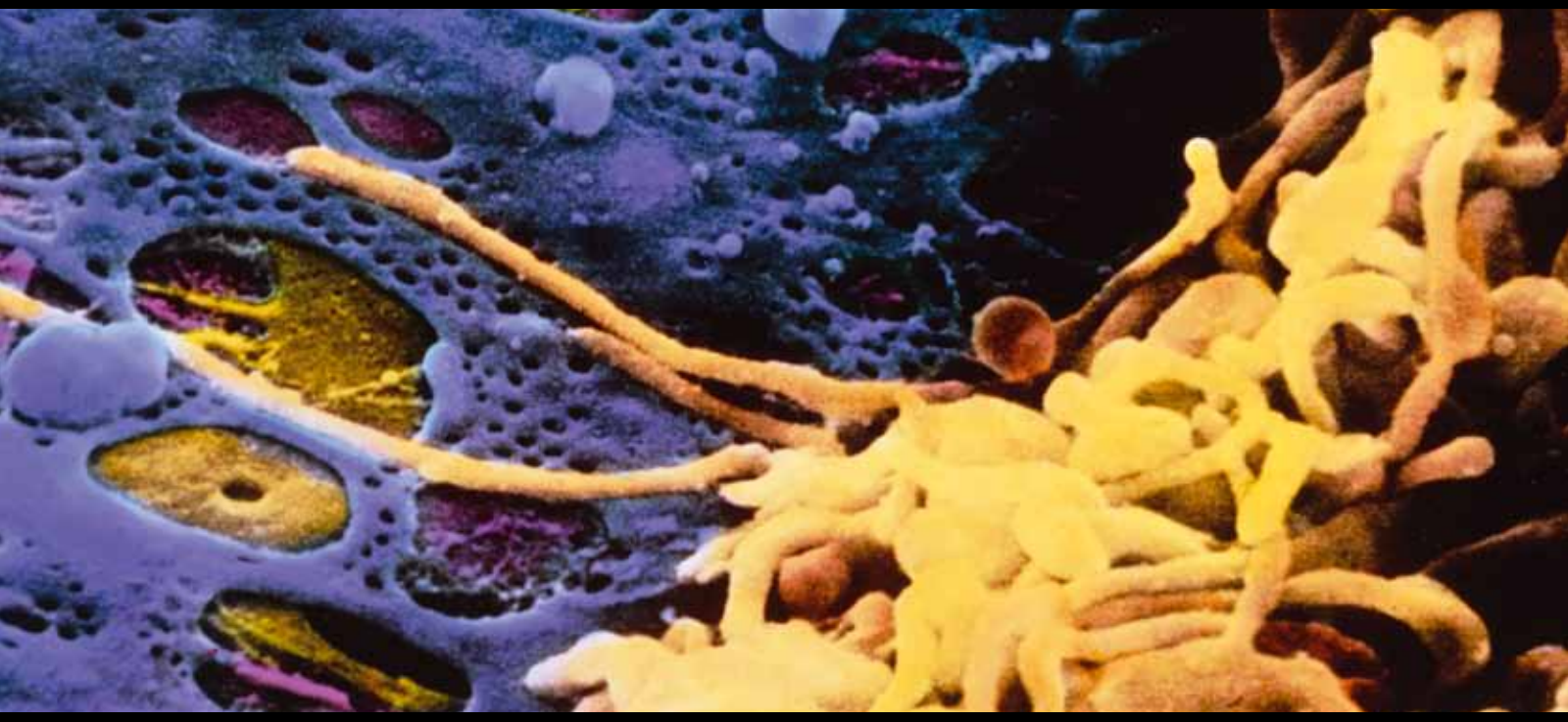
International Journal of Hepatology

Metastatic Lesions to the Liver

Guest Editors: Jorge Ortiz, David K. Imagawa, Roberto Verzaro, Francesco Serafini, and Liise K. Kayler



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Editorial

Metastatic Lesions to the Liver

Jorge Ortiz,[1] David K. Imagawa,[2] Roberto Verzaro,[3] Francesco Serafini,[4] and Liise K. Kayler[5]

[1] *Einstein Medical Center, USA*
[2] *Department of Surgery, University of California, USA*
[3] *Surgery Department ISMETT, Italy*
[4] *Downstate Medical Center, USA*
[5] *Department of Surgery, University of Florida Medical Center, USA*

Correspondence should be addressed to Jorge Ortiz; jorgeortiz2275@gmail.com

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Welcome to this issue of International Journal of Hepatology. The focus will be on metastatic lesions to the liver. We are hopeful that this topic will be of interest to hepatobiliary surgeons, surgical oncologists, medical oncologists, and CT, MR, and interventional radiologists.

Liang et al. review hepatic arterial infusion for liver lesions. This therapeutic modality has been propounded since the 1990s by Margaret and Nancy Kemeny, a surgical and medical oncologist, respectively. Liang et al. relate that hepatic arterial infusion may provide good locoregional control of liver tumors. It may be particularly beneficial for colorectal tumors in combination with systemic chemotherapy. Exciting new medications infused through the device may one day lead to stunning advances in this field.

Kelly et al. review hepatobiliary contrast-enhanced magnetic resonance imaging for liver metastasis from colorectal cancer. They provide a succinct summary of this topic which should improve the surgeon's ability to plan the appropriate surgical approach and consent patients correctly.

Kele et al. revealed a lack of anatomical concordance between preablation and postablation CT images, which may be a risk factor related to ablation site recurrence. This is very important since accurate ablation of metastatic lesions remains the cornerstone of excellent long-term outcomes. Additionally, early detection of recurrence and risk factors for said recurrence are necessary in order to initiate timely retreatment.

Bacchetti et al. review, via a meta-analysis,surgical treatment and survival for metastatic neuroendocrine tumors. They found a significantly longer survival in patients treated surgically compared to those treated with embolization. This meta-analysis is another example of advances made in this field including transplantation and new medications.

Nguyen-Khac et al. review hepatotoxicity (particularly sinusoidal dilatation) associated with chemotherapy. This is particularly important since many patients receive many courses of chemotherapy before and after surgical intervention. Hopefully, with the advent of new medications, these side effects will be attenuated.

We believe this issue is just the beginning in a long line of special issues which will lead to greater understanding of complex hepatologic issues and improved outcomes for our patients.

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Review Article

Modern Prospection for Hepatic Arterial Infusion Chemotherapy in Malignancies with Liver Metastases

Yi-Hsin Liang,[1,2] Yu-Yun Shao,[2,3] Jia-Yi Chen,[2] Po-Chin Liang,[4] Ann-Lii Cheng,[2,3,5] and Zhong-Zhe Lin[2,5]

[1] *Department of Hemato-Oncology, E-Da Hospital, No. 1, Yi-da Road, Jiaosu Village, Yanchao, Kaohsiung 82445, Taiwan*
[2] *Department of Oncology, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei City 10002, Taiwan*
[3] *Graduate Institute of Oncology, College of Medicine, National Taiwan University, No. 1, Section 1, Ren-Ai Road, Taipei City 10051, Taiwan*
[4] *Department of Medical Imaging, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei City 10002, Taiwan*
[5] *Department of Internal Medicine, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei City 10002, Taiwan*

Correspondence should be addressed to Zhong-Zhe Lin; zzlin7460@ntu.edu.tw

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Malignancy with liver metastasis plays an important role in daily oncology practice, especially for primary cancers of the gastrointestinal tract and hepatopancreatobiliary system. On account of the dual vascular supply system and the fact that most metastatic liver tumors are supplied by the hepatic artery, hepatic artery infusion chemotherapy (HAIC) is an appealing method for the treatment of liver metastases. Herein, we summarize recent study results reported in the literature regarding the use of HAIC for metastatic liver tumors, with special focus on colorectal cancer.

1. Introduction

Malignancy with liver metastasis plays an important role in daily oncology practice, especially for primary cancers of the gastrointestinal (GI) tract and hepatopancreatobiliary system [1]. The liver is commonly the first site of distant metastasis. For example, about three-quarters of patients with stage IV colorectal cancer (CRC) have liver metastases [2]. Many of these patients have metastatic disease confined to the liver only. It has been demonstrated that for patients with such limited distant metastases, locoregional therapy such as surgery may be helpful [3, 4]. However, usually the liver metastases are too advanced to be resected by hepatectomy. Fewer than 15% of these patients receive hepatectomy to a curative extent [5].

On account of the dual vascular supply system and the fact that most metastatic liver tumors are supplied by the hepatic artery [6, 7], hepatic artery infusion chemotherapy (HAIC) is an appealing method for the treatment of liver metastases. HAIC has several advantages over intravenous chemotherapy. First, chemotherapeutic agents can be delivered more specifically to malignant cells. Normal hepatocytes that mostly rely on the portal venous system are thus exposed to fewer chemotherapeutic agents. Second, many chemotherapy agents used in HAIC have a high first-pass hepatic clearance effect, such as 5-fluorouracil (5-FU) and floxuridine (FUDR), a prodrug of 5-FU. Over 90% of FUDR and 19%–50% of 5-FU are cleared by the liver when they are administered by HAIC [8]. Systemic exposure to chemotherapeutic agents is thus decreased.

These two mechanisms enable HAIC to provide a higher exposure of chemotherapy to malignant cells with minimized toxicities. The higher drug level may also overcome drug resistance. For example, intravenous (IV) anthracyclines are generally considered ineffective for CRC. HAIC with pirarubicin, an anthracycline that is an analogue of doxorubicin, has been demonstrated to have a fair efficacy in CRC patients with liver metastases [9–11].

The equipment and skills related to HAIC have been in development for more than 5 decades. With advances in implantable catheters and ports, external infusion pumps can be avoided to decrease catheter-related complications. Catheter implantation is generally performed via the femoral, axillary, or subclavian arteries under fluoroscopic guidance [12–15]. The angiography should be carefully reviewed before and after catheter implantation to identify any anomalous vasculature. The tips of HAIC catheters are fixed at the gastroduodenal artery or proper hepatic artery. The HAIC ports are then immobilized subcutaneously. Finally, a perfusion scan is usually performed for HAIC catheters to detect any unexpected shunting to other organs.

Adverse reactions to HAIC can be divided into catheter-related complications and chemotherapy-related complications. Common catheter-related complications include catheter displacement, hepatic artery occlusion, and catheter-related infection [16–18]. The complication rates for these issues have been reported to be lower than 7% in recent studies, compared to 22–35% in earlier studies. The most common chemotherapy-related complication is gastrointestinal symptoms. Nausea and vomiting can occur in 25–35% patients [17, 19]. Hepatobiliary toxicity, including elevation of serum hepatic transaminase levels, and hyperbilirubinemia are also important problems [20–23].

Although the rationale for the use of HAIC for metastatic liver tumors is appealing, the actual benefit of HAIC is not wholly clear. The lack of large randomized clinical trials makes it difficult to examine the overall survival benefits. However, results from previous studies are accumulating gradually and could provide some hints as to the actual efficacy of HAIC for metastatic liver tumors. Herein, we summarize recent study results reported in the literature with regards to the use of HAIC for metastatic liver tumors, with special focus on CRC.

2. Colorectal Cancer

2.1. HAIC Combined with Systemic Chemotherapy. CRC is the third most prevalent malignant disease around the world [24, 25]. Despite screening and early surgery, many patients eventually suffer from metastatic disease. The liver is the most frequent metastatic site of CRC. CRC with liver metastasis becomes an important issue for treatment of metastatic CRC, and HAIC potentially provides good local control with a response rate (RR) ranging from 34% to 92% (Table 1) when combined with systemic chemotherapy.

Mancini et al. conducted a clinical trial that enrolled 123 CRC patients with unresectable liver metastasis [27]. The patients were randomized into two arms. In arm one, patients received intravenous 5-FU chemotherapy and infusional cisplatin via HAIC. In arm two, patients received intravenous 5-FU chemotherapy and bolus cisplatin via HAIC. There was no significant difference in response between the two arms, and thus, treatment response was presented as a combination of all patients in the two arms. The overall RR was 52%, which included a 17% complete response rate. The median overall survival (OS) was 18 months and 28 months for all patients and responders, respectively. Kemeny et al. conducted a clinical trial that enrolled 49 patients with CRC who had unresectable liver-confined metastasis only [31]. The patients received intravenous oxaliplatin and irinotecan (CPT-11) combined with FUDR via HAIC. The overall RR was 92%, which included a 8% complete response rate [31]. The median OS was 50.8 months for chemotherapy-naïve patients and 35 months for previously-treated patients.

Although these studies did not incorporate targeted therapy agents, the reported response rates are comparable to current standards using combination therapy with targeted and cytotoxic chemotherapy. However, whether the addition of HAIC to current standard treatment, which generally provides a high response rate of 47%–64%, is useful remains unclear [32–35]. Recently, targeted therapy has also been used with HAIC in some small series. Bouchahda et al. demonstrated that HAIC could be combined with intravenous cetuximab in two patients in a retrospective study [36]. Further research with different combinations of novel targeted therapy is warranted.

2.2. Reversing Inoperable Disease to Operable Disease. For patients with CRC and liver-only metastatic disease, complete resection provides the chance of a cure. When liver metastatic disease develops, complete resection can provide a potential cure for CRC patients. However, only 10–15% of these patients are eligible for such surgery upon diagnosis [5]. Because of the high response rate, HAIC may reverse inoperable liver metastatic disease to an operable status.

Kemeny et al. conducted a clinical trial examining the use of intravenous oxaliplatin and CPT-11 combined with FUDR via HAIC for patients with CRC-related unresectable liver-confined metastasis only [31]. Initially, 98% of these resectable cases had bilobar metastatic lesions, and 73% of them had >5 hepatic lesions. The overall RR was high at 92%. Twenty-three (47%) patients eventually received hepatectomy to a curative extent. Yamaguchi et al. conducted a clinical trial that enrolled 22 patients who had CRC and unresectable liver metastasis to receive intravenous CPT-11 with oral tegafur/uracil in combination with 5-FU via HAIC [26]. The definition of unresectability included (1) tumors involved all liver segments, (2) inadequate liver reservation after resection, and (3) tumors involved all main hepatic veins or both inflow pedicles. The overall RR was 86.4%, and eventually 14 patients (63.6%) underwent complete resection of liver tumors.

Other than 5-FU, oxaliplatin and CPT-11 have also been tested in HAIC. Ducreux et al. conducted a clinical trial that enrolled 28 patients who had CRC-related inoperable liver-confined metastatic diseases only [37]. Twenty-one of these patients had received previous intravenous 5-FU therapy. The patients then received intravenous 5-FU and leucovorin (LV) with oxaliplatin infused via HAIC. The RR was 64%, and the median overall survival (OS) was 27 months. Approximately 18% of patients' diseases became operable following therapy. The same group then further applied this regimen in a second-line setting [38]. Boige et al. conducted a clinical trial that enrolled 44 patients who had CRC-related inoperable

Table 1: Selective studies of combining HAIC with systemic chemotherapy for colorectal cancer.

Authors	Year	Setting	Treatment	Line	Inclusion population	Patient no. (treat[a])	Median OS (months)	RR	Note
Yamaguchi et al. [26]	2011	Pro, phase I/II	HAIC → 5-FU IV → CPT-11 + LV Oral tegafur/uracil	First line	Unresectable hepatic mets	Phase 1: 12 (12) Phase 2: 22 (22)	Not reach	86.4%	RCR: 63.6%
Mancini et al. [27]	2003	Pro, Ran	Arm1: HAIC → continuous cisplatin IV → 5-FU Arm2: HAIC → bolus cisplatin IV → 5-FU	First line	Unresectable hepatic mets	58 (58) 65 (65)	18	52%	
Goéré et al. [28]	2010	Ret	HAIC → oxaliplatin IV → 5-FU + LV	First line: 18 Second line: 69	Unresectable hepatic mets	87 (87)	NM	55%	5-year survival: 56%
Gallagher et al. [29]	2007	Ret	HAIC → FUDR + Dexa IV → CPT-11	Failed oxaliplatin	Unresectable hepatic mets	39 (39)	18	44%	
Pilati et al. [30]	2009	Ret	Arm1: HAIC → FUDR + LV Arm2: HAIC → FUDR + LV IV → 5-FU + LV	NM	Unresectable hepatic mets	72 (72) 81 (81)	18 19.1	52.7% 50.6%	

Selected studies that enroll patients with colorectal cancer to receive systemic chemotherapy in combination with HAIC are listed here. Studies designed for patients with colorectal cancer-related liver-confined metastatic disease were listed in Table 2.

*With statistical significance.

[a]Actual patients' number who received treatment.

Abbreviations—OS: overall survival, RR: response rate, Pro: prospective, Ran: randomized, Ret: retrospective, NM: not mentioned, HAIC: hepatic artery infusion chemotherapy, IV: intravenous, FUDR: floxuridine, LV: leucovorin, Dexa: dexamethasone, CPT-11: irinotecan, Mets: metastasis, and RCR: resectability conversion rate.

liver-confined metastatic diseases only and in whom first-line chemotherapy failed [38]. Treatment of twenty-eight of these patients with 5-FU, oxaliplatin, and CPT-11 had previously failed. For only one patient, 5-FU alone failed, and in the others both 5-FU and either CPT-11 or oxaliplatin treatment failed. The RR was 62% and the median overall survival (OS) was 16 months. Similarly, 18% of patients' disease became operable following therapy.

For HAIC, the hepatic resectability conversion rate is worthy of emphasis. The current standard treatment, combined targeted and cytotoxic chemotherapy, usually generates a less than 10% hepatic resectability conversion rate according to post hoc analysis [32, 35, 39]. Folprecht et al. conducted the CELIM study that enrolled 114 patients who had CRC and inoperable liver-confined metastatic diseases who received intravenous cetuximab and combination cytotoxic chemotherapy [40]. Overall, 38% of patients eventually received curative hepatectomy. It is worthy of note that 32% of patients with paired images before and after surgery in CELIM trial were considered operable prior to chemotherapy when the images were reviewed centrally. Although there has been no large-scale phase III trial to prove the concept that HAIC might improve the liver resectability conversion rate, the above results are promising, with high response rates and good conversion rates of reversing inoperable disease to operable disease. The outcome is even more encouraging considering that these studies did not incorporate novel targeted agents, such as bevacizumab and cetuximab.

2.3. Liver-Confined Disease. Some patients who receive local therapy for early CRC may suffer from recurrence, with liver metastasis as the only disease site (liver-confined disease). Although systemic chemotherapy is the standard treatment for metastatic CRC, some of these patients had had their primary cancer treated previously and suffered from liver-confined metastatic disease. For these patients, it is reasonable to develop a local therapy with an enhanced efficacy against liver metastases. The mechanism of HAIC suits this purpose.

HAIC exhibits a high RR, ranging from 22% to 92%, albeit with an unclear effect on overall survival in this setting (Table 2). In the CALGB 9481 trial, 135 CRC patients with inoperable liver-confined disease were randomly assigned to receive FUDR via HAIC or intravenous bolus 5-FU and LV [41]. Patients who received HAIC compared to patients who received IV chemotherapy had a significantly higher RR (47% versus 24%, $P = 0.012$) and a longer median OS (24.4 months versus 20.0 months; $P = 0.003$). Patients treated with HAIC had a significantly longer time to hepatic progression compared to patients who received IV chemotherapy (9.8 months versus 7.3 months; $P = 0.034$), but a significantly shorter time to extrahepatic progression (7.7 months versus 14.8 months; $P = 0.029$).

Besides FUDR or 5-FU, mitomycin-C (Mit-C) has also been used in HAIC [47, 49]. Kemeny et al. randomly assigned 63 CRC patients with inoperable liver-confined disease to receive high-dose Mit-C and FUDR/LV via HAIC [47].

Table 2: Selective studies of HAIC for liver-confined metastatic disease from colorectal cancer.

Authors/ Year	Setting	Treatment	Line	Inclusion population	Patient no. (treat)[a]	Median OS (months)	RR	Note
Kemeny et al. 2006 [41]	Pro, Ran	Arm1: HAIC → FUDR + LV + Dexa Arm2: IV → 5-FU + LV	First line	Unresectable liver confined	68 (59) 67 (58)	24.4* 20	47%* 24%	QOL improvement
Fiorentini et al. 2006 [42]	Pro, phase III	Arm1: HAIC → 5-FU + LV Arm2: HAIC → 5-FU + LV IV → 5-FU + LV	First line	Unresectable liver confined	40 (36) 42 (40)	14 20	41.7% 47.5%	
Fallik et al. 2003 [11]	Pro, phase II	HAIC → pirarubicin IV → 5-FU + LV	First line	Unresectable liver confined	75 (69)	20	34.4%	
Kerr et al. 2003 [43]	Pro, Ran	Arm1: HAIC → 5-FU + LV Arm2: IV → 5-FU + LV	First line	Unresectable liver confined	145 (95) 145 (126)	14.7 14.8	22% 19%	
Allen-Mersh et al. 2000 [44]	Pro, Ran	Arm1: HAIC → FUDR IV → 5-FU + LV Arm2: IV → 5-FU	First line	Unresectable liver confined	41 (39) 43 (42)	NM	45% 23%	No QOL difference
Lorenz et al. 2000 [45]	Pro, Ran	Arm1: HAIC → 5-FU + LV Arm2: IV → 5-FU + LV Arm3: HAIC → FUDR	First line	Unresectable liver confined	57 (40) 57 (71)[b] 54 (37)	18.7 17.6 12.7	45% 19.7% 43.2%	
Kemeny et al. 2009 [31]	Pro, phase I	HAIC → FUDR + Dexa IV → oxaliplatin + CPT-11	First line: 23 Second line: 26	Unresectable liver confined	49 (49)	First line: 50.8 Second line: 35	92%	RCR: 47%
Ducreux et al. 2005 [37]	Pro	HAIC → Oxaliplatin IV → 5-FU + LV	First line: 7 Second line: 21	Unresectable liver confined	28 (26)	27	64%	RCR: 18%
Kemeny et al. 2005 [46]	Pro, phase I	Arm1: HAIC → FUDR + DEXA IV → oxaliplatin + CPT-11 Arm2: HAIC → FUDR + DEXA IV → oxaliplatin + 5-FU + LV	First line: 4 After first line: 32	Unresectable liver confined	36 (36)	36 22	90% 87%	
Kemeny et al. 2009 [31]	Pro, phase I	HAIC → FUDR + Dexa IV → Oxaliplatin + CPT-11	First line: 23 Second line: 26	Unresectable liver confined	49 (49)	First line: 50.8 Second line: 35	92%	RCR: 47%
Kemeny et al. 2005 [47]	Pro, phase II	HAIC → FUDR + Dexa + Mit-C	First line: 26 Second line: 37	Unresectable liver confined	63 (63)	First line: 23 Second line: 20	First line: 73% Second line: 70%	
Lorenz et al. 2001 [48]	Pro, phase II	HAIC → 5-FU + LV	First line: 40 Second line: 10	Unresectable liver confined	50 (50)	22.3	56%	

Table 2: Continued.

Authors/ Year	Setting	Treatment	Line	Inclusion population	Patient no. (treat)[a]	Median OS (months)	RR	Note
Boige et al. 2008 [38]	Pro	HAIC → oxaliplatin IV → 5-FU + LV	After first line	Unresectable liver confined	44 (43)	16	62%	RCR: 18%
Fazio et al. 2003 [49]	Ret	HAIC → cisplatin + Mit-C + 5-FU	After first line	Hepatic mets predominent[c]	45 (44)	NM	35%	
Kemeny et al. 2001 [50]	Pro, phase I	HAIC → FUDR + DEXA IV → CPT-11	After first line	Unresectable liver confined	46 (46)	17.2	74%	
Van Riel et al. 2000 [51]	Ret	HAIC → 5-FU	All	Hepatic mets predominent[c]	145 (145)	14.3 m	34%	Hepatic artery thrombosis (48%)
Fujimoto et al. 2009 [52]	Ret	HAIC → 5-FU	NM	Unresectable liver confined	72 (72)	18	38%	
Sameshima et al. 2007 [53]	Ret	HAIC → 5-FU	NM	Unresectable liver confined	42 (42)	29.1	57%	

Selected studies that enroll patients with colorectal cancer-related liver-confined metastatic disease are listed here. Studies designed for patients with colorectal cancer to receive systemic chemotherapy in combination with HAIC are listed in Table 1.

[*] With statistical significance.

[a] Actual patients' number who received treatment.

[b] Patients who did not receive treatment in arm1 and arm3 received treatment as arm2.

[c] Trial enrolled patients with liver-confined disease or "minimal" extrahepatic disease.

Abbreviations—OS: overall survival, RR: response rate, Pro: prospective, Ran: randomized, Ret: retrospective, NM: not mentioned, HAIC: hepatic artery infusion chemotherapy, IV: intravenous, FUDR: floxuridine, LV: leucovorin, Dexa: dexamethasone, Mit-C: mitomycin C, CPT-11: irinotecan, QOL: quality of life, Mets: metastasis, and RCR: resectability conversion rate.

The RR was 73% in the chemotherapy-naïve patients and 70% in previously-treated patients. However, the expense was a high biliary toxicity. Elevation of the serum bilirubin level >3 mg/dL occurred in 22.5% patients. Half of the patients suffered from at least a doubling of the serum hepatic transaminase level. Besides, biliary sclerosis was noted in 6 patients (9.5%) and liver bilomas in 5 (7.9%) patients.

Fallik et al. enrolled 75 patients with CRC and inoperable liver-confined metastatic diseases in a phase II trial [11]. All patients received intravenous 5-FU and LV in combination with HAIC using pirarubicin, an anthracycline analog. The overall RR was 31.9% and the median OS was 19 months. Most important was that grade 4 neutropenia was reported for 27 cycles (23%). The toxicity profile seemed acceptable in this trial and no cardiac toxicity was reported.

Several small studies in the literature have addressed the use of HAIC in liver-confined disease of CRC. The study designs and results were heterogeneous across these trials. Therefore, Mocellin et al. conducted a meta-analysis to compare HAIC and intravenous chemotherapy for liver-confined metastatic diseases of CRC [54, 55]. Ten randomized controlled trials, including a total of 1277 patients, were enrolled in the analysis. All studies used 5-FU or FUDR as single agents via HAIC or intravenous chemotherapy. Although the RR was significantly higher in patients receiving HAIC than in patients receiving intravenous chemotherapy (42.9% versus 18.4%, $P < 0.001$), the median OS was not significantly longer (15.9 months versus 12.4 months, $P = 0.240$).

The result of this meta-analysis should be interpreted cautiously. The analyzed ten clinical trials were mostly conducted a decade ago and used 5-FU only in intravenous chemotherapy, which is clearly inadequate as compared with present therapies. This explains the inferior OS outcome of 12 months only in either treatment arm and the uncertainty regarding the interpretation of this meta-analysis result. On the contrary, many patients who were allocated into the HAIC arms in these trials did not receive HAIC mainly due to catheter-related complications. Some of them were allowed to cross over into intravenous chemotherapy arms but still analyzed as HAIC in an intent-to-treat manner. All these reasons suggest difficulty in interpretation of this meta-analysis.

According to current evidence, HAIC demonstrates better locoregional control for CRC patents with liver-confined disease, at the expense of poor extrahepatic disease progression. Although there was a survival benefit for HAIC-treated patients reported in the CALGB 9481 study, this OS benefit became nonsignificant when ten studies were enrolled into a meta-analysis. Evidence as to whether HAIC provides a better survival benefit than systemic therapy is thus still lacking, and further large-scale clinical trials are warranted. Except for 5-FU and FUDR, some other cytotoxic agents such as Mit-C and pirarubicin are also applied via HAIC. As we know, anthracycline drugs were thought to be ineffective in the treatment of CRC. However, anthracycline analogs demonstrated potential efficacy in CRC via HAIC because of their special mechanism, which provides a greater drug selection for the treatment of CRC.

2.4. HAIC after Curative Hepatectomy. With improvement in surgical techniques, more and more CRC patients with liver-confined metastasis receive surgery for both the primary CRC and liver tumors with a curative intent. Prevention of disease recurrence is crucial in these patients. Some physicians use a local treatment, HAIC, in this adjuvant setting.

Kemeny et al. enrolled 156 CRC patients who received complete resection of liver metastatic disease [56, 57]. These patients were randomized into groups receiving either intravenous 5-FU alone or in combination with HAIC using FUDR. In an updated result after a median follow-up duration of 10.3 years, patients who received combination therapy with HAIC had a significantly longer progression-free survival than patients who received intravenous therapy alone (31.3 months versus 17.2 months, $P = 0.02$) [57]. Although the OS was not significantly different, the trend still favored combination therapy with HAIC (68.4 months versus 58.8 months, $P = 0.10$).

Oxaliplatin is the current standard for adjuvant treatment of stage III CRC [58]. When the efficacy of newer agents for the treatment of CRC has been proven, they have been tested for HAIC. Alberts et al. conducted a phase II trial that enrolled 76 patients with CRC who had liver-confined metastasis [59]. After curative surgery for both the primary tumor and liver metastases, patients received adjuvant intra-venous oxaliplatin and oral capecitabine alternated with HAIC FUDR plus dexamethasone. Although 3 treatment-related deaths were reported, the median disease-free survival was 32.7 months and only 30 patients developed recurrent malignancies after median follow-up time of 4.8 years.

In addition to oxaliplatin, CPT-11 has also shown a fair efficacy for stage 4 CRC and thus was also examined in combination with HAIC. Kemeny et al. conducted a phase I/II trial that enrolled 96 patients with CRC who had liver-confined metastasis [60]. After curative surgery, patients received adjuvant intravenous CPT-11 combined with HAIC FUDR plus dexamethasone. With a median follow-up time of 26 months, the 2-year survival rate was 89%, and 1.5-year hepatic disease-free survival rate was 88%.

In the targeted therapy era, a combination of HAIC with novel targeted agents was also tested in some series. Kemeny et al. randomly assigned 73 CRC patients with resected liver-confined disease to receive curative hepatectomy [61]. All patients received intravenous oxaliplatin or CPT-11 plus infusional 5-FU in combination with FUDR plus dexamethasone via HAIC. Patients were randomized into two arms, receiving intravenous bevacizumab or not. The 4-year recurrence-free survival rate was 46% and 37% for the no bevacizumab arm and the bevacizumab arm ($P = 0.4$), respectively, after a median follow-up duration of 30 months.

There have recently been some convincing results showing a lower recurrence rate for HAIC in combination with systemic therapy after curative hepatectomy. Systemic chemotherapy after curative surgery for liver metastatic disease is still the standard treatment, and HAIC might provide enhanced locoregional control for the liver. Further large-scale phase III trials are warranted.

3. Other Malignancies

3.1. Gastric Cancer. The prognosis of gastric cancer with liver metastases is extremely poor, with median OS of only 2–6 months if untreated [62]. The standard treatment is combination systemic chemotherapy including platinum analogs and 5-FU. For better palliation, some case series reported the efficacy of HAIC as a liver-directed therapy. Tarazov reported the results of HAIC using 5-FU and doxorubicin in 12 patients with unresectable gastric cancer-related bilobar liver metastases [62]. The RR was 25% and the median OS was 23 months. One patient had 60 months of stable disease after 7 courses of HAIC treatment. Kumada et al. conducted a phase II trial that tested HAIC with 5-FU, epirubicin, and Mit-C in 63 patients with gastric cancer who had unresectable liver metastasis [63]. Only 36 patients were documented to have liver-confined metastatic diseases. The response rate was 55.6%, with three complete responders. For patients with liver-confined disease, the median OS was 13 months.

As a treatment for synchronous multiple liver metastases from gastric cancer after palliative gastrectomy to maintain quality of life, Ojima et al. retrospectively analyzed 18 patients who received HAIC with 5-FU [64]. The RR was 83% with a response duration of 7.6 months. The median OS was 19.2 months.

According to the limited data above, HAIC potentially provides high response rates in patients with liver metastases of gastric cancer. The median OS in these small groups of patients seemed longer given that the best survival in patients receiving systemic chemotherapy has been reported to be 13.8 months [65]. Therefore, HAIC might have the potential to be a feasible local treatment for gastric cancer with unresectable liver metastases.

3.2. Uveal Melanoma. Uveal melanoma usually hematogenously spreads into the liver in up to 95% patients [66]. Once liver metastases occur, the life expectancy is less than 5 months. Because no systemic therapy is proved to have definite efficacy for metastatic uveal melanoma, regional therapy to control liver metastases and delay extrahepatic spread

becomes one of the treatment choices. Melichar et al. performed HAIC with the combination of cisplatin, vinblastine, and dacarbazine in 10 liver metastatic uveal melanoma patients [67]. Two patients had partial response, and four patients achieved stable disease. Those who had clinical benefit survived for more than one year. Becker et al. conducted a phase II prospective clinical trial that enrolled 48 patients with metastatic uveal melanoma [66]. HAIC with fotemustine was given to the 23 patients who had liver metastases alone. Intravenous fotemustine was given to the 25 patients who had metastases other than liver. All patients received subcutaneous interleukin-2 and interferon α. The overall RR was significantly higher for patients who received HAIC than those patients who received intravenous chemotherapy (21.7% versus 8.0%). However, the median OS was similar (369 days versus 349 days).

With the therapeutic activity demonstrated above, HAIC might play a role to control liver-confined metastatic uveal melanoma. Comparing with the cumulating results from chemoembolization in uveal melanoma with liver metastases, the evidence for the better efficacy of HAIC is still scarce and needs more studies [68].

3.3. Pancreatic Cancer. The prognosis of pancreatic cancer is extremely poor because of the low resection rate at diagnosis, rapid progression, and frequent metastasis even after curative surgery. Despite the advances of cancer therapy generally, the survival of patients with pancreatic cancer did not improve significantly in the past decades. Liver is the most common site of metastasis, and thus, HAIC was examined as a strategy for palliation or prevention of liver metastasis. For unresectable pancreatic cancer without metastasis, HAIC was also examined as a primary treatment modality for primary tumors from pancreatic body and tails [69].

Homma et al. also enrolled 16 patients with pancreatic cancer-related liver metastases who received cisplatin and 5-FU via HAIC [70]. The RR was 68.8% with median survival 16.25 months.

There were few studies focusing on HAIC in the adjuvant setting. Hashimoto et al. conducted a retrospective analysis that enrolled 42 patients with pancreatic cancer who received curative pancreatectomy and subsequent 5-FU via HAIC [71]. Hepatic recurrence rate was 7.1% with a median 19-month followup.

From the above studies, HAIC for pancreatic cancer is a way for local treatment. Besides, HAIC also provides potential benefit to reduce recurrence after pancreatectomy, compared to the 36% recurrent rate reported by CONKO-001 study using systemic gemcitabine alone [72]. The cost of relative high complication rate remains the problem. Common complications include high probability of hepatic arterial stenosis (19.6%) and liver abscess (3.6%). Due to the limitation of various HAIC techniques and different vasculatures of each patient, large prospective trial is required for further investigation.

3.4. Biliary Tree Cancer. Due to limited effective therapy for unresectable and metastatic biliary tract cancers, HAIC was also applied in several studies. These studies of biliary tract cancer were heterogeneous in patient population, and most studies included more than one cancer type. Inaba et al. conducted a phase I/II trial for patients with unresectable intrahepatic cholangiocarcinoma [73]. HAIC with gemcitabine was applied in 13 patients. One patient had partial response and 8 patients had stable disease. The response rate was 7.7%. In addition to gemcitabine, cisplatin and epirubicin combination were also examined. Cantore et al. conducted a phase II study that enrolled 25 patients with metastatic intrahepatic cholangiocarcinoma and 5 patients with gallbladder carcinoma to receive intravenous 5-FU and HAIC with cisplatin and epirubicin [74]. Overall RR was 40% including 1 patient who achieved complete remission. Median OS was 13.2 months. Mambrini et al. conducted a phase II trial that enrolled 20 patients with unresectable metastatic intra- or extra-hepatic biliary tree cancers to receive oral capecitabine and HAIC using cisplatin and epirubicin [75]. The overall RR was 31.5%, and median OS was 18 months.

From the evidence of these phase II studies, combination HAIC with oral or intravenous chemotherapy seems to be a safe and effective treatment modality. With the advance of intervention radiology and radiotherapy techniques, multimodality treatment incorporating radiation, drug-eluting beads, and chemoembolization were also developing in combination with HAIC [76, 77]. Further comparison of different treatments modality and large scale phase III trials are needed.

3.5. Neuroendocrine Tumor. Gastroenteropancreatic neuroendocrine tumors often metastasize to liver and contribute substantially to one of the most important noncolorectal causes of liver metastases [78]. Due to limited patients numbers, HAIC for unresectable liver metastases from neuroendocrine tumors has mostly been studied retrospectively.

Christante et al. collected 77 patients with extensive liver metastases with disease progression after octreotide treatment [79]. Fifty-nine patients received four cycles of 5-FU via HAIC with the addition of selective chemoembolization at the end of third and fourth cycles. However, 18 patients received HAIC alone due to the concern of hepatotoxicity. Overall response rate was 80%, and median progression-free survival was 19 months, and all the responders were treated with combination of HAIC and chemoembolization.

Most of the HAIC studies in neuroendocrine tumors were conducted in combination with chemoembolization. Due to the limitation of scarce retrospective studies with HAIC treatment alone, the efficacy of HAIC for neuroendocrine tumors seems to be difficult to clearly be identified based on current evidences. Further studies are warranted.

4. Conclusion

In this article, we presented the current lines of evidence of HAIC as a treatment of liver metastases. HAIC provides a good locoregional control to liver tumors. Most of evidences mainly came from studies of CRC. For patients with CRC and inoperable liver metastasis, HAIC has potentials to

enhance the treatment response of the liver metastases when combined with systemic chemotherapy. For CRC patients who had failed previous intravenous chemotherapies, HAIC still provides fair efficacy of control to liver tumors. Patients with initially considered inoperable liver metastases could have a chance to receive surgery if HAIC converts the tumors back to operable status. However, the evidence to support if HAIC could totally replace the intravenous chemotherapies is still not strong enough across previous trials. Therefore, current standard for liver metastatic CRC is still intravenous chemotherapy, and HAIC could be provided as local control focusing on liver. As for CRC patients with initially operable liver metastatic tumors who received curative operation, HAIC in combination with intravenous chemotherapies demonstrated good competence to reduce liver recurrent and to subsequently prolong the overall survival. Some new agents could be used in HAIC in combination to systemic agents, such as pirarubicin, which is initially considered ineffective for CRC. With the emergent novel agents and targeted agents in the 21 century, more studies are needed for different combinations with HAIC.

HAIC is also applied for other malignant diseases with liver metastases, especially for those malignancies which have poor response to systemic chemotherapy, such as melanoma or pancreatic cancer. Although the results for large-scale prospective phase III trials are warranted, HAIC seems to become an attractive procedure for hepatic metastatic diseases in the future.

Abbreviations

CRC: Colorectal cancer
HAIC: Hepatic artery infusion chemotherapy
OS: Overall survival
5-FU: 5-Fluorouracil
FUDR: Floxuridine
RR: Response rate
CPT-11: Irinotecan
LV: Leucovorin
TACE: Transarterial chemoembolization
MIT-C: Mitomycin C
IV: Intravenous
GI: Gastrointestinal.

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Review Article

Gd-EOB-DTPA-Enhanced MRI for Detection of Liver Metastases from Colorectal Cancer: A Surgeon's Perspective!

Kelly J. Lafaro, Panayota Roumanis, Aram N. Demirjian, Chandana Lall, and David K. Imagawa

University of California, Irvine, 333 The City Boulevard West, Suite 1205, Orange, CA 92868, USA

Correspondence should be addressed to David K. Imagawa; dkimagaw@uci.edu

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Colorectal cancer affects over one million people worldwide annually, with the liver being the most common site of metastatic spread. Adequate resection of hepatic metastases is the only chance for a cure in a subset of patients, and five-year survival increases to 35% with complete resection. Traditionally, computed tomographic imaging (CT) was utilized for staging and to evaluate metastases in the liver. Recently, the introduction of hepatobiliary contrast-enhanced magnetic resonance imaging (MRI) agents including gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Eovist in the United States, Primovist in Europe, or Gd-EOB-DTPA) has proved to be a sensitive method for detection of hepatic metastases. Accurate detection of liver metastases is critical for staging of colorectal cancer as well as preoperative planning.

1. Introduction

Colorectal cancer is one of the most common cancers worldwide with nearly one million people diagnosed each year. The liver is the most common site of distant metastases from colorectal cancer. Up to 70% of all patients with colorectal cancer will develop hepatic metastases at some point in their lifetime, and one-third of these will have metastases confined only to the liver [1, 2].

In metastases from colorectal adenocarcinoma, locoregional therapies are available including radiofrequency ablation and resection, which provide a survival benefit for patients with limited disease. Hepatectomy for liver metastases from colorectal cancer is the gold standard of treatment and provides the only chance for cure. Complete resection of all disease has been associated with a five-year survival ranging between 22% and 58% [3]. However, incomplete resection does not increase patient survival [4, 5]. Median survival for patients with untreated but potentially resectable metastases is 8 months, with a 5-year survival of less than 5% [2]. The paradigm for resection of colorectal metastases has changed from excluding patients with more than 3-4 liver metastases, periportal lymphadenopathy, or metastases within 1 cm of major vessels to only excluding those in which a margin-free resection cannot be achieved without preserving at least a 20% future liver remnant, or 30% if the patient has undergone chemotherapy [6–8]. Identification and resection of liver lesions often rely on high-quality cross-sectional imaging studies, and these images are an indispensable tool in the treatment planning process [9].

Historically, computed tomography (CT) has been used to stage and evaluate the liver in patients with colorectal adenocarcinoma. However, the introduction of magnetic resonance imaging (MRI) has proven to be a highly effective way to evaluate liver parenchyma [10–12]. In 1997, the introduction of specific hepatobiliary contrast agents for MRI further enhanced and strengthened this imaging modality. In addition to a more sensitive way to image metastatic lesions, the introduction of MRI allowed radiologists to avoid the risk of contrast-induced nephropathy in patients with eGFR <40 mL/min in healthy patients and <60 mL/min in diabetic patients [13].

Early publications evaluating the use of gadolinium-based contrast agents showed an advantage of MRI over CT

[14]. Recently, multiple studies have demonstrated the superiority of Gd-EOB-DTPA-enhanced MR over CT for detection of liver metastases [15].

2. Hepatobiliary Contrast Agents

Mangafodipir trisodium (MT) was the first specific hepatobiliary contrast agent. It was introduced in 1997 and approved as "an adjunct to MRI in patients to enhance the T1w images used in the detection, localization, characterization, and evaluation of lesions in the liver" (package insert, [16]). MT is a manganese-based agent, which shows hepatic enhancement as well as some biliary contrast. The agent had limited assessment of vascular structures due to its inability to be administered as a bolus and the agent was taken off the market in the United States in 2005 due to concerns regarding toxicity [16, 17].

Gadobenate dimeglumine (MultiHance, Gd-BOPTA) was approved by the FDA in 2004 for use as an MRI contrast agent. Gd-BOPTA acts as both an extracellular agent as well as a hepatobiliary contrast agent. While it is approved for hepatobiliary imaging in Europe, it is used off-label in the United States. 3% to 5% is taken up by hepatocytes and excreted into the biliary system which allows for its hepatobiliary specificity [18, 19].

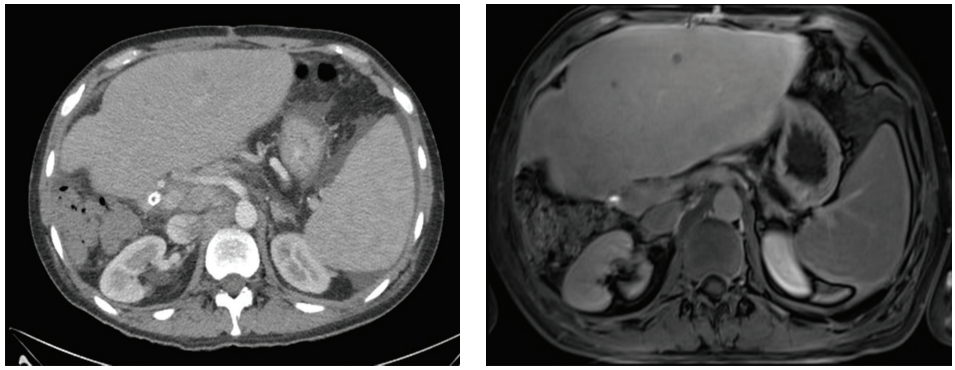
In 2008, gadoxetic acid (Gd-EOB-DTPA, Eovist, Primovist) was FDA approved in the United States for the detection and characterization of liver lesions. It had previously been approved in Europe in 2004 as Primovist. Eovist is a gadolinium-based contrast agent with approximately 50% uptake into hepatocytes and subsequent biliary excretion [9]. After administration, it is distributed into the vascular and extravascular spaces allowing for arterial, portal venous, and late dynamic phases. This is similar to nonspecific extracellular gadolinium contrasts; however, it adds information during the hepatobiliary phases [20–23]. It offers strong, early intravascular contrast allowing for dynamic phase imaging facilitated by 11% protein binding. This leads to increased relaxivity, thereby leading to increased signal enhancement in the blood and liver [24]. Due to its high relaxivity, dosing is also much lower than with other gadolinium compounds. Gd-EOB-DTPA is approved at a dose of 0.1 mL/kg to 0.025 mmol/kg body weight, This is one-fourth the dose of other gadolinium agents used in liver MRI. It is thought to be absorbed into hepatocytes by the canalicular multispecific organic anion transporter 8 (OATP8) with subsequent excretion into the bile via multidrug resistant protein 3 (MRP3) [25]. The hepatobiliary phase contrast enhancement peaks at 20 minutes and persists for more than 2 hours [26]. Gd-EOB-DTPA demonstrates earlier onset, as well as longer duration of contrast than Gd-BOPTA, which facilitates imaging and image quality [27].

Gd-EOB-DTPA's elimination half-life in healthy patients is roughly 55 to 57 minutes. Its elimination pathway is unique compared to other gadolinium agents. It is eliminated equally (50%) through the renal and hepatobiliary systems. In patients with one impaired pathway, the other elimination pathway will remove a larger percentage of the dose. For this reason, patients with renal or hepatic impairment do not require dose adjustment [24]. It does carry the black box warning given to all gadolinium-based contrast agents because of its association with nephrogenic fibrosing dermopathy. This is a rare occurrence and tends to affect those with end-stage renal disease already on dialysis, and therefore it is recommended to avoid the use of Gd-EOB-DPTA in patients with an eGFR <25 [28]. The most frequent adverse reactions include nausea, vasodilation, headache, taste perversion, and injection site pain [29]. Eleven patients out of 162 (6.8%) in a phase III trial reported a total of 21 adverse events. Of these, one was determined to be definitely related to GD-EOB-DPTA administration, 5 probably related, seven possibly related, one unlikely to be related, and seven not related. Eovist-enhanced MRI is invaluable in patients with severe allergies to iodinated contrast agents, such as prior anaphylaxis, who should not receive Iodine during CT imaging. Gadolinium-based agents tend to be fairly safe in this subset of patients.

3. Characterization of Liver Lesions with MRI

The use of dynamic contrast-enhanced MRI with gadolinium-based contrast agents for the characterization of benign and malignant liver lesions has been well described in a growing body of literature [30, 31]. Liver lesions with minimal or no hepatocyte function do not show accumulation of Eovist. These lesions include cysts, hemangiomas, metastases, the majority of hepatocellular carcinomas, and hepatic adenomas. In these cases, liver lesions will be more easily detected secondary to increased contrast between the lesions and the normal enhancing hepatocytes in the liver. On the other hand, hepatic lesions with functioning hepatocytes—including focal nodular hyperplasia and a small percentage of well-differentiated hepatocellular carcinomas—generally take up Eovist during the hepatocyte phase. These lesions will be enhanced during the hepatocyte phase and demonstrate a distinct pattern of enhancement. From this, a variety of algorithms to characterize liver lesions based on enhancement patterns have been developed. However, when interpreting images acquired with gadolinium-based contrast agents, understanding the pathophysiology and pharmacokinetics is important for image interpretation.

Gd-EOB-DTPA has unusual pharmacokinetics in that it is the only gadolinium agent which is taken up in equal amounts by the extracellular space and functioning hepatocytes, demonstrating a biphasic action. The dynamic phase of gadoxetic acid occurs during the first 2 minutes after injection. During this phase, normal hepatocytes as well as lesions containing hepatocytes exhibit contrast enhancement due to hepatocellular uptake. The enhancement pattern depends on vascular supply, the presence of functioning hepatocytes, and characteristics of the biliary structures within the lesion. The normal hepatocytes then slowly excrete the contrast agent into the biliary tree, which is referred to as the "hepatobiliary phase." For gadoxetic acid, the duration of this phase is 20–120 minutes where hepatocytes have excreted the contrast into the bile and have reached a level optimal for interpreting



(a) (b)

Figure 1: Contrast CT compared with Gd-EOB-DTPA-enhanced MRI. 65 y. male after right hepatic lobe resection. Routine follow-up CT scan (a) shows subtle low attenuation lesions in the left hepatic lobe, clearly seen on MRI with Eovist (b).

images of both the biliary system and hepatic lesions [26, 27, 32].

4. Metastatic Disease

Metastatic lesions are typically present on gadolinium-based contrast-enhanced imaging with peripheral rim enhancement and lack of central enhancement in the dynamic phase when central tumor necrosis is present. During the hepatobiliary phase, contrast uptake by hepatocytes provides contrast between the liver parenchyma and metastatic disease causing metastases to appear hypointense. In addition, during the hepatobiliary phase, rim enhancement [33] and a "target sign" [34] have been described in metastases. Initially, as mentioned previously, gadopentetate dimeglumine was the only gadolinium-based contrast available. The introduction of Gd-EOB-DPTA allowed for increased uptake by hepatocytes, and Vogl et al. (1996) demonstrated lesion to liver contrast superiority of Gd-EOB-DPTA over gadopentetate dimeglumine, and a statistically significant improvement in detection rate in metastases, hepatocellular carcinoma, and hemangiomas [35].

Initial studies using gadolinium-based contrast agents showed advantages of MR over CT, but with some mixed results [14]. Since the initial studies, multiple groups have evaluated Gd-EOB-DPTA-enhanced MRI for detecting liver metastases.

In 2004, Kim et al. demonstrated improved tumor to liver contrast using gadobenate dimeglumine in the hepatobiliary phase, leading to detection of more metastases compared to dynamic imaging alone [34]. In their paper, they describe the appearance of a "target sign" with central hyperenhancement and a hypointense rim [34].

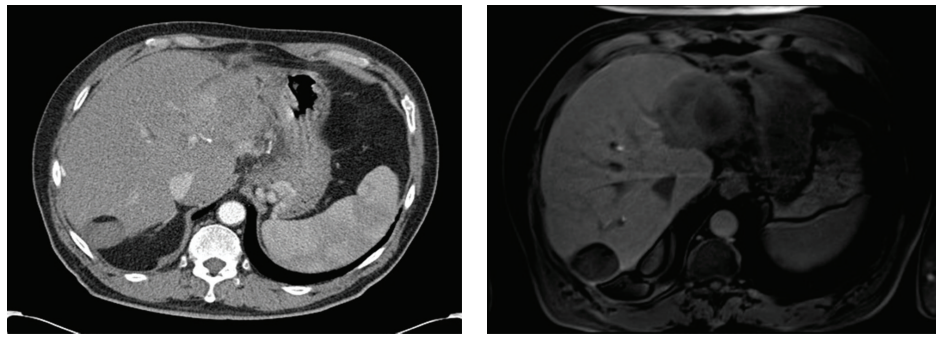
The European EOB Study Group (Huppertz et al. 2004) looked at 302 lesions in 13 patients with biopsy or intraoperative ultrasound proven focal liver lesions. 81 of these patients had metastases from a colorectal tumor primary. T1 and T2 phase MRIs, pre- and post-Gd-EOB-DTPA, were performed and evaluated in a blinded fashion by three radiologists. In 21 of the 129 patients, results differed between pre- and postcontrast MRI, and 19 of these were correct in the Gd-EOB-DTPA group, resulting in a significant ($P < 0.001$) difference in the correct detection with Gd-EOB-DTPA. It also showed a 7% increase in correct lesion classification with Gd-EOB-DTPA as compared to precontrast MRI [36].

Bluemke et al. (2005) showed that the percentage of lesions that were correctly classified as malignant or benign was 2–15% greater for blinded readers comparing MR images with Gd-EOB-DTPA with helical CT images of the same patients, with an increase in false positive lesions identified using CT. False positive results in liver imaging for metastases from colorectal cancer can impact surgical planning, delay excision of the primary tumor, and result in unnecessary surgery [37].

In 2006, Halavaara et al. showed superiority of Gd-EOB-DPTA compared to CT and diffusion weighted MR. They found increased lesion identification (95% versus 89%), sensitivity (95 versus 92%), and specificity (94 versus 90%) with MRI compared to CT [38]. This was further supported by Hammerstingl et al. (2008) who looked at 302 lesions and showed that the frequency of correctly detected lesions was significantly higher (10.44%) on Gd-EOB-DPTA-enhanced MRI compared with biphasic helical CT scan using histopathology or intraoperative ultrasound as confirmation. This superiority held true when looking at lesions with a diameter <1 cm. Interestingly, a change in surgical therapy was documented in 19 of 131 patients (14.5%) after Gd-EOB-DTPA-enhanced MRI [29]. This superiority of Gd-EOB-DTPA to CT scan has been witnessed in multiple studies, as well as at our own institution. Contrast of metastases from colorectal cancer on CT imaging versus Gd-EOB-DTPA-enhanced MRI is clearly demonstrated in Figures 1 and 2.

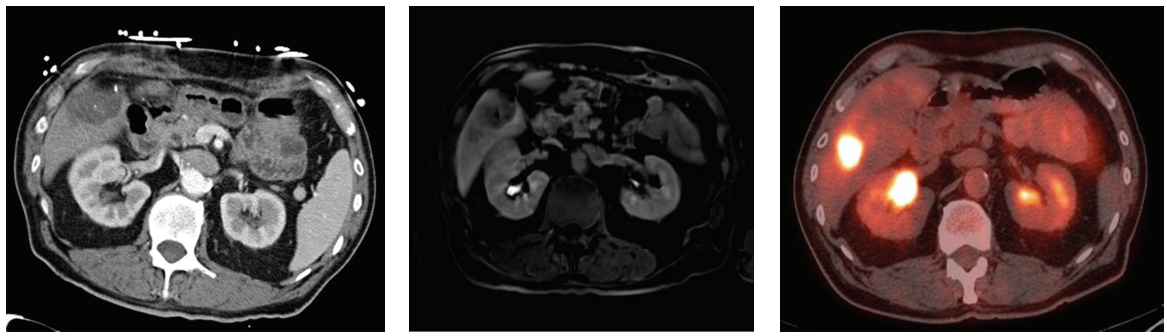
Studies by Ichikawa et al. (2010) have demonstrated superiority of gadoxetic-acid-enhanced MR over unenhanced MR and triphasic contrast-enhanced spiral CT for detection of metastases with regard to sensitivity. This was true for lesions <20 mm in diameter; however, the lesions <20 mm were not broken down by lesion type [15].

In the same year, Shimada et al. looked at 45 patients undergoing abdominal MRI. A total of 51 hepatic metastases



(a) (b)

Figure 2: Contrast-enhanced CT compared to Gd-EOB-DTPA-enhanced MRI in the same patient. 69 y. male with colorectal cancer after RFA of segment 6 lesion. New CT and MRI with Eovist ordered for elevated CEA. CT (a) shows a mildly heterogeneous area in segment 2. MRI with Eovist (b) shows a clearly demarcated lesion measuring over 7 cm consistent with metastasis.



(a) (b) (c)

Figure 3: Liver metastases in the same patient compared with contrast-enhanced CT, Gd-EOB-DTPA-enhanced MRI and PET/CT scan. 76 y. male with history of rectal cancer after neoadjuvant chemotherapy and radiation followed by low anterior resection. Segment 5 and caudate lesions, now with segment 6 lesion not seen on CT scan (a) but present on PET (c) and MRI with Eovist (b).

were examined by two independent observers. 7 of these lesions were seen on Gd-EOB-DTPA but were missed on DWI by both observers. 2 metastases very close in proximity to hepatic vessels were difficult to detect on Gd-EOB-DTPA but were seen clearly on DWI. In this study, Gd-EOB-DTPA-enhanced MRI showed statistically significant higher accuracy in detection of small lesions (<2 cm) than DWI. However, only slightly more than half of these metastases were confirmed histologically; the remainder were considered to be metastases on the basis of tumor growth on follow-up radiologic examinations [39].

Two studies have compared Gd-EOB-DTPA-enhanced MRI with PET/CT. Donati et al. (2010) looked at 85 liver lesions in 29 patients. 45 of these were metastases from a colorectal primary. The metastases were not divided out by primary cancer type [40]. When looking at the lesions as a whole, there was a significant difference in lesion detection between PET/CT and Gd-EOB-DTPA MRI (64% and 85% resp., $P = 0.002$). There was also a significant difference in detection (29% and 71% $P = 0.013$) for lesions less than 1 cm in diameter. This study is very limited by the fact that it did not differentiate between benign and malignant lesions [40]. Following this study, Seo et al. (2011) compared the diagnostic accuracy of Gd-EOB-DTPA MRI to 18F-flourodeoxyglucose positron emission tomography/computed tomography (CE-PET/CT) for the detection of liver metastases, specifically from colorectal cancer. This study retrospectively looked at 135 metastases from 68 patients who underwent both imaging studies and were reviewed by 2 radiologists independently. They found significantly higher diagnostic accuracy and sensitivity of EOB-MRI than CE-PET/CT ($P < 0.001$). On subset analysis, 25 small lesions less than 1 cm in diameter were detected only with EOB-MRI [41]. This difference in lesion detection between PET/CT and Gd-EOB-DTPA-enhanced MRI is clearly demonstrated from a patient at our own institution as seen in Figure 3.

Löwenthal et al. (2011) demonstrated the superiority of Gd-EOB-DTA-enhanced MR in the hepatobiliary phase to MR-DWI and MR for the detection of focal liver lesions when looking at 332 lesions (94.4%/100%, 78.3%/97.5%, and 81.5%/89.9% resp.). However, unlike Hammerstingl et al., this study did note that sensitivity for lesions <1 cm was higher for MR-DWI than for MR hepatobiliary phase images (0.98 versus 0.92) [42].

Chung et al. (2011) looked at a series of 47 patients with a total of 78 confirmed colorectal metastases comparing DWI and Gd-EOB-DTPA-enhanced MRI. In this study, regardless of lesion size (greater or less than 2 cm in diameter),

significantly more lesions were detected when looking at both DWI and Gd-EOB-DTPA-enhanced images than with DWI imaging alone [43]. All lesions in this study were confirmed as metastases histopathologically. Interestingly, in this study, positive predictive value was higher in the DWI group compared to Gd-EOB-DTPA or the combined DWI and Gd-EOB-DTPA.

Muhi et al. (2011) broadened the comparison and looked at the diagnostic accuracy of contrast-enhanced CT (CE-CT), contrast-enhanced ultrasound (CE-US), and superparamagnetic iron oxide-enhanced MRI (SPIO-MRI) for detecting colorectal hepatic metastases. 112 metastases in 46 patients were evaluated. For all lesions combined, sensitivity and area under the receiver operating characteristic curve of Gd-EOB-DTPA-enhanced MRI were significantly greater (95%) than CE-CT (63%) and CE-US (73%). For lesions less than 1 cm in diameter, sensitivity of Gd-EOB-DTPA-enhanced MRI was significantly greater than for CE-CT and CE-US. However, they did not find a significant difference in positive predictive value between any of the imaging modalities [44].

Most recently, Chen et al. performed a meta-analysis of 1900 lesions from 13 studies showing the sensitivity of Gd-EOB-DTPA-enhanced MRI for detection of liver metastases to be 93% and specificity 95% with statistically significant decreased sensitivities with lesions less than 10 mm in size ($P = 0.001$) [45].

The issue of imaging patients following neo-adjuvant chemotherapy who have developed hepatic steatosis was evaluated by Berger-Kulemann et al. (2012). In this study, 68 metastases were evaluated with triphasic MDCT and Gd-EOB-DTPA-enhanced MRI. All patients underwent surgical resection of liver metastases after evaluation. For lesions <1 cm diameter, MDCT detected only 41.9% while MRI detected 93% of metastases ($P < 0.001$). There was not a significant difference in lesions >1 cm in diameter between MDCT and Gd-EOB-DPTA enhanced MRI (97% and 100% resp.) [46].

While there have been multiple studies looking at the sensitivities and specificities of Gd-EOB-DPTA contrast enhanced MRI compared to other imaging techniques, economic considerations have become an increasingly important aspect of patient care in the United States. Zech et al. performed a cost analysis comparing MRI with Eovist, extracellular enhanced MRI, and three-phase MDCT as the initial evaluation of patients with metachronous colorectal liver metastases in Germany, Italy, and Sweden. It demonstrated that MRI with Eovist required fewer additional imaging studies (8.6%) than extracelluar-enhanced MRI (18.5%) and MDCT (23.5%). While MRI with Eovist has the highest initial imaging cost of the three modalities studied, it was in fact cost saving when reimaging, and the cost of modified and unnecessary surgical procedures was factored into the equation [47].

5. Conclusions

The ideal preoperative imaging study would provide diagnostic information which is highly sensitive and has a low rate of false positives. The studies described above have shown that hepatobiliary phase imaging with gadoxetic acid is safe and offers increased sensitivity in the detection of metastases due to the superior liver-lesion contrast generated by the avid uptake of gadolinium into the background of liver parenchyma. In addition, it has a lower rate of false positives than helical CT scan. These are important aspects of imaging in preoperative planning for resection of metastases from colorectal cancer.

Accurately mapping the location and number of metastases from colorectal cancer is crucial for the surgeon's preoperative planning process. Not only can it dramatically alter an operation from a minor wedge resection to a much larger anatomic procedure, but also it allows the surgeon to counsel the patient more accurately regarding the procedure they will require to excise the metastases. This is supported by the studies discussed previously where operative plans changed after reviewing Gd-EOB-DPTA enhanced MRI imaging [29]. In addition, false positive results can lead to unnecessary procedures for patients, and in a time when "liver first" surgery is accepted and increasingly popular, it can unnecessarily delay the resection of the primary tumor. Eovist-enhanced MRI is superior to other imaging modalities in the detection, localization, delineation, and management of patients with liver metastases from colorectal cancer.

Disclosure

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Clinical Study

A Reappraisal of Chemotherapy-Induced Liver Injury in Colorectal Liver Metastases before the Era of Antiangiogenics

Eric Nguyen-Khac,[1] Céline Lobry,[1] Denis Chatelain,[2] David Fuks,[3] Jean Paul Joly,[1] Marie Brevet,[2] Blaise Tramier,[4] Charlotte Mouly,[3] Vincent Hautefeuille,[1] Bruno Chauffert,[5] and Jean Marc Regimbeau[3]

[1] *Department of Hepatology, Amiens University Hospital, Place Victor Pauchet, 80054 Amiens Cedex 01, France*
[2] *Department of Pathology, Amiens University Hospital, Place Victor Pauchet, 80054 Amiens Cedex 01, France*
[3] *Department of Digestive Surgery, Amiens University Hospital, Place Victor Pauchet, 80054 Amiens Cedex 01, France*
[4] *Biostatistic Department, Amiens University Hospital, Place Victor Pauchet, 80054 Amiens Cedex 01, France*
[5] *Department of Medical Oncology, Amiens University Hospital, Place Victor Pauchet, 80054 Amiens Cedex 01, France*

Correspondence should be addressed to Eric Nguyen-Khac; nguyen-khac.eric@chu-amiens.fr

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Background and Aims. Chemotherapy of colorectal liver metastases can induce hepatotoxicity in noncancerous liver. We describe these lesions and assess risk factors and impacts on postresection morbidity and mortality in naive patients to chemotherapy before the era of bevacizumab. *Methods.* Noncancerous liver tissue lesions were analysed according to tumour, chemotherapy, surgery, and patient characteristics. *Results.* Fifty patients aged 62 ± 9.3 years were included between 2003 and 2007. Thirty-three (66%) received chemotherapy, with Folfox (58%), Folfiri (21%), LV5FU2 (12%), or Xelox (9%) regimens. Hepatotoxicity consisted of 18 (36%) cases of severe sinusoidal dilatation (SD), 13 (26%) portal fibrosis, 7 (14%) perisinusoidal fibrosis (PSF), 6 (12%) nodular regenerative hyperplasia (NRH), 2 (4%) steatosis >30%, zero steatohepatitis, and 16 (32%) surgical hepatitis. PSF was more frequent after chemotherapy (21% versus 0%, $P = 0.04$), especially LV5FU2 ($P = 0.02$). SD was associated with oxaliplatin (54.5% versus 23.5%, $P = 0.05$) and low body mass index ($P = 0.003$). NRH was associated with oxaliplatin ($P = 0.03$) and extensive resection ($P = 0.04$). No impact on mortality and morbidity was observed, apart postoperative elevation of bilirubin levels in case of PSF ($P = 0.03$), longer hospitalization in case of surgical hepatitis ($P = 0.03$), and greater blood loss in case of portal fibrosis ($P = 0.03$). *Conclusions.* Chemotherapy of colorectal liver metastases induces sinusoidal dilatation related to oxaliplatin and perisinusoidal fibrosis related to 5FU, without any impact on postoperative mortality.

1. Introduction

Synchronous or metachronous liver metastases (LMs) complicate the course of colorectal cancers (CRCs) in 40% of cases. Surgical resection of LM is the standard treatment, allowing a 5-year survival rate estimated to be between 25 and 44% [1]. Over the past decade, substantial improvement has been obtained in terms of systemic chemotherapy for CLM including perioperative [2] and induction [3] chemotherapies. For patients with initially unresectable disease, induction chemotherapy is offered with a goal of converting these patients to a resectable situation with a 5-year survival rate after resection reaching 35% [1, 3]. However, regardless of its benefit, subsequent toxicity on the nontumorous liver parenchyma has been recently reported in this setting. Various authors have reported increased morbidity and mortality rates after liver resection in patients who received preoperative oxaliplatin or irinotecan-based regimens [4–6]. Several arguments support that irinotecan-based chemotherapy is involved in a histopathologic entity defined as chemotherapy-associated steatohepatitis which manifests as liver steatosis, lobular inflammation, and ballooning of hepatocytes [7–10] that seems to increase both morbidity and mortality after liver resection. Oxaliplatin has been associated with

the sinusoidal obstruction syndrome (SOS) and, less frequently, with regenerative nodular hyperplasia [11, 12]. In the context of liver surgery, SOS could increase the risk of intraoperative bleeding [10, 13] and postoperative liver insufficiency [2]. However, the correlation between chemotherapy (type and number of cycles), liver injury (frequency and type of lesions), and clinical outcome (postoperative morbidity and mortality) after liver resection for CLM is currently under debate. In addition, we did not observe that much liver injury after neoadjuvant CT in our experience. Data concerning the effect of antivascular endothelial growth factor (VEGF) and antiepidermal growth factor receptor (EGFR) on nontumoral hepatic parenchyma are more limited [14–17]. Adding bevacizumab to chemotherapy does not increase the injury in non-tumoral hepatic parenchyma: SOS was observed in 27% of patients who received preoperative bevacizumab versus 53% in patients receiving 5-FU and oxaliplatin in a recent series [18]. Therefore, some authors have even stated that anti-VEGF has a protective effect, based on the fact that circulating VEGF is correlated to the severity of SOS [19, 20].

The primary objective of this retrospective study was to describe histological lesions of the liver in patients with colorectal cancer treated by neoadjuvant chemotherapy followed by liver resection before the era of bevacizumab in patients naive to chemotherapy. The secondary objectives were to identify factors associated with this liver injury and estimate the impact on postoperative morbidity and mortality.

2. Patients and Methods

2.1. Patient's Selection. This was a retrospective analysis of data collected from patients with CLM managed in our Federation in the Amiens University Hospital from February 2003 to July 2007. A prospective database of 485 hepatectomies was used to identify all patients who underwent liver resection for CLM. Among them, 50 patients met the inclusion criteria which were the following: hepatectomy for documented CLM, no underlying chronic liver disease (non-alcoholic, hepatitis B or C virus, or autoimmune chronic liver disease or genetic haemochromatosis), and with sufficient non-tumorous liver parenchyma for pathologic analysis. Among these 50 patients, 33 received preoperative systemic chemotherapy (induction or perioperative CT excluding patients receiving adjuvant CT after primary colorectal resection) within 4 months before hepatectomy (Chemo+) and were compared to the 17 remaining patients who did not receive any chemotherapy (Chemo−). The patients who received bevacizumab were not included. The study was performed in line with the 2000 Declaration of Helsinki. All patients signed an informed consent form.

2.2. Preoperative Evaluation. All patients underwent a preoperative evaluation including an abdominal and thoracic CT scan. Patients were considered for hepatectomy if all detected tumors could be removed completely with grossly negative surgical margins and a safe liver remnant volume. In selected patients in whom the amount of future remnant liver was considered insufficient (less than 30% of total liver volume) [21, 22], a preoperative portal vein embolization was performed [23]. Biologic data assessed before surgery were the following: platelet count, serum creatinine level, serum aspartate aminotransferase level (AST), serum alanine aminotransferase level (ALT), gamma glutamyl transferase level (γGT), alkalin phosphatase level (AP), serum total bilirubin level (Bili), and prothrombin time (PT).

2.3. Indication and Regimens of Systemic Chemotherapy in Chemo+ Group. In resectable patients ($n = 5$), indication for preoperative chemotherapy were to downsize the tumors preoperatively in view of a function-sparing resection or to ensure negative margins ($n = 3$) and to assess tumor's response to chemotherapy ($n = 2$). The patients with nonresectable CLM at presentation ($n = 28$) received "induction" chemotherapy which aimed at downsizing the CLM to switch the patients from a "non-resectable" status to a "resectable" status.

2.4. Surgical Technique. Liver resections were performed at least 4 weeks after the last course of chemotherapy in the Chemo+ group. During operation, a thorough exploration of the abdomen and the liver (intraoperative ultrasound) was carried out to rule out any contraindication to liver resection. Vascular clamping was not performed routinely, but if necessary resections were performed preferentially under intermittent portal triad clamping. Liver resection was achieved with a macroscopic tumor-free margin of 1 cm or larger whenever possible. Major hepatectomies were defined as the resection of three or more segments. Liver resection was performed by the same experienced liver surgeon (JMR).

2.5. Intraoperative and Postoperative Course. Intraoperative appearance of the liver, blood loss, use of vasopressive drugs, and blood requirement were recorded. Intra- and postoperative transfusions were taken into account. Mortality was defined as death occurring within 90 days after surgery, and morbidity was defined as a complication occurring during the hospital stay. Complications were stratified in accordance with Dindo's classification [22]: grade I was complications that induce any deviation from the normal postoperative course, grade II was complications that require pharmacological treatment, grade III was complications that require surgical, endoscopic, or radiological intervention, grade IV was life-threatening complications that require intermediate or intensive care unit management, and grade V was complications that result in the death of the patient. Liver dysfunction was defined as follows: ascites (volume > 500 mL per day) and/or PT < 50% on day 5 and/or Bilirubin > 50 μmol/L on postoperative day 5 and/or PT < 30% at any time [22]. The combination of a PT < 50% and a Bilirubin >50 μmol/L on postoperative day 5 was defined as liver failure [24, 25].

As for preoperative management, adjuvant chemotherapy was decided on by a multidisciplinary committee that included oncologists, pathologists, gastroenterologists, radiologists, and surgeons.

2.6. Pathologic Analysis. All slides, which were originally prepared from formalin-fixed and paraffin-embedded tissues,

were reviewed. Representative slides of non-tumorous hepatic tissue located as far as possible from the tumor were selected for the study. The morphological analyses were performed using slides stained with hematoxylin and eosin, Masson trichrome, and reticulin stain. The slides were examined by a single pathologist with hepatobiliary expertise (DC), who was unaware of the clinical data. *Hepatic steatosis* was classified into 3 grades: less than or equal to 30%, between 30% and 60%, and greater than 60% [26]. *Steatohepatitis* was evaluated according to the semiquantitative score of Kleiner et al. [27] and the NASH activity score (NAS) obtained by the addition of the steatosis ($0 \leq 5\%$, $1 = 5$–33%, $2 = 33$–66%, and $3 \geq 66\%$), lobular inflammation (0 = no site, $1 \leq 2$ sites, 2 = two to four sites, and $3 \geq$ four sites per ×200 field), and hepatocyte ballooning (0 = absent, 1 = several ballooned hepatocytes, 2 = numerous ballooned hepatocytes, or predominant hepatocyte ballooning) scores. A NAS score ≥ 5 was in favour of steatohepatitis, and a score less than 3 excluded steatohepatitis [27]. Sections were examined for the presence of vascular lesions such as *sinusoidal dilatation* (SD) classified into grade I (minimal centrilobular dilatation), II (dilatation occupying 2/3 of the lobule), and III (dilatation occupying all of the lobule) [11]. The presence of *nodular regenerative hyperplasia* was investigated by specific reticulin stain. *Perisinusoidal fibrosis* (PSF) was classified as minimal, moderate, or severe [28]. *Portal fibrosis* was estimated according to the Metavir score: absent (F0), portal fibrosis without septa (F1), portal fibrosis with several septa (F2), numerous septa without cirrhosis (F3), and cirrhosis (F4) [29]. Finally, lesions secondary to intraoperative manipulation of the surgical specimen were defined by periportal or centrilobular hepatocyte necrosis with polymorphonuclear neutrophile infiltrate [13] and were called "*surgical hepatitis*".

2.7. Studied Criteria. Demographic data (age, gender, body mass index, and ASA score (American Society of Anesthesiologists)), associated comorbidities (smoking, diabetes mellitus, arterial hypertension, and hypercholesterolaemia), pathological variables (number and size of CLM, pTNM stage), chemotherapy characteristics (type of chemotherapy, number of courses, dose and duration of chemotherapy, and interval between the end of chemotherapy and liver surgery), surgical modalities (extension of resection, vascular clamping, preoperative portal embolization, macroscopic appearance of the liver, blood loss, number of units of packed cells transfused, and operating time), and postoperative outcomes (mortality, morbidity, and length of stay) were recorded. The laboratory assessment prior to any chemotherapy, then before and after liver surgery, including transaminases, gammaglutamyl transferase, alkaline phosphatase, total serum bilirubin, prothrombin time, and complete blood count and platelets were also recorded.

2.8. Statistical Analysis. All results are expressed as the mean ± standard deviation, or median and range. Statistical comparisons were performed by Mann-Whitney, Wilcoxon Kruskal-Wallis and Student's t tests for continuous variables, Fisher's exact test for binary variables and Pearson's Chi-square test for ordinal variables. A P value < 0.05 was considered to be significant. All statistical analyses were performed using SPSS 18.0 (SPSS, Inc., Chicago, IL).

3. Results

3.1. Patients. From 2003 to 2007, a total of 182 patients underwent hepatectomy for CLM in our department. Among these 182 patients, 111 (61%) received neoadjuvant chemotherapy. Sixty-one patients had adjuvant CT after primary colorectal resection and were not analysed (Figure 1). Fifty patients satisfying the inclusion criteria were analysed. There were 34 males and 16 females with a mean age of 62 years (range: 36–82 years). Thirty-three (66%) patients had a primary colonic cancer. CLM was synchronous in 62% of patients. The mean number of metastases was 2.3 (range: 1–7) with a mean diameter of 55.3 mm (range: 47–190). Preoperative characteristics of these patients are summarized in Table 1. In the Chemo+ group, 28 had initially nonresectable CLM, and the remaining 5 patients with resectable CLM received neoadjuvant chemotherapy. In the Chemo− group, 17 patients had primary colorectal tumor with synchronous resectable CLM.

3.2. Regimens of Systemic Chemotherapy in Chemo+ Group. Details of CT are reported in Table 2. The mean number of cycles of CT was 9.5 ± 5.5 (range 3–27). Twelve (36%) patients received more than six cycles. The mean time interval between administration of CT and surgery was 25.2 ± 17 days (range 15–41).

3.3. Surgical Procedures. Fifteen (30%) patients underwent major hepatectomy (after preoperative portal vein embolization $n = 3$), and 15 (30%) required vascular clamping. The mean operating time was 334 minutes (range 140–600), and 5 (10%) had intraoperative transfusion. Intra-operative liver appearance was normal in 30 (60%) patients, steatotic in 12 (24%), and congested in 8 (16%) patients. There was no difference between Chemo+ and Chemo− groups.

3.4. Postoperative Outcomes. Postoperative mortality was 4% ($n = 2$), and overall morbidity was 40% ($n = 20$). Dindo's III-IV complications included 6 patients. No liver or renal failure was reported. There was postoperative ascites in one patient who had major hepatectomy. The median length of hospitalization was 15.2 days (range 5–48).

3.5. Description of Histological Lesions of the Liver. Histological examination of non-tumorous liver parenchyma demonstrated hepatic steatosis $\leq 30\%$ in 40 (80%) and steatosis >30% in 2 (4%) patients. No patients had NASH (median NAS score of 2 (range: 0–4)). Six (25%), 10 (42%), and 8 (33%) patients had grade I, II, and III sinusoidal dilatation, respectively. Nodular regenerative hyperplasia was observed in 6 (12%) patients. Perisinusoidal fibrosis was minimal in 9 (18%) and moderate to severe in 7 (14%) patients. Thirty seven patients had F0 fibrosis and 13 (26%) had more than F2

Table 1: Baseline characteristics of the 50 included patients.

	Parameters	Total n (%)	Chemo+ ($n = 33$)	Chemo− ($n = 17$)	P
Demography	Age (years)	62 ± 9.3	60	63	NS
	Male gender	34 (68)	22 (66)	12 (71)	NS
	ASA score (I/II/III)	8 (16)/26 (52)/16 (32)	7/15/11	1/11/5	NS
	BMI	28 ± 4.7	27	28	NS
Comorbidities	Hypertension	21 (42)	14 (44)	7 (41)	NS
	Diabetes mellitus	4 (8)	3 (9)	1 (6)	NS
	Smoking	16 (32)	11 (33)	5 (29)	NS
	Hyperlipidemia	14 (28)	10 (30)	4 (24)	NS
Liver tests	AST (IU/L)	30.5 ± 15.2	29	33	NS
	ALT (IU/L)	31.2 ± 19	24	38	NS
	γ-Glutamyl transferase (IU/L)	86 ± 97	82	90	NS
	Alkaline phosphatase (IU/L)	110 ± 47.7	110	108	NS
	Prothrombin time (%)	89.6 ± 2.6	90.6	88.4	NS
	Total bilirubin (μmol/L)	9.2 ± 5.6	8.4	10.0	NS
	Platelets count ($\times 10^3/mm^3$)	247 ± 111	220	251	NS

ASA: anesthesiologist score association.
BMI: body mass index.
NS: not significant.

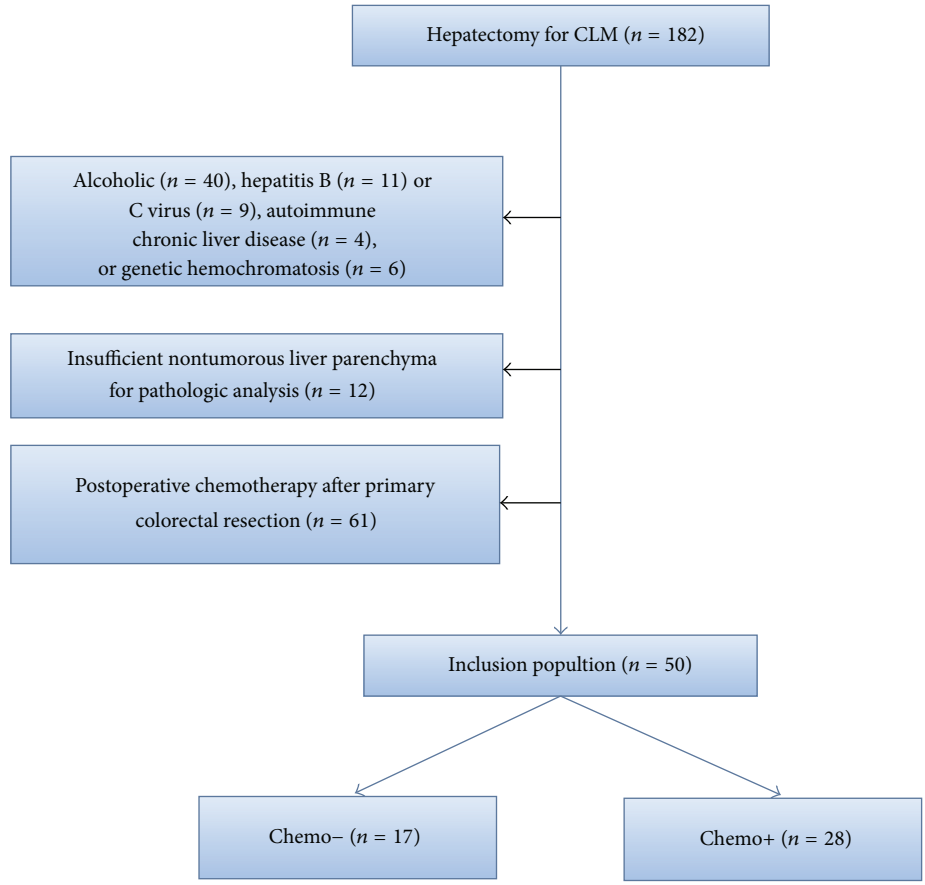

Figure 1: Flow chart of the study.

Table 2: Characteristics of chemotherapy in the Chemo+ group (n = 33).

	Parameters	n (%) Mean ± SD
Type of CT	LV5-FU2 n (%)	4 (12)
	Folfox n (%)	19 (58)
	Xelox n (%)	3 (9)
	Folfiri n (%)	7 (21)
Number of courses	Fluorouracil	10.4 ± 5.7
	Fluorouracil plus irinotecan	8 ± 6.7
	Fluorouracil plus oxaliplatin	8.2 ± 3.8
Cumulative dose	Fluorouracil (mg)	51580 ± 29520
	Irinotecan (mg)	2767 ± 2250
	Oxaliplatin (mg)	1250 ± 626

portal fibrosis. "Surgical hepatitis" lesions were described in 16 (33%) cases. Only perisinusoidal fibrosis was significantly higher in Chemo+ group than in Chemo− group (P = 0.04) (Table 3).

When the surgeon intraoperatively observed macroscopic steatosis, the histological steatosis was 21 ± 42%, whereas it was 9.6 ± 10.3% when the macroscopic appearance was normal (P = 0.02). On the contrary, the macroscopic appearance of the liver was not associated with presence of sinusoidal dilatation on the specimen (P = 0.08).

3.6. Association between Hepatic Lesions and the Various Chemotherapy Protocols. Only LV5FU2 chemotherapy was significantly associated with perisinusoidal fibrosis, compared to patients not receiving chemotherapy (P = 0.02) (Table 4). Patients with PSF received an average of 12.8 courses of 5FU-based chemotherapy versus 8.8 courses for patients without PSF, but the difference was not significant (P = 0.15).

Grade II and III sinusoidal dilatation was present in 54.5% of patients who had received oxaliplatin-based chemotherapy (Folfox or Xelox) versus 23.5% in Chemo− patients (P = 0.05), while no difference was observed with the other chemotherapy protocols used. The mean number of courses of oxaliplatin-based chemotherapy was 8.8 in the group of patients with sinusoidal dilatation versus 9 in the absence of sinusoidal dilatation (P = NS). Five (22.7%) of the 22 patients who had received oxaliplatin-based chemotherapy (Folfox or Xelox) presented features of NRH versus only 1/17 (5.9%) patients in Chemo− group, but this difference was not significant (P = 0.20). However, patients with NRH received more courses of oxaliplatin-based chemotherapy than patients without NRH (10.2 ± 4 courses versus 7.6 ± 3.7 courses, P = 0.03).

Hepatic steatosis greater than 30% and significant portal fibrosis ($F \geq 2$) were not associated with chemotherapy. Surgical hepatitis lesions were not associated with chemotherapy, but appeared to be more frequent in patients who had received Folfox (42.1%) or Folfiri (42.9%), versus 29.4% in the absence of chemotherapy, but the differences were not statistically significant.

3.7. Association between Hepatic Lesions and other Risk Factors. Among the demographic factors related to the patient (age, gender, BMI, smoking, hypercholesterolaemia, and diabetes mellitus), the primary tumor, the CLM (number and size of LM), and timing of chemotherapy (duration and interval between end of chemotherapy and surgery), only diabetes mellitus was significantly associated with hepatic steatosis greater than 30% (P = 0.02). BMI was significantly lower in patients with sinusoidal dilatation compared to patients without sinusoidal dilatation (25.6 ± 4.7 versus 29 ± 3.7, P = 0.003). Perisinusoidal fibrosis, NRH and portal fibrosis were not associated with any of these factors (Figure 2). Finally, patients with surgical hepatitis lesions had a shorter interval between the end of chemotherapy and surgery than patients without this type of lesion (59 ± 29.8 days versus 191 ± 212.2 days, P = 0.019).

3.8. Consequences of Histological Lesions on Surgery, Liver Function Tests, Mean Length of Stay, and Postoperative Outcomes. Intra-operative blood loss was increased in the presence of portal fibrosis $F \geq 2$, compared to patients with $F0$-$F1$ fibrosis (1,045 ± 880 versus 541 ± 652 mL, P = 0.03). Major hepatectomy was associated with a higher incidence of NRH (P = 0.04). The only significant postoperative modification of liver function tests was a more marked elevation of serum bilirubin levels in the presence of PSF (bilirubin increased by 18.6 ± 28.3 versus 13.7 ± 26.4 μmol/L, P = 0.05).

The mean length of hospital stay was not influenced by steatosis (P = 0.99), perisinusoidal fibrosis (P = 0.16), sinusoidal dilatation (P = 0.56), NRH (P = 0.80), or portal fibrosis $F2$ (P = 0.20), but the mean length of hospital stay was significantly longer in case of surgical hepatitis (18 ± 10.7 versus 14 ± 10.3 days, P = 0.03). Among the 50 patients, postoperative morbidity was not modified by hepatic lesions: steatosis (P = 0.99), PSF (P = 0.82), sinusoidal dilatation (P = 0.69), surgical hepatitis lesions (P = 0.36), or NRH (P = 0.35) on the Mann-Whitney test. No difference in postoperative morbidity was observed between Chemo+ and Chemo- groups. Among Chemo+ patients, there was no difference in postoperative morbidity in patients who presented at least one liver injury compared to patients with no liver injury (median Dindo's score: 1.8 ± 1.2 versus 1.14 ± 0.37, P = 0.45). We did not find any difference of postoperative morbidity with or without PSF (P = 0.48) or sinusoidal dilatation (P = 0.056). We did not demonstrate any impact of histological lesions on postoperative mortality. Two patients died during the postoperative period with no signs of vascular lesions (SD, NRH, or PSF) or portal fibrosis $F \geq 2$. Both patients presented signs of surgical hepatitis with steatosis scores of 30% and 10%, respectively.

3.9. Postoperative Outcomes and the Various Chemotherapy Protocols. Post-operative mortality was 4% (n = 2) with no correlation with the number of courses of oxaliplatin-based

Table 3: Histological lesions of the non-tumorous liver parenchyma.

Histological lesions of the non-tumorous liver parenchyma	All	Chemo+ ($n = 33$) n (%)	Chemo– ($n = 17$) n (%)	P
Steatosis ≤ 30%	40 (80)	29 (88)	11 (65)	NS
Steatosis > 30%	2 (4)	1 (3)	1 (6)	NS
Steatohepatitis (NASH), NAS ≥ 5	0 (0)	0 (0)	0 (0)	—
Grade II and III sinusoidal dilatation	18 (36)	14 (42)	4 (24)	NS
Nodular regenerative hyperplasia (NRH)	6 (12)	5 (15)	1 (6)	NS
Moderate to severe perisinusoidal fibrosis	7 (14)	7 (21)	0 (0)	0.04
Portal fibrosis ≥ F2	13 (26)	10 (31)	3 (18)	NS
Mild/severe postoperative lesions	9 (18)/16 (32)	7 (21)/12 (36)	2 (12)/4 (24)	NS/NS

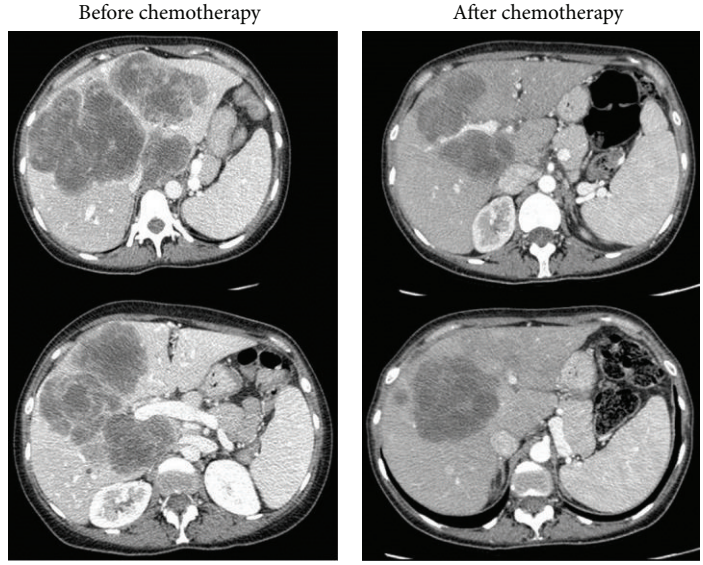

Figure 2: Example of a 41-year-old patient who developed HNR with portal hypertension after induction chemotherapy (FOLFOX, IV 12 cycles). An increase of the size of the spleen and an apparition of portal hypertension was observed after chemotherapy.

chemotherapy ($P = 0.51$) and irinotecan-based chemotherapy ($P = 0.9$).

Overall morbidity was 40% ($n = 20$) included 6 patients with Dindo's III-IV. There was no association between the overall morbidity and the number of courses of chemotherapy included oxaliplatin-based chemotherapy and irinotecan-based chemotherapy ($P > 0.05$). The number of courses >6 (or >8) for oxaliplatin-based chemotherapy and the number of courses >6 (or >8) for irinotecan were not associated with a higher incidence of morbidity. Finally, the number of course of chemotherapy protocol did not influence postoperative outcomes.

4. Discussion

Over the past decade, preoperative chemotherapy is being increasingly used before hepatic resection for colorectal liver metastases [3, 30]. Several arguments support its use in selected patients: [3] by downsizing the tumors preoperatively, it may increase the rate of curative resection with negative margin, [31] some patients with unresectable disease at presentation may become eligible for hepatic resection, [30] good responders may be identified preoperatively, and [2] response to chemotherapy may be a good evaluation of tumors biologic aggressiveness as those who progress under chemotherapy may not benefit from resection [10, 32]. Hepatotoxicity induced by the chemotherapy protocols used in colorectal cancer is an emerging problem and raises the question of whether this hepatotoxicity may interfere with the results of management of CLM in terms of postoperative morbidity and mortality. The present study population was comparable to those of other published series in terms of age, gender, BMI, colorectal tumour characteristics, mean number of CLM, and history of chemotherapy prior to surgery [7, 11, 13, 33]. However, this series included all types of neoadjuvant and adjuvant chemotherapy except bevacizumab and patients who had postoperative chemotherapy after primary tumor resection, regardless of the date of administration in relation to liver surgery, while other studies excluded from the Chemo+ group patients who had received chemotherapy more than 6 months before surgery [13] and

Table 4: Characteristics of liver impairment according to the type of chemotherapy.

Chemotherapy	Steatosis > 30% ($n = 2$)			Portal fibrosis ≥ 2 ($n = 13$)			Perisinusoidal fibrosis ($n = 7$)			Sinusoidal dilatation ($n = 18$)			NRH ($n = 6$)		
	Chemo+	Chemo−	*P*	Chemo+	Chemo−	*P*	Chemo+	Chemo−	*P*	Chemo+	Chemo−	*P*	Chemo+	Chemo−	*P*
LV5FU2	0/4 (0)	1/17 (6)	1	2/4 (50)	3/17 (17.6)	0.22	2/4 (50)	0/17 (0)	0.02	1/4 (25)	4/17 (23.5)	1	0/4 (0)	1/17 (5.9)	1
Folfox	1/19 (5.3)	1/17 (6)	1	5/18 (27.8)	3/17 (17.6)	0.69	4/19 (21.1)	0/17 (0)	0.10	10/19 (52.6)	4/17 (23.5)	0.07	4/19 (21)	1/17 (5.9)	0.34
Xelox	0/3 (0)	1/17 (6)	1	0/3 (0)	3/17 (17.6)	1	0/3 (0)	0/17 (0)	1	2/3 (66.6)	4/17 (23.5)	0.20	1/3 (33.3)	1/17 (5.9)	0.28
Folfox and Xelox	1/22 (4.5)	1/17 (6)	1	5/21 (24)	3/17 (17.6)	0.70	4/22 (18.2)	0/17 (0)	0.11	12/22 (54.5)	4/17 (23.5)	0.05	5/22 (22.7)	1/17 (5.9)	0.20
Folfiri	0/7 (0)	1/17 (6)	1	2/6 (33.3)	3/17 (17.6)	0.57	2/7 (28.6)	0/17 (0)	0.07	2/7 (28.6)	4/17 (23.5)	1	1/7 (14.3)	1/17 (5.9)	0.50

sometimes even more than 2 months before surgery [34]. The mean interval between the end of chemotherapy and liver surgery was longer in our series than in other studies [7, 11], which could influence the prevalence of reversible lesions such as steatosis. Finally, the nonrandomized retrospective nature of our study is limitations common to all recently published studies [7, 9, 11, 13, 34, 35], apart from a European prospective study [36].

Perisinusoidal fibrosis and sinusoidal dilatation were observed in 7 (14%) and 18 (36%) patients, respectively, and were significantly correlated with previous chemotherapy. PSF was significantly more frequent in the group of patients that had received chemotherapy ($P = 0.04$), particularly 5FU monotherapy ($P = 0.02$). Patients with PSF had received a greater number of courses of 5FU-based chemotherapy than patients without PSF, but the difference was not significant. This result must be interpreted cautiously in view of the small sample size. PSF has been reported in only one other study [11] and was interpreted by the authors to be a late consequence of sinusoidal dilatation. PSF can be either isolated or associated with sinusoidal dilatation and obstruction [37]. It can also be due to nonalcoholic steatohepatitis [26, 38], but these two risk factors were not associated with PSF in our study. To our knowledge, no previous study has reported an association between PSF and 5FU. This hypothetical association, therefore, needs to be confirmed. PSF did not induce any postoperative morbidity or mortality and did not even increase the mean hospital length of stay, although a more marked elevation of total serum bilirubin was observed during the postoperative period in patients with PSF. Elevation of serum bilirubin could be due to capillarization of sinusoids, secondary to fibrosis, which interferes with metabolic exchanges.

This study also confirms the existence of sinusoidal dilatation in noncancerous liver with a prevalence of 36%. This rate was 54.5% for patients who had received oxaliplatin-based chemotherapy versus 23.5% for patients without chemotherapy ($P = 0.05$). Previous studies have reported an association between sinusoidal dilatations and chemotherapy and no chemotherapy [13, 34], not confirmed in the present study, and between the use of oxaliplatin [7, 11] exclusively in severe grade II and III lesions, as demonstrated in the present study. The reported prevalence of sinusoidal dilatations is between 8% [7] and 50% [11, 34] among patients receiving neoadjuvant chemotherapy, increasing to 19% and 79% for patients treated with oxaliplatin [11, 36]. Rubbia-Brandt et al. were the first to report the development of sinusoidal dilatation after chemotherapy and proposed the following hypothesis: the initially damaged endothelial cells induce activation of stellate cells, leading to fibrosis and aggregation of erythrocytes and cytoplasmic blebs in the perisinusoidal space, which results in obstruction of the junction between sinusoids and centrilobular venules [11]. Apart from chemotherapy, sinusoidal dilatation was also significantly more frequent in patients with a lower BMI ($P = 0.003$), but this was not confirmed by another study [36]. This result could suggest differences in the metabolism of chemotherapeutic agents related to BMI. No other risk factor was associated with the presence of sinusoidal dilatation in our study: neither duration or number of courses of chemotherapy, the interval between the end of treatment and surgery, the extent of liver resection, nor the use of vascular clamping. Similarly, other authors also did not report any correlation between sinusoidal dilatations and the duration of chemotherapy [7, 13] or the cumulative dose of oxaliplatin [11]. Only Farges et al. reported a tendency to a greater number of severe sinusoidal dilatation in the case of intraoperative vascular clamping, but the difference was not significant ($P = 0.09$) [33]. As reported in other series, sinusoidal dilatation did not have any impact on the mean length of hospital stay [34], transfusion [13, 34], or postoperative morbidity and mortality [7, 34, 36].

None of the other hepatic lesions observed were associated with any of the chemotherapy protocols used. The incidence of 12% of NRH in this study was comparable to the rates reported in the literature [11, 13, 34]. Patients with NRH had received significantly more courses of oxaliplatin-based chemotherapy ($P = 0.03$). This confirms the results of Rubbia-Brandt et al. [11], whom described NRH as secondary to the use of oxaliplatin, frequently associated with sinusoidal dilatation. This is coherent with our results concerning sinusoidal dilatations and oxaliplatin. The presence of NRH did not influence the postoperative course, transfusion requirements, or survival rate, as reported by Farges et al. [33]. NRH lesions, therefore, appeared to have an identical risk profile to that of sinusoidal dilatation, as they also belong to the spectrum of vascular lesions, suggesting a continuum of these oxaliplatin-induced lesions [38, 39].

Hepatic steatosis in non-tumoral liver parenchyma was frequent in our population, observed in almost 80% of cases, despite the fact that our patients had a slightly high BMI. However, steatosis >30% was much rarer, observed in only 8% of cases, while other studies have reported frequencies between 9% and 20% [7, 11, 13] with no significant association with chemotherapy [11, 13, 34, 36], except for the series by Pawlik et al. in which hepatic steatosis was significantly correlated with the use of irinotecan [35]. As in the setting of liver transplantation, steatosis >30% could increase the postoperative morbidity after resection of CLM [40, 41], but this remains controversial [34, 42]. No conclusions can be drawn from the present study due to the low rate of steatosis >30% in this population. While steatohepatitis has been significantly associated with irinotecan use, inducing increased mortality on the 90th postoperative day from liver failure ($P = 0.01$) [17], no case of this complication was observed in our study based on the use of the NAS score proposed by Kleiner et al. Similarly, Fernandez et al. [9], based on a small sample size ($n = 37$), noted that chemotherapy, with no distinction between oxaliplatin or irinotecan, was a risk factor for steatohepatitis, independent of BMI, compared to patients who had not received chemotherapy or who received 5FU alone ($P = 0.003$). However, no consensus has been reached concerning the histological criteria for the diagnosis of steatohepatitis. Vauthey et al. [7] used a NAS score > 4, while Fernandez et al. [9] used the inflammatory activity score of Brunt et al. Finally, other authors did not report any association between steatohepatitis and oxaliplatin or increased morbidity or mortality [34–36]. Data concerning steatosis and steatohepatitis, therefore, vary from study to

study related to population differences in terms of metabolic risk factors, interval after the end of chemotherapy, or even the use of irinotecan.

Portal fibrosis, $F \geq 2$, was not associated with chemotherapy in this study, confirming several previous reports [13, 34]. It was not related to extended liver resection or the operating time. However, an increased blood loss ($P = 0.03$) and a tendency to greater transfusion requirement ($P = 0.09$) were observed in the presence of $F \geq 2$, not confirmed by other series [13, 33].

Lastly, the pathophysiology of "surgical hepatitis" remains poorly defined, but could correspond to zones of infarction related to ischaemia. When major resections with total vascular exclusion were performed, surgical hepatitis lesions were observed in 97% of cases in one study [34]. Thirty-three percent of our patients presented surgical hepatitis, but it was not correlated with major resection, vascular clamping, operating time, or blood loss; postoperative liver function tests and postoperative course did not differ from those of the other patients, apart from a significantly longer length of hospital stay ($P = 0.03$). Furthermore, the 2 patients who died during the postoperative period presented surgical hepatitis and no other histological lesion apart from steatosis scores of 10 and 30%. Surgical hepatitis was not associated with chemotherapy in our study, as in the series by Karoui et al. [34], but a correlation with chemotherapy was observed in another series [13]. However, surgical hepatitis was significantly more frequent in our study when the interval between the end of chemotherapy and surgery was shorter ($P = 0.019$), suggesting a possible impact of chemotherapy on the susceptibility of non-tumoral liver parenchyma to ischaemia.

Regarding duration of chemotherapy exposure prior to resection, Karoui et al. reported that patients receiving systemic chemotherapy (mostly oxaliplatin) had a significantly higher rate of sinusoidal dilatation (49 versus 13.6%, $P = 0.005$) and postoperative complications (38 versus 13.5%, $P = 0.03$) compared with controls. This correlated with the number of chemotherapy cycles administered. Patients who received >6 cycles had considerably higher postoperative complications, as compared with those treated with <6 cycles (54 versus 19%, $P = 0.047$) [34]. Moreover, in the study of Kneuertz et al. [43], postoperative liver failure was observed in five patients who received more than ten cycles of chemotherapy. However, in our study we found that a number of courses >6 for oxaliplatin-based chemotherapy and a number of courses >8 for irinotecan were not associated with a higher incidence of morbidity.

In conclusion, hepatic sinusoidal dilatation is probably the most frequently reported and demonstrated chemo-induced liver injury in patients receiving chemotherapy for CLM. Oxaliplatin is usually responsible [7, 11, 35]. Other lesions such as steatosis [7, 11, 13, 34, 35] have been less clearly demonstrated, while in 3 studies [7, 9, 35] steatohepatitis was associated with the use of irinotecan. The impact of all of these lesions on postoperative morbidity and mortality remains controversial [7, 13, 34, 35]. At the present time, the benefit-risk balance remains in favour of chemotherapy for colorectal LM. However, a short window after the last course of chemotherapy to perform the liver resection, giving time for regeneration the non-tumorous liver parenchyma would be considered, but not too long time for tumor escaping.

Abbreviations

CT: Chemotherapy
CLM: Colorectal liver metastases
NRH: Nodular regenerative hyperplasia.

Conflict of Interests

The authors stated neither financial relationship nor conflict of interests to disclose.

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Review Article

Surgical Treatment and Survival in Patients with Liver Metastases from Neuroendocrine Tumors: A Meta-Analysis of Observational Studies

Stefano Bacchetti,[1] Serena Bertozzi,[1] Ambrogio P. Londero,[2] Alessandro Uzzau,[1] and Enrico Maria Pasqual[1]

[1] *Department of Surgery, AOU "Santa Maria della Misericordia", Piazzale SM della Misericordia 15, I-33100 Udine, Italy*
[2] *University of Udine and AOU "Santa Maria della Misericordia", Piazzale SM della Misericordia 15, I-33100 Udine, Italy*

Correspondence should be addressed to Stefano Bacchetti; stefano.bacchetti@uniud.it

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Introduction. The role of hepatic resection in patients with liver metastases from gastroenteropancreatic neuroendocrine tumors (GEP-NETs) is still poorly defined. Therefore, we examined the results obtained with surgical resection and other locoregional or systemic therapies by reviewing the recent literature on this topic. We performed the meta-analysis for comparing surgical resection of hepatic metastases with other treatments. *Materials and Methods*. In this systematic review and meta-analysis of observational studies, the literature search was undertaken between 1990 and 2012 looking for studies evaluating the different survivals between patients treated with surgical resection of hepatic metastases and with other surgical or nonsurgical therapies. The studies were evaluated for quality, publication bias, and heterogeneity. Pooled hazard ratio (HR) estimates and 95% confidence intervals (CI.95) were calculated using fixed-effects model. *Results*. We selected six studies in the review, five of which were suitable for meta-analysis. We found a significant longer survival in patients treated with hepatic resection than embolisation HR 0.34 (CI.95 0.21–0.55) or all other nonsurgical treatments HR 0.45 (CI.95 0.34–0.60). Only one study compared surgical resection with liver transplantation and meta-analysis was not feasible. *Conclusions*. Our meta-analysis provides evidence supporting the hypothesis that hepatic resection increases overall survival in patients with liver metastases from GEP-NETs. Further randomized clinical trials are needed to confirm these findings and it would be desirable to identify new markers to properly select patients for surgical treatment.

1. Introduction

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a heterogeneous group of malignancies with various clinical presentation and growth rates [1–3]. In the current literature, the vast majority of GEP-NETs fall into two nearly distinct categories: pancreatic neuroendocrine tumors, also known as islet cell tumors, and gastrointestinal neuroendocrine tumors, usually grouped in carcinoids [4–6]. In the clinical fashion, gastrointestinal NETs tend to grow much more slowly than pancreatic NETs and also differ in the tumor biology and prognosis [6–8]. It is common to find these tumors in advanced stage, with metastases frequently involving the liver [9–12]. In particular, for gastrointestinal NETs, it is reported that nearly 50–75% of small bowel NETs develop hepatic metastases [13–15]. Although there is uniform consensus for the treatment of primary tumor, there is still debate over how to manage patients with metastatic disease. Many medical and surgical treatments have been proposed for patients with liver metastases from NETs [10, 16–18]. However, the exact role of liver surgery for patients with metastatic NETs is still poorly defined because, frequently, the presence of unresectable hepatic secondaries and the inert growth, and the long-term natural history of the disease make many problems to the evaluation of the real effectiveness of hepatic surgical approach. Moreover, a valid set of criteria for selecting patients to resection has not been established. In the present meta-analysis, our aim

was to examine the survival differences of patients treated with surgical resection of hepatic metastases and with other therapies.

2. Materials and Methods

2.1. Search Strategy for Review. The literature search was carried out, by three authors independently, by gathering information from Medline, Embase, Ovid, Google Scholar, and Cochrane database for studies published form January 1990 to August 2012. Search terms included "neuroendocrine tumour" or "carcinoid tumour" or "gastrointestinal NETs" or "liver metastases" or "hepatic metastases" or "neuroendocrine metastases" and "hepatectomy" or "liver resection" or "liver transplantation." Then, we examined all the titles and the abstracts of the resulting articles. The first step was the selection of papers referring to the surgical treatment of liver metastases from NETs. After that, we analyzed the full articles. In addition, bibliographies and citations from full articles and previous review publications were used to identify other additional pertinent articles.

2.2. Inclusion and Exclusion Criteria. We considered for inclusion all experimental and observational studies that evaluated survival in patients affected by NET liver metastases and treated by hepatic surgical resection or liver transplantation or other therapies (somatostatin analogues, hepatic embolisation/chemoembolisation, peptide receptor therapy, chemotherapy, etc.) and submitted to watchful waiting. All relevant studies were observational (level III or IV of evidence, CEBM) [25] because randomized trials comparing partial hepatectomy versus liver transplantation or other nonsurgical therapies have never been attempted. In this meta-analysis we considered a Cox proportional hazards regression model or Kaplan-Meier curves to calculate the survival difference among patients treated with resection of liver metastases and other treatments. Moreover, we included only articles written in English on human subjects with the full text available for data retrieval. We recorded geographic locations, time frame for NET diagnosis, and treatment in order to avoid any possible population overlap. When two or more studies presented possible overlap, the one of better quality or with more detailed data was included. In case of discrepancies among the three reviewers they were addressed by a joint reevaluation of the original article. Specific exclusion criteria were studies considering <20 patients, or nonhuman subjects, and non-English written articles. Furthermore, we excluded also reviews, letters to the editor without original data, editorials, and case reports. Conference abstracts were also excluded due to a lack of details regarding the study design and survival data.

2.3. Data Extraction. Three reviewers independently extracted data for selected studies using a standard data extraction form. They discussed any discrepancies in appropriateness for inclusion in the present meta-analysis and data extraction. The following information was then extracted from every single study: authors, year of publication, geographical area, population characteristics (age, sex, etc.), study design, number of patients, type of procedure applied, hazards ratios with 95% confidence interval (CI.95), or hazards ratios extracted from Kaplan-Meier curves. The hazard ratio in our meta-analysis was calculated from data obtained from published reports, using methods previously described [26].

2.4. Quality Assessment for Included Studies. Three authors assessed independently the quality of each included study by using the Newcastle-Ottawa Scale [27]. The Newcastle-Ottawa Scale evaluates the quality of studies analyzing three items: selection, comparability, and outcome (cohort studies) or exposure (case-control studies). This scale assigns a maximum of nine points to each study: a maximum of four points for selection, two points for comparability, and three points for exposure/outcome. Therefore, the highest quality is achieved by scoring nine points. In our analysis studies of high quality were defined those that scored nine or eight points and studies of medium quality those that scored seven or six points on the Newcastle-Ottawa Scale. Any discrepancy in quality assessment was addressed by a joint evaluation of the original article.

2.5. Data Analysis. The data was analyzed by R (version 2.15.0), considering significant $P < 0.05$. In the meta-analysis, a summary statistic was calculated considering the hazards ratio for survival analysis. We used rank correlation test of funnel plot asymmetry to test the presence of any publication bias [28, 29]. We used I2 index and Cochran Q to assess the heterogeneity among studies. We considered an I2 index value > 50% a measure of heterogeneity and, for Q statistic, a P value < 0.10 was considered statistically significant for heterogeneity [30]. The fixed- and random-effect models were applied to calculate the pooled estimate where appropriate. The primary outcome in this meta-analysis was reported as HR (with CI.95) of overall survival in patients treated with hepatic resections. We considered MOOSE (Meta-Analysis Of Observational Studies in Epidemiology) guidelines for accurately performing meta-analysis of observational studies [31] and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines checklist [32].

3. Results

3.1. Search Results. We identified a total of 2293 articles during the initial search (Figure 1). After reviewing the titles and abstracts of these publications, 2259 were found to be not eligible as they were case reports, review articles, editorials, nonhuman studies, or non-English articles, not focusing on the review topic, and not meeting the inclusion criteria. In total, 34 articles were identified as potentially eligible for this review. According to a subsequent evaluation of full-text articles, 28 of these articles either described only the outcome of patients treated with surgical management or did not report any HR or Kaplan-Meier curves to compare surgical resection of hepatic metastases with other treatments (Supplemental List 1) (see Supplementary Material available online at http://dx.doi.org/10.1155/2013/235040). We

Table 1: Description of the included studies.

Labels	Location (city, country)	Publication year	Study period	Number of patients (liver resection/other)	5 ys OS (liver resection/other)
Surgical resection versus other conservative treatments					
Chen et al., 1998 [19]	Baltimore (USA)	1998	1984–1995	15/23	73%/29%
Grazi et al., 2000 [20]	Bologna (Italy)	2000	1981–1997	19/9	92.6%/18.5%*
Ahmed et al., 2009 [21]	Basingstoke, London, Liverpool, Belfast, and Southampton (UK)	2009	1973–2007	50/269	78%/52%
Surgical resection versus embolization					
Yao et al., 2001 [22]	Chicago (USA)	2001	1992–2000	16/20	70%/40%
Osborne et al., 2006 [23]	Tampa (USA)	2006	2000–2004	38 complete and 23 palliative/53	78% complete and 64% palliative/35%
Surgical resection versus liver transplant					
Coppa et al., 2001 [24]	Milan (Italy)	2001	1987–1999	20/9	67%/70%

*Four years OS.

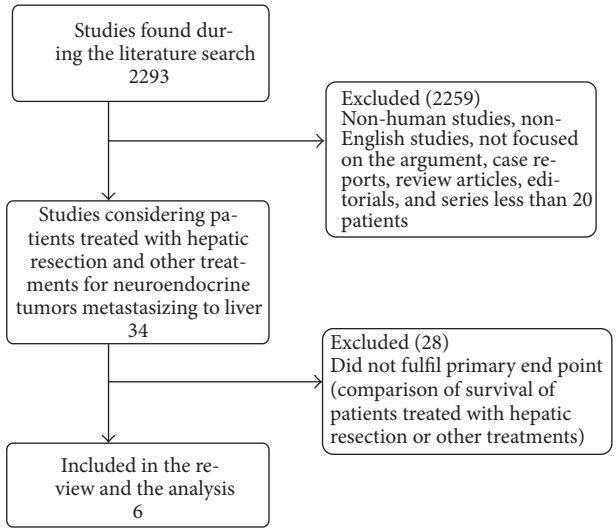

Figure 1: Flow-chart of the literature search and selection.

finally selected six eligible articles that compared survival between the groups using Kaplan-Meier curves (Figure 1) [19–24]. All included studies were observational retrospective studies. Five studies compared hepatic metastases resection with other conservative treatments and one study compared surgical resection with liver transplantation.

3.2. Characteristics of the Studies. This meta-analysis included retrospective observational studies that evaluated survival in patients affected by NET comparing surgical resection of hepatic metastases with conservative management or other treatments (Table 1) [19–24]. Five studies compared surgical resection with conservative treatments and one study compared surgical resection with liver transplantation. Among the five studies comparing surgical resection with conservative treatments two studies compared surgery to embolisation. In Table 1 we present the characteristics of the included studies. None of the studies presented Cox proportional hazards multivariate regression models and HR was extracted from Kaplan-Meier curves. We could not perform any meta-analysis about surgical resection versus liver transplantation, because there was only one eligible study. In this study, Coppa et al. found a non significant increased OS in the group treated with liver transplantation versus surgical resection of liver metastases alone [24]. In Supplemental List 1 we show also the excluded studies after analyzing the full paper during the second step of our study selection process. All these studies were observational and retrospective and HR extraction to perform the meta-analysis was not possible. The majority of the excluded studies were accurately described and summarized by a recent systematic review by Saxena et al. [33].

3.3. Quality Assessment of the Included Studies. The quality of the evidence on the influence of surgical treatment on survival of patients with NET liver metastases is quite low (levels III-IV, CEBM) [25].

All studies in our meta-analysis consistently showed an increased survival in the groups treated with surgery but none of the studies was randomized. The three independent reviewers agreed that all studies were graded six or seven points on the nine-point Newcastle-Ottawa scale for quality (medium quality). We regarded our results to be the basis to plan randomized clinical trials on this field.

3.4. Main Analysis. The meta-analysis was performed on five studies as reported in Figure 2 and considered 374 patients affected by NET liver metastases and treated in a conservative manner and 161 patients treated with liver metastases. The heterogeneity among the studies was not significant and we used fixed-effect model to calculate the

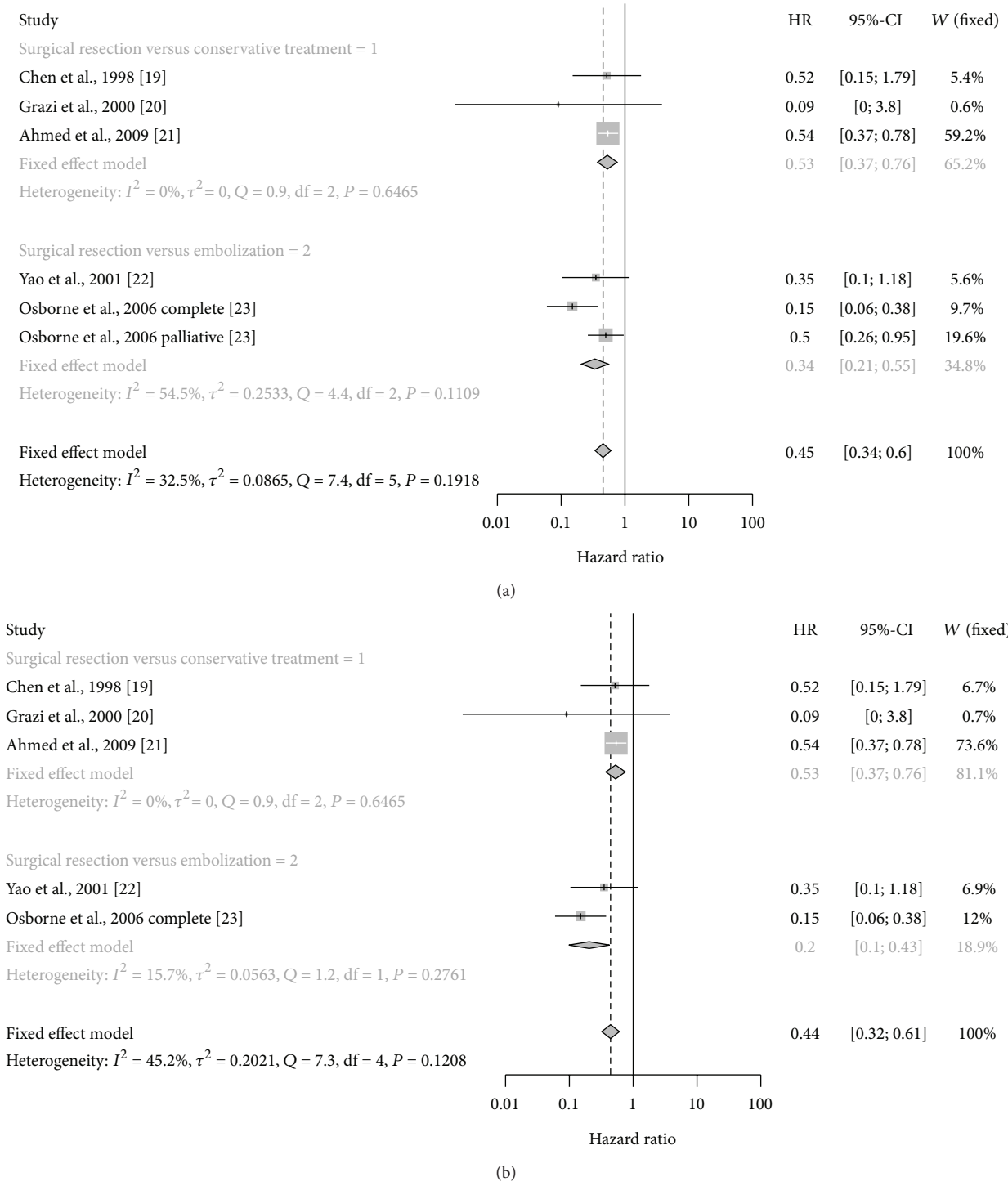

Figure 2: (a) Forest plot of overall survival comparison between hepatic metastasis resection versus expectant or other conservative/minimally invasive managements. (b) Analysis of OS excluding palliative surgery from data published by Osborne et al. [23].

pooled estimate. Only considering data from incomplete cytoreduction group published by Osborne et al. we found significant heterogeneity but fixed- and random-effect models were similar and for this study we considered the fixed-effect model [23]. We found a significant increased survival in thea group of patients treated with surgical hepatic resections HR 0.45 (CI.95 0.34–0.60) in comparison to conservative treatments and to embolization HR 0.34 (CI.95 0.21–0.55) (Figure 2(a)). In Figure 2(b) we reported the same analysis excluding only the cases treated with palliative surgery by Osborne et al. and the results were similar [23].

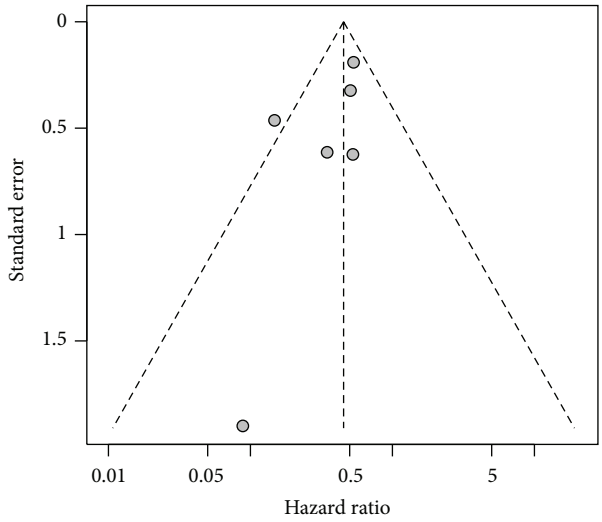

Figure 3: Funnel plot.

3.5. Risk of Bias Assessment. All the observational retrospective studies were classified as medium quality. We did not find any randomized clinical trial on this argument. The main limit to consider observational retrospective studies was to suppose a possible selection bias for the patients treated with surgical resection (limited disease in comparison to the group treated with conservative treatments). The articles of Yao et al. and Chen et al. stated that surgical resection and conservative treatment groups presented comparable disease characteristics [19, 22] and the study of Osborne et al. showed comparable pretreatment status between surgical resection and embolization [23]. The article published by Ahmed et al. presented the widest population and the patients treated in a conservative manner were older, with low proliferative index and high Chromogranin A [21]. The study of Grazi et al. did not specify the differences between the group treated with surgical liver resection of NET metastases and the conservative treatment group [20].

3.6. Publication Bias. We show in Figure 3 a funnel plot examining possible publication bias. These results should be interpreted with caution, because our meta-analysis calculation included only five studies (Figure 2, six dots because one study considered separately complete and palliative cytoreduction), and current guidelines do not recommend testing for funnel plot asymmetry in analysis of a limited number of studies (<10) [34]. The study with the smallest number of controls seems to be out of the symmetry in the plot (Figure 3). Also the comparison between complete cytoreductive surgery and embolization seems out of the symmetry. Nevertheless, the rank correlation test of funnel plot asymmetry with a P value of 0.189 does not indicate significant asymmetry in the funnel plot.

4. Discussion

In patients with NETs, occurrence of hepatic secondaries is one of the most important prognostic factors for survival [10, 35–37]. Due to the high prevalence of distant metastases and recurrences, NETs must be considered to have malignant potential [2, 38–41]. In particular, pancreatic NETs showed the lowest 5-year survival rates (34.1–37.6%), whereas gastrointestinal NETs exhibited the highest survival (85.9–88.5% at 5 years) [2, 35, 42]. Even if these neoplasms are quite uncommon, 2% of all malignancies [3], the incidence of NETs has increased exponentially (overall 500%) over the last three decades [3]. So the traditional assumption that these cancers are rare is incorrect [2]. Actually, the medical and surgical therapy of NETs is a hot topic and during the last two years at least four reviews of the literature have been published on this subject [6, 33, 43, 44].

The most recent classifications of the 7th American Joint Committee on Cancer/Union International Contre le Cancer 2009 (AJCC/UICC) and of the European Neuroendocrine Tumor Society 2006 (ENETS), associated with the WHO classification 2010, segregate NETs into well-differentiated neuroendocrine tumors (low and intermediate grade based on the Ki67 labeling index, also named NET-G1 or carcinoid and NET-G2, resp.) and into the group of neuroendocrine carcinomas (high grade, poorly differentiated, also named NEC) [40]. These classifications have provided means to better grade and stage NETs, but although these classifications may be useful for primary tumors, they do not allow the stratification of patients with hepatic neuroendocrine metastases [8, 45].

Considerable controversy exists regarding the best approach to patients with NET hepatic metastases. The management of these patients varies from control of symptoms only to more aggressive surgical or conservative therapies. For patients with unresectable liver disease, biotherapy with somatostatin analogues, peptide-mediated radioreceptor therapy, transarterial chemoembolisation, selective intra-arterial radiotherapy, or new molecular target-directed therapy can be employed [4, 44, 46], but these therapies are considered as palliative [18]. For localized hepatic metastases, surgical therapy appears as the most efficient approach [5, 16, 17, 36, 37, 47–49]. Furthermore, surgical resection of hepatic metastases could significantly reduce carcinoid symptoms [33].

Many studies that evaluate the outcome following surgical management of liver metastases from NETs have focused solely on resection rather than combined-modality approaches that include resection and ablation or surgery and chemotherapy. It is well known that neuroendocrine liver metastases recur in the most patients after hepatic resection, with high recurrence rates up to 70–94% at 5 years [8, 22, 35, 37, 49–51] and the liver is the most common site of progression of disease (69%) [49]. Therefore, the true curative role of liver-directed surgery was questionable and new strategies in association to surgery should be studied. It is important to underline that data on repeated liver surgery for recurrent disease have been extremely limited, and the role of repeated operations remains ill defined [51].

In our review and meta-analysis, we found five studies comparing surgical resection of NET liver metastases with conservative management and we observed a significant increased survival in patients treated with liver resection. It

is important to underline that all the included studies were observational and so the clinical evidence was low.

A recent systematic review considering 29 studies (between 1980 and 2009) found a 5-year OS of 70.5% (range 31–100%) and a 5-year progression-free survival of 29% (range 6–66%) [33]. Histological grade, extrahepatic disease, and macroscopically incomplete resection of liver metastases were associated with poor prognosis. Moreover, it was found that the predominant histological type was carcinoid (71%) and the most common origin was the small/large intestine (52%) [33]. In another multi-institutional study evaluating 339 patients, Mayo et al. demonstrated with multivariate analysis that synchronous disease, nonfunctional NET hormonal status, and extrahepatic disease were the most important predictive factors of worse survival [51]. Concerning other prognostic parameters for primary NETs and liver metastases, Katz et al. demonstrated that the robust presence of tumour-infiltrating lymphocytes is a significant predictor of outcome [52]. Moreover, it is demonstrated that Ki67 staining of core biopsies provides an adequately reliable method of proliferation assessment for prognosis of metastatic NETs to the liver [45].

The symptomatology is the most important consequence of NETs liver metastases (particularly for carcinoid tumors). Normally serotonin produced by a carcinoid tumor from a primary gut localization is secreted into the portal circulation and metabolized within the liver. The presence of multiple bilobar liver metastases will cause carcinoid syndrome because the serotonin is not metabolized and directly secreted into the systemic circulation. Furthermore, Saxena et al. found that 95% of patients (range 50–100%) will benefit from liver surgical resection by reducing symptomatology. They concluded that hepatic resection was safe and effective in symptomatic relief and favorable survival outcomes although the majority of patients develop recurrence of disease. It was hypothesized that the recognition of new markers could better identify which patients will be selected for surgery [33].

As previously stated, we agree that data about the survival benefit must be interpreted with caution because they could likely just to be the product of prudent patient selection. Probably, in the majority of published studies, there was a selection bias because many patients with a large number of hepatic tumors tend to be managed without surgical resection. Likewise, patients with synchronous disease are more likely to be treated without surgery. As randomized controlled trials are not available yet, the question about the effectiveness of surgical resection and other treatment modalities remains unanswered. Anyway, in our meta-analysis, at least two studies considered comparable disease in surgical and nonsurgical groups [19, 22]; in the study of Osborne et al. pre-treatment statuses between surgical resection and embolization were similar, and in the study of Ahmed et al. the difference is unlikely to be due only to patient selection [21]. Even the analysis of the two studies with comparable characteristics was in the same direction of the global analysis, and thus in favour of hepatic resection [19, 22]. Another weakness of our study is related to the great heterogeneity and wide variety in conservative therapies undertaken for NETs, which is due to the observational nature of the included studies. To overcome this weakness we subdivided the analysis considering separately the two studies comparing only surgery and embolization. Also in these two studies we found an advantage of surgical resection over conservative treatment (only embolization in this subgroup) in terms of overall survival. This further analysis resulted in the same direction as the overall analysis thus in favor of surgical resection. Therefore, we found a significant increased survival in the surgical hepatic resection group, and this data requires further evidence from randomized clinical trials in order to obtain a definitive answer to a really important question like the survival gain in these patients.

Our literature search results included only one study about liver transplant and we could not do any meta-analysis [24]. Recurrence after liver transplantation to treat NETs remains a significant concern, and considering the high morbidity and mortality associated with this procedure the indication of symptom relief alone must outweigh the significant risks [53]. Appropriate selection criteria and further international multicentric studies are needed to demonstrate survival and clinical benefits of this procedure.

5. Conclusion

Liver metastases are frequently encountered in patients with NETs; these secondaries have an important role in the prognosis. The published observational studies and our paper were supporting the surgical solution for NET hepatic metastases. But the observational and retrospective nature of these studies was limiting the level of evidence to support this solution. Since no randomized trial has been published, which could inform meaningfully about the sustained advantages of hepatic resection, no certain conclusion on the impact of this aggressive approach can be achieved. Our meta-analysis based on observational studies found a significant increased survival after surgical hepatic resection, but randomized clinical trials must be undertaken to achieve more evidence about the role of surgical treatment in patients with liver metastases from NETs.

Abbreviations

NET: Neuroendocrine tumor
RCT: Randomized controlled trial.

Conflict of Interests

The authors declare that they have no potential conflict of interests relevant to this paper.

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Clinical Study

Lack of Anatomical Concordance between Preablation and Postablation CT Images: A Risk Factor Related to Ablation Site Recurrence

Petra G. Kele,[1] Eric J. Van der Jagt,[1] Paul F. M. Krabbe,[2] and Koert P. de Jong[3]

[1] *Department of Radiology, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9700 RB Groningen, The Netherlands*
[2] *Health Technology Assessment Unit, Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands*
[3] *Division of Hepato-Pancreatico-Biliary Surgery and Liver Transplantation, Department of Surgery, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands*

Correspondence should be addressed to Petra G. Kele, p.g.kele@umcg.nl

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Objective. Variation in the position of the liver between preablation and postablation CT images hampers assessment of treatment of colorectal liver metastasis (CRLM). The aim of this study was to test the hypothesis that discordant preablation and postablation imaging is associated with more ablation site recurrences (ASRs). *Methods*. Patients with CRLM were included. Index-tumor size, location, number, RFA approachs and ablative margins were obtained on CT scans. Preablation and postablation CT images were assigned a "Similarity of Positioning Score" (SiPS). A suitable cutoff was determined. Images were classified as identical (SiPS-id) or nonidentical (SiPS-diff). ASR was identified prospectively on follow-up imaging. *Results*. Forty-seven patients with 97 tumors underwent 64 RFA procedures (39 patients/63 tumors open RFA, 25 patients/34 tumours CT-targeted RFA, 12 patients underwent >1 RFA). Images of 52 (54%) ablation sites were classified as SiPS-id, 45 (46%) as SiPS-diff. Index-tumor size, tumor location and number, concomitant partial hepatectomy, and RFA approach did not influence the SiPS. ASR developed in 11/47 (23%) patients and 20/97 (21%) tumours. ASR occurred less frequently after open RFA than after CT targeted RFA ($P < 0.001$). ASR was associated with larger index-tumour size (18.9 versus 12.8 mm, $P = 0.011$). Cox proportional hazard model confirmed SiPS-diff, index-tumour size >20 mm and CT-targeted RFA as independent risk factors for ASR. *Conclusion*. Variation in anatomical concordance between preablation and postablation images, index-tumor size, and a CT-targeted approach are risk factors for ASR in CRLM.

1. Introduction

Liver metastases develop in approximately 50% of patients with colorectal carcinoma. Partial hepatectomy is a potential curative treatment, but only 10–20% of the patients are eligible for partial hepatectomy. Radiofrequency ablation (RFA) is an alternative for patients with unresectable tumours and is often used as an adjunct to partial hepatectomy [1–4]. By using an image-guided approach, electrodes are positioned in the tumour either percutaneously or by an open approach [5–8]. One of the major problems with RFA is incomplete ablation, leading to ablation site recurrences (ASRs) [9]. Factors associated with low ASR rates are small index-tumour size [10], low number of treated tumours [11], at least 10 mm margins of coagulation around the tumour [1, 12], open surgical approach (versus percutaneous CT-targeted approach) [2, 3], and tumor location distant from large vessels [2, 3]. The purpose of post-RFA imaging is the early detection of ASR, providing the opportunity to repeat the RFA procedure. Strategies used for post-RFA evaluation include measuring the ablative margins or focusing on contrast enhancement in the ablation zone. A disadvantage of these techniques is the variation that can occur in the position of the liver between the pre-RFA scan and the post-RFA scan, resulting in an inaccurate quantitative assessment of the ablative margin. This may give false reassurance to

the adequacy of the treatment and might thus be an indirect risk factor for development of ASR. In this study, we test the hypothesis that variation in the position of the liver between pre-RFA scan and post-RFA scan makes the assessment of completeness of ablation of colorectal liver metastases difficult, and as an indirect risk factor is associated with the development of future ablation site recurrences (ASRs).

2. Patients and Methods

2.1. Patients. The study was approved by our institutional review board. Between July 2000 and July 2008, 142 RFA procedures were performed for primary (benign and malignant) and secondary liver tumours in our center. Sixty-five percent of these procedures were done with an open approach, 35% was performed percutaneously under CT targeting. Open procedures were performed in patients who also underwent a partial hepatectomy or if the tumour could not be safely reached using the percutaneous route. Laparoscopic procedures were not performed. All procedures were performed by one of the authors, an experienced hepatobiliary surgeon in collaboration with dedicated radiologists. CT-targeted RFA was performed in collaboration with a radiologist. Fifty-two patients (37%) underwent RFA for colorectal liver metastases. Five patients were excluded—missing pre-RFA images ($n = 2$), multiple and widespread liver metastases shortly after RFA making assessment of ASR impossible ($n = 2$), and lost to followup ($n = 1$). Thus, 47 patients who underwent 64 RFA procedures for 97 liver metastases were included in the study. Partial hepatectomy was performed as described previously and is considered the gold standard [13]. It is standard praxis to fix the liver remnant after partial hepatectomy with the aim to keep the liver remnant in the same position in order to prevent rotation of the remaining liver lobe. Rotation can lead to torsion of the draining hepatic vein and congestion of the liver lobe. RFA was only performed if partial hepatectomy was not able to render the liver tumor-free.

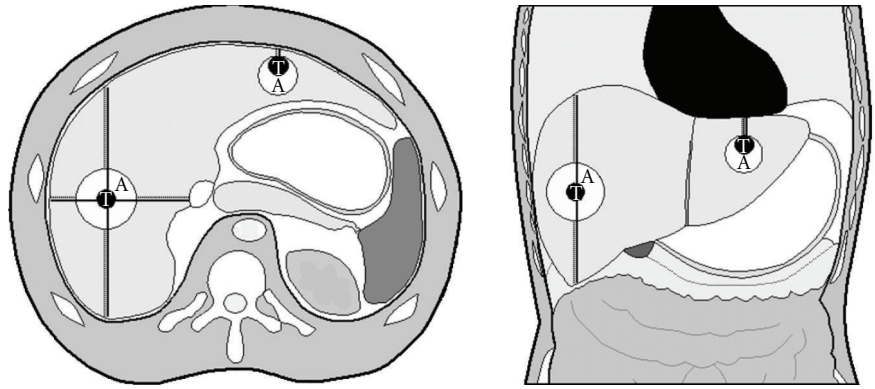
2.2. RFA Procedure. RFA was performed by one staff HPB surgeon (K. P. de Jang) in collaboration with a staff radiologist (E. J. Van der Jagt) for the CT-guided procedures. Ablation procedures are performed in our hospital since 1995 with about 20 procedures per year for colorectal liver metastases. We used the RF 3000 TM Radio Frequency Ablation System (Boston Scientific, Boston, MA, USA). A LeVeen electrode of 2, 3.5, 4, or 5 cm diameter was used, depending on tumour diameter. The RFA electrode was positioned using ultrasonography in open and CT-guided in CT-targeted RFA. RFA was applied according to the protocol of the manufacturer. RFA was continued until the generation of radiofrequency waves was blocked by the rise in tissue impedance. Large tumours were treated by several overlapping positions of the deployed RFA electrode. Terminology used in this paper is in accordance to the guidelines given by Goldberg et al. [14].

2.3. CT Protocol. Patients underwent triphasic CT scanning before the RFA procedure, one week after the RFA procedure, then at three-monthly intervals during the first two years and every six months thereafter. CT was performed on a 16- or 64-slice multidetector CT scanner (SOMATOM Sensation 64, Siemens, Erlangen, Germany). Intravenous contrast was used, 120 mL iodixanol 320 mg I/mL (Visipaque 320, GE Healthcare, Chalfont St Giles, UK), with a flow rate of 4.0 mL/sec. All subjects were scanned in craniocaudal direction during inspiratory breath-holding. CT images were acquired in a supine position using a 16×1.5 (16-slice) or 24×1.2 (64-slice) collimation, tube potential 120 kV, tube current time product 130 mAs, pitch 1, slice thickness of 2 mm, reconstruction Kernel B30f, and reconstruction increment 1.5.

2.4. Followup. Followup of the ablated tumours consisted of CT imaging or F18-fluorodeoxyglucose positron emission tomography (FDG-PET) when CT imaging was inconclusive. Patients were considered to have recurrences when there was a typical pattern of contrast enhancement on CT imaging and/or pathological glucose uptake on PET scanning.

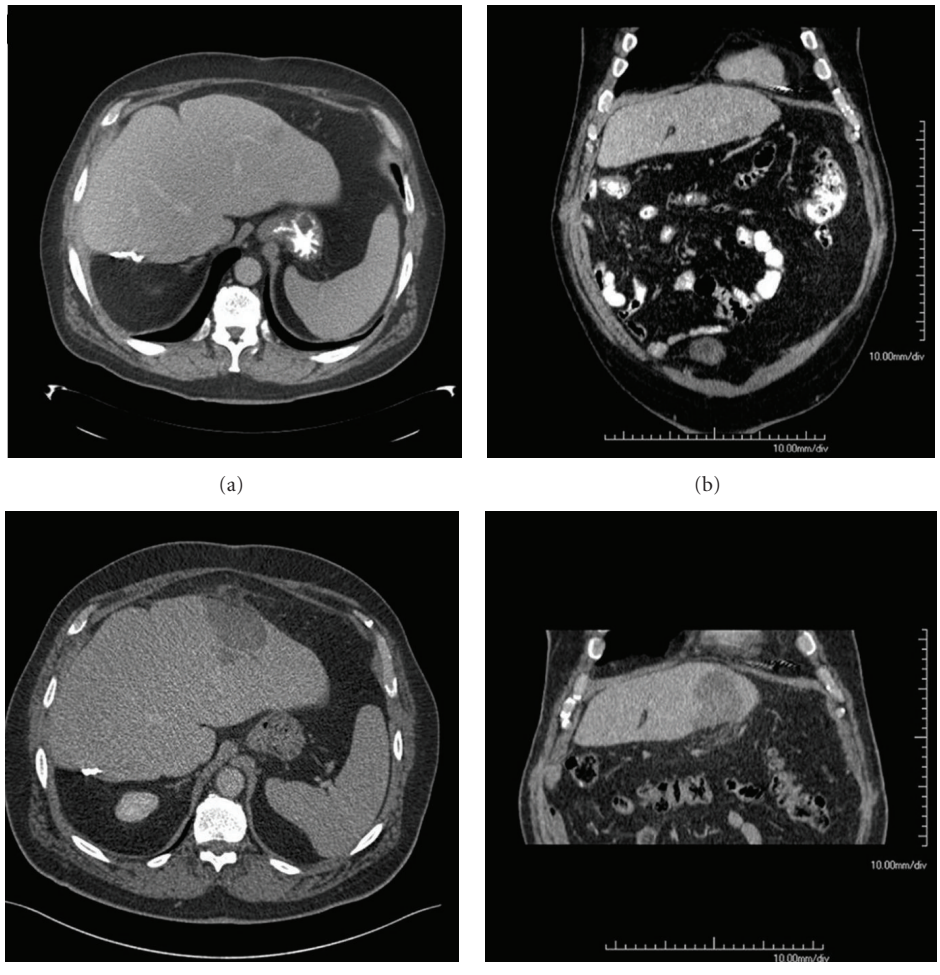
2.5. Post-RFA Evaluation. Radiological evaluation of the tumours before and one week after the RFA procedure was performed on an Aquarius Workstation (version 1.8.3.6, TeraRecon Inc., San Mateo, CA, USA). Images in axial and reconstructed coronal planes were used for three-dimensional measurements and comparison of the pre-RFA scan and the post-RFA scan (explanation in Figure 1). This was done by two of the authors (P. G. Kele, E. J. Van der Jagt). Reliable comparison was only possible when the position of the liver was identical or almost identical on the pre-RFA scan and the post-RFA scan. Therefore, a dichotomous "Similarity of Positioning Score" (SiPS) was developed in which post-RFA scans were compared to pre-RFA scans. Post-RFA scans were centrally and blindly classified as SiPS-identical (SiPS-id, i.e., comparable to the pre-RFA scans, Figure 2) or SiPS-different (SiPS-diff, i.e., not comparable to the pre-RFA scan, Figure 3). A post-RFA scan was considered SiPS-id when the vascular configuration (especially hepatic and portal veins) was identical or nearly identical to that on the pre-RFA scan. In addition, the projection of the abdominal organs, bony structures (vertebrae and ribs), and the position of previously placed surgical clips had to be identical or nearly identical. When these criteria were not met, a scan was regarded as SiPS-diff. For validation of SiPS, one of the authors (P. G. Kele) classified all tumours twice for intra-observer agreement. Another radiologist with two years CT experience performed the same classifications to obtain the interobserver agreement. Ablative margins >10 mm were considered sufficient. The smallest margin in one of the six directions was considered the most imperfect one. Therefore, tumours with an ablative margin <10 mm in only one of the six directions were regarded as having an insufficient ablative margin.

2.6. Definition of Ablation Site Recurrence. Progression at the site of a previously RFA-treated tumour was considered ASR



Axial Coronal

Figure 1: Explanation of the method of measurement. Schematic representation of the method of measurement of the ablation zone. Figure 1 representing the axial and coronal view respectively of the tumour (black circle with white T) and the ablation zone (white circle with black A). Ablative margins were calculated as follows. The distance from the edge of the tumour to the surface of the liver was measured in all six directions on the pre-RFA scan (continuous line). The same measurements were performed for the post-RFA scan from the edge of the ablation zone scan to the surface of the liver (dotted line). The ablative margins are the difference between both distances. The tumour in the left liver lobe is considered to be incompletely ablated because in one of the six directions the difference between both distances is zero.



(a) (b)

(c) (d)

Figure 2: Similarity of Positioning Score-identical (SiPS-id). Example of identical (concordant) pre-RFA CT images and post-RFA CT images, classified as Similarity of Positioning Score-identical (SiPS-id). The pre-RFA CT scan ((a) axial, (b) coronal) and the post-RFA CT scan ((c) axial, (d) coronal) are well comparable.

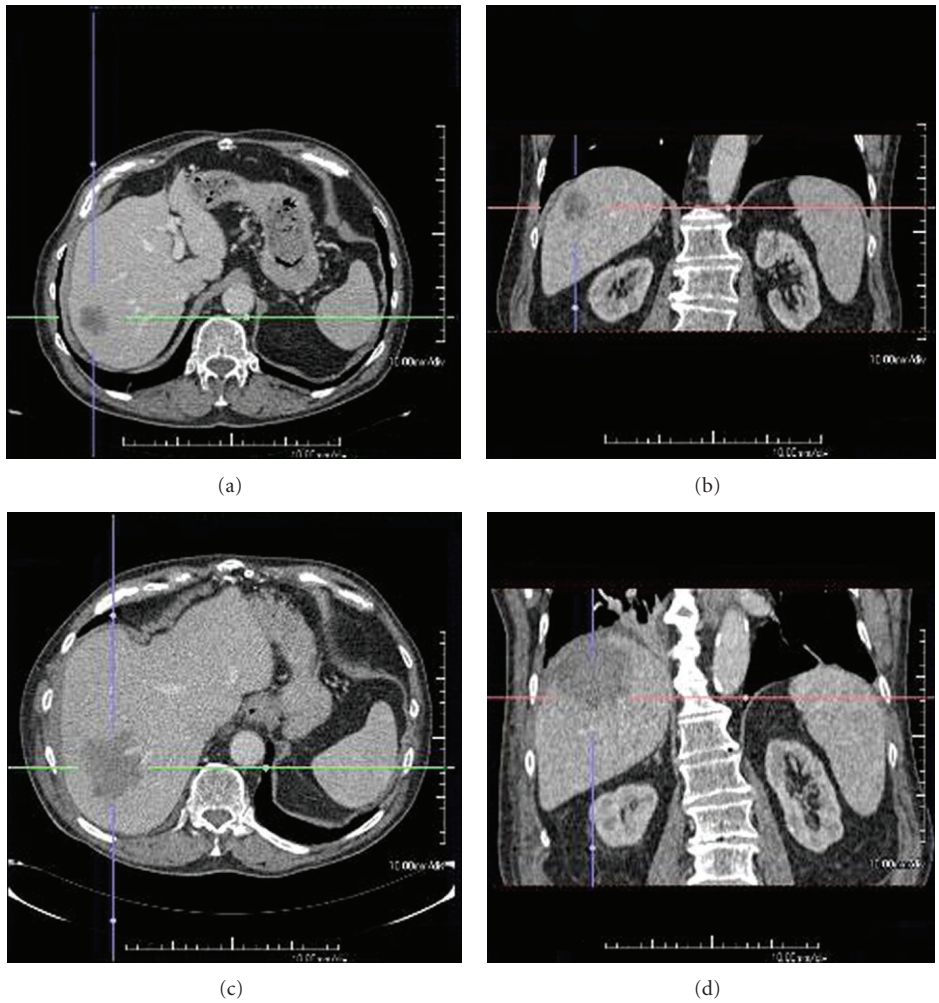


Figure 3: Similarity of Positioning Score-different (SiPS-diff). Example of nonidentical (discordant) pre-RFA CT-images and post-RFA CT-images, classified as Similarity of Positioning Score-different (SiPS-diff). The pre-RFA CT-scan ((a) axial, (b) coronal) and post-RFA CT-scan ((c) axial, (d) coronal) are not comparable.

when it met both of the following criteria: (1) growth of a contrast-enhancing lesion within or directly adjacent to the ablation zone and (2) the largest diameter of the lesion was in direct contact with the ablation zone. The latter prerequisite is to exclude the outgrowth of satellite lesions in the vicinity of the ablated tumour (Figure 4).

2.7. Statistical Analysis. Chi-square and Fisher's exact test were applied to assess the relationship between categorical variables SiPS (identical versus different), RFA approach (open versus CT-targeted), partial hepatectomy in the history (yes versus no), number of tumours ablated (<3 versus ≥3), localization of tumours (subcapsular, i.e., <10 mm under the liver capsule, versus central), ablative margins (>10 mm versus <10 mm and >5 mm versus <5 mm), and ASR (yes versus no). For comparing the continuous variable index-tumour size between tumours with and without ASR, Student's *t*-test was used after correction for nonnormal distribution (log transformation). Survival was assessed with Kaplan-Meier analysis. Variables possibly contributing to ASR were analyzed by using log-rank test. Cox proportional hazard model was used to identify independent risk factors for ASR. Kappa statistics were calculated to test the intraobserver and interobserver agreement of SiPS. Agreement was rated as poor (kappa 0–0.2), fair (kappa 0.21–0.40), moderate (kappa 0.41–0.60), substantial (kappa 0.61–0.80), or excellent (kappa 0.81–1.0) [15]. The significance level was set at a $P < 0.05$ for all tests. Statistical analysis was performed using SPSS (Statistical Package for Social Sciences version 16.0 Inc., Chicago, IL, USA).

3. Results

3.1. General Characteristics and Recurrence Patterns. In 47 patients with 97 colorectal liver metastases, 64 RFA procedures were performed. An open approach was used in 39 patients with 63 metastases. Percutaneous CT-targeted RFA was performed in 25 patients with 34 metastases. There

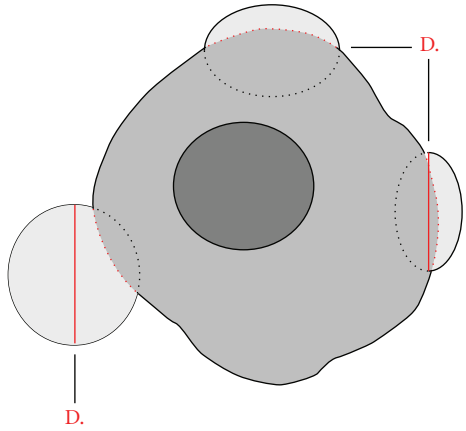


Figure 4: Definition of ablation site recurrence. Examples of ablation site recurrences (ASRs). The largest diameter of both lesions on the right is in direct contact with the ablation zone. The lesion on the left is not an ASR, because the center of the line representing the largest diameter is not in direct contact with the ablation zone. It is more probably a satellite metastasis which was already present at the time of the ablation. Outgrowth of this lesion took place after the RFA procedure. This prerequisite is necessary to prevent erroneously identified outgrowing satellite lesions in the close vicinity of the ablated tumour as ASR.

were 12 patients who underwent one or more further RFA procedures, of which 5 patients had repeat RFA for ASR. ASR was seen in 11 patients (23%) with 20 metastases (21%). There were 2 patients (4%) with 3 metastases (3%) who showed ASR without recurrences elsewhere. Recurrent disease elsewhere occurred in 33 patients (70%) with 74 ablated liver metastases (76%) and was concomitant with ASR in 9 patients (19%) with 17 metastases (18%). Recurrence without ASR was seen in 24 patients (51%) with 57 tumours (59%) (Table 1). Mean index-tumour size before RFA was 13.9 mm (SD 1.8, range 3.9–78.0 mm).

3.2. Similarity of Positioning Score (SiPS). After CT-targeted RFA, 15 of the 34 tumours (44%) were classified as SiPS-id, the remaining 56% as SiPS-diff. After open RFA, 37 of the 63 tumours (59%) were classified as SiPS-id, the remaining 41% as SiPS-diff. After open RFA with concomitant partial hepatectomy, 24 tumours were classified as SiPS-id (56%), the remaining 44% as SiPS-diff. Kappa statistics for intraobserver agreement were excellent (kappa 0.834, $P < 0.001$) and substantial for interobserver agreement (kappa 0.752, $P < 0.001$). Index-tumour size, RFA approach, concomitant partial hepatectomy, number of ablated tumours, and tumour localization were not different in the SiPS-diff group versus the SiPS-id group (Table 2).

3.3. ASR. ASR occurred in 20 of 97 metastases (21%). Tumours with ASR were larger than tumours without ASR (18.9 mm versus 12.8 mm, $P = 0.011$). ASR was seen in 17 (50%) tumours treated with CT-targeted RFA and 3 (5%) tumours with open RFA ($P < 0.001$). ASR was seen in 6 (12%) tumours classified as SiPS-id and 14 (31%) tumours classified as SiPS-diff ($P = 0.017$). ASR was not different in tumours with ablative margins <5 mm ($P = 0.464$).

Univariate analysis showed more ASR in tumours treated with CT-targeted RFA ($P < 0.001$), in tumours classified

Table 1: Patient and tumour characteristics.

	Patients	Tumours
Number	47	97
Gender ♂/♀	30/17 (64%/36%)	—
Age (mean, range)	61.8 years (39–81)	—
Deceased	12/47 (26%)	—
Partial hepatectomy	34 (72%)	73 (75%)
Before RFA[a]	5 (15%)	20 (27%)
During RFA	25 (73%)	43 (59%)
After RFA	4 (12%)	10 (14%)
Type of partial hepatectomy ($n = 34$)		
Right-sided hemihepatectomy	12 (35%)	—
Left-sided hemihepatectomy	8 (24%)	—
Segment 2 and 3 resection	12 (35%)	—
Other	2 (6%)	—
Synchronous/metachronous disease	26/21 (55%/45%)	57/40 (59%/41%)
Indication RFA		
Bilobar disease	29 (62%)	—
Recurrence after partial hepatectomy	8 (17%)	—
Major comorbidity	7 (15%)	—
Minimal residual disease	2 (4%)	—
Severe steatosis	1 (2%)	—
RFA procedures		
1 RFA	35 (75%)	—
2 RFAs	9 (19%)	—
3 RFAs	1 (2%)	—
4 RFAs	2 (4%)	—
RFA approach (64 procedures)		
Open	39 (61%)	63 (65%)
CT targeted[b]	25 (39%)	34 (35%)
No. of tumors ablated (64 procedures)		
1 tumor	44 (69%)	—
2 tumors	13 (20%)	—
≥3 tumors	7 (11%)	—
Recurrence	33 (70%)	74 (76%)
ASR[c]	11 (23%)	20 (21%)
Repeat RFA for ASR		
Yes	5 (11%)	10 (10%)[d]
No	42 (89%)	87 (90%)
Partial hepatectomy for ASR		
Yes	1 (2%)	2 (2%)
No	46 (98%)	95 (98%)

[a]RFA: radiofrequency ablation.
[b]CT targeted: computer tomography targeted.
[c]ASR: ablation site recurrence.
[d]CT targeted RFA was performed initially in all tumours which underwent repeated RFA for ASR.

Table 2: Effect of different factors on the Similarity of Positioning Score (SiPS).

	SiPS-id[a] ($n = 52$)	SiPS-diff[a] ($n = 45$)	P value
Index-tumor size (mean ± SD)[b]	14.1 mm (1.9)	13.6 mm (1.8)	0.773
RFA approach[c]			
Open RFA ($n = 63$)	37 (59%)	26 (41%)	0.203
CT-targeted RFA ($n = 34$)	15 (44%)	19 (56%)	
Partial hepatectomy during RFA[c]			
Yes ($n = 43$)	24 (56%)	19 (44%)	0.838
No ($n = 54$)	28 (52%)	26 (48%)	
No. of tumours ablated[c]			
1-2 ($n = 70$)	40 (57%)	30 (43%)	0.364
≥3 ($n = 27$)	12 (44%)	15 (56%)	
Localization[c]			
Subcapsular ($n = 76$)	44 (58 %)	32 (42 %)	0.140
Central ($n = 21$)	8 (38 %)	13 (62 %)	

[a] SiPS: Similarity of Positioning Score, identical (SiPS-id) or different (SiPS-diff).
[b] Student's t-test.
[c] Chi-square or Fisher's exact test.

Table 3: Cox proportional hazard model showing the relative risk for development of ablation site recurrence compared to the reference standard (1.0).

	Relative risk (95% CI)	P value
RFA approach		
Open RFA	1.0	0.001
CT-targeted RFA	9.5 (2.6–34.0)	
Similarity of Positioning Score (SiPS)		
SiPS-identical	1.0	0.019
SiPS-different	3.9 (1.2–12.3)	
Index-tumour size		
<20 mm	1.0	0.010
≥20 mm	3.6 (1.4–9.4)	

as SiPS-diff ($P = 0.023$), and in tumours with an index-tumour size >20 mm ($P = 0.009$). Tumour localization (subcapsular versus central) and ablative margins were not associated with ASR ($P = 0.483$ and $P = 0.576$, resp.). Cox proportional hazard model identified RFA approach, SiPS, and index-tumour size as independent predictors of ASR. CT-targeted RFA was associated with the highest risk for developing ASR, followed by SiPS-diff and an index-tumor size >20 mm (Table 3).

3.4. Survival. Median time of followup was 36 months (interquartile range 25–49). Median overall survival in the open RFA group was 40.7 months (95%-CI 23.3–58.2) and was not statistically different for the CT-targeted RFA group ($P = 0.23$). As the proportion of disease-free patients in the latter group was more than 50% at the end of the study, the median survival could not be estimated. After open RFA, median disease-free survival was 35.2 months (95%-CI 29.7–40.7) and 32.6 months (95%-CI 15.8–49.5) after CT-targeted RFA ($P = 0.50$).

4. Discussion

RFA is increasingly used in patients with malignant liver tumors in whom partial hepatectomy is not able to render the liver tumor-free. RFA seems to be a highly attractive treatment modality since it is associated with lower morbidity and mortality compared to partial hepatectomy. However, a major concern is the reported high incidence of ablation site recurrences (ASRs). Early evaluation of the completeness of RFA—followed by immediate repeated RFA in case of an incomplete procedure—is essential to reduce the high incidence of ASR. A prerequisite for evaluation of the completeness of RFA is the anatomical concordance or comparability of the pre-RFA scan with the post-RFA scan. In the present study, we hypothesized that incomparability of the pre-RFA scan and the post-RFA scan may result in an increased number of future ASR, since completeness of ablation cannot be evaluated reliably. Indeed we found that this incomparability is a risk factor associated with ASR. Other risk factors were CT-targeted RFA approach (as opposed to open RFA) and an index-tumour size >20 mm.

The reason for using the Similarity of Positioning Score (SiPS) in this study was to evaluate the problem and consequences of incomparable pre-RFA imaging and post-RFA imaging. Fifty-four percent of the post-RFA scans were classified as anatomically concordant or SiPS-identical (SiPS-id), the remaining 46% as anatomically discordant or SiPS-different (SiPS-diff). Open RFA and CT-targeted RFA were equally represented, suggesting that SiPS is not influenced by RFA approach and concomitant partial hepatectomy. Although intuitively it seems reasonable to expect that partial hepatectomy is associated with a change in position and configuration of the liver and thus influence SiPS, we did not encounter this. A probable explanation is that the liver remnant is fixed in position at the end of the operation. This means that SiPS is determined by other factors, for example, changes in the position of the liver as a result of longitudinal or rotational movements of the liver related to variations in diaphragm position. These factors could result in substantial organ position differences. These issues are well known in the field of radiotherapy and nuclear medicine. In radiotherapy, this problem is improved by using implanted markers which optimize accurate tumour targeting and advanced scanning techniques such as four-dimensional CT planning [16, 17]. In nuclear medicine, movements—particularly respiratory movements—can result in mismatch between PET and CT images. Respiratory-motion tracking systems, mathematical correction models, or scanning correction models and post-processional motion-correction methods are used to minimize this problem [18, 19]. These techniques could

be useful in reducing organ position differences between subsequent scans in the post-RFA followup.

Radiological evaluation of RFA procedures can be performed by different strategies. Firstly, ablative margins can be estimated by fusing pre-RFA images and post-RFA images. Unfortunately, this method is often hindered by incomparable pre-RFA images and post-RFA images. Secondly, comparing surfaces, volumes, or diameters of the index tumor and post-RFA ablation zone is often not reliable because of geometrical constraints or incomplete overlap of the index tumor and ablation zone [7, 20]. Thirdly, evaluation can be performed by focusing on post-RFA contrast enhancement, which might be misleading because of contrast enhancement associated with post-RFA inflammation and contrast enhancement due to residual tumour origin. Differentiation between these entities can be performed by their different morphological characteristics and contrast-enhancement patterns on multiphase CT scanning [21, 22], but remains difficult.

A possible solution to detect residual tumour after RFA without being hindered by incomparable pre-RFA images and post-RFA images is to perform PET-CT. PET is reported to have a high diagnostic accuracy in detecting residual tumour after RFA compared to contrast-enhanced CT and even MRI, modalities which are more readily available [21, 23]. Until now, only few studies with small patient populations assessed the usefulness of PET-CT after RFA. Based on our study it might be that PET-CT is the preferred imaging modality to detect incomplete ablations in patients with discordant pre-RFA scans and post-RFA scans. A potential limitation might be a false-positive result because of glucose uptake associated with post-RFA inflammation in the early post-RFA period [24]. Another possibility to evaluate the completeness of the ablation is to monitor ablation zone volume on consecutive CT scans, since an ongoing decline in ablation zone volume on consecutive scans is highly predictive of complete ablation and that an increase in volume is associated with ASR [25]. However, this is only noticed later in the followup and not on the first postprocedural scan. Therefore, we recommend that in case of SiPS-id, patients undergo regular followup with multiphase CT scanning every three months in the first two years after the RFA procedure and biannually thereafter. Patients with SiPS-diff should be followed in a similar fashion, but it might be advisable in these patients to perform additional PET-CT scanning three to six months after the RFA procedure, when the post-RFA inflammation has subsided and eventual glucose uptake can be attributed to the residual tumour.

We report an ASR rate of 23% per patient and 21% on a tumour basis. Previously reported ASR rates vary widely between 1.8 and 55% [2, 3, 11, 26–28]. We found more ASR in tumours with SiPS-diff classified scans, CT-targeted RFA treated tumours and tumours with a diameter of >20 mm. Although some studies have shown a higher incidence of ASR with ablation margins <10 mm [29–31], our findings are in line with that of others who have reported that ASR is not related to ablative margins [31, 32]. Unfortunately, authors often do not mention their evaluation methods, which may lead to contradictory reports because of the use of different techniques.

It has been reported that CT-targeted RFA is associated with a higher risk of ASR [2, 3, 12, 26, 28, 33–35], which is in accordance with our results. The most important explanation for the higher ASR rate in CT-targeted RFA is limited access to the tumour compared to open RFA, leading to inadequate ablation. Open RFA allows complete mobilization of the liver, better electrode accessibility, additional manoeuvres (Pringle), and tumour visibility (using intraoperative ultrasound). Especially relevant is our finding that despite the higher incidence of ASR in CT-targeted RFA, survival is not different from patients treated with open RFA. This can very likely be explained by thorough postprocedural followup. By carefully monitoring patients, early detection of ASR offers the possibility of timely interventions such as repeat RFA or partial hepatectomy.

This study has certain limitations. Firstly, the newly introduced SiPS classification system is used in a small patient population. We are planning to validate the SiPS classification in a larger patient cohort. Secondly, we did not perform biopsies to confirm the diagnosis of ASR. However, the reason not to do so is well founded—biopsies can be associated with tumour seeding. This risk outweighs the benefit of the procedure [36, 37]. Although SiPS was described in a relative small population encompassing 97 tumours, it is highly reproducible as reflected by the excellent intraobserver and substantial interobserver agreement.

In conclusion, lack of anatomical concordance between pre-RFA images and post-RFA images, CT-targeted RFA, and index-tumour size >20 mm are independent risk factors associated with future ablation site recurrences. Anatomical concordance of pre-RFA images and post-RFA images, expressed in the Similarity of Positioning Score, is important in evaluating the RFA procedure. In discordant scans, no reliable judgement can be made about the completeness of ablation and thus whether an additional RFA is necessary. Therefore, it is associated with an indirect increased risk of future ablation site recurrences.

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