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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

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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).

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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-)

Table 1
Prospective trials with TACE for treatment of unresectable CRLM.

Author	Sample size	Drugs used	Median OS (months)	1year-OS (%)
(Lang and Brown, 1993)	46	Doxorubicin	–	65
(Sanz-Altamira et al., 1997)	40	FU, Mitomycin C	10	–
(Tellez et al., 1998)	30	Cisplatin, Doxorubicin Mitomycin C	8.6	20
(Vogl et al., 2009)	463	Mitomycin C *v.s.* Mitomycin C + Gemcitabine *v.s.* Mitomycin C + IRI	14	62
(Albert et al., 2011)	121	Cisplatin, Doxorubicin Mitomycin C	12 (first or second-line)	41%

and 13 months (for those with progressive disease –PD-) without statistically significant difference between the three different regimens (Vogl et al., 2009).

Subsequently a second single-institution large case-series of 121 patients treated with cisplatin, doxorubicin, mitomycin C–based TACE showed confirmed safety and interesting DCR of 43%. Overall survival was significantly better when TACE was performed after first or second line systemic treatment (11–12 months; 52% of the cohort) than after three or more lines of chemotherapy (6 months) ($p = 0.03$) (Albert et al., 2011).

Clinical data reported in mainly uncontrolled case series, although encouraging, require confirmation in prospective controlled studies compared with new-generation systemic approaches with the aim of identifying those patients who may derive greater benefit from this procedure.

2.2. Drug Eluting Beads (DEB)

TACE using drug eluting beads is an alternative technique that uses highly absorbent polyvinyl alcohol beads, modified with sulfonate groups, which are able to sequester cytotoxic compounds in their salt form. Drug-eluting beads, which deliver higher concentrations of chemotherapy directly to the tumor via its arterial vasculature, have recently garnered scientific interest. In this review, we focus on the studies with IRI-loaded beads (also known as DEBIRI) in CRLM. The beads possess static charge, allowing for oppositely charged molecules to bind and release through ion exchange. These physical properties are important for physicochemical stability and the controlled release of chemotherapeutic agents within the proximity of the tumor (Taylor et al., 2007). After drug loading, IRI is released into the vicinity of the tumor tissue, where the prodrug is activated to SN38 mostly by the normal liver parenchyma (Kawato et al., 1991). In spite of published preclinical data supporting the rationale of DEBIRI administration, there is currently insufficient evidence available about survival and toxicity profile in the clinical setting and further standardization of the technique across different institutions is needed (Lencioni et al., 2014; Akinwande et al., 2015).

In a Phase II prospective trial, 82 pretreated patients (61% having received at least two lines of chemotherapy) were treated with DEBIRI, loaded with dose of either 100 or 200 mg IRI. The medium duration of response was 6 months with manageable toxicity (fever in 80%, reversible transaminases increased-levels in 70%, right quadrant pain in 40% and nausea in 27% of patients) (Aliberti et al., 2011). Subsequently a multicenter Phase III trial evaluated 74 patients randomized to DEBIRI or FOLFIRI for the management of pretreated, liver-only CRC with <50% hepatic parenchyma involvement. Response rate was 69% versus (vs) 30%, and PFS was 7 months vs 4 months ($p = 0.006$) for DEBIRI and FOLFIRI, respectively. Extrahepatic progression had occurred in all patients, at a median time of 13 months in the DEBIRI group and 9 months in the FOLFIRI group. Although there was no statistical difference in the time to extrahepatic progression between the two treatment groups, at two-years OS rates were significantly higher in the experimental arm (56% vs. 32%, $p < 0.031$). Median survival was 22 months for DEBIRI and 15 months for FOLFIRI (Fiorentini et al., 2012).

Despite promising results, the results of this Phase III trial has not changed clinical practice and, to date, no international guidelines have recommended DEB-TACE as a standard treatment for CRLM. It is expected that ongoing trials will add further information to support the use of DEB-TACE with concomitant systemic chemotherapy also in the first-line setting (Table 2).

2.3. Selective internal radiation therapy (SIRT)

SIRT using yttrium-90 resin microspheres, is a radio-therapeutic device approved for treatment of patients with unresectable CRLM. The microspheres containing the radionuclide yttrium-90 deliver SIRT (^{90}Y-SIRT) to the tumor-feeding hepatic arterioles, resulting in high doses of radiation (>120 Gy) to be selectively targeted to tumors with minimal injury to surrounding tissue.

Data from the Phase III international, multicenter, open-label study (SIRFLOX study) compared the efficacy and safety of combining T SIR-Spheres® with FOLFOX chemotherapy (with or without bevacizumab) as first-line treatment for unresectable liver-dominant CRLM. The patients were randomized to receive chemotherapy (Arm A: 263 patients) or SIRT plus chemotherapy (Arm B: 267 patients) With 40% of patients presenting with extrahepatic disease at baseline, overall PFS was similar in both treatment arms (10.7 vs 10.2 months; $p = 0.428$), but liver-PFS was significantly prolonged when SIRT was added to systemic chemotherapy (20.5 months in arm B vs 12.6 months in arm A $p = 0.002$). Median liver PFS was 21.1 *v.s.* 12.4 months in arm B *v.s.* A ($p = 0.003$) for patients with liver-only metastases and 16.7 *v.s.* 12.6 ($p = 0.147$) for those with also extrahepatic metastases. Correspondingly, the response rates (defined by RECIST 1.0) in the liver, for both the complete response (6.0% *v.s.* 1.9%; $p = 0.02$) and DCR (78.7% *v.s.* 68.8%; $p < 0.042$) were significantly greater with combined treatment modality. More than 1 in 10 patients with unresectable CRLM in this study were down-staged and received R0 resection (14.2% *v.s.* 13.7%). Common toxicities were mainly hematologic (32.9% *v.s.* 51.2%) and gastrointestinal (32.9% *v.s.* 21.2%), with a higher incidence of severe (grade ≥3) gastric or duodenal ulcer (3.7% *v.s.* 0.0%) in the SIRT arm *v.s.* chemotherapy alone arm (Van Hazel et al., 2016).

Two other studies are ongoing on SIR-Spheres® combination in first-line setting: FOXFIRE, a UK clinical trial and FOXFIRE Global, an international study. The results of all-three- studies, which together enrolled more than 1100 patients, will be combined in a pre-planned assessment of the overall survival and are expected in 2017.

In second-line setting a Phase III trial (EPOCH study) evaluating the effectiveness and safety of TheraSphere® (glass microspheres) associated to systemic standard care *v.s.* systemic treatment alone, in patients with liver-dominant CRLM, is currently ongoing.

Several clinical trials have been also investigated this procedure in combination with, different lines of treatment (Table 3). In a meta-analysis of 18 studies with 681 patients median survival after ^{90}Y SIRT, across a range of settings (from salvage to first-line) varied between 6.7 and 17.0 months (Vente et al., 2009).

In a phase III trial comparing protracted intravenous fluorouracil infusion alone or with Yttrium-90 Resin Microspheres Radioem-

Table 2
Ongoing trials with liver-directed drug eluting beads for unresectable CRLM.

Trial	Study Design	Phase
NCT01839877	Intra-arterial Hepatic Beads Loaded With IRI With Concomitant Chemotherapy With Folfox in Patients With Colorectal Cancer With Unresectable Liver Metastases: a Phase II Multicenter Study	II
NCT01891552	Observational Study on Second Line Treatment of Hepatic Metastases With Intra-arterial Infusion of IRI-loaded Drug-eluting Beads (DEBIRI) and Cetuximab (TACETUX)	observational
NCT02350400	Pilot Study to Assess the Safety and Pharmacokinetics of 70–150 μm Drug Eluting Beads Loaded With IRI (DEBIRI).	I

bolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy, Hendliz et al. demonstrated that combined treatment significantly improved time to liver progression and time to progression compared with FU alone. This procedure is also safe and is a valid therapeutic option for chemotherapy-refractory liver-limited mCRC. No differences in OS was observed presumably due to cross over effect; anyway 10 months OS observed in the sperimental arm is promising; even if this survival time could be explained by population selection (liver only disease; most patient have not received anti EGFR therapy in previously lines) (Hendlitz et al., 2010). This trial led to the inclusion of SIRT in the ESMO guidelines.

In the salvage setting, prospective phase II trial was published by the SITILO- group, reporting DCR in 48% of patients with 12,6 months median survival (CI 7.0–18.3) and 19.6% 2-year survival, similar to those obtained with second-line systemic therapy (Cosimelli et al., 2010).

Great efforts for allowing better patients selection by pre-therapeutic work-up (by exploring hepatic vasculature to assess lung shunting and by establishing liver radio-dosimetry – the latter is a technical issue non yet solved-) and by evaluating clinical factors predictive of outcome (as liver-only disease), may improve outcome and prevent patients from unnecessary toxicity.

2.4. Hepatic artery infusion chemotherapy (HAI) in unresectable CRLM

Like to other liver-directed therapies, the primary goal of HAI is to selectively deliver high concentrations of drugs to cancer cells. To maximize efficacy, agents used must have optimal pharmacokinetic profile characterized by high first-pass metabolism in the liver (limiting systemic exposure), short plasma half-life, and first-order kinetics The most common agent (in U.S. but difficult to supply in Europe) which responds to all these characteristics is Floxuridine (FUDR) a pyrimidine antimetabolite which is transformed to FU in the liver (hepatic extraction FUDR >90% while FU <50%) (Ensminger and Gyves, 1983). Since the early 1990s at least 3- large randomized trials with HAI FUDR *v.s.* systemic chemotherapy have been conducted. These trials although reporting significant gain in terms of response rate in favour of locoregional therapy have not translated into survival benefits (Chang et al., 1987; Kemeny et al., 1987; Wagman et al., 1990; Kerr et al., 2003).

Three meta-analysis, evaluating the role of HAI with FUDR or FU compared with systemic (older-generation) treatments, are published reporting conflicting results. The most recent was conducted nearly ten years ago (involving 10 studies/1277 patients) and observed a response rate in favour of HAI (42,9% *v.s.* 18,4%) but once again did not demonstrate statistical advantage in terms of survival (15,9 vs 12,4 months, HR = 0,90, p = 0.24) (Mocellin et al., 2007).

More recent Phase I–II trials conducted in second line setting have achieved some impressive improvements with HAI plus systemic chemotherapies using FUDR plus Ox, Folfox and/or IRI (Kemeny et al., 2001, 2005; Ducreux et al., 2005; Boige et al., 2008) (Fig 1). An Italian single-institution experience in 44 heavily pretreated patients demonstrated the feasibility and efficacy of HAI with a chemotherapy regimen containing cisplatin, FU and mitomycin C administered through a temporary percutaneous arterial catheter (instead of surgically positioned intra-abdominal portable pump). The study reported PR of 35% and SD in 33% of cases against grade 3–4 neutropenia in 22% and thrombocytopenia in 15% of cases (Fazio et al., 2003).

2.4.1. The role of HAI in neo-adjuvant setting

HAI has also been investigated in the neo-adjuvant setting. Interesting results documented in prospective Phase Ib-II trial conducted with HAI combined with systemic Ox and IRI in 49 patients recorded a response rate of 92% (enabling 57% of chemotherapy naïve patients to undergo liver resection) with median survival of 50.8 months. For previously treated patients, the response rate was 85% and the median survival was 35 months. (Kemeny et al., 2009a). In a large study, a total of 373 patients with unresectable CRLM treated with HAI and modern systemic treatments including bevacizumab treated between 2000 and 2009 were retrospectively analyzed. In this study, 79% of patients have received one line of systemic chemotherapy and 93 patients (25%) underwent complete resection; median OS was 59 months in patients radically resected, compared with 16 months in those who did not perform surgery. (Ammori et al., 2013) Finally, HAI with Ox has been widely used in France, with small published trials of HAI Ox plus systemic therapy in the unresectable setting achieving conversion rates of approximately 15–20%. (Ducreux et al., 2005; Boige et al., 2008).

2.4.2. Post-operative HAI

The role of systemic chemotherapy in the adjuvant and neoadjuvant setting in resectable CRLM is currently hotly debated because the criteria of resectability are not uniformly standardized and on depends by surgeon-specific experience. Adjuvant FU alone or in combination with Ox in perioperative setting provides an improvement in terms of recurrence free survival without statistically advantage on OS (Portier et al., 2006; Parks et al., 2007; Nordlinger et al., 2013). Unfortunately postoperative IRI-containing regimens and the perioperative introduction of cetuximab in an Ox-containing schedule, has been associated with a significant worsening of toxicity without any better outcome (Delbaldo et al., 2015; Primrose et al., 2014).

Based on promising results obtained with HAI in unresectable disease, its combination with systemic treatment in adjuvant setting has been evaluated to assess its role in early prevention/treatment of micro-metastases.

Seven Phase III trials have evaluated adjuvant HAI with/without systemic therapy in patients with CRLM but only 3 studies included a meaningful sample size (Boige et al., 2008; Kemeny et al., 1999, 2002; Lorenz et al., 1998; Lygidakis et al., 1995; Rudroff et al., 1999; Tono et al., 2000). Data from two randomized trials conducted in Germany and in the USA have reported an increased time to treatment failure as well as a decrease in hepatic recurrence compared to resection alone. However neither studies have shown significant

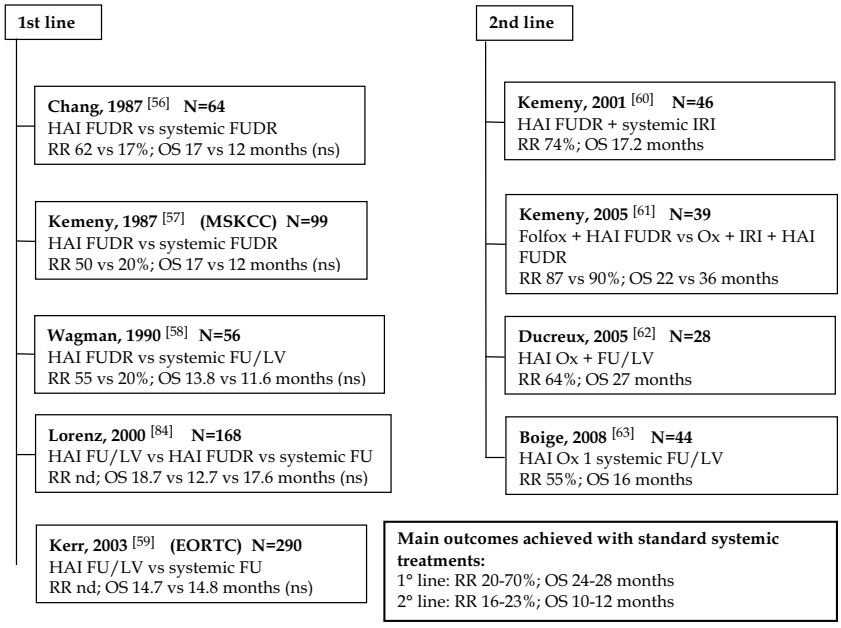

Fig. 1. Main trials of HAI for unresectable CRLM.

improvement in overall survival if compared with surgery alone (in the German study only 31% of patients completed the planned treatment with HAI) (Lorenz et al., 1998; Kemeny et al., 2002).

In another U.S. multicenter study, 156 patients were randomized to systemic chemotherapy plus HAI-FUDR *v.s.* systemic chemotherapy alone (bolus or continuous infusion FU). The median survival was 68.4 months *v.s.* 58.8 months and two years liver-free relapse was 90% *v.s.* 60%, $p < 0.001$, in favour of combined approach. However, extrahepatic recurrence appeared to be similar in both treatment arms, emphasizing the role of systemic therapy in this setting (Kemeny et al., 1999; Kemeny and Gonen, 2005).

More recently, several trials have investigated adjuvant HAI-FUDR added to modern systemic chemotherapy (Kemeny et al., 2003, 2009b). The first of these trials was led by the NCCTG-NSABP CI-66- with capecitabine/Ox alternating with HAI-FUDR. This Phase II trial met the pre-specified endpoint of >85% survival at 2 years and reported manageable toxicity (Alberts et al., 2010). Subsequently a retrospective comparison of adjuvant HAI-FUDR and concurrent systemic Ox- or IRI-containing-regimens *v.s.* systemic chemotherapy alone confirmed an improved overall RR (48% *v.s.* 25%), liver recurrence-free survival (75% *v.s.* 55%) and disease-specific survival (79% *v.s.* 55%), justifying future prospective randomized trials (House et al., 2011).

A Phase II study of adjuvant HAI plus Ox-based therapy with/without bevacizumab was conducted and, despite the promising rationale, no improvement in relapse-free survival, but increase in biliary toxicity was observed (Kemeny et al., 2011).

Finally, despite these intriguing results, the applicability of HAI is limited by lack of standardized chemotherapeutic regimens and by its high complication rates. Technical side effects (arterial thrombosis 5–6%, catheter occlusion or dislodgment 6%, extra hepatic perfusion 3%) or drug-related toxicity (biliary sclerosis 5% with FUDR alone and 10–20% in poly-chemotherapy) or a combination of both are reported in a range of 16–36% of patients treated and need qualified expertise for its management (Ko and Karanicolas, 2014).

2.4.3. *The role of ablation and stereotactic body radiation therapy*

Surgery is the reference standard treatment for CRLM with 5-year survival rates of up to 40% and cure rates of approximately 20% (Abdalla et al., 2013; Kingham et al., 2015; Tomlinson et al., 2007). Unfortunately in many cases surgical approach cannot be offered because of underlying liver disease, other co-morbidities, or extensive tumour involvement. In carefully selected patients with liver limited disease, ablative techniques are a potentially alternative approach by using different mechanisms of focal destruction: radiofrequency ablation (RFA), cryoablation, laser ablation, microwave ablation, focused ultrasound ablation that induce thermal cell damage while stereotactic body radiation therapy (SBRT) and irreversible electroporation determine a non-thermal injury. RFA is the most extensively used and well-studied ablation modality with-morbidity reported in <10% of cases and mortality <1%,regardless of the approach (either percutaneously or during laparoscopy/laparotomy) (Mulier et al., 2002).

To date no randomized trial comparing RFA and surgery in resectable liver disease is available and its conventional use is supported by only Phase II single-arm prospective or retrospective trials (Mulier et al., 2008; Bai et al., 2015; Tanis et al., 2014).

Therefore this procedure is mainly employed for palliative use in outpatient setting, in case of recurrent hepatic disease (with relapsed free survival <6 months) previously treated with liver surgery and/or in patients with iatrogenic liver damage caused by intensive or prolonged chemotherapy or in patients unfit for surgery (Wong et al., 2010; Petre et al., 2015).

Clinical benefit in terms of local-disease control vary widely between studies with local recurrence ranging between 2% and 60% of cases and appreciable OS (>30 months) in patients with small size (<3 cm), limited number of lesions, clear ablation margins (at least 1 cm all around lesion) (Tanis et al., 2014; Berber et al., 2005; Solbiati et al., 2001; Gillams and Lees, 2009).

In patients with bilateral, multiple hepatic metastases, ablative therapies (RFA or microwave ablation) combined with resection has been shown to extend the number of patients eligible for resection with curative intent, with improved perioperative outcomes without compromising long-term survival compared with bilateral resection (Karanicolas et al., 2013).

Furthermore in recently published ESMO Guidelines ablative techniques, such as RFA or SBRT have been recognized as a complement to surgery R0 or as an alternative for resection in the case of

Table 3
Main trials on SIRT in CRLM.

Author, year	Phase/Sample size	Trial Design	Line	EHD	PR	SD	PD	Other outcomes	Median OS (months)
(Van Hazel et al., 2004)	Phase II (N = 21)	SIRT + FU/LV *v.s.* FU/LV	I	23%	91%	9%	0%	mTTP 18.6 *v.s.* 3.6 HR = na	29.4 *v.s.* 12.8 HR 0.33
(Sharma et al., 2007)	Phase I (N = 20)	SIRT + Folfox	I	65%	90%	10%	0%	PFS 9.3 mTTLP 12.3	–
(Van Hazel et al., 2009)	Phase I (N = 25)	SIRT + CPT-11	>II	48%	48%	39%	13%	PFS 6.0	12.2
(Seidensticker et al., 2012)	Matched Pair Comparison (N = 58)	SIRT + BSC *v.s.* BSC	>II	Liver dominant disease	41.4%	17.2%	37.9%	PFS 5.5 *v.s.* 2.1%	8.3 *v.s.* 3.5% HR 0.26
(Lim et al., 2005)	Phase II (N = 30)	SIRT	>II	20%	33%	27%	40%	mTTP 5.3	–
(Cosimelli et al., 2010)	Phase II (N = 50)	SIRT	>III	22%	22%	24%	44%	mTTP 3.7	12.6
(Hendlitz et al., 2010)	Phase III (N = 44)	SIRT + FU c.i. *v.s.* FU c.i.	>III	38%	0	85	–	mTTLP 5.5 *v.s.* 2.1	10.0 *v.s.* 7.3 (ns)

BSC = best supportive care; EHD = extra-hepatic disease; PR = partial response; SD = stable disease; PD = progressive disease; mTTP = median time to progression; mTTLP = median time to liver progression; PFS = progression free survival; c.i. = continuous infusion; ns = not statistically significant.

tumours with a poor anatomical localization for resection, in order to preserve sufficient remnant liver (Van Cutsem, 2014).

To date is matter of debate whether RFA combined with first-line chemotherapy gives advantage if compared to systemic therapy alone. The randomized EORTC Intergroup 40004 (CLOCC) Phase II study evaluated the benefit of combining systemic chemotherapy (consisted of 6 months FOLFOX) with local tumor destruction by RFA in patients with unresectable CRLM up to 9 lesions and without extrahepatic disease. The study conducted on 119 patients found that RFA plus systemic treatment resulted in significant longer 3 years PFS rate for combined treatment (27.6% *v.s.* 10.6% for systemic treatment only; HR = 0.63, 95% CI 0.42-0.95, p = 0.025) and median PFS of 16.8 months *v.s.* 9.9 months, respectively. After a median follow-up of 9.7 years there was a significant difference in OS in favour of the combined arm (p = 0.01) with median OS of 45.6 months (95% CI: 30.3–67.8) *v.s.* 40.5 months (95% CI: 27.5–47.7) in favour of RFA plus systemic therapy arm (Ruers et al., 2015).

Irreversible electroporation (by using high-voltage electric current) and microwave ablation (heat destruction induced by electromagnetic field) has also been investigated in larger tumours with aim of minimizing the collateral damage caused by tumour proximity to bile ducts, vascular wall or other structures and to overcome high risk for local recurrence. Currently few prospective trials are available, but no definitive conclusions about survival advantage neither targeted indications for appropriate use of these procedures can be drawn (Shibata et al., 2000; Groeschl et al., 2014; Scheffer et al., 2014).

In SBRT highly ablative radiation doses are delivered directly and accurately to CRLM with a limited number of fractions: 1–6 fractions with total doses between 46 and 52 Gy (Chang et al., 2011).

In a recent small dose-escalation study, two-year local control was obtained in nearly all patient treated at a dose of 60 Gy administered in 5 fractions (Rule et al., 2011).

For difficult-to-reach tumours, these new methodologies appear to be promising and deserve further evaluation in controlled clinical trials (Ahmed et al., 2014).

3. Discussion

Liver surgery should be considered as gold standard in patients with CRLM with the aim to remove "radically and safely" all macroscopic evidence of tumor involvement based on resection criteria remarkably evolved during last decades. In this context it is crucial the role of correct staging of liver and distant disease (c.e. CT scan, epatospecific c.e. MRI and FDG-PET scan) for selecting patients with liver-only or liver-dominant disease (minimal extraepatic involvement should be well defined), candidates for surgery with curative intent.

Several techniques are used to improve resectability in patients who fail to meet resection criteria. These include portal vein occlusion, two-stage hepatectomy, local ablation techniques, and downstaging chemotherapy. These techniques can be used as single approach, but are more effective when considered in a multimodality approach and could be contribute to improve OS, mainly in patients with potentially resectable disease.

Minimally invasive techniques (such as RFA) may be considered in addition to surgery to obtain R0 intent with the aim to improve OS.

There are no published randomized controlled trials examining the use of RFA versus surgery in CRLM but only single arm, retrospective and prospective studies. This trials reported variable local efficacy but demonstrated that when RFA of CRLM is performed with curative intent in patients with unresectable liver-only disease, survival rate is directly affected by size, number (best outcome in solitary CRLM) and location of lesions. In selected cases

with resectable lesions with low chance of cure (technically possible but clinically critical), the use of these treatments may limit unnecessary, expensive and high morbidity surgery. Thereafter in case of underlying liver disease, patients comorbidities, or subsequent liver recurrences after surgery, these local techniques may primarily be offered as palliative approach. However, recently, the addition of RFA to systemic chemotherapy in first line setting confer improved OS compared to chemotherapy alone. So the combined approach seems to be a good option especially in CRLM with no extensive liver involvement.

Other liver-directed therapies (chemoembolization, radioembolization, intra-arterial chemotherapy) have been developed to control liver metastases, but no large phase III trials have been undertaken to fully assess the clinical usefulness of such therapies.

Selective internal radiotherapy (90Y-SIRT), selectively delivered to CRLM, has reported a wide range in tumor response rates and toxicities across different treatment settings, in retrospective non-randomized trials, meta-analysis and case series. The procedure seems to be active with median OS ranging from 8.8 and 14.5 months, also in patients refractory to chemotherapy and in palliative setting (THER-RAD.00006, 2016).

Recently the results of the first phase III trial of the addition of SIRT to standard chemotherapy in first-line treatment of CRLM were published. The SIRFLOX study results show that the radioembolization added to FOLFOX regimen failed to improve PFS, but demonstrate a statistically significant improvement in median PFS in the liver (20.5 *v.s.* 12.6 months, p = 0.002 h = 0.69). Despite the increased liver response rate, no statistically difference for resection was observed. Data regarding OS are awaiting. The possible reasons of the failure in improvement PFS and liver resection rate is probably explain by some unfavourable selection criteria as high burden liver involvement, presence of extrahepatic disease and non resected primary CRC.

The high rate of hepatic relapse in patients treated with surgery provides a rationale for proposing locoregional liver approaches as unique procedure or in combination with systemic treatments in the peri-operative setting. The data regarding intra-arterial chemotherapy with FUDR or 5FU show modest (if any) OS benefit.

'Intensifed' combination of HAI plus systemic treatments results in improved response rate (ORR > 80%, DCR ~100%), even after systemic chemotherapy failure, with a percentage of conversion to resectability up to 74% of patients with CRLM. Nevertheless this procedure is now recommend only in clinical trials.

Furthermore, due to the lack of standardized approach for arterial catheter/port or surgically implantable pump and for chemotherapy regimens, this procedure remains the domain of few specialized institutions.

Chemo-embolization for CRLM is an interesting treatment strategy, supported mostly by uncontrolled clinical studies, with debatable benefits for the each of different chemotherapies types and dimension of bead combined various embolic agents. DEBIRI has recently been evaluated for treating liver-only or liver-dominant disease and further large scale validation are expected.

4. Conclusion

Interventional local and locoregional liver-directed approach are effective and well-manageable oncologic procedure for treating selected patients with unresectable and resectable CRLM.

Optimal outcomes with these therapies should be achieved through: greater efforts for allowing better patients selection by improving baseline local (morphological and functional) and distal staging, standardization of technical work-up and by promoting constant education and training of team-work. New study design for evaluating optimal integration of target- and immunotherapy-agents are awaited. The investigations of the clinical-biological factors, which are predictive of outcomes are also essential for future prospective trials.

Conflict of interest statment

No author declares conflict of Interest.

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Biographies

Maria Giulia Zampino is deputy Director of the Unit of Gastrointestinal Medical Oncology and Neuroendocrine Tumors at IEO. She is actively part of a multidisciplinary team dedicated to gastrointestinal tumors, and focused on the management and research in the topic of lower gastrointestinal tract cancers.

Elena Magni graduated in Medicine at University of Milan in 1999 and has specialized in Oncology at University of Milan in November 2003. From 2004 to 2013 she worked as a medical oncologist at the European Institute of Oncology in Milan dealing in clinical and research of gastrointestinal cancers. Since 2014, she has been working as medical oncologist at Niguarda Cancer Center in Milan.

Paola Simona Ravenda earned her medical degree in 2005 from University of Medicine in Messina (Italy) and completed her training in Medical Oncology in 2011 at the University of Pavia (Italy). In 2010 she attended Medical Oncology department

at the Moffitt Cancer Center in Tampa (FL, USA) and, in 2011, at the Memorial Sloan Kettering Cancer Center in New York City (NY, USA). Since 2012, she has been working as medical oncologist at IEO within the Unit of Gastrointestinal Medical Oncology and Neuroendocrine Tumors.

Chiara Alessandra Cella graduated from Faculty of Medicine at University of Naples Federico II (Italy) in September 2008 and obtained post-graduate degree in Medical Oncology in November 2014. She is working currently as a research fellow at the Unit of Gastrointestinal Medical Oncology and Neuroendocrine Tumors of IEO.

Guido Bonomo is deputy Director of the Interventional Radiology Division at IEO. He is strictly involved in a multidisciplinary team dedicated to gastrointestinal tumors. His field of working is focused on the management and research of gastrointestinal tract cancers, and liver neoplasms, primary and metastatic

Paolo Della Vigna is Deputy Director of the Interventional Radiology Division at IEO. He is actively part of a multidisciplinary team dedicated to gastrointestinal tumors. His field of working is focused on Interventional Oncology in the management of gastrointestinal tract cancers, liver and renal neoplasms, primary and metastatic.

Salvatore Galdy achieved his graduation in Medicine in October 2004 at University of Parma (Italy) and completed its training in Medical Oncology in November 2008. He is working currently as a research fellow at the Unit of Gastrointestinal Medical Oncology and Neuroendocrine Tumors of European Institute of Oncology (IEO) in Milan (Italy), where he is involved in clinical research projects mainly in the field of upper gastrointestinal cancer.

Francesca Spada graduated in Medicine at University of Cagliari (Italy) in July 2004. She was involved in Regional Emergency Medical Services and completed her training in Medical Oncology at University of Sassari (Italy) in July 2011. Since 2011, she has been dealing with clinical practice and research activity in the field of neuroendocrine and gastrointestinal tumors at the Unit of Gastrointestinal Medical Oncology and Neuroendocrine Tumors of IEO, where she is currently working.

Gianluca Maria Varano graduated from Faculty of Medicine at Sapienza University of Rome in October 2009 and complete his training in Radiology in May 2015. Currently he works as Interventional Radiologist at European Institute of Oncology (IEO) within Division of Interventional Oncology.

Giovanni Mauri graduated at University of Milan, where he received his Board Certification in Radiology in 2012. During his training he attended a Fellowship in Interventional Radiology in London (University of London) and a Research Fellowship in Boston (Harward Medical School). Since graduation he worked as an Interventional Radiologist, mainly in the field of Interventional Oncology and Vascular Interventional Radiology, and he is actually part of the staff of the Division of Interventional Oncology of IEO. He publilshed more than 40 papers in peer-reviewed international journals, and presented more than 100 abstracts at national or international meetings.

Nicola Fazio, consultant in Internal Medicine and Medical Oncology with PhD in Digestive Oncology, has been leading the Unit of Gastrointestinal Medical Oncology and Neuroendocrine Tumors at IEO since July 2011. With more than 80 scientific publications in peer reviewed journals, he is a member of all the main national and international oncological societies and he is recognized as opinion leader in neuroendocrine tumors management.

Franco Orsi, Interventional Radiologist, chairs the Division of Interventional Radiology at IEO since 2006, where more than 3000 interventional procedures in cancer patients are performed every year. He is part of the Executive Committee of the Italian-European Society of Interventional Radiology (IESIR) and permanent faculty of the most important international meetings of Interventional Radiology. Together with his staff developed several new procedures in the Interventional Oncology field.