European Journal of Radiology Open 7 (2020) 100236

Contents lists available at ScienceDirect

European Journal of Radiology Open

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

Transarterial chemoembolisation of colorectal liver metastases with irinotecan-loaded beads: What every interventional radiologist should know

Roberto Iezzi[a,b,*], Attila Kovacs[c], Hans Prenen[d], Patrick Chevallier[e], Philippe L. Pereira[f]

[a] Fondazione Policlinico Universitario A. Gemelli IRCCS, Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia – Istituto di Radiologia, l.go A gemelli 8, 00168 Rome, Italy
[b] Università Cattolica del Sacro Cuore, Rome, Italy
[c] Klinik für Diagnostische und Interventionelle Radiologie und Neuroradiologie, Mediclin Robert Janker Klinik, Bonn, Germany
[d] UZ Antwerp, Oncology Department, Wilrijkstraat 10, 2650 Edegem, Belgium
[e] Imagerie interventionnelle Oncologique, Hôpital Archet, 151 route de saint antoine de ginestière, 06202 Nice, France
[f] SLK-Kliniken Heilbronn GmbH, Klinik für Radiologie, Minimal-invasive Therapien und Nuklearmedizin, Am Gesundbrunnen 20-26, 74078 Heilbronn, Germany

ARTICLE INFO

Keywords:
Chemoembolization
Colorectal liver metastases
Irinotecan
Pain management

ABSTRACT

The last decade has seen important developments in the treatment of metastatic colorectal cancer (mCRC). In this scenario, interventional locoregional treatments could play an expanding role offering safe and effective integrated options in the continuum-of-care offering curative as well as palliative approaches.

Based on ESMO guidelines, the toolbox of ablative treatments also includes intra-arterial palliative options, like chemoembolization, that can be offered as an alternative option in patients failing the available chemotherapeutic regimens.

However, to date, there is still a limited use of chemoembolization in clinical practice.

Based on this background, a comprehensive review of the methodologic and technical considerations as well as clinical indications and future perspectives seems to be useful with the aim to demonstrate the field's value of the procedure, highlight their advantages, and ensure an increased role in treatment management of patients with colorectal liver metastases.

1. Introduction

The last decade has seen important developments in the treatment of metastatic colorectal cancer (mCRC), particularly in the use of newer multidrug regimens and their combination with targeted locoregional therapies [1–3]. Increasing data on the ability to treat liver metastases with locoregional therapies has also solidified this treatment management. Understanding the timing and role of these techniques in the multidisciplinary care of the patient is critical [4,5]. In this scenario, interventional radiologists (IRs) could play an expanding role offering safe and effective integrated options in the continuum-of-care as curative or palliative approaches, helping to improve local control of tumours with a multimodality treatment. In detail, catheter-directed therapies, such as transarterial chemoembolization, are potential techniques for managing patients with unresectable liver metastases to selectively deliver high doses of chemotherapy to the tumour bed and to embolize the target vessels, with minimal systemic bioavailability while sparing the surrounding liver tissues [6,7]. ESMO guidelines showed that chemoembolization may be considered as a treatment option for patients with liver-limited disease failing the available chemotherapeutic options, even if characterized by low level of evidence, mainly based on a retrospective cohort of case–control studies, and recommended with a limited clinical benefit [8,9]. However, to date, there is still a limited use of chemoembolization in clinical practice.

The aim of this article is to integrate evidence-reported literature and experience-based perceptions on chemoembolization with irinotecan-loaded beads in the treatment of patients with colorectal cancer liver metastases, while attempting to make the information easy to access using a point format, to assist not only residents and fellows who are training in interventional oncology but also practicing colleagues who are attempting to gain further expertise and to improve their involvement in these procedures.

2. Improve your procedure knowledge

Standardization of technique and protocols is mandatory, being

* Corresponding author at: Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli – IRCCS, Università Cattolica del Sacro Cuore, Istituto di Radiologia, L. go A. Gemelli 8, 00168 Rome, Italy.
E-mail address: roberto.iezzi@policlinicogemelli.it (R. Iezzi).

https://doi.org/10.1016/j.ejro.2020.100236
Received 28 February 2020; Received in revised form 27 April 2020; Accepted 28 April 2020

expected to lead to improved safety and efficacy [10–12].

All intra-arterial chemoembolizations are performed in an angiographic suite with the structural characteristics of an operating room, with monitoring of vital signs and anaesthesia care, under local anaesthesia, through a femoral or a radial approach, using a 4–5 F arterial introducer sheath. Trans-radial approach could represent an attractive accepted alternative, characterized by several advantages, such as shorter post-procedural monitoring, earlier ambulation, shorter hospital stay and less discomfort, associated with potentially reduced bleeding risks, improving patient preference as also demonstrated by recent literature [13–16].

Diagnostic angiography is usually performed with a 4–5 F diagnostic catheter with Cobra, Simmons, or Multipurpose shapes. The first objective is to identify the appropriate anatomy of the hepatic artery and of any possible branches related to non-target structures, and exclude any arteriovenous fistulae. If identified, these vessels must be embolized or avoided by placing the catheter tip well beyond the origin of these vessels. In addition, forward flow into the desired vessel must be maintained because inadvertent administration or reflux of beads into these extrahepatic vessels would be undesirable. After diagnostic angiography, a selective lobar catheterization is usually performed with a coaxial technique placing a micro-catheter in the right or left hepatic artery that is feeding the tumour lesions.

Under fluoroscopic guidance, a solution of 2 mL of micro-particles with a size $\leq$100 μm loaded with Irinotecan at 50 mg/mL (for a total dose of 100 mg per syringe), 5 mL water for injection and 10 mL of non-ionic contrast medium/mL is slowly infused until the complete expected dose is delivered. Procedural endpoint is to deliver the planned dose of anticancer agent, not to occlude the vessel, obtaining a “near-stasis” flow [10,11].

On the basis of extent and distribution of the disease, it is decided to carry out a single lobe (two treatments at 4 weeks interval) or a bilobar treatment (four treatments, at 2 weeks interval), with the first targeted to the lobe more involved by disease.

3. Improve your knowledge on peri/intra-procedural pain management

The most frequent adverse event is represented by post embolization syndrome (PES), which include one or more of the following: fatigue, nausea, vomiting, mild fever, and laboratory values indicative of tumour necrosis. In detail, abdominal pain is generally seen in as many as 40% of patients after treatment, being severe in 25% of patients. The pathogenesis of PES is complicated and unclear, involving multiple mechanisms, with the main ones being the toxicities of chemotherapy agents and embolization-induced ischemia, necrosis, and hypoxia in normal cells with the consequent release of inflammatory factors and activation of the body’s stress response [10–12].

These symptoms often last for 1–2 days. In the setting of moderate to severe symptoms, if not treated promptly, great effects on the prognosis and quality of life in patients can occur. Thus, an adequate knowledge on peri/intra-procedural pain management, necessitating a systemic approach, is mandatory to increase the number of patients treated and to reduce the rate of uncompleted treatment cycle.

Intra-procedural pain is usually controlled by continuous infusion of opioids (20 mg morphine/24 h) and non-steroidal anti-inflammatory agents (i.e. ketorolac 20 mg/24 h).

Antibiotic prophilaxis (before and after treatment for seven days – ciprofloxacin, second-generation fluoroquinolone at dosage of 500 mg once-daily) is administered at the physician’s discretion [17]. Among pain management strategies, intra-arterial lidocaine administration (1%–2.5% – 5 mL) into the hepatic artery, immediately before microparticles injection, can also be considered; in addition, lidocaine is a potent vasodilator of the arterial system increasing drug uptake, useful in hypovascular lesions as CRC metastases (Table 1).

Table 1
Recommendations for a peri-interventional management.

Prior to IRI-Beads TACE
• i.v. access for hydratation 2l/24H of fluids (Sodium Chloride 0.9% intravenously)
• Hydroxyzine (Atarax25 mg) or Midazolam (Dormicum 1 − 3 mg iv) against anxiety
• Etoricoxib (Arcoxia 60 − 90 mg D1-3) (Cave: not in patients with high risk of renal insufficiensy)
• or Diclofenac 75 mg (Voltaren resinat, 75 mg, D1-3) 2 h before procedure. (Cave in patients with renal insufficiency or gastric ulcer)
• Dexamethasone (4 − 8 mg, Cave: not in patients with diabetes) or 100 mg Prednisolon or Decortin H 250 mg.
During IRI-Beads TACE
• Patient’s monitoring
• Dexamethasone (4 − 8 mg, not in patients with diabetes)
• i.a. intra-arterial Lidocaine 1% 2.5 − 5 mL given immediately prior to beads.
• Granisetron (Kevatril) up to 3 mg or Ondansetron (Zofran) 4 mg slow infusion
• Prevention of pain: Piritramid (0.05 − 0.1 mg/kg, Dipidolor, 15 mg in 250 mL over 30 − 45 min, can be repeated during intervention) Cave: Patient-monitoring, in the elderly or patients < 50 kg, dosis should be reduced.
• Additionally Paracetamol 1 mg iv (15 mg/kg/Day).
• In case of vegetative reaction: Atropin i.v. Bolus
• In case of gastric spasms: Phlorogucinol
Post IRI-Beads TACE
• i.v. hydratation 2 l/24H of fluids (Sodium Chloride 0.9% intravenously)
• until good oral intake.
• Dexamethasone (4 − 8 mg, not in patients with diabetes)
• Ondansetron 4 − 8 mg (Zofran) slow infusion (up to 6 h after DEBIRI) or Granisetron (Kevatril) 1 mg (maximum per day 3 mg)
• Piritramid iv (up to 15 mg in 250 mL) Cave: Patient-monitoring, in the elderly or patients < 50 kgs, dosis should be reduced
Additional management
• Consider patient-monitoring after intervention in symptomatic patients.
• Pain documentation (e.g. VAS scala)
• Surveillance of diuresis
• Full blood count (FBC), electrolytes and liver function’s parameters to be checked at least before discharge.
• Optional: US or triple-phase CT-Control (unenhanced, arterial, portal/venous phase) post interventional
• Dynamic MRI-post control after 4 − 6 weeks
Factors that influence AEs after IRI-Beads TACE
• No hepatic arterial lidocaine
• > 3 bilobar treatments with IRI-Beads
• Complete stasis
• > 100-mg IRI in 1 treatment session.
• Bilirubin > 2.0
• > 50% liver involvement

4. Improve your oncological knowledges

Approximately 25% of patients with CRC have synchronous liver metastases and up to 60% will develop them during the course of the disease [18]. In the last decade major advances in systemic chemotherapy have expanded the therapeutic options for these patients and improved median survival from less than 1 year in the era of 5-fluorouracil (5-FU) more than 30 months for selected patients, mainly driven by the availability of new cytotoxic agents other than 5-FU, and biologic agents targeting angiogenesis and the epidermal growth factor receptor (EGFR) [19]. Disease stage, mutational status, side location of the primary, as well as the liver function, the general condition, and performance status of the patient are strong prognostic and predictive factors [8]. To date, surgery provides a potentially curative option for patients with limited metastatic disease, especially if located in one organ system (such as liver or lung), an isolated local recurrence, or limited intraabdominal disease. With aggressive management integrating chemotherapy and surgery, long-term survival can be achieved in as many as 50% of cases [20,21]. However approximately 80% of patients with liver metastases are initially not suitable for curative resection. Even with liver-limited disease, the majority are not surgical candidates because of tumor location, multifocality, or inadequate hepatic reserve. Achieving secondary resectability is the treatment goal in patients with initially unresectable hepatic metastases

to obtain better long-term outcome [22–26]. A strategic treatment goal rendering technically unresectable colorectal metastases resectable is called conversion therapy [27]. Beyond systemic chemotherapy, which is the most common approach to convert initially non-resectable or borderline resectable liver metastases, locally distributed chemotherapies via the hepatic artery, like hepatic artery infusion (HAI) and transarterial chemoembolization (TACE) are further techniques to achieve later hepatic resection [28–31].

On the other hand, despite the curative intent of surgical resection, the majority of patients, around 65% develop intrahepatic recurrence within three years, even with the addition of systemic chemotherapy [32]. Surgical strategies should therefore be adopted to maximize the potential for repeat resections in the event of recurrence [33]. In addition, local ablative treatment (LAT) strategies for patients either unresectable or post-surgical recurrences as well as alternative to surgery in selected patients with oligometastatic disease are rapidly evolving, also to retain sufficient future liver remnant [33–35].

All these informations are also part of European curriculum for interventional oncology, proposed by CIRSE, with knowledge mandatory for all colleagues involved in the management of these cancer patients [36].

5. Be part of a Multidisciplinary Tumour Board (MDTB)

The indication for intra-arterial chemoembolization in patients with colorectal cancer liver metastases should come from a MDTB discussion and should be clearly articulated in a concurrent manner by the interventional and diagnostic radiologists, medical and radiation oncologists, hepatologist, pathologists, and surgeons preferably with expertise in colorectal, hepatobiliary and lung surgery.

Multidisciplinary evaluation will take into consideration the clinical specificities beyond liver tumour burden, such as comorbidities, compliance to treatment, general performance status, and history of the disease in order to select the best approach for the individual patient following the principles of the precision medicine.

In the presence of *colorectal metastatic disease to the liver*, the decision whether a patient has initially resectable or initially unresectable metastatic disease should be made at the first meeting of the MDTB. Furthermore, it is mandatory to evaluate the response rate of standard systemic therapies and the possibility to combine these options with locoregional treatments. It needs to be highlighted that the goal in these patients is not necessarily to cure but to achieve long-term disease control, potentially contributing to overall survival [3–5].

Interdisciplinarity in oncology imply a synergistic application of medical therapy concepts with focus on prolongation of survival and prevention of tumor progression and of locoregional therapies aiming to achieve local tumour control as well as controlling tumour-related symptoms and maintenance of quality of live (QoL). For this reasons, patients with colorectal liver metastases (CRLM) are usually discussed in a multidisciplinary expert team (MDTB), in order to identify an individually optimized treatment strategy. Furthermore, an MDT-managed treatment strategy has to be maintained for the duration of a patient's treatment, to allow the refinement of treatment strategies according to on-treatment information (e.g. response to a selected treatment) and evaluation of the potential need for the integration of ablative as well as intra-arterial treatments [8–37].

6. Follow the best treatment indication

Oligometastatic disease (OMD) is characterised by the localisation of the disease to only a few sites and with a limited number of lesions and is associated with the option to use local ablative treatment (LAT) approaches in patient treatment strategies with aiming to improve disease control and therefore clinical outcome in these patients. Generally, OMD may be characterised by the existence of metastases at up to 2 or occasionally 3 sites and up to 5 lesions, predominantly visceral and occasionally lymphonodal [35]. For patients with a limited size of the metastases (usually < 3 cm), local control per lesion is similar with thermal ablation compared with surgery, so that LAT strategies could be used and meaningfully contribute to the prognosis [38].

Thus, treatment strategies for patients with OMD should be based on the possibility of achieving complete eradication of all tumour masses, using surgical R0 resection (complete resection with clear resection margins and no evidence of microscopic residual tumour) and/or LAT, either initially or possibly after induction treatment with systemic therapy, for both the primary tumour and metastases. For patients with OMD confined to a single organ (most frequently the liver), or a few organs (pre-dominantly visceral metastases, e.g. lung), a potentially curative approach exists. Numerous case series have shown that in this setting, ten year survival, rated as cure can be attained in up to 25% of patients who undergo complete R0 resection of their metastases [25,26]. For patients with more extensive OMD involving $>$ 4 organs, the value of a surgical approach is controversial. In these patients, surgery may contribute to long-term survival but is rarely curative [33]. For this group of patients, the consideration of LATs becomes relevant, in combination with systemic therapy (as part of a multimodal therapy approach), following a careful MDT discussion and assessment. The goal for this group of patients is to achieve long-term disease control, potentially contributing to OS with well-controlled sites of metastases, discontinuing systemic chemotherapy ("chemo-holidays"). Liver-directed therapy is probably the best established of the LAT interventions; however, the increasing use of the appropriate ablative treatment strategy from a 'toolbox' of options, including, for example, stereotactic ablative body radiotherapy (SBRT) and radiofrequency ablation (RFA) for visceral or nodal involvement, peritonectomy with or without hyper thermic intraperitoneal chemotherapy (HIPEC) for peritoneal disease, and nodal dissection, sees the management of this subgroup of patients becoming increasingly complex. The toolbox of LATs contain thermal ablations (RF-, Microwave-, and Cryo-ablation) and non-thermal ablations (electroporation, EP and, brachytherapy, BT and EBRT). Locoregional treatments comprise mostly endovascular techniques, like transarterial chemoembolisation (TACE), chemoperfusion, selective internal radiation therapy, SIRT) as well as locally enhanced chemotherapies (e.g. electrochemotherapy, ECT).

Sub-characterisation of OMD according to site also impacts on the treatment options and the timing of treatment. Patients with liver and lung metastases have a much better prognosis than those with other metastatic disease locations.

However for patients with OMD, systemic therapy is the standard of care and should be considered as the initial part of every treatment strategy (exception: patients with single/few liver or lung lesions).

A treatment goal of LATs is a relatively new concept for patients with mCRC and involves an attempt to eradicate all visible metastatic lesions using the best instrument from the toolbox of LATs, in combination with systemic therapy. The CLOCC trial, a prematurely terminated randomised phase II trial, has shown that the combined approach with surgery and RFA of unresectable metastases plus systemic therapy may be associated with a significant improvement in OS [35]. The most important discriminator for the usage of different toolbox instruments is, after tumour location, the type of energy administered. Current technologies comprise invasive thermal ablation with distinct size limitations (e.g. RFA), conformal radiation techniques which are directed against isolated lesions, and chemoembolisation or radioembolisation with yttrium or holmium-labelled microspheres, both of which are limited to the liver for use in the management of CLM that are rather diffuse.

7. Develop the best treatment indication (for TACE)

Hence steady re-evaluation of patients during treatment in a MDT including interventional radiologists and radiation oncologists is

recommended, to adapt the therapies. Any patient with limited liver metastases should be considered a candidate for potential secondary resection as currently there are no criteria that allow us to distinguish between those patients for whom purely palliative treatment and those for whom potentially curative treatment is appropriate [37].

To date, the data on chemoembolisation for liver metastases from CRC are mostly observational series in various treatment situations [38,39]. Comparative data are limited to irinotecan-based drug-eluting beads showing a benefit versus systemic chemotherapy [40]. In potentially resectable patients with the goal of conversion, a regimen leading to high response rate (RR) and/or a large tumour size reduction is recommended [level of evidence: II, A] [3]. Intra-arterial chemotherapy and chemoembolization have been shown to achieve high RRs and R0 resection rates in small series and may be used to shrink a larger tumour so that it can be removed by surgery or LAT [18]. A further recommendation of the ESMO Guidelines is that, for patients with liver-limited disease failing the available chemotherapeutic options TACE may be considered as a treatment option [level of evidence: IV, B]) [3].

Irinotecan-based TACE in the treatment of CRC liver metastases requires further investigation in the context of the entire oncologic treatment. In detail, it could be useful to highlight its potential use as first-line treatment or as consolidation or closing treatment with or without systemic therapy after a stable disease for more than 3 months, in order to also provide a “chemo-holidays”. Furthermore, following improvement in HCC disease setting, chemoembolization could also be combined with ablative procedures with a potential curative intent.

8. Be involved in the follow-up

Being involved in the follow-up of the patients is mandatory in order to suggest eventual treatment repetition that can be proposed based on treatment response rate and clinical conditions.

Contrast-enhanced CT or MRI are recognized as the standard modalities with which to assess treatment outcome. The current interpretation of CT and MRI results is of outmost importance. At CT and MRI images obtained *4–6 weeks after completion of the treatment* cycle, successful necrosis shows as a non-enhancing area with or without a peripheral enhancing rim, that may represent a benign physiologic response to chemical injury. Residual as well as recurrent tumours are detected as neoplastic tissue in the treatment area, eventually near the necrotic portion.

Later follow-up imaging studies should be aimed at detecting local tumour progression, development of new hepatic lesions, or emergence of extrahepatic disease. A recommended follow-up protocol could include CT or MRI studies at 1, 6, and 12 months after treatment and at 6-month intervals thereafter for at least the next 3 years. However, in patients where chemo-embolization is done in a palliative setting to provide chemo-holidays, a more intensive follow could be needed, with CT or MRI control performed every 3 months for the first 2 years.

9. Check your results

Quality improvement (QI) in Interventional Radiology is currently a very hot topic, that also involved the Cardiovascular Interventional Radiological Society of Europe (CIRSE) as well as American Society of Interventional Radiology (SIR). Both societies created dedicated committee to develop quality improvement guidelines for locoregional treatments with the final aim of improving patient care. They recommended procedure-specific benchmarks such as appropriateness, safety, and efficacy to be monitored providing indicator thresholds for specific procedures. When appropriateness of indications or success rates (technical and clinical) are below the minimum threshold, or when complication rates exceed a maximum threshold, a review should be performed to determine causes and to implement changes as necessary. Finally, consolidation and standardization of changes and new processes into the permanent workflow is needed.

10. Conclusions

Locoregional therapies and in particular chemoembolization with irinotecan-loaded beads are minimally invasive procedures with an emerging role for the management of colorectal liver metastases. The range of treatments and applications for image-directed therapy has expanded to meet the growing demand from referring clinicians. Interventional oncology progressively continues to establish itself as a key pillar of cancer care, alongside with medical oncology, surgery, and radiation oncology.

Factors that contribute to success include: appropriate patient selection, enrolment in a Multidisciplinary Tumour Board management program, a thorough knowledge of procedural aspects as well intra-peri-procedural pain management. Furthermore, the crucial role of follow-up in order to obtain an early detection of local recurrences or new lesions needing prompt treatment must be highlighted. In conclusion, chemoembolization for the treatment of patients with colorectal liver metastases requires familiarization and practice of all these aspects to provide the most optimal effective and safe treatment. The era of quality-driven health care provides tremendous opportunities for interventional radiologists to showcase the field’s value, build credibility, and ensure the survival and growth of the specialty.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Institutional Review Board (IRB) approval of our study was obtained.

Informed consent

For this type of study informed consent is not required.

Consent for publication

For this type of study consent for publication is not required.

Funding

This study was not supported by any funding.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

References

[1] Felix Che-Lok Chow, Kenneth Siu-Ho Chok, Colorectal liver metastases: an update on multidisciplinary approach, World J. Hepatol. 11 (2) (2019) 150–172.
[2] G. Fiorentini, D. Sarti, C. Aliberti, R. Carandina, A. Mambrini, S. Guadagni, Multidisciplinary approach of colorectal cancer liver metastases, World J. Clin. Oncol. 8 (3) (2017) 190–202, https://doi.org/10.5306/wjco.v8.i3.190.
[3] E.P. Weledji, Centralization of liver Cancer surgery and impact on multidisciplinary teams working on stage IV colorectal Cancer, Oncol. Rev. 11 (2017) 331.
[4] R. Adam, A. de Gramont, J. Figueras, N. Kokudo, F. Kunstlinger, E. Loyer, G. Poston, P. Rougier, L. Rubbia-Brandt, A. Sobrero, C. Teh, S. Tejpar, E. Van Cutsem, J.N. Vauthey, Påhlman L of the EGOSLIM (Expert Group on OncoSurgery management of LIver Metastases) group. Managing synchronous liver metastases from colorectal cancer: a multidisciplinary international consensus, Cancer Treat. Rev. 41 (2015) 729–741.
[5] J. Oxenberg, W. Papenfuss, I. Esemuede, K. Attwood, M. Simunovic, B. Kuvshinoff, V. Francescutti, Multidisciplinary cancer conferences for gastrointestinal malignancies result in measureable treatment changes: a prospective study of 149 consecutive patients, Ann. Surg. Oncol. 22 (2015) 1533–1539.
[6] M.E. Clark, R.R. Smith, Liver-directed therapies in metastatic colorectal cancer, J. Gastrointest. Oncol. 5 (5) (2014) 374–387.
[7] K. Malagari, R. Iezzi, S.N. Goldberg, J.I. Bilbao, A. Sami, O. Akhan, F. Giuliante,

M. Pompili, L. Crocetti, V. Valentini, A. Gasbarrini, C. Colosimo, R. Manfredi, The ten commandments of chemoembolization: expert discussion and report from Mediterranean Interventional Oncology (MIOLive) congress 2017, Eur. Rev. Med. Pharmacol. Sci. 22 (2) (2018) 372–381, https://doi.org/10.26355/eurrev20180114184.

[8] E. Van Cutsem, A. Cervantes, R. Adam, A. Sobrero, J.H. Van Krieken, D. Aderka, E. Aranda Aguilar, A. Bardelli, A. Benson, G. Bodoky, F. Ciardiello, A. D'Hoore, E. Diaz-Rubio, J.Y. Douillard, M. Ducreux, A. Falcone, A. Grothey, T. Gruenberger, K. Haustermans, V. Heinemann, P. Hoff, C.H. Köhne, R. Labianca, P. Laurent-Puig, B. Ma, T. Maughan, K. Muro, N. Normanno, P. Österlund, W.J. Oyen, D. Papamichael, G. Pentheroudakis, P. Pfeiffer, T.J. Price, C. Punt, J. Ricke, A. Roth, R. Salazar, W. Scheithauer, H.J. Schmoll, J. Tabernero, J. Taïeb, S. Tejpar, H. Wasan, T. Yoshino, A. Zaanan, D. Arnold, ESMO consensus guidelines for the management of patients with metastatic colorectal cancer, Ann. Oncol. 27 (2016) 1386–1422.

[9] National Comprehensive Cancer Network, NCCN Clinical Practice in Oncology: Colon Cancer, version 3. Available from: NCCN.org, 2018, https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.

[10] O. Akinwande, M. Dendy, J.M. Ludwig, H.S. Kim, Hepatic intra-arterial injection of irinotecan drug eluting beads (DEBIRI) for patients with unresectable colorectal liver metastases: a systematic review, Surg. Oncol. 26 (3) (2017) 268–275, https://doi.org/10.1016/j.suronc.2017.05.003 Epub 2017 May 22.

[11] R. Lencioni, C. Aliberti, T. de Baere, et al., Transarterial treatment of colorectal cancer liver metastases with irinotecan-loaded drug-eluting beads: technical recommendations, J. Vasc. Interv. Radiol. 25 (3) (2014) 365–369.

[12] R. Iezzi, V.A. Marsico, A. Guerra, et al., Transarterial Chemoembolization with Irinotecan-loaded Drug-eluting Beads (DEBIRI) and capecitabine in refractory liver prevalent colorectal Metastases: a pahse II single-center study, Cardiovasc. Interv. Radiol. 38 (6) (2015) 1523–1531.

[13] Lb Liu, Ma Cedillo, V. Bishay, M. Ranade, Rs Patel, E. Kim, Sf Nowakowski, Ra Lookstein, Am. Fischman, Patient experience and preference in transradial versus transfemoral access during transarterial radioembolization: a randomized single-center trial, J. Vasc. Interv. Radiol. 30 (3) (2019) 414–420, https://doi.org/10.1016/j.jvir.2018.10.005.

[14] J. Loewenstern, C. Welch, S. Lekperic, V. Bishay, M. Ranade, Rs Patel, E. Kim, Fs Nowakowski, Ra Lookstein, Am. Fischman, Patient radiation exposure in transradial versus transfemoral Yttrium-90 radioembolization: a retrospective propensity score-matched analysis, J. Vasc. Interv. Radiol. 29 (7) (2018) 936–942, https://doi.org/10.1016/j.jvir.2018.02.011 Epub 2018 May 9.

[15] R. Yamada, S. Bracewell, B. Bassaco, J. Camacho, Mb Anderson, A. Conrad, C. Lynn, P. Burns, H. Collins, M. Guimaraes, Transradial versus transfemoral arterial access in liver Cancer embolization: randomized trial to assess patient satisfaction, J. Vasc. Interv. Radiol. 29 (1) (2018) 38–43, https://doi.org/10.1016/j.jvir.2017.08.024 Epub 2017 Nov 15.

[16] R. Iezzi, M. Pompili, A. Posa, E. Annicchiarico, M. Garcovich, B. Merlino, E. Rodolfino, V. Di Noia, M. Basso, A. Cassano, C. Barone, A. Gasbarrini, R. Manfredi, C. Colosimo, Transradial versus transfemoral access for hepatic chemoembolization: intrapatient prospective single-center study, J. Vasc. Interv. Radiol. 28 (9) (2017) 1234–1239, https://doi.org/10.1016/j.jvir.2017.06.022 Epub 2017 Jul 27.

[17] G. Fiorentini, C. Aliberti, G. Benea, et al., TACE of liver metastases from colorectal cancer adopting irinotecan-eluting beads: beneficial effect of palliative intra-arterial lidocaine and post-procedure supportive therapy on the control of side effects, Hepatogastroenterology 55 (88) (2008) 2077–2082.

[18] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2019, CA Cancer J. Clin. 69 (2019) 7–34, https://doi.org/10.3322/caac.21551.

[19] V. Heinemann, L.F. von Weikersthal, T. Decker, et al., FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial, Lancet Oncol. 15 (2014) 1065–1075, https://doi.org/10.1016/s1470-2045(14)70330-4.

[20] G. Zimmitti, J. Shindoh, Y. Mise, et al., RAS mutations predict radiologic and pathologic response in patients treated with chemotherapy before resection of colorectal liver metastases, Ann. Surg. Oncol. 22 (2015) 834–842, https://doi.org/10.1245/s10434-014-4042-6.

[21] S.A. Shah, R. Haddad, W. Al-Sukhni, et al., Surgical resection of hepatic and pulmonary metastases from colorectal carcinoma, J. Am. Coll. Surg. 202 (2006) 468–475, https://doi.org/10.1016/j.jamcollsurg.2005.11.008.

[22] R.L. Jamison, J.H. Donohue, D.M. Nagorney, et al., Hepatic resection for metastatic colorectal cancer results in cure for some patients, Arch. Surg. 132 (1997) 505–510, https://doi.org/10.1001/archsurg.1997.01430290051008 discussion 511.

[23] E.K. Abdalla, J.N. Vauthey, L.M. Ellis, et al., Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases, Ann. Surg. 239 (2004) 818–825, https://doi.org/10.1097/01.sla.0000128305.90650.71 discussion 825-817.

[24] D.F. Dunne, R.P. Jones, H.Z. Malik, et al., Surgical management of colorectal liver metastases: a European perspective, Hepat. Oncol. 1 (2014) 121–133, https://doi.org/10.2217/hep.13.3.

[25] J.S. Tomlinson, W.R. Jarnagin, R.P. DeMatteo, et al., Actual 10-year survival after resection of colorectal liver metastases defines cure, J. Clin. Oncol. 25 (2007) 4575–4580, https://doi.org/10.1200/jco.2007.11.0833.

[26] R.P. Jones, S. Stattner, P. Sutton, et al., Controversies in the oncosurgical management of liver limited stage IV colorectal cancer, Surg. Oncol. 23 (2014) 53–60, https://doi.org/10.1016/j.suronc.2014.02.002.

[27] R.P. Jones, S. Hamann, H.Z. Malik, et al., Defined criteria for resectability improves rates of secondary resection after systemic therapy for liver limited metastatic colorectal cancer, Eur. J. Cancer 50 (2014) 1590–1601, https://doi.org/10.1016/j.ejca.2014.02.024.

[28] T. Gruber-Rouh, C. Marko, A. Thalhammer, et al., Current strategies in interventional oncology of colorectal liver metastases, Br. J. Radiol. 89 (2016) 20151060, , https://doi.org/10.1259/bjr.20151060.

[29] V.W. Lam, J.M. Laurence, E. Johnston, et al., A systematic review of two-stage hepatectomy in patients with initially unresectable colorectal liver metastases, HPB (Oxford) 15 (2013) 483–491, https://doi.org/10.1111/j.1477-2574.2012.00607.x.

[30] R.C. Martin 2nd, C.R. Scoggins, D. Tomalty, et al., Irinotecan drug-eluting beads in the treatment of chemo-naive unresectable colorectal liver metastasis with concomitant systemic fluorouracil and oxaliplatin: results of pharmacokinetics and phase I trial, J. Gastrointest. Surg. 16 (2012) 1531–1538, https://doi.org/10.1007/s11605-012-1892-8.

[31] R.P. Jones, H.Z. Malik, S.W. Fenwick, et al., PARAGON II – a single arm multicentre phase II study of neoadjuvant therapy using irinotecan bead in patients with resectable liver metastases from colorectal cancer, Eur. J. Surg. Oncol. 42 (2016) 1866–1872, https://doi.org/10.1016/j.ejso.2016.07.142.

[32] R.P. Jones, R. Jackson, D.F. Dunne, et al., Systematic review and meta-analysis of follow-up after hepatectomy for colorectal liver metastases, Br. J. Surg. 99 (2012) 477–486, https://doi.org/10.1002/bjs.8667.

[33] R.P. Jones, G.J. Poston, Resection of liver metastases in colorectal Cancer in the era of expanding systemic therapy, Annu. Rev. Med. 68 (2017) 183–196, https://doi.org/10.1146/annurev-med-062415-093510.

[34] T. Ruers, C. Punt, F. Van Coevorden, et al., Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004), Ann. Oncol. 23 (2012) 2619–2626, https://doi.org/10.1093/annonc/mds053.

[35] M.R. Meijerink, R.S. Puijk, A. van Tilborg, et al., Radiofrequency and microwave ablation compared to systemic chemotherapy and to partial hepatectomy in the treatment of colorectal liver metastases: a systematic review and meta-analysis, Cardiovasc. Intervent. Radiol. 41 (2018) 1189–1204, https://doi.org/10.1007/s00270-018-1959-3.

[36] European Curriculum and Syllabus for Interventional Oncology, (2018) https://www.cirse.org/wp-content/uploads/2019/03/cirse_IOcurriculum_syllabus_2018_web.pdf.

[37] C.J. van de Velde, P.G. Boelens, J.M. Borras, et al., EURECCA colorectal: multidisciplinary management: European consensus conference colon & rectum, Eur. J. Cancer 50 (2014) 1.e1–1.e34, https://doi.org/10.1016/j.ejca.2013.06.048.

[38] E. Tanis, B. Nordlinger, M. Mauer, et al., Local recurrence rates after radiofrequency ablation or resection of colorectal liver metastases. Analysis of the European Organisation for Research and Treatment of Cancer #40004 and #40983, Eur. J. Cancer 50 (2014) 912–919, https://doi.org/10.1016/j.ejca.2013.12.008.

[39] R.P. Jones, D. Dunne, P. Sutton, et al., Segmental and lobar administration of drug-eluting beads delivering irinotecan leads to tumour destruction: a case-control series, HPB (Oxford) 15 (2013) 71–77, https://doi.org/10.1111/j.1477-2574.2012.00587.x.

[40] G. Fiorentini, C. Aliberti, M. Tilli, et al., Intra-arterial infusion of irinotecan-loaded drug-eluting beads (DEBIRI) versus intravenous therapy (FOLFIRI) for hepatic metastases from colorectal cancer: final results of a phase III study, Anticancer Res. 32 (2012) 1387–1395.