Predictive value of biological markers in loco-regional recurrence of breast cancer after mastectomy and radiotherapy

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Objective
To assess the prognostic usefulness of the human epidermal growth factor receptor-2 (Her 2), the progestin receptor (PR), and the oestrogen receptor (ER) in locoregional recurrence following mastectomy radiotherapy in Egyptian breast cancer patients.
Patients and methods
This retrospective analysis comprised 432 female patients who had received radiation and had a mastectomy and immunohistochemistry reports. The Ethics Committee's clearance was required before this study could be carried out at the Ain-Shams University hospitals.
Results
A total of 24 individuals developed LRR after a median follow-up period of 68.9 months. Although lymph nodes with more than three exhibited a statistically significant risk for LLR, tumour grade and pT were not significant risk factors. LRR risk rose for those who were HER2-positive and those with TNBC, but Luminal B had a non-significantly greater risk than Luminal A.
Conclusion
For breast cancer patients receiving PMRT, the biological subtype based on the categorization standard from the St. Gallen International Breast Cancer Conference (2013) Expert Panel acts as an accurate prognostic predictor. In HER2-positive and hormonal receptor-positive individuals, trastuzumab treatment significantly reduced the risk of LRR.

Keywords:
biological markers, breast cancer, mastectomy and radiotherapy, recurrence

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Introduction

According to the national cancer institute, Breast cancer is the most common site of cancer in Egyptian women as it accounts for about 38.8% of total malignancies among females in Egypt; it is an important cause of mortality among them [1]. It is the second leading cause of cancer-related death in women, accounting for about 14% of cancer-related deaths [2]. Breast cancer may recur decades after the primary therapy. Patients undergoing breast-conserving therapy (BCT) for operable breast cancer have approximately 10 to 15 percent chance of developing a loco-regional recurrence within 10 years [3]. Patients undergoing mastectomy have a lower risk of loco-regional recurrence (5–10 percent) [4].

A few specific biomarkers, such as the oestrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2), have been utilised for several years to determine the prognosis of breast cancer and direct treatment [5]. Radiotherapy is commonly used as a local treatment for breast cancer patients having mastectomy surgery in order to lessen local and regional recurrence (LRR). 10% of breast cancer patients who got post-mastectomy radiation (PMRT) still have a local recurrence, which suggests that these patients are not receiving enough care. It is crucial to identify individuals who need more severe therapy and are at a higher risk of recurrence. [6].

Biological subtypes

HER2-positive (HER2 overexpressed or amplified-ER and PR absent), HER2-positive (HER2 overexpressed or amplified-ER and PR absent), Luminal A-like (ER-positive, PR-positive, HER2-negative, and low Ki-67), and Luminal B-like (ER-positive, HER2-negative, and at least one of high Ki-67 or negative or (ER-negative, PR negative, HER2 negative, and any Ki-67). This category has been extensively used in clinical decision-making for the

systemic treatment of breast cancer [7]. The immunohistochemical (IHC) staining profile is a popular and reasonably priced substitute. Around 70% of breast tumours express oestrogen receptor (ER), a potent predictor of responsiveness to treatments that stop the production of oestrogen or stop its receptor from doing its job [8].

To reduce the financial burden and side effects of chemotherapy, it is critical to identify between individuals with ER-positive tumours at high risk for recurrence who need further chemotherapy and those for whom adjuvant endocrine treatment alone may be sufficient. Although HER2 overexpression identifies cancers susceptible to trastuzumab, multi-gene tests are potent potential tools for predicting the likelihood of recurrence in individuals with ER-positive disease [9].

Multi-gene expression analysis should not be used in routine clinical practise. Ki67 may be used as a proliferative index in addition to ER and PR status to reliably distinguish between "luminal A" (more endocrine-sensitive, more indolent, and better prognosis) and "luminal B (HER2-negative)" (less endocrine-sensitive, more aggressive, and worse prognosis) breast cancer subtypes. Ki67's threshold for high proliferation is yet unknown, however, it is generally agreed that a number of 20 or above is high. Ki67 must be used with laboratory-specific techniques and cut-off values in order to be a reliable prognostic marker. High Ki67 expression in breast cancer is linked to poorer prognoses [10].

Aim of the work

The purpose of this study is to assess the usefulness of the human epidermal growth factor receptor-2 (Her 2), the progestin receptor (PR), and the oestrogen receptor (ER) as indicators of locoregional recurrence following surgery and radiation in Egyptian breast cancer patients.

Patients and methods

Type of the study: It is a Retrospective analytical study.

1076 patients who underwent modified radical mastectomy and PMRT at the Department of General Surgery, AIN SHAMS UNIVERSITY, were retrospectively examined from March 2020 to January 2023. Their medical histories were amassed sequentially. The department's ethics committee gave its approval for the review of the data used in our analysis. Having invasive breast cancer that was pathologically proven was the first requirement for inclusion. Complete and readily available information on IHC staining for the HER2 receptor, the progesterone receptor and the oestrogen receptor. Individuals who were receiving therapy and had distant metastases were not included in the research. For restaging, we used the AJCC Cancer Staging Manual, ninth edition [11]. A total number of 432 patients fulfilled the inclusion criteria and were included in the study.

LRR is short for localised regional relapse, and it occurs when the ipsilateral chest wall, axillary nodes, supraclavicular lymph nodes, or intramammary chain of LN are affected. Data from the outpatient department and direct patient contact were used for follow-up. Imaging or pathology data were used to make the diagnosis of LRR (such as CT, MRI, or ultrasonography).

Statistical analysis

Gray's competing risks data analysis method was used to determine the cumulative incidence of LRR, with fatalities and distant metastases alone serving as the competing risks. To compare cumulative incidence curves, we employed Gray's test. A smoothing technique called the Kernel approach was used to predict rates of yearly LRR danger. All statistical analyses were performed using R software version 2.11.1 and SPSS version 25.0 (SPSS, Chicago, IL, USA) [12].

Results

All patients got radiation and a modified radical mastectomy. The majority of patients—96.0%—received chemotherapy. Seventy-three percent of individuals who tested positive for either ER or PR received hormonal therapy. The median dosage, including boost, for the whole cohort of patients receiving radiation to the chest wall and/or nearby lymph nodes was 50 Gy (range 40–60). In 73% of patients, recurrence was identified using both pathology and images. Only a photograph was used to diagnose others. A total of 24 individuals developed LRR after a median follow-up period of 68.9 months. The 3-year cumulative incidence of LRR (synchronous distant metastasis) for the entire study group was 5.55%. Just four individuals had an independent LRR diagnosis, while 20 patients had LRR together with distant failure, there were many sites of recurrence, including supraclavicular area ($n = 13$), chest wall ($n = 11$), internal mammary area ($n = 3$).

According to Table 1, the median age of the patient group at diagnosis was 51.66 12.763 years (range, 21–82 years). The findings of the ER, PR, Her2, and Ki 67 markers are displayed in Tables 2–5, respectively. Table 1 displays the IHC results, which revealed that 138 patients (32%), 174 patients (40.3%), 81 patients (18.7%), and 39 patients (9%) were, respectively, Luminal A, Luminal B, HER2-positive, and TNBC (Table 6**)**.

13% of the patients were T3, whereas 87% of the patients were T1-2. 47 patients (11%) were found to not have lymph nodes involved; 125 patients (29%) had 1–3 nodes involved, and 260 patients (60%) had more than 3.

The 3-year LRR cumulative incidence rates were For Luminal A 1.5%, Luminal B 4%, HER2-positive 10.5%, and TNBC patients 11%. The time of LRR, all LRR occurred in the first 3 years in the TNBC subtype, while for HER2-positive subtype, 89% LRR occurred in the first 3 years. After the fifth year of follow-up, the luminal subtype population had an 18% LRR rate. This also revealed earlier relapse peak in TNBC and later in luminal subtypes. Table 7. 60-month cumulative incidence rate of LRR among Luminal A, TNBC, and HER2-positive subtype with and without trastuzumab showed a statistically significant difference in favor of trastuzumab as with using trastuzumab the LLR falls dramatically to near Luminal A, while without it rises close to TNBC. Table 8.

The risk factors for LLR are shown in Tables 9–12. Although lymph nodes with more than three exhibited a statistically significant risk for LLR, tumour grade and pT were not significant risk factors. LRR risk rose for those who were HER2-positive and those with TNBC, but Luminal B had a non-significantly greater risk than Luminal A.

Table 1 Mean age of the study

Age	No.=432
Mean±SD	12.763±51.63
Range	21–82

Table 2 Results of estrogen receptor markers

ER	No. (%)
Negative	102 (23.6%)
Positive	330 (76.4%)
Total	432 (100.0%)

Table 3 Results of progesterone receptor markers

PR	No. (%)
Negative	142 (33%)
Positive	290 (67%)
Total	432 (100.0%)

Table 4 Results of HER 2 NEU receptor markers

HER 2 NEU	No. (%)
Negative	227 (52.5%)
Positive	205 (47.5%)
Total	432 (100.0%)

Table 5 Results of KI 67 receptor markers

KI 67	No. (%)
Low	163 (37.7%)
High	269 (62.3%)
Total	432 (100.0%)

Table 6 Results of Intrinsic subtypes of biological markers

Intrinsic subtypes	No. (%)
Luminal A	138 (32%)
Luminal B	174 (40.3%)
HER2 positive	81 (18.7%)
Tiple Negative Breast Cancer	39 (9.0%)
Total	432 (100.0%)

Table 7 Cumulative rates for LRR by molecular subtypes after 24, 36, 60 and >60 months follow-up

	Luminal A	Luminal B	HER2-positive	TNBC
24 M	1.5	2.8	5	8
36 M	1.5	4	7	10.5
60 M	1.5	4	11	10.5
>60 M	4.7	13.25	11	10.5
P 0.027				

Table 8 60month cumulative incidence rate of LRR among Luminal A, TNBC, and HER2-positive subtypes with and without trastuzumab

	Rate in %	*P* value
Luminal A	1.5	0.0035
HER2-positive subtype without trastuzumab	19.43	
HER2-positive subtype with trastuzumab	3.57	
TNBC	10.5	

Table 9 Risk of biological subtypes

		95% confidence interval		
Subtype	HR	Lower	Upper	*P* value
Luminal A	1			
Luminal B	2.03	0.587	6.95	0.26
Her-2 Positive	4.27	1.312	16.03	0.021
TNBC	4.65	1.532	17.331	0.21

Table 10 Risk of tumor grade

		95% confidence interval		
Grade	HR	Lower	Upper	*P* value
1-2	1			
3	1.22	0.596	2.48	0.65

Table 11 Risk of pT

		95% confidence interval		
pT	HR	Lower	Upper	*P* value
1	1			
2	0.927	0.411	1.68	0.71
3	2.03	0.492	7.82	0.37

Data were analyzed by Microsoft Office 2010(Excel) and Statistical Package for social science (SPSS) version 20. Comparing the 2 groups was done using the Chi-Square test

$$\text{Mean} = \sum \chi / \text{n}$$

Standard deviation (SD)

$$\text{SD} = \sqrt{\sum (\text{X} - \text{X})^2 / \text{n} - 1}$$

Discussion

A patient's prognosis must be accurately anticipated in the era of precision medicine to avoid overtreating or undertreating them [13]. Carmen *et al.* discovered 1241 patients with Luminal B early-stage breast cancer and 1-3 axillary positive nodes who had surgery. Patients with Ki67 expression who have Luminal B and node-positive breast cancer may benefit from combining adjuvant chemotherapy with hormone therapy [14].

Only a few studies explored the relationship between biological subtype and locoregional recurrence after PMRT. Wright and his colleagues demonstrated that biological subtype might predict the fate of various biological subtypes of breast cancer by looking at 582 consecutively treated patients who got PMRT. One drawback of this study was that it only examined patient populations from specific ethnic groups (black and white) [15].

According to the criteria outlined at the 2013 St. Gallen conference, the current study demonstrated that molecular subtype was a prognostic predictor for patients who had PMRT that may stand alone and even exceed more traditional prognostic markers including tumour size and tumour grade. The targeted treatment markedly reduced LRR.

Table 12 Risk of pN

		95% confidence interval		
pN	HR	Lower	Upper	*P* value
0	1			
1	1.26	0.247	5.73	0.75
2	1.62	0.312	8.13	0.531
3	5.91	1.140	22.19	0.o21

Patients with triple-negative and HER2+ expression profiles had a considerably higher 3-year LRR rate than those with positive hormone receptors and negative HER2 profiles, according to Wang *et al.*'s study of 835 node-positive breast cancer patients who underwent mastectomy [16]. Tseng *et al.* found that TNBC patients had the highest incidence of LRR compared to other biological subtypes in a research where only 30% of patients underwent PMRT [17].

Among the subtypes, many striking relapse patterns were seen. All local recurrences occurred within the first 3 years, which was 1 to 3 years sooner than HER2-positive and luminal subtypes. This was found despite TNBC having the greatest risk of LRR. Dent *et al.* discovered the same outcomes in a cohort of 1601 patients with breast cancer and examined the timing of relapse across several biological subgroups. Compared to other subtypes, TNBC patients experienced a local recurrence sooner (2.8 vs. 4.2 years, respectively; $P = 0.02$) [18]. Local relapses in TNBC patients were also observed by Meena to occur during the first five years, which was substantially sooner than the luminal subtypes. (between five and fifteen or more years of experience) [19]. Our findings imply that necessary regular follow-up in the first three to five years and more aggressive and efficient local therapy are crucial for TNBC patients.

Our investigation revealed that a higher percentage of LRRs were located in the supraclavicular area and the ipsilateral chest wall with regard to their anatomical distribution. As a result, the supraclavicular area and chest wall should be closely observed.

Radio resistance, invasiveness, and breast proliferation are all tightly correlated with HER2 overexpression. The prognosis of breast cancer patients may be improved with the assistance of suitable treatment, as trastuzumab treatment increases survival for breast cancer patients with HER2 overexpression, particularly when paired with normal chemotherapy or neoadjuvant chemotherapy [20]. There may not be a therapy target for TNBC, the most aggressive form of breast cancer [21].

This retrospective observational analysis has certain inherent limitations that need to be taken into account. Removal of certain patients from this research because to incomplete IHC staining data for the markers ER, PR, HER2, or Ki-67. Hence, with 432 patients included, the sample size of the current study was quite modest. The results should be further investigated in multicenter studies because, secondly, the patient group comes from a single cancer centre, which might introduce bias to the current study. Finally, the follow-up period was, in some ways, brief. Longer follow-up is required to adequately compare the rate of LRR among the four subtypes.

Conclusion

Biological subtype acts as an accurate prognostic predictor for breast cancer patients getting PMRT based on the categorization criteria from the St. Gallen International Breast Cancer Conference (2013) Expert Panel. In patients who tested positive for HER2 and/or a hormonal receptor, the risk of LRR was significantly reduced by trastuzumab and endocrine treatment.

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Data Availability: Data is available on request. Please contact the corresponding author (Heba Tharwat Abd El Aziz, MD).

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Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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