
Lumpectomy	114	36
Axillary surgery (n = 309)		
Clearance	295	95
Sampling	14	5
Dissected LN (339)		
0–9	74	22
10–20	165	49
More than 20	100	29
Chemotherapy (n = 304)		
Neoadjuvant	42	14
Adjuvant	194	64
Both	51	17
Palliative	17	5
Type of chemotherapy (n = 304)[a]		
Anthracycline-based	266	87
Taxane-based	144	47

[a] Some patients received both agents.

Table 3 – Pattern of failure (n = 100).

Site of recurrence		% of all cases
Local recurrence	39	10.7
Bone metastasis	28	7.7
Lung metastasis	28	7.7
Liver metastasis	19	5.2
Brain metastasis	14	3.8
Contra-lateral breast cancer	8	2.2

Table 4 – Patient characteristics in different studies.

	Prevalence (%)	Mean age	Premenopausal (%)	Parity (more than 3) (%)	OCP (%)	Smoking history (%)	Family history of cancer (%)
Kuwait[a]	12.2	48	61	50.2	44	7.7	20
Lebanon[26]	9.3	52	48				10
Turkey[29]	10.6	44	70		35		
Singapore[23]	11	53					
Korea[27]	16	45					
Japan[24]		56					
Mayo Clinic[34]		59.7					
Bauer et al.[16]		50		64.6			
Dent et al.[28]		50					
Phipps et al.[37]				57	55		28
Kwan et al.[36]				34	72	49	20

[a] Current study.

cancer in general, independent of phenotype (52 years in Kuwait).[13] Korea and Turkey have the youngest cohort of TNBC patients (44–45),[28,30] while Japan has the oldest (mean age was 56 years).[25] Fifteen percent were younger than 40 years in the study from Singapore versus 24% in our study.[24]

Premenopausal status varied from 70% of patients in Turkey,[30] 48% in Lebanon[27] to 61% of TNBC patients in our study. Parity was considered as a characteristic in TNBC that deserve reporting in many studies (Table 5).[17,37,38] In our study, only 4% were nulliparous (vs. 13% in Yang meta-analysis[26]). This may be related to cultural reasons rather than a fertility issue. Breast feeding was not documented in 41% of our cohort. However, 37.4% of the documented cases lack breast feeding similar to that documented by Millikan et al.[20]

5.4. *History of hormone Intake and smoking*

Forty-four percent gave history of oral contraceptives(OCP) in our cohort as compared by 72% in Kwan et al.[37] study, 55% in Phipps et al. study,[38] and 35% in the Turkish study.[30] Only 7.7% of our study cohort gave history of smoking versus 49% in Kwan et al.[37]

5.5. *Family history*

A positive family history was found in 10% of patients with TNBC in Lebanon compared with 1% of patients with breast cancer when all phenotypes are included.[27,39] In our study, 20% gave that history, similar to that documented by Kwan et al.[37] It was 28% in Phipps et al.[38]

In Yang meta-analysis,[26] having a positive family history of breast cancer was more frequent in case of patients with basal-type tumors compared with patients with ER+/HER2- or PR+/HER2-tumors (25% vs. 22%) in spite of the absence of this difference when classification was based on IHC only (19% vs. 18%). On the other hand, the family history of breast cancer was the same between TNBC and non-TNBC in the Turkish study.[30] It seems that genetic inheritance and family history is an important risk factor in TNBC in Kuwait.

5.6. *Tumor characteristics Table 5*

5.6.1. *Histological presentation of TNBC*

More than 90% of TNBCs exhibit an invasive ductal histology (IDC).[32,40–44] In current study, 81% were IDC. IDC was most predominant in Singapore and Japan (93% and 95%, respectively).[24,25] ILC was interestingly documented in 2% of patients in Singapore[24] vs. about 4% in our current study. This was lately highlighted in an Italian study as 2.3% of their patients expressed the ILC phenotype.[45] This may represent the pleomorphic subtype of ILC.[46] We were very concerned about these 13 patients and pathology review was done.

Additional characteristics of TNBC are frequent metaplastic elements and medullary/atypical medullary features.[40,41,47,48] In our study, 12.9% had metaplastic and/or medullary carcinomatous features of their tumors.

Triple negative cancers are predominately of high histological grade.[10,28,29,40,49–53] In our study, similar to many others, 57% were of high histological grade.[29,47,48,54–58] In Singapore, they documented a higher rate of high grade (77%),[24] similar to a study from Kansas.[23]

But Japan showed the highest predominance of high grade tumors (92%).[25]

5.7. *Ki67*

The high frequency of more aggressive expression profile with low Bcl-2 but high p53 and Ki67 expression was documented in many studies.[15,21,40,49–51,53,52] In our study, 65% of examined specimens showed high mitotic index. Both the Lebanese study and Dent et al.[29] study documented Ki-67 positivity in 50% of patients.[27]

5.8. *Lymphovascular invasion (LVI)*

In the study from Mayo Clinic, LVI was less common in TNBC when compared with HER2+ (18% and 24%, respectively), but both had higher rates than that seen with ER+ (15%, $P = 0.006$).[35] However, in a Turkish trial, there was no difference among both groups.[30]

In our cohort, LVI was documented in 28% of examined specimens; a much higher rate than that in both studies but close to that recorded in the Kansas study (33%).[23]

Table 5 – Tumor characteristics in TNBC in different studies.

	IDC (%)	High grade (%)	Ki67 (%)	LVI (%)	Mean tumor size (cm)	T2 lesion (%)	Stages I and II	LN + ve (%)
Kuwait[a]	81	57	65	28	3	43	56	58
Lebanon[26]	85	63	50				64	50
Turkey[29]		53		19				29.4
Singapore[23]	93	77				70		
Korea[27]		53.7					90	
Japan[24]	95	92				43	86.5	34
Mayo Clinic[34]	88			18				
Bauer et al.[16]								
Dent et al.[28]		63	50		3			54.6
Phipps et al.[37]								
Kwan et al.[36]					2			48
Kansas, US[22]		75		33				

[a] Current study.

5.9. *Size of tumor*

At diagnosis, TNBCs are commonly of larger tumor size.[35,40,49–51,53,52] In our study, the mean tumor size was 3 cm in TNBC group; similar to that in Dent et al.[29] study and larger than other non-TNBC group in the same study (3.0 versus 2.1 cm, respectively; $P < 0.0001$). It was smaller (2 cm) in Tawfik et al.[23] study. Most of tumors were T2 in Singapore study (70%).[24] In both our study and in Japan, T2 represents about 43% of cases of TNBC.[25]

5.10. *Stage*

Ghosn et al.[27] compared the staging of TNBC as found in the Lebanese study with the staging of breast cancer of all phenotypes in Lebanon (stages I and II, 64% versus 75%; stage III, 24% versus 20%. They concluded that TNBC is more often locally advanced at diagnosis.[59,60] In our study, stages I and II represents 56% while stage III represents 37% of TNBC in Kuwait; which means that TNBC patients are diagnosed at a later stage in our community. In Japan, 86.5% have stages I and II while only 10.3% has stage III,[25] while it is 90% and 10%, respectively, in Korea,[28] which may result from more strict and nation-wide screening systems.

In a series of 1263 women diagnosed with invasive breast cancer in the Henry Ford Health System, women with advanced stage (stages III and IV) were 16 times more likely to have triple-negative tumors than those with early-stage [odds ratio (OR) 16.4; 95% confidence interval (CI): 7.8–34.2].[54]

5.11. *Lymph node metastasis*

The presence of positive lymph nodes in the Lebanese study was 50%, while it was detected in 58% in our study. With almost a similar percentage, Dent et al.[29] found that the rate of node positivity was slightly higher in the triple-negative group compared with the other group (54.6% versus 45.6%, respectively; $P = 0.02$). In contrast, non-significant difference was documented by Tawfik et al.[23] in the study from Kansas (48 vs. 41%). Interestingly, the ratio was reversed in the Turkish study (29.4 in TNBC vs. 38.5% in non-TNBC)[11,30] found it to be higher in their study (68%) while it was much lower in Japanese patients (34%).[25]

5.12. *Survival*

5.12.1. *DFS and OS (Fig. 1)*

TNBC accounts for a disproportionate number of BC deaths; the majority of studies indicate a negative impact of a TN.[10,18,20,21,29,61–65] Patients with TNBC typically have a high risk of early recurrence that sharply increases in years 1–4 after diagnosis, and the majority of deaths occur in the first 5 years after treatment.

However, differences between TNBC and non-TNBC regarding overall survival (OS) wear off at 10 years of follow-up.[66]

The risk for late recurrences (i.e. beyond 5 years of diagnosis) is decreased by 50% compared with HR-positive disease.[67] In other words, for women with triple negative disease, a substantial number appear to be cured if they remain recurrence free for the first five years after diagnosis.[68]

Follow-up of about 200 patients diagnosed with TNBC in Toronto between 1987 and 1997 showed a peak of recurrence rate much greater than that of non-TNBC tumors during the first and third years, as well as a higher 5-year mortality rate.[29] This was subsequently confirmed in patients treated with neoadjuvant therapy at M.D. Anderson,[69] who showed a higher 3-year relapse and mortality rates.

In both the Lebanese [27] and US studies (Dent's [29] and Haffty et al.[70] studies), the peak of recurrence occurred after 6–18 months. In our study, this peak was noticed later; at 30 months (81% of recurrence).

In the Mayo Clinic Study, local or regional recurrence developed significantly more often with TN tumors (5.7%) vs. 10.7% in our study. In the same study, at 5 years after surgery, TN patients exhibited an overall survival of 85% vs. 81.5 in our study.[35]

In Korea, during the median 73.3 months of follow-up, the 5-year relapse rates among TNBC was 30.1% vs. 26% in our study, and the 5-year OS rate was 83.1%[28] vs. 77% in the California study.[17]

5.12.2. *Aggressiveness*

The poor prognosis of high-grade TNBC relates to poor disease-free interval in the adjuvant setting,[29,71] shortened progression-free survival in the metastatic setting,[29,72] and the

lack of targeted therapy. However, not all TNBCs are associated with a poor prognosis.[73]

5.12.3. *Locoregional recurrence*

In a study by Haffty et al.[70], they found that the locoregional relapse rate for TNBC appears to be identical to that of other molecular subgroups after conservative surgical management; however, the TN phenotype appears to be associated with a higher rate of distant metastases.

There was no difference between the Lebanese[27] and Haffty et al.[70] studies regarding the sites of metastasis, which were, in order of frequency, the lungs, brain, then liver. Dent and colleagues [29] found few cases in which local recurrence preceded distant metastases; these, in turn, are more common in the viscera and soft tissues than in bone.[74,75]

Several studies have supported a significantly increased rate of visceral versus bone metastasis[57,69] among patients with TNBC compared with non-TNBC. In the largest report to date, data on 12,858 patients indicate an increased risk for lung [odds ratio (OR) 2.27 and brain (OR 5.32) metastasis as first sites of recurrence and lower risk for bone recurrence (OR 0.23) in patients with TNBC.[32]

However, in our cohort, the most common site of recurrence was local recurrence in 10.7% of cases (39% of all recurrences). This was followed by bone and lung metastasis that occurred in 7.7% of cases each (28% of all recurrences each). Then comes liver metastasis in 5.2%, brain metastasis 3.8%, and contra-lateral breast recurrence in 2.2%, (19%, 14%, 8% of all recurrences, respectively).

5.12.4. *Central nervous system metastases*

Patients with TNBC compared with other subtypes reportedly experience an increased risk of central nervous system metastases (CM) of 6–46% of those experiencing metastatic spread of disease.[75–77] Similarly, in a single-institution study among 3193 patients, a significantly elevated risk of CM among patients with TNBC and HER-2-positive BC compared with other phenotypes was reported (HR 4.5 and 4.9 for TNBC and HER-2+, respectively)[76]; the risk of CM was particularly pronounced among young patients with node positive disease: the incidence of CM among patients <50 years of age and node positive was 20.0% for TNBC compared with 4.8% for HER-2 positive. In our study, CM represents the site of metastasis in 14% of the patients experienced metastasis.

Recently, a nomogram has been indicated[78] to calculate the probability for developing cerebral metastasis, particularly for patients with TNBC, the clinical implications and validation of which, however, remain unclear.

6. Conclusion

From the above overview, it seems that TNBC has another aspect of heterogeneity; that is the demographic characteristics of patients.

- A step forward toward genetic studies for TNBC is needed as phenotypic and molecular classifications lake explanation for variable responses and prognosis.
- Regional collaborative studies should be performed in TNBC to define underlying molecular unique characteristics that may affect treatment options in every ethnicity or population.
- Another point is the proper evaluation of the TNBC problem in relation to the whole breast cancer patients in view of cost-effectiveness; especially in middle and low-income countries.

Conflict of interest

None declared.

Disclaimer

None.

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None declared.

REFERENCES

1. Glass AG, Lacey Jr JV, Carreon JD, et al. Breast cancer incidence, 1980–2006: combined roles of menopausal hormone therapy, screening mammography, and estrogen receptor status. *J Natl Cancer Inst* 2007;**99**:1152–61.
2. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;**365**:1687–717.
3. Goldhirsch A, Wood WC, Gelber RD, et al. Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. *Ann Oncol* 2007;**18**:1133–44.
4. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005;**353**:1659–72.
5. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005;**353**:1673–84.
6. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;**344**:783–92.
7. Sparano JA, Goldestin LJ, Childs BH, et al. Genotypic characterization of phenotypically defined triple-negative breast cancer. *J Clin Oncol (Meeting Abstracts)* 2009;**27** [Abstr 500].
8. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature* 2000;**406**:747.
9. Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci U S A* 2001;**98**:10869–74.
10. Rakha E, El-Sayed M, Green A, et al. Prognostic markers in triple-negative breast cancer. *Cancer* 2007;**109**:25–32.
11. Rakha EA, Elsheikh SE, Aleskandarany MA, et al. Triple-negative breast cancer: distinguishing between basal and nonbasal subtypes. *Clin Cancer Res* 2009;**15**:2302–10.

12. Gnanta M, Harbeckb N, Thomssen C. St. Gallen 2011: summary of the consensus discussion. *Breast Care* 2011;**6**:136–41.
13. Motawy M, El Hattab O, Fayaz S, et al. Multidisciplinary approach to breast cancer management in Kuwait, 1993–1998. *J Egypt Natl Canc Inst* 2004;**16**(June 2):85–91.
14. Perez EA, Roche PC, Jenkins RB, et al. HER2 testing in patients with breast cancer: poor correlation between weak positivity by immunohistochemistry and gene amplification by fluorescence in situ hybridization. *Mayo Clin Proc* 2002;**77**:148–54.
15. Brenton JD, Carey LA, Ahmed AA, Caldas C. Molecular classification and molecular forecasting of breast cancer: ready for clinical application? *J Clin Oncol* 2005;**23**:7350–60.
16. Foulkes WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer: review article. *N Engl J Med* 2010;**363**(November 20):1938–48.
17. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California Cancer Registry. *Cancer* 2007;**109**:1721–8.
18. Carey LA, Perou CM, Livasy CA, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. *JAMA* 2006;**295**:2492–502.
19. Morris GJ, Naidu S, Topham AK, et al. Differences in breast carcinoma characteristics in newly diagnosed African-American and Caucasian patients. *Cancer* 2007;**110**:876–84.
20. Millikan R, Newman B, Tse C-K, et al. Epidemiology of basal-like breast cancer. *Breast Cancer Res Treat* 2008;**109**:123.
21. Nielsen TO, Hsu FD, Jensen K, et al. Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma. *Clin Cancer Res* 2004; **10**:5367–74.
22. Viale G, Bottiglieri L. Pathological definition of triple negative breast cancer. *Eur J Cancer* 2009;**45**(Suppl. 1):5–10.
23. Tawfik O, Davis K, Kimler BF, et al. Clinicopathological characteristics of triple-negative invasive mammary carcinomas in African-American versus Caucasian women. *Ann Clin Lab Sci* 2010;**40**(4):315–23 [Fall].
24. Thike AA, Cheok PY, Jara-Lazaro AR, Tan B, Tan P, Tan PH. Triple-negative breast cancer: clinicopathological characteristics and relationship with basal-like breast cancer. *Mod Pathol* 2010;**23**(January 1):123–33 [Epub 2009 Oct 23].
25. Ishikawa Y, Horiguchi J, Toya H, et al. Triple-negative breast cancer: histological subtypes and immunohistochemical and clinicopathological features. *Cancer Sci* 2011;**102**(March 3):656–62, http://dx.doi.org/10.1111/j.1349-7006.2011.01858.x.
26. Yang XR, Chang-Claude J, Goode EL, et al. Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the Breast Cancer Association Consortium studies. *J Natl Cancer Inst* 2011;**103**(February 3):250–63 [Epub 2010 Dec 29].
27. Ghosn M, Hajj C, Kattan J, et al. Triple-negative breast cancer in Lebanon: a case series. *Oncologist* 2011;**16**(11):1552–6 [Epub 2011 Oct 21].
28. Park YH, Lee SJ, Cho EY, et al. Clinical relevance of TNM staging system according to breast cancer subtypes. *Ann Oncol* 2011;**22**(July 7):1554–60 [Epub 2011 Jan 17].
29. Dent R, Trudeau M, Pritchard KI, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. *Clin Cancer Res* 2007;**13**(August 15 Pt 1):4429–34.
30. Aksoy S, Dizdar O, Harputluoglu H, Altundag K. Demographic, clinical, and pathological characteristics of Turkish triple-negative breast cancer patients: single center experience. *Ann Oncol* 2007;**18**(November 11):1904–6.
31. Cheang MC, Voduc D, Bajdik C, et al. Basal-like breast cancer defined by five biomarkers has superior prognostic value than triple-negative phenotype. *Clin Cancer Res* 2008;**14**:1368–76.
32. Lin C, Chien SY, Chen LS, et al. Triple negative breast carcinoma is a prognostic factor in Taiwanese women. *BMC Cancer* 2009;**9**(June):192.
33. Razzak AR, Lin NU, Winer EP. Heterogeneity of breast cancer and implications of adjuvant chemotherapy. *Breast Cancer* 2008;**15**:31–4.
34. Yang XR, Sherman ME, Rimm DL, et al. Differences in risk factors for breast cancer molecular subtypes in a population-based study. *Cancer Epidemiol Biomarkers Prev* 2007;**16**:439–43.
35. Billar JA, Dueck AC, Stucky CC, et al. Triple-negative breast cancers: unique clinical presentations and outcomes. *Ann Surg Oncol* 2010;**17**(Suppl. 3):384–90 [Epub 2010 Sep 19].
36. Rhee J, Han SW, Oh DY, et al. The clinicopathologic characteristics and prognostic significance of triple-negativity in nodenegative breast cancer. *BMC Cancer* 2008;**8**:307, http://dx.doi.org/10.1186/1471-2407-8-307.
37. Kwan ML, Kushi LH, Weltzien E, et al. Epidemiology of breast cancer subtypes in two prospective cohort studies of breast cancer survivors. *Breast Cancer Res* 2009;**11**:R31.
38. Phipps AI, Chlebowski RT, Prentice R, et al. Body size, physical activity, and risk of triple-negative and estrogen receptor-positive breast cancer. *Cancer Epidemiol Biomarkers Prev* 2011;**20**(March 3):454–63 [Epub 2011 Mar 1].
39. Fakhoury W. *Prognostic factor in breast cancer; correlation with other factors; estrogen and progesterone receptors, MIB and histoprognostic grade*. Beirut, Lebanon: Saint-Joseph University; 1996–1997. p. 1–50 [Thesis].
40. Fulford LG, Easton DF, Reis-Filho JS, et al. Specific morphological features predictive for the basal phenotype in grade 3 invasive ductal carcinoma of breast. *Histopathology* 2006;**49**:22–34, http://dx.doi.org/10.1111/j.1365-2559.2006.02453.x.
41. Lakhani SR, Reis-Filho JS, Fulford L, et al. Prediction of BRCA1status in patients with breast cancer using estrogen receptor and basal phenotype. *Clin Cancer Res* 2005;**11**:5175–80.
42. Livasy CA, Karaca G, Nanda R, et al. Phenotypic evaluation of the basal-like subtype of invasive breast carcinoma. *Mod Pathol* 2006;**19**:264–71.
43. Tsuda H, Takarabe T, Hasegawa T, et al. Myoepithelial differentiation in highgrade invasive ductal carcinomas with large central acellular zones. *Hum Pathol* 1999;**30**:1134–9.
44. Tsuda H, Takarabe T, Hasegawa F, et al. Large, central acellular zones indicating myoepithelial tumor differentiation in high-grade invasive ductal carcinomas as markers of predisposition to lung and brain metastases. *Am J Surg Pathol* 2000;**24**:197–202.
45. Montagna E, Maisonneuve P, Rotmensz N, et al. Heterogeneity of triple negative breast cancer: histologic subtyping to inform the outcome. *Clin Breast Cancer* 2013;**13**(1):31–9.
46. Monhollen L, Morrison C, Ademuyiwa FO, et al. Pleomorphic lobular carcinoma: a distinctive clinical and molecular breast cancer type. *Histopathology* 2012;**61**(3):365–77.
47. Reis-Filho JS, Milanezi F, Steele D, et al. Metaplastic breast carcinomas are basal-like tumours. *Histopathology* 2006;**49**:10–21.
48. Jacquemier J, Padovani L, Rabayrol L, et al. Typical medullary breast carcinomas have a basal/myoepithelial phenotype. *J Pathol* 2005;**207**:260–8.
49. Foulkes WD, Brunet JS, Stefansson IM, et al. The prognostic implication of the basal-like (cyclin E high/p27 low/p53+/glomeruloid-microvascularproliferation+) phenotype of BRCA1-related breast cancer. *Cancer Res* 2004;**64**:830–5.

50. Tian XS, Cong MH, Zhou WH, Zhu J, Chen YZ, Liu Q. Clinicopathologic and prognostic characteristics of triple-negative breast cancer. *Onkologie* 2008;**31**:610–4.
51. Dogan L, Atalay C, Yilmaz KB, Ozaslan C. Prognosis in hormon receptor negative breast cancer patients according to ERBB2 status. *Neoplasma* 2008;**55**:544–8.
52. Nishimura R, Arima N. Is triple negative a prognostic factor in breast cancer? *Breast Cancer* 2008;**15**:303–8.
53. Chivukula M, Striebel JM, Ersahin C, Dabbs DJ. Evaluation of morphologic features to identify "basal-like phenotype" on core needle biopsies of breast. *Appl Immunohistochem Mol Morphol* 2008;**16**:411–6.
54. Stark A, Kapke A, Schultz D, Brown R, Linden M, Raju U. Advanced stages and poorly differentiated grade are associated with an increased risk of HER2/neu positive breast cancer only in white women: findings from a prospective cohort study of African-American and white-American women. *Breast Cancer Res Treat* 2008;**107**:405–14.
55. Rakha EA, Reis-Filho JS, Ellis IO. Basal-like breast cancer: a critical review. *J Clin Oncol* 2008;**26**:2568–81.
56. Reis-Filho JS, Tutt ANJ. Triple negative tumours: a critical review. *Histopathology* 2008;**52**:108–18.
57. Rodriguez-Pinilla SM, Sarrio D, Honrado E, et al. Vimentin and laminin expression is associated with basal-like phenotype in both sporadic and BRCA1-associated breast carcinomas. *J Clin Pathol* 2007;**60**:1006–12.
58. Vincent-Salomon A, Gruel N, Lucchesi C, et al. Identification of typical medullary breast carcinoma as a genomic subgroup of basal-like carcinomas, a heterogeneous new molecular entity. *Breast Cancer Res* 2007;**9**:R24.
59. El Saghir NS, Seoud M, Khalil MK, et al. Effects of young age at presentation on survival in breast cancer. *BMC Cancer* 2006;**6**:194.
60. El Saghir NS, Shamseddine AI, Geara F, et al. Age distribution of breast in Lebanon: Increased percentages and age adjusted incidence rates of younger-aged groups at presentation. *J Med Liban* 2002;**50**:3–9.
61. Dolle JM, Daling JR, White E, et al. Risk factors for triple-negative breast cancer in women under the age of 45 years. *Cancer Epidemiol Biomarkers Prev* 2009;**18**: 1157–66.
62. Sorlie T, Tibshirani R, Parker J, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. *Proc Natl Acad Sci U S A* 2003;**100**:8418–23.
63. Abd El-Rehim D, Graham B, Pinder S, et al. High-throughput protein expression analysis using tissue microarray technology of a large well-characterised series identifies biologically distinct classes of breast cancer confirming recent cDNA expression analyses. *Int J Cancer* 2005;**116**:340–50.
64. Carey LA, Dees EC, Sawyer L, et al. The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes. *Clin Cancer Res* 2007;**13**:2329–34.
65. Williams DJ, Cohen C, To TV, et al. Triple-negative breast carcinoma in women from Vietnam in the United States: characterization of differential maker expression by tissue microarray. *Hum Pathol* 2009;**40**:1176–81.
66. Gluz O, Liedtke C, Gottschalk N, Pusztai L, Nitz U, Harbeck N. Triple-negative breast cancer – current status and future directions. *Ann Oncol* 2009;**20**:1913–27.
67. Nofech-Mozes S, Trudeau M, Kahn H, et al. Patterns of recurrence in the basal and non-basal subtypes of triple-negative breast cancers. *Breast Cancer Res Trea* 2009;**118**:131–7.
68. Anderson WF, Pfeiffer RM, Dores GM, Sherman ME. Comparison of age distribution patterns for different histopathologic types of breast carcinoma. *Cancer Epidemiol Biomarkers Prev* 2006;**15**(10):1899–905.
69. Liedtke C, Mazouni C, Hess KR, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. *J Clin Oncol* 2008;**26**:1275–81.
70. Haffty BG, Yang Q, Reiss M, et al. Locoregional relapse and distant metastasis in conservatively managed triple negative early-stage breast cancer. *J Clin Oncol* 2006;**24**:5652–7.
71. Tischkowitz M, Brunet J-S, Begin L, et al. Use of immunohistochemical markers can refine prognosis in triple negative breast cancer. *BMC Cancer* 2007;**7**:134.
72. Harris L, Broadwater G, Lin N, et al. Molecular subtypes of breast cancer in relation to paclitaxel response and outcomes in women with metastatic disease: results from CALGB 9342. *Breast Cancer Res* 2006;**8**:R66.
73. Ismail-Khan R, Bui MM. A review of triple-negative breast cancer. *Cancer Control* 2010;**17**(July 3):173–6.
74. Smid M, Wang Y, Zhang Y, et al. Subtypes of breast cancer show preferential site of relapse. *Cancer Res* 2008;**68**:3108–14.
75. Lin NU, Claus E, Sohl J, Razzak AR, Arnaout A, Winer EP. Sites of distant recurrence and clinical outcomes in patients with metastatic triple-negative breast cancer: high incidence of central nervous system metastases. *Cancer* 2008;**113**:2638–45.
76. Heitz F, Harter P, Traut A, et al. Cerebral metastases (CM) in breast cancer (BC) with focus on triple-negative tumors. Presented at the 44th Annual American Society of Clinical Oncology Meeting; May 30–June 3, Chicago, IL. *J Clin Oncol* 2008;**26**(May 20 Suppl.) [Abstract 1010].
77. Dawood S. Triple-negative breast cancer epidemiology and management options. *Drugs* 2010;**70**(17):2247–58.
78. Pusztai L, Rouzier R, Pusztai L, et al. A specific nomogram to predict subsequent brain metastasis in metastatic triple-negative breast cancer patients. *J Clin Oncol* 2009;**27** (Abstr 1028).