Centrally Located Breast Cancer Is More Aggressive in Bahraini Patients

Hamdi Al Shenawi, ACS, FRCSI* Rami Yaghan, FRSCI, JBSO** Noor Al Shenawi*** Amer Almarabheh, PhD**** Lamees Yaghan, MBBS***** Fatima Al Shenawi*** Suhair AlSaad, ACS, FRCSI*

ABSTRACT

Introduction: Breast cancer behaves differently according to the primary tumor location. Medially located breast tumors were thought to have a worse prognosis than laterally located breast tumors. Studies showed that central tumors tend to present at a relatively more advanced stage with more features of a locally advanced disease. Lateral, medial, and central breast tumors are not well studied in Bahrain and worldwide; therefore, we aimed to clarify the incidence & clinicopathological characteristics of each and to explore the impact of primary tumor location on the prognosis.

Materials and Methods: This is a cross-sectional, retrospective review involving 233 consecutive breast cancer Bahraini female patients that were divided into 3 groups in relation to primary tumor location: lateral, medial, and central. Pertinent clinicopathological variables were analyzed in relation to the primary tumor localization in the breast.

Results: Lateral breast cancer patients (N=133, 57.1%), medial breast cancer patients (N=64, 27.5%), and central breast cancer patients (N=36, 15.4%). Chi-square test showed a significant association between central tumor location and tumor size (p-value=0.008), lymph node status (p-value=0.010), and tumor stage (p-value=<0.001).

Conclusion: This is the first study from Bahrain regarding the possible impact of primary tumor location on the outcome of breast cancer. Although the lateral breast tumors have the highest incidence, the central tumors were more likely to present with a locally advanced disease, larger than 5 cm tumor size, and axillary lymph node metastasis. They also tended to have a higher ratio of lymphovascular invasion and HER2 over expression. Multicenter meta-analysis is needed to evaluate the real impact of primary tumor location and internal mammary lymph node evaluation on the outcome of breast cancer.

Key words: Breast cancer, Lateral, Medial, Central, Bahrain, Size of tumor, Tumor stage

INTRODUCTION

Breast cancer is the most common malignancy in females worldwide. It surpasses lung cancer and has accounted for about 2.3 million new cases in 2020 (11.7% of all cancers)[1]. In Bahrain, breast cancer had the highest incidence among all malignancies. In the year 2020, 244 new breast cancer cases were diagnosed, constituting 20.1% of all the newly diagnosed cancers in Bahrain[2]. In recent years, breast cancer mortality in the developed countries has decreased, yet it is still one of the most common causes of death from cancer in less developed countries[3,4]. In Bahrain, breast cancer attributed to 11.1% of cancer related mortality in 2020, only second to lung cancer[2].

The prognosis of breast cancer is related to several clinicopathological variables. Factors associated with worse prognosis include: younger age at diagnosis, primary tumor size, tumor grade, negative hormonal receptors, overexpression of human epidermal growth factor (HER2), ipsilateral positive axillary lymph node involvement, lymphovascular invasion. Therefore, it is important to stratify breast cancer according to the clinicopathological characteristics to improve management strategies[5-8].

* Department of Surgery
College of Medicine and Medical Sciences
Arabian Gulf University, Bahrain.
E-mail: hamdims@agu.edu.bh
** Department of Surgery
College of Medicine and Medical Sciences
Arabian Gulf University, Bahrain.
Department of Surgery and Urology
Faculty of Medicine
Jordan University of Science and Technology, Irbid, Jordan.
*** Undergraduate medical student
College of Medicine and Medical Sciences
Arabian Gulf University, Bahrain.
**** Department of Family and Community Medicine
College of Medicine and Medical Sciences
Arabian Gulf University, Bahrain.
***** Medical Skills & Simulation Center
Arabian Gulf University, Bahrain.

The impact of tumor location on prognosis is less understood both quantitively and qualitatively. The most frequent site of tumor location is in the upper outer quadrant (UOQ) of the breast. It is associated with better survival when compared with other quadrants[5,9]. While if the tumor is located primarily in the medial quadrants of the breast it is associated with lower survival rates than the lateral ones, despite a lower incidence of axillary lymph node metastasis[3]. This fact could be explained based on the proximity to internal mammary lymph nodes, which are not usually evaluated or biopsied in breast cancer management[5,10,11]. On the other hand, centrally located breast cancer (subareola & nipple) has shown a higher incidence of axillary lymph node metastasis in some studies[5,12].

This study aims to report the distribution of breast cancer according to location of the primary tumor among Bahraini women, the clinicopathological characteristics of each location, and to explore the impact of primary tumor location on the prognosis.

MATERIALS AND METHODS

This is a cross-sectional, retrospective review of a particular ethnic population that involved 238 consecutive Bahraini breast cancer patients diagnosed between August 1999 and October 2021. All patients were treated by the first, second, and last author in governmental and private hospitals affiliated to the Arabian Gulf University (AGU) (Salmaniya Medical Complex, Al Kindi Hospital and Al Salam Specialist Hospital). Three synchronous bilateral breast cancer and two malignant phyllodes patients were excluded leaving 233 patients who were subjected to this study. The patients were divided into 3 groups according to the primary tumor location: lateral (includes upper outer and lower outer quadrant tumors), medial (includes upper inner and lower inner quadrant tumors), and central (includes all central subareolar and nipple tumors) groups. (Figure 1)

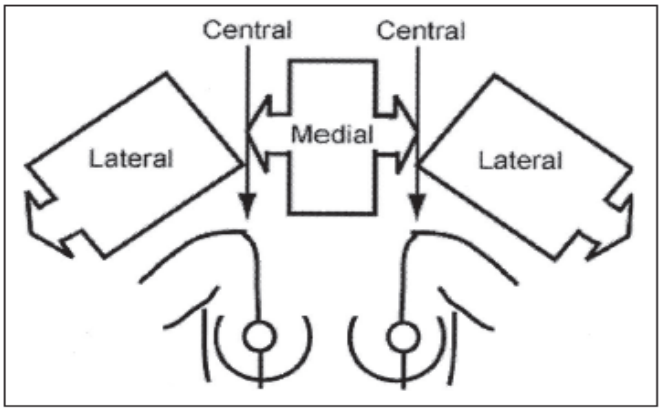

Figure 1: Primary breast tumor location map adopted in this study

The following clinical variables were analyzed in each location: mean age at diagnosis (below 40 and above or equal to 40 years of age), nulliparity, history of breast feeding, early menarche (11 years and below), late menopause (50 years and above), age at first delivery (less than 30 and above or equal to 30 years of age), prolonged use of oral contraceptive pills (OCP), use of hormonal replacement therapy (HRT), past history of malignancy, and family history of malignancy for breast, ovarian, colonic, and prostate cancers, menopausal status, recurrence of the primary tumor, site of recurrence (local or distant) and five-year survival rate.

The following pathological variables were analyzed in each location: tumor size (5 cm and below and above 5 cm), lymph node status, metastasis at presentation (M0 or M1), vascular and lymphatic invasion, estrogen and progesterone receptors (ER/PR), HER2 status, tumor stage: early (T0, T1, T2, N0-N2, M0), locally advanced (T3, T4, N0-N2, M0) or distant metastasis (Any T, any N, M1), and tumor grade (grade I, II and III).

Statistical analysis was performed using SPSS software for Windows version 28.0 (SPSS Inc., Chicago, IL, USA). Qualitative variables were summarized using descriptive statistics and were reported as frequencies and percentages. Quantitative variables were presented as means and standard deviations. Clustered bar chart was used to present the association between two categorical variables. Chi-Square test was used to determine whether there is a significant association between two categorical variables. Two-sided p-value < 0.05 was considered statistically significant.

RESULTS

The 233 patients were divided into three groups; the lateral breast cancer patients (N=133, 57.1%), the medial breast cancer patients (N=64, 27.5%), and the central breast cancer patients (N=36, 15.4%). (Table 1)

Table 1: Distribution of tumor location

Tumor Location	N (%)
Lateral	133 (57.1)
Medial	64 (27.5)
Central	36 (15.4)

Clinical Variables: The results of Chi-Square test of the association between all clinical variables analyzed and tumor location (lateral, medial and central) showed no statistically significant differences (p-value). (Table 2)

Late menopause was in 23.2% of breast cancer patients but was noticed higher in the central breast cancer patients (N=5, 38.5).

Recurrence was higher in the medial breast cancer patients (N=14, 25%) and similar in the lateral and the central breast cancer patient groups (N=25, 20.8%, N=7, 20.6%). Local recurrence was higher in the medial breast cancer patients (N=5, 8.5%) but distant recurrence was higher in the central and the lateral breast cancer patients' groups (N=5, 16.7%, N=18, 14.6%), respectively.

Regarding the mean age between the three locations showed that central breast cancer patients presented 4 years younger than the lateral breast cancer patients.

Pathological Variables

The results of Chi-Square test of the association between pathological characteristics and tumor location (Table 3) showed a significant association between tumor location (lateral, medial and central) and tumor size:(χ^2=9.712, df=2; p-value=0.008), lymph node status: (χ^2=9.271, df=2; p-value=0.010), and tumor stage:(χ^2=27.861, df=6; p-value<0.001).

Regarding tumor size, p-value was 0.008. Tumors with sizes less than or equal to 5cm were higher in the medial and the lateral breast cancer patients, (N=56, 87.5%, N=116, 87.2%), respectively. The tumor with sizes above 5 cm was highest in the central breast cancer patients (N=12, 33.3%), while the lateral and the medial were almost the same (around 12.5% each). (Figure 2)

Regarding positive axillary lymph node status, p-value was 0.010. It was the highest in the central breast cancer patients (N=25, 69.4%), followed by the lateral breast cancer patients (N=74, 55.6%). The

Table 2: Association between clinical variables and tumor location

Clinical Characteristics	Classification	Tumor Location						Total		P-value
		Lateral		Medial		Central				
		No. of Patients	%	No. of Patients	%	No. of Patients	%	No.	%	
Age at diagnosis (Years)	< 40	23	17.3	12	18.8	12	33.3	47	20.2	0.098
	>= 40	110	82.7	52	81.3	24	66.7	186	79.8	
Nulliparity	Yes	31	23.3	12	18.8	9	25	52	22.3	0.707
	No	102	76.7	52	81.3	27	75	181	77.7	
History of breastfeeding	Yes	95	71.4	46	73	25	69.4	166	71.5	0.930
	No	38	28.6	17	27	11	30.6	66	28.4	
Early menarche	Yes	21	18.1	12	22.2	6	17.1	39	19	0.778
	No	95	81.9	42	77.8	29	82.9	166	81	
Late menopause	Yes	13	22.4	4	16.7	5	38.5	22	23.2	0.317
	No	45	77.6	20	83.3	8	61.5	73	76.8	
Age at 1st delivery	<30 year	84	66.1	45	73.8	27	75.0	156	69.6	0.610
	>=30 year	12	9.5	4	6.5	1	2.8	17	7.6	
	No children	31	24.4	12	19.7	8	22.2	51	22.8	
Use of OCP	Yes	28	21.7	21	34.4	6	16.7	55	24.3	0.082
	No	101	78.3	40	65.6	30	83.3	171	75.7	
Use of HRT	Yes	3	2.3	3	4.8	1	2.8	7	3.1	0.646
	No	127	97.7	60	95.2	35	97.2	222	96.9	
Past history of malignancy	Yes	2	1.5	4	6.3	0	0.0	6	2.6	0.085
	No	129	98.5	60	93.7	36	100	225	97.4	
Family history of malignancy	Yes	41	31.1	26	40.6	11	30.6	78	33.6	0.387
	No	91	68.9	38	59.4	25	69.4	154	66.4	
Menopause status	Yes	61	45.9	28	44.4	15	41.7	104	44.8	0.902
	No	72	54.1	35	55.6	21	58.3	128	55.2	
Recurrence of tumor	Yes	25	20.8	14	25	7	20.6	46	21.9	0.807
	No	95	79.2	42	75	27	79.4	164	78.1	
Site of recurrence	Local	5	4.1	5	8.5	2	6.7	12	5.6	0.759
	Distant Metastasis	18	14.6	7	11.9	5	16.7	30	14.2	
	No	100	81.3	47	79.7	23	76.7	170	80.2	
Five-year survival rate	Yes	90	81.1	43	76.8	25	89.3	158	81	0.618
	No	17	15.3	9	16.1	2	7.1	28	14.4	
	Lost follow up	4	3.6	4	7.1	1	3.6	9	4.6	
Mean Age at diagnosis (Years) Mean±S.D		50.92±11.54		49.19±10.70		47.44±11.66				

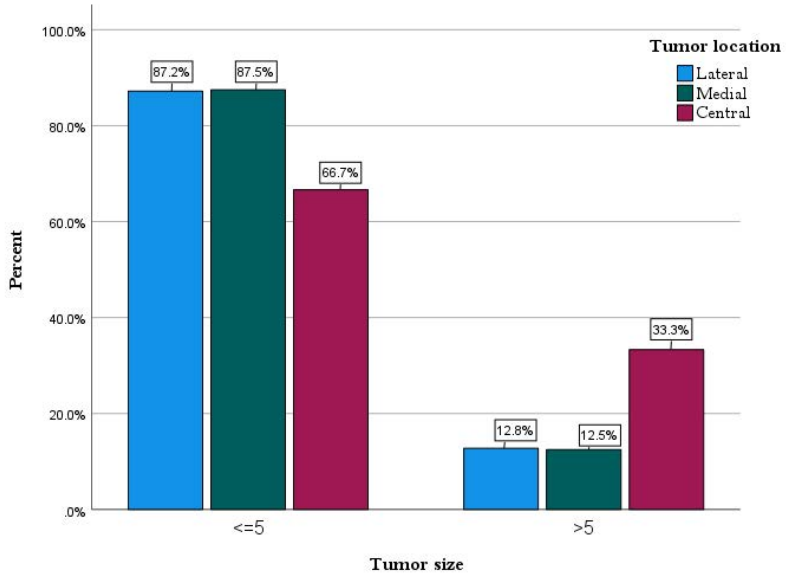

Figure 2: Association between tumor location and tumor size

Table 3: Association between pathological variables and tumor location

Pathological Characteristics	Classification	Tumor Location						P-value
		Lateral		Medial		Central		
		No. of Patients	%	No. of Patients	%	No. of Patients	%	
Tumor size	≤5	116	87.2	56	87.5	24	66.7	**0.008**
	>5	17	12.8	8	12.5	12	33.3	
Lymph node status	Positive	74	55.6	25	39.1	25	69.4	**0.010**
	Negative	59	44.4	39	60.9	11	30.6	
Metastasis	M_O	61	45.9	33	51.6	23	63.9	0.439
	M_1	5	3.8	2	3.1	1	2.8	
	M_x	67	50.4	29	45.3	12	33.3	
Vascular and lymph invasion	Positive	54	43.5	27	44.3	18	52.9	0.432
	Negative	68	54.8	33	54.1	14	41.2	
	Unknown	2	1.6	1	1.6	2	5.9	
ER/PR receptors	Positive	77	62.1	40	65.6	23	69.7	0.697
	Negative	47	37.9	21	34.4	10	30.3	
HER2 status	Positive	47	36.4	23	35.9	14	43.8	0.719
	Negative	82	63.6	41	64.1	18	56.3	
Tumor Stage	Early	97	72.9	50	78.1	15	41.7	**<0.001**
	Locally Advanced	18	13.5	6	9.4	16	44.4	
	Distant metastasis (M1)	14	10.5	7	10.9	2	5.6	
	Early multi focal	4	3	1	1.6	3	8.3	
Grade of primary tumor	Grade i	14	11.5	6	10.2	0	0	0.452
	Grade ii	56	45.9	28	47.5	20	60.6	
	Grade iii	47	38.5	21	35.6	11	33.3	
	Not assessable	5	4.1	4	6.8	2	6.1	

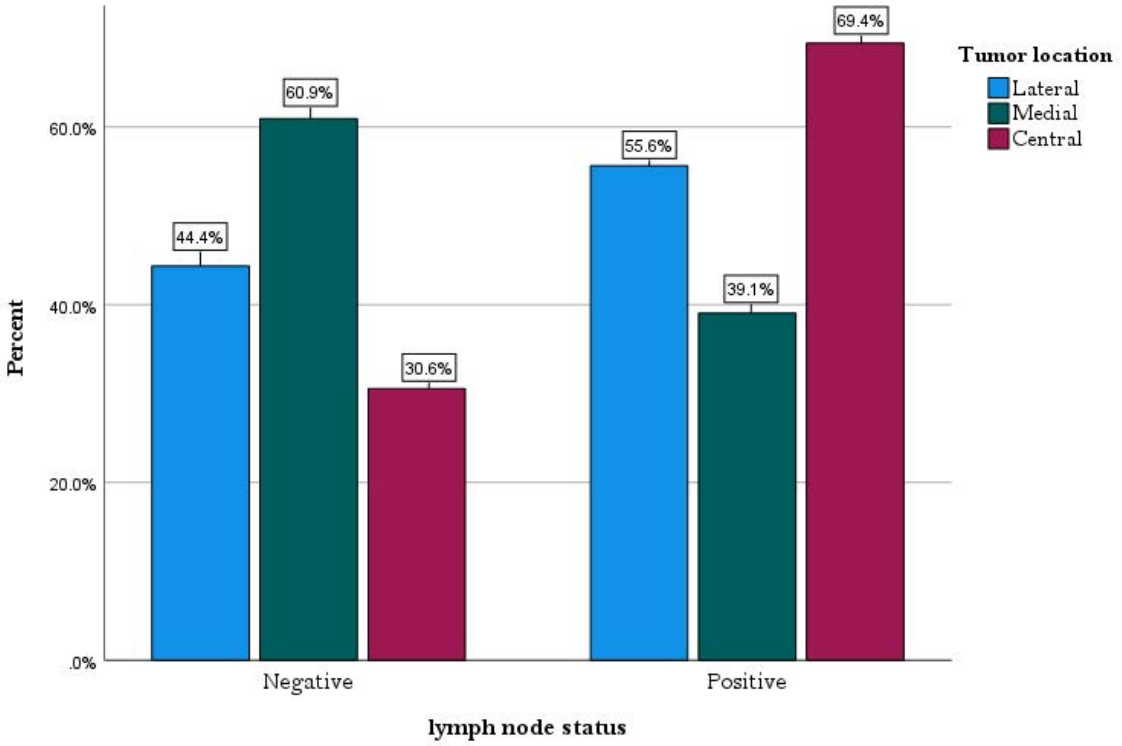

Figure 3: Association between tumor location and lymph node status

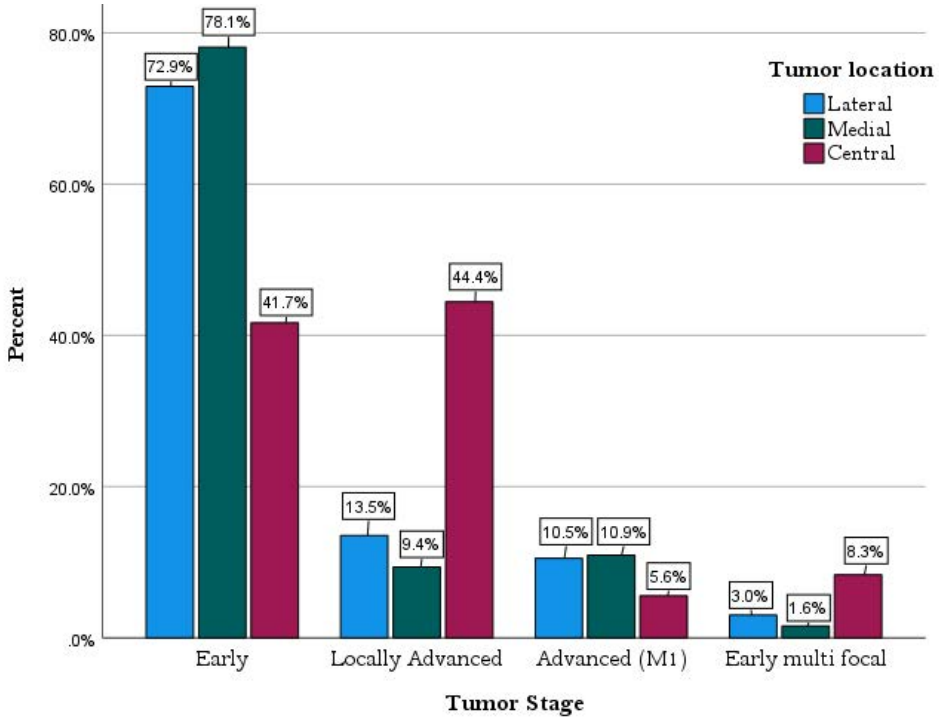

Figure 4: Association between tumor location and tumor stage

lowest positive axillary lymph node status was in the medial breast cancer patients (N=25, 39.1%). (Figure 3)

Regarding tumor stage analysis was statistically significant (p-value=<0.001). The early tumor stage was higher in both the medial and lateral breast cancer patients (N=50, 78.1%; N=97, 72.9%). (Figure 4)

The locally advanced tumor stage was higher in the central breast cancer patients (N=16, 44%), followed by the lateral (N=18, 13.5%) and the medial (N=6, 9.4%) respectively. The distant metastasis stage (M1) was high in both the medial and the lateral breast cancer patients (N=7, 10.9%, N=14, 10.5%) respectively. (Figure 4)

The other pathological variables did not show significant p-value but showed higher incidence of vascular and lymphatic invasion in the central breast cancer patients (N=18, 52.9%) while the medial and the lateral breast cancer patients were similar (N=27, 44.3%, N=54, 43.5%) respectively. HER2 was highest in the central breast cancer patients (N=14, 43.8%), Grade of the tumor, showed highest grade II results in the central breast cancer patients (N=20, 60.6%), while grade III results were almost the same in the three locations.

Regarding metastasis and ER/PR, those variables did not show any difference between different locations.

DISCUSSION

Location of the primary tumor is considered one of the auxiliary factors that might affect the prognosis of breast cancer. There is relatively good evidence in the literature that central tumors tend to be associated with a more locally advanced disease, a higher risk of local recurrence, a higher risk of distant metastasis, and thus a reduced prognosis[13-16]. However, the current standard of care management limits the impact of primary tumor location to the choice of the most appropriate type of surgery for local control and cosmetic considerations, with no impact on the type of systemic treatment modalities. This study revisits this issue by reviewing the pertinent clinicopathological aspects in a group of Bahraini population.

In this study, two-thirds of the patients (57.1%) were in the lateral group, and less than one third were in the medial group, and one-sixth of the patients were in the central group. This is consistent with medical literature. Lohrisch et al[13] and Zucali et al[17], reported a 65.7% and 61.5% lateral location, respectively. It has been suggested that the higher incidence of benign and malignant diseases of the breast in the lateral location is due to the presence of the largest amount of breast tissue in this location[18]. Despite the fact that the central group included the lowest number of patients in this study, the most important observations were related to this group.

Among our study group, the ratio of patients presenting at an age younger than 40 years was highest in the centrally located tumors (33%), compared to around 18 % in both of the medial and lateral location groups. Younger age at diagnosis is usually associated with more aggressive features of breast cancer[19-21].

Among our study group, the relative ratio of tumor size larger than 5 cm was the highest in the central group. This is similar to the report by Rummel et al., they suggested that central breast tumors present with larger tumor sizes because they are more difficult to detect mammographically[22]. Patients might also find difficulties in detecting tumors below the nipple areola complex leading to a delay in medical consultation[23].

Our results showed that central tumors had the highest risk of positive axillary lymph nodes. The ratio of axillary lymph node involvement was 69.4%, 55.6%, 39.1%in the central, lateral, and medial groups respectively. This finding is similar to many other published studies[5,9,12,24].

The propensity of central and lateral tumors to have a higher ratio of axillary lymph node involvement is most likely a reflection of a closer proximity to the axillary lymph nodes rather than a less aggressive

nature of tumors in the medial location. In fact, some researchers believe that medial location might be associated with a higher chance of occult or overt internal mammary lymph node metastases[11,14,25-28]. According to the current protocols of breast cancer management, internal mammary lymph node are usually ignored, either due to habit, lack of a specific investigation, or difficulty in obtaining biopsies[11,25,27]. A Korean study on medial tumors with negative axillary lymph nodes showed a poorer prognosis[10]. They suggested that because internal mammary lymph nodes were not evaluated, patients with negative axillary lymph nodes but potentially positive internal mammary lymph nodes might had a lower chance of receiving chemotherapy[10]. To improve the algorithm of treatment in medial breast cancer patients, this fact is worth considering. Two studies published in 2001 showed that sentinel lymph node biopsies of the internal mammary lymph nodes might be positive in 9-45% of cases[29,30]. Marco Colleoni et al. recommended to evaluate the sentinel internal mammary nodes in medial tumors either by biopsy or new imaging techniques such as lymphoscintigraphy and positron emission tomography scanning[26]. Targeting internal mammary lymph nodes with radiotherapy showed a favorable outcome and improved local control in high-risk early breast cancer patients[13]. The expected hazard, however, will be a potentially higher radiotoxicity to the pericardium.

Among our study group, the presence of a locally advanced disease was 44.4%, 13.5%, 9.4% in the central, lateral and medial groups respectively. Recurrence with distant metastases was highest in the central location (16.7%). Lateral breast cancer patients presented at an early stage in 72.9%, tumor size less 5cm in 87.2 %, and positive axillary lymph nodes in 55.6%. If compared with medial and central locations, lateral location can be considered the best prognosis of the three locations. This was also concluded in other studies[22].

Among our study group, the centrally located tumors were found to have a higher incidence of vascular and lymphatic invasion and HER-2 overexpression yet it was statistically not significant.

Critiques: Although a statistically significant association between a central location and a locally advanced disease, a larger than 5 cm tumor size, and axillary lymph nodes metastasis was demonstrated in this study, the low number of patients limited statistically based conclusions of the other clinical pertinent variables. A global limitation in literature is that some studies stratified locations to a medial hemisphere and a lateral hemisphere of the breast, while others (like our study) used the lateral, medial, and central stratifications. This calls for further multicenter meta-analysis to explore the prognostic impact of primary breast cancer location.

CONCLUSION

This is the first study from Bahrain regarding the possible impact of primary tumor location on the outcome of breast cancer. Although the lateral breast tumors have the highest incidence, the central tumors were more likely to present with a locally advanced disease, larger than 5 cm tumor size, and axillary lymph nodes metastasis. They also tended to have a higher ratio of lymphovascular invasion and HER2 overexpression. Multicenter meta-analysis is needed to evaluate the real impact of primary tumor location and internal mammary lymph node evaluation on the outcome of breast cancer.

Authors' Contributions: "HA, SKA-S, and RY contributed to conception and design of the study. SKA-S and NA organized the database. AA performed the statistical analysis. HA and SKA-S wrote the first draft of the manuscript. HA, RY, NA, AA, LY, FA and SKA-S wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version."

Availability of Data and Materials: The datasets generated and/or analysed during the current study are not publicly available due to patients' privacy could be compromised but are available from the corresponding author on reasonable request.

Ethical Considerations: This research was approved by the Ethical committee of CMMS-AGU, Bahrain. (Reference number: E006-PI-9/20).

All methods were performed in accordance with the relevant guidelines and regulations.

Consent for participation, our research was approved by Ethical committee of CMMS-AGU which include exemption from consent as it is not applicable.

Potential Conflict of Interest: None

Competing Interest: None

Acceptance Date: 24 February 2023

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: Cancer J Clin 2021;71(3):209-49.
2. The Global Cancer Observatory, Gco.iarc.fr.2021. 2021.
3. Harbeck N, Gnant M. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet 2017;389(10074):1134-50.
4. DeSantis CE, Ma J, Goding Sauer A, et al. Breast cancer statistics, 2017, racial disparity in mortality by state. CA: Cancer J Clin 2017;67(6):439-48.
5. Ji F, Xiao WK, Yang CQ, et al. Tumor location of the central and nipple portion is associated with impaired survival for women with breast cancer. Cancer Manag Res 2019;11:2915-25.
6. Nicolini A, Ferrari P, Duffy MJ. Prognostic and predictive biomarkers in breast cancer: Past, present and future. Semin Cancer Biol 2018;52(1):56-73.
7. Denkert C, Liedtke C, Tutt A, et al. Molecular alterations in triple-negative breast cancer—the road to new treatment strategies. Lancet 2017;389(10087):2430-42.
8. Győrffy B, Hatzis C, Sanft T, et al. Multigene prognostic tests in breast cancer: past, present, future. Breast Cancer Res 2015;17(1):1-7.
9. Sohn VY, Arthurs ZM, Sebesta JA, et al. Primary tumor location impacts breast cancer survival. Am J Surgery 2008;195(5):641-4.
10. Hwang KT, Kim J, Kim EK, et al. Poor prognosis of lower inner quadrant in lymph node–negative breast cancer patients who received no chemotherapy: a study based on nationwide Korean breast cancer registry database. Clin Breast Cancer 2017;17(4):e169-84.
11. Bräutigam E, Track C, Seewald DH, et al. Medial tumor localization in breast cancer–an unappreciated risk factor? Strahlentherapie und Onkologie 2009;185(10):663-8.
12. Desai AA, Hoskin TL, Day CN, et al. Effect of primary breast tumor location on axillary nodal positivity. Ann Surgical Oncol 2018;25(10):3011-8.
13. Lohrisch C, Jackson J, Jones A, et al. Relationship between tumor location and relapse in 6,781 women with early invasive breast cancer. J Clin Oncol 2000;18(15):2828-35.

14. Wang YT, Chen ZJ, Zhang D, et al. Effect of the primary tumor location on the prognosis of breast invasive ductal carcinoma patients treated with radical mastectomy. Zhonghua zhong liu za zhi. Chinese J Oncol 2019;41(9):686-92.
15. Siotos C, McColl M, Psoter K, et al. Tumor site and breast cancer prognosis. Clin Breast Cancer 2018;18(5):e1045-52.
16. Montagna E, Bagnardi V, Rotmensz N, et al. Outcome and medial presentation of breast cancer: European Institute Of Oncology Experience. Clin Breast Cancer 2015;15(6):440-7.
17. Zucali R, Mariani L, Marubini E, et al. Early breast cancer: evaluation of the prognostic role of the site of the primary tumor. J Clin Oncol 1998;16(4):1363-6.
18. Lee AH. Why is carcinoma of the breast more frequent in the upper outer quadrant? A case series based on needle core biopsy diagnoses. Breast 2005;14(2):151-2.
19. Anders CK, Johnson R, Litton J, et al. Breast cancer before age 40 years. Semin Oncol 2009;36(3):237-49.
20. Al Saad SK, Al Shenawi HM, Shamsi NM. Risk factor of breast cancer in Bahrain. Bahrain Med Bull 2009.
21. Al Saad SK, Jalal AA. Breast cancer risk factors and stage at presentation. Bahrain Med Bull 2006;28(3):1-8.
22. Rummel S, Hueman MT, Costantino N, et al. Tumour location within the breast: Does tumour site have prognostic ability? Cancer Med Science 2015;9.
23. Del Riego J, Pitarch M, Codina C, et al. Multimodality approach to the nipple-areolar complex: a pictorial review and diagnostic algorithm. Insights Imag 2020;11(1):1-27.
24. Lewis EI, Ozonoff A, Nguyen CP, et al. Breast cancer close to the nipple: does this increase the risk of nodal metastasis at diagnosis? Canadian Assoc Radiologists J 2011;62(3):209-14.
25. Sarp S, Fioretta G, Verkooijen HM, et al. Tumor location of the lower-inner quadrant is associated with an impaired survival for women with early-stage breast cancer. Ann Surgical Oncol 2007;14(3):1031-9.
26. Colleoni M, Zahrieh D, Gelber RD, et al. Site of primary tumor has a prognostic role in operable breast cancer: the international breast cancer study group experience. J Clin Oncol 2005;23(7):1390-400.
27. Lohrisch C, Jackson J, Jones A, et al. Relationship between tumor location and relapse in 6,781 women with early invasive breast cancer. J Clin Oncol 2000;18(15):2828-35.
28. Gaffney DK, Tsodikov A, Wiggins CL. Diminished survival in patients with inner versus outer quadrant breast cancers. J Clin Oncol 2003;21(3):467-72.
29. Uren RF, Howman-Giles R, Renwick SB, et al. Lymphatic mapping of the breast: locating the sentinel lymph nodes. World J Surg 2001;25(6):789-93.
30. Van der Ent FW, Kengen RA, van der Pol HA, et al. Halsted revisited: internal mammary sentinel lymph node biopsy in breast cancer. Ann Surg 2001;234(1):79.