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REVIEW

Evidence-based medical oncology and interventional radiology paradigms for liver-dominant colorectal cancer metastases

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Abstract

Colorectal cancer metastasizes predictably, with liver predominance in most cases. Because liver involvement has been shown to be a major determinant of survival in this population, liver-directed therapies are increasingly considered even in cases where there is (limited) extrahepatic disease. Unfortunately, these patients carry a known risk of recurrence in the liver regardless of initial therapy choice. Therefore, there is a demand for minimally invasive, non-surgical, personalized cancer treatments to preserve quality of life in the induction, consolidation, and maintenance phases of cancer therapy. This report aims to review evidence-based conceptual, pharmacological, and technological paradigm shifts in parenteral and percutaneous treatment strategies as well as forthcoming evidence regarding next-generation systemic, locoregional, and local treatment approaches for this patient population.

Key words: Colonic neoplasms; Rectal neoplasms; Neoplasm metastasis; Antineoplastic agents; FOLFOX protocol; Irinotecan, 5-flurouracil, and leucovorin protocol; Radiofrequency ablation; Microwave ablation; Chemoembolization; Therapeutic; Immunotherapy

Core tip: Survival is increasing in patients with colorectal cancer because of major advances in the domain of modern chemotherapy and personalized biological agents. As a result, there is increased demand for minimally-invasive non-surgical strategies to treat liver metastases and their recurrences. Non-surgical Interventional Radiology treatments such as percutaneous ablation

and endovascular-directed therapy have emerged as adjuncts or alternatives to other forms of treatment in this population.

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INTRODUCTION

Cancer is the second most common cause of death in the United States, and may surpass heart diseases (the most common cause) within the next decade[1]. Cancers of the gastrointestinal tract include esophagus, stomach, small intestine, colon, rectum, and anus. If not only by anatomic proximity, cancers of the colon and rectum have traditionally been grouped as colorectal cancer (CRC). However, a growing body of work discriminates colon and rectum cancers on the basis of: (1) differing oncogenic molecular mechanism - microsatellite/chromosomal instability *vs* microsatellite stability/TP53/APC/β-catenin pathway[2]; (2) different metastatic patterns - rectal cancer can spread directly to the lungs without going through the liver because the inferior rectal veins drain directly into inferior vena cava; and (3) different treatment approaches for the primary tumor - for example, rectal cancer often involves radiation therapy early in treatment, which can confound studies trying to determine the effects of chemotherapy in this time period.

In the future, perhaps new subcellular insights will continue to discriminate our treatment approaches for metastases from colonic primaries *vs* rectal primaries. Until then, the term metastatic colorectal cancer (mCRC) persists in the literature and in ongoing clinical trials.

Fewer people are being diagnosed with CRC than before. This is because screening colonoscopy allows removal of lesions while they are still pre-cancerous. For example, in the United States, where screening colonoscopy use has increased from 19% to 55% in adults aged 50-75 years[3], the incidence of colorectal cancer declined by at least 4% per year as recently as 2008-2011[1].

Colon cancer is curable, but only if detected early. Unfortunately, many patients have distant metastatic disease at the time of presentation, for example 20% of patients in the United States have distant metastatic disease at presentation[1].

Therefore, this report aims to summarize current state-of-the-art treatment options for these patients, and to set forth the new frontiers in treatment and high-impact research trends that will effect treatment in upcoming decade.

Before beginning, it is important to note that the diagnosis, staging, treatment, and follow-up of patients with CRC is optimally done not just in a multidisciplinary, but truly an interdisciplinary setting. For example, there is strong international consensus[4] that an interventional oncologist should be a standing member of the institutional colorectal metastasis tumor board, because access to ablation is still uneven and advice given to patients does not always originate with an interventional oncologist qualified in percutaneous ablation[4].

Moreover, as physicians we must acknowledge that evidence-based medicine cannot aid all of our medical decisions. This is because the majority of methodologically sound studies serve the purpose of promoting a single intervention in a controlled clinical trial with exacting patient selection criteria. "Real-world" patient scenarios rarely fit into the sterile criteria of randomized controlled trials.

Finally, when proposing treatments, we must remember the impact on quality of life. Quality of life remains under-represented in evidence-based medicine.

MEDICAL ONCOLOGY APPROACH TO METASTATIC COLORECTAL CANCER

In 1957, Dr. Charles Heidelberger synthesized the cytotoxic agent 5-fluorouracil (5-FU). Since then and especially over the last four decades, therapies including 5-FU have remained the mainstay of treatment for patients with stage Ⅲ colon cancer. There is level Ⅰ evidence for this. Indeed, the basis for 5-FU (usually given with folinic acid (FA) intravenously for a 6-mo treatment period) is founded in pooled data from seven randomized controlled studies showing that patients receiving 5-FU/FA after resection of stage Ⅱ or Ⅲ colon cancer have increased 5-year disease-free survival (DFS) (67% *vs* 55%) and overall survival (OS) (71% *vs* 64%). Of note, for rectal cancer, although we believe that the benefit of 5-FU should be similar, concurrent radiation therapy often confounds studies for these patients and the available evidence is weaker at this time.

For a long time, 5-FU was the only available option. Currently, 5-FU alone is considered best supportive care in palliative situations. This is because several new medications have been developed and supported with level Ⅰ evidence after the turn of the century. It is now a very exciting time for systemic therapy of mCRC.

Current state-of-the-evidence

The goals of treatment determine the role of systemic agents. Treatment goals for patients with mCRC can be classified as: (1) curative (sometimes referred to

Table 1 Chemotherapy for advanced or metastatic disease (NCCN and ESMO guidelines)

Options for	Options for therapy	Options for therapy
Initial therapy	After first progression	After second progression
FOLFOX +/- bmab or cetux/pmab[1]	Irinotecan +/- bmab or aflib or cmab/pmab[1]	Irinotecan + cmab or pmab[1]
CAPOX +/- bmab or cmab/pmab[1]	FOLFIRI +/- bmab or aflib or cmab/pmab[1]	Regorafenib
		Clinical trial
		Best supportive care
FOLFIRI +/- bmab or cmab/pmab[1]	FOLFOX +/- bmab	CAPOX
	CAPOX +/- bmab	FOLFOX
	Irinotecan + cmab/pmab[1]	Irinotecan + cmab/pmab[1]
		Regorafenib
		Clinical trial
		Best supportive care
Bmab + 5-FU/LV or Cape or FOLFOXIRI	Bmab + FOLFOX/FOLFIRI/Irinotecan/CAPOX	Irinotecan + cmab/pmab1
	Bmab + Irinotecan + Oxaliplatin	FOLFOX
	Aflib + FOLFIRI/Irinotecan	CAPOX
	Irinotecan + cmab/pmab[1]	Regorafenib
	Regorafenib	

[1](KRAS/NRAS WT gene only). Bmab: Bevacizumab; Cape: Capecitabine; Cmab: Cetuximab; Pmab: Panitumumab; Aflib: Aflibercept.

as "resectable" or "operable"); (2) potentially curative; (3) non-curative with active treatment intent (most patients fall into this group); and (4) non-curative with palliative intent (best supportive care)

As previously described, the liver is the most common site of hematogenous metastases for gastrointestinal tumors colorectal liver metastases (CLMs). Other common sites are lungs, peritoneum, lymph nodes, bones, and the central nervous system.

Treatment of the resectable patient (curative intent)

According to the surgical literature, up to 25% of patients diagnosed with CRC are found to have synchronous CLMs[5,6]. Up to 50% of patients without CLM at presentation will develop CLM during their lifetime[7]. In about one third of patients with mCRC, metastatic disease appears confined to the liver; about one third of these patients are deemed resectable by expert liver surgeons. Of those who get surgery, about 25% are cured (live for 10 years and do not have recurrence) while 10% are long-term survivors up to 5 years post-resection with recurrence[8,9].

As a result of the success of modern surgery (staged resections, newer vascular reconstruction techniques, assistance from complex hepatic interventional radiology), the terms resectable and unresectable will probably become outdated as we move towards a clinical decision of who will benefit from surgery (curative intent) and who will not (uncurable). Cure is most commonly defined in the literature as survival of 10 years with no recurrence.

There are three surgical approaches around which systemic treatment will be designed. The classic approach is resection of the colorectal primary, followed by adjuvant chemotherapy, then CLM resection. However, patients can decompensate between surgeries and may miss the opportunity for CLM resection. More commonly used today, the combined approach, includes same-session primary and CLM resection. Finally, the reverse approach places CLM resection before colon tumor resection. Brouquet *et al*[10] showed no significant difference in survival among these three groups. The combined approach has a higher risk of postoperative complications[11-13].

What happens when neoadjuvant chemotherapy is too successful? The problem of disappearing metastases becomes a big issue in patients who are potentially curable but receiving neoadjuvant therapy. The incidence of disappearing metastases (complete radiological response) can be as high as 38%[14-19]. Unfortunately, the natural history of patients with disappearing metastases is unknown. What *is* known is that microscopic disease is expected in up to 80% of patients with disappearing metastases[14,16-19] Placement of a fiduciary marker by an interventional oncologist should be considered for patients with metastases at risk of disappearing.

Patients who are resectable will often receive approximately 3 mo of neoadjuvant and 3 mo of adjuvant chemotherapy under the combined surgical approach, for example. Although the number of combinations is vast (Table 1), FOLFOX-4 (folinic acid, fluorouracil, oxaliplatin) is a standard first-line treatment with three recent landmark studies that constitute the frontier for neoadjuvant chemotherapy in patients treated with curative intent.

The most recent landmark study for perioperative chemotherapy was published in 2013. EORTC 40983 (funded in part by Sanofi-Aventis, the makers of oxaliplatin) was a phase Ⅱ study that asked the question "In patients with resectable CLM, does neoadjuvant plus adjuvant FOLFOX4 improve OS at 8.5 years follow-up" The answer to this was no. However, the FOLFOX4 group did show improved progression-free survival (PFS) in the intergroup trial short-term data from EORTC 40983[20].

Can neoadjuvant chemotherapy facilitate resection? The concept of anti-epidermal growth factor receptor (EGFR) agents combined with chemotherapy was studied in the CELIM phase Ⅱ study (funded in part by Merck-Serono, the makers of cetuximab) which asked "In patients with resectable CLM, does neoadjuvant cetuximab plus FOLFOX/FOLFIRI increase resectability compared to historic controls?" The answer was yes; resectability rates increased from 32% (22/68 patients) to 60% (41/68) after chemotherapy (P < 0.0001). Cetuximab is a monoclonal antibody that targets EGFR[21].

Moreover, OPUS, a phase Ⅱ study (funded in part by Merck-Serono, the makers of cetuximab) showed that adding cetuximab to FOLFOX in chemotherapy-naïve patients increases the response rate and time to cancer progression compared to chemotherapy alone. Only patients who were KRAS wild type were found to benefit from cetuximab, but this is expected because KRAS mutant cells send growth signals independent of EGFR activation[22].

Treatment of the potentially operable patient

Response rates to modern chemotherapy have increased up to 60%-70%, and initially unresectable patients who are closely followed by their specialists during chemotherapy may become surgical candidates.

The concepts of down-sizing and down-staging" follow from the above discussion; if surgery is currently our only modality that is shown to be potentially curative, then we need to work to convert unresectable patients to surgical candidates with neoadjuvant chemotherapy (or interventional oncology methods, to be discussed later).

Importantly, chemotherapy can induce steatosis, fibrosis, and functional liver derangements, which need to be factored in to the regimen planning. For example, even a short 3-mo course of oxaliplatin regimens (*e.g.*, FOLFOX) increase liver morbidity after hepatic resection, as shown by Nordlinger *et al*[20] in the EORTC Intergroup 4098 trial.

Currently the strongest evidence guiding chemotherapy selection for these patients is randomized phase Ⅲ data showing that KRAS wild-type subgroups have the highest RECIST (radiological) response rates for EGFR inhibitors (cetuximab). Therefore, triple therapy using cetuximab in addition to irinotecan (CRYSTAL study)[23] is probably the best choice for patients with a goal of downsizing for potential resection. Furthermore, in a randomized controlled trial of 138 unresectable patients, Ye *et al*[24] found that cetuximab combined with chemotherapy improved resectability (25.7% *vs* 7.4%, P < 0.01) of liver metastases and improved 3-year OS (41% *vs* 18%, P = 0.013) compared with chemotherapy alone. Of note, panitumumab is a humanized version of cetuximab that simply has a different dosing schedule and can be used in the case of cetuximab allergy. Panitumumab was established in the PRIME study showing significant PFS increase (9.6 mo *vs* 8 mo)[25,26].

Treatment of the patient with limited extrahepatic disease

These patients will most commonly have three or fewer lung metastases or peritoneal implants. This remains an area of controversy. The surgical (or ablative) control of these lesions remains understudied, as does the role of systemic therapy in these patients.

Treatment of the unresectable patient

Despite all modern efforts described above, < 5% of all patients with mCRC will be cured; usually due to relapse before reaching 10 years of DFS. Moreover, the 5-year OS for patients with mCRC is 7%[5,26]. The goal of care from these patients moves from cure to control.

The paradigm shift in treating these patients will be demonstrating the impact of liver-directed therapies in the context of extrahepatic disease. It makes sense that the vast synthetic and filtration functions of the liver (a vast understatement of the complex biophysiology of this organ) serve a vital role in patient morbidity and mortality. Stated differently, it makes sense, but has not yet been rigorously proven, that patients with widespread mCRC benefit from a focus on the CLM, whether it be with chemotherapy or locoregional treatments (to be discussed later). Moreover, the liver especially makes sense for mCRC (especially colon cancer metastases) given the predictable metastatic pattern for these tumors.

Globally, contemporary standard of care is the use of doublet or triplet regimens. Doublet regimens involve combination of irinotecan and oxaliplatin (which is not useful alone[27]) with 5-FU/leucovorin (LV)[28-31]. All trials comparing first-line combination superiority between oxaliplatin and irinotecan have shown equivalent survival. Capecitabine[32,33], S1[34], and UFT-tegafur are oral fluoropyrimidines with established non-inferiority to 5-FU, and can be used in doublet/triplet combinations based on toxicity profiles. Specifically, CAPIRI and FOLFIRI had similar efficacy and adverse event profiles in a meta-analysis of the six major trials available[35]. Randomized controlled trials on triplet and quadruplet regimens are forthcoming, but the quadruplet regimens stand the risk of being limited by toxicity.

Unfortunately, de Gramont and the GERCOR group showed that the majority of patients treated with continuous FOLFOX will discontinue for neurotoxicity before progression. OPTIMOX 1 showed that an "oxaliplatin holiday" with just infusional 5-FU could be used to gain maximal time on oxaliplatin and reach progression before abandoning the drug (so called "stop and go" oxaliplatin regimen). OPTIMOX 2 aimed to study whether the infusional 5-FU was even necessary, but remained underpowered with 216

patients once bevacizumab was approved in France, which effectively dismantled OPTIMOX 2. Nonetheless, patients receiving maintenance therapy had improved PFS and OS.

Doublet regimens are often enhanced with a choice of two additional targeted biological agents that benefit from specificity and reduced toxicity profiles (but can be cost-prohibitive). These are an anti-vascular endothelial growth factor (VEGF) monoclonal antibody, bevacizumab, and another monoclonal antibody targeted for the human epidermal growth factor receptor (HER-1 or EGFR).

In the second line, the phase Ⅲ VELOUR trial[36] showed that FOLFIRI plus aflibercept (a fusion protein of human IgG Fc1 and VEGF receptors 1 and 2 that functions as a VEGF-trap and blocks all human VEGF-A isoforms, VEGF-B, as well as placental growth factor PIGF-2) provided significant survival advantage, which was even seen in patients with resistance at prior bevacizumab (a pure VEGF ligand inhibitor as opposed to a VEGF trap) treatment. The European TML study showed that patients who progressed on first-line chemotherapy plus bevacizumab benefitted from having bevacizumab included in their second-line chemotherapy as well, with significant PFS and OS differences (5.7 mo *vs* 4.1 mo and 11.2 mo *vs* 9.8 mo, respectively)[37]. In a related study, the RAISE study (presented at ASCO 2015) showed that second-line FOLFIRI ramucirumab (a human IgG1 monoclonal antibody targeting the extracellular domain of VEGFR-2) also leads to a statistically significant improvement in OS in comparison to FOLFIRI plus bevacizumab (13.3 mo *vs* 11.7 mo, respectively).

In the salvage setting, the CORRECT trial[38] stands out as a landmark trial, where regorafenib (an oral multikinase inhibitor) showed a significant survival advantage compared to best supportive care. The newest frontier in this setting was announced at 2015 ASCO GI with famitinib, a multi-target receptor tyrosine kinase inhibitor primarily acting against angiogenesis which had favorable phase Ⅰ data, with further studies forthcoming.

Treatment of patients with recurrent or progressive disease

As chemotherapy improves, patients are now living longer. Median survival now exceeds 30 mo, with many patients living up to 4-5 years with advanced disease. In fact, patients are living so long that we must begin to consider the cumulative toxicities from multiple lines of chemotherapy[39].

The contemporary approach for patients who progress on doublet therapy is to "flip the doublet", that is, irinotecan and oxaliplatin based doublets are interchanged. The E3200 study showed that adding bevacizumab to the second-line in bevacizumab-naïve patients increased progression-free (7.3 mo *vs* 4.7 mo) and overall (12.9 mo *vs* 10.8 mo) survival. The TML study has been described above but supports continuation of bevacizumab in the second line. As described above, VELOUR[36] added aflibercept to the list of medications with phase Ⅲ survival improvement data in the second line. As above, EPIC[40] showed that cetuximab improved PFS (4 mo *vs* 2.6 mo) in patients with EGFR-expressing tumors.

Data regarding third-line therapies are relatively slim. Regorafenib was studied in the CORRECT trial as detailed above, and shown to improve OS in patients progressing on anti-EGFR therapy (6.4 mo *vs* 5 mo). This comes at the risk of hand-foot syndrome which can be seen with regorafenib[38].

SUMMARY: MEDICAL ONCOLOGY

Somatic mutation testing at initial tissue diagnosis

KRAS and BRAF at a minimum, in the future multi-gene testing systems for targetable mutations.

For advanced metastatic disease, chemotherapy-first as opposed to surgery-first

As CRC approaches designation as a chemosensitive disease, and is increasingly facilitated by palliative endoluminal stenting for concurrent obstruction, surgery will be used less frequently as the first treatment[41,42].

More removal of the primary tumor in systemic disease

In the correct patient population, there is increasing evidence that, even in systemic disease, removal of the primary tumor improves survival. This is retrospective at this point.

Metastatic equivalents

The concept that heavy node-positive disease at primary resection may be treated as if the patient has distant metastases.

Stage Ⅱ colorectal cancer patients

The benefits of chemotherapy will become more established for patients with stage Ⅱ tumors that are high risk (lymphovascular invasion/emergent presentation with obstruction or perforation/poor differentiated/T4 N0). Already there is level Ⅰ evidence for survival benefit with chemotherapy for stage Ⅲ tumors.

Complexity

As the number of agents and patient survival increase (Table 2), choosing an optimal chemotherapy strategy becomes more complex, limited by expense as well as cumulative toxicity profiles.

Table 2 Highlights of ongoing clinical trials (National Cancer Institute) regarding systemic treatment for metastatic colorectal cancer

Protocol ID	Principle investigator	Phase, purpose, and relevance
NCT02149108	Boehringer Ingelheim	Phase Ⅲ study of salvage nindetanib
NCT02305758	AbbVie	Phase Ⅱ study of first-line veliparib (PARP inhibitor) added to FOLFIRI +/- bmab
NCT02060188	Bristol-Myers Squibb	Phase Ⅱ study of nivolumab (anti-PD1 antibody) +/- Ipilimumab in recurrent and microsatellite high (MSI-H) colon cancer
NCT02119676	Incyte	Phase Ⅱ study of salvage ruxolitinib (a JAK1 and JAK2 inhibitor) in combination with regorafenib
NCT02260440	University of Pittsburgh	Phase Ⅱ study of salvage pembrolizumab (anti-PD1) in combination with azacitidine
NCT01661972	Duke University Medical Center	Phase Ⅰ/Ⅱ study of capecitabine plus aflibercept ("X-TRAP study")
NCT02168777	Bayer	Phase Ⅰ/Ⅱ study of remafetinib with regorafenib
NCT02079740	National Cancer Institute, United States	Phase Ⅰb/Ⅱ study of trametinib (a MEK inhibitor) and navitoclax (BCL-2 Family Inhibitor) in KRAS mutant advanced tumors
NCT00940316	Genentech, OSI Pharmaceuticals, Amgen	Phase Ⅰ/Ⅱ study of dual epidermal growth factor receptor inhibition With Erlotinib and Panitumumab with or without chemotherapy
NCT01985763	Mt. Sinai School of Medicine, New York City	Phase Ⅰ/Ⅱ study of first line genistein (a soy derivative that interrupts Wnt signaling) in addition to standard regimens
NCT01471353	University of Florida	Phase Ⅱ study of salvage sorafenib plus capecitabine (SorCape)
NCT01750918	GlaxoSmithKline	Phase Ⅰ/Ⅱ study of trametinib and dabrafenib in combination with panitumumab in BRAF-mutation V600E colorectal cancer and in patients with resistance to prior anti-EGFR therapy

INTERVENTIONAL RADIOLOGY APPROACH TO MCRC

Standing at the forefront of minimally invasive cancer therapies, interventional oncology is positioned alongside medical oncology, radiation oncology, and surgical oncology as one of the four pillars of care for the patient with cancer. Interventional oncology is the super-specialization of interventional radiology sub-specialists in the care of the patient with cancer. Interventional oncology physicians bring a clinical - not purely technical - approach to patient care and are a key component of multidisciplinary cancer treatment teams.

The interventional oncologist uses therapies that fall into two main categories when treating solid tumors: ablation and embolization. Ablation is the deposition of energy into a tumor using percutaneous electrodes, antennae, or probes with the intent of destroying the tumor and a margin of normal surrounding tissue. Embolization refers to the endovascular delivery of any agent including bland particles, or particle-bound pharmaceuticals/biological agents/chemotherapy/radiopharmaceuticals, or even biological agents (for example, antineoplastic mutant virus pharmaceuticals) with the intent of a focused volume of distribution into target tumor with minimal collateral damage to normal parenchyma, and sometimes a secondary goal of causing ischemia (although, as described later, tissue anoxia is sometimes undesirable for example in radioembolization where the mechanism of tumor destruction is oxygen free radical formation).

While reviewing the forthcoming data regarding interventional oncology therapy for mCRC, it is important to note that ablation is already recognized as a curative[43] modality (the other two curative modalities being surgical resection and transplantation) for hepatocellular carcinoma (HCC) per the BCLC (Barcelona Clinic Liver Cancer) Criteria that are widely endorsed by scientific organizations including EASL, ESMO, and AASLD (European Association for the Study of the Liver, European Society for Medical Oncology, and the American Association for the Study of Liver Diseases, respectively). Moreover there is level 1 evidence to support the use of chemoembolization in HCC patients. Level 1 evidence is a high quality randomized trial or prospective study, including systematic reviews of other level 1 studies.

Interventional oncology therapies have provided treatment options for patients in the salvage setting with low volumes of healthy liver parenchyma, for example, patients with underlying cirrhosis, steatohepatitis after multiple lines of chemotherapy and/or prior extensive hepatic resection. Importantly, outcomes in the salvage setting should not be used as a benchmark for the outcomes of all interventional oncology therapies. This is because: (1) studies of interventional oncology patients in the salvage setting commonly suffer from severe selection bias, including poorer baseline performance status; and this limits external generalizability of these studies; and (2) the tumor biology of salvage patients is categorically worse (greater accumulation of tumor DNA mutations, more aggressive behavior) after multiple lines of treatment compared to patients receiving first-line therapies.

Interventional oncology combines a utilization of local and locoregional therapies. Local therapies are treatments directed at tumors we can see on imaging and target with resection, intraoperative ablation, or percutaneous ablation. However, it is no longer controversial that patients with macroscopic CLM also must be assumed to have microscopic CLM. Locoregional therapies (for example yttrium-90 radioembolization, and chemoembolization) allow

minimally invasive organ-directed treatment with a field effect that can result in fewer side effects than systemic therapy and are less invasive than open surgery.

The need for interventional oncology in the treatment of patients with colon and rectum cancer is increasing. Patients are living longer post-treatment, developing lesions during survival that need biopsy, and ultimately recurrence that may require local or locoregional therapies. Finally, as life expectancy continues to rise, older patients diagnosed with cancer will seek treatment even if they are not candidates for surgery.

Interventional radiology and the "test-of-time" concept

The test-of-time approach is a crucial concept in the management of mCRC that can spare patients from unnecessary surgery. This concept was popularized by Livraghi *et al*[44] in 2003, and sought to ask the question: for resectable patients awaiting surgery, what happens if ablation is done first, with the plan of still taking them to surgery? In their study, ablated patients who had complete tumor necrosis with margins [with necrosis defined as non-enhancement at contrast-enhanced computed tomography (CT) on postoperative day 1], 98% (52/58) were spared surgical resection, 23/52 (44%) because they remained disease free, and 29/52 (56%) because they manifested with widespread disease. Had these patients undergone surgical resection, it would have resulted in unnecessary morbidity because they would have developed those new liver metastases anyway. All patients received chemotherapy before radiofrequency ablation (RFA) unless they refused; in total, 70/88 patients (80%) received chemotherapy before RFA.

To summarize, Livraghi *et al*[44] showed that if RFA with margins can be performed for resectable oligometastatic CLM, 98% of patients are spared unnecessary surgery. The concept that today's "resectable" will come to mean "ablatable" is a visionary guiding principle for all interventional oncologists seeking to treat patients in a percutaneous minimally invasive fashion.

Interventional radiology and the "chemotherapy holiday" concept

Ablation is a repeatable and minimally invasive therapy that is directly complementary to surgical resection in principle. Induction chemotherapy does not always result in a complete visual disappearance of all lesions at imaging. The initial "induction" response of first-line chemotherapy can be "consolidated" by percutaneous image-guided ablation in a minimally invasive fashion. Depending on local practice patterns, the eradication of visible tumor may allow for the patient to take a "holiday" from receiving chemotherapy (which can involve frequent visits to the hospital, side effects, and expense, all of which may affect quality of life). As above, this can be used with the test-of-time approach.

Interventional radiology and the concept of PFS as a surrogate of OS

In randomized controlled trials, the gold standard endpoint is overall survival. However, this endpoint requires extended follow-up and is often confounded by subsequent lines of treatment. Even though the United States Food and Drug Administration (FDA) will approve treatments based on the endpoint of PFS, it is becoming less controversial to use PFS as a surrogate for OS as a primary endpoint in studies in medical oncology and interventional oncology.

The use of PFS as a surrogate for OS should be cancer-specific. In this regard, for patients with mCRC and CLM, liver progression of disease is what will usually affect survival. In 2002, the FDA approved SIR-spheres for mCRC CLM on the basis of statistically significantly improved PFS. Recently, the FDA published regulation 21CFR813, subpart H allowing the use of PFS in the accelerated approval of new drugs for serious illnesses.

PERCUTANEOUS ABLATION

Interventional radiology and the concept of an "A0" ablation

Ablation is defined as the delivery of energy into a tumor to destroy that tumor. Just like a margin of normal tissue must be removed for R0 resection, it makes sense that a margin of normal tissue must be ablated to perform A0 ablation.

The concept of A0 ablation, as well as objective criteria to document the performance of it, is a subject being pioneered at selected centers worldwide, for example, by work including Interventional Oncologists Sofocleous, Erinjeri, and Solomon and colleagues at Memorial Sloan Kettering Cancer Center (MSKCC) in New York City. For example, immediate post-ablation biopsy of the peritumoral margin can be evaluated using YO-PRO-1 as a biomarker of cell death[45].

Strategies to document A0 ablation using immediate procedural imaging are also being studied but will benefit from the aforementioned histological verification prior to rigorous clinical application. Makino *et al*[46] performed a pilot feasibility study of pre-ablation and post-ablation contrast-enhanced CT [or magnetic resonance imaging (MRI), respectively] images, showing that MR fusion provided technically acceptable image registration for ablation volume comparison in 86/92 (93.5%) while CT did so for 62/92 (68%), noting that shrinkage of the ablation zone during the $\leqslant$ 28 d between pre- and post-ablation scans may need attention in future studies. In another feasibility pilot study, Rempp *et al*[47] showed that ablation performed under MR guidance can be followed

with MR thermometry and diffusion-weighted imaging to document tumoricidal temperatures in real time and establish the margins of cellular destruction. Finally, while not FDA-approved for this indication, Mauri *et al*[48] have performed a substantial pilot study of sulfur hexafluoride microbubble ultrasound intravascular contrast for intraprocedural rapid assessment of ablation volume, showing that contrast-enhanced ultrasound spared retreatment in 29/93 (31%) of patients who had incomplete ablation with an approximately 22% cost reduction for overall interventional treatment. Of note, unfortunately, gas bubbles seen at routine B-mode ultrasound during thermal ablation do not indicate complete ablation of the gas-emitting region[49], and the zone of gas bubbles does not correlate accurately with the zone of necrosis[49].

Image guidance, fusion, and navigation

Guidance options for probe placement include ultrasound, CT, CT fluoroscopy, positron emission tomography (PET)/CT, and MRI (with compatible ablation systems). Augmented reality systems including fusion imaging and volumetric spatial navigation are emerging as adjunct technologies.

Ultrasound is well suited for mCRC in the liver because the lesions are usually conspicuously hypoechoic relative to the surrounding liver parenchyma. Using the sensitivity of diffusion-weighted MRI to detect lesions non-invasively, cognitive fusion with ultrasound provides the benefits of real-time needle/probe tracking with the respiratory cycle. Additionally, ultrasound provides real-time vascular assessment with Doppler ultrasound as well as omniplanar vector planning, which is difficult for CT. Intraoperative ultrasound is especially sensitive for lesion detection. One unsolved dilemma with ultrasound guidance during ablation is that water vapor and nitrogen gas released during tissue boiling (RFA, microwave) or ice formation (cryoablation) cause acoustic scattering, acoustic refraction, and acoustic shadowing of an already-hypovascular lesion. Therefore, given the option to ablate a deep lesion and a superficial lesion in sequence, experienced operators ablate the deeper lesion first to avoid acoustic shadowing of the second lesion.

Body habitus may limit ultrasound capabilities because the subcutaneous adipose layer scatters the otherwise-organized sound waves originating from the cutaneous piezoelectric crystals, distorting image quality. This becomes especially important for deep liver lesions. CT is helpful in this setting. Fluoroscopic CT can be used to safely guide the needle/probe/antenna to the target and confirm the zone of ablation. Iodinated contrast can be given that will provide a time window of 5 min or less for targeting of inconspicuous lesions. PET/CT using fluorodeoxyglucose (FDG) (or any other radiotracer that emits positrons) is a powerful technique to target the metabolically active portions of tumors. Indeed Shyn *et al*[50] have shown that a reasonable 20-s breath-hold PET acquisition (shorter than that usual 3-min summed breath-hold acquisition) can safely be used for intrahepatic lesion targeting. In practice, it is important to remember that lead aprons do not block positrons, so in-room time should be limited once the FDG dose is given. Finally, not all ablation equipment is MRI compatible but MRI does provide exquisite anatomic detail, with Rempp *et al*[47] demonstrating technical success of MRI-guided ablation in 210/213 lesions (98.6%) when using wide-bore MR-guided RFA. Especially for patients with large body habitus, the wide-bore magnet is preferable, and in practice the patient can be positioned asymmetrically in the bore to open up space on the right side of the patient.

Electromagnetic tracking-based image fusion is a powerful technique combining the spatial/metabolic/physiological sensitivity and specificity of PET/CT, contrast-enhanced CT or MRI, with the real-time imaging and handheld convenience of ultrasound. Example software provides "plug-and-play" fusion whereby images from any CD-ROM or PACS can be registered to ultrasound by the operator by selecting mutual anatomic landmarks in a series of images. The magnetic field generator tower that tracks ultrasound probe positioning may not be compatible with cardiac pacing devices. Respiratory motion (which can vary later in the case due to sedatives) remains an issue for this fusion - the anatomy is fused at a single point in the respiratory cycle (preferably expiration which lasts longer than inspiration and provides a longer window for needle/probe positioning). Mauri *et al*[51] have performed one of the largest series regarding fusion guidance during thermal ablation in 295 ablation cases, demonstrating correct tumor targeting and ablation in 266/295 (90.2%) of cases. Of note, this technology is most valuable for lesions that are poorly visualized by ultrasound but require ultrasound for appropriate positioning (for example liver dome lesions).

Navigation is important to differentiate from fusion. Fusion simply refers to overlay of two image sets (usually a real-time ultrasound to a static hybridized PET/CT for example), which are spatially registered to vary in the x, y and z axes of ultrasound scanning. Navigation refers specifically to tracking of the operator's instrument (needle/probe/antenna) in space toward a target and can be performed even on unfused images. Improved lesion targeting with navigation systems may one day become the standard of care, with emerging studies such as that from Bale *et al*[52] showing that use of an optical frameless stereotactic navigation system with percutaneous RFA achieves similar OS and DFS rates as surgical

resection, directly challenging surgical resection as the first-line treatment of choice for CLM.

Percutaneous ablation: Patient selection

After clinical factors have been addressed, technical factors guiding patient selection include the following. (1) the number of tumors is limited, usually ⩽ 4 tumors; (2) the size of tumor appropriate for ablation. There is no strict absolute cutoff and tumor histology and ablation technology must be considered. Broadly, 3 cm is not controversial, while ⩽ 5 cm is acceptable. A new frontier ripe for study is the combination of embolization and ablation for this patient population, which has already shown promise for HCC based on data from MSKCC; and (3) tumor location near major vessels will designate the ablational at-risk margin regarding incomplete ablation due to heat sink and current sink (detailed below) and should prompt percutaneous temperature probe placement to document tumoricidal temperatures along the at-risk margin.

Contraindications to ablation include: (1) uncorrectable coagulopathy; and (2) no safe window for access vector to the tumor, even after considering strategic patient repositioning and temporary organ displacement maneuvers.

Percutaneous RFA

RFA involves delivery of energy with a frequency of less than 900 kHz using needle electrodes of varying geometry. The energy agitates ions resulting in temperature elevation. At 60 ℃, coagulation necrosis occurs. At 100 ℃, undesirable carbonization occurs, limiting heat distribution throughout the tumor. Tumors near blood vessels pose a challenge for RFA, as the nearby blood flow will remove electrical current and heat from the ablation zone (heat sink and current sink). Nearby biliary structures risk stricture formation as well.

The ideal candidate for RFA is a patient with a solitary CLM < 3 cm in size. Although rigorous evidence is forthcoming, it is believed that A0 ablation requires at least a 5-mm margin of normal tissue (based on imaging follow-up 1-2 mo post ablation).

Although major literature is forthcoming, the available retrospective data suggest that carefully selected RFA patients do just as well as resected patients. For example, Gillams *et al*[53] showed in their series of 167 patients undergoing percutaneous RFA, for patients with ⩽ 5 metastases, maximum diameter ⩽ 5 cm and no extrahepatic disease, the 5-year survival from the time of diagnosis was 30%, and the 5-year survival from the time of first RFA was 26%. This compares favorably to the 5-year survival for operable patients of a median of 32%.

Future frontiers with RFA will include pre-medication or pre-embolization (see Bland Embolization section below). For example, Devun *et al*[54] have shown that systemic pretreatment of mice with the DNA repair inhibitor Dbait improves the efficacy of radiofrequency ablation.

The literature regarding RFA of CLM is highlighted in Table 3.

Percutaneous cryoablation

Cryoablation uses a special probe applying the Joule-Thompson principle to argon gas to cause rapid tissue cooling. Cancer cells contain more water than non-cancer cells. Freezing leads to the formation of intracellular ice crystals. At -40 ℃, tissue death occurs. Early generation devices have limited the implementation of this modality for the liver due to adverse event reports of cryoshock, a condition similar to diffuse intravascular coagulation. Despite the availability of effective thermal ablation methods in the liver, cryoablation remains the oldest method of tumor ablation and has been used with success in other organs[55-57]. Furthermore, the ability to visualize a clear ablation margin under CT using cryoablation makes it an attractive option, and for this reason forthcoming literature regarding cryoablation in the liver constitutes a new frontier for mCRC CLM.

The available literature regarding cryoablation of CLM is highlighted in Table 4.

Percutaneous microwave ablation

Microwave ablation (MWA) was developed to overcome limitations with RFA. MWA uses high-frequency waves (900 MHz and 2.4 GHz) to oscillate water molecules, creating friction, tissue heating, and tissue destruction by coagulation necrosis. MWA does not rely on electrical current to generate heat, and therefore a current sink is not an issue. Due to the power of the microwave generator, MWA can overcome the heat sink even if it does not fully avoid it. MWA is superior to RFA in treating larger tumors, with lower recurrence rates (as low as 6%)[58].

There is only one randomized trial comparing MWA to resection in mCRC patients with CLM. No statistically significant difference was found as the study was underpowered (40 patients). The mean survival time was greater in the MWA group (27 mo *vs* 25 mo) while the mean disease-free interval was slightly shorter (11.3 mo *vs* 13.3 mo)[59]. The available literature regarding MWA of CLM is highlighted in Table 5.

Percutaneous irreversible electroporation

Irreversible electroporation was developed to overcome limitations presented by thermal ablation (RFA and MWA), namely, collateral damage to bile ducts or other important structures that could be damaged due to heat. Irreversible electroporation is a new technology and much of the data is forthcoming. Studies that have

Table 3 Highlights of radiofrequency ablation literature for colorectal liver metastases

Ref.	Level of evidence	Year	Study details	1 yr OS%	3 yr OS%	5 yr OS%	7 yr OS%	10 yr OS%	Median OS (mo)	Procedure-related complications
[1]Gillams *et al*[53]	Ⅱ-2	2004	Prospective, 167 patients Percutaneous (ValleyLab) Mean 4 lesions Mean 4 cm max diameter	91	28	25			38	< 1% (1/167)
Hildebrand *et al*[108]	Ⅱ-2	2006	Prospective, 88 pts/420 lesions Percutaneous (RITA/ValleyLab) Mean 3.5 lesions Median 2.7 cm max diameter	92	42				28	3.4% (3/88)
Siperstein *et al*[109]	Ⅱ-2	2007	Prospective, 234 patients Laparoscopic Mean 3 lesions Median 4 cm max diameter		20.2	18.4			24	Not reported
Berber *et al*[110]	Ⅱ-2	2008	Prospective, 68 pts/68 lesions Laparoscopic All solitary lesions Median 3.7 cm max diameter		20.6	30			20.5	2.9% (2/68)
Veltri *et al*[111]	Ⅱ-2	2008	Retrospective, 122 pts/199 lesions Percutaneous (RITA/ValleyLab /LeVeen) Mean 1.6 lesions Median 3 cm max diameter	79	38	22			31.5	1% (2/199)
Gleisner *et al*[112]	Ⅱ-2	2008	Prospective, 66 patients Intraoperative (RITA) Median 2 lesions Median 3 cm max diameter	92.3	51.1	28.3			38.1	Not reported
[1]Gillams and Lees[113]	Ⅱ-2	2009	Prospective, 309 pts/617 lesions Percutaneous (Covidien/RITA) Mean 4 lesions Median 2.3 cm max diameter		49	24			36	3.7% (23/617)
Sofocleous *et al*[114]	Ⅱ-2	2011	Prospective, 56 pts/71 lesions Percutaneous (LeVeen/Valleylab/ RITA) Mean 1.4 lesions Median 1.9 cm max diameter	91	41				31	4% (2/56)
Solbiati *et al*[115]	Ⅱ-2	2012	Retrospective, 99 pts/202 lesions Percutaneous (Covidien) Mean 2 lesions Mean 2.1 cm diameter +/- 0.75 cm std deviation	98	69.3	47.8	25	18	53.2	1.3% (2/156)
Bale *et al*[52]	Ⅱ-2	2012	Retrospective, 63 pts/189 lesions Percutaneous (Covidien) with Treon Navigation Mean 2 lesions Mean 2 cm diameter	87	44	27			27 mo for unresectable patients, 58 mo for resectable patients (P = 0.002)	17% (17/98)
Hamada *et al*[116]	Ⅱ-2	2012	Retrospective 84 pts/141 lesions Percutaneous (Valleylab) Mean 1.7 lesions Mean 2.3 cm max diameter +/- 1.4 cm	90.6	44.9	20.8			34.9	2.2% (3/138)

[1]Partially redundant series. Level of Evidence based on the United States Agency of Healthcare Research and Quality Classification of Levels of Evidence. OS: Overall survival.

Table 4 Highlights of cryoablation literature for colorectal liver metastases

Ref.	Level of evidence	Year	Study details	1 yr OS%	3 yr OS%	5 yr OS%	Median OS (mo)	Procedure-related Complications
Rivoire *et al*[117]	Ⅱ-2	2002	Retrospective, 24 patients, 69 lesions Laparotomy (Erbokryo CS-6) 10-15 min freeze, 5 min thaw, 5-10 min freeze, occasionally with Pringle maneuver Mean 3 lesions Mean 4.5 cm max diameter	92	58		39	21% (5/24) had iceball fracture, successfully treated with suture (all cryoablation performed at laparotomy)
Yan *et al*[118]	Ⅱ-2	2003	Prospective, 172 pts/420 lesions Laparotomy (L.C.S. 3000/Erbe) 1 cm margin, freeze-partial thaw-freeze Mean 4 lesions Median 3.6 cm max diameter	89	41	19	28	28% (48/172) (all cryoablation performed at laparotomy, not percutaneously) Gelfoam packed into every tract
Brooks *et al*[119]	Ⅱ-2	2005	Prospective, 93 patients Laparotomy (L.C.S. 3000/Erbe) Median 2 lesions	85	43	19	33	Cryoablation-related complications not specifically reported
Niu *et al*[120]	Ⅱ-2	2007	Prospective, 124 pts/124 lesions Laparotomy (L.C.S. 3000/Erbe) 1 cm margin, freeze-partial thaw-freeze For lesions > 3 cm, two probes always used Mean 4 lesions Mean 4 cm max diameter	84	43	24	29	Not reported Gelfoam was packed into every tract
Paganini *et al*[121]	Ⅱ-2	2007	Retrospective, 49 pts Laparotomy (CMS AccuProbe/Erbe) Mean 5 lesions Median 3 cm max diameter	87	43	23	31	22% (11/49)
Ng *et al*[122] (Part 1)	Ⅱ-2	2012	Retrospective, 211 pts Laparotomy (L.C.S. 3000/Erbe) Single-freeze thaw performed except for "smaller" lesions where partial double freeze-thaw performed Mean 4.4 lesions	87	21	12	27	Cryoablation-related complications not specifically reported
Ng *et al*[122] (Part 2)	Ⅱ-2	2012	Mean size 4 cm Retrospective, 93 pts Laparotomy-assisted cryoablation of inadequate resection margins as determined by operator; (L.C.S. 3000/Erbe)	87	31	17	34	Cryoablation-related complications not specifically reported
Shyn *et al*[123]	Ⅱ-2	2014	Mean 2.2 lesions Mean lesion size 5.7 cm Retrospective, 39 patients, 54 lesions Percutaneous (Galil) Median 4 probes (range 1-7) each 17 Gauge, 15 min freeze, 10 min passive thaw, 15 min freeze cycle Mean 1.4 lesions Mean lesion size 3 cm	Local progression at a mean interval of 30.3 mo (range 13-72 mo) was seen in 14/54 patients (26%). Survival not reported				Not reported

Level of Evidence based on the United States Agency of Healthcare Research and Quality Classification of Levels of Evidence.

included mCRC patients with CLM have shown primary efficacy of up to 100% for tumors adjacent to vascular and biliary structures[60-63]. In this setting, similar to that shown in the microwave setting[59] a tumor size of ⩾ 3 cm seems to be an independent risk factor for local recurrence.

Post-ablation patient follow-up

The exact timing and modality of follow-up imaging after ablation varies on an institutional basis. There are three main systems used in evaluating treatment response by these patients: the World Health Organization criteria, the Response Evaluation Criteria in Solid Tumors and the Positron Emission Evaluation Response Evaluation Criteria in Solid Tumors.

The treatment team should be aware that there is one major nuance to the application of all of these criteria. With percutaneous ablation, the ablation creates a volume of imaging abnormality larger than the target tumor. Therefore, for proper evaluation of response to treatment and early detection of local tumor progression, a post-ablation scan at 4-8 wk is considered the new baseline for future comparisons. The next scan can be timed for 2-4 mo, and will be used to detect local, near local, and distant disease progression. Ideally the interventional oncologist should see these patients in their clinic and review imaging directly with the patient.

Table 5 Highlights of microwave ablation literature for colorectal liver metastases

Ref.	Level of evidence	Year	Study details	1 yr OS%	3 yr OS%	5 yr OS%	Median OS (mo)	Procedure-related complications
Shibata *et al*[59]	Ⅱ-1	2000	Prospective, randomized, 14 pts, 58 lesions Laparotomy (Azwell HSD-20M) Mean 4 lesions Mean 2.7 cm	71	14		27	14% (2/14) - one biliary fistula and one hepatic abscess
Liang *et al*[124]	Ⅱ-2	2003	Retrospective, 74 patients, 149 lesions Laparotomy (Microtaze AZM-520) Mean 2 lesions Mean 0.8 cm max diameter	91.4	46.4	29	20.5	4% (3/74) skin burns (in patients with tumors with extracapsular extension)
Tanaka *et al*[125]	Ⅱ-2	2006	Retrospective, 16 patients, 35 lesions Laparotomy (Microtaze AZM-520) Mean 2 lesions Mean 0.8 cm max diameter	80	51	17	28	19% (3/16) Bleeding, biliary fistula, wound infection. (all patients underwent MWA *via* laparotomy, none percutaneous)

SUMMARY: PERCUTANEOUS ABLATION

Immunomodulation is the next major topic in ablation research. The underlying mechanisms are already under investigation by Erinjeri *et al*[64] at MSKCC and selected institutions worldwide.

Until immunomodulation mechanisms are determined and translated to the bedside, existing technology will be studied clinically. Based on similar experiences with level 1 HCC data for interventional oncology therapies, forthcoming mCRC data will likely prove that ablation, performed by skilled operators in carefully selected patients, rivals or outperforms surgery when accounting for morbidity, cost, and quality of life of the patient.

Metabolic-imaging guidance during ablation, as pioneered by Ryan, Sofocleous, Solomon and colleagues at MSKCC, may become standard of care for establishing A0 ablation and for anatomically challenging marginal ablations[65].

Patient safety during anatomically challenging percutaneous ablations will be enhanced by mainstream implementation of image-guided navigation systems[66].

The same tumor biology that affects the outcomes of medical and surgical treatments will determine the outcomes from interventional treatments. Therefore, smaller and fewer tumors, as well as CLM in the absence of significant extrahepatic disease, and low nodal involvement of the resected primary tumor are all positive predictive factors that should guide interventional oncologists in multidisciplinary tumor conferences and in the clinic.

ENDOVASCULAR ANTINEOPLASTIC INTERVENTIONS

The fundamental limitation of local therapies (surgery and ablation) is that only tumors that are seen (visually or radiologically) are targeted. However, our ability to see tumors is limited. For example, even the best imaging technologies currently in use have a liver resolution in the order of millimeters at best. In other words, in order to see a tumor by imaging, 10^7 cancer cells must be present. Even using the only mainstream molecular imaging technology of PET, this is reduced at best to 10^6 cells. Furthermore, there is a growing body of research regarding circulating tumor cells. In summary, there is an opportunity to benefit patients if we recognize that microscopic tumor probably plays a role in tumor recurrence or treatment resistance. The EORTC Intergroup Trial 40983 showed that, of resectable patients (1-4 visible metastases) who underwent surgery, 70% developed intrahepatic recurrence at 3 years (long-term follow-up). Thus the burden of micrometastatic disease can be estimated to be approximately 70% in patients with mCRC and resectable CLM.

Locoregional therapies expand on local therapies by treating the field of parenchyma surrounding tumors. A mystery in oncology is why liver metastases (presumably reaching the liver *via* the portal vein) derive most or all of their blood from the hepatic artery. However, interventional oncologists depend on this fortuitous anatomical relationship to deliver particles to the tumor blood supply in a selective fashion while sparing nearby normal parenchyma. If particles are delivered, this procedure is called embolization.

CLMs are usually hypovascular relative to the normal nearby liver parenchyma. If an arterially directed therapy depends on flow-directed embolization (whereby particles preferentially enter the tumor vasculature due to their usually increased blood flow), can it still benefit patients with hypovascular CLMs? The brief answer is yes, although the hemodynamics and vascular fluidics of microparticle delivery in this setting have not yet been fully established.

Locoregional therapies carry the benefit of treating the field, that is, treating micrometastases that are not yet visible using current imaging technology.

There are four settings in which arterially directed

therapies are commonly used. (1) induction treatment - downsizing potentially curable patients in preparation for surgery; (2) combined with percutaneous ablation - embolization reduces the heat sink and creates an ischemic tumor environment that is primed for ablation. If embolization is performed with lipiodol, an oily embolic, it is thought to greatly enhance heat delivery to tumor cells. Elnekave and colleagues have shown that this method equals surgical outcomes for HCC (not mCRC) up to 7 cm in their series at MSKCC[67]; (3) salvage treatment - high response rates can be seen by adding arterially directed therapies to chemotherapy, even in settings where patients have previously been resistant to the same chemotherapy agent; and (4) early-line treatment - this concept is a natural evolution from use in the salvage setting and follows from organ-directed therapy concepts previously described. In addition, it is thought that locoregional therapies can have a greater effect before reaching a multi-line-resistant tumor with more aggressive biology. SIRFLOX and FIREFOX trials are two example studies looking at radioembolization as an early-line treatment.

Hepatic arterial chemotherapy

Relying on high-first-pass extraction of chemotherapeutic agent from the bloodstream, hepatic arterial infusion (HAI) of chemotherapy utilizes a subcutaneous injection port with a thin intra-arterial indwelling catheter that has its tip in the proper hepatic artery at the origin of the gastroduodenal artery. The port can be placed surgically or percutaneously. The skeletonization *via* the percutaneous route is thought to be more complete although no rigorous studies have demonstrated this. Maintenance Tc-99 microalbumin aggregate studies and angiograms are occasionally performed during the dwell time of the device to ensure there is no extrahepatic drug delivery.

HAI improves OS. This finding supports the concept of a liver-directed approach in patients with widespread mCRC, and also supports the concept of organ-directed approaches for metastatic cancers. A meta-analysis of six HAI trials showed improved response rates as well as OS advantage (14.5 mo *vs* 10.1 mo, $P = 0.0009$)[8].

Portal vein infusion chemotherapy

It would make sense that treatment of the "field" of radiologically uninvolved parenchyma would optimally be done *via* the portal vein, where the "normal" parenchyma derives the majority of its blood supply. This procedure is different from portal vein "embolization", which is done to hypertrophy a contralateral lobe prior to resection. The infusion of portal venous chemotherapy and evaluation of first-pass extraction has been studied. The group SAKK from Switzerland showed that adjuvant portal vein infusion of mitomycin C + 5-FU improved OS but did not reduce the recurrence of liver metastases[68]. A subsequent prospective three-arm randomized multicenter trial of 753 patients with stages Ⅰ-Ⅲ colorectal cancer (surgery only *vs* adjuvant portal vein chemotherapy *vs* adjuvant peripheral vein chemotherapy) showed that portal vein infusion did not improve DFS and OS. Actually, PVI was shown to have potentially harmful effects with a statistically significant increase in early death in the PVI group[69]. This technique remains investigational at the time of this report.

Bland embolization

Bland embolization is the injection of particles with the goal of causing selective tumor ischemia. The practice has evolved from use of PVA toward the use of calibrated microspheres in ascending sequential order of sphere diameter to reach full stasis.

When compared to chemoembolization, there are no level Ⅰ studies demonstrating superiority of chemoembolization to bland embolization for patients with CLM. Proponents of bland embolization believe that tumor death is caused by anoxia and that chemoembolization achieves its endpoints by this route. Bland embolization is thought to be more repeatable owing to better preservation of the hepatic arterial vasculature. This may be due to reduced caustic effect of chemotherapeutic agents on the intima. Though head-to-head studies are not available, the ability of bland embolization to facilitate extended repeat treatments has been shown[70]. Bland embolization is cheaper than chemoembolization, although this cost may be offset by the brief hospital stay for the management of post-embolization syndrome (categorized by fevers, chills, nausea, and abdominal pain), which is more pronounced for bland embolization than conventional chemoembolization. Conventional chemoembolization still results in a high systemic dose of chemotherapeutic agent, which can result in systemic side effects, although this has changed with the advent of drug-eluting bead technologies. The intra-arterial use of outdated or biologically irrelevant chemotherapeutic regimens (*e.g.*, doxorubicin) intra-arterially has been challenged when these agents are not necessarily used peripherally for the same tumor. However, with the advent of drug-eluting bead irinotecan chemoembolization this has changed specifically to mCRC as described later. Bland embolization can be effectively used to "paint" tumors for post-embolization targeting and ablation under CT guidance, similar to lipiodol in conventional transcatheter arterial chemoembolization (TACE). In the salvage setting, the cumulative toxicities of TACE chemotherapeutic agent with prior lines of chemotherapy, as well as possible resistance of aggressive tumor biology to the chemotherapeutic

regimens classically used in TACE, may weigh in favor of the more repeatable bland embolization procedure.

On the new frontiers of bland embolization, in Japan where they reported DEBIRI and radioembolization to be less available, Tanaka *et al*[71] have recently undertaken a pilot study of questions relevant to the current discussion. First, how does bland embolization, a flow-directed procedure dependent on causing ischemia, fare with tumors that are hypovascular (as colorectal metastases classically are) relative to liver parenchyma? Second, since bland embolization is repeatable and preserves hepatic vasculature, can it be performed less invasively through an implantable port? Tanaka and colleagues have documented the effects of 100-μm microspheres on a patient with metastatic rectal cancer with OS approaching 6 mo, using no other therapies. Future systematic studies might specify outcomes of bland embolization in hypovascular liver metastases.

Another new frontier for bland embolization will be the pre-ablation embolization setting. For example, Tanaka *et al*[72] have shown in pigs that bland embolization pre-ablation is more effective than bland embolization post-ablation, and that bland embolization with 40-μm microspheres enhances the efficacy of RFA more than bland embolization with 250-μm particles. Future work might include embolization with novel particles.

Chemoembolization

The literature regarding chemoembolization is the strongest of all transcatheter methods. However, it is important to note that the term chemoembolization is a vast over-simplification given the variety of methods used to perform this procedure [including for example, the choice and dose of chemotherapeutic agents, endpoint of treatment (stasis, near-stasis, or neither), conventional *vs* drug-eluting bead utilization, and post-treatment embolization with gelfoam or other methods]. This non-standardization has made meaningful meta-analysis of the chemoembolization literature challenging. However, as will be described later, the advent of drug-eluting beads may standardize chemoembolization for patients with mCRC CLM.

The premise of chemoembolization is to combine ischemia and chemotherapeutic penetration for enhanced (ideally, synergistic) tumor destruction. Conventional chemoembolization delivers the agent mixed with lipiodol, which proponents believe penetrates into the deepest vessels of the tumor and allows embolization while slowly leeching chemotherapeutic agent into the tumor. This method also causes failure of the transmembrane pump[73] thought to trap chemotherapeutic agent in cells. This is sometimes followed by a proximal embolization to reduce the pressure head of inflow and prolong the interaction time between the embolic bolus and tumor cells. The chemotherapeutic agent and lipiodol are prepared in the form of an emulsion in a method described by Lo *et al*[74] in their randomized trial of lipiodol TACE for HCC (not mCRC). However there are other ways to chemoembolize. For example, the original randomized controlled trial providing level 1 evidence for HCC (not mCRC) was performed by Llovet *et al*[75] and used gelatin sponge with doxorubicin (a technique no longer widely performed). In contradistinction, drug-eluting beads are thought to be a more reproducible mode of chemotherapeutic agent delivery, achieving the endpoint of ischemia as well as a more reliable chemical interaction with the chemotherapeutic agent and reduced systemic leeching of chemotherapy. For example, drug-eluting beads bound to irinotecan were introduced in 2006. DEBIRI has been shown to reduce systemic plasma levels by 75% when compared to intra-arterial irinotecan[76].

Factors that predict adverse events and hospital length of stay after TACE are embolization to complete stasis (P = 0.04), treatment with > 100 mg DEBIRI in a single session (P = 0.03), lack of pre-treatment with hepatic arterial lidocaine (P = 0.005), third or more repeated TACE (P = 0.05), > 50% liver involvement (P = 0.05), and pre-TACE bilirubin of > 2.0 g/dL[77-82].

The only phase 3 randomized controlled trial performed thus far by Fiorentini *et al*[79] randomized 74 patients with mCRC CLM to DEBIRI *vs* FOLFIRI. The DEBIRI group had improved survival (22 mo *vs* 15 mo, P = 0.031) and higher response rate (68.6% *vs* 20%) and longer life (8 mo *vs* 3 mo, P < 0.001).

Most recently in 2015, Iezzi *et al*[83] have shown phase Ⅱ study results with DEBIRI + capecitabine (PFS 4 mo, OS 7.3 mo) that are comparable to those shown in the CORRECT trial (where regorafenib was compared to best supportive care in 760 patients with PFS 1.9 mo and OS 6.4 mo in the regorafenib group). The available literature regarding TACE of CLM is highlighted in Table 6.

Chemosaturation

Isolated liver perfusion is a complex open surgical procedure requiring a perfusionist. In contrast, isolated liver infusion, or chemosaturation is a minimally invasive equivalent of isolated liver perfusion that maintains normal hepatic arterial and portal vein inflow. Instead, the hepatic vein drainage is isolated and the chemotherapeutic agent is extracted from the blood (with the newest filtration system extracting approximately 93% of the melphalan) before returning the blood to the systemic circulation. The procedure is performed using triple access (right common femoral and right jugular vein access for blood extraction/filtration and re-entry respectively) and left hepatic artery access (for infusion catheter placement into the hepatic artery).

The proprietary device used for hepatic chemo-

Table 6 Highlights of chemoembolization literature for colorectal liver metastases

Ref.	Level of evidence	Year	Study details	Response rate (SD, CR, PR)	PFS/TTP (mo)	1 yr OS	2 yr OS	Median OS (mo)
Lang and Brown[126]	Ⅱ-2	1993	TACE, Doxorubicin Prospective cohort, 46 patients	63		65%	22%	
Hong *et al*[127]	Ⅱ-2	2009	TACE, cisplatin + doxorubicin + mitomycin C Retrospective cohort, 21 patients			43%	10%	7.7
Vogl *et al*[82]	Ⅱ-2	2009	TACE, mitomycin C alone or with gemcitabine *vs* irinotecan Prospective cohort, 463 patients	63		62%	28%	14
Albert *et al*[77]	Ⅱ-2	2011	TACE, cisplatin, doxorubicin, mitomycin C Retrospective cohort, 121 patients	43	3	36%	13%	9
Martin *et al*[128]	Ⅱ-2	2011	DEB-TACE (DEBIRI) Prospective cohort, 55 patients			75%		19
Fiorentini *et al*[79]	Ⅰ	2012	DEB-TACE (DEBIRI) Randomized Controlled Trial, 74 patients, DEBIRI *vs* FOLFIRI	80	7		56%	15
Narayanan *et al*[129]	Ⅱ-2	2013	DEB-TACE (DEBIRI) Retrospective cohort, 28 patients	68.6	3			13.3
Iezzi *et al*[83]	Ⅱ-1	2015	DEB-TACE (DEBIRI) + Capecitabine Prospective Phase Ⅱ Trial, 20 patients	60	4			7.3

OS: Overall survival; TACE: Transcatheter arterial chemoembolization; TTP: Time to progression.

saturation is a 16 Fr system made by Delcath and has two balloons on either side of a 7-cm fenestrated catheter segment. Delcath performed a Phase Ⅱ clinical study of melphalan chemosaturation at the National Cancer Institute in the United States enrolling 16 patients with late-stage CLMs. While the safety profile was similar to the Delcath melanoma trial, the efficacy signal from the mCRC study was inconclusive, mainly because melphalan usage in the salvage setting was limited due to cumulative toxicities from prior lines of chemotherapy.

Of note, the isolated hepatic perfusion literature is more robust, using mitomycin C, oxaliplatin, and melphalan with and without tumor necrosis factor-α. For example, Reddy *et al*[84] studied 120 patients and showed overall response rate of 59% with median time to hepatic progression of 7 mo and median OS of 17.4 mo; patients receiving hepatic artery infusion of floxuridine benefited from a longer time to hepatic progression (13 mo *vs* 6 mo). Perhaps this and other surgical studies will continue to motivate research into the future outlook of isolated hepatic infusion (chemosaturation).

Radioembolization

Kennedy, one of the pioneers of the utilization of radioembolization in CLMs, showed microdosimetry results of intratumoral radiation delivery up to 1000 Gy[84]. This dose is made possible by the limited penetrance of beta radiation. Radioembolization is generally accepted to deliver 100 Gy to intrahepatic tumors; a dose that is impossible using external beam radiation due to radiation-induced liver disease (which occurs at 30 Gy). The curative dose for adenocarcinoma mCRC is 70 Gy. It is important for interventional oncologists to understand that the dosimetry of radioembolization cannot be directly compared to the absorbed dosimetry of external beam radiation due to differences in radiobiology between a continuous low dose-rate beta radiation and intense but brief external beam photon radiation pulsation[85,86].

In 2002, the FDA approved radioembolization with SIR-spheres (20-60-μm spheres, while terminal arterioles are usually 10-40 μm in diameter while capillaries average 8 μm in diameter for humans, and 3 μm in rodents) based on a study by Gray *et al*[87] that administered resin microspheres through a hepatic arterial infusion pump (whole liver treatment) in the context of floxuridine (FUDR) and compared this to FUDR alone. Tumor volume response (50% *vs* 24%), carcinoembryonic antigen response (72% *vs* 47%), median liver time to local progression (16 mo *vs* 10 mo) and survival (39% *vs* 29% at 2 years, 17% *vs* 6.5% at 3 years, and 3.5% *vs* 0% at 5 years) all reached statistical significance. There were no significant differences in grade 3/4 toxicities or quality of life measures. Unfortunately, the company funding the trial did not extend this trial until reaching the OS endpoint.

The summary of current evidence for yttrium-90 is that there is a strong trend toward prolongation of liver PFS, PFS, and the universal endpoint of OS when yttrium-90 is added to systemic treatments in early and late lines of treatment based on small randomized controlled trials. The safety profile of yttrium 90 treatments, especially regarding gallbladder and biliary complications, has matured over time and this procedure has very low morbidity when done by well-

Table 7 Highlights of yttrium-90 radioembolization literature for colorectal liver metastases

Ref.	Level of evidence	Year	Study details	Median OS (mo)	Median PFS (mo)
Kennedy *et al*[86]	Ⅱ-2	2006	Phase Ⅱ Prospective study 208 patients	10.5	
Sharma *et al*[130]	Ⅱ-2	2007	Phase Ⅰ, 20 patients No prior chemotherapy SIRT + FOLFOX4 SIR-Spheres only		9.3 (14.2 if had only liver-confined disease)
Benson *et al*[131]	Ⅱ-2	2013	Phase Ⅱ Prospective study 151 patients (61 colorectal) Theraspheres only	8.8	2.9
Lewandowski *et al*[132]	Ⅱ-2	2014	Phase Ⅱ Prospective study 214 patients Theraspheres only	10.6	
Sofocleous *et al*[133]	Ⅱ-2	2014	Phase Ⅰ, 19 patients Prior hepatic arterial and peripheral chemotherapy SIR-Spheres only	14.9	5.2
Gray *et al*[87]	Ⅰ	2001	Phase Ⅲ Randomized controlled trial 74 patients First-line SIRT +/- Regional chemotherapy 46 patients	17 *vs* 15.9 (P = 0.18)	15.9 *vs* 9.7 (P = 0.001) Liver PFS
Van Hazel *et al*[90]	Ⅰ	2004	Phase Ⅱ Randomized Controlled trial 21 patients First-line SIRT +/- 5-FU/LV	29.4 *vs* 11.8 (P = 0.008)	11.5 *vs* 4.6 (P < 0.004)
Hendlisz *et al*[134]	Ⅰ	2010	Phase Ⅲ Randomized controlled trial First-Line SIRT +/- 5-FU	10 *vs* 7.3 (P = 0.8)	5.5 *vs* 2.1 (P = 0.001)
SIRFLOX[135]	Ⅰ	Ongoing	Phase Ⅲ Randomized controlled trial Primary Endpoint: Progression free survival Size: 532 patients		
FOXFIRE[136]	Ⅰ	Ongoing	Phase Ⅲ Randomized controlled trial Primary Endpoint: Overall survival Size: 490 patients		
EPOCH[137]	Ⅰ	Ongoing	Phase Ⅲ Randomized controlled trial Primary Endpoint: Progression free survival		

trained operators at experienced centers[88,89].

The only randomized controlled trial comparing SIRT + chemotherapy to systemic chemotherapy alone was done by Van Hazel *et al*[90] who showed statistically significant doubling in PFS when SIRT was used as a first-line therapy. The forthcoming FOXFIRE and SIRFLOX studies will carry this concept into the modern chemotherapy regimens by using oxaliplatin in combination with SIRT. EPOCH will investigate the use of Theraspheres, glass microspheres that have a higher per-sphere radiation dose and are less embolic than SIR-Spheres resin microspheres. Some hypothesize that Theraspheres may fare better because the treatment is less embolic, which allows consistent delivery of the entire radioactive dose without concern for reflux, and facilitates oxygenation of the irradiated tissue (tumor destruction in radioembolization occurs by oxygen free-radical formation, therefore embolization is actually counterintuitive in this setting). The literature regarding radioembolization for mCRC CLM is highlighted in Table 7.

Viroembolization

Herpes simplex virus (HSV)-1 is a virus that has been extensively studied and is known to use host cell machinery to replicate upon gaining entry into cells. Interestingly, the genome of HSV-1 is large but only a few genes are necessary for replication. This leaves space for genetic engineering to create a mutant virus that can selectively infect tumor cells and, if needed, be neutralized by administration of acyclovir (a routinely available antiviral agent).

Specific to CLMs, interventional oncology will continue to play a role in advanced anti-cancer therapy due to the value of the biological payload and the need for organ-directed delivery, especially with the relatively hypovascular CLMs. A phase Ⅰ open-label dose escalation study at MSKCC demonstrated safety of delivery of neoadjuvant NV1020 *via* the right hepatic artery in a tumor-specific fashion[91].

INTERVENTIONAL RADIOLOGY MANAGEMENT OF CONCURRENT COLORECTAL METASTASES TO THE LUNG

The biological basis for an organ-directed treatment plan focused on liver progression has already been

established above regarding mCRC. However, the liver is not the only location to receive a metastatic burden. Rectal cancer can metastasize directly to the lungs *via* its own venous drainage that bypasses the liver to drain directly into the inferior vena cava. Colon cancer metastases typically go first to the liver then to the lung soon thereafter.

Surgical metastasectomy (sublobar; wedge or segmental resection) for patients with limited (a term not yet consistently defined) pulmonary metastases can yield 5-year OS of up to 60%[92-95].

However, ablation already is comparable to surgery for these patients: (1) RFA series of colorectal lung metastases have yielded 1-, 2- and 3-year survival rates of up to 95%, 72% and 57%, respectively[96-101]; (2) cryoablation, similarly, 1- and 3-year survival rates of 91% and 60%, respectively[102]; and (3) microwave ablation with 1- and 2-year survival rates of 91.3% and 75%[103].

Moreover, the goals of therapy must be kept in mind. Most of these patients are not candidates for cure, which means that repeated interventions will be necessary in the future. Repeat thoracotomies could be considered, but are technically challenging, expensive, carry risk of morbidity, and remove more normal lung tissue. Even so, if surgery is preferred, some patients will not be surgical candidates, especially if they have had previous lung resections, comorbid medical conditions, or even pulmonary toxicity from irinotecan, oxaliplatin, tyrosine kinase inhibitors, and monoclonal antibodies. Toxicity is not commonly reported but may increase as survival increases and patients undergo multiple lines of chemotherapy[104-107]. Although radiation therapy can be honed to a specific location (SABR; Stereotactic ABlative Radiotherapy), the toxicity of pulmonary fibrosis in the region can cause extensive morbidity with repeated infections and remains understudied. Furthermore, repeated thoracotomy and post-radiation thoracotomy (with fused tissue planes) are technically challenging procedures. Proponents of surgery indicate that palpation of the lung can detect nodules that are below the imaging threshold, however, the survival impact of "drive-by" resection of subclinical nodules newly detected at surgery has not yet been validated in the literature, nor has it been compared to simply following these nodules and ablating them later in this population, which is not curable and will likely need further interventions during survival. Percutaneous ablation can provide chemotherapy holidays of up to 20 mo in the setting of oligometastatic disease and close CT follow-up[100].

Compared to surgery, interventional percutaneous CT-guided ablation is fast, minimally invasive, preserves quality of life (can be done as an outpatient procedure), repeatable as necessary, does not interfere with chemotherapy, and has limited effects on pulmonary reserve and function. The lungs have natural properties that facilitate ablation, in that air is a natural thermal insulant (for heat or cold), the regional blood vessels are conspicuous without contrast enhancement, and the parenchymal background allows CT tracking of ablation volume.

For ablation of lung metastasis from colorectal cancer, RFA remains the most studied technique with local recurrence of 9% in a series by Lencioni *et al*[96]. Yan *et al*[97] reported a local recurrence rate of 38% but included more tumors of larger size, showing local PFS of approximately 74% at 1 year and 57% at 2 years. Technical factors do play a role in outcome, as carbonization has a more detrimental effect in the lungs. An oversized active zone relative to the tumor can cause charring of the adjacent lung penumbra, which can rapidly increase impedance and shut off certain RFA systems. This may lead to undertreatment of the tumor and therefore probe selection is paramount.

CONCLUSION

Patients with advanced mCRC are living longer than they did previously due to major advances in treatment. Next-generation systemic therapies, coupled with modern, minimally invasive percutaneous ablative and transcatheter angiographic treatments supported by forthcoming large clinical trials will define the new frontiers of management for patients with metastatic colon and rectum adenocarcinomas.

REFERENCES

1 **Siegel RL**, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015; **65**: 5-29 [PMID: 25559415 DOI: 10.3322/caac.21254]

2 **Li FY**, Lai MD. Colorectal cancer, one entity or three. *J Zhejiang Univ Sci B* 2009; **10**: 219-229 [PMID: 19283877 DOI: 10.1631/jzus.B0820273]

3 Centers for Disease Control and Prevention, National Center for Health Statistics. National Health Interview Surveys, 2000, 2013. Public use data files: 2001, 2014

4 **Gillams A**, Goldberg N, Ahmed M, Bale R, Breen D, Callstrom M, Chen MH, Choi BI, de Baere T, Dupuy D, Gangi A, Gervais D, Helmberger T, Jung EM, Lee F, Lencioni R, Liang P, Livraghi T, Lu D, Meloni F, Pereira P, Piscaglia F, Rhim H, Salem R, Sofocleous C, Solomon SB, Soulen M, Tanaka M, Vogl T, Wood B, Solbiati L. Thermal ablation of colorectal liver metastases: a position paper by an international panel of ablation experts, The Interventional Oncology Sans Frontières meeting 2013. *Eur Radiol* 2015; **25**: 3438-3454 [PMID: 25994193 DOI: 10.1007/s00330-015-3779-z]

5 **Almersjö O**, Bengmark S, Hafström L. Liver metastases found by follow-up of patients operated on for colorectal cancer. *Cancer* 1976; **37**: 1454-1457 [PMID: 4218]

6 **Bengmark S**, Hafström L. The natural history of primary and secondary malignant tumors of the liver. I. The prognosis for patients with hepatic metastases from colonic and rectal carcinoma by laparotomy. *Cancer* 1969; **23**: 198-202 [PMID: 5763253]

7 **Pawlik TM**, Choti MA. Surgical therapy for colorectal metastases

to the liver. *J Gastrointest Surg* 2007; **11**: 1057-1077 [PMID: 17530336 DOI: 10.1007/s11605-006-0061-3]
8 **Kemeny N**, Fata F. Arterial, portal, or systemic chemotherapy for patients with hepatic metastasis of colorectal carcinoma. *J Hepatobiliary Pancreat Surg* 1999; **6**: 39-49 [PMID: 10436236]
9 **Seifert JK**, Junginger T, Morris DL. A collective review of the world literature on hepatic cryotherapy. *J R Coll Surg Edinb* 1998; **43**: 141-154 [PMID: 9654872]
10 **Brouquet A**, Mortenson MM, Vauthey JN, Rodriguez-Bigas MA, Overman MJ, Chang GJ, Kopetz S, Garrett C, Curley SA, Abdalla EK. Surgical strategies for synchronous colorectal liver metastases in 156 consecutive patients: classic, combined or reverse strategy? *J Am Coll Surg* 2010; **210**: 934-941 [PMID: 20510802 DOI: 10.1016/j.jamcollsurg.2010.02.039]
11 **Bolton JS**, Fuhrman GM. Survival after resection of multiple bilobar hepatic metastases from colorectal carcinoma. *Ann Surg* 2000; **231**: 743-751 [PMID: 10767796]
12 **Reddy SK**, Pawlik TM, Zorzi D, Gleisner AL, Ribero D, Assumpcao L, Barbas AS, Abdalla EK, Choti MA, Vauthey JN, Ludwig KA, Mantyh CR, Morse MA, Clary BM. Simultaneous resections of colorectal cancer and synchronous liver metastases: a multi-institutional analysis. *Ann Surg Oncol* 2007; **14**: 3481-3491 [PMID: 17805933 DOI: 10.1245/s10434-007-9522-5]
13 **Tanaka K**, Shimada H, Matsuo K, Nagano Y, Endo I, Sekido H, Togo S. Outcome after simultaneous colorectal and hepatic resection for colorectal cancer with synchronous metastases. *Surgery* 2004; **136**: 650-659 [PMID: 15349115 DOI: 10.1016/j.surg.2004.02.012]
14 **Benoist S**, Brouquet A, Penna C, Julié C, El Hajjam M, Chagnon S, Mitry E, Rougier P, Nordlinger B. Complete response of colorectal liver metastases after chemotherapy: does it mean cure? *J Clin Oncol* 2006; **24**: 3939-3945 [PMID: 16921046 DOI: 10.1200/jco.2006.05.8727]
15 **Auer RC**, White RR, Kemeny NE, Schwartz LH, Shia J, Blumgart LH, Dematteo RP, Fong Y, Jarnagin WR, D'Angelica MI. Predictors of a true complete response among disappearing liver metastases from colorectal cancer after chemotherapy. *Cancer* 2010; **116**: 1502-1509 [PMID: 20120032 DOI: 10.1002/cncr.24912]
16 **Elias D**, Goere D, Boige V, Kohneh-Sharhi N, Malka D, Tomasic G, Dromain C, Ducreux M. Outcome of posthepatectomy-missing colorectal liver metastases after complete response to chemotherapy: impact of adjuvant intra-arterial hepatic oxaliplatin. *Ann Surg Oncol* 2007; **14**: 3188-3194 [PMID: 17705091 DOI: 10.1245/s10434-007-9482-9]
17 **Elias D**, Youssef O, Sideris L, Dromain C, Baton O, Boige V, Ducreux M. Evolution of missing colorectal liver metastases following inductive chemotherapy and hepatectomy. *J Surg Oncol* 2004; **86**: 4-9 [PMID: 15048673 DOI: 10.1002/jso.20039]
18 **Tanaka K**, Takakura H, Takeda K, Matsuo K, Nagano Y, Endo I. Importance of complete pathologic response to prehepatectomy chemotherapy in treating colorectal cancer metastases. *Ann Surg* 2009; **250**: 935-942 [PMID: 19953712]
19 **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**: 1691-1700 [PMID: 20839072 DOI: 10.1007/s11605-010-1348-y]
20 **Nordlinger B**, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, Bechstein WO, Primrose JN, Walpole ET, Finch-Jones M, Jaeck D, Mirza D, Parks RW, Collette L, Praet M, Bethe U, Van Cutsem E, Scheithauer W, Gruenberger T. 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**: 1007-1016 [PMID: 18358928 DOI: 10.1016/S0140-6736(08)60455-9]
21 **Folprecht G**, Gruenberger T, Bechstein W, Raab HR, Weitz J, Lordick F, Hartmann JT, Stoehlmacher-Williams J, Lang H, Trarbach T, Liersch T, Ockert D, Jaeger D, Steger U, Suedhoff T, Rentsch A, Köhne CH. Survival of patients with initially unresectable colorectal liver metastases treated with FOLFOX/cetuximab or FOLFIRI/cetuximab in a multidisciplinary concept (CELIM study). *Ann Oncol* 2014; **25**: 1018-1025 [PMID: 24585720 DOI: 10.1093/annonc/mdu088]
22 **Bokemeyer C**, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, de Braud F, Donea S, Ludwig H, Schuch G, Stroh C, Loos AH, Zubel A, Koralewski P. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2009; **27**: 663-671 [PMID: 19114683 DOI: 10.1200/JCO.2008.20.8397]
23 **Van Cutsem E**, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, D'Haens G, Pintér T, Lim R, Bodoky G, Roh JK, Folprecht G, Ruff P, Stroh C, Tejpar S, Schlichting M, Nippgen J, Rougier P. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009; **360**: 1408-1417 [PMID: 19339720 DOI: 10.1056/NEJMoa0805019]
24 **Ye LC**, Liu TS, Ren L, Wei Y, Zhu DX, Zai SY, Ye QH, Yu Y, Xu B, Qin XY, Xu J. Randomized controlled trial of cetuximab plus chemotherapy for patients with KRAS wild-type unresectable colorectal liver-limited metastases. *J Clin Oncol* 2013; **31**: 1931-1938 [PMID: 23569301 DOI: 10.1200/JCO.2012.44.8308]
25 **Van Cutsem E**, Siena S, Humblet Y, Canon JL, Maurel J, Bajetta E, Neyns B, Kotasek D, Santoro A, Scheithauer W, Spadafora S, Amado RG, Hogan N, Peeters M. An open-label, single-arm study assessing safety and efficacy of panitumumab in patients with metastatic colorectal cancer refractory to standard chemotherapy. *Ann Oncol* 2008; **19**: 92-98 [PMID: 17785764 DOI: 10.1093/annonc/mdm399]
26 **Amado RG**, Wolf M, Peeters M, Van Cutsem E, Siena S, Freeman DJ, Juan T, Sikorski R, Suggs S, Radinsky R, Patterson SD, Chang DD. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol* 2008; **26**: 1626-1634 [PMID: 18316791 DOI: 10.1200/jco.2007.14.7116]
27 **Rothenberg ML**, Oza AM, Bigelow RH, Berlin JD, Marshall JL, Ramanathan RK, Hart LL, Gupta S, Garay CA, Burger BG, Le Bail N, Haller DG. Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: interim results of a phase III trial. *J Clin Oncol* 2003; **21**: 2059-2069 [PMID: 12775730 DOI: 10.1200/jco.2003.11.126]
28 **de Gramont A**, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, Boni C, Cortes-Funes H, Cervantes A, Freyer G, Papamichael D, Le Bail N, Louvet C, Hendler D, de Braud F, Wilson C, Morvan F, Bonetti A. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000; **18**: 2938-2947 [PMID: 10944126]
29 **Grothey A**, Deschler, B., Kroening, H. Phase III study of bolus 5-fluorouracil (5-FU)/folinic acid (FA) (Mayo) vs weekly high-dose 24h 5-FU infusion/FA oxaliplatin in advanced colorectal cancer. *Proc Am Soc Clin Oncol* 2002; **21**: 129a (abstr 512)
30 **Giacchetti S**, Perpoint B, Zidani R, Le Bail N, Faggiuolo R, Focan C, Chollet P, Llory JF, Letourneau Y, Coudert B, Bertheaut-Cvitkovic F, Larregain-Fournier D, Le Rol A, Walter S, Adam R, Misset JL, Lévi F. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. Linchuang *Zhongliu Zazhi* 2000; **18**: 136-147
31 **Douillard JY**, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, Jandik P, Iveson T, Carmichael J, Alakl M, Gruia G, Awad L, Rougier P. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000; **355**: 1041-1047 [PMID: 10744089]

32 **Hoff PM**, Ansari R, Batist G, Cox J, Kocha W, Kuperminc M, Maroun J, Walde D, Weaver C, Harrison E, Burger HU, Osterwalder B, Wong AO, Wong R. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. *J Clin Oncol* 2001; **19**: 2282-2292 [PMID: 11304782]

33 **Van Cutsem E**, Twelves C, Cassidy J, Allman D, Bajetta E, Boyer M, Bugat R, Findlay M, Frings S, Jahn M, McKendrick J, Osterwalder B, Perez-Manga G, Rosso R, Rougier P, Schmiegel WH, Seitz JF, Thompson P, Vieitez JM, Weitzel C, Harper P. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. *J Clin Oncol* 2001; **19**: 4097-4106 [PMID: 11689577]

34 **Muro K**, Boku N, Shimada Y, Tsuji A, Sameshima S, Baba H, Satoh T, Denda T, Ina K, Nishina T, Yamaguchi K, Takiuchi H, Esaki T, Tokunaga S, Kuwano H, Komatsu Y, Watanabe M, Hyodo I, Morita S, Sugihara K. Irinotecan plus S-1 (IRIS) versus fluorouracil and folinic acid plus irinotecan (FOLFIRI) as second-line chemotherapy for metastatic colorectal cancer: a randomised phase 2/3 non-inferiority study (FIRIS study). *Lancet Oncol* 2010; **11**: 853-860 [PMID: 20708966 DOI: 10.1016/s1470-2045(10)70181-9]

35 **Guo Y**, Shi M, Shen X, Yang C, Yang L, Zhang J. Capecitabine plus irinotecan versus 5-FU/leucovorin plus irinotecan in the treatment of colorectal cancer: a meta-analysis. *Clin Colorectal Cancer* 2014; **13**: 110-118 [PMID: 24461997 DOI: 10.1016/j.clcc.2013.12.004]

36 **Van Cutsem E**, Tabernero J, Lakomy R, Prenen H, Prausová J, Macarulla T, Ruff P, van Hazel GA, Moiseyenko V, Ferry D, McKendrick J, Polikoff J, Tellier A, Castan R, Allegra C. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol* 2012; **30**: 3499-3506 [PMID: 22949147 DOI: 10.1200/jco.2012.42.8201]

37 **Bennouna J**, Sastre J, Arnold D, Österlund P, Greil R, Van Cutsem E, von Moos R, Viéitez JM, Bouché O, Borg C, Steffens CC, Alonso-Orduña V, Schlichting C, Reyes-Rivera I, Bendahmane B, André T, Kubicka S. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol* 2013; **14**: 29-37 [PMID: 23168366 DOI: 10.1016/s1470-2045(12)70477-1]

38 **Grothey A**, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, Humblet Y, Bouché O, Mineur L, Barone C, Adenis A, Tabernero J, Yoshino T, Lenz HJ, Goldberg RM, Sargent DJ, Cihon F, Cupit L, Wagner A, Laurent D. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013; **381**: 303-312 [PMID: 23177514 DOI: 10.1016/s0140-6736(12)61900-x]

39 **Kopetz S**, Chang GJ, Overman MJ, Eng C, Sargent DJ, Larson DW, Grothey A, Vauthey JN, Nagorney DM, McWilliams RR. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. *J Clin Oncol* 2009; **27**: 3677-3683 [PMID: 19470929 DOI: 10.1200/jco.2008.20.5278]

40 **Sobrero AF**, Maurel J, Fehrenbacher L, Scheithauer W, Abubakr YA, Lutz MP, Vega-Villegas ME, Eng C, Steinhauer EU, Prausova J, Lenz HJ, Borg C, Middleton G, Kröning H, Luppi G, Kisker O, Zubel A, Langer C, Kopit J, Burris HA. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. *J Clin Oncol* 2008; **26**: 2311-2319 [PMID: 18390971 DOI: 10.1200/jco.2007.13.1193]

41 **Damjanov N**, Weiss J, Haller DG. Resection of the primary colorectal cancer is not necessary in nonobstructed patients with metastatic disease. *Oncologist* 2009; **14**: 963-969 [PMID: 19819916 DOI: 10.1634/theoncologist.2009-0022]

42 **Poultsides GA**, Servais EL, Saltz LB, Patil S, Kemeny NE, Guillem JG, Weiser M, Temple LK, Wong WD, Paty PB. Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment. *J Clin Oncol* 2009; **27**: 3379-3384 [PMID: 19487380 DOI: 10.1200/jco.2008.20.9817]

43 **Liccioni A**, Reig M, Bruix J. Treatment of hepatocellular carcinoma. *Dig Dis* 2014; **32**: 554-563 [PMID: 25034288 DOI: 10.1159/000360501]

44 **Livraghi T**, Solbiati L, Meloni F, Ierace T, Goldberg SN, Gazelle GS. Percutaneous radiofrequency ablation of liver metastases in potential candidates for resection: the "test-of-time approach". *Cancer* 2003; **97**: 3027-3035 [PMID: 12784338 DOI: 10.1002/cncr.11426]

45 **Fujisawa S**, Romin Y, Barlas A, Petrovic LM, Turkekul M, Fan N, Xu K, Garcia AR, Monette S, Klimstra DS, Erinjeri JP, Solomon SB, Manova-Todorova K, Sofocleous CT. Evaluation of YO-PRO-1 as an early marker of apoptosis following radiofrequency ablation of colon cancer liver metastases. *Cytotechnology* 2014; **66**: 259-273 [PMID: 24065619 DOI: 10.1007/s10616-013-9565-3]

46 **Makino Y**, Imai Y, Igura T, Hori M, Fukuda K, Sawai Y, Kogita S, Fujita N, Takehara T, Murakami T. Comparative evaluation of three-dimensional Gd-EOB-DTPA-enhanced MR fusion imaging with CT fusion imaging in the assessment of treatment effect of radiofrequency ablation of hepatocellular carcinoma. *Abdom Imaging* 2015; **40**: 102-111 [PMID: 25052767 DOI: 10.1007/s00261-014-0201-2]

47 **Rempp H**, Clasen S, Pereira PL. Image-based monitoring of magnetic resonance-guided thermoablative therapies for liver tumors. *Cardiovasc Intervent Radiol* 2012; **35**: 1281-1294 [PMID: 21785888 DOI: 10.1007/s00270-011-0227-6]

48 **Mauri G**, Porazzi E, Cova L, Restelli U, Tondolo T, Bonfanti M, Cerri A, Ierace T, Croce D, Solbiati L. Intraprocedural contrast-enhanced ultrasound (CEUS) in liver percutaneous radiofrequency ablation: clinical impact and health technology assessment. *Insights Imaging* 2014; **5**: 209-216 [PMID: 24563244 DOI: 10.1007/s13244-014-0315-7]

49 **Olaf Dössel WCS**. IFMBE Proceedings, World Congress on Medical Physics and Biomedical Engineering 7-12 September, 2009 Munich Germany. Surgery, Minimal Invasive Interventions, Endoscopy, and IMage Guided Therapy, 2009: Volume 25/6

50 **Shyn PB**, Tatli S, Sahni VA, Sadow CA, Forgione K, Mauri G, Morrison PR, Catalano PJ, Silverman SG. PET/CT-guided percutaneous liver mass biopsies and ablations: targeting accuracy of a single 20 s breath-hold PET acquisition. *Clin Radiol* 2014; **69**: 410-415 [PMID: 24411824 DOI: 10.1016/j.crad.2013.11.013]

51 **Mauri G**, Cova L, De Beni S, Ierace T, Tondolo T, Cerri A, Goldberg SN, Solbiati L. Real-time US-CT/MRI image fusion for guidance of thermal ablation of liver tumors undetectable with US: results in 295 cases. *Cardiovasc Intervent Radiol* 2015; **38**: 143-151 [PMID: 24806953 DOI: 10.1007/s00270-014-0897-y]

52 **Bale R**, Widmann G, Schullian P, Haidu M, Pall G, Klaus A, Weiss H, Biebl M, Margreiter R. Percutaneous stereotactic radiofrequency ablation of colorectal liver metastases. *Eur Radiol* 2012; **22**: 930-937 [PMID: 22071776 DOI: 10.1007/s00330-011-2314-0]

53 **Gillams AR**, Lees WR. Radio-frequency ablation of colorectal liver metastases in 167 patients. *Eur Radiol* 2004; **14**: 2261-2267 [PMID: 15599547 DOI: 10.1007/s00330-004-2416-z]

54 **Devun F**, Biau J, Huerre M, Croset A, Sun JS, Denys A, Dutreix M. Colorectal cancer metastasis: the DNA repair inhibitor Dbait increases sensitivity to hyperthermia and improves efficacy of radiofrequency ablation. *Radiology* 2014; **270**: 736-746 [PMID: 24475822 DOI: 10.1148/radiol.13130805]

55 **Sag AA**, Maybody M, Comstock C, Solomon SB. Percutaneous

image-guided ablation of breast tumors: an overview. *Semin Intervent Radiol* 2014; **31**: 193-202 [PMID: 25049447 DOI: 10.1055/s-0034-1376159]

56 **Erinjeri JP**, Clark TW. Cryoablation: mechanism of action and devices. *J Vasc Interv Radiol* 2010; **21**: S187-S191 [PMID: 20656228 DOI: 10.1016/j.jvir.2009.12.403]

57 **Maybody M**. An overview of image-guided percutaneous ablation of renal tumors. *Semin Intervent Radiol* 2010; **27**: 261-267 [PMID: 22550365 DOI: 10.1055/s-0030-1261784]

58 **Groeschl RT**, Pilgrim CH, Hanna EM, Simo KA, Swan RZ, Sindram D, Martinie JB, Iannitti DA, Bloomston M, Schmidt C, Khabiri H, Shirley LA, Martin RC, Tsai S, Turaga KK, Christians KK, Rilling WS, Gamblin TC. Microwave ablation for hepatic malignancies: a multiinstitutional analysis. *Ann Surg* 2014; **259**: 1195-1200 [PMID: 24096760 DOI: 10.1097/sla.0000000000000234]

59 **Shibata T**, Niinobu T, Ogata N, Takami M. Microwave coagulation therapy for multiple hepatic metastases from colorectal carcinoma. *Cancer* 2000; **89**: 276-284 [PMID: 10918156]

60 **Cannon R**, Ellis S, Hayes D, Narayanan G, Martin RC. Safety and early efficacy of irreversible electroporation for hepatic tumors in proximity to vital structures. *J Surg Oncol* 2013; **107**: 544-549 [PMID: 23090720 DOI: 10.1002/jso.23280]

61 **Kingham TP**, Karkar AM, D'Angelica MI, Allen PJ, Dematteo RP, Getrajdman GI, Sofocleous CT, Solomon SB, Jarnagin WR, Fong Y. Ablation of perivascular hepatic malignant tumors with irreversible electroporation. *J Am Coll Surg* 2012; **215**: 379-387 [PMID: 22704820 DOI: 10.1016/j.jamcollsurg.2012.04.029]

62 **Silk MT**, Wimmer T, Lee KS, Srimathveeravalli G, Brown KT, Kingham PT, Fong Y, Durack JC, Sofocleous CT, Solomon SB. Percutaneous ablation of peribiliary tumors with irreversible electroporation. *J Vasc Interv Radiol* 2014; **25**: 112-118 [PMID: 24262034 DOI: 10.1016/j.jvir.2013.10.012]

63 **Thomson KR**, Cheung W, Ellis SJ, Federman D, Kavnoudias H, Loader-Oliver D, Roberts S, Evans P, Ball C, Haydon A. Investigation of the safety of irreversible electroporation in humans. *J Vasc Interv Radiol* 2011; **22**: 611-621 [PMID: 21439847 DOI: 10.1016/j.jvir.2010.12.014]

64 **Erinjeri JP**, Thomas CT, Samoilia A, Fleisher M, Gonen M, Sofocleous CT, Thornton RH, Siegelbaum RH, Covey AM, Brody LA, Alago W, Maybody M, Brown KT, Getrajdman GI, Solomon SB. Image-guided thermal ablation of tumors increases the plasma level of interleukin-6 and interleukin-10. *J Vasc Interv Radiol* 2013; **24**: 1105-1112 [PMID: 23582441 DOI: 10.1016/j.jvir.2013.02.015]

65 **Ryan ER**, Sofocleous CT, Schöder H, Carrasquillo JA, Nehmeh S, Larson SM, Thornton R, Siegelbaum RH, Erinjeri JP, Solomon SB. Split-dose technique for FDG PET/CT-guided percutaneous ablation: a method to facilitate lesion targeting and to provide immediate assessment of treatment effectiveness. *Radiology* 2013; **268**: 288-295 [PMID: 23564714 DOI: 10.1148/radiol.13121462]

66 **Maybody M**, Stevenson C, Solomon SB. Overview of navigation systems in image-guided interventions. *Tech Vasc Interv Radiol* 2013; **16**: 136-143 [PMID: 23993075 DOI: 10.1053/j.tvir.2013.02.008]

67 **Elnekave E**, Erinjeri JP, Brown KT, Thornton RH, Petre EN, Maybody M, Maluccio MA, Hsu M, Sofocleous CT, Getrajdman GI, Brody LA, Solomon SB, Alago W, Fong Y, Jarnagin WR, Covey AM. Long-term outcomes comparing surgery to embolization-ablation for treatment of solitary HCC& lt; 7 cm. *Ann Surg Oncol* 2013; **20**: 2881-2886 [PMID: 23563960 DOI: 10.1245/s10434-013-2961-2]

68 Long-term results of single course of adjuvant intraportal chemotherapy for colorectal cancer. Swiss Group for Clinical Cancer Research (SAKK). *Lancet* 1995; **345**: 349-353 [PMID: 7845115]

69 **Laffer U**, Metzger U, Aeberhard P, Lorenz M, Harder F, Maibach R, Zuber M, Herrmann R. Adjuvant perioperative portal vein or peripheral intravenous chemotherapy for potentially curative colorectal cancer: long-term results of a randomized controlled trial. *Int J Colorectal Dis* 2008; **23**: 1233-1241 [PMID: 18688620 DOI: 10.1007/s00384-008-0543-8]

70 **Erinjeri JP**, Salhab HM, Covey AM, Getrajdman GI, Brown KT. Arterial patency after repeated hepatic artery bland particle embolization. *J Vasc Interv Radiol* 2010; **21**: 522-526 [PMID: 20188589 DOI: 10.1016/j.jvir.2009.12.390]

71 **Tanaka T**, Nishiofuku H, Maeda S, Masada T, Anai H, Sakaguchi H, Kichikawa K. Repeated bland-TAE using small microspheres injected via an implantable port-catheter system for liver metastases: an initial experience. *Cardiovasc Intervent Radiol* 2014; **37**: 493-497 [PMID: 23839008 DOI: 10.1007/s00270-013-0691-2]

72 **Tanaka T**, Isfort P, Braunschweig T, Westphal S, Woitok A, Penzkofer T, Bruners P, Kichikawa K, Schmitz-Rode T, Mahnken AH. Superselective particle embolization enhances efficacy of radiofrequency ablation: effects of particle size and sequence of action. *Cardiovasc Intervent Radiol* 2013; **36**: 773-782 [PMID: 23070107 DOI: 10.1007/s00270-012-0497-7]

73 **Kruskal JB**, Hlatky L, Hahnfeldt P, Teramoto K, Stokes KR, Clouse ME. In vivo and in vitro analysis of the effectiveness of doxorubicin combined with temporary arterial occlusion in liver tumors. *J Vasc Interv Radiol* 1993; **4**: 741-747 [PMID: 8280994]

74 **Lo CM**, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, Fan ST, Wong J. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002; **35**: 1164-1171 [PMID: 11981766 DOI: 10.1053/jhep.2002.33156]

75 **Llovet JM**, Real MI, Montaña X, Planas R, Coll S, Aponte J, Ayuso C, Sala M, Muchart J, Solà R, Rodés J, Bruix J. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002; **359**: 1734-1739 [PMID: 12049862 DOI: 10.1016/s0140-6736(02)08649-x]

76 **Taylor RR**, Tang Y, Gonzalez MV, Stratford PW, Lewis AL. Irinotecan drug eluting beads for use in chemoembolization: in vitro and in vivo evaluation of drug release properties. *Eur J Pharm Sci* 2007; **30**: 7-14 [PMID: 17030118 DOI: 10.1016/j.ejps.2006.09.002]

77 **Albert M**, Kiefer MV, Sun W, Haller D, Fraker DL, Tuite CM, Stavropoulos SW, Mondschein JI, Soulen MC. Chemoembolization of colorectal liver metastases with cisplatin, doxorubicin, mitomycin C, ethiodol, and polyvinyl alcohol. *Cancer* 2011; **117**: 343-352 [PMID: 20830766 DOI: 10.1002/cncr.25387]

78 **Aliberti C**, Tilli M, Benea G, Fiorentini G. Trans-arterial chemoembolization (TACE) of liver metastases from colorectal cancer using irinotecan-eluting beads: preliminary results. *Anticancer Res* 2006; **26**: 3793-3795 [PMID: 17094403]

79 **Fiorentini G**, Aliberti C, Tilli M, Mulazzani L, Graziano F, Giordani P, Mambrini A, Montagnani F, Alessandroni P, Catalano V, Coschiera P. 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 [PMID: 22493375]

80 **Martin RC**, Howard J, Tomalty D, Robbins K, Padr R, Bosnjakovic PM, Tatum C. Toxicity of irinotecan-eluting beads in the treatment of hepatic malignancies: results of a multi-institutional registry. *Cardiovasc Intervent Radiol* 2010; **33**: 960-966 [PMID: 20661569 DOI: 10.1007/s00270-010-9937-4]

81 **Tellez C**, Benson AB, Lyster MT, Talamonti M, Shaw J, Braun MA, Nemcek AA, Vogelzang RL. Phase II trial of chemoembolization for the treatment of metastatic colorectal carcinoma to the liver and review of the literature. *Cancer* 1998; **82**: 1250-1259 [PMID: 9529016]

82 **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. *Radiology* 2009; **250**: 281-289 [PMID: 19092099 DOI: 10.1148/radiol.2501080295]

83 **Iezzi R**, Marsico VA, Guerra A, Cerchiaro E, Cassano A, Basso M, Devicienti E, Rodolfino E, Barone C, Bonomo L. Trans-Arterial Chemoembolization with Irinotecan-Loaded Drug-Eluting Beads (DEBIRI) and Capecitabine in Refractory Liver Prevalent Colorectal Metastases: A Phase II Single-Center Study. *Cardiovasc Intervent Radiol* 2015; **38**: 1523-1531 [PMID: 25799948 DOI: 10.1007/s00270-015-1080-9]

84 **Reddy SK**, Kesmodel SB, Alexander HR. Isolated hepatic perfusion for patients with liver metastases. *Ther Adv Med Oncol* 2014; **6**: 180-194 [PMID: 25057304 DOI: 10.1177/1758834014529175]

85 **Kennedy A**. Radioembolization of hepatic tumors. *J Gastrointest Oncol* 2014; **5**: 178-189 [PMID: 24982766 DOI: 10.3978/j.issn.2078-6891.2014.037]

86 **Kennedy AS**, Coldwell D, Nutting C, Murthy R, Wertman DE, Loehr SP, Overton C, Meranze S, Niedzwiecki J, Sailer S. Resin 90Y-microsphere brachytherapy for unresectable colorectal liver metastases: modern USA experience. *Int J Radiat Oncol Biol Phys* 2006; **65**: 412-425 [PMID: 16690429 DOI: 10.1016/j.ijrobp.2005.12.051]

87 **Gray B**, Van Hazel G, Hope M, Burton M, Moroz P, Anderson J, Gebski V. 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**: 1711-1720 [PMID: 11843249]

88 **Sag AA**, Savin MA, Lal NR, Mehta RR. Yttrium-90 radioembolization of malignant tumors of the liver: gallbladder effects. *AJR Am J Roentgenol* 2014; **202**: 1130-1135 [PMID: 24758670 DOI: 10.2214/AJR.13.10548]

89 **Atassi B**, Bangash AK, Lewandowski RJ, Ibrahim S, Kulik L, Mulcahy MF, Murthy R, Ryu RK, Sato KT, Miller FH, Omary RA, Salem R. Biliary sequelae following radioembolization with Yttrium-90 microspheres. *J Vasc Interv Radiol* 2008; **19**: 691-697 [PMID: 18440457 DOI: 10.1016/j.jvir.2008.01.003]

90 **Van Hazel G**, Blackwell A, Anderson J, Price D, Moroz P, Bower G, Cardaci G, Gray B. Randomised phase 2 trial of SIR-Spheres plus fluorouracil/leucovorin chemotherapy versus fluorouracil/leucovorin chemotherapy alone in advanced colorectal cancer. *J Surg Oncol* 2004; **88**: 78-85 [PMID: 15499601 DOI: 10.1002/jso.20141]

91 **Fong Y**, Kim T, Bhargava A, Schwartz L, Brown K, Brody L, Covey A, Karrasch M, Getrajdman G, Mescheder A, Jarnagin W, Kemeny N. A herpes oncolytic virus can be delivered via the vasculature to produce biologic changes in human colorectal cancer. *Mol Ther* 2009; **17**: 389-394 [PMID: 19018254 DOI: 10.1038/mt.2008.240]

92 **Mori M**, Tomoda H, Ishida T, Kido A, Shimono R, Matsushima T, Kuwano H, Sugimachi K. Surgical resection of pulmonary metastases from colorectal adenocarcinoma. Special reference to repeated pulmonary resections. *Arch Surg* 1991; **126**: 1297-1301; discussion 1302 [PMID: 1929833]

93 **Pastorino U**, Buyse M, Friedel G, Ginsberg RJ, Girard P, Goldstraw P, Johnston M, McCormack P, Pass H, Putnam JB. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. *J Thorac Cardiovasc Surg* 1997; **113**: 37-49 [PMID: 9011700]

94 **Saito Y**, Omiya H, Kohno K, Kobayashi T, Itoi K, Teramachi M, Sasaki M, Suzuki H, Takao H, Nakade M. Pulmonary metastasectomy for 165 patients with colorectal carcinoma: A prognostic assessment. *J Thorac Cardiovasc Surg* 2002; **124**: 1007-1013 [PMID: 12407386 DOI: 10.1067/mtc.2002.125165]

95 **Watanabe K**, Nagai K, Kobayashi A, Sugito M, Saito N. Factors influencing survival after complete resection of pulmonary metastases from colorectal cancer. *Br J Surg* 2009; **96**: 1058-1065 [PMID: 19672932 DOI: 10.1002/bjs.6682]

96 **Lencioni R**, Crocetti L, Cioni R, Suh R, Glenn D, Regge D, Helmberger T, Gillams AR, Frilling A, Ambrogi M, Bartolozzi C, Mussi A. Response to radiofrequency ablation of pulmonary tumours: a prospective, intention-to-treat, multicentre clinical trial (the RAPTURE study). *Lancet Oncol* 2008; **9**: 621-628 [PMID: 18565793 DOI: 10.1016/S1470-2045(08)70155-4]

97 **Yan TD**, King J, Sjarif A, Glenn D, Steinke K, Al-Kindy A, Morris DL. Treatment failure after percutaneous radiofrequency ablation for nonsurgical candidates with pulmonary metastases from colorectal carcinoma. *Ann Surg Oncol* 2007; **14**: 1718-1726 [PMID: 17285398 DOI: 10.1245/s10434-006-9271-x]

98 **Gillams A**, Khan Z, Osborn P, Lees W. Survival after radiofrequency ablation in 122 patients with inoperable colorectal lung metastases. *Cardiovasc Intervent Radiol* 2013; **36**: 724-730 [PMID: 23070108 DOI: 10.1007/s00270-012-0500-3]

99 **Hiraki T**, Gobara H, Iishi T, Sano Y, Iguchi T, Fujiwara H, Tajiri N, Sakurai J, Date H, Mimura H, Kanazawa S. Percutaneous radiofrequency ablation for pulmonary metastases from colorectal cancer: midterm results in 27 patients. *J Vasc Interv Radiol* 2007; **18**: 1264-1269 [PMID: 17911517 DOI: 10.1016/j.jvir.2007.06.027]

100 **Petre EN**, Jia X, Thornton RH, Sofocleous CT, Alago W, Kemeny NE, Solomon SB. Treatment of pulmonary colorectal metastases by radiofrequency ablation. *Clin Colorectal Cancer* 2013; **12**: 37-44 [PMID: 23026111 DOI: 10.1016/j.clcc.2012.07.003]

101 **Yamakado K**, Hase S, Matsuoka T, Tanigawa N, Nakatsuka A, Takaki H, Takao M, Inoue Y, Kanazawa S, Inoue Y, Sawada S, Kusunoki M, Takeda K. Radiofrequency ablation for the treatment of unresectable lung metastases in patients with colorectal cancer: a multicenter study in Japan. *J Vasc Interv Radiol* 2007; **18**: 393-398 [PMID: 17377185 DOI: 10.1016/j.jvir.2006.11.003]

102 **Yamauchi Y**, Izumi Y, Kawamura M, Nakatsuka S, Yashiro H, Tsukada N, Inoue M, Asakura K, Nomori H. Percutaneous cryoablation of pulmonary metastases from colorectal cancer. *PLoS One* 2011; **6**: e27086 [PMID: 22096520 DOI: 10.1371/journal.pone.0027086]

103 **Vogl TJ**, Naguib NN, Gruber-Rouh T, Koitka K, Lehnert T, Nour-Eldin NE. Microwave ablation therapy: clinical utility in treatment of pulmonary metastases. *Radiology* 2011; **261**: 643-651 [PMID: 22012906 DOI: 10.1148/radiol.11101643]

104 **Shah A**, Udwadia ZF, Almel S. Oxaliplatin-induced lung fibrosis. *Indian J Med Paediatr Oncol* 2009; **30**: 116-118 [PMID: 20838550 DOI: 10.4103/0971-5851.64259]

105 **Chan AK**, Choo BA, Glaholm J. Pulmonary toxicity with oxaliplatin and capecitabine/5-Fluorouracil chemotherapy: a case report and review of the literature. *Onkologie* 2011; **34**: 443-446 [PMID: 21934344 DOI: 10.1159/000331133]

106 **Shimura T**, Fuse N, Yoshino T, Minashi K, Tahara M, Doi T, Joh T, Ohtsu A. Clinical features of interstitial lung disease induced by standard chemotherapy (FOLFOX or FOLFIRI) for colorectal cancer. *Ann Oncol* 2010; **21**: 2005-2010 [PMID: 20305036 DOI: 10.1093/annonc/mdq061]

107 **Dimopoulou I**, Bamias A, Lyberopoulos P, Dimopoulos MA. Pulmonary toxicity from novel antineoplastic agents. *Ann Oncol* 2006; **17**: 372-379 [PMID: 16291774 DOI: 10.1093/annonc/mdj057]

108 **Hildebrand P**, Kleemann M, Roblick UJ, Mirow L, Birth M, Leibecke T, Bruch HP. Radiofrequency-ablation of unresectable primary and secondary liver tumors: results in 88 patients. *Langenbecks Arch Surg* 2006; **391**: 118-123 [PMID: 16604376 DOI: 10.1007/s00423-006-0024-x]

109 **Siperstein AE**, Berber E, Ballem N, Parikh RT. Survival after radiofrequency ablation of colorectal liver metastases: 10-year experience. *Ann Surg* 2007; **246**: 559-565; discussion 565-567 [PMID: 17893492 DOI: 10.1097/SLA.0b013e318155a7b6]

110 **Berber E**, Tsinberg M, Tellioglu G, Simpfendorfer CH, Siperstein AE. Resection versus laparoscopic radiofrequency thermal ablation

of solitary colorectal liver metastasis. *J Gastrointest Surg* 2008; **12**: 1967-1972 [PMID: 18688683 DOI: 10.1007/s11605-008-0622-8]

111 **Veltri A**, Sacchetto P, Tosetti I, Pagano E, Fava C, Gandini G. Radiofrequency ablation of colorectal liver metastases: small size favorably predicts technique effectiveness and survival. *Cardiovasc Intervent Radiol* 2008; **31**: 948-956 [PMID: 18506519 DOI: 10.1007/s00270-008-9362-0]

112 **Gleisner AL**, Choti MA, Assumpcao L, Nathan H, Schulick RD, Pawlik TM. Colorectal liver metastases: recurrence and survival following hepatic resection, radiofrequency ablation, and combined resection-radiofrequency ablation. *Arch Surg* 2008; **143**: 1204-1212 [PMID: 19075173 DOI: 10.1001/archsurg.143.12.1204]

113 **Gillams AR**, Lees WR. Five-year survival in 309 patients with colorectal liver metastases treated with radiofrequency ablation. *Eur Radiol* 2009; **19**: 1206-1213 [PMID: 19137310 DOI: 10.1007/s00330-008-1258-5]

114 **Sofocleous CT**, Petre EN, Gonen M, Brown KT, Solomon SB, Covey AM, Alago W, Brody LA, Thornton RH, D'Angelica M, Fong Y, Kemeny NE. CT-guided radiofrequency ablation as a salvage treatment of colorectal cancer hepatic metastases developing after hepatectomy. *J Vasc Interv Radiol* 2011; **22**: 755-761 [PMID: 21514841 DOI: 10.1016/j.jvir.2011.01.451]

115 **Solbiati L**, Ahmed M, Cova L, Ierace T, Brioschi M, Goldberg SN. Small liver colorectal metastases treated with percutaneous radiofrequency ablation: local response rate and long-term survival with up to 10-year follow-up. *Radiology* 2012; **265**: 958-968 [PMID: 23091175 DOI: 10.1148/radiol.12111851]

116 **Hamada A**, Yamakado K, Nakatsuka A, Uraki J, Kashima M, Takaki H, Yamanaka T, Inoue Y, Kusunoki M, Takeda K. Radiofrequency ablation for colorectal liver metastases: prognostic factors in non-surgical candidates. *Jpn J Radiol* 2012; **30**: 567-574 [PMID: 22664831 DOI: 10.1007/s11604-012-0089-0]

117 **Rivoire M**, De Cian F, Meeus P, Négrier S, Sebban H, Kaemmerlen P. Combination of neoadjuvant chemotherapy with cryotherapy and surgical resection for the treatment of unresectable liver metastases from colorectal carcinoma. *Cancer* 2002; **95**: 2283-2292 [PMID: 12436433 DOI: 10.1002/cncr.10973]

118 **Yan DB**, Clingan P, Morris DL. Hepatic cryotherapy and regional chemotherapy with or without resection for liver metastases from colorectal carcinoma: how many are too many? *Cancer* 2003; **98**: 320-330 [PMID: 12872352 DOI: 10.1002/cncr.11498]

119 **Brooks AJ**, Wang F, Alfredson M, Yan TD, Morris DL. Synchronous liver resection and cryotherapy for colorectal metastases: survival analysis. *Surgeon* 2005; **3**: 265-268 [PMID: 16121772]

120 **Niu R**, Yan TD, Zhu JC, Black D, Chu F, Morris DL. Recurrence and survival outcomes after hepatic resection with or without cryotherapy for liver metastases from colorectal carcinoma. *Ann Surg Oncol* 2007; **14**: 2078-2087 [PMID: 17473951 DOI: 10.1245/s10434-007-9400-1]

121 **Paganini AM**, Rotundo A, Barchetti L, Lezoche E. Cryosurgical ablation of hepatic colorectal metastases. *Surg Oncol* 2007; **16** Suppl 1: S137-S140 [PMID: 18055196 DOI: 10.1016/j.suronc.2007.10.031]

122 **Ng KM**, Chua TC, Saxena A, Zhao J, Chu F, Morris DL. Two decades of experience with hepatic cryotherapy for advanced colorectal metastases. *Ann Surg Oncol* 2012; **19**: 1276-1283 [PMID: 21913018 DOI: 10.1245/s10434-011-2025-4]

123 **Shyn PB**, Mauri G, Alencar RO, Tatli S, Shah SH, Morrison PR, Catalano PJ, Silverman SG. Percutaneous imaging-guided cryoablation of liver tumors: predicting local progression on 24-hour MRI. *AJR Am J Roentgenol* 2014; **203**: W181-W191 [PMID: 24555531 DOI: 10.2214/ajr.13.10747]

124 **Liang P**, Dong B, Yu X, Yang Y, Yu D, Su L, Xiao Q, Sheng L. Prognostic factors for percutaneous microwave coagulation therapy of hepatic metastases. *AJR Am J Roentgenol* 2003; **181**: 1319-1325 [PMID: 14573427 DOI: 10.2214/ajr.181.5.1811319]

125 **Tanaka K**, Shimada H, Nagano Y, Endo I, Sekido H, Togo S. Outcome after hepatic resection versus combined resection and microwave ablation for multiple bilobar colorectal metastases to the liver. *Surgery* 2006; **139**: 263-273 [PMID: 16455336 DOI: 10.1016/j.surg.2005.07.036]

126 **Lang EK**, Brown CL. Colorectal metastases to the liver: selective chemoembolization. *Radiology* 1993; **189**: 417-422 [PMID: 8210369 DOI: 10.1148/radiology.189.2.8210369]

127 **Hong K**, McBride JD, Georgiades CS, Reyes DK, Herman JM, Kamel IR, Geschwind JF. Salvage therapy for liver-dominant colorectal metastatic adenocarcinoma: comparison between transcatheter arterial chemoembolization versus yttrium-90 radioembolization. *J Vasc Interv Radiol* 2009; **20**: 360-367 [PMID: 19167245 DOI: 10.1016/j.jvir.2008.11.019]

128 **Martin RC**, Joshi J, Robbins K, Tomalty D, Bosnjakovik P, Derner M, Padr R, Rocek M, Scupchenko A, Tatum C. Hepatic intra-arterial injection of drug-eluting bead, irinotecan (DEBIRI) in unresectable colorectal liver metastases refractory to systemic chemotherapy: results of multi-institutional study. *Ann Surg Oncol* 2011; **18**: 192-198 [PMID: 20740319 DOI: 10.1245/s10434-010-1288-5]

129 **Narayanan G**, Barbery K, Suthar R, Guerrero G, Arora G. Transarterial chemoembolization using DEBIRI for treatment of hepatic metastases from colorectal cancer. *Anticancer Res* 2013; **33**: 2077-2083 [PMID: 23645758]

130 **Sharma RA**, Van Hazel GA, Morgan B, Berry DP, Blanshard K, Price D, Bower G, Shannon JA, Gibbs P, Steward WP. Radioembolization of liver metastases from colorectal cancer using yttrium-90 microspheres with concomitant systemic oxaliplatin, fluorouracil, and leucovorin chemotherapy. *J Clin Oncol* 2007; **25**: 1099-1106 [PMID: 17369573 DOI: 10.1200/JCO.2006.08.7916]

131 **Benson AB**, Geschwind JF, Mulcahy MF, Rilling W, Siskin G, Wiseman G, Cunningham J, Houghton B, Ross M, Memon K, Andrews J, Fleming CJ, Herman J, Nimeiri H, Lewandowski RJ, Salem R. Radioembolisation for liver metastases: results from a prospective 151 patient multi-institutional phase II study. *Eur J Cancer* 2013; **49**: 3122-3130 [PMID: 23777743 DOI: 10.1016/j.ejca.2013.05.012]

132 **Lewandowski RJ**, Memon K, Mulcahy MF, Hickey R, Marshall K, Williams M, Salzig K, Gates VL, Atassi B, Vouche M, Atassi R, Desai K, Hohlastos E, Sato K, Habib A, Kircher S, Newman SB, Nimeiri H, Benson AB, Salem R. Twelve-year experience of radioembolization for colorectal hepatic metastases in 214 patients: survival by era and chemotherapy. *Eur J Nucl Med Mol Imaging* 2014; **41**: 1861-1869 [PMID: 24906565 DOI: 10.1007/s00259-014-2799-2]

133 **Sofocleous CT**, Garcia AR, Pandit-Taskar N, Do KG, Brody LA, Petre EN, Capanu M, Longing AP, Chou JF, Carrasquillo JA, Kemeny NE. Phase I trial of selective internal radiation therapy for chemorefractory colorectal cancer liver metastases progressing after hepatic arterial pump and systemic chemotherapy. *Clin Colorectal Cancer* 2014; **13**: 27-36 [PMID: 24370352 DOI: 10.1016/j.clcc.2013.11.010]

134 **Hendlisz A**, Van den Eynde M, Peeters M, Maleux G, Lambert B, Vannoote J, De Keukeleire K, Verslype C, Defreyne L, Van Cutsem E, Delatte P, Delaunoit T, Personeni N, Paesmans M, Van Laethem JL, Flamen P. 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 [PMID: 20567019 DOI: 10.1200/jco.2010.28.5643]

135 **Gibbs P**, Gebski V, Van Buskirk M, Thurston K, Cade DN, Van Hazel GA. Selective Internal Radiation Therapy (SIRT) with yttrium-90 resin microspheres plus standard systemic chemotherapy regimen of FOLFOX versus FOLFOX alone as first-line treatment of non-resectable liver metastases from colorectal cancer: the SIRFLOX study. *BMC Cancer* 2014; **14**: 897 [PMID:

25487708 DOI: 10.1186/1471-2407-14-897]
136 **Dutton SJ**, Kenealy N, Love SB, Wasan HS, Sharma RA. FOXFIRE protocol: an open-label, randomised, phase III trial of 5-fluorouracil, oxaliplatin and folinic acid (OxMdG) with or without interventional Selective Internal Radiation Therapy (SIRT) as first-line treatment for patients with unresectable liver-only or liver-dominant metastatic colorectal cancer. *BMC Cancer* 2014; **14**: 497 [PMID: 25011439 DOI: 10.1186/1471-2407-14-497]
137 EPOCH Clinical Trial Information. Available from: URL: http://www.theraspheretrials.com/epoch-102

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