MANAGEMENT OF METASTATIC COLORECTAL CANCER TO LIVER

Essay

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in General Surgery

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List of Abbreviations

5-FU	Fluorouracil
5-FU/LV	Fluorouracil and leucovorin
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CA 19.9	Carbohydrate Antigen 19-9, also called Cancer Antigen 19-9
CEA	Carcinoembryonic antigen
CEUS	Contrast enhanced ultrasonography
CNS	Central nervous system
CRP	C-reactive protein
CRLMs	Colorectal liver metastases
CRS	Clinical risk score
CSA-P	Colon-specific antigen-P
CT	Computed tomography
CVP	Central venous pressure
DIC	Disseminated intravascular coagulapathy
DNA	Deoxyribonucleic acid
EGF	Epidermal growth factor receptor-targeted agents
EHD	Extrahepatic disease
EMA	Epithelial membrane antigen
FDG	Fluoro-2-deoxyglucose
FDG-PET	Fluoro-2-deoxyglucose- positron emission tomography
FLR	Future liver remnant
FNH	Focal nodular hyperplasia
FOLFIRI	5-fluorouracil (5-FU), leucovorin, and irinotecan
FOLFOX	5-fluorouracil (5-FU), leucovorin, and

	oxaliplatin
HAI	Hepatic artery infusion
HCC	Hepatocellular carcinoma
ICG	Indocyanine green retention
IL-8	Interleukin-8
IOUS	Intraoperative ultrasound
IRT	Inflammatory response to tumor
IVC	Inferior vena cava
KRASgene	Kirsten rat sarcoma viral oncogene homolog
MAC	Modified Astler-Coller system
MAP kinase	Mitogen-activated protein kinases
MDCT	Multidetector computed tomography
MR	Magnetic resonance
MRCP	Magnetic resonant cholicystopancreatography
mRNA	Messenger ribonucleic acid
NC	Neoadjuvant chemotherapy
NIH	National Institutes of Health Consensus Development Program
NLR	Neutrophil-to-lymphocyte ratio
OS	Overall survival
PCA	Patient-controlled analgesia
PD-ECGF	Platelet-derived endothelial cell growth factor
PET	Positron emission tomography
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
PLF	Post-resectional liver failure
PT	Prothrombin time
PVE	Portal vein embolisation
R0	Margin-negative resection
R1	Margin-posetive microscopically

RECIST	Response evaluation criteria in solid tumors criteria
RFA	Radiofrequency ablation
RLV	Remnant liver volume
SGOT	Serum glutamic oxalacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SPECT	Single Photon Emission Computerized Tomography
TLV	Total liver volume
TNM	Tumor, lymph Node, and distant Metastasis
TSP	Thrombospondin
US	Ultrasonogragpy
VEGF	Vascular endothelial growth factor
VWF	Von Willebrand Factor

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Introduction

Colorectal cancer is the third most common malignancy worldwide, with over 1.2 million new cases diagnosed each year. Despite decreasing mortality rates in several western countries, this neoplasm still represents the second leading cause of cancer-related mortality, with 608,700 deaths attributed to this disease in 2008. ***(Jemal A et al., 2011)***

Epidemiologic data indicate that more than half of the patients develop distant metastases during the course of their disease, with the liver involved in most cases. In such patients, hepatic resection has become the standard of care and, currently, it remains the only single treatment modality offering hope for a cure. Rather disappointingly, only a minority of patients are suitable for resection. ***(De Jong MC et al., 2009)***

The complex decisions required to determine respectability are best made in the setting of an interdisciplinary team that includes surgeons experienced in liver surgery. Preoperative evaluation requires a complete medical evaluation to determine the patient's suitability for surgery as well as detailed anatomic imaging to determine the location of the liver tumors and to exclude extra hepatic metastasis. Radiological evaluation is needed not only to identify extra hepatic disease but also to assess the adequacy of liver parenchyma after surgery. In addition to the patient evaluation, liver function tests are evaluated to assess the synthetic function of the liver; combined with radiological findings, these tests can aid in the decision-making process. ***(Taylor R and Fong Y, 2007)***

Margin-negative (R0) resection of limited metastatic disease, in conjunction with systemic antineoplastic agents, is the primary treatment strategy, leading to long survival times for appropriately selected patients. There is debate over whether the primary tumor and secondaries should be removed at the same time or in a staged manner. ***(Aloia TA et al., 2007)***

Chemotherapy is effective in converting some unresectable liver metastases into resectable disease, with a correspondingly better survival outcome. However, the ideal chemotherapy with or without biological agents and when it should be administered in the course of treatment are uncertain. The role of neoadjuvant chemotherapy in initially resectable liver metastases is controversial. Local delivery of chemotherapy, with and without surgery, can lead to longer disease-free survival times, but it is not routinely used with curative intent. ***(Abdalla EK et al., 2004)***

In recent years, the number of surgical candidates has increased to approximately 20% of all stage IV patients. This change has occurred owing to the recognition that surgically resecting colorectal liver metastases (CRLMs) may substantially improve long-term survival and, mostly, as a consequence of the evolution of the definition of resectability. ***(Kopetz S et al., 2009)***

In fact, as the safety of liver resection has improved, advanced surgical techniques have been introduced and efficient chemotherapy regimens have become available, surgeons have challenged the traditional criteria used to define which patients can be considered resectable. Nowadays, selection criteria focus only on the remaining liver and on the possibility of completely resecting all tumors with one or two consecutive operations. ***(Charnsangavej C et al., 2006)***

As the indications for hepatectomy broaden, the possibility of accurately predicting outcomes within the wide spectrum of the disease is essential to guide treatment decisions and to stratify patients for clinical trials based on the individual risk of recurrence or death. ***(House MG et al., 2010)***

Aim of the Work

To review the recent modalities in diagnosis and surgical treatment of liver metastases from colorectal cancer.

Anatomy of Colorectal Liver Metastasis

Embryology:

The liver primordium is formed in the third week of gestation as an outgrowth of endodermal epithelium (known as the hepatic diverticulum, or liver bud). The connection between the hepatic diverticulum and the future duodenum narrows to form the bile duct, and an outpouching of the bile duct forms into the gallbladder and cystic duct. Hepatic cells develop cords and intermingle with the vitelline and umbilical veins to form hepatic sinusoids. Simultaneously, hematopoietic cells, Kupffer cells, and connective tissue form from the mesoderm of the septum transversum. The mesoderm of the septum transversum connects the liver to the ventral abdominal wall and to the foregut. As the liver protrudes into the abdominal cavity, these structures are stretched into thin membranes, ultimately forming the falciform ligament and the lesser omentum, respectively. The mesoderm on the surface of the developing liver differentiates into visceral peritoneum except superiorly, where contact between the liver and mesoderm (future diaphragm) is maintained, forming a bare area devoid of visceral peritoneum. ***(Ruiz-Casado A and Pereira F, 2006)***

Incidence and prevalence:

Colorectal cancer is the third most common cancer and the third leading cause of cancer related mortality in the United States. Colorectal cancer is also very common in Western Europe, Australia and New Zealand, whereas the age standardized incidence rate of colorectal carcinoma is very low in India and Africa. There seems to be an association of higher incidence rates in colorectal cancer with increasing affluence. Over the past decade, colorectal cancer rates have modestly decreased or