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Treatment of liver metastases, an update on the possibilities and results

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Abstract

Long-term results after liver resection for colorectal liver metastases show 5-year survival rates between 35 and 40%. However, only a limited number of patients appear to be candidates for resection, far more patients prove to have unresectable disease. Present challenges in liver surgery for colorectal metastases are to improve patient selection, to increase the resectability rate and to improve survival by multimodality treatment approaches. The variables most consistently associated with a poor prognosis and tumour recurrence are tumour-positive resection margins and the presence of extra-hepatic disease. Hence, patient selection and preoperative staging should concentrate on accurate imaging of the liver lesions and the detection of extrahepatic disease. For liver imaging, spiral computed tomography (CT) scan or magnetic resonance imaging (MRI), supplemented by intra-operative ultrasound, are currently regarded as the best methods for evaluating the anatomy and resectability of colorectal liver metastases. Extrahepatic disease should be investigated by spiral CT of the chest and abdomen and when possible by 2-fluouro-2-deoxy-D-glucose-positron emission tomography (FDG-PET). Resection remains the gold standard for the surgical treatment of colorectal liver metastases. In experienced centres, resection is a safe procedure and mortality rates are below 5%. The aim of resection should be to obtain tumour-negative resection margins. Edge cryosurgery should be considered in cases where very close resection margins are anticipated. The role of adjuvant chemotherapy after resection is still controversial, although two recent studies show a clear benefit. For the moment, local tumour ablative therapies such as cryotherapy and radiofrequency therapy should be considered as an adjunct to hepatic resection in those cases in which resection can not deal with all of the tumour lesions. In these cases, there seems a beneficial effect of a combined treatment consisting of resection and local tumour ablation. At this stage, there are no randomised data that local tumour ablation is as effective as resection. For a selected group of patients with unresectable liver metastases, there may be a chance to turn unresectable disease to resectable disease by aggressive neo-adjuvant chemotherapy or portal vein embolisation. For patients with unresectable disease, many different chemotherapy schedules may be used based on systemic drug administration. Regional chemotherapy and isolated liver perfusion should only be used within a study design.
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1. Introduction

Colorectal cancer ranks second as a cause of death due to cancer in the Western world. The cumulative lifetime risk is approximately 5%, the incident rate in the Western world 50/100 000 [1]. Liver metastases form the main cause of death in patients with colorectal cancer. Already at the time of detection of the primary tumour, 15–25% of the patients present with liver metastases, another 20% will develop these metastases following treatment of the colorectal primary [2,3]. Without any treatment, the median survival after the detection of liver metastases is approximately 9 months, depending on the extent of the disease at the time of diagnosis [4].

In contrast to many other solid tumours, resection of liver metastases from colorectal origin has been shown to result in long-term survival and even cure. In selected patients with metastatic disease confined to the liver, 5-year survival rates are generally reported between 35 and 40%, depending on the extent of liver involvement

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[5–8]. Unfortunately, only a minority of patients (10–15%) with liver metastases are considered to be candidates for resection. Most patients have liver metastases that are unresectable. Present challenges in liver surgery are to improve patient selection, to increase resectability rates, and to improve survival by multimodality approaches of treatment.

2. Patient selection

In the past, several factors were identified that determined clinical outcome after resection of colorectal liver metastases (Table 1). The variables most consistently associated with poor prognosis and tumour recurrence are tumour-positive resection margin of the removed specimen and extrahepatic disease at the time of surgery for liver metastases [6–11].

2.1. Radical resection

In patients with positive resection margins, survival after resection hardly differs from natural history and hence positive resection margins or residual tumour should be avoided at any time [6–11]. Unfortunately, the parameter of a histologically-positive resection margin is not particularly useful during preoperative patient selection. The understanding, however, that it is a strong prognostic factor should force every surgeon to critical judgement before surgery whether there is a fair chance that all of the tumour tissue can be adequately removed.

2.2. Extrahepatic disease

The presence of extrahepatic disease is generally considered a contra-indication to resection [6–11]. However, in the presence of resectable lung metastases or locally invasive disease that can be removed together with the liver lesions (e.g. the involvement of the diaphragm) resection of all metastatic disease still has a positive impact on survival. Several series report a 5-year survival rate of more than 20% after combined resection of liver and lung metastases [12,13].

In patients with peritoneal metastases or intra-abdominal lymph node metastases, surgical treatment does not seem to prolong survival and resection of liver metastases is generally not indicated. In patients with positive lymph nodes, Hughes reported a 5-year survival rate of only 4% while, in two other studies, there were no patients who survived more than 4 years [14–16]. Some Japanese studies show slightly better results after liver resection and resection of positive lymph nodes [17].

2.3. Other factors

Other factors that are related to survival after resection are the number of metastases, the size of the metastases, synchronous presentation of the metastases with the primary tumour, the time interval between the primary tumour and metastases, the original staging of the primary tumour and high preoperative carcino-embryonic antigen (CEA) levels [5–11]. Each of these factors has only a limited impact on survival and should not be considered an absolute contra-indication to resection. To direct clinical decision-making, several scoring systems have been proposed based on these prognostic factors [5,18]. These systems combine several prognostic indicators resulting in a sum that can be used to select patients for surgery or to allow stratification of patients in order to evaluate and compare the results of clinical trials. In a scoring system using five variables (size of metastases >5 cm, disease-free interval <12 months, number of metastases >1, lymph node positive primary tumour, preoperative CEA >200 ng/ml) Fong and colleagues showed favourable outcome with a 5-year survival rate of $>40\%$ after resection in patients with up to two of these criteria [18]. 5-year survival dropped to $<20\%$ in those patients with three or more of these variables.

From recent literature, it can be concluded that there is an increasing tendency to resect liver metastases from a colorectal origin. Synchronous metastases, multiple metastases or bilobar disease which were considered contra-indications for resection in the past, no longer are considered an obstruction for resection. Today, the main guidelines for patient selection and hence preoperative staging for hepatic surgery is to exclude

Table 1
Prognostic factors for survival after resection of colorectal liver metastases

Author (Ref.)	Patients (*n*)	Size lesions	Synchronous metachronous	Stage primary tumour	Metastasis (*n*)	Extrahepatic disease	Resection margin
Hughes [6]	859	Yes	Yes	Yes	Yes	Yes	Yes
Scheele [7]	350	No	Yes	Yes	No	Yes	Yes
Jaeck [9]	747	Yes	No	Yes	Yes	Yes	Yes
Jamison [10]	280	No	No	No	No	Yes	Yes
Fong [8]	456	Yes	Yes	Yes	Yes	Yes	Yes
Elias [11]	270	No	No	No	No	Yes	Yes

extrahepatic disease and to judge whether negative resection margins can be obtained.

3. Preoperative staging

Preoperative staging of patients with colorectal liver metastases should concentrate on the accurate imaging of the number, size and location of the metastatic lesions within the liver, as well as on the detection of possible extrahepatic disease.

3.1. Liver

For imaging of the liver spiral computed tomography (CT) scan with intravenous (i.v.) contrast is currently regarded as the best method for evaluating the anatomy and resectability of colorectal liver metastases [19,20]. The sensitivity of CT scan for the detection of colorectal liver metastases is approximately 80% [21]. Only peroperative ultrasound shows a higher sensitivity and sometimes better image of the relationship of the lesions to vessels or bile ducts [22] For this reason, several studies promote the use of laparoscopic ultrasound prior to laparotomy [23,24]. For example, in a study of Rahusen and colleagues 25% of the patients scheduled for laparotomy and liver resection were found to have unresectable disease during laparoscopic ultrasound [24].

Other forms of CT scan, such as CT arterial portography (CTAP) and CT hepatic arteriography (CTA), require catheterisation and do not generally lead to a better judgement with regard to the feasibility of resection. Although the sensitivity of these forms of CT scan is reported to be higher, false-positive results due to perfusion defects are generally higher than for spiral CT and hence may lead to unjustified conservative treatment [25]. In addition, the results of magnetic resonance imaging (MRI) are, at this stage, not superior to spiral CT, although the use of new contrast agents may result in improved imaging [19,26].

The role of the 2-fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) scan in the detection of colorectal liver metastases is still under investigation. In most series, the sensitivity for the detection of liver lesions is lower for FDG-PET than for CT, although several studies report a higher sensitivity for FDG-PET [27–32]. Given the limited anatomical information provided by a FDG-PET scan, FDG-PET by itself will not become a substitute for the excellent anatomical imaging provided by spiral CT scan. Further development of combined modalities of CT and PET imaging, thereby presenting overlays of anatomical (CT) and functional (PET) information, may lead to significant improvements in pre-operative liver staging and pre-operative judgement on the feasibility of resection [33].

With the present imaging techniques, there is no place for liver biopsies to confirm the diagnosis. Liver biopsies may lead to metastatic seeding and hence may interfere with the purpose of the later curative resection.

3.2. Extrahepatic

At this stage, spiral CT scans of the chest and abdomen (including the pelvic area after rectal carcinoma) is generally standard practice to exclude extra-hepatic disease. Chest X-ray is unreliable in detecting pulmonary metastases and hence no longer indicated. Whole body survey and analysis of metabolic activity, as performed during FDG-PET, may substantially add to the conventional anatomical imaging by CT scan. In several series, FDG-PET led to clinically relevant extrahepatic findings that were different from conventional imaging in 20–30% of the cases [27,30,34]. The precise role of FDG-PET in the selection of patients for liver resection needs further evaluation.

To exclude large bowel recurrence or any new primary colon malignancy, X-ray or colonoscopy should performed.

4. Resection

4.1. Survival

Resection is still the gold standard for the surgical treatment of colorectal liver metastases. It should be considered in all patients with metastatic disease confined to the liver which can be removed adequately, while leaving enough functional liver reserve.

Many studies over the last two decades have demonstrated long-term survival after liver resection for colorectal liver metastases (Table 2). 5-year survival rates after resection in these series varies from 21 to 50% [6–11,35–40]. Differences in survival are mainly related to patient selection. Moreover, multicentre studies often report lower survival data compared with single centre studies emphasising the importance of the experience that is present in the high volume centres. On the other, hand single-centre studies often suffer from long inclusion periods in which inclusion of the first patients in the study dates back more than 25 years. Hence, recent studies that include only patients during the last 15 years will give the best impression of the results that can be obtained by resection today. In all of these studies, a 5-year survival rate of more than 33% is reported [8,11,40]. Data on longer follow-up are still rare:two studies report 10 year survival rates of 20 and 23%, indicating that liver resection can cure patients with colorectal liver metastases [7,10].

4.2. Resection margins

It should be stressed that these good results apply only for those patients in whom resection margins of the

Table 2
Results after resection of colorectal liver metastases

Author (Ref.)	Patients (*n*)	Years of follow-up	Centers (*n*)	Operative mortality (%)	5-year survival (%)	10-year survival (%)
Nordlinger [35]	80	16	2	5	25	
Hughes [6]	859	37	24	–	33	
Van Ooijen [36]	118	10	15	7.6	21	
Doci [37]	100	9	1	5	30	
Rosen [16]	280	27	1	4	25	
Gayowski [38]	204	11	1	0	32	
Scheele [7]	350	33	1	4.4	38	23
Jaeck [9]	747	33	85	2.4	26	
Jamison [10]	280	27	1	4	27	20
Fong [8]	456	6	1	2.8	38	
Elias [11]	270	12	1	2	34	
Nakamura [39]	66	–	1	3	50	
Taylor [40]	123	16	1	0	34	

resected specimen are negative for tumour. As stated earlier, patients with positive resection margins hardly benefit from resection. For these patients, 5-year survival rates vary in different studies between 0 and 17% [6–9,11].

Although in general a resection margin of 1 cm or more is aimed for, the location of tumour deposits does not always allow such a margin. It should be realised that long-term survival is still significantly improved as long as the resection margins are microscopically free of disease. In a prospective study, Elias described a 5-year survival rate of 25% for patients who had undergone resection with a margin <1 cm compared with a 5-year survival rate close to zero in patients with a positive resection margin [11]. Patients with a resection margin >1 cm showed a 5-year survival rate of 42% in this study.

There is a close relationship between the prognostic relevance of the number and size of metastases and the histological status of the resection margin. Fong and colleagues described a 5-year survival rate of 47% for patients with less than four metastases compared with 24% for patients with more than four metastases [8]. These differences in survival related to the number of metastases were, however, not observed in studies by Elias and Scheele who both analysed only those patients with negative margins [7,11]. This means that as long as all of the liver lesions can be removed adequately, the number of lesions is of less importance. The same principle applies for the diameter of the metastases. Patients with larger lesions show generally higher recurrence rates. However, this difference in survival becomes smaller when these lesions can be removed adequately with a negative margin.

With an increasing tendency to perform hepatic resection for a second or even third time in cases of recurrence, there is a trend to avoid extensive resections when not absolutely indicated to obtain adequate margins. Several liver surgeons prefer segment resections or even atypical resections, as long as adequate margins can be obtained. Extensive resections such as hemihepatectomy for one solitary lesion should be avoided when possible. A liver-sparing approach offers significantly better opportunities for secondary liver surgery.

4.3. Edge cryotherapy

Several studies describe the use of cryosurgery in case a very close or histologically-positive resection margin is anticipated [41]. During this procedure, flat cryoprobes are held against the resection edge of the remaining liver. Adequate freezing is obtained for at least 1.5 cm into the remaining liver tissue. Seifert described a series of 44 patients with involved or inadequate resection margins treated by edge cryotherapy [42]. Median overall survival in the series was 33 months with only five recurrences at the resection edge. In addition, other authors mention the successful use of edge cryotherapy under these circumstances [11,42,43].

4.4. Perioperative mortality and morbidity

Hepatic resection has become an increasingly safe procedure during the last two decades. Mortality in a recent series was below 5% despite increasing aggressiveness to treat patients at an older age and patients with more extensive liver involvement [6–11,35–40]. In most series, mortality is related to the extent of liver resection. For example, in a series of 456 patients, mortality after local and segment resections was 0.5% compared with 4.6% after more extensive resections [8].

Reported morbidity in most series of liver resections varies from 20 to 40% [7,8]. Pulmonary complications, which are often related to upper abdominal surgery, such as pneumonia and atelectasis, are observed in 5–10% of the patients, cardiac complications are encountered in 3–5% of the cases. Pleural effusion is often encountered after hepatic surgery, but treatment is seldom necessary. Wound problems occur in approxi-

mately 5%, while abscesses, bile fistula and biloma are described in 2–5% of the patients. Liver failure and haemorrhage also vary between 1 and 5%, depending on the extent of hepatic resection.

4.5. Recurrences

In approximately two-thirds of the patients, tumour recurrence will occur [6–11,35–40]. In half of these cases, the first site of recurrence is within the remaining liver. The other half shows extrahepatic recurrence in the lungs and at intra-abdominal sites. In the patients suffering from recurrence, recurrent disease is initially limited to the liver in approximately 30% of the cases [8,35,44,45]. In this group of patients, as well as in those who show only lung metastases, surgery should be considered. Several studies show a 5-year survival rate close to 30% after secondary resection of liver metastases from colorectal cancer [45,46]. In addition, local ablative techniques may be indicated in this group of patients.

4.6. Adjuvant treatment

Whether the use of adjuvant chemotherapy after resection of the metastases can decrease the recurrence rate is still a matter of dispute. Several retrospective and prospective studies have investigated the effectiveness of adjuvant chemotherapy after resection of colorectal liver metastases. Results from retrospective studies using 5-fluorouracil (5-FU)-based chemotherapy is conflicting, with two studies demonstrating no benefit and two suggesting some advantages [47–50]. A multicentre prospective German study failed to show any survival benefit following adjuvant postoperative arterial treatment using 5-FU and folinic acid [51]. In this study, the percentage of patients who did not receive the assigned treatment was high (35%). Two recent studies from the United States could demonstrate a significant beneficial effect of adjuvant chemotherapy (5-FU-based) after resection of colorectal liver metastases. One study demonstrated a significant improvement in 3-year survival comparing surgery plus adjuvant systemic chemotherapy (5-FU) and hepatic arterial infusion (FUDR) with surgery alone. 3 year survival in the adjuvant chemotherapy arm was 58% versus 34% in the surgery alone arm [52]. The other study compared adjuvant hepatic arterial infusion plus systemic chemotherapy to only adjuvant systemic chemotherapy and showed an improved 2-year survival rate after combined therapy compared with systemic therapy alone (86% versus 72%) [53]. At the moment, a European Organization For Research and Treatment of Cancer (EORTC) study is running comparing surgery alone with surgery plus pre- and post-resection chemotherapy using 5-FU, leucovorin and oxaliplatin.

5. Local tumour ablation

In many patients with colorectal liver metastases confined to the liver, resection of the metastases can not result in an adequate clearance of all of the tumour tissue from the liver. This may be the case either because of the number of metastatic liver lesions or because of the location of the metastases. Examples are patients with more diffuse bilobar disease or with unresectable recurrence after previous liver surgery. It is in this group of patients with unresectable colorectal liver metastases in which local ablative techniques like, radiofrequency and cryoablation, can be used to clear the liver from all metastatic tumour lesions [54–68]. Both techniques can be used alone or in combination with resection. During this last approach, which is most often used, lesions easily accessible to resection are resected by surgery, while local tumour ablative techniques are used to treat all unresectable lesions. To date, there are no data that local tumour ablative techniques are as efficient as resection, and hence local tumour ablation should for the moment be reserved for unresectable lesions.

5.1. Techniques

During recent years, several new techniques have been developed such as cryoablation [54–61], radiofrequency [62–68], microwave and laser [69]. Of these methods, cryoablation and radiofrequency are the most widely used. During cryosurgery, tumours are frozen with the aid of liquid nitrogen circulating through a probe which is placed within the tumour. Tumour destruction during cryoablation is obtained by a freeze-thaw process of the tumour tissue resulting in direct cell death and microvascular thrombosis. During radiofrequency, a small electrode is placed within the tumour and used to deliver radiofrequency energy to the tissue. The radiofrequency current generates ionic agitation, which is converted into frictional heat and results in the subsequent breakdown of proteins and cell membranes.

Both techniques have been shown to be effective in the local destruction of colorectal liver metastases. For cryoablation, local tumour control can be obtained for metastatic lesions up to 8–9 cm in size [54–61]. For radiofrequency, adequate local tumour control has been described for tumours up to 4–5 cm in size [62–68]. The accuracy of both techniques is mainly determined by adequate imaging of the procedure by ultrasound. During cryosurgery, an ice ball is formed around the tip of the cryoprobe which is clearly visible by ultrasound. The ice ball should exceed the diameter of the metastatic lesion by approximately 1 cm. During radiofrequency, a hyperechoic area is formed around the tip of the needle which corresponds to the area treated. Judgement on whether complete tumour treatment is obtained

(including a rim of normal liver tissue) is generally more difficult for radiofrequency than for cryosurgery.

For both techniques, local recurrence rates at the treated site of between 5 and 30% have been reported [54–68]. Local failure rates are directly related to the diameter of the lesion treated and may start to increase for lesions over 4 cm [43,55,63,67,68]. Generally, when failure occurs after treatment mainly other areas of the liver are involved as well as extrahepatic sites.

In contrast to cryoablation, for which probes of up to 10 mm are used, radiofrequency can be performed as a minimally-invasive technique by percutaneous or laparoscopic use [62–65]. Needle electrodes used for radiofrequency treatment are thin (15-gauge) and can easily be introduced into tumour tissue without significant harm to normal liver. The diameter of the lesions that can be treated by presently available radiofrequency techniques is, however, considerably smaller than with cryosurgery.

Radiofrequency has proven to be an extremely safe procedure with a complication rate lower than $<10\%$ [64,65]. Cryoablation can induce some serious complications such as haemorrhage and cryo shock. The complication rate after cryosurgery is generally reported to be between 10 and 20% [41].

5.2. Survival

Up to now, local tumour ablative techniques have mainly been used in patients with unresectable colorectal liver metastases. In these patients, tumour ablative therapy was used either alone or in combination with hepatic resection, in which case hepatectomy dealt with the main tumour mass and some residual tumour, that could not be resected, was treated with local tumour ablative therapy. Using this combined approach of local tumour destruction and resection, most series using cryosurgery describe 1 and 2 year survival rates of 80 and 60%, respectively (Table 3). Median survival times vary from 26 to 32 months [43,54–56,58,59]. For radiofrequency, follow-up in the different series is still too short. Only two series are reported with a longer follow-up which show 1- and 2-year survival rates of 81 and 67%, respectively [66,67]. It has been claimed that these results are better than those obtained during chemotherapy alone. For chemotherapy treatment, the results strongly depend on the regimen used, but generally a 1-year survival rate of around 60% is reported, with a 2-year survival below 30%.

Because disease recurrence after local ablative tumour treatment is mainly outside the area treated by local ablative therapy, a combined treatment regimen of local tumour destruction and systemic chemotherapy is encouraged by many centres at this stage. In a study by the group of Morris, a clear benefit in 2-year survival was observed after combined treatment (cryoablation + intra-arterial chemotherapy) compared with cryoablation alone in a historical control group (2-year survival 56% versus 13%) [55,61].

Although many studies show effective treatment responses after cryoablation or radiofrequency, the precise impact of local tumour ablative therapy on survival in colorectal liver metastases is still unclear. No randomised studies have been performed investigating local aggressive treatment of liver metastases in combination with chemotherapy versus chemotherapy alone. Hence, the superior results of local ablative treatment of liver metastases compared with chemotherapy, as reported in literature, may be due to patient selection. Especially, since patients selected for aggressive local treatment often show only a limited number of metastatic deposits (generally less than 10), while patients treated with

Table 3
Results of local ablative therapy for colorectal liver metastases

Author/year	Patients (*n*)	Indication	Other treatment	Mortality rate of procedure (%)	Survival (%)		
					1 year	2 year	5 year
Cryosurgery							
Adam [43]	25	$\leqslant$10 lesions $\leqslant$6 cm	Resection Chemotherapy	Not given	77	52	
Seifert [55]	116	$\leqslant$12 lesions $\leqslant$15 cm	Resection i.a. chemotherapy	1	82	56	13
Weaver [56]	136	$\leqslant$10 lesions $\leqslant$13 cm	Resection	4	82	62	20
Ruers [58]	30	$\leqslant$10 lesions $\leqslant$9 cm	Resection	3	76	61	
Radiofrequency							
Solbiati [67]	109	$\leqslant$4 lesions generally $<$3 cm	None		–	67	33 (3 years)
De Baere [66]	54	$\leqslant$5 lesions $\leqslant$4.5 cm	Resection		81% (mean follow-up of 14 months)		

i.a., intra-arterial.

chemotherapy may show widespread liver involvement. An EORTC study is starting that compares radiofrequency ablation plus chemotherapy with chemotherapy alone for unresectable colorectal liver metastases.

6. Ways to increasing resectability rates

6.1. Preoperative chemotherapy

Obviously there are many patients with metastastic disease confined to the liver and with a good performance status in whom liver involvement by tumour is either too extensive for surgery or in which tumour lesions are situated at unresectable sites. Several studies have shown that in some of these patients combination chemotherapy may alter unresectable lesions into resectable ones. In these studies, a schedule with 5-FU/LV/oxaliplatin has generally been used [70–74]. In analyses after chronomodulation therapy, 15–30% of the patients who initially had unresectable colorectal liver metastases underwent macroscopically curative resection of these metastases [73,74]. For fixed rate combination chemotherapy, this figure is 12% (73), although recently preliminary results have been reported that during fixed rate chemotherapy with FOLFOX 4 the percentage of patients that becomes resectable is close to 30% [75]. The benefit in survival after combined treatment of preoperative chemotherapy and resection seems comparable to that obtained with primary liver resection. In a study of Bismuth and colleagues the 5-year survival rate after chronomodulation chemotherapy and resection was 40% [72].

6.2. Staged resection and portal vein embolisation

Resection of liver metastases may lead to severe postoperative liver failure if the functional reserve of the remaining liver remnant is too small [76]. To overcome this problem, preoperative portal vein embolisation (PVE) or staged resection of liver metastases can be considered.

Portal vein occlusion leads to atrophy of the homolateral liver lobe and compensatory hypertrophy of the contralateral liver lobe [77,78]. Hepatocyte regeneration starts within 1 day after PVE and reaches a peak at 12–14 days [79,80]. The increase in volume of the remnant liver ranges from 7 to 27% (median 12%) after PVE [81]. In this way, the functional reserve of the liver can be increased within 2–4 weeks.

Makuuchi and colleagues were the first who applied PVE to prevent major liver insufficiency, 2–3 weeks before major liver resection for hepatocellular carcinoma [81]. In their series, portal embolisation did not produce major side-effects. The embolised lobe atrophied in 12 of the 14 patients. 13 patients underwent extended right or left lobectomy and 1 a trisegmentectomy with bilio-intestinal reconstruction. One patient died as a result of jaundice and cholangitis, another patient died of hepatitis, 3 months after resection. The other patients had no major liver insufficiency. From 1986 to 2000, 16 series have been published about PVE including 409 patients. These studies were summarised by Abdalla and colleagues in Ref. [82]. The complication rate of PVE ranged from 0 to 10%. From 24 of the 409 patients, it is not known if a liver resection was performed. Of the remaining 385 patients, 316 (82%) underwent a resection. Mortality ranged from 0 to 6.5% in non-cirrhotic and from 6 to 7% in cirrhotic patients. The complication rate ranged from 0 to 15%, and complications were mostly of a technical or infectious nature. Hepatitis was reported in 2 patients and transient liver insufficiency in 8 patients. In two series, long-term follow-up of PVE and liver resection is reported in patients with metastases of colorectal origin. 5-Year survival rate in the series of Elias and colleagues was 29% and was 40% in the series of Azoulay and colleagues [83,84]. From these studies, it is obvious that PVE is a safe technique that may increase the safety of major liver resection and resectability rate of liver tumours. When applied in patients with colorectal metastases, overall survival is comparable to metastasectomy without PVE [83].

In patients with diffuse multinodular metastases, staged liver resection can be an alternative for conservative treatment. During the first operation, the highest possible number of metastases are resected. After operation, the liver remnant regenerates accompanied by an increase of the functional capacity of the liver. During this period, systemic chemotherapy is given to hamper outgrowth of metastases. At a later stage, as the functional capacity has been restored, a second stage curative resection of the residual liver metastases is performed. This strategy was followed by Adam and colleagues [85] in 13 patients, in whom curative resection was not feasible at the first operation and who had a partial response or stable disease on preoperative systemic chemotherapy. 2 of the 13 patients died after the repeat hepatectomy. The 3-year survival rate after two-stage hepatectomy was 35%, with a median survival of 31 months. In patients with diffuse metastases in the liver, a two-stage hepatectomy can offer a chance of long-term remission.

7. Chemotherapy

7.1. 5-FU/LV

In Europe, until recently the standard first-line treatment in advanced colorectal cancer consisted of

5-fluorouracil (5-FU)-based schedules, in which almost invariably leucovorin (LV) is incorporated [86–90]. Leucovorin enhances the activity of 5-FU which results in response rates of approximately 20% and a median overall survival of approximately 12 months. Many different schedules have been compared in randomised studies, showing differences in response rates and toxicity, but no schedule has shown a benefit in terms of overall survival. Schedules of 5-FU continuous infusion may be tolerated somewhat better and may result in a higher response rate compared with bolus 5-FU schedules, which should be balanced against the extra costs and morbidity of central venous access devices [91,92]. The choice for a regimen is mostly dependent on the experience of the oncologist with a particular regimen. In addition, there are sometimes specific preferences within countries.

7.2. Irinotecan/oxaliplatin

Given the positive results of two phase III studies of second-line treatment with irinotecan in patients with advanced colorectal cancer progressing after first-line 5-FU treatment [93,94], the logical next step was to incorporate irinotecan into first-line regimens. To date, the results of two randomised trials comparing 5-FU/LV to 5-FU/LV/irinotecan in the first-line have been published [95,96]. In both studies, a small (3.2 and 2.2 months), but significant, survival advantage for the irinotecan-containing treatment arms was observed. Differences in the response rates (49% versus 31%, and 39% versus 21%, respectively) and progression-free survival (6.7 versus 4.4 months, and 7.0 versus 4.3 months, respectively) also reached statistical significance. In several countries, this has resulted in the acceptance of 5-FU/LV/irinotecan, which results in a median survival of 15–17 months, as the new first-line standard treatment in advanced colorectal cancer. However, since in both trials the second-line treatment with irinotecan in the control arm was not planned in a prospective way, there is still a matter of debate whether first-line 5-FU/LV/irinothecan should be widely accepted as first-line treatment.

In addition, oxaliplatin in combination with 5-FU/LV has shown promising results in terms of response rate and progression-free survival. In two recent randomised studies, the addition of oxaliplatin to either the de Gramont schedule [97] or a chronomodulated 5-FU/LV schedule [70] resulted in a significant improvement in the response rate (50.7% versus 22.3%, and 53% versus 16%, respectively) as well as in progression-free survival (9.0 versus 6.2 months and 8.7 versus 6.1 months, respectively) . However, in neither study did the addition of oxaliplatin to 5-FU/LV result in an overall survival benefit. Again second-line treatment in both studies was not randomised which may account for the fact that differences in disease-free survival were not translated into differences in overall survival. In several countries the above results has led to the acceptance of 5-FU/LV/oxaliplatin as first-line treatment.

Since the addition of either irinotecan or oxaliplatin to 5-FU/LV increases the overall incidence of toxic events, many medical oncologists still consider 5-FU/LV as the standard first-line regimen and postpone the use of irinotecan or oxaliplatin to 2nd- or 3rd-line regimens.

7.3. Regional chemotherapy

Another, already long-lasting debate, is the use of regional chemotherapy [98–101]. The use of hepatic arterial infusion chemotherapy is based on the principle that the regional administration of certain drugs can lead to higher drug concentrations within the tumour with less systemic side-effects. Although response rates of hepatic arterial chemotherapy are significantly higher in most randomised studies of intrahepatic versus systemic chemotherapy, these studies fail to show a significant benefit in overall survival. Crossover of patients who failed systemic chemotherapy to intra-arterial chemotherapy may partly explain these results. At this stage, regional chemotherapy should not be considered standard and should only be performed in a study design.

7.4. Isolated liver perfusion

To increase the response rates of chemotherapy, several forms of infusion or perfusion techniques of the liver have been developed. Isolated hepatic perfusion (IHP) was first applied in 1961 by Ausman [102]. Aigner and colleagues treated 29 patients with colorectal metastases with IHP using 5-FU under hyperthermic conditions [103]. The median survival was 8 months.

Marinelli and colleagues reported a median survival of 17 months after IHP with mitomycin under normothermic conditions [104]. However, treatment was complicated by veno-occlusive disease in 4 of the 9 patients, 1 with fatal outcome. Therefore, IHP with mitomicin was stopped and replaced by melphalan by the group from Leiden. Vahrmeijer and colleagues found an overall response rate of 29% and a median survival of 19 months in 24 patients treated with IHP using melphalan in a phase I trial using high dose melphalan therapy in patients with colorectal metastases [105]. 3 patients died in this group. Addition of tumour necrosis factor (TNF) to the perfusate may improve the response rate. In a series of 50 patients, Alexander and colleagues found an overall response rate of 74% across virtually all types of tumours treated, including colorectal metastases [106]. The median duration of response was 9 months, with some long-term survivors. The results of IHP do not justify IHP for routine use in patients with colorectal metastases.

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