Effect of Chemotherapy on Tumor Marker (Ca 15.3) and Serum in Breast Cancer Patients of Southern Eastern Region of Chhattisgarh; 6 Years Follow up Study

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Abstract

Background: At many centers tumor markers are used to detect disease recurrence and to monitor response to chemotherapy therapy in patients with advanced disease, although the real value of serial observation of marker levels remains disputed. In this study, we evaluated the changes in biochemical and tumor maker (CA 15.3) with respect to Chemotherapy among breast cancer patients.

Aim: The present study was aimed to ascertain the changes in biochemical and tumor maker (CA 15.3) with respect to Chemotherapy among breast cancer patients.

Material & Methods: 40 breast cancer patients and 10 cancer patient other than breast cancer (control subject) from regional cancer center were studied. All the cancer patients were aged between 27 to 56 years old with BSA and BMI ranged between 1.30-1.98 and 13.06-39.51 respectively. Tumor marker CA 15.3 level was done by ELISA, haematological test was measured by cell counter and biochemical assay was measured by Auto analyzer. Tumor size was measured before and after chemotherapy. Patients were followed 6 years. Survival at 6 years is 60%. The data were analyzed using SPSS (20.0).

Results: The result revealed that as compared to control patients the CA 15.3 maker was statistically significantly higher among breast cancer patients in before as well as in after chemotherapy cycles as well as it accessed the normal range of CA 15.3 (9-36 U/ml). Further, results of Chi-square test revealed statistically significant changes in serum parameters after chemotherapy. Glucose, urea, creatinine, bilirubin (total), bilirubin (direct), ALT (Alanine amino transferase), AST (Aspartate amino transferase), ALP (Alkaline phosphatase) and globulin were found to be significantly increase whereas, CA (15.3), WBC, Hb (haemoglobin), platelets, serum serum sodium, serum potassium, total protein and albumin were found to be significantly decreased, after chemotherapy. 83.3% tumour reduction in case group reported. The 6-year overall survival was 51% in the case group. Overall survival in operated group was 49.4 % and non-operated group was 52.1%.

Conclusion: It is concluded that CA (15.3) is specific and sensitive maker for breast cancer. Further, prominent fluctuations in serum parameters due to chemotherapy specify consequent side-effects among breast cancer patients.

Keywords: Chemotherapy, CA (15.3), breast cancer, AST, ALT, ALP, T. Protein

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Introduction

Cancer is a general term that refers to cells that grow and multiply out of control and possibly spread to other parts of the body[1]. There are many different types of breast cancer. Each may have different characteristics, and each one may require a different treatment[2,3]. Cancer is a significant cause of mortality and morbidity throughout the world[4]. Early detection of cancer is essential for best chance of cure[5]. Serum tumour markers (TM) are widely used for cancer diagnosis, evaluation of cancer status, and monitoring treatment[6]. TM is considered as the proteins that ideally indicate the presence of malignancy[7]. This marker can be found in tumour cells, or in normal cells and over expressed in malignant cells[8]. TM is associated with cancer development although slightly higher levels of TM are detected in benign disorders[9]. Breast cancer is a common cancer among women in United states and second only to skin cancer, affecting about 178,480 women in the United States in 2007[10]. Most breast cancer begins in the milk ducts. These ducts connect the milk-producing glands (called lobules) to the nipple. Some breast cancer begins in the lobules themselves, and the rest begins in other tissues. Breast cancer is not just a woman's disease. It is quite possible for men to get breast cancer, although it occurs less frequently in men than in women[11]. Our discussion will focus primarily on breast cancer as it relates to women but it should be noted that much of the information is also applicable for men[12]. CA 15-3 have been applied for monitoring treatment in patients with breast cancer and the relationship between the initial marker levels and the changes of the markers during chemotherapy has been established. ELISA is a quantitative assay based on specific antibody-antigen binding and is commonly used to analyse biomarkers due to its specificity, sensitivity, and simplicity. We had

to determine whether induction chemotherapy could reduce the number of mastectomies for tumours which would otherwise be treated by initial mastectomy because they were too large for conserving surgery[13,14,15]. Moreover, we wanted to verify whether disease-free and overall survivals are as favourable with induction chemotherapy as with classical adjuvant chemotherapy following mastectomy.

Aim

The study was aimed to ascertain the changes in tumor maker (CA 15-3) and biochemical parameters with respect to Chemotherapy among breast cancer patients of south eastern region of Chhattisgarh. To compare the CA 15-3 & biochemical blood parameters before and after Chemotherapy.

Material & Methods

The present study conducted under Department of Biochemistry, Pt. J.N.M. Medical College, Raipur. The study is designed to include 40 patients with breast cancer and 10 other cancer patients. The study has been planned in OPD of Department of Radiotherapy in Dr. B.R. Ambedkar Memorial Hospital, Raipur (C.G.). The case-control study was conducted between October 2009 and February 2015 at the Pt. J.N.M. Medical College, Raipur (Chhattisgarh). It comprised 40 women diagnosed with breast cancer with no malignant pathology by biopsy and 10 other cancer patients' women were enrolled from the outpatient department (OPD) to serve as the control group. Written Informed consent was also obtained from both the cases and the controls. 5ml blood samples were collected in twice in these studies from the cases and controls i.e. prior and after 5th cycles chemotherapy and processed generally within an hour. Separate the serum by centrifugation and stored in multiple tubes at -20°C. Chemotherapy was scheduled every 23rd days interval of the treatment. Random selection of the patients was applied. This study followed some inclusion and exclusion criteria.

The mean age group of case group and control group was respectively 41.83 and 36.2 years. Average BSA of both the groups was respectively 1.69 and 1.59 and BMI was respectively 24.42 and 26.26. Karnofsky Performance Status (PS) was also assessed of both the groups. Socio-demographics, addictive habits and clinical characteristics of case and control group were listed in Table 1. Staging of the disease was performed for them by specialists and followed up for survival of case group as well as control for a period of 1-5 years. Haematological parameters WBC, Hb, Platelets was measured by using Mindray Automated cell counter & biochemical parameters Sodium, Potassium, Glucose, Urea, Creatinine, Total & Direct Bilirubin, ALT, AST, ALP, T. Protein, Albumin, Globulin was measured by using ILab-650 Auto analyzer before and 5th cycle after chemotherapy. Tumor size was also measured by using ultra sonography technique in before and after chemotherapy treatment. Tumor reduction was analysed by arc sine transformation technique. CA 15:3 was investigated in two steps: in pre and post chemotherapy, the validity of the tumour marker was evaluated and its variations were analyzed at two stages of the disease. Serum CA15-3 concentration was determined by CA15-3 Enzyme Immunoassay Kit based on the principle of a solid phase enzyme-linked immunosorbent assay (ELISA), purchased from Bio Check, Inc, 323Vintage Park Drive, Foster City, CA 94404. The CA15-3 conjugate reagents prepared by the entire 1ml of conjugate concentrate to 21ml of the enzyme conjugate diluents. Washing buffer was prepared by adding 50ml of the buffer to 950ml of distilled water. Statistical analysis was performed by SPSS 20. Pearson test was used for the determination of correlation between the measured parameters. One-way analysis of variance (ANOVA) test was used for the determination of relation between different breast cancer and the control group. $P<0.05$ was considered statistically significant.

Observation & Results

In case group we compared tumour size before and after chemotherapy in 40 breast cancer patients and the result reveals 83.3% reduction in tumour size after chemotherapy. (Fig. 1) There have been 12 deaths in the case group in 6 years. The 6-year overall survival was 51% in the case group. Case group showed survival frequency from 1st to 6th years was respectively 98%, 98%, 93%, 83%, 70% and 70% (Fig. 2). In this study 16 patients were operated and rests were non-operated. Overall survival in operated group was 49.4% and non-operated group was 52.1% (Fig. 3). We compared operative and non-operative group from one to six years, it reveals that in 1st year operative group showed 100% survival, in 2nd year again 100%, in 3rd year 94%, in 4th year 75%, in 5th year 63% and in 6th year 63% respectively non-operative group showed 96%, 96%, 92%, 88%, 75% and 75% (Fig. 4).

Table 1: Socio-demographics, addictive habits and clinical characteristics of case and control group

Characteristic	Case	Control
Number (%)	40 (100)	10 (100)
Age, median/ mean (SD) years	45/41.83 (7.45)	40/36.2 (7.94)
BSA, mean (SD) m^2	1.69 (0.16)	1.59 (0.12)
BMI, mean (SD) kg/m^2	24.42 (5.40)	26.26 (6.41)
Marital status *(MS), n* (%)	33 (82.5)	7 (70)
Education (ED), n (%)		
Illiterate	7 (17.5)	3 (30)
Primary	15 (37.5)	00
Middle	9 (22.5)	00
HSSC	6 (15)	7 (70)
Graduate	3 (7.5)	00
Profession (PR), n (%)		
Home wife	16 (40.0)	8 (80)
Worker	7 (17.5)	00
Farmer	6 (15)	00
Student	6 (15)	00
Self employed	5 (12.5)	2 (20)
Alcohol users *(AU), n* (%)	2 (5)	00
Sleeping pill users *(SU), n* (%)	13 (32.5)	7 (70)
Chronotype (CHT), n (%)		
Morning type	22 (55.0)	6 (60)
Intermediate type	11 (27.5)	2 (20)
Evening type	7 (17.5)	2 (20)
Karnofsky Performance Status (PS), n (%)		
100	23 (57.5)	3 (30)
90	17 (42.5)	7 (70)
Background (BG), n (%)		
Rural	25 (62.5)	6 (60)
Urban	15 (37.5)	4 (40)
Family type (FT), n (%)		
Joint	17 (42.5)	2 (20)
Nuclear	23 (57.5)	8 (80)
Source of income (SI), n (%)		
Agriculture	24 (60)	9 (90)
Govt. sector	7 (17.5)	00
Private sector	9 (22.5)	1 (10)
Chemotherapy *(CT), n* (%)	40 (100.0)	10 (100)
Disease progression	5 (12.5)	
Stable disease	2 (5)	
Partial response	9 (22.5)	
Complete response	34 (85)	
Clinical tumor size, length (cm) (%)		
4 ≥	6 (15)	
4.1-6.0	17 (42.5)	
Mean tumor size ± standard deviation	17 (42.5)	

Table 2: Correlation before chemotherapy

		Pearson Correlation (r)	p value
Hb	ALT	.334*	0.035
S. Sodium	S. Potassium	.621**	0
S. Sodium	Creatinine	.323*	0.042
S. Sodium	Albumin	.351*	0.026
S. Potassium	S. Sodium	.621**	0
Creatinine	S. Sodium	.323*	0.042
T. Bilirubin	D. Bilirubin	.461**	0.003
T. Protein	Albumin	.537**	0
Albumin	S. Sodium	.351*	0.026
Albumin	T. Protein	.537**	0
D. Bilirubin	ALP	-.376*	0.017
ALT	S. Sodium	-.424**	0.006
ALP	D. Bilirubin	-.376*	0.017
S. Sodium	D. Bilirubin	-.366*	0.02
S. Sodium	ALT	-.424**	0.006
D. Bilirubin	S. Sodium	-.366*	0.02

Table 3: Correlation after chemotherapy

		Pearson Correlation (r)	p value
Albumin	AST	.517**	0.001
Albumin	ALP	.972**	0
Albumin	Hb	.330*	0.037
ALP	AST	.546**	0
ALP	Albumin	.972**	0
ALP	Hb	.330*	0.038
Urea	Creatinine	.332*	0.036
AST	ALP	.546**	0
AST	Albumin	.517**	0.001
T. Bilirubin	CA 15-3	.317*	0.047
Tumour redu.	Glucose	.373*	0.018
CA 15-3	T. Bilirubin	.317*	0.047
T. Protein	Globulin	.885**	0
Platelets	Hb	.582**	0
Creatinine	Urea	.332*	0.036
Globulin	T. Protein	.885**	0
Glucose	D. Bilirubin	.373*	0.018

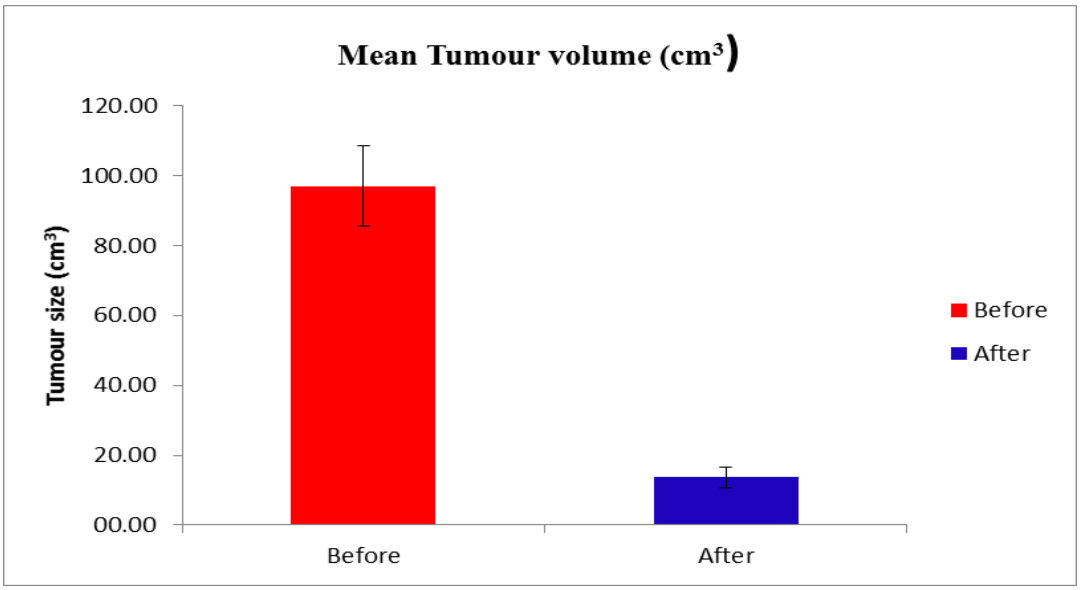

Fig. 1: Tumour reduction (83.3%) before and after chemotherapy

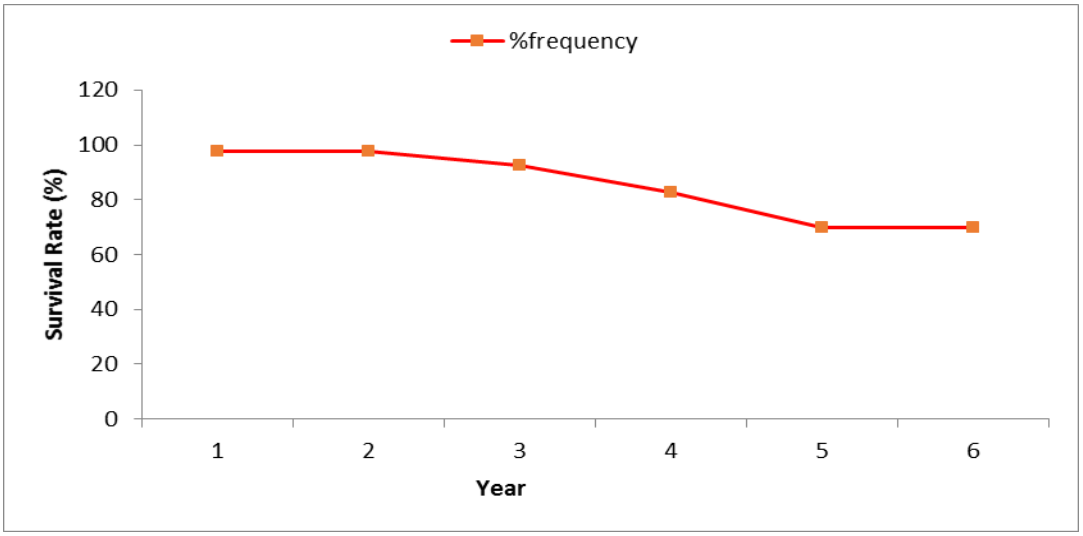

Fig. 2: Overall survival rate of case group (n=40)

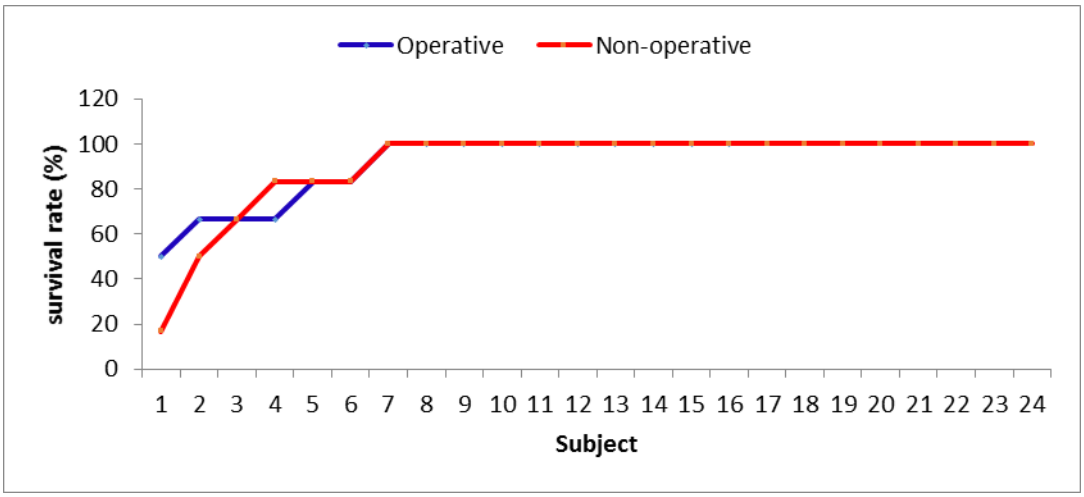

Fig. 3: Comparative survival rates in operated and non-operated group

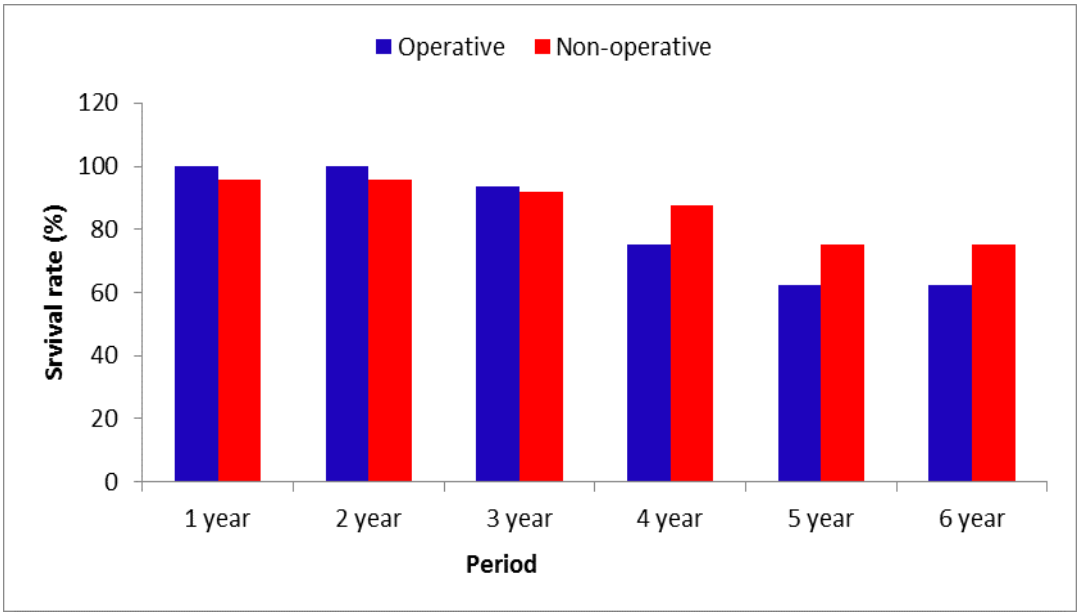

Fig. 4: Year wise comparative survival rate in operative and non-operative group

Discussion

We compared the cancer antigen level pre and post chemotherapy. These values are increased or decreased in some cases. These levels are the parameter for primary diagnosis. The power of CA 15.3 to predict survival was compared to established prognostic markers, namely stage, grade, receptor status, and histological subtype. CA 15.3 was abnormal (≥300U/ml) in some patients [16]. Out of 40, 10 patients were post-operative and they suffered with same problem that is the pain over the operated sites. In 6 patients the serum marker values were decreased after treatment [17]. Out of only one male patient and 3 were post-operative patients. These results indicate that CA 15.3 can predict survival in primary breast cancer. A significant relationship was found between disease response and CA 15.3 variations, although many individual discrepancies were also observed. We can monitor serum CA 15.3 levels during first-line chemotherapy in advanced breast cancer patients provides prognostic information independently from tumour response[18]. Breast cancer is the leading type of cancer in women[19]. It is commonly accepted that the earlier the detection of the disease, the better the prognosis[20]. Therefore the present study is undertaken to evaluate the clinical significance of tumour marker CA 15.3[21]. Our study confirms that serum CA 15.3 measurements are hardly valuable for screening of breast cancer[22]. However high values have diagnostic significance. In conclusion, monitoring serum CA 15.3 levels during first-line chemotherapy or in advanced breast cancer patients provides prognostic information independently from tumour response.

Conclusion

CA 15:3 is a good tumour marker because only one control in 100 had an abnormal CA 15:3 levels. Various authors have set the significant threshold value between 30 and 50Uml-1 to avoid overestimation due to false positives. In breast cancer follow-up, the main problem is detection of local recurrence or distant metastasis; as false negatives must be avoided in these cases, we recommend a threshold value of 25Uml-1. (Value of CA 15:3 in the follow-up of breast cancer patients.

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Conflicts of Interest

None of the funding source influenced the study design, collection, analysis, interpretation of data, and decision to submit the manuscript. We state that we have had full access to all the data in the study and that we agree to allow the journal to review our data if requested.

Authors' Contributions

Priyanka Chandel supervised the data collection, analysed the data and write this paper. Harish Uraon contributes in designing and in statistical interpretation. Prof. Dr. Vivek Choudhary contributes in literature review, editing and paper writing.

References

1. Liang, QL., Shi, HZ., Qin, XJ., Liang, XD., Jiang, J., Yang, HB., (2008). Diagnostic accuracy of tumour markers for malignant pleural effusion: a meta-analysis. *Thorax. Jan.,* 63(1):35-41.
2. Abe, H., Naitoh, H., Kodama, M., Umeda, T., Shiomi, H., Okabe, H., (2000). Occult Breast Cancer Presenting Axillary Nodal Metastasis: A Case Report. *Jpn. J. Clin. Oncol.,* 30 (4):185-187. doi: 10.1093/jjco/hyd047.
3. Bartsch, R., Wenzel, C., Pluschnig, A., S., Hussian, D., Sevelda, U., Altorjai, G., Locker, GJ., Mader, R., Zielinski, CC., Stege, GG., (2006). Prognostic value of monitoring tumour markers CA 15-3 and CEA during fulvestra treatment. *BMC Cancer*, 6:81 doi:10.1186/1471-2407-6-81.
4. Michael J. Duffy., Nicolini, A., Carpi, A., Tarro, G., (2006). Serum Tumor Markers in Breast Cancer: Are Biomolecular markers of breast cancer. *Biosci.,*11:1818-43.
5. Klee, GG., Schreiber, WE., (2004). MUC1 gene-derived glycoprotein assays for monitoring breast cancer (CA 15-3, CA 27.29, BR): are they measuring the same antigen?. *Arch Pathol Lab Med*.,128(10):1131-5.
6. Gülsen, Y., Fatma, MY., Mehmet, S., Dogan, Y., (2007). Tumor marker requests in a general teaching teaching turkish hospital. *Indian Journal of Clinical Biochemistry*, 22(1):52-56.
7. Lamerz, R., Stieber, P., Fateh-Moghadam, A., (1993). Serum marker combinations in human breast cancer (review). *In Vivo.,* 7(6B):607-13.
8. Kumpulainen, EJ., Keskikuru, RJ., Johansson, RT., (2002). Serum tumor marker CA 15.3 and stage are the two most powerful predictors of survival in primary breast cancer. *Breast Cancer Res Treat*., 76(2):95-102.
9. Hamid, UM., Royle, L., Saldova, R., Radcliffe, CM., Harvey, DJ., Storr, SJ., Pardo, M., Antrobus, R., Chapman, CJ., Zitzmann, N., Robertson, JF., Dwek, RA., Rudd, PM. (2008). A strategy to reveal potential glycan markers from serum glycoproteins associated with breast cancer progression. *Glycobiology*, 18(12):1105-18. doi: 10.1093/glycob/cwn095.
10. Berent, R., Auer, J., Porodko, M., Lamm, G., Weber, T., Wimmer, E., Seier, J., Aspöck, G., Eber, B., (2006). Influence of cardiopulmonary resuscitation on levels of tumour markers. *Eur J Cancer Care (Engl)*, 15(3):252-6.
11. Keshaviah, A., Dellapasqua, S., Rotmensz, N., Lindtner, J., Crivellari, D., Collins, J., Colleoni, M., Thürlimann, B., Mendiola, C., Aebi, S., Price, KN., Pagani, O., Simoncini, E., Castiglione GM., Gelber, RD., Coates, AS., Goldhirsch, A., (2007). CA15-3 and alkaline phosphatase as predictors for breast cancer recurrence: a combined analysis of seven International Breast Cancer Study Group trials. *Ann Oncol.* 18(4):701-8.
12. Gion, M., Mione, R., Leon, AE., Dittadi, R. (1999). Comparison of the diagnostic accuracy of CA27.29 and CA15.3 in primary breast cancer. *Clin Chem*, 45(5):630-7.
13. Stearns, V., Yamauchi, H., Hayes, DF., (1998). Circulating tumor markers in breast cancer: accepted utilities and novel prospects. *Breast Cancer Res Treat.*, 52(1-3):239-59.
14. Berberoglu, U., Ceyhan, B., Erçakmak, N., Sezerdogdu, V. (1989). The value of new tumour marker CA 15-3 in diagnosis and monitoring of patients with breast cancer. *J Islamic Academy Sci.,* 6:81.
15. Bon, GG., Von Mensdorff-Pouilly S, Kenemans, P., van Kamp GJ., Verstraeten, RA., Hilgers, J., Meijer, S., Vermorken, JB., (1997). Clinical and technical evaluation of ACS BR serum assay of MUC1 genederived glycoprotein in breast cancer, and comparison with CA 15-3 assays. *Clin Chem*, 43(4):585-93.
16. Cohen, A., D., Cohen, Y., Maislos, M., Buskila, D., (200). Prolactin serum level in patients with breast cancer. *Isr Med Assoc J.* 2(4):287-9.
17. De La Lande, B., Hacene, K., Floiras, JL., Alatrakchi, N., Pichon, MF., (2002). Prognostic value of CA 15.3 kinetics for metastatic breast cancer. *Int J Biol Markers*. 17(4):231-8.
18. Pathak, KA., Khanna, R., Khanna, HD., Khanna, S., Gupta, S., Khanna, NN., (1996). Carcinoembryonic antigen: an invaluable marker for advanced breast cancer. *J Postgrad Med*., 42(3):68-71.
19. Pectasides, D., Pavlidis N, Gogou L, Antoniou F, Nicolaides C, Tsikalakis D., (1996). Clinical value of CA 15-3, mucin-like carcinoma-associated antigen, tumor polypeptide antigen, and carcinoembryonic antigen in monitoring early breast cancer patients. *Am J Clin Oncol.*, 19(5):459-64.
20. Stearns, V., Yamauchi, H., Hayes, DF., (1998). Circulating tumor markers in breast cancer: accepted utilities and novel prospects. Breast Cancer Res Treat., 52(1-3):239-59.
21. Sobin, LH., Gospodarowicz, MK., Wittekind, C., (2009). TNM Classification of Malignant Sölétormos, G., Hyltoft PP., Dombernowsky, P., (2000). Progression criteria for cancer antigen 15.3 and carcinoembryonic antigen in metastatic breast cancer compared by computer simulation of marker data. *Clin Chem.* 46(7):939-49.
22. Park, BW., Oh, JW., Kim, JH., Park, SH., Kim, KS., Kim, JH., Lee, KS., (2008). Preoperative CA 15-3 and CEA serum levels as predictor for breast cancer outcomes. *Ann Oncol.* 19(4):675-81.