Current Colorectal Cancer Reports (2018) 14:12–21
https://doi.org/10.1007/s11888-018-0397-6

SURGERY AND SURGICAL INNOVATIONS IN COLORECTAL CANCER (S HUERTA, SECTION EDITOR)

Current Management of Liver Metastasis From Colorectal Cancer

Forat Swaid[1,2] · Allan Tsung[1,2]

Published online: 8 February 2018

Abstract
Purpose of Review To describe the main components of modern treatment for colorectal cancer (CRC) metastatic to the liver.
Recent Findings Liver metastasis occurs in 50–60% of patients with CRC, and surgery is the only potentially curative treatment. Surgery should be performed where a complete (R0) resection of all radiologically visible metastases is possible. The presence of extra-hepatic disease no longer precludes liver metastectomy, and combined metastectomy in the liver and the extra-hepatic site can result in acceptable long-term survival. Peri-operative chemotherapy significantly improves PFS and DFS, but not OS. Modern cytotoxic regimens can convert a significant percentage of unresectable patients to resectable status, and the addition of biologic agents can increase the rate of conversion. Several local treatment modalities serve as alternatives, or sometimes as adjuncts, to resection of CRC liver metastasis and systemic chemotherapy.
Summary The modern approach to CRC with liver metastasis combines surgery, modern cytotoxic and biologic agents, and modern technologies in the field of ablation, radiation, and endovascular access. The result is that long-term survival, and even cure, is now possible.

Keywords Colorectal cancer · Liver metastasis · Overall survival

Introduction

Liver metastasis occurs in 50–60% of patients with colorectal cancer (CRC) [1, 2]. Although 20–34% of CRC patients presented with synchronous liver metastasis [3], the majority of metastatic CRC patients are presented with metachronous liver disease, diagnosed months to years after surgical resection of the primary cancer [4, 5].

Even with modern chemotherapy regimens, surgery is still the only potentially curative treatment option for patients with CRC metastatic to the liver, and long-term survival is rare without an R0 resection [6, 7]. Following complete resection, 5- and 10-year survival rates are 40 and 20%, respectively, and median survival exceeds 40 months [8–10], as compared to a median survival of 5–10 months without any treatment [11]. Recent studies report even more encouraging results, with a 5-year survival as high as 70%, when combining resection, modern chemotherapy, and other loco-regional treatment modalities [12–15]. Of those who survive 5 years after resection, one-third will still have a cancer-related death, while those who survive 10 years rarely die of the disease and are virtually cured [16].

It is this solid and abundant medical literature that explains the rationale behind the surgical treatment of CRC with liver metastasis and drives the continuous effort to improve outcome of this disease. In this review, we will cover the main components of modern treatment for CRC metastatic to the liver, with emphasis on surgical resection and other loco-regional treatment modalities.

Surgical Resection

Since a complete R0 resection of liver metastasis is the only treatment option associated with prolonged survival and potential cure, it is now considered the treatment of choice, when feasible. The main principles of surgical resection are discussed here.

This article is part of the Topical Collection on *Surgery and Surgical Innovations in Colorectal Cancer*

✉ Forat Swaid
foratola@gmail.com

[1] Department of Surgery, University of Pittsburgh, 3459 Fifth Avenue, Pittsburgh, PA 15213-2582, USA

[2] UPMC Liver Cancer Center, Kaufmann Medical Building, 3471 Fifth Avenue, Suite 300, Pittsburgh, PA 15213, USA

Goal of Surgery

Surgery should be performed exclusively in patients where a complete resection of all radiologically visible metastases seems to be realistic and feasible. Resections associated with macroscopically positive margins, or R2 resections, lack any survival benefit [2, 17]. Achieving a microscopically positive resection margin, i.e., R1 resection, is often the result of intra-operative considerations, such as close proximity of the metastatic mass to vital structures. The significance of R1 resections is controversial. While several studies showed that it is associated with worse survival as compared to R0 resections [8, 18, 19], a study from 2008 by de Haas et al. suggested that an R1 resection did not adversely affect 5-year survival, although it was associated with a higher recurrence rate [20]. Nonetheless, as a general rule, an R0 resection should always be sought.

Extent of Negative Margin

Traditionally, a 1-cm rim of normal liver tissue around the metastatic mass was required [21]. More recently, it is believed that much smaller margins are acceptable, and that as long as the cut margin is truly negative, a rim of normal liver tissue of any width gives the same oncologic outcome [18, 22–25]. This is in concordance with a recent trend in several other oncologic resections, such as in lumpectomy for breast cancer.

Anatomic Versus Non-anatomic Resections

In the long-standing debate of whether anatomic resections result in better outcomes compared to wedge resections, the principle that should be kept in mind is that an R0 resection should be the goal of surgery. Although some studies showed better outcomes with anatomic resections [26], this is believed to result indirectly from the lower rate of positive margins associated with anatomic resections. In other words, as long as a negative margin can confidently be achieved, either a wedge resection or an anatomic resection is acceptable. The size and location of the metastatic mass, as well as its proximity and relations to vital structures, are factors that often influence the extent and type of resection.

Presence of Extra-hepatic Disease

Traditionally, the presence of extra-hepatic disease, i.e., an additional location of metastasis, had precluded surgery as a curative option, and those patients were generally treated with palliative chemotherapy [8, 30]. However, this paradigm has been challenged in the last two decades. In highly selected patients, combined or staged metastectomy in the liver and the extra-hepatic site, particularly ovarian or low-volume lung metastasis, has been shown to result in acceptable long-term survival, with a reported 5-year survival rate as high as 30% [28–30].

The presence of portal lymphadenopathy in association with liver metastasis from CRC indicates poor prognosis, and recurrence was reported in the majority of patients in which positive portal lymphadenopathy was confirmed [31]. To date, there is no convincing evidence that performing portal lymphadenectomy during metastectomy improves survival, and thus, it is not routinely performed [27].

It is reported that 17% of patients with metastatic CRC have evidence of peritoneal carcinomatosis. In most cases, this finding renders the disease unamenable to R0 resection, and these patients are generally treated with palliative systemic chemotherapy [32]. However, in highly selected cases with limited peritoneal disease, when an R0 resection is deemed possible, patients at experienced centers might benefit from cytoreductive surgery with peri-operative hyperthermic intraperitoneal chemotherapy (HIPEC). In a landmark randomized study by Verwaal et al., this strategy had resulted in a statistically significant prolonged overall survival in comparison to palliative chemotherapy with 5FU alone [33••]. Nonetheless, this study is criticized for not administering more efficient chemotherapies in the control group, and for including cases where the carcinomatosis was of appendiceal origin, such as pseudomyxoma peritonei, which is classically associated with better prognosis than classic CRC. Additionally, as shown in a meta-analysis from 2006, morbidity and mortality rates associated with this approach are high, reaching 23–44 and 0–12%, respectively [34].

Determining Resectability

Defining patient selection criteria for metastectomy is a topic of evolving debate, and limits are frequently being pushed further, thus expanding the pool of patients that might ultimately benefit from resection. However, there is a consensus that several scenarios are considered absolute contra-indications for liver metastectomy, e.g., the presence of unresectable extra-hepatic disease, unfitness for surgery, and insufficient remnant liver volume [35]. Main trunk or bilateral involvement of the hepatic artery, portal vein, or major bile ducts, as well as visible and gross aorto-caval lymphadenopathy, are also factors that usually preclude resection [36].

Several risk scoring systems have been proposed in an attempt to determine who will benefit from metastectomy [8, 37, 38]. However, these have limited ability to predict disease-free survival after resection, and their implementation in the clinical setting is complicated [39••]. Recent trends favor clear and simple definitions of resectability; in the modern era, resectability of CRC with metastasis to the liver is defined as the ability to completely resect all visible disease, with acceptable morbidity and mortality, and with an adequate liver remnant

after resection [40]. Obviously, the primary CRC should be resectable, and any extra-hepatic disease should be amenable to complete resection [41].

When evaluating patients for resectability, PET scans can play an important role in pre-operative planning, specifically to rule out the presence of unresectable extra-hepatic disease, a scenario that will define the case as unresectable. However, PET scan results should be interpreted carefully, especially in patients who have been treated with neoadjuvant chemotherapy; tumor metabolic rates can decrease significantly following chemotherapy, making them undetectable as hypermetabolic lesions on PET scans, despite continuous viability within the tumor mass [42–44]. These false negative results can mislead surgical decision making if previous chemotherapy treatments are not taken into consideration. Additionally, multiple radiologic systems aim at assessing response to treatment, the most commonly used being the European Organization for Research and Treatment of Cancer (EORTC) criteria and PET Response Criteria in Solid Tumors (PERCIST) systems. Furthermore, there is lack of agreement regarding the ideal timing of obtaining repeat PET scans for assessing response following chemotherapy. Thus, further research is needed before the best strategy for following treatment response can be determined.

Treating Recurrent Liver Metastasis After Resection

Several studies have shown that recurrent disease in the liver following prior metastectomy can be safely resected in highly selected patients [45–49], with 5-year survival as high as 42% [45]. Importantly, 5-year survival rates decreased steadily with each additional resection [46], and patient selection for re-resection is critical. Patients will benefit most from re-resection if they have long disease-free intervals, if the recurrence is solitary or unilobar, and when recurrence is confined to the liver, without evidence of extra-hepatic disease [50].

Role of Peri-operative Chemotherapy in Initially Resectable Disease

The role of peri-operative chemotherapy in the surgical management of CRC with initially resectable metastasis to the liver is still a subject of active debate in the literature. In the landmark EORTC intergroup trial 40,983, Nordlinger et al. compared surgery alone to pre-operative and post-operative systemic chemotherapy with FOLFOX [51]. Although the combined modality group had a better 3-year PFS, they had significantly more post-operative complications, and the OS rates were similar among the two groups. Several recent large meta-analyses uniformly reached a conclusion that peri-operative chemotherapy for CRC with resectable metastasis to the liver significantly improves PFS and DFS, but not OS [52–55]. However, the timing of chemotherapy administration in relation to resection is controversial, and chemotherapy can be given in a neo-adjuvant, adjuvant, or combined peri-operative setting; the total duration of administration should not exceed 6 months [41].

Giving chemotherapy in a neo-adjuvant setting has the potential advantage of early treatment of occult micrometastases. Additionally, it can reveal a subset of patients in whom early disease progression during active chemotherapy is demonstrated; surgery is unlikely to benefit these patients, and they are spared major futile resection. On the other hand, opponents of this strategy point to the risk of delaying surgery to the point where the "window of opportunity" for a potentially resectable disease is lost due to tumor progression during chemotherapy, or due to major morbidity caused by chemotherapy, to the point where the patient cannot tolerate resection any more. An additional potential risk is that the metastatic masses might respond "too-favorably" to the chemotherapy, to the point that they disappear on imaging, and the ability of confidently and accurately resecting them no longer exists, thus risking leaving viable cancer cells unresected. In the last scenario, complete "radiologic response" correlates poorly with true complete "biologic response," and several reports showed that masses that disappeared radiologically still contained viable cancer tissue upon resection in 25–83% of the cases [56–58].

Modern peri-operative chemotherapy regimens are usually based on a combination of agents, most commonly FOLFOX (infusional 5-FU, LV, oxaliplatin), FOLFIRI (infusional 5-FU/LV/irinotecan), or FOLFOXIRI (infusional 5-FU, LV, oxaliplatin, irinotecan). In general, according to NCCN guidelines, oxaliplatin-containing combinations are considered first line treatment in the peri-operative setting of resectable metastatic CRC [41]. However, a detailed discussion of the different chemotherapy regimens and options is beyond the scope of this review. Biologic agents, such as epidermal growth factor receptor (EGFR) inhibitors and monoclonal antibodies to vascular endothelial growth factor (anti-VEGF), are not recommended in the peri-operative metastatic setting, except when attempting to convert an unresectable metatstatic disease to a resectable state [41], as discussed below.

Converting Unresectable to Resectable Disease

Patients presenting with liver metastases that involve major structures, e.g., main portal vein, but are otherwise good surgical candidates, may benefit from a trial of neo-adjuvant chemotherapy aiming at shrinking the metastatic mass off the vital structures, thus potentially converting the disease to a resectable status. However, modern chemotherapy regimens, that mostly include oxaliplatin and/or irinotecan, can frequently result in liver toxicity. Oxaliplatin can cause severe hepatic vascular changes, commonly described as "blue liver," that might increase the risk of operative bleeding. Irinotecan

commonly causes liver steatosis and steatohepatitis, potentially leading to impaired hepatic regeneration after resection, and increasing the risk for post-operative liver failure. In any case, no more than six cycles of pre-operative chemotherapy should be administered, as exceeding that has been shown to increase post-operative complications [59]. Therefore, the use of these regimens should be limited in time, frequent re-assessment of resectability should be performed, and resection should be undertaken as soon as sufficient downsizing of the metastatic mass has been achieved [41].

Several studies showed that irinotecan- or oxaliplatin-based regimens resulted in converting significant percentage of unresectable patients to resectable status, with conversion rates ranging between 13 and 40% [60–62]. Combining irinotecan with oxaliplatin, in the form of FOLFOXIRI, has been shown to be superior to regimens using irinotecan alone, i.e., FOLFIRI, and resulted in both better rate of conversion to resectability (15 vs. 6%, respectively), and in longer median overall survival (23.4 vs. 16.7 months, respectively) [63–65].

The addition of biologic agents to conventional chemotherapy regimens in this regard was also extensively reported. Several reports and meta-analyses showed that in patients with wild-type KRAS tumors, the addition of EGFR inhibitors, e.g., cetuximab or panitumumab, resulted in almost doubling the rate of conversion to resectability and of the R0 resection rates, but did not change overall survival compared to patients treated with resection following chemotherapy alone [26, 66, 67]. Interestingly, it has been reported that EGFR inhibitors were only beneficial when the primary CRC is left sided, i.e., at or distal to the splenic flexure, while adding no benefit in the setting of right-sided primary CRC [68••]. Anti-VEGF agents, e.g., bevacizumab, have been shown to result in better response and higher rates of conversion to resectability when added to irinotecan-based regimens, but had no benefit when added to oxaliplatin-based regimens [69, 70]. It is well established that bevacizumab is associated with delayed wound healing [71, 72]. Excessive wound healing complications were successfully avoided by spacing resection and bevacizumab administration by 6 weeks, which corresponds to two half-lives of bevacizumab [72]. Therefore, the National Comprehensive Cancer Network (NCCN) guidelines recommend an interval of at least 6 weeks between the last dose of bevacizumab and any elective surgery [41].

Timing of Resection for Synchronous Liver Disease

Patients presenting with CRC and synchronous resectable liver metastasis were traditionally treated according to the "colon first" paradigm, where the primary CRC was resected first, and liver metastectomy was done at a later stage through a separate operation [73]. However, in the last decade, other treatment paradigms were proposed, such as the "liver first" approach, or the "simultaneous" resection of the primary and metastasic masses during the same operation [74, 75]. None of the different approaches has shown any clear-cut significant advantages over the others [74], and the choice of strategy frequently depends on the size, location, and number of the liver metastases, as well as the characteristics of the primary CRC, available expertise, and institution preference. Incorporating neo-adjuvant, adjuvant, or combined peri-operative chemotherapy into these strategies has also been extensively described in the literature. The three main strategies recommended by NCCN [41] are (1) synchronous or staged colectomy with liver resection, followed by adjuvant chemotherapy; (2) neo-adjuvant chemotherapy for 2 to 3 months, followed by synchronous or staged colectomy with liver resection; or (3) colectomy followed by adjuvant chemotherapy and then resection of metastatic disease. Overall, combined neo-adjuvant and adjuvant treatments should not exceed 6 months.

Other Local Treatment Modalities

Several local treatment modalities serve as alternatives, or sometimes as adjuncts, to resection of CRC liver metastasis and systemic chemotherapy. The most commonly used modalities include regional tumor ablation, e.g., radiofrequency ablation (RFA), direct chemotherapy administration via the hepatic artery, internal radiation (e.g., using beta-emitting microspheres), and external beam radiation. These modalities are needed in cases where complete R0 metastectomy is not feasible due to the number, size, or location of some of these metastases, patient un-fitness to complete surgical resection, or due to insufficient liver remnant if a full metastectomy is to be performed.

Tumor Ablation

The main tumor ablation techniques are RFA, microwave ablation, and cryoablation.

RFA is the most commonly used ablative technique, and the most frequently reported in medical literature. It can be performed surgically, either open or laparoscopic, or percutaneously (with US or CT guidance). There is no clear evidence of any of these approaches being superior to the others [76], and the choice depends on patient surgical risk, tumor characteristics, and available expertise. However, it is important to keep in mind that RFA should not be utilized as an alternative to resection when the latter is feasible and safe, since several reports comparing RFA and resection showed that resection was associated with better OS survival and lower recurrence rates [77, 78].

In the setting of unresectable liver metastasis, there is no evidence that adding RFA to systemic palliative chemotherapy has any OS benefit, although it has been shown to improve local control of the liver disease and DFS [79••]. However, in

cases where the majority of liver disease can be cleared with resection, adding RFA to the liver resection can be considered, with the goal of treating minor residual disease that is not amenable to resection, e.g., due to deep location, proximity to major structures, or concerns of inadequate future liver remnant. These decisions are often complex and are made on a case by case basis.

Since the current available technology produces necrosis of a diameter of 4–5 cm, best results are achieved when the ablated lesions are 3 cm or smaller, which permits a 1–2 cm of necrosed normal parenchyma around it, serving as a "safety margin" [80–82].

The location within the liver of the metastatic mass is also an important consideration. Close proximity of the mass to large blood vessels decreases the efficiency of RFA, because the rapid blood flow in these vessels causes the heat sink effect, where the heat generated by the probe during ablation is cooled down instantly by the blood flow, thus decreasing the chance of achieving necrosis [82]. Furthermore, lesions located at the dome or at the inferior edge of the liver are usually better ablated surgically (than percutaneously), since better control and isolation can be achieved to avoid potential diaphragmatic injury or bowel perforation, respectively [83, 84]. RFA is generally safe, with a reported complication rate of 6–9% and mortality rate of 0–2% [76]. Potential complications include liver abscess, subcapsular hematoma, diaphragmatic injury, bowel perforation, pneumothorax, and pleural effusion.

Microwave ablation (MWA) in the setting of CRC liver metastasis is gaining more popularity recently. Special probes are inserted to the mass either percutaneously or surgically, delivering microwave radiation between 900 MHz and 2.4 GHz and causing polarized water molecules within the tissue to oscillate, generating friction that produces heat, which in turn causes coagulative necrosis of the treated tissue [85]. MWA has several advantages over RFA, the most prominent of which is the ability to ablate lesions located in close proximity to large blood vessels, being less affected by the heat sink phenomenon [86]. Additionally, greater and faster heat can be achieved with MWA as compared to RFA, thus allowing more efficient tissue destruction and facilitating ablation of larger lesions, up to 6 cm in diameter [85]. Although data is still limited, a few reports have shown encouraging results, with local recurrence rates as low as 3–6% [87–89].

Hepatic Intra-arterial Chemotherapy

In contrast to normal hepatocytes, that derive the majority of their blood supply from the portal vein, CRC metastases receive over 80% of their blood supply from the hepatic artery. Hence, the administration of chemotherapy directly to the hepatic artery is hypothesized to preferentially reach tumor cells, with relative sparing of normal hepatocytes [90]. Furthermore, since the liver serves as a "filter" by metabolizing many of the modern chemotherapy drugs, higher concentrations of these medications can be administered directly into the hepatic artery, thus achieving augmented drug concentration and effect in the liver, with minor systemic toxicity [90].

Hepatic intra-arterial (HIA) chemotherapy is administered through a surgically implantable pump system; after laparotomy, exploration, and cholecystectomy, ligation of all branches of the hepatic artery supplying the distal stomach and duodenum is performed, in order to minimize the risk of misperfusion, i.e., high concentration chemotherapy regimens reaching these organs, which might result in inflammation and ulceration [91]. Additionally, any accessory right or left hepatic arteries must be ligated. After ligating the gastro-duodenal artery (GDA) as distally as possible, the catheter tip is inserted and secured to the GDA's proximal takeoff from the common hepatic artery. The other end of the catheter, passing through the abdominal wall, is connected to the pump, which is secured in a subcutaneous pocket. Intra-operatively, fluorescein injection and examination with Woods lamp is performed to ensure adequate liver perfusion and to rule-out misperfusion. Possible complications include hepatic artery thrombosis, misperfusion to the stomach and duodenum leading to ulceration, biliary toxicity, and pump site-related complications, such as hematoma and infection. Several randomized trials have shown HIA chemotherapy alone (usually fluorodeoxyuridine) to be superior to systemic chemotherapy in terms of response rates, but whether this increased OS was controversial [92, 93]. However, the largest meta-analysis to date, that included ten randomized trials that compared HIA to systemic chemotherapy, showed no survival benefit associated with HIA [94].

A landmark study from MSKCC showed a survival advantage for systemic 5-FU/LV plus HAI over systemic 5-FU/LV when used in an adjuvant setting after resection [95].

Trans-arterial Chemo-Embolization

This is an interventional radiology modality in which hepatic artery branches feeding the tumor are selectively catheterized percutaneously, and drug-eluting beads (usually gelatin sponge particles) are injected, thus achieving a combined effect of tumor ischemia and intra-arterial extended-release chemotherapy administration. Data about the efficacy of trans-arterial chemo-embolization (TACE) is still limited, and a few studies on the effect of intra-arterial administration of drug-eluting beads loaded with irinotecan (DEBIRI®; Biocompatibles United Kingdom Ltd., Farnham, UK) showed benefit in response rate, and even in OS [96, 97].

Radioembolization

An additional interventional radiology modality involves percutaneous hepatic artery catheterization and administration of radioactive isotopes (most commonly yttrium-90 [Y90]-tagged

glass or resin microspheres) directly to branches feeding the liver mass, thus delivering focal high-dose radiation to the desired liver area. The radiation is very focused due to the low tissue penetration of betta radiation emitted off the Y90 (about 1 cm), thus sparing normal liver parenchyma. Y90 was shown to improve response rate and time to progression when added to HIA chemotherapy in patients with unresectable CRC liver metastases, without a clear added benefit in terms of survival [98].

In 2016, the widely cited randomized controlled SIRFLOX trial compared the combination of Y90 and systemic chemotherapy (FOLFOX+/− bevacizumab) with systemic chemotherapy alone in patients with unresectable metastatic CRC. Overall, PFS was not significantly different in both groups. However, liver-specific PFS was significantly longer in the Y90 arm [99••]. In other words, Y90 contributed to significantly better disease control in the liver, but metastases in other locations progressed more rapidly. One possible explanation for that is the dose reductions in systemic chemotherapy that the researchers had to perform in the Y90 arm in order to reduce liver toxicity, which might have led to early progression of lung and other metastases. Nonetheless, these results are encouraging, and applying Y90 treatment in cases with exclusive liver metastasis might result in prolonged overall PFS. This hypothesis is still to be tested by clinical trials.

External Radiation

Traditional external beam radiation therapy (EBRT) has limited use in the liver because the maximal dose of radiation that normal liver parenchyma can tolerate is 35 Gy, which is about half the dose required for treating adenocarcinoma metastases. Hence, stereotactic body radiation therapy (SBRT), which focuses external radiation beams very precisely to the tumor mass with sparing of normal surrounding parenchyma, is a more tolerable modality for treating liver metastases, and is gaining popularity.

Tumor location is determined using four-dimensional imaging, which takes into consideration patient movements during breathing, and gold fiducials are inserted percutaneously and placed in the target mass, under image-guidance. Using the pre-determined location and the fiducials, high-dose radiation can be precisely directed to the target lesion over a short duration, thus avoiding extensive exposure to radiation, and sparing normal liver parenchyma. Although data is still limited, initial reports show encouraging results, with local control rates of 55–91% at 2 years [100–102]. No data is available yet regarding survival benefits.

Conclusions

The approach to CRC with liver metastasis has undergone a revolutionary change in the last three decades. With the advances in surgical techniques and the introduction of modern cytotoxic and biologic agents, long-term survival, and even cure, is now possible. The addition of modern technologies in the field of ablation, radiation, and endovascular access has widened the spectrum of treatment modalities available for these patients, in both palliative and curative settings. Active clinical and molecular research, combined with promising emerging technologies and medications, is expected to further improve the management of this disease, once considered invariably lethal.

Compliance With Ethical Standards

Conflict of Interest The authors declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Van Cutsem E, Nordlinger B, Adam R, Köhne CH, Pozzo C, Poston G, et al. Towards a pan-European consensus on the treatment of patients with colorectal liver metastases. Eur J Cancer. 2006;42(14):2212–21. https://doi.org/10.1016/j.ejca.2006.04.012.
2. Yoo PS, Lopez-Soler RI, Longo WE, Cha CH. Liver resection for metastatic colorectal cancer in the age of neoadjuvant chemotherapy and bevacizumab. Clin Colorectal Cancer. 2006;6(3):202–7. https://doi.org/10.3816/CCC.2006.n.036.
3. Fong Y, Cohen AM, Fortner JG, Enker WE, Turnbull AD, Coit DG, et al. Liver resection for colorectal metastases. J Clin Oncol. 1997;15(3):938–46. https://doi.org/10.1200/JCO.1997.15.3.938.
4. Muratore A, Zorzi D, Bouzari H, Amisano M, Massucco P, Sperti E, et al. Asymptomatic colorectal cancer with un-resectable liver metastases: immediate colorectal resection or up-front systemic chemotherapy? Ann Surg Oncol. 2007;14(2):766–70. https://doi.org/10.1245/s10434-006-9146-1.
5. Hayashi M, Inoue Y, Komeda K, Shimizu T, Asakuma M, Hirokawa F, et al. Clinicopathological analysis of recurrence patterns and prognostic factors for survival after hepatectomy for colorectal liver metastasis. BMC Surg. 2010;10(1):27. https://doi.org/10.1186/1471-2482-10-27.
6. Stang R, Altendorf-Hofmann A, Charnley RM, Scheele J. Factors influencing the natural history of colorectal liver metastases. Lancet. 1994;343(8910):1405–10. https://doi.org/10.1016/S0140-6736(94)92529-1.
7. Rougier P, Milan C, Lazorthes F, Fourtanier G, Partensky C, Baumel H, et al. Prospective study of prognostic factors in patients with unresected hepatic metastases from colorectal cancer. Fondation Française de Cancérologie Digestive. Br J Surg. 1995;82(10):1397–400. https://doi.org/10.1002/bjs.1800821034.
8. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann

Surg. 1999;230(3):309–18; **discussion 318-21**. https://doi.org/10.1097/00000658-199909000-00004.

9. Choti MA, Sitzmann JV, Tiburi MF, Sumetchotimetha W, Rangsin R, Schulick RD, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg. 2002;235(6):759–66. https://doi.org/10.1097/00000658-200206000-00002.
10. Jamison RL, Donohue JH, Nagorney DM, Rosen CB, Harmsen WS, Ilstrup DM. Hepatic resection for metastatic colorectal cancer results in cure for some patients. Arch Surg. 1997;132(5):505–10; **discussion 511**. https://doi.org/10.1001/archsurg.1997.01430290051008.
11. Norstein J, Silen W. Natural history of liver metastases from colorectal carcinoma. J Gastrointest Surg. 1997;1(5):398–407. https://doi.org/10.1016/S1091-255X(97)80126-6.
12. Nikfarjam M, Shereef S, Kimchi ET, Gusani NJ, Jiang Y, Avella DM, et al. Survival outcomes of patients with colorectal liver metastases following hepatic resection or ablation in the era of effective chemotherapy. Ann Surg Oncol. 2009;16(7):1860–7. https://doi.org/10.1245/s10434-008-0225-3.
13. Aloia TA, Vauthey JN, Loyer EM, Ribero D, Pawlik TM, Wei SH, et al. Solitary colorectal liver metastasis: resection determines outcome. Arch Surg. 2006;141(5):460–6; **discussion 466-7**. https://doi.org/10.1001/archsurg.141.5.460.
14. Hur H, Ko YT, Min BS, Kim KS, Choi JS, Sohn SK, et al. Comparative study of resection and radiofrequency ablation in the treatment of solitary colorectal liver metastases. Am J Surg. 2009;197(6):728–36. https://doi.org/10.1016/j.amjsurg.2008.04.013.
15. Lee WS, Yun SH, Chun HK, Lee WY, Kim SJ, Choi SH, et al. Clinical outcomes of hepatic resection and radiofrequency ablation in patients with solitary colorectal liver metastasis. J Clin Gastroenterol. 2008;42(8):945–9. https://doi.org/10.1097/MCG.0b013e318064e752.
16. Tomlinson JS, Jarnagin WR, DeMatteo RP, Fong Y, Kornprat P, Gonen M, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. J Clin Oncol. 2007;25(29):4575–80. https://doi.org/10.1200/JCO.2007.11.0833.
17. Altendorf-Hofmann A, Scheele J. A critical review of the major indicators of prognosis after resection of hepatic metastases from colorectal carcinoma. Surg Oncol Clin N Am. 2003;12(1):165–92. https://doi.org/10.1016/S1055-3207(02)00091-1.
18. Pawlik TM, Scoggins CR, Zorzi D, Abdalla EK, Andres A, Eng C, et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. Ann Surg. 2005;241(5):715–22, **discussion 722-4**. https://doi.org/10.1097/01.sla.0000160703.75808.7d.
19. Nuzzo G, Giuliante F, Ardito F, Vellone M, Giovannini I, Federico B, et al. Influence of surgical margin on type of recurrence after liver resection for colorectal metastases: a single-center experience. Surgery. 2008;143(3):384–93. https://doi.org/10.1016/j.surg.2007.09.038.
20. de Haas RJ, Wicherts DA, Flores E, Azoulay D, Castaing D, Adam R. R1 resection by necessity for colorectal liver metastases: is it still a contraindication to surgery? Ann Surg. 2008;248(4):626–37. https://doi.org/10.1097/SLA.0b013e31818a07f1.
21. Shirabe K, Takenaka K, Gion T, Fujiwara Y, Shimada M, Yanaga K, et al. Analysis of prognostic risk factors in hepatic resection for metastatic colorectal carcinoma with special reference to the surgical margin. Br J Surg. 1997;84(8):1077–80. https://doi.org/10.1002/bjs.1800840810.
22. Are C, Gonen M, Zazzali K, Dematteo RP, Jarnagin WR, Fong Y, et al. The impact of margins on outcome after hepatic resection for colorectal metastasis. Ann Surg. 2007;246(2):295–300. https://doi.org/10.1097/SLA.0b013e31811ea962.
23. Scheele J, Stang R, Altendorf-Hofmann A, Paul M. Resection of colorectal liver metastases. World J Surg. 1995;19(1):59–71. https://doi.org/10.1007/BF00316981.
24. Hamady ZZ, Cameron IC, Wyatt J, Prasad RK, Toogood GJ, Lodge JP. Resection margin in patients undergoing hepatectomy for colorectal liver metastasis: a critical appraisal of the 1cm rule. Eur J Surg Oncol. 2006;32(5):557–63. https://doi.org/10.1016/j.ejso.2006.02.001.
25. Figueras J, Burdio F, Ramos E, Torras J, Llado L, Lopez-Ben S, et al. Effect of subcentimeter nonpositive resection margin on hepatic recurrence in patients undergoing hepatectomy for colorectal liver metastases. Evidences from 663 liver resections. Ann Oncol. 2007;18(7):1190–5. https://doi.org/10.1093/annonc/mdm106.
26. DeMatteo RP, Palese C, Jarnagin WR, Sun RL, Blumgart LH, Fong Y. Anatomic segmental hepatic resection is superior to wedge resection as an oncologic operation for colorectal liver metastases. J Gastrointest Surg. 2000;4(2):178–84. https://doi.org/10.1016/S1091-255X(00)80054-2.
27. Abdalla EK, Adam R, Bilchik AJ, Jaeck D, Vauthey JN, Mahvi D. Improving resectability of hepatic colorectal metastases: expert consensus statement. Ann Surg Oncol. 2006;13(10):1271–80. https://doi.org/10.1245/s10434-006-9045-5.
28. Headrick JR, Miller DL, Nagorney DM, Allen MS, Deschamps C, Trastek VF, et al. Surgical treatment of hepatic and pulmonary metastases from colon cancer. Ann Thorac Surg. 2001;71(3):975–9; **discussion 979-80**. https://doi.org/10.1016/S0003-4975(00)02522-4.
29. Miller G, Biernacki P, Kemeny NE, Gonen M, Downey R, Jarnagin WR, et al. Outcomes after resection of synchronous or metachronous hepatic and pulmonary colorectal metastases. J Am Coll Surg. 2007;205(2):231–8. https://doi.org/10.1016/j.jamcollsurg.2007.04.039.
30. Pulitano C, Bodingbauer M, Aldrighetti L, et al. Liver resection for colorectal metastases in presence of extrahepatic disease: results from an international multi-institutional analysis. Ann Surg Oncol. 2011;18(5):1380–8. https://doi.org/10.1245/s10434-010-1459-4.
31. Carpizo DR, Are C, Jarnagin W, Dematteo R, Fong Y, Gönen M, et al. Liver resection for metastatic colorectal cancer in patients with concurrent extrahepatic disease: results in 127 patients treated at a single center. Ann Surg Oncol. 2009;16(8):2138–46. https://doi.org/10.1245/s10434-009-0521-6.
32. Klaver YL, Leenders BJ, Creemers GJ, et al. Addition of biological therapies to palliative chemotherapy prolongs survival in patients with peritoneal carcinomatosis of colorectal origin. Am J Clin Oncol. 2013;36(2):157–61. https://doi.org/10.1097/COC.0b013e3182438c55.
33.•• Verwaal VJ, Bruin S, Boot H, van Slooten G, van Tinteren H. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. Ann Surg Oncol. 2008;15(**9**):2426–32. **A landmark randomized trial that showed that cytoreduction followed by HIPEC improves survival in patients with peritoneal carcinomatosis of colorectal origin**. https://doi.org/10.1245/s10434-008-9966-2.
34. Yan TD, Black D, Savady R, Sugarbaker PH. Systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma. J Clin Oncol. 2006;24(24):4011–9. https://doi.org/10.1200/JCO.2006.07.1142.
35. Poston GJ, Adam R, Alberts S, Curley S, Figueras J, Haller D, et al. OncoSurge: a strategy for improving resectability with curative intent in metastatic colorectal cancer. J Clin Oncol. 2005;23(28):7125–34. https://doi.org/10.1200/JCO.2005.08.722.

36. 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;26(22):3672–80. https://doi.org/10.1200/JCO.2007.15.7297.
37. Konopke R, Kersting S, Distler M, Dietrich J, Gastmeier J, Heller A, et al. Prognostic factors and evaluation of a clinical score for predicting survival after resection of colorectal liver metastases. Liver Int. 2009;29(1):89–102. https://doi.org/10.1111/j.1478-3231.2008.01845.x.
38. Nagashima I, Takada T, Matsuda K, Adachi M, Nagawa H, Muto T, et al. A new scoring system to classify patients with colorectal liver metastases: proposal of criteria to select candidates for hepatic resection. J Hepato-Biliary-Pancreat Surg. 2004;11(2):79–83.
39.•• Roberts KJ, White A, Cockbain A, Hodson J, Hidalgo E, Toogood GJ, et al. Performance of prognostic scores in predicting long-term outcome following resection of colorectal liver metastases. Br J Surg. 2014;101(7):856–66. **A study that assessed the performance of several score systems in predicting DFS and DSS, and found that none does so with sufficient discriminatory accuracy**. https://doi.org/10.1002/bjs.9471.
40. Berri RN, Abdalla EK. Curable metastatic colorectal cancer: recommended paradigms. Curr Oncol Rep. 2009;11(3):200–8. https://doi.org/10.1007/s11912-009-0029-z.
41. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
42. Akhurst T, Kates TJ, Mazumdar M, Yeung H, Riedel ER, Burt BM, et al. Recent chemotherapy reduces the sensitivity of [18F]fluorodeoxyglucose positron emission tomography in the detection of colorectal metastases. J Clin Oncol. 2005;23(34):8713–6. https://doi.org/10.1200/JCO.2005.04.4222.
43. 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(4):340–5; discussion 345. https://doi.org/10.1001/archsurg.2010.41.
44. van Kessel CS, Buckens CF, van den Bosch MA, et al. Preoperative imaging of colorectal liver metastases after neoadjuvant chemotherapy: a meta-analysis. Ann Surg Oncol. 2012;19(9):2805–13. https://doi.org/10.1245/s10434-012-2300-z.
45. Nagakura S, Shirai Y, Suda T, Hatakeyama K. Multiple repeat resections of intra- and extrahepatic recurrences in patients undergoing initial hepatectomy for colorectal carcinoma metastases. World J Surg. 2002;26(2):141–7. https://doi.org/10.1007/s00268-001-0196-z.
46. de Jong MC, Mayo SC, Pulitano C, Lanella S, Ribero D, Strub J, et al. Repeat curative intent liver surgery is safe and effective for recurrent colorectal liver metastasis: results from an international multi-institutional analysis. J Gastrointest Surg. 2009;13(12):2141–51. https://doi.org/10.1007/s11605-009-1050-0.
47. Homayounfar K, Bleckmann A, Conradi LC, Sprenger T, Lorf T, Niessner M, et al. Metastatic recurrence after complete resection of colorectal liver metastases: impact of surgery and chemotherapy on survival. Int J Color Dis. 2013;28(7):1009–17. https://doi.org/10.1007/s00384-013-1648-2.
48. Neeff HP, Drognitz O, Holzner P, Klock A, Bronsert P, Hopt UT, et al. Outcome after repeat resection of liver metastases from colorectal cancer. Int J Color Dis. 2013;28(8):1135–41. https://doi.org/10.1007/s00384-013-1670-4.
49. Salah S, Watanabe K, Park JS, Addasi A, Park JW, Zabaleta J, et al. Repeated resection of colorectal cancer pulmonary oligometastases: pooled analysis and prognostic assessment. Ann Surg Oncol. 2013;20(6):1955–61. https://doi.org/10.1245/s10434-012-2860-y.
50. Luo LX, Yu ZY, Huang JW, Wu H. Selecting patients for a second hepatectomy for colorectal metastases: a systemic review and meta-analysis. Eur J Surg Oncol. 2014;40(9):1036–48. https://doi.org/10.1016/j.ejso.2014.03.012.
51. Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet. 2008;371(9617):1007–16. https://doi.org/10.1016/S0140-6736(08)60455-9.
52. Ciliberto D, Prati U, Roveda L, Barbieri V, Staropoli N, Abbruzzese A, et al. Role of systemic chemotherapy in the management of resected or resectable colorectal liver metastases: a systematic review and meta-analysis of randomized controlled trials. Oncol Rep. 2012;27(6):1849–56. https://doi.org/10.3892/or.2012.1740.
53. Wang ZM, Chen YY, Chen FF, Wang SY, Xiong B. Peri-operative chemotherapy for patients with resectable colorectal hepatic metastasis: a meta-analysis. Eur J Surg Oncol. 2015;41(9):1197–203. https://doi.org/10.1016/j.ejso.2015.05.020.
54. Araujo RL, Gonen M, Herman P. Chemotherapy for patients with colorectal liver metastases who underwent curative resection improves long-term outcomes: systematic review and meta-analysis. Ann Surg Oncol. 2015;22(9):3070–8. https://doi.org/10.1245/s10434-014-4354-6.
55. Khoo E, O'Neill S, Brown E, Wigmore SJ, Harrison EM. Systematic review of systemic adjuvant, neoadjuvant and perioperative chemotherapy for resectable colorectal-liver metastases. HPB (Oxford). 2016;18(6):485–93. https://doi.org/10.1016/j.hpb.2016.03.001.
56. van Vledder MG, de Jong MC, Pawlik TM, Schulick RD, Diaz LA, Choti MA. Disappearing colorectal liver metastases after chemotherapy: should we be concerned? J Gastrointest Surg. 2010;14(11):1691–700. https://doi.org/10.1007/s11605-010-1348-y.
57. Benoist S, Brouquet A, Penna C, Julié C, el Hajjam M, Chagnon S, et al. Complete response of colorectal liver metastases after chemotherapy: does it mean cure? J Clin Oncol. 2006;24(24):3939–45. https://doi.org/10.1200/JCO.2006.05.8727.
58. Bischof DA, Clary BM, Maithel SK, Pawlik TM. Surgical management of disappearing colorectal liver metastases. Br J Surg. 2013;100(11):1414–20. https://doi.org/10.1002/bjs.9213.
59. Karoui M, Penna C, Amin-Hashem M, Mitry E, Benoist S, Franc B, et al. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. Ann Surg. 2006;243(1):1–7. https://doi.org/10.1097/01.sla.0000193603.26265.c3.
60. Alberts SR, Horvath WL, Sternfeld WC, Goldberg RM, Mahoney MR, Dakhil SR, et al. Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group phase II study. J Clin Oncol. 2005;23(36):9243–9. https://doi.org/10.1200/JCO.2005.07.740.
61. Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg. 2004;240:644–57. **discussion 657-648**
62. Pozzo C, Basso M, Cassano A, Quirino M, Schinzari G, Trigila N, et al. Neoadjuvant treatment of unresectable liver disease with irinotecan and 5-fluorouracil plus folinic acid in colorectal cancer patients. Ann Oncol. 2004;15(6):933–9. https://doi.org/10.1093/annonc/mdh217.
63. Falcone A, Ricci S, Brunetti I, Pfanner E, Allegrini G, Barbara C, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as

first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. J Clin Oncol. 2007;25(13):1670–6. https://doi.org/10.1200/JCO.2006.09.0928.

64. Souglakos J, Androulakis N, Syrigos K, Polyzos A, Ziras N, Athanasiadis A, et al. FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): a multicentre randomised phase III trial from the Hellenic Oncology Research Group (HORG). Br J Cancer. 2006;94(6):798–805. https://doi.org/10.1038/sj.bjc.6603011.
65. Masi G, Vasile E, Loupakis F, Cupini S, Fornaro L, Baldi G, et al. Randomized trial of two induction chemotherapy regimens in metastatic colorectal cancer: an updated analysis. J Natl Cancer Inst. 2011;103(1):21–30. https://doi.org/10.1093/jnci/djq456.
66. Folprecht G, Gruenberger T, Bechstein WO, Raab HR, Lordick F, Hartmann JT, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. Lancet Oncol. 2010;11(1):38–47. https://doi.org/10.1016/S1470-2045(09)70330-4.
67. Petrelli F, Barni S. Resectability and outcome with anti-EGFR agents in patients with KRAS wild-type colorectal liver-limited metastases: a meta-analysis. Int J Color Dis. 2012;27(8):997–1004. https://doi.org/10.1007/s00384-012-1438-2.
68.•• Moretto R, Cremolini C, Rossini D, Pietrantonio F, Battaglin F, Mennitto A, et al. Location of primary tumor and benefit from anti-epidermal growth factor receptor monoclonal antibodies in patients with RAS and BRAF wild-type metastatic colorectal cancer. Oncologist. 2016;21(8):988–94. **A study that showed that patients with right-sided RAS and BRAF wild-type mCRC seemed to derive no benefit from single-agent anti-EGFRs**. https://doi.org/10.1634/theoncologist.2016-0084.
69. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350(23):2335–42. https://doi.org/10.1056/NEJMoa032691.
70. Saltz LB, Clarke S, Diaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol. 2008;26(12):2013–9. https://doi.org/10.1200/JCO.2007.14.9930.
71. Hochster HS, Hart LL, Ramanathan RK, Childs BH, Hainsworth JD, Cohn AL, et al. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE study. J Clin Oncol. 2008;26(21):3523–9. https://doi.org/10.1200/JCO.2007.15.4138.
72. Scappaticci FA, Fehrenbacher L, Cartwright T, Hainsworth JD, Heim W, Berlin J, et al. Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab. J Surg Oncol. 2005;91(3):173–80. https://doi.org/10.1002/jso.20301.
73. Adam R, Miller R, Pitombo M, Wicherts DA, de Haas RJ, Bitsakou G, et al. Two-stage hepatectomy approach for initially unresectable colorectal hepatic metastases. Surg Oncol Clin N Am. 2007;16(3):525–36. https://doi.org/10.1016/j.soc.2007.04.016.
74. Baltatzis M, Chan AK, Jegatheeswaran S, et al. Colorectal cancer with synchronous hepatic metastases: systematic review of reports comparing synchronous surgery with sequential bowel-first or liver-first approaches. Eur J Surg Oncol. 2016;42(2):159–65. https://doi.org/10.1016/j.ejso.2015.11.002.
75. Chen J, Li Q, Wang C, Zhu H, Shi Y, Zhao G. Simultaneous vs. staged resection for synchronous colorectal liver metastases: a metaanalysis. Int J Color Dis. 2011;26(2):191–9. https://doi.org/10.1007/s00384-010-1018-2.
76. Wong SL, Mangu PB, Choti MA, Crocenzi TS, Dodd GD 3rd, Dorfman GS, et al. American Society of Clinical Oncology 2009 clinical evidence review on radiofrequency ablation of hepatic metastases from colorectal cancer. J Clin Oncol. 2010;28(3):493–508. https://doi.org/10.1200/JCO.2009.23.4450.
77. de Jong MC, Pulitano C, Ribero D, Strub J, Mentha G, Schulick RD, et al. Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1669 patients. Ann Surg. 2009;250(3):440–8. https://doi.org/10.1097/SLA.0b013e3181b4539b.
78. Abdalla EK. Commentary: radiofrequency ablation for colorectal liver metastases: do not blame the biology when it is the technology. Am J Surg. 2009;197(6):737–9. https://doi.org/10.1016/j.amjsurg.2008.06.029.
79.•• Ruers T, Punt C, Van Coevorden F, Pierie JP, Borel-Rinkes I, Ledermann JA, 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. 2012;23(**10**):2619–26. **This is the first randomized study on the efficacy of RFA in treating metastatic CRC that showed that RFA plus systemic treatment resulted in significant longer PFS compared to systemic chemotherapy alone**. https://doi.org/10.1093/annonc/mds053.
80. van Duijnhoven FH, Jansen MC, Junggeburt JM, van Hillegersberg R, Rijken AM, van Coevorden F, et al. Factors influencing the local failure rate of radiofrequency ablation of colorectal liver metastases. Ann Surg Oncol. 2006;13(5):651–8. https://doi.org/10.1245/ASO.2006.08.014.
81. Montgomery RS, Rahal A, Dodd GD 3rd, Leyendecker JR, Hubbard LG. Radiofrequency ablation of hepatic tumors: variability of lesion size using a single ablation device. AJR Am J Roentgenol. 2004;182(3):657–61. https://doi.org/10.2214/ajr.182.3.1820657.
82. Machi J, Uchida S, Sumida K, Limm WM, Hundahl SA, Oishi AJ, et al. Ultrasound-guided radiofrequency thermal ablation of liver tumors: percutaneous, laparoscopic, and open surgical approaches. J Gastrointest Surg. 2001;5(5):477–89. https://doi.org/10.1016/S1091-255X(01)80085-8.
83. Head HW, Dodd GD 3rd, Dalrymple NC, Prasad SR, El-Merhi FM, Freckleton MW, et al. Percutaneous radiofrequency ablation of hepatic tumors against the diaphragm: frequency of diaphragmatic injury. Radiology. 2007;243(3):877–84. https://doi.org/10.1148/radiol.2433060157.
84. Tanabe KK, Curley SA, Dodd GD, Siperstein AE, Goldberg SN. Radiofrequency ablation: the experts weigh in. Cancer. 2004;100(3):641–50. https://doi.org/10.1002/cncr.11919.
85. Pathak S, Jones R, Tang JM, Parmar C, Fenwick S, Malik H, et al. Ablative therapies for colorectal liver metastases: a systematic review. Color Dis. 2011;13:252–65.
86. Wright AS, Sampson LA, Warner TF, Mahvi DM, Lee FT. Radiofrequency versus microwave ablation in a hepatic porcine model. Radiology. 2005;236(1):132–9. https://doi.org/10.1148/radiol.2361031249.
87. Shibata T, Niinobu T, Ogata N, Takami M. Microwave coagulation therapy for multiple hepatic metastases from colorectal carcinoma. Cancer. 2000;89(2):276–84. https://doi.org/10.1002/1097-0142(20000715)89:2<276::AID-CNCR11>3.0.CO;2-0.
88. Iannitti DA, Martin RC, Simon CJ, Hope WW, Newcomb WL, McMasters KM, et al. Hepatic tumor ablation with clustered microwave antennae: the US phase II trial. HPB (Oxford). 2007;9(2):120–4. https://doi.org/10.1080/13651820701222677.

89. 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(1):171–8. https://doi.org/10.1245/s10434-009-0686-z.
90. Collins JM. Pharmacologic rationale for regional drug delivery. J Clin Oncol. 1984;2(5):498–504. https://doi.org/10.1200/JCO.1984.2.5.498.
91. Hohn DC, Stagg RJ, Price DC, Lewis BJ. Avoidance of gastroduodenal toxicity in patients receiving hepatic arterial 5-fluoro-2′-deoxyuridine. BJ J Clin Oncol. 1985;3(9):1257–60. https://doi.org/10.1200/JCO.1985.3.9.1257.
92. Harmantas A, Rotstein LE, Langer B. Regional versus systemic chemotherapy in the treatment of colorectal carcinoma metastatic to the liver. Is there a survival difference? Meta-analysis of the published literature. Cancer. 1996;78(8):1639–45. https://doi.org/10.1002/(SICI)1097-0142(19961015)78:8<1639::AID-CNCR1>3.0.CO;2-9.
93. Kemeny N, et al. Hepatic arterial infusion versus systemic therapy for hepatic metastases from colorectal cancer: a randomized trial of efficacy, quality of life, and molecular markers (CALGB 9481). J Clin Oncol. 2006;24(9):1395–403. https://doi.org/10.1200/JCO.2005.03.8166.
94. Mocellin S, Pilati P, Lise M, Nitti D. Meta-analysis of hepatic arterial infusion for unresectable liver metastases from colorectal cancer: the end of an era? J Clin Oncol. 2007;25(35):5649–54. https://doi.org/10.1200/JCO.2007.12.1764.
95. Kemeny N, Huang Y, Cohen AM, Shi W, Conti JA, Brennan MF, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. N Engl J Med. 1999;341(27):2039–48. https://doi.org/10.1056/NEJM199912303412702.
96. 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(4):1387–95.
97. Martin RC, 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(20):3649–58. https://doi.org/10.1002/cncr.29534.
98. Gray B, Van Hazel G, Hope M, Burton M, Moroz P, Anderson J, et al. Randomised trial of SIR-spheres plus chemotherapy vs. chemotherapy alone for treating patients with liver metastases from primary large bowel cancer. Ann Oncol. 2001;12(12):1711–20. https://doi.org/10.1023/A:1013569329846.
99.•• van Hazel GA, Heinemann V, Sharma NK, Findlay MPN, 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(**15**):1723–31. **A landmark RCT that showed that the combination of Y90 and systemic chemotherapy resulted in a significantly longer liver-specific PFS when compared to systemic chemotherapy alone**. https://doi.org/10.1200/JCO.2015.66.1181.
100. Scorsetti M, Comito T, Tozzi A, Navarria P, Fogliata A, Clerici E, et al. Final results of a phase II trial for stereotactic body radiation therapy for patients with inoperable liver metastases from colorectal cancer. J Cancer Res Clin Oncol. 2015;141(3):543–53. https://doi.org/10.1007/s00432-014-1833-x.
101. Hoyer M, Roed H, Traberg Hansen A, Ohlhuis L, Petersen J, Nellemann H, et al. Phase II study on stereotactic body radiotherapy of colorectal metastases. Acta Oncol. 2006;45(7):823–30. https://doi.org/10.1080/02841860600904854.
102. van der Pool AE, Méndez Romero A, Wunderink W, Heijmen BJ, Levendag PC, Verhoef C, et al. Stereotactic body radiation therapy for colorectal liver metastases. Br J Surg. 2010;97(3):377–82. https://doi.org/10.1002/bjs.6895.