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Evaluation of Pattern of Relapse in Luminal Breast Cancer

Mohamed Ahmed Abdelaziz
Department of Clinical Oncology and Nuclear Medicine, Al Azhar University,Cairo,
moha_abdelaziz@outlook.com

Eslam Mohamed Ebrahim
Department of Clinical Oncology and Nuclear Medicine, Al Azhar University,Cairo

Mohsen Salah El-Din Zikry
Department of Clinical Oncology and Nuclear Medicine, Al Azhar University,Cairo

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Cover Page Footnote

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ORIGINAL ARTICLE

Evaluation of Pattern of Relapse in Luminal Breast Cancer

Mohamed Ahmed Abdelaziz*, Eslam Mohamed Ebrahim, Mohsen Salah El-Din Zikry

Department of Clinical Oncology and Nuclear Medicine, Al Azhar University, Cairo, Egypt

Abstract

Background: **The most common molecular subtype of breast cancer worldwide is luminal breast cancer. It has shown a good prognostic profile compared to other types. Despite the immense development of adjuvant treatment in the past years, around 20% of patients with early-stage disease relapse.**

Aim of the study: **To evaluate the relapse pattern in luminal breast cancer and the correlation between luminal types and (AJCC 8th edition).**

Subject and methods: **A total of 230 luminal breast cancer patients treated at Al-Hussein University Hospital between 2013 and 2018 were analyzed. Patients have been divided into the following groups: luminal A (31%) and B (32.6%), luminal B HER2+ve (18.6%), and luminal UC (17.3%).**

Results: **The median follow-up was 66.7 months, and the relapse rate of luminal breast cancer was 27.8%. Although statistically not significant, luminal A had the lowest relapse rate (19.4%), while luminal B (36%), HER2 positive luminal B (23.2%), and luminal UC (32.5%) ($P = 0.117$). The predominant organ relapse was bone (29.6%) mainly observed in luminal A and B, 35.7% and 32.3% of patients respectively ($P = 0.048$). Luminal Correlation with the AJCC staging system was significant, luminal A was most often observed in early stages with 81.9% presented in Stages I to II ($P = 0.008$).**

Conclusion: **Luminal breast cancer has a wide discrepancy in relapse rate and pattern. Luminal A seems to have the best prognosis for DFS. Ki-67% and HER2 testing would give a prognostic factor in luminal subcategorization and could be beneficial in the intensification of adjuvant therapy.**

Keywords: Breast cancer, Luminal type, Adjuvant, Relapse, AJCC

1. Introduction

The most prevalent type of cancer in the world is breast cancer. It represents about 11.7% of all malignant tumors globally, with an estimated incidence of 2.3 million cases around the world.[1] Breast cancer is the most common malignancy in Egyptian women, representing 38.8% of malignancies in this demographic, with a projected number of cases of breast cancer of over 23,000 by 2020.[2] Our understanding of the biology of breast cancer has changed as a result of gene expression profiling.[3] The past several years have seen the classification of four primary basic molecular subtypes of breast cancer: luminal A, luminal B, HER2-enriched, and basal-like. Each of these subtypes has unique characteristics, clinical behaviors, and therapeutic response profiles.[4] The St. Gallen expert consensus panel endorsed a molecular-based strategy and sub-categorization of luminal and nonluminal breast cancer in 2011, and in 2021, the panel agreed to spare adjuvant chemotherapy in early luminal breast cancer with ki67% less than 30%.[5,6] Luminal subcategorization has had a lot of changes in the past years. Luminal A is currently described as having ER positive (ER+), PgR positive (PR+), and HER2 negative (HER2-) with less than 30% Ki67 expression,[7] however in 2011 luminal A was early defined by ki67% as less than 14%, and

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* Corresponding author at: Clinical oncology and nuclear medicine, Clinical Oncology, and nuclear medicine Department, Al Hussein University Hospital, Cairo, Egypt.
E-mail address: Moha_abdelaziz@outlook.com (M.A. Abdelaziz).

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have been updated in 2013 to 20%.[8,9] Luminal breast cancer has shown a very good prognostic profile compared to other types of breast cancer, with a relapse rate of almost 20% of cases in the first 10 years.[10] Pattern of relapse has a wide discrepancy between luminal subtypes and that discrepancy has affected the choice of further lines of treatment in advanced setting.[11,12] Also the choice of adjuvant endocrine treatment has recently been updated with the introduction of novel target therapies with CDK4/6 inhibitors in high-risk patients or PARP inhibitors in high-risk germline BRCA mutant patients.[13,14] Accordingly, the present study's goal was to assess the pattern of relapse in luminal breast cancer and the correlation between luminal types and the 2018 American Joint Committee on Cancer Staging Version (AJCC 8th edition).

2. Patient and methods

Patients having a diagnosis that has been pathologically proven will be included in this retrospective study with breast invasive carcinomas, ER + ve, PR + ve, HER2 −ve, HER2 +ve (Luminal Breast Cancer) referred to the Clinical Oncology and Nuclear Medicine department at the Al Hussein University Hospital, Al-Azhar University's faculty of medicine, between January 1, 2013, and December 31, 2018.

In our study, we analyzed 354 pathologically proven women with breast cancer for eligibility. Women having de-novo metastatic breast cancer ($n = 12$), breast lymphoma or sarcoma ($n = 3$), patients who were referred for postoperative radiotherapy ($n = 38$), triple-negative patients ($n = 32$), HER2 enriched cases ($n = 21$), lost follow-up cases ($n = 11$), age more than 70 ($n = 3$), synchronous dual malignancy ($n = 2$) and ductal carcinoma in situ DCIS ($n = 2$) were excluded from our study (Fig. 1).

2.1. Molecular classification

According to the immunohistochemistry profile, the following breast cancer molecular subtypes were classified: luminal A (ER/PR + ve, HER2 -ve, Ki67 < 30%), luminal B (ER/PR positive, HER2 negative, ki67 ≥ 30%) or (ER positive, PR negative, HER2 negative, regardless of ki67%), luminal B HER2 positive (ER/PR + ve, HER2 +ve), HER2 enriched subtype (ER/PR -ve, HER2 +ve) and triple negative (ER/PR -ve, HER2 -ve).[7] We found luminal cases with non-identified Ki67% or HER2 status, and they were considered luminal unclassified subtype (luminal UC) ($n = 40$).

2.2. Statistical methods

SPSS Version 26.0 (SPSS, Chicago, IL, USA) was used to conduct the statistical calculations. The Chi-square, or Fisher's exact test, was used to compare patient and tumor characteristics amongst breast cancer subtypes. The chi-square test was used to evaluate the relationship between the relapse site and the tumor subtype. The cumulative incidence curves of recurrence have been estimated using a competing risk approach. The Kaplan–Meier method was used to study the probability distribution for DFS and OS. The statistical analyses were two-sided, and statistical significance was determined by P values less than 0.05.

3. Results

This study had 230 cases in all, and the median follow-up was 66.7 months. Patients have been classified according to luminal subtypes as luminal A 72/230 (31.3%), luminal B 75/230 (32.6%), luminal B HER2 positive (luminal BH) 43/230 (18.7%) and luminal UC 40/230 (17.4%) patients. As regard the age at the time of presentation, it ranged between 21 and 70 years luminal A mean age was 51.3 years, while luminal B, luminal B HER2 +ve, and luminal UC were 47, 47.15, and 47.67 years, respectively.

Luminal types and their relation with menopausal status, family history, and grade showed no significant association, on the other hand, tumor size, nodal status and histological types showed high significant associations (Table 1).

The Association of luminal types and AJCC 8th edition was significant ($P = 0.008$). Luminal A had a predominance in early stages I to II with 81.7% of cases being in those stages, while luminal B and B HER2 positive were markedly observed in stages II and III (Fig. 2).

Among our luminal breast cancer patients, DFS and OS weren't significantly different, luminal A had the highest 5 years disease-free survival with 83%, however luminal B 66%, luminal B HER2 positive 76%, and luminal UC 75% ($P = 0.091$) (Fig. 3 and Table 2).

Incidence of relapse in our studied population was 27.8%, although no significant difference, luminal A had the lowest relapse rate (19.4%), luminal B (36%), luminal B HER2 (23.2%), and luminal unclassified (32.5%) ($P = 0.117$) (Table 3, Fig. 4).

As regard overall survival, again no significant difference between luminal types, 5 years overall survival for luminal A was 95%, luminal B 87%,

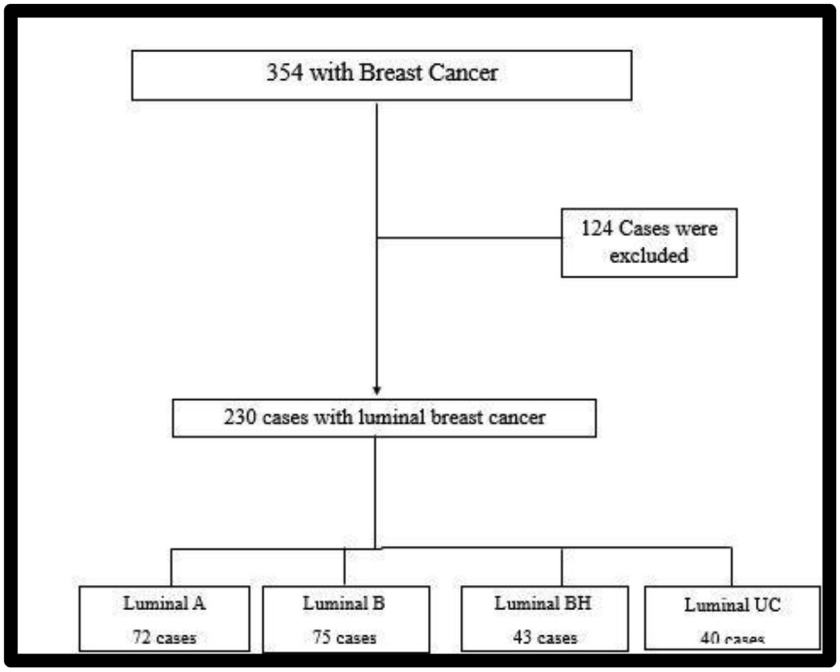

Fig. 1. Study design.

Table 1. Association between luminal types and all parameters in our patients.

Parameters	Luminal A ($n = 72$) N (%)	Luminal B ($n = 75$) N (%)	Luminal BH ($n = 43$) N (%)	Luminal UC ($n = 40$) N (%)	P value
Menopausal					
Pre	35 (48.6%)	44 (58.6%)	19 (44.1%)	28 (70%)	**0.064**
Post	37 (51.3%)	31 (41.3%)	24 (55.8%)	12 (30%)	
Family History					
Yes	14 (19.4%)	14 (18.6%)	9 (20.9%)	8 (20%)	**0.992**
No	58 (80.5%)	61 (81.3%)	34 (79.06%)	32 (80%)	
Histology type					
IDC	64 (88.88%)	71 (94.67%)	41 (95.34%)	36 (90%)	**0.02**
ILC	4 (5.55%)	1 (1.33%)	0 (0)	1 (2.5%)	
Mixed	0 (0%)	0 (0%)	2 (4.65%)	1 (2.5%)	
Mucinous	0 (0%)	0 (0%)	0 (0%)	2 (5%)	
Others	4 (5.55%)	3 (4%)	0 (0%)	0	
Tumor grade					
I	2 (2.7%)	0 (0)	0 (0)	0 (0)	**0.422**
II	67 (93%)	70 (93.3%)	42 (97.6%)	37 (92.5%)	
III	3 (4.1%)	5 (6.67%)	1 (2.3%)	3 (7.5%)	
T Stage					
T0	2 (2.8)	0 (0%)	1 (2.3%)	2 (5)	**0.003**
T1	19 (26.4%)	9 (12%)	7 (16.3%)	7 (17.5%)	
T2	40 (55.6%)	47 (62.6%)	15 (34.9%)	25 (62.5%)	
T3	9 (12.5%)	7 (9.3%)	14 (32.6%)	3 (7.5%)	
T4	2 (2.8%)	9 (12%)	6 (14%)	3 (7.5%)	
T missing	0 (0%)	3 (4%)	0 (6.9%)	0 (0%)	
N Stage					
N0	41 (56.9%)	17 (22.6%)	15 (34.9%)	15 (37.5%)	**0.001**
N1	20 (27.8%)	22 (29.3%)	13 (30.2%)	9 (22.5%)	
N2	5 (6.9%)	26 (34.6%)	7 (16.3%)	11 (27.5%)	
N3	6 (8.3%)	7 (9.3%)	8 (18.6%)	5 (12.5%)	
N missing	0 (0%)	3 (4%)	0 (0%)	0 (0%)	

Significant results if p value less than 0.05, for menopausal statues it is not significant.

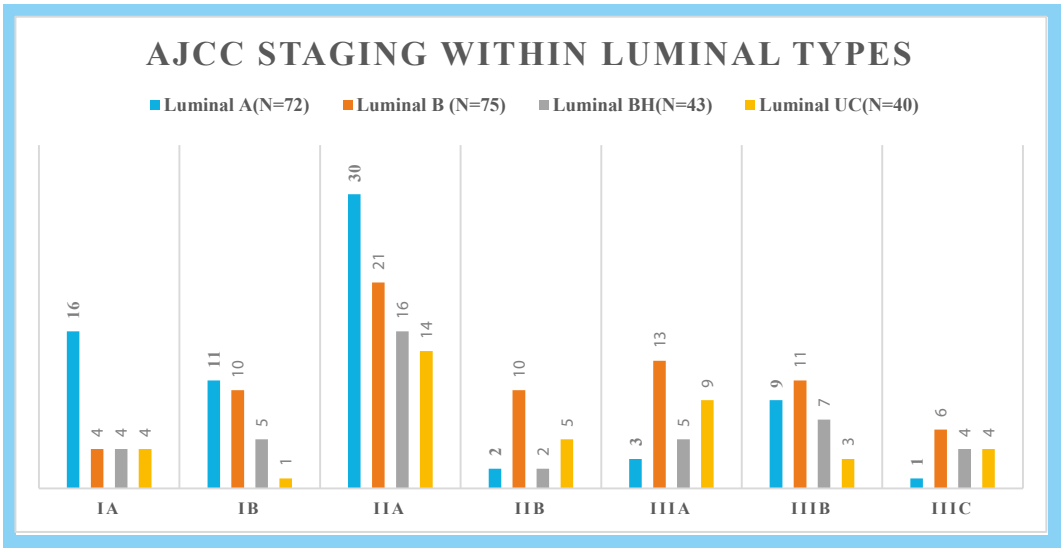

Fig. 2. AJCC 8th stages within luminal types.

luminal B HER2 positive 90%, and luminal unclassified 97% ($P = 0.434$) (Table 4, Fig. 5).

The pattern of relapse in patients with relapsed disease was analyzed. Luminal subtypes had a significant difference in relapse pattern, luminal A most observed relapse pattern was bone 35.7%, luminal B HER2 positive was often observed with more than 2 relapsed organs 20% and it was the only subtype reported brain relapse ($P = 0.048$) (Table 5, Fig. 6).

Table 2. DFS analysis of luminal types. Non-significant between all types as p value more than 0.05

Luminal type	Relapse/month	95% confidence interval		*P* value
		Lower bound	Upper bound	
A	92.8	85.2	100.4	0.091
B	81.1	71.2	91.1	
BH	87.9	77.4	98.5	
UC	81.5	71.5	91.61	
Overall	89.09	83.9	94.2	

4. Discussion

Luminal breast cancer is a predominant molecular subtype in western countries; it represents almost 70% of all breast cancer cases.[15] Luminal A tumors are considered low-grade, slow-growing, and have the best prognosis, in contrast to luminal B tumors, which are worse in prognosis and rapidly growing tumors.[16] In our study, luminal breast cancer represented about 80% of patients with early breast

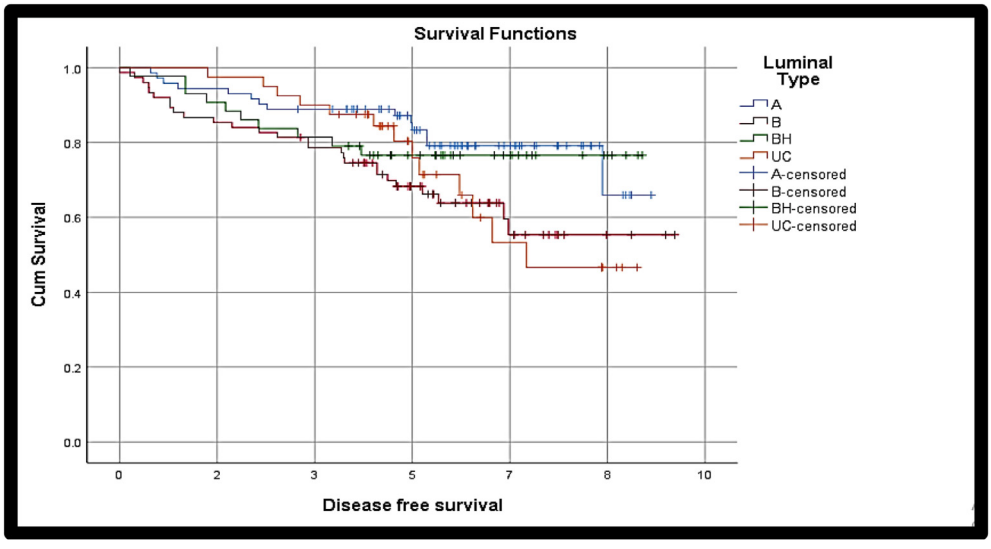

Fig. 3. DFS Kaplan–Meier curve.

Table 3. Relapse status in luminal types.

Relapse status	Luminal A ($N = 72$) N (%)	Luminal B ($N = 75$) N (%)	Luminal BH ($N = 43$) N (%)	Luminal UC ($N = 40$) N (%)	P value
Yes	14 (19.4%)	27 (36%)	10 (23.2%)	13 (32.5%)	**0.117**
No	58 (80.56%)	48 (64%)	33 (76.6%)	27 (67.5%)	

cancer, including patients who were referred for postoperative radiotherapy. In a cross-sectional retrospective study done in Iran with a total of 142 patients with early breast cancer, they found no significant differences between family history ($P = 0.42$) and menopause state ($P = 0.36$) in luminal breast cancer.[17] These findings are correlated with our study as we found no significant difference in family history ($P = 0.992$) and menopausal status ($P = 0.064$). In our study, the association between luminal types and the AJCC 8th staging system was significant ($P = 0.008$). Luminal A had (81.9%) patients in (Stage I and Stage II), while luminal B (39.9%) patients were presented in Stage III, and for luminal B HER2+, the majority of patients had been presented in Stage II (41.8%). The AMAZONA study retrospectively analyzed a group of Brazilian breast cancer patients and found that early stages (I and II) were the most prevalent in luminal A (82%), while the majority of patients with luminal B and luminal B HER2 positivity were presented in stage II (60.6%) and (52.1%), respectively.[18] The recurrence rate was 59.7% at a median follow-up of 24.2 years in the international breast cancer study groups trial (I to V), as well as being lower in ER-positive patients in comparison with ER-negative patients.[19] In our study (27.8%) of patients relapsed during our median follow-up period. Although not statistically significant ($P = 0.117$), luminal A had the lowest rate of relapse (19.4%), while luminal B and luminal B HER2 +ve had (36%) and (23.2%) respectively. Bone as a solitary organ relapse was the predominant

Table 4. OS analysis of luminal types.

Luminal type	Overall survival/month	95% confidence interval		P value
		Lower bound	Upper bound	
A	103.6	99.07	108.15	0.434
B	100.8	93.67	107.9	
BH	100.7	94.83	106.7	
UC	102.9	95.92	109.8	
Overall	104.4	100.99	107.8	

pattern of relapse among our relapsed cases (29.6%), luminal A bone relapse was (35.7%), while luminal B (33.3%) and luminal B HER2 positive (20%), in contrary luminal unclassified, had contralateral breast as the most observed relapse pattern with (38.4%) ($P = 0.048$). An Indian observational analyzed 468 patients, 11.7% had disease relapse, (7.27%) patients were in Luminal A, Luminal B (18.18%) and HER2 enriched types (41.8%), these differences may be due and they didn't sub classify HER2 enriched either luminal or non-luminal type. Bone was also the most common solitary organ relapse (50.9%) with the highest rate of incidence in Luminal A and B, however, results weren't statistically significant ($P = 0.064$).[20] The rates of DFS and OS among our patients weren't significantly varied. The 5 years DFS for luminal A was 83%, while luminal B, B HER2 positive, and luminal UC were 66%, 76%, and 75%, respectively ($P = 0.091$). Five years OS was 95% for luminal A, 87% for luminal B, 90% for luminal B HER 2 positive and 97% for luminal UC ($P = 0.434$). With a median follow-up of 80.8 months in a large prospective trial with 12,053

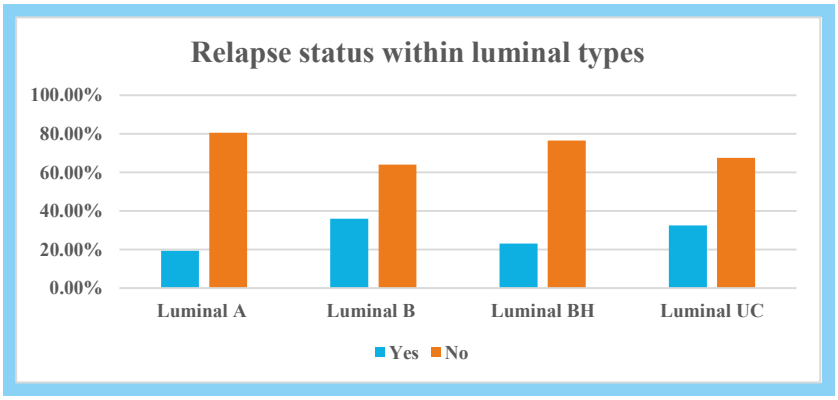

Fig. 4. Relapse rate in luminal types.

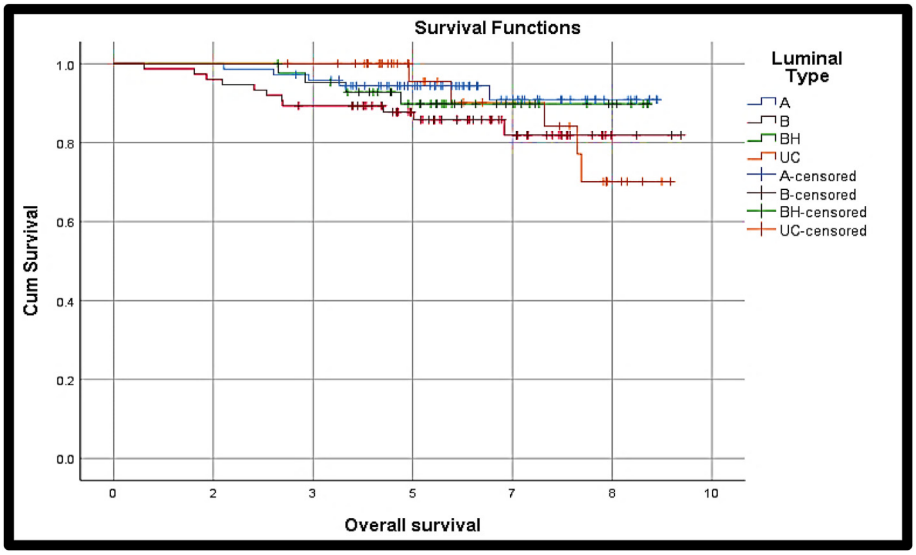

Fig. 5. OS Kaplan–Meier curve.

Table 5. Pattern of relapse in luminal types, significant correlation between pattern of relapse and luminal types as p value less than 0.05

Pattern of relapse	Total ($N = 64$) N (%)	Luminal A ($N = 14$) N (%)	Luminal B ($N = 27$) N (%)	Luminal BH ($N = 10$) N (%)	Luminal UC ($N = 13$) N (%)	P value
>2 Metastasis	10 (15.6%)	2 (14.2%)	5 (18.5%)	2 (20%)	1 (7.6%)	**0.048**
Bone	19 (29.6%)	5 (35.7%)	9 (33.3%)	2 (20%)	3 (23.07%)	
Brain	1 (1.5%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)	
Contralateral Breast	9 (14%)	3 (21.4%)	1 (3.7%)	0	5 (38.4%)	
Liver	6 (9.3%)	4 (28.5%)	1 (3.7%)	1 (10%)	0 (0%)	
Lymph node	6 (9.3%)	0 (0%)	2 (7.4%)	2 (20%)	2 (15.3%)	
Local Recurrence	10 (15.6%)	0 (0%)	7 (25.9%)	1 (10%)	2 (15.3%)	
Lung	1 (1.5%)	0 (0%)	1 (3.7%)	0 (0%)	0 (0%)	
Shoulder	2 (3.1%)	0 (0%)	1 (3.7%)	1 (10%)	0 (0%)	

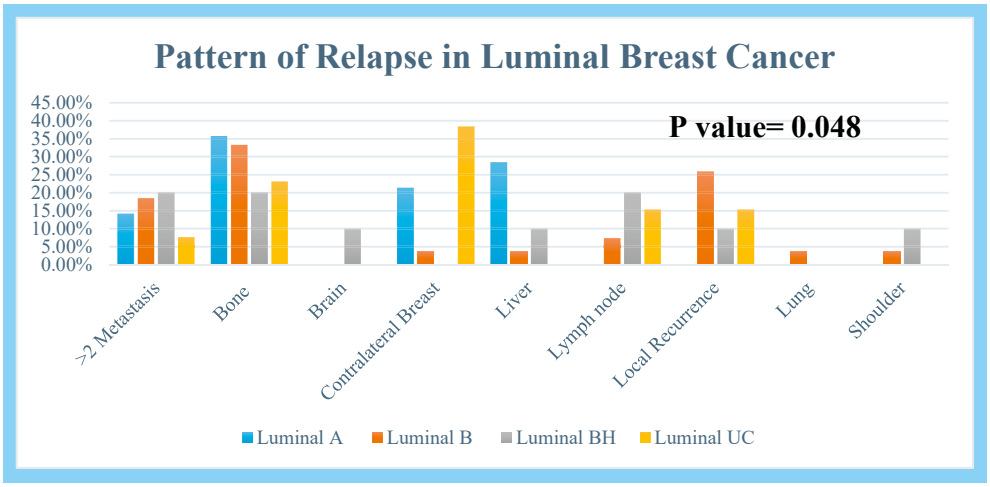

Fig. 6. Pattern of relapse in luminal types.

patients, the 10 year DFS was statistically significant. Luminal A exhibited the best 10 year DFS (95.5%), followed by luminal B HER2 positive (84.9%) ($P=<0.0001$) and the predicted 10 year OS for luminal A was (89.2%), luminal B (79%), luminal B HER2 positive (74.4%) ($P=<0.0001$).[11] This huge discrepancy in survival has a lot of factors such as a prospective trial, large sample size, and different luminal subcategorization methods.

4.1. Conclusion

In spite of the small sample size, women having luminal breast cancer had a greater percentage of single bone relapse. The risk of relapse in women having luminal breast cancer during and after the adjuvant hormonal treatment period was still present. After receiving appropriate therapy, women with luminal A breast cancer showed a superior prognosis. The relapse patterns and clinical outcomes of women with luminal breast cancer as per the different luminal subtypes were also somewhat different Ki-67% and HER2 testing would give a prognostic factor in luminal subcategorization and could be beneficial in deciding intensification of adjuvant treatment.

Authors' contributions

All authors are involved in the design, writing, revising of the manuscript and approval of the final version, involved in conception design, data collection, literature review, writing the manuscript, and approval of the final version, additionally, all authors have read and approved the final manuscript.

Conflicts of interest

There are no conflicts of interest.

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