حسام مغربى

شبكة المعلومات الجامعية

بسم اللّه الرحمن الرحيم

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التوثيق الالكتروني والميكروفيلم

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جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

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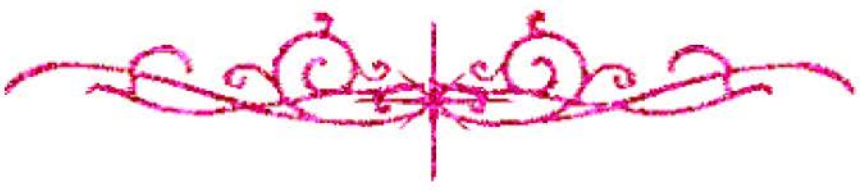

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بالرسالة صفحات لم ترد بالأصل

MALIGNANCY OF THE BILIARY DUCTS AND PERIAMPULLARY REGION: STUDY OF DIAGNOSTIC AND THERAPEUTIC MODALITIES

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By

WAEL NABIL ABDEL-SALAM

M.B.B.Ch.(Alex.)

M.S.(Alex.)

Faculty of Medicine

University of Alexandria

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SUPERVISORS

Prof. Dr. Mostafa M. El-Hennawy

Professor of Surgery

Faculty of Medicine

University of Alexandria

Prof. Dr. Ahmed El-saied Basiouni

Professor of Surgery

Faculty of Medicine

University of Alexandria

Prof. Dr. El-Said Abbass El-Kayal

Professor of Surgery

Faculty of Medicine

University of Alexandria

CO-WORKERS

Prof. Dr. Mohamed Yousry Taher

Professor of Internal Medicine

Faculty of Medicine

University of Alexandria

Dr. Ahmed Mostafa Shawky

Assistant Professor of Surgery

Faculty of Medicine

University of Alexandria

EXAMINERS

Prof. Dr. Mostafa M. El-Hennawy

Professor of Surgery

Faculty of Medicine

University of Alexandria

Prof. Dr. Medhat Mostafa Sabet

Professor of Surgery

Faculty of Medicine

University of Elmenia

Prof. Dr. Mahmoud Aly El-Khishen

Professor of Surgery

Faculty of Medicine

University of Alexandria

CONTENTS

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INTRODUCTION

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Carcinoma of the extrahepatic biliary tract has always been associated with a dismal prognosis. This is essentially the result of the slow and asymptomatic growth of the neoplasm that infiltrates the surrounding structures, such as the portal vein and hepatic artery, making a curative surgical treatment almost impossible[1]. However in the last decade, improvements in surgical, anesthetic, and intensive care techniques have allowed to ameliorate both the pre- and postoperative general condition of the patient, and offer a wider range of surgical options[1].

Investigations into the molecular and cellular biology of carcinogenesis continue to elucidate potential mechanisms for the initiation and progression of biliary tract cancer. There is an evidence for a possible link between chronic inflammation and malignant transformation through the relation between nitric oxide and DNA repair enzymes [2].

Bile duct tumors (cholangiocarcinoma):

Biliary tract cancers are rare malignancies involving the bile ducts and/or the gallbladder. In 1997, 7000 cases of biliary tract cancer were diagnosed, of these 2000 were of bile ducts origin and the remaining 5000 were of gallbladder origin [3]. Cholangiocarcinoma has been reported to affect 6 % to 11 % of patients with primary sclerosing cholangitis (PSC)[4,5]. In a case - control study of 113 patients with PSC, [26 patients of them (23%) was associated with

cholangiocarcinoma], alcohol consumption was the only risk factor identified among PSC patients developing cholangiocarcinoma[4] Smoking, inflammatory bowel disease, and the severity of liver disease were not associated with an increased risk of cholangiocarcinoma in these patients [4].

The etiology of cholangiocarcinoma is unknown. Several reviews summarize the factors associated with an increased risk for biliary tract cancer; symptomatic gall stones, female sex, obesity. bacterial infection, polyps > 1 cm in size, porcelain gallbladder and adenomas of the ampulla of Vater [6,7]. In addition, biliary tract carcinogenesis has been linked to anatomic anomalies such as congenital bile duct cysts, Caroli disease, pancreatico-biliary maljunction, chronic inflammatory conditions such as infections with Clonorchis Sinensis and Salmonella Typhi, autoimmune diseases such as PSC, primary biliary cirrhosis, and chronic ulcerative colitis [6-9].

Chronic inflammation appears to be a key component in all of the entities that predispose patients to cholangiocarcinoma [10]. Cytokines (tumor necrosis factor-α and interleukin-λ) produced by activated macrophages during the inflammatory process may be responsible for the induction of cytotoxic and mutagenic effects inducing carcinogenesis [6].

Iaiswal et al [10] examined the possible link between chronic inflammation and malignant transformation by examining the relation between nitric oxide (NO) and DNA repair enzymes. They demonstrated that, human cholangiocarcinoma express inducible nitric

oxide synthase (INOS) and that cytokines can stimulate the production of NO in cholangiocarcinoma cell lines [10]. The NO levels produced were sufficient to cause DNA damage and inhibit DNA repair activity. Although the exact mechanism is not yet elucidated, the authors concluded that, NO may play an important role in the initiation, progression and/or promotion of cholangiocarcinoma [10].

Whatever the initiating event, oncogenic mutations have been postulated to provoke an imbalance between cell proliferation and apoptosis, leading to uncontrolled cellular proliferation [6]. Mutations in a variety of oncogenes including K-ras, C-nyc, C-new, C-erb-b2, and C-met as well as the tumor suppressor genes P53 and bel-2 have been shown to be associated with biliary cancer [6,7,11]. Pan et al [12] have suggested that Fas/APO-l (CD 95) and the Fas ligand system, which is a key regulator of apoptosis, also may be a candidate signaling pathway involved in the pathogenesis of cholangiocarcinoma.

Hui et al [13], examined the postoperative outcome of 32 patients with resectable extrahepatic bile duct carcinoma by measuring the level of the cell cycle regulators cyclin Dl (a positive regulator) and P27 Kipl (a negative regulator). In this study, normal bile duct epithelial cells exhibited high levels of immunoreactivity to the negative regulator, whereas bile duct carcinomas exhibit a decreased expression.

Decreased P27 Kipl expression also predicted frequent recurrence and shortened survival time in patients with

cholangiocarcinoma. Expression of P27 Kipl was identified as a novel independent predictor for death. Patients with a decreased P27 Kipl had 18 % 5 - year survival rate as compared with 46 % survival rate for the preserved P27 Kipl group [13].

Conversely, cyclin Dl, which has been identified as a cancer-specific gene, that functions primarily in cell - cycle progression, was frequently (68 %) over expressed in extrahepatic bile duct carcinoma tissues as compared with normal bile duct epithelium [13]. This over expression was significantly associated with relapse and survival. Thus, both decreased inhibition of cell cycle (decreased P27 Kip 1) expression and over-expression of positive cell cycle regulator (increased cyclin Dl) were associated with decreased survival rates and shown to predict poor prognosis independently of other factors including tumor differentiation and TNM stage[13]. They suggested that detection of P27 Kipl and cyclin Dl on surgically resected specimens indicates the need for close follow - up evaluation and adjuvant therapy [13].

Gohongi et al [14] demonstrated that human gallbladder tumors express transforming growth factor TGF - B 1 which creates a systemic environment that maintains metastatic tumor cells dormant when implanted in a mouse model. TGF - B 1 secreted by the primary gallbladder tumor suppressed vessel formation, leukocyte endothelial cell interactions, and tumor growth at a distant site [14].

Anti - angiogenic therapies that modulate TGF - B 1 may be important in the future therapy of gallbladder cancer by affecting