Local chemotherapy in the treatment of colorectal liver secondaries

THESIS

Submitted for Partial Fulfillment of

MD. Degree in Radiology

Investigator

Hebat allah Mohamed saad El- Din Fouad

MB.B.CH, M.SC

Assistant lecturer of Radiology

Faculty of Medicine

Cairo University

Under Supervision of

Prof. Ahmed Sami Saeed

Professor of Radiology

Faculty of Medicine

Cairo University

Prof. Magda Moustafa Kamal Hussein

Professor of Clinical oncology

Faculty of Medicine

Cairo University

A.Prof. Ayman Ismail Kamel

Assistant Professor of Radiology

Faculty of Medicine

Cairo University

2012

2012

2012

Acknowledgement

*First and foremost I feel always indebted to **ALLAH**, the most kind and most merciful.*

*I would like to express my deep gratitude and thankfulness to **Prof. Dr. Ahmad Sami Saeed**, Professor of Radiology at Cairo University for his enormous effort, help and support which extend far beyond this work. No enough words can do him justice for his meticulous and keen supervision. He spent unlimited time and a lot of patience guiding me in every minute detail regarding this work which was not possible to be complete without his invaluable guidance.*

*I owe sincere and earnest thankfulness to **Prof. Dr. Magda Moustafa Kamal**, Professor of Clinical Oncology at Cairo University for her kind help in facilitating the provision of cases for this work as well as clinical guidance.*

*I would like to show my gratitude to **A. Prof. Dr. Ayman Ismail Kamel**, Assistant Professor of Radiology at Cairo University who has made available his support in a number of ways starting from basic teaching of technical practice up to his help in performing the cases and providing continuous care.*

*This work would not have been possible without the embracement and generous help of **Prof. Dr. Robert CG Martin**, Director of Division of Surgical, Oncology, Professor of Surgery, University of Louisville, Kentucky, USA. He allowed me to participate in the multi-institutional registry research on treatment of metastatic colorectal cancer to liver using drug eluting beads, providing me with the raw data for the patients in it from which it was possible to do the statistical analysis for this thesis. Also he taught me basic principles of research and was continuously encouraging me.*

*I am obliged to many of my colleagues who supported me to get this work done. **Dr. Ahmed Hosni**, Lecturer of Radiology at Cairo University, who helped in providing some cases images and was offering his help all through.*

Also I am grateful to the courageous patients who were fighting liver secondaries from colorectal cancer who accepted to participate in the thesis and try a new way of therapy for not losing hope in cure. May the mercifulness of Allah be on them for those who died and those who are still alive.

Last but not least remains the appreciation and thankfulness of the hidden supporters, mother, brother and dear husband for their unlimited care and continuous help.

Keywords:
Chemotherapy – Hepatic Transarterial chemoembolization-
Colorectal Liver metastases

The first-line treatment for unresectable hepatic metastases from colorectal cancer is chemotherapy, which may be administered systemically or with a hepatic arterial infusion. Local response results of patients treated with drug eluting beads loaded with Irinotecan after 1 year were stable disease in 38%, complete resolution in 12%, while progressive disease in 23%. The results of our study show that it is a safe and effective way in the treatment of metastatic colorectal cancer.

CONTENTS

List of Abbreviations

APC	Adenomatous Polyposis Coli
ASCO	American Society of Clinical Oncology
CEA	Carcinoembryonic antigen
CEUS	Contrast enhanced Ultrasound
CE IOUS	Contrast enhanced Intra operative Ultrasound
CLOCC	Chemotherapy + Local ablation versus Chemotherapy
CRC	Colorectal cancer
CRLM	Colorectal Liver Metastases
CTAP	CT Arterioportography
DEBIRI	Drug Eluting Beads - Irinotecan
DEB	Drug Eluting Beads
EORTC	European Organization for Research and Treatment of Cancer
FAP	Familial Adenomatous Polyposis
FOLFIRI	Folinic acid (leucovorin), Fluorouracil (5-FU), Irinotecan
FOLFOX	Folinic acid (leucovorin), Fluorouracil (5-FU), Oxaliplatin
FUDR	Floxuridine
Gd-BOPTA	Gadolinium benzyloxypropionictetraacetate
Gd-DTPA-BMA	Gadolinium diethylenetriaminepentaacetic-acid-bis-methylamide
Gd-EOB-DTPA	Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid
HAIP	Hepatic Artery Infusion Pump
HNPCC	Hereditary non-polyposis colon cancer
INR	International Normalized Ratio
LMs	Liver metastases
MDCT	Multi-detector Computed Tomography
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
RECIST	Response Evaluation Criteria In Solid Tumors
RFA	Radiofrequency ablation
TACE	Transarterial chemoembolization

List of Tables

List of Figures

Introduction

Colorectal cancer is the 3rd most common malignancy worldwide. Colorectal cancer metastasizes to various organs, with the lymph nodes being the most frequent, followed by the liver and lungs. By the time of diagnosis, about 25% of patients have liver metastases (synchronous metastases); another 25-30% will present hepatic lesions in the following 2-3 years (metachronous metastases). The overall life expectancy is mainly determined by the progression of liver secondary disease and not by the primary carcinoma, even in patients with an isolated hepatic tumor. Without treatment, life expectancy is less than 1 year ***(McMillan DC and McArdle CS, 2007)***.

Surgery is the only therapy that offers a possibility of cure for the patients with hepatic metastatic diseases. Unfortunately, only 25% of patients with colorectal liver metastases are candidates for liver resection, while the others are not amenable to surgical resection ***(Liu LX et al, 2003)***. Several modalities have been developed for local treatment of liver tumors, including cryotherapy, radiofrequency ablation, percutaneous ethanol injection, laser and photodynamic therapy ***(van de Velde, 2005)***.

Techniques for regional hepatic therapy for metastatic colon cancer to the liver include hepatic arterial infusion chemotherapy, chemoembolization, infusion radiotherapy with yttrium-90 labeled

particles and isolated hepatic perfusion. While these approaches have been available for a long time, their role in the management of metastatic colon cancer continues to evolve ***(Bartlett DL et al, 2006)***.

Transarterial therapies take advantage of the dual blood supply of the liver. Approximately 80% of the blood supply to hepatic metastases from colorectal cancer arrives via the hepatic artery, whereas three-fourths of the blood supply to normal hepatic parenchyma is portal venous. Hence, cytotoxic agents that are infused selectively into the hepatic artery preferentially target tumor cells over normal hepatic tissue. Traditional transarterial therapies are based on the infusion of chemotherapeutic drugs into the hepatic artery either intermittently or through a surgically implanted hepatic artery pump ***(Sanjeeva P. Kalva et al, 2008)***.

The concept of hepatic artery infusion (HAI) dates back to the early 1960s when it was tried in a few patients with gastrointestinal tumors metastatic to the liver and was associated with favorable outcomes. The rationale for HAI is to expose the metastases to high chemotherapy concentrations while minimizing systemic toxicity. The other rational is the high first pass hepatic extraction of the drug used for this approach ***(Homsi J and Garrett CR, 2006)***. For many years, fluorouracil (5-FU) in combination with Leucovorin (LV) was the standard therapy for metastatic colorectal cancer, yielding a response rate

of 20%-30% and median survival time of 11-12 months. Newer systemic chemotherapy regimens incorporating the platinum agent have increased both response rates and overall survival ***(Steven R. Alberts and Lawrence D. Wagman, 2008)***.

Transarterial chemoembolization (TACE) is a catheter-based technique that combines both regional chemotherapy and embolization to increase the dwell time of cytotoxic agents and induce ischemia in the tumor. The use of drug-eluting microspheres in a new variation of the TACE method is designed to improve the precision of drug delivery. Another recent advance, a form of brachytherapy, involves the administration via the hepatic artery of yttrium- 90 (90Y) microspheres, which preferentially are deposited within hypervascular tumors and emit beta radiation. Experimental techniques in gene therapy also are being tested ***(Sanjeeva P. Kalva et al, 2008)***.

Aim of the work

Study the effect of loco regional chemotherapy on metastatic colorectal cancer in the context of;

1. Effect on tumor size and viability.
2. Effect on the patient's quality of life (functional status).

Pathophysiology and Epidemiology of Colorectal Cancer

Colorectal cancer (CRC) is very common worldwide, with 850,000 people developing it annually and 500,000 dying of the disease. Its prevalence and preventable nature makes CRC a primary focus in the oncology community. In fact, estimates indicate that gastrointestinal cancers represent about 20% of all cancers. The broad diversity in the types of patients and stages at which the disease is diagnosed creates multidisciplinary challenges ***(Ries LAG et al, 2000)***.

Risk Factors for Colorectal Cancer

1. Age older than 50 years.
2. Previous CRC.
3. Polyps.
4. Family history of CRC or adenomatous polyp.
5. Inflammatory bowel disease:

- Ulcerative Colitis.
- Chron's disease.

6. Preventable risk factors:

- High-fat diet.
- Diet low in fruits and vegetables.
- Physical inactivity.
- Obesity.
- Smoking.

- Alcohol.

7. Possible chemoprevention:

NSAIDs, COX-2 inhibitors. (NSAIDs: Non-steroidal anti-inflammatory drugs, COX-2: cyclooxygenase isoenzyme) ***(AL B. Benson, 2007)***.

Approximately 70% of CRCs are nonhereditary or sporadic, and about 20% are familial. Two key hereditary syndromes are familial adenomatous polyposis (FAP) and hereditary non-polyposis colon cancer (HNPCC). The FAP syndrome develops from inherited mutations of the adenomatous polyposis coli (APC) gene, and accounts for approximately 1% to 2% of all CRC cases. Patients with FAP develop hundreds to thousands of polyps before age 30, and inevitably develop CRC. Usually, CRC develops at an early age (average, 39 years) in FAP patients, but it can be prevented by surgically removing the colon ***(Giardiello FM et al, 1997)***.

Lynch syndrome, or HNPCC, is caused by inherited mutation in any 1 of 5 mismatch repair (MMR) genes, and accounts for 3% to 5% of all CRC cases. The term non-polyposis does not mean that the cancer does not emanate from polyps; it is used to distinguish HNPCC from FAP. Polyps do not develop earlier in people with HNPCC, but once they do, their tendency to become malignant more rapidly leads to a 70% to 80% lifetime risk of CRC. In these patients, CRC occurs at early age (average 44 years). Some patients with HNPCC also elect to have a