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Risk Factors That Have Effect on Breast Cancer Recurrence in Rizgary Oncology Center in Erbil

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Abstract

Background and objectives: Breast cancer is a heterogeneous disease with variations in clinical behavior and biological features that lead to variations in response to treatments and survival. The aim of this study was to look for the histopathological and therapeutic factors associated with breast cancer recurrence. **Methods:** In this retrospective study, 100 locally recurrent or distant metastatic breast cancer cases were reviewed between 2008 -2016 in Rizgary Oncology Center in Erbil to find out the most important risk factors that have effect on breast cancer recurrence.

Results: The current study revealed that, grade of disease has a great effect on breast cancer recurrence, when 64.9% of patients with grade III disease have had disease recurrence within the first 2 years from the date of diagnosis. Also, this study showed that, within the first two years from the date of diagnosis, 57.9% of stage III cases have had disease recurrence. Adding more, within the first two years, 36.4% of the triple negative subtype and 41% of human epidermal growth factor receptor 2 enriched subtype had disease recurrence within that period. Concerning the effect of delay in receiving adjuvant radiotherapy, 65.2% of those patients that were waited for more than two months to receive adjuvant radiotherapy had disease recurrence within the first two years. **Conclusions:** Several factors have important effect on the disease recurrence like stage of the disease, grade, molecular subtypes and delays in receiving adjuvant radiotherapy. All of them are independently causing earlier recurrence of breast cancer.

Keywords: Breast Cancer; Recurrence; Radiation therapy.

Introduction

Breast cancer is the most frequent cancer and is the second most common cancer related death, just after lung cancer, among women in the world[1]. Incidence rates vary across the world regions, it range from 27 per 100,000 in Middle Africa and Eastern Asia to 96 in Western Europe, but inversely, Breast cancer mortality rates are highest in Western Africa and lowest in Eastern Asia, this partly reflects varying data quality worldwide[2]. This variation in survival rates between world regions is lower than that for incidence because of the more favorable survival from breast cancer in developed regions with high incidence[3]. These variations in incidence, mortality, and survival may be due to several underlying complex factors including age, ethnicity, diet, lifestyles, early detection program, and advances in treatment[4, 5].

Five years survival rate for female patients with breast cancer has improved in the past three decades, because of improvements in treatment (i.e., adjuvant chemotherapy, hormone therapy, radiotherapy and targeted drugs) and earlier detection through increased awareness and widespread use of mammography[6]. Therefore, these treatment modalities should be tailored as soon as possible, as delays in their initiation may affect clinical outcomes[7, 8].

The size of the tumor and the status of the axillary lymph nodes provide accurate information on the likelihood of tumor relapse[9, 10]. Tumor histology and grade are proved to be associated with survival[11, 12]. Histological grading, when carried out in an adequate manner, provides a simple, inexpensive, and highly accurate method to assess biological characteristics of the disease and patient prognosis[13]. Molecular subtypes like Luminal A and Luminal B, Human Epidermal Growth Factor receptor 2 (HER2) and triple negative breast cancer (TNBC) at presentation is another prognostic and predictive marker in treatment selection in breast[14].

Many studies had been carried out internationally to discover the factors that affects the survival of breast cancer,

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but in our country the risk factors for breast cancer recurrences is far from clear. The aim of this study was to look for the histopathological and therapeutic factors associated with breast cancer recurrence.

Patients and methods

In this retrospective study, a hundred of locally recurrent and distant metastatic breast cancer patients who had disease recurrence between 2008 -2016 in Rizgary Oncology Center in Erbil. The data of this study were retrospectively retrieved from archived patient's case material at the registry unit. Eligible subjects included all female patients who have been diagnosed previously as a case of breast cancer, operated on and received adjuvant therapy. Exclusion criteria included those patients who were presented as a stage IV breast cancer at presentation. For this study, a written official permission has been taken from Rizgary Oncology Center as the main Center for collecting study samples. All the files were reviewed to provide the following data on each subject: Histopathology, Immunohistochemistry, Imaging reports, date and site of recurrence. Also, their Radiotherapy archived materials reviewed separately at the Rizgary Radiotherapy center registry unit for further information and specifically to find out waiting time for receiving adjuvant radiotherapy after completing the adjuvant chemotherapy protocol.

Regarding the Histopathological subtype, grade, lymphovascular invasion (LVI), Perineural invasion (PNI) and staging of the disease of almost all of the patients were taken from their pathology reports. For the others, the information was taken from the case files. Regarding molecular subtype; ER, PR, and HER 2 have been detected by immunohistochemistry, but concerning HER-2 tumors that exhibited an IHC score of +2 were verified by fluorescence in situ hybridization (FISH).

Times to Relapse (TTR) or disease-free survival (DFS) defined as the interval between the diagnosis and the first tumor local recurrence or occurrence of metastases either by imaging or biopsy results or both. Then the results were compared with published international and regional data.

Results

The results of this study showed that, 60% of the involved patients were diagnosed with breast cancer at the age of 40-60 years while only 5% of them were diagnosed at the age of 20-29 years and 2% of them diagnosed at the age of more than 70 years. Their mean ages at diagnosis were 46.1 (S.D.±10.182) years.

Regarding their histopathologies, 94% of the patients presented with infiltrative ductal carcinoma (IDC) but only 1% presented with infiltrative lobular carcinoma (ILC) and ductal carcinoma in situ (DCIS). Furthermore, the remained 4% of the patients presented witha mixture of both IDC + ILC.

When grade of disease was examined alone, 64.9% of patients with grade III disease have had disease recurrence within the first 2 years from the date of diagnosis, while 32.4% of grade III diseases had disease recurrence within 2-5 years and only 2.7% of the grade III diseases had disease recurrence after 5 years from the date of diagnosis, Table (1).

Table (1): Correlation between grade and Time to Relapse

		Time to Relapse by year		
		Within 2 years	2-5 years	>5 years
Grade	G I	0.0%	50.0%	50.0%
	G II	32.7%	49.1%	18.2%
	G III	64.9%	32.4%	2.7%

Regarding the patient's molecular subtype, Luminal, HER2 enriched and TNBC molecular subtypes were 38.7%, 39.8 and 21.5%, respectively. All the patients within the age of 20-29 years were HER2 enriched or TNBC molecular subtype. Also 50% of the patients between the age of 30-39 presented with stage III and 56% of the patients within this range of age presented with either HER2 enriched or TNBC molecular subtype.

By comparing molecular subtype to time to relapse, 57% of the luminal subtype patients remained disease free for more than 5 years, while 35% of HER2 enriched subtype and only 7% of TNBC subtype remained disease free for more than 5 years, Table (2).

Table (2): Correlation between Molecular Subtype and Time to relapse by years

	Time to relapse by years					
	Within 2 years		2-5 years		>5 years	
Molecular subtype	N	%	N	%	N	%
Luminal	9	20.5%	21	50.0%	8	57.1%
HER2 enriched	19	43.1%	15	35.7%	5	35.7%
Triple negative	16	36.4%	6	14.3%	1	7.1%

N: number of patients %: percentage of patients

The results showed that 0-9 lymph nodes were removed in 29 patients when axillary lymph node dissection was undergone as the primary surgical treatment. Adding more, 42 patients were undergoing lymph node dissection by removing 10-19 lymph nodes. For the remaining cases 20 or more lymph nodes were removed, Figure 1. The numbers of removed lymph nodes of 11 cases were unknown.

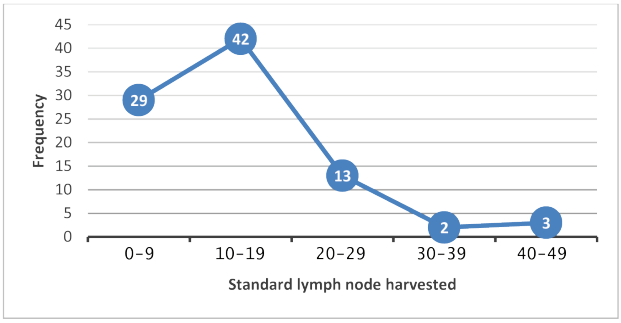

Figure (1): Number of removed lymph nodes within recurrent breast cancer cases.

By looking the effect of stage on recurrence, Table (3), 57.9% of stage III, and 24.3% of stage II cases had disease recurrence within the first two years of diagnosis. While no any case of stage I had disease recurrence within that period.

Table (3): Correlation between Stage at presentation and Time to Relapse

		Time To relapse by years		
		< 2 years	2-5 years	>5 years
Stage	I	0.00%	63.30%	36.70%
	II	24.30%	51.20%	24.50%
	III	57.90%	33.70%	8.40%

Regardless of the stage at presentation, those patients who have had disease recurrence within the first 2 years from the date of diagnosis, 20.5% of them were luminal subtypewhile 36.4% of them were TNBC subtype and 43.1% of them were HER2 enriched subtype.

Regarding the type of operation, 82% of the patients had mastectomy and axillary lymph node dissection (ALND), 15% of patients had BCS and ALND and for the other 3% of patients ALND has not been done; (2 patients had mastectomy only and one patient had BCS only).

Concerning the effect of delay in receiving Radiotherapy on breast cancer recurrence, this study demonstrated that 65% of the patients who were waited to receive radiotherapy for more than 2 months developed disease recurrence with first two years, in contrast 45% of those patients who were waited to receive radiotherapy less than two months had recurrence within two years Table (4). In follow up of the studied cases, 10% of patients, who received adjuvant radiotherapy in less than 2 months, were remain free from disease for more than 5 years while only 4.3% of those who waited for more than two months after completing chemotherapy remain free from disease for more than 5 years.

Table (4): The effect of delay in receiving radiotherapy on breast cancer recurrence

		Time to Relapse		
		< 2 years	2-5 years	> 5 years
Waiting to receive RT	<2 months	45.0%	45.0%	10.0%
	>2 months	65.3%	30.4%	4.3%

RT: Radiotherapy

Discussion

Breast cancer is a heterogeneous disease, and it has different biologic features with different clinical outcomes and responses to therapy depending on the available risk factors like age, grade, stage of disease at presentation and molecular subtype. Breast cancer in young age women present with higher stage tumors, hormone receptor negative, higher grade with higher rate of lymphovascular invasion, Ki-67 and p53 mutations[15]. By looking at the age distribution of the involved patients in this study, it is noticed that our patients have got breast cancer in a younger age in comparison to other studies that have been conducted in other Middle East and Gulf countries[16,17]. The reason behind this difference is that this study has been done on recurrent cases not on newly diagnosed case. As if the younger age group of our recurrent cases may represent that, age is an independent adverse prognostic factor

which has been confirmed in other studies[18].

Independent of lymph node status and tumor size, Grade of disease in invasive breast cancer is a powerful indicator of disease recurrence and patient death[19, 20]. Interestingly the results of this study is concordant with international data when it is found that, high grade diseases have earlier recurrence in comparison with low and intermediate grade diseases, Table (1).

Molecular subtyping is a good indicator to assess the aggressiveness of breast cancer at presentation and it is another important prognostic factor to identify patients at increased risk of Loco-regional recurrence and distant metastases[21]. When Luminal A subtype has lowest recurrence rate but the other subtypes like HER2 enriched and TNBC have higher recurrence rate after either breast conserving therapy or mastectomy[22, 23]. This study find out that, 48.1% of stage IIIC diseases were HER2 enriched subtype at presentation, while only 16.7% of the patients with stage IA diseases presented with HER2 enriched subtype. Adding to that, 60% of TNBCs present with stage III when diagnosed at presentation. That is why HER2 enriched and TNBC subtypes should be staged thoroughly at the beginning. Also, there is a racial and geographical variation within the molecular subtypes too[24]. So, it is worthy to do further studies on molecular subtypes at least in our locality.

One of the most significant prognostic factors for patients with invasive breast cancer is Axillary lymph node involvement[25]. The NCCN panel recommends level 1 or 2 axillary dissections when sentinel nodes are not identified[26]. Traditional level 1 and 2 evaluation of axillary lymph nodes requires that at least 10 lymph nodes should be provided for pathologic evaluation to accurately stage the axilla[27]. In contrast, this study showing that 29 out of 89 patients were staged by removing less than 10 lymph nodes, Figure 1, it means that a large number of our patients are not adequately staged surgically at presentation.

There is a large volume data showing that the effect of radiation therapy in improving breast cancer treatment results[28]. Beside the importance of post mastectomy and BCS adjuvant radiotherapy, some studies determine that delay in the initiation of RT is associated with increased risk of local recurrence in breast cancer [29-31]. Although there are many studies couldn't find association between waiting times for radiotherapy and survival32. This study demonstrated that those patients who are waited to receive radiotherapy for more than two months have earlier local recurrence in comparison to those received radiotherapy within 2 months after completing 4-8 cycles of chemotherapy. Although this subject is still controversial and we have a small sample size data, but our result goes with that delay in receiving radiotherapy have bad effect on breast cancer local recurrence.

Conclusions

This study showed that grade of cell differentiation, stage of the disease at presentation and molecular subtype were independent risk factors for breast cancer recurrence. Furthermore, waiting time for receiving Radiotherapy was an important factor for local recurrence. The study finds out that there is long waiting list to receive adjuvant radiotherapy post mastectomy or breast conserving surgeries that have negative effect on breast cancer recurrence however this issue is still debatable and needs more studies with big sample sizes. In addition, there are a number of patients undergoing inadequate lymph node removing at the operation according to the international guidelines (NCCN Clinical Practice Guidelines in Oncology).

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics. CA: a cancer journal for clinicians. 2016; 66(1):7-30.

2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA: a cancer journal for clinicians. 2015; 65(2):87-108.

3. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. International journal of cancer. 2015; 136(5) E359-E86.

4. Hortobagyi GN, de la Garza Salazar J, Pritchard K, et al. The global breast cancer burden: variations in epidemiology and survival. Clinical breast cancer. 2005; 6(5):391-401.

5. De La Rochefordiere A, Campana F, Fenton J et al. Age as prognostic factor in premenopausal breast carcinoma. The Lancet. 1993; 341(8852):1039-43.

6. Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. New England Journal of

Medicine. 2005; 353(17):1784-92.

7. Chen Z, King W, Pearcey R, Kerba M, Mackillop WJ. The relationship between waiting time for radiotherapy and clinical outcomes: a systematic review of the literature. Radiotherapy and Oncology. 2008; 87(1):3-16.

8. Gagliato Dde M, Gonzalez-Angulo AM, Lei X, et al. Clinical impact of delaying initiation of adjuvant chemotherapy in patients with breast cancer. J Clin Oncol. 2014; 32 (8): 735-44.

9. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. Cancer. 1989; 63(1):181-7.

10. Sohrabi A, Sandoz J, Spratt JS, Polk HC. Recurrence of breast cancer: Obesity, tumor size, and axillary lymph node metastases. JAMA. 1980; 244(3):264-5.

11. Makki J. Diversity of breast carcinoma: histological subtypes and clinical relevance. Clinical Medicine Insights: Pathology. 2015; 8:23-31

12. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with longşterm followşup. Histopathology. 1991;19(5):403-10.

13. Rakha EA, Reis-Filho JS, Baehner F, et al. Breast cancer prognostic classification in the molecular era: the role of histological grade. Breast Cancer Research. 2010; 12(4):207.

14. Onitilo AA, Engel JM, Greenlee RT, Mukesh BN. Breast cancer subtypes based on ER/PR and Her2 expression: comparison of clinicopathologic features and survival. Clinical medicine & research. 2009; 7(1-2):4-13.

15.Klauber-DeMore N. Tumor biology of breast cancer in young women. Breast disease. 2006 ;23(1):9-15.

16. Al-Moundhri M, Al-Bahrani B, Pervez I, et al. The outcome of treatment of breast cancer in a developing country—Oman. The Breast. 2004;13(2):139-45.

17.Nissan A, Spira RM, Hamburger T, et al. Clinical profile of breast cancer in Arab and Jewish women in the Jerusalem area. The American journal of surgery. 2004;188(1):62-7.

18. El Saghir NS, Seoud M, Khalil MK, et al. Effects of young age at presentation on survival in breast cancer. BMC cancer. 2006; 6(1):194.

19. Ivshina AV, George J, Senko O et al. Genetic reclassification of histologic grade delineates new clinical subtypes of breast cancer. Cancer research. 2006; 66(21):10292-301.

20. Lundin J, Lundin M, Holli K et al. Omission of histologic grading from clinical decision making may result in overuse of adjuvant therapies in breast cancer: results from a nationwide study. Journal of clinical oncology. 2001;19(1):28-36.

21. Voduc KD, Cheang MC, Tyldesley S, Gelmon K, Nielsen TO, Kennecke H. Breast cancer subtypes and the risk of local and regional relapse. Journal of Clinical Oncology. 2010; 28(10):1684-91.

22.Lowery AJ, Kell MR, Glynn RW, Kerin MJ, Sweeney KJ. Locoregional recurrence after breast cancer surgery: a systematic review by receptor phenotype. Breast cancer research and treatment. 2012; 133(3):831-41.

23. Dawood S, Hu R, Homes MD, et al. Defining breast cancer prognosis based on molecular phenotypes: results from a large cohort study. Breast cancer research and treatment. 2011; 126(1):185-92.

24.Carey LA, Perou CM, Livasy CA, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. Jama. 2006; 295(21):2492-502.

25.Lyman GH, Giuliano AE, Somerfield MR, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. Journal of clinical oncology. 2005; 23(30):7703-20.

26. National Comprehensive Cancer Network. Breast Cancer (Version 3.2017). Available from https://www.nccn. org/professionals/physician_gls/pdf/breast.pdf. Accessed November 11, 2017.

27. Kiricuta CI, Tausch J. A mathematical model of axillary lymph node involvement based on 1446 complete axillary dissections in patients with breast carcinoma. Cancer. 1992; 69(10):2496-501.

28. Recht A, Comen EA, Fine RE, et al. Postmastectomy radiotherapy: an american society of clinical oncology, american society for radiation oncology, and society of surgical oncology focused guideline update. Practical radiation oncology. 2016; 6(6):e219-34

29. Huang J, Barbera L, Brouwers M, Browman G, Mackillop WJ. Does delay in starting treatment affect the outcomes of radiotherapy? A systematic review. Journal of clinical oncology. 2003; 21(3):555-63.

30. Benk V, Joseph L, Fortin P, et al. Effect of delay in initiating radiotherapy for patients with early stage breast cancer. Clinical Oncology. 2004; 16(1):6-11.

31.Faculty of Radiation Oncology Quality Improvement Committee. Management of waiting lists in radiation oncology "Quality in the timeliness of patient care"–Version 2. The Royal Australian and New Zealand College of Radiologists. 2013. Available from http://ranzcr.edu.au/about/faculty-of-radiation-oncology/899-faculty-publication.

32.Downing A, Gilthorpe MS, Dodwell D, Lawrence G, Forman D. Waiting times for radiotherapy after breast-conserving surgery and the association with survival: a path analysis. Clinical Oncology. 2011; 23(7):442-8.