Evaluation of the Significance of CA-125 Levels in Patients of Epithelial Ovarian Cancer in Bihar, India



Dr. Ranjit Kumar

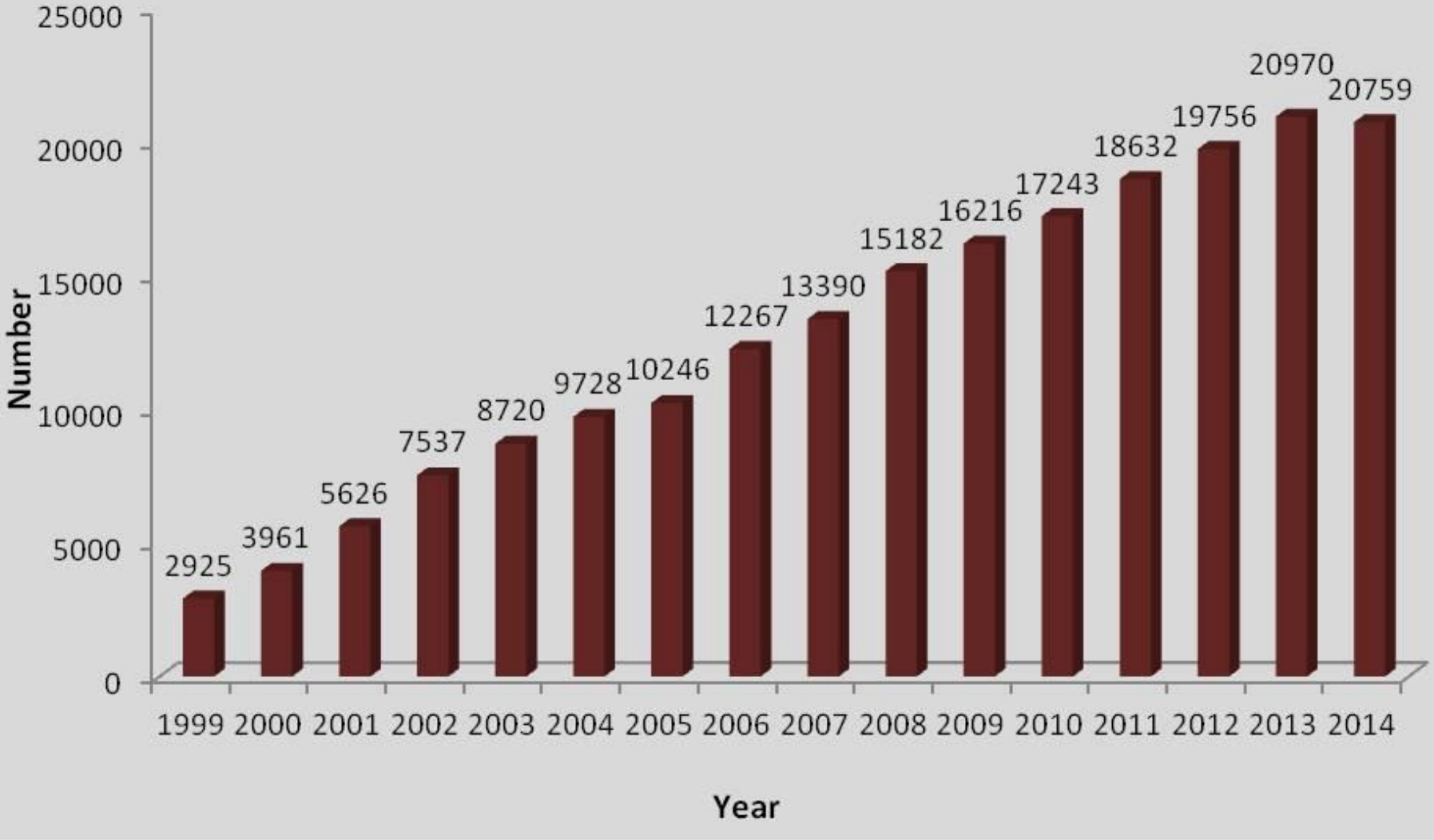
Scientist - I

Mahavir Cancer Sansthan

Patna, India

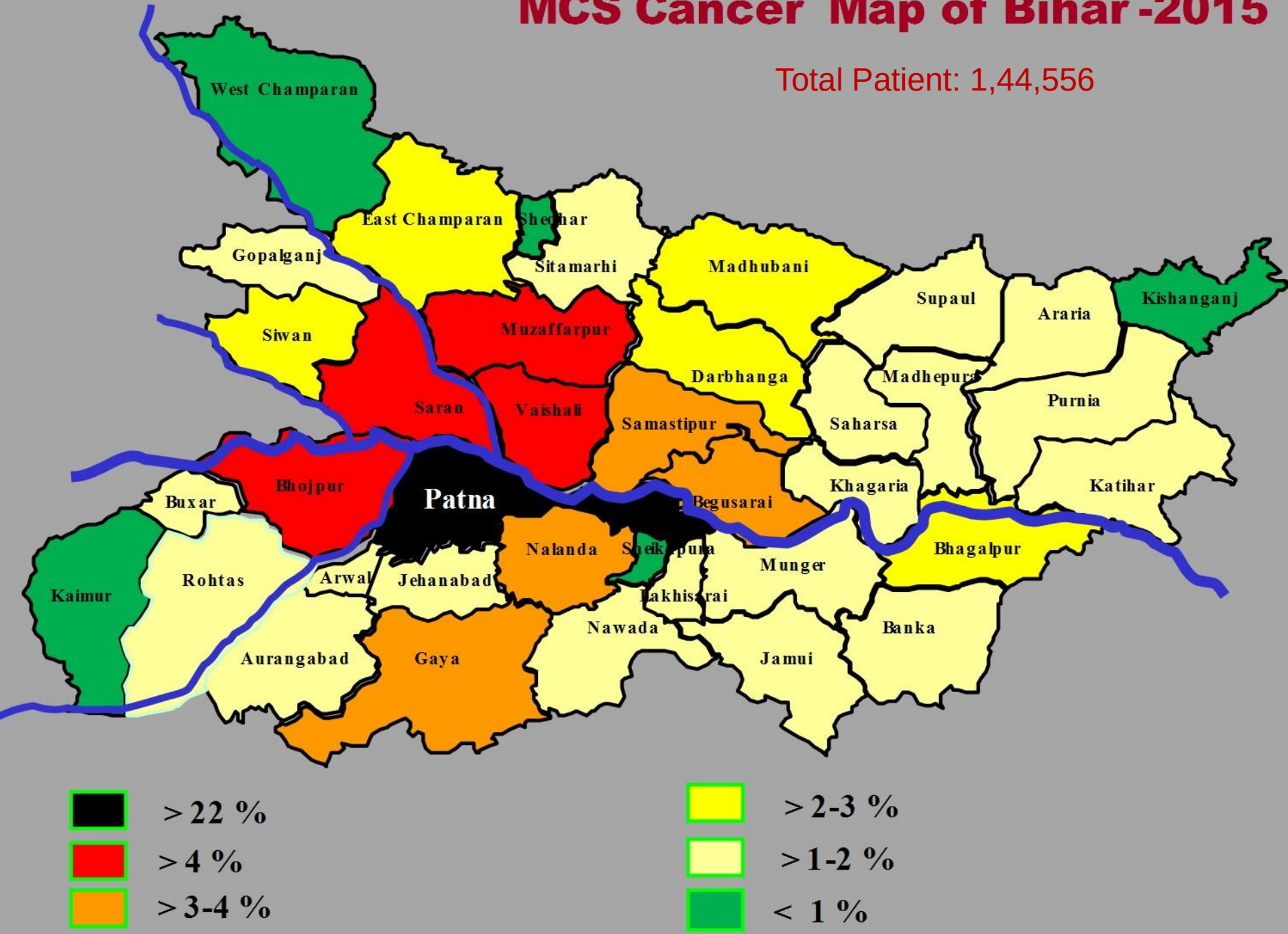
MAHAVIR
CANCER SANSTHAN

Number of New Patients at Mahavir Cancer Sansthan



MCS Cancer Map of Bihar -2015

Total Patient: 1,44,556



Ovarian Cancer Epidemiology

- 9th most common cancer among women
  - 21,880 (3%)
- 5th most common cause of cancer death
  - 13,850 (5%)
- Leading malignancies among women: Breast, Lung, Colon, cervix, gall bladder etc.

Jemal. Cancer Statistics 2010

Epithelial Ovarian Cancer (EOC)

- Most common type of ovarian cancer
  - Epithelial (75%)
  - Germ cell (15-20%)
  - Sex-cord Stromal (5%)
- Median age of presentation 65 years
- Overall lifetime risk is 1 in 70
- 75-80% of patients are diagnosed with Stage III or IV disease

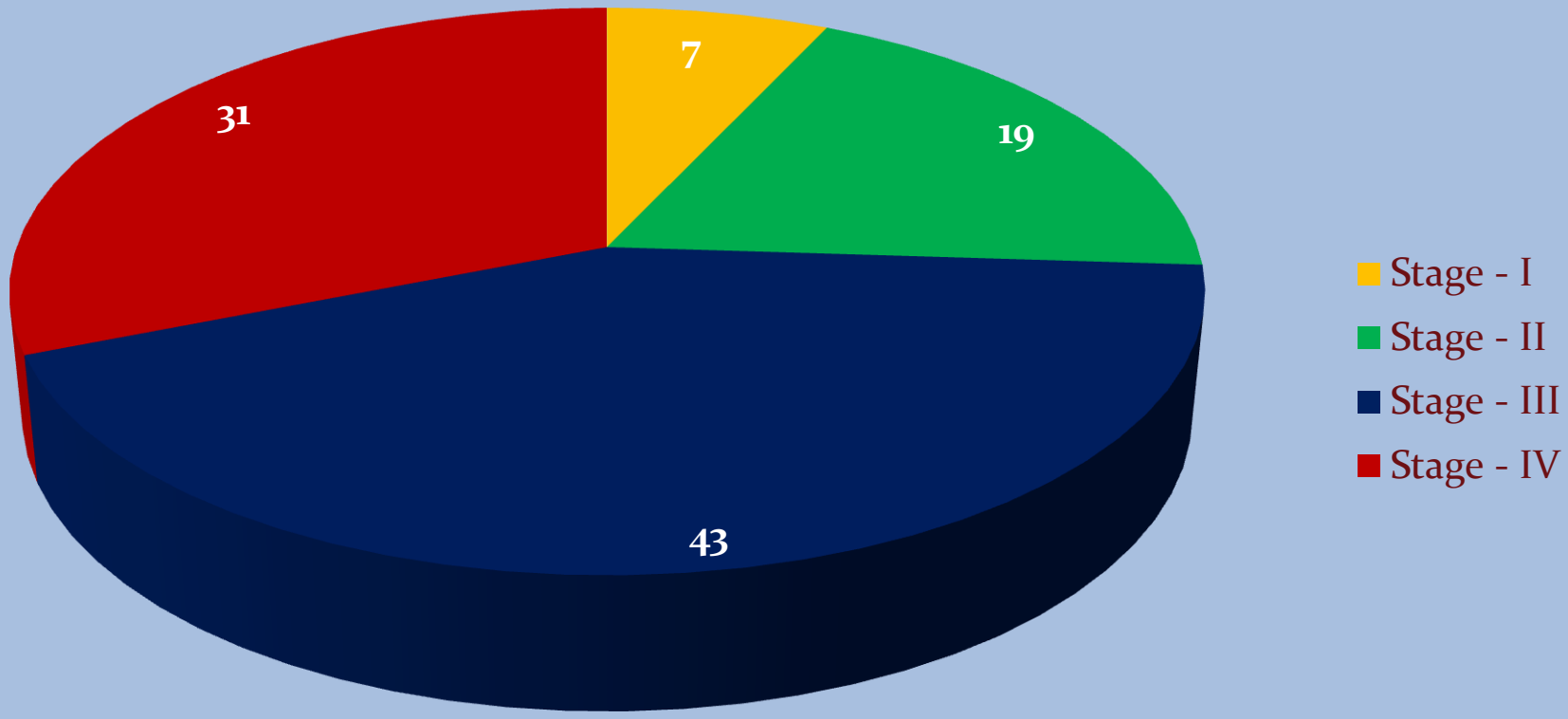
Clinical Tests

- Ultrasound
  - Size
  - Consistency- solid, cystic, mixed
  - Septations
  - Papillary excrescences
  - Pelvic fluid
- Color Doppler
- Other Imaging Modalities
  - CT scan should be used to evaluate for metastatic lesions
- Serum Markers
  - CA125

Screening for Ovarian Cancer

- *There is **no evidence*** that screening for Ovarian Cancer leads to earlier detection or improved survival…
- Commonly the following *have been* or *are being used for EOC* screening
  - TVS
  - CA125
  - Multimodal
  - Symptoms
  - Biomarkers

Stages of Ovarian Cancer Patient at MCS



Screening (CA125/MUC-16)

- Tumor associated antigen
  - Not expressed in mucinous tumors
  - Normal value in 50-70% of stage I tumors and 20-25% of advanced tumors
- Associated with a variety of common, benign conditions including: endometriosis, fibroids, PID, adenomyosis, pregnancy and possibly menstruation
- Better predictive value in postmenopausal patients
- *Abnormal*
  - >35 u/ml: postmenopausal
  - >100 u/ml: premenopausal

CA 125 FOR EARLY DETECTION OF OVARIAN CANCER

- Elevated 10-60 Months Prior to Diagnosis
- Detects 50 - 60% of Stage I Disease
- Specificity of a Single Determination is 99%, but This is Still Inadequate
- Combination with Ultrasonography can increase Specificity

CA-125/MUC 16

- The cancer antigen (CA) -125 is a high molecular mass glycoprotein produced both by ovarian cancer cells as also by normal cells of tissues derived from coelomic epithelium.

- Serum CA-125 levels are used as a marker of tumor activity in patients known to have ovarian carcinoma1 and commercial tests for serum CA-125 have been available since 1983.

- In women with histologically proven ovarian carcinoma, levels of serum CA-125 are elevated >35 U/ml in more than 80 per cent of cases.

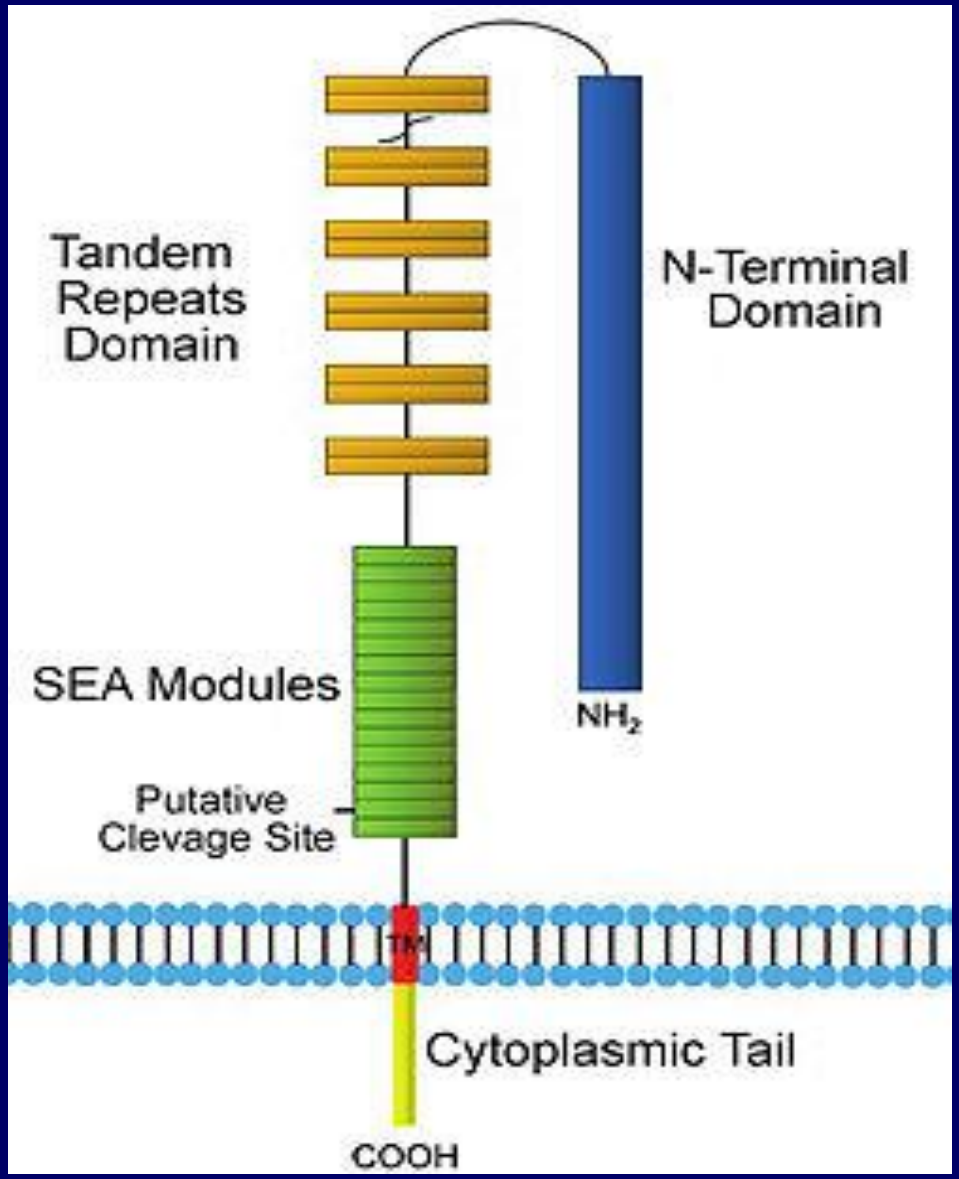
Structure of CA-125/Mucin 16

- Mucin 16 is a membrane associated mucin that possesses a single transmembrane domain.
- A unique property of MUC16 is its large size.
- MUC16 contains about 22,000 Amino acid , making it the largest membrane associated mucin.
- MUC16 is composed of three different domains:
- An N-terminal domain
- A Tandem repeat domain
- A C-terminal domain

Structure of CA-125/Mucin 16 contd…..

- The N-terminal and tandem repeat domains are both entirely extracellular and highly O-Glycosylated.
- All mucins contain a tandem repeat domain that has repeating amino acid sequences high in serine, threonine and proline.
- The C-terminal domain contains multiple extracellular SEA (sea urchin sperm protein, enterokinase, and agrin) modules,a transmembrane domain, and a Cytoplasmic tail.
- The extracellular region of MUC16 can be released from the cell surface by undergoing Proteolytic cleavage.
- MUC16 is thought to be cleaved at a site in the SEA modules.

Mucin 16 (CA-125), cell surface association

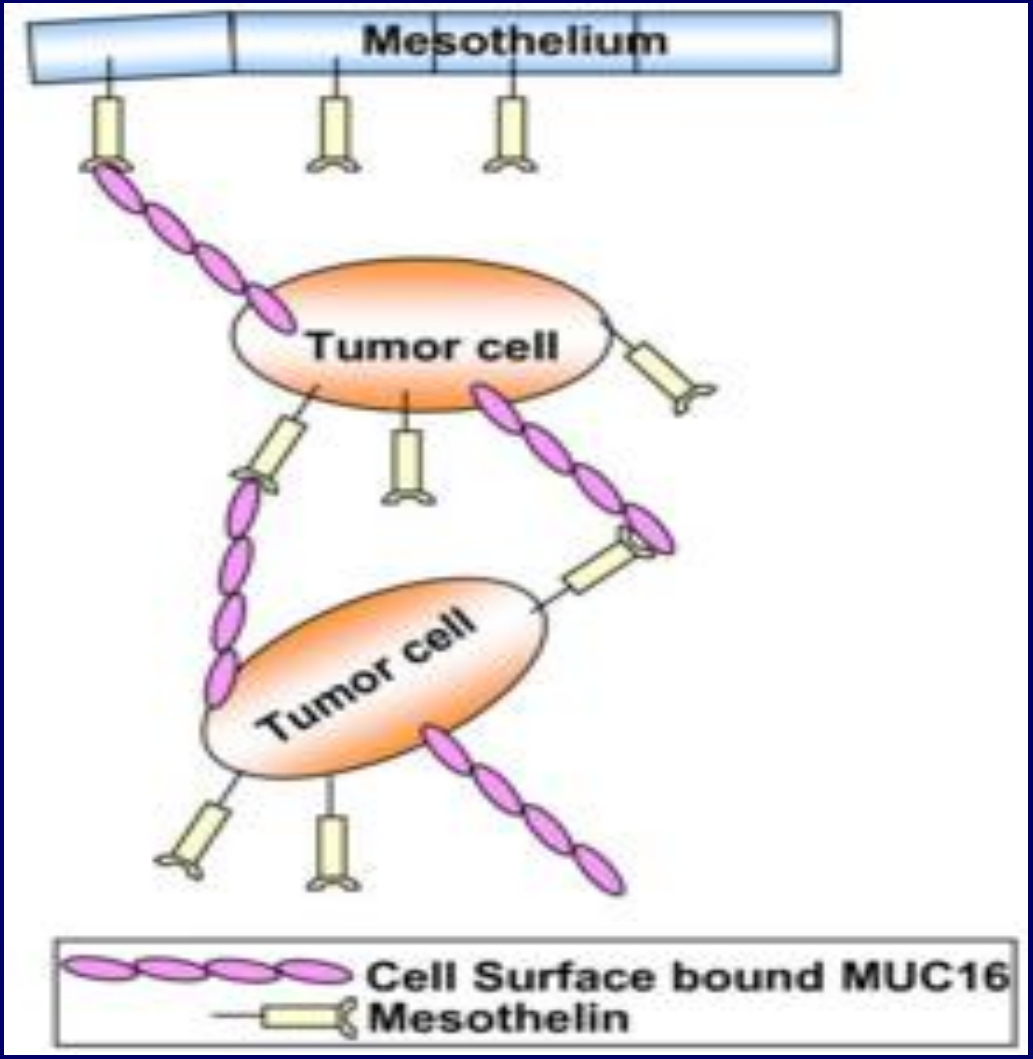


Immune system evasion

- One way that MUC16 helps the growth of tumors is by suppressing the response of Natural Killar cells, which protects the cancer cells from the immune response.

- MUC16 can protect tumor cells from the immune system is the discovery that the heavily glycosylated tendem repeat domain of MUC16 can bind to galectin-1 (an immunosuppressive protein).

Tumor metastasis initiated by interactions between MUC16 and mesothelin



This study is designed to finds out significance of CA-125 for ovarian cancer patients residing near rivers.

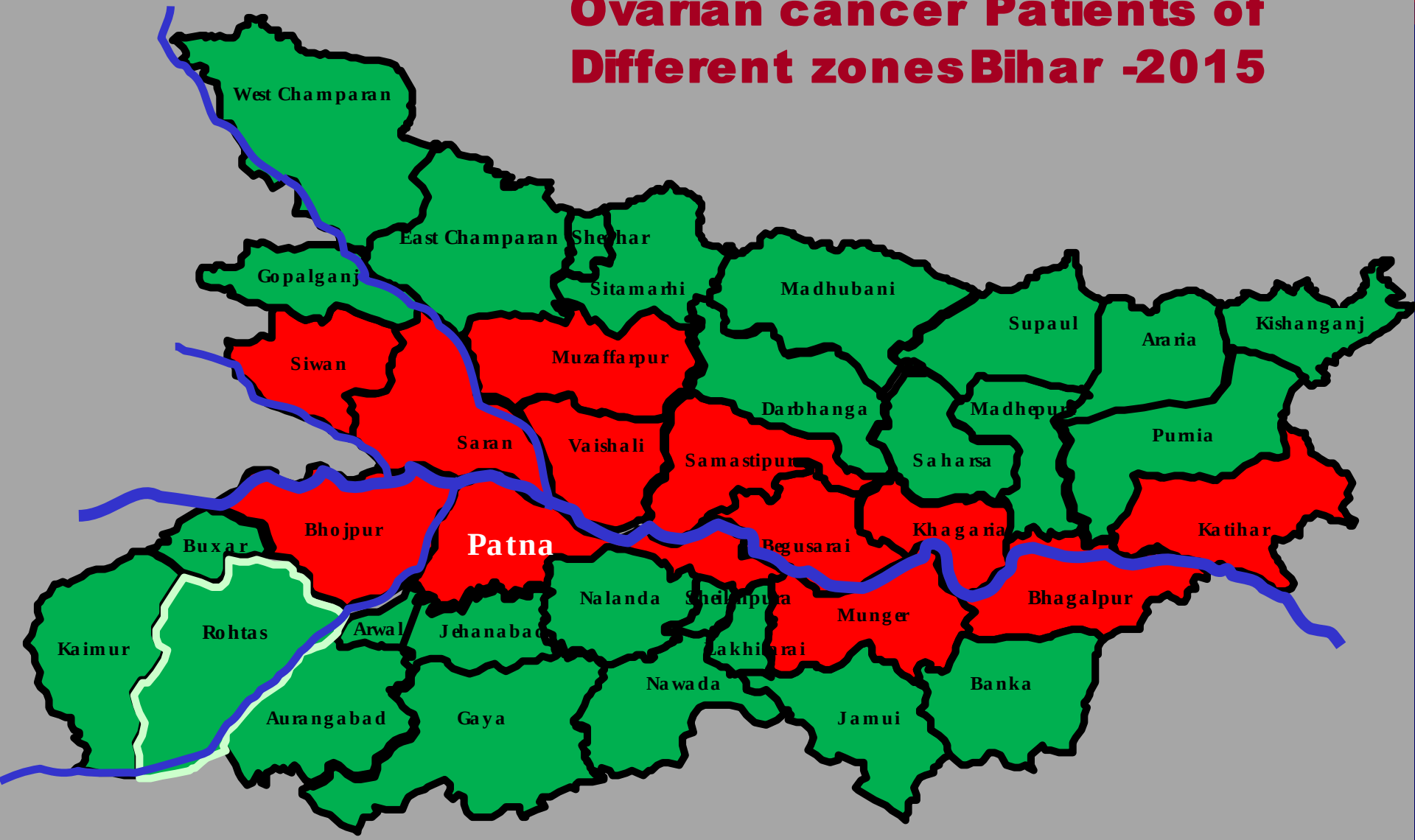
Materials and Methods

- The medical records of 80 patients treated at the Mahavir Cancer Institute and research Centre for ovarian cancer between 2005 and 2007 with preoperative serum CA 125 levels were reviewed.

- Only patients with epithelial ovarian cancer were included in this study.

- Patients were evaluated for their preoperative CA 125 level, age, histology, grade, International Federation of Gynecologists and Obstetricians (FIGO) stage.

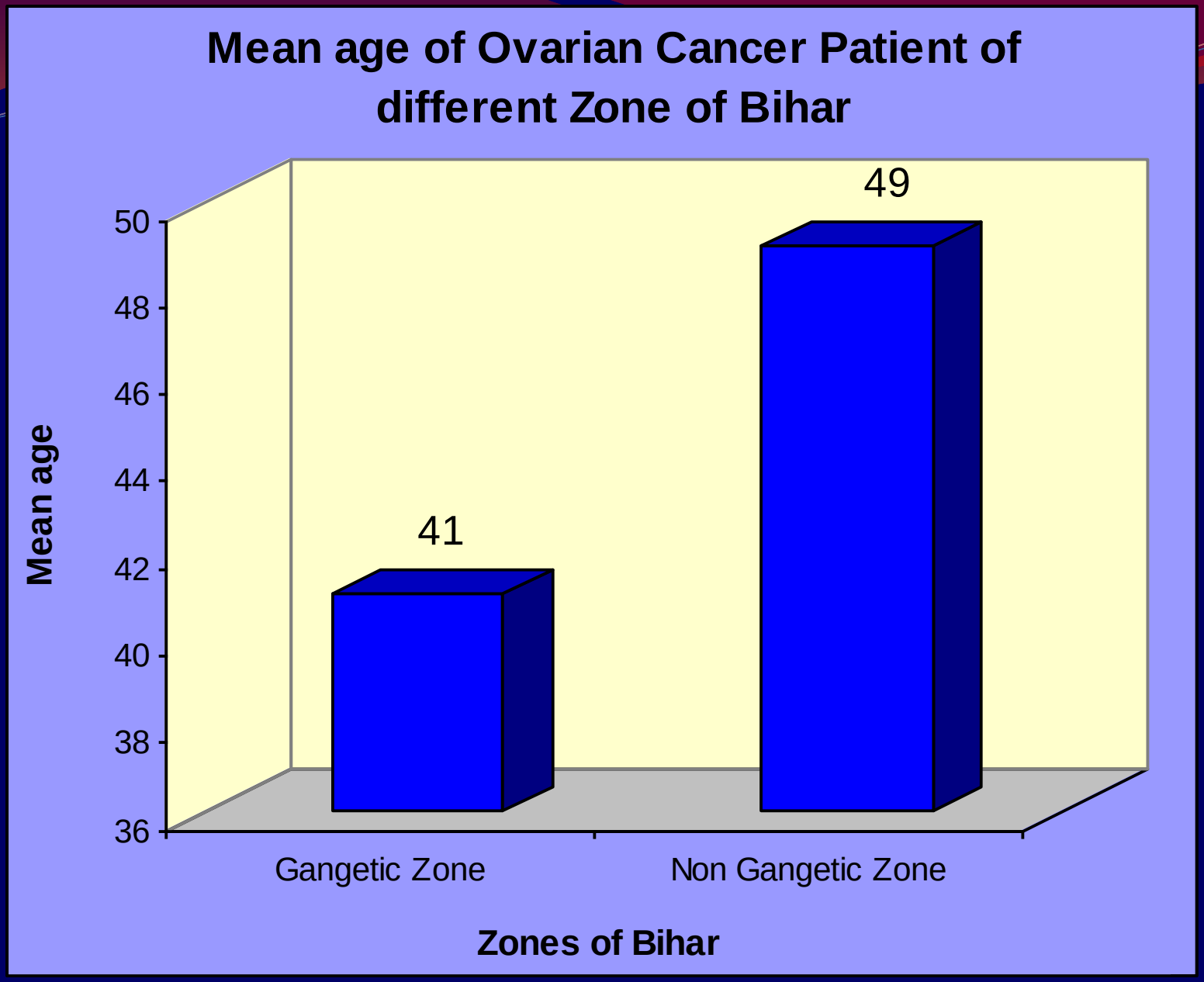
Ovarian cancer Patients of Different zones Bihar -2015



Gangetic Zone

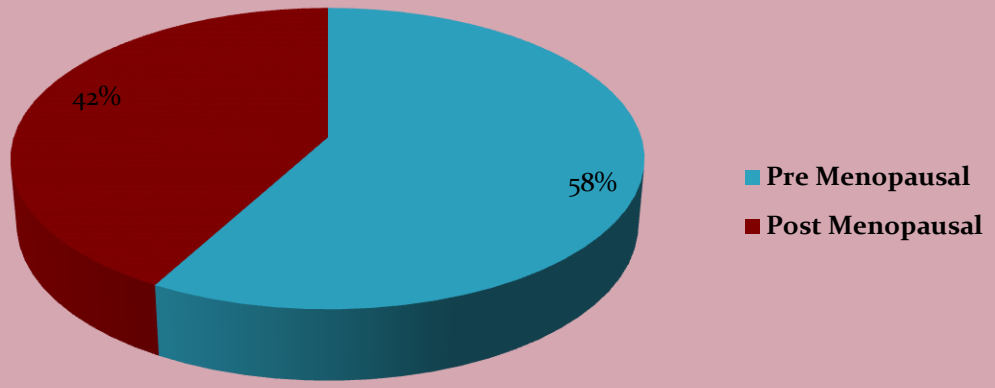
Non Gangetic Zone

Results

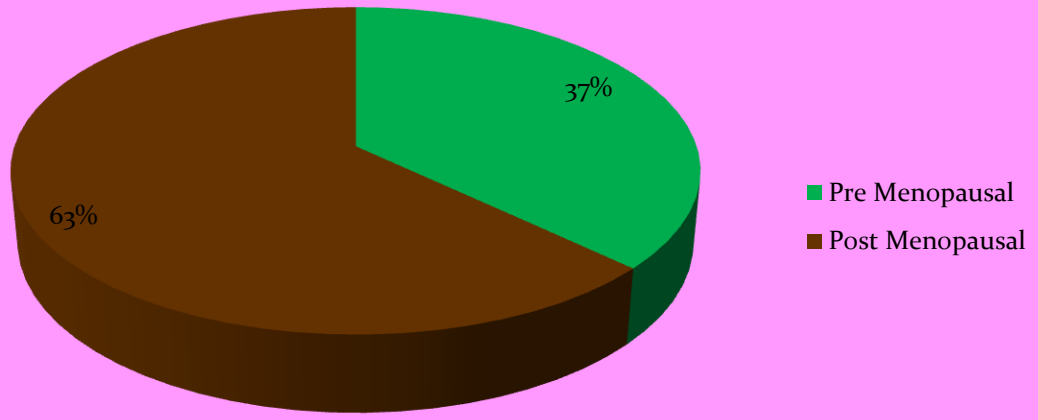


Mean Age of Ovarian Cancer Patients was 45 years

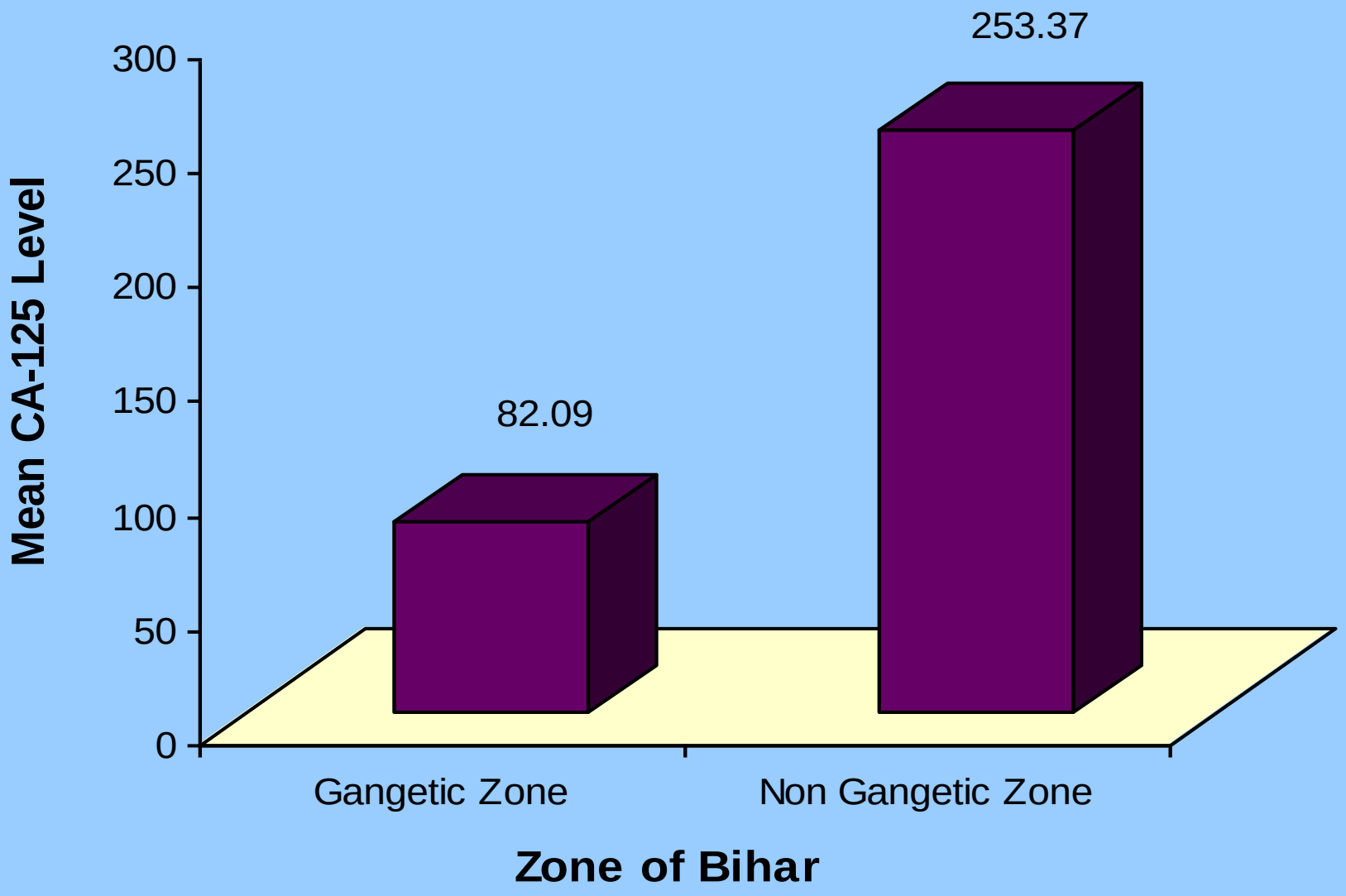
Menstrual History of Gangetic zone EOC patients



Menstrual History of Non Gangetic zone EOC patients

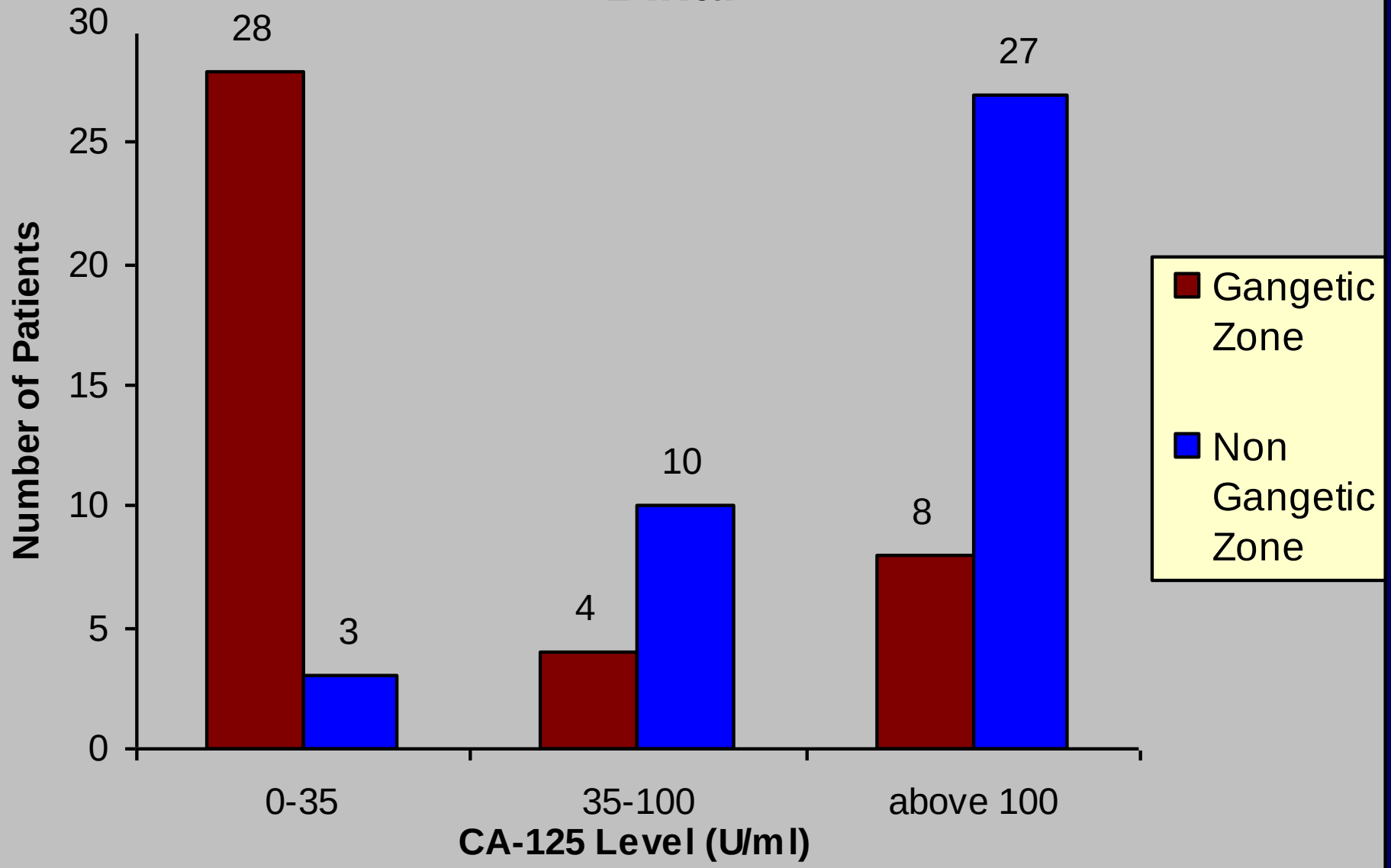


Mean CA-125 Level in Ovarian Cancer Patients of Different zone of Bihar

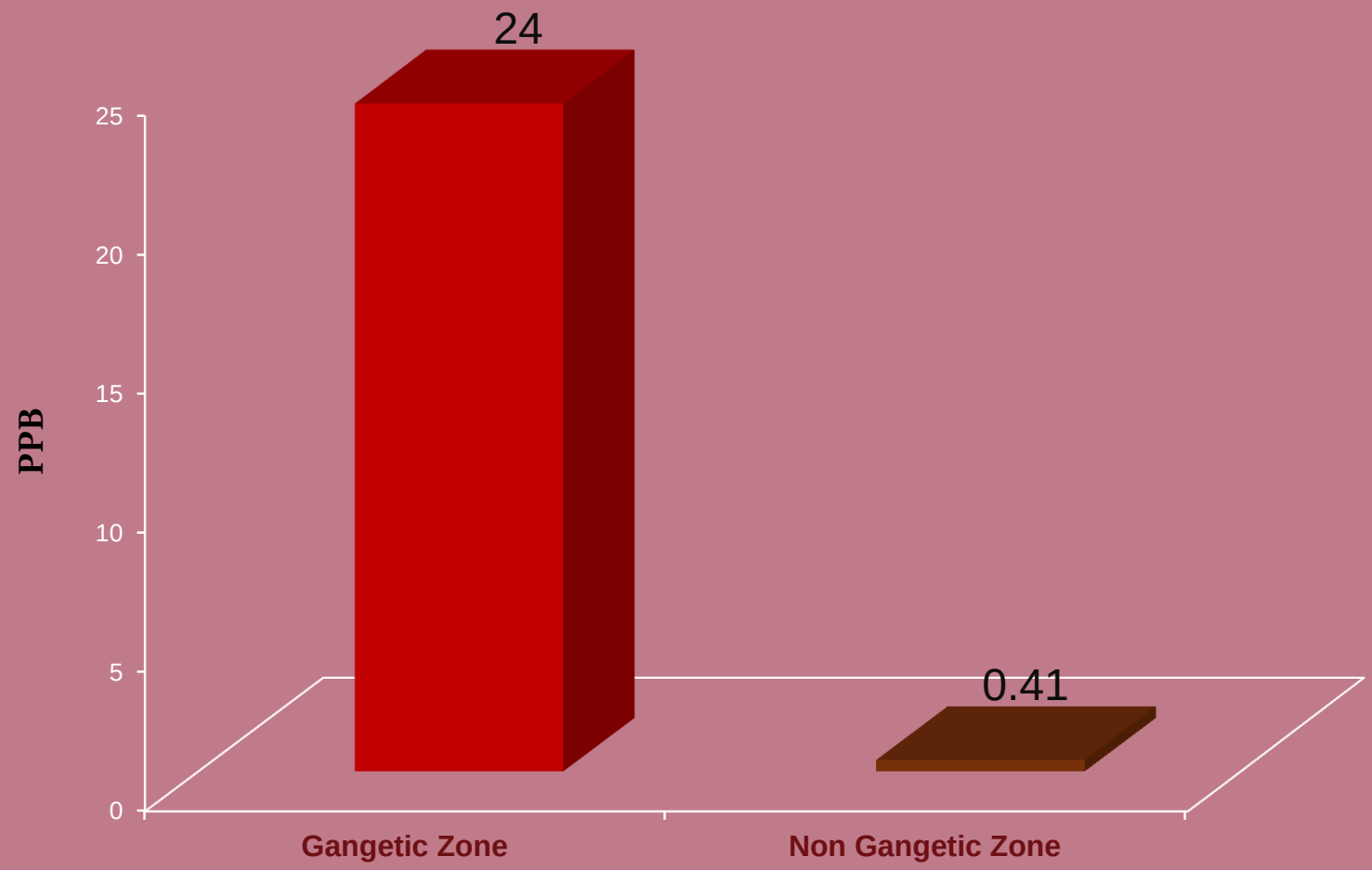


Zones of	Number of Subjects	Mean Ca 125 Level	Standard Deviation
Gangetic Zone	40	82.09	177.18
Non Gangetic Zone	40	353.37	350.23
Total	**80**	**217.73**	**307.71**

CA-125 Level in Ovarian Cancer Patients of Bihar

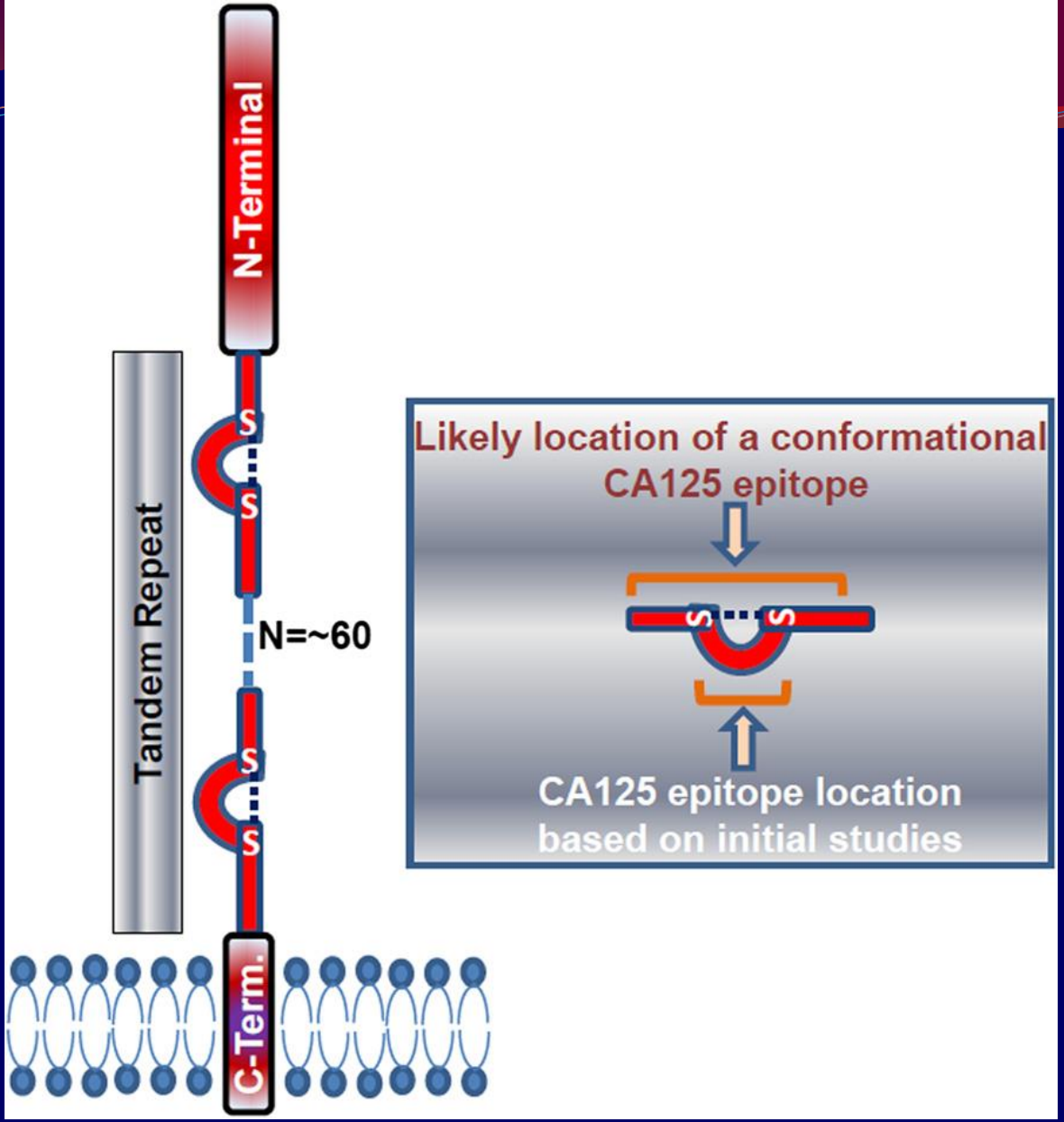


Arsenic Level in Different zones of Bihar



CA-125/MUC 16 non expression

- MUC16 is a component of the female reproductive tract epithelia.
- Since MUC16 is highly Glycosylated it creates a hydrophilic environment that acts as a lubricating barrier against foreign particles and infectious agents on the apical membrane of epithelial cells.
- This hydrophilic environment facilitate its interaction with Arsenic or heavy Metals
- The cytoplasmic tail of MUC16 has been shown to interact with cytoskeleton by binding members of the Protein family.
- Arsenic also acts in depolymerisation of microtubules and adversely affects its interaction with membrane protein.



MUC16 structure. Model shows the three domains of MUC16 and potential location of the CA125 epitope in a tandem repeat.

Conclusion

- Although CA 125 is the best available single marker for ovarian cancer, its sensitivity and specificity may not be sufficient for screening of epithelial ovarian cancer patients of Bihar residing in Gangetic zone.

- While it is find significant for patients residing in non Gangetic region.

- It is found that Arsenic level is very high in water of Gangetic zone that may bind with Cancer Antigen – 125 glycoprotein and increases its molecular weight.

Conclusion

- CA-125/MUC-16 has four negatively charged binding site at its tendem repeat on which positively charged contaminant (Arsenicale) binds and increases its molecular weight.
- Due to increased molecular weight of CA-125 it is not detected.
- That's why even in Advanced stage of ovarian cancer many patients has CA-125 level 0.1 U/ml.
- Heavy metal estimation is also recommended with CA-125 to get accuracy in patients residing near river zones.

Brief Communication

Evaluation of the Significance of CA-125 Levels in Patients With Epithelial Ovarian Cancer in Bihar, India

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Abstract

Epithelial ovarian cancer (EOC) is the leading cause of death among all gynecologic cancers around the world. This is so because women diagnosed with early-stage disease have a better prognosis and hence better chances of survival. Cancer antigen (CA)-125 is a high-molecular-mass glycoprotein produced both by ovarian cancer cells and also by the normal cells of tissues derived from coelomic epithelium. This study explores the significance of CA-125 for patients with ovarian cancer residing near rivers. The medical records of 80 patients treated at the Mahavir Cancer Institute and Research Centre for ovarian cancer between 2006 and 2007 with preoperative serum CA-125 levels were reviewed. Study reveals that the patients residing in the Gangetic region have the lowest mean CA-125 level (82.09 IU/mL), whereas the ovarian cancer not patients residing in the Gangetic zone have a higher mean CA-125 level (353.37 IU/mL). Although CA-125 is the best available single marker for ovarian cancer, its sensitivity and specificity might not be sufficient for the screening of patients from Bihar residing in the Gangetic zone who have epithelial ovarian cancer.

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Keywords: FIGO, Gangetic zone, Epithelial ovarian cancer

Introduction

Epithelial ovarian cancer (EOC) is the leading cause of death among all gynecologic cancers around the world. This is so because women diagnosed with early-stage disease have a better prognosis and hence better chances of survival than women diagnosed with late-stage disease. Early detection of ovarian cancer is not yet possible; hence, it escapes identification in most cases, leading to higher rates of mortality in this disease.[1] Early detection represents a potentially practical approach to reducing the mortality associated with EOC. Serum cancer antigen (CA)-125 has evolved as one of the biomarkers of ovarian cancer[2] and is currently being used as a marker for identification of this disease.

Cancer antigen-125 is a high-molecular-mass glycoprotein produced by both ovarian cancer cells and also by normal cells of tissues derived from the coelomic epithelium.[3] Serum CA-125 levels are used as a marker of tumor activity in patients known to have ovarian carcinoma,[4] and commercial tests for serum CA-125 have been available since 1983. In women with histologically proven ovarian carcinoma, levels of serum CA-125 are elevated > 35 U/mL in > 80% of cases.[5] CA-125 assessment can identify 85% of clinically advanced carcinomas[4,6]; several studies have shown that deviations in CA-125 might occur.

Elevation of CA-125 levels may occur in malignant conditions other than ovarian cancer, in benign diseases, and in 1%-2% of normal healthy individuals.[7] Some of the malignant conditions associated with the elevated tumor marker include lung, bladder, gastric, hepatic, and pancreatic cancers; leukemia; non-Hodgkin lymphoma; and mediastinal teratoma.[8] This tumor marker is also elevated in pleural effusion associated with Meigs syndrome secondary to ovarian fibroma and pseudo-Meigs syndrome related to other benign pelvic tumors.[6]

The best available marker for EOC is the mucin CA-125. The reference interval most frequently quoted for CA-125 is 0-35 kU/L, although 99% of apparently healthy postmenopausal women have levels below 20 kU/L.[9] In apparently healthy premenopausal women, levels of 100 kU/L or higher can occur during menses.[10]

Over more than 2 decades of clinical use, CA-125 has proven itself to be one of the most useful tumor markers in cancer medi-

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Thank You