The Value of Fecal M2PK in Colorectal Cancer

Ehesis

Submitted For Partial Fulfillment of Master Degree in Tropical Medicine

By

Hani Ezzat Sadik

(M.B., B.Ch)

Under Supervision of

Professor/ Hisham Khalil Dabbous

Professor of Tropical Medicine Faculty of Medicine Ain Shams University

Professor/ Yosry Abd El-Rhaman Mohammed

Professor of Tropical Medicine Theodor Bilharz Research Institute

Doctor/ Runia Fouad EL- Folly

Assistant Professor of Tropical Medicine Faculty of Medicine Ain Shams University

Faculty of Medicine

Ain Shams University

2016



سورة البقرة الأية: ٣٢





First and foremost, praise and thanks must be to ALLAH, Who guides me throughout life.

I would like to express my deepest gratitude and thanks to **Prof. Dr. Hisham Khalil Dabbous,** Professor of Tropical Medicine, Faculty of Medicine, Ain Shams University for his kind continuous encouragement and great support throughout the work. It was a great honor to be a student working under his supervision.

I am also greatly indebted and grateful to **Prof. Dr. Yousry Abd El Rahaman Mohamed,** Professor of Hepatology and Gastroenterology, Theodor Bilharz Research Institute, for his great help, valuable time, careful supervision and continuous advices and his efforts that made this work come to light.

I am also greatly indebted to **Dr. Runia Fouad El-Folly,** Assistant Professor of Tropical Medicine, Faculty of Medicine, Ain Shams University, it was impossible for me to finish this work without her wise instructions and guidance. No words would ever fulfill my deepest gratitude towards her support.

Also I am really deeply grateful to **Dr. Mohammed Darwish**, Assistant Professor of Hepatology and Gastroenterology, Theodor Bilharz Research Institute, for his careful and great support.

I am really thankful to endoscopy unit of Hepatology and Gastroenterology department and Pathology department, Theodor Bilharz Research Institute who took part in exhibiting this work to light.

Candidate



List of Contents

| Subject | Page No. |
|--------------------------------|----------|
| List of Abbreviations | i |
| List of Tables | v |
| List of Figures | viii |
| Abstract | X |
| Introduction | 1 |
| Aim of the Work | 5 |
| Review of Literature | 6 |
| Colorectal Polyps | 6 |
| Colorectal Cancer | 42 |
| CRC Screening and Surveillance | 51 |
| Patients and Methods | 71 |
| Results | 80 |
| Discussion | 106 |
| Summary | 118 |
| Conclusions | |
| Recommendations | 124 |
| References | 125 |
| Arabic Summary | ••••• |

List of Abbreviations

| Abbr. | Full-term |
|-------------|---|
| ACG | : American College of Gastroenterology |
| AGA | : American Gastroenterological Association |
| APC | : Adenomatous polyposis coli |
| ASGE | : American Society for Gastrointestinal Endoscopy |
| ATP | : Adenosine triphosphate |
| AVMs | : Arteriovenous Malformations (AVMs) |
| BMP3 | : Methylated Bone Morphogenetic Protein 3 |
| BMPR1A | : Bone morphogenetic protein receptor, type IA |
| BRAF | : v-Raf murine sarcoma viral oncogenes homolog B1 |
| BSG | : British Society of Gastroenterology |
| CD | : Crohn's colitis |
| CIMP | : CpG island methylator phenotype |
| CRC | : Colorectal cancer |
| CT | : Computed tomography |
| CTC | : Computed tomography colonography |
| DALM | : Dysplasia Associated Lesion or Mass |
| DCBE | : Double contrast barium enema |
| DCC | : Deleted in cancer colon |
| DNA | : Deoxy Ribonucleic acid |
| EDTA | : Ethylenediaminetetraacetic acid |
| ERUS | : endorectal ultrasonography |
| ESD | : Endoscopic sub-mucosal dissection |
| FS | : Sigmoidoscopy |
| | |

FAP : Familial adenomatous polyposis

FIT : Fecal immunochemical tests

FOBTs: Fecal occult blood tests

gFOBT : Guaiac-based Fecal occult blood tests

GISTs : Gastro-intestinal stromal tumors

GIT : Gastro intestinal tract

HHT : Hereditary Hemorrhagic Telangiectasia

HIF1 : Hypoxia-Inducible Factor (HIF)-1

hMLH1: Human MutL Homolog 1

hMLH3: Human MutL Homolog 3

HMPS: Hereditary mixed polyposis syndrome

hMSH2: Human MutS Homolog 2

hMSH3: Human MutS Homolog 3

hMSH6 : Human MutS Homolog 6

HNPCC: Hereditary Non-Polyposis Colorectal Cancer

HNSCC: Head and Neck Squamous Cell Carcinoma

HPV-16 E7: Human Papiloma Virus Type 16 E7 protein

IARC : International Agency for Research on Cancer

IBD : Inflammatory bowel disease

Kras : Kirsten rat sarcoma viral oncogene homologue

L PK : Liver pyruvate kinase

M1PK : Muscle pyruvate kinase

M2PK : M2Pyruvate Kinase

MHC : Major Histocompatibility Complex

MLH1 : MutL Homolog 1

MRC : Magnetic resonance colonography

MSH2 : MutS Homolog 2 MSH6 : MutS Homolog 6

MSI : Microsatellite instability

MSI-H: High-frequency microsatellite instability

MUC : Mucosal Ulcerative Colitis

MYC : Myc proto-oncogene protein

NBI : Narrow-band imaging

NCI : National Cancer Institute

NDRG4 : NDRG family member 4

NHL: Non Hodgkin lymphomal

NIR AF : near-infrared autofluorescence

NSAID : Non Steroidal Anti Influmatory Drugs

P53 : Protein 53

PEP: Phosphoenolpyruvate

PHTS: PTEN hamartomatous tumor syndromes

PILLcam: PillCam Capsule Endoscopy

pp60v-src kinase : pp60v-src tyrosine kinase

PSC: Primary sclerosing cholangitis

PTEN: phosphatase and tensin homolog protein

R PK : erythrocyte pyruvate kinase

SMAD2 : SMA protein- mothers against decapentaplegic 2SMAD3 : SMA protein- mothers against decapentaplegic 3

SMAD4 : SMA protein- mothers against decapentaplegic 4

SMAD4 : SMA protein- mothers against decapentaplegic 4

Sp1 : specificity protein 1

SPS : Serrated polyposis syndrome

List of Abbreviations

SSAs : Sessile Serrated AdenomasSTK11 : Serine/threonine kinase 11

TAC-IRA: total abdominal colectomy with ileorectal anastomosis

TGF- β : Transforming growth factor-βTSAs : Traditional Serrated Adenomas

UC : Ulcerative colitis

List of Tables

| Eable No | v. Citle | Page No. |
|--------------------|--|-------------------|
| <u>Tables in F</u> | <u>Review</u> | |
| Table (I): | Summary of Major Risk Factors for C Cancer | |
| Table (II): | The protective factors for colorecta risk | |
| Table (III): | Current Recommendations for the Prev Colorectal Cancer | |
| Table (IV): | Risk stratification and methods of s and surveillance: | • |
| Table (V): | The following options are recommendated cancer screening in men and aged 50 and older at average risk | d women |
| Table (VI): | Recommendations for individuals with history of CRC or adenomatous polyps | • |
| Table (VII): | Recommendations for individuals with cancer syndromes | • |
| Table (VIII) | : Surveillance recommendations for inc with significant personal history of c neoplasia | olorectal |
| Table (IX): | Summary of the main differences recommendations for colorectal surveillance programs in inflammator disease patients | cancer y bowel |

List of Tables (Cont.)

| Eable N | o. Eitle Page N | o. |
|--------------------|--|----|
| Tables in | Results | |
| Table (1): | Demographic characteristics and medical history among the study groups | 81 |
| Table (2): | Main presenting complains among the study groups | 82 |
| Table (3): | Clinical presentations among the study groups: | 83 |
| Table (4): | Per-rectum examination findings among the study groups | 84 |
| Table (5): | Hemoglobin, TLC and platelets among the study groups | 85 |
| Table (6): | Tumor markers among the study groups: | 86 |
| Table (7): | Diagnostic characteristics of tumor marker cut off points in differentiating CRC group from CRP group | 88 |
| Table (8): | Diagnostic characteristics of tumor marker cut off points in differentiating CRC group from control group: | 89 |
| Table (9): | Radiological findings among the study groups: | 90 |
| Table (10): | Colonoscopy findings among the study groups: | 91 |
| Table (11): | Pathological findings among the study groups: | 92 |
| Table (12): | Correlation between markers among the study groups. | 94 |
| Table (13): | Correlation between CEA marker and other quantitative variables among the study groups: | 96 |
| Table (14): | Correlation between CA19-9 marker and other quantitative variables among the study groups: | 98 |

| Table (15): | Correlation between M2PK marker and other quantitative variables among the study groups: | . 99 |
|--------------------|---|------|
| Table (16): | Comparison smoking conditions regarding tumor markers among study groups: | 100 |
| Table (17): | Comparison clinical conditions regarding tumor markers among CRC group: | 101 |
| Table (18): | Diagnostic performance of tumor markers in differentiating study groups | 102 |
| Table (19): | Diagnostic characteristics of serial application of M2PK>25.0 followed by CA19-9>25.0 cut off points in differentiating CRC group from CRP and control groups | 105 |

List of Figures

| Figure Na | v. Eitle | Page No. |
|---------------|---|-----------------------|
| Figures in | <u>Review</u> | |
| Figure (I): | Colonoscopic view of sessile pedunculated (b) polyps | |
| Figure (II): | Tubular adenoma: low (400,a) a (2000,b) power magnification vie hematoxilin—eosin stain. The hi appearance is of branched tubular gla | ws of a stological |
| Figure (III): | Villous adenoma | 11 |
| Figure (IV): | Colonic mucosa carpeted with ade polyps in a patient with familial ade polyposis | nomatous |
| Figure (V): | Endoscopic view of each type of colorectal carcinoma | |

List of Figures

| Figure No | v. Citle Po | age No | ٧. |
|---------------------|--|--------|----|
| Figures in | Results | | |
| Figure (1): | Main presenting complains among the s groups | - | 2 |
| Figure (2): | (a) CEA, (b) CA19-9, (c) M2PK among study groups | - | 7 |
| Figure (3): | Colonoscopy findings among the cogroup | | 1 |
| Figure (4): | Pathological findings among the co groups | | 3 |
| Figure (5): | Pathological findings among the CRP grou | ıps 93 | 3 |
| Figure (6): | Correlation between CEA and Ca19-9 and the group CRC | _ | 5 |
| Figure (7): | Correlation between CEA and Ca19-9 and the group CRP | | 5 |
| Figure (8): | Correlation between CEA and age among CRP group | - | 7 |
| Figure (9): | Diagnostic performance of tumor marked differentiating in differentiating CRC g from CRP group | roup | 3 |
| Figure (10): | Diagnostic performance of tumor marked differentiating in differentiating CRC g from control group | roup | 3 |
| Figure (11): | Diagnostic performance of tumor marked differentiating in differentiating CRP g from control group | roup | 4 |
| | | | |

The Value of Fecal M2PK in Colorectal Cancer

Thesis

Submitted For Partial Fulfillment of Master Degree
In Tropical Medicine

By

Hani Ezzat Sadik

(M.B., B.Ch)

Supervisors

Prof. Hisham Khalil Dabbos, MD
Professor of Tropical Medicine
Faculty of Medicine
Ain Shams University

Prof. Yosry Abd El-Rahman Mohamed, MD
Professor of Tropical Medicine
Theodor Bilharz Research Institute

Dr. Runia Fouad El-Folly, MD Assistant professor of Tropical Medicine Ain Shams University

Faculty of Medicine
Ain Shams University
2015