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ORIGINAL PAPER

Basal vs. luminal a breast cancer subtypes: a matched case-control study using estrogen receptor, progesterone receptor, and HER-2 as surrogate markers

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Abstract Breast cancer is a heterogeneous disease that encompasses several distinct entities with different biological characteristics and clinical behavior. Basal subtype is considered as a prognostically unfavorable subset. The purpose of this study is to compare the clinico-pathological characteristics and outcome of basal vs. luminal A subtype, as approximated by ER, PR, and HER-2. Sixty-four patients with basal breast cancer were matched for age, stage, and year of diagnosis with 64 patients having luminal A disease. Basal tumors were immunohistochemically defined by a lack of expression of estrogen receptor (ER), progesterone receptor (PR), and HER-2, while luminal A cancers were ER+ or PR+, and HER-2−. As compared with luminal A, basal subtype patients had significantly larger primary tumor size, higher percentage of grade III tumor, more tumor that showed lymphovascular invasion, less presence of non-invasive disease, and higher proportion of extranodal extension. There was no statistically significant difference in metastatic sites, pathology type, or in the axillary lymph nodal status. A few patients received neoadjuvant chemotherapy—13 and 9 patients in basal and luminal A groups, respectively). The complete pathological response was 20% and 14%, respectively (not significant). At a median follow-up of approximately 2 years, there was no statistically significant difference in the overall survival rate between basal and luminal A patients. Analysis of disease-free survival (DFS) for stage I–III (53 patients in each group) showed that the median DFS for basal patients was 41.4 months (95% CI, 26.5–55.3 months), whereas the DFS for the luminal A patients was not reached ($P = 0.014$). After adjusting for several significant prognostics variables identified in a univariate analysis, a multivariate conditional logistic regression analysis identified the negative effect of lymphovascular invasion and the favorable influence of the use of neoadjuvant and/or adjuvant chemotherapy. This matched case–control study confirmed the poor clinical and pathological characteristics of patients with basal subtype and their unfavorable outcome compared with luminal A disease. Management of basal tumors remains a challenging task, and new therapeutic strategies are warranted.

Keywords Breast cancer · Basal · Luminal A · Triple negative

Introduction

Recently, a group at Stanford has pioneered the study that led to the demonstration of the morphological heterogeneity of breast cancer [1, 2]. These studies have allowed classification of breast cancer into five main groups, two of them hormone receptor positive (luminal A and B) and three hormone receptor negative groups (normal breast-like, HER-2+, and basal-like). In those, and in subsequent studies, it has been shown that the basal-like group is enriched for tumors that lack expression of hormone receptors and of HER-2, has a more aggressive clinical behavior [3, 4], a distinctive metastatic pattern [5], and a poor prognosis despite responding to conventional neoadjuvant and adjuvant

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chemotherapy regimens [6, 7]. That subtype which accounts for approximately 15% of all the patients with breast carcinoma, is defined as the subset that does not express hormone receptors and HER-2.

The main characteristics of basal cancers that have emerged from the literature illustrate the similarities between basal-like and triple-negative (TN) diseases [8, 9]. Although some investigators have concluded that basal breast cancer is synonymous with basal-like breast cancer [10], nevertheless, it should be noted that only about 85% of phenotypic TN breast cancers are deemed basal-like when tested by appropriate immunohistochemical means [11].

On the other hand, luminal A phenotype is defined as a tumor that is estrogen receptor (ER)-positive or progesterone receptor (PR) positive, and HER-2−. Because of each marker's pattern, each subtype carries a more favorable prognosis [12, 13].

The purpose of this study is to compare the clinicopathological features and outcome of patients with basal breast cancer with those of matched controls of breast cancer patients with luminal A disease.

Patients and methods

Patients and controls

Included in the hospital-based cancer registry database were 76 women with pathologically confirmed basal-like breast cancer (ER−, PR−, and HER-2−). Using the same database, 1:1 matching controls of patients with luminal A subtype (ER+ or PR+, and HER-2−), were selected. Patients were matched for age (±3 years), stage, and same year of diagnosis. Out of the 76 basal subtype patients, only 64 had luminal A-matched controls. All the patients received their management at our facility from January 2002 to December 2007. Initial evaluation included clinical examination, mammography, and breast ultrasonography. Computed tomography of chest, bone scan, and breast magnetic resonance imaging were performed if indicated. The data on hormone receptors assessed by routine immunohistochemical staining were obtained through pathology reports. We reviewed the electronic and paper medical records and the cancer registry database to retrieve demographic data, clinical information, treatment details, and outcome.

Immunohistochemistry analysis

Immunohistochemical staining was carried out using standard streptavidin–biotin-peroxidase method on 3–5-mm thick tissue sections. Stainings were performed with antibodies raised against the following markers: ER, PR, and HER-2. ER and PR statuses were recorded according to the pathologist's interpretation of the assays. ER and PR were considered negative if immunoperoxidase staining of tumor cell nuclei is less than 5%. A negative HER-2 expression using HercepTest (Dako, Glostrup, Denmark) was defined as cases that displayed no membranous staining (negative) or those that either had some staining in <10% of tumor cells or had weak-to-moderate staining (1+). Those who had moderate staining in >10% of cells (2+) were further evaluated by fluorescence in situ hybridization (FISH) for gene amplification. FISH is scored on a quantitative scale with less than two copies of the HER-2 gene classified as negative.

Statistical analysis

Conditional logistic regression was used to compare covariates in the two groups. Each matched case was paired with the corresponding control to enable differences between the cases and controls to be computed. Response to neoadjuvant therapy or to systemic therapy in metastatic disease was measured according to the Response Evaluation Criteria in Solid Tumors [14]. Comparison between disease-free survival (DFS) and overall survival (OS) was carried out using the Kaplan–Meier method [15]. Difference between survival rates was tested with the log-rank test [16]. P-values <0.05 were considered indicative of statistical significance. To test a multivariate model, variables were evaluated for independent correlations with survival by Cox's conditional logistic regression analysis [17]. Variables with $P > 0.10$ in the univariate analysis were dropped. Next, variables with $P \leq 0.05$ were selectively added to the model, starting with the variable with the lowest P-value. At the next stage, variables with $P > 0.05$ were selectively dropped from the model, one at a time, beginning with the variable with the highest P-value. The model was then reassessed, followed by dropping of the variable with the next highest P-value until all the variables with $P > 0.05$ were eliminated from the final multivariate model. Wald's statistics, odd ratios (ORs), and 95% confidence intervals (CIs) are reported. DFS for non-metastatic disease was calculated as the duration from the date of diagnosis to the date of initial relapse, or the date of last follow-up evaluation. On the other hand, OS was computed from the date of diagnosis to the date of death from any cause or the date of last contact. SPSS software (SPSS version 15.0.0, SPSS Inc., Chicago, IL) was used for all the statistical evaluations. The study was approved by the Institutional Review Board.

Results

Patient characteristics

Table 1 shows the patient characteristics of the 64 basal patients and their matched controls. Most basal and luminal A patients were young premenopausals and their median age was similar. As compared with luminal A patients, basal group had significantly larger primary tumor size, higher percentage of grade III tumor (66% vs. 46%), more tumor that showed lymphovascular invasion (65% vs. 43%), less presence of non-invasive disease (28% vs. 67%), and higher proportion of extranodal extension (54% vs. 25%). On the other hand, there was no statistically significant difference in age, family history of breast cancer, stage, metastatic sites, pathology type, or in the axillary lymph nodal status.

Therapy details

Table 2 depicts the initial treatment for non-metastatic disease in both subtypes. Among the few patients who received neoadjuvant chemotherapy, the complete pathological response (pCR) among basal patients (23%) was double that in luminal A patients (11%), although that difference was not statistically significant. With the expected difference in the administration of adjuvant hormonal therapy, no significant difference was noted in the initial management of the two groups. A few patients received neoadjuvant plus adjuvant chemotherapy (nine patients in each group), while 12 and five patients in the luminal A and basal groups, respectively, did not receive any chemotherapy. The reason for non-receiving chemotherapy in the basal subtype was patient's refusal.

Among basal patients presenting with metastatic disease, two patients had no palliative systemic treatment while six patients received systemic chemotherapy. On the other hand, for luminal A patients with metastatic disease, five and three patients received initial palliative hormonal therapy and chemotherapy, respectively.

Survival analysis

As of May 2008, the median follow-up (95% CI) was 23.5 (18.9–36.7) and 25.4 (20.5–39.8) months for basal and luminal A patients, respectively (difference was not significant). At follow-up, 38 (59%), 21 (33%), and 5 (8%) basal patients were alive with no evidence of disease, alive with disease, and dead, respectively. The corresponding survival status for the luminal A group was 46 (72%), 9 (14%), and 9 (14%), respectively.

Table 1 Univariate analysis comparing basal and luminal A patients

	Basal no. (%)	Luminal A no. (%)	*P*-value
Number	64 patients	64 patients	
Median age in years (range)	45.5 (22–73)	47.0 (24–73)	0.59
Family history			0.08
Yes	8 (12)	13 (20)	
No	35 (55)	39 (61)	
Unknown	21 (33)	12 (19)	
Stage			NA
Stage I	5 (8)	5 (8)	
Stage II	28 (44)	28 (44)	
Stage III	20 (31)	20 (31)	
Stage IV	8 (12)	8 (12)	
Unknown	3 (5)	3 (5)	
Metastatic sites			
Lung	3 (5)	3 (5)	0.10
Bone	3 (5)	6 (10)	0.36
Liver	2 (3)	2 (3)	0.10
Other	5 (8)	4 (6)	0.60
Mean primary tumor size in cm (95% CI)	3.5 (3.8–5.3)	3.1 (2.6–3.6)	0.003
Pathology			
Infiltrative ductal	59 (92)	53 (83)	0.64
Other	5 (8)	11 (17)	
Grade			0.007
I	0 (0)	2 (3)	
II	16 (25)	27 (42)	
III	42 (66)	29 (46)	
Unknown	6 (9)	6 (9)	
Lymphovascular invasion (when known)			0.03
Positive	31 (65)	21 (43)	
Negative	17 (35)	28 (57)	
Non-invasive component			<0.0001
None	46 (72)	21 (33)	
Yes	18 (28)	43 (67)	
Known axillary lymph nodes status			0.27
0	24 (39)	20 (35)	
1–3	23 (38)	17 (29)	
4 or more	14 (23)	21 (36)	
Extranodal extension (when known)			0.009
Positive	19 (54)	10 (25)	
Negative	16 (46)	30 (75)	
Hormonal receptors			
ER+	0 (100)	64 (100)	NA
PR+	0 (100)	51 (80)	NA
Negative Her-2	64 (100)	64 (100)	NA

NA not applicable

Table 2 Univariate analysis of initial management of stage I–III basal and luminal A patients

	Basal no. (%)	Luminal A no. (%)	*P*-value
Neoadjuvant chemotherapy	13 (20)	9 (14)	0.48
Anthracycline-based	11 (17)	7 (11)	
Anthracycline–taxen based	2 (3)	2 (3)	
Pathologic response to neoadjuvant chemotherapy			0.52
pCR	3/13 (23)	1/9 (11)	
pPR	6/13 (46)	6/9 (57)	
pSD + pPD	4/13 (31)	2/9 (22)	
Primary surgery			0.07
Conservative surgery	39 (74)	29 (55)	
Modified radical mastectomy	14 (26)	24 (45)	
Adjuvant hormonal therapy (Stage I–III)			<0.0001
Tamoxifen	0	35 (66)	
Aromatase inhibitor (AI)	0	13 (25)	
Tamoxifen then AI	0	5 (9)	
Adjuvant chemotherapy			0.38
None	12 (23)	16 (30)	
Yes	41 (77)	37 (70)	
Adjuvant chemotherapy type			0.33
None	12 (22)	16 (30)	
Anthracycline-based	29 (55)	21 (40)	
Anthracycline–taxen based	10 (19)	11 (21)	
Taxen + other	1 (2)	3 (5)	
Other	1 (2)	2 (4)	
Combined neoadjuvant and adjuvant chemotherapy			1.00
No	44 (73)	44 (73)	
Yes	9 (17)	9 (17)	
Any chemotherapy (neoadjuvant or adjuvant)			0.052
None	5 (9)	12 (23)	
Yes	48 (91)	41 (77)	
Adjuvant radiotherapy			0.59
None	12 (23)	13 (25)	
Yes	41 (77)	40 (75)	

pCR, complete pathological response; pPR, partial pathological response; pSD, pathologic stable disease; pPD, pathologic progressive disease

For basal patients, the median OS was not reached; however, the actuarial probability of the 3-year OS was 82.5% with the lower probability of the 95% CI estimated as 66.7%. Similarly, the median survival for luminal A group was not reached with an actuarial probability of the 3-year OS of 90% with lower probability of the 95% CI estimated as 80.2%. Comparison between the OS curves did not demonstrate a statistically significant difference between basal and luminal A patients. Various clinical and pathological variables were tested to assess their relation to OS. Table 3 shows the univariate logistic regression analysis of the statistically significant covariates. Due to small number of events, only larger pathological primary tumor size, and presence of lymphovascular invasion were found significant as adverse factors. Moreover, the 95% CI of the latter variable was wide; therefore, multivariate analysis was not attempted.

Table 3 Univariate analysis of the significant covariates for overall survival for all the patients

Factor	Wald statistics	OR	95% CI		*P*-value
			Lower	Upper	
Pathological primary tumor size	4.21	1.23	1.01	1.50	0.04
Lymphovascular invasion	4.66	9.80	1.24	77.79	0.03

OR odd ratio; *CI* confidence interval

Analysis of DFS was restricted to stage I–III (53 patients in each group). In the basal group, 17 (32%) patients experienced relapse. Local or locoregional relapse, distant relapse, and local or locoregional combined with distant relapse occurred in 5 (9.4%), 9 (17%), and 3 (6%) patients, respectively. The median DFS for basal patients was 41.4 months (95% CI, 26.5–55.3 months). On the other hand, in the luminal A patients 9 (17%) developed relapse. The relapse in the latter group was 6 (11%) distant and 3 (6%) combined locoregional and distant. The median DFS for luminal A was not reached. Comparison between the DFS curves (Fig. 1) showed a statistically significant difference in favor of luminal A ($P = 0.014$). After excluding the five patients in the basal group that did not receive any chemotherapy and their matched controls, the difference remained significant ($P = 0.027$).

Various clinical and pathological variables have been tested to assess their relation to DFS. Table 4 shows the univariate conditional logistic regression analysis of the statistically significant covariates. Adverse prognostic factors included positive family history, large clinical or pathological primary tumor, stage III, grade III, and the presence of lymphovascular invasion. Conversely, ER+ or PR+ tumors, and the use of neoadjuvant or adjuvant chemotherapy were favorable. Comparison of DFS for basal vs. non-basal patients adjusted for the significant variables shown in Table 4 was performed using multivariate conditional logistic regression to identify prognostic variables that independently explain the DFS difference (Table 5). The model identified the presence of lymphovascular invasion as an adverse variable, whereas the use of any chemotherapy (neoadjuvant and/or adjuvant chemotherapy) as a favorable factor.

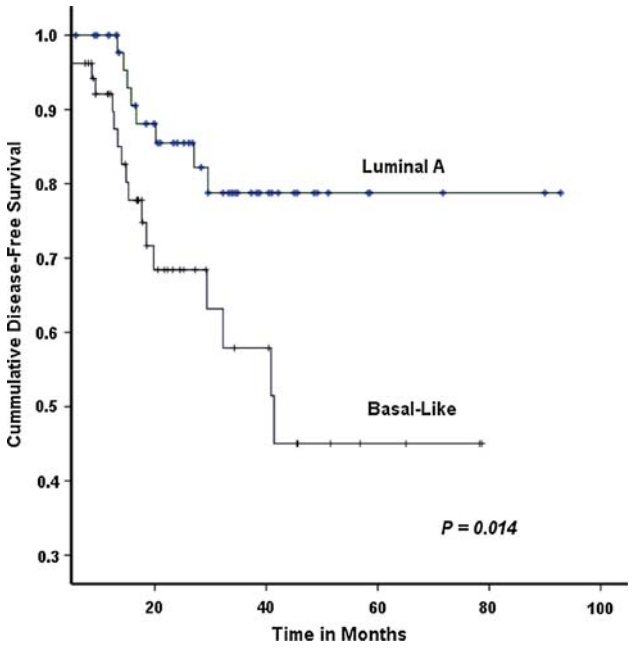

Fig. 1 Kaplan–Meier plot of disease-free survival for stages I–III

Salvage therapy for stage I–III disease

On relapse, 14 basal patients received first-line while two received first- and second-line salvage chemotherapy. The corresponding numbers for luminal A patients were seven and two patients, respectively. Moreover, in the latter group seven patients received salvage hormonal therapy.

Discussion

Recent advances in genetic profiling have led to the identification of distinct prognostic groups in breast cancer [1–4]. Due to growing interest in this subgroup, we examined the clinico-pathological features and outcome of the 64 patients with basal breast cancer as compared with that for luminal A matched controls.

Despite being matched for age, stage, and year of diagnosis, basal group demonstrated adverse pathological features as compared with luminal A controls. In concordance with other series [8, 13], basal patients in this current study had larger mean tumor size as compared with those who had luminal A. The higher prevalence of tumors with higher grade and lymphovascular invasion seen in our basal subtype has also been described in the literature [8, 13, 18, 19].

Lymph node involvement in basal breast cancer and TN tumors is an interesting feature. It has been reported that these cancers disseminate to axillary lymph nodes less frequently; however, they favor a hematogenous spread [5, 13, 20, 21]. In another study, however, the rate of node positivity was slightly higher in the basal group compared with the other cancer types [8]. In this study, there was no difference in axillary nodal status between basal and luminal A patients.

Analysis of systemic therapy of stage I–III patients showed the expected high exposure to adjuvant hormonal treatment in luminal A patients (91%). On the other hand, there was no significant difference in the frequency of administration of neoadjuvant or adjuvant chemotherapy, the nature of systemic chemotherapy, or the administration of adjuvant radiotherapy. Though not statistically significant, more basal patients attained pCR as compared with luminal A (23% vs. 11%). The small number of patients receiving neoadjuvant

Table 5 Multivariate analysis model for disease-free survival

Factor	Wald statistics	OR	95% CI		*P*-value
			Lower	Upper	
Lymphovascular invasion	10.13	5.76	1.96	16.91	0.001
Neoadjuvant and/or adjuvant chemotherapy	6.55	0.29	0.11	0.75	0.01

OR odd ratio; *CI* confidence interval

Table 4 Univariate analysis of the significant covariates for disease-free survival for all patients

Factor	Wald statistics	OR	95% CI		*P*-value
			Lower	Upper	
Family history (yes vs. no)	3.96	1.10	1.00	1.22	0.05
Clinical T stage (T3/T4 vs. T1/T2)	6.64	1.65	1.13	2.41	0.01
Pathological primary tumor size	13.33	1.29	1.13	1.49	0.00
Stage III vs. stage I + II	7.55	2.77	1.34	5.73	0.01
Grade III vs. grade I + II	4.78	2.92	1.12	7.64	0.03
Lymphovascular invasion	6.02	3.56	1.29	9.81	0.01
ER+ vs. ER−	5.49	0.36	0.15	0.84	0.01
PR+ vs. PR−	4.82	0.36	0.14	0.89	0.03
Neoadjuvant and/or adjuvant chemotherapy	6.66	0.35	0.15	0.77	0.01

OR odd ratio; *CI* confidence interval

chemotherapy may account for the lack of significant effect, as basal tumors are known to show a significant responsiveness to neoadjuvant chemotherapy [6, 7].

Analysis of OS could not demonstrate a significantly significant difference between basal and luminal A patients. However, the actuarial probability of the 3-year OS was 82.5% and 90%, respectively. The lack of OS survival difference may be attributed to the fact that more basal patients received salvage chemotherapy. Moreover, matching the two subtypes for known prognostic variables (age and stage) may have eliminated an expected survival difference. The univariate analysis identified larger pathological primary tumor and the presence of lymphovascular invasion as the only adverse prognostic variables that predict OS. The multivariate analysis was not attempted.

On the other hand, DFS among basal patients was significantly worse than that in luminal A controls ($P = 0.014$). All the relapses in the luminal A were distant with or without locoregional recurrence. However, among basal patients, relapse was distant with or without locoregional in 12 out of 17 patients (71%). It is known that basal patients have high likelihood of distant recurrence [8, 13, 22]; however, the risk of distant recurrence tends to peak at 3 years and declines rapidly thereafter [8]. Although the pattern of relapse in our basal group appears different from that the expected for that subtype, the relatively short follow-up may suggest that a larger proportion may unfortunately demonstrate distant recurrence on longer follow-up. Moreover, the relatively small number of documented events may also explain the inconsistency with published reports.

The univariate conditional logistic regression analysis identified several significant variables that could prognosticate DFS (Table 4). Analysis of the difference in DFS between basal and luminal A patients adjusted for the significant factors identified the presence of lymphovascular invasion as an adverse variable, whereas the use of neoadjuvant and/or adjuvant chemotherapy as a favorable factor.

There may be several limitations to this study. First, classifications using ER, PR, and HER-2 statuses as surrogate markers for the underlying genotype-based breast cancer subtype, and conclusions based on the receptor-based approximations cannot necessarily be applied to the genotype-based subtypes. However, because receptor status information is much more readily available than genotyping, this method appears to have the most clinical practicality. Moreover, it has recently been shown that a combination of simple immunohistochemical markers could be used for proper molecular subtyping [8, 11, 13, 23, 24]. Second, our patients had a rather short follow-up to allow more accurate survival comparison. However, one could appropriately expect that on longer follow-up a statistically significant OS difference might emerge in favor of luminal A as predicted from the actuarial 3-year survival. Nevertheless, we intend to re-analyze the same patients' population or perhaps larger matched groups at median follow-up of 3–4 years. Third, five patients in the basal refused neoadjuvant or adjuvant chemotherapy, and that may have compromised their survival outcome. However, excluding those patients together with their matched luminal A controls did not influence the poorer DFS in the basal subtype ($P = 0.027$).

Despite these shortcomings, our study is of value because: (1) to the best of our knowledge, this is the only study that analyzes basal disease in the Middle East; (2) the matched case–control design allowed adjustment for age, stage, and year of diagnosis, and therefore enhanced the robustness of the comparison; (3) it highlighted the importance of the triple negative phenotype as a surrogate marker for basal-like breast cancer; (4) it confirmed the adverse clinico-pathological features of basal breast cancer disease and ascertained its poor DFS compared with luminal A; (5) it identified that the presence of lymphovascular invasion adversely affected DFS, although the use of neoadjuvant and/or adjuvant chemotherapy was favorable.

Basal cancer phenotype remained as challenging subtype of breast cancers. The adverse pathological features, besides, the poor outcome of basal tumors as shown in our analysis and by others, suggest that new therapeutic strategies for the management of such patients are warranted. Retrospective analysis of two randomized studies based on cyclophosphamide and thiotepa suggested that basal patient benefited from high-dose chemotherapy [25, 26]. Another strategy is to test the efficacy of humanized anti-EGFR monoclonal antibodies and EGFR tyrosine kinase [18]. Greater understanding of the pathological and molecular characteristics of this phenotype may lead us to tailor the treatment for these patients.

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