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Clinical utility of serum CA15-3 in patients with breast cancer: A systematic review

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Abstract
Breast cancers often produce tumor marker CA15.3 which can be estimated through immunoassays available commercially. So, the aim of this study is to asses the clinical utility of this tumor marker test for daily practice. The utility of measuring CA15-3 levels for breast cancer patients remains controversial. The ASCO and the NCCN guidelines do not currently recommend the use of serum CA15-3 for breast cancer screening and directing treatment post-operative surveillance Metastatic disease (ASCO, NCCN, EGTM, ESMO) and monitoring treatment response. There were limitations to utility in clinical practice. Further prospective studies will be essential for the validation of these results in our own clinical setting.

Keywords: CA15.3, ASCO, NCCN, ESMO, MUC-1

Introduction
Carcinoma of the breast is the most prevalent form of cancer in women. These tumors often produce mucinous antigen, which is large molecular weight glycoprotein with O-linked oligosaccharide chains. Tumor-associated antigen encoded by the human *MUC-1* gene are known by CA 15-3. Estimation of CA15.3 done by Automated Immunoassay (CLIA, CMIA) and this was Noninvasive, Inexpensive. Normal reference values are < 30U/mL.

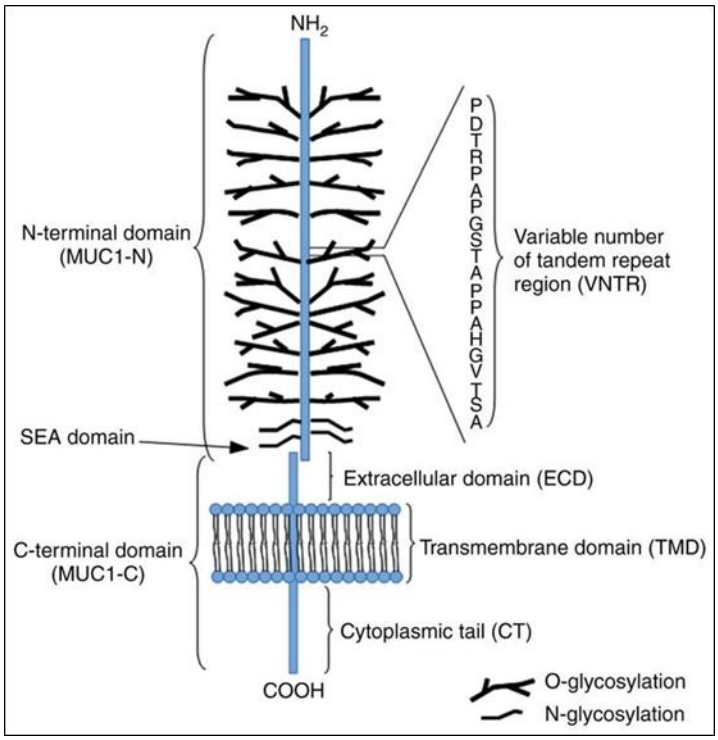

Fig 1: Structure of MUC1

Mucin -1 antigen contains cytoplasmic carboxy terminal and extra cellular N terminal domain. Extra cellular domain combines with oligosaccharide through glycosylation. Mutation in the extracellular domain leads to aberrant and over expressed mucin antigen and secreted into the blood. MUC1 interacts with several oncogenic pathways like NF-Kb and inhibit apoptosis.

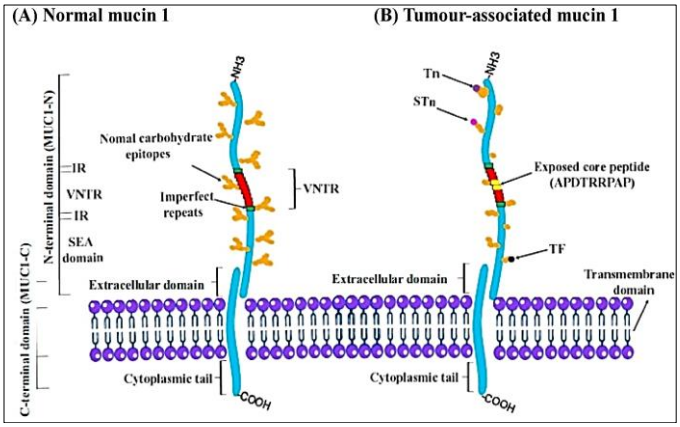

Fig 2: Abnormal mutated mucin -1 antigen

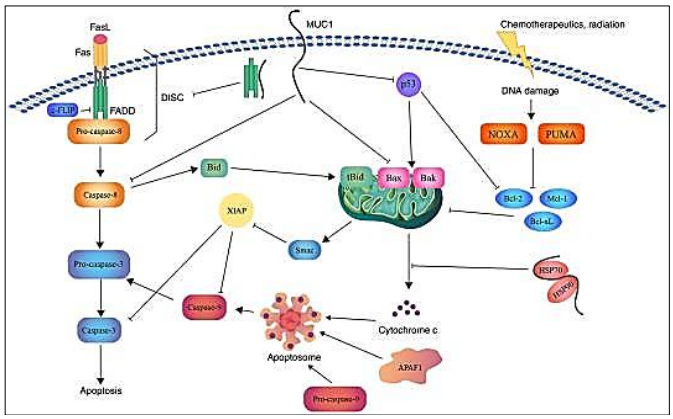

Fig 3: Schematic representation of the role of MUC1 in apoptosis.

Discussion

The utility of measuring CA15-3 levels for breast cancer patients remains controversial. The ASCO and the NCCN guidelines do not currently recommend the use of serum CA15-3 for breast cancer screening and directing treatment. In contrast to the ASCO Panel, both the NACB and EGTM Panels recommended use of CA 15-3 for monitoring therapy in patients with advanced breast cancer. The FDA has approved both CA 15-3 and CA 27.29 for monitoring therapy of advanced or recurrent breast cancer. The potential uses of CA15.3 in breast cancer include aiding diagnosis of metastatic disease and determining prognosis, predicting response or resistance to specific therapies, surveillance after primary surgery for recurrence monitoring therapy in patients with advanced disease.CA 15-3 concentrations are increased in 10% of patients with stage I disease, 20% with stage II disease, 40% with stage III disease, 75% with stage IV disease. According to ASCO Expert Panel, a CA 15-3 concentration 5- to10-fold above the upper limit of the reference interval could alert a physician to the presence of metastatic disease.

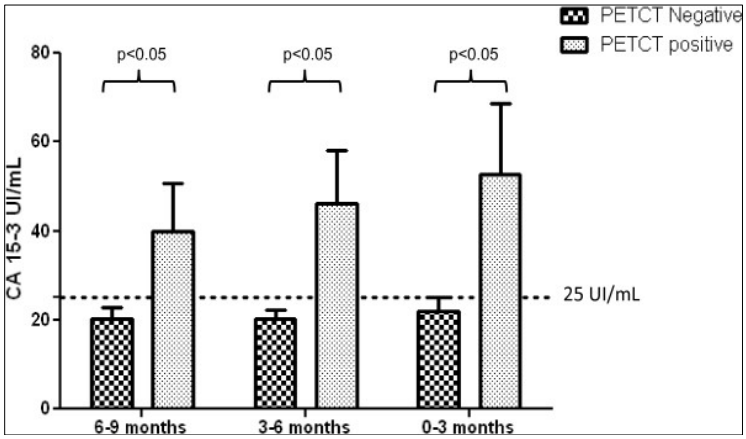

Fig 4: Relation between CA15-3 and PETCT (BMC Cancer. 2014; 14: 356)

Elevated levels of tumor marker CA 15-3 are strongly correlated with positive bone scan. Bone scan is highly sensitive to detect bone metastasis but need assistance of chemical biomarkers. CA 15-3 as a tumor marker proved a help full determinant of tumor burden in metastatic breast cancer. Its significance is more to detect bone metastasis than to pulmonary and then to liver metastasis. Study shows that CA 15-3 is both an independent prognostic factor and prognostic in different subgroups of patients with breast cancer.

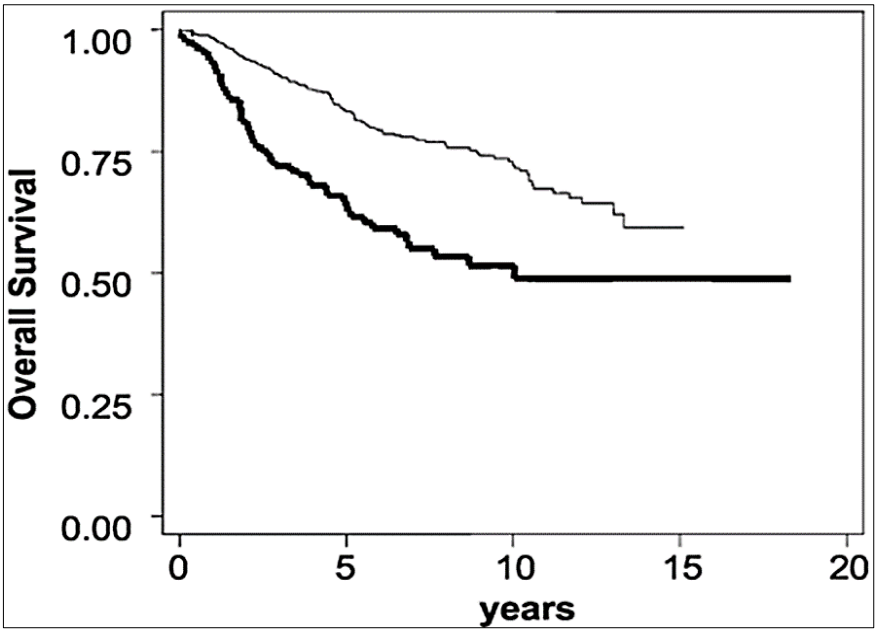

Fig 5: Overall survival according to serum CA 15-3 concentrations in 600 patients with breast cancer. (Clin Chem, Volume 50, Issue 3, 1 March 2004, Pages 559–563)

High Preoperative CA 15-3 Concentrations Predict Adverse Outcome in Node-Negative and Node-Positive Breast Cancer: Study of 600 Patients with Histologically Confirmed Breast Cancer. *Thin line*, CA 15-3 ≤30 units/L (n = 489); *thick line*, CA 15-3 >30 units/L (n = 111). HR = 2.16 (CI, 1.55–3.03); *P* <0.0001.

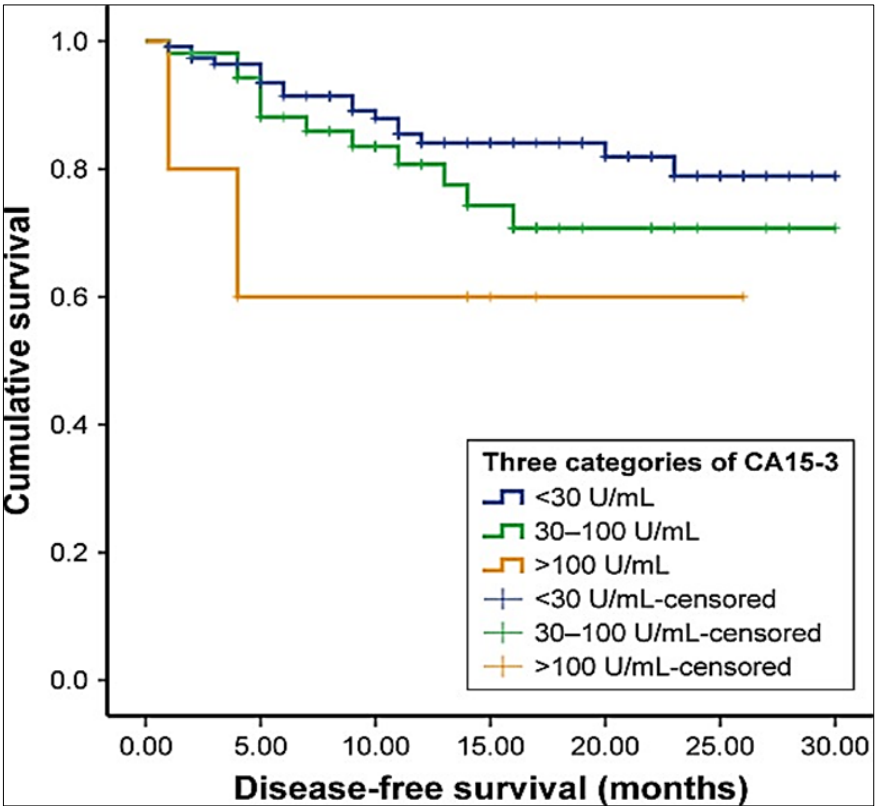

Fig 6: Elevated pre-surgical CA15-3 and disease-free survival (Elevated pre-surgical CA15-3: Int J Women's Health. 2018)

Despite poor prognosis associated with an initially high value, scientific societies have not yet recommended its determination in the initial evaluation as regards the extent of disease. At least 10 published studies involving 4000

patients have addressed the relationship between preoperative concentrations of CA 15-3 (cutoff-30IU/L) and patient outcome, all of the identified studies apart from one concluded that high concentrations of the marker at initial presentation predicted adverse patient outcome. Although most studies relating CA 15.3 to prognosis have used preoperative values, concentrations during follow-up can also provide prognostic information. Reported that patients with CA15.3 values 30 IU/L at the time of first recurrence survived significantly longer than those with higher concentrations.

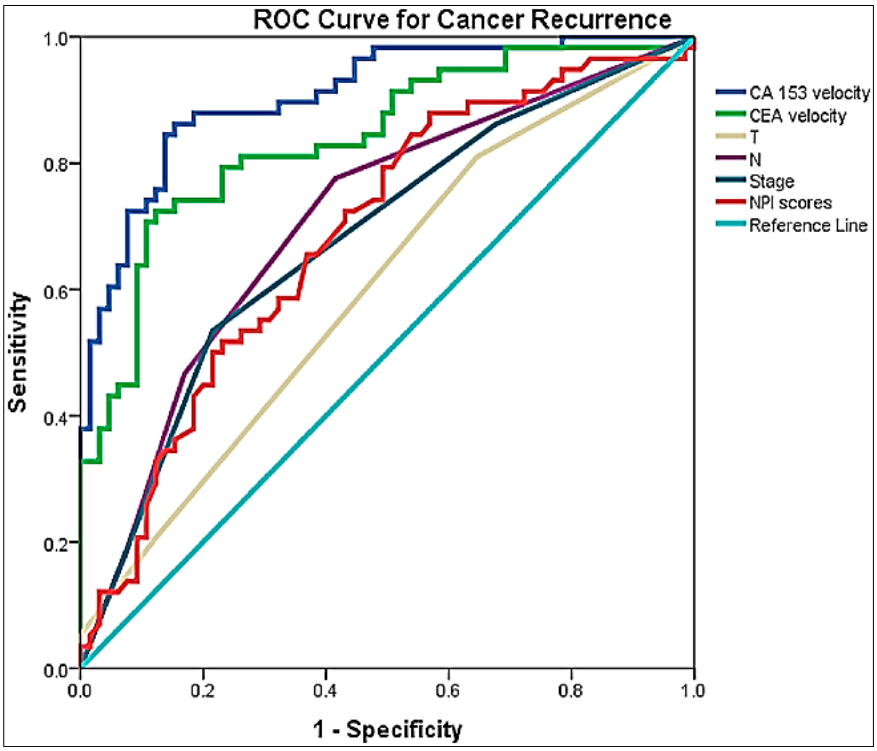

Fig 7: Receiver operator characteristics curve (0.84) for CA 15–3 tumor marker velocity exceeding threshold value of2.5U/mL/year respectively against tumor status, nodal status, TNM staging and NPI scores. (J. Breast_2020 Aug; 52: 95–101)

CA 15-3 and other MUC-1–related markers may also have a role in predicting response to therapy (Ren *et al*.). This resistance appeared to result from the ability of MUC-1 to inhibit apoptosis. Clearly, studies should now be carried out to determine whether either tumor tissue or serum concentrations of MUC-1–related markers predict response/resistance in patients undergoing treatment with platinum-based therapies. The combination of increased serum HER-2/neu and increased serum CA 15-3 predicts a worse prognosis than does increased CA 15-3 alone. In multivariate analysis, increased serum CA 15-3 and increased serum HER-2/neu were both independently associated with a shorter survival. According to the EGTM Panel, marker should be measured before every chemotherapy course and at 3-month intervals for patients receiving hormone therapy. This Panel defined a clinically significant increase in marker concentration as an increase of at least 25% over the previous value. This increased concentration should be confirmed with a second sample taken within 1 month.

Conclusion

The Panel also stated that a confirmed decrease in marker concentration of 50% was consistent with tumor regression. The CA 15-3 marker is often false-positive in benign conditions like chronic hepatitis, liver cirrhosis, tuberculosis, sarcoidosis, systemic lupus erythematosus, hypothyroidism and megaloblastic anemia, and may be elevated in other malignancies, e.g., lung, ovarian, endometrial, gastrointestinal and bladder carcinomas (Seregni *et al*. 2004, Duffy 2006) [5]. Currently available breast cancer biomarkers in the circulation, such as CA15–3 and the associated antigen CA27.29, which recognize different epitopes on the same antigen (Mucin 1) such as a 30% sensitivity for early-stage disease, 60%–70% sensitivity in advanced cases.

These biomarkers do not have a place in early-disease diagnosis or in population screening. Primary disease (EGTM) prognostic post-operative surveillance Metastatic disease (ASCO, NCCN, EGTM, ESMO) monitoring treatment response. There were limitations to utility in clinical practice. Further prospective studies will be essential for the validation of these results in our own clinical setting. In the future, more studies with uniform cut-off values, large-scale data, and good designs are needed to validate utility of serum CA15.3 for detecting, monitoring the prognosis and recurrence breast cancer along with other pathological and radiological parameters.

Abbreviations

ASCO - American Society of Clinical Oncology
NCCN -National Comprehensive Cancer Network
ESMO -European Society for Medical Oncology

Conflict of Interest: No conflict of interest

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