Abstract

Background: The aim of this work is to assess the recurrence (primary site and distant metastases) after hepatic resection for metastatic colorectal cancer according to the preoperative prognostic factors, for the selection of patients who may benefit from hepatic resection.

Patients and methods: During the period of August 2009 through August 2013, 44 patients with liver metastases from colorectal cancer underwent hepatic resection at Eldemerdash and Ainshams Specialized Hospitals, Ain Shams Universty.Faculty of Medicine. All 44 patients were regularly followed and monitored for recurrence; disease free survival (DFS) and overall survival (OS), within a median follow up of 18 month after hepatic resection.

In this study we investigated the recurrence, disease free survival (DFS) and overall survival (OS) according to 12 perioperative prognostic risk factors, these factors related to the clinicopathologic variables pertaining to patient characteristics, clinical data and histopathologic finding

The mean age of the whole group was 50.7±12.0 ranging from 24 to 75 years. Twenty-seven patients were males (61.4%) and the remaining 17 females constituted 38.6% of the studied group. At presentation 5 patients (11.4%) had colonic obstruction and 2 patients received perioperative blood transfusion. Preoperatively, 36 patients (81.8%) received chemotherapy; 28 patients (63.6%) responded to chemotherapy. In addition 6 patients (13.6%) had portal vein embolization

Results: Solitary metastatic focus was detected in 18 patients (40.9%). The median number of metastatic foci was 2 (range: 1-7) Only two patients had other metastasis outside the liver where the ovarian metastases were discovered during exploration in both patients;. Histopathological type in all cases was adenocarcinoma. Grade of liver metastasis ; the majority of cases had grade II disease. The median size of overall tumor burden of hepatic metastases was 9 cm ranging from 2 to 15 cm. The median size of the largest tumor focus of hepatic metastases was 5 cm ranging from 2 to 12 cm. Nearly One-half of the cases had right lobe lesions. Lymph node metastasis of the primary colon cancer was present in 25 patients (56.8%). CRLM were synchronous in 23 patients (52.3%), while 21 patients (47.7%) had metachronous CRLM.

Carcinoembryonic antigen (CEA) and Cancer antigen (CA) 19.9 were measured in all patients as a part of preoperative assessment. All patients had elevated serum level of CEA except 2 (4.5%), while 5 patients had CEA serum level > 200 μg/L. CA 19.9 serum level were elevated in 21 patient (47.7%); 8 of them had levels > 200 IU/ml.

Preoperatively, 36 patients (81.8%) received chemotherapy; 28 patients (63.6%) responded to chemotherapy. In addition 6 patients (13.6%) had portal vein embolization

The operation done was major in 34 patients (77.3%). The median number of resected segments was 2 (range: 1-6). Only two patients (4.6%) had positive margins of the resected liver segment. The two patients with extrahepatic metastasis had right and left oophorectomy in addition to hepatic resection

5 factors adversely affecting survival and recurrence after hepatic resection for colorectal liver metastases.These are non response to neoadjuvent chemotherapy. Positive lymph node status of the primary colon tumor and advanced nodal stage,the major hepatic resection (more or equal to 2 segments), the diameter of the largest tumor>5cm and disease free interval from diagnosis of the primary to discovery of liver metastases< one year.

Conclusion: In the present study, the Disease free survival and recurrence after hepatic resection in patients with preoperative prognostic risk factor 0 (without risk factors), was superior to that in resection patients with 1, 2, 3, 4 or 5 factors respectively and in non resection patient and the 5 factors adversely affecting survival and recurrence after hepatic resection for colorectal liver metastases.These are non response to neoadjuvent chemotherapy. Positive lymph node status of the primary colon tumor and advanced nodal stage,the major hepatic resection (more or equal to 2 segments), the diameter of the largest tumor>5cm and disease free interval from diagnosis of the primary to discovery of liver metastases< one year.

Keywords: Hepatic resection, liver resection, recurrence after hepatic resection, colorectal cancer, liver metastases, metastatic colorectal cancer.

INTRODUCTION

Colorectal cancer is the third most common cancer worldwide ***(Abdalla et al., 2006);*** 15-20% of patients have synchronous liver metastases at the time of diagnosis and 50% of patients will develop liver metastases within 5 years of the initial "curative" resection of the primary tumor ***(Nordlinger et al., 1996).*** Surgical resection (hepatectomy) of colorectal liver metastases (CRLM) remains the only potentially curative modality of therapy ***(Pawlik et al., 2005).*** The outcome of untreated CRLM is dismal, with median survival of 5-12 months ***(Alberts et al., 2005);*** hepatectomy can result in a 5-year survival rate of 35-40% ***(Ruers and Bleichrodt, 2002)***

When traditional criteria of resectability are applied, only 10-15% of patients are eligible for curative resection at the time of diagnosis ***(Wanebo et al., 1996).*** Over the last decade, improvements in surgical technique, imaging and systemic therapy have led many institutions to expand the criteria of resectability; indeed, some centers consider the only contraindication for hepatic resection is the inability to achieve margin-negative resection while ensuring sufficient hepatic reserve ***(Abdalla et al., 2006).***

The use of multidetector helical CT scans improved resolution and has increased the- sensitivity of detecting CRLM to 70%-90 %.Positron emission tomography using fluoro-18-deoxyglucose (FDG-PET) has recently emerged as a supplemental modality in the diagnosis of hepatic metastasis. A recent analysis has reported the sensitivity and specificity of FDG-PET at 88% and 96%, respectively, for detecting hepatic metastasis and 90% and 95% for detecting extra hepatic disease. The results of FDG-PET scan are particularly impressive for detecting extra hepatic disease and have the potential to change the overall management plan in 20%-25% of the patients ***(Kamel et al., 2003).***

Portal vein embolization (PVE), by causing ipsilateral atrophy and contralateral hypertrophy, can be used to expand the patient base undergoing curative liver resection for CRLM. It is used for patients where the extent of surgical resection will result in less than the optimal functional liver volume of *25%-40%* necessary to prevent postoperative liver failure ***(Di Stefano et al., 2005)***.

Surgical resection of the primary tumor was always associated with nodal dissection in compliance with current guidelines. Liver resection was either performed at the same time as the resection of the primary tumor or later anatomic or nonanatomic hepatic resection depended on the type of tumor and the requirement for healthy resection margins and preservation of the hepatic parenchyma. Resections of extra hepatic localizations were performed before or after liver surgery ***(Ziparo et al., 2002)***

The prognostic factors are largely established; patients with four or more metastases have a worse outlook as do patients with larger metastases and where the primary tumour is poorly differentiated or has lymph node involvement. Extra-hepatic disease and a high CEA are also adverse features and after operation a positive resection margin has prognostic significance. These factors emerge from most of the studies that have been undertaken ***(Simmonds et aL 2006; Rees et aL 2008).*** At present liver resection is the only modality shown to convincingly cure liver metastasis, although ablative treatments are currently showing some promise ***(Mulier et al., 2008).***

AIM OF THE WORK

The aim of this work is to assess the recurrence (primary site and distant metastases) after hepatic resection for metastatic colorectal cancer according to the preoperative prognostic factors, for the selection of patients who may benefit from hepatic resection.

LIVER ANATOMY

Couinauds liver segmentation

The Couinaud segmentation system is based on the distribution in the liver of both the portal vein and the hepatic veins **(Champetier, 1994)** and shows a specific consideration for the caudate lobe. Fissures of the three hepatic veins (portal scissurae) divide the liver into four sectors (segments), lateral and paramedian, on the right and left sides, respectively. The planes containing portal pedicles are called hepatic scissurae. Eight segments are described, one for the caudate lobe (segment I), three on the left (segments II, III, and IV), and four on the right (segments V, VI, VII, and VIII). In general, the segments of this classification correspond to subsegments of Healey and Schroy **(Healey and Schroy, 1953).**

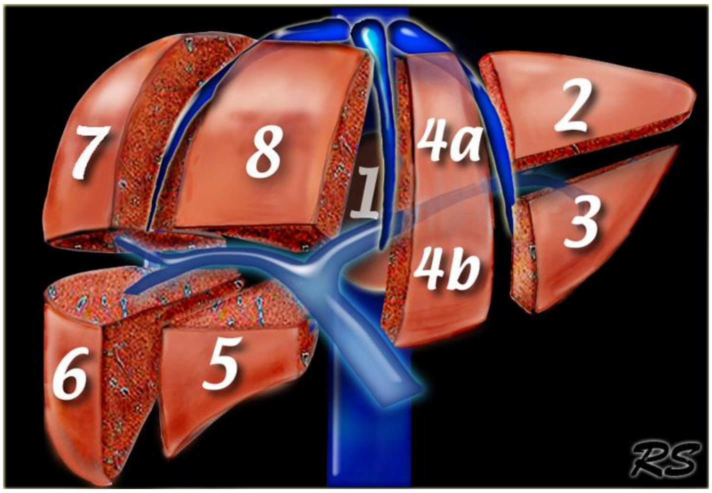

Fig.1: Segmental anatomy according to couinaud, 1957.

Couinaud's system of liver segmentation differs from Healey and Schroy's system in several ways, however. According to Couinaud, a subdivision of segment IV and the caudate lobe into two parts is not justified. Furthermore, Couinaud asserted that a study of organogenesis and comparative anatomy suggests that the umbilical fissure is the hepatic scissura between segments III and IV **(Couinaud, 1957**).For Healy and Schroy **(Healey and Schroy, 1953),** however, the umbilical fissure is the plane of separation between territories of biliary (and consequently portal vein) branches between the medial and lateral segment of the left lobe **(Champetier, 1994).**

Segmental anatomy of the liver by computed tomography

Computed Tomography:

CT scans illustrate the Couinaud classification of numbering of liver segments. The longitudinal plane of the right hepatic vein divides VIII from VII in the superior portion of the liver and V from VI in the inferior portion of the liver. The longitudinal plane of the middle hepatic vein through the gallbladder fossa separates IVa from VIII in the superior liver and IVb from V in the inferior liver. The longitudinal plane of the left hepatic vein and fissure of the ligamentum teres separates IVa from II in the superior liver and IVb from III in the inferior liver. The axial plane of the left portal vein separates IVa superiorly from IVb inferiorly and II superiorly from III inferiorly in the left lobe. The axial plane of the right portal vein separates VIII and VII superiorly from V and VI inferiorly in the right lobe. The caudate lobe (segment I) extends between the fissure of the ligamentum venosum anteriorly and the inferior vena cava posteriorly ***(Harshavardhan.andSuresh, 2012)*.**

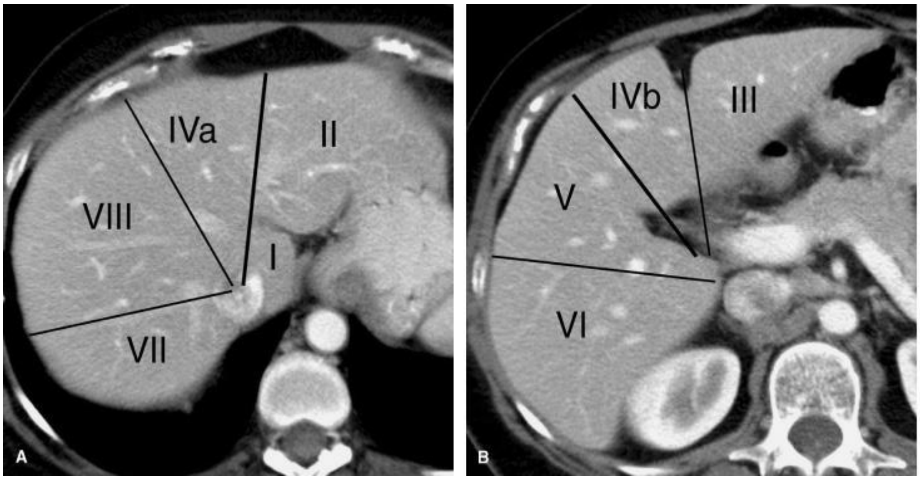

Fig. 2: A) Superior portion of the liver (B) inferior portion of the liver ***(Harshavardhan.andSuresh, 2012)***

Liver vasculature

The liver has a dual blood supply from the portal vein and common hepatic artery.The portal vein is responsible for approximately 70% and the hepatic artery for 30% of the blood flow of the liver. In the liver, arteries, portal veins, and bile ducts are surrounded by a fibrous sheath, the Glissonian sheath. Hepatic veins in the hepatic parenchyma lack such protection **(Ger, 1989).**

Arteries

Common hepatic artery

The common hepatic artery take origin from the celiac trunk (86%); other sources are the superior mesenteric artery (2.9%), the aorta (1.1%), and, very rarely, the left gastric artery **(Van Damme and Bonte, 1985).** The common hepatic artery then runs horizontally along the upper border of the head of the pancreas covered by the peritoneum of the posterior wall of the omental bursa. The gastroduodenal artery branches off the common hepatic artery posterior and superior to the duodenum. The common hepatic artery continues as the proper hepatic artery and turns upward to ascend in the lesser omentum, enveloped by the hepatoduodenal ligament, in front of the epiploic (Winslow's) foramen. Within the hepatoduodenal ligament, the proper hepatic artery lies to the left of the common bile duct and anterior to the portal vein. The portal vein, however, is located posteriorly or deeper to the proper hepatic artery and the common bile duct. Within the ligament the proper hepatic artery divides into right and left branches, called right and left hepatic arteries. Arterial distribution to different functional segments is identical to the distribution of portal vein **(Champetier et al, 1994).**

Left hepatic artery

In 25% to 30% of cases, the left hepatic artery arises from the left gastric artery. In 40% of subjects the left hepatic artery branches into a medial and a lateral segmental artery. Other patterns often occur, however. The medial segmental artery supplies the quadrate lobe. The lateral segmental artery divides into superior and inferior arteries for the respective subsegments as described by the Bismuth classification.Furthermore, the left hepatic artery gives off a branch for the caudate lobe, supplying its left side. **(Healey, 1970).**

Right hepatic artery

In about 17% of subjects, the right hepatic artery branches from the superior mesenteric artery. The right hepatic artery passes to the right behind (or occasionally in front of) the hepatic duct in front of the portal vein. Before entering the liver, the right hepatic artery gives off the cystic artery in the hepatocystic triangle located between the cystic duct and the common bile duct within the liver or extrahepatically in the porta, the right hepatic artery divides into anterior and posterior segmental arteries, which divide further into superior and inferior arteries to supply the respective subsegments. An artery for the caudate lobe also originates from the right hepatic artery and supplies the caudate process and the right side of the caudate lobe. These arteries are found under the respective bile duct branches **(Healey and Schwartz, 1964).**

Aberrant hepatic arteries

Aberrant hepatic arteries are found in about 45% of subjects. If the arteries arise entirely from some source other than the celiac arterial distribution, they are called ′ 'replacing" arteries and can supply an entire lobe of the liver or even the entire liver. Although atypical hepatic arteries are commonly called ″accessory" arteries if they arise from some aberrant source and are additive to lobar branches, it is evident that they provide the primary arterial supply to a specific part of the liver (lobe, segment, or subsegment); therefore, they are not "accessory" arteries **(Smith et al., 1971).**

Veins

Portal vein

The portal vein is between 7 and 10 cm long and between 0.8 and 1.4cm in diameter and is without valves. It is formed by the confluence of the superior mesenteric vein and the splenic vein behind the neck of the pancreas. At the porta hepatis, the portal vein bifurcates into right and left branches before entering the liver. In general, portal veins are found posterior to hepatic arteries and the bile ducts in their lobar and segmental distribution ***(Skandalakis* et *al, 2004*).**

The right branch of the portal vein is located anterior to the caudate process and is shorter than the contralateral branch. Near its origin it gives off a branch for the caudate lobe, It follows the distribution of the right hepatic artery and duct and bifurcates into anterior and posterior segmental branches as soon as it enters the hepatic parenchyma. Each segmental branch further divides into inferior and superior subsegmental branches for its respective parenchyma subsegments.

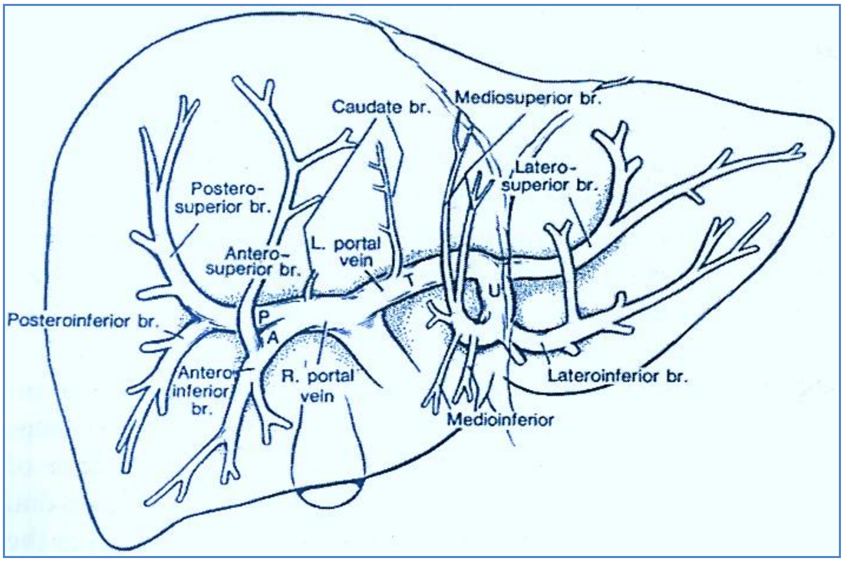

Fig.3: Intrahepatic distribution of the hepatic portal vein.A, anterior segment; br, branch; P, posterior segment; T, pars transversus; U, pars umbilicus, the site of the embryonic ductus venosus .***(Skandalakis* et al*, 1987).***

Parallel to the segmental branches of the portal vein are a corresponding segmental branch of the proper hepatic artery and of the hepatic duct. At the porta hepatis, connective tissue, together with the blood vessels, enters the liver as the perivascular fibrous capsule (formerly known as Glisson's capsule). The three parallel vessel systems are always bound together within the perivascular connective tissue forming the portal triad (earlier known as Glisson's triad) ***(Skandalakis* et al*, 2004)*.**

Hepatic veins

The liver is drained by a series of dorsal hepatic veins.Three major and between 10 and 50 smaller veins open into the 1VC. **(Nakamura and Suzuki, 1981).**

The three major veins have an extrahepatic length of 0.5 to 1.5 cm. In contrast to hepatic arteries, portal veins, and bile ducts, these veins are found intrahepatically within the (intersegmental) planes separating lobes and segments (intersegmental). They drain adjacent segments and subsegments. The right hepatic vein is the largest. It lies in the right fissure, draining the entire posterior segment (superior and inferior subsegments) and the superior subsegment of the anterior segment of the right lobe. It serves segments V, VI, VII, and part of VIII. The middle hepatic vein lies in the median fissure and drains the inferior subsegment of the anterior segment of the right lobe and the inferior area of the medial subsegment of the left lobe. The middle hepatic vein also drains the right anterior superior subsegment. This vein mainly serves the left liver,together with the left hepatic vein **(Champetier, 1994).The** middle hepatic vein serves mainly segments IV, V, and VIII. The left hepatic vein lies in the upper part of the left fissure. It drains the superior area of the medial subsegment (segment IV) and the left anterior superior and inferior subsegments (segments II and III). In about 60% of individuals, the left and middle veins unite to enter the IVC as a single vein **(Healey and Schwartz, 1964).**

Lymphatics

The hepatic lymphatic network, superficial and deep, does not follow the functional vasculobiliary organization. The superficial lymphatic system, located within the Glissonian sheath, travels toward the thorax and the abdominal regional lymph nodes. Lymph vessels pass the diaphragm mainly in the bare area or through Morgagni's foramen to reach anterior or lateral phrenic nodes. These trunks join the internal thoracic artery lymph pathway as well as anterior and posterior mediastinal lymphatics **(Champetier, 1994).**

Intrahepatic biliary tract

Understanding the surgical anatomy of the biliary ductal system, including the gallbladder, is of great consequence in the study of hepatic anatomy. Following is a brief overview of the intrahepatic biliary tract Bile canaliculi are formed by parts of the membrane of adjacent parenchymal cells, and they are isolated from the perisinusoidal space by junctions. Bile flows from the canaliculi through ductules (canals of Hering) into the interlobular bile ducts found in portal pedicles. In the segmental and subsegmental pedicles surrounded by the Glissonian sheath, bile ducts are found above and veins and arteries beneath **(Champetier, 1994).** Biliary segmentation is identical to portal vein segmentation.In contrast to portal vein branches, which may communicate, no communication is observed in biliary branches **(Anderhuber and Lechner, 1986).**

The right hepatic duct

The right hepatic duct has an average length of 0.9 cm and is formed by the union of the anterior and posterior branches at the