الاهميه الاكلينيكيه لذائب CD44v6
في مرضى سرطان القولون والمستقيم

رساله

توطئه للحصول على درجة الماجستير
في الباثولوجيا الاكلينيكيه والكيميائيه

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CLINICAL SIGNIFICANCE OF SOLUBLE CD44V6 IN PATIENTS WITH COLORECTAL CANCER

Thesis

Submitted for Partial Fulfillment of Master Degree
In **Clinical and Chemical Pathology**

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SUMMARY

Colorectal cancers, among other neoplasms are in the third place in morbidity and mortality after the breast and lung cancers in women and prostate and lung cancers in men. Colorectal cancer is also the third cause of death among all neoplasmal diseases.

The incidence of this disease has been rising especially in developed countries. The survival rate after radical operative treatment and chemo- or radiotherapy is still unsatisfactory. The 5-year survival after radical treatment was about 60% in the Unites States and Western Europe, whereas it was only about 40% in Eastern Europe. The recurrence of the disease is dependent on the progression of neoplasmal metastases to lymph nodules and distal organs and is the most common cause of death.

The routine examinations of specimens with the estimation of the histopathological grade of malignancy, clinical evaluation and even the changes in CEA, CA19.9 levels in the serum evaluation all still have limited ability and require serial measurements to identify patients with colorectal cancer.

Therefore, there is a desperate need for an early and sensitive marker for detection of colorectal cancer in order to interfere early and thus improve the prognosis. A candidate marker for detection of colorectal cancer is CD44.


بسم الله الرحمن الرحيم
وَأَنْزَلَ اللهُ عَلَيْكَ
الْكِتَابَ والْحِكْمَةَ
وَعَلَّمَكَ مَا لَمْ
تَكُنْ تَعْلَمُ وَكَانَ
فَضْلُ اللهِ عَلَيْكَ
عَظِيمًا
صدق الله العظيم
سورة النساء آية
(١١٣)

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LIST OF ABBREVIATIONS

Abbrev.	Full term
APC	Adenomatous Polyposis Coli
Bcl-2	B-cell Lymphoma 2 Proto-oncogene.
CSCs	Cancer Stem Cells.
CA 19.9	Carbohydrate Antigen 19-9.
CEA	Carcinoembryonic Antigen.
CD44v	CD44 Variant.
CLIA	Chemiluminescence Immunoassay.
CD44	Cluster of Differentiation 44.
CV	Coefficient of Variation.
CCSA	Colon Cancer–specific Antigen.
CRC	Colorectal Carcinoma.
CT	Computed Tomography.
CI	Confidence Interval.
DNA	Deoxyribonucleic Acid
DK	Dermokine.
ELISA	Enzyme-linked Immunosorbent Assay.
EGFR	Epidermal Growth Factor Receptor.
CD44e	Epithelial CD44.
ECM	Extracellular Matrix.
FAP	Familial Adenomatous Polyposis.
FOBT	Fecal Occult Blood Test.
CD44H	Hematopoietic CD44.
HNPCC	Hereditary Non Polyposis Colorectal Cancer.
HPLC	High Performance Liquid Chromatography.
HRP	Horseradish Peroxidase.
HEV	Human Endothelial Vessels.
HA	Hyaluronic Acid.
IHC	Immunohistochemistry.

LIST OF ABBREVIATIONS (Cont....)

Abbrev.	Full term
IR	Interquartile Range.
Kb	Kilobase
kDa	Kilo Dalton.
K-Ras	Kirsten Rat Sarcoma Gene.
LLD	Lower Limit of Detection.
$\overline{X}$	Mean.
mRNA	Messenger RNA.
mAb	Monoclonal Antibody.
BCIP/NBT	5-Bromo-4-Chloro-3-Indolyl Phosphate System/Nitro Blue Tetrazolium.
O.D.	Optical Density.
OPN	Osteopontin.
PBS	Phosphate Buffer Saline.
PLSCR1	Phospholipid Scramblase 1.
p	Probability.
PSGL-1	P-Selectin Glycoprotein Ligand-1.
RIA	Radioimmunoassay.
RTK	Receptor of Tyrosin Kinase.
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction.
SDS-PAGE	Sodium Dodecyl Sulphate Polyacrylamide Gel Electrophoresis.
r_s	Spearman's Rank Correlation Coefficient.
CD44s	Standard CD44.
SD	Standard Deviation.
Σ	Sum of Observed Values.
TBS	Trisbuffered Saline.
TNM	Tumor Node Metastasis.
VEGF	Vascular Endothelial Growth Factor.
Z	Wilcoxon's Rank Sum Test.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide, with an annual incidence of approximately 1 million cases and an annual mortality of more than 500,000 **(*Parkin et al., 2005)***. It contributes for 8.9% of all cancers in the world, and 6.5% of all cancers in Egypt ***(El-Bolkainy et al., 2006)***.

Fecal occult blood test, sigmoidoscopy, colonoscopy, virtual colonoscopy, digital rectal examination are reliable methods for diagnosis of colorectal cancer ***(Adolfo, 2009)***.

Although histopathology is the most important tool in the diagnosis of colorectal cancer, tumor markers as CEA and CA19.9 are important as diagnostic markers, prognostic markers and surveillance markers ***(Yamashita et al., 2009)***.

The American Society for Clinical Oncology recommends that CEA is the only marker of choice for monitoring the response of metastatic disease to systemic therapy at present ***(Yamashita et al., 2009)***.

On the other hand CA19.9 was evaluated as a prognostic marker for colorectal cancer. Simultaneous use of the two markers is useful in evaluating the therapeutic effect and monitoring the recurrence of advanced colorectal cancer ***(Park et al., 2009)***.

Short for cluster of differentiation 44(CD44) is an adhesion molecule of the hyaluronan receptor family. It has 10 splice variants take the numbers from 1 to 10. CD44 has in recent years been intensively studied in connection with different forms of cancer, where CD44 may regulate invasiveness and tumor progression. Although major functions involve adhesion and migration, CD44 also affects leukocyte homing, recruitment, phagocytosis, matrix remodeling, proliferation and apoptosis ***(Alexandra et al., 2009).***

CD44v6 is the soluble CD44 splice variant containing exon v6. Several studies found it higher in patients with metastasis than in primary patients implying the role of this molecule in tumor progression ***(Amirghofran et al., 2008)***.