Recent Strategies and Paradigm Shift in Management of Hepatic Metastasis from Colorectal Cancer

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Abstract

The liver is the most common site for metastasis from colorectal cancers (CRCs). There are so many new armamentarium, which have increased the life expectancy and progression-free survival. There are various available guidelines, such as NCCN, ESMO, and ASCO, which provide an insight into the latest modalities and new protocols. We have tried to elucidate into paradigm shift of the management.

Keywords Colorectal cancer · Hepatic metastasis · Multimodal treatment

Introduction

The liver is the most common site for metastasis from colorectal cancers (CRCs). One quarter of the patients with primary colorectal carcinoma presents with synchronous hepatic metastasis, and 50% of patients who underwent resection for colorectal as a primary will eventually develop metachronous liver metastasis [1]. The survival for untreated colorectal hepatic metastasis (CHM) is dismal with median survival estimated in only 6–9 months [2]. In the past few decades, multimodal management of CHM has resulted in a paradigm shift in the way we manage them now. Overall survival has dramatically increased from less than 6 months to nearly 2 years. Five years of survival has increased from < 8%, using palliative chemotherapy (CT) to 25–40% using multimodal management. Hepatic resection of metastases has become much safer, as mortality rates have decreased from 10% to approximately 1% in experienced centers [3]. In this review, we tried to elucidate this shift and describe the evolving guidelines in the management of CHM, advancements in surgical technique, chemotherapeutic regimens, and adjuncts.

Methods

We did a thorough review of Cochrane databases, PubMed, 2016 NCCN guidelines, ESMO guidelines, and ASCO recommendations for metastatic colorectal cancer. We have also included contemporary studies from LiverMetSurvey. LiverMetSurvey is a large prospective international Internet-based registry, collecting and regularly updating clinical data from all consecutive patients undergoing surgery for CLM, and was designed to assess the efficacy of multimodality treatment of CLM [4]. We have outlined herein the major changes in management in terms of patient selection for surgery, pre-operative imaging studies, type of surgical resection, and chemotherapy with addition of molecular agents. Further, our synopsis was stratified according to level of evidence to reflect its role of implication in daily clinical practice.

Results

Colorectal liver metastasis (CRLM) is classified into three groups according to resectability (level of evidence IIA; ESMO).

- 1) Group I: liver lesion(s) are clearly resectable.
- 2) Group II: liver lesion(s) are unresectable but potentially exchangeable to resection after conversion chemotherapy or liver-directed therapy.
- 3) Group III: liver lesion(s) are unresectable and are likely to remain so even with effective chemotherapy or liver-directed therapy [5].

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The management algorithm based on this classification is shown in Fig. 1;

- 4) Selection criteria for surgery: Fitness for surgery is judged by ASA & POSSUM score. Patients being considered for a hepatic resection are assessed for preoperative liver dysfunction, i.e., Child-Pugh score, portal hypertension, and synthetic function of liver based on indocyanine green (ICG) dye test. Two most important criteria for surgical consideration includes the following:
 - a. ability to achieve R0 resection and
 - b. adequate viable future liver remnant (FLR), with a vascular inflow and outflow and biliary drainage.

FLR is the percentage of liver that remains after surgery. It is a strong, independent predictor of postsurgical hepatic dysfunction and complications [6] (level I; strength of recommendation B, NCCN). The older criteria, based on number, size, and location of lesions, are not significant factors for surgical planning.

Preoperative Workup/Imaging (Level IIA, Strength if Recommendation B)

Preoperative imaging studies aim to delineate the extent of hepatic metastases, determine their best management plan, and to identify extrahepatic disease, taking into account lymph node, and peritoneal involvement, local or regional recurrence.

- 1) Multidetector CT (MDCT) in portal venous phase is most commonly used imaging modality for detection and characterization of hepatic metastases. Liver volumetry is

done with CT scan to assess FLR. Healthy liver tolerates reducing its volume to 20%, chemotherapy induced injury or cirrhosis will require a FLR of 30% [7].

- 2) Magnetic resonance imaging (MRI), with liver specific contrast Gd EOB-DTPA (gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid) is utilized for detecting and characterizing liver lesions, particularly those < 1 cm in size. This is of paramount value in patients with preexisting steatosis or chemotherapy-induced changes.
- 3) Intraoperative ultrasound (IOUS): It identifies new subcentimetric liver lesions intraoperatively that were missed during preoperative imaging, thus changing the live time surgical resectability. The development of contrast enhanced ultrasound (CEUS) has dramatically increased the potential of sonography in the assessment of focal liver lesions. Contrast is non-nephro/cardiotoxic. CEUS is utilized as a dynamic study in questionable hepatic lesions intraoperatively. In a comprehensive LiverMetSurvey on 6025 patients by Vigano et al., it concluded that IOUS reduces the hepatic early recurrence rate [8].
- 4) PET-CT: It is recommended for preoperative detection of unrecognized additional metastatic liver lesions and to detect extra hepatic disease. PET-CT should not be used in clearly unresectable disease.

Timing, Surgical Resectability, and Interventional Modalities for Safe Maximal Resection

1. Timing of resection: There are two strategies with respect to the timing of liver resection for synchronous CRLM. One of these methods is resection at the same time as the primary tumor is removed; this is termed as synchronous resection. The second is performed 2–3 months after

Fig. 1 Management algorithm

removal of the primary colorectal tumor and the resection is performed if curative liver resection is possible, termed as metachronous resection. NCCN guidelines strongly favor synchronous resection [9]. (level IIA, B).

2. Timing of resection and chemotherapy: Classical management (CM) includes resection of the primary tumor, followed by chemotherapy. Metastases were subsequently removed, after appropriate response to chemotherapy. Reversed management (RM) begins with a liver-directed neoadjuvant chemotherapy, followed by the resection of all CRLM and finally treatment of the primary cancer. In a LiverMetSurvey on 787 patients, survival were similar in the RM and CM groups (48 vs. 46% at 5 years, $P = 0.965$ and 30 vs. 26%, $P = 0.992$). This study concluded that classical and reversed managements of metastatic liver disease in colorectal cancer are associated with similar survival when successfully completed [10].
3. Segmental resections along hepatic veins, obtaining clear surgical margins of 1 cm and preservation of native liver parenchyma are associated with improved perioperative outcomes without jeopardizing oncological principles.
4. Portal vein embolization: It is a very effective strategy to increase FLR; it is indicated if FLR as determined by volumetric studies is found below threshold. The goal of PVE is to achieve complete portal occlusion of targeted segments. Embolizing the entire portal tree including distal branches is important to prevent porto-portal shunts [11]. The treatment algorithm based on FLR and Child-Pugh score as discussed previously is shown in Fig. 2.
5. Extrahepatic disease: NCCN & ESMO guidelines are unanimous on the surgical criteria of carefully selected patients having concomitant pulmonary metastasis. Patients should not have more than two metastatic nodules and a maximum diameter of the largest metastatic lung nodule should be less than 3 cm [12]. (III, C). Surgery for extra-hepatic metastasis has been extended to portal lymph node metastasis and small volume peritoneal carcinomatosis in some small studies.

Role of Genetics: (Category IIA, NCCN)

KRAS/NRAS and BRAF (optional) mutation testing are recommended at the diagnosis of liver metastases in colorectal cancer. Its major implication is in the patients without KRAS mutations (wild KRAS). These patients have shown better overall survival with cetuximab and panitumumab via the EGFR inhibition as compared to those patients with KRAS mutation. Major chemotherapeutic and molecularly targeted agents—cytotoxic and biological agents may be used in perioperative period to decrease tumor volume and risk of relapse. They are used in adjuvant

setting to decrease the micrometastatic burden. Combination chemotherapy with 5-FU/LV/oxaliplatin (FOLFOX) or 5-FU/LV/irinotecan (FOLFIRI) provides higher response rates, longer progression-free survival (PFS), and better survival than any other regimen [13]. The recommendations are a total of 6 months of chemotherapy that should be given before (neoadjuvant chemotherapy), between or after surgery (adjuvant) (IIA, B, NCCN). Bevacizumab (VEGFR inhibitor) has been shown to increase the survival, PFS and RR in first-line treatment in combination with 5-FU/LV/irinotecan, and FOLFOX regimen as first-line treatment [1, B].

Panitumumab and cetuximab are EGFR inhibitors that have demonstrated benefits in treating patients with metastatic CRC. Benefits have particularly been found using cetuximab in chemorefractory patients, improving survival compared to standard therapies. In a prospective trial on 46 patients with unresectable liver metastasis neoadjuvant chemotherapy with cetuximab was given to 34 patients and R0 resection was performed in 28 patients (60.9%). This study concluded that cetuximab yields high response rates compared with historical controls, and leads to significantly increased resectability [14].

Liver-Directed Therapies (Ablative Therapies)

They are predominantly used in non-resectable liver mets with aim to provide continuum of care. The data is mixed regarding the outcome so current guidelines are not clear on their definite role.

1. Trans arterial chemoembolization (TACE)/trans arterial radioembolization (TARE): Hepatic metastases derive its blood supply preferentially from hepatic artery. Trans arterial catheter-based therapies deliver the chemotherapeutic agents to these foci, while minimizing systemic exposure and treatment associated toxicities. Options include radioembolization (RE) with yttrium-90 (90Y). TACE is done using either emulsions of ethiodized oil and chemotherapy solution or drug-eluting beads loaded with irinotecan (DEBIRI-TACE). NCCN, ESMO, & ASCO panels lack consensus for arterially directed therapies. Their use is still restricted to clinical trials and multi-institutional studies are awaited (level of evidence III, category of recommendation C, NCCN).
2. Chemical and thermal ablative therapies: They cause tumor necrosis by injection of cytotoxic or ischemia-inducing chemicals or transmission of thermal energy into the tumor tissue itself. Although reported local recurrence rates have been extremely variable ranging from 3 to 50% [15].
 - A) Cryoablation: It is thermal ablative modality attempted to treat unresectable hepatic malignancies.

Fig. 2 Surgical planning based on liver function, imaging and portal vein embolization

Local delivery of liquid nitrogen or argon on a probe tip to the CHM, resulting in tumor destruction by intracellular ice crystals that form.

- B) Radio-frequency ablation: RFA is being used to treat unresectable CHM only, with no extrahepatic metastatic disease. Tumors amenable to successful treatment with RFA have typically been solitary CHM or a few, which are not close to large hepatic vessels. Tumor size in particular has been limited to 3 cm.
- C) Microwave ablation: MWA is applied via a microwave probe delivered into the tumor via image-guided percutaneous or ultrasound-guided surgical approaches. Via these probes, microwave radiation between 900 MHz and 2.4 GHz is delivered that causes polarized water molecules within the tissue to oscillate generating friction that produces heat that destroys tissue by coagulative necrosis.

Surveillance: (IIA, B NCCN, ESMO)

1. CT chest, abdomen, and pelvis are recommended every 3–6 months in first 2 years followed by every 12 months for next 5 years.
2. Monitoring of serum CEA levels is suggested every 3–6 months in first 2 years followed by every 6 months for the next 5 years.

Predicting Oncological Outcome

A useful clinical risk score (CRS) was proposed based on a retrospective multivariate analysis that identified five preoperative variables to predict outcome following hepatic resection. One point each was assigned for node positive disease, disease-free interval < 12 months, number of tumors > 1, preoperative CEA level > 200 ng/dL, and size of tumor > 5 cm. CRS is useful in predicting survival as well as the likelihood of disseminated disease and resectability [16].

Conclusion

Multimodal treatment strategies have suggested improved outcomes in the patients with CRLM. Growing innovations and increased surgical anatomical understanding have resulted in safe maximal resection, establishing a standard of care for resectable lesion(s). Systemic therapies with the advent of novel cytotoxic systemic chemotherapeutic agent has boosted the surgical management strategies and improved the survivability in these patients. This approach needs careful selection of surgical candidates, which could be subjected to multidisciplinary treatments;

however, further randomized trials are needed for robust selection criteria and surgical outcomes.

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