Comparative Effectiveness in Hepatic Malignancies

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Abstract

The benefits of applying comparative effectiveness research (CER) strategies to the management of cancer are important. As the incidence of cancer increases both in the United States and worldwide, accurate analysis of which tests and treatments should be applied in which situations is critical, both in terms of measurable and meaningful clinical outcomes and health care costs. In the last 20 years alone, multiple controversies have arisen in the diagnosis and treatment of primary and metastatic tumors of the liver, making the management of liver malignancies a prime example of CER. Contributing factors to the development of these controversies include improvements in molecular characterization of these diseases and technological advances in surgery and radiology. The relative speed of these advances has outpaced data from clinical trials, in turn making robust data to inform clinical practice lacking. Indeed, many of the current treatment recommendations for the management of liver malignancies are based primarily on retrospective data. We herein review select CER issues concerning select decision-making topics in the management of liver malignancies.

Keywords

Comparative effectiveness · Hepatocellular carcinoma · Colorectal metastasis · Hepatectomy · Neuroendocrine metastasis

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1 Hepatocellular Carcinoma (HCC)

Hepatocellular carcinoma (HCC) is the seventh most common cancer in the world and its incidence is increasing [1, 2]. The presentation of patients with HCC is broad, both in terms of tumor burden and extent of liver dysfunction. Tumor burden may range from small and solitary HCC, to multinodular and metastatic disease; the degree of liver dysfunction can also be extensive with cirrhosis, or be absent without any evidence of liver function compromise. The management of HCC must be directed to patients anywhere along this spectrum, and includes systemic chemotherapy, non-resection local therapies (NRLT), liverl resection (LR), and liver transplant (LT). Given the broad spectrum of presentation, combined with multiple emerging treatment modalities, expectedly, there are CER dilemmas.

1.1 Unresectable HCC: The Role of Local Therapies

Unfortunately, many patients with HCC present with disease that is unresectable secondary either to advanced stage, or with evidence of liver dysfunction that cannot tolerate resection. For those patients with advanced HCC that is unresectable, less invasive therapies like NRLT have been incorporated into the management of HCC. The common examples of NRLTs include percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), transarterial chemoembolization (TACE), drug-eluting bead transarterial chemoembilzation (DEB-TACE), and transarterial radio-embolization (TARE) with yttrium-90 (Y90). Over the past 20 years, each type of these therapies has been studied and applied to patients with varying levels of disease burden and liver dysfunction. Recently, the comparative data supporting the use of these less-invasive therapies in unresectable HCC has grown rapidly.

Prior to the 1990s, there was no evidence-based algorithm for applying local therapies in HCC and most guidelines were based on small retrospective reviews [3, 4]. This was especially true for unresectable patients with a low burden of disease, but who had evidence of significant cirrhosis. In 2003, Lencioni et al. [5] were one of the first groups to examine the role of NRLT in a prospective randomized study involving patients with HCC deemed to be not appropriate for LT or LR. In a sample of 102 patients, all patients with cirrhosis and single HCC <5 cm or three HCCs each <3 cm were randomized to PEI or RFA. At 2 years, the authors noted that patients treated with RFA had a trend toward improved overall survival and significantly better recurrence-free survival compared with patients treated with PEI (98 % vs. 88 %, $p = 0.138$, and 96 % vs. 62 %, RR = 0.17, $p = 0.002$, respectively). On multivariate analysis, RFA remained an independent prognostic factor associated with an improvement in local recurrence-free survival (RR 0.20, $p = 0.015$). Lin et al. [6] reported similar trends in a larger prospective trial with longer follow-up in which the authors noted improvements in both overall survival and recurrence-free survival with RFA. At 3 years, overall survival was 74 % versus 51 % ($p = 0.31$), with recurrence-free survival (43 % vs. 21 %; $p = 0.038$) also favoring the RFA versus PEI group. While overall survival was equivocal, the aggregate data seemed to support RFA over PEI for small HCC in terms of recurrence-free survival.

Some patients will present with HCC that has progressed to a more advanced stage where ablation cannot be utilized. In this scenario, the HCC typically has reached a larger size and transitioned to receive the majority of its blood flow from the hepatic artery [7]. With the HCC being larger in size, treatments like RFA and PEI do not have the same efficacy as when the lesion is smaller [8, 9]. As such, alternative NRLTs that utilize the vascular supply of the HCC to deliver therapy have been incorporated into the management of more advanced HCC. These intra-arterial therapies include bland embolization, embolization with chemotherapy (TACE), or embolization with drug-eluting beads with chemotherapy (DEB-TACE).

There are a number of CER issues relating to intra-arterial therapy of HCC, including but not limited to: (1) what type of chemotherapy (if any) should be given with TAE, (2) is there a role for DEB, (3) what agent should be used for embolization, (4) how many treatments or sessions should be offered, and (5) which patients will benefit from this type of therapy. Despite the many questions around the evolving treatment modalities for advanced HCC, some data do exist to guide our current understanding for the role of intra-arterial therapies for more advanced HCC. One early study, performed by the D'Etude [10] evaluated the effect of TACE on unresectable, larger HCC compared with conservative treatment/best supportive care. The authors noted that TACE reduced tumor growth (decreased >50, 16 % vs. 5 %, $p = 0.001$) and decreased serum AFP (decreased >50, 23 % vs. 8 %, $p = 0.001$). The effect of TACE on overall survival was not pronounced, with 4-year overall survival of 12 % versus 15 % ($p = 0.13$). Other studies have explored the role of TACE in unresectable HCC and similarly failed to demonstrate a dramatic improvement in survival with intra-arterial therapy [11–14]. In a separate study, however, Llovet et al. [15] demonstrated that TACE did indeed lead to a survival benefit. In this prospective study, patients with advanced HCC (i.e. lesions not amenable to resection or transplantation) were randomized to TACE, bland embolization, or conservative therapy/best supportive care. The investigators noted an overall survival benefit for TACE over bland embolization and conservative therapy (2-year overall survival: 63 % vs. 50 % vs. 27 %, respectively; $p = 0.009$). On multivariate analysis, TACE was the only variable independently associated with survival (OR 0.45, $p = 0.02$). The authors attributed this improvement to strict patient selection, gelfoam as their embolization agent, and doxorubicin as the chemotherapeutic agent. The trial was stopped early so that patients in this setting could receive TACE. Based on these data, TACE is now part of the standard therapeutic armamentarium for patients with advanced HCC [16–18].

1.2 Imaging and Tumor Response After Local Therapies

An area that has evolved dramatically both in terms of technological advancement and CER has been the adoption of standardized and objective radiological response criteria after NRLT. Radiologic response to local therapies is critical to the management of HCC as it may be a surrogate marker for survival [19]. The two earliest suggested recommendations for standardization of objective response to NRLT were the World Health Organization (WHO) criteria and the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines [20, 21]. Both of these guidelines were based on tumor response being correlated with changes in tumor size. However, treatment with these types of NRLT of HCC often results in change in tumor vascularity and viability, but not necessarily changes in tumor size. As such, the WHO and RECIST criteria have been criticized as being limited and unreliable. Subsequently, the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) proposed additional guidelines to assess tumor response following NRLT [22, 23]. These criteria specifically took into account tumor necrosis by examining the reduction in viable tumor area using contrast-enhanced radiologic imaging. Viable tumor was defined as the part of the tumor that took up contrast in the arterial phase, while the role of overall tumor size was made a secondary consideration in the assessment of the tumor response [23]. Another proposed set of criteria to assess response include the modified RECIST (mRECIST) criteria, which bases assessment of overall response on target lesions characteristics noted on contrast enhanced imaging, non-target lesions response, and the presence or absence of new lesions. The field of imaging assessment for tumor response after NRLT will continue to evolve as treatment and radiological modalities improve and will need to be a topic of future CER.

1.3 Resectable HCC: Non-resection Local Therapies Versus Resection

Patients with HCC may present with early stage disease/resectable lesion and optimal liver function with minimal to no comorbidities. For these patients, LR represents a potential therapeutic option. The long-term outcome with certain

NRLT, such as ablation that can spare higher risk surgical patients from potential perioperative complications, is not well-defined and represents a subject of CER interest [24, 25]. Chen et al. [24] compared LR versus RFA for patients with a solitary small HCC. In this prospective series, 180 patients were randomized to RFA or LR. Inclusion criteria for the study were solitary HCC <5 cm in diameter, no vascular involvement, no evidence of liver dysfunction, and patients had to be suitable for either LR or RFA. At 4 years, overall survival was equivalent among patients undergoing RFA or LR at 65.9 % versus 64.0 %, respectively. In terms of disease-free survival, results were also similar with 4-year recurrence-free survival being 48.2 % versus 51.6 %, respectively. The authors concluded that RFA and LR were equally effective in the treatment of solitary and small HCC, with RFA being associated with decreased morbidity. Huang et al. [25] also prospectively examined the issue of LR versus RFA, but with expanded guidelines and came to different conclusions. In this study, patients with 3 lesions <3 cm or one lesion <5 cm were included. LR had improved survival and decreased recurrence over RFA. The 5-year overall survival was 54.8 % versus 75.7 % for RFA and LR, respectively (p = 0.001). In terms of disease-free survival, the same trend of better outcomes with LR over RFA was observed (5-year disease-free survival: 51.3 % vs. 28.7 %, respectively; $p = 0.024$). Direct comparisons of the different outcomes in the Chang and Huang studies is difficult as the studies varied in their inclusion criteria. Of note, in the Huang study, patients were not blinded to their treatment plan and 7 patients chose LR over RFA. In addition, the tumor size of the HCC was different between groups and the rate of loss of follow-up between groups was higher in the LR group (15.6 % vs. 6.1 %, $p < 0.05$). The comparison of these studies represents a key component to CER—understanding differences in study design, inclusion/exclusion criteria, as well as recognizing limitations in analysis. Furthermore, applying this CER perspective is necessary as more treatment modalities become available, e.g. the role of microwave versus RFA [26].

1.4 Resection Versus Transplant

Another source of treatment of CER interest is the debate over when to offer LR versus LT for early HCC. Theoretically, for most patients with HCC, LT represents the best treatment for survival because it removes both the tumor and underlying liver disease. There are, however, obstacles preventing LT from being offered to all patients with HCC including a limited availability of donor organs [27]. Historically in the 1980s and 1990s, the broad criteria utilized in organ allocation for patients with HCC led to a variety of outcomes for patients transplanted with HCC. In fact, the 90-day mortality, tumor recurrence, and long-term survival were not equivalent among all patients who were transplanted and some results were actually quite poor [28]. As such, attempts were made to identify the specific subset of patients who would benefit the most from LT [29]. In the seminal report by Mazzaferro et al. [30] the authors reported on a subset of patients with specific HCC characteristics who were proposed as a select patient population who would benefit from LT. This so-called “Milan criteria” included patients with one lesion smaller than 5 cm, up to 3 lesions smaller than 3 cm, no extra-hepatic manifestations, and no vascular invasion [30]. Since the adoption of the Milan criteria, additional guidelines have been suggested to broaden the inclusion of patients eligible for LT [31, 32]. These proposed guidelines include increasing the acceptable tumor size for transplantation. The ideal patient population to benefit from LT is still evolving and only with persistent CER re-assessment will refinements in the allocation system be possible.

Despite the identification of patient populations who benefit from LT, there are still limitations of donor organ availability, making application of LT to all patients with HCC not feasible. In turn, LR is a feasible alternative for some patients. Improvements in patient selection and perioperative management have made LR safe and relatively effective. While patients with end-stage liver disease and early stage tumors are most appropriate for LT, patients with compensated liver disease and early stage tumors can be appropriate for LT or LR. Choosing LT or LR for patients with compensated cirrhosis and early stage HCC remains challenging and often debated. In a retrospective review, Margarit et al. [33] examined the issue of when to offer LT versus LR for patients with early stage HCC and compensated cirrhosis. In this study, the authors reviewed patients with a single tumor <5 cm and Child’s class A liver disease and noted 10-year disease-free survival was worse after LR versus LT (18 % vs. 56 %, $p = 0.001$), with mean disease-free survival of 52 months versus 86 months, respectively ($p = 0.04$). Only 2.7 % in the LT group had local, hepatic recurrence versus 48.6 % in the LR cohort ($p = 0.001$). In terms of overall survival, there were no differences between the two groups (46 % vs. 36 %, LR vs. LT, $p = 0.3$) (Fig. 1a). Other studies have examined the same topic, with larger cohorts and intention-to-treat analyses [34–37] (Table 1). For example, Bellavance et al. [38] reported on 245 patients who underwent hepatic resection and 134 patients who underwent liver transplantation for early stage HCC. All patients had well-compensated cirrhosis. Compared with transplantation, patients undergoing resection had larger tumors and a higher incidence of microscopic vascular invasion. Transplantation was associated with better 5-year disease-free and overall survival compared with resection (Fig. 1b). Hepatitis status, presence of microscopic vascular invasion, and tumor size were predictors for recurrence, while the presence of microscopic vascular invasion and tumor size conferred an increased risk of death. The disease-free survival advantage with transplantation was more pronounced in hepatitis C patients compared with non-hepatitis and hepatitis B patients. The overall survival advantage with transplantation persisted in cases of solitary lesions ≤3 cm, but was attenuated in patients with a MELD score ≤8.

Final consensus on the comparative debate between LR and LT for early stage HCC with compensated liver disease remains lacking. While disease-free survival is clearly better among patients undergoing LT, the relative overall survival benefit of LT over LR remains ill defined. While LT has benefits over LR, it remains unclear whether patients who recur following LR can be salvaged with LT and experience the same long-term survival [39–41]. Prospective, randomized studies taking into

Fig. 1 **a**, **b** Actuarial patient survival after liver resection and liver transplant. Used with permission [33, 38]

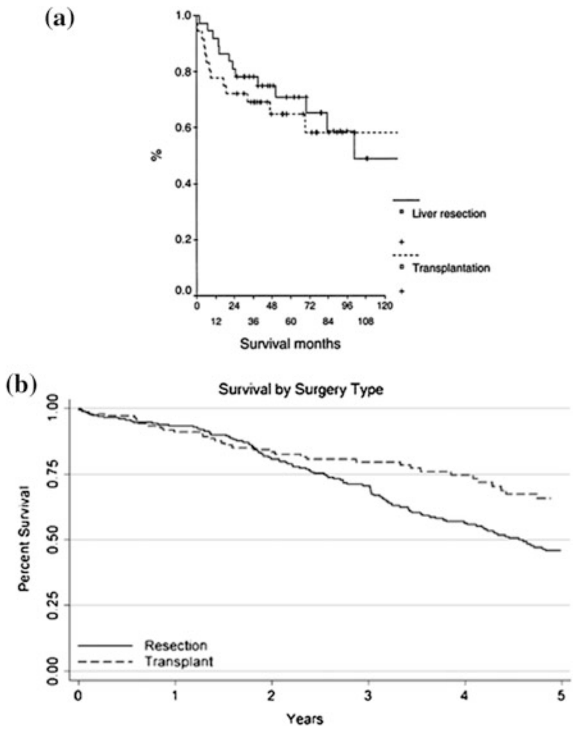

Table 1 Summary of studies examining liver resection versus liver transplant for early hepatocellular cancer

First author (year)	Treatment groups	Total patients	Childs A/B/C or average MELD	Mean maximal tumor size (cm)	5-year disease free survival (%)	5-year overall survival (%)
Figueras (2000) [35]	Resection	35	31/4/0	4.8	31	51
	Transplant	85	43/35/7	2.8	60	60
Margarit (2005) [33]	Resection	37	37/0/0	3.2	39	70
	Transplant	36	36/0/0	3.0	64	65
Poon (2007) [34]	Resection	204	195/9/0	<5	42	68
	Transplant	43	8/15/20	<5	84	81
Del Gaudio (2008) [36]	Resection	80	55/14/0	3.1	41	66
	Transplant	293	23/139/131	1.3	71	73
Bellavance (2008) [38]	Resection	245	9.1	NR	40	48[a]
	Transplant	134	11.0		82	79[a]
Lee (2010) [111]	Resection	130	113/17/0	4.5	50	52
	Transplant	78	35/43/0	3.8	75	68
Koniaris (2011) [37]	Resection	106	7.3	6.1	45	53
	Transplant	257	12.9	3.0	60	62

Adapted from and used with permission [110]
NR not reported
[a] For solitary lesions, ≤3 cm

account tumor size, multifocality, waitlist time and organ availability, and comorbidities, with appropriate long-term follow-up are needed to better address the LR versus LT debate.

2 Colorectal Liver Metastases

In the United States, colorectal metastases to the liver (CRLM) are probably the most common secondary malignancy involving the liver [42]. Approximately 140,000 Americans are diagnosed with colon cancer annually, with more than half of these patients eventually developing metastases [43]. Most of these metastases are found in the liver, and the presentation may vary from disease that is isolated to the liver and resectable to disease with tumor burden that is extensive and unresectable [44]. Given the heterogeneity of this patient population with metastatic disease, combined with developments in NRLTs and a paucity of prospective data, numerous CER issues have arisen in the surgical oncology literature.

2.1 Role of Loco-regional Therapies in Patients with Unresectable Disease

Unfortunately, most patients with CRLM have unresectable disease [45]. There are numerous reasons why a patient may be unresectable and not be an appropriate candidate for LR, including multiple small tumors, vascular involvement of the tumor, a small future liver remnant (FLR), medical comorbidities, or extra-hepatic disease. Typically patients with unresectable disease are treated with systemic therapy, with an associated median survival of 2 years and 5-year survival around 10–15 % [46, 47]. For those patients with liver predominant or liver only disease that is unresectable, local therapies may have a possible therapeutic role over systemic therapy. These options include RFA, TARE with Yttrium-90 microspheres, TACE with irinotecan eluting beads (DEBIRI), and hepatic artery infusion (HAI) pumps [48, 49].

The role for RFA has been examined frequently as one of the more common alterative or adjunct therapeutic options for patients with unresectable advanced disease [50–55]. Siperstein et al. [56] examined a retrospective cohort of patients with unresectable CRLMs that were treated with RFA. A unique strength to this study was its extensive 10-year follow-up. In the cohort of 234 patients—all of whom were treated with RFA—the 5-year survival was 18.4 %, which the authors noted was better than the 5-year survival or 10 % for historical controls treated with systemic therapy alone [57]. In a separate study, as part of the Intergroup 40,004 trial contrast, Ruers et al. [58] reported their findings for patients with unresectable CRLM. In this prospective study, the investigators compared systemic FOLFOX-based chemotherapy combined with RFA versus systemic therapy alone for patients with advanced CRLM. The authors noted that 30-month overall survival was similar: 61.7 % in the combined arm versus 57.6 % in the systemic therapy alone arm (p = NS). Median overall survival was also similar: 40.5 months in the systemic arm versus 45.3 months in the combined treatment arm (p = NS). While overall survival was the same in both groups, 3-year progression free survival was worse in the systemic alone arm (10.6 % vs. 27.6 %, HR = 0.63, $p = 0.025$). Therefore, the authors concluded that overall survival for patients with unresectable disease treated with systemic therapy alone versus ablation plus systemic therapy was similar, while progression free survival was improved with the use of ablation.

Other local therapies have also shown promise, however the data supporting their use is not as robust and therefore is a focus on CER. One such therapy is the HAI pump. First proposed in 1984, the role for HAI has been controversial, and its efficacy has been compared to systemic therapies in multiple prospective studies [59–62]. Many of these studies, however, have been criticized due to low sample size, patient cross-over, and the single-center nature of the trials [63]. In an effort to address these issues, Kemeny et al. [63] prospectively compared HAI pump therapy with systemic therapy in a large multi-institutional trial that did not allow cross-over. The authors reported that overall survival was improved for patients who received HAI versus systemic chemotherapy (median, 24.4 months vs. 20 months, $p = 0.0034$). Additionally, response rates were higher (47 % vs. 24 %, $p = 0.012$) and time to hepatic progression was longer (9.8 months vs. 7.3 months, $p = 0.034$) with HAI therapy. While these data were promising, other studies have challenged the survival benefit of HAI. In a meta-analysis of 10 randomized controlled trials performed comparing HAI with systemic chemotherapy, Mocellin et al. recently suggested that there is no evidence supporting the use of HAI. In the pooled analysis, while tumor response rate was expectedly better in the HAI group (42.9 % vs. 18.4 %, RR 2.3, <0.001), overall survival was not different comparing HAI versus systemic therapy (15.9 months vs. 12.4 months, HR 0.9, $p = 0.24$, respectively). While HAI therapy may provide some benefit in the treatment of advanced colorectal liver metastasis, more CER is needed to determine the role for HAI.

Other newer local therapies such as TACE with irinotecan beads (DEBIRI) and TARE with Yttrium-90 (Y-90) have posed CER issues in the context of unresectable CRLM. There are emerging data for the use of transarterial DEBIRI in the treatment of unresectable liver metastasis [64–66]. Many studies, however, incorporate TACE or TARE only for patients who are refractory to systemic therapies. Martin et al. [66] reported 55 patients who had received prior systemic chemotherapy and who underwent DEBIRI treatment. In this series, response rates were 66 % at 6 months and 75 % at 12 months. TARE with Y-90 has also been investigated for patients refractory to chemotherapy [67, 68]. Cosimelli et al. [68] in a prospective multicenter phase II trial, evaluated the effect of TARE on patients who had failed previous oxaliplatin and ironotecan based chemotherapies. Based on RECIST criteria, 2 % had a complete response, 22 % a partial response, 24 % had stable disease, 44 % had progressive disease, and 8 % were non-evaluable. Because of these promising results, a phase III multicenter clinical trial, Efficacy Evaluation of TheraSphere following Failed First-Line Chemotherapy in Metastatic Colorectal Cancer (EPOCH) trial will soon open to elucidate the effect of TARE on not just response rates, but also overall survival. Final consensus on the optimal management of patients with unresectable CRLM is still developing, but progress is being made with emerging meta-analyses and prospective studies.

2.2 Ablation Versus Liver Resection

For the 10–25 % of patients with resectable CRLM, LR is the standard treatment approach with 5-year survival following surgery now approaching 60 % [42, 69, 70]. The role of ablation versus surgery among patients with CRLM potentially amenable to either therapy has been debated. The median overall survival associated with LR of CRLM reported in the literature ranges from 24 to 59 months whereas the data on survival following ablation are more limited [52, 71]. Several studies have sought to compare outcomes for patients who underwent ablation versus patients who underwent resection for CRLM [72–76]. Abdalla et al. [52] reported on 358 consecutive patients who underwent hepatic resection with or without RFA for CRLM. In this cohort, LR provided a significantly better overall 4-year survival over RFA alone, (65 % vs. 22 %, $p < 0.001$). Similarly, Hur et al. [77] noted a 5-year survival advantage for patients who underwent LR versus RFA (25.1 % for RFA vs. 50.0 % for LR). Based on the available data, it appears that patients managed with ablation have a worse outcome compared with patients who underwent hepatic resection (Table 2) [72, 74–76, 78].

The difference in the outcomes may, however, not be solely attributable to the type of therapy delivered (i.e. LR versus ablation), but also an issue of disparate underlying tumor biology among each patient population. Specifically, patients who undergo ablation as treatment for their CRLM often represent a distinct subgroup of patients with otherwise advanced disease who are not amenable to surgical extirpation [79]. In fact, many of the clinicopathologic features such as tumor size and number are often different in the group of patients receiving LR versus ablation. To achieve more comparable groups, subgroup analyses of patients undergoing either LR or ablation for CRLM have been performed, which have commonly been stratified by tumor number [78]. For example, Aloia et al. [78] examined a cohort of patients all of whom had only a solitary lesion. In this study, 150 patients treated with resection were compared with 30 patients treated with RFA. The authors reported that patients who underwent resection had a significantly better 5-year survival (resection: 71 % vs. RFA: 27 %; $p < 0.001$). However, patients managed with RFA likely had worse tumor biology as indicated by a higher proportion of patients with concomitant extrahepatic disease. In a separate study, Gleisner et al. [80] sought to examine how discordant clinicopathologic factors might play a crucial role in comparing patients who underwent resection versus ablation. Specifically, Gleisner et al. compared overall survival between patients who underwent resection with survival of patients who underwent RFA using three distinct statistical methods. The authors reported that patients managed with resection alone had an improved long-term overall survival compared with patients treated with

Table 2 Summary of studies comparing RFA with resection for colorectal liver metastases

First author (Year)	Treatment groups	Total patients	Mean maximal tumor size (cm)	Median time to local recurrence (months)	Median survival (months)	5-year local recurrence free survival	5-year overall survival
Oshowo (2003) [72]	RFA	25	3	NR	37	NR	52.6[a]
	Resection	20	4	NR	41		55.4[a]
Aloia (2006) [78]	RFA	30	3.0	18	NR	60	27
	Resection	150	3.5	31	NR	92	71
White (2007) [74]	RFA	22	2.4	NR	31	NR	0
	Resection	30	2.7	NR	80	NR	58
Berber (2008) [75]	RFA	68	3.7	NR	34	NR	30.0
	Resection	90	3.8	NR	57	NR	40.0
Lee (2008) [76]	RFA	37	2.25	NR	NR	42.6	48.5
	Resection	116	3.29	NR	NR	84.6	65.7
Hur (2009) [77]	RFA	25	2.5	NR	NR	69.7	25.5
	Resection	42	2.8	NR	NR	89.7	50.1
Reuter (2009) [113]	RFA	66	3.2	12.2	27.0	NR	NR
	Resection	126	5.3	31.1	36.4	NR	NR

Adapted and used with permission [112]
NR not reported
[a] At 3 years

resection plus ablation. The authors noted, however, that there were many differences in the clinicopathologic profile of each group. To examine the comparability of the baseline characteristics of the two treatment groups, Gleisner and colleagues utilized propensity score methodology. The authors noted that the aggregate distribution of the clinical and pathologic characteristics of patients undergoing resection alone versus RFA ± resection were markedly different and therefore direct comparisons of these groups may not be appropriate. The work of Gleisner and colleagues serves therefore to highlight the significant shortcomings of using retrospective data to compare outcomes following resection versus ablation in cohorts of patients who are very different and whose choice of treatment was undoubtedly based in part based of very different baseline characteristics.

In 2009, as part of an American Society of Clinical Oncology (ASCO) evidence-based review, Wong et al. [81] attempted to examine all data available at that time on ablation and LR for CRLM. The authors concluded that the available data were insufficient to form the basis of an evidence-based recommendation. Specifically, the authors noted that there was wide variability in 5-year survival (14–55 %) and local tumor recurrence (3.6–60 %) with ablation compared with LR. In turn, the investigators commented that the question of ablation versus LR could only be answered by a prospective, randomized trial. Such a trial, while ideal, would be challenging for a variety of reasons, most significantly, accrual would be required to be multi-institutional, and the ablation procedure itself would need to be standardized [45]. In an attempt to simulate such a trial, Khajanchee et al. [45] used a Markov and Monte Carlo analysis comparing RFA and LR. The authors reported that the model estimated 5-year survival among those patients who underwent LR over RFA alone to be 38.2 % versus 27.2 %, respectively. Five-year disease-free survival was also superior in the LR group (LR: 29.8 % vs. RFA: 15.5 %). While there are no prospective data comparing ablation with LR in the resectable population, from the limited data available, LR should remain the preferred approach with ablation being used as an adjunct second line therapy.

2.3 Systemic Therapy, Neoadjuvant Chemotherapy and the Disappearing Liver Metastasis

While local therapies such as ablation and resection are important treatment options for patients with CRLM, systemic chemotherapy plays a critical role in the multimodal therapy of these patients. Systemic therapy has the potential of treating micrometastatic disease, evaluating tumor response, and downstaging unresectable tumors to resectability. The benefits of chemotherapy come with some possible consequences, including hepatotoxicity such as sinusoidal dilation, steatosis, or steatohepatitis [47, 57, 82, 83].

In an attempt identify which patients may benefit the most from systemic chemotherapy, several predictive models have been designed to identify patients at high risk for recurrence after hepatectomy. Fong et al. [42] were one of the first groups to propose a clinical risk score for predicting recurrence and survival. This study identified several prognostic factors for recurrence including: extra-hepatic disease, node-positive primary tumor, disease free interval from primary to metastases <12 months, CEA level >200, largest hepatic tumor >5 cm, and number of hepatic tumors >1. Similarly, Adam et al. [84] also created a prognostic model, examining initially unresectable CRLM that received chemotherapy and that were downstaged to resectability. In this study, the investigators identified a rectal primary, ≥3 CRLMs, maximum CRLM size of ≥10 cm, and CA19-9 >100 as independent factors of poor prognosis. Capussotti et al. [85] in 2007 suggested their own prognostic model. These authors identified patients with T4 primary colon cancers, metastases with infiltration of neighboring structures, and patients with more than three metastases as being potential indicators of poor prognosis and, in turn, may indicate a potential benefit from systemic chemotherapy. Despite these large retrospective series, there are still no specific consensus guidelines to indicate which patients with resectable CLRM should receive systemic chemotherapy either in the adjuvant or neoadjuvant setting [86].

Among the cohort of patients treated with neoadjuvant or preoperative systemic chemotherapy, there are several CER issues that remain debatable. Most data would suggest that those patients who have progressive disease on preoperative chemotherapy have a very poor prognosis [84]. Whether these patients should categorically be refused potential surgery even if the disease is technically still resectable remains controversial. Among patients who have a response to neoadjuvant/preoperative chemotherapy, surgery is typically performed with the goal of resecting all sites of disease. Up to 10–25 % of patients with CRLM who are treated with preoperative chemotherapy, however, will have a complete response with radiographic “disappearance” of some or all CRLM lesions in the liver [87, 88]. The so called “disappearing liver metastasis” (DLM) raises a number of CER issues.

From a radiologic perspective, there is no consensus regarding which imaging modality (CT, MRI, FDG-PET, or FDG-PET-CT) is most appropriate to determine whether the DLM is simply “missing” due to low sensitivity of the chosen imaging modality versus whether it has truly “disappeared.” Most medical oncologists and surgeons currently use CT in the treatment of patients with CRLM. The widespread use of dual phase helical CT is based on clinician familiarity and a high degree of reproducibility with excellent sensitivity and specificity up to 90 % when diagnosing CRLM [89, 90]. In the setting of a DLM, when the liver has been exposed to systemic chemotherapy—often many cycles—the background liver can appear darker with less contrast between the liver and any hypovascular metastases [91]. PET-CT has been considered as adjunct to CT alone, however PET-CT has limited sensitivity in its ability to detect lesions <1 cm and chemotherapy decreases hexokinase activity, thereby inhibiting glucose uptake for CRLM [92, 93]. Recently, there has been increasing data to suggest that MRI should be the imaging modality of choice in the setting of DLM. MRI, has increased sensitivity compared with CT, particularly in the setting of chemotherapy induced hepatic parenchymal changes (Fig. 2) [88]. In a recent meta-analysis, van Kessel et al. [94] compared various imaging modalities in the detection of CRLM after preoperative chemotherapy and found that the sensitivity of MRI was 85.7 % versus 69.9 % for CT, 54.5 % for PET, and 51.7 % for PET-CT. As such, MRI seems to be the imaging modality of choice for patients treated with preoperative chemotherapy—especially those with DLM. Future CER to understand better the role of different imaging modalities in treating patients with CRLM will be needed.

In addition to radiological issues in management of DLM, there is also is also a lack of consensus about the surgical management of DLM. As with other CER dilemmas, this primarily stems from the lack of reliable data. van Vledder et al. [87] attempted to examine the question of how to manage DLM using retrospective data; the authors noted that patients with untreated DLM had an increased local recurrence rate compared with patients who underwent LR of the DLM ($p = 0.04$). Despite these findings, the 1-, 3-, and 5-year overall survival was not different for patients undergoing LR versus those patients who had DLM left in situ (92.3 % vs. 93.8 %, 70.8 % vs. 63.5 %, 46.2 % vs. 63.5 % respectively) (Fig. 3a, b). The CER issues raised by the management of DLM were recently addressed by Bischof et al. [88]. In their review of DLM, the authors concluded that among patients who had a complete radiographic response, only 20–50 % had a durable long-term remission.

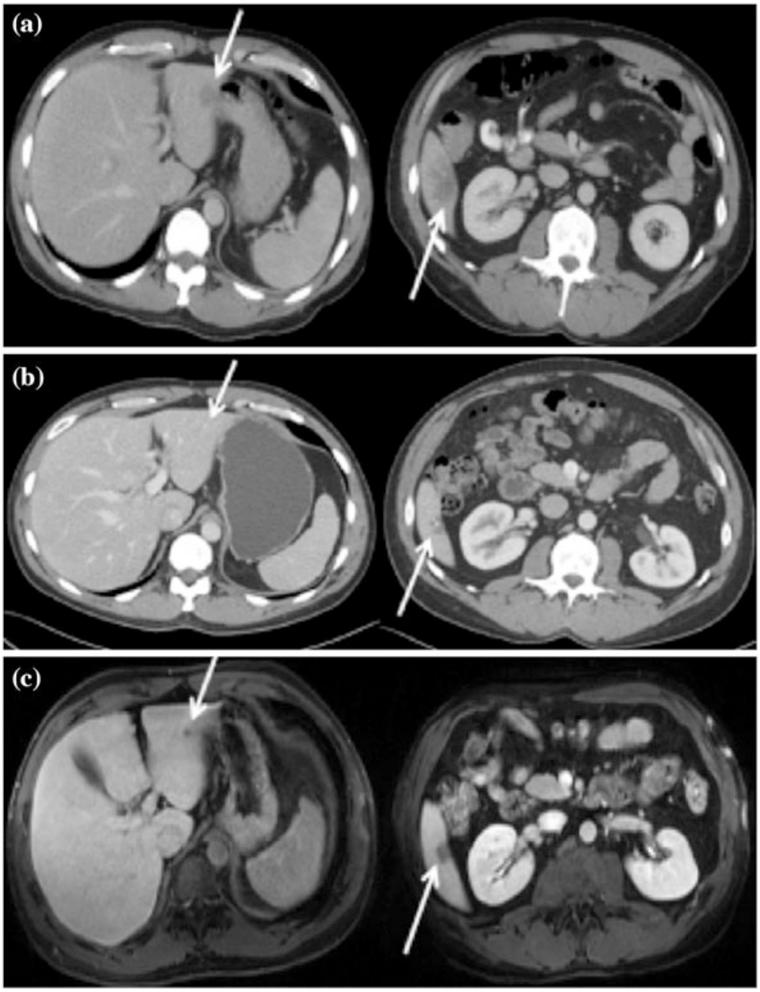

Fig. 2 **a** Computed tomography (CT) image demonstrating colorectal liver metastases in segments II and VI (*arrows*) before systemic chemotherapy. **b** After 6 cycles of FOLFOX (folinic acid, 5-fluorouracil, oxaliplatin) therapy, CT showed that the lesion in segment II had 'disappeared', whereas the lesion in segment VI was significantly smaller and calcified. **c** Magnetic resonance imaging similarly identified the lesion in segment VI, but also demonstrated a residual 7-mm lesion in segment II. Used with permission [88]

In addition, among patients who had the DLM resected, residual tumor was present in 25–45 % of patients. Therefore, more CER is need to understand which patients need surgery for a DLM after receipt of preoperative chemotherapy.

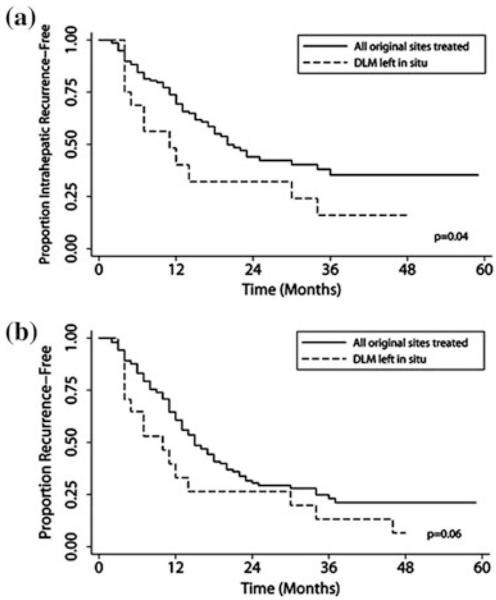

Fig. 3 **a** Kaplan–Meier curve of overall survival in patients with untreated DLM when compared to patients in whom all original disease sites were resected. **b** Kaplan–Meier curve showing overall survival in 99 patients with a complete or partial radiological response (RECIST) to preoperative chemotherapy stratified by the presence of untreated DLM. Used with permission [87]

3 Neuroendocrine Liver Metastases

Neuroendocrine tumors (NETs) represent another important topic in the context of liver surgery and CER. NETs are of particular interest as these tumors are increasing in incidence and 40–95 % of cases are metastatic at diagnosis [95]. Treatment strategies for NETs once they have metastasized to the liver (NELM) are similar to those employed for the aforementioned liver tumors, and options include systemic chemotherapy, various NRLT, and LR. Also similar to other hepatic tumors, there is an absence of data from rigorous trials [96]. To further exacerbate the issue of reliable long-term data is the often indolent biologic behavior of these tumors compared to other liver tumors [97].

3.1 Cytoreductive Therapy—Liver Resection and Non-surgical Local Therapies

While the standard of care for NELM is LR, the data guiding this recommendation are surprisingly limited. In 2000, Chamberlain et al. [98] argued in presenting the results of their surgical series that LR improved survival. In this study, the authors demonstrated on multivariate analysis that LR prolonged 5-year survival versus NRLT (bland embolization) and best supportive care (76 % vs. 50 % vs. <25 %, respectively; $p < 0.05$). In a separate study, Sarmiento et al. [99] from the Mayo Clinic reported on an experience with 170 patients who underwent LR for NELM.

The authors noted that overall 5- and 10-year survival were 61 and 35 %, respectively. Similarly, in a large multi-center study, Mayo et al. [100] reported excellent long-term results following surgery with 5- and 10-year survival of 74 and 51 %, respectively. As such, based on these data, surgical resection of NELM is widely utilized as it is believed to offer patients improved long-term survival. While most surgeons agree with an approach to resect patients with a low-disease burden, the role of surgical debulking of patients with larger disease-burdens is more controversial. For example, some groups have even suggested that patients with a high tumor burden may have a survival benefit after palliative debulking, as long as the majority (>75–80 %) of the liver disease can be removed [99, 101].

Despite the long-term survival associated with LR for NELM, recurrence following surgical management of NELM is almost universal. Specifically, in the largest retrospective review to date by Mayo et al. [100] the authors reported a 94 % recurrence at 5 years and 99 % recurrence rate at 10 years. Because of this remarkably high incidence of recurrence, there has been an increased interest in NRLT for NELM, including such intra-arterial therapies (IAT) as TACE and TARE. In a large, multi-institutional respective review, Mayo et al. [102] compared outcomes among patients with NELM based on treatment by LR versus IAT. Not surprisingly, the authors noted significant differences in the baseline characteristics of patients who underwent LR versus IAT, with the IAT group having more hormonally active tumors (48 % vs. 28 %, $p < 0.001$) and a larger hepatic tumor burden (>25 %: 76 % vs. 52 %, $p < 0.001$). The selection bias obviously calls into question any conclusions that can be drawn from retrospective comparisons of these two treatment modalities and highlights the CER challenges in answering this question. The authors did attempt to address the issue of selection bias by using propensity score matching. Propensity scoring provides a means to design and analyze a nonrandomized, retrospective dataset in an attempt to mimic some of the characteristics of a randomized controlled trial [103]. In the study, quintiles were created from their entire cohort with similar clinicopathologic characteristics and used in a matched analysis. With propensity matching, the authors noted that the analytic cohort comparing LR versus IAT groups now had much similar baseline characteristics. While LR was still associated with an improved survival over IAT, the difference was less pronounced (Fig. 4a, b). Furthermore, on stratified analyses, it was noted that symptomatic patients with a small burden of liver disease benefited the most from surgery. While symptomatic patients with a large burden of liver disease (>25 % hepatic tumor involvement) had improved median survival with LR over IAT (87 months vs. 51 months, $p < 0.001$, respectively), patients who were asymptomatic did not seemingly benefit from surgery resection (LR, 16.7 months vs. IAT, 18.5 months, $p = 0.78$). While propensity matching can assist with the comparison of groups with disparate baseline characteristics, more effective methodology and prospective trials will be necessary to answer better the CER question around which patients benefit from LR versus IAT.

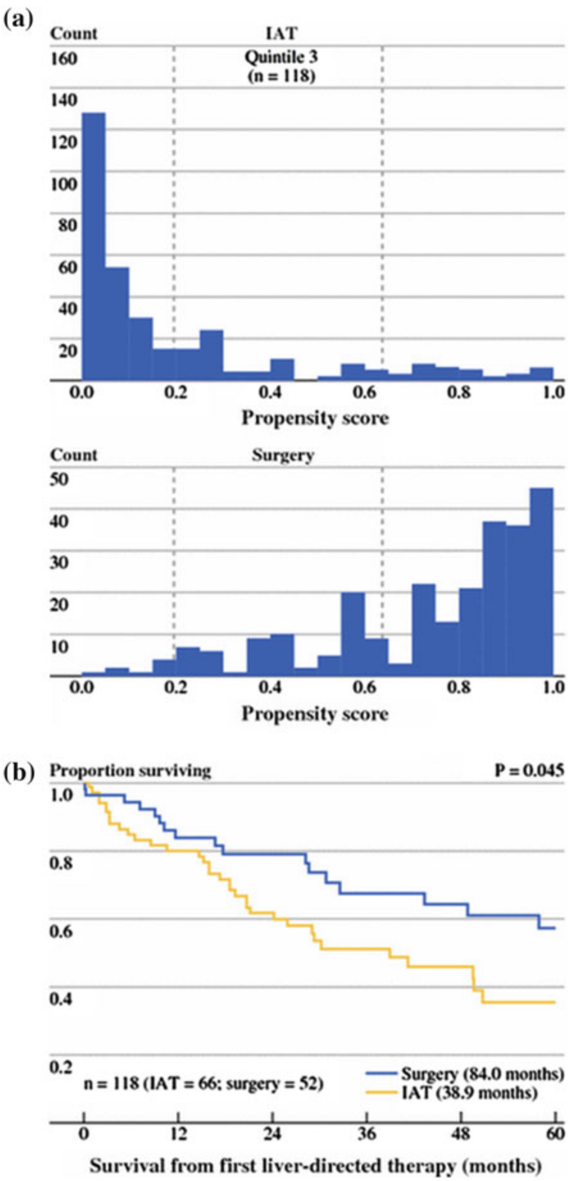

Fig. 4 **a** Histograms demonstrating the distribution of the propensity scores in the surgical and intra-arterial therapy (*IAT*) patient cohorts. The area of greatest overlap (quintile 3) corresponds to group of patients most likely have undergone either treatment based on baseline characteristics. **b** Overall survival of propensity-matched patients in quintile 3 stratified by receipt of surgery versus IAT. Used with permission [102]

3.2 Role of Resecting the Small Bowel Primary in the Unresectable NELM Setting

An additional area of CER contention is the question whether to leave an asymptomatic small bowel (SB) primary NET in place in the setting of unresectable NELMs. For patients with SB-NET, this scenario is not uncommon, as 15–80 % of these primary tumors develop unresectable NELM [104]. The proposed goals of primary tumor resection are to provide relief from hormonal and local tumor-related symptoms (e.g., pain, perforation, bleeding, and obstruction), limit disease solely to the liver so that it may be treated with IAT, and potentially improve overall survival. Unfortunately, the data for the role of resection in this scenario is particularly sparse, and current management is based on personal experience and local practice patterns [95, 105–108]. Therefore, in an attempt to create evidence-based recommendation for this scenario, both meta-analyses and consensus panels have been used. Capurso et al. [109] recently performed a meta-analysis and examined the role of resecting SB-NET in the setting of unresectable NELM. The authors found that the only studies reported to date were solely retrospective and that the quality and type of data included in these small cohort studies did not meet the inclusion criteria for the meta-analysis (Table 3). In particular, Capuso et al. noted that some studies included patients with other primary tumor sites and the role of resection was also not appropriately analyzed in each study.

Frilling et al. [96] also attempted to examine the role of primary tumor resection in a recent European-African Hepato-Pancreato-Biliary (E-AHPBA) consensus conference. Similar to the aforementioned meta-analysis, the authors concluded that many variables made a consensus statement impossible. The investigators noted that significant confounding factors included biases to operate on less advanced tumors, as well as a selection bias to operate on patients with better performance status—thereby making the actual benefit of the surgery itself impossible to discern. Because of the paucity of unbiased data, there are only weak evidence to recommend resection and more rigorous retrospective and prospective CER studies are needed.

Table 3 Summary of studies examining resection or unresected primary midgut carcinoid tumors in patients with unresectable liver metastases

First author (year)	Treatment groups	Total patients	Median progression-free survival (months)	Median overall survival (months)	5-year survival
Givi (2006) [106]	Resected	66	54	108	81
	Unresected	18	27	50	21
Strosberg (2009) [105]	Resected	100	NR	110	NR
	Unresected	35	NR	88	NR
Ahmed (2009) [107]	Resected	209	NR	119	74
	Unresected	76	NR	57	46
Norlen (2012) [108]	Resected	493	NR	NR	75
	Unresected	86	NR	NR	28

Adapted and used with permission [109]

4 Conclusion

Examining current treatment recommendations through the prism of CER is challenging and humbling, as it sheds light on areas that lack robust data and rigorous analysis. The management of liver malignancies is an ideal example of how CER has led to reliable treatments, but also where progress is urgently needed. When prospective, randomized controlled trials can be completed, these data will remain the gold standard for practice. However, in those scenarios where such trials are not feasible, clinicians must be cautious when adopting conclusions drawn from retrospective analyses.

References

1. El-Serag HB, Mason AC (1999) Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 340(10):745–750
2. Yang JD, Roberts LR (2010) Hepatocellular carcinoma: a global view. Nat Rev Gastroenterol Hepatol 7(8):448–458
3. Bruix J, Sherman M, Llovet JM et al (2001) Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. J Hepatol 35(3):421–430
4. Livraghi T, Goldberg SN, Lazzaroni S, Meloni F, Solbiati L, Gazelle GS (1999) Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection. Radiology 210(3):655–661
5. Lencioni RA, Allgaier H-P, Cioni D et al (2003) Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection1. Radiology 228(1):235–240
6. Lin S, Lin C, Lin C, Hsu C, Chen Y (2005) Randomised controlled trial comparing percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less. Gut 54(8):1151–1156
7. Caturelli E, Siena DA, Fusilli S et al (2000) Transcatheter arterial chemoembolization for hepatocellular carcinoma in patients with cirrhosis: evaluation of damage to nontumorous liver tissue—long-term prospective study 1. Radiology 215(1):123–128
8. Veltri A, Moretto P, Doriguzzi A, Pagano E, Carrara G, Gandini G (2006) Radiofrequency thermal ablation (RFA) after transarterial chemoembolization (TACE) as a combined therapy for unresectable non-early hepatocellular carcinoma (HCC). Eur Radiol 16(3):661–669
9. Livraghi T (2003) Radiofrequency ablation, PEIT, and TACE for hepatocellular carcinoma. J Hepato-Biliary-Pancreatic Surg 10(1):67–76
10. d'Etude G, Hépatocellulaire TDC (1995) A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. N Engl J Med 332:1256–1261
11. Lin D, Liaw Y, Lee T, Lai C (1988) Hepatic arterial embolization in patients with unresectable hepatocellular carcinoma—a randomized controlled trial. Gastroenterology 94 (2):453–456
12. Pelletier G, Roche A, Ink O et al (1990) A randomized trial of hepatic arterial chemoembolization in patients with unresectable hepatocellular carcinoma. J Hepatol 11 (2):181–184
13. Madden M, Krige J, Bailey S et al (1993) Randomised trial of targeted chemotherapy with lipiodol and 5-epidoxorubicin compared with symptomatic treatment for hepatoma. Gut 34 (11):1598–1600

14. Llovet JM, Fuster J, Bruix J (1999) Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology 30(6):1434–1440
15. Llovet JM, Real MI, Montaña X et al (2002) Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 359(9319):1734–1739
16. Sergio A, Cristofori C, Cardin R et al (2008) Transcatheter arterial chemoembolization (TACE) in hepatocellular carcinoma (HCC): the role of angiogenesis and invasiveness. Am J Gastroenterol 103(4):914–921
17. Pinter M, Hucke F, Graziadei I et al (2012) Advanced-stage hepatocellular carcinoma: transarterial chemoembolization versus sorafenib. Radiology 263(2):590–599
18. Becker G, Soezgen T, Olschewski M, Laubenberger J, Blum HE, Allgaier H-P (2005) Combined TACE and PEI for palliative treatment of unresectable hepatocellular carcinoma. World J Gastroenterol 11(39):6104
19. Bhagat N, Reyes DK, Lin M, et al. (2013) Phase II study of chemoembolization with drug-eluting beads in patients with hepatic neuroendocrine metastases: high incidence of biliary injury. Cardiovasc Intervent Radiol: 1–11
20. Miller A, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47(1):207–214
21. Therasse P, Arbuck SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92(3):205–216
22. Llovet JM, Bruix J (2008) Novel advancements in the management of hepatocellular carcinoma in 2008. J Hepatol 48:S20–S37
23. Bruix J, Sherman M (2011) Management of hepatocellular carcinoma: an update. Hepatology 53(3):1020–1022
24. Chen M-S, Li J-Q, Zheng Y et al (2006) A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg 243(3):321
25. Huang J, Yan L, Cheng Z et al (2010) A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. Ann Surg 252(6):903–912
26. Qian G-J, Wang N, Shen Q et al (2012) Efficacy of microwave versus radiofrequency ablation for treatment of small hepatocellular carcinoma: experimental and clinical studies. Eur Radiol 22(9):1983–1990
27. Merion RM, Pelletier SJ, Goodrich N, Englesbe MJ, Delmonico FL (2006) Donation after cardiac death as a strategy to increase deceased donor liver availability. Ann Surg 244(4):555
28. Earl TM, Chapman WC (2013) Hepatocellular carcinoma: resection versus transplantation. In: Seminars in liver disease. Thieme Medical Publishers, Stuttgart, pp 282–292
29. Yao F, Xiao L, Bass N, Kerlan R, Ascher N, Roberts J (2007) Liver transplantation for hepatocellular carcinoma: validation of the UCSF-expanded criteria based on preoperative imaging. Am J Transplant 7(11):2587–2596
30. Mazzaferro V, Regalia E, Doci R et al (1996) Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 334(11):693–700
31. Yao F (2008) Liver transplantation for hepatocellular carcinoma: beyond the Milan criteria. Am J Transplant 8(10):1982–1989
32. Belghiti J, Durand F (2011) Criteria for liver transplantation for hepatocellular carcinoma: what is an acceptable outcome? Liver Int 31(s1):161–163
33. Margarit C, Escartín A, Castells L, Vargas V, Allende E, Bilbao I (2005) Resection for hepatocellular carcinoma is a good option in Child-Turcotte-Pugh class A patients with cirrhosis who are eligible for liver transplantation. Liver Transpl 11(10):1242–1251
34. Poon RT, Fan ST, Lo CM, Liu CL, Wong J (2007) Difference in tumor invasiveness in cirrhotic patients with hepatocellular carcinoma fulfilling the Milan criteria treated by resection and transplantation: impact on long-term survival. Ann Surg 245(1):51

35. Figueras J, Jaurrieta E, Valls C et al (2000) Resection or transplantation for hepatocellular carcinoma in cirrhotic patients: outcomes based on indicated treatment strategy. J Am Coll Surg 190(5):580–587
36. Del Gaudio M, Ercolani G, Ravaioli M et al (2008) Liver transplantation for recurrent hepatocellular carcinoma on cirrhosis after liver resection: University of Bologna experience. Am J Transplant 8(6):1177–1185
37. Koniaris LG, Levi DM, Pedroso FE et al (2011) Is surgical resection superior to transplantation in the treatment of hepatocellular carcinoma? Ann Surg 254(3):527–538
38. Bellavance EC, Lumpkins KM, Mentha G et al (2008) Surgical management of early-stage hepatocellular carcinoma: resection or transplantation? J Gastrointest Surg 12(10):1699–1708
39. Belghiti J, Cortes A, Abdalla EK et al (2003) Resection prior to liver transplantation for hepatocellular carcinoma. Ann Surg 238(6):885
40. Poon RT-P, Fan ST, Lo CM, Liu CL, Wong J (2002) Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. Ann Surg 235(3):373–382
41. Belghiti J, Carr B, Greig P, Lencioni R, Poon R (2008) Treatment before liver transplantation for HCC. Ann Surg Oncol 15(4):993–1000
42. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH (1999) Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 230(3):309
43. Tzeng C-WD, Aloia TA (2013) Colorectal liver metastases. J Gastrointest Surg 17(1):195–202
44. Mansour J, Fong Y (2007) Timing of the liver resection for patients with synchronous metastases: practical and outcome considerations. Ann Surg Oncol 14(9):2435–2436
45. Khajanchee YS, Hammill CW, Cassera MA, Wolf RF, Hansen PD (2011) Hepatic resection vs minimally invasive radiofrequency ablation for the treatment of colorectal liver metastases: a Markov analysis. Arch Surg 146(12):1416
46. Kopetz S, Chang GJ, Overman MJ et al (2009) Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol 27(22):3677–3683
47. Saltz LB, Clarke S, Díaz-Rubio E et al (2008) Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 26(12):2013–2019
48. Narayanan G, Barbery K, Suthar R, Guerrero G, Arora G (2013) Transarterial chemoembolization using DEBIRI for treatment of hepatic metastases from colorectal cancer. Anticancer Res 33(5):2077–2083
49. Martin RC, Joshi J, Robbins K, Tomalty D, O'Hara R, Tatum C (2009) Transarterial chemoembolization of metastatic colorectal carcinoma with drug-eluting beads, irinotecan (DEBIRI): multi-institutional registry. J Oncol 2009:539795
50. Mulier S, Miao Y, Mulier P et al (2005) Electrodes and multiple electrode systems for radiofrequency ablation: a proposal for updated terminology. Eur Radiol 15(4):798–808
51. Goldberg SN, Hahn PF, Tanabe KK et al (1998) Percutaneous radiofrequency tissue ablation: does perfusion-mediated tissue cooling limit coagulation necrosis? J Vasc Interv Radiol 9 (1):101–111
52. Abdalla EK, Vauthey J-N, Ellis LM et al (2004) Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg 239(6):818
53. Mulier S, Ruers T, Jamart J, Michel L, Marchal G, Ni Y (2009) Radiofrequency ablation versus resection for resectable colorectal liver metastases: time for a randomized trial? Dig Surg 25(6):445–460
54. Mulier S, Ni Y, Jamart J, Ruers T, Marchal G, Michel L (2005) Local recurrence after hepatic radiofrequency coagulation: multivariate meta-analysis and review of contributing factors. Ann Surg 242(2):158–171

55. Gillams A, Lees W (2009) Five-year survival in 309 patients with colorectal liver metastases treated with radiofrequency ablation. Eur Radiol 19(5):1206–1213
56. Siperstein AE, Berber E, Ballem N, Parikh RT (2007) Survival after radiofrequency ablation of colorectal liver metastases: 10-year experience. Ann Surg 246(4):559–567
57. Wicherts DA, Miller R, de Haas RJ et al (2008) Long-term results of two-stage hepatectomy for irresectable colorectal cancer liver metastases. Ann Surg 248(6):994–1005
58. Ruers T, Punt C, Van Coevorden F et al (2012) Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004). Ann Oncol 23(10):2619–2626
59. Kemeny N, Daly J, Oderman P et al (1984) Hepatic artery pump infusion: toxicity and results in patients with metastatic colorectal carcinoma. J Clin Oncol 2(6):595–600
60. Hohn DC, Stagg RJ, Friedman MA et al (1989) A randomized trial of continuous intravenous versus hepatic intraarterial floxuridine in patients with colorectal cancer metastatic to the liver: the Northern California Oncology Group trial. J Clin Oncol 7(11):1646–1654
61. Chang AE, Schneider PD, Sugarbaker PH, Simpson C, Culnane M, Steinberg SM (1987) A prospective randomized trial of regional versus systemic continuous 5-fluorodeoxyuridine chemotherapy in the treatment of colorectal liver metastases. Ann Surg 206(6):685
62. Lorenz M, Müller H-H (2000) Randomized, multicenter trial of fluorouracil plus leucovorin administered either via hepatic arterial or intravenous infusion versus fluorodeoxyuridine administered via hepatic arterial infusion in patients with nonresectable liver metastases from colorectal carcinoma. J Clin Oncol 18(2):243
63. Kemeny NE, Niedzwiecki D, Hollis DR et al (2006) Hepatic arterial infusion versus systemic therapy for hepatic metastases from colorectal cancer: a randomized trial of efficacy, quality of life, and molecular markers (CALGB 9481). J Clin Oncol 24(9):1395–1403
64. Fiorentini G, Aliberti C, Tilli M et al (2012) Intra-arterial infusion of irinotecan-loaded drug-eluting beads (DEBIRI) versus intravenous therapy (FOLFIRI) for hepatic metastases from colorectal cancer: final results of a phase III study. Anticancer Res 32(4):1387–1395
65. Martin RC II, Scoggins CR, Tomalty D et al (2012) Irinotecan drug-eluting beads in the treatment of chemo-naive unresectable colorectal liver metastasis with concomitant systemic fluorouracil and oxaliplatin: results of pharmacokinetics and phase I trial. J Gastrointest Surg 16(8):1531–1538
66. Martin RC, Joshi J, Robbins K et al (2011) 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 18(1):192–198
67. Gray B, Van Hazel G, Hope M et al (2001) Randomised trial of SIR-Spheres® plus chemotherapy vs. chemotherapy alone for treating patients with liver metastases from primary large bowel cancer. Ann Oncol 12(12):1711–1720
68. Cosimelli M, Golfieri R, Cagol P et al (2010) Multi-centre phase II clinical trial of yttrium-90 resin microspheres alone in unresectable, chemotherapy refractory colorectal liver metastases. Br J Cancer 103(3):324–331
69. Nordlinger B, Guiguet M, Vaillant JC et al (1996) Surgical resection of colorectal carcinoma metastases to the liver: a prognostic scoring system to improve case selection, based on 1568 patients. Cancer 77(7):1254–1262
70. Fernandez FG, Drebin JA, Linehan DC, Dehdashti F, Siegel BA, Strasberg SM (2004) Five-year survival after resection of hepatic metastases from colorectal cancer in patients screened by positron emission tomography with F-18 fluorodeoxyglucose (FDG-PET). Ann Surg 240 (3):438
71. Berber E, Flesher N, Siperstein AE (2002) Laparoscopic radiofrequency ablation of neuroendocrine liver metastases. World J Surg 26(8):985–990
72. Oshowo A, Gillams A, Harrison E, Lees W, Taylor I (2003) Comparison of resection and radiofrequency ablation for treatment of solitary colorectal liver metastases. Br J Surg 90 (10):1240–1243

73. Aloia TA, Vauthey J-N, Loyer EM et al (2006) Solitary colorectal liver metastasis: resection determines outcome. Arch Surg 141(5):460–467
74. White R, Avital I, Sofocleous C et al (2007) Rates and patterns of recurrence for percutaneous radiofrequency ablation and open wedge resection for solitary colorectal liver metastasis. J Gastrointest Surg 11(3):256–263
75. Berber E, Tsinberg M, Tellioglu G, Simpfendorfer CH, Siperstein AE (2008) Resection versus laparoscopic radiofrequency thermal ablation of solitary colorectal liver metastasis. J Gastrointest Surg 12(11):1967–1972
76. Lee W-S, Yun SH, Chun H-K et al (2008) Clinical outcomes of hepatic resection and radiofrequency ablation in patients with solitary colorectal liver metastasis. J Clin Gastroenterol 42(8):945–949
77. Hur H, Ko YT, Min BS et al (2009) Comparative study of resection and radiofrequency ablation in the treatment of solitary colorectal liver metastases. Am J Surg 197(6):728–736
78. Aloia TA, Vauthey J-N, Loyer EM et al (2006) Solitary colorectal liver metastasis: resection determines outcome. Arch Surg 141(5):460
79. Tsai S, Pawlik TM (2009) Outcomes of ablation versus resection for colorectal liver metastases: are we comparing apples with oranges? Ann Surg Oncol 16(9):2422–2428
80. Gleisner AL, Choti MA, Assumpcao L, Nathan H, Schulick RD, Pawlik TM (2008) Colorectal liver metastases: recurrence and survival following hepatic resection, radiofrequency ablation, and combined resection-radiofrequency ablation. Arch Surg 143 (12):1204
81. Wong SL, Mangu PB, Choti MA et al (2010) American Society of Clinical Oncology 2009 clinical evidence review on radiofrequency ablation of hepatic metastases from colorectal cancer. J Clin Oncol 28(3):493–508
82. Goldberg RM, Sargent DJ, Morton RF et al (2004) A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 22(1):23–30
83. Vauthey J-N, Pawlik TM, Ribero D et al (2006) Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol 24(13):2065–2072
84. Adam R, Delvart V, Pascal G et al (2004) Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg 240(4):644
85. Capussotti L, Luca VM, Ferrero A, Tesoriere RL, Ribero D, Polastri R (2007) Timing of resection of liver metastases synchronous to colorectal tumor: proposal of prognosis-based decisional model. Ann Surg Oncol 14(3):1143–1150
86. Pawlik TM, Cosgrove D (2011) The role of peri-operative chemotherapy for resectable colorectal liver metastasis: what does the evidence support? J Gastrointest Surg 15(3):410–415
87. van Vledder MG, de Jong MC, Pawlik TM, Schulick RD, Diaz LA, Choti MA (2010) Disappearing colorectal liver metastases after chemotherapy: should we be concerned? J Gastrointest Surg 14(11):1691–1700
88. Bischof D, Clary B, Maithel S, Pawlik T (2013) Surgical management of disappearing colorectal liver metastases. Br J Surg 100(11):1414–1420
89. Bhattacharjya S, Bhattacharjya T, Baber S, Tibballs J, Watkinson A, Davidson B (2004) Prospective study of contrast-enhanced computed tomography, computed tomography during arterioportography, and magnetic resonance imaging for staging colorectal liver metastases for liver resection. Br J Surg 91(10):1361–1369
90. Kamel IR, Choti MA, Horton KM et al (2003) Surgically staged focal liver lesions: accuracy and reproducibility of dual-phase helical CT for detection and characterization1. Radiology 227(3):752–757

91. Oliva MR, Mortele KJ, Segatto E et al (2006) Computed tomography features of nonalcoholic steatohepatitis with histopathologic correlation. J Comput Assist Tomogr 30 (1):37–43
92. Tan MC, Linehan DC, Hawkins WG, Siegel BA, Strasberg SM (2007) Chemotherapy-induced normalization of FDG uptake by colorectal liver metastases does not usually indicate complete pathologic response. J Gastrointest Surg 11(9):1112–1119
93. Fong Y, Saldinger PF, Akhurst T et al (1999) Utility of $_{18}$F-FDG positron emission tomography scanning on selection of patients for resection of hepatic colorectal metastases. Am J Surg 178(4):282–287
94. van Kessel CS, Buckens CF, van den Bosch MA, van Leeuwen MS, van Hillegersberg R, Verkooijen HM (2012) Preoperative imaging of colorectal liver metastases after neoadjuvant chemotherapy: a meta-analysis. Ann Surg Oncol 19(9):2805–2813
95. Modlin IM, Oberg K, Chung DC et al (2008) Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol 9(1):61–72
96. Frilling A, Modlin IM, Kidd M et al (2014) Recommendations for management of patients with neuroendocrine liver metastases. Lancet Oncol 15(1):e8–e21
97. Hashim YM, Trinkaus KM, Linehan DC et al (2014) Regional lymphadenectomy is indicated in the surgical treatment of pancreatic neuroendocrine tumors (PNETs). Ann Surg 259(2):197–203
98. Chamberlain RS, Canes D, Brown KT et al (2000) Hepatic neuroendocrine metastases: does intervention alter outcomes? J Am Coll Surg 190(4):432–445
99. Sarmiento JM, Heywood G, Rubin J, Ilstrup DM, Nagorney DM, Que FG (2003) Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. J Am Coll Surg 197(1):29–37
100. Mayo SC, de Jong MC, Pulitano C et al (2010) Surgical management of hepatic neuroendocrine tumor metastasis: results from an international multi-institutional analysis. Ann Surg Oncol 17(12):3129–3136
101. McEntee G, Nagorney D, Kvols L, Moertel C, Grant C (1990) Cytoreductive hepatic surgery for neuroendocrine tumors. Surgery 108(6):1091–1096
102. Mayo SC, de Jong MC, Bloomston M et al (2011) Surgery versus intra-arterial therapy for neuroendocrine liver metastasis: a multicenter international analysis. Ann Surg Oncol 18 (13):3657–3665
103. Austin PC (2011) An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivar Behav Res 46(3):399–424
104. John BJ, Davidson BR (2012) Treatment options for unresectable neuroendocrine liver metastases. Expert Rev Gastroenterol Hepatol 6(3):357–369
105. Strosberg J, Gardner N, Kvols L (2009) Survival and prognostic factor analysis of 146 metastatic neuroendocrine tumors of the mid-gut. Neuroendocrinology 89(4):471–476
106. Givi B, Pommier SJ, Thompson AK, Diggs BS, Pommier RF (2006) Operative resection of primary carcinoid neoplasms in patients with liver metastases yields significantly better survival. Surgery 140(6):891–898
107. Ahmed A, Turner G, King B et al (2009) Midgut neuroendocrine tumours with liver metastases: results of the UKINETS study. Endocr Relat Cancer 16(3):885–894
108. Norlén O, Stålberg P, Öberg K et al (2012) Long-term results of surgery for small intestinal neuroendocrine tumors at a tertiary referral center. World J Surg 36(6):1419–1431
109. Capurso G, Rinzivillo M, Bettini R, Boninsegna L, Fave GD, Falconi M (2012) Systematic review of resection of primary midgut carcinoid tumour in patients with unresectable liver metastases. Br J Surg 99(11):1480–1486
110. Rahman A, Assifi MM, Pedroso FE et al (2012) Is resection equivalent to transplantation for early cirrhotic patients with hepatocellular carcinoma? A meta-analysis. J Gastrointest Surg 16(10):1897–1909
111. Lee KK, Kim DG, Moon IS, Lee MD, Park JH (2010) Liver transplantation versus liver resection for the treatment of hepatocellular carcinoma. J Surg Oncol 101(1):47–53

112. Wu Y-Z, Li B, Wang T, Wang S-J, Zhou Y-M (2011) Radiofrequency ablation vs hepatic resection for solitary colorectal liver metastasis: a meta-analysis. World J Gastroenterol: WJG 17(36):4143
113. Reuter NP, Woodall CE, Scoggins CR, McMasters KM, Martin RC (2009) Radiofrequency ablation vs. resection for hepatic colorectal metastasis: therapeutically equivalent? J Gastrointest Surg 13(3):486–491