Discordance of Diagnostic Core Biopsy and Final Histopathology Performed after Surgical Resection of Breast Cancer

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ABSTRACT

Objective: To determine the frequency of discordance of receptor status in our breast cancer patients, find out its causes, and suggest remedial measures.

Study Design: Retrospective longitudinal study.

Place and Duration of Study: Breast clinic and Radiation Oncology Department of Combined Military Hospital Rawalpindi Pakistan from Jan 2018 to Nov 2021.

Methodology: Estrogen Receptor, Progesterone Receptor and Her2 Neu status differences between diagnostic tru-cut biopsy and surgical specimen were compared.

Results: Receptor status between initial core biopsy and final histopathology of 63 patients were compared. Discordance rates of 05 (7.90%), 13 (20.60%) and 12 (19%) were noted for Estrogen receptor, progesterone receptor and Her2, respectively. The highest discordance noted was for the progesterone receptor, followed by the HER2 receptor and the Estrogen receptor.

Conclusion: The highest discordance noted was for the progesterone receptor, followed by the HER2 receptor and the Estrogen receptor. Further studies are required to know more about the causes of receptor status discordance, its impact on treatment decisions and its impact on disease progression and survival.

Keywords: Receptor discordance, Estrogen Receptor, Progesterone receptor, Her2 receptor.

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INTRODUCTION

Her2 neu [epidermal growth factor receptor 2 (EGFR-2)] targeted therapy and hormonal treatment are an integral part of the treatment of carcinoma of the breast.[1] These may be given in the form of neoadjuvant and adjuvant therapy in the curative setting and for palliation in the metastatic setting.[1] Although these agents are beneficial, they have many drug-related side effects, toxicities, and financial implications.[2] Their cost ranges from thousands to millions of rupees per month. So determining the receptor status of all patients is very important and compulsory to find out which patients will benefit from them. Patients wrongly labelled as HER2 neu positive will receive treatment for up to twelve months (if cancer is localized) or maybe for many years (if the disease is metastatic) with drugs which will not benefit them and instead will cause them drug toxicity and "financial toxicity". Receptors' status, such as ER, PR, HER2 Neu and Ki-67%, is mainly determined by Immunohisto-chemistry (IHC).[3] For her2 neu status of 2+ on IHC being equivocal, the dual-probe FISH test is performed to clarify whether her2 neu status is negative or positive.[4] The experience and competence of the histo-pathologist play a pivotal role in determi-ning the receptor status on IHC.

In this study, receptor status performed on initial core biopsy was compared with the receptors performed on final histopathology of the specimen removed after surgery and discordance rate was measured.[5] In addition, an effort was made to determine the reason or risk factors responsible for the discordance.[6] A change of receptor status, either from negative to positive or positive to negative, was considered discordance. In addition, any change in Allred score, either decrease or increase (for example, from 5 to 6, which still as a whole is positive), was also considered discordance.[7,8]

The rationale of our study was to avoid the futile efforts, conserve the cost and protect patients from the economic and health effects of overtreatment when it is not required. In addition, this study will also help to modify and enhance the diagnostic yield and decision power, and capabilities of clinicians.

METHODOLOGY

This retrospective longitudinal study was conducted at the Radiation Oncology Department and Breast Clinic, Combined Military Hospital, Rawalpindi

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Pakistan, from January 2018 to November 2021. The sample size was calculated using the WHO sample size calculator using a 95% confidence interval, Absolute precision was 10%, and the prevalence of discordance is taken as 20% in estrogen receptors.[7] The probable sample size was 62 patients. Non-probability consecutive sampling technique was used.

Inclusion Criteria: The cases included in the study were those who had invasive breast cancer with available previous data of receptors on core biopsy and final histopathology and had reports of AFIP histopathology.

Exclusion Criteria: Cases were excluded whose receptor status, whether pre-op or post-op, was missing and whose histopathology reports were from laboratories other than AFIP.

Two hundred patients from the Breast clinic and Radiation Oncology outpatient department (OPD) at Combined Military Hospital (CMH) Rawalpindi Pakistan fulfilling the inclusion criteria were selected after permission from Hospital Ethical Committee and informed written consent (222/11/21). In addition, OPD registration numbers, name, age, gender, and histopathology reports were noted. All patients were subjected to the following diagnostic workup: physical examination, radiological examinations (mammogram and ultrasound of breasts and axillae), biochemical profile (cell counts, total bilirubin, alkaline phosphatase, alanine transaminase, urea, creatinine) and ER, PR, Her2 neu and Ki-67 status both pre-op and post-op. Histopathology was done or re-checked at the Armed Forces Institute of Pathology, Rawalpindi. All data was counter checked by another colleague before being recorded in a proforma to reduce observer bias (Figure).

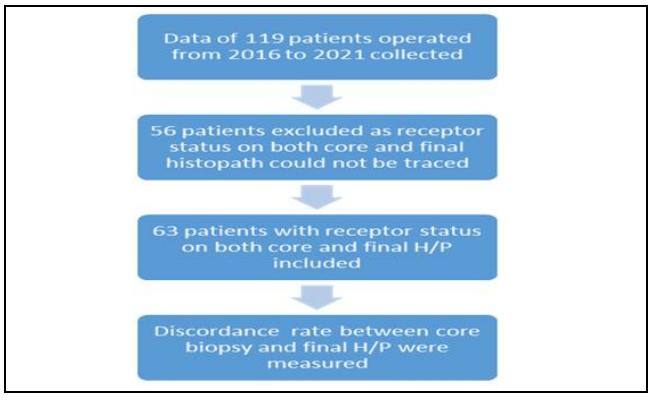

Figure: Flowchart.

Data was analyzed using Statistical Package for the social sciences (SPSS) version 23.00 and MS Excel 2016 software. Mean ± SD was calculated for the continuous variable. In addition, frequency and percentage were calculated for categorical variables.

RESULTS

A total of 63 breast cancer patients were included; the mean age was 53.02 ± 12.95 years, ranging from 22 to 85 Years, 61 (98.4%) were females, and 1 (1.60%) male, Out of a total, 53 (84.12%) patients were estrogen receptor-positive on core biopsy, and 10 (15.87%) patients were negative for estrogen receptors, On final histopathology 48 (76.19%) patients were positive, and 15 (23.80%) patients were negative for estrogen receptors, On core biopsy 44 (69.84%) patients were tested positive for progesterone receptor and 10 (15.87%) patients were found negative. On final histopathology, 39 (61.90%) patients were positive, while 24 (38.09%) patients were negative for progesterone receptors. Her2 status on the core was 11 (17.50%) positive, 34 (53.96%) negative, and 08 (12.69%) equivocal, while on final histopathology, 11 (17.50%) were positive, 47 (74.60%) were negative, and 05 (7.90%) were equivocal for her2 receptor, of total 08 cases found equivocal for her2 receptor on core biopsy, FISH was positive in 01 (1.58%) case while negative in remaining 07 (11.11%) cases. On final histopathology, FISH was performed for 05 (7.92%) cases that were found equivocal for her2 receptor, 04 (6.34%) of which were positive and 1 (1.58%) was negative, shown in Table-I.

The grade change for Estrogen receptors was 32 (50.80%), while a change of status was 5 (7.90%). Out of these 5 cases, a change from positive to negative was present in 4 (80%) cases, while the change from negative to positive was found in 1 (20%) cases. For progesterone receptors, a grade change was noted in 32 (50.80%) cases, and a status change was noted in 13 (20.60%) cases. 9 (69.23%) out of 13 changed status from positive to negative, and 04 (30.76) changed from negative to positive. For her2 neu, a change of grade was noted in 29 (46%) cases, while status changed in 12 (19%) cases (Table-II).

Table-II: Frequency of discordance rates.

Parameters	Grade Change	Status Change
Estrogen Receptor	32 (50.80)	05 (7.90)
Progesterone Receptor	32 (50.80)	13 (20.60)
Her2 Receptor	29 (46.00)	12 (19.00)

Of these 12 patients with discordance, 05 (41.66%) were a change of status from positive to negative, and 7 (58.33%) were cases of status change from negative to positive.

DISCUSSION

Determination of receptor status on a specimen obtained after surgical resection of breast carcinoma is as vital as the initial determination of receptor status on core biopsy at the time of diagnosis.[9] Receptor status discordance occurs in substantial numbers of cases of cancers.

Table-I: Demographic and reproductive variables.

Parameters	n (%)
Age (Mean ± SD)	53.02 ± 12.95 Years
Gender	
Male	62 (98.40)
Female	1 (1.60)
Estrogen receptor	
Positive on core	53 (84.12)
Negative on core	10 (15.87)
Positive on final histopathology	48 (76.19)
Negative on final histopathology	15 (23.80)
Progesterone receptor	
Positive on core	43 (68.25)
Negative on core	20 (31.74)
Positive on final histopathology	39 (61.90)
Negative on final histopathology	24 (38.09)
HER2 status	
Neg on core	11 (17.50)
Equivocal on core	34 (53.96)
Positive on final H/P	08 (12.96)
Neg on final H/P	11 (17.50)
Equivocal on final H/P	47 (74.60)
	05 (7.90)
FISH on core biopsy	
Positive	01 (1.58)
Negative	07 (11.11)
Not done	55 (87.30)
FISH on final histopathology	
Positive	04 (6.34)
Negative	01 (1.58)
Not done	58 (92.06)

Routinely, a patient presenting into a breast clinic with complaints of a breast lump undergoes triple assessment, including history and examination, imaging and core biopsy if indicated. Once the core biopsy confirms it is cancer, further tests are conducted, including receptor status of ER, PR, HER2 neu, and Ki-67 on the already submitted core biopsy sample.[10] The 2015 European Society for Medical Oncology (ESMO) guideline recommended that ER, PR and HER2 status be first tested by core biopsy sample. This will dictate further systemic treatment.[8] After all, investigations are concluded, including staging workup for metastasis, the case is presented and discussed in a Multi-disciplinary cancer meeting (MDT), where a decision is taken regarding treatment. Keeping in mind all parameters, some patients are directed for up-front surgery followed by adjuvant therapy, while some undergo neoadjuvant chemotherapy followed by surgery.

Many surgeons and oncologists do not determine receptor status on the final specimen obtained during surgery and continue treatment based on the initial receptor status performed on core biopsy. This can result in a continuation of a therapy which may give no advantage to the patient but instead may be detrimental for her/him with the futile financial burden. In contrast, some patients may be denied a therapy that may be advantageous to her/him and may add survival benefits.[11]

A discordance rate of 7.9%, 20.6%, and 19% were noted in our study for ER, PR, and Her2 neu, respectively. This is in accordance with several other studies with varying discordance rates of (1-22.2%) for ER, (3-31%) for PR, and (3-36%) for Her2.[11]. The discordance was mainly loss of receptors expression for ER, PR and Her2. The gain was more than the loss. This trend of losses more than gains is reported by other studies.[12,13] The highest discordance rate in our study was noted for PR (20.6%) was also in accordance with similar other studies.[9–11,14] Other studies also reported that the discordance rate is highest for PR, followed by Her2 and ER.[6] The same trend is found in our study as well.

Multiple causes of discordance include inter-laboratory variation, technical and analytical variability in IHC interpretation, tumour heterogeneity, biological evolution of tumour with time and evolution of tumour in response to neoadjuvant chemotherapy.

Despite many advances in receptor status determination, inter-laboratory variation still subsists.[15] Even intra laboratory variation occurs, and the same specimen, when reviewed by two independent histopathologists of the same department, may sometimes give diverse results as the cut-off values for ER and PR positivity may differ.[16] The method of tissue processing and fixation, the choice of method (IHC vs RT-PCR), and the assay used (dual vs single antibody ER assay) may all donate to discordance.[17] The fixation may be overdue. There may be under fixation or over fixation of the surgical specimen with formalin before IHC, which may interfere with the actual results. The amount of tissue taken in core biopsy is small compared to the sample after surgical resection. Due to nominal sample size and tumour heterogeneity, a core biopsy may not be as reliable. Due to tumour heterogeneity, the sample on core biopsy may not be the true

representative of the whole tumour and may culminate in discordance.

Another foundation for receptor status discordance may be neo-adjuvant chemotherapy.[18] Literature shows discordance in ER, PR and ki-67 pre and post neoadjuvant chemotherapy.[18] However, in our study, patients who received neoadjuvant chemotherapy before surgery were excluded from the study.

Several recent studies showed that the failure to detect negative-to-positive expression alterations in tumours is more likely to significantly influence treatment decisions than the failure to identify positive-to-negative expression changes.

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LIMITATION OF THE STUDY

As it was a retrospective analysis of receptor status discordance for cases operated between 2018 and 2021 so the following data of all patients included in our study could not be traced like tumour type, stage, type of surgery, whether the patient received adjuvant or neo-adjuvant chemotherapy, radiotherapy, whether the method of specimen processing in the laboratory was standardized or not. In addition, we were unable to gather details of further treatment in those patients in which discordance occurred and whether discordance impacts disease progression and survival.

RECOMMENDATIONS

The following recommendations have been made based on our study.

A: Receptor status must be repeated/determined on the final surgical specimen recovered after surgical resection.

B: The decision already taken at the MDT meeting at the start of the treatment should be modified accordingly if final histopathology shows receptor discordance.

C: When in doubt, the receptor status should be reviewed from another standard laboratory.

D: The method of specimen processing, method of fixation, and time frame for fixation and analysis should be standardized and supervised in each laboratory.

E: Further studies are required to know more about the causes of receptor status discordance, its impact on treatment decisions, and its impact on disease progression and survival.

CONCLUSION

The maximum discordance noted was for the progesterone receptor, followed by the HER2 receptor and the Estrogen receptor. Several causes that may lead to discordance were discussed, including technical errors in the laboratory, tumour heterogeneity, size of the biopsy specimen, tumour evolution with time and tumour evolution with neo-adjuvant chemotherapy. In addition, further studies are required to know more about the causes of receptor status discordance, its impact on treatment decisions and its impact on disease progression and survival.

Conflict of Interest: None.

Author's Contribution

SZK: Main Author, data collection, introduction writing, results analysis, discussion writing, SRQ:, MSN: Editing, Proof reading, supervision, AK: Discussion writing, AM: Data collection, MMJ: introduction writing.

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