Volume 3, Issue 1, 2025

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

SERUM UREA/CREATININE LEVELS; ER/PR STATUS AND GRAYSCALE ULTRASOUND IN DETERMINATION OF RENAL METASTASIS OF BREAST CANCER

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DOI: https://doi.org/10.5281/zenodo.15093929

Keywords

Article History
Received on 19 February 2025
Accepted on 19 March 2025
Published on 27 March 2025

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Abstract

Objectives: *To analyzing serum levels of urea /creatinine and gray scale ultrasound in patients of breast cancer to check renal metastasis. A correlation of tumor markers ER/PR with TNM staging was also done.*

Study Design: *Cross-sectional study*

Place and Duration of Study: *This study was conducted at the JINNAH POST GRADUATE MEDICAL CENTER; KARACHI; PAKISTAN from August 2017 to November 2018.*

Methods: *Study design was approved by Board of Advance Studies, University of Karachi and ethical committee of Jinnah Post Graduate Medical Centre. Tumor markers ER/PR status was checked by stained tissue histology under microscope received embedded in formalin. Serum urea and creatinine were estimated via using Selectra –E ,XL semi auto biochemical analyzer. Gross kidney metastasis evaluated by ultrasound which is routinely done of each patient.*

RESULT: *Creatinine gives significant negative correlation with T ($p<0.01$), Urea gives significant negative correlation with T ($p=0.01$), significant negative correlation with N ($p<0.01$) and significant negative correlation with M ($p=0.01$), ER gives significant positive correlation with T ($p<0.01$), significant negative correlation with M ($p=0.02$), whereas PR gives 20.6% negative correlation with N ($p<0.01$). The results using multivariate analysis, increase in T will give 0.05 unit decrease in Creatinine ($p=0.02$), no significant effect of T, N and M was observed on Urea, patients with higher T, N, and M values were found significantly more likely for positive ER and patients with higher N were significantly less likely to be found with positive PR ($p<0.01$).*

Volume 3, Issue 1, 2025

Frontier in Medical & Health Research

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CONCLUSIONS: *As result of study showed no significant effect of T,N and M was observed on serum Urea, creatinine values. Positive ER cases showed higher N values although were significantly less likely to be found with positive PR). Ultrasound findings were negative for metastasis almost in all patients.*

INTRODUCTION

New era brought the challenge for human health. Breast cancer appear as a big monster in field of medicine and irrupting globally. Cohort projects are still being done to trace breast cancer etiology and presence in early stages to enhance and maintain community health levels.in protection from breast cancer. Mammogram, ultrasound, and MRI are routinely available imaging tests. Available techniques are sensitive but not cost effective. Skill full hands and experienced analyst are required. Conclusively it is hardly difficult to make sensitive test rational. If patients and physicians utilize test in start of disease can get benefit more. [1] Continually used system for staging of breast cancer is the American Joint Committee on Cancer (AJCC) TNM system. The most recent AJCC system, is effective since January 2018, including clinical and pathologic staging systems. The addition of information related with ER, PR, and HER2 status plus grade is detailed, informative but rather complex [2] Biomarkers are biological chemicals released from diseased cancer tissues in response to abnormal body ambient or immunity which leak information regarding cancer transformation and spread. Estimate of tumor markers level in serum can be done by different modalities in single or combination. Other factors are size, mass, expression degree, catabolic, excretion rates, tumor bloody supply, and drug resistance. [3]

Estrogen receptor (ER) is an active and specific biological marker for estrogen. Estrogen nuclear receptor located in the nucleus, and its messenger RNA are for the time being post translation modification move in cytoplasm. Advantage of estrogen receptor estimation is either selection of endocrine therapy or check after effects. It is benefiting marker in diagnosis and metastasis evaluation of breast cancer. [4 5 6] Predominantly aging process and chronic diseases affect kidney function alternatively cancer patient renal parenchyma may develop chronic kidney disease because of nephrotoxic potential of chemotherapy or radiation. Cancer and its medicines slowly damage the normal kidney function and may result in parenchyma replacement with nonfunctioning fibrous tissues. Recently onco-nephrology emerged as sub-specialty to resolve the health issues involving the renal parenchyma. The subspecialty onco-nephrology may comprehend and treat this long and puzzled process. [7 8 9] A data base of 4684 cancer patients CKD with GFR < 60ml/min/1.73m^2 (MDRD formula) was identified. Austria 2014, the prevalence of CKD in a cohort of 1100 patients was 16.1% [10 11] It is anticipated that 13.1 million cancer-related deaths by the year 2030 would be possible by CKD. The role of tumor markers in assessing diagnosis and prognosis is elaborated by many studies. A serial monitoring of disease, its resurge and outcome is important and make possible by estimation of endocrine markers levels. Few markers are found positive in one type of cancer and others are positive in others. Hal mark of super tumor marker is to be highly sensitive as well specific, and reliable along with perfect prognostic results. Extra perspective for an ideal tumor marker are tissue specificity and correlation of marker with staging. Basically hemodialysis, peritoneal dialysis, and kidney transplantation may change the impact of tumor markers. Combination of serum tumor markers enhances its value in diagnostic field of medicine. Few literatures highlight the clinical significance of serum tumor markers in screening, diagnosis, end result or possibility of cancer in chronic kidney disease and renal allograft recipients. [12] The B-mode ultrasound is primary imaging applied in breast cancer detection. It is proved successful in guided needle core biopsy of cancer tissues. Advancement in field of ultrasound is making it more beneficial. It is now recommended as first line imaging modality in breast related problems specially below age of thirty. A frequency above 10 MHz is now recommended for adequate spatial resolution by

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ISSN: (e) 3007-1607 (p) 3007-1593

The American College of Radiology (ACR) suggest B-mode imaging with center frequency above 10 MHz. Compound ultrasonography is innovative. Harmonic imaging techniques is an integral of multiple pulses with higher frequency and velocity which throw image of good quality on screen and lowers the noise to signal ratio. Color Doppler ultrasound is another sonographic facility which enables the sonographer to notice the presence, consistency of mass and difference of benign from malignant by the pattern of color flow. [13] [14] [15] [16] Secondary metastases usually present disseminated fasion. Clear cell carcinoma is a tumor with smooth edged and uniform internal texture is commonest reported cancer. In Contrast-enhanced CT it appear as a hyper vascular lesion. In contrast, papillary renal cell carcinoma and chromo phobe cell carcinoma show hypo vascular characteristics on contrast-enhanced CT scan. [17]

METHODOLOGY

RESEARCH DESIGN: Cross Sectional Observational Study.

METHODOLOGY: Selection of Patients:

The present study was carried out on 280 known patients of breast cancer taken from Jinnah Post Graduate Medical Centre, (department of oncology).

Inclusion Criteria:

Clinically and histopathologically diagnosed cases of breast cancer (any stage) were selected for the study. The staging was done on the basis of TNM staging system of breast cancer. TNM staging criteria describes observations related to tumor size (T), degree of involvement of regional lymph nodes (N) and metastasis (M).

Exclusion Criteria:

Male patients, Patients suffering from primary Bone diseases, Diabetes, Hepatobiliary disease and previous history of any other type of malignancy were excluded from the study.

Consent form was described orally to every patient and signature was taken.

Study design was approved by Board of Advance Studies, University of Karachi and ethical committee of Jinnah Post Graduate Medical Centre.

Collection of Samples:

Trained staff were hired for sample collection. Sterilized materials were used. Evacuated tubes were commercially prepared with additives. Polyurethane boxes containing dry ice are used to ship and transport samples and stored at –70 degree C. Formalin-fixed paraffin-embedded tissue specimens were examined for tumor characteristics at molecular level at JPMC and BMSI.

Biochemaical Markers:

SERUM UREA AND CREATININ were estimated via using Selectra –E ,XL semi auto biochemical analyzer.

Reference : Kaplan A Urea. Kaplan A et al. clinical chemistry. Princeton 984; 1257-1260 and 437 and 418.

Tumor markers ER/PR status was checked by Formalin-fixed paraffin-embedded tissue specimens. Histology is done under microscope.

Sample collection: samples 3ml, were collected in heparinized syringe

KIDNEY METASTSSIS:

Gross kidney metastasis evaluated by ultrasound which is routinely done of each patient.

RESULTS:

Statistical Analysis:

Data were stored and analyzed using IBM-SPSS version 23.0; Spearman rank correlation was used to study the correlation of Creatinine, Urea, ER and PR with T,N and M. Multi variable regression analysis technique was used to study the effect of these dependent variables on T,N, and M. P-values less than 0.05 were considered statistically significant. Bar diagram was reported for ER and PR outcomes, Scatter plot was used to display the significant relationships of dependent variables with independent variables.

Results:

Table-1 reports the correlation analysis of Creatinine, Urea, ER and PR with T,N and M; results showed Creatinine gives 21.5% significant negative correlation with T ($p<0.01$), Urea gives 13.9% significant negative correlation with T ($p=0.01$), 16% significant negative correlation with N ($p<0.01$) and

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ISSN: (e) 3007-1607 (p) 3007-1593

14.2% significant negative correlation with M (p=0.01), ER gives 22% significant positive correlation with T (p<0.01) , 13.6% significant negative correlation with M (p=0.02) ,whereas PR gives 20.6% negative correlation with N (p<0.01).

Table-2 reports the results using multivariate analysis, increase in T will give 0.05 unit decrease in Creatinine (p=0.02), no significant effect of T,N and M was observed on Urea, patients with higher T, N, and M values were found significantly more likely for positive ER and patients with higher N were significantly less likely to be found with positive PR (p<0.01).

Table 1: Correlation Analysis of Studied Parameters using Spearman Rank Correlation

Parameters		T	N	M
Creatinine	Correlation Coefficient	-0.215	0.041	-0.041
	p-value	<0.01*	0.49	0.491
Urea	Correlation Coefficient	-0.139	-0.160	-0.142
	p-value	0.01*	<0.01*	0.01*
ER	Correlation Coefficient	0.220	0.096	-0.136
	p-value	<0.01*	0.10	0.02*
PR	Correlation Coefficient	-0.068	-0.206	0.018
	p-value	0.25	<0.01*	0.76
*p<0.05 was considered statistically significant for Spearman Rank Correlation				

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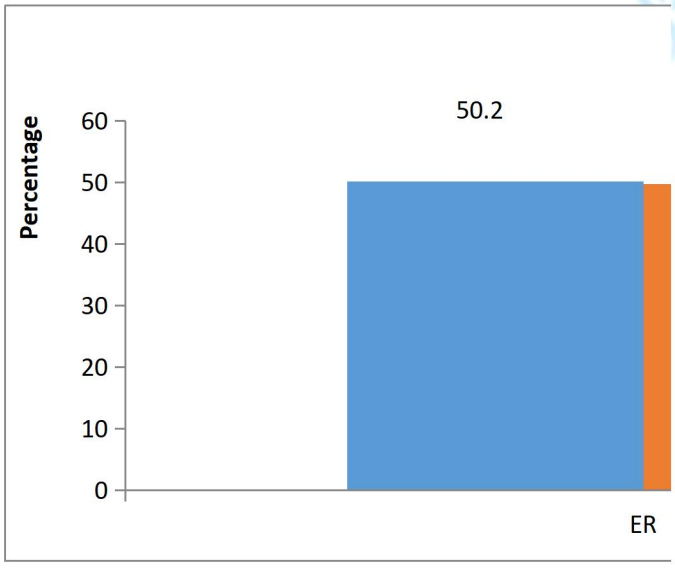
Table 2: Effect of Creatinine, Urea, ER and PR on

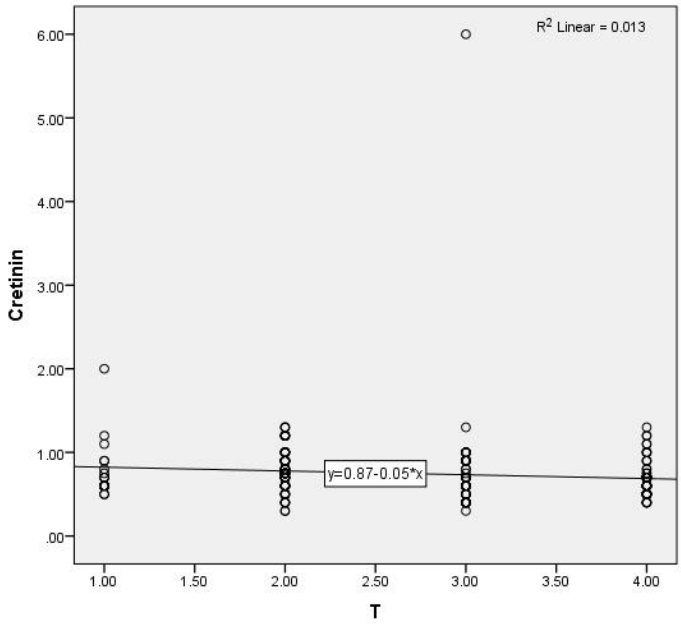
Dependent Variable	Independent Variables	Beta	S.E	t-value	p-value	95% Confidence Interval	
						Lower Bound	Upper Bound
Creatinine	Intercept	0.858	0.079	10.877	<0.01*	0.702	1.013
	T	-0.055	0.025	-2.234	0.02*	-0.103	-0.007
	N	0.001	0.026	.037	0.97	-0.051	0.053
	M	0.026	0.014	1.865	0.06	-0.001	0.054
urea	Intercept	32.674	3.234	10.103	<0.01*	26.307	39.040
	T	-1.422	1.005	-1.414	0.15	-3.401	0.557
	N	-1.542	1.074	-1.436	0.15	-3.657	0.572
	M	-1.084	0.576	-1.884	0.06	-2.217	0.049
ER	Intercept	0.038	0.097	.396	0.69	-.152	0.229
	T	0.150	0.030	4.983	<0.01*	0.091	0.209
	N	0.122	0.032	3.782	<0.01*	0.058	0.185
	M	-0.064	0.017	-3.709	<0.01*	-0.098	-0.030
PR	Intercept	0.711	0.099	7.216	<0.01*	0.517	0.905
	T	-0.056	0.031	-1.842	0.06	-0.117	0.004
	N	-0.139	0.033	-4.234	<0.01*	-0.203	-0.074
	M	0.010	0.018	.548	0.58	-0.025	0.044

T, N, and M using Multivariate Regression

Bar Diagram



Scatter Plot 1:



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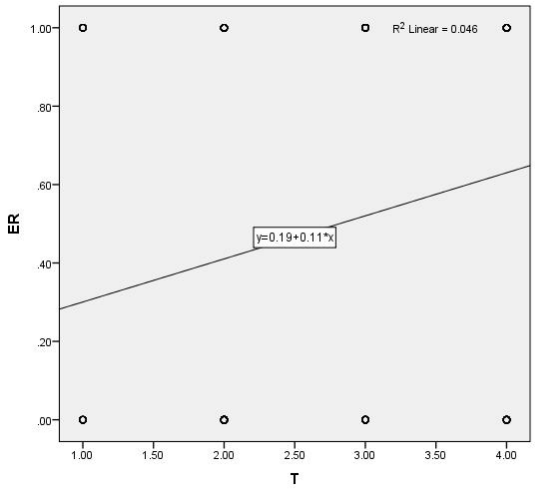
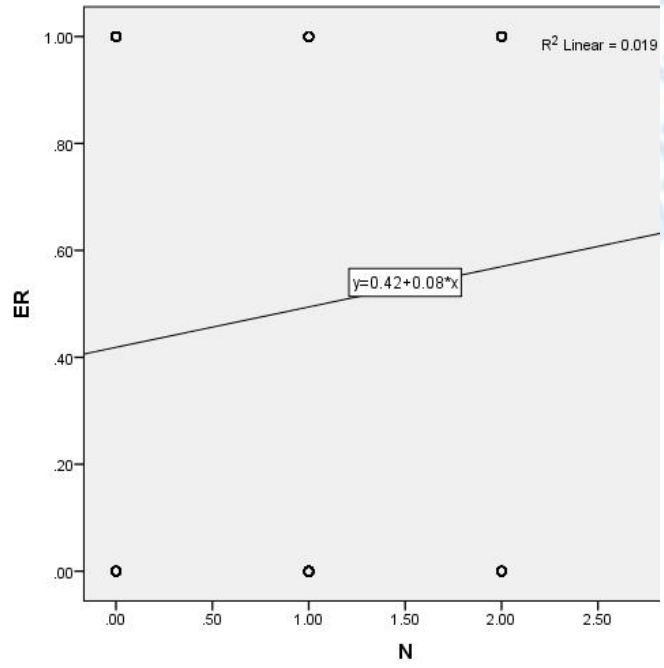
Scatter plot -1 showing a negative effect of T on Creatinine, R^2 showed 1.3% variation in Creatinine was explained by T.

Scatter Plot 2:



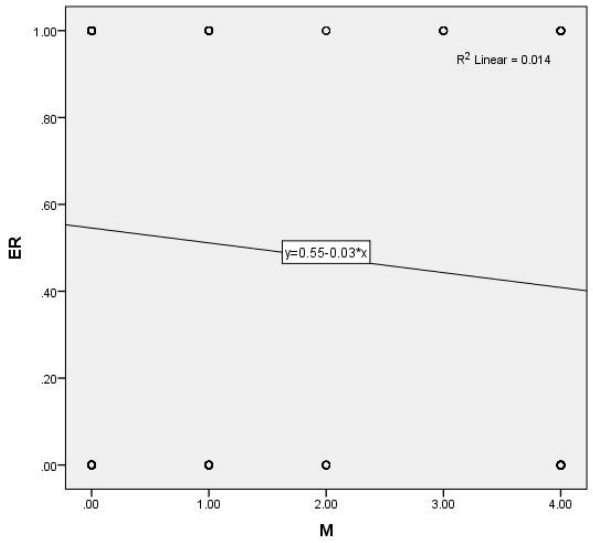
Scatter plot -1 showing a positive effect of T on ER, R^2 showed 4.6% variation in ER was explained by T.

Scatter Plot 3:



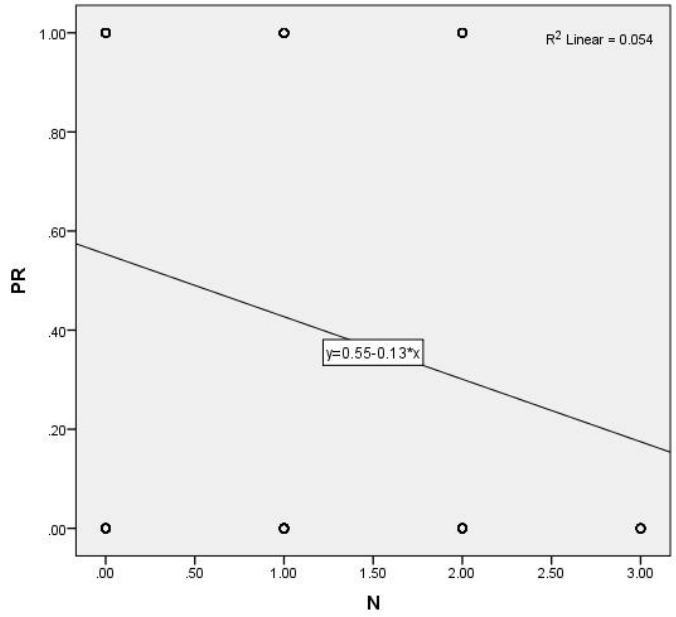
Scatter plot -3 showing a positive effect of N on ER, R^2 showed 1.9% variation in ER was explained by N.

Scatter Plot 4:



Scatter plot -4 showing a positive effect of M on ER, R^2 showed 1.4% variation in ER was explained by M.

Scatter Plot 5:



Scatter plot -5 showing a negative effect of N on PR, R^2 showed 5.4% variation in PR was explained by N.

FIGURE 1: Showing serum levels of creatinine and different stages in breast cancer patients. All serum creatinine values are within normal range in all stages.

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ISSN: (e) 3007-1607 (p) 3007-1593

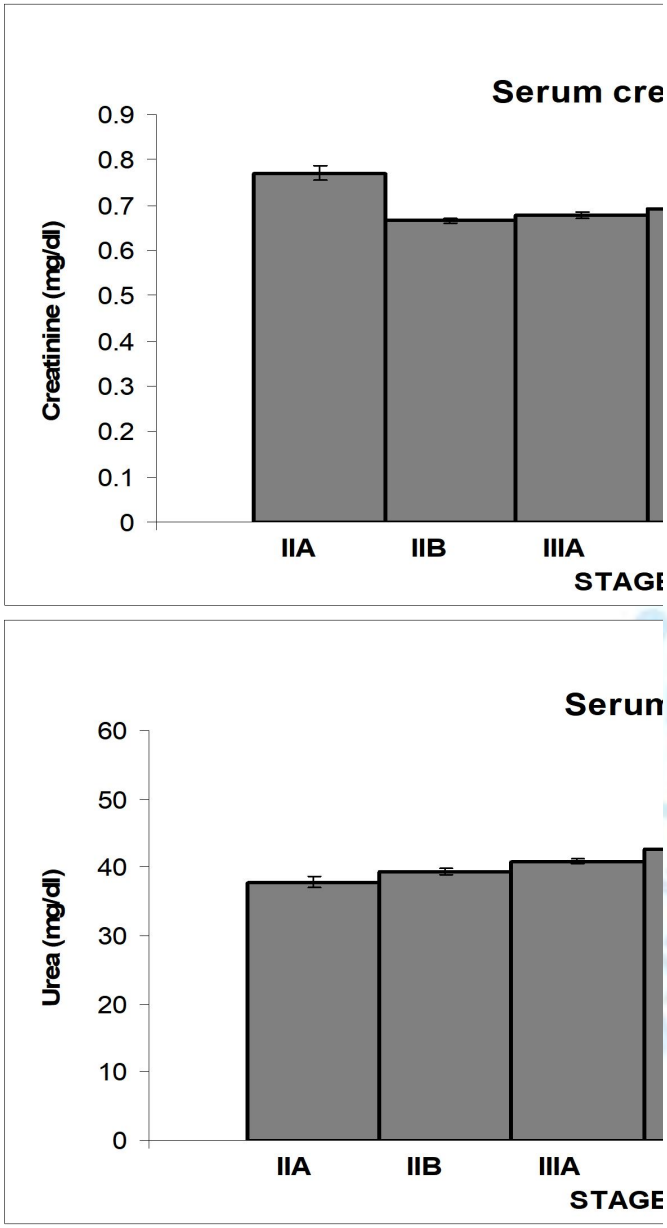

FIGURE 2: Showing serum levels of urea and different stages in breast cancer patients. All serum urea values are within normal range in all stages.

8.4. DISCUSSION

A complex relation is expected between cancer and the renal function. Patients suffer in chronic kidney disease are victims of cancer. Advanced bio-molecular formulas are facilitating the improvement in renal function and a longer disease free survival. Kidney physicians may guide the onco-physician about the selection of therapy specially in renal impairment patients. Physician must be care full when going to prescribe medicine for any complication. A mutual team work between oncologists and nephrologists is optimal for controlled and safer management of cancer patients. [18 19] Onco- nephrology team co-work is mandatory to provide excellent chemotherapy and nephrotic management to the patients. The disribution of CKD was higher in patients with renal (50%), urinary tract (33.6%) and pancreatic cancers (19.6%) lower in patients with colonic cancers (5.3%) and brain tumors (2.5%). At the end of our 2-year survey period, 0, 7% of the CKD cases had an eGFR around 6 ml/min/1.73m^2 –an indication for renal replacement therapy. [20] Estrogen proved as tumor growth factor in estrogen positive cases but not in estrogen receptor negative cases. ER positive breast cancer patients usually show improvement with hormonal therapy and anti-estrogen works efficiently to suppress tumor growth. Literature evidence are required to make it justified that cancers devoid of ER expression should receive hormonal treatment or not. [21 22] Progesterone receptor (PR) is also a hormone receptor biomolecule. PR activation is influence by ER activity. The interaction between PR and chromatin will change the binding position of ER and chromatin and then lead to the change in cell gene regulation from proliferation to cell cycle arrest, apoptosis, and differentiation. When breast cancer cells enter into the blood stream, it is called the circulating tumor cells (CTC). CTC has the property to facilitate translation of more tumor cells . CTC cells presence it - self serve as tumor marker and can provide help to stage and grade patients and select treatment. CTC cells can also helpful in determining the prognosis and decision for postoperative additional radiation therapy. [5 23 24 25 26] Much more new tumor markers are introduced. They have vast property and singnificance in the diagnosis and treatment of breast cancer. These functions include the early detection of breast cancer, the choice of treatment and the targets of targeted therapy [27]

. CONCLUSIONS: As result of study showed no significant effect of T,N and M was observed on serum Urea, creatinine values. Positive ER cases showed higher N values although were significantly less likely to be found with positive PR). Ultrasound

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ISSN: (e) 3007-1607 (p) 3007-1593

findings were negative for metastasis almost in all patients

Ethics approval and consent to participate

Ethical approval for publication of this study was obtained from the Ethics Committee of JPMC. And consent to participate was obtained.

Consent for publication

Informed consent was obtained for publication of this case report.

Conflict of authors: There is no conflict of authors

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