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Original Research Article

DISCORDANCE OF ESTROGEN RECEPTOR, PROGESTERONE RECEPTOR, AND HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 EXPRESSION IN BREAST CANCER - A SYSTEMIC REVIEW AND META-ANALYSIS

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Abstract

Background: The option of hormonal therapy is now offered to every patient of breast cancer irrespective of age based on the tumor receptor status. Hence, biomarkers estimation needs to be carried out in every patient diagnosed with breast cancer. Hence, the present systemic review was conducted to study the incidence of expression of various molecular subtypes. **Materials and Methods:** The inclusion criteria were framed as per internationally standardized PICOS framework, as recommended by PRISMA guidelines. The study population included cases of surgical resection of mammary carcinomas which were assessed immunohistochemically for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expressions.Primary outcomes of the study were to assess expression of ER, PR and HER2+ in breast cancer among various studies anddiscordance rate (DR) if any of estrogen receptor (ER), progesterone receptor (PR), HER-2 in primary breast tumors and paired metastases. **Result:** Total cases analysed qualitatively in the present study was 9485 from 12 studies that fulfilled the inclusion criteria.For the quantitative analysis of biomarkers among total 12 studies, 9 studies reported complete analysis of ER+, PR+ and HER+ values. Among total cases of 7247, 5191 were ER+, 5103 were PR+ and 1904 were HER2+. The clinically used biomarkers were highly unstable between the primary tumor and the metastatic lesion. **Conclusion:** Estrogen receptor was most frequently expressed. Thus, the hormone receptor-positive tumors are predominant and hence the majority of breast cancer patients could benefit from hormone therapy. HER2 subtype presents an aggressive tendency, suggesting the importance of anti-HER2 therapy. Discordance of receptor status between primary tumor and metastasis, where possible, metastatic lesions should be biopsied in accordance with current guidelines. Identification of various biologically and clinically distinct subtypes is important for treatment planning and target therapy.

INTRODUCTION

The most frequent type of cancer and the most common cause of cancer-related death in women is breast cancer.[1]Breast cancer is the most generally reported cancer worldwide and second leading cause of mortality.Incidence of breast cancer is progressively increasing over last decades, and specially Asian countries have shown marked increase in the incidence. It is a malignancy with varied molecular and clinical characteristics.[2]

In 2000, a molecular classification of breast cancer based on gene expression profiles was proposed for the first time by Perou and his colleagues and four breast cancer subgroups can be identified based on this molecular classification i.e., Luminal A and Luminal B (which are positive for the hormone receptors), HER2 (which overexpresses the HER2 growth factor), and Basal-like (which is triple negative: estrogen receptor-negative (ER-), progesterone receptor-negative (PR-), and HER2-negative (HER2-).[3]The detection of estrogen, progesterone and HER-2 neu receptors on the surface of the tumour cell is a significant prognostic factor, alone or in combination. The presence or absence of these receptors on the surface of the tumour cell is associated with the conditional gene expression in the tumour cell itself. Later on, in St. Gallen International Expert Consensus in 2011, based on these genetically determined expressions

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of the tumour cell, five molecular subtypes of breast cancer were classified on the that can be immunohistochemically detected, with each subtype manifesting certain prognosis and aggression.[4]Breast carcinoma subtypes based on immunohistochemical markers are (a) Luminal A – Estrogen Receptor (ER) and/or Progesterone Receptor (PR) positive and Human Epidermal Growth Factor Receptor 2 (Her2) negative, (b) Luminal B – ER and/or PR positive and Her2 positive, (c) Her2neu subgroup – ER and PR negative and Her2 positive, (d) Basal like – ER, PR and Her2 negative, cytokeratin (CK) 5/6 positive and/or Epidermal Growth Factor Receptor (EGFR) positive, and (e) Unclassified/Penta negative (PN) – ER, PR, Her2neu, CK 5/6 and EGFR all negative.[2]
The identification of these breast cancer molecular subgroups provides important information on the prognosis and the response to treatment of the disease.[3]The Early Breast Cancer Trialists Collaborative Group has confirmed that the amount of benefit from adjuvant endocrine therapy in breast cancer is proportional to the amount of ER present in the primary tumor. The option of hormonal therapy is now offered to every patient of breast cancer irrespective of age based on the tumor receptor status. Hence, ER/PR estimation needs to be carried out in every patient diagnosed with breast cancer.[5] Hence, the present systemic review was conducted to study the incidence of expression of various molecular subtypes.

MATERIALS AND METHODS

The inclusion criteria were framed as per internationally standardized PICOS framework, as recommended by PRISMA guidelines:
Participants/population: The study population included cases of surgical resection of mammary carcinomas which were assessed immunohistochemically for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expressions and cases reporting if any discordance of receptor status between primary tumor and metastasis.
Intervention: Smears from paraffin sections from cases of surgical resection of mammary carcinomas were assessed immunohistochemically for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expressions were included in the review.
Comparator(s)/control: Studies of any of the above-mentioned interventions was included, including studies with no comparator group
Outcome: the key outcomes consider were:
1) assessment of expression of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 expression in breast cancer among various studies
2) discordance rate (DR) of estrogen receptor (ER), progesterone receptor (PR), HER-2 in primary breast tumors and paired metastases
Tumors were classified into molecular subtypes based on IHC markers status findings [Kondov B et al[4], Goldhirsch A[6]. Thus, four subtypes were defined:
Luminal A:ER-positive, PR-positive (>20%), HER2-negative, Ki-67 < 14%.
Luminal B:ER-positive, HER2-negative, and at least one of: Ki-67 ≥ 14%, PR < 20%.
ER-positive, HER2-positive, Any Ki-67, Any PR.
HER2:ER-negative, PR-negative, HER2-positive.
Triple Negative:ER-negative, PR-negative, HER2-negative.
Study Design: The review included all types of observational studies and case series which have reported the outcomes of the above-mentioned diagnostic methodology.
Inclusion Criteria
Studies conducted anywhere in the world and articles published during and after 2012 through March2023reporting expression of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 in breast cancer and studies assessing discordance rate (DR) of estrogen receptor (ER), progesterone receptor (PR), HER-2 in primary breast tumors and paired metastases was included in the study.
Only those studies published in English language, academic peer-reviewed journals were included in the review.
Exclusion Criteria
Case studies was excluded from the study.
Studies conducted on animals were excluded from the study.
Literature Search: A systematic literature search was performed in PubMed, Embase, clinical trial.gov and Cochrane Library from January 2012 through March 2023 in the English language by two independent authors using a structured search strategy. The literature search used the following terms (with synonyms, MeSH terms, and closely related words):“breast cancer” “estrogen receptor/ERα,” “progesterone receptor/PR,” “HER2/neu,” “metastasis,” “immunohistochemistry/IHC” and “receptor conversion/dis- or concordance.” The searches were screened by the references of selected articles to find those that did not appear in the search databases. Additional references were not obtained by free internet search from Google as the number of studies were large. The detail search strategy is given in [Table 1].
Process of screening and selection of articles: All the citations along with the title and abstract was added to a specified endnote library and final list of studies to be screened for inclusion in the study wasprepared by removing the duplicates. Two researchers carefully screened the articles by assessment of the title and thorough reading the abstracts to shortlist the studies which are likely to

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satisfy the inclusion criteria of the review. Attempts were made to obtain full-text articles for all these shortlisted studies, and thorough assessment was done for the satisfaction of inclusion and exclusion criteria. Studies not satisfying inclusion criteria was excluded further. The list of excluded studies and the reasons for exclusion were presented in the "characteristics of excluded studies" table. "PRISMA flow chart" was used to clearly represent the screening and selection process. [Figure 1].

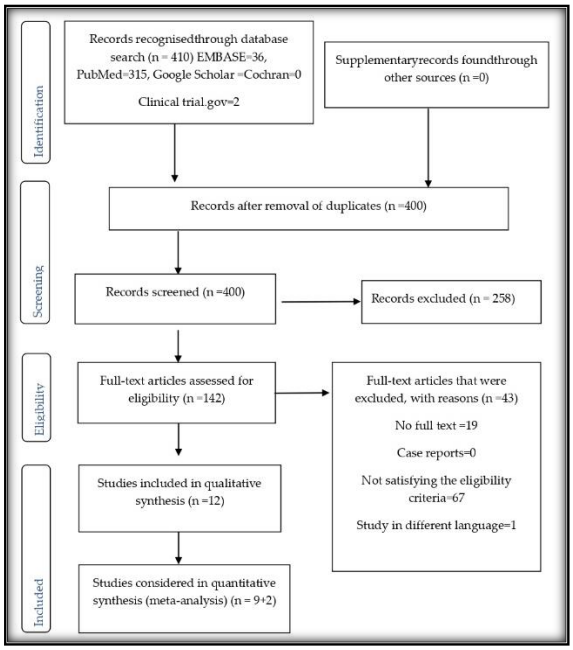

Figure 1: PRISMA 2009 Flow Diagram

Data Extraction: Data was thoroughly read through and were extracted from included studies manually on to a structured data extraction form.

Risk of bias in individual studies: The methodological quality of studies included in the systemic review was assessed according to Fowkes and Fulton quality assessment.[7]

RESULTS

Total cases analysed in the present study was 9485 from 12 studies that fulfilled the inclusion criteria.11 studies were retrospective analysis and 1 study by Kondov B et al [4] was prospective immunohistochemical analysis. The time period of data or patient recordanalysis varied from 1 year to 16 years. 42% of studies were conducted among Asian population, 17% studiesamong African, 33% among European and 8% among American population [Table 1].

Total cases analysed in the present study was 9485 from 12 studies that fulfilled the inclusion criteria [Table 1 and 2]. For analysis of biomarkers among total 12 studies, 9 studies reported complete analysis of ER+, PR+ and HER+ values; study by Pandit P et al reported combined values of ER+ and PR+ cases, in study by Kumar et al value of PR+ cases were not given and study by Ibrahim T et al reported only discordance values between primary and metastatic cases.The analysis reported total cases of 7247, out of which 5191 were ER+, 5103 were PR+ and 1904 were HER2+ [Table 3 and Figure2]. Thus, the present study does not find any discordance between various studies on expression of Estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 expression in breast cancer. Estrogen receptor was most frequently expressed along with loss of HER2 receptor. Thus, the hormone receptor-positive tumors are predominant and hence the majority of breast cancer patients could benefit from hormone therapy. HER2 subtype presents an aggressive tendency, suggesting the importance of anti-HER2 therapy.

Graph 2 reported the discordance of biomarkers in primary tumor and metastatic analysis.The discordance of biomarkers in primary tumor and metastatic analysis was found with higher change PR+ status.Ibrahim T et al evaluated the discordance rate (DR) of estrogen receptor (ER), progesterone receptor (PgR), HER-2, and Ki67 in breast cancer patients and change in ER status was observed in 19 cases (DR 16.4%), while PgR status was modified in 48 cases (DR 41.7%). HER-2 was altered in 21 cases (DR 17.5%). Walter P et al found that clinically used biomarkers were highly unstable between the primary tumor and the metastatic lesion. ER, PR, and HER2 status changed in 14%, 32%, and 15%, respectively.

The most common type of carcinoma was the luminal A type [Table 2 and 4]. The molecular expression of Luminal A type comprises of ER-positive, PR-positive (>20%), HER2-negative, Ki-67 < 14%.Therefore, the most common molecular subtype in India is Luminal-like disease. Identification of Basal like breast cancer, a highly aggressive, biologically and clinically distinct subtype different than its non-basal variant, is important for treatment planning and target therapy. The prognostic indicators significantly predicted a worse overall survival in premenopausal patients, triple negative subtype HER2-enriched status.

In the study by Pandit P et al, the overall incidence of Hormonal Receptor-positive patients (either estrogen-receptor (ER) or progesterone-receptor (PR) or both) was 1162 (56.4%). The Mean tumor size was 3.8cm (range 0–18cm). Luminal type A was positive in 762 (37%) patients while Luminal type B was present in 157 (7.6%) patients. Basal-like subtype was observed in 537 (26%) patients while HER2 rich subtype was seen in 229 (11.1%). The incidence of Luminal A subtype increased with age. The highest observed among patients (72%) aged 70 years or more. Incidence of Basal like subtype was highest in patients less than 30 years (52%). In another study by Elidrissi Errahhali M et al, most tumors were hormone receptor-positive (73%) and 28.6% were HER2 positive. 86.1% of patients with hormone receptor-positive breast cancer were given hormone therapy, while 68.9% of

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patients with HER2+ breast cancer received targeted therapy with Herceptin. Luminal A was the commonest molecular subtype, followed by Luminal B, Triple Negative and HER2. The highest prevalence of premenopausal patients was observed in Triple Negative subtype (72.2%), followed by HER2 (64.1%), Luminal B (62.2%), and Luminal A (55.1%). Luminal B subtype had a poorer prognosis than Luminal A. Compared with Triple Negative, HER2 subtype tend to spread more aggressively and is associated with poorer prognosis.

In the study by Vohra P et al, a total of 134 cases of breast carcinoma were identified from 2002 through 2014 with both FNA cell blocks (fixed in 10% formalin) and corresponding available tissue blocks and ER, PR, and HER2 were characterized in both specimens.Amanat A et al reported that the mean age of the patients was 46.31 years and most of the cases were seen in the age group of 55 to 64 years. The frequency of ER-positive cases was 29(64.4%) while the frequency of ER-negative cases was 16(35.6%), the frequency of PR-positive cases was 19(42.2%), and PR-negative cases was 26(57.8%). In contrast, the frequency of HER2-positive cases was 13(28.9%) and the frequency of HER2-negative cases was 28(62.2%). Most ER-positive cases were observed in the age group 45 to 64 years and most of the HER2-negative cases were seen in the age group 55 to 64 years. The majority of the cases (95.6%) were invasive ductal carcinoma. Most of the cases of breast cancer were of grade II (87%) and luminal A type (40%) was the most frequent one. In the mastectomy specimens, the size of the tumor in most of the cases (55.6%) was 2 to 5 cm and a majority of the cases (33.3%) had ≥4 lymph nodes positive.The hormone receptor-positive tumors are predominant and hence the majority of breast cancer patients could benefit from hormone therapy. HER2 subtype presents an aggressive tendency, suggesting the importance of anti-HER2 therapy.

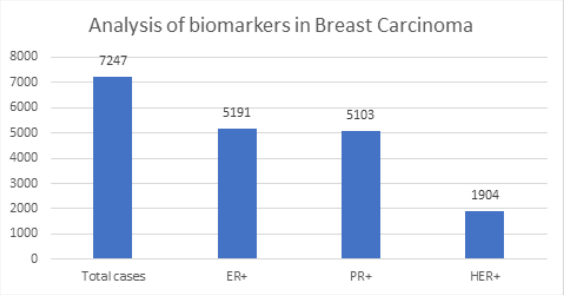

Figure 2: Analysis of biomarkers in Breast Carcinoma

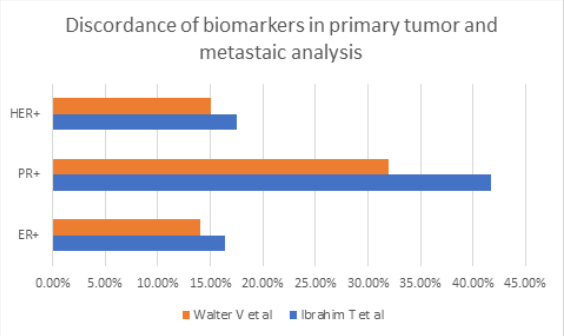

Figure3: Discordance of biomarkers in primary tumor and metastatic analysis

Table 1: Evaluation of studies reporting molecular expression among breast cancer patients

Author	Year	Type of study/database	Country	No. of participants in study group	Duration of analysis of data
Amanat A et al.[8]	2022	Retrospective record-based study	Pakistan	45	January 2021 to May 2022 (1 year 5 months)
Kakudji BK et al.[9]	2021	Retrospective record-based study	South Africa	136	1st January 2012 to 31st December 2018 (7 years).
Pandit P et al.[10]	2020	Retrospective observational study, hospital database	India	2062	Between March 2007 to March 2019 (12 years)
Walter V et al.[11]	2020	Retrospective observational study, hospital database	Germany	541	between 1982 and 2018 (36 years)
Tubtimhin S et al,[1]	2018	Population based Retrospective study, cancer registry in Uboratchathai, Thailand	Thailand	523	2002-2011 (10 years)
Kondov B et al,[4]	2018	Prospective, immunohistochemical analysis	Republic of Macedonia (Europe)	290	1 year
ElidrissiErrahhali M et al,[3]	2017	Retrospective, immunohistochemical analysis	Eastern Morocco (Africa)	2260 breast cancer cases	Between October 2005 and December 2012 (7 years)
Vohra P et al,[12]	2016	Retrospective / Comparative analysis	California, USA	134 cases of breast carcinoma	-
Kumar N et al,[2]	2015	Retrospective analysis	India	56 breast carcinoma cases	Between May 2012 and Apr 2014 (2 years)
Zhu X et al,[13]	2014	Retrospective analysisof cases at National Cancer Center (NCC), China	China	3,198 cases of surgical resection mammary carcinomas	July 1, 2010-July 1, 2012 (2 years)

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Ibrahim T et al,[14]	2013	Retrospective analysis	Italy	120 with samples available from both primary tumors and paired metastases	Not reported
Duchnowska R et al,[15]	2012	Retrospective analysis	Poland	120breast cancer patients	between 1996 and 2011 (16 years)

Table 2:Evaluation of studies reporting clinical features,ER,PR and HER2 expression and type of carcinoma

Author	Reported clinical features	ER, PR and HER2 expression	Type of Carcinoma and biomarkers expression
Amanat A et al (2022).[8]	Mean age of the patients was 46.31 years	ER-positive cases: 29(64.4%), ER-negative cases: 16(35.6%), PR-positive cases: 19(42.2%), PR-negative cases: 26(57.8%), HER2-positive cases: 13(28.9%), HER2-negative cases 28(62.2%).	Most common type:Luminal A type carcinoma. The triple negative cases comprised 22.2%.
Kakudji BK et al (2021).[9]	mean age: 56.35	ER+: 71.6%, PR+: 64.7%HER2-: 75.9%.	Luminal type A and B are the preponderant molecular subtypes.
Pandit P et al (2020).[10]	Mean tumor size: 3.8cm (range 0–18cm). Axillary nodes: positive in 62.5%.	Hormonal Receptor-positive patients (either estrogen-receptor (ER) or progesterone-receptor (PR) or both) was 1162 (56.4%), HER2 rich subtype was seen in 229 (11.1%).	Luminal type Apositive: 762 (37%),Luminal type B: 157 (7.6%), Basal-like subtype was observed in 537 (26%) patients while HER2 rich subtype was seen in 229 (11.1%).
Walter V et al (2020),[11]	Not reported	For primary tumor: ER+ in 421 (78%) patients, PR+ in 385 (72%), and HER2+ in 92 (20%). ER, PR, and HER2 status changed in 14%, 32%, and 15%, respectively.	Not reported
Tubtimhin S et al (2018),[1]	Patient's average age:49.6 years	ER+: 338 (64.6%) PR+: 248 (47.4%) Her-2+:149 (28.5%)	Molecular subtypes: Luminal A: 165 (31.6%) Luminal B: 82 HER2-enriched: 52 (9.9%) Triple negative: 59 (11.3%) Unknown: 165 (31.6%)
Kondov B et al (2018),[4]	Patient's average age:57.6 years, mean size of a primary tumour: 30.27 + 18.3 mm, axillary lymph nodes metastases in 59% of the patients.	ER+: 215 (74.14%) PR+: 226 (77.93%) HER2+: 95 (32.76%)	Luminal A was present in 77 (26.55%) patients, Luminal B HER-2 negative was present in 91 (31.38%) patients, Luminal B HER-2 positive was present in 70 (24.14%) patients, HER-2 enriched was present in 25 (8.62%) patients and basal-like (or triple negative) was present in 27 (9.31%) patients.
ElidrissiErrahhali M et al (2017),[3]	Mean age at diagnosis was 48.7 years ±11.4. The mean size of breast tumors was 3.5 cm ± 1.96, and 84% of our patients are diagnosed with tumors of more than 2 cm.	64.2% were ER+, 66.5% were PR+ and 28.6% were HER2+	Luminal A was the commonest molecular subtype, followed by Luminal B, Triple Negative and HER2. Luminal B subtype had a poorer prognosis than Luminal A. Compared with Triple Negative, HER2 subtype tend to spread more aggressively and is associated with poorer prognosis.
Vohra P et al (2016),[12]	Not reported	On tissue block: ER+98; PR+ :60; HER2+14:	-
Kumar N et al (2015),[2]	Average age of patients was 50.5 years. Histological grade and ER negative status showed strong correlations with basal markers.	ER+: 28 (50%) HER2+: 10 (17.8%)	Luminal A subtype was most prevalent 34%, followed by Basal like/Triple negative subtype 25%. Luminal B and Her2/neu subtypes had same prevalence i.e. 18% each and Breast Tissue like/Unclassified subtype/Penta Negative subtype was 5%.
Zhu X et al (2014),[13]	Median age of 51 years, a mean tumor size of 2.1 cm, and 42.3 % lymph node positivity.	Of all cases, ER+ were 2,506 (78.4 %), PR+ were 2,548 (79.7 %), HER2+ were 816 (25.5 %)	luminal A were the majority accounting for 65.3 %, and triple-negative breast cancer accounted for 9.2 %.
Ibrahim T et al (2013),[14]	Not reported	Change in ER status was observed in 19 cases (DR 16.4%), while PgR status was modified in 48 cases (DR 41.7%). HER-2 was altered in 21 cases (DR	Not reported

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		17.5%	
Duchnowska R et al (2012),[15]	Not reported	ER+:42%,PR+: 34%,and HER2+: 47% in primary tumors. Conversion of ERα status occurred in 35 (29%), PR status changed in 34 (29%), Conversion of HER2 occurred in 14% cases.	Triple-negative cases: 29%.

Table 3: Summarized table of present study

Author	Year	Total sample	ER+	PR+	HER+
Amanat A et al,[8]	2022	45	29	19	13
Kakudji BK et al,[9]	2021	136	83	75	28
Walter V et al,[11]	2020	541	421	385	92
Tubtimhin S et al,[1]	2018	523	338	248	149
Kondov B et al,[4]	2018	290	215	226	95
ElidrissiErrahhali M et al,[3]	2017	2260	1450	1502	646
Vohra P et al,[12]	2016	134	98	60	14
Zhu X et al,[13]	2014	3,198	2506	2548	816
Duchnowska R et al,[15]	2012	120	51	40	51
Total		7247	5191	5103	1904

Table 4: Intervention and conclusion of present studies

Author	Intervention	Conclusion
Amanat A et al (2022),[8]	The frequencies were calculated for ER, PR, and HER2 status and tumor characteristics	Estrogen receptor was most frequently expressed along with loss of HER2 receptor. The most common type of carcinoma was the luminal A type.
Kakudji BK et al (2021),[9]	To study prevalence of receptor status and molecular subtypes in women with breast cancer	The most common breast cancer was receptor-positive; approximately one-quarter were triple-negative.
Pandit P et al (2020),[10]	Patient's characteristic, histological features and molecular subtypes were collected and analyzed.	Most common molecular subtype in India: Luminal-like disease. Identification of Basal like breast cancer, a highly aggressive, biologically and clinically distinct subtype different than its non-basal variant, is important for treatment planning and target therapy.
Walter V et al (2020),[11]	Not reported	Discordance of receptor statuses between primary tumor and metastasis, where possible, metastatic lesions should be biopsied in accordance with current guidelines.
Tubtimhin S et al (2018),[1]	Molecular subtypes and prognostic factors for survival of pre- and post-menopausal breast cancer patients.	The prognostic indicators significantly predicted a worse overall survival in premenopausal patients, triple negative subtype HER2-enriched status. Statistically significant increased risk of death in postmenopausal patients was noted for chemotherapy after mastectomy, and for a Luminal B status
Kondov B et al (2018),[4]	To determine if the subtypes and the clinical stage are somehow correlated.	Detecting the subtype of breast cancer is important for disease prognosis, but also for determining and providing an adequate therapy.
ElidrissiErrahhali M et al (2017),[3]	Molecular subtypes were determined and their associations with the clinico-pathological characteristics of the tumors were examined.	The hormone receptor-positive tumors are predominant and hence the majority of breast cancer patients could benefit from hormone therapy. HER2 subtype presents an aggressive tendency, suggesting the importance of anti-HER2 therapy.
Vohra P et al (2016),[12]	compared the concordance of ER, PR, and HER2 markers as determined on fine-needle aspiration (FNA) cell blocks compared with tissue blocks prepared from surgical specimens.	Excellent concordance for ER and HER2 and moderate concordance for PR expression as determined by IHC on cell blocks compared with the same expression determined on tissue blocks.
Zhu X et al (2014),[13]	Smears from paraffin sections from 3,198 cases of surgical resection mammary carcinomas were assessed immunohistochemically for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expressions	ER, PR, and HER2 status showed a direct correlation to tumor onset age, tumor type, and grade of ductal carcinoma
Ibrahim T et al (2013),[14]	Discordance rate (DR) of estrogen receptor (ER), progesterone receptor (PR), HER-2 in primary breast tumors and paired metastases	Changes in the cell biology of breast cancer metastasis seems to occur and hence biopsy could potentially guide the choice of treatment and provide useful information on prognosis.
Duchnowska R et al (2012),[15]	Status of estrogen receptor alpha (ERα),	Receptor conversion i.e., loss of hormone receptors in

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	progesterone receptor (PR), and epidermal growth factor receptor 2 (HER2) in primary tumor and in the corresponding brain metastases in a consecutive series of breast cancer patients.	particular is a common occurrence in brain metastases from breast cancer, and endocrine therapy may increase its incidence.

DISCUSSION

Breast cancer is a complex disease with various subtypes that have different cellular structures, molecular changes, and clinical manifestations. In addition, the prognosis and response to breast cancer treatment depend on multiple variables, including tumor grade & size, lymph node infiltration, ER receptors, PR receptors, and HER-2/neu receptors.[16]The present study does not find any discordance between various studies on expression of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 expression in breast cancer. however, studies reporting comparison ofbiomarkers reported discordance among results of primary lesion and metastatic lesion. Estrogen receptor was most frequently expressed along with loss of HER2 receptor. Thus, the hormone receptor-positive tumors are predominant and hence the majority of breast cancer patients could benefit from hormone therapy. HER2 subtype presents an aggressive tendency, suggesting the importance of anti-HER2 therapy.The most common type of carcinoma was the luminal A type.ER, PR, and HER2 status revealed a direct correlation to tumor onset age, tumor type, and grade of ductal carcinoma. Hence, detecting the subtype of breast cancer is important for disease prognosis, but also for determining and providing an adequate therapy. Detection of the subtype of breast cancer is important for evaluating the prognosis of the disease, but also for determining and providing an adequate therapy. Luminal-like disease is the most common molecular subtype in India.

Vohra P et al,[12] found the usefulness of cell blocks prepared from FNA material obtained from breast carcinomas as a substrate for the characterization of ER, PR, and HER2 expression by IHC asthere was an excellent concordance for ER and HER2 and moderate concordance for PR expression as determined by IHC on cell blocks compared with the same expression determined on tissue blocks. Kondov B et al,[4] found that luminal A was present in 77 (26.55%) patients, Luminal B HER-2 negative was present in 91 (31.38%) patients, Luminal B HER-2 positive was present in 70 (24.14%) patients, HER-2 enriched was present in 25 (8.62%) patients and basal-like (or triple negative) was present in 27 (9.31%) patients. Pandit P et al,[10] reported that the luminal-like disease is the most common molecular subtype in India. Identification of basal like breast cancer, a highly aggressive, biologically and clinically distinct subtype different than its non-basal variant, is important for treatment planning and target therapy.Indeed, Luminal tumors are associated with a better prognosis compared with basal-like or HER2 tumors which have a more aggressive clinical outcome.[3]

There are various markers used to identify breast cancer including estrogen and progesterone receptors. Breast cancers with positive ER and PR status are associated with improved outcomes and response to therapy. On the contrary, another marker is a tyrosine kinase receptor (HER2) related to the epidermal growth factor receptor family. If HER2 is over-expressed, it is associated with relapse and resistance to therapies as 5 compared to ER & PR-positive cases. Therefore, it is imperative to evaluate ER, PR, and HER2 status of breast carcinomas diagnosed on hematoxylin and eosin 8 (H & E) staining.[1]Human EGFR 2 (HER2) amplification occurs in 20% to 25% of women and is associated with a poor prognosis. Elevated EGFR expression has been correlated with a poor prognosis in breast cancer specimens and in laboratory models.[17]Furthermore, gain of HER2 positivity was associated with a significantly more favorable prognosis than concordantly negative receptor status which may reflect benefit from adjustment of therapy.[11]

In another study, Walter P et al,[11] found that clinically used biomarkers were highly unstable between the primary tumor and the metastatic lesion. ER, PR, and HER2 status changed in 14%, 32%, and 15%, respectively. Although the change of HER2 status was not statistically significant, the percentage of discordant patients is clinically meaningful. Patients who lost HR positivity had a significantly poorer prognosis than concordantly receptor-positive patients.[11]In another study by Ibrahim T et al,[14] of 145 cases reviewed, 120 with samples available from both primary tumors and paired metastases were included in the study. For each receptor, the DR was calculated as the proportion of discordant cases with respect to the total number of patients.A change in ER status was observed in 19 cases (DR 16.4%), while PR status was modified in 48 cases (DR 41.7%). HER-2 was altered in 21 cases (DR 17.5%). There has been controversy about the importance of PR receptor estimation in breast cancer, with a strong opinion that PR estimation should be stopped. But, several studies have shown that patients with PR+ tumors benefit with endocrine therapy although PR is a weaker predictor of response to endocrine therapy than ER.[5] Preliminary data form study by Bernoux A et al,[18] suggested that there is no difference in disease free survival between tamoxifen and anastrozole in the subgroup of patients with ER- and PR+ tumors, while anastrozole was found to be

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significantly superior to tamoxifen in the subgroup of ER+ and PR− patients.

The estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) statuses of primary breast cancer tissue are used clinically to approximate biological subtypes, to predict outcome, and to guide therapy decisions, especially for endocrine and HER2-targeted regimens. However, numerous studies have shown substantial discordance rates in ER, PR, and HER2 receptor profiles between primary and metastatic tumors.[11]Estrogen receptor alpha (ERα), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status have proven their clinical utility in guiding therapeutic decision-making in (metastatic) breast cancer. Prescription of endocrine or HER2-targeted therapies is mainly directed at the biomarker status of the primary tumor. However, increasing evidence shows extensive differences between immunohistochemically assessed tissue characteristics of primary breast tumors and their paired metastases. For ERα, PR, and HER2, widely varying discordance rates have been reported so far: 3%–54% for ERα, 5%–78% for PR, and 0%–34% for HER2. This change of hormone receptor and/or HER2 status between primary tumor and paired metastasis within a patient is usually denoted receptor conversion.[19]Thus, biopsy and re-assessment of receptor status in distant metastases whenever possible at each progression or change in therapy should be conducted in order to get more insight into the patterns and dynamics of hormone receptor conversion.

The limitation of the present study is the exclusion of those with incomplete data is potential source of bias.

CONCLUSION

The present study concludes that discordance of receptor status between primary tumor and metastasis, hence, where possible, metastatic lesions should be biopsied in accordance with current guidelines. Estrogen receptor was most frequently expressed. Thus, the hormone receptor-positive tumors are predominant and hence the majority of breast cancer patients could benefit from hormone therapy. HER2 subtype presents an aggressive tendency, suggesting the importance of anti-HER2 therapy.The most common type of carcinoma was the luminal A type. Identification of various biologically and clinically distinct subtypes is important for treatment planning and target therapy. The prognostic indicators significantly predicted a worse overall survival in premenopausal patients, triple negative subtype HER2-enriched status.

Therefore, determining the subtype of breast cancer is necessary for the routine histopathological assay.Moreover, biopsy and re-assessment of receptor status in distant metastases whenever possible at each progression or change in therapy should be conducted in order to get more insight into the patterns and dynamics of hormone receptor conversion.

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