



## The Prognostic Value of Luminal Subtypes of Breast Cancer and their Impact on the Patient's Outcome

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### Abstract

**Background:** Breast cancer is the major cause of death by cancer among females in developing countries. Although the overall breast cancer incidence rate in the developed countries is double that seen in developing countries, the mortality rates from the disease are generally similar. However, survival following breast cancer tends to be poorer in developing countries, this is attributed to late diagnosis and limited access to standard treatment. One of the challenges in treating the disease is addressing the biological heterogeneity evident in the presence of several histologic and molecular subtypes.<sup>(1-4)</sup>

Despite advances, about 20% to 30% of patients with early breast cancers will experience distant metastatic relapse.<sup>(5)</sup> Risk of recurrence is enhanced by the stage at initial presentation and the underlying molecular biology of the tumor. Nodal, Tumor size, grade, lympho-vascular and perineural invasion, and estrogen receptor (ER)<sup>(6)</sup> and human epidermal growth factor receptor 2 (HER2)<sup>(7)</sup> status are all major risk factors for relapse.

The response of breast cancer patients to hormonal therapy is currently guided by the expression of two steroid hormonal receptors (HR): estrogen receptor- $\alpha$  (ER- $\alpha$ ), progesterone receptor (PR) and proliferation marker Ki-67. Expression of PR, in fact, has been reported to confer good prognosis to breast cancer patients.<sup>(8)</sup> Another molecular marker that is increasingly being examined in breast cancer for therapeutic potential as well as a prognostic indicator is the human epidermal growth factor receptor type 2 (Her-2/neu) oncoprotein.<sup>(9-11)</sup> Although several subtype classifications have been developed, the different classifications generally agree on four subtypes (luminal A, luminal B, HER2-enriched and basal-like).<sup>(12)</sup>

**Aim of the study:** The aim of this study is to assess the hormonal receptors and molecular subtypes for their impact on management in breast cancer patients.

**Patients:** This study was carried out retrospectively on 400 patients presented to Surgical oncology unit; Alexandria Main University Hospital, Medical and Surgical Oncology units; Gamal Abdel-Nasser Health Insurance Hospital was obtained within 3 years from January 2010 to January 2013.

**Subjects and Methods:** The patients data were collected from Surgical oncology unit; Alexandria Main University Hospital, Medical and Surgical Oncology units; Gamal Abdel-Nasser Health Insurance Hospital within 3 years from January 2010 to January 2013 and filtered into flow sheets.

**Results:** The age was varying between 32.0 - 86.0 years with a mean age of  $55.27 \pm 9.24$  years. Luminal A subtype was found to be the most frequent type presenting 74.3% of patients followed by Luminal B (12.3%), Triple -ve (10.5%) and Her2 type, the least common, presenting 3.0% of patients. Infiltrating duct carcinoma

(NOS) (IDC) was the most commonly diagnosed histopathological type presenting 93.8% of cases. There was no history of recurrence of the primary tumor in 80.3% of cases, 8.7% of cases presented with loco-regional recurrence (LRR) and 11.0% of cases presented with distant recurrence within four years after excision of the primary tumor. The Triple –ve group had the highest incidence of recurrence with 48.0% and 16.0% of cases with loco-regional recurrence and distant recurrence respectively, followed by Luminal B and Luminal A subtypes. Her2-enriched subtype showed no distant recurrence among the group patients.

**Conclusion:** Luminal A subtype is the most frequent biological subtype and Her2 type is the least common. Triple –ve group has the highest incidence of recurrence with 48.0% and 16.0% of cases with loco-regional recurrence and distant recurrence respectively, followed by Luminal A and B subtypes and Her2 enriched subtype showed no distant recurrence among the group patients.

## Introduction

Breast cancer is the major cause of death by cancer among females in developing countries. Although the overall breast cancer incidence rate in the developed countries is double that seen in developing countries, the mortality rates from the disease are generally similar. However, survival following breast cancer tends to be poorer in developing countries, this is attributed to late diagnosis and limited access to standard treatment. One of the challenges in treating the disease is addressing the biological heterogeneity evident in the presence of several histologic and molecular subtypes.<sup>(1-4)</sup>

## Prognostic factors of breast cancer:

### 1. Axillary Lymph-nodal Status

The presence or absence of axillary lymph node involvement is considered as the most significant prognostic indicator for patients with breast cancer. Furthermore, there is a direct relationship between the number of involved axillary nodes and the risk for distant recurrence<sup>(13,14)</sup>. The 5-year survival for patients with node-negative disease (N0) is about 82.8% compared with 73% for 1- 3 positive nodes (N1), 45.7% for 4-9 positive nodes (N2), and 28.4% for  $\geq 10$  positive nodes (N3)<sup>(15)</sup>. These data show that the risk of recurrence is significant with lymph node positive disease to require adjuvant systemic therapy.

### 2. Age at Diagnosis

Two relatively large trials have demonstrated that patients younger than 35 years of age with breast cancer have worse prognosis than older ones, even after adjustment for other prognostic factors.<sup>(16, 17)</sup>

Moreover, very young women have higher incidence of advanced stages at time of diagnosis and poorer 5-year survival than older premenopausal patients.<sup>(18-20)</sup>

### 3. Tumor Size

Tumor size correlates with the presence and number of involved axillary lymph nodes. It is also an independent prognostic factor, with distant recurrence rates increasing with larger tumor size. Rosen et al. examined the relationship between the size of the tumor and 20-year recurrence-free survival and found that there is a significant association, with a 20-year recurrence-free survival of 88% for tumors  $\leq 1$  cm, 72% for tumors 1.1 cm to 3 cm, and 59% for tumors between 3.1 cm and 5 cm<sup>(21)</sup>. For patients with negative lymph nodes, tumor size is the most important prognostic factor and is routinely used to make adjuvant treatment decisions.

### 4. Tumor Type/Grade

The pathological characteristics of the tumor have prognostic significance. Certain subtypes such as tubular, mucinous, and medullary have a more favorable prognosis than unspecified breast cancer<sup>(22-24)</sup>. The most widely used grading system is the Scarff-Bloom-Richardson (SBR) classification<sup>(25)</sup>. Degree of differentiation, mitotic index and pleomorphism are scored from 1 to 3 and the scores from each category are totaled.

### 5. Lympho-vascular and peri-neural Invasion

Lymphatic vessel and vascular invasion (LVI) has been demonstrated to have prognostic importance for the risk of local and distant recurrence. At 20 years of follow-up, Rosen et al. noted a correlation between lympho-vascular invasion and

the risk of recurrence. The recurrence rate for women with LVI-positive stage I disease was 38% compared with 22% for those with LVI-negative disease. Lympho-vascular invasion does have prognostic significance and is used essentially to make decisions for nodal-negative patients with borderline tumor sizes.<sup>(26)</sup>

## 6. ER/PR Status

The presence of estrogen and progesterone receptors in an invasive breast carcinoma have both prognostic and predictive significance. Its prognostic effect is difficult to evaluate in that it must be assessed in the absence of adjuvant tamoxifen.<sup>(27)</sup>

## 7. Ki67 (New prognostic factor)

Ki-67 protein (also known as MKI67) is a cellular proliferation marker. The Ki-67 expression as detected by immunohistochemistry is one of the most reliable indicators of the proliferative status of cancer cells<sup>(28)</sup>. In 2011, Ki-67 was considered as one of the factors affecting molecular subtypes<sup>(29)</sup>. Ki-67 expression is closely associated with the growth and invasion of breast cancer: Ki-67-positive breast cancers are more active in growth, more aggressive in invasion, and more metastatic. Cheang et al.<sup>(30)</sup> integrated Ki-67 expression as a prognostic factor into molecular typing, and their results showed that Luminal B breast cancer patients (ER and/or PR positive, HER-2 positive,  $\geq 14\%$  Ki-67 positive cells) with positive axillary lymph nodes had a poorer 10-year recurrence free survival rate (64%) and a poorer overall survival rate (74%) when compared with Luminal A breast cancer patients (ER and/or PR positive, HER2 negative,  $< 14\%$  Ki-67 positive cells). Furthermore, two meta-analyses showed that Ki-67 is an important factor affecting the recurrence of early breast cancer and the survival of breast cancer patients<sup>(31,32)</sup>. The prognostic value of Ki-67 has been associated with poorer prognosis in breast cancer patients with negative axillary lymph nodes in most studies<sup>(33-35)</sup>.

## Patients and Methods

This retrospective study was carried out on 400 patients presented to Surgical Oncology unit; Alexandria Main University Hospital, Medical and Surgical Oncology units; Gamal Abdel-Nasser Health Insurance Hospital.

The patient's data was randomly obtained from patient's oncology files within 3 years from January 2010 to January 2013 or as back as we need to reach the number of patients wanted.

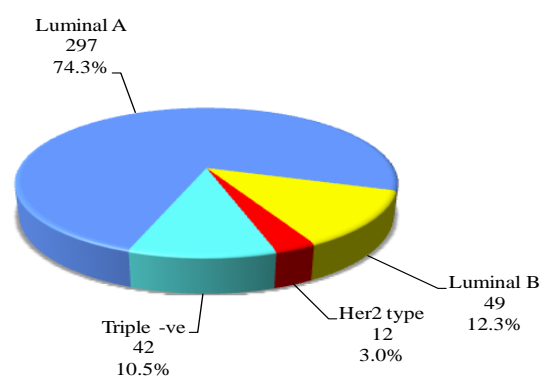
The data was be filtered and collected into flow sheets including the personal data, history of presenting symptoms, reproductive history, history of oral contraceptive pill use, past medical history, clinical examination, investigations, treatment received and follow up.

The patients were classified according to the hormonal receptor status into the four biological subtypes of breast cancer (luminal A, luminal B, HER2-enriched and triple negative).

## Results

According to age, the age of the patients was varying between 32.0 and 86.0 years with a mean age of  $55.27 \pm 9.24$  years with no statistically significant difference between groups.

According to the distribution of biological types among the studied cases, comparison between various biological types shows that Luminal A type presents 74.3%, Luminal B type 12.3%, Her2 type 3.0% and Triple -ve type 10.5% of cases. (Figure 1)

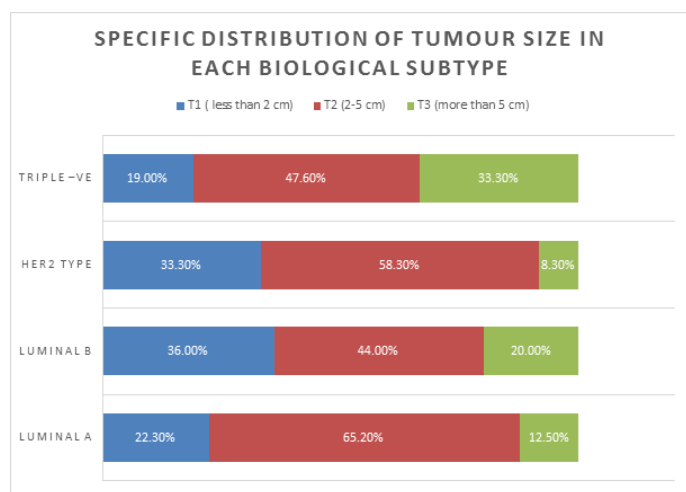


**Figure (1):** Distribution of the studied cases according to biological type

According to history of oral contraceptive pills, 18% of patients gave history of OCP intake and 82% gave no history of OCP intake with no statistically significant difference between groups.(Table 1)

Infiltrating duct carcinoma (IDC) (NOS) is the most common type presenting 93.8%of cases.IDC (NOS) was histo-pathologically diagnosed in 93.8% of cases while invasive lobular carcinoma accounts for 4.5%, mixed ductal and lobular carcinoma accounts for 1.0% and mucoid adenocarcinoma accounts for 0.7% of total cases with no statistically significant difference. (Table 1)

As regards to the size of the tumors in our study, T2 tumors (2-5 cm in size) were the commonest presenting tumors in all molecular subtypes where they represented 60.5% of total number of patients, T1 (less than 2 cm) represented 24.0% of patients and T3 (more than 5 cm) represented 15.5% of total number of patients which is statistically significant (p value=0.003).(Figure 2)



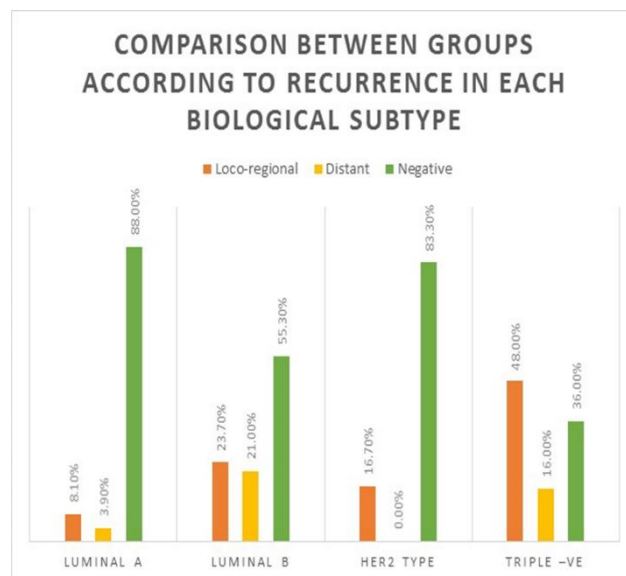
**Figure (2):** Comparison between groups according to tumor size in each biological subtype

Axillary LN dissection of the 400 study cases showed that 24.3% of cases had negative axillary LN spread (N0), 31.3% with 1-3 positive LNs (N1), 33% with 4-9 positive LNs (N2) and 11.5% with 10 or more positive LNs (N3) with no statistically significant difference. (Table 1)

Also, the study showed that 335 cases (83.8%) had no distant metastasis (M0) while 65 cases (16.3%) had distant metastasis (M1) at the time of presentation; 40.5% of Triple -ve, 24.0% of Luminal B and 12.2% of Luminal A patients had M1 tumors while Her2 enriched group reported no primary distant metastasis among the study cases which is statistically significant (p=0.000). (Table 1)

As regards to staging in our study, 9.75% of cases found to be as stage I, 34% as stage II, 40% as stage III and 16.25% as stage IV (p value=0.002). (Table 1)

According to recurrence, 66 patients reported the occurrence of recurrence representing 19.7% of total number of study patients; with 29 cases of loco-regional recurrence and 37 cases with distant relapse; while 269 patients had no relapse till the time of study representing 80.3% of total study patients which is statistically significant (p=0.000). (Figure 3)



**Figure (3)** Comparison between groups according to recurrence in each biological subtype

**Table (1):** Comparison between different biological subtype groups

		Luminal A	Luminal B	Her2-enriched	Triple -ve
Mean age		55.67 ± 8.93	55.47 ± 10.58	53.50 ± 10.93	52.69 ± 9.06
History of OCPs	Positive	13.9%	32.0%	25.0%	28.6%
	Negative	86.1%	68.0%	75.0%	71.4%
Incidence		74.3	12.3	3.0	10.5
Histopathological type	IDC (NOS)	93.5%	96.0%	100.0%	93.8%
	Invasive lobular	4.4%	4.0%	0.0%	4.5%
	Mixed IDC & lobular	1.4%	0.0%	0.0%	0.0%
	Mucoid adenocarcinoma	0.6%	0.0%	0.0%	0.7%
Tumor size (in cm)	T1 (less than 2 cm)	22.3%	36.0%	33.3%	19.0%
	T2 (2-5 cm)	65.2%	44.0%	58.3%	47.6%
	T3 (more than 5 cm)	12.5%	20.0%	8.3%	33.3%
Lymph-node metastasis	N0 (No LN metastasis)	26.4%	18.0%	16.7%	19.0%
	N1 (1-3 LN metastasis)	30.1%	36.0%	33.3%	33.3%
	N2 (4-9 LN metastasis)	32.4%	32.0%	25.0%	40.5%
	N3 (≥10 LN metastasis)	11.1%	14.0%	25.0%	7.1%
Distant metastasis (M)	M0 (No distant metastasis)	87.8%	76.0%	100.0%	59.5%
	M1 (Distant metastasis)	12.2%	24.0%	0.0%	40.5%
Stage	I	11.1%	10.0%	0.0%	2.4%
	II	34.8%	30.0%	50.0%	28.5%
	III	41.9%	36.0%	50.0%	28.6%
	IV	12.2%	24.0%	0.0%	40.5%
Recurrence	Loco-regional	8.1%	23.7%	16.7%	48.0%
	Distant	3.9%	21.0%	0.0%	16.0%
	Negative	88.0%	55.3%	83.3%	36.0%

## Discussion

Molecular classification of breast cancer is an important prognostic factor. <sup>(36)</sup> Gene expression profiling has a significant impact on our understanding of breast cancer biology. During the last 15 years, four molecular subtypes of breast cancer were identified; Luminal A, Luminal B, HER-2 enriched and Triple negative (Basal like). These subtypes have shown significant differences in terms of their incidence, risk factors, prognosis and treatment sensitivity. <sup>(37-41)</sup>

The hormonal receptor status of the thestudy patients showed that Luminal A subtype was found to be the most frequent type presenting 74.3% of patients followed by Luminal B (12.3%), Triple –ve (10.5%) and Her2 type, the least common, presenting 3.0% of patients. Several studies including study by Cadoo KA et al, Park S et al and Haibe-Kains B et al. reported that luminal A/B tumors were the most frequently observed subtype (56%–63%), followed by the basal-like (19%– 27%) and HER2-enriched (13%–15%) subtypes. <sup>(42-44)</sup> This also reported by Sørli T et al and Calza S et al. They showed

that Luminal A subtype is the most commonly diagnosed subtype and the HER2-enriched subtype is the least common one. <sup>(45-46)</sup>

As regards to the histopathological type in our study, Infiltrating duct carcinoma (NOS) (IDC) was the most commonly diagnosed histopathological type presenting 93.8% of cases with no statistically significant difference. Studies by Carter CL et al, Rao C et al and Chakrabarti S et al also reported that IDC was the most commonly diagnosed histopathological type of breast cancer. <sup>(47-49)</sup>

As regards to the size of the tumors in our study, T2 tumors (2-5 cm in size) were the commonest presenting tumors in all molecular subtypes where they represented 60.5% of total number of patients, T1 (less than 2 cm) represented 24.0% of patients and T3 (more than 5 cm) represented 15.5% of total number of patients. Rakha EA et al conducted a study on 2,219 cases. The study showed that 412 cases (18.6%) were T1, about 790 were T2 (35.6%), and 1,017 cases (45.6%) were T3. <sup>(139)</sup> Similar findings were observed by

Carter CL et al, Liu ZF et al and Widodo et al. (47,50-51)

As regards to distant metastasis at the time of presentation in our study, 16.3% of patients diagnosed with distant metastasis (M1), distributed in the different groups as follow; 40.5% of Triple –ve, 24.0% of Luminal B and 12.2% of Luminal A patients had M1 tumors while Her2 enriched group reported no primary distant metastasis among the study cases which is statistically significant (p value =0.000). In the study of Kast K et al between 2006 and 2011, metastatic disease was mostly found in Her2-enriched (29.4 %) and triple negative breast cancer (20.2 %) among 2284 breast cancer cases, while fewer cases with metastatic disease were found in luminal A breast cancer compared to all other subtypes. It also observed that Her2-enriched subtype presented with primary and secondary metastatic disease in the same time, whereas triple negative breast cancer more likely developed metastatic disease as a secondary event, while the luminal A subtype cases with primary metastatic disease were diagnosed more frequently than cases with secondary metastases. (52)

Similar results were reported by Sanpaolo P et al, Savci-Heijink CD et al and GarcíaFernández A et al. (53-55)

As regards to staging in our study, 9.75% of cases found to be as stage I, 34% as stage II, 40% as stage III and 16.25% as stage IV (p value=0.002). In a study by Jung HA et al, a total of 1145 patients were diagnosed with breast cancer and received curative surgery. Of these, 463 (40.4 %) patients were stage I, and 682 (59.6%) were stage II or III. (56)

As regards to recurrence in our study, 80.3% of cases gave no history of recurrence of the primary tumor, 8.7% of cases presented with loco-regional recurrence (LRR) and 11.0% of cases presented with distant recurrence within four years after excision of the primary tumor (p value=0.000). The Triple –ve group had the highest incidence of recurrence with 48.0% and 16.0% of cases with

loco-regional recurrence and distant recurrence respectively, followed by Luminal B with 23.7% of LRR and 21.0% of distant metastasis. Luminal A group also showed LRR in 8.1% of cases and distant recurrence in 3.9% of cases. Her2 type group showed no distant recurrence among the group patients. Lowery AJ et al. showed that Patients with luminal subtype tumors (A/B) had a lower risk of recurrence than both triple-negative and HER2/neu-overexpressing tumors. (57) Nofech-Mozes S et al, de Ruijter TC et al and Rhee J et al found that patients with triple-negative breast cancer (TNBC) suffer from poor prognosis compared to other breast cancer subtypes, TNBC develop earlier in life, and consequently more often in pre-menopausal women. (58-60) Tobin NP et al. study showed that basal-like and HER2-enriched subtypes were associated with the worst survival outcome and the highest incidence of relapse compared with the luminal A subtype. Overall, 32% of the metastases were HER2-enriched, 25% basal-like, 10% luminal A and 28% luminal B. (61) Oakman C et al and Rubovszky G et al also reported that Triple negative breast cancer (TNBC) accounts for approximately 15% of breast cancer cases. TNBC occurs in younger women and is marked by high rates of visceral and CNS metastases, relapse and early death. (62-63)

## Conclusions

Luminal A subtype is the most frequent biological subtype and Her2 type is the least common. Triple –ve group has the highest incidence of recurrence with 28.6% and 9.5% of cases with loco-regional recurrence and distant recurrence respectively, followed by Luminal A and B subtypes and Her2 enriched subtype showed no distant recurrence among the group patients.

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