We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

186,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Histopathological Characteristics: Clinical Course of Breast Cancer Subtypes Depending on the ER(+) (−)/ PR(+) (−) Receptor Status

Nilufer Bulut

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/66176

Abstract

Breast cancer patients were divided into separate groups, which were the estrogen receptor (ER)+/progesterone receptor (PR)+ HER2−, the ER or PR+ HER2−, the ER+/ PR+ HER2+, the ER or PR+ HER2+, the ER−/PR− HER2−, and the ER−/PR− HER2+ groups. Patients with the ER/PR(+)/HER2− subtype breast cancers show better clinical prognosis compared to the hormone-negative, triple-negative (TN), and HER2+ subtypes. TN, HER2+ tumors in postmenopausal women were of higher grade, showing lymph node and lymphovascular invasion with poor prognosis in all case series. However, the ER+/PR−/HER2+ subgroup had the lowest survival rates in 2- and 5-year follow-ups. Comparison between the ER+PR+HER2+ and ER+PR−HER2− subgroups showed that HER2− status is an indicator of improved prognosis in long-term follow-up. Single hormone receptor (HR)(+) status, particularly HER2(−) cases, was in between the favorable and poor survival subgroups. The ER−, PR−, and HER2+ properties were found to be risk factors for frequent recurrences. In this chapter, breast cancer subtypes are compared with each other. Results from different studies highlight the importance of ER/PR/HER2 receptor variations in the choice of treatment and prognosis of breast cancer.

Keywords: breast cancer subtype, estrogen/progesterone receptor, survival, treatment

1. Introduction

Breast cancer is common among women between the ages of 50 and 60 years and is one of the leading causes of disease-related deaths [1]. There is no single marker that determines the clinical

properties and treatment of breast cancer. The main factors affecting the choice of treatment, prognosis of the disease, and the predictability of the tumor include size, invasion into the lymph nodes, lymphovascular invasion (LVI), grade, age at diagnosis, menopausal status, surgical margins, estrogen and progesterone receptors (ER/PR), and HER2 oncogene [2–7].

About 70% of all breast cancers are hormone receptor (HR)-positive [4]. PR is the gene which regulates estrogen, and single hormone receptor positivity increases aggressiveness compared to ER+PR+ tumors, and is an indicator of poor prognosis [4]. Receptor positivity is often inversely related to the presence of HER2 oncogene [6]. ER/PR-negative HER2+ tumors, high grade, large tumor volume, and invasion into the lymph nodes indicate the need for an aggressive course of treatment [6]. Hormone receptor positivity is responsive to hormonal treatment, while HER2 positivity is responsive to trastuzumab treatment, and this helps guide clinicians in the optimal choice of treatment. Recently developed diagnostic methods, the definition of subtypes, goal-directed therapy, intensive chemotherapy, and hormonal therapies have increased the survival rates in breast cancers.

The biological properties of breast cancers tend to vary depending on ER, PR, and HER2 expression [5]. Breast cancers are divided into four subgroups based on ER and PR gene heterogeneity: luminal A (ER or PR+, HER2-negative), luminal B (ER- or PR-positive, HER2-positive), ER-PR-HER2-positive, and triple-negative (ER-PR-HER2−) types [8].

Adjuvant endocrine therapy and/or chemotherapy are given in luminal A (HR+/HER2−) cancers depending on tumor volume, lymph node status, and 21-gene recurrence score [9]. On the other hand, luminal B (HR+/HER2+) tumors are more aggressive, and anthracycline- and trastuzumab-based multichemotherapeutic agents are preferred in their treatment [9]. In luminal cancers, short-term prognosis and response to hormonal therapy are better compared to the other subgroups [9].

Luminal A tumors show the best progression, while TN tumors have the worst [10]. Luminal B type exhibits poor ER expression compared to luminal A tumors. The possibility of early relapse is also higher than with luminal A tumor [8]. With luminal B tumors, insensitivity to endocrine treatment is also higher than with HR+/HER2−, while chemotherapy resistance is more frequent than with TN and HER2+ tumors [8]. Invasion into the lymph nodes is also more common in luminal B tumors compared to that in luminal A [11, 12].

Triple negative and HER2 (+) breast cancers also exhibit poor clinical features and prognosis [13]. Recurrence and metastasis rates in TN breast cancers are particularly higher than in other subgroups due to their high grade and proliferative properties [13].

The aim of this section is to divide breast cancers into subgroups based on their receptor status, to compare ER (+) breast cancers with other subgroups (ER-PR+/− HER2+/−, ER-PR− HER2−, and ER-PR-HER2+), to determine the risk factors affecting the prognosis of the disease, and to compare the overall survival (OS) periods. Aside from the aforementioned risk factors, the study also aimed to evaluate the effects of the ER and PR status on tumor characteristics, as well as their impact on prognosis during long-term follow-up. Furthermore, the study emphasized that multiple chemotherapy combined with hormonal treatment cannot ensure the expected survival rates in the HR+ patients.

2. Clinical features and differences of tumor subgroups

The clinical, histopathological, and genetic subtypes of patients with breast cancer are important in the prognosis of the disease and in the choice of chemotherapy. Breast cancers have a considerably heterogeneous structure, and they are divided into at least four subtypes. Among these, luminal A cancers have the best prognosis, whereas TN and ER-PR-HER2+ subgroups possess the poorest prognosis. The prognosis of ER or PR (+) HER2 (+) luminal B subtype falls somewhat in between these subgroups. ER+PR-HER2− tumors, in particular, are associated with aggressive biology, hormonal treatment unresponsiveness resulting from PR gene loss, and resistance to chemotherapy [8]. PR negativity is related to a high relapse rate despite chemotherapy and endocrine treatment. However, in a meta-analysis performed by Early Breast Cancer Trialists' Collaborative Group (EGCTCG), hormonal treatment administration in ER(+) tumors regardless of the PR status was shown to improve the disease-free survival (DFS) [8].

ER positivity is a good predictive factor for the effectiveness of hormonal treatment, and 5-year hormonal therapy decreases the mortality rate by 5.6% [7]. In a previous study, prognosis in the first 3 years of ER(+) tumors was shown to be good, although survival in the longer term was fairly poor. Gradually, endocrine therapy resistance is the main factor that blocks the success of hormonal treatment [14].
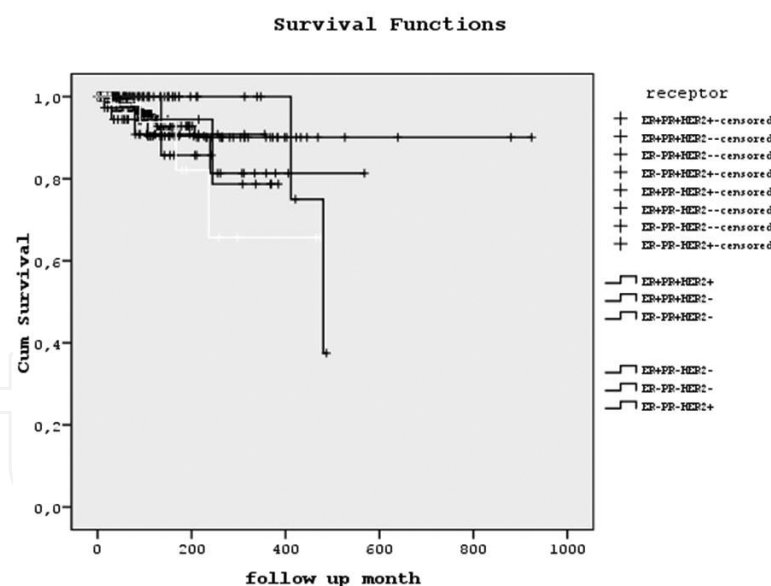
Figure 1. Analysis of overall survival of breast cancer subtypes by log-rank test [15].

Chemotherapy in HR-negative patients is known to improve DFS and OS [7]. In one study where HR+ patients with early-stage breast cancer received chemotherapy followed by subsequent 5-year hormonal treatment, the best survival rates were observed in the ER+/PR +HER2− and ER+/PR-HER2− subgroups (2-, 5-, and 10-year survival rates for these two groups were 96%, 83%, 68% and 87%, 81%, 81%, respectively). The shortest survival was observed in

the ER+PR− and HER2+ cases (2-, 5-, and 10-year survival: 66, 33, and 0%, respectively), followed by TN (2-, 5-, and 10-year survival: 71, 64, and 64%, respectively) and HER2+ (2-, 5-, and 10-year survival: 82, 71, and 0%, respectively) cases. ER+PR+HER2− cases exhibited the longest survival (2-, 5-, and 10-year survival: 96, 83, and 68%, respectively). Meanwhile, single HR+/HER2+ cases (2-, 5-, and 10-year survival: 90, 90, and 0%, respectively) and HER2− cases (2-, 5-, and 10-year survival: 92, 92, and 46%, respectively) were found to have survival rates in between those of other subgroups [15] (**Figure 1** and **Table 1**). However, Bae et al. [4] surprisingly demonstrated that PR(+) tumors have poor prognosis compared to PR(−) tumors.

	ER+PR+ HER2− N = 1360 (47.7%)	ER-PR+ HER2− N = 76 (2.7%)	ER+PR− HER2− N = 150 (5.3%)	ER+PR+ HER2+ N = 221 (7.8%)	ER-PR+ HER2+ N = 44 (1.5%)	ER+PR− HER2+ N = 59 (2.1%)	ER-PR− HER2− N = 311 (10.9%)	ER-PR− HER2+ N = 220 (7.7%)	*p*-Value
Age									
≤40	4.0%	0.3%	0.5%	1.1%	0.1%	0.2%	1.3%	0.8%	0.001
41-59	26.8%	1.7%	2.1%	4.8%	0.9%	1.0%	5.9%	3.7%	
≥60	17%	0.7%	2.7%	1.9%	0.5%	0.8%	3.7%	3.2%	
Menopause									
Pre	23.9%	1.4%	1.4%	4.3%	0.7%	0.8%	5.4%	3.5%	0.001
Peri	2.9%	0.2%	0.3%	0.6%	0.1%	0.2%	0.7%	0.6%	
Post	20.7%	1.0%	3.5%	2.8%	0.7%	1.1%	4.9%	3.7%	
Stage									
I	12%	0.4%	1.0%	1.2%	0.1%	0.3%	1.9%	0.9%	0.001
II	19.1%	1.1%	1.7%	2.8%	0.4%	0.7%	4.9%	2.1%	
III	10%	0.6%	1.5%	2.4%	0.5%	0.8%	2.1%	2.7%	
IV	7.1%	0.5%	1.2%	1.5%	0.5%	0.3%	2.2%	2.0%	
Lymph node									
N0	23.1%	1.2%	2.1%	3.1%	0.2%	0.8%	5.4%	2.2%	0.001
N1	14.4%	0.8%	1.9%	2.1%	0.6%	0.5%	3.3%	2.1%	
N2	6.6%	0.6%	0.8%	1.3%	0.3%	0.4%	1.5%	1.5%	
N3	4.4%	0.2%	0.6%	1.6%	0.4%	0.4%	1.2%	2.0%	
Grade									
I	8.8%	0.2%	0.6%	0.3%	0%	0.1%	0.2%	0.2%	0.001
II	27.5%	0.7%	2.9%	3.2%	0.4%	1.0%	2.4%	2.6%	
III	17.3%	1.8%	2.1%	4.7%	1.2%	1.1%	8.8%	5.4%	
Lymphovascular invasion (LVI)									
Yes	30.4%	1.9%	3.4%	7.1%	1.3%	1.9%	7.1%	7.6%	0.001
No	17.7%	0.8%	2.4%	3.3%	0.9%	0.4%	4.2%	2.1%	
Survival									
2 y	96%	92%	87%	97%	90%	66%	71%	82%	0.001
5 y	83%	92%	81%	86%	90%	33%	64%	71%	
10 y	68%	46%	81%	46%	0%	0%	64%	0%	

Table 1. Subtype features and clinical course of breast cancer [15].

In a previous study, it was determined that 1974 patients (69.3%), including those with lymph node invasion or who underwent breast-protective surgery, were treated with radiotherapy [15], while a total of 2797 patients received chemotherapy and/or hormonal therapy. Hormonal therapy included tamoxifen and aromatase inhibitors or switch combinations. Patients received chemotherapy regimens combined with endoxan, anthracycline, fluorouracil, taxane, trastuzumab, platine, cyclophosphamide, and methotrexate [15]. In another study, it was determined that, compared to the HR+ subtype, the HR− subtype is less commonly treatable by surgery, and more often treated through radiotherapy [16]. Nowadays, the main treatment for HR− tumors is surgery, radiotherapy, and chemotherapy [16]. The different treatment options that are available, as well as racial reasons and tumor subgroups, help explain the observed differences in survival rates [16].

2.1. Demographic and ethnic characteristics

Luminal A (ER-PR+)-type tumors are large volume and advanced stage tumors that are more common among young women of nonhispanic, black, and hispanic races [9]. Luminal B (ER+/PR+ or PR−) tumors, on the other hand, are high-incidence tumors that are observed among young people of nonhispanic, Asian, and hispanic races [9]. When the ER+PR− and ER+PR+ subgroups are compared independently of the HER2 status, it can be seen that ER-PR+ tumors are generally observed among women less than 50 years old, and that these tumors are generally advanced stage upon diagnosis. However, these tumors also have a low incidence among women of nonhispanic, white race. ER-PR+ subtype occurrence is higher among nonhispanic black women. Compared with nonhispanic white women, ER-PR+ subtype among nonhispanic black women also exhibits poorer prognosis [9]. Thus, the heterogeneity in genes also affects prognosis.

The location of the tumor, as well as tumor stage, and the presence of axillary lymph node involvement are all closely interrelated with breast cancer subtypes [17]. Luminal A tumors show the highest axillaries lymph involvement [17]. Late identification of tumor hypothetically explains the high mortality rate [17]. In one study, a relationship between the location and type of tumor was identified, and luminal A tumors were found to frequently occur in the upper outer quadrant of the breast [17]. Again, oral contraceptive use was found to be meaningfully associated with breast cancer subtype. Oral contraceptive use was observed more frequently in the luminal A group compared with the luminal B, basal, and HER2(+) groups [17]. While ovarian hormones and reproductive pattern appear in many studies to play a significant role in breast cancer growth, another study performed on 1326 Mexican women described that the number of pregnancies, gestational age, and menopause status were not risk factors for breast cancer [17].

Luminal A tumors are commonly observed among high-income, nonhispanic black race women living in cities. Compared with the ER+PR+ subtype, the incidence of the ER-PR+ is 1.7 times higher among individuals under the age of 50 [9]. The clinic and demographic characteristics of luminal A and B subtypes are different [9]. These differences are due to the effects of estrogen and progesterone in tumor progression [9]. Estrogen suppresses progression, while progesterone causes tumors to progress aggressively. In ER(−) tumors, high

progesterone levels cannot be balanced by the estrogen levels, and this leads to the progression of the tumor [9].

A limited number of studies have researched the relationship between subtype of breast cancer and the socioeconomic and health-care conditions of the patients [16]. The study determined that good health care is closely associated with higher socioeconomic conditions, and that living in larger cities it facilitates patients' access to and compliance with treatment [16].

2.2. Prognosis, survival, and risk factors that affect them

In one study population, ER-PR+HER2 (+)/(−) patients showed poorer survival compared to the ER+PR+HER2 (+)/(−) group [15]. Similarly, other studies showed PR-HER2+ tumors to have high recurrence scores [18]. Recurrence risk (RR) in the ER-PR+ and ER+PR− tumors was determined as 2.1 and 1.4%, respectively [19]. Single hormone receptor positivity results in a poor prognosis and affects treatment response [20]. Additionally, lymph node invasion is seen more frequently in luminal B tumors compared to luminal A tumors, and is associated with poor prognosis [11]. A high Ki-67 index is characterized by lower patient age, larger tumor volume, positive lymph nodes, ER/PR negativity, and HER2 positivity [11, 13, 20, 21].

In most studies, TN and HER2+ tumors showed the poorest survival rates [22, 23]. In a study by You et al. [1], early-stage tumors without lymph node invasion and with improved histological appearance resulted in better survivals in all molecular subtypes. High-stage disease and HR negativity were associated with poor survival rates. As HR (−) subtypes develop and advance more rapidly than HR (+) tumors, they are usually detected in advanced stages [16]. Breast cancer mortality in HR (−) subtypes is two times more than HR (+) subtypes (HR: 1.91; 95% confidence interval (CI): 1.88–1.94) [16]. TN cases have the lowest survival rates, with 5- and 10-year survival being 63 and 44%, respectively [20].

In one study, both ER+PR-HER2+ and ER-PR-HER2+ subgroups received combined regimens such as trastuzumab and anthracycline/or taxane, carboplatine chemotherapies. However, the study found that ER+PR− leads to poorer prognosis with these treatment regimens. This result may have been due to the following factors: choice of treatment not being specific enough for the group, or not applied in sufficient or equal numbers, unresponsiveness to hormonal maintenance treatment due to ER positivity, small number of patients, and response to chemotherapy that varies according to the intrinsic profile of the tumor and HER2 positivity [5, 12, 15, 24].

The longer survival rate of ER+PR+/HER2 (+)(−) tumors compared to HER2+ and TN− tumors is due to their early-stage detection, absence of lymph node invasion, and the ability to administer hormonal treatment for at least 5 years (aromatase inhibitor following 2- or 3-year tamoxifen therapy) in addition to a combined chemotherapy regimen, no matter what the intrinsic profile of the tumor is.

In some studies, HR+HER2− tumors were found to have shorter OS and DFS periods, while their overall recurrence was more frequent than the single HR+HER2+ luminal B tumors [12]. Ki-67 indices of these tumors were high due to their high-grade property and lymph node invasion. Although HER2 positivity is a criterion of poor prognosis, anti-HER2 treatments may

decrease the negative effects of this factor. Thus, high Ki-67 index in ER+ tumors is an important criterion which determines prognosis [12]. Additionally, 25–50% of ER+PR+ tumors are resistant to hormonal treatment. Genetic and non-genetic interferences between the ER and growth factors may lead to hormone resistance [14], but the exact mechanism that is implicated has not yet been understood. Genetic testing is not commonly performed to determine tumor subtypes or select treatment, and treatment alternatives are usually applied based on the receptor and clinicopathological data. However, genetic variations and ethnic differences may alter the prognosis of the disease [25]. Consequently, different response rates have been observed in many of the studies. These findings suggest that oncogenes in different pathways should be investigated to further improve treatment alternatives.

One study evaluated ER+, ER-PR+, TN, and HER2+ patients who were mostly premenopausal. As such, 54.1% of the patients in the study were premenopausal, while 45.1% were postmenopausal. In other studies, triple-negative breast cancer (TNBC) or PR− subtypes were found to be more frequent in postmenopausal women [2, 15, 26]. PR-negative breast cancers are frequently observed during the postmenopausal period. Some studies have shown that, due to the higher level of progesterone in premenopausal women, the incidence of ER-PR+ subtypes is considerably higher among individuals under the age of 50 [9]. The high levels of progesterone increase the invasiveness of breast cancer cells, and hence the risk of metastasis in premenopausal patients [9].

The initial metastatic site was bone in the HR+ (56.5%) patients, followed by liver, lung, and multiple organ invasions. In TN (12.9%) and HER2+ patients (11.5%), the disease progressed into multiple organ metastases. Recurrences were observed at the following rates in different tumor subtypes: in 215 (44.9%) of the patients with luminal A tumors, in 56 (11.6%) of the patients with luminal B tumors, in 61 (12.9%) of the patients with TN tumors, and in 54 (11.5%) of the patients with HER2+ tumors [15]. When HR+/HER2(+)(−) patients were compared to ER-PR-HER2− and ER-PR-HER2+ patients, the TN and HER2+ patients were found to be mostly postmenopausal, N+, high-stage and high-grade ($p = 0.001$) (**Table 2**) [15]. Each increase of age by a decade also raised the risk of recurrence (RR = 0.4, 95% CI, 0.3–0.6, $p = 0.001$) (**Table 2**). High-stage, high-grade tumors with node positivity and LVI showed higher recurrence risk. ER negativity led to a 1.5-fold increase in recurrence risk (RR = 1.5, 95% CI, 1.3–1.9, $p = 0.001$), while PR negativity led to a 1.4 fold increase (RR = 1.4, 95% CI, 1.2–1.8, $p = 0.001$) (**Table 2**). HER2 positivity (RR = 0.7, 95% CI, 0.6–0.9, $p = 0.025$) was also associated with a higher recurrence risk.

However, the Carolina Breast Cancer Study Group did not identify any differences in menopausal status between the molecular subtypes [2]. Devi et al. [26] reported high frequency of TNBC among postmenopausal women, which may have been due to ethnic differences and gene heterogeneity. Jenkins et al. [3] also reported increased luminal A and B tumors and decreased basal-like tumors with increasing age. TN and the basal-like subtype are particularly more common in the young population, whereas the HR+/HER2+ luminal B subtype is more frequent in patients above 60 years of age [3].

|	RR	95% CI	*p*-Value
Age			
41–59/<40	0.6	0.4–0.8	**0.003**
>60/<40	0.4	0.3–0.6	**0.001**
Stage (2,3,4)/1			
3/1	2.1	0.3–15	**0.027**
2/1	0.4	0.2–0.9	**0.040**
Grade (III/II)/I			
III/I	1.7	1.1–2.6	**0.014**
II/I	1.2	0.8–1.9	0.311
LVI (yes/no)	0.6	0.5–0.8	**0.003**
Node (3,2,1/0)			
3/0	1.8	1.4	**0.001**
2/0	1.6	1.2–2.1	**0.001**
1/0	1.1	0.8–1.4	0.386
ER negative	1.5	1.3–1.9	**0.001**
PR negative	1.4	1.2–1.8	**0.001**
HER2 positive	0.7	0.6–0.9	**0.025**

Table 2. Univariate Cox-regression analysis of factors associated with recurrence in patients with subgroups [15].

Furthermore, PR negativity is not related with age and menopausal status; however, it is associated with high grade and proliferation index [8]. Ki-67 index is described as being more than 30% in ER+PR-HER2− tumors ($p = 0.006$) [8]. Epidermal growth factor (EGFR) expression is higher in PR− tumors [4]. PR negativity in our patients resulted in different survival rates depending on the HER2+/− status (2-, 5-, and 10-year survival being 66%, 33%, 0% and 87%, 81%, 81%, respectively) [15]. In addition, ER-PR+ tumors had poorer prognosis compared to ER+PR+ tumors. ER-PR+ tumor incidence has been reported as 1.5–3.4% [4]. In addition, ER-PR+ and ER+PR− tumor incidences were reported to be 4.2 and 7.4%, respectively. Altogether, ER+PR+HER2− tumors were the most frequent in younger women below 40 years of age, and in older women above 60 years of age (4.0 and 17.0%, respectively).

HR+ tumors have often lower grade compared to TN and HER2+ subgroups, showing a slow progression in the long term [27]. Recurrence in these slowly enlarging tumors after a 10-year follow-up appears to be associated with the 5–10-year hormonal treatments that continue after chemotherapy. In ER+HER2− tumors, the mortality rate increases in the 10–15-year follow-ups [27].

In one study, HER2 positivity was found to be 7.8% in ER+PR+ patients and 3.6% in patients with single HR positivity. This ratio was found to vary from 10 to 20% in other studies [15, 21, 28]. In agreement with the findings of other studies, we observed similar survival rates in ER +HER2+ and ER+HER2− groups, despite HER2 positivity [29]. When luminal A (mean survival: 5030 day) and luminal B (mean survival:4718 day) patients were compared, HER2+ (mean survival:3149 day) patients were found to have lower survival rates (**Figure 2** and **Table 3**).

The California Breast Cancer Study Group also reported the highest mortality rates for ER-HER2+ tumors in the 10-year or longer follow-up [29].
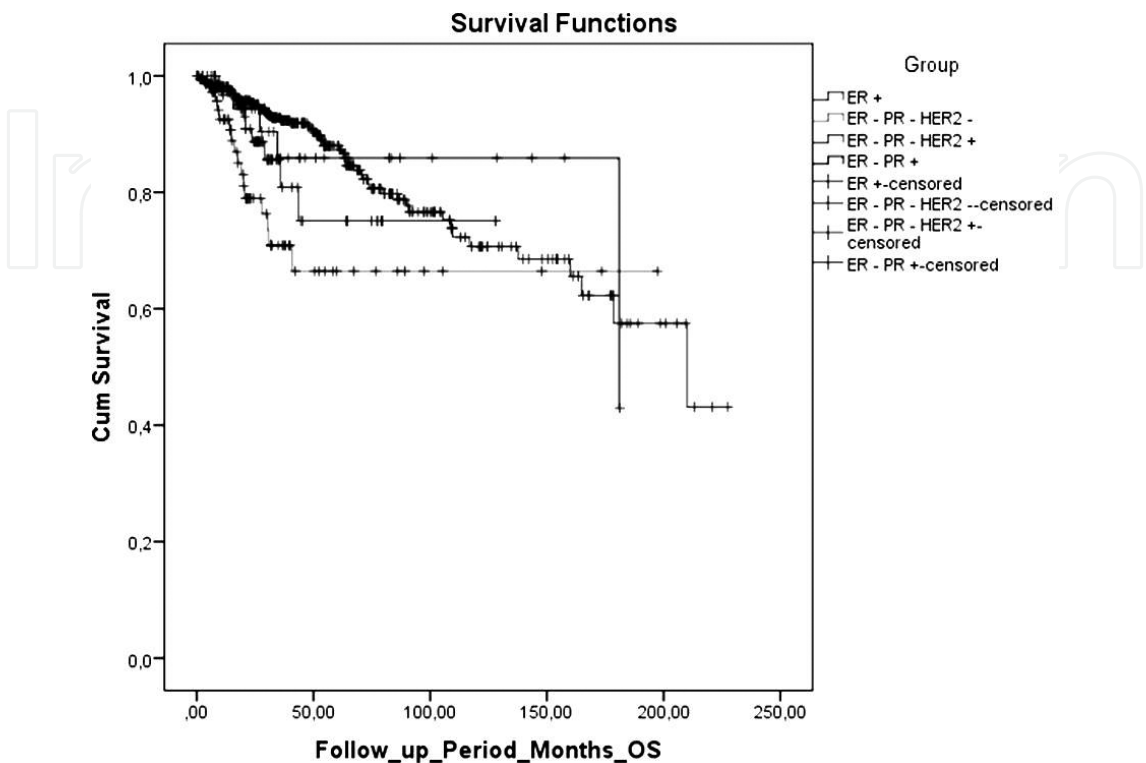
Figure 2. Analysis of overall survival of breast cancer subtypes by Kaplan-Meier. ER+ cases were determined to have longer survival rates when compared to non-luminal HER2+, HR-HER2–, and luminal B tumors. HER2+, HR-HER2–, and luminal B tumors [15].

	Number of patients	Number of case observed	Percent of case observed	Mean survival (day)	*P*-value
ER+	396	57	85.6	5030.747	**0.010***
ER-PR+	78	5	86.5	4718.160	
HER2+	37	9	87.0	3149.519	
TN	69	16	79.5	4150.100	
Total	**580**	**87**	**85%**	**4940.640**	

* HER2+ patients were found to have lower survival rates than others p<0.05

Table 3. Survival analysis of tumor subgroups [15].

3. Conclusion

HR+ tumors are the most frequently observed breast cancer subtype. ER+PR− and ER-PR+ tumors have a particularly poorer prognosis compared to the ER+PR+ subtypes. In addition

to the poor prognosis factor (i.e., due to HER2 positivity), being ER− or PR− may further reduce the tumor's treatment responsiveness and survival, while increasing the risk of recurrence. In the clinical practice, the receptor status of the tumor should be determined to elucidate the intrinsic gene profile of the tumor, as this will assist and provide guidance in choosing the appropriate treatment.

Abbreviations

EGFR	epidermal growth factor
EGCTCG	early breast cancer trialists
ER	estrogen receptor
DFS	disease-free survival
HR	hormone receptor
LVI	lymphovascular invasion
OS	overall survival
PR	progesterone receptor
RR	recurrence risk
TNBC	triple-negative breast cancer

Author details

Nilufer Bulut

Address all correspondence to: ferlut@hotmail.com

Kanuni Sultan Suleyman Education and Search Hospital, Istanbul, Turkey

References

[1] You JM., Kim YG., Moon HG., Nam SJ., Lee JW., Lim W., et al. Survival improvement in Korean breast cancer patients due to increases in early-stage cancers and hormone receptor positive/HER2 negative subtypes: A nationwide registry-based study. J Breast Cancer 2015; 18(1): 8–15.

[2] Song Q., Huang R., Li J., Fan J., Zheng S., Zhang B, et al. The diverse distribution of risk factors between breast cancer subtypes of ER, PR and HER2: A 10-year retrospective multi-center study in China. PLoS One 2013;8:1–7.

[3] Jenkins EO., Deal AM., Anders CK., Prat A., Perou CM., Carey LA., et al. Age-specific changes in intrinsic breast cancer subtypes: A focus on older women. Oncologist 2014; 19:1076–83.

[4] Bae SY., Kim S., Lee JH., Lee H., Lee SK., Kil WH., et al. Poor prognosis of single hormone receptor-positive breast cancer: similar outcome as triple-negative breast cancer. BMC Cancer 2015; 15(138): 1–9.

[5] Yang XR., Claude CJ., Goode EL., Couch FJ., Nevanlinna H., Milne RL., et al. Associations of breast cancer risk factors with tumor subtypes: A pooled analysis from the breast cancer association consortium studies. J Natl Cancer Inst 2011; 103(3):250–63.

[6] Mahmood H., Faheem M., Mahmood S., Sadiq M., Irfan J. Impact of age, tumor size, lymph node metastasis, stage, receptor status and menopausal status on overall survival of breast cancer patients in Pakistan. Asian Pac J Cancer Prev 2015;16: 1019–24.

[7] He J., Wang H., Ma F., Feng F., Lin C., Qian H. Prognosis of lymph node-negative breast cancer: Association with clinicopathological factors and tumor associated gene expression. Oncol Lett 2014; 8:1717–24.

[8] Zong Y., Zhu L., Wu J., Chen X., Huang O., Fei X., et al. Progesterone receptor status and Ki-67 index may predict early relapse in luminal B/HER2 negative breast cancer patients: A retrospective study. PLoS One 2014;9:1–8.

[9] Andreana NH., Julie JR., Manohar R., David HG., Michele LC. HER2 status and disparities in luminal breast cancers. Cancer Med 2016; 1–7.

[10] Andrade ACM., Ferreira JCA., Guimaraes BD., Barros AWP., Almeida GS., Weller M. Molecular breast cancer subtypes and therapies in a public hospital of Northeastern Brazil. BMC Women's Health. 2014; 14(110): 1–9.

[11] Inic Z., Zegarac M., Inic M., Marcovic I., Kozomara Z., Djurisic I., et al. Difference between luminal A and luminal B subtypes according to Ki-67, tumor size, and progesterone receptor negativity providing prognostic information. Clin Med Insights Oncol 2014; 8: 107–11.

[12] Yan J., Liu XL., Han LZ., Xiao G., Li NL., Deng YN., et al. Relation between Ki-67, ER, PR, Her2/neu, p21, EGFR, and TOPII-α expression in invasive ductal breast cancer patients and correlations with prognosis. Asian Pas J Cancer Prev 2015; 16: 823–29.

[13] Galukande M., Wabinga H., Mirembe F., Karamagi C., Asea A. Molecular breast cancer subtypes prevalence in an indigenous Sub Saharan African population. Pan Afr Med J 2014; 17: 1–7.

[14] Jamshed A., Shah MA., Murtaza G., Mehmood T., Chaudry SJ., Loya A., Hameed S. Clinical outcome of primary non-metastatic breast cancer: A single institution experience. Indian J Cancer 2016; 52: 191–25.

[15] Nilufer B., Kadri A. Does estrogen receptor determination affect prognosis in early stage breast cancers? Int J Clin Exp Med 2015; 8(11): 21454–9.

[16] Tomi A., Justin XM., Akinyemi IO., John WW., Sean FA. Racial disparities in individual breast cancer outcomes by hormone-receptor subtype, area-level socio-economic status and healthcare resources. Breast Cancer Res Treat 2016; 157(3): 575–86.

[17] Gabriel PR., Catalina AM., Ivonne MOC., Jose RGS. The association of subtypes of breast cancer with tumour characteristic and reproductive factors in 1326 Mexican women. Contemp Oncol(pozn) 2015; 19(6): 462–6.

[18] Bharti JN., Rani P., Kamal V., Agarwal N. Angiogenesis in breast cancer and its correlation with estrogen, progesterone receptors and other prognostic factors. J of Clin Diagn Res 2015;9(1): 5–7.

[19] Dunnwald LK., Rossing MA., Li CI. Hormone receptor status, tumor characteristics and prognosis: a prospective cohort of breast cancer patients. Breast Can Res 2007; 9: 1–10.

[20] Dong G., Wang D., Liang X., Gao H., Wang L., Yu X., et al. Factors related to survival rates for breast cancer patients. Int J Clin Exp Med 2014; 7(10): 3719–24.

[21] Mahyari HM., Khosravi A., Monfared ZE. Human epidermal growth factor receptor 2 and estrogen receptor status in respect to tumor characteristics in non-metastatic breast cancer. Tanaffos 2014; 13(1): 26–34.

[22] Onitilo AA., Engel JM., Greenlee RT., Mukesh BN. Breast cancer subtypes based on ER/PR and HER2 expression: comparison of clinicopathologic features and survival. Clin Med Res 2009; 7: 1–13.

[23] Pal S., Lüchtenborg M., Davies EA., Jack RH. The treatment and survival of patients with triple negative breast cancer in a London population. Springerplus 2014; 3(553): 1–5.

[24] Prat A., Carey LA., Adamo B., Vidal M., Tabernero J., Cortes J., et al. Molecular features and survival outcomes of the intrinsic subtypes within HER2-positive breast cancer. J Natl Cancer Inst 2014; 106(8): 1–8.

[25] Song N., Choi JY., Sung H., Jeon S., Chung S., Park SK., et al. Prediction of breast cancer survival using clinical and genetic markers by tumor subtypes. PLoS One 2015; 13: 1–15.

[26] Devi CR., Tang TS., Corbex M. Incidence and risk factors for breast cancer subtypes in three distinct South-East Asian ethnic groups: Chinese, Malay and natives of Sarawak, Malaysia. Int J Cancer 2012; 131: 2869–77.

[27] Kontani K., Hashimoto S., Murazawa C., Norimura S., Tanaka H., Ohtani M., et al. Factors responsible for long term survival in metastatic breast cancer. World J Surg Oncol 2014; 12(344): 1–9.

[28] Yan M., Schwaederle M., Arguello D., Millis SZ., Gatalica Z., Kurzrock R. HER2 expression status in diverse cancers: review of results from 37,992 patients. Cancer Metastasis Rev 2015; 34: 157–64.

[29] Keegan THM., Press DJ., Tao L., DeRouen C., Kurian AW., Clarke CA., et al. Impact of breast cancer subtypes on 3-year survival among adolescent and young adult women. Breast Cancer Res 2013;15: 1–12.