

A Study of the Prognostic Value of Protein COX-2 in Colorectal Carcinoma

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Contents

▪ Introduction	١
▪ Aim of the work	٣
▪ Review of the literature	٤
- Risk factors of colorectal carcinoma	٤
- Colorectal carcinogenesis	١٧
- Pathology of colorectal carcinoma	٢٢
- Staging of colorectal carcinoma	٢٨
- Diagnosis of colorectal carcinoma	٣١
- Prognostic factors in colorectal carcinoma	٣٣
- Cyclooxygenase-٢ and Prostaglandins	٤١
▪ Material and methods	٤٨
▪ Results	٥٤
▪ Discussion	٨٦
▪ Summary	٩٢
▪ Conclusion and recommendation	٩٥
▪ References	٩٦
▪ Arabic Summary	

List of Tables

No	Subject	Page
١	WHO histological classification of CRC	٢٣
٢	TNM classification of CRC	٢٩
٣	Stage grouping of CRC	٣٠
٤	Age group of the studied cases of CRC	٥٤
٥	Distribution of the studied cases of CRC according to sex	٥٤
٦	The site of the studied cases of CRC	٥٤
٧	The tumor size of the studied cases of CRC	٥٥
٨	The gross appearance of the studied cases of CRC	٥٥
٩	Histological types of the studied cases of CRC	٥٥
١٠	Tumor grade of the studied cases of CRC with adenocarcinoma	٥٦
١١	Depth of invasion of the studied cases of CRC according to TNM classification	٥٦
١٢	Lymph node metastasis of the studied cases of CRC	٥٦
١٣	Distant metastasis of the studied cases of CRC according to TNM classification	٥٧
١٤	Tumor stage of the studied cases according to TNM staging	٥٧
١٥	COX-٢ expression in the studied cases of CRC	٥٧
١٦	Relationship between COX-٢ expression and age in years of the studied cases of CRC	٥٨
١٧	Relationship of COX-٢ expression with sex of the studied cases of CRC	٦٠
١٨	Relationship between COX-٢ expression and tumor site in the studied cases of CRC	٦١
١٩	Relationship between COX-٢ expression and tumor size of the studied cases of CRC	٦٣
٢٠	Relationship between COX-٢ expression and tumor gross appearance	٦٤

٢١	Relationship between COX-٢ expression and tumor type of the studied cases of CRC	٦٦
٢٢	Relationship between COX-٢ expression and tumor grade of the studied cases of CRC	٦٨
٢٣	The relationship between COX-٢ expression and depth of invasion of the studied cases of CRC	٧٠
٢٤	Relationship between lymph node metastasis and COX-٢ expression in the studied cases of CRC	٧٢
٢٥	Relationship between COX-٢ expression and distant metastasis (M) in the studied cases of CRC	٧٤
٢٦	The relationship between COX-٢ expression and different tumor stages in the studied cases of CRC	٧٦

List of Diagrams

No	Subject	Page
١	Relationship between COX-٢ expression and age in years of the ٢٠ cases of CRC	٥٩
٢	Relationship between COX-٢ expression and sex of the ٢٠ cases of CRC	٦٠
٣	Relationship between COX-٢ expression and tumor site in the ٢٠ cases of CRC	٦٢
٤	Relationship between COX-٢ expression and tumor size of CRC in the ٢٠ cases	٦٣
٥	Relationship between COX-٢ expression and tumor gross appearance of CRC in ٢٠ cases	٦٥
٦	COX-٢ expression in different tumor types of CRC in the ٢٠ cases	٦٧
٧	COX-٢ expression in different tumor grade of the adenocarcinoma of ١٢ cases of CRC	٦٩
٨	COX-٢ expression in different depths of invasion (T) of CRC in the ٢٠ cases	٧١
٩	COX-٢ expression and lymph node metastasis in ٢٠ cases of CRC	٧٣
١٠	COX-٢ expression and distant metastasis of ٢٠ cases of CRC	٧٥
١١	COX-٢ expression in different tumor stage in the ٢٠ cases of CRC	٧٧

List of Figures

NO	Figure	Page
١	A case of moderately differentiated adenocarcinoma H&E (X ١٠٠)	٧٨
٢	A case of moderately differentiated adenocarcinoma showing moderate diffuse cytoplasmic staining of COX-٢ (X١٠٠)	٧٨
٣	A case of moderately differentiated adenocarcinoma H&E (X٤٠٠)	٧٩
٤	A case of moderately differentiated adenocarcinoma showing moderate diffuse cytoplasmic staining for COX-٢ (X٤٠٠)	٧٩
٥	A case of moderately differentiated adenocarcinoma showing moderate cytoplasmic staining for COX-٢ (X١٠٠)	٨٠
٦	A case of moderately differentiated adenocarcinoma showing moderate diffuse cytoplasmic staining for COX-٢ (X٤٠٠)	٨٠
٧	A case of poorly differentiated adenocarcinoma H&E (X١٠٠)	٨١
٨	A case of poorly differentiated adenocarcinoma H&E (X٤٠٠)	٨١
٩	A case of poorly differentiated adenocarcinoma showing strong cytoplasmic COX-٢ staining (X٤٠٠)	٨٢
١٠	A case of mucinous adenocarcinoma H&E (X١٠٠)	٨٢
١١	A case of mucinous adenocarcinoma H&E (X٤٠٠)	٨٣
١٢	A case of mucinous adenocarcinoma showing strong granular cytoplasmic staining for COX-٢ (X٤٠٠)	٨٣
١٣	A case of signet ring adenocarcinoma H&E (X١٠٠)	٨٤
١٤	A case of signet ring adenocarcinoma showing COX-٢ staining expression COX-٢ (X١٠٠)	٨٤

١٥	A case of signet ring adenocarcinoma H&E (X٤٠٠)	٨٥
١٦	A case of signet ring adenocarcinoma showing strong granular cytoplasmic staining for COX-٢ (X ٤٠٠)	٨٥

List of Abbreviations

ACF	Aberrant Crypt Foci
APC	Adenomatous polyposis coli
CEA	Carcinoembryonic Antigen
COX	Cyclooxygenase
COX - α	Cyclooxygenase- α
COX - β	Cyclooxygenase- β
COX - γ	Cyclooxygenase- γ
CRC	Colorectal carcinoma
DCC	Deleted in Colon Cancer
FAP	Familial Adenomatous Polyposis
hCG	human Chorionic Gonadotropin
HIF α	Hypoxia-inducible factor- α
HNPCC	Hereditary Non polyposis Colorectal Cancer
IL- β	Interleukin- β
IL- γ	Interleukin- γ
MMP	Matrix-Metalloproteinase
MMR	Mismatch Repair
MSI	Microsatellite instability
MSS	Microsatellite Stable
NO	Nitric Oxide
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PGs	Prostaglandins
TxA β	Thromboxane A β
VEGF	Vascular endothelial growth factor

Introduction

Colorectal cancer is the third leading cause of cancer death in Western Countries. Between 20% and 50% of patients with colorectal cancer will probably die within five years of diagnosis as the result of extensive disease metastasis. In the United States, colorectal cancer affects nearly 150,000 people each year, with as many as 56,730 deaths anticipated in 2004 (**Hawk et al., 2004**).

In Egypt, colorectal cancers constituted 5.0% of total malignancies in the period from 1980 to 1989 in National Cancer Institute (**Mokhtar, 1991**). Colorectal cancer constituted 4.3% of total malignancies in National Cancer Institute during the years 2003 and 2004 (**Mokhtar et al., 2007**).

In Gharbiah, Colorectal Cancer constituted 3.8% of total cancers during the year 1999 (**Ibrahim et al., 2002**). And Colorectal cancer constituted 4.1% of total cancers, 3.6% of total cancers in males and 4.5% of total cancers of females during the period from 2000 to 2002 (**Ibrahim et al., 2007**).

Because of its aggressiveness as a fatal disease, many studies were done to assess the prognostic factors of colorectal cancer; one of these factors is COX-2 (Cyclooxygenase-2).

Cyclooxygenase (COX) is a key regulator enzyme in the synthesis of prostaglandins (PGs). The two iso enzymes of COX, termed Cyclooxygenase-1 (COX-1) and Cyclooxygenase-2 (COX-2), have been identified. COX-1 is constitutively expressed in virtually all tissues and regulates normal physiological functions (**Wiese et al., 2001**).

Introduction

COX- γ is the best defined molecular target of NSAIDs (non-steroidal anti-inflammatory drugs) and regulates the synthesis of prostaglandins (PGs), COX- γ (also known as prostaglandin H synthase-1) is upregulated in response to inflammatory cytokines, growth factors and tumor promoters (***Thun et al., 2002***).

COX- γ overexpression in other epithelial cancers including pancreas (***Tucker et al., 1999***), esophagus (***Shamma A et al., 2000***), breast (***Ristimaki A et al., 2002***), stomach (***Van Rees et al., 2002***) and lung (***Altorki et al., 2002***), is also found primarily in the malignant epithelial cells.

Potential mechanisms by which COX- γ may contribute to tumorigenesis including promoting cell division (***Fosslien, 2000***), increased cell invasiveness (***Reddy et al., 2002***), alternating cell adhesion and enhancing metastasis (***Chen et al., 2001***), inhibiting apoptosis (***Nzeako et al., 2002***) and stimulation of angiogenesis (***Leahy et al., 2000 and Rao et al., 2004***).

COX- γ expression is gradually up regulated in the development from normal epithelium to adenomas and from early colorectal cancers to advanced colorectal cancers, so COX- γ expression can be regarded as independent risk factor of poor prognosis for postoperative patients with advanced colorectal cancers (***Zhan et al., 2004***).

Finally COX- γ overexpression may confer prognostic information in human colorectal cancers, as its overexpression in primary tumors was associated with more advanced tumor stage, increased tumor size and positive lymph node status (***Zhang and Sun, 2002***).

Aim of the Work

Aim of the Work

The aim of this work is to study COX- γ expression in colorectal carcinoma and its value as a prognostic factor in colorectal carcinoma.

Conclusion and Recommendation

From this study, we conclude that strong positive COX-2 expression was correlated with the most important prognostic parameters including, tumor stage, depth of invasion as well as lymph nodes metastasis; and this relation was statistically significant. So, positive COX-2 expression might predict tumors with more aggressive behavior. Thus COX-2 expression maybe useful in selection of patients of CRC at high risk of tumor progression.

We recommend further follow-up studies on COX-2 expression on large number of cases of CRC to confirm its prognostic value in relation to survival and other effective prognostic factors such as tumor stage, tumor invasion and presence of lymph node metastasis, in order to select CRC patients who would benefit from adjuvant therapeutic management.

Discussion

Colorectal carcinoma is the third most common cancer in the world and the second most common cause of cancer related death (**Ricchi et al., ۲۰۰۳**) (**Jemal, ۲۰۰۵**) . During the year ۲۰۰۰, in the United States, ۱۳۰,۲۰۰ new cases of colon cancer and rectal cancer were reported (**Nelson et al., ۲۰۰۱**). Colorectal cancer affects nearly ۱۵۰,۰۰۰ people each year with as many as ۵۶,۷۳۰ deaths anticipated in ۲۰۰۴ (**Hawk et al., ۲۰۰۴**). In Japan, ۳۶,۰۰۰ patients died of this cancer in ۲۰۰۱ (**Kotake et al., ۲۰۰۳**).

In Egypt, the median age is ۶۵ years, but younger (۵۰ years) in cases complicating polyposis and ulcerative colitis. Male predominance is ۲:۱ in the rectum and ۱,۳:۱ in the colon (**El-Bolkainy et al., ۲۰۰۵**).

The overall prognosis of colorectal carcinoma remains poor, despite the improving survival of patients with surgically operable tumors, and use of main conventional prognostic factors such as tumor stage, depth of tumor invasion and the presence of lymph node metastasis. So, attempts to find new biologic markers that could identify patients with poor prognosis remain under investigation.

COX-۲ overexpression has been detected in several other carcinomas including the breast cancer (**Rozic et al., ۲۰۰۱**), in the