Significance of tumoral and stromal ALDH 1A1 expression in breast invasive duct carcinoma in Egyptian female patients

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Background
Cancer is considered a stem cell disease. Many stem cell markers are recently well known to have main roles in carcinogenesis and tumor progression. Aldehyde dehydrogenase 1A1 (ALDH1A1) is a stem cell marker that thought to have a role in many cancers. This study aimed to evaluate the expression of ALDH1A1 in different molecular types of breast invasive ductal carcinomas (NOS), and its relation to clinicopathological data.
Materials and methods
This is a retrospective study carried out on 40 cases of NOS of the breast. The cases were collected from archives of Early Cancer Detection Unit, Benha Faculty of Medicine and Pathology Department, International Medical Center, between the years 2007 and 2013. Previously estrogen receptor, progesterone receptor, Her2/neu and Ki-67 stained slides were reevaluated for each case. Both tumoral and stromal expression of ALDH1A1 was also evaluated for each case.
Results
A significant positive correlation of ALDH1A1 tumoral expression was observed in patients with age more than 55 years ($P<0.05$), higher tumor grade ($P<0.05$), large tumor size (T) ($P<0.05$), lymph node metastasis ($P<0.01$), distant metastases, and advanced TNM stage ($P<0.05$). A significant association of tumoral ALDH1A1 with estrogen receptor and progesterone receptor negativity was noted ($P<0.05$) while the expression of ALDH1A1 in tumor cells appeared more frequently in Her2/neu-positive cases ($P<0.05$). Expression of ALDH1A1 in stromal cells correlated inversely with the presence of distant metastasis and advanced tumor stage ($P<0.05$ for both). Tumoral ALDH1A1 expression showed inverse highly significant correlations ($P<0.0001$) with patient's survival. Increased stromal expression of ALDH1A1 showed a significant relation to disease-free survival and overall survival ($P<0.05$). Tumoral ALDH1A1 expression correlated inversely with the overall survival and disease-free survival of luminal A and luminal B cases ($P<0.05$ for all).
Conclusion
ALDH1A1 may have a dual role in NOS progression. Also, ALDH1A1 could be used to predict chemoresistant cases among different molecular subtypes. Induction of stromal ALDH1A1 expression could be a possible therapeutic target in the future to suppress tumor progression.

Keywords:
aldehyde dehydrogenase 1A1, breast cancer, invasive ductal carcinoma

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Introduction

Breast cancer is the most common malignancy affecting women. It accounts for 19.3% of total primary malignant tumors in Egypt as reported by the Egyptian National Cancer Institute (Mokhtar *et al.*, 2016). According to Ain-Shams Pathology Registry, breast carcinoma was most frequent in the sixth decade of life. Invasive ductal carcinoma (NOS) represented 91.3% of studied cases with higher positivity of estrogen receptor (ER) and progesterone receptor (PR), while Her2/neu positivity was higher in cases of in-situ ductal carcinoma (Helal *et al.*, 2015).

Molecular studies have classified breast carcinomas into four subtypes based on immunohistochemical staining: luminal A, luminal B, triple negative breast carcinoma and Her2/neu-positive to predict the prognosis (Reddy *et al.*, 2017). However, the response to treatment and survival is still controversy. Many cases of disease relapse and cancer death are still reported (Cid *et al.*, 2018).

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Cancer stem cells (CSCs) are self-renewing cells. They can promote tumor growth, and though they are very important in tumor recurrence, occurrence of distant metastasis, and resistance to therapy (Alferez *et al.*, 2018).

Aldehyde dehydrogenase is a family of enzymes, which has a role in the biosynthesis of retinoic acid and other genetic regulators of different cell functions. Aldehyde dehydrogenase 1A1 (ALDH1A1) is an enzyme that regulates cell functions in normal stem cells and also in CSCs, to promote tumor growth and develop resistance to therapy (Vassalli, 2019).

ALDH1A1 has been identified as a CSC marker in many cancers including those of the breast (Liu *et al.*, 2014). However, its prognostic significance and its value in predicting the disease recurrence in breast cancer patients is still unknown (Miyoshi *et al.*, 2016).

This study aimed at assessment of the role of ALDH1A1 in different molecular subtypes of breast NOS and correlate it with the clinicopathological data.

Human tissue sampling and immunohistochemical analysis

This retrospective study was carried out on 40 selected cases, diagnosed as breast NOS, during 2007–2013. Formalin-fixed, paraffin-embedded blocks of tumor specimens were collected from Early Cancer Detection Unit, Pathology Department, Faculty of Medicine, Benha University and International Medical Center. All collected specimens were of female patients, who had undergone modified radical mastectomy. Previously ER, PR, Her2/neu, and Ki-67 stained slides were obtained from the patient archives and reassessed. Follow-up of only 25 patients was obtained for 5 years or until the time of death.

Modified Scarff–Bloom–Richardson grading system was used to assess the tumor grade. TNM staging was applied according to the AJCC and the molecular subtype each case was recorded based on the evaluation of obtained slides of ER, PR, and Her2 and Ki-67 (Kondov *et al.*, 2018).

From each block, one section of 4 μm thickness was cut on a positively charged slide. The avidin–biotin complex technique was applied according to the manufacturer guidelines for immunohistochemical staining (Genemed, South San Francisco, California, USA) (Hsu *et al.*, 1981). Antigen retrieval was performed by microwave heating in 10 mmol/l citrate monohydrate (neo-markers, cat. AP-9003), pH 6.0. Slides were incubated with the primary mouse monoclonal anti-ALDH1A1 antibody (cat no. YPA1390; Chongqing Biopsies Co., Chongqing, China), at a 1/50 dilution, at room temperature for 1 h. Freshly prepared DAB was applied as a chromogen.

Immunohistochemical assessment

Stromal and tumoral ALDH1A1 expressions were evaluated in stained breast carcinoma cases. ALDH1A1 positively stained tumor cells were characterized by the presence of brownish cytoplasmic coloration and was scored as reported by Khalifa *et al.* (2018), while ALDH1A1 expression in stromal cells were assessed according to Bednarz-Knoll *et al.* (2015).

Normal liver tissue samples were used as positive controls. Negative controls were obtained by replacing primary antibody with PBS (Zhou *et al.*, 2012).

Statistical analyses

Statistical package for the social sciences (SPSS) program, version 16 (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis. Quantitative data are expressed as mean±SD. Pearson correlation coefficient was used to correlate ALDH1A1 expression with clinicopathological data. Univariate survival analysis was carried out by Kaplan–Meier and log-rank statistics, to assess the prognostic significance of overall survival (OS) and disease-free survival (DFS). Relations, represented by *P* values, were considered significant when *P* value was less than 0.05 and highly significant when *P* value less than 0.01.

Results

The ages of the 40 cases studied having breast NOS, ranged from 40 to 69 years with a mean age of 55.8 ±7.58. All studied cases (100%) were women (Table 1).

Immunohistochemical results

Aldehyde dehydrogenase 1A1 expression in tumor cells

When detected, ALDH1A1 was localized to the cytoplasm of tumor cells. Thirteen (32%) breast cancer patients exhibited high expression for ALDH1A1 staining in primary tumor cells, whereas 27 (68%) breast cancer patients exhibited low expression.

Relationship between tumoral aldehyde dehydrogenase 1A1 expression and clinicopathological parameters

A significant positive correlation of tumoral ALDH1A1 expression was observed in the age group of more than 55 years ($P<0.05$), higher grade of tumor ($P<0.05$), larger tumor size (T) ($P<0.05$), greater possibility of lymph node metastasis ($P<0.01$),

Table 1 Demographic and clinicopathological characteristics of the studied cases

Characteristics	*N* (%)
Total patients	40 (100)
Age (years)	
≤55	16 (40)
>55	24 (60)
Sex (female)	40 (100)
Grade	
G2	26 (65)
G3	14 (35)
Primary tumor	
T1	6 (15)
T2	11 (27.5)
T3	17 (42.5)
T4	6 (15)
Regional lymph nodes	
N0	11 (27.5)
N1	13 (32.5)
N2	10 (25)
N3	6 (15)
Distant metastasis	
M0	34 (85)
M1	6 (15)
TNM stage	
I	2 (5)
II	13 (32.5)
III	19 (47.5)
IV	6 (15)
Molecular subtype	
Luminal A	16 (40)
Luminal B	
Her2 negative	5 (12.5)
Her2 positive	5 (12.5)
Her2 enriched	6 (15)
Triple negative	8 (20)
Prognosis (of 25 cases only)	
5 year disease-free survival	8 (32)
Metastasis/or local recurrence	6 (24)
Cancer-related death	11 (44)

presence of distant metastases ($P<0.05$), and advanced TNM stage ($P<0.05$; Table 2).

A significant association of tumoral ALDH1A1 with ER and PR negativity was noted ($P<0.05$ for both), while tumoral ALDH1A1 appeared significantly correlated with Her2/neu-positive cases ($P<0.05$; Table 2). The rate of ALDH1A1 positivity varied significantly among different molecular subtypes. The Her2-enriched subtype exhibited the highest expression rate as 66.7% of Her2-enriched cases showed high tumoral ALDH1A1 expression, followed by triple negative subtypes (50%) ($P<0.001$; Fig. 1a and b).

Prognostic study

Survival curves were plotted against tumoral ALDH1A1 expression. Log-rank test showed inverse significant correlations in respect to DFS ($P<0.0001$) and OS ($P<0.05$). So, breast cancer cases with ALDH1A1-positive tumor cells had a poorer prognosis than those with ALDH1A1-negative cases. Tumoral ALDH1A1 expression was found to be associated with high recurrence rate and shorter DFS in breast cancer (Table 3).

As regards the hormonal status, tumoral ALDH1A1 expression correlated inversely with OS and DFS of luminal A ($P<0.01$ for both) and luminal B ($P<0.05$ for both). However, the prognosis of Her2-enriched or triple-negative subtype was not affected ($P>0.05$; Table 4 and Fig. 2).

Aldehyde dehydrogenase 1 A1 expression in primary tumor-associated stroma

ALDH1A1 expression was detected in primary tumor-associated stroma in 22 (55%) of breast carcinoma patients. It was reported as brown cytoplasmic staining either moderate (12 cases, 30%) or strong (10 cases, 25%), in spindled- and/or polygonal-shaped stromal cells (Fig. 1c).

Relations of stromal aldehyde dehydrogenase 1A1 expression to clinicopathological parameters

Stromal ALDH1A1 expression was correlated inversely with the presence of distant metastasis and advanced tumor stage ($P<0.05$ for both), but there were no correlations to other clinicopathological parameters (Table 2).

Prognostic study

Univariate survival analysis showed longer DFS and OS in patients with positive stromal ALDH1A1 expression than patients with negative stromal ALDH1A1 expression (Kaplan–Meier log-rank analysis, $P<0.0001$; Table 3). In respect to the hormonal status, stromal ALDH1A1 was not significantly related to the survival of any of the molecular subtypes.

Relation between tumoral and stromal aldehyde dehydrogenase 1A1 expression

Fifteen (37.5%) cases expressed ALDH1A1 staining only in stromal cells, while six (15%) cases expressed it only in tumor cells. Combined tumoral and stromal ALDH1A1 expression was detected in seven (17.5%) patients. Tumoral and stromal ALDH1A1 expression had no statistical correlation with each other.

Discussion

Breast cancer is the first cancer affecting women worldwide, and the most leading cause of death

Table 2 Relations between aldehyde dehydrogenase 1A1 expressions and clinicopathological findings

Clinical data	Tumoral ALDH1A1			Stromal ALDH1A1			
	Low expression	High expression	*P* value	No expression	Moderate expression	Strong expression	*P* values
Age							
>55	15 (37.5)	1 (2.5)	<0.05*	5 (12.5)	6 (15)	5 (12.5)	**>0.05**
<55	12 (30)	12 (30)		13 (32.5)	6 (15)	5 (12.5)	
Tumor grade							
Grade 2	20 (50)	6 (15)	<0.05*	16 (40)	4 (10)	6 (15)	**>0.05**
Grade 3	7 (17.5)	7 (17.5)		2 (5)	8 (20)	4 (10)	
Primary tumor size							
T1	5 (12.5)	1 (2.5)	<0.05*	3 (7.5)	0	3 (7.5)	**>0.05**
T2	9 (22.5)	2 (5)		3 (7.5)	4 (10)	4 (10)	
T3	12 (30)	5 (10)		9 (22.5)	5 (12.5)	3 (7.5)	
T4	1 (2.5)	5 (12.5)		3 (7.5)	3(7.5)	0 (10)	
LN status							
N0	11 (27.5)	0	<0.01**	5 (12.5)	4 (10)	2 (5)	**>0.05**
N1	12 (30)	1 (2.5)		5 (12.5)	4 (10)	4 (10)	
N2	4 (10)	6 (15)		6 (15)	2 (5)	2 (5)	
N3	0	6 (15)		2 (5)	2 (5)	2 (5)	
Distant metastasis							
M0	27 (67.5)	7 (17.5)	<0.05*	12 (30)	12 (30)	10 (25)	<0.05*
M1	0	6 (15)		6 (15)	0	0	
TNM stage							
I	1 (2.5)	1 (2.5)	<0.01**	0	0 (10)	2 (5)	<0.05*
II	12 (30)	1 (2.5)		2 (5)	5 (12.5)	6 (15)	
III	14 (35)	5 (12.5)		11 (27.5)	6 (15)	2 (2.5)	
IV	0	6 (15)		5 (12.5)	1 (2.5)	0	
Molecular subtype							
Luminal A	14 (35)	2 (5)		6 (15)	6 (15)	4 (10)	
Luminal B							
Her2 negative	4 (10)	1 (2.5)	<0.05*	2 (5)	2 (5)	1 (2.5)	**>0.05**
Her2 positive	3 (7.5)	2 (5)		2 (5)	2 (5)	1 (2.5)	
Her2 enriched	2 (5)	4 (10)		2 (5)	2 (5)	2 (5)	
Triple negative	4 (10)	4 (10)		6 (15)	0	2 (5)	
Total	27	13		18	12	10	

ALDH1A1, aldehyde dehydrogenase 1A1. *Significant. **Highly significant. The bold values are non significant.

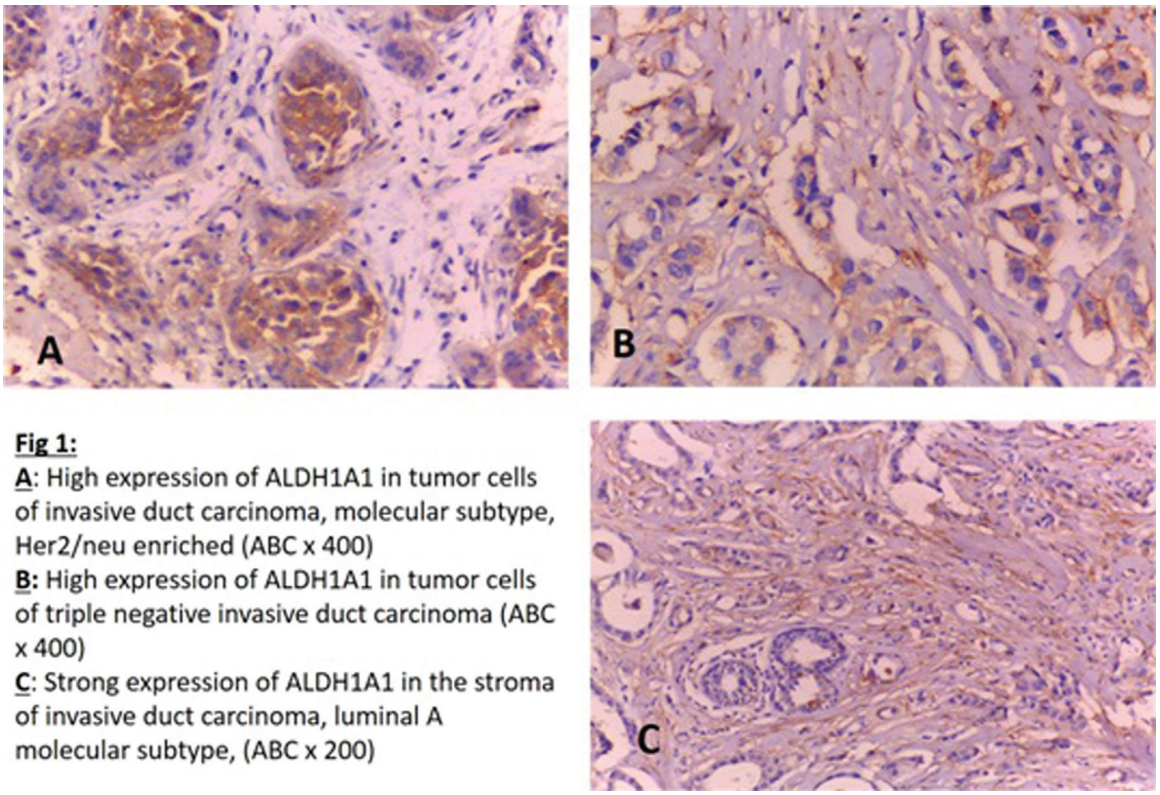
(Torre *et al.*, 2015). Well-known prognostic factors related to survival in breast cancer are the clinicopathological factors. Other important prognostic factors are the biological markers used clinically as ER, PR, and Her2/neu receptor status. Predictive markers that are used to determine treatment options and evaluate response to treatment are also included (Bandyopadhyay *et al.*, 2018).

ALDH1A1 is a CSC marker which is now known by its poor prognostic value in many tumors such as colorectal cancer, and ovarian and prostatic carcinomas (Bednarz-Knoll *et al.*, 2015). In this study, we detected the presence of ALDH1A1 in both tumor epithelial cells and stromal cells of breast NOS and searched for the relation between ALDH1A1 expression and clinicopathological data.

In tumoral epithelial cells, ALDH1A1 was detected in the cytoplasm of tumor cells with the majority of patients (68%) exhibiting low expression while (32%) breast cancer patients exhibited high expression. These results were in concordance with those of Miyoshi *et al.* (2016). We could explain these results by the fact that CSCs represent a small proportion of cancer tumoral cells. CSCs divide asymmetrically into two daughter cells, one becomes stem cell to ensure self-renewal and the second is a progenitor to proliferate. The proportion between both types is uncontrolled in tumor genesis (Douville *et al.*, 2009).

In this study, there was a significant association of tumoral ALDH1A1 with clinicopathological factors such as age more than 55 years ($P<0.05$), higher tumor grade ($P<0.05$), larger size of tumor (T) ($P<0.05$), positive lymph node metastasis ($P<0.01$), distant metastases ($P<0.05$), and advanced TNM stage ($P<0.01$). A significant correlation with ER and PR negativity was detected ($P<0.05$), in contrast to a significant positive correlation between tumoral cell ALDH1A1 expression

Fig. 1



(a) High expression of aldehyde dehydrogenase 1A1 (ALDH1A1) in tumor cells of invasive ductal carcinoma, molecular subtype, Her2/neu enriched [avidin–biotin complex (ABC) ×400]. (b) High expression of ALDH1A1 in tumor cells of triple-negative invasive ductal carcinoma (ABC ×400). (c) Strong expression of ALDH1A1 in the stroma of invasive ductal carcinoma, luminal A molecular subtype, (ABC ×200).

Table 3 Aldehyde dehydrogenase 1A1 expression in relation to survival

Tumoral ALDH1A1 expression	*N*	DFS (mean±SD) (months)	Disease-free patients [*n* (%)]	Patients with recurrence [*n* (%)]
Low expression	12	51.08±4.34	8 (66.7)	4 (33.3)
High expression	13	28.00±4.30	0	13 (100)
		$P<0.01$		
Stromal ALDH1A1 expression				
No expression	9	21.89±3.39	0	9 (100)
Moderate	9	41.67±5.79	2 (22.2)	7 (77.8)
Strong	7	57.86±1.98	6 (85.7)	1 (14.3)
		$P<0.01$		

Tumoral ALDH1A1 expression	*N*	OS (mean±SD) (months)	Alive [*n* (%)]	Dead [*n* (%)]
Low expression	12	52.54±4.31	9 (75)	3 (25)
High expression	13	31.78±4.78	5 (38.5)	8 (61.5)
		$P<0.05$		
Stromal ALDH1A1 expression				
No expression	9	24.58±4.06	2 (22.2)	7 (77.8)
Moderate	9	46.74±6.64	6 (66.7)	3 (33.3)
Strong	7	57.86±1.98	6 (85.7)	1 (14.3)
		$P<0.01$		

ALDH1A1, aldehyde dehydrogenase 1A1; DFS, disease-free survival; OS, overall survival.

and Her2/neu-positive cases ($P<0.05$). These results were in keeping with Morimoto *et al.* (2009) and Ricardo *et al.* (2011). These results suggested the role of ALDH1A1 in the aggressiveness of the tumor. It is not only CSC marker but also has a role in cell biology and propagation of the tumor through many biological functions. It acts through retinoic acid cell signaling and causes tumoral cell proliferation and differentiation (Marcato *et al.*, 2011).

In this study, it was observed also that the rate of ALDH1A1 positivity varied significantly among different molecular subtypes with the highest

Table 4 Tumoral aldehyde dehydrogenase 1A1 expression in the studied breast cancer molecular subtypes in relation to survival

DFS in respect to ALDH1A1 expression in luminal A subtype				
Tumoral ALDH1A1 expression	*N*	DFS (mean±SD) (months)	Cases in remission [*n* (%)]	Cases with relapse [*n* (%)]
Low expression	7	52.7±1.9	2 (28.6)	5 (71.4)
High expression	2	10.00±2.00	0	2 (100)
		P<0.01		
DFS with respect to ALDH1A1 expression in luminal B subtype				
Tumoral ALDH1A1 expression	*N*	DFS (mean±SD) (months)	Cases in remission [*n* (%)]	Cases with relapse [*n* (%)]
Low expression	3	58.33±1.36	2 (66.7)	1 (33.3)
High expression	3	16.7±3.3	0	3 (100)
		P<0.05		
OS with respect to ALDH1A1 expression in luminal A subtype				
Tumoral ALDH1A1 expression	*N*	OS (mean±SD) (months)	Alive [*n* (%)]	Dead [*n* (%)]
Low expression	7	58.14±1.34	5 (71.4)	2 (28.6)
High expression	2	20.50±0.50	0	2 (100)
		P<0.01		
OS with respect to ALDH1A1 expression in luminal B subtype				
Tumoral ALDH1A1 expression	*N*	OS (mean±SD) (months)	Alive [*n* (%)]	Dead [*n* (%)]
Low expression	3	59.6±0.27	2 (66.7)	1 (33.3)
High expression	3	28.00±6.20	0	3 (100)
		P<0.05		

ALDH1A1, aldehyde dehydrogenase 1A1; DFS, disease-free survival; OS, overall survival.

expression level was observed in Her2-enriched subtype (66.7%), followed by triple negative subtype (50%) ($P<0.001$) and these results were compatible with results of Schmitt *et al.* (2012), Liu *et al.* (2014), and Pan *et al.* (2015) who found that tumors with positive ALDH1A1 expression had more aggressive phenotypes, such as HER2-positive and triple-negative cancers, also those cancers with higher histological grade, higher Ki-67 expression, and more advanced TNM stage. Kim *et al.* (2014) results demonstrated that ALDH1A1 expression may have a role in the heterogeneity and breast cancer aggressiveness.

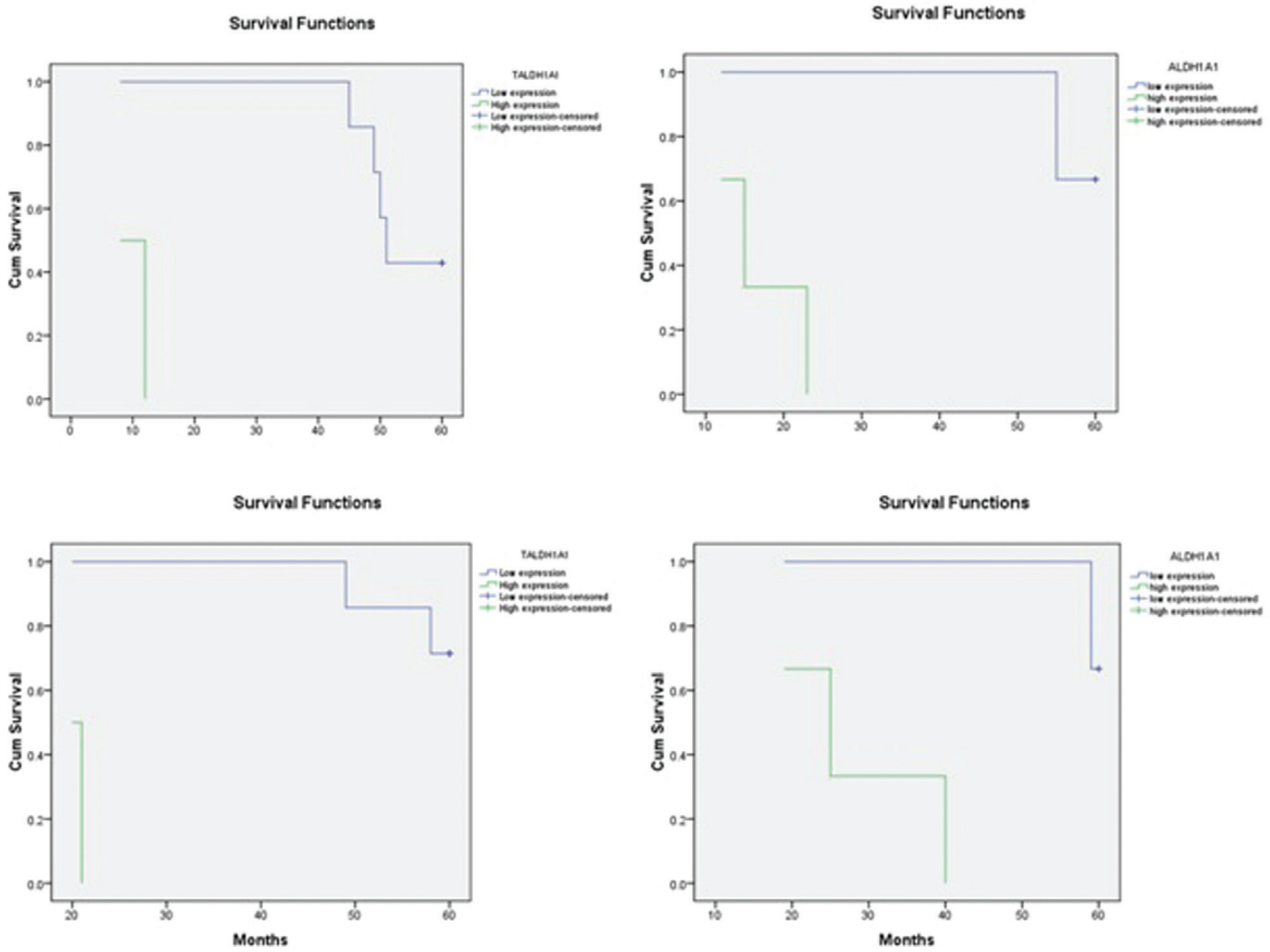
Another finding in this study was an inverse significant correlation of tumoral ALDH1A1 in respect to OS and DFS ($P<0.05$ and < 0.01, respectively). The prognosis of breast cancer cases with ALDH1A1-positive cells was poorer than that of the ALDH1A1-negative cells as tumoral ALDH1A1 was associated with high recurrence rate and shorter DFS in breast cancer. These results agree with those of Miyoshi *et al.* (2016), Bednarz-Knoll *et al.* (2015), Morimoto *et al.* (2009), and Ricardo *et al.* (2011). These results support the hypotheses that both normal and CSCs are relatively resistant to irradiation or common chemotherapeutic drugs that help cancer recurrence and later metastasis development as it targets rapidly dividing cells while leaving stem cells. CSCs grows slowly, and is usually in the quiescent state, therefore they does not respond to chemotherapeutics that target the fast-growing cancer cells (Dalerba *et al.*, 2007). Another hypothesis is that cancer breast is originated from transformed stem cell which help them escape from commonly used chemotherapy and grow back after remission (Dontu *et al.*, 2003).

Tumoral ALDH1A1 expression correlated inversely with OS and DFS of both luminal A ($P<0.01$) and luminal B cases ($P< 0.05$) and this could be attributed to the possible role of ALDH1A1 in the creation of resistance to treatment and aggressiveness of the tumor and this explanation is matching with the results of Miyoshi *et al.* (2016).

Tumoral ALDH1A1 expression did not affect the prognosis of Her2-enriched or the triple-negative subtype and these results match with Kim *et al.* (2014), who reported that shorter DFS in ALDH1A1+ tumor cells may be attributed to the triple-negative features than ALDH1A1 expression itself .This also can be explained by the theory that breast cancer is considered a heterogeneous disease, and though, it exhibits variable prognosis among its different types as regards positivity to ALDH1A1 (Miyoshi *et al.*, 2016).

In contrast to our results, the results of Kahlert *et al.* (2011) on pancreatic cancer stated that decreased

Fig. 2



(a) Log-rank curve regarding tumoral aldehyde dehydrogenase 1A1 (ALDH1A1) expression luminal A subtype with respect to disease-free survival (DFS) ($P<0.01$). (b) Log-rank curve regarding tumoral ALDH1A1 expression luminal B subtype with respect to DFS ($P<0.05$). (c) Log-rank curve regarding tumoral ALDH1A1 expression luminal A subtype with respect to overall survival (OS) ($P<0.01$). (d) Log-rank curve regarding tumoral ALDH1A1 expression luminal B subtype with respect to OS ($P<0.05$).

ALDH1A1 expression was considered a poor prognostic marker in pancreatic cancer. This diversity may be due to the difference in the tissue and the different isoform of ALDH responsible for activity as it varies according to the type of cancer (Marcato *et al.*, 2011).

Regarding tumor stroma, in the current study ALDH1A1 was detected in stromal cells in 55% of patients as moderate and strong cytoplasmic staining. Unlike tumoral ALDH1A1 expression, stromal ALDH1A1 was inversely correlated with presence of distant metastasis ($P<0.05$), and advanced tumor stage ($P< 0.05$). For us it was surprising as it is well known that the epithelial-to-mesenchymal transition is a requirement for dissemination and metastasis of tumor cells. Disseminated cells lose their epithelial features and then acquire more mesenchymal properties which help in dissemination and metastasis. These results are matching with those of Bednarz-Knoll *et al.* (2015) who explained their results by the hypothesis that these stromal cells may be a type of fibroblasts or dendritic cells recruited by the tumor. These cells have the ability to attenuate the outgrowth of the tumor. Another explanation is that stromal positive ALDH1A1 may secrete retinoic acid into the microenvironment and thus increase differentiation and reduce proliferation and inhibit migration abilities of the tumor by regulating other immune cells (Tang and Gudas, 2011).Unlike the study performed by Kahlert *et al.* (2012) on colon and rectal carcinomas which observed that the increasing stromal ALDH1A1 expression is correlated with poor prognosis. This raised the hypothesis that cancer breast is originated from a transformed stem cell which has different properties (Dontu *et al.*, 2003).

Conclusion

ALDH1A1 may play a dual role in NOS progression. Tumoral ALDH1A1 is a marker for unfavorable prognosis, while its stromal expression gives an

opposite impression. Tumoral ALDH1A1 could be used to predict chemoresistant cases among different molecular subtypes of breast cancer, in order to apply a different treatment regimen. Induction of stromal ALDH1A1 expression could be a possible therapeutic target in the future to suppress tumor progression. Further studies to explore genetic regulation of stromal ALDH1A1 expression are recommended.

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Conflicts of interest
There is no conflicts of interest.

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