Critical Reviews in Oncology/Hematology 108 (2016) 154–163

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

# Treatments for colorectal liver metastases: A new focus on a familiar concept

M.G. Zampino[a,*], E. Magni[b], P.S. Ravenda[a], C.A. Cella[a], G. Bonomo[c], P. Della Vigna[c], S. Galdy[a], F. Spada[a], G.M. Varano[c], G. Mauri[c], N. Fazio[a], F. Orsi[c]

[a] Unit of Gastrointestinal Medical Oncology and Neuroendocrine Tumors, European Institute of Oncology, Italy
[b] Niguarda Cancer Center, Ospedale Niguarda Ca' Granda, 20162 Milan, Italy
[c] Division of Interventional Radiology, European Institute of Oncology, Italy

**Contents**

1. Introduction ..... 155
2. Liver-directed treatments for unresectable liver CRC ..... 155
   2.1. Chemoembolization ..... 155
   2.2. Drug Eluting Beads (DEB) ..... 156
   2.3. Selective internal radiation therapy (SIRT) ..... 156
   2.4. Hepatic artery infusion chemotherapy (HAI) in unresectable CRLM ..... 157
      2.4.1. The role of HAI in neo-adjuvant setting ..... 157
      2.4.2. Post-operative HAI ..... 157
      2.4.3. The role of ablation and stereotactic body radiation therapy ..... 158
3. Discussion ..... 159
4. Conclusion ..... 160
Conflict of interest statment ..... 160
References ..... 160
Biographies ..... 162

ARTICLE INFO

*Article history:*
Received 7 March 2016
Received in revised form 9 October 2016
Accepted 13 November 2016

*Keywords:*
Liver metastases
Loco-regional therapies
Intra-arterial chemotherapy
Radio-embolization
Ablative therapies

ABSTRACT

A major challenge for the management of advanced-colorectal-cancer is the multidisciplinary approach required for the treatment of liver metastases. Reducing the burden of liver metastases with liver-directed therapy has an important impact on both survival and health-related quality of life. This paper debates the rationale and current liver-directed approaches for colorectal liver metastases based on the evidence of literature and new clinical trials. Surgery is the gold standard, when feasible, and it's the main treatment goal for patients with potentially-resectable disease as a means of prolonging progression-free survival. Better tumor response rates with modern systemic therapy mean that more unresectable patients are now down-staged for radical resection following conversion therapy but for other patients, additional procedures are needed. In multiple unilobar disease, when the projected remnant liver is <30% of the total liver, portal embolization or selective-internal-radiation-therapy (SIRT) can induce hypertrophy of the healthy liver, leading to resectability. In multiple bilobar disease, in situ destruction of non-resectable lesions by minimally invasive techniques may be associated with liver resection to achieve potential curative intent. Other palliative liver-directed approaches, such as SIRT or intra-hepatic chemotherapy (HAI), which are associated with higher response rates, may also have role in down-staging patients for resection. Until recently, such technologies have not been validated in prospective controlled trials.

* Corresponding author at: Unit of Gastrointestinal Medical Oncology and Neuroendocrine Tumors, European Institute of Oncology, Via Ripamonti 435, Milan, Italy.
*E-mail address:* maria.zampino@ieo.it (M.G. Zampino).

http://dx.doi.org/10.1016/j.critrevonc.2016.11.005

However in the light of new Phase 3 data for SIRT as well as for HAI combined with modern therapies or radiofrequency ablation in the first- and second-line setting, the clinical value of these treatments needs to be re-appraised.



## 1. Introduction

Multidisciplinary approach for liver metastases represents the major challenge in the management of patients with colorectal cancer (CRC). The liver is the main site of tumour involvement in patients with advanced CRC and is evident in approximately 20–35% of patients at the time of diagnosis and in up to 70% of patients with CRC at death (Hugen et al., 2014).

Surgery (R0 resection) is the standard, when feasible, and the main goal for increasing 5-year survival up to 40–50% (Pawlik et al., 2006). But the majority (70–80%) of patients are unsuitable candidates for resection due to clinical and/or surgical technical reasons (severe co-morbidities or unresectable extra-hepatic disease).

Over the past 3 decades, the historical criteria for resectability have been defined by: lesion size (<5 cm), number (<4 lesions) and spread (unilateral) although conflicting opinion remains on the optimal approach ("how and when"), due to heterogeneity of the clinical picture, especially in patients with synchronous presentation (Ihnát et al., 2015). The current definition of resectability "the ability to remove all metastatic deposits, leaving adequate liver remnant" is obviously influenced by the technical skills of the surgeon and his team and any decisions, based on achieving parenchyma preservation, are of vital importance if we are to continue seeing improvements in liver resection outcomes (Charnsangavej et al., 2006; Abdalla et al., 2013; Kingham et al., 2015). In patients with metastatic resectable disease at diagnosis, a sequential "liver first" or classical "primary-first" approach versus simultaneous surgery have been shown to be equally feasible with similar long-term outcomes (Mentha et al., 2008; Silberhumer et al., 2015; Bigourdan et al., 2014).

Systemic chemotherapy with fluoropyrimidines (FU) plus oxaliplatin (Ox) and/or irinotecan (IRI) combined to biologic agents such as antiangiogenetics or epidermal growth factor receptor (EGFR)-inhibitors has significantly contributed to increase the percentage of patients candidates for curative surgery and with potentially better outcome (Folprecht et al., 2010). Both the rate and depth of response to chemotherapy represents an important prognostic indicator to aid the clinical decision making process for the selection of patients, especially in cases of extensive disease (>4 metastases) (Adam et al., 2004a; Pawlik et al., 2009).

For other patients, additional procedures are needed to achieve resectability. In multiple unilobar disease, when the projected remnant liver is <30% of the total liver, portal embolization or SIRT can induce hypertrophy of the healthy liver, leading to resectability (Garlipp et al., 2014; Vouche et al., 2013). In multiple bilobar disease, *in situ* destruction of residual non-resectable metastases by radiofrequency or cryosurgery may be associated with liver R0 resection.

In unresectable disease, systemic therapy is considered the standard approach for the conversion of unresectable to R0 resection for approximately 12.5%–34% of patients (plus a further 12% of patients who may be considered eligible for R1 with/without radiofrequency ablation). The number of R0 resection may be further increased if combined with HAI or other liver-directed approaches, such as SIRT (Adam et al., 2004b; Kemeny et al., 2009a; Goéré et al., 2010; Sharma et al., 2007).

Chemotherapy when administered by HAI reaches increased concentrations able to maximize tumour control with minimal systemic toxicity, but complex management and not easily reproducible results, have limited its widespread application.

Other liver-directed approaches (chemo-embolization, radiotherapy) have been currently employed mainly with palliative intent in patients with unresectable liver-dominant disease.

The aim of this review is to update the "state of the art" of liver-directed technologies and strategies.

## 2. Liver-directed treatments for unresectable liver CRC

Despite significant gains in survival achieved with systemic regimens that combine FU and leucovorin (LV) with Ox (Folfox regimen) and/or IRI (Folfiri) as well as targeted biological agents, such as bevacizumab, cetuximab, panitumumab and regorafenib, most patients with metastatic unresectale CRC eventually develop progressive disease (Table 1). In patients with liver-dominant or liver-only CRC, refractory to frontline systemic treatments there is the current opportunity to integrate liver-directed locoregional approaches.

First described in late the 1970s, liver-directed therapies are still evolving for the management of primary hepatic tumors as well as of liver metastases. Particularly, the management of colorectal liver metastasis (CRLM) has been significantly improved with recent data showing that transarterial therapies such as transarterial chemoembolization (TACE), particularly Drug Eluting Beads (DEB)-TACE, SIRT, HAI chemotherapy contributing to gains in 5-years survival rates up to 50% (Lencioni et al., 2014; Mocellin et al., 2007; Hendlitz et al., 2010).

### 2.1. Chemoembolization

Conventional TACE consists of administration of different types of chemotherapy mixed to different types of microspheres and embolic particles as lipiodol oil, collagen particles, trisacryl gelatin microspheres or polyvinyl alcohol particles, producing a shutdown of blood flow and the simultaneous release of high doses of the drug (Fiorentini, 2011). It has been shown that ischemia increases vascular permeability and thereby promotes penetration of chemotherapeutic agents into the tumor with the advantage to maximized local cytotoxic/ischemic damage and minimizing systemic side effects.

TACE is currently approved for hepatocellular carcinoma without portal vein invasion, and recently some trials (including 2 large case series, have been published in CRLM) (Llovet et al., 2002; Lang and Brown, 1993; Sanz-Altamira et al., 1997; Tellez et al., 1998; Vogl et al., 2009) (Table 1).

Vogl et al. published in 2009 the largest series of cases: 463 patients with unresectable CRLM –who were either refractory, or unable to tolerate systemic chemotherapy- received intra-hepatic mitomycin C as single agent or combined with gemcitabine or IRI. The best response was observed 12 weeks after the first TACE; disease control rate (DCR) was 62% and median survival (calculated from the start of TACE) was 14 months. Median survival differed according to the response to treatment: 18.2 (for patients with partial response-PR-), 13.5 months (for those with stable disease –SD-)