Surgical Oncology & Clinical Practice Journal

Review Article
Published: 07 Nov, 2016

Current Management of Colorectal Cancer with Liver Metastasis

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Abstract

Colorectal cancer is a worldwide public health problem. More than 20% of patients with colorectal cancer present at an advanced stage, and the liver is the most common site of metastases. More recently, selection criteria for resectability have been expanded, but definition of resectability still remains challenging. Since the presence of metastases is the most relevant prognostic factor, surgical resection of liver metastases is the mainstay of treatment. The most appropriate resection approach remains controversial, but both staged and simultaneous resection has been shown to have comparable survival advantages and long-term outcomes. The advent of new chemotherapeutic agents and the development of loco-regional therapies (embolization, ablation, and infusion chemotherapy) have contributed to better outcomes. It is deemed reasonable to adopt combination therapy for unresectable metastases. In view of the lack of standardized evidence-based protocols, optimal management of hepatic metastases should be individualized to the single patient and decided through a multidisciplinary approach. Early detection is always the ultimate goal to reduce metastatic colorectal cancer burden worldwide. In this overview, the current management of liver metastases originating from colorectal cancer is presented.

Keywords: Colorectal cancer; Liver metastases; Liver resection; Hepatic resection; CRLM

Introduction

Colorectal cancer (CRC) is an increasingly global health issue [1]. According to the most recent epidemiological data, it accounts for more than 1.4 million newly diagnosed cases each year [2]. CRC is the most common gastrointestinal tumor and the third most frequently diagnosed malignancy in men and women worldwide, however, there is a wide geographical variation in incidence and mortality [1-3]. Liver is the most common site of distant metastases from CRC [4]. More than 50% of patients will develop liver metastases sometime in the course of their disease; in addition, presentation of liver metastases at the time of diagnosis (stage IV disease) is reported in 15 to 20% of cases [5]. Traditionally, patients with metastatic liver disease were deemed inoperable; however, surgical resection for liver metastases has more recently been shown possibility to achieve cure or prolong survival [5]. In fact, recent modifications of resectability criteria for liver metastasis have significantly improved outcomes with five-year and ten-year survival rates reaching up to 40% and 25% respectively [6,7]. However, 1-year recurrence rate after metastases resection has been reported in up to 30% of cases [7]. When surgical treatment of liver metastases is not feasible, chemotherapy, radiation therapy and/or ablation techniques can be used with satisfactory outcomes [8]. This review examines the current management of colorectal cancer with liver metastases (CRLM). Comments about effectiveness, complications as well as survival benefits are discussed.

Perioperative evaluation

In order to minimize postoperative complications, perioperative assessment of patient's fitness for surgery and liver status are crucial. Presence of co-morbidities and patient's performance must be carefully assessed as these affect resection outcomes and treatment plan through a dedicated multidisciplinary team. Comprehensive blood investigations should be routinely obtained before surgical resection including liver function tests, coagulation profile, bilirubin, creatinine and carcinoembryonic antigen (CEA) [9]. The 'Patient Safety in Surgery Study' has highlighted that advanced age, male gender, low serum albumin, presence of underlying liver disease (hepatitis or alcoholic hepatitis), ascites, kidney failure, bleeding disorders, cardiomyopathy, and chronic obstructive pulmonary disease are associated with substantial morbidity and mortality following liver resection [10].

OPEN ACCESS

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Received Date: *25 Sep 2016*
Accepted Date: *24 Oct 2016*
Published Date: *07 Nov 2016*

Citation:
Al-Qahtani M, Alqahtani S, Privitera A, Al-Rashid F, Osian G. Current Management of Colorectal Cancer with Liver Metastasis. Surg Oncol Clin Pract J. 2016; 1(1): 1001.

Radiological evaluation

Radiological assessment of CRLM is mandatory to plan surgical resection [11]. The three main radiological modalities to evaluate CRLM as well as extra-hepatic disease (EHD) are: computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) scan [11]. Hepatic metastases are easily detected as hypoattenuating lesions using contrast-enhanced CT scan with 85% sensitivity rate in most references [11-14]. However, a higher detection rate (reaching up to 90%) can be obtained using contrast-enhanced multi-detector CT scan [13]. In cases of underlying liver disease (steatosis, cirrhosis), following chemotherapy, or to identify sub-centimetric lesions, MRI with liver-specific contrast agents is superior to CT scan with more than 90% sensitivity [14].

Specificity of the three diagnostic modalities is high and has been reported as 95%, 93%, and 97% for CT, MRI and PET CT respectively [15]. PET scan is used to obtain whole body map to identify EHD that could rule out liver resection [15]. A recent meta-analysis has shown FDG PET scan to be the best radiological modality for detection of liver lesions from gastrointestinal origin [16]. Moreover, adding CT to FDG PET improves sensitivity up to 97% [15]. In patients with recent chemotherapy treatment PET scan has high false-negative rates [17]. More recently, intra-operative ultrasound (IOUS) has been increasingly used in surgical practice. It is safe, inexpensive and a very useful adjunct to preoperative investigations, being able to detect new lesions in up to 20% of cases [18].

Current Treatment Strategies

Chemotherapy

Neo-adjuvant Chemotherapy for Resectable CRLM: The use of neoadjuvant chemotherapy in resectable CRLM is still controversial [19]. Many authors claim that upfront induction chemotherapy has many advantages. [19]In fact, it can assess tumor sensitivity, downstage large or multiple liver lesions leading to easier resection, and more importantly may treat potential micrometastases [19]. However, a potential drawback of induction chemotherapy includes possibility of delayed surgical treatment for a subset of patients in whom disease will continue to progress [19,20]. Also, chemotherapy carries a substantial risk of hepatic toxicity with steatohepatitis that is associated with increased 90-day postoperative mortality [21]. In addition, it can make liver metastases undetectable on preoperative imaging, a relatively new clinical problem that can be seen in 5-25% of patients with the use of current chemotherapy agents [22]. In a recent multicentric randomized trial comparing surgery alone to perioperative chemotherapy (6 cycles of preoperative and post operatively of FOLFOX4) in a cohort of 364 patients with initially resectable CRLM, no major differences were found in five-year overall survival between both groups (48% in the surgery-alone group versus 51% in the perioperative chemotherapy group) [23]. However, there was an absolute increase of 7.3% in the rate of progression-free survival (PFS) at 3 years in the perioperative chemotherapy group [23].

In current practice, it is widely acceptable that patients with resectable CRLM receive perioperative chemotherapy; however, no clinical trial has shown that this practice would prolong overall survival (OS) [24]. Due to the lack of clear evidence of overall survival improvement with chemotherapy, it has been suggested to limit chemotherapy to 6 cycles given for no longer than 3 month due to the substantial associated side effects [25], especially when a major hepatectomy is needed [26].

Adjuvant Chemotherapy for Resectable CRLM: The ultimate dilemma after complete CRLM resection is the rate of recurrence that is reported as high as 70% after complete surgical excision. Unlike neoadjuvant treatment, several studies have shown benefit of adjuvant chemotherapy in terms of longer disease-free-survival (DFS) [27]. More than one study has demonstrated that that use of adjuvant chemotherapy FOLFOX4 (folinic acid, fluorouracil, and oxaliplatin) after liver resection is superior to liver resection alone [28]. A recent meta-analysis has shown that adjuvant chemotherapy is associated with longer OS when compared to surgery alone, although the difference has not been found to be statistically significant [29]. The classic four chemotherapeutic agents studied as adjuvant treatment are: 5-fluorouracil/leucovorin (5-FU/LV), capecitabine (the oral fluoropyrimidine carbamate), oxaliplatin and irinotecan [30,31]. More recently, molecular-targeted agents including anti-angiogenic drugs (bevacizumab, regorafenib and aflibercept) and anti-epidermal growth factor receptors agents (anti-EGFR), such as cetuximab and panitumumab, have been introduced in the market [30,31].

Generally, adjuvant chemotherapy after resection of metastases is highly recommended, however the best regimen protocol remains controversial [29]. There is also a lack of consensus about the impact of adjuvant chemotherapy on OS in the setting of resectable CRLM [28]. The National Comprehensive Cancer Network (NCCN) guidelines accredited more than one chemotherapy line [30,31]. According to most trials, 5-fluorouracil/leucovorin (5-FU/LV) with or without oxaliplatin remains the recommended first-line [28]. However, during the last few decades, a trend into combination therapy has emerged and more than one combination has been investigated. A recent trial has identified no significant difference in OS and median DFS when FOLFIRI (5-fluorouracil/leucovorin and irinotecan) and 5FU/LV (5-fluorouracil/ leucovorin) administered after complete resection of CRLM, were compared (22 months for the 5FUlLV group vs. 25 months for the FOLFIRI group). However, a trend was observed for improved DFS in the patients receiving FOLFIRI. Additionally, grade 3/4 toxic side effects were more common in the FOLFIRI group (47% vs. 30%) [32].

Chemotherapy for Unresectable CRLM: About 80% of patients with CRLM have unresectable disease at the time of presentation [33]. This group of patients has complex disease, and therefore may require a combination of loco-regional therapy regimens including ablation, embolization or radiation. However, systemic chemotherapy is the mainstay of treatment and several lines known to have good response rate are available [30,31]. In a recent study, infusional 5FU/LV, oxaliplatin an irinotecan (FOLFOXIRI) followed by surgical resection has been shown to be associated with a high response rate (70.4%) with 19% of patients achieving an R0 surgical resection. OS at 5 years and 8 years were reported as 42% and 33% respectively. At 5 years, 29% of patients were disease free [34]. Conversion rates of unresectable disease to resectable differ in the literature ranging from 5% to 38%. This variation in final outcomes is due to several factors including disease extent, type and duration of chemotherapy treatment [35]. Failed response to first line chemotherapy is an extremely poor prognostic factor. In fact, best response rate after second line chemotherapy does not exceed 10% [35].

The use of anti-EGFR and anti-vascular endothelial growth factors (anti-VEGF) is becoming more common in cases of unresectable metastases [36]. However, various studies have identified only a slight

gain in response rate when bevacizumab is added to FOLFOXIRI (fluorouracil - leucovorin, oxaliplatin, and irinotecan) as first line chemotherapy regimen [36].

Surgical Excision of Metastases

Surgery is the mainstay of treatment for liver metastases from colorectal cancers, and can provide up to 55% five-year survival [37]. Metastases are not considered a contraindication to surgery if excision of all metastatic deposits can be achieved with an adequate future liver remnant (FLR) [38].

Criteria for resectability

There has been a paradigm shift in the CRLM resectability criteria over the last few decades [6]. In fact, criteria have expanded and they are less dependent on the presence, number, size and location of the lesions; in addition, more emphasis has been placed on the volume and function of the future liver remnant (FLR) rather than the extent of resection [25]. The presence of EHD is currently no longer considered to be a contraindication [6]. Currently, the minimum requirements needed prior to resection of liver metastases are: 1) Achieving an R0 resection of both intrahepatic as well as EHD. 2) At least two adjacent liver segments should be spared with blood and bile inflow and outflow preservation 3) Adequate future remnant liver volume and function (at least 25% estimated normal liver parenchyma and 30% in case of impaired liver function tests) [27,39,40].

Timing of colon and Liver resection

The sequence and best timing of CRLM resection is still controversial and several approaches have been proposed, especially with chemotherapy being increasingly used. Strong evidence is still lacking and there is no randomized controlled trial comparing different methods [41,42].

There are several approaches described in the surgical literature. The classic surgical approach is "primary first" in which resection of the primary colorectal cancer is followed by chemotherapy and eventually by resection of metastases after 3 to 6 months. This staged resection is best for patients with significant co-morbidities, symptomatic colorectal cancers, inadequate FLR, and advanced primary cancer. In fact, when the tumor is advanced, a higher complication rate may be observed during chemotherapy, and there is possibility of progression of disease leading to inoperability [41]. Another main advantage of this approach is to identify patients with occult liver metastases that may become detectable during adjuvant chemotherapy avoiding the morbidity of a liver resection [42]. However, some patients might experience progression of liver disease especially if delays are encountered due to complications after resection of the primary [41,42]. The other approach is the simultaneous resection of liver metastases and primary tumor. This approach avoids delays in treatment since all cancerous lesions are removed in one single procedure and chemotherapy treatment can be started earlier if no complications occur. However, increased postoperative morbidity and mortality due to bacterial contamination of the surgical field is a potential issue that should be taken into consideration [43]. This approach suits best colon cancers and single group of patients who can tolerate longer operative times [8]. The third known approach is the alternative staged "liver-first" approach. This approach consists of liver metastases resection (usually following 3 to 6 cycles of systemic chemotherapy) followed by resection of the colorectal tumor (adjuvant chemotherapy might be given in between both procedure). Recent data showed that liver-first approach is better for selected patients with advanced CRLM when chemotherapy might provide better results if given before [44].

Extra-Hepatic Disease (EHD)

The presence of EHD is associated with a poor prognosis [45]. Lungs are the second most common sites of metastases (after lymph nodes) from CRC, followed by the peritoneum, brain and bone [45]. EHD is no longer a contraindication to surgery [6]. Recent reports show longer DFS and five-year-survival rates in patients with resection of pulmonary metastases compared to those receiving chemotherapy alone [7].

Regarding lymph nodes involvement, the OS following resection of specific groups of lymph nodes differs according to site and number [46]. In fact, worse outcomes have been reported after resection of aortocaval or celiac lymph nodes compared to hepatic pedicle nodes. Similarly, the higher the number of lymph nodes involved, the poorer the outcome [46]. However, when the median survival of individuals with chest lymph nodes involvement were compared, intra-thoracic metastases found to have better five-year-survival than mediastinal ones [47].

Other surgical approaches

FLR is the utmost limiting factor to perform major hepatectomies. Therefore, surgeons have developed innovative techniques to accelerate liver growth in order to increase resectability. Those strategies include (but not limited to), Associated Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) and two-stage hepatectomy (TSH).

ALPPS is one of the main novel techniques in recent years. ALPPS was first described in 2012 to achieve sufficient hypertrophy prior to major hepatectomy [47]. The main idea is to divert the venous blood flow away from the lobe where tumor is located with portal vein ligation to induce hypertrophy in the contralateral lobe, then to resects the tumor-bearing lobe. Use of ALPPS, indications, and safety is still a controversial among hepatobiliary surgeons [48]. Some centers reported high morbidity and mortality reaching up to 30%, in opposite to that, several studies demonstrated ALPPS to achieve up to 90% increase in the FLR [49-51]. Due to this huge variability in long-term outcomes and lack of standardization, we cannot draw firm conclusions if ALPPS is to be considered a treatment choice for marginally resectable or initially non-resectable CRLM. The other relatively new surgical procedure is TSH. To date, TSH is the standard of care for extensive CRLM. It has been found that TSH significantly improved resectability rates (up to 50%) but associated with high rates of drop out (up to 30%) after the first procedure due to disease progression remains a concern [52]. Therefore, Trozilli G. et al. [53] encouraged one-stage hepatectomy (OSH) approach with no local recurrence in a median follow up of 14 months. Clearly, this short median follow up time precludes any conclusions regarding the safety and feasibility of OSH for extensive CRLM. More recently, laparoscopic approach was examined in TSH and found be safe and feasible by Fuks D. and his colleagues [54]. In regard to 90-days mortality of TSH in comparison to ALPPS, Adam R. et al. [55] reported higher 90-days mortality with ALPPS approach in a propensity matching score analysis of 58 patients with multiple liver metastases.

Loco-Regional Therapies

Over the last several decades, more patients with unresectable

CRLM at presentation are being treated with ablative techniques with good outcomes. In addition to chemotherapy, they have been shown to prolong OS by approximately 20 months in comparison to chemotherapy alone [56,57]. Selection of the best loco-regional treatment has to be tailored to every case through a multidisciplinary approach [57].

Ablation techniques

Radiofrequency ablation (RFA) is a widely used form of ablation allowing application of extreme temperature for ablation of the tumor with minimal toxicity to the surrounding liver parenchyma. Published data show low toxicity rates, less than 1% mortality and less than 10% morbidity regardless of the route of administration [58]. The "heat sink effect" remains a major downside of RFA with possibility of significant hepatic or vascular injury [59]. Hence, RFA is not recommended for unresectable lesions, lesions located near blood vessels or diaphragm due to the substantial risk of perforation [60]. Another limitation of RFA is the recurrence rate especially with lesions higher than 3 cm or if it was delivered percutaneosly [61]. External Beam Radiation (EBRT) using high frequency microwave radiation is another modern technique, which causes coagulation and necrosis of the tumor deposits. This technique is not well studied and there are concerns about its safety [62]. One of the largest series reported a 6% local recurrence rate [63]. The potential role of EBRT has increased over the years with advances in imaging techniques [63]. Due to its low therapeutic window, toxicity remains a major concern. However, for liver tumors in general and in selected patients, EBRT has shown to be safe and effective as a loco-regional treatment modality [57]. A dose of 60 Gy (gray) for local disease control has been reported to be a safe [57]. In light of the limitation of the RFA and EBRT, a newer technique has been used emerged in the field. The Irreversible electroporation (IRE) uses a Nano-knife to deliver high-voltage electricity directly to the tumor to induce cell death under radiological control. Since IRE is a non-thermal technique, the area of ablation will not suffer from 'heat-sink effect'; therefore, IRE is relatively safe for metastases close to vital structure [64]. Short-term response rate is about 50% and was associated with lesions < 1 cm [65,66] and the lowest effectiveness was associated with tumors of colorectal origin [67]. IRE uses high velocity of electoral pulses; so, it has to be performed under general anesthesia and patients need to be monitored not to develop cardiac arrhythmias [64]. To our knowledge, COLDFIRE-2 is the only one single-arm phase II clinical trial that has been done to assess the efficacy of IRE to treat CRLM. It showed that IRE is a promising modality of treatment with good safety index for the difficult to reach lesions [68]. At this time of development, there are no studies comparing IRE to other ablation techniques. Likewise, there are many questions unanswered about IRE in the treatment of CRLM, therefore, larger prospective clinical research is needed [66].

Embolic intra-arterial therapies

As a new liver-directed locoregional technique, they showed sufficient control of liver metastases in first and later lines of patients with CRLM. In comparison to the systemic chemotherapy regimens offered to patients with CRLM, they were found to be superior to systemic chemotherapy in hepatic PFS. Trans-arterial chemoembolization in general offered higher concentration of the chemotherapy agent than the infusion route. To date, there is no consensus on what is the standard protocol for chemoembolization but varies between centers [69]. Trans-Arterial Chemoembolization (TACE) has serious complications like 'tumor-lysis syndrome' and 'post-embolization syndrome'; both are self-limiting and resolve within short period of time [70]. Due to median survival benefits (8 to 12 months) of TACE, it will remain a preferable treatment option for unresectable CRLM, provided a preserved liver function however, different strategies of chemoembolization need further prospective studies [71]. More recently, there is growing literature supporting the use of TACE along with the drug-eluting beads with irinotecan (DEBIRI). It has been found to have a longer overall survival (7 months) when compared to systemic FOLFIRI in a phase III randomized trial [72]. Furthermore, can down stage non-resectable metastases when combined with first-line systemic chemotherapy (FOLFOX), however, a technical aspect of the procedure is still debated [73]. Selective Intra-arterial radiation therapy (SIRT) is another intra-arterial embolic treatment for CRLM. There is a sufficient body of evidence indicating that SIRT is a safe, however, some authors reported serious hematological and gastrointestinal complications, such as bleeding, radiation induced cholecystitis or radiation-induced liver disease [74]. SIRT uses yttrium-90 (^{90}Y) bound to resin microspheres to be injected into the metastatic lesion through the hepatic artery. In a randomized phase III control trial for patients with liver-limited metastatic lesions who have failed chemotherapy, Hendlisz A. et al. [75] compared fluorouracil infusion versus radio-embolization against intravenous fluorouracil and found a prolonged time to tumor progression in the radio-embolization arm. Furthermore, SIRFLOX-study showed around 30% decreases in disease progression in the liver when SIRT using ^{90}Y is added to Folfox as a first line chemotherapy [76]. Also, in a recent review of the current evidence by Towsend A. et al. [77] SIRT showed neither survival benefit nor a better quality of life. Clearly, majority of studies showed either tumor response or slowing down tumor progression [78]. To date, there are four randomized clinical trials comparing the effectiveness of SIRT with chemotherapy to chemotherapy alone, none examined OS [65]. Therefore, data of OS from SIRFLOX combined with FOXFIRE and FOXFIRE Global will be necessary before implementation into standard practice.

Conclusions

Recent advances in the treatment of metastatic colorectal liver disease have allowed expansion of resectability criteria with an increased number of patients being cured or living with better disease control. There is currently no consensus regarding the sequence of surgical resection of the primary cancer and metastatic disease. However, the use of neoadjuvant chemotherapy is generally accepted as a primary step. Surgical resection is feasible as long as complete removal of cancer is achievable and adequate residual functioning liver parenchyma is preserved. Adjuvant chemotherapy is highly recommended, though protocols are not yet well standardized. In case of unresectable disease, combination chemotherapy treatment may induce regression of disease and allow for possibility of resection and cure. In the battle against liver metastases from colorectal origin, loco-regional treatments are gaining more support and may achieve good local control, however, not recommended as first-line treatment options for resectable metastases. For all patient with liver metastases, a multidisciplinary approach is to be emphasized for optimal management and an individualized evidence-based approach must be adopted to achieve best clinical and survival outcomes.

References

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al.

Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015; 136: E359-E386.

2. Siegel R, Desantis C, Jemal A. Colorectal cancer statistics. CA Cancer J Clin. 2014; 64: 104-117.

3. Renehan AG, Egger M, Saunders MP, T O'Dwyer S. Impact on survival of intensive follow up after curative resection for colorectal cancer: systematic review and meta-analysis of randomised trials. BMJ. 2002; 324: 813.

4. Nordlinger B, Van Cutsem E, Rougier P, Köhne CH, Ychou M, Sobrero A, et al. Does chemotherapy prior to liver resection increase the potential for cure in patients with metastatic colorectal cancer? A report from the European Colorectal Metastases Treatment Group. Eur J Cancer. 2007; 43: 2037-2045.

5. Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M. Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. Br J cancer. 2006; 94: 982-999.

6. Pawlik TM, Schulick RD, Choti MA. Expanding criteria for resectability of colorectal liver metastases. Oncologist. 2008; 13: 51-64.

7. Hadden WJ, de Reuver PR, Brown K, Mittal A, Samra JS, Hugh TJ. Resection of colorectal liver metastases and extra-hepatic disease: a systematic review and proportional meta-analysis of survival outcomes. HPB. 2016; 18: 209-220.

8. Abdalla EK, Vauthey JN, Ellis LM, Ellis V, Pollock R, Broglio KR, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg. 2004; 239: 818-827.

9. Read JA, Boris Choy ST, Beale PJ, Clarke SJ. Evaluation of nutritional an inflammatory status of advanced colorectal cancer patients and its correlation with survival. Nutrition and Cancer. 2006; 55: 78-85.

10. Virani S, Michaelson JS, Hutter MM, Lancaster RT, Warshaw AL, Henderson WG, et al. Morbidity and mortality after liver resection: results of the patient safety in surgery study. J Am Coll Surg. 2007; 204: 1284-1292.

11. Glover C, Douse P, Kane P, Karani J, Meire H, Mohammadtaghi S, et al. Accuracy of investigations for asymptomatic colorectal liver metastases. Dis Colon Rectum. 2002; 45: 476-484.

12. Tan AG, Thng CH. Current status in imaging of colorectal liver metastases. Ann Acad Med Singapore. 2003; 32: 185-190.

13. Scharitzer M, Ba-Ssalamah A, Ringl H, Kölblinger C, Grünberger T, Weber M, et al. Preoperative evaluation of colorectal liver metastases: comparison between gadoxetic acid-enhanced 3.0-T MRI and contrast-enhanced MDCT with histopathological correlation. Eur Radiol. 2013; 23: 2187-2196.

14. Choi DJ, Kwak JM, Kim J, Woo SU, Kim SH. Preoperative chest computerized tomography in patients with locally advanced mid or lower rectal cancer: its role in staging and impact on treatment strategy. J Surg Oncol. 2010; 102: 588-592.

15. Niekel MC, Bipat S, Stoker J. Diagnostic Imaging of Colorectal Liver Metastases with CT, MR Imaging, FDG PET, and/or FDG PET/CT: A Meta-Analysis of Prospective Studies Including Patients Who Have Not Previously Undergone Treatment 1. Radiology. 2010; 257: 674-684.

16. Kinkel K, Lu Y, Both M, Warren RS, Thoeni RF. Detection of hepatic metastases from cancers of the gastrointestinal tract by using noninvasive imaging methods (US, CT, MR imaging, PET): a meta-analysis 1. Radiology. 2002; 224: 748-756.

17. Glazer ES, Beaty K, Abdalla EK, Vauthey JN, Curley SA. Effectiveness of positron emission tomography for predicting chemotherapy response in colorectal cancer liver metastases. Arch Surg. 2010; 145: 340-345.

18. Lucchese AM, Kalil AN, Schwengber A, Suwa E, Rolim de Moura GG. Usefulness of intraoperative ultrasonography in liver resections due to colon cancer metastasis. Int J Surg. 2015; 20: 140-144.

19. Chua TC, Saxena A, Liauw W, Kokandi A, Morris DL. Systematic review of randomized and nonrandomized trials of the clinical response and outcomes of neoadjuvant systemic chemotherapy for resectable colorectal liver metastases. Ann Surg Oncol. 2010; 17: 492-501.

20. Power DG, Kemeny NE. Role of adjuvant therapy after resection of colorectal cancer liver metastases. J Clin Oncol. 2010; 28: 2300-2309.

21. Vauthey JN, Pawlik TM, Ribero D, Wu TT, Zorzi D, Hoff PM, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol. 2006; 24: 2065-2072.

22. Bischof DA, Clary BM, Maithel SK, Pawlik TM. Surgical management of disappearing colorectal liver metastases. Br J Surg. 2013; 100: 1414-1420.

23. Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol. 2013; 14: 1208-1215.

24. Beppu T, Sakamoto Y, Hayashi H, Baba H. Perioperative chemotherapy and hepatic resection for resectable colorectal liver metastases. Hepatobiliary Surg Nutr. 2015; 4: 72-75.

25. Mattar RE, Al-alem F, Simoneau E, Hassanain M. Preoperative selection of patients with colorectal cancer liver metastasis for hepatic resection. World Gastroenterol. 2016; 22: 567-581.

26. Karoui M, Penna C, Amin-Hashem M, Mitry E, Benoist S, Franc B, et al. B. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. Ann Surg. 2006; 243: 1-7.

27. Adam R, de Gramont A, Figueras J, Kokudo N, Kunstlinger F, Loyer E, et al. Managing synchronous liver metastases from colorectal cancer: a multidisciplinary international consensus. Cancer Treat Rev. 2015; 41: 729-741.

28. Mitry E, Fields AL, Bleiberg H, Labianca R, Portier G, Tu D, et al. Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. J Clin Oncol. 2008; 26: 4906-4911.

29. Brandi G, De Lorenzo S, Nannini M, Curti S, Ottone M, Dall'Olio FG, et al. Adjuvant chemotherapy for resected colorectal cancer metastases: Literature review and meta-analysis. World J Gastroenterol. 2016; 22: 519-533.

30. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Colon Cancer (version 2. 2016) http://www.nccn.org. [Accessed Jan 24, 2016]

31. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Rectal Cancer (version 1. 2016). http://www.nccn.org. [Accessed Jan 24, 2016]

32. Ychou M, Hohenberger W, Thezenas S, Navarro M, Maurel J, Bokemeyer C, et al. A randomized phase III study comparing adjuvant 5-fluorouracil/folinic acid with FOLFIRI in patients following complete resection of liver metastases from colorectal cancer. Ann Oncol. 2009; 20: 1964-1970.

33. Adam R, Wicherts DA, de Haas RJ, Ciacio O, Lévi F, Paule B, et al. Patients with initially unresectable colorectal liver metastases: is there a possibility of cure?. J Clin Oncol. 2009; 27: 1829-1835.

34. Masi G, Loupakis F, Pollina L, Vasile E, Cupini S, Ricci S, et al. Long-term outcome of initially unresectable metastatic colorectal cancer patients treated with 5-fluorouracil/leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) followed by radical surgery of metastases. Ann Surg. 2009; 249: 420-425.

35. Adam R, De Gramont A, Figueras J, Guthrie A, Kokudo N, Kunstlinger F, et al. The oncosurgery approach to managing liver metastases from colorectal cancer: a multidisciplinary international consensus. Oncologist. 2012; 17: 1225-1239.

36. Loupakis F, Cremolini C, Masi G, Lonardi S, Zagonel V, Salvatore L, et al. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. N Engl J Med. 2014; 371: 1609-1618.

37. De Ridder JA, van der Stok EP, Mekenkamp LJ, Wiering B, Koopman M, Punt CJ, et al. Management of liver metastases in colorectal cancer patients: A retrospective case-control study of systemic therapy versus liver resection. Eur J Cancer. 2016; 59: 13-21.

38. Misiakos EP, Karidis NP, Kouraklis G. Current treatment for colorectal liver metastases. World J Gastroenterol. 2011; 17: 4067-4075.

39. Ihnát P, Vávra P, Zonča P. Treatment strategies for colorectal carcinoma with synchronous liver metastases: Which way to go?. World J Gastroenterol. 2015; 21: 7014-7021.

40. Ferrero A, Viganò L, Polastri R, Muratore A, Eminefendic H, Regge D, et at. Postoperative liver dysfunction and future remnant liver: where is the limit?. World j Surg. 2007; 31: 1643-1651.

41. Waisberg J, Ivankovics IG. Liver-first approach of colorectal cancer with synchronous hepatic metastases: A reverse strategy. World J Hepatol. 2015; 7: 1444-1449.

42. Ruers TJ, Hagendoorn J. Treatment dilemmas in patients with synchronous colorectal liver metastases. Recent Results Cancer Res. 2012; 196: 37-49.

43. Feng Q, Wei Y, Zhu D, Ye L, Lin Q, Li W, et al. Timing of Hepatectomy for Resectable Synchronous Colorectal Liver Metastases: For Whom Simultaneous Resection Is More Suitable-A Meta-Analysis. PLoS one. 2014; 9: e104348.

44. Lykoudis PM, O'Reilly D, Nastos K, Fusai G. Systematic review of surgical management of synchronous colorectal liver metastases. Br J Surg. 2014; 101: 605-612.

45. Chua TC, Saxena A, Liauw W, Chu F, Morris DL. Hepatectomy and resection of concomitant extrahepatic disease for colorectal liver metastases–a systematic review. Eur J cancer. 2012; 48: 1757-1765.

46. Adam R, de Haas RJ, Wicherts DA, Aloia TA, Delvart V, Azoulay D, et al. Is hepatic resection justified after chemotherapy in patients with colorectal liver metastases and lymph node involvement? J Clin Oncol. 2008 Aug 1; 26: 3672-3680.

47. Torres OJ, Moraes-Junior JM, Lima NC, Moraes AM. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): a new approach in liver resections. Arq Bras Cir Dig. 2012; 25: 290-292.

48. Buac S, Schadde E, Schnitzbauer AA, Vogt K, Hernandez-Alejandro R. The many faces of ALPPS: surgical indications and techniques among surgeons collaborating in the international registry. HPB (Oxford). 2016; 18: 442-448.

49. Schadde E, Ardiles V, Slankamenac K, Tschuor C, Sergeant G, Amacker N, et al. ALPPS offers a better chance of complete resection in patients with primarily unresectable liver tumors compared with conventional-staged hepatectomies: results of a multicenter analysis. World J Surg. 2014; 38: 1510-1519.

50. Schadde E, Ardiles V, Robles-Campos R, Malago M, Machado M, Hernandez-Alejandro R, et al. Early survival and safety of ALPPS: first report of the International ALPPS Registry. Ann Surg. 2014; 260: 829-838.

51. Oldhafer KJ, Donati M, Jenner RM, Stang A Stavrou GA. ALPPS for patients with colorectal liver metastases: effective liver hypertrophy, but early tumor recurrence. World J Surg. 2013; 38: 1504-1509.

52. Chun YS, Vauthey JN, Ribero D, Donadon M, Mullen JT, Eng C, et al. Systemic chemotherapy and two-stage hepatectomy for extensive bilateral colorectal liver metastases: perioperative safety and survival. J Gastrointest Surg. 2007; 11: 1498-1505.

53. Torzilli G, Procopio F, Botea F, Marconi M, Del Fabbro D, Donadon M, et al. One-stage ultrasonographically guided hepatectomy for multiple bilobar colorectal metastases: a feasible and effective alternative to the 2-stage approach. Surgery. 2009; 146: 60-71.

54. Fuks D, Nomi T, Ogiso S, Gelli M, Velayutham V, Conrad C, et al. Laparoscopic two-stage hepatectomy for bilobar colorectal liver metastases. Br J Surg. 2015; 102: 1684-1690.

55. Adam R, Imai K, Castro-Benitez C, Allard MA, Ciacio O, Pittau G, Vibert E, Cunha AS, Cherqui D, Baba H, Castaing D. Two-stage hepatectomy versus ALPPS procedure: A propensity score-matching analysis of early oncological outcomes. HPB. 2016; 18: e33-e34.

56. Hwang M, Jayakrishnan TT, Green DE, George B, Thomas JP, Groeschl RT, et al. Systematic review of outcomes of patients undergoing resection for colorectal liver metastases in the setting of extra hepatic disease. Eur J Cancer. 2014; 50: 1747-1757.

57. Abdalla EK, Bauer TW, Chun YS, D'Angelica M, Kooby DA, Jarnagin WR. Locoregional surgical and interventional therapies for advanced colorectal cancer liver metastases: expert consensus statements. HPB (Oxford). 2013; 15: 119-130.

58. Mulier S, Mulier P, Ni Y, Miao Y, Dupas B, Marchal G, et al. Complications of radiofrequency coagulation of liver tumours. Br J Surg. 2002; 89: 1206-1222.

59. Stang A, Fischbach R, Teichmann W, Bokemeyer C, Braumann D. A systematic review on the clinical benefit and role of radiofrequency ablation as treatment of colorectal liver metastases. Eur J Cancer. 2009; 45: 1748-1756.

60. Mulier S, Ni Y, Jamart J, Ruers T, Marchal G, Michel L. Local recurrence after hepatic radiofrequency coagulation: multivariate meta-analysis and review of contributing factors. Ann Surg. 2005; 242: 158-171.

61. Martin RC, Scoggins CR, McMasters KM. Safety and efficacy of microwave ablation of hepatic tumors: a prospective review of a 5-year experience. Ann Surg Oncol. 2010; 17: 171-178.

62. Swaminath A, Dawson LA. Emerging role of radiotherapy in the management of liver metastases. Cancer J. 2010; 16: 150-155.

63. Rule W, Timmerman R, Tong L, Abdulrahman R, Meyer J, Boike T, et al. Phase I dose-escalation study of stereotactic body radiotherapy in patients with hepatic metastases. Ann Surg Oncol. 2011; 18: 1081-1087.

64. Scheffer HJ, Nielsen K, de Jong MC, van Tilborg AA, Vieveen JM, Bouwman AR, et al. Irreversible electroporation for nonthermal tumor ablation in the clinical setting: a systematic review of safety and efficacy. J Vascu Interv Radiol. 2014; 25: 997-1011.

65. Wagstaff PG, Buijs M, van den Bos W, de Bruin DM, Zondervan PJ, de la Rosette JJ, Pes MP. irreversible electroporation: state of the art. OncoTargets Ther. 2016; 9: 2437-2446.

66. Wichtowski M, Nowaczyk P, Kocur J, Murawa D. Irreversible electroporation in the treatment of locally advanced pancreas and liver metastases of colorectal carcinoma. Contemp Oncol (Pozn). 2016; 20: 39-44.

67. Thomson KR, Cheung W, Ellis SJ, Federman D, Kavnoudias H, Loader-Oliver D, et al. Investigation of the safety of irreversible electroporation in humans. J Vasc Interven Radiol. 2011; 22: 611-621.

68. Scheffer HJ, Vroomen LG, Nielsen K, van Tilborg AA, Comans EF, van Kuijk C, et al. Colorectal liver metastatic disease: efficacy of irreversible electroporation—a single-arm phase II clinical trial (COLDFIRE-2 trial). BMC cancer. 2015; 15: 772.

69. Vogl TJ, Gruber T, Balzer JO, Eichler K, Hammerstingl R, Zangos S. Repeated Transarterial Chemoembolization in the Treatment of Liver Metastases of Colorectal Cancer: Prospective Study 1. Radiology. 2009; 250: 281-289.

70. Wasser K, Giebel F, Fischbach R, Tesch H, Landwehr P. [Transarterial chemoembolization of liver metastases of colorectal carcinoma using degradable starch microspheres (Spherex): personal investigations and review of the literature]. Radiology. 2005; 45: 633-643.

71. Gruber-Rouh T, Marko C, Thalhammer A, Nour-Eldin NE, Langenbach M, Beeres M, et al. Current strategies in interventional oncology of colorectal liver metastases. Br J Radiol. 2016; 89: 20151060.

72. Fiorentini G, Aliberti C, Tilli M, Mulazzani L, Graziano F, Giordani P, 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. 2012; 32: 1387-1395.

73. Martin RC 2nd, Scoggins CR, Schreeder M, Rilling WS, Laing CJ, Tatum CM, et al. Randomized controlled trial of irinotecan drug-eluting beads with simultaneous FOLFOX and bevacizumab for patients with unresectable colorectal liver-limited metastasis. Cancer. 2015; 121: 3649-3658.

74. Cosimelli M, Golfieri R, Cagol PP, Carpanese L, Sciuto R, Maini CL, et al. Multicentre phase II clinical trial of yttrium-90 resin microspheres alone in unresectable, chemotherapy refractory colorectal liver metastases. Br J Cancer. 2010; 103: 324-331.

75. Hendlisz A, Van den Eynde M, Peeters M, Maleux G, Lambert B, et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. J Clin Oncol. 2010; 28: 3687-3694.

76. Van Hazel GA, Heinemann V, Sharma NK, Findlay MP, Ricke J, Peeters M, et al. SIRFLOX: Randomized Phase III Trial Comparing First-Line mFOLFOX6 (Plus or Minus Bevacizumab) Versus mFOLFOX6 (Plus or Minus Bevacizumab) Plus Selective Internal Radiation Therapy in Patients With Metastatic Colorectal Cancer. J Clin Oncol. 2016; 34: 1723-1731.

77. Townsend AR, Chong LC, Karapetis C, Price TJ. Selective internal radiation therapy for liver metastases from colorectal cancer. Cancer Treat Rev. 2016; 50: 148-54.

78. Geschwind JF. Interventional Oncology: Principles and Practice of Image-Guided Cancer Therapy. Cambridge University Press; 2016. Chapter 18. 163.