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Research Article

Pattern of Breast Cancer in Young Females in Minia Governorate

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Abstract
Background: Breast cancer is the most common cause of cancer in women worldwide. Although it is a disease of postmenopausal and elderly age group, approximately 5.6% of breast cancer patients are ≤40 years. It has aggressive clinical behavior with poor outcomes as compared to the elderly group. This study was carried out to determine the pattern of breast cancer in young females in Minia district. **Methods:** This is a retrospective cohort study collecting data in Minia university hospital and Minia oncology center from 2017 to 2021, for patients with primary breast cancer who were diagnosed and pathologically proven breast cancer below age of 40. Patients were staged according to TNM staging system (according to American Joint Committee on Cancer AJCC 2017) Immunohistochemistry was used for molecular classification. **Results:** Total number of cases of breast cancer cases below age of 40 was 279 which represent 10% of 2760 cases. About 10.8% of patients had family history, 91% of patients presented with infiltrating ductal carcinoma and (82.4%) had Grade II disease . About 98 (35.7%) cases were luminal A, 30.5% were luminal B. HER2 positive in 47cases (16.8%) and triple negative patients 49 cases (17.6%). Majority of patients had negative ovulation induction, stage II 45.9%, nodal status N1 34.1% . **Conclusion:** The reflection of molecular subtypes on overall survival was not statistically significant but ki67 and association of primary tumor stage T and the prevalence of metastasis to lymph nodes were statistically significant.

Keywords: Breast cancer, Young females, Pattern.

Introduction
Breast cancer (BC) is the most common cancer in women. Although the incidence of BC is age-dependent, a constant increase in BC diagnoses in women younger than 40 years has been recently reported in several countries, with approximately 11% of new cases diagnosed in women who are 45 years of age or younger. A variety of risk factors for breast cancer have been well-established by epidemiologic studies including race, ethnicity, family history of cancer, and genetic traits, as well as modifiable exposures such as increased alcohol consumption, physical inactivity, exogenous hormones, and certain female reproductive factors. Younger age at menarche, parity, and older age at first full-term pregnancy may influence breast cancer risk through long-term effects on sex hormone levels or by other biological mechanisms.

Different types of breast cancer diagnostic examinations are also available, such as mammography, breast MRI, biopsy, ultrasound and molecular imaging appropriate workup of physical symptoms is essential in these patients. (1)

Breast cancer can be broadly categorized on the basis of histological outcome into in situ carcinoma and *invasive* carcinoma. Breast carcinoma in situ is further sub-classified as either ductal (DCIS; more common) or lobular (LCIS; less common). Among the invasive carcinomas IDC is the most common subtype accounting for 70–80% of all invasive lesions.

IDC is further sub-classified as well-differentiated (grade 1), moderately differentiated (grade 2) or poorly differentiated (grade 3) based on the levels of nuclear pleomorphism, glandular/tubule formation and mitotic index.
Breast cancers are then classified with respect to the presence or absence of these receptors as Luminal A (ER and PR positive, and HER2 negative); Luminal B (ER and/or PR positive, HER2 negative and high KI67); HER2-enriched (ER and PR negative, and HER2 positive) and Basal Like (Triple negative breast cancer- ER, PR and HER2 negative). [2]

The therapeutic approaches that are employed for breast cancer management include cytoreductive surgery, radiation treatment, targeted endocrine/molecular therapy and chemotherapy Due to the heterogeneity of the disease the treatment protocol requires rationalized therapy in individual cases according to the characterization and stage of the disease.

There are two major types of surgical procedures enabling the removal of breast cancerous tissues and those include (1) breast-conserving surgery (BCS) and (2) mastectomy. BCS-also called partial/segmental mastectomy, lumpectomy, wide local excision, or quadrant-ectomy the removal of affected lymph nodes involves sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND).

Chemotherapy is a systemic treatment of BC and might be either neoadjuvant or adjuvant. Choosing the most appropriate one is individualized according to the characteristics of the breast tumor; chemotherapy might also be used in the secondary breast cancer. Neoadjuvant chemotherapy is used for locally advanced BC, inflammatory breast cancers, for downstaging large tumors to allow BCS or in small tumors with worse prognostics molecular subtypes (HER2 or TNBC) which can help to identify prognostics and predictive factors of response. [3]

Radiotherapy is local treatment of BC, typically provided after surgery and/or chemotherapy. It is performed to ensure that all of the cancerous cells remain destroyed, minimizing the possibility of breast cancer recurrence. Further, radiation therapy is favorable in the case of metastatic or unresectable breast cancer.

Endocrinal therapy might be used either as a neoadjuvant or adjuvant therapy in patients with hormonal positive Breast Cancer; it is effective in cases of breast cancer recurrence or metastasis Drugs that block ERs while treatments that aim to lower the estrogen levels include aromatase inhibitors (AIs) .In the case of pre-menopausal women, ovarian suppression induced by oophorectomy, luteinizing hormone-releasing hormone analogs, or several chemotherapy drugs, are also effective in lowering estrogen levels.[4]

Biological therapy (targeted therapy) can be provided at every stage of breast therapy– before surgery as neoadjuvant therapy or after surgery as adjuvant therapy. Biological therapy is quite common in HER2-positive breast cancer patients; major drugs include trastuzumab, pertuzumab, trastuzumab deruxtecan, lapatinib, and neratinib.

Among breast cancer survivors, 32–93% of women report sexual problems and 27% to 88% report body image concerns. For women of reproductive age, treatments for breast cancer may also negatively impact fertility. Breast cancer treatment-related changes in sexual and reproductive health are associated with significant distress and often negatively impact women's emotional well-being, relationships, sense of self, and overall quality of life.[5]

Aim of the study

This study will be carried out to determine the pattern of breast cancer in young females in our community regarding hormonal manipulation, age of marriage, consanguinity, site, pathology, grade, Tumor size, lymph node status, molecular classification (ER, PR, HER2 neu positive, Triple negative , basal like,), KI67 and reflection on overall survival from year 2017 to 2021.

Patients and methods

The data for patients with primary breast cancer who were diagnosed by pathologically proven breast cancer below age of 40 years collecting from female cases from Minia university hospital and Minia oncology center from period 2017 to 2021. TNM staging system (according to American Joint Committee on Cancer AJCC 2017) was used for staging. Immunohistochemistry was used for molecular classification.

Inclusion criteria:

Female ageed below 40y, with biopsy-proven invasive lobular or ductal carcinoma.

1. Staging by (TNM staging system).
2. Hormonal manipulation (Contraceptive usage, ovulation induction).
3. Time of menarche.
4. Family history.
5. consanguinity
6. Molecular classification.

Ethical consideration:

An ethical approval was taken from Research Ethics Committee of faculty of Medicine, Minia University and Minia oncology center.

Statistical analysis:

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 20. The qualitative data Molecular classification of these cases was luminal A in 98 case (35.7%), luminal B 85 case (30.5%), HER2 positive 47case (16.8%) and Triple negative patients 49 case (17.6%).
161 patients (57,7%) were still alive, 118 patients (42.3%) dead . Our results showed that, OAS range was (6-87months) and mean ± SD (43.5 ± 17.4).

Cox regression analysis for prediction of mortality revealed that ki67 level was a significant predictor of the overall survival with HR (95% CI); 1.64 (1.135-2.375)
There was association of primary tumor stage T and the prevalence of metastasis to lymph nodes.

were presented as number and percentages while quantitative data were presented as mean, standard deviations and ranges for normally distributed data. Cox regression analysis was used for prediction of mortality
The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following:
P> 0.05 = non significant (NS)
P < 0.05 = significant (S)
P < 0.001 = highly significant (HS).

Results

A total of 279 cases were included. In this study, there were 34 patients were Age < 30 years (12.2%) and 245 were in age between 30 – 40 years (87.8%) , The median age of enrolled patients was 34.6±4.5 years (range 22–40 years). Sixty sex (23.7%) patients had positive family history of breast cancer, and 160 patients (57.3%) used hormonal contraceptive, patients were 225 (91.4%) with no consanguinity. There were 227 (81.4%) patients with negative ovulation induction**.** Time of first Menarche < 13 years was recorded in 32.3% of patients.
The majority of patients has invasive duct carcinoma (254 cases (91%)) while invasive lobular carcinoma ILC represent only 14 cases (5.0%), other pathology like DCIS , LCIS , phylloid tumor represent minority of cases and
TNM staging revealed that 230 (82.4%) of patients with Grade II, 128 (45.9%) with **T2** and 95 (34.1%) with **N1** status.

Table 1: Baseline characteristic of the studied group

		Descriptive statistics N=279
Age	Range Mean ± SD	(22-40) 34.6±4.5
Age group	< 30 y 30-40 y	34(12.2%) 245(87.8%)
Family history	-Ve +Ve	213(76.3%) 66(23.7%)
Contraceptive usage	-Ve +Ve	119(42.7%) 160(57.3%)
Consanguinity	-Ve +Ve	255(91.4%) 24(8.6%)
Site	RT LT Bilateral	149(53.4%) 122(43.7%) 8(2.9%)
Pathology	IDC LDC Others	254(91%) 14(5%) 11(3.9%)
Grade	Grade I Grade II Grade III	10(3.6%) 230(82.4%) 39(14%)
ER	-Ve +Ve	100(35.8%) 179(64.2%)
PR	-Ve +Ve	89(31.9%) 190(68.1%)
HER2	-Ve +Ve	201(72%) 78(28%)
KI67	Low High	121(43.4%) 158(56.6%)
Progresion	-Ve +Ve	166(59.5%) 113(40.5%)
Ovarian induction	-Ve +Ve	227(81.4%) 52(18.6%)
Time of Menarche	< 13 y 13 y > 13 y	90(32.3%) 118(42.3%) 71(25.4%)
T	T1 T2 T3 T4	46(16.5%) 128(45.9%) 87(31.2%) 18(6.5%)
N	N0 N1 N2 N3	70(25.1%) 95(34.1%) 79(28.3%) 35(12.5%)
Molecular classification	Luminal A Luminal B Her 2 Base like	98(35.7%) 85(30.5%) 47(16.8%) 49(17.6%)
Death	Live Dead	161(57.7%) 118(42.3%)
OAS	Range Mean ± SD	(6-87) 43.5±17.4

Table 2: Cox regression analysis for prediction of mortality

		HR	95% CI	P value
Age group	< 30 y	Ref.		
	30-40 y	0.956	0.555-1.647	0.872
Family history	-Ve	Ref.		
	+Ve	1.086	0.695-1.697	0.717
Contraceptive usage	-Ve	Ref.		
	+Ve	1.304	0.901-1.888	0.159
Consanguinity	-Ve	Ref.		
	+Ve	1.363	0.728-2.552	0.333
Site	RT	Ref.		
	LT	1.064	0.385-2.936	0.905
	Bilateral	1.253	0.452-3.477	0.664
Pathology	IDC	Ref.		
	LDC	0.916	0.372-2.253	0.848
	Others	0.852	0.270-2.690	0.785
Grade	Grade I	Ref.		
	Grade II	0.958	0.461-1.994	0.909
	Grade III	0.825	0.348-1.956	0.662
ER	-Ve	Ref.		
	+Ve	0.835	0.575-1.212	0.343
PR	-Ve	Ref.		
	+Ve	0.816	0.564-1.183	0.283
HER2	-Ve	Ref.		
	+Ve	0.850	0.553-1.307	0.459
KI67	Low	Ref.		
	High	**1.642**	**1.135-2.375**	**0.009***
Progression	-Ve	Ref.		
	+Ve	1.018	0.709-1.463	0.922
Ovarian induction	-Ve	Ref.		
	+Ve	1.323	0.834-2.097	0.235
Time of Menarche	< 13 y	Ref.		
	13 y	0.899	0.58-1.384	0.629
	> 13 y	1.044	0.639-1.708	0.863
T	T1	Ref.		
	T2	1.265	0.743-2.152	0.386
	T3	1.453	0.846-2.496	0.176
	T4	1.126	0.416-3.052	0.815
N	N0	Ref.		
	N1	0.985	0.608-1.597	0.952
	N2	1.212	0.759-1.937	0.421
	N3	0.826	0.450-1.518	0.538
Molecular classification	Luminal A	Ref.		
	Luminal B	1.183	0.741-1.89	0.482
	Her 2	0.860	0.490-1.509	0.600
	Base like	1.490	0.911-2.437	0.112

Table 3: Association between tumor size and prevelance of nodal metastasis

		T				Total	P value
		T1	T2	T3	T4		
N	N0	26	42	2	0	70	<0.001*
	N1	20	53	20	2	95	
	N2	0	29	47	3	79	
	N3	0	4	18	13	35	
Total		46	128	87	18	279	

Table 4: Lymph node metastasis and its relation to tumor size

	Tumor size	
	r	P value
Nodal status	*0.647*	*<0.001**

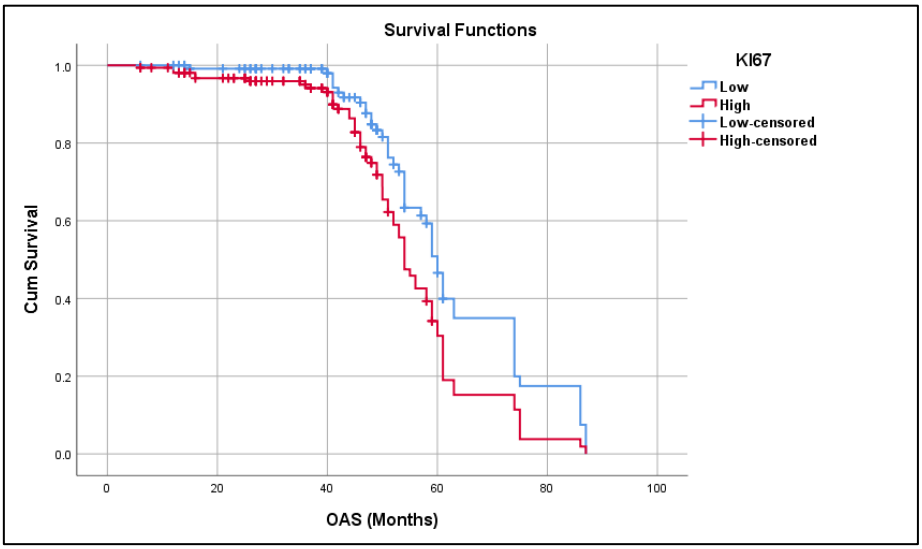


Figure (1): overall survival regarding ki67.

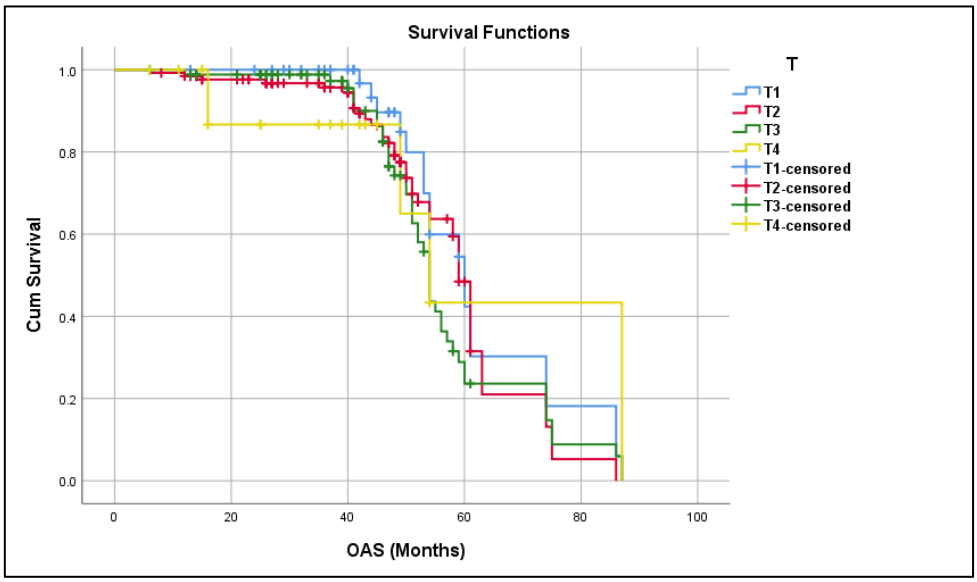


Figure (2): overall survival regarding tumor size.

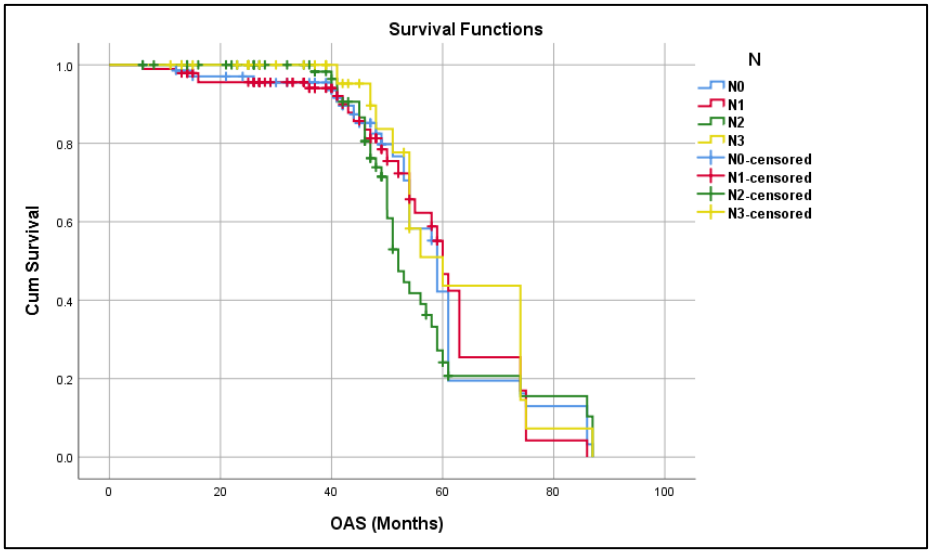
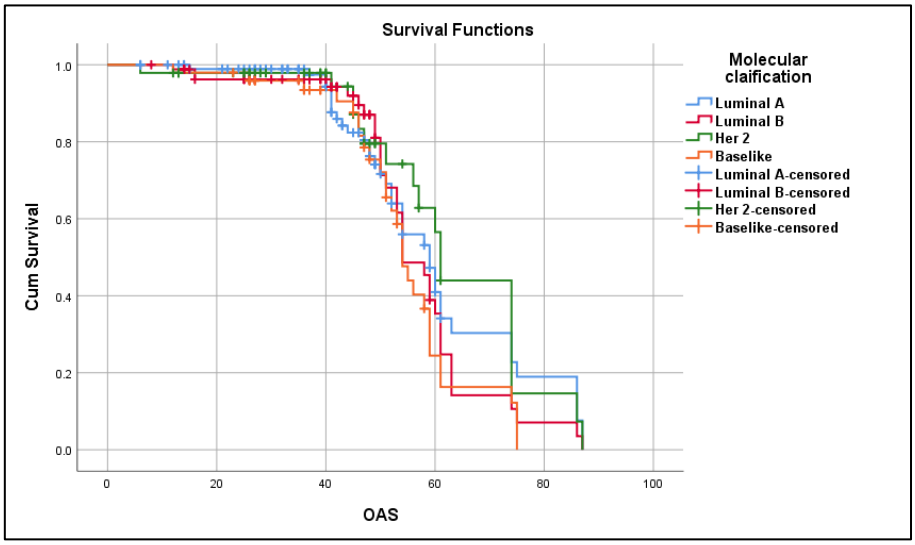


Figure (3) overall survival and lymph node status.



Figure(4) overall survival and molecular classification

Discussion

Breast cancer is considered as a heterogeneous condition and so requires evaluation of as many clinical and pathological features as possible to allow for best prediction of survival.

Our results showed that, there were 254(91%) patients with IDC, 14(5.0%) patients with ILC and 11(3.9%) patients with other pathological subgroup.This agreed with a study that aimed to compare the characteristics of breast cancer in a group of young women with a group of postmenopausal women and confirm the higher malignant potential of cancer in the population of young women. They reported that Invasive ductal carcinoma was the most frequent histologic type of tumor. The second most common type was invasive lobular carcinoma (6).

The age of the patient is a well-defined prognosis factor for local recurrence. It is well established that patient age greater than 35 or 40 is associated with an increased frequency of local recurrence due to presence of various adverse pathologic features, such as lymph vascular invasion, grade 3 histology, absence of Estrogen Receptor (ER) and Progesterone

Receptor (PR), presence of HER2 and presence of extensive intra-ductal component. [7]

Turkish study showed the molecular sub-type analysis of the tumors that 57.7% of the tumors were luminal A (ER and/or PR positive, HER-2 negative, low KI67), 20.6% were luminal B (ER and/or PR positive, HER-2 positive, high KI67), 9.6% were HER-2 type (ER and PR negative, HER-2 positive) and 12.1% were triple negative which agreed with our study. [8]
Lymph node involvement has long been recognized as an important prognostic factor in breast cancer. The presence of positive axillary lymph nodes is a predictor of increased risk of local and distant recurrence, directly affecting mortality. The association between lymph node involvement and survival has been previously demonstrated and it has been shown that overall survival rates are up to 40% lower in node-positive patients compared with node-negative ones .[9]

Retrospective cohort study of node-positive stage II and III breast cancer patients diagnosed and treated between 2008 and 2009 at the Brazilian National Cancer Institute the median overall survival times of low-, intermediate-, and high-risk LNR patients were 55.6, 52.9, and 48.8 months, respectively ($p<0.001$) [10]

In our study we found lymph node negative were (N0) 70 patients with estimated mean 58.6% and CI (53.9- 63.3). N1 95 patients estimated mean 58.7 and CI (54.3 – 63.1), N2 79 patients estimated mean 57.6 and CI (52, 9-62, 3) and N3, 35 patients estimated mean 62.8 and CI (56.2 -69.4)

In the current study the impact of molecular classification luminal A 98 cases (35.7%), luminal B 85 cases (30.5%), HER2 positive 47cases (16.8%) and Triple negative patients 49 cases (17.6%) and that is not statistically significant on overall survival.

There are also studies investigating influence of reproductive factors on tumor characteristics and breast cancer survival in women. An association had been found between early age at menarche and reduced survival. Age at menarche was also shown to be significantly associated with tumor grade and lymph node involvement**.** [11]

Breast cancer survival varies substantially by stage at diagnosis. Pinheiro et al., showed the 5-year relative survival for patients diagnosed during 2012–2018 was >99% for stage I disease, 93% for stage II, 75% for stage III, and 29% for stage IV. Except for stage I, for which survival is similar, Black women have the lowest survival for every stage of diagnosis, with the largest Black–White disparities among those diagnosed with stages III and IV disease. [12]

And the 5-year overall survival According to the Iranian study, Ki67 could not be used as an independent prognostic factor for invasive breast cancers. It was also concluded that there is no significant relationship between Ki67 and some prognostic factors such as hormonal receptors and HER2. In addition, no significant difference was observed between Ki67 and 3- and 5-year DFS with 5-year OS. In our study ki67 level was a significant predictor of the overall survival with HR (95% CI); 1.64 (1.135-2.375)

There is an association of primary tumor stage T and the prevalence of metastasis to lymph nodes was statistically significant with p value < 0.001 .

Conclusion

More cases of breast cancer were recorded among those 30 - 40 years. 10.8% of patients had family history of breast cancer. 91% presented with infiltrating ductal carcinoma. Molecular classification of these cases was luminal A in 98 of cases (35.7%) , luminal B in 85 of cases (30.5%) , HER2 positive 47cases (16.8%) and Triple negative patients 49 cases (17.6%). Reflection of molecular subtypes not statistically significant while ki67 status and association of primary tumor stage T and the prevalence of metastasis to lymph nodes were statistically significant.
Facilities should be provided for screening, early diagnosis and management especially in the low- and middle-income countries.

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