New strategies for advanced colorectal liver metastases
No more a fatality

D.A. Wicherts

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No more a fatality

Nieuwe strategieën voor uitgebreide colorectale levermetastasen: geen infauste prognose meer
(met een samenvatting in het Nederlands)

Proefschrift

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Prof.dr. R. Adam
Prof.dr. I.H.M. Borel Rinkes

Aan mijn ouders

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Chapter 1

General outline and introduction of the thesis

Worldwide, colorectal carcinoma remains one of the most common causes of cancer related death. Nearly one million new cases are diagnosed each year and liver metastases will develop in approximately 50% of patients.[1,2] Notably, 25% of these patients already present with liver metastases at the time of diagnosis of the primary tumor. Colorectal liver metastases may therefore currently be regarded as a major health problem.

Resectability

Until recently, very few patients with colorectal liver metastases were considered for resection. Owing to strict selection criteria, only 10% to 20% of patients were amenable for partial hepatectomy. The remaining proportion of patients received palliative chemotherapy with a median survival of only 6 to 12 months.[3] These patients usually have large or multinodular tumor deposits, closely related to major vascular or biliary structures *(Figure 1)*.

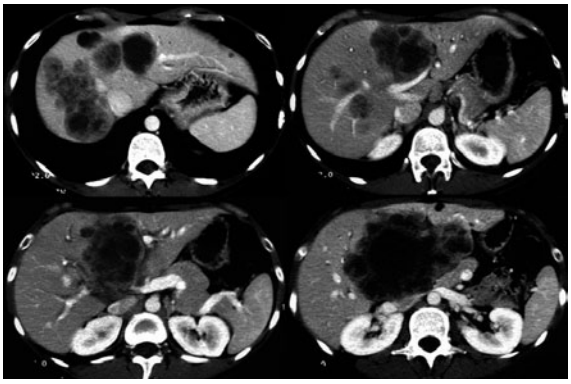

Figure 1.
Example of a patient with extensive colorectal liver metastases (computed tomography images).

Conventional criteria for resection included less than four metastases, unilobar distribution, maximum tumor size of 5 cm, and a potential tumor-free resection margin of at least 1 cm.[4-6] However, initial studies have shown that hepatectomy offers the only chance of long-term survival with 5-year survival rates around 30% to 40%.[5-7] In addition, long-term analyses have now been reported that suggest that previous selection criteria are not as important factors in determining outcome as previously thought.[8,9] Complete tumor resection, even in poor prognostic groups, results in a significant chance of long-term survival.[10]

In the last decade, important progress has been made in the field of treatment of colorectal liver metastases: more effective chemotherapy, new surgical strategies for safer hepatic resections, and additional techniques such as portal vein embolization (PVE) and local ablation therapies to increase the possibility of curative therapy. The combination of these developments has increased the

resectability rate of patients with colorectal liver metastases to almost 30% and led to increased chances of survival for patients with advanced metastatic disease.[11]

Advances in chemotherapy and liver surgery

With the traditional regimen of 5-fluorouracil (5-FU) and leucovorin (LV), tumor response rate was approximately 20% for metastatic colorectal disease.[1] Modern regimens, however, combine 5-FU/LV with oxaliplatin or irinotecan and result in response rates of around 50%. Subsequently, median survival of unresectable patients has increased to almost 24 months.[12-14] As these more effective chemotherapeutic regimens are capable of inducing major tumor shrinkage, it was thought to be of critical importance in rendering initially inoperable patients amenable to potentially curative resection. The first results of this strategy appeared in 1996. Bismuth et al. reported a 40% 5-year survival rate in patients with initially unresectable liver metastases treated with chemotherapy followed by liver resection.[15] With the development of biological agents such as cetuximab and bevacizumab, tumor response rates have increased even further, hereby significantly enlarging the proportion of patients achieving a possibility of liver surgery.[16-19]

Concerning the limits of liver surgery, resections as large as 70% of the total functional liver volume have been shown to be safe without the risk of postoperative liver insufficiency.[20] These results have led to the current opinion that the technical inability to completely resect all tumor deposits, while leaving at least 30% of functional liver volume, remains the only cause of unresectability. Even the presence of extrahepatic disease, if limited and resectable, no longer is an absolute contraindication for surgery. The development of advanced surgical techniques to increase the feasibility of hepatic resection was consequently largely stimulated.

PVE, by inducing ipsilateral liver atrophy and contralateral hypertrophy, enables resection in case of an insufficient volume of the future remnant liver.[21,22] Following a 4 to 6 weeks interval, parenchymal hypertrophy is generally adequate to obtain a safe situation for hepatic resection. Another development evolved with the introduction of sequential liver resections. The concept of two-stage hepatectomy was first described in the year 2000.[23] This approach uses two sequential liver resections, with or without PVE, to clear the liver of all its metastases. Because of a bilobar distribution of multiple metastases, complete tumor resection during a single operation is unable in these patients. As with PVE, this strategy relies on the compensatory regenerative capability of the liver. Perioperative chemotherapy has an important additional role in tumor control.

Intraoperatively, tumor involvement of the inferior vena cava or hepatic veins may hamper complete resection of metastases. In specialized centers, however, total vascular exclusion of the liver and vascular reconstruction techniques currently make surgery possible, with an acceptable risk of complications.[24-26] Nevertheless, in patients selected for extended left hepatectomy metastases are frequently located centrally in the liver, close to vascular and biliary structures. Besides a higher morbidity rate, the risk of incomplete tumor resection with impaired survival is suggested to be elevated in these patients. Local ablation techniques such as radiofrequency ablation and cryosurgery further help in the treatment of deeply located, otherwise unresectable metastases.[27,28]

When combining all aforementioned advances in chemotherapy and surgery, resectability rates of initially unresectable patients between 13% and 38% have been reported by different authors depending on their selection criteria.[29,30] By this way, this group of patients can now be offered a real chance of curative surgery. Short- and long-term outcomes following these multimodal strategies remain however to be confirmed in large cohorts with longer follow-up before establishing these strategies as general treatment options for patients with extensive metastases.

Operative risks related to chemotherapy

Due to the developments in chemotherapy and liver surgery, individual patients with colorectal liver metastases are increasingly exposed to multimodal treatment strategies. Although higher resectability rates may be achieved, evaluation of related perioperative risks is essential.

The use of most optimal chemotherapy regimens requires continuing evaluation in terms of response rates and liver toxicity. With the improved efficacy of modern chemotherapy, adverse side-effects such as steatosis or sinusoidal obstruction syndrome may occur in the liver.[31,32] Results on the impact of these chemotherapy-associated lesions on surgical outcome are still preliminary. Steatotic livers have a characteristic yellow appearance and current data suggest that moderate steatosis contributes to increased postoperative morbidity.[31] Steatohepatitis, mainly related to the use of irinotecan, was reported to be associated with increased mortality after major hepatic resection.[33] Vascular toxicities range from sinusoidal congestion to regenerative nodular hyperplasia and are characterized by blue liver discoloration *(Figure 2)*.[34] These lesions are mainly related to the use of oxaliplatin and may result in increased blood transfusions during surgery and a higher risk of postoperative lifer failure.[32,34,35] The effect of individual toxic lesions, however, still needs to be evaluated.

The new biological agent bevacizumab, which is a vascular endothelial growth factor (VEGF) antibody, results in higher response rates of colorectal metastases,

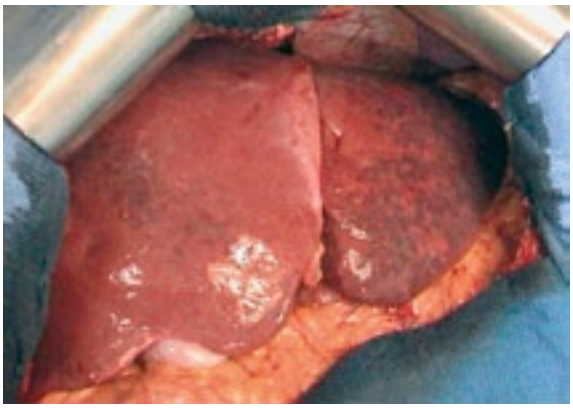

Figure 2.
Blue liver discoloration caused by vascular parenchymal lesions related to chemotherapy treatment.

but its effect on normal liver tissue is still largely unknown. Recent reports suggest a decreased incidence of sinusoidal lesions compared to patients receiving conventional chemotherapy alone.[36] Additionally, because of its anti-VEGF working mechanism, impaired liver regeneration after hepatectomy was suggested but never investigated thoroughly. With current increased resection volumes and massive chemotherapy treatment, this issue is nevertheless important to consider.

Outcome

Although long-term survival is increasingly reported after resection of colorectal liver metastases, the possibility of cure remains doubtful, especially in case of advanced metastatic disease. This thought is related to the fact that this entity represents a widespread, systemic disease, for which cure would be unlikely to occur.

High response rates to current chemotherapy regimens sometimes result in a complete radiological disappearance of metastases. This has, however, been shown to be of limited predictive value of pathologic tumor destruction.[37] A complete pathologic tumor response (necrosis) would, on the contrary, be much more interesting in terms of cure of the disease. The effect of complete pathologic response on long-term survival as well as its predictive factors remain to be analyzed.

Ten year survivors following hepatectomy for colorectal metastases have been reported for selected patients in different series.[10,11] Whether or not these patients are definitively free of disease is unknown. As recurrences mostly occur within the first 5 years after hepatectomy, a 5-year disease-free survival could be an appropriate and practical definition of cure.[38] The possibility of cure, especially for patients with initially unresectable metastases, would further confirm the value of current advanced treatment protocols for metastatic colorectal

disease. However, the amount of initial tumor load and degree of response to chemotherapy are likely to be related with the chance of cure. Nevertheless, the combined efficacy of current chemotherapy and advanced surgery necessitates a new evaluation of long-term outcome of this multimodality treatment for patients with colorectal liver metastases.

Outline of the thesis

This thesis analyses current multimodal treatment strategies for patients with advanced colorectal liver metastases. We address the important value of the combination of surgery and chemotherapy in achieving long-term survival for this specific patient group. Part I focusses on surgical techniques, while Part II highlights oncological aspects of these strategies.

The central research questions in this thesis are:

- What is the current role of PVE *(chapter 3)* and two-stage hepatectomy *(chapter 4)* in the multimodal treatment of patients with advanced colorectal liver metastases?

- What are the results of extended left hepatectomy with or without caudate lobectomy for patients with colorectal metastases *(chapter 5)*?

- What is the impact of regenerative nodular hyperplasia of the liver related to chemotherapy on postoperative outcome after hepatic resection of colorectal metastases *(chapter 6)*?

- What is the effect of preoperative bevacizumab treatment on functional recovery and histology of the liver after resection of colorectal metastases *(chapter 7)*?

- What is the value of a complete pathologic response of colorectal liver metastases in achieving long-term survival after hepatic resection *(chapter 8)*?

- Is there a possibility of cure for patients with advanced colorectal liver metastases treated by a combination of chemotherapy and surgery *(chapter 9)*?

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Chapter 2

Bringing unresectable liver disease to resection with curative intent

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ABSTRACT

The majority of patients with colorectal liver metastases present with unresectable disease. Without resection, the prognosis for these patients is extremely poor. The technical inability to completely remove all metastases while leaving at least 30% of remnant normal functioning liver parenchyma is nowadays regarded as the only absolute contraindication to resection.

Chemotherapy regimens containing combinations of 5-fluorouracil, leucovorin, oxaliplatin and/or irinotecan can provide significant downstaging of liver disease enabling curative rescue resection and resulting in improved long-term survival. The addition of cetuximab and bevacizumab may result in higher resectability rates that may offer curative surgery in a larger amount of patients. In addition, different surgical techniques like portal vein embolization, two-stage hepatectomy and local ablation are available to achieve a resectable situation. Due to vascular exclusion and reconstruction techniques, tumoral involvement of the hepatic veins and inferior vena cava no longer limits the indication of resection.

Overall, surgery should be performed as soon as liver metastases become resectable. Collaboration between oncologists and surgeons is essential to optimize individual therapeutic strategies.

INTRODUCTION

Liver metastases are found in approximately 50% of patients with colorectal cancer.[1] In addition, up to 30% of these patients present with liver metastases at the same time of the primary tumor diagnosis. Complete surgical resection of colorectal liver metastases (CLM) can offer long-term survival and even cure, with reported 5-year survival rates between 21% and 48%.[2,3] The median survival of nonresected patients, however, ranges between 6 and 18 months.[4-6] Noteworthy, prognosis after incomplete resection is the same as for nonresected patients.[7] At the time of diagnosis, only a minority of patients with CLM (10% to 20%) present with resectable tumors.[8] For approximately 80% of patients it is impossible to completely remove all liver metastases in first instance, while leaving at least 30% of remnant functional liver parenchyma.

The presence of multiple, large metastases is classically associated with decreased patient survival.[9,10] However, provided that all metastases can be completely resected, the total number as well as the size of the metastases are nowadays no longer arguments contraindicating resection.[11] Similar conclusions can be made regarding a narrow resection margin and the presence of extrahepatic disease. Both factors are predictive of poor outcome.[9,10] Complete resection in these poor prognostic groups, however, results in a significant proportion of long-term survivors, while no patients would be expected to be alive if the metastatic disease had not been resected.[12-14] These results emphasize that the technical inability to achieve radical resection, due to the extent of liver involvement, should now be regarded as the only cause of unresectability, even in patients with poor prognostic factors.

The poor outlook of an unresectable disease situation has stimulated the development of methods to improve resectability. In this article, we describe all currently available oncological and surgical options to convert patients with technical unresectable liver metastases to a resectable situation.

CHEMOTHERAPY AND SURGERY

Substantial improvements in combination chemotherapy including 5-fluorouracil (5-FU), leucovorin (LV), oxaliplatin and irinotecan have led to increased response rates and survival in patients with metastatic colorectal cancer. Response rates between 39% and 66% can now be achieved with median overall survivals up to 21 months *(Table 1)*.[15-25] The efficacy of systemic chemotherapy is further improved by a four drug regimen adding both oxaliplatin and irinotecan to 5-FU and LV (response rate 71% and median overall survival 27 months).[18] Chemotherapy regimens based on oxaliplatin and irinotecan are nowadays the standard of care in the first-line treatment of patients with unresectable liver disease.

Table 1. Literature overview of combination chemotherapy for metastatic colorectal cancer.

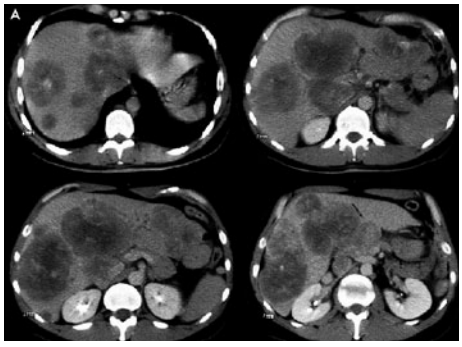
Author	Year	Study design	No. of patients	Regimen	Line	Response rate (%)	Median time to progression (months)	Median overall survival (months)
Oxaliplatin-based								
Lévi[21]	1992	Phase II	93	FOLFOX	*a*	58	10	15
Bertheault[15]	1996	Phase II	50	FOLFOX	*b*	48	9.3	17.8
Lévi[22]	1997	RCT	186	FOLFOX chrono *vs* FOLFOX constant-rate	1st	51 *vs* 29[c]	6.4 *vs* 4.9[d]	15.9 *vs* 16.9[e]
Lévi[23]	1999	Phase II	90	FOLFOX	1st	66	8.4	18.5
de Gramont[16]	2000	RCT	420	FOLFOX *vs* 5-FU/LV	1st	50.7 *vs* 22.3[f]	9.0 *vs* 6.2[g]	16.2 *vs* 14.7[h]
Giacchetti[19]	2000	RCT	200	FOLFOX *vs* 5-FU/LV	1st	53 *vs* 16[j]	8.7 *vs* 6.1[k]	19.4 *vs* 19.9[e]
Irinotecan-based								
Douillard[17]	2000	RCT	387	5-FU/CF+irinotecan *vs* 5-FU/CF	1st	49 *vs* 31[j]	6.7 *vs* 4.4[j]	17.4 *vs* 14.1[m]
Saltz[24]	2000	RCT	683	FOLFIRI *vs* 5-FU/LV *vs* irinotecan	1st	39 *vs* 21[n]	7.0 *vs* 4.3[r]	14.8 *vs* 12.6[s]
Köhne[20]	2005	RCT	430	FOLFIRI *vs* 5-FU/LV	1st	62.2 *vs* 34.4[t]	8.5 *vs* 6.4[t]	20.1 *vs* 16.9[w]
Oxaliplatin/Irinotecan-based								
Falcone[18]	2002	Phase II	42	FOLFIRIFOX	1st	71.4	10.4	26.5
Tournigand[25]	2004	RCT	220	FOLFIRI/FOLFOX6 *vs* FOLFOX6/FOLFIRI	1st	56 *vs* 54[y]	8.5 *vs* 8.0[y]	21.5 *vs* 20.6[z]

a: 49% had previously received chemotherapy and/or radiation therapy; *b*: 37 previously treated patients and 13 chemotherapy-naive patients; *c*: $P = 0.003$; *d*: $P = 0.006$; *e*: P = not significant; *f*: $P = 0.0001$; *g*: $P = 0.0003$; *h*: $P = 0.12$; *j*: $P < 0.001$; *k*: $P = 0.048$; *m*: $P = 0.03$; *n*: $P < 0.001$ (FOLFIRI *vs* 5-FU/LV); *r*: $P = 0.004$ (FOLFIRI *vs* 5-FU/LV); *s*: $P = 0.04$ (FOLFIRI *vs* 5-FU/LV); *t*: $P < 0.0001$; *w*: $P = 0.28$; *y*: $P = 0.26$ (after first line); *z*: $P = 0.99$ (with both lines). Abbreviations: RCT = randomized controlled trial; chrono = chronomodulated therapy; FOLFOX = 5-fluorouracil (5-FU), leucovorin (LV) and oxaliplatin; CF = calcium folinate; FOLFIRI = 5-FU, LV and irinotecan; FOLFIRIFOX = 5-FU, LV, oxaliplatin and irinotecan.

Conventional preoperative chemotherapy

Chemotherapy alone does not allow for complete eradication of the metastatic disease and therefore carries a relatively poor prognostic outcome. On the contrary, hepatic resection after downstaging of initially unresectable liver disease has been shown to provide a significant improvement in long-term survival.[26,27]

An important issue in this subject is the close relationship observed between response rate and resectability rate.[28] Advances in the efficacy of chemotherapy regimens with higher response rates now allow an increasing proportion of patients to be considered for hepatic resection *(Figure 1)*. Published reports show resectability rates between 13% and 54% after downstaging of unresectable metastatic disease *(Table 2)*.[12,26,27,29-35] Resectability rates differ between papers which is mainly due to differences in patient selection and definition of (un) resectability between centers. Some reports include only selected patients with metastases confined to the liver. Subsequently, higher resection rates are generally reported in these studies (above 30% in most cases) when compared to studies that also included patients with more widespread metastatic disease (unselected patients) (13% to 26%) *(Table 2)*. Survival rates after hepatic resection range from 33% to 58% at 5 years and are clearly superior compared to nonresected patients.[27,33]



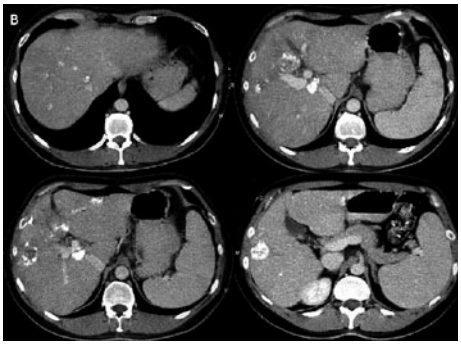


Figure 1.
Example of unresectable large bilobar colorectal liver metastases (A) downstaged by chemotherapy (B) allowing for curative liver resection after right portal vein embolization.

Table 2. Literature overview of conventional preoperative chemotherapy for initially unresectable liver metastases followed by surgery.

Author	Year	No. of patients	Regimen	Response rate (%)	Resection rate (%)[a]	5-year overall survival (%)[b]	Median overall survival (months)[b]
Unselected							
Bismuth[30]	1996	53	FOLFOX	-	16.1	40	-
Adam[12,c]	2001	701	FOLFOX	-	13.6	34	36
Adam[26,d]	2004	1104	[e]	-	12.5	33	39
Masi[33]	2006	74	FOLFIRIFOX	71.6	25.7	[f]	36.8[g]
Selected							
Giacchetti[27]	1999	151	FOLFOX	58.9	38.4	58	-
Pozzo[34]	2004	40	FOLFIRI	47.5	32.5	-	-
de la Camara[31]	2004	212	FOLFIRIFOX	64	43	-	-
Quenet[35]	2004	26	FOLFIRIFOX	73	54	-	-
Alberts[29]	2005	42	FOLFOX4	59.5	33.3	[h]	-
Ho[32]	2005	40	FOLFIRI	55	10	-	-

Unselected studies included patients with widespread metastatic disease. Selected studies included patients with only liver metastases.

a: R0/R1 resection; *b*: after resection; *c*: update of previous report[30]; *d*: update of previous report[12]; *e*: 5-fluorouracil (5-FU) and leucovorin (LV) alone or combined with oxaliplatin, irinotecan or both; *f*: 4-year overall survival of 37% from the onset of chemotherapy; *g*: from the onset of chemotherapy; *h*: 3-year overall survival of 67%. Abbreviations: FOLFOX = 5-FU, LV and oxaliplatin; FOLFIRI = 5-FU, LV and irinotecan; FOLFIRIFOX = 5-FU, LV, oxaliplatin and irinotecan.

The strategy to resect initially unresectable patients after effective chemotherapy is nowadays increasingly used. Since long-term survival is not achieved in all patients, individual expected benefit of surgery is of great clinical importance. Recently, a predictive model was proposed, based on four prognostic factors of survival, that enables selection of patients most likely to benefit from this strategy.[26] Five-year survival was found to range from 59% to 0% depending on the presence of a primary rectal tumor, more than 3 liver metastases at the time of resection, a preoperative maximum tumor size of more than 10 cm, and a preoperative CA 19.9 level of more than 100 IU/L.

New advances in chemotherapy treatment: biological agents

Although chemotherapy regimens with 5-FU, LV and oxaliplatin or irinotecan have led to increased response rates, there still remains a need for more efficient treatment regimens to optimize the achievement of resectability. The recent development of biological agents like cetuximab and bevacizumab has brought new possibilities for improved response rates that might enable potentially curative surgery of colorectal liver metastases in a larger amount of patients.

Cetuximab

Cetuximab is a monoclonal antibody specifically targeting the epidermal growth factor receptor (EGFR), resulting in inhibition of cell proliferation and stimulation of cell death, hereby preventing metastasis formation.[36]

Many studies have evaluated the efficacy of cetuximab-based therapy for metastatic colorectal cancer in first or higher lines, either in monotherapy or combination therapy regimens *(Table 3)*.[37-49] In first-line treatment, objective response rates (ORR) between 41% and 72% are reported in combination with irinotecan or oxaliplatin.[37,40,41,43,45] Response rates around 20% and 25% are achieved with combination therapy in second and higher lines,[38,39,42,47-49] superior to the results of cetuximab monotherapy (ORR 9% to 12%).[44,46] However, as expected, median overall survivals in all reports still remain inferior to those achieved after surgical resection *(Table 3)*. The results of these preliminary trials have warranted further investigation of the application of cetuximab, especially in first-line therapy, in ongoing large phase III studies.

Table 3. Literature overview of cetuximab-based chemotherapy for metastatic colorectal cancer.

Author	Year	Study design	No. of patients	Regimen	Line	Response rate (%)	Median time to progression (months)	Median overall survival (months)
Cunningham[39,a]	2004	RCT	329	irinotecan+cetux *vs* cetux	2nd,*b*	22.9 *vs* 10.8*c*	4.1 *vs* 1.5*d*	8.6 *vs* 6.9*e*
Rougier[45]	2004	Phase II	23	FOLFIRI+cetux	1st	46	10.9	-
Saltz[46]	2004	Phase II	57	cetuximab	2nd,*b*	9	1.4	6.4
Díaz Rubio[40]	2005	Phase II	43	FOLFOX4+cetux	1st	72	-	-
Chung[38]	2005	RS	16	irinotecan+cetux*f*	3rd,*b*	25	-	-
Wilke[49,g]	2006	Phase II	1123	irinotecan+cetux	2nd,*b*	-	-	9.2
Gebbia[42]	2006	RS	60	irinotecan+cetux	3rd,*b*	20	3.1	6
Souglakos[47]	2006	Phase II	40	CAPOX+cetux	2nd,*b*	20	3	10.7
Lenz[44]	2006	Phase II	346	cetuximab	2nd,*b*	12.4	1.4	6.6
Borner[37]	2006	Phase II	74	CAPOX+cetux *vs* CAPOX	1st	53 *vs* 33	-	-
Heinemann[43]	2006	Phase II	92	CCI *vs* CCO	1st	41 *vs* 71	-	-
Folprecht[41]	2006	Phase II	21	FOLFIRI+cetux	1st	67	9.9	33
Vincenzi[48]	2006	Phase II	55	irinotecan+cetux	3rd	25.4	4.7	9.8

a: BOND I study; *b*: or higher; *c*: $P = 0.007$; *d*: $P < 0.001$; *e*: $P = 0.48$; *f*: two patients received cetuximab monotherapy; *g*: MABEL study. Abbreviations: RCT = randomized controlled trial; cetux = cetuximab; RS = retrospective study; CAPOX = capecitabine and oxaliplatin; CCI = cetuximab, capecitabine and irinotecan; CCO = cetuximab, capecitabine and oxaliplatin; FOLFIRI = 5-fluorouracil, leucovorin and irinotecan.

Seen in the light of the prognostic impact of surgical resection, it is of utmost importance to take resectability into acount as a new endpoint in future trials to assess the potential of a given chemotherapy regimen to impact patient survival.

Resection rates of 19% to 30% have been reported for patients with unselected metastatic disease treated with cetuximab in first-line regimens.[40,41,45] We recently evaluated our experience with cetuximab-based therapy to determine the degree of cetuximab response in second or higher lines after progression on conventional chemotherapies, that allowed for surgical resection of liver metastases. The significant finding of this evaluation was that 7% of patients refractory to conventional chemotherapy could still be converted to resectability using cetuximab-based regimens, increasing the total proportion of unresectable patients who become eligible for surgery to 20%.[50] Cetuximab combined to irinotecan is currently the only approved therapy for patients refractory to previous irinotecan-based regimens.

Bevacizumab

The monoclonal antibody bevacizumab, targeting vascular endothelial growth factor (VEGF), has also shown promising results in the treatment of metastatic colorectal cancer. In a first-line setting, overall responses were between 45% and 70% when combined to 5-FU, LV and irinotecan.[51,52] One study evaluated the combined administration of bevacizumab and cetuximab with and without irinotecan in irinotecan-refractory patients.[53] Response rate was 35% when the three drugs were combined and toxicity was acceptable. These results may favor the addition of both bevacizumab and cetuximab to conventional regimens to further increase response rates and related resectability.

SURGICAL TECHNIQUES

In addition to preoperative chemotherapy, a broad armamentarium of surgical techniques is available to achieve a situation of resectability. These different options will be described below.

Portal vein embolization (PVE)

Resection of 60% to 70% of liver parenchyma can normally be performed with minimal risks of postoperative liver failure, which is the most important cause of death after liver resection.[54-56] When the amount of hepatic disease necessitates an extended resection to obtain a curative situation that exceeds 60% to 70% of liver parenchyma, surgical treatment is generally contraindicated.

Embolization of one side of the portal venous system induces hypertrophy of the contralateral liver lobe, i.e. the future remnant liver. A cutoff point of 25% to 30% of remaining normal functioning liver parenchyma after surgery is usually used to indicate PVE in healthy livers.[56] However, 40% of total normal functioning volume should remain in case of previous multiple courses of chemotherapy with anticipated decreased liver function.[57]

PVE can be performed by a percutaneous transhepatic approach as well as by a transileocolic approach during laparotomy.[58,59] The percutaneous method consists of accessing the portal vein via a transhepatic route under sonographic and fluoroscopic guidance.[58] Venous portography then allows selective catheterization and embolization of one of the portal branches. The transileocolic approach consists of direct cannulation of the ileocolic vein, after which selective embolization of a portal branch can be performed.[59] Several agents, such as fibrin glue, ethanol, gel foam, metal coils, and cyano-acrylate have been used for embolization, but none of them emerged as superior to the others.[60] After PVE, hepatic volume is routinely evaluated using computed tomography volumetric analysis. This imaging modality enables the surgeon to determine the degree of compensatory hypertrophy of the future remnant liver as well as to re-evaluate metastatic disease. Generally, 4 to 6 weeks after embolization adequate hypertrophy has occurred to enable safe hepatic resection.[60]

When PVE is used in patients presenting multiple bilobar liver metastases, local treatment of metastatic disease in the future remnant liver and/or systemic chemotherapy is advocated to prevent accelerated outgrowth of the metastases after PVE.[61] Systemic chemotherapy usually starts after 2 to 3 weeks following PVE, to prevent interference with initial liver regeneration.[62]

Feasibility and influence on long-term outcome of PVE in patients requiring an extended hepatectomy has been described in several studies, but only few of them specifically aimed at patients with colorectal metastases.[57,63-65] All four studies used the percutaneous technique. By this way, a gain of future remnant

liver volume up to 43% could be achieved.[57] No postoperative deaths related to the PVE procedure were reported, and morbidity rates varied between 3% and 18%.[57,63-65] Five-year survival rates up to 40% after subsequent hepatectomy are achieved.[57]

The compensatory hypertrophy of the future remnant liver caused by PVE increases the resectability of colorectal liver metastases in patients in whom liver resection would otherwise be contraindicated because of an insufficient remnant liver volume. PVE is a safe technique, and survival rates are similar to that observed in patients with initially resectable liver disease.

Two-stage hepatectomy

A two-stage procedure is indicated when colorectal liver metastases remain unresectable after preoperative chemotherapy because of multinodular, large metastases involving both liver lobes, which cannot be removed in a single procedure owing to a too small volume of the future remnant liver.

The two-stage procedure consists of two subsequent hepatectomies, and takes advantage of physiological liver regeneration to achieve radicality. The objective of the first hepatectomy is to make the second hepatectomy potentially curative.[62] During the first hepatectomy, the highest number of liver metastases is cleared from the less-invaded hepatic lobe. After regeneration of the future remnant liver, the remaining tumoral tissue in the contralateral lobe is resected during a second operation. To control tumor growth between the two hepatectomies, chemotherapy is administered, generally starting 3 weeks after the first hepatectomy to prevent interference with liver regeneration. If the estimated future remnant liver volume after the second hepatectomy is below 30% (40% if heavily treated with chemotherapy), PVE can be performed as additional procedure during the first operation.

The first results of two-stage hepatectomy were described in 2000.[62] After the first hepatectomy, the second hepatic resection could be performed in 81% of patients, with a 3-year survival of 35%. No perioperative deaths occurred at the first hepatectomy, compared to a perioperative mortality of 15% at the second hepatectomy. Morbidity rates were higher after the second hepatectomy compared to the first operation (45% *vs* 31%, respectively). These results are afterwards confirmed by others.[64,66] The higher mortality and morbidity rates related to the second hepatectomy most logically reflect the heaviness of preoperative treatment and the increased complexity of the second procedure.

For patients with multiple, bilobar colorectal liver metastases, a two-stage hepatectomy can offer long-term remission. However, this approach can only be recommended to highly selected patients.

Local ablation techniques

When hepatic resection alone cannot be curative, local treatment modalities such as radiofrequency ablation (RFA), cryosurgery, and laser-induced interstitial thermotherapy (LITT), can be added to obtain a curative situation.

RFA is based upon the deliverance of a high-frequency (460 to 500 kHz) alternating current through a probe positioned in the tumor, which is turned into heat (> 50°C) that causes tissue hyperthermia and cellular destruction.[67] Cryosurgery is based upon the cyclic application of extremely low temperatures (-196°C) to the tumor. Tumor death occurs by direct cellular freezing and indirectly through vascular thrombosis and tissue anoxia.[68] LITT consists of the application of light-energy through optical fibers which is absorbed by the tumoral tissue, causing tissue temperatures exceeding 60°C, resulting in local tissue destruction.

Within the literature, RFA is associated with low mortality and morbidity rates, and favorable survival rates when combined to hepatic resection.[69,70] Similarly, cryosurgery is reported to be a safe technique with mortality rates up to 4% and acceptable morbidity and survival rates.[71-73] Only few publications exist in which LITT for colorectal liver metastases is evaluated.[74,75] Nevertheless, results reported after LITT for initially unresectable colorectal liver metastases are similar to that described after cryosurgery and/or RFA. However, LITT was not combined to resection in these studies.

Local treatment modalities should be regarded as complementary to hepatectomy when complete resection cannot be achieved. By this way, the number of patients initially unresectable in whom curative treatment can be accomplished can be increased.

Extreme liver surgery

Involvement of the inferior vena cava and/or confluence of the hepatic veins by liver metastases used to be a contraindication for surgery. Currently, total vascular exclusion (TVE) of the liver and vascular reconstruction techniques can make surgery possible, without the risks of massive intraoperative blood loss and gas embolism.

TVE was first described by Heaney et al.[76] in 1966, and in current practice it is a safe procedure with acceptable morbidity and mortality rates, enabling surgical treatment in a larger number of patients.[77-85] Conventional TVE consists of clamping of the portal triad to occlude inflow, combined to clamping of the inferior vena cava below and above the liver.[80] To prevent hypotension caused by clamping of the inferior vena cava, outflow control achieved by clamping of the major hepatic veins with preservation of the caval flow can be performed in patients without tumoral invasion of the inferior vena cava.[81] When hemodynamic

instability occurs during caval clamping, a venovenous bypass, by which venous blood from a femoral vein and the portal vein is redirected to an axillary vein, might overcome this complication.[86]

Interruption of hepatic blood flow in normothermia is safe for at least 60 minutes.[87] However, the need for a vascular reconstruction can necessitate a longer ischemic period, and in these cases hypothermic perfusion of the liver can be useful. The combination of TVE and in situ hypothermic perfusion was first described by Fortner et al., and was recently evaluated in our center.[77,88] In the latter study, TVE combined to hypothermic perfusion was associated with a significantly better tolerance to ischemia, a better liver function, and a significantly lower number of complications, compared to standard TVE of 60 minutes or more.[77]

In addition, liver resection can be combined to resection of the inferior vena cava and, if necessary, replacement by a prosthetic material. In our institute, 22 patients underwent combined liver resection and surgery of the inferior vena cava.[89] One patient (4.5%) died during the perioperative course, and complications occurred in 14 patients (morbidity rate 64%). Overall 5-year survival of this patient group was 38%. Our results compare favorably to those reported by others.[90-93]

By using TVE and vascular reconstruction techniques, surgery is not necessarily contraindicated when colorectal liver metastases involve the inferior vena cava and/or confluence of the hepatic veins. However, it should only be performed in selected cases in which the increased risk associated with these procedures is carefully balanced against the possible benefits.

CONCLUSIONS

Hepatic resection of colorectal metastases after downstaging by chemotherapy provides the only chance of long-term survival for patients with initially unresectable disease. Additional surgical techniques can be combined to chemotherapy to further improve resectability. At this moment, the only absolute contraindication for resection is the inability to completely resect all metastases, avoiding postoperative liver failure by leaving enough functional liver tissue. The presence of poor prognostic factors no longer limits the indications for resection.

A close collaboration between oncologists and surgeons is essential when treating patients with unresectable colorectal liver metastases. Frequent re-evaluations and adequate timing are necessary to optimize therapeutic strategies on an individual basis. A crucial condition for long-term survival after hepatic resection is control of the metastatic disease by chemotherapy prior to surgery. Tumor progression during chemotherapy is associated with a 5-year survival rate of only 8% after curative resection, significantly lower compared to tumor response or stabilization.[94]

The paradoxal risk of prolonged chemotherapy is the disappearance of metastases on all imaging modalities. A complete radiologic response does not mean cure in approximately 83% of lesions.[95] Additionally, complete clinical response limits the possibilities of the surgeon to detect all remnant metastatic lesions during surgery, endangering the chance of a curative resection.

Prolonged chemotherapy may further produce histologic changes in the liver parenchyma that may influence surgical outcome.[96-98] Overall, a fast tumor response should be pursued, lowering the risks of liver toxicity.

Surgery of initially unresectable disease should be performed as soon as metastases become resectable, hereby ultimately using the advantages of chemotherapy, but avoiding the potential hazards of its prolonged duration. A decisional algorithm for the treatment of unresectable liver metastases is proposed in *Figure 2*.

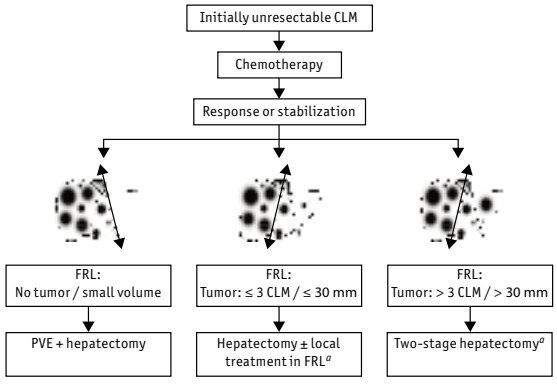


Figure 2.

Decisional algorithm for the treatment of patients with unresectable colorectal liver metastases. *a*: combined to PVE if volume of FRL < 30%. Abbreviations: CLM = colorectal liver metastases; FRL = future remnant liver; PVE = portal vein embolization.

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Part I

Surgery-related aspects in the treatment of advanced colorectal liver metastases

Chapter 3

Impact of portal vein embolization on long-term survival of patients with primarily unresectable colorectal liver metastases

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ABSTRACT

Background

Portal vein embolization (PVE) increases the resectability of initially unresectable colorectal liver metastases (CLM). This study evaluated long-term survival in patients with CLM who underwent hepatectomy following PVE.

Methods

In a retrospective analysis, patients treated by PVE before major hepatectomy were compared with those who did not have PVE, and with those who had PVE without resection.

Results

Of 364 patients who underwent hepatectomy, 67 had PVE beforehand and 297 did not. Those who had PVE more often had more than three liver metastases (68% *vs* 41%) (P<0.001) that were more frequently bilobar (78% *vs* 56%) (P<0.001), and a higher proportion underwent extended hepatectomy (63% *vs* 19%) (P<0.001). Postoperative morbidity rates were 55% and 41% (P=0.04), respectively, and overall 3-year survival rates were 44% and 61% (P=0.001). Thirty-two other patients who were treated by PVE but did not undergo resection all died within 3 years.

Conclusion

PVE increases the resectability rate of initially unresectable CLM. Among patients who had PVE, long-term survival was better in those who had resection than in those who did not. PVE is of importance in the multimodal treatment of advanced CLM.

Introduction

For patients with colorectal liver metastases (CLM), complete resection of all tumor nodules provides the only chance of long-term survival, with 5- and 10-year survival rates exceeding 50% and 20% for patients with clearly resectable tumors.[1-3] Unfortunately, up to 80% of patients with CLM present with unresectable disease at the time of diagnosis.

When tumor characteristics, such as vascular contact, large volume, multinodularity, bilaterality or extrahepatic disease, make metastases unresectable, curative resection can be achieved in a significant subset of patients after dowstaging by chemotherapy.[4,5] This strategy has increased the 5-year survival rate of this patient group to 33% after liver resection, approaching that of patients with initially resectable disease.[5] Without complete surgical treatment, long-term survival is rare, with a 5-year survival rate of around 2%.[6]

In patients requiring a major hepatectomy for complete tumor removal, liver resection, even when technically feasible, may still be contraindicated owing to an insufficient future remnant liver and the subsequent risk of fatal postoperative liver failure. Portal vein embolization (PVE), first described by Makuuchi and colleagues,[7] was developed for patients with extensive liver metastases to induce ipsilateral atrophy and contralateral compensatory hypertrophy of the remnant liver, thereby preventing severe postoperative liver failure.

In a previous publication almost 10 years ago that concerned a small number of patients with advanced CLM, survival rates were similar in patients who underwent PVE and in those who had resection without previous PVE.[8] Furthermore, chemotherapy regimens have become more effective and indications for PVE have expanded during recent years, as more extended resections are performed for more advanced disease. The aim of this study was to analyze long-term outcome after hepatectomy following PVE and to define the current place of PVE in the multimodal treatment of patients with extensive CLM.

PATIENTS AND METHODS

Patients who underwent partial liver resection for colorectal metastases at the Centre Hépato-Biliaire, Hôpital Paul Brousse, between January 1990 and January 2006 were identified from the hospital information system. From this large cohort, patients requiring a major hepatectomy (three or more segments) for complete tumor resection were selected for analysis. Patients treated by PVE before hepatectomy were compared with those who underwent hepatectomy without previous PVE. An additional group of patients who had PVE but did not subsequently undergo hepatic resection was also identified.

Preoperative management

Preoperative chemotherapy

Systemic chemotherapy was administered to patients with technically unresectable liver metastases owing to multinodularity, large tumor size, or a close relation to major vascular structures. Preoperative chemotherapy was routinely indicated for patients with concomitant extrahepatic disease. For those with primarily resectable metastases, chemotherapy has become increasingly more common during recent years before surgery to assess tumor chemoresponsiveness and to facilitate margin-negative resections.

Response to chemotherapy, assessed by computed tomography (CT) and/or magnetic resonance imaging, was discussed every four cycles of treatment in a multidisciplinary meeting of surgeons, oncologists and radiologists. Surgery was considered only when complete resection of intrahepatic and extrahepatic metastases could be achieved by single or multiple resections.

Portal vein embolization

PVE was indicated for patients whose estimated remnant liver was too small in relation to the extent of the planned resection. An estimated remnant functional liver parenchyma of less than 40% evaluated by CT volumetry determined the need for PVE. This cutoff point was chosen because most of these patients had received chemotherapy, which is known to be a major risk factor for liver failure.[9,10] Liver volumes were assessed before and after PVE by CT volumetric measurements as described previously.[8]

PVE was performed before surgery by a percutaneous or ileocolic technique depending on the surgeon's preferred approach. For the percutaneous technique, portal branches contralateral or ipsilateral to the tumor were catheterized selectively under ultrasonographic guidance.[11] After control venous portography, a guidewire was placed in the portal branch and embolization was performed. With the ileocolic technique, portal branches were catheterized through an ileocolic vein by minilaparotomy.[7] In selected patients, PVE was performed during resection of the primary colorectal tumor or the first step of a planned two-stage

hepatectomy by both embolization and ligation of the indicated portal branch. A time-interval of 4 to 6 weeks was generally considered necessary to obtain adequate parenchymal hypertrophy.

Chemotherapy was usually stopped at the time of PVE to avoid interfering with initial regeneration of the future liver remnant. Hepatectomy was reconsidered when the degree of hypertrophy had stabilized on repeated CT. For patients who underwent PVE at the first stage of a planned two-stage hepatectomy, three to four cycles of chemotherapy were routinely proposed after a 3-week chemotherapy-free interval to prevent tumor progression before the second hepatectomy.

Liver resection

The objective of surgery was to resect completely all lesions detected during surgery with tumor-free margins. Local ablative techniques were used only to treat unresectable remnant metastases of 3 cm or smaller. A two-stage hepatectomy approach was used for multiple bilobar metastases that were unresectable by a single procedure.[12]

All postoperative complications occurring within two months after surgery were recorded. An increase in serum bilirubin level above 50 µmol/L and a decrease in prothrombin time to less than 50% were used to define liver failure.[13]

Follow-up after surgery

All patients were followed by clinical examination, serum carcinoembryonic antigen (CEA) and CA 19.9 levels, and abdominal ultrasound one month after resection and then at 4-month intervals. CT of the chest, abdomen and pelvis was done every 8 months. Postoperative chemotherapy was recommended routinely. Repeat intrahepatic and extrahepatic resections were performed only if they could be complete oncologically.

Statistical analysis

Continuous data were reported as mean (standard deviation) or median (range) depending on whether the variable was distributed normally. Quantitative variables were compared using the independent-samples *T* test and qualitative variables by means of the X^2 test. The Kaplan-Meier method was used to determine survival probabilities, which were compared using the log-rank test. Univariate analysis was done using the log-rank test. Variables with a *P* value ≤0.10 were selected for multivariate analysis. Multivariate analysis of prognostic factors of survival was performed with a Cox regression model. A hazard ratio of more than 1 was associated with poor survival. $P \leq 0.05$ was considered statistically significant. Statistical analysis was performed with SPSS® software version 13.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

A total of 802 patients underwent partial liver resection for CLM, and 364 consecutive patients who underwent major hepatectomy for metastases were included in this study *(Figure 1)*. This group comprised 210 men (58%) and 154 women (42%) with a median age of 60.5 years (range: 27.9 to 83.0 years). The median number of metastases was 3 (range: 1 to 25) with a median diameter of 50 mm (range: 10 to 290 mm). Sixty-eight patients (19%) had concomitant extrahepatic disease. The majority of patients (63%) were initially considered to have unresectable tumors. Preoperative chemotherapy was administered to 307 patients (84%) with a median number of 1 type of chemotherapy regimen (line) (range: 1 to 5 lines) and 8 cycles (range: 1 to 43 cycles). Sixty-seven (18%) of the 364 patients underwent PVE before hepatectomy and 297 (82%) did not.

In the same period, 32 other patients underwent PVE. However, no liver resection was performed in these patients owing to tumor progression (27 patients), insufficient hypertrophy (less than 40% remnant liver volume) (three) or for other reasons (two), and therefore this group was excluded from the present analysis. Overall, 67 of 99 patients who underwent PVE had a liver resection (resectability rate 68%).

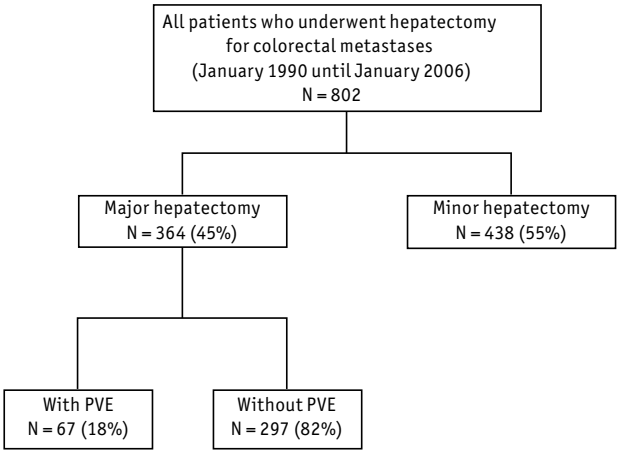


Figure 1.
Flowchart of patient selection.
Abbreviations: PVE = portal vein embolization.

Baseline characteristics

No differences were observed in age, sex or primary tumor characteristics between patients who had liver resection with or without previous PVE *(Table 1)*. Patients in the PVE group more often had more than three liver metastases (68% *vs* 41%, respectively) (P<0.001). Most patients who had PVE had liver metastases

synchronous to the primary tumor (75% *vs* 59% in the no-PVE group) (*P*=0.02). Metastases were more frequently bilobar in the PVE group (78% *vs* 56%) (*P*<0.001). Extrahepatic metastases were present in 19% of patients in both groups.

Table 1. Patient, primary tumor and liver metastases data in patients who did or did not have portal vein embolization (PVE) before liver resection.

	No PVE (N = 297)	PVE (N = 67)	*P*
Patients			
Mean age ± SD, years	59.0 ± 11.4	59.4 ± 10.6	0.77
Male/Female	168 (57%) / 129 (43%)	42 (63%) / 25 (37%)	0.36
Primary tumor			
Colon/Rectum	233 (79%) / 63 (21%)	52 (78%) / 15 (22%)	0.84
T stage			
1/2	25 (12%)	5 (13%)	0.90
3/4	176 (88%)	33 (87%)	
N stage			
0	71 (36%)	13 (32%)	0.63
1/2	128 (64%)	28 (68%)	
Liver metastases			
Synchronous[a]	175 (59%)	50 (75%)	0.02
Mean number ± SD	4.0 ± 3.9	5.5 ± 3.9	0.007
1	73 (26%)	8 (12%)	< 0.001
2 - 3	92 (33%)	13 (20%)	
> 3	114 (41%)	44 (68%)	
Mean maximum size ± SD, mm	56.2 ± 36.1	52.6 ± 27.0	0.44
Bilobar	164 (56%)	52 (78%)	< 0.001
Initially unresectable	163 (56%)	67 (100%)	< 0.001
Cause of initial unresectability			
Multinodularity	77 (48%)	30 (53%)	0.20
Large size	51 (32%)	20 (35%)	
Close vascular relation	22 (14%)	7 (12%)	
Extrahepatic disease	12 (7%)	0 (0%)	
Median CEA level (range), ng/mL	33.5 (0.4-7400)	69.8 (1.2-2215)	-
Concomitant extrahepatic disease	55 (19%)	13 (19%)	0.87
Resection	31 (56%)	5 (39%)	0.25

a: synchronous metastases were diagnosed before or within 3 months after resection of the primary colorectal tumor. Abbreviations: SD = standard deviation; CEA = carcinoembryonic antigen.

Preoperative chemotherapy

Fifty-six patients (84%) received preoperative chemotherapy in the PVE group and 251 (85%) in the control group (*P*=0.85). For selected patients with unilobar metastases (eleven), embolization of one hemiliver was sufficient to allow

resectability without the need for preoperative chemotherapy. The number of lines and cycles of preoperative chemotherapy were comparable between the two groups *(Table 2)*. Last line regimens most often consisted of a combination of 5-fluorouracil, leucovorin and oxaliplatin (56% and 50% in the PVE and no-PVE groups, respectively) (*P*=0.53).

Table 2. Details of preoperative chemotherapy.

	No PVE (N = 297)	PVE (N = 67)	*P*
Preoperative chemotherapy	251 (85%)	56 (84%)	0.85
Number of lines			
1	173 (69%)	39 (70%)	0.92
> 1	78 (31%)	17 (30%)	
Mean number of cycles ± SD	9.7 ± 5.9	8.6 ± 5.3	0.19
Last line regimen			
5-FU/LV	48 (20%)	7 (13%)	0.53
5-FU/LV Oxaliplatin	123 (50%)	30 (56%)	
5-FU/LV Irinotecan	34 (14%)	10 (19%)	
Other	39 (16%)	7 (13%)	
Clinical response			
Complete/Partial	138 (58%)	27 (48%)	0.38
Stabilization	76 (32%)	23 (41%)	
Progression	24 (10%)	6 (11%)	

Abbreviations: PVE = portal vein embolization; SD = standard deviation; 5-FU = 5-fluorouracil; LV = leucovorin.

Portal vein embolization

PVE was performed percutaneously in most patients (67%) and an ileocolic procedure was performed in 12%. The remaining 21% underwent PVE intraoperatively. In all but one, this comprised the first stage of a planned two-stage hepatectomy. The median time-interval between PVE and hepatectomy was 8.1 weeks (range: 2.0 to 26.9 weeks).

Hepatectomy and postoperative complications

Resection of the right hemiliver was the most frequently performed resection (88%) in patients who underwent PVE. Patients in the PVE group more often underwent extended right (enlarged to segments IV and/or I) or left (enlarged to segments I, V and/or VIII) hepatectomy compared with patients in the no-PVE group (63% *vs* 19%) (*P*<0.001) *(Table 3)*. Total vascular exclusion (32% *vs* 18%) (*P*=0.007) and two-stage hepatectomy (25% *vs* 3%) (*P*<0.001) were more frequently used in the PVE group. R0, R1 and R2 resections were performed in

74%, 24% and 2% of patients respectively in the PVE group, and in 59%, 38% and 4% of those who did not have PVE (*P*=0.12).

Table 3. Comparison of data concerning liver resection and postoperative outcome.

	No PVE (N = 297)	PVE (N = 67)	*P*
Hepatectomy			
Mean number of detected metastases ± SD	4.0 ± 3.6	4.5 ± 3.5	0.43
1	63 (23%)	11 (23%)	0.28
2 - 3	96 (35%)	11 (23%)	
> 3	118 (43%)	25 (53%)	
Mean number of resected segments ± SD	3.8 ± 0.7	4.3 ± 0.8	< 0.001
Resection type			
Anatomical	158 (54%)	31 (46%)	0.28
Anatomical and nonanatomical	137 (46%)	36 (54%)	
Resection classification			
Right hepatectomy	153 (52%)	23 (34%)	< 0.001
Left hepatectomy	52 (18%)	0 (0%)	
Extended right hepatectomy	28 (10%)	36 (54%)	
Extended left hepatectomy	25 (9%)	6 (9%)	
Central hepatectomy	8 (3%)	1 (2%)	
Other	27 (9%)	1 (2%)	
Vascular occlusion			
None	16 (6%)	5 (8%)	0.007
Total pedicular	145 (54%)	34 (54%)	
Vascular exclusion	47 (18%)	20 (32%)	
Selective	60 (22%)	4 (6%)	
Combined local treatment			
None	270 (91%)	64 (96%)	0.42
RFA	13 (4%)	2 (3%)	
Cryotherapy	14 (5%)	1 (2%)	
Two-stage resection	8 (3%)	17 (25%)	< 0.001
Median red blood cell transfusions (range), units	0 (0-28)	2 (0-28)	-
Postoperative outcome			
Mortality (within 60 days)	2 (1%)	1 (2%)	0.50
Morbidity	122 (41%)	37 (55%)	0.04
General complications[a]	67 (24%)	17 (25%)	0.79
Hepatic complications	88 (31%)	31 (46%)	0.02
Biliary leak	12 (14%)	4 (13%)	0.06
Hemorrhage	13 (15%)	1 (3%)	
Infected collection	16 (19%)	3 (10%)	
Noninfected collection	26 (31%)	7 (23%)	
Liver insufficiency[13]	16 (19%)	13 (43%)	
Combination	2 (2%)	2 (7%)	
Relaparotomy	17 (6%)	6 (9%)	0.40
Percutaneous drainage	42 (17%)	18 (27%)	0.05
Mean hospital stay ± SD, days	14.2 ± 6.9	18.0 ± 13.8	0.001
Postoperative chemotherapy	248 (86%)	48 (74%)	0.02

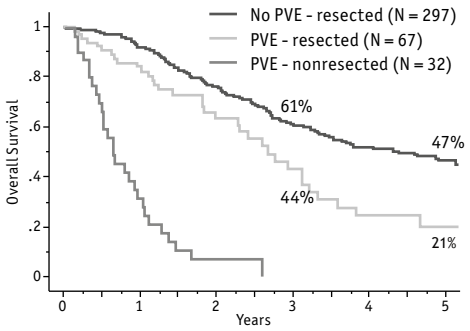
a: as general complications were considered: pulmonary, cardiovascular, urinary tract, infectious (other than local hepatic) and iatrogenic complications. Abbreviations: PVE = portal vein embolization; SD = standard deviation; RFA = radiofrequency ablation.

One of 67 patients who had liver resection after PVE died within 60 days from severe liver insufficiency after a right hepatectomy as the second step of a two-stage hepatectomy. Postoperative morbidity occurred in 37 patients (55%) in the PVE group and in 122 (41%) in the no-PVE group (*P*=0.04) *(Table 3)*. This difference was mainly due to a higher incidence of hepatic complications (46% *vs* 31%, respectively) (*P*=0.02). Postoperative liver failure was more frequent after hepatectomy in patients who underwent PVE (43% *vs* 19%) (*P*=0.06).

Long-term outcome and survival

Median follow-up was 27.7 months (range: 0.4 to 192.8 months) for the whole group and 30.3 months (range: 0.4 to 179.5 months) for survivors. Recurrences developed in 46 patients (69%) in the PVE group and in 232 (78%) in the no-PVE group (*P*=0.24). In the PVE group, recurrences were intrahepatic in 7 (18%), extrahepatic in 12 (31%), and both intrahepatic and extrahepatic in 20 (51%) of the patients. However, for 7 patients with recurrence, the exact localization was unknown. Localization of recurrences was similar in patients who did not have PVE. Repeat hepatic and extrahepatic resections were comparable between groups, being carried out in 16% (eleven) and 22% (fifteen), respectively, of patients who underwent PVE, and in 25% and 30% of patients in the no-PVE group.

Overall 3- and 5-year survival was 44% and 21% for patients who underwent PVE, and 61% and 47% for patients in the no-PVE group (*P*=0.001) *(Figure 2)*. However, the overall survival rate for patients who underwent hepatectomy after PVE was significantly higher compared to that of the 32 patients who underwent

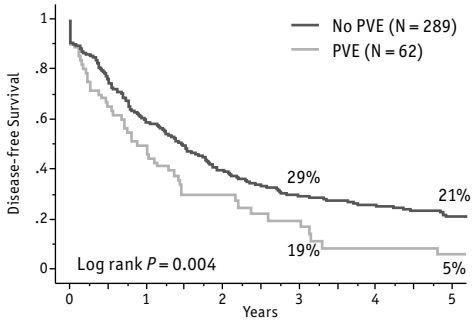


Patients at risk	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
No PVE - resected	297	252	178	108	77	56
PVE - resected	67	48	25	14	8	3
PVE - nonresected	32	10	2	-	-	-

Figure 2.
Overall survival curves of the different patient groups. Survival is significantly different between resected patients with and without previous PVE (*P*=0.001), and between resected and nonresected patients who underwent PVE (*P*<0.001).

PVE but did not undergo hepatic resection in the same time period (P<0.001) *(Figure 2)*. All of these patients died within 3 years after PVE, mainly because of tumor progression.

Among patients who underwent tumor resection, disease-free survival at 3 and 5 years was 19% and 5% for those who had PVE compared with 29% and 21% for those who did not (P=0.004) *(Figure 3)*.



Patients at risk	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
No PVE	289	165	102	66	55	42
PVE	62	28	12	7	3	2

Figure 3.
Disease-free survival curves of resected patients with and without previous PVE.

Subanalysis: (extended) right hepatectomy

As right and extended right hepatectomy constitute the classical indications for PVE, postoperative outcome was analyzed separately in this group (with the exclusion of patients who had a two-stage hepatectomy). The morbidity rate was 49% among 43 patients who had PVE and 43% among 173 patients who had resection without PVE (P=0.47). One patient died after right hepatectomy in the no-PVE group. The 5-year overall survival rate was 18% in the PVE group and 43% in the no-PVE group (P=0.008).

Prognostic factors of survival

In univariate analysis, eight factors were related to decreased overall survival (P≤0.10): more than three metastases, initial unresectability, CEA level over 10 ng/mL, concomitant extrahepatic disease, preoperative chemotherapy, more than four resected liver segments, PVE and intraoperative red blood cell transfusion. Multivariate analysis subsequently identified concomitant extrahepatic disease, preoperative chemotherapy and PVE as independent predictors of poor survival *(Table 4)*.

Table 4. Univariate and multivariate analysis of overall survival.

		Survival				
Variable	**N**	**3 Yrs (%)**	**5 Yrs (%)**	**UV *P***	**MV *P***	**HR (95% CI)**
All patients	364	58	43	-	-	-
Patients						
Gender						
Male	210	58	39	0.14	-	-
Female	154	59	47			
Age at hepatectomy						
≤ 40 years	30	55	30	0.20	-	-
> 40 years	334	59	44			
Primary tumor						
Localization						
Colon	285	58	44	0.46	-	-
Rectum	78	59	38			
T stage						
1/2	30	72	36	0.74	-	-
3/4	209	55	42			
N stage						
0	84	64	43	0.26	-	-
1/2	156	53	37			
Liver metastases						
Timing						
Synchronous	225	57	39	0.38	-	-
Metachronous	138	61	47			
Number[a]						
≤ 3	186	64	47	0.05	NS	-
> 3	158	50	39			
Maximum size						
≤ 30 mm	86	62	43	0.30	-	-
> 30 mm	237	56	41			
Localization						
Unilobar	143	63	45	0.34	-	-
Bilobar	216	55	41			
Initial resectability[a]						
No	230	54	35	0.04	NS	-
Yes	130	67	46			
CEA level[a]						
≤ 10 ng/mL	73	69	55	0.003	NS	-
> 10 ng/mL	179	52	35			
Concomitant extrahepatic disease[a]						
No	296	61	48	0.003	0.01	1.8 (1.1-2.8)
Yes	68	48	21			
Preoperative chemotherapy[a]						
No	57	80	64	< 0.001	0.03	1.5 (1.1-2.2)
Yes	307	54	38			
Number of lines						
1	212	57	41	0.15	-	-
> 1	95	47	30			

Continuation of table 4.

		Survival				
Variable	**N**	**3 Yrs (%)**	**5 Yrs (%)**	**UV *P***	**MV *P***	**HR (95% CI)**
Number of cycles						
≤ 10	189	53	41	0.40	-	-
> 10	85	48	30			
Last line regimen						
5-FU/LV	55	49	30	0.93	-	-
5-FU/LV Oxaliplatin	153	54	40			
5-FU/LV Irinotecan	44	53	45			
Other	46	62	37			
Clinical response						
Complete/Partial	165	57	45	0.11	-	-
Stabilization	99	48	31			
Progression	30	48	28			
Hepatectomy						
Number of resected segments[a]						
≤ 4	284	59	45	0.01	NS	-
> 4	49	46	26			
Resection type						
Anatomical	189	57	41	0.56	-	-
Anatomical and nonanatomical	173	59	45			
Pedicular clamping						
No	85	58	50	0.68	-	-
Yes	246	58	41			
Combined local treatment						
No	334	58	42	0.84	-	-
Yes	30	66	45			
PVE[a]						
No	297	61	47	0.001	0.02	1.6 (1.1-2.4)
Yes	67	44	21			
Two-stage hepatectomy						
No	338	59	43	0.47	-	-
Yes	25	47	34			
Intraoperative RBC transfusion[a]						
No	167	62	47	0.10	NS	-
Yes	135	54	34			
Postoperative chemotherapy						
No	58	63	46	0.50	-	-
Yes	296	58	42			
Resection margin						
R0	184	55	38	0.39	-	-
R1	106	63	49			
R2	11	62	48			

a: variables entered in Cox regression model. Abbreviations: UV = univariate; MV = multivariate; HR = hazard ratio; CI = confidence interval; NS = not significant; CEA = carcinoembryonic antigen; 5-FU = 5-fluorouracil; LV = leucovorin; PVE = portal vein embolization; RBC = red blood cell.

Discussion

The important finding of this study was that PVE increased the resectability rate of advanced CLM. The majority of patients who had hepatectomy after PVE had also received preoperative chemotherapy. In the PVE group, 3- and 5-year survival rates of 44% and 21% were achieved. Although these rates were lower than those in patients who had resection without the need for PVE, long-term survival of this group was significantly better than that of patients who underwent PVE but still had unresectable tumors. Together, these results confirm the importance of PVE in the achievement of resection and long-term survival of selected patients with initially unresectable CLM.

Several studies have reported that PVE is a safe and efficient method for inducing sufficient hypertrophy of the future remnant liver in patients with metastatic and primary hepatobiliary malignancies.[7,8,14-19] Although the feasibility of PVE for achieving complete resection of initially unresectable CLM is clearly described, limited data are available concerning the long-term outcome after hepatectomy.[8,20-25] Resectability rates varied from 60% to 82% after PVE, and 5-year survival from 25% to 46%.[20-22,25]

Progression of intrahepatic and extrahepatic disease is the main reason for failure to achieve resection, indicating a possible role for the administration of chemotherapy following PVE to control the disease and to increase the proportion of patients referred for surgery. The influence of chemotherapy on initial liver regeneration owing to toxic injury of the nontumoral parenchyma has been suggested previously, but recent studies now question its negative effect on parenchymal hypertrophy.[16,21,26,27] When chemotherapy is administered after PVE in the authors' practice, it is generally delayed for 3 to 4 weeks to allow maximal liver hypertrophy.[26] In this study, most patients received preoperative chemotherapy. As a consequence, the interval between PVE and hepatectomy was relatively long, probably reflecting a slower rate of liver hypertrophy.[16] Nevertheless, an insufficient degree of hypertrophy prevented surgery in only 9% of patients. Overall, 18% of patients who underwent major hepatectomy were treated by PVE. This result is comparable with published rates of 19%, 20% and 37%.[8,22,25]

The finding that the survival rate was lower in those who had PVE before resection than in those who had resection alone can largely be explained by the increased initial tumor load in the PVE group. However, on multivariate analysis, PVE was found to be an independent prognostic factor for decreased survival, which suggests that PVE itself can contribute to tumor progression. Previous studies also reported that PVE may stimulate the growth of metastases,[28,29,30] associated with a decreased disease-free survival after resection.[29] This is also in line with the concept that tumor control by chemotherapy after PVE may play an

important role in achieving long-term outcome after hepatectomy.[31] Possible underlying mechanisms of stimulated tumor growth include changes in growth factors and cytokines or changes in portal and arterial blood flow after PVE, but the exact causes still need to be identified. If indeed PVE contributes to tumor progression, patients with bilobar disease (the majority in this series) are particularly at risk of stimulated tumor growth in the future remnant and nonembolized liver.

Besides PVE, concomitant extrahepatic disease and preoperative chemotherapy were also found to be predictors of poor survival. Extrahepatic disease is a commonly reported indicator of poor survival owing to the presence of advanced metastatic disease.[32] Similarly, preoperative chemotherapy is related to a high tumor burden. Interestingly, long-term survival was not influenced by R0 or R1 resections. This result is in agreement with a recent observation that effective chemotherapy and repeat hepatectomy may achieve similar survival rates in both groups.[33]

In other recent series including the authors' preliminary report, overall survival was comparable after resection with or without previous PVE.[8,20,22-24] For patients who underwent PVE, 5-year survival rates between 37% and 46% were reported. However, most series included few patients (not more than 41) with more limited tumor load. One study that reported a decreased intrahepatic recurrence rate after right hepatectomy following embolization of the right portal vein compared with patients who underwent a right hepatectomy without previous PVE included only patients with unilobar metastases.[20] In the present series, patients who underwent PVE had significantly more metastases than those in the no-PVE group, most often located in both liver lobes. This clearly reflects a relatively aggressive approach in offering a possibility of curative resection to patients with highly advanced disease. Nevertheless, long-term survival was achieved in a significant proportion of these patients, who otherwise would have had a very poor prognosis.

Postoperative morbidity rates were higher in the PVE group than in the no-PVE group in this study, mainly owing to a larger number of local hepatic complications. Although patients in the PVE group were referred for surgery only when liver regeneration was considered sufficient, a significant number experienced transient postoperative liver insufficiency. PVE was not reported to influence morbidity rates after hepatectomy for CLM in most series.[20,22] Additionally, two studies reported a lower complication rate in the PVE group.[21,23] In recent years, however, the authors have expanded the indications for hepatectomy provided that complete resection could be achieved while leaving sufficient nontumoral parenchyma. As a result, patients with PVE had more advanced disease requiring

more extensive resections than patients who did not need PVE. This may also contribute to the differences found in postoperative morbidity.

A proportion of patients included in this study underwent a planned two-stage hepatectomy. It has recently been shown that these patients who, in addition, generally receive prolonged preoperative chemotherapy, have increased morbidity after the second hepatectomy, reflecting the aggressiveness of the total strategy.[12] When patients who had a two-stage procedure were excluded from the analysis in this series, the difference in postoperative morbidity between the PVE and no-PVE group disappeared. Although the achievement of complete resection should be the most important issue to consider, careful patient selection for these treatment strategies remains essential.

The use of PVE as part of a two-stage hepatectomy is at present an established treatment strategy for patients with multiple bilobar metastases.[34-37] Between 70% and 100% of patients generally complete this treatment with reported 3-year survival rates up to 86%.[34-37] Although it has been shown recently that embolization as well as ligation of the portal vein results in a comparable degree of hypertrophy of the nonembolized liver,[38,39] at this center both types of portal vein occlusion are performed routinely during the first stage of a planned two-stage hepatectomy. By this means, irreversible occlusion of the total portal tract of one hemiliver is secured (embolization with alcohol), while incidental embolization of the contralateral portal branches is avoided (ligation). Furthermore, the additional use of embolization prevents the development of portoportal collateral vessels.

In conclusion, PVE is an efficient means of increasing the resectability rate among selected patients with initially unresectable CLM owing to insufficient remnant liver volume. In recent years, improvements in systemic chemotherapy and surgical techniques have increased the number of tumors that can become resectable. In a specialized multidisciplinary setting including surgeons and oncologists, this technique offered significant long-term survival (3- and 5-year rates of 44% and 21%) to patients with advanced metastatic disease, who would have had a dismal prognosis without resection. Nevertheless, owing to the risk of disease progression and associated unresectability, the indications for PVE should remain strict and its overuse for primarily resectable patients should be avoided. The routine use of preoperative chemotherapy after PVE in the near future will probably result in an increased proportion of patients in whom complete tumor resection can be achieved.

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Chapter 4

Long-term results of two-stage hepatectomy for irresectable colorectal cancer liver metastases

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ABSTRACT

Objective

To assess feasibility, risks, and long-term outcome of two-stage hepatectomy as a means to improve resectability of colorectal liver metastases (CLM).

Summary Background Data

Two-stage hepatectomy uses compensatory liver regeneration after a first noncurative hepatectomy to enable a second curative resection.

Methods

Between October 1992 and January 2007, among 262 patients with initially irresectable CLM, 59 patients (23%) were planned for two-stage hepatectomy. Patients were eligible when single resection could not achieve complete treatment, even in combination with chemotherapy, portal embolization, or radiofrequency, but tumors could be totally removed by two sequential resections. Feasibility and outcomes were prospectively evaluated.

Results

Two-stage hepatectomy was feasible in 41 of 59 patients (69%). Eighteen patients failed to complete the second hepatectomy because of disease progression (N=17) or bad performance status (N=1). The 41 successfully treated patients had a mean number of 9.1 metastases (mean diameter: 48.5 mm at diagnosis). Chemotherapy was delivered before (95%), in between (78%), and after (78%) the two hepatectomies. Mean delay between the two liver resections was 4.2 months. Postoperative mortality was 0% and 7% (3/41) after the first and second hepatectomy, respectively. Morbidity rates were also higher after the second procedure (59% *vs* 20%) (P<0.001). Five-year survival was 31% on an intention to treat basis, and all but 2 patients who did not complete the two-stage strategy died within 19 months. After a median follow-up of 24.4 months (range: 3.7 to 130.3 months), overall 3- and 5-year survivals for patients who completed both hepatectomies were 60% and 42%, respectively, after the first hepatectomy (median survival: 42 months from first hepatectomy and 57 months from metastases diagnosis). Disease-free survivals were 26% and 13% at 3 and 5 years, respectively.

Conclusions

Two-stage hepatectomy provides a 5-year survival of 42% and a hope of long-term survival for selected patients with extensive bilobar CLM, irresectable by any other means.

INTRODUCTION

The majority of patients with colorectal liver metastases (CLM) present with irresectable disease at the time of diagnosis, and only 15% to 25% can be offered complete resection of metastases according to currently used criteria.[1] However, curative hepatectomy remains the only treatment option providing long-term survival for patients with CLM, with 5-year survival rates reaching 67% for highly selected patients.[2] Neither chemotherapy nor local ablative treatment alone can achieve long-term survival rates similar to that of radical surgery.[3-6]

Improved response rates of CLM to chemotherapy regimens consisting of 5-fluorouracil (5-FU), leucovorin (LV), oxaliplatin and/or irinotecan, have offered a possibility of curative hepatectomy to patients with initially irresectable metastases after tumor downsizing. For 10% to 54% of these patients, sufficiently responding to chemotherapy, 5-year survival can be achieved in 33% to 58% of cases after hepatic resection.[7-14] In some patients in whom chemotherapy alone is not sufficient, specific surgical techniques as portal vein embolization (PVE) and local treatment modalities can be used additionally to allow complete resection of the metastases.[15,16]

The concept and initial results of two-stage hepatectomy were first described by our group in 2000.[17] This strategy was proposed to patients with multiple bilobar CLM that were unable to be resected by a single hepatectomy, even in combination with preoperative chemotherapy and specific surgical techniques. The two-stage procedure consists of the resection of metastases of one hemiliver during a first hepatectomy, with the objective to make a second hepatectomy of the contralateral hemiliver potentially curative. The overall strategy relies on compensatory regeneration of the remnant liver after the first hepatic resection, allowing to safely perform the second curative hepatectomy without the risk of postoperative liver failure. Systemic chemotherapy is regularly administered after the first resection to control tumor progression promoted by growth factors involved in liver regeneration. Overall, two-stage hepatectomy has been shown to provide a survival benefit in an additional proportion of patients with multiple bilobar metastases, otherwise unable to be curatively treated.[17] However, feasibility and long-term survival are still under scrutiny, and only limited series have been reported so far.

The aim of this study was to evaluate the feasibility, risks, and long-term results of two-stage hepatectomy as a means to improve the resectability of multinodular bilobar CLM.

PATIENTS AND METHODS

Study population

Between October 1992 and January 2007, 817 consecutive patients with CLM underwent hepatectomy at our hospital, 262 of which (32%) were initially considered irresectable. Initial irresectability was defined as the inability to resect all metastases with tumor-free margins while saving 25% to 30% of remnant liver volume to prevent postoperative liver failure. Causes for irresectability were either multinodular disease (55%), large size (19%) or unfavorable vascular localization (16%) of metastases, or extensive extrahepatic disease (10%).

In 59 of the 262 initially irresectable patients (23%), a widespread intrahepatic diffusion of the disease prevented a complete resection of all metastases by a single hepatectomy, even in combination with additional techniques. A complete removal of the metastases could, however, be possible by two sequential resections, and these patients were therefore selected for two-stage hepatectomy. The decision to perform a two-stage procedure was a planned strategy decided either before or during the first hepatectomy in all cases.

Two-stage hepatectomy: the procedure

Preoperative evaluation

Patients were generally treated with preoperative chemotherapy because of the extent of the disease. This allowed to assess tumor biology, avoiding hepatic resection in patients with progressive disease, a situation associated with poor long-term survival.[18] The response to chemotherapy was evaluated with computed tomography (CT) after every 4 cycles of treatment. The decision for hepatectomy was taken in a multidisciplinary meeting, including surgeons, medical oncologists, and radiologists, when the overall surgical strategy could achieve complete tumor resection and the disease was controlled by chemotherapy. The presence of extrahepatic disease was evaluated by CT of the chest, abdomen, and pelvis, and colonoscopy, and if resectable, was not considered a contraindication to hepatic resection. Recent patients also had a positron emission tomography (PET)-CT scan.

The first hepatectomy

The majority of metastases was located in the right liver in most patients. During the first hepatectomy, either the most invaded right hemiliver was resected ('right first') or the less-invaded left liver was cleared from its metastases ('left first'). Detailed inspection, palpation and intraoperative ultrasound were standardly performed to precisely localize all metastases. Radiofrequency ablation or cryotherapy was only used in combination with surgery to treat

irresectable deeply located remnant lesions. Noteworthy, attention was paid not to dissect the future hemiliver to be resected, in a way not to compromise the second hepatectomy.

Portal vein embolization
PVE was performed if there was a risk of insufficient liver regeneration to safely enable a second resection. The risk of liver failure especially existed when less than 25% to 30% of normal functioning parenchyma would remain after resection.[19] Moreover, in case of intensive previous chemotherapy treatment, an estimated remnant liver volume of 40% was pursued.

Chemotherapy treatment between the two liver resections
Chemotherapy was usually started 3 weeks after the first hepatectomy to avoid interference with initial liver regeneration, and normally the same drug protocol was used as before surgery. Three to 4 cycles were delivered to prevent tumor progression. In case of progression, the chemotherapy protocol was changed, and the second hepatectomy was postponed.

The second hepatectomy
Timing of the second hepatectomy depended on the degree of liver hypertrophy and was only performed if it could be curative and the remaining disease was controlled by chemotherapy. Preoperative evaluation was similar to that described for the first hepatectomy. Owing to the extensiveness of the metastatic disease and associated high risk of recurrence, postoperative chemotherapy was routinely recommended.

Resection of extrahepatic disease
Limited extrahepatic disease located in the abdomen was usually resected at the time of the first hepatectomy. When extrahepatic metastases were located outside the abdomen, resection was performed 2 to 3 months after the second hepatectomy if the disease remained controlled by chemotherapy.

Follow-up

Tumor recurrence was regularly assessed by serum tumor markers (CEA and CA 19.9), clinical examination, and hepatic imaging (ultrasound and CT). Follow-up of patients occurred at one month postoperatively and then every 4 months. Recurrences were resected only when an overall curative resection was considered possible.[20]

Statistical analysis

Comparison of data between groups was performed using the X^2 test for categorical data and the independent-samples *T* test for continuous data. Survival probabilities were determined with the Kaplan-Meier method and compared using the log-rank test. Uni- and multivariate analysis of survival was performed by using the log-rank test and a Cox regression model. Differences with a *P* value ≤0.05 were considered significant. All statistical calculations were performed with SPSS® software, version 13.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Two-stage hepatectomy: evolution in time

An increasing rate of two-stage hepatectomies was observed over time in the total cohort of patients who underwent hepatectomy for CLM at our institute *(Figure 1)*. Although two-stage hepatectomy constituted only 2% to 7% of all hepatectomies during the initial study period, this percentage increased to 14% during most recent years.

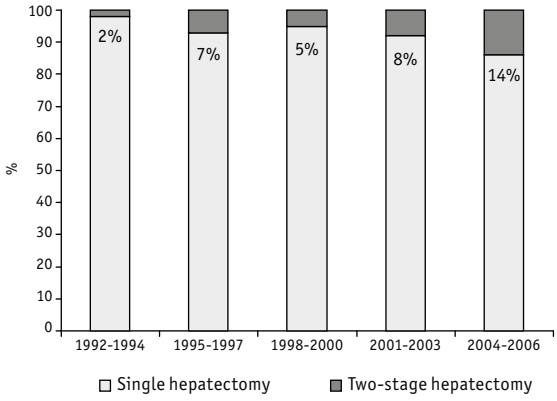


Figure 1.
Evolution in time of two-stage hepatectomy compared with single hepatectomy.

Feasibility

Of all 59 patients who were planned for a two-stage resection, 41 completed the second-stage hepatectomy (69%). Seventeen patients failed to complete the second procedure because of intrahepatic disease progression after the first hepatectomy, including 11 patients who also developed extrahepatic metastases. One patient could not complete the procedure because of a bad performance status. Compared with patients who completed both resections, failed patients did not demonstrate any difference in tumor characteristics, but they received more lines of preoperative chemotherapy (3 or more lines: 33% *vs* 8%) (P=0.05) *(Table 1)*.

Patient characteristics

Among the 41 patients who completed both resections, there were 22 men and 19 women with a median age of 58.2 years (range: 32.8 to 83.7 years) *(Table 1)*. Patients had a median number of 8 metastases (range: 2 to 23) that were synchronous to the primary colorectal tumor in 33 cases (81%). Median size of the largest metastasis was 50 mm (range: 10 to 130 mm) at diagnosis. Concomi-

tant extrahepatic disease was present in 7 patients (17%) and was located in the lungs in 4 patients (10%). Two patients had a local recurrence of their primary tumor (5%), 1 of whom also had lung metastases. One additional patient presented with a single lung metastasis and localized peritoneal and para-aortic lymph node metastases.

Table 1. Comparison of patients who completed and failed the two-stage hepatectomy procedure.

	Completed two-stage hepatectomy (N = 41)	Failed two-stage hepatectomy (N = 18)	*P*
Patients			
Mean age ± SD, years	58.4 ± 9.9	58.6 ± 9.4	0.93
Male/Female	22 (54%) / 19 (46%)	11 (61%) / 7 (39%)	0.60
Primary tumor			
Colon/Rectum	33 (81%) / 8 (20%)	14 (78%) / 4 (22%)	0.81
T stage			
1/2	6 (25%)	3 (20%)	0.72
3/4	18 (75%)	12 (80%)	
N stage			
0	5 (22%)	3 (21%)	0.98
1/2	18 (78%)	11 (79%)	
Liver metastases			
Synchronous[a]	33 (81%)	14 (78%)	0.81
Mean number ± SD	9.1 ± 5.4	8.5 ± 4.7	0.71
Mean maximum size ± SD, mm	48.5 ± 25.8	37.9 ± 15.8	0.16
Mean maximum CEA level ± SD, ng/mL	319.4 ± 686.1	236.5 ± 343.9	0.71
Concomitant extrahepatic disease	7 (17%)	4 (22%)	0.64
Chemotherapy			
Before first hepatectomy	39 (95%)	18 (100%)	0.34
Number of lines			
1	21 (55%)	7 (39%)	0.05
2	14 (37%)	5 (28%)	
≥ 3	3 (8%)	6 (33%)	
Mean number of cycles ± SD	11.1 ± 4.0	13.6 ± 9.0	0.16
Before second hepatectomy	32 (78%)	-	-
Mean number of cycles ± SD	4.0 ± 1.8	-	-
After second hepatectomy	32 (78%)	-	-

a: synchronous metastases were diagnosed before or within 3 months after resection of the primary colorectal tumor.
Abbreviations: SD = standard deviation; CEA = carcinoembryonic antigen.

Chemotherapy treatment

Before the first hepatectomy, 39 patients (95%) were administered systemic chemotherapy with a median number of 1 line (range: 1 to 3 lines) and 10 cycles

(range: 4 to 19 cycles) *(Table 1)*. Partial response and stabilization of the disease were observed in 26 (67%) and 13 (33%) patients, respectively.

The 32 patients (78%) who continued chemotherapy after the first resection received a median number of 4 cycles (range: 1 to 9 cycles) between the two procedures *(Table 1)*. Chemotherapy was continued after the second hepatectomy in 32 patients (78%).

Surgery

The median duration between resection of the primary tumor and the first hepatectomy was 9.2 months (range: 0 to 43.4 months). Resection of the primary colorectal tumor was integrated within the first stage hepatectomy in 8 patients (20%). First hepatectomies were minor resections (less than 3 segments) in the majority of patients (90%), and 63% were nonanatomical hepatectomies *(Table 2)*. Cryotherapy was used additionally to resection in 2 patients (5%) for deeply located irresectable lesions, to completely clear the future remnant liver of metastases. In 32 patients (78%), PVE was used to increase the volume of the remnant liver. This procedure was performed either before, during, or after the first hepatectomy in one (3%), 23 (72%), and 8 (25%) patients, respectively. The first hepatectomy consisted of clearance of the left hemiliver in 32 patients (78%). The 9 other patients (22%) underwent resection of the right hemiliver.

The median time interval between the two liver resections was 3.3 months (range: 1.0 to 15.7 months), with the majority of patients (86%) resected for the second time within 6 months.

At the second operation, anatomical resections were performed in 35 patients (86%), and were combined to nonanatomical resections in 18 of them *(Table 2)*. Second hepatectomies were more often major resections (3 or more segments) (76% *vs* 10% for first hepatectomies) ($P<0.001$). Consequently, vascular occlusion was used more frequently than during the first procedure (88% *vs* 46%) ($P<0.001$). The number of transfused blood units was also higher than during the first resection (mean: 2.2 *vs* 0.8 units) ($P=0.02$), and the operation time was longer (mean: 368 *vs* 313 minutes) ($P=0.01$). Finally, hospital stay was also longer after the second hepatectomy (mean: 19.0 *vs* 11.4 days) ($P=0.01$).

Surgical complications and mortality

More complications occurred after the second hepatectomy, both complications located distant from the field of liver surgery (general complications) (29% *vs* 7% after the first hepatectomy) ($P=0.01$), and complications located on the field of liver surgery (hepatic complications) (51% *vs* 15%, respectively) ($P=0.01$) *(Table 2)*. According to the recently reported classification of surgical complications by Clavien and coworkers,[21] general complications after the first hepatec-

tomy consisted of grade I (33%) or II (67%) complications only, while after the second hepatectomy, 33% of these complications were grade III events. Similarly, 17% of hepatic complications were classified as grade III after the first hepatectomy, without any grade IV or V events, compared with 14% grade III, 5% grade IV and 14% grade V hepatic complications after the second resection. Both general and hepatic complications occurred in 2% and 22% of patients after the first and second hepatectomy, respectively (*P*=0.01). Relaparotomy was necessary after the first hepatectomy in one patient for local hepatic hemorrhage (2%), and after the second hepatectomy in two patients (5%), one for small bowel occlusion and one for a biliary leak.

Table 2. Comparison of operative data between the first and second hepatectomy (N=41).

	First hepatectomy	Second hepatectomy	*P*
Hepatectomy			
Major hepatectomy (≥ 3 segments)	4 (10%)	31 (76%)	< 0.001
Type of resection			
Anatomical	7 (17%)	17 (42%)	< 0.001
Nonanatomical	26 (63%)	6 (15%)	
Both	8 (20%)	18 (44%)	
Vascular occlusion			
None	22 (54%)	5 (12%)	< 0.001
Total pedicular	18 (44%)	28 (68%)	
Vascular exclusion	0 (0%)	2 (5%)	
Selective	1 (2%)	6 (15%)	
Combined local treatment			
None	39 (95%)	36 (88%)	0.41
RFA	0 (0%)	1 (2%)	
Cryotherapy	2 (5%)	4 (10%)	
Mean red blood cell transfusions ± SD, units	0.8 ± 1.8	2.2 ± 3.3	0.02
Mean duration ± SD, minutes	313 ± 100	368 ± 98	0.01
Postoperative outcome			
Postoperative morbidity	8 (20%)	24 (59%)	< 0.001
General complications[a]	3 (7%)	12 (29%)	0.01
Hepatic complications			
None	35 (85%)	20 (49%)	0.01
Biliary leak	0 (0%)	5 (12%)	
Hemorrhage	1 (2%)	0 (0%)	
Infected collection	0 (0%)	1 (2%)	
Noninfected collection	2 (5%)	5 (12%)	
Liver insufficiency	2 (5%)	9 (22%)	
Combination	1 (2%)	1 (2%)	
Relaparotomy	1 (2%)	2 (5%)	0.56
Percutaneous drainage	1 (2%)	9 (22%)	0.01
Mean hospital stay ± SD, days	11.4 ± 4.0	19.0 ± 16.5	0.01

a: as general complications were considered: pulmonary, cardiovascular, urinary tract, infectious (other than local hepatic) and iatrogenic complications. Abbreviations: RFA = radiofrequency ablation; SD = standard deviation.

Three patients (7%) died within 2 months after the second hepatectomy. These patients succumbed of progressive liver failure and died 24, 53 and 60 days after major resections. All three patients received prolonged systemic chemotherapy for a mean number of 11 and 5 cycles before the first and second hepatectomy, respectively.

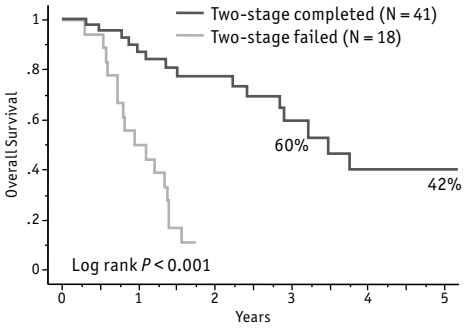
Outcome

After a median follow-up of 24.4 months (range: 3.7 to 130.3 months) (mean follow-up: 30.5 months for the total group and 35.0 months for surviving patients), disease recurrence was diagnosed in 20 patients (49%). This involved isolated hepatic or extrahepatic sites in 5 (12%) and 3 (7%) patients. Combined intra- and extrahepatic recurrences occurred in 12 patients (29%). Overall, recurrences could be resected in 13 patients (32%). A third hepatectomy was performed in 9 patients (22%), 2 of whom also had a fourth hepatectomy. Three of these patients also underwent resection of extrahepatic recurrence. In 4 patients (10%), only extrahepatic recurrent disease was resected. Extrahepatic disease was resected once in 4 patients (10%), twice in 2 patients (5%) and four times in one patient (2%). At last follow-up, 26 patients are alive (63%), of whom 11 (27%) are disease-free. Fifteen patients (37%) have died of disease progression. Overall, the 41 patients who completed the total two-stage procedure underwent 93 hepatectomies, 15 extrahepatic resections, and 39 adjuvant surgical techniques, totalizing 147 procedures (3.6 procedures per patient).

Overall and disease-free survival

On an intention-to-treat basis, 5-year survival was 31%. Three- and 5-year overall survivals for patients who completed both hepatectomies were 60% and 42%, respectively, after the first hepatectomy *(Figure 2)*. Median survivals were 42 and 39 months after the first and the second hepatectomy, respectively, and 57 months from metastases diagnosis. Disease-free survivals were 26% and 13% at 3 and 5 years after the first hepatectomy. Overall survival was significantly higher as compared with the 18 patients who did not complete the two-stage strategy (P<0.001) *(Figure 2)*. Median survival was 11.4 months for these failed patients. Sixteen of the 18 patients have died after a median duration of 10.6 months (range: 3.6 to 18.8 months) after hepatectomy.

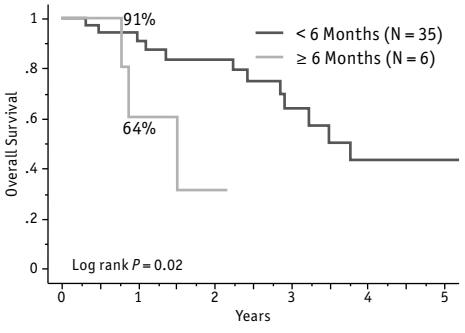
Interestingly, overall survival of patients who completed the two-stage procedure was increased in case of a time interval of less than 6 months between the two hepatic resections *(Figure 3)*. Overall and disease-free survivals of the 41 successfully treated patients were not different compared with those of all other patients with CLM who underwent a single hepatectomy in the same study period (N=758) *(Figure 4 & 5)*.



Patients at risk	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
Two-stage completed	41	29	21	11	6	4
Two-stage failed	18	9	-	-	-	-

Figure 2.

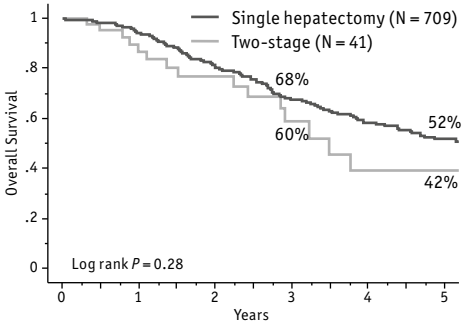
Kaplan-Meier overall survival curves after the first hepatectomy of patients who failed and completed two-stage hepatectomy.



Patients at risk	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
< 6 Months	35	26	20	11	6	4
≥ 6 Months	6	3	1	-	-	-

Figure 3.

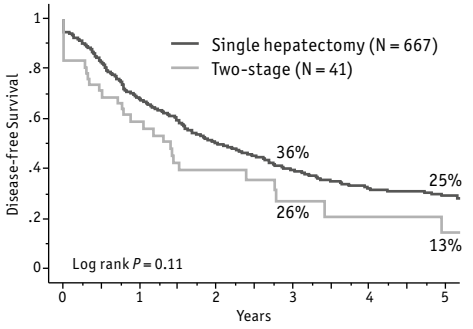
Kaplan-Meier overall survival curves after the first hepatectomy of patients who completed two-stage hepatectomy related to the time interval between the two hepatic resections.



Patients at risk	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
Single hepatectomy	709	549	366	252	176	120
Two-stage	41	29	21	11	6	4

Figure 4.

Kaplan-Meier overall survival curves after the first hepatectomy of patients who completed two-stage hepatectomy and patients who underwent a single hepatectomy in the same study period (October 1992-January 2007).



Patients at risk	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
Single hepatectomy	667	379	239	159	112	84
Two-stage	41	21	12	5	3	2

Figure 5.
Kaplan-Meier disease-free survival curves after the first hepatectomy of patients who completed two-stage hepatectomy and patients who underwent a single hepatectomy in the same study period (October 1992-January 2007).

Prognostic factors of survival

Six factors were related to decreased overall survival at univariate analysis ($P \leq 0.10$): 6 or more metastases at diagnosis, concomitant extrahepatic disease, 2 or more chemotherapy lines before the first hepatectomy, the absence of chemotherapy after the second hepatectomy, a time interval of 6 or more months between the two hepatic resections, and the absence of repeat hepatectomy after the second operation *(Table 3)*. Independent association with decreased overall survival was demonstrated at multivariate analysis for only 3 factors: 6 or more metastases at diagnosis, concomitant extrahepatic disease, and the absence of chemotherapy after the second hepatectomy *(Table 3)*.

Illustrative case-report

A 51-year-old male patient presented with 5 bilobar liver metastases 20 months after resection of a rectal adenocarcinoma (T3N0). The disease was stabilized after 11 cycles of chronomodulated chemotherapy with 5-FU, LV, and oxaliplatin. Owing to the distribution of the tumors within the liver, a right hepatectomy and left lobectomy were considered necessary to completely clear the liver from metastases *(Figure 6A)*. This patient was therefore planned for two-stage hepatectomy and underwent a left lobectomy with right portal vein embolization during the first operation. Pathological examination revealed 3 metastases with a maximum diameter of 12 mm. Postoperative liver regeneration resulted in a marked hypertrophy of segments I and IV *(Figure 6B)*. No chemotherapy was administered before the second operation, which consisted of a right hepatectomy for 4 remnant metastases (maximum diameter: 55 mm). Postoperatively, only segments I and IV remained *(Figure 6C)*.

Table 3. Univariate and multivariate analysis of overall survival in patients who completed two-stage hepatectomy.

		Survival				
Variable	**N**	**3 Yrs (%)**	**5 Yrs (%)**	**UV *P***	**MV *P***	**HR (95% CI)**
All patients	41	60	42	-	-	-
Patients						
Gender						
Male	22	52	37	0.59	-	-
Female	19	67	46			
Age at first hepatectomy						
< 60 years	23	68	44	0.27	-	-
≥ 60 years	18	47	47			
Primary tumor						
Localization						
Colon	33	63	42	0.64	-	-
Rectum	8	52	52			
T stage						
1/2	6	100	-	0.30	-	-
3/4	18	67	52			
N stage						
0	5	50	-	0.89	-	-
1/2	18	77	61			
Liver metastases						
Timing						
Synchronous	33	59	39	0.98	-	-
Metachronous	8	71	71			
Number[a]						
< 6	11	88	56	0.09	0.01	18.4 (2.1-161.3)
≥ 6	27	44	35			
Maximum size						
< 30 mm	7	100	50	0.39	-	-
≥ 30 mm	31	52	37			
CEA level						
< 40 ng/mL	12	58	58	0.27	-	-
≥ 40 ng/mL	18	54	30			
Concomitant extrahepatic disease[a]						
No	34	69	54	0.01	0.02	5.3 (1.3-21.0)
Yes	7	21	0			
Chemotherapy before first hepatectomy						
No	2	50	-	0.28	-	-
Yes	39	60	42			
Number of lines[a]						
< 2	21	74	65	0.02	NS	-
≥ 2	17	33	0			
Number of cycles						
< 12	21	71	59	0.16	-	-
≥ 12	16	46	23			
Clinical response						
Complete/Partial	26	51	42	0.49	-	-
Stabilization	13	81	45			
Chemotherapy before second hepatectomy						
No	9	67	45	0.63	-	-
Yes	32	58	41			

Variable	N	Survival 3 Yrs (%)	Survival 5 Yrs (%)	UV *P*	MV *P*	HR (95% CI)
Number of cycles						
< 6	24	55	33	0.54	-	-
≥ 6	4	75	75			
Chemotherapy after second hepatectomy[a]						
No	9	42	0	0.002	0.001	12.8 (2.9-56.0)
Yes	32	66	57			
Hepatectomy						
Time between first and second operation[a]						
< 6 months	35	64	45	0.02	NS	-
≥ 6 months	6	38	-			
Strategy						
Left first	32	56	33	0.13	-	-
Right first	9	73	59			
Repeat hepatectomy after second operation[a]						
No	32	50	25	0.02	NS	-
Yes	9	86	71			

a: variables entered in Cox regression model. Abbreviations: UV = univariate; MV = multivariate; HR = hazard ratio; CI = confidence interval; CEA = carcinoembryonic antigen; NS = not significant.

Although the patient received 8 cycles of chronotherapy after the second resection, a single lung metastasis was diagnosed 8 months later, which was successfully resected after 3 cycles of 5-FU, LV, and irinotecan. A partial (third) hepatectomy of segment IV for a hepatic recurrence was performed 5 months after the pulmonary resection. Unfortunately, the patient recurred for a third time with both hepatic and pulmonary metastases. At last follow-up, 4.8 years after the first hepatectomy, the patient is alive with recurrence, which is controlled by chemotherapy.

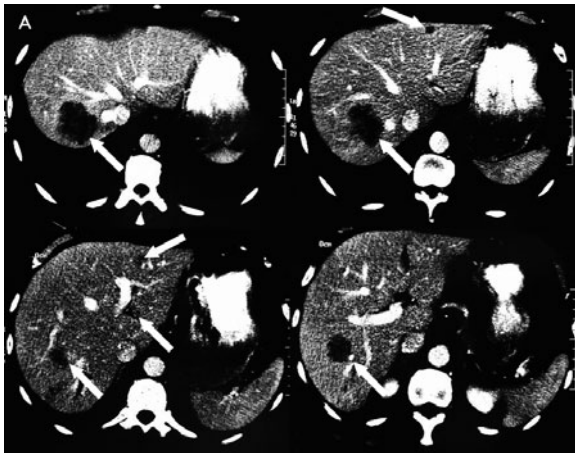
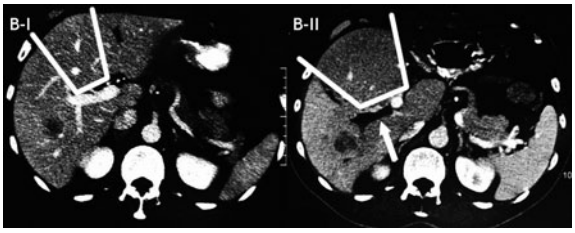
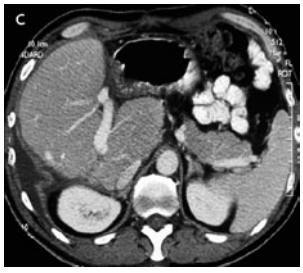


Figure 6.
A: multiple bilobar liver metastases (arrows) requiring both a right hepatectomy and a left lobectomy.



B: computed tomography scans before (B-I) and after (B-II) left lobectomy and right portal vein embolization illustrating right liver atrophy and compensatory hypertrophy of segments I and IV. Note the absence of blood flow in the right portal vein (arrow) after embolization.



C: only segments I and IV remain after the second operation (right hepatectomy).

Discussion

In recent years, potentially curative treatment strategies have emerged for patients with irresectable liver metastases that combine systemic chemotherapy, surgery, local ablation and portal embolization.[7-16] However, for a proportion of patients with widespread bilobar distribution of the disease, a single curative hepatectomy may still remain impossible due to a too small remnant liver. In the present series, we present the long-term results of two-stage hepatectomy, a multidisciplinary treatment strategy increasingly proposed for patients with extensive bilobar metastases. To our knowledge, these results constitute the largest available single center experience to date.

For patients who completed the two-stage approach, 3- and 5-year survivals of 60% and 42% were reached, allowing 27% of patients to be alive without disease at last follow-up. Two important aspects have to be noticed in relation to this result. First of all, it is only in case of successful completion of this strategy that long-term survival can be achieved. When no second curative resection can be performed and a proportion of metastases remains *in situ*, survival rates are poor and similar to those reported for nonresected patients.[22,23] This is not surprising because our patients selected for two-stage hepatectomy had extensive multinodular disease, reflected by a mean number of 9 metastases with a maximum size of 50 mm. The second important aspect concerns the fact that we demonstrated a comparable survival between patients who completed two-stage hepatectomy and patients who underwent a single curative hepatectomy during the same time period. Because of the extent of the disease, lower survival would be expected for the two-stage patients. However, our results confirm that this strategy has the potential to offer a similar survival benefit for patients with advanced bilobar disease.

Of all patients selected for two-stage hepatectomy, only 69% could complete the total strategy in this series. In the literature, success rates between 70% and 100% have been reported with 3-year survivals between 33% and 86%, and selection of patients most suitable for this approach is therefore still a critical question.[24-28] In our series, we reserved two-stage hepatectomy only for patients with more than 3 metastases and a maximum tumor size larger than 3 cm in the future remnant liver.[29] These criteria are based on the fact that local treatment is not indicated for more than 3 lesions of more than 3 cm owing to the risk of treatment failure and related local recurrence.[30-32] Patients with 3 or less metastases of 3 cm or less in the less-involved hemiliver are usually offered a single hepatectomy, with local ablation of otherwise irresectable deeply located remnant lesions. Other authors have, however, been less stringent in patient selection for two-stage hepatectomy and only used an expected insufficient remnant liver volume after single hepatectomy (without PVE) as criterion for

patient inclusion, irrespective of the number and size of metastases of the future liver remnant.[24]

Selection of patients by preoperative chemotherapy also appears crucial for success rate and patient outcome. Compared with patients who completed the total strategy, failed patients more often received multiple lines of chemotherapy before hepatectomy. This was the reflection of an aggressive tumor biology, difficult to control by chemotherapy. Furthermore, according to the well known poor prognosis related to disease progression before hepatic resection, at least tumor stabilization must be recommended to achieve a two-stage approach.[18]

The role of chemotherapy between the two hepatectomies and its effect on survival and perioperative morbidity is still under scrutiny. The rationale to continue chemotherapy after the first hepatectomy relies on the evidence that growth factors that induce hypertrophy of parenchymal cells after liver resection and portal embolization also have the potential to stimulate tumor cells.[33-35] Since chemotherapy may inhibit the proliferation of both normal and tumor cells,[36,37] we have chosen to delay it for 3 to 4 weeks after the first resection to allow maximal liver regeneration,[38] while minimizing the risk of tumor progression. However, recent data suggest that chemotherapy has no impact on liver proliferation after PVE,[39] and therefore the real value of a chemotherapy-free interval is yet to be defined. The decreased survival of patients with a time interval exceeding 6 months between the two hepatectomies reflects more difficult control of the tumor by chemotherapy. This result would promote the upfront use of highly effective regimens. Accordingly, the duration of chemotherapy treatment will be shorter, hereby lowering the risks of hepatic toxicity and related perioperative morbidity.

In terms of risks of the procedure, we observed a postoperative mortality rate of 7% due to three surgical deaths within 60 days after the second hepatectomy. All cases were related to progressive liver failure. Mortality in these patients relied most probably on the severity of the disease in combination with an aggressive management consisting of prolonged chemotherapy, extensive liver surgery, and adjuvant procedures. Together with a high morbidity rate, these results reflect the heaviness of this strategy in patients with highly advanced tumors.

Concerning the first site of the liver to be treated, our preferred strategy for two-stage hepatectomy now is to start with clearance of the left liver of its metastases, with or without local ablation, and simultaneous embolization of the right portal vein. After sufficient regeneration of the remnant left lobe, a major right hepatectomy is performed to complete the resection of all metastases.[24] A limited first resection facilitates the dissection at the second hepatectomy, as massive adhesions to the cut section of the liver are avoided. In addition, as the

first stage of this approach is often a minor hepatectomy, it could be safely combined to the resection of the primary tumor. Furthermore, clearance of the future remnant liver during the first stage seems logical in relation to the risk of tumor proliferation caused by high levels of growth factors involved in liver regeneration. Of course, the distribution of metastases is different in each patient. In practice, we advise not to leave metastases in the future remnant liver at the first operation. Also, dissection and mobilization of the hemiliver to be resected at the second stage should be avoided.

The presence of 6 or more metastases and extrahepatic disease at initial diagnosis were found to be independent predictors of poor survival in successfully treated patients. A high number of metastases is generally considered as a well known poor prognostic factor for patients with CLM.[1,7] In contrast to the presence of pulmonary metastases, intra-abdominal extrahepatic metastases were previously associated with a decreased risk to complete a two-stage strategy.[24] Together with our results (no 5-year survivors in case of extrahepatic disease), the indication of two-stage hepatectomy for patients with extensive extrahepatic metastases could be questionned and preoperative evaluation with PET-CT or staging laparoscopy should be encouraged. Interestingly, adjuvant chemotherapy after the second hepatectomy also emerged as independent prognostic factor of survival in this study, which justifies its standard use in patients who present with highly advanced disease.

Taken together, the increasingly used technique of two-stage hepatectomy can be considered as an established potentially curative treatment option in selected patients with extensive bilobar CLM. As part of a multidisciplinary approach, this strategy can achieve long-term outcome in up to 70% of cases with a 5-year survival of 42%, which is not different from patients who undergo a single curative hepatectomy. Mortality and morbidity rates are, however, increased in these aggressively treated patients. Nevertheless, this approach offers the only chance of remission in patients otherwise promised to a very poor prognosis.

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Chapter 5

Short- and long-term results of extended left hepatectomy for colorectal metastases

Submitted

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ABSTRACT

Background

Extended left hepatectomies involve complex resections for centrally located tumors. Operative outcomes of this resection for colorectal liver metastases (CLM) remain unclear owing to the inclusion of mixed tumor etiologies in previous series.

Methods

We analyzed short- and long-term outcome following extended left hepatectomy for CLM in a large single center cohort. Consecutive patients who underwent extended left hepatectomy between January 1990 and January 2006 were included. The impact of caudate lobectomy on postoperative morbidity and survival was also assessed.

Results

From a consecutive series of 802 resected patients, 31 patients who underwent extended left hepatectomy were included. Maximum tumor size at diagnosis was more than 60 mm in the majority of patients (54%). Twenty-six patients (84%) presented with initially unresectable metastases, mainly related to large tumor size (42%) or close relation with major vascular structures (23%). Preoperative chemotherapy was administered to 29 patients (94%). Combined vascular resection was performed in 5 patients (16%). Mortality rate at 90 days was zero with a morbidity rate of 55%. Three- and five-year overall survival were 38% and 27%. Morbidity did not differ between patients with and without caudate lobectomy (53% *vs* 57%, respectively) (P=0.82). Three- and five-year overall survival rates were 45% and 26% for patients with caudate lobectomy versus 29% and 29% in the control group (P=0.90).

Conclusions

Extended left hepatectomy for CLM can be performed with acceptable morbidity and significant long-term survival. Caudate lobectomy does not impact surgical outcome.

INTRODUCTION

In current liver surgery, resections up to 70% of functional liver volume have been shown to be safe without the risk of postoperative liver failure.[1] The most important indication for major hepatectomies is the presence of extensive intrahepatic tumor, either caused by multinodular disease or large tumor size. Extended left hepatectomies are, however, not comparable to any other liver resection due to their technical complexity related to a large resection surface, central liver dissection and resection of the caudate lobe. Nevertheless, patients with centrally located metastases with close contact to major vascular or biliary structures often require extended left hepatectomies to achieve complete tumor clearance with an increased risk of microscopically incomplete tumor resection.

Recently, we have shown that major liver resections combined with vascular resection and reconstruction can safely be performed in selected patients.[2] However, extended left hepatectomies are still suggested to have higher morbidity and mortality rates compared to other resections due to the complexity of the procedure.[3-5] Yet, the inclusion of mixed patient groups in all previous series interferes with an objective analysis of surgical morbidity following extended left hepatectomy in patients with colorectal liver metastases (CLM).[3,6-8] Different diseases with various underlying conditions, such as cirrhosis in patients with hepatocellular carcinoma or jaundice in patients with Klatskin tumors, all relate with surgical outcome.[9] Critical analysis of associated risks and results of this challenging procedure is however crucial when offering it to patients as a potentially curative treatment.

The objective of our study was to assess short-term outcome of patients with CLM following extended left hepatectomy in a large single center cohort. We furthermore determined the impact of caudate lobectomy on postoperative morbidity. Additionally, long-term survival was evaluated.

PATIENTS AND METHODS

All consecutive patients who underwent extended left hepatectomy for CLM between January 1990 and January 2006 were included. Patients were selected from a prospectively maintained hepatobiliary database. Extended hepatectomies were defined as resections exceeding the boundaries of a standard left hepatectomy (segments II-IV).[10,11] Extended left hepatectomies therefore included segments II-IV with segment I, with segments V and VIII or with segments I, V and VIII.

Preoperative chemotherapy

Systemic chemotherapy was administered to patients with technically unresectable liver metastases due to multinodularity, large tumor size, or a close relation to major vascular structures. Initial unresectability was defined as the inability to completely resect all liver metastases while leaving at least 30% to 40% of functional liver volume. Preoperative chemotherapy was furthermore routinely indicated for patients with concomitant extrahepatic disease (oncological unresectability). Chemotherapy was also increasingly administered to patients with upfront resectable metastases to assess tumor chemoresponsiveness and to facilitate margin-negative resections.

Response to chemotherapy was assessed by computed tomography (CT) and/or magnetic resonance imaging in a multidisciplinary meeting with surgeons, oncologists and radiologists every 4 cycles of treatment. Surgery was considered only when complete resection of intra- and extrahepatic metastases could be achieved.

Hepatectomy

During surgery, the abdominal cavity was searched for extrahepatic metastases and every suspicious lesion was examined by frozen section. Intraoperative ultrasound of the liver was used in all patients to confirm the number and size of metastases, to define their relation with intrahepatic vascular structures, and to search for occult lesions. Liver resections were performed with the objective of radical resection, either achieved by single or multiple procedures. When tumor-free margins could not be obtained, owing to vascular proximity or multinodularity, resection was still performed provided that it was macroscopically complete. Prophylactic abdominal drains were placed in all patients following hepatectomy.

Portal vein embolization (PVE) and two-stage hepatectomy procedures were used accordingly for patients with estimated resections of more than 60% to 70% of liver parenchyma (based on preoperative CT volumetrics) or with multiple metastases unable to be resected by a single hepatectomy.[12,13] PVE was performed preoperatively by a percutaneous or ileocolic technique decided by the

treating surgeon.[14,15] In selected patients, portal vein embolization and ligation was performed intraoperatively during resection of the primary tumor or the first step of a two-stage hepatectomy approach.[13] Local ablative techniques (RFA or cryotherapy) were only used in combination to resection for three or less, otherwise unresectable metastases up to 3 cm in diameter in the future remnant liver. Vascular reconstruction was considered in cases with tumoral encasement of major vascular structures. For these resections, total vascular exclusion of the liver with or without venovenous bypass was generally used.[2,16-18]

All postoperative complications occurring within two months after surgery were recorded and graded according to the Dindo-Clavien classification.[19] An increase in serum bilirubin level to more than 50 µmol/L and a decrease in prothrombin time to less than 50% on postoperative day 5 were used to define liver insufficiency.[20] Postoperative mortality was assessed at 90 days.

Follow-up

Regular postoperative follow-up started at one month from hepatectomy, and then every 4 months, consisting of routine blood tests, serum tumor markers evaluation (CEA and CA19.9), and hepatic ultrasound. Thoracoabdominal CT imaging was performed every 8 months. Our general policy was to continue postoperative chemotherapy for 6 to 8 cycles to reduce the risk of recurrence. Resection of intra- or extrahepatic disease recurrence was performed only when it could be globally curative and was generally preceeded by chemotherapy to control the disease process.[21]

Statistical analysis

The X^2 test was used to compare categorical data (number of patients with percentages) and continuous data (means ± standard deviation) were compared using the independent-samples *T* test. Survival curves were generated by the Kaplan-Meier method and compared by the log-rank test. Statistical significance was defined as $P \leq 0.05$. All statistical analyses were performed with SPSS® version 13.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Between January 1990 and January 2006, a consecutive series of 802 patients underwent partial hepatectomy for CLM with curative intent. Major hepatectomies (3 or more segments) were performed in 364 patients (45%). Thirty-one patients (9%) underwent extended left hepatectomies and were included in this study *(Figure 1)*.

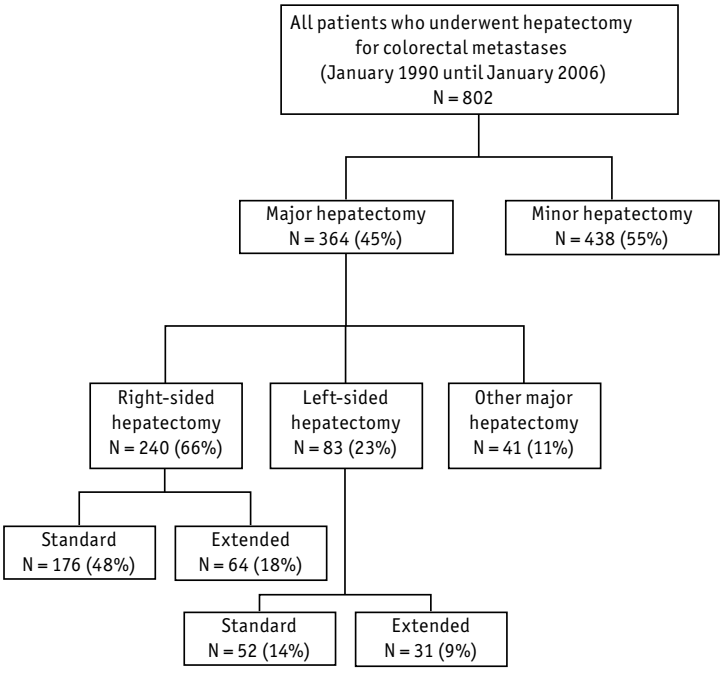


Figure 1.
Flowchart of patient selection. Standard right hepatectomies include segments V-VIII, and extended right hepatectomies include segments V-VIII with segment IV, segment I, or both. Standard left hepatectomies include segments II-IV, and extended left hepatectomies include segments II-IV with segment I, segments V and VIII or segments I, V and VIII.

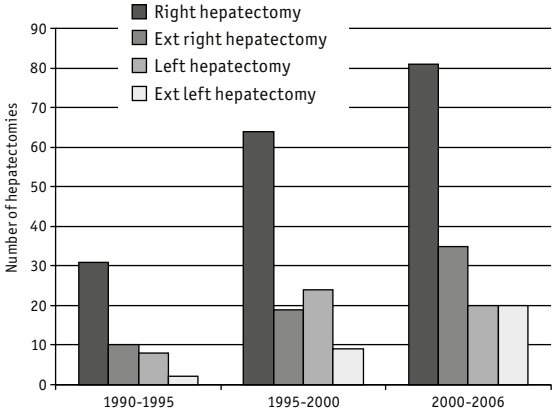


Figure 2.
Evolution of major left- and right-sided hepatectomies within time (*P*=0.23).

The majority of extended left hepatectomies was performed in most recent years *(Figure 2)*. For example, 65% of extended left hepatectomies was done within the last six years of the present 16-year study (2000 to 2006) (P=0.23).

Patient and tumor characteristics

Patients who underwent extended left hepatectomy had a median age of 59 years (range: 42 to 79 years). Liver metastases were synchronous to the primary tumor in the majority of patients *(Table 1)*. The median number of metastases was 3 (range: 1 to 20) with a median maximum diameter of 68 mm (range: 20 to 160

Table 1. Patient, tumor and chemotherapy characteristics.

	Extended left hepatectomy (N = 31)
Patients	
Mean age ± SD, years	58.9 ± 8.7
Male/Female	17 (55%) / 14 (45%)
Primary tumor	
Colon/Rectum	25 (81%) / 6 (19%)
T stage	
1/2	1 (5%)
3/4	21 (96%)
N stage	
0	8 (35%)
1/2	15 (65%)
Liver metastases	
Synchronous[a]	18 (58%)
Mean number ± SD	3.8 ± 3.8
≤ 3	15 (54%)
> 3	13 (46%)
Mean maximum size ± SD, mm	76.5 ± 43.6
Bilobar	26 (84%)
Initially unresectable	26 (84%)
Cause of initial unresectability	
Multinodularity	8 (31%)
Large size	11 (42%)
Close vascular relation	6 (23%)
Extrahepatic disease	1 (4%)
Concomitant extrahepatic disease	5 (16%)
Resection	3 (60%)
Preoperative chemotherapy	29 (94%)
Number of lines	
1	21 (72%)
> 1	8 (28%)
Mean number of cycles ± SD	10.7 ± 6.6
Last line regimen	
5-FU/LV	1 (3%)
5-FU/LV Oxaliplatin	19 (66%)
5-FU/LV Irinotecan	5 (17%)
Other	4 (14%)
Clinical response	
Complete/Partial	19 (66%)
Stabilization/Progression	10 (35%)

a: synchronous metastases were diagnosed before or within 3 months after resection of the primary colorectal tumor.
Abbreviations: SD = standard deviation; 5-FU = 5-fluorouracil; LV = leucovorin.

mm). In more than half of patients (54%), maximum tumor size was more than 60 mm at diagnosis. Consequently, large tumor size was the most frequent cause of initial unresectability in this patient group (42%), followed by a close vascular localization of metastases (23%).

Preoperative chemotherapy

Preoperative chemotherapy was administered to all but two patients (94%) *(Table 1)*. Most patients received 5-fluorouracil and leucovorin combined to oxaliplatin. Chemotherapy was administered as conversion therapy for initially unresectable metastases in 26 of 31 patients (84%). The median number of chemotherapy cycles was 8 (range: 3 to 27 cycles).

Liver surgery

PVE was performed before hepatectomy in 6 patients (19%). Extended left hepatectomy constituted the second step of a two-step hepatectomy approach in only one patient *(Table 2)*. The majority of patients (97%) required vascular occlusion to reduce intraoperative blood loss. For this purpose, intermittent pedicular clamping was most frequently used. Vascular resection and reconstruction were performed in 5 patients (16%). Fifteen patients (52%) received intraoperative red blood cell transfusions.

Short- and long-term outcome

Half of patients (55%) experienced postoperative morbidity *(Table 2)*. Noninfected collections were the most frequently observed complication located near the field of liver surgery. Postoperative liver failure occurred only in two patients. Postoperative mortality at 90 days was nil.

R0 (margin-free) and R1 resections occurred in 61% and 39% of patients in the extended left hepatectomy group. Recurrences were diagnosed in 26 patients (87%) after a median follow-up of 27.4 months (mean: 30.5 ± 20.9 months). Mean time to first recurrence was 13.1 ± 10.3 months. Intrahepatic recurrences occurred in 15 patients (68%), which were combined to extrahepatic recurrences in 7 of them. Three patients (10%) underwent a second liver resection. Localized extrahepatic disease recurrence was resected once in 5 patients, twice in one patient and three times in another patient.

Three- and 5-year overall survivals were 38% and 27%. Disease-free survivals at 3 and 5 years were 9% and 4% *(Figure 3)*.

Caudate lobectomy

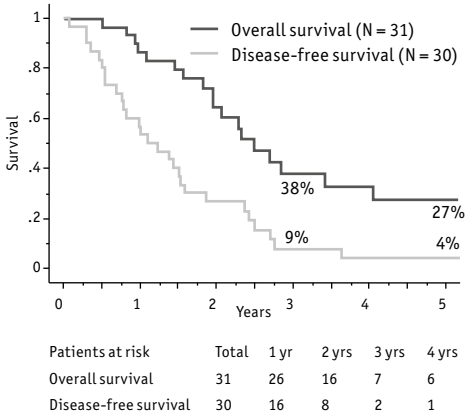
Of all patients who underwent extended left hepatectomy, 17 (55%) also had resection of the caudate lobe (segment I). Patient groups with and without

Table 2. Data concerning liver resection and short-term outcome.

	Extended left hepatectomy (N = 31)
Hepatectomy	
Mean number of detected metastases ± SD	4.1 ± 3.5
1	6 (21%)
2 - 3	12 (41%)
> 3	11 (38%)
Resection type	
Anatomical	13 (42%)
Anatomical and nonanatomical	18 (58%)
Vascular occlusion	29 (97%)
Pedicular clamping	19 (66%)
Vascular exclusion	9 (31%)
Selective	1 (3%)
Vascular resection and reconstruction	5 (16%)
Portal vein	2 (40%)
Inferior vena cava	1 (20%)
Hepatic vein	2 (40%)
Combined local treatment	
None	28 (90%)
RFA	2 (7%)
Cryotherapy	1 (3%)
Two-stage resection	1 (3%)
Portal vein embolization	6 (19%)
Mean red blood cell transfusions ± SD, units	3.3 ± 5.9
Postoperative outcome	
Mortality (within 90 days)	0 (0%)
Morbidity	17 (55%)
General complications[a]	7 (23%)
Hepatic complications	13 (42%)
Biliary leak	2 (15%)
Hemorrhage	0 (0%)
Infected collection	3 (23%)
Noninfected collection	6 (46%)
Liver insufficiency[20]	2 (15%)
Dindo-Clavien classification[19]	
Grade I/II	5 (42%)
Grade III/IV	7 (58%)
Relaparotomy	2 (7%)
Percutaneous drainage	7 (23%)
Mean hospital stay ± SD, days	14.8 ± 6.0
Postoperative chemotherapy	27 (87%)

a: as general complications were considered: pulmonary, cardiovascular, urinary tract, infectious (other than local hepatic) and iatrogenic complications. Abbreviations: SD = standard deviation; RFA = radiofrequency ablation.

caudate lobectomy were similar in terms of age, sex distribution, primary tumor site and stage, and synchronicity of metastases *(Table 3)*. Maximum tumor size at diagnosis tended to be higher in patients requiring caudate lobectomy (P=0.15). Furthermore, patients in this subgroup more often had initially unresectable metastases, which was mainly related to a close relationship with major hilar structures.



Patients at risk	Total	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
Overall survival	31	26	16	7	6	4
Disease-free survival	30	16	8	2	1	1

Figure 3.
Overall- and disease-free survival curves following extended left hepatectomy for CLM.

Of all 5 patients who underwent vascular resection and reconstruction, 4 had resection of the caudate lobe (24% *vs* 7% in patients without caudate lobectomy) (*P*=0.22). Total vascular exclusion was used in 6 patients (38%) with caudate lobectomy and in 3 patients (21%) without caudate lobectomy (*P*=0.34). Intra-operative red blood cell transfusions were necessary in 63% of patients with caudate lobectomy (compared to 39% in the control group) (*P*=0.20).

Morbidity rates were 53% and 57% in patients with and without caudate lobectomy, respectively (*P*=0.82). Although R1 resections were more frequent in the caudate lobectomy group (53% *vs* 23%) (*P*=0.10), recurrences occurred in a similar proportion of patients in both groups (88% and 86% of patients with and without caudate lobectomy, respectively) (*P*=0.89). Three- and five-year overall survival rates were 45% and 26% versus 29% and 29% with and without caudate lobe involvement (*P*=0.90).

Table 3. Comparison of patient, tumor and chemotherapy characteristics between groups with and without caudate lobectomy.

	With caudate lobectomy (N = 17)	Without caudate lobectomy (N = 14)	*P*
Patients			
Mean age ± SD, years	59.2 ± 9.6	58.7 ± 7.7	0.87
Male/Female	10 (59%) / 7 (41%)	7 (50%) / 7 (50%)	0.62
Primary tumor			
Colon/Rectum	15 (88%) / 2 (12%)	10 (71%) / 4 (29%)	0.24
T stage			
1/2	1 (7%)	0 (0%)	0.44
3/4	13 (93%)	8 (100%)	
N stage			
0	5 (33%)	3 (38%)	0.84
1/2	10 (67%)	5 (63%)	
Liver metastases			
Synchronous[a]	9 (53%)	9 (64%)	0.52
Mean number ± SD	3.1 ± 2.4	4.8 ± 5.1	0.27
≤ 3	9 (56%)	6 (50%)	0.74
> 3	7 (44%)	6 (50%)	
Mean maximum size ± SD, mm	86.9 ± 50.9	62.7 ± 28.0	0.15
Bilobar	13 (77%)	13 (93%)	0.22
Initially unresectable	16 (94%)	10 (71%)	0.09
Cause of initial unresectability			
Multinodularity	5 (31%)	3 (30%)	0.39
Large size	6 (38%)	5 (50%)	
Close vascular relation	5 (31%)	1 (10%)	
Extrahepatic disease	0 (0%)	1 (10%)	
Concomitant extrahepatic disease	4 (24%)	1 (7%)	0.22
Resection	2 (50%)	1 (100%)	0.36
Preoperative chemotherapy	16 (94%)	13 (93%)	0.89
Number of lines			
1	12 (75%)	9 (69%)	0.73
> 1	4 (25%)	4 (31%)	
Mean number of cycles ± SD	9.2 ± 4.4	12.8 ± 8.5	0.17
Last line regimen			
5-FU/LV	0 (0%)	1 (8%)	0.71
5-FU/LV Oxaliplatin	11 (69%)	8 (62%)	
5-FU/LV Irinotecan	3 (19%)	2 (15%)	
Other	2 (13%)	2 (15%)	
Clinical response			
Complete/Partial	11 (65%)	8 (67%)	0.91
Stabilization/Progression	6 (35%)	4 (33%)	

a: synchronous metastases were diagnosed before or within 3 months after resection of the primary colorectal tumor.
Abbreviations: SD = standard deviation; 5-FU = 5-fluorouracil; LV = leucovorin.

Discussion

Owing to the significant development of surgical techniques as well as the extended indications for partial hepatectomy in patients with CLM, major hepatectomies are now increasingly performed. Extended left hepatectomies, however, represent a specific category of liver surgery owing to the technical difficulty related to the dissection of hilar structures as well as resection of the caudate lobe. Until now, specific analysis of short-term outcome of this procedure in a sufficient cohort of patients with CLM was lacking.[3,4,7,8]

The main result of our study is that extended left hepatectomies for patients with CLM can be performed with acceptable morbidity. Furthermore, postoperative mortality was nil and long-term survival could be achived in a significant proportion of patients. Three-year survival could be achieved in 38% of patients, not so different from general survival rates reported in the literature.[22-24]

Previous reports describing extended left hepatic resections all included mixed populations of patients with cholangiocarcinomas (including patients with jaundice), hepatocellular carcinomas (usually in cirrhotic patients) and colorectal metastases. Owing to the inclusion of small patient numbers, information on morbidity and mortality rates for patients with CLM is absent or very limited.[3,4,7,8] The present study, to our knowledge, is the first to specifically address short-term outcome of extended left hepatectomy in a homogeneous group of patients with CLM only.

Patients usually had central, large metastases in close relation with major hilar structures, reflecting the technical complexity of this procedure. Resection of centrally located metastases in close proximity with main vascular structures often needs vascular resection and reconstruction with total vascular exclusion to control intraoperative blood loss. Herefore, operative characteristics of extended left liver resections generally differ from those of major right-sided resections. In a natural way, colorectal liver metastases are most frequently located in the right lobe, owing to anatomical differences in weight and portal venous inflow of both hemilivers.[25,26] This natural distribution of metastases results in a tumor presentation which is more often multinodular in patients selected for right hepatectomy. Right-sided resections usually include more liver segments, and additional strategies like PVE and two-stage approaches are more frequently required to achieve complete tumor resection. Our recent report describing the results of PVE also mainly included right-sided resections.[12] On the contrary, vascular resection is much less frequently performed in extended right hepatectomies (8% of cases in our series; data not shown).

Owing to the large resection surface in case of extended left hepatectomy, biliary leakage and (non)infected collections are more likely to occur in this group. Previous papers also found that bile leakage was a frequent complication

in left hepatectomy patients because of the difficult parenchymal transection.[3,4,7] The high incidence of collections could be related to the difficulty to have a declive drainage after left-sided hepatectomy compared to right-sided ones. Patients with right hepatectomies, however, generally experience more cases of postoperative liver insufficiency due to the resection of higher liver volumes. In combination with massive preoperative chemotherapy, the risk of liver failure is known to be elevated.[27,28] Postoperative liver insufficiency, on the other hand, occurred only in two patients in our study.

The frequent central localization of metastases in left hepatectomy patients could suggest a higher risk of microscopically involved resection margins and local recurrences with decreased overall survival. Although R1 resections as well as recurrences occurred in a large proportion of patients, survival rates were favorable and not different from generally reported results.[22-24] Extended left hepatectomies should therefore not be denied when technically feasible, since it may provide similar oncological benefit and chance for cure as compared with other resections for CLM.

Liver metastases involving the caudate lobe add to the complexity of curative hepatectomy caused by its difficult anatomical localization. The caudate lobe lies in close relation with the inferior vena cava, the portal bifurcation and the confluence of the left and middle hepatic veins.[29] Its mobilization from the inferior vena cava with the ligation of its short hepatic veins during resection increases the risk of intraoperative blood loss and associated morbidity. However, due to surgical refinements, resection of the caudate lobe is increasingly performed.[30] The fact that surgical margin width is of limited influence on survival has also contributed to this development.[31,32]

In this study, patients who underwent caudate lobectomy more often presented with initially unresectable metastases due to vascular proximity. Combined vascular resection was frequently performed, but surgical morbidity was not increased compared to a control group without caudate lobectomy. Recurrences occurred in a similar proportion as in patients without caudate lobe involvement, although patients with caudate lobe resection more often presented with R1 resections. Khan et al. found similar results, confirming that patients with metastases in the caudate lobe can be offered similar short- and long-term outcomes as other patients with CLM.[30] Others suggested a decreased survival in case of caudate lobe involvement due to a early spreading of tumor cells through direct venous drainage in the vena cava.[33,34] This was, however, not confirmed in the present cohort.

In conclusion, extended left hepatectomy for CLM is technically challenging with a high risk of microscopically involved margins and tumor recurrence.

However, in a multidisciplinary setting, it can be performed with acceptable morbidity and significant long-term outcome. Due to the complexity of this procedure and the so-called volume-outcome relationship in this field, patients should be referred to specialized liver surgery centers.

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Part II

Chemotherapy-related aspects in the treatment of advanced colorectal liver metastases

Chapter 6

Regenerative nodular hyperplasia of the liver related to chemotherapy: impact on outcome of liver surgery for colorectal metastases

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ABSTRACT

Background

Regenerative nodular hyperplasia (RNH) represents the end-stage of vascular lesions of the liver induced by chemotherapy. The aim was to evaluate its incidence and impact on the outcome of patients resected for colorectal liver metastases (CLM).

Methods

Patients who underwent hepatectomy for CLM after 6 cycles or more of first-line chemotherapy, between January 1990 and November 2006, were included. Detailed histopathologic analysis of the nontumoral liver was performed according to a standard format.

Results

From a cohort of 856 resected patients at our institution, 771 (90%) received preoperative chemotherapy. Of these, 146 fulfilled the selection criteria and were included: 24 (16%) received 5-fluorouracil (5-FU) and leucovorin (LV) alone, 92 (63%) had 5-FU/LV and oxaliplatin, 18 (12%) had 5-FU/LV and irinotecan, and 12 (8%) were treated by 5-FU/LV, oxaliplatin and irinotecan. RNH occurred in 22 of 146 patients (15%). Twenty of these patients (91%) received oxaliplatin, of whom six (30%) had chronomodulated therapy. Patients treated by oxaliplatin more often had RNH compared with oxaliplatin-naïve patients (22% *vs* 4%). Although operative mortality was nil, the presence of RNH was associated with increased postoperative hepatic morbidity (50% *vs* 29%). Elevated preoperative gamma-glutamyltransferase (GGT) (more than 80 U/L;>1N) and total bilirubin levels (more than 15 µmol/L;>1N) were independent predictors of RNH.

Conclusions

Patients with CLM who receive preoperative oxaliplatin have an increased risk of RNH and associated postoperative morbidity. Increased serum GGT and bilirubin are useful markers to predict the presence of RNH.

INTRODUCTION

During recent years, the intensity of preoperative systemic chemotherapy for patients with colorectal liver metastases (CLM) has increased significantly. Patients with unresectable metastatic disease frequently receive prolonged chemotherapy treatment in an attempt to convert them to resectability. With this approach, long-term survival can be achieved when liver resection becomes feasible after tumoral downsizing.[1] In addition, neoadjuvant chemotherapy is applied for resectable liver metastases to facilitate margin-free resections, and this approach has shown recently to improve progression-free survival after hepatectomy.[2,3]

Our group and others have reported a relationship between the use of preoperative chemotherapy and histopathologic changes of the nontumoral liver with consequently an increased risk of perioperative morbidity.[3-11] This mainly concerns the prolonged use of oxaliplatin and associated vascular lesions. However, close evaluation of direct relations between specific vascular lesions and postoperative outcome remains limited *(Table 1)*.[3,6-15] Only three studies have correlated specific chemotherapy-related vascular changes in the nontumoral liver with an increased intraoperative transfusion rate or longer hospital stay.[8-10]

Table 1. Review of publications evaluating the effect of preoperative chemotherapy and hepatic chemotoxicity on short-term outcome after resection of colorectal liver metastases.

Author	Year	Number of patients[a]	Type of chemotherapy	Related histology nontumoral liver	Short-term perioperative outcome
Studies of no effect:					
Parikh[12]	2003	61	Irinotecan	Steatosis	Unaffected
Hewes[13]	2007	46	Miscellaneous[b]	None	Unaffected
Pawlik[14]	2007	153	Oxaliplatin	Sinusoidal dilatation	Unaffected
			Irinotecan	Steatosis/Steatohepatitis	Unaffected
Scoggins[15]	2009	112	Miscellaneous[c]	None	Unaffected
Studies of effect - Outcome related to chemotherapy:					
Karoui[6]	2006	45	Miscellaneous[d]	Sinusoidal dilatation	Increased morbidity
Nordlinger[3]	2008	151	Oxaliplatin	*Not analyzed*	Increased morbidity
Studies of effect - Outcome related to liver histology:					
Vauthey[7]	2006	248	Oxaliplatin	Sinusoidal dilatation	Unaffected
			Irinotecan	Steatohepatitis	Increased 90-day mortality
Aloia[8]	2006	75	Oxaliplatin	HCN/RNH	Increased transfusion rate
Mehta[9]	2007	130	Oxaliplatin	Sinusoidal dilatation	Longer hospital stay and increased transfusion rate
Nakano[10]	2008	90	Oxaliplatin	Sinusoidal injury	Longer hospital stay and increased morbidity[e]
Kandutsch[11]	2008	50	Oxaliplatin	Fibrosis	Increased transfusion rate
				Sinusoidal dilatation	Unaffected

a: treated with preoperative chemotherapy; *b*: 5-fluorouracil and leucovorin alone or combined with oxaliplatin; *c*: 5-fluorouracil with various combinations of other agents; *d*: 5-fluorouracil and leucovorin alone or combined with oxaliplatin, irinotecan or both; *e*: in patients that underwent major hepatectomy (3 or more segments). Abbreviations: HCN = hemorrhagic centrilobular necrosis; RNH = regenerative nodular hyperplasia.

Regenerative nodular hyperplasia (RNH) is considered the end-stage of vascular lesions induced by chemotherapy, but its effect on the outcome of hepatic resection for colorectal metastases remains unclear. However, with the increasing indications of preoperative chemotherapy, especially oxaliplatin, RNH is observed more frequently, necessitating an evaluation of its consequences. Furthermore, with the high incidence of recurrences observed in patients resected of CLM, repeat hepatectomies are increasingly performed.[16-18] Knowledge concerning the consequences of RNH, as well as its potential to regress, is crucial in evaluating the risks of repeat surgery with the continuing administration of chemotherapy.

In this study, we evaluated the incidence of RNH and its impact on postoperative outcome in patients resected of CLM. In addition, we assessed the evolution of RNH by analyzing the pathologic specimens of patients submitted to repeat hepatectomy.

Patients and methods

Patients

From January 1990 to November 2006, 856 consecutive patients underwent partial hepatectomy for colorectal metastases at our institute. Sevenhundred seventy-one (90%) of these patients were treated by preoperative chemotherapy, whereas 85 patients (10%) underwent hepatic resection without preoperative chemotherapy treatment. Of all 771 patients treated by preoperative chemotherapy, this study focused only on patients who received 6 or more cycles of first-line therapy. In addition, patients treated with preoperative intra-arterial chemotherapy were excluded.

Preoperative chemotherapy

Chemotherapy was most often administered before surgery for patients with initially unresectable metastases. Technical unresectability was defined as the inability to completely resect all metastases while leaving at least 30% of normal liver parenchyma, resulting from a multinodular tumor distribution, large tumor size, or a close relation with major vascular or biliary structures. The presence of extrahepatic metastases determined oncological unresectability. The rationale to administer preoperative chemotherapy to patients with upfront resectable metastases was to assess tumor chemoresponsiveness and to facilitate margin-negative resections.

Response to chemotherapy was evaluated in a multidisciplinary meeting with surgeons, oncologists and radiologists, and surgery was only performed when the overall strategy could result in complete intra- and extrahepatic tumor clearance.

Liver resection

The aim of liver surgery was to resect completely all detectable lesions. Detailed inspection, palpation, and intraoperative ultrasound of the liver were routinely performed in each patient. Local ablation, portal vein embolization, and two-stage hepatectomy were used as described before to increase the possibility of radical tumor resection.[19-21] General and local hepatic complications occuring within 2 months after surgery were recorded and classified.[22,23]

Histopathologic examination

Detailed histopathologic assessment of the nontumoral liver was performed by a single hepatobiliary pathologist, blinded for the information regarding preoperative chemotherapy and perioperative outcome. Liver tissue was analyzed according to a standard format previously described.[8] Briefly, vascular lesions were categorized as sinusoidal alterations (vasodilatation and congestion), peliosis, hemorrhagic centrilobular necrosis (HCN), RNH, and veno-occlusive disease. The

presence of macrovacuolar steatosis was graded as mild (less than 30% of hepatocytes), moderate (30% to 60%), or severe (more than 60%). Steatohepatitis included steatosis with signs of local inflammation and apoptotic hepatocytes. Fibrosis was divided into portal fibrosis, portoportal fibrosis, septal fibrosis, and cirrhosis. Surgical necrosis was also noted.

Repeat surgery

The development of recurrences was assessed by physical examination, serum CEA and CA 19.9 levels, and abdominal ultrasound at 4-month intervals after hepatectomy. CT imaging of the chest, abdomen and pelvis was performed every 8 months. Repeat resection of intra- and/or extrahepatic recurrences was only considered if it could be macroscopically complete.[17] For patients who underwent repeat liver surgery, histopathologic examination of the nontumoral liver was performed in a similar way as described above to evaluate the evolution of initial lesions.

Statistical analysis

All statistical analyses were performed using SPSS® software version 13.0 (SPSS Inc., Chicago, Illinois, USA). Categorical data were reported as the number of patients with percentages and compared by the X^2 test. For continuous data, reported as means ± standard deviation, the independent-samples *T* test was used to compare groups. Logistic regression was done to define independent predictive factors of hepatic morbidity as well as preoperative predictive factors of RNH. Herefore, factors with $P \leq 0.10$ at univariate analysis were included. *P* values ≤ 0.05 were considered significant.

RESULTS

Of all 771 consecutively resected patients treated by preoperative chemotherapy, 155 received 6 or more cycles of first-line therapy, delivered by intravenous route. Due to an insufficient amount of nontumoral liver parenchyma available for histopathologic analysis, 9 patients were excluded, resulting in a cohort of 146 patients *(Figure 1)*.

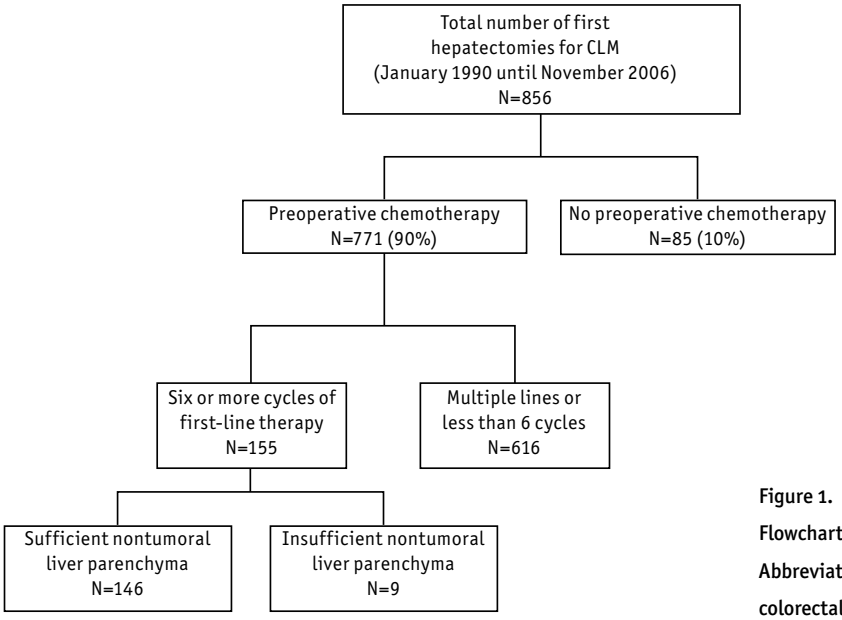

Figure 1.
Flowchart of patient selection.
Abbreviations: CLM = colorectal liver metastases.

Patient and tumor characteristics

Included patients had a median age of 61 years (range: 34 to 79 years) and 76% presented with synchronous liver metastases *(Table 2)*. Most patients (54%) had more than 3 metastases at diagnosis with a median diameter of 40 mm (range: 6 to 160 mm). Metastases were located in both liver lobes in 70% of patients and 20 patients (14%) had concomitant extrahepatic disease.

Preoperative chemotherapy

Chemotherapy was indicated for initially unresectable metastases in the majority of patients (72%). Unresectability was related to multinodular disease (59%), large tumor size (29%), close vascular relation (10%) and extrahepatic disease (3%). The remaining 28% of patients received preoperative chemotherapy for resectable disease. The median number of administered cycles for the total group

Table 2. Characteristics of 146 included patients.

	Chemotherapy group (N = 146)
Patients	
Mean age ± SD, years	59.1 ± 9.5
Male/Female	85 (58%) / 61 (42%)
Mean body mass index ± SD, kg/m^2	24.1 ± 3.6
Diabetes mellitus	8 (6%)
Primary tumor	
Colon/Rectum	114 (79%) / 31 (21%)
T stage	
1/2	19 (17%)
3/4	92 (83%)
N stage	
0	43 (38%)
1/2	70 (62%)
Liver metastases diagnosis	
Synchronous[a]	111 (76%)
Number	
≤ 3	62 (46%)
> 3	73 (54%)
Mean maximum size ± SD, mm	45.2 ± 28.6
Bilobar	102 (70%)
Mean CEA ± SD, ng/mL	293.2 ± 643.1
Concomitant extrahepatic disease	20 (14%)
Resection	11 (58%)
Hepatectomy	
Major resection (≥ 3 segments)	73 (50%)
Resection type	
Anatomical	47 (32%)
Nonanatomical	34 (23%)
Both	65 (45%)
Vascular occlusion	
No	21 (15%)
Total pedicular	73 (54%)
Vascular exclusion	20 (15%)
Selective	22 (16%)
Combined local ablation	
No	129 (88%)
RFA	10 (7%)
Cryotherapy	7 (5%)
Portal vein embolization	18 (12%)
Two-stage hepatectomy	10 (7%)
Red blood cell transfusions	
No	78 (59%)
Yes	54 (41%)

Continuation of table 2.

	Chemotherapy group (N = 146)
Postoperative outcome	
Mortality (within 60 days)	1 (1%)
Morbidity	63 (43%)
General complications[b]	43 (30%)
Hepatic complications	47 (32%)
Biliary leak	3 (6%)
Hemorrhage	2 (4%)
Infected collection	5 (11%)
Noninfected collection	21 (45%)
Liver insufficiency[23]	8 (17%)
Combination	8 (17%)
Relaparotomy	5 (3%)
Drainage	14 (10%)
Mean hospital stay ± SD, days	12.9 ± 5.9
Nontumoral liver	
Macrovacuolar steatosis (≥ 30%)	12 (8%)
Steatohepatitis	1 (1%)
Fibrosis	69 (47%)
Portal	57 (83%)
Portoportal	11 (16%)
Septal	0 (0%)
Cirrhosis	1 (1%)
Vascular lesions[c]	82 (56%)
Sinusoidal alterations[d]	16 (11%)
Peliosis	45 (31%)
HCN	36 (25%)
RNH	22 (15%)
Veno-occlusive disease	18 (14%)
Surgical necrosis	8 (6%)

a: synchronous metastases were diagnosed before or within 3 months after resection of the primary colorectal tumor; *b*: as general complications were considered: pulmonary, cardiovascular, urinary tract, infectious (other than local hepatic) and iatrogenic complications; *c*: patients with one or more individual vascular changes (percentages for specific vascular lesions are related to the total number of 146 patients); *d*: vasodilatation or congestion. Abbreviations: SD = standard deviation; CEA = carcinoembryonic antigen; RFA = radiofrequency ablation; HCN = hemorrhagic centrilobular necrosis; RNH = regenerative nodular hyperplasia.

was 8 (range: 6 to 21 cycles) and chemotherapy delivery was chronomodulated in 41% of patients.[24] Twenty-four patients (16%) received 5-fluorouracil (5-FU) and leucovorin (LV) alone (9.0 ± 2.0 cycles), 92 patients (63%) had 5-FU/LV and oxaliplatin (8.6 ± 2.8 cycles), 18 patients (12%) had 5-FU/LV and irinotecan (8.9 ± 3.0 cycles), and 12 patients (8%) were treated by 5-FU/LV, oxaliplatin and irinotecan (9.6 ± 3.6 cycles). The number of chemotherapy cycles did not differ between different regimens (P=0.70).

Hepatectomy characteristics

Major hepatectomies (3 or more segments) were performed in 50% of patients *(Table 2)*. Red blood cell transfusions were required in 41% of patients, of whom 94% needed more than one blood unit. Postoperative morbidity occurred in 43% of patients and one patient (1%) died within 60 days after surgery. Hepatic complications were classified as Grade III or IV complications in 34% of patients. Median duration of hospital stay was 11 days (range: 6 to 42 days).

Nontumoral liver parenchyma

Vascular liver lesions constituted the most frequent type of histopathologic lesion and were present in 82 patients (56%) *(Table 2)*. Peliosis was most often observed (31%). RNH *(Figure 2)* occurred in 22 of 146 patients (15%) and was more frequent than sinusoidal alterations (11%). Steatohepatitis occurred in only one patient (1%).

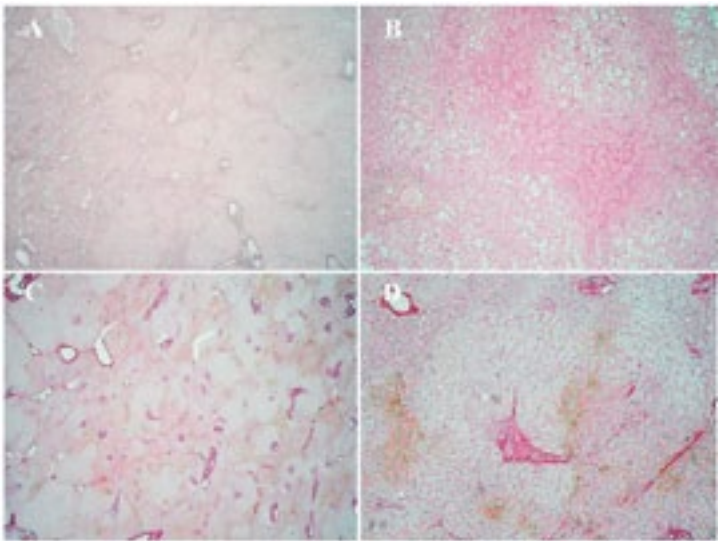

Figure 2.
Example of regenerative nodular hyperplasia. Nodules of hyperplastic hepatocytes replace the normal liver parenchyma and are surrounded by atrophic plates without evidence of fibrosis (note the hemorrhagic changes close to atrophic plates). A: Gordon and Sweet stain (x20). B: Hematoxylin-Eosin stain (x10).
C: Picrosirius stain (x20).
D: Picrosirius stain (x10).

RNH versus non-RNH patients

Patients with RNH more often presented with more than 3 metastases at diagnosis compared with patients without RNH (78% *vs* 50%) (P=0.03) *(Table 3)*. Twenty RNH patients (91%) preoperatively received 5-FU/LV and oxaliplatin (9.2 ± 2.6 cycles). The two remaining patients were treated by 5-FU/LV and irinotecan (12 cycles) (one) and 5-FU/LV, oxaliplatin and irinotecan (6 cycles) (one). Chemotherapy was chronomodulated in six patients (27%) (all oxaliplatin). RNH

occurred in 22% of patients treated by oxaliplatin compared to 4% of oxaliplatin-naïve patients (P=0.003). The number of chemotherapy cycles was not increased in RNH patients compared with the control group (9.1 ± 2.7 *vs* 8.8 ± 2.8) (P=0.55).

RNH patients had lower platelet counts at hospital admission ($150 \cdot 10^3$/µL or less: 48% *vs* 17%) (P=0.002). Mean alkaline phosphatase, gamma-glutamyltransferase (GGT) and total bilirubin levels before surgery were higher in RNH patients *(Table 3)*.

Major hepatectomies were performed in a similar percentage of patients with and without RNH (55% *vs* 49%, respectively) (P=0.64) *(Table 3)*. None of the RNH patients died within 60 days postoperatively. However, hepatic complications occurred in 50% of RNH patients compared to 29% of patients without RNH (P=0.05). This difference was mainly caused by an increased incidence of biliary leaks (27% *vs* 0%).

Uni- and multivariate analysis of hepatic morbidity

Seven factors, including RNH, were associated with hepatic morbidity at univariate analysis *(Table 4)*. However, only 4 factors were independent predictors at multivariate analysis: a preoperative platelet count of less than $150 \cdot 10^3$/µL, major hepatectomy, two-stage hepatectomy and intraoperative red blood cell transfusion.

Predictive factors of RNH

Multivariate logistic regression analysis identified elevated preoperative GGT (more than 80 U/L; >1N) and total bilirubin levels (more than 15 µmol/L; >1N) as independent factors predictive for the presence of RNH. Risk ratios were 6.6 (95% confidence interval 2.0 to 21.4) for GGT (P=0.002) and 3.3 (95% confidence interval 1.1 to 10.0) for total bilirubin (P=0.04).

Evolution of RNH within time

Fifteen of 82 patients (18%) with vascular changes of the nontumoral liver at first hepatectomy underwent repeat liver surgery. This included two of 22 patients (9%) with RNH at first hepatectomy. RNH was replaced by HCN at second hepatectomy in both patients following interruption of oxaliplatin and subsequent treatment with irinotecan. These patients received 11 and 12 cycles of irinotecan-based chemotherapy between both hepatectomies, respectively. No new cases of RNH were found at repeat hepatectomy in the remaining cases.

Table 3. Characteristics of patients with and without RNH.

	No RNH (N = 124)	RNH (N = 22)	*P*
Patients			
Mean age ± SD, years	59.1 ± 9.9	59.1 ± 7.6	0.99
Male/Female	73 (59%) / 51 (41%)	12 (55%) / 10 (46%)	0.71
Mean body mass index ± SD, kg/m^2	24.0 ± 3.5	24.4 ± 4.0	0.60
Diabetes mellitus	6 (5%)	2 (10%)	0.43
Liver metastases diagnosis			
Synchronous[a]	91 (73%)	20 (91%)	0.08
Number			
≤ 3	58 (50%)	4 (22%)	0.03
> 3	59 (50%)	14 (78%)	
Mean maximum size ± SD, mm	44.5 ± 28.4	49.0 ± 30.2	0.52
Bilobar	84 (68%)	18 (82%)	0.19
Preoperative chemotherapy			
Chronotherapy	53 (43%)	6 (27%)	0.16
Mean number of cycles ± SD	8.8 ± 2.8	9.1 ± 2.7	0.55
≤ 9	75 (63%)	12 (55%)	0.45
> 9	44 (37%)	10 (46%)	
Regimen			
5-FU/LV Oxaliplatin	72 (58%)	20 (91%)	0.003
Other	52 (42%)	2 (9%)	
Preoperative biochemical variables			
Mean ICG-R15 ± SD, %	15.0 ± 7.3	13.0 ± 5.7	0.35
Mean hemoglobin level ± SD, g/dL	12.3 ± 1.5	11.9 ± 1.5	0.27
Mean platelet count ± SD, 10^3/μL	217.8 ± 74.7	158.7 ± 63.3	0.001
≤ 150	19 (17%)	10 (48%)	0.002
> 150	92 (83%)	11 (52%)	
Mean prothrombin time ± SD, %	90.2 ± 12.2	91.8 ± 8.9	0.59
Mean AST ± SD, U/L	48.0 ± 64.7	58.6 ± 36.2	0.46
Mean ALT ± SD, U/L	46.9 ± 81.0	60.2 ± 49.6	0.46
Mean AP ± SD, U/L	133.6 ± 124.7	208.8 ± 154.5	0.03
≤ 100	52 (52%)	2 (12%)	0.002
> 100	49 (49%)	15 (88%)	
Mean GGT ± SD, U/L	96.1 ± 125.2	235.2 ± 284.8	< 0.001
≤ 80	75 (65%)	4 (20%)	< 0.001
> 80	40 (35%)	16 (80%)	
Mean total bilirubin ± SD, μmol/L	11.8 ± 10.1	15.0 ± 8.5	0.17
≤ 15	100 (86%)	14 (64%)	0.01
> 15	16 (14%)	8 (36%)	

Continuation of table 3.

	No RNH (N = 124)	RNH (N = 22)	*P*
Hepatectomy			
Major resection (≥ 3 segments)	61 (49%)	12 (55%)	0.64
Vascular occlusion			
No	20 (17%)	1 (5%)	0.47
Total pedicular	60 (52%)	13 (62%)	
Vascular exclusion	16 (14%)	4 (19%)	
Selective	19 (17%)	3 (14%)	
Portal vein embolization	13 (11%)	5 (23%)	0.11
Two-stage hepatectomy	7 (6%)	3 (14%)	0.17
Mean red blood cell transfusions ± SD, units	1.5 ± 2.4	1.4 ± 1.5	0.90
No	68 (61%)	10 (48%)	0.24
Yes	43 (39%)	11 (52%)	
Postoperative outcome			
Mortality (within 60 days)	1 (1%)	0 (0%)	0.67
Morbidity	50 (40%)	13 (59%)	0.10
General complications[b]	35 (28%)	8 (36%)	0.44
Hepatic complications	36 (29%)	11 (50%)	0.05
Biliary leak	0 (0%)	3 (27%)	0.04
Hemorrhage	2 (6%)	0 (0%)	
Infected collection	4 (11%)	1 (9%)	
Noninfected collection	18 (50%)	3 (27%)	
Liver insufficiency[23]	6 (17%)	2 (18%)	
Combination	6 (17%)	2 (18%)	
Relaparotomy	5 (4%)	0 (0%)	0.34
Drainage	11 (9%)	3 (14%)	0.48
Mean hospital stay ± SD, days	12.7 ± 5.7	13.9 ± 7.3	0.36
Nontumoral liver			
Sinusoidal alterations[c]	13 (11%)	3 (14%)	0.66
Peliosis	38 (31%)	7 (32%)	0.91
HCN	30 (24%)	6 (27%)	0.77

a: synchronous metastases were diagnosed before or within 3 months after resection of the primary colorectal tumor; *b*: as general complications were considered: pulmonary, cardiovascular, urinary tract, infectious (other than local hepatic) and iatrogenic complications; *c*: vasodilatation or congestion. Abbreviations: RNH = regenerative nodular hyperplasia; SD = standard deviation; ICG-R15 = indocyanine green retention rate at 15 minutes; AST = aspartate aminotransferase; ALT = alanine aminotransferase; AP = alkaline phosphatase; GGT = gamma-glutamyltransferase; HCN = hemorrhagic centrilobular necrosis.

Table 4. Univariate and multivariate analysis of hepatic morbidity.

		Hepatic morbidity				
Variable	**N**	**Yes (N = 47)**	**No (N = 99)**	**UV *P***	**MV *P***	**RR (95% CI)**
Patient factors						
Gender						
Male	85	25 (53%)	60 (61%)	0.40	-	-
Female	61	22 (47%)	39 (39%)			
Age at hepatectomy, years						
≤ 60	78	22 (47%)	56 (57%)	0.27	-	-
> 60	68	25 (53%)	43 (43%)			
Liver metastases						
Synchronous[a]						
No	35	7 (15%)	28 (28%)	0.08	NS	-
Yes	111	40 (85%)	71 (72%)			
Number						
≤ 3	62	17 (43%)	45 (47%)	0.60	-	-
> 3	73	23 (58%)	50 (53%)			
Maximum size, mm						
≤ 30	50	17 (40%)	33 (38%)	0.90	-	-
> 30	79	26 (61%)	53 (62%)			
Localization						
Unilobar	44	13 (28%)	31 (31%)	0.65	-	-
Bilobar	102	34 (72%)	68 (69%)			
Initial resectability						
No	105	36 (77%)	69 (70%)	0.39	-	-
Yes	41	11 (23%)	30 (30%)			
Concomitant extrahepatic disease						
No	125	40 (87%)	85 (86%)	0.86	-	-
Yes	20	6 (13%)	14 (14%)			
Preoperative chemotherapy						
Number of cycles						
≤ 9	87	26 (57%)	61 (64%)	0.38	-	-
> 9	54	20 (44%)	34 (36%)			
Regimen						
5-FU/LV Oxaliplatin	92	33 (70%)	59 (60%)	0.21	-	-
Other	54	14 (30%)	40 (40%)			
Preoperative biochemical variables						
ICG-R15, %						
≤ 10	22	10 (35%)	12 (21%)	0.19	-	-
> 10	63	19 (66%)	44 (79%)			
Platelet count[a], 10^3/μL						
≤ 150	29	13 (33%)	16 (17%)	0.05	0.01	3.5 (1.3-9.2)
> 150	103	27 (68%)	76 (83%)			
Prothrombin time, %						
≤ 90	50	18 (41%)	32 (36%)	0.58	-	-
> 90	83	26 (59%)	57 (64%)			
AST[a], U/L						
≤ 30	63	16 (36%)	47 (51%)	0.10	NS	-
> 30	75	29 (64%)	46 (50%)			
ALT, U/L						
≤ 30	76	23 (51%)	53 (57%)	0.52	-	-
> 30	62	22 (49%)	40 (43%)			

Continuation of table 4.

		Hepatic morbidity				
Variable	**N**	**Yes (N = 47)**	**No (N = 99)**	**UV *P***	**MV *P***	**RR (95% CI)**
AP, U/L						
≤ 100	54	19 (48%)	35 (45%)	0.79	-	-
> 100	64	21 (53%)	43 (55%)			
GGT, U/L						
≤ 80	79	28 (64%)	51 (56%)	0.40	-	-
> 80	56	16 (36%)	40 (44%)			
Total bilirubin, µmol/L						
≤ 15	114	35 (78%)	79 (85%)	0.30	-	-
> 15	24	10 (22%)	14 (15%)			
Hepatectomy						
Major resection[a] (≥ 3 segments)						
No	73	17 (36%)	56 (57%)	0.02	0.05	2.6 (1.0-6.4)
Yes	73	30 (64%)	43 (43%)			
Pedicular clamping						
No	43	10 (23%)	33 (36%)	0.12	-	-
Yes	93	34 (77%)	59 (64%)			
Combined local treatment						
No	129	43 (92%)	86 (87%)	0.42	-	-
Yes	17	4 (9%)	13 (13%)			
Portal vein embolization						
No	128	40 (85%)	88 (89%)	0.52	-	-
Yes	18	7 (15%)	11 (11%)			
Two-stage hepatectomy[a]						
No	136	41 (87%)	95 (96%)	0.05	0.03	5.7 (1.2-27.2)
Yes	10	6 (13%)	4 (4%)			
Intraoperative RBC transfusion[a]						
No	78	19 (43%)	59 (67%)	0.01	0.03	2.6 (1.1-6.1)
Yes	54	25 (57%)	29 (33%)			
Nontumoral liver						
Macrovacuolar steatosis (≥ 30%)						
No	134	44 (94%)	90 (91%)	0.58	-	-
Yes	12	3 (6%)	9 (9%)			
Fibrosis						
No	77	28 (60%)	49 (50%)	0.25	-	-
Yes	69	19 (40%)	50 (51%)			
Sinusoidal alterations						
No	130	43 (92%)	87 (88%)	0.51	-	-
Yes	16	4 (9%)	12 (12%)			
Peliosis						
No	101	31 (66%)	70 (71%)	0.56	-	-
Yes	45	16 (34%)	29 (29%)			
HCN						
No	109	37 (79%)	72 (74%)	0.49	-	-
Yes	36	10 (21%)	26 (27%)			
RNH[a]						
No	124	36 (77%)	88 (89%)	0.05	NS	-
Yes	22	11 (23%)	11 (11%)			

a: variables entered in Cox regression model. Abbreviations: UV = univariate; MV = multivariate; RR = risk ratio; CI = confidence interval; NS = not significant; 5-FU/LV = 5-fluorouracil/leucovorin; ICG-R15 = indocyanine green retention rate at 15 minutes; AST = aspartate aminotransferase; ALT = alanine aminotransferase; AP = alkaline phosphatase; GGT = gamma-glutamyltransferase; RBC = red blood cell; HCN = hemorrhagic centrilobular necrosis; RNH = regenerative nodular hyperplasia.

DISCUSSION

Although previous reports have correlated preoperative chemotherapy for CLM with increased postoperative complications, evidence for a direct relation between specific nontumoral liver lesions and postoperative morbidity remains preliminary.[7-10,25,26] With the increasing use of preoperative chemotherapy, especially oxaliplatin, it is nevertheless important to know the incidence and impact of different vascular lesions on postoperative outcome, and to know how these lesions can be predicted to adjust patient monitoring and to identify patients at risk of increased morbidity.

Our present study shows that RNH may occur in 15% of patients treated with preoperative chemotherapy. RNH is associated with increased hepatic morbidity and occurs most frequently in patients receiving oxaliplatin. Interestingly, its presence can be predicted preoperatively by elevated levels of GGT and total bilirubin.

The fact that RNH was related with increased postoperative hepatic morbidity was an important finding of our study. However, only a preoperative platelet count of less than $150 \cdot 10^3/\mu L$, major hepatectomy, two-stage hepatectomy and intraoperative red blood cell transfusion, were independent predictors of hepatic morbidity at multivariate analysis in the total study population. Major hepatectomy, two-stage hepatectomy and intraoperative red blood cell transfusions were equally distributed between RNH and non-RNH patients. However, RNH patients had relatively low platelet counts compared with non-RNH patients. We may assume that a low platelet count was related to splenomegaly owing to portal hypertension caused by RNH, with subsequent platelet trapping. These results all strengthen the association of RNH with increased hepatic morbidity observed in our study.

In a recent study, sinusoidal liver injury was related with increased morbidity following major hepatectomy for CLM after preoperative chemotherapy.[10] Our inclusion of both minor and major hepatectomies confirms the importance of recognizing RNH in all patients scheduled for hepatectomy after preoperative chemotherapy treatment. Furthermore, our result was independent of the number of chemotherapy cycles.

Interestingly, we identified preoperative elevated levels of GGT and total bilirubin as predictive factors of RNH. A recent study also found that high levels of GGT predicted the presence of sinusoidal lesions.[27] Surprisingly, mean ICG-R15 values, known to be more sensitive and reliable for hepatic injury, were not altered in our patients with RNH. For patients at risk for RNH, efforts should be made to reduce the risks of liver surgery. Techniques such as portal vein embolization and two-stage hepatectomy may be helpful to spare the highest amount of

liver parenchyma as possible, thereby maximizing the chances of an uneventful postoperative course.

In relation with the increased risk of hepatic morbidity and the enlarging number of patients who undergo repeat hepatectomy with perioperative chemotherapy, it is important to consider the evolution of RNH within time. RNH may have deleterious long-term consequences related to the development of portal hypertension. One case study reported the development of RNH and portal hypertension in three patients treated with oxaliplatin that finally contraindicated curative liver surgery.[28] Recently, the development of portal hypertension in patients with RNH with deleterious postoperative complications and even death was reported by another group.[29] Other reports on RNH as a result of preoperative chemotherapy are rare.[30] When we evaluated the evolution of vascular lesions in patients who underwent repeat hepatectomy, previously diagnosed RNH was replaced by HCN in two patients. Because RNH is distributed throughout the liver in a regular pattern, sample variation is unlikely to cause the absence of RNH at subsequent hepatectomies.[31] Furthermore, all nontumoral liver specimens were evaluated by the same hepatobiliary pathologist. The natural history of RNH remains largely unknown.[28] However, as it is a noncirrhotic liver disease without fibrosis, RNH can theoretically regress, as was demonstrated in our study.[27]

Interestingly, in both patients in whom RNH disappeared, oxaliplatin was stopped and irinotecan was administered before the second hepatectomy. This may suggest that irinotecan may be a good alternative of oxaliplatin to treat these patients. Previously, RNH had already been associated with the use of oxaliplatin.[4] Recently, different authors have suggested a protective effect of bevacizumab on the development of vascular toxicity.[32-34] Therefore, its addition to conventional chemotherapy may reduce the risk of RNH and associated morbidity. However, this issue lies beyond the scope of the present study and needs further evaluation. Conclusions on the evolution of vascular lesions other than RNH into less or more severe types at repeat hepatectomy are difficult, because of their irregular distribution throughout the liver with the subsequent risk of sample variation.

Our study represents a selected patient group that received only one line of chemotherapy. By this way, we were able to correlate RNH with different chemotherapy regimens most accurately. However, with the large amount of patients receiving multiple chemotherapy regimens before surgery, RNH may be even more frequent in daily practice. The potential negative effect of portal hypertension related to RNH on patient outcome should therefore not be underestimated.

A final interesting remark of our study is that we observed only one patient with steatohepatitis, who received oxaliplatin before hepatectomy. Previous large series have associated steatohepatitis mainly with irinotecan,[7,14] one of whom even found that steatohepatitis was related with an increased 90-day mortality rate.[7] The low incidence of obese patients and patients with diabetes probably is one of the reasons for the low frequency of steatohepatitis in our current study. The precise causes and consequences of this entity should nevertheless be investigated more extensively.

In conclusion, an increasing number of patients with CLM currently receive oxaliplatin-based chemotherapy, including adjuvant treatment after stage III colon cancer, induction therapy to convert extensive metastases to resectability or perioperative treatment in patients with resectable metastases.[1,3,35] RNH may occur in one of five patients, with an increased risk of postoperative morbidity after hepatectomy. Elevated serum GGT and bilirubin are useful markers to detect RNH that does not contraindicate hepatic resection. Clinical recommendations regarding preoperative chemotherapy treatment based on these results should be evaluated further, taking into account the availability and consequences of new biological agents.

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Chapter 7

Impact of bevacizumab on functional recovery and histology of the liver after resection of colorectal metastases

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ABSTRACT

Background

The impact of bevacizumab on functional recovery and histology of the liver was evaluated in patients undergoing hepatic resection for colorectal liver metastases (CLM) following bevacizumab treatment.

Methods

Consecutive patients who had resection of CLM between July 2005 and July 2009 following preoperative chemotherapy were identified retrospectively from a prospectively collected database. Patients who had received bevacizumab before the last chemotherapy line were excluded. Postoperative liver function and histology were compared between patients with and without bevacizumab treatment. Recorded parameters included serum prothrombin time, total bilirubin concentration, and levels of aspartate and alanine aminotransferase and gamma-glutamyltransferase.

Results

Of 208 patients identified, 67 had received last line bevacizumab, 44 were excluded and 97 had not received bevacizumab. Most patients in the bevacizumab group (66%) received a single line of chemotherapy. Bevacizumab was most often combined with 5-fluorouracil/leucovorin and irinotecan (68%). The median number of bevacizumab cycles was 8.6 (range: 1 to 34 cycles). Bevacizumab administration was stopped at a median of 8.3 weeks before surgery (range: 3.0 to 19.1 weeks). There were no deaths. Postoperative morbidity occurred in 43% and 36% of patients in the bevacizumab and no-bevacizumab group, respectively (P=0.35). The mean degree of tumor necrosis was significantly higher in the bevacizumab group (55 ± 27% *vs* 32 ± 29%) (P=0.001). Complete pathologic response rates were comparable (3% *vs* 8%) (P=0.31). Postoperative changes in functional parameters and objective signs of hepatic toxicity were similar in both groups.

Conclusion

Preoperative administration of bevacizumab does not seem to affect functional recovery of the liver after resection of CLM. Tumor necrosis is increased following bevacizumab treatment.

Introduction

The combination of oxaliplatin- and irinotecan-based chemotherapy with bevacizumab has led to improved response rates, progression-free survival and overall survival for patients with metastatic colorectal cancer in large randomized trials.[1-3] However, hepatic resection still remains the only potentially curative therapy for colorectal liver metastases (CLM), with almost 25% of patients now surviving for at least 10 years after hepatectomy in experienced centers.[4,5]

The improved effectiveness of cytotoxic chemotherapy combined with molecular targeted therapy for CLM has resulted in an increasing number of patients receiving bevacizumab before hepatectomy. For initially unresectable metastases, objective response to chemotherapy is the main determinant of subsequent resectability.[6] Following tumor downsizing, curative hepatectomy may result in 5-year survival rates up to 58%, compared with 2% in patients without resection.[7,8] In addition, for upfront resectable metastases, neoadjuvant chemotherapy is more frequently used to assess tumor biology and to facilitate margin-negative resections. The administration of chemotherapy before and after surgery has been shown to improve progression-free survival after hepatectomy in this patient group.[9]

Bevacizumab acts by inhibition of vascular endothelial growth factor (VEGF), and has been associated with increased risks of thrombosis, bleeding and gastrointestinal perforations.[1] Recently, the influence of bevacizumab on perioperative morbidity has been evaluated in patients with CLM undergoing hepatectomy.[10-12] None of these series provided evidence of an increased risk of perioperative complications with the addition of bevacizumab to oxaliplatin- or irinotecan-containing regimens. However, bevacizumab has been implicated in impaired liver regeneration after hepatic resection or portal vein embolization (PVE).[13,14]

The present study investigated this issue by evaluating postoperative functional recovery and histology of the liver, as well as perioperative morbidity in patients undergoing resection of CLM following bevacizumab treatment.

PATIENTS AND METHODS

Patient inclusion criteria

Consecutive patients undergoing hepatectomy following chemotherapy between July 2005 and July 2009 were identified retrospectively from a prospectively collected database. Patients who received bevacizumab as part of the last chemotherapy line before hepatic resection formed the population of the study. Patients undergoing hepatectomy following systemic chemotherapy without bevacizumab were used as a control group. Those patients who had received bevacizumab as part of a previous chemotherapy regimen were excluded. The type of preoperative chemotherapy regimen was decided by the medical oncologist.

Evaluation of chemotherapy response

Patients treated with chemotherapy routinely received bevacizumab by intravenous infusion at a dose of 5 mg/kg every 2 weeks. Response to chemotherapy was evaluated every 4 cycles (2 months) by computed tomography or magnetic resonance imaging of the chest, abdomen and pelvis according to RECIST criteria.[15] Surgery was undertaken only when an overall curative resection of both intra- and extrahepatic metastases could be achieved, either by single or staged procedures. Bevacizumab was usually discontinued 6 to 8 weeks before surgery to avoid perioperative complications. Subsequently, usually one or two cycles of chemotherapy without bevacizumab were given to prevent tumor progression.

Hepatic resection and postoperative outcome

The aim of surgery was to completely resect all remaining intra- and extrahepatic lesions. Anatomical or nonanatomical resections were performed according to the extent of intrahepatic metastatic disease, sparing as much liver parenchyma as possible. Limited extrahepatic disease, resectable by combined or staged surgery, was not considered a contraindication to partial hepatectomy. For advanced bilobar liver metastases, additional procedures, including PVE, local ablation and two-stage hepatectomy were used as necessary to achieve complete tumor clearance.[16] Patients received standard prophylactic abdominal drains following hepatectomy. In patients undergoing two-stage hepatectomy, functional recovery and histology were analyzed after the second resection.

Preoperative hepatic functional reserve was assessed by standard indocyanine green retention rate at 15 minutes (ICG-R15) determined at hospital admission. Biochemical variables were used to assess liver functional recovery and were obtained from serum on the day before surgery, postoperatively on the day of surgery, and during subsequent days of admission according to the patient's individual clinical progress. Recorded functional parameters included prothrombin time (PT) and serum total bilirubin level. Serum levels of aspartate amino-

transferase (AST), alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT) were also measured as markers of cellular damage.

Surgical complications and mortality rates were stratified according to the Clavien classification.[17] Postoperative morbidity was classified as 'local hepatic' or 'general' complications (located near or distant from the field of liver surgery, respectively), occurring within 2 months after hepatectomy. Liver insufficiency was noted when the serum bilirubin level exceeded 50 µmol/L and prothrombin time decreased to below 50%.[18] For patients treated with bevacizumab, the medical records were reviewed to evaluate potential treatment-related complications.

Liver histology

To determine the impact of bevacizumab on the nontumoral liver parenchyma, only patients undergoing first hepatectomies and with one line of chemotherapy from each group were compared. Histopathologic assessment of the resection specimen was performed by a specialized hepatobiliary pathologist, unaware of the preoperative chemotherapy treatment and perioperative outcome. Pathology reports were reviewed for the presence of fibrosis (portal, portoportal, septal, and cirrhosis), macrovacuolar steatosis and vascular lesions. Vascular lesions were categorized as sinusoidal alterations (vasodilatation and congestion), peliosis, hemorrhagic centrilobular necrosis and regenerative nodular hyperplasia (RNH). In addition, the degree of tumor necrosis and fibrosis in resected specimens was assessed.

Statistical analysis

Patients treated with and without preoperative bevacizumab were compared with respect to patient and treatment characteristics, postoperative morbidity and functional recovery and histology of the liver. Continuous data were compared using the independent-samples *T* test, and categorical data using the X^2 test. The ANOVA test for repeated measures was used to compare recovery of liver function with time between patient groups. Additionally, areas under the curve (AUC) were calculated. *P* values ≤0.05 were considered statistically significant. SPSS® software (SPSS Inc., Chicago, Illinois, USA), version 13.0, was used for all statistical analyses.

RESULTS

Patient and tumor characteristics

A total of 208 patients were identified who underwent partial hepatectomy for CLM *(Figure 1)*. Some 111 patients had received bevacizumab, of whom 44 were excluded because bevacizumab had been received in an earlier chemotherapy regimen. The remaining 67 patients were compared with a control group of 97 patients who had not received bevacizumab. The bevacizumab group consisted of 42 men (63%) and 25 women (37%) with a median age of 59 years (range: 31 to 82 years) at hepatectomy *(Table 1)*. The median number of metastases was 4 (range: 1 to 20). Liver metastases were synchronous in 72% of patients and had a median maximum size of 30 mm (range: 10 to 290 mm). Concomitant extrahepatic metastases were present in 18 patients (27%).

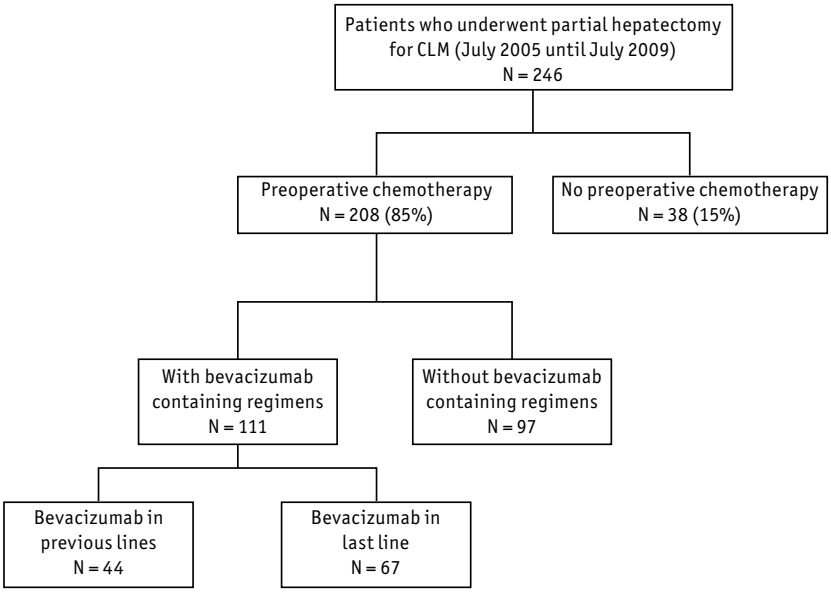

Figure 1. Flowchart illustrating study patient selection.

Preoperative chemotherapy

Chemotherapy was administered to 42 patients (63%) in the bevacizumab group to achieve resectability. Tumors in the remaining 25 patients (37%) were considered resectable at diagnosis and preoperative chemotherapy was given in a neoadjuvant setting *(Table 2)*. Most patients received only one line of chemotherapy before surgery. Patients were administered more than 6 cycles of chemo-

Table 1. Comparison of patient and tumor characteristics between study groups.

	With bevacizumab (N = 67)	Without bevacizumab (N = 97)	*P*
Patients			
Mean age ± SD, years	58 ± 11	62 ± 11	0.03
Male/Female	42 (63%) / 25 (37%)	61 (63%) / 36 (37%)	0.98
Primary tumor			
Colon/Rectum	50 (76%) / 16 (24%)	74 (76%) / 23 (24%)	0.94
T stage			
1/2	7 (14%)	10 (13%)	0.79
3/4	42 (86%)	69 (87%)	
N stage			
0	18 (38%)	28 (36%)	0.86
1/2	30 (63%)	50 (64%)	
Liver metastases			
Synchronous[a]	48 (72%)	67 (69%)	0.72
Mean number ± SD	5.6 ± 4.5	4.5 ± 4.6	0.14
≤ 3	26 (39%)	54 (58%)	0.02
> 3	40 (61%)	39 (42%)	
Mean maximum size ± SD, mm	49 ± 46	46 ± 33	0.73
Bilobar	45 (67%)	56 (58%)	0.22
Concomitant extrahepatic disease	18 (27%)	15 (16%)	0.07
Lung	13 (72%)	9 (60%)	0.46
Peritoneum	1 (6%)	1 (7%)	0.89
Lymph node	2 (11%)	4 (27%)	0.25
Combination	2 (11%)	1 (7%)	0.66

a: synchronous metastases were diagnosed before or within 3 months after resection of the primary colorectal tumor. Abbreviations: SD = standard deviation.

Table 2. Comparison of preoperative chemotherapy characteristics between study groups.

	With bevacizumab (N = 67)	Without bevacizumab (N = 97)	*P*
Main indication			
Neoadjuvant	25 (37%)	44 (45%)	0.31
Initial irresectability	42 (63%)	53 (55%)	
Multinodular	25 (60%)	34 (64%)	0.64
Size	6 (14%)	13 (25%)	0.22
Close vascular relation	4 (10%)	5 (9%)	0.99
Extrahepatic disease	7 (17%)	1 (2%)	0.01
Number of lines			
1	44 (66%)	60 (62%)	0.62
> 1	23 (34%)	37 (38%)	
Mean number of cycles ± SD	11 ± 7	10 ± 6	0.46
Last line regimen			
Conventional			
5-FU/LV	5 (8%)	1 (2%)	0.03
5-FU/LV Oxaliplatin	15 (23%)	38 (56%)	0.02
5-FU/LV Irinotecan	44 (68%)	25 (37%)	< 0.001
5-FU/LV Oxaliplatin Irinotecan	1 (2%)	2 (3%)	0.79
Other	0 (0%)	2 (3%)	0.24
Cetuximab	2 (3%)	29 (30%)	< 0.001
Clinical response			
Complete/Partial	47 (70%)	60 (62%)	0.27
Stabilization/Progression	20 (30%)	37 (38%)	

Abbreviations: SD = standard deviation; 5-FU = 5-fluorouracil; LV = leucovorin.

therapy in 75% and 61% of patients in the bevaczumab and control group, respectively (*P*=0.08).

Bevacizumab treatment

Of 67 patients who received bevacizumab, 25 (37%) were treated at another institution and were referred to the authors' center for partial hepatectomy.

Bevacizumab was administered as first-line therapy in 50 patients (75%). The other 17 patients switched to bevacizumab-containing regimens in second or higher lines, owing to insufficient response (12 patients; 18%) or tumor progression on bevacizumab-free therapy (5 patients; 8%).

In most patients, bevacizumab was combined with 5-fluorouracil (5-FU), leucovorin (LV) and irinotecan (68%) or oxaliplatin (23%) *(Table 2)*. Patients in the bevacizumab group more often received 5-FU and LV in combination with irinotecan than those in the control group (*P*<0.001). More patients in the control group received cetuximab (*P*<0.001).

Bevacizumab administration was stopped at a median of 8 weeks before surgery (range: 3 to 19 weeks). The median number of administered bevacizumab cycles was 8.6 (range: 1 to 34 cycles).

Operative characteristics

Thirty-one patients (46%) in the bevacizumab group underwent major hepatectomy (3 or more segments) as compared with 38 patients (39%) in the control group (*P*=0.37). Of all resections performed, 24% and 17% were repeat hepatectomies in the bevacizumab and control group, respectively (*P*=0.24). PVE (40% *vs* 21%) (*P*=0.006) and two-stage hepatectomy (33% *vs* 16%) (*P*=0.009) were more common in the bevacizumab group. Radiofrequency ablation combined with resection was used similarly in both groups (5% *vs* 3%) (*P*=0.64). Total pedicular clamping was used in 61% and 64% of bevacizumab and control patients, respectively (*P*=0.83). Pure anatomical resections were performed in 42% and 70% of patients, respectively (*P*=0.04). Intraoperative red blood cell transfusions were administered in 45% of patients treated with bevacizumab compared with 32% of patients in the control group (*P*=0.11) (mean number of units: 1.5 ± 2.3 *vs* 1.2 ± 2.4) (*P*=0.43). The duration of surgery was longer in the bevacizumab group (mean: 414 ± 146 *vs* 341 ± 110 minutes) (*P*=0.001).

Surgical morbidity and mortality

There were no deaths within 60 days of hepatectomy. Postoperative morbidity occurred in 29 patients (43%) treated with preoperative bevacizumab and in 35 patients (36%) in the control group (*P*=0.35). No differences were observed between the two groups when general and local hepatic complications were

analyzed separately. These results were not related to the duration of the bevacizumab-free interval before surgery. Details on postoperative complications are outlined in *Table 3*. Of note, postoperative liver insufficiency occurred in only one patient in the bevacizumab group (2%) and in two patients (2%) in the control group.

Table 3. Comparison of postoperative outcome between study groups.

	With bevacizumab (N = 67)	Without bevacizumab (N = 97)	*P*
General complications	13 (19%)	21 (22%)	0.73
Pleural effusion	3 (23%)	10 (48%)	0.54
Pneumonia	3 (23%)	1 (5%)	
Cardiac arrhythmia	1 (8%)	2 (10%)	
Prolonged ileus	1 (8%)	1 (5%)	
Wound abscess	1 (8%)	3 (14%)	
Abdominal wall hematoma	1 (8%)	0 (0%)	
Venous thrombosis	1 (8%)	1 (5%)	
Urinary tract infection	0 (0%)	1 (5%)	
Other	2 (15%)	1 (5%)	
Combination[a]	0 (0%)	1 (5%)	
Hepatic complications[b]	21 (31%)	21 (22%)	0.16
Biliary leak	4 (19%)	3 (14%)	0.20
Hemorrhage	0 (0%)	0 (0%)	
Infected collection	10 (48%)	4 (19%)	
Noninfected collection	4 (19%)	11 (52%)	
Liver insufficiency only[18]	0 (0%)	1 (5%)	
with noninfected collection	1 (5%)	1 (5%)	
Other combination[c]	2 (10%)	1 (5%)	
Dindo-Clavien classification[d,17]			
Grade I	4 (19%)	12 (57%)	0.07
Grade II	6 (29%)	4 (19%)	
Grade III	10 (48%)	5 (24%)	
Grade IV	1 (5%)	0 (0%)	
Relaparotomy	3 (5%)	1 (1%)	0.16
Percutaneous drainage	10 (15%)	7 (7%)	0.11
Mean hospital stay ± SD, days	13.6 ± 14.4	11.3 ± 7.1	0.17

a: pleural effusion and urinary tract infection; *b*: infected and noninfected collections were differentiated according to the presence of fever and elevated serum levels of infective parameters; *c*: biliary leak and infected collection; *d*: of hepatic complications.
Abbreviations: SD = standard deviation.

Potential bevacizumab treatment-related complications

Two of 67 patients (3%) experienced venous thrombotic events. One patient developed thrombosis of the superior mesenteric vein and another patient developed thrombosis of the left and right brachiocephalic trunk. Bevacizumab treatment was discontinued in both patients. Mild arterial hypertension occurred before surgery in one patient (2%) after 8 cycles of treatment, necessitating dose

reduction and treatment with beta-blocker therapy. Another patient (2%), who had received 9 cycles of preoperative bevacizumab, showed delayed wound healing more than 3 months after hepatectomy.

Thirteen of the 67 patients received bevacizumab with the primary colorectal tumor *in situ*. No spontaneous bowel perforations occurred in these patients. Colorectal and hepatic resections were performed synchronously in 7 patients. Anastomotic leakage with localized peritonitis occurred in one, requiring reintervention and construction of a protective ileostomy 8 days after the initial surgery. Bevacizumab treatment had been discontinued 5 weeks before surgery in this patient. Two other patients underwent hepatic resection first, followed by delayed resection of the primary tumor. Four additional patients died of tumor progression with the primary tumor *in situ*.

Postoperative recovery of liver function

On hospital admission, mean ICG-R15 values were comparable between patients treated with or without bevacizumab (8 ± 5% *vs* 9 ± 7%, respectively) (P=0.39). No differences in serum liver function parameters were observed between both groups immediately before surgery. Minimum postoperative PT levels were 58 ± 15% and 59 ± 15% in the bevacizumab and control group, respectively (P=1.00), and were reached one day after surgery. PT levels increased progressively thereafter *(Figure 2)*. Areas under the curve were 728.7 and 696.4 in the bevacizumab and control group, respectively. Peak postoperative total bilirubin levels (µmol/L) were higher in patients that received bevacizumab (38 ± 29 *vs* 30 ± 22 in the control group on the day after surgery), although there was no significant difference (AUC: 313.6 *vs* 273.4, respectively) *(Figure 3)*.

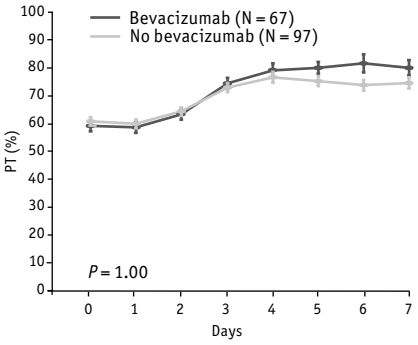

Figure 2.
Evolution of postoperative serum prothrombin time (PT) in patients treated with and without preoperative bevacizumab (means ± SE). Day 0 indicates the day of hepatectomy.

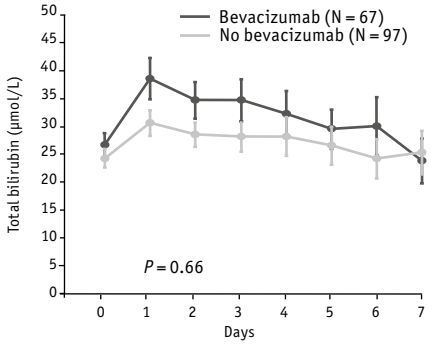

Figure 3.
Evolution of postoperative serum total bilirubin level in patients treated with and without preoperative bevacizumab (means ± SE). Day 0 indicates the day of hepatectomy.

Peak postoperative AST and ALT levels (U/L) were higher in the bevacizumab group (510 ± 326 *vs* 407 ± 415 for AST and 512 ± 328 *vs* 409 ± 338 for ALT), but subsequent recovery in both groups was not statistically significant (*P*=0.82 for AST and *P*=0.86 for ALT). Serum levels of GGT increased from postoperative day 3 in a similar way in both groups (*P*=0.93).

Postoperative recovery of liver function was analyzed separately in the subgroup of patients who underwent major hepatectomy. Changes over time were similar in both groups. Postoperative PT levels decreased to 49 ± 11% and 49 ± 12% on day 1 in the bevacizumab and control group, respectively, and increased thereafter in a similar manner (*P*=0.58). There was no difference in total bilirubin levels in the postoperative period between both groups (*P*=0.37).

Postoperative changes in PT and total bilirubin levels did not differ between patients in both groups treated with oxaliplatin or irinotecan alone. For example, *P* was 0.99 for the changes in total bilirubin in patients treated with irinotecan with or without bevacizumab.

Pathology

The number and size of resected metastases were similar in both patient groups *(Table 4)*. Macroscopically complete tumor resections (R0 or R1) were obtained in 55 patients (82%) treated with bevacizumab. With the exception of the 12 patients who underwent the first-step of a two-stage hepatectomy, there were no R2 resections in the bevacizumab group.

The degree of hepatotoxicity and tumor necrosis and fibrosis was analyzed separately in 35 patients treated with bevacizumab and 47 control patients (first hepatectomies with only one line of preoperative chemotherapy). Vascular lesions were less common in the bevacizumab group (*P*=0.04). Of 16 patients who had sinusoidal alterations, 11 were treated with oxaliplatin (69%). The degree of tumor necrosis was significantly higher in the bevacizumab group *(Table 4)*. Complete pathologic tumor response was observed in one patient (3%) in the

Table 4. Comparison of pathologic features between study groups.

	With bevacizumab (N = 67)	Without bevacizumab (N = 97)	*P*
Number of resected metastases			
≤ 3	40 (60%)	63 (66%)	0.44
> 3	27 (40%)	33 (34%)	
Mean maximum size ± SD, mm	42 ± 45	35 ± 26	0.20
Resection margin			
R0	28 (42%)	51 (53%)	0.15
R1	27 (40%)	38 (40%)	0.93
R2	0 (0%)	1 (1%)	0.40
Rx[a]	12 (18%)	6 (6%)	0.02
Complete response[b]	1 (3%)	4 (8%)	0.31
Mean tumor necrosis[b] ± SD, %	55 ± 27	32 ± 29	0.001
< 50%	15 (43%)	36 (77%)	0.002
50-80%	15 (43%)	8 (17%)	0.01
> 80%	5 (14%)	3 (6%)	0.23
Mean tumor fibrosis[b] ± SD, %	27 ± 22	28 ± 22	0.90
Nontumoral liver[b]			
Fibrosis	19 (53%)	21 (45%)	0.46
Portal	16 (84%)	19 (91%)	0.55
Portoportal	3 (16%)	2 (10%)	
Steatosis[c]	5 (14%)	6 (13%)	0.84
Vascular lesions[d]	11 (31%)	25 (53%)	0.04
Sinusoidal alterations	6 (17%)	10 (21%)	0.60
Peliosis	4 (11%)	9 (19%)	0.32
RNH	1 (3%)	7 (15%)	0.06

a: concerned patients that underwent the first-step of a two-stage hepatectomy approach; *b*: only patients with first hepatectomies and one line of chemotherapy were included (thirty-five with bevacizumab and forty-seven without bevacizumab); *c*: moderate or severe macrovacuolar steatosis (30% or more of hepatocytes); *d*: one or more individual vascular lesions may be present per patient.
Abbreviations: SD = standard deviation; RNH = regenerative nodular hyperplasia.

bevacizumab group and in 4 patients (8%) in the control group (*P*=0.31). Mean percentages of tumor fibrosis were similar in both groups.

Among patients treated with oxaliplatin with (nine) or without (twenty-seven) bevacizumab, mean tumor necrosis (%) was 48 ± 30 in the bevacizumab group and 41 ± 29 in the control group (*P*=0.56). Vascular lesions were similarly distributed (56% *vs* 67%) (*P*=0.55). Sinusoidal alterations occurred in 3 of 9 patients (33%) in the bevacizumab group and in 8 of 27 patients (30%) in the control group (*P*=0.84).

For patients treated with irinotecan with (twenty-four) or without (eleven) bevacizumab, mean tumor necrosis (%) was 57 ± 27 and 19 ± 19, respectively (*P*=0.001). Vascular lesions occurred in 5 patients (21%) in the bevacizumab group and in 3 patients (27%) in the control group (*P*=0.46).

Discussion

Bevacizumab is increasingly being administered in combination with conventional systemic chemotherapy to patients with CLM, with subsequent improved tumor responses. Although several trials have associated bevacizumab with an increased risk of bleeding and intestinal perforation, experience with bevacizumab administration before hepatectomy remains limited.[1,3,10-12] The possible adverse effect of VEGF inhibition by bevacizumab on hepatic regeneration has furthermore been noted, but has never been evaluated extensively in clinical studies. This study investigated the impact of preoperative bevacizumab treatment on recovery of liver function after hepatic resection for colorectal metastases by analysis of biochemical parameters, an issue that has hitherto received little attention.

In the present study postoperative recovery of liver function in patients treated with preoperative bevacizumab was comparable to that of patients who had not received bevacizumab. A similar evolution of serum liver parameters, with early impairment after hepatectomy and subsequent normalization, was noted in both groups, irrespective of the extent of hepatectomy (major or minor). In addition, baseline preoperative estimates of liver function and liver functional reserve (ICG-R15) did not differ before surgery, confirming that the additional administration of bevacizumab had no negative impact on clinical hepatic function.

It could be argued that conventional chemotherapy agents differed between both groups. Irinotecan was more commonly used in the bevacizumab group, whereas patients in the control group more often received oxaliplatin. However, subanalyses of patients who received irinotecan or oxaliplatin also showed comparable recovery of hepatic function in both groups.

A previous preliminary analysis showed that bevacizumab did not impair liver regeneration after PVE.[19] The negative impact of bevacizumab on liver hypertrophy has, however, been described by others, but the mechanisms involved are not clearly understood.[14,20] In the present study, interestingly, a high percentage of bevacizumab patients underwent major hepatectomy (46%) and PVE (40%). The equivalent liver function recovery in both groups suggests that any differences in regeneration did not impair clinical outcome. Pre- and postoperative liver volumetric analysis was beyond the scope of this study, but could be used to further examine this question. Similarly, new developments such as the LiMAx test may be useful in determining functional liver capacity more accurately.[21]

Histologic changes in the nontumoral liver owing to prolonged chemotherapy treatment may impact liver function, thereby impairing the objective analysis of the influence of preoperative bevacizumab.[22,23] No differences in the incidence of fibrosis and steatosis were found in the nontumoral liver between the two groups in the present study. Nevertheless, vascular lesions were observed in a high proportion of patients overall and were more common in the control group. This

can be explained by the higher incidence of oxaliplatin use in this group. The difference in vascular lesions disappeared, however, in the subgroup analysis of patients treated with oxaliplatin with or without bevacizumab. These results strenghten the conclusion that recovery of liver function is not impaired following preoperative bevacizumab treatment. In line with the high incidence of vascular lesions, more than 30% of patients in both groups required intraoperative red blood cell transfusions.[22]

Interestingly, recent publications have reported a decreased incidence of sinusoidal dilatation in patients treated with bevacizumab.[24,25] These series contained patients all treated with 5-FU and oxaliplatin. This study found, in a more heterogeneous population, a relatively higher incidence of mild compared to severe vascular lesions in the bevacizumab group, suggesting a protective effect of bevacizumab on the development of such lesions. For example, RNH was noted in 15% of patients in the control group, but in only 3% of patients treated with bevacizumab (P=0.06). However, this difference disappeared on subgroup analysis of patients treated with oxaliplatin. Other papers have, nevertheless, confirmed the protective effect of bevacizumab concerning the presence of RNH.[26]

An increased incidence of complete tumor destruction might be expected with increased efficacy of conventional chemotherapy in combination with targeted agents.[27] Indeed, several authors have reported a significantly improved degree of pathologic tumor response when bevacizumab was administered.[24,28] However, the incidence of complete pathologic response was similar to that in patients treated without bevacizumab.[24] In the present study, a complete pathologic response was observed in only one patient in the bevacizumab group. Owing to the relatively low incidence of complete pathologic response expected in patients treated with preoperative chemotherapy, a greater number of patients will probably be required to provide conclusive evidence of the added value of bevacizumab in achieving such a response.[27] Nevertheless, the degree of tumor necrosis was significantly higher in patients treated with bevacizumab. Interestingly, this effect mainly occurred in combination with irinotecan-based regimens, suggesting that this is the most effective strategy in achieving tumor response.

Previous publications reported a similar pattern of surgical morbidity in patients who did or did not receive preoperative bevacizumab treatment, with an overall morbidity rate around 40% to 50%.[10-12] Furthermore, treatment with bevacizumab did not increase the need for intraoperative blood transfusion. Other preliminary reports are in agreement with these results and suggest that bevacizumab can be administered safely before hepatic resection.[20,29] The present study confirmed in a relatively large patient cohort that the preoperative administration of bevacizumab was not associated with an increased rate of complications

or blood transfusions, despite even more two-stage hepatectomies. Of note, grade III and IV complications appeared to occur more frequently in patients who had received bevacizumab, but this difference was not statistically significant. Cases of liver insufficiency were few and similarly distributed, reflecting comparable postoperative changes in liver function in both groups.

An increased incidence of wound healing complications after surgery for metastatic colorectal cancer has been suggested previously after preoperative treatment with bevacizumab.[30] In this series, only a small proportion of the patients underwent hepatic resection. In the present study, potential bevacizumab-related complications were mild and occurred in only a minority of patients.

This study shows that preoperative treatment with bevacizumab has no impact on recovery of clinically relevant liver function after hepatic resection for CLM. There is no specific hepatic toxicity related to bevacizumab. The degree of tumor necrosis in patients treated with bevacizumab is increased compared with patients who did not receive bevacizumab, with however no higher incidence of complete pathologic response.

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Chapter 8

Complete pathologic response after preoperative chemotherapy for colorectal liver metastases: myth or reality?

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ABSTRACT

Background

Complete clinical response (CCR) of colorectal liver metastases (CLM) following chemotherapy is of limited predictive value for complete pathologic response (CPR) and cure of the disease. The objective of this study was to determine predictive factors of CPR as well as its impact on survival.

Patients and Methods

From January 1985 to July 2006, 767 consecutive patients with CLM underwent liver resection after systemic chemotherapy. Patients with CPR were compared with patients without CPR.

Results

Twenty-nine of 767 patients (4%) had CPR, and none of these 29 patients had CCR. Patients with CPR (mean age: 54 years) had a mean number of 3.3 metastases at diagnosis (mean size: 29.3 mm). Objective response and stable disease were observed in 79% and 21% of cases, respectively. Postoperative mortality rate was 0%. After a median follow-up of 52.2 months (range: 1.1 to 193.0 months), overall 5-year survival was 76% for patients with CPR compared with 45% for patients without CPR (P=0.004). Independent predictive factors for CPR were: age 60 years or less, size of metastases 3 cm or less at diagnosis, carcinoembryonic antigen (CEA) level at diagnosis 30 ng/mL or less, and objective response following chemotherapy. The probability of CPR ranged from 0.2% when all factors were absent to 30.9% when all were present.

Conclusion

CPR was observed in 4% of patients with CLM treated with preoperative chemotherapy. However, CPR may occur in almost one-third of objective responders aged 60 years or less with metastases of 3 cm or less and low CEA values. CPR is associated with uncommon high survival rates.

Introduction

More than 50% of patients with colorectal cancer will develop liver metastases.[1] Hepatic resection today offers the only chance for cure, with 5-year survival rates ranging from 21% to 48%.[2,3] For patients with initially unresectable metastases, modern chemotherapy treatment allows the conversion of approximately 13% of these patients to a resectable situation, with 5-year survival rates after resection reaching 35%.[4] In addition, preoperative chemotherapy is increasingly being administered to patients with resectable disease. The objective of this approach is to control the metastatic disease, in order to avoid surgery in patients with rapidly progressive disease associated with a poor outcome after hepatic resection.[5] Furthermore, reduction of tumor size facilitates the possibility for curative resection.

The combination of 5-fluorouracil (5-FU) and leucovorin (LV) with oxaliplatin or irinotecan has increased the response rates of colorectal liver metastases (CLM) up to 60%.[6-8] Preliminary results show that the addition of biological agents to conventional chemotherapy may further increase these response rates and, subsequently, the proportion of patients referred for surgery.[9-11]

With these advances in chemotherapy efficacy, the frequency of a complete clinical response (CCR) of metastases has increased. Although still rare, CCR has recently created debate in the surgical and medical oncology communities.[12,13] CCR has, however, been shown to be of limited predictive value for complete pathologic response (CPR) and disease cure.[12] By contrast, a complete tumor destruction is observed in some cases, whether the initial tumor sites have disappeared (CCR) or still persist (no CCR) radiologically, and from an oncologic perspective, CPR may have much more clinical relevance than CCR.

Currently, no data exists concerning the long-term outcome and predictive factors of CPR. The aim of our study was to determine the incidence of CPR, to assess its relationship with CCR, and to evaluate its predictive factors and long-term survival.

PATIENTS AND METHODS

Patient selection

From January 1985 to July 2006, 945 consecutive patients with CLM were operated on at our institution and prospectively included in a database.

Of all 945 patients, 767 (81%) received preoperative systemic chemotherapy and underwent hepatectomy. This group consisted of 450 (59%) men and 317 (41%) women with a median age of 59.5 years (range: 27.6 to 84.8 years). The median number of metastases at diagnosis was 3 (range: 1 to 25) with a median maximum size of 35 mm (range: 1 to 250 mm). Concomitant extrahepatic disease was present in 162 patients (21%).

At diagnosis, disease was unresectable in 262 (34%) patients. Chemotherapy for resectable metastases was indicated for synchronous metastases with the primary tumor in place, or for marginally resectable disease (5 or more bilobar nodules or limited concomitant extrahepatic disease). Unresectability was defined as the technical inability to completely remove all metastases while leaving at least 30% of normal liver parenchyma. Patients received a median number of two lines of chemotherapy (range: 1 to 6 lines), with 350 patients (46%) receiving one line, 329 patients (43%) receiving two lines, 58 patients (8%) receiving three lines, and 26 patients (4%) receiving more than three lines. Last preoperative chemotherapy consisted of 5-FU and LV alone (25%) or combined with oxaliplatin (48%), irinotecan (14%) or both (7%). Miscellaneous systemic regimens were administered in the remaining 7% of patients. Patients received a median number of nine cycles (range: 1 to 54 cycles).

Preoperative management

The response to chemotherapy was evaluated every four cycles of treatment with computed tomography (CT) of the liver according to the RECIST criteria.[14] CCR was defined as the absence of any lesion or residual calcification at the site of the initially detected metastases, on all imaging modalities. Preoperative imaging was reviewed by a radiologist for all patients with CPR.

Hepatic resection

During surgery, our policy was to radically resect all remaining lesions, including remnant calcifications and scar lesions, with the aim to completely clear the liver of palpable and visible tumoral tissue, sparing the highest amount of liver parenchyma as possible.

Pathologic examination

Surgical liver specimens were cut in successive slices 0.5 cm thick. Localization, size, and gross evaluation of the percentage of necrosis were described for all

nodules. Each nodule was sampled for histologic examination: the number of paraffin blocks per nodule was proportional to the size of the nodule (one block for each cm of diameter).

At microscopic level, CPR was defined by the absence of any viable tumor cell irrespective of the proportions of necrosis and fibrosis. In case of any doubt, especially for the differential diagnosis with dystrophic biliary structures, additional immunohistochemistry for CK7 and CK20 was performed. CPR was only considered in patients following a complete resection of all CLM.

Follow-up

Patients were followed at one month postoperatively and then every 4 months with serum tumor markers (CEA and CA 19.9), clinical examination and hepatic imaging (ultrasound and/or CT). Repeat resection of intra- and/or extrahepatic disease recurrence was performed when curative resection could be achieved.[15]

Statistical analysis

Data were compared between patients with and without CPR using the X^2 test for categoric data and the independent-samples *T* test for continuous data. Overall and disease-free survival probabilities were determined with the Kaplan-Meier method and compared using the log-rank test. A *P* value ≤0.05 was considered significant. Predictive factors of CPR were analyzed using a multivariate risk model including factors with a *P* value ≤0.10 at univariate analysis. A predictive model was subsequently constructed to identify patients with the highest likelihood of achieving CPR following treatment with preoperative chemotherapy.[16,17] Statistical analyses were performed using SPSS® version 13.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Of all 767 resected patients receiving preoperative chemotherapy, 29 patients (4%) presented with CPR. The remaining 738 patients formed the comparison group for the study population.

Patient and tumor characteristics

Among the 29 patients with CPR there were 16 men and 13 women with a median age of 54.6 years (range: 35.1 to 70.1 years). The median number of liver metastases was 2 (range: 1 to 13) with a maximum diameter of 3 cm or less for most patients (71%) at diagnosis. For patients without CPR, the median number of metastases was 3 (range: 1 to 25) with a median maximum size of 35 mm (range: 5 to 250 mm). Compared with patients without CPR, patients with CPR were younger (P=0.02) and had a smaller maximum tumor size (P=0.01) *(Table 1)*.

In nine patients with CPR (31%), extrahepatic disease was diagnosed before or during liver surgery, compared with 153 patients (21%) in the group without CPR (P=0.18). For patients with CPR, extrahepatic metastases were present in the lungs in four patients (44%) and in intra-abdominal lymph nodes in two patients (22%). In the other three patients (33%), extrahepatic disease was located in the ovaries (one patient), bone (one patient), and peritoneum (one patient). Only one of the six patients with CPR that underwent extrahepatic disease resection also had a complete necrosis of resected extrahepatic metastases. For the three patients who did not undergo extrahepatic disease resection, chemotherapy (two patients) and radiotherapy (one patient) resulted in the radiological disappearance of the disease. Localization and resection of extrahepatic disease were not different for both patient groups *(Table 1)*.

Chemotherapy details

In the CPR group, preoperative chemotherapy was most commonly administered for technically resectable metastases (55%), either synchronous (23%), multinodular (13%), or associated to limited extrahepatic disease (19%). In the remaining 45% of patients, chemotherapy was administered for initially unresectable disease, related to multinodularity (31%), vascular ill-location (7%), or extensive extrahepatic disease (7%).

Eighteen patients (62%) received one line, six patients (21%) had two lines, and two patients (7%) had three lines of chemotherapy. Only three patients (10%) received more than three lines. The majority of patients (66%) received 5-FU, LV and oxaliplatin in the last preoperative line *(Table 1)*. Two of 29 patients (7%) had received cetuximab. However, no patients were treated with bevacizumab before hepatectomy. The median number of cycles was 8 (range: 3 to 29 cycles) for patients with CPR, compared with 9 (range: 1 to 54 cycles) for patients

Table 1. Comparison of clinical and chemotherapeutical features of the study population.

	Complete pathologic response (N = 29)	No complete pathologic response (N = 738)	*P*
Patients			
Mean age ± SD, years	54.0 ± 9.7	58.7 ± 10.8	0.02
Male/Female	16 (55%) / 13 (45%)	434 (59%) / 304 (41%)	0.70
Primary tumor			
Colon	22 (76%)	521 (74%)	0.85
Rectum	7 (24%)	180 (26%)	
T stage			
1/2	5 (22%)	38 (16%)	0.48
3/4	18 (78%)	200 (84%)	
N stage			
0	11 (46%)	70 (32%)	0.18
1/2	13 (54%)	147 (68%)	
Liver metastases			
Synchronous/Metachronous[a]	16 (55%) / 13 (45%)	450 (61%) / 288 (39%)	0.53
Mean number ± SD	3.3 ± 3.3	3.6 ± 3.3	0.63
Mean maximum size ± SD, mm	29.3 ± 19.6	44.3 ± 31.8	0.01
Distribution			
Unilobar	15 (52%)	345 (48%)	0.72
Bilobar	14 (48%)	369 (52%)	
Mean CEA level ± SD, ng/mL	60.6 ± 168.0	338.3 ± 1794.3	0.50
Concomitant extrahepatic disease	9 (31%)	153 (21%)	0.18
Localization			
Lung	4 (44%)	71 (46%)	0.87
Peritoneum	1 (11%)	21 (14%)	
Lymph nodes	2 (22%)	25 (16%)	
Other	2 (22%)	23 (15%)	
Combination	0 (0%)	13 (9%)	
Resection	6 (67%)	71 (46%)	0.24
Preoperative chemotherapy			
Indication			
Initial unresectability	13 (45%)	249 (34%)	0.23
Resectable disease	16 (55%)	481 (66%)	
Mean number of lines ± SD	1.7 ± 1.2	1.7 ± 0.8	0.83
Mean number of cycles ± SD	9.2 ± 6.1	10.8 ± 6.8	0.29
Chemotherapy regimen last line			
5-FU/LV Oxaliplatin	19 (66%)	321 (47%)	0.14
5-FU/LV Irinotecan	2 (7%)	97 (14%)	
Other	8 (28%)	264 (39%)	
Response			
Complete/Partial	23 (79%)	253 (53%)	0.005
No change/Progression	6 (21%)	228 (47%)	

a: synchronous metastases were diagnosed before or within 3 months after resection of the primary colorectal tumor.
Abbreviations: SD = standard deviation; CEA = carcinoembryonic antigen; 5-FU = 5-fluorouracil; LV = leucovorin.

without CPR. In the majority of patients with CPR (79%), a partial response was observed before surgery. The other 21% of patients had disease stabilization. CPR was observed in 19 of 340 patients treated with 5-FU, LV and oxaliplatin (6%) and in 2 of 99 patients (2%) receiving 5-FU, LV and irinotecan (P=0.14). No significant

differences in chemotherapy characteristics were observed between patients with and without CPR *(Table 1)*.

Relation between CCR and CPR

Following the last preoperative line of chemotherapy, two of the 767 patients of the total study population (0.3%) presented with CCR. In both patients, small remnant lesions were detected intraoperatively, and neither of these two patients had CPR. Interestingly, all 29 patients with CPR came from the group without CCR. An objective response was, however, more frequent in patients with CPR as compared with the control group (79% *vs* 53%) (P=0.005) *(Table 1)*.

Hepatectomy characteristics

CPR was found at first hepatectomy in 20 patients (69%) and at repeat hepatectomy in nine patients (31%: 24% at second and 7% at third hepatectomy).

Portal vein embolization was performed before hepatectomy in three patients to increase the volume of the future remnant liver *(Table 2)*.[18] For two patients in the CPR group, the selected hepatic resection constituted the second step of a two-stage resection.[19]

The 60-day mortality rate was 0%, and hepatic and general complications were observed in 16% and 24% of patients with CPR, respectively. Chemotherapy was continued postoperatively in 82% and 84% of patients with and without CPR, respectively (P=0.75).

Pathology details

Compared with patients without CPR, patients with CPR had fewer metastases in the resection specimen (mean: 1.9 *vs* 3.4) (P=0.005) with a smaller maximum tumor size (mean: 13 *vs* 43 mm) (P<0.001) *(Table 3)*. A margin-free resection (R0) was performed in 72% of patients with CPR versus 56% of patients without CPR (P=0.18).

Survival

Overall 3- and 5-year survivals for patients with CPR were 91% and 76%, respectively, and were significantly higher when compared with patients without CPR (61% and 45%, respectively) (P=0.004) *(Figure 1)*. Ten-year survivals were 68% and 29% with and without CPR, respectively. Disease-free survivals were also different between both groups (69% and 19% at 5 years) (P<0.001) *(Figure 2)*.

A comparison of both patient groups solely considering patients with liver-only metastases revealed 5-year overall survival rates of 65% and 44% (P=0.05) with and without CPR *(Figure 3)*. After a median follow-up of 52.2 months (range: 1.1 to 193.0 months), less recurrences occurred in patients with CPR (41% *vs* 62% for

Table 2. Comparison of operative and postoperative features of the study population.

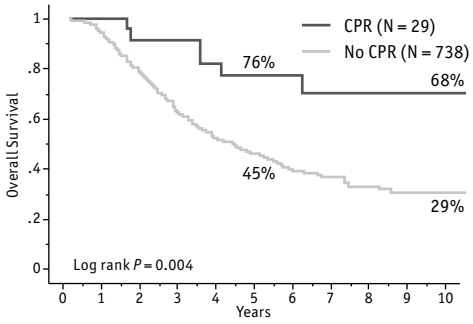
	Complete pathologic response (N = 29)	No complete pathologic response (N = 738)	*P*
Hepatectomy			
Mean prehepatectomy CEA level ± SD, ng/mL	2.1 ± 1.2	93.1 ± 398.9	0.26
Mean number of resected segments ± SD	1.1 ± 1.5	1.5 ± 1.8	0.24
Type of resection			
Anatomical	9 (31%)	225 (31%)	0.06
Nonanatomical	14 (48%)	218 (30%)	
Both	6 (21%)	289 (40%)	
Vascular occlusion			
None	9 (31%)	117 (21%)	0.01
Total pedicular	12 (41%)	360 (64%)	
Vascular exclusion	5 (17%)	73 (13%)	
Selective	3 (10%)	13 (2%)	
Combined local treatment			
None	28 (97%)	657 (89%)	0.45
RFA	1 (3%)	20 (3%)	
Cryotherapy	0 (0%)	58 (8%)	
Both	0 (0%)	3 (0%)	
Portal vein embolization	3 (10%)	41 (7%)	0.53
Two-stage resection	2 (7%)	44 (6%)	0.85
Mean red blood cell transfusions ± SD, units	1.5 ± 2.6	1.7 ± 3.1	0.74
Postoperative outcome			
Mortality (within 60 days)	0 (0%)	6 (1%)	0.61
General complications[a]	7 (24%)	127 (19%)	0.48
Hepatic complications			
None	24 (83%)	538 (84%)	0.18
Biliary leak	0 (0%)	22 (3%)	
Hemorrhage	0 (0%)	6 (1%)	
Infected collection	1 (3%)	27 (4%)	
Noninfected collection	3 (10%)	15 (2%)	
Liver insufficiency	0 (0%)	18 (3%)	
Combination	1 (3%)	17 (3%)	
Relaparotomy	0 (0%)	34 (5%)	0.21
Percutaneous drainage	2 (7%)	9 (6%)	0.85
Mean hospital stay ± SD, days	11.6 ± 2.9	13.3 ± 6.0	0.12
Postoperative chemotherapy	22 (82%)	528 (84%)	0.75

a: as general complications were considered: pulmonary, cardiovascular, urinary tract, infectious (other than local hepatic) and iatrogenic complications. Abbreviations: CEA = carcinoembryonic antigen; SD = standard deviation; RFA = radiofrequency ablation.

Table 3. Comparison of pathologic features of the study population.

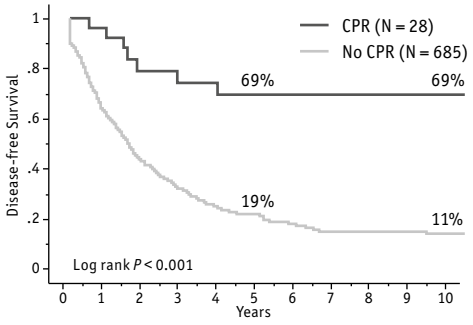
	Complete pathologic response (N = 29)	No complete pathologic response (N = 738)	*P*
Mean number of resected metastases ± SD	1.9 ± 1.1	3.4 ± 2.8	0.005
Mean maximum size ± SD, mm	13.0 ± 12.1	43.0 ± 38.0	< 0.001
Resection margin			
R0	21 (72%)	330 (56%)	0.18
R1	8 (28%)	248 (42%)	
R2	0 (0%)	15 (3%)	
Metastatic lymph nodes			
None	28 (97%)	100 (75%)	0.08
Pedicular	0 (0%)	20 (15%)	
Celiac	1 (3%)	12 (9%)	
Other	0 (0%)	1 (1%)	

Abbreviations: SD = standard deviation.



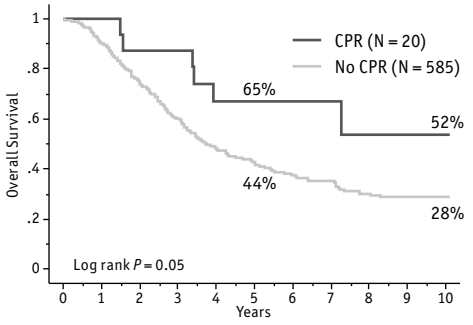
Patients at risk	Total	1 yr	3 yrs	5 yrs	6 yrs	8 yrs	10 yrs
CPR	29	25	19	11	11	8	5
No CPR	738	545	222	104	71	36	20

Figure 1.
Overall survival curves (Kaplan-Meier) of patients with and without complete pathologic response (CPR).



Patients at risk	Total	1 yr	3 yrs	5 yrs	6 yrs	8 yrs	10 yrs
CPR	28	23	15	9	9	8	5
No CPR	685	349	130	70	46	26	15

Figure 2.
Disease-free survival curves (Kaplan-Meier) of patients with and without complete pathologic response (CPR).



Patients at risk	Total	1 yr	3 yrs	5 yrs	6 yrs	8 yrs	10 yrs
CPR	20	17	13	6	6	4	2
No CPR	585	456	202	101	71	39	27

Figure 3.
Overall survival curves (Kaplan-Meier) of patients with liver-only metastases with and without complete pathologic response (CPR).

patients without CPR) (P=0.03). Hepatic recurrences were less frequent in the CPR group (17% *vs* 57%, respectively) (P=0.003). Isolated extrahepatic or combined intra- and extrahepatic recurrences both occurred in 42% of patients with CPR. Repeat hepatectomy was performed in six patients, two of whom also underwent extrahepatic disease resection. Three additional patients only had resection of extrahepatic disease recurrence. At last follow-up, 20 patients with CPR are alive disease-free (69%), of whom nine more than 5 years and five more than 10 years after hepatectomy. Two patients are alive with disease (7%) and seven patients (24%) have died from recurrence.

Analysis of predictive factors

Univariate analysis identified seven preoperative variables with statistical difference (P≤0.10) between both groups *(Table 4)*. At multivariate analysis, four of the univariate factors were found to be independent predictive factors of CPR: age 60 years or less, maximum size of metastases 3 cm or less at diagnosis, CEA level 30 ng/mL or less at diagnosis, and objective response following chemotherapy.

Table 4. Univariate and multivariate analysis of predictive factors of complete pathologic response.

	Complete pathologic response (N = 29)	No complete pathologic response (N = 738)	UV *P*	MV *P*	RR	95% CI
Clinical characteristics						
Age						
≤ 60 yrs	24 (83%)	403 (55%)	0.003	0.03	4.1	1.1-15.1
> 60 yrs	5 (17%)	335 (45%)				
Maximum size of metastases at diagnosis						
≤ 3 cm	20 (71%)	262 (44%)	0.004	0.05	3.1	1.0-9.5
> 3 cm	8 (29%)	339 (56%)				
CEA level at diagnosis						
≤ 30 ng/mL	17 (90%)	148 (48%)	< 0.001	0.03	5.6	1.2-26.3
> 30 ng/mL	2 (11%)	160 (52%)				
Chemotherapy characteristics						
Number of lines						
≤ 3	26 (90%)	714 (97%)	0.04	NS	-	-
> 3	3 (10%)	23 (3%)				
Number of cycles						
≤ 10	17 (77%)	272 (59%)	0.09	NS	-	-
> 10	5 (23%)	188 (41%)				
Last line regimen						
5-FU/LV Oxaliplatin	19 (66%)	321 (47%)	0.05	NS	-	-
Other	10 (35%)	361 (53%)				
Response						
Complete/Partial	23 (79%)	253 (53%)	0.005	0.04	3.9	1.1-14.4
No change/Progression	6 (21%)	228 (47%)				

Abbreviations: UV = univariate; MV = multivariate; RR = risk ratio; CI = confidence interval; CEA = carcinoembryonic antigen; NS = not significant; 5-FU = 5-fluorouracil ; LV = leucovorin.

Predictive model for CPR

To predict the presence of CPR in individual patients treated with preoperative chemotherapy, the four multivariate predictive factors were each assigned one point. For patients without any of the predictive factors, the probability to present with CPR was 0.2%. The addition of subsequent factors increased this probability to 0.9% for one factor, 3.6% for two factors, 12.7% for three factors, and 30.9% for four factors *(Table 5)*.

Table 5. Probability of complete pathologic response based on four predictive factors in patients treated with preoperative chemotherapy.

Age ≤ 60 years	Size ≤ 3 cm	CEA ≤ 30 ng/mL	OR	Probability (%)	Factors
-	-	-	-	0.2	0
+	-	-	-	0.7	1
-	+	-	-	0.5	
-	-	+	-	0.9	
-	-	-	+	0.6	
+	+	-	-	2.0	2
+	-	+	-	3.6	
+	-	-	+	2.6	
-	+	+	-	2.7	
-	+	-	+	1.9	
-	-	+	+	3.4	
+	+	+	-	10.3	3
+	+	-	+	7.5	
+	-	+	+	12.7	
-	+	+	+	9.8	
+	+	+	+	30.9	4

Abbreviations: CEA = carcinoembryonic antigen; OR = objective radiological response.

DISCUSSION

The use of highly effective chemotherapy regimens in patients with CLM has resulted in an increased frequency of CCR. Recent studies have shown that most of the lesions that disappear on imaging are still found to have viable tumor when resected, or recur *in situ* when not resected.[12] Based on these findings, it appears that CPR could be of more important prognostic value than CCR. To date, outcomes in patients with CPR have remained unexplored.

In this study, we evaluated the long-term survival of patients with CPR after hepatic resection. Overall, CPR was identified in 4% of resected patients. Noteworthy, CPR was more than 10 times more frequent than CCR (0.3%). Previously, we showed CCR and CPR percentages of 3% and 7%, respectively, in more selected patients with initially unresectable disease, converted to resection after chemotherapy treatment.[20] By definition, these patients were high responders to chemotherapy, resulting in a logically higher frequency of CCR. The strict definition of CCR used in the present series might be another explanation for the lower percentage of CCR, and a proportion of remnant metastatic lesions can now be detected by better preoperative imaging modalities. The fact that in our experience CPR was more than 10 times more frequent than CCR indicates that total necrosis does not imply disappearance of metastases on preoperative imaging. Conversely, in this study, none of the patients with CCR had CPR.

CPR was associated with a remarkable 5-year overall survival of 76% with a still not reached median survival. Survival was not only significantly higher than for patients without CPR, but constitutes the highest rate of 5-year survival ever reported after resection of CLM. To eliminate the influence of extrahepatic metastases on long-term outcome, survivals of both groups were also compared considering patients with liver-only metastases. Five-year survival for patients with CPR decreased to 65% due to the exclusion of five of 11 patients who survived more than 5 years. However, survival remained higher than that of patients without CPR, confirming that CPR is a strong predictor of prolonged survival and cure.

The favorable long-term results for patients with CPR could question the utility of surgery in this setting. However, in our opinion surgery should be proposed for several reasons. First, confirmation of CPR ultimately depends on the accuracy of gross pathologic examination and on the exhaustivity of histologic sampling, and few undetected malignant cells could therefore still be present in resected lesions. By resecting all metastases, the possibility of leaving active tumor cells untreated is secured. Second, additional metastatic lesions may be found at laparotomy, that otherwise would have remained undetected.[21] Finally, no imaging technique, even positron emission tomography-CT, is currently reliable to diagnose CPR.[22] In the absence of any reliable preoperative assessment tool for

CPR, only surgical resection with concomitant pathologic examination of the specimen is able to make the definitive diagnosis. In addition, the complete disappearance of metastases on imaging should not contraindicate surgery, since a majority of these patients will not have CPR. Paradoxically, patients treated with chemotherapy should be referred to surgeons before CCR to avoid the therapeutically difficult situation associated with the inability to localize previous radiologically apparent lesions. In these situations, remnant malignant lesions might be missed, risking disease progression when chemotherapy is withdrawn.

Few studies have dealed with complete response: three concerning clinical response with controversial results, and two approaching pathologic findings. Recent data have clarified that for 83% of CLM showing CCR, macro- or microscopic disease persists or *in situ* recurrence occurs within one year postoperatively.[12] On the contrary, another study, evaluating the evolution of nonresected disappeared CLM in 11 patients, found that 73% of patients did not present with *in situ* recurrence after a median follow-up of 31 months.[13] However, the limited number of patients and the use of intra-arterial chemotherapy in a large percentage of these patients makes it difficult to draw definitive conclusions on the clinical significance of these disappeared lesions. Additionally, a recent analysis from the Intergroup N9741 trial found a remarkable median survival of 44 months for patients with CCR after systemic chemotherapy alone.[23] This concerned, however, a mixed patient population with different types of advanced colorectal cancer.

With regard to pathologic response, a first study concluded that different types of remnant lesions can be present after chemotherapy treatment with a still undefined impact on outcome and recurrence.[24] In another study, five of 112 patients pretreated with chemotherapy (4%) presented with CPR, which is in agreement with our series.[25] A higher degree of pathologic tumor regression was associated with improved overall and disease-free survival. However, both studies lack the evaluation of predictive factors of CPR and of the impact of CPR on long-term survival.

Interestingly, in the latter study, patients treated with oxaliplatin experienced a higher degree of tumor regression compared with patients treated with irinotecan.[25] In our experience, the number of lines, cycles, and type of chemotherapy treatment did not influence the incidence of CPR. CPR occurred more frequently in patients treated with oxaliplatin, however, this difference did not reach statistical significance.

In clinical practice, an important issue is to appreciate the possibility of CPR. Owing to the overall incidence of 4%, it could be argued that this situation is anecdotal. However, by analyzing the predictive factors of CPR, our study determined that patients presenting with small tumors (3 cm or less) and/or a relatively low CEA value (30 ng/mL or less) were more likely to present with CPR

following preoperative chemotherapy treatment. This can be related to a limited amount of intrahepatic tumor burden, facilitating the cytotoxic effect of chemotherapeutic agents. As expected, radiological response also predicted the presence of CPR. Finally, young patients (60 years or less) were found to have an increased probability for CPR. This finding was independent of primary tumor and chemotherapy characteristics. Overall, the presence of predictive factors was associated with an increase in the proportion of patients with CPR up to 31%, confirming its clinical relevance.

In conclusion, CPR is observed in 4% of patients resected for CLM following preoperative chemotherapy. When combined with an aggressive oncosurgical approach, CPR is associated with an exceptional high survival. The emergence of still more active chemotherapy regimens and biotherapies will certainly increase the frequency of CPR in the near future raising the need of a better comprehension of this entity. Further work should be encouraged to identify chemotherapeutic factors that increase the chance of CPR in resected patients, which is obviously associated with a real hope of cure.

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Chapter 9

Patients with initially unresectable colorectal liver metastases: is there a possibility of cure?

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ABSTRACT

Background

Although oncosurgical strategies have demonstrated increased survival in patients with unresectable colorectal liver metastases (CLM), their potential of cure is still questioned. The aim of this study was to evaluate long-term outcome after combining downsizing chemotherapy and rescue surgery and to define prognostic factors of cure.

Patients and Methods

All patients with initially unresectable CLM who underwent rescue surgery and had a minimum follow-up of 5 years were included. Cure was defined as a disease-free interval of 5 years or more from last hepatic or extrahepatic resection until last follow-up.

Results

Mean age of 184 patients who underwent resection (April 1988 until July 2002) was 56.9 years. Patients had a mean number of 5.3 metastases (bilobar in 76%), associated to extrahepatic disease in 27%. Surgery was possible after one (74%) or more (26%) lines of chemotherapy. Five- and 10-year overall survival rates were 33% and 27%, respectively. Of 148 patients with a follow-up of 5 years or more, 24 patients (16%) were considered cured (mean follow-up: 118.6 months), six (25%) of whom were considered cured after repeat resection of recurrence. Twelve cured patients (50%) had a disease-free interval more than 10 years. Cured patients more often had 3 or fewer metastases less than 30 mm (P=0.03), responding to first-line chemotherapy (P=0.05). Multivariate analysis identified maximum size of metastases less than 30 mm at diagnosis, number of metastases at hepatectomy 3 or fewer, and complete pathologic response as independent predictors of cure.

Conclusion

Cure can be achieved overall in 16% of patients with initially unresectable CLM resected after downsizing chemotherapy. In addition to increased survival, this oncosurgical approach has real potential of disease eradication.

INTRODUCTION

Approximately 80% of patients with colorectal liver metastases (CLM) present with unresectable disease at diagnosis. For patients who do not undergo resection, survival rates are poor and do not exceed 2% at 5 years.[1,2] The introduction of novel chemotherapeutic regimens, including oxaliplatin and irinotecan, has increased the median survival of these patients.[3,4] However, the results of chemotherapy still remain inferior to those of curative hepatic resection, which results in 5-year survival rates of 40% overall (www.livermetsurvey.org) and even exceeds 50% in selected patients.[5,6]

The potential value of resectability for long-term survival has resulted in the development of oncosurgical strategies for initially unresectable disease. When used in combination with surgery, chemotherapy, radiofrequency ablation and portal vein embolization (PVE) may now result in potentially curative treatment and long-term survival of these patients. We previously reported a 13% conversion rate to resectability of patients with unresectable disease after tumor downsizing by chemotherapy, associated with a 5-year survival rate of 33% after hepatectomy.[7] Comparable experience has later been reported by others with different chemotherapy regimens, with results largely depending on variety in patient selection.[8-10]

It is well known, that patients with extensive tumor involvement experience less favorable outcome after hepatic resection as compared with patients with limited disease.[11-13] Nevertheless, long-term survival is increasingly reported after surgery, even in the presence of poor prognostic factors.[14,15] The potential of cure for patients with liver metastases, especially when initially unresectable, is however still questioned, owing to the fact that it represents a widespread, advanced systemic disease.

To date, cure has only been evaluated in patients treated by surgery alone.[16] Furthermore, although long-term disease-free survival is the most appropriate definition of cure, it is usually defined as long-term overall survival only. In this study, we evaluated the possibility of cure by taking into account disease-free survival and a multidisciplinary treatment strategy combining surgery and chemotherapy in patients with initially unresectable CLM. The additional objective was to determine predictive factors of disease cure.

PATIENTS AND METHODS

Cohort description

All patients with unresectable CLM at the time of diagnosis who underwent rescue surgery after downsizing chemotherapy and had a minimum follow-up of 5 years from surgery were included. Patients considered to have technically unresectable disease had a too small remnant liver volume in relation to the extent of the resection that was needed for complete resection of all metastases. This was defined by the need of a resection leaving less than 30% of liver remnant, or less than 40% when patients received intensive preoperative chemotherapy.[17]

Preoperative management

Response to chemotherapy was evaluated every 2 months by a multidisciplinary team that included surgeons, oncologists, and radiologists by computed tomography (CT) according to the WHO guidelines during the initial study period and to the RECIST criteria during the final period.[18,19] Patients responding to chemotherapy were reconsidered for surgery when the overall strategy could achieve complete clearance of intra- and extrahepatic metastases. Preoperative workup included CT of the chest, abdomen and pelvis to evaluate liver and extrahepatic disease, as well as colonoscopy to assess local recurrence of the primary tumor.

Hepatic resection

Resection of all detectable lesions with tumor-free margins was the objective of surgery in all patients. However, when tumor-free margins were not possible owing to major vascular or biliary contact, resection was still indicated provided that all tumors could be macroscopically resected.

When downsizing by chemotherapy was not sufficient to allow a curative treatment, surgery might include three specific techniques aimed at increasing resectability. First, PVE was performed 4 to 6 weeks before surgery in cases of too small estimated remnant liver volume after the planned hepatectomy.[20] Second, for bilobar metastases, hemihepatectomy could be combined with the use of radiofrequency ablation or cryotherapy for few contralateral, unresectable, deeply located lesions of 3 cm or less. Third, when multinodular bilobar metastases could neither be completely resected by a single procedure nor treated with hepatectomy combined with ablation, two-stage hepatectomy was considered.[21] Postoperative complications within two months after hepatectomy were recorded and classified according to the classification by Clavien.[22] Liver insufficiency was defined as an increase in serum bilirubin level to more than 50 µmol/L and a decrease in prothrombin time to less than 50%.[23]

The presence of resectable extrahepatic metastases was not a contraindication to liver resection. When located in the abdomen, resection of extrahepatic disease

was performed at the same time as the hepatectomy. For extrahepatic disease outside the abdomen, resection was generally delayed for 2 to 3 months, with chemotherapy treatment during the time-interval to prevent disease progression.

Postoperative management

Follow-up after hepatectomy included physical examination, serum tumor markers (CEA and CA 19.9), and abdominal ultrasound one month after surgery and then every 4 months. CT imaging of the chest, abdomen and pelvis was performed every 8 months. As a routine policy, chemotherapy was recommended postoperatively for 6 to 8 cycles to decrease the risk of disease recurrence.

Definition of cured and noncured patients

Cure was defined as a disease-free interval of 5 years or more after the last hepatectomy or last resection of extrahepatic metastases. Furthermore, patients had to be free of disease at last follow-up. Patients who died of not curatively resected metastases or disease recurrence were defined noncured.

Statistical analysis

Cured patients were compared with noncured patients using the X^2 test for categorical data and the independent-samples *T* test for continuous data. A multivariate risk model of factors likely to predict cure and expressing a *P* value ≤0.10 at univariate analysis was used to define independent predictors of cure. *P* values ≤0.05 were considered significant. SPSS® software version 13.0 was used for all statistical calculations (SPSS Inc., Chicago, Illinois, USA).

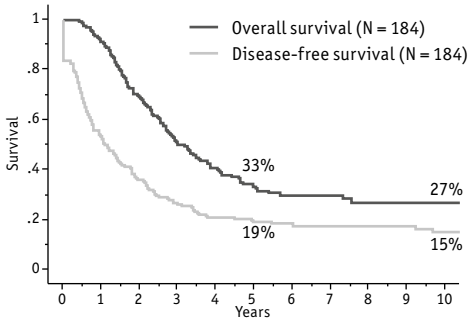
RESULTS

Between April 1988 and July 2002, 184 consecutive patients with initially unresectable CLM underwent hepatic resection at our institution after tumor downsizing by systemic chemotherapy. This group consisted of 102 men (55%) and 82 women (45%) with a median age of 58.3 years (range: 30.8 to 79.2 years). Patients had a median number of 5 metastases (range: 1 to 22) with a median size of 50 mm at diagnosis (range: 6 to 160 mm). Metastases were bilobar in 76% of cases.

Reasons for unresectability were multinodular disease (50%), large size of metastases (21%), vascular ill-location of metastases (18%) or extensive concomitant extrahepatic disease (12%). Metastases became resectable after a median number of 1 line (range: 1 to 4 lines) and 10 cycles (range: 2 to 43 cycles) of chemotherapy. The last preoperative regimen consisted most often of 5-fluorouracil (5-FU) and leucovorin (LV) alone (18%), or combined with oxaliplatin (62%), irinotecan (6%), or both (9%). Other regimens were administered in the remaining 5% of patients.

Cured and noncured patients

For the 184 patients who underwent resection, 5- and 10-year survival rates were 33% and 27%, respectively *(Figure 1)*. Disease-free survival rates were 19% and 15% at 5 and 10 years, respectively.



Patients at risk	Total	1 yr	3 yrs	5 yrs	6 yrs	8 yrs	10 yrs
Overall survival	184	161	78	41	25	18	14
Disease-free survival	184	96	45	31	22	17	12

Figure 1.
Overall and disease-free survival curves of patients with initially unresectable disease who underwent resection after downsizing chemotherapy.

A total of 148 patients (80%) had a follow-up of 5 years or more after hepatectomy. Of these, 24 patients (16%) were considered cured. One of the 24 patients died of a second primary tumor 16 years after hepatectomy and was therefore still

considered cured of the initial disease. Another 112 patients (76%) had died of disease and formed the noncured patient group. Twelve remaining patients (8%) were excluded because of a disease-free interval of less than 5 years after last resection (three), the presence of disease recurrence at last follow-up (eight), or death from a nontumoral cause (one) (9 months after hepatectomy).

Patient, primary tumor and metastases characteristics

Cured patients had a median age of 61.2 years (range: 30.8 to 73.1 years) and presented with synchronous metastases in 58% of cases *(Table 1)*. The median number of metastases was 3 (range: 1 to 15) with a mean maximum size of 50.5 mm at diagnosis. Metastasis size was smaller for cured than for noncured patients (less than 30 mm: 30% *vs* 12%) (P=0.03). Sixty-seven percent of cured patients had metastases in both liver lobes. Four patients (17%) had concomitant extrahepatic disease, which included lung metastases (one patient), peritoneal metasta-

Table 1. Patient, primary tumor and metastases characteristics of cured and noncured patients.

	Cured patients (N = 24)	Noncured patients (N = 112)	*P*
Patients			
Mean age ± SD, years	58.7 ± 10.5	56.6 ± 10.5	0.38
Male/Female	14 (58%) / 10 (42%)	65 (58%) / 47 (42%)	0.98
Primary tumor			
Colon/Rectum	23 (96%) / 1 (4%)	91 (81%) / 21 (19%)	0.08
T stage			
1/2	0 (0%)	10 (13%)	0.15
3/4	15 (100%)	70 (88%)	
N stage			
0	5 (33%)	24 (29%)	0.71
1/2	10 (67%)	60 (71%)	
Liver metastases			
Synchronous/Metachronous[a]	14 (58%) / 10 (42%)	82 (73%) / 30 (27%)	0.15
Number			
1	6 (25%)	16 (16%)	0.19
2 - 3	7 (29%)	18 (18%)	
> 3	11 (46%)	66 (66%)	
Mean maximum size ± SD, mm	50.5 ± 32.2	59.6 ± 32.5	0.23
Unilobar/Bilobar	8 (33%) / 16 (67%)	23 (21%) / 89 (80%)	0.18
Cause of unresectability			
Multinodular	9 (38%)	57 (51%)	0.68
Size	5 (21%)	20 (18%)	
Vascular ill-location	6 (25%)	22 (20%)	
Extrahepatic disease	4 (17%)	13 (12%)	
Mean CEA level ± SD, ng/mL	114.8 ± 236.3	258.6 ± 510.0	0.23
Concomitant extrahepatic disease	4 (17%)	36 (32%)	0.13
Resection	2 (50%)	23 (62%)	0.64

a: synchronous metastases were diagnosed before or within 3 months after resection of the primary colorectal tumor. Abbreviations: SD = standard deviation; CEA = carcinoembryonic antigen.

ses (one patient), pedicular lymph node metastases (one patient) and a bone metastasis located in the scapula (one patient). Unresectability was related to multinodular (38%), large (21%), or vascular ill-located (25%) metastases, or extrahepatic disease (17%).

Chemotherapy treatment

Surgery was allowed after one line of chemotherapy in 88% of cured patients *(Table 2)*. Noncured patients more often received two or more lines of chemotherapy before hepatectomy could be reconsidered (33% *vs* 13%) (*P*=0.05). Patients who achieved cure were administered a median number of 8 cycles (range: 4 to 29 cycles) and a last preoperative regimen that most often consisted of 5-FU/LV and oxaliplatin (75%). Chronomodulated therapy was used in 19 patients (79%).[24] None of the cured patients were treated with targeted agents in the last preoperative line.

Table 2. Comparison of preoperative chemotherapy characteristics for cured and noncured patients.

	Cured patients (N = 24)	**Noncured patients (N = 112)**	***P***
Number of lines			
1	21 (88%)	75 (67%)	0.05
> 1	3 (13%)	37 (33%)	
Mean number of cycles ± SD	10.6 ± 6.3	10.9 ± 5.3	0.85
Last line regimen			
5-FU/LV	1 (4%)	24 (22%)	0.25
5-FU/LV Oxaliplatin	18 (75%)	66 (60%)	
5-FU/LV Irinotecan	2 (8%)	7 (6%)	
Other	3 (13%)	14 (13%)	
Chronotherapy	19 (79%)	77 (69%)	0.34
Clinical response			
Complete/Partial	20 (83%)	94 (84%)	0.94
Stabilization	4 (17%)	18 (16%)	

Abbreviations: SD = standard deviation; 5-FU = 5-fluorouracil; LV = leucovorin.

Hepatectomy characteristics

During surgical exploration, more than three metastases were detected more frequently in noncured patients compared to cured patients (63% *vs* 33%) (*P*=0.02). Major hepatectomies (3 or more segments) were performed in 42% of cured patients. Most hepatectomies (75%) included anatomical resections *(Table 3)*. Combined local treatment, PVE, and two-stage hepatectomy were necessary in 21%, 8%, and 4% of cured patients, respectively, to achieve complete resection. Operative data concerning the initial hepatectomy did not differ

between both groups *(Table 3)*. Postoperative chemotherapy was administered in 92% and 93% of cured and noncured patients, respectively.

Table 3. Comparison of data concerning initial liver resection and postoperative outcome of cured and noncured patients.

	Cured patients (N = 24)	Noncured patients (N = 112)	*P*
Hepatectomy			
Mean prehepatectomy CEA level ± SD, ng/mL	8.7 ± 18.5	121.7 ± 633.3	0.43
Mean prehepatectomy CA 19.9 level ± SD, U/L	26.2 ± 50.8	193.1 ± 707.5	0.35
Number of detected metastases			
1	5 (21%)	18 (16%)	0.02
2 - 3	11 (46%)	23 (21%)	
> 3	8 (33%)	70 (63%)	
Major resection (≥ 3 segments)	10 (42%)	55 (49%)	0.51
Type of resection			
Anatomical	7 (29%)	28 (25%)	0.90
Nonanatomical	6 (25%)	28 (25%)	
Both	11 (46%)	56 (50%)	
Vascular occlusion			
None	7 (29%)	19 (17%)	0.27
Total pedicular	8 (33%)	54 (49%)	
Vascular exclusion	3 (13%)	20 (18%)	
Selective	6 (25%)	17 (16%)	
Mean duration of pedicular clamping ± SD, min	45 ± 24	49 ± 27	0.64
Combined local treatment			
None	19 (79%)	94 (84%)	0.23
RFA	2 (8%)	2 (2%)	
Cryotherapy	3 (13%)	16 (14%)	
PVE	2 (8%)	29 (26%)	0.06
Two-stage resection	1 (4%)	16 (14%)	0.17
Mean red blood cell transfusions ± SD, units	1.6 ± 4.7	2.7 ± 5.0	0.40
Mean duration ± SD, minutes	294 ± 140	349 ± 118	0.23
Postoperative outcome			
Mortality (within 90 days)	0 (0%)	0 (0%)	-
General complications[a]	4 (17%)	30 (27%)	0.30
Hepatic complications			
None	18 (75%)	75 (67%)	0.20
Biliary leak	0 (0%)	7 (6%)	
Hemorrhage	0 (0%)	2 (2%)	
Infected collection	0 (0%)	4 (4%)	
Noninfected collection	6 (25%)	12 (11%)	
Liver insufficiency[23]	0 (0%)	4 (4%)	
Combination	0 (0%)	8 (7%)	
Relaparotomy	0 (0%)	4 (4%)	0.35
Percutaneous drainage	4 (17%)	17 (15%)	0.86
Mean hospital stay ± SD, days	12.8 ± 5.7	14.0 ± 6.4	0.42
Postoperative chemotherapy	22 (92%)	103 (93%)	0.85

a: as general complications were considered: pulmonary, cardiovascular, urinary tract, infectious (other than local hepatic) and iatrogenic complications. Abbreviations: CEA = carcinoembryonic antigen; SD = standard deviation; CA 19.9 = carbohydrate antigen 19.9; min = minutes; RFA = radiofrequency ablation; PVE = portal vein embolization.

Resection of extrahepatic metastases

Extrahepatic metastases were resected in 2 of 4 cured patients (50%) who presented with extrahepatic disease. In one patient, pedicular lymph node metastases were resected at the same time as the hepatectomy. The other patient had lung metastases that regressed under chemotherapy and were resected 3 months after hepatectomy. For the remaining two patients, radiotherapy for a single bone metastasis and chemotherapy for localized peritoneal carcinomatosis resulted in complete disappearance of the extrahepatic disease. Comparatively, extrahepatic disease resection was performed in 23 (62%) of 36 noncured patients that presented with metastases outside the liver (P=0.64).

Pathology

The number and size of resected metastases was similar between the two groups *(Table 4)*. The first hepatectomy was incomplete in two (8%) of the cured patients, related to a two-stage hepatectomy approach in one of them. Remnant liver metastases were completely resected by a second hepatectomy in both cases.

Table 4. Comparison of pathologic features after initial hepatectomy excluding patients who underwent two-stage hepatectomy.

	Cured patients (N = 24)	**Noncured patients (N = 112)**	***P***
Number of resected metastases			
1	7 (32%)	27 (29%)	0.15
2 - 3	10 (46%)	26 (28%)	
> 3	5 (23%)	41 (44%)	
Mean maximum size ± SD, mm	32.5 ± 19.5	44.4 ± 33.4	0.13
Resection margin			
R0	11 (48%)	31 (34%)	0.34
R1	11 (48%)	59 (64%)	
R2	1 (4%)	2 (2%)	
Complete pathologic response	5 (21%)	1 (1%)	< 0.001

Abbreviations: SD = standard deviation.

Complete pathologic tumor response was present in 5 (21%) of 24 patients in whom cure was achieved. To the contrary, complete pathologic response was found in only one (1%) of the noncured patients (P<0.001).

Postoperative complications

No postoperative mortality was observed in either group within the 3 months after hepatectomy. Postoperative morbidity occurred in 33% of cured patients after initial hepatectomy *(Table 3)*, and included only general complications in

8%, only hepatic complications in 17%, and both general and hepatic complications in 8%. General and hepatic complications were classified as grade I or II events in all cases that occurred in cured patients.[22]

Achievement of cure and causes of noncure

Median follow-up of cured patients was 121.2 months (range: 60.2 to 201.4 months). Sixteen (67%) of the 24 cured patients were cured after the initial hepatectomy. One patient (4%) who underwent a two-stage hepatectomy was cured after resection of concomitant pulmonary metastases. Another patient (4%) was cured after repeat hepatectomy of a single nodule that was missed at the initial hepatectomy. The six remaining patients (25%) were cured after resection of recurrent disease *(Figure 2)*.

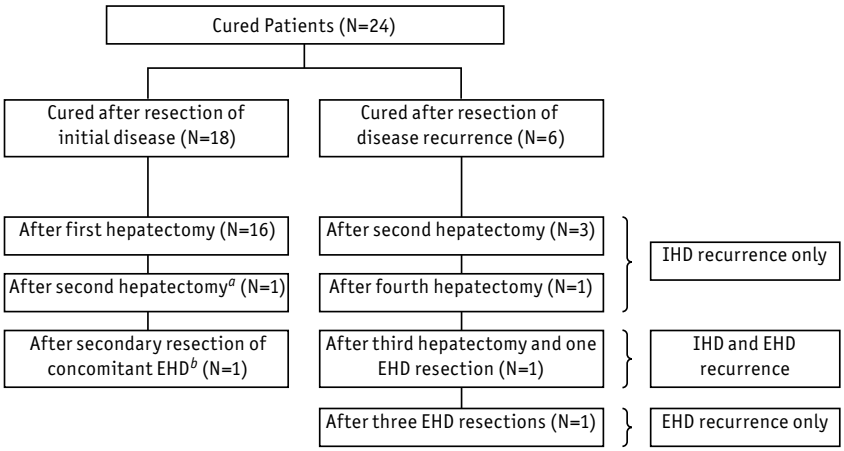


Figure 2.

Flowchart of cured patients detailing the different moments at which cure was achieved.

***a*: of a single tumor nodule missed at first hepatectomy; *b*: this patient underwent a two-stage hepatectomy approach. Abbreviations: EHD = extrahepatic disease; IHD = intrahepatic disease.**

Recurrences were both intra- and extrahepatic in one patient (4%), only intrahepatic in 4 patients (17%), and only extrahepatic in another patient (4%). Time to first recurrence tended to be longer for patients in the cured group as compared with those in the noncured group (mean: 16.0 *vs* 9.4 months, respectively) (P=0.09). Three patients with isolated intrahepatic recurrence were cured after a second hepatectomy, and one patient was cured after a fourth hepatectomy. The patient with isolated extrahepatic recurrence required three repeat

extrahepatic resections. The sixth patient was cured after a third hepatectomy combined with one repeat extrahepatic resection. The last curative resection was performed within 3.5 years after initial hepatectomy for all six patients. Of note, none of the 24 patients defined as cured by the study definition presented a further recurrence after the initial 5-year disease-free interval. Among the 24 cured patients, 12 (50%) have reached a disease-free interval of 10 years or more with currently available follow-up.

From the 112 noncured patients, 24 patients (21%) died of incompletely resected intra- or extrahepatic metastases. The other 88 patients (79%) succumbed of recurrent disease. This concerned only intrahepatic recurrence in 23 patients (21%), only extrahepatic recurrences in 14 patients (13%), and combined intra- and extrahepatic recurrences in 51 patients (46%). Localization of recurrent disease for noncured patients was not different from that of cured patients (P=0.08). None of the noncured patients experienced a disease-free interval of 5 years or more in the course of their disease. Noncured patients died after a median of 2.1 years (range: 0.4 to 7.5 years) after initial hepatectomy.

Predictive factors of cure

When comparing cured and noncured patients at univariate analysis, five variables likely to predict cure were significantly different between both groups (P≤0.10). Multivariate analysis identified three of these variables as independent predictors of cure: maximum size of metastases at diagnosis less than 30 mm, number of metastases at hepatectomy 3 or fewer, and complete pathologic tumor response *(Table 5)*.

Table 5. Univariate and multivariate analysis of predictive factors of cure.

	Cured patients (N = 24)	Noncured patients (N = 112)	UV *P*	MV *P*	RR	95% CI
Clinical characteristics						
Primary tumor						
Colon	23 (96%)	91 (81%)	0.08	NS	-	-
Rectum	1 (4%)	21 (19%)				
Maximum size of metastases at diagnosis						
< 30 mm	7 (30%)	12 (12%)	0.03	0.03	3.8	1.1-13.0
≥ 30 mm	16 (70%)	85 (88%)				
Hepatectomy characteristics						
Prehepatectomy CEA level						
< 10 ng/mL	18 (90%)	61 (60%)	0.01	NS	-	-
≥ 10 ng/mL	2 (10%)	40 (40%)				
Number of metastases at hepatectomy						
≤ 3	16 (67%)	41 (37%)	0.007	0.02	3.6	1.2-10.4
> 3	8 (33%)	70 (63%)				
Pathologic characteristics						
Complete pathologic response						
No	19 (79%)	110 (99%)	< 0.001	0.01	17.9	1.9-163.8
Yes	5 (21%)	1 (1%)				

Abbreviations: UV = univariate; MV = multivariate; RR = risk ratio; CI = confidence interval; NS = not significant; CEA = carcinoembryonic antigen.

Discussion

Considerable developments in chemotherapy and surgery have led to improved outcomes for patients with CLM.[5,25] Long-term survival after hepatectomy is increasingly reported and has long been regarded as the most appropriate definition of cure, considering that cancer-related death more than 10 years after hepatectomy is rare.[16] However, as CLM represent a systemic disease, 5-year survival without evidence of disease recurrence may be more appropriate and clinically more practical to define cure.[26] This study is the first to assess long-term disease-free survival in patients with initially unresectable CLM treated with a combination of chemotherapy and surgery.

The present study demonstrates that the combination of chemotherapy and surgery can result in cure of 16% of patients with primarily unresectable metastases. This observation is of significant importance because these patients were considered for palliative chemotherapy only some years ago, without any hope for long-term survival. After demonstrating that liver resection could offer a possibility of long-term survival in 13% of patients who respond to chemotherapy[7], we now know that cure can be achieved in a similar percentage of patients who undergo resection. Our results therefore support again that liver surgery should be proposed to all patients with unresectable metastases responding to chemotherapy.

An additional important aspect of our study is that 5-year disease-free survival seems to be the most appropriate definition of cure. This is reflected by the fact that none of the patients defined as cured by the study definition presented further recurrence after the initial 5-year disease-free interval. Of 12 patients with a minimum follow-up of 10 years after surgery, all remained free of disease. Conversely, six patients who survived more than 5 years after initial hepatectomy were part of the noncured group, confirming that 5-year survival per se does not mean cure. Nevertheless, it is still unclear whether cured patients in our study are definitely cured. It is rather impossible to exclude that some patients develop late recurrences with longer follow-up. However, this risk is small because most patients experience recurrence within the first 5 years after hepatectomy.[27-29]

Because of the fact that disease recurrence most often occurs during the first years after hepatectomy, 10-year survival may reflect cure in a similar way as a disease-free interval of 5 years. Indeed, using 10-year survival as a surrogate of cure, a similar percentage of cure (17%) was recently reported in patients with liver-only metastases.[16] Nevertheless, this definition of cure necessitates at least 10 years of follow-up in individual patients, which may limit its use in daily practice. In addition, in our study, two of 14 actual 10-year survivors (14%) developed extensive intra- and extrahepatic recurrences at last follow-up. None of these two patients had experienced a disease-free interval of 5 years in the course of their disease, confirming the value of our proposed definition of cure.

Obviously, cure in this study was achieved by an aggressive surgical and oncological approach. A proportion of patients (33%) were only cured after multiple repeat resections from the initial hepatectomy. However, all patients had advanced metastatic disease with or without extrahepatic disease, and the observation of a possibility of cure reinforces the use of oncosurgery in these selected patients having poor prognostic factors. This result furthermore assumes that the combination of chemotherapy and surgery may have a similar or even greater value in patients with less extensive, resectable disease. In our opinion, the use of chemotherapy is indispensable in the treatment of a systemic disease that is unlikely to be cured by local surgery alone. Adverse side effects of preoperative chemotherapy should nevertheless be taken into consideration[30], and prolonged administration should be avoided in upfront resectable patients.

An important objective of our study was to define predictive factors of cure. Apparently, patients presenting with 3 or fewer metastases at hepatectomy that did not exceed 3 cm in diameter at diagnosis had an increased probability to be cured. Additionally, complete pathologic response was a strong independent predictor of cure. This result is in agreement with our previous observation that complete pathologic response is related with an uncommonly high 5-year survival rate of 76% after hepatectomy.[31] It furthermore confirms the important value of

combining chemotherapy and surgery in the achievement of cure for patients with CLM, especially in those with a high probability of complete pathologic response.

To our knowledge, no previous study has been able to demonstrate independent predictive factors of cure. Nevertheless, the presence of more than 3 metastases was recently associated with a low probability of cure.[16] In the same study, none of the patients with a positive resection margin achieved cure. However, most patients were treated by surgery alone, and modern chemotherapy agents were not used. In our study, initial hepatectomies were R1 resections in 46% of cured patients, emphasizing the efficiency of postoperative chemotherapy and repeat surgery.

In conclusion, this study highlights the current potential of an oncosurgical approach for patients with initially unresectable CLM. In addition to long-term survival, it offers a chance of total eradication of the disease in a subgroup of patients. The potential of cure of this advanced metastatic disease is closely related to the amount of tumor and its response to chemotherapy. With the development of more efficient chemotherapy and targeted therapies used in combination with curative surgery, probably more patients with CLM will be cured in the near future. It is obvious, however, that this critical objective will only be achieved through close collaboration between oncologists and surgeons.

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Chapter 10

Summary

The natural course of colorectal liver metastases is associated with poor survival. Although chemotherapy regimens for metastatic colorectal disease have evolved significantly during recent years, complete tumor resection offers the only possibility of long-term survival.

This thesis has focussed on current multimodal treatment strategies for advanced colorectal liver metastases. Different surgical and oncological aspects are highlighted.

Surgical aspects

In recent years, indications for liver surgery for colorectal metastases have largely expanded. The presence of limited extrahepatic disease or microscopically involved resection margins are no longer considered absolute contraindications for partial hepatectomy.[1-5] The technical ability to resect all metastases while leaving sufficient remnant liver is the only criterion determining (un)resectability. Subsequently, different strategies have been developed to increase the number of patients amenable for surgery.

Portal vein embolization (PVE) uses compensatory ipsilateral atrophy and contralateral hypertrophy to increase the remnant liver volume.[6] By this way, complete tumor resections by major hepatectomies can be performed safely, with a limited risk of postoperative liver insufficiency. PVE may be performed percutaneously, by minilaparotomy (ileocolic technique) or during resection of the primary colorectal tumor or the first step of a two-stage hepatectomy.[6,7] In *chapter 3*, we analyzed the role of PVE in the multimodal treatment of patients with extensive colorectal metastases to the liver. Interestingly, 18% of patients who underwent major hepatectomy in our series required PVE to achieve resectability. Long-term survival of this subgroup (3-year survival rate of 44%) was significantly higher compared to that of nonresected patients. These results confirm the important value of PVE in the treatment of patients with advanced colorectal liver metastases. Not surprisingly, tumor load was high in PVE patients, requiring extensive resections and hereby increasing postoperative morbidity. Nevertheless, without PVE, this group of patients would have a dismal prognosis.

Chapter 4 describes two-stage hepatectomy for bilobar metastatic disease. This strategy was developed for patients with multinodular metastases unable to be resected by a single hepatectomy, even with the use of PVE.[8] Compensatory regeneration after partial resection of the first hemiliver allows for a safe second curative resection of the contralateral lobe. Until now, available data was too limited to establish this strategy in the treatment of advanced metastatic colorectal disease.[9-13] In this thesis, we have reported a 3- and 5-year survival rate of 60% and 42% for patients who complete the total strategy. For these patients, survival was similar as for those achieving complete tumor clearance by a single

hepatectomy in the same time period, confirming that two-stage hepatectomy can provide a real survival benefit for patients with advanced bilobar metastases. Increased morbidity and mortality rates should, however, be anticipated. Selection of patients, therefore, remains crucial for success. Relative unresponsiveness to chemotherapy and the presence of extrahepatic disease, reflecting aggressive tumor biology, appear to be important factors.[14]

Metastases located centrally in the liver, in close relation with major hilar structures, often require extended left hepatectomies to achieve complete tumor resection. Owing to frequent vascular invasion and involvement of the caudate lobe (segment I), extended left hepatectomies are generally considered complex procedures with a high risk of complications.[15-19] To elucidate this issue, we analyzed short- and long-term outcome of this type of liver resection *(chapter 5)*. Interestingly, extended left hepatectomies were increasingly performed during most recent years, reflecting the development of liver surgery techniques. Nevertheless, it still constituted only 9% of all major hepatectomies performed in this time period. Postoperative morbidity occurred in 55% of patients without any 90-day mortality. Microscopically involved resection margins were relatively frequent (39%) and 87% of patients experienced recurrent disease. However, within a multidisciplinary treatment strategy combining liver surgery and chemotherapy in a specialized hepatobiliary center, long-term survival was achieved in a significant number of patients (5-year survival 27%). In addition, combined resection of the caudate lobe did not result in different outcomes. Therefore, although technically challenging, extended left hepatectomy should not be denied for patients with advanced colorectal liver metastases.

Oncological aspects

Median overall survival for metastatic colorectal cancer is less than 6 months with best supportive care. With the introduction of 5-fluorouracil and leucovorin only few years ago, median survival reached 12 months.[20] The sequential administration of oxaliplatin or irinotecan further increased long-term survival up to 20 months.[21] The improved efficacy of chemotherapy subsequently resulted in improved tumor response and stimulated the development of advanced treatment strategies combining chemotherapy and secondary surgery for initially unresectable colorectal liver metastases. Initial results were promising and confirmed in following publications with longer follow-up.[22-24]

Although modern efficient chemotherapy agents improve tumor response rates, their impact on the nontumoral liver parenchyma should not be denied. In *chapter 6* we assessed the impact of regenerative nodular hyperplasia (RNH) on postoperative outcome. This vascular entity was related to oxaliplatin treatment and associated with increased postoperative hepatic morbidity. Different authors have

described the development of portal hypertension as a consequence of RNH, which may contraindicate repeat liver surgery.[25,26] Interestingly, we observed that RNH may disappear at repeat hepatectomy when oxaliplatin is stopped. Although clinical recommendations regarding the pre- and postoperative administration of chemotherapy need to be evaluated further, this observation provides an opportunity to reduce the risks of RNH. Also, elevated serum levels of gamma-glutamyltransferase and total bilirubin predicted the presence of RNH in our series. For patients at risk for RNH, efforts should be made to reduce the risks of liver surgery.

Better understanding of tumor biology in recent years led to the development of specific therapies targeting biological mechanisms of tumor growth. The epidermal growth factor receptor (EGFR) antibody cetuximab has demonstrated high response rates in combination with irinotecan for patients with progressive disease after previous conventional chemotherapy.[27] Bevacizumab, targeting angiogenesis by blocking vascular endothelial growth factor (VEGF), also improves response rates, progression-free survival and overall survival in combination with irinotecan.[28] However, its influence on functional recovery and histology of the liver after hepatic resection of colorectal metastases has received only little attention. In *chapter 7*, we reported that postoperative recovery of liver function is not impaired by preoperative bevacizumab treatment. Furthermore, mild compared to severe vascular lesions were more frequent in the bevacizumab group, suggesting a protective effect of bevacizumab on the evolution of these lesions. Also, degrees of tumor necrosis were significantly increased. These findings, confirmed in other reports, have resulted in an increased use of bevacizumab in the first-line treatment of patients with colorectal metastases to the liver.[29-31]

Limited initial tumor burden facilitates the cytotoxic effect of chemotherapy. Not surprisingly, the presence of multiple or large metastases is frequently reported as prognostic factor of survival.[24,32] However, larger efficacy of new chemotherapeutical agents has led to improved tumor response and higher degrees of tumor necrosis. In our series, complete tumor necrosis at pathologic examination (complete pathologic response) was observed in 4% of resected patients treated by preoperative chemotherapy *(chapter 8)*. Five-year survival of this patient group was remarkable (76%). Interestingly, complete necrosis did not imply disappearance of metastases on preoperative imaging. In clinical practice, this means that patients should be referred for surgery in an early stage to avoid a situation in which remnant malignant lesions could be missed. Of note, the possibility of complete pathologic response increased in the presence of small metastases with a high degree of chemoresponsiveness. The continuing develop-

ment of new chemotherapeutical agents will therefore certainly increase the incidence of complete pathologic response, hereby improving patient outcome.

The importance of complete pathologic response for long-term survival was confirmed in *chapter 9*. Here, we defined cure of the disease as 5-year survival without evidence of disease recurrence. This hypothesis was based on the fact that recurrences occur in the first 5 years after hepatectomy in most patients.[33,34] We found that 16% of patients with initially unresectable metastases could be cured by the combination of chemotherapy and surgery. Interestingly, complete pathologic response was found to be a strong predictor of cure. One can assume that chemotherapy is indispensable in the achievement of cure of a systemic, widespread disease. For patients with upfront resectable metastases, the use of chemotherapy will therefore most likely be inevitable to achieve similar results. Again, the degree of chemotherapy efficacy and associated tumor response is of critical importance.

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Chapter 11

Conclusions, general discussion and future perspectives

CONCLUSIONS

Based on the results described in this thesis, the following conclusions can be made in relation to our central research questions:

What is the current role of PVE and two-stage hepatectomy in the multimodal treatment of patients with advanced colorectal liver metastases?
PVE increases the resectability rate of patients with initially unresectable colorectal liver metastases owing to an insufficient remnant liver volume, and long-term survival of resected patients who underwent PVE is significantly higher compared with nonresected patients. Similarly, two-stage hepatectomy can provide long-term survival in selected patients with multiple bilobar metastases unable to be treated by a single resection.

What are the results of extended left hepatectomy with or without caudate lobectomy for patients with colorectal metastases?
In experienced liver surgery centers, extended left hepatectomy for colorectal metastases can be performed with acceptable morbidity and long-term outcome. Combined resection of the caudate lobe does not result in worse outcome.

What is the impact of regenerative nodular hyperplasia of the liver related to chemotherapy on postoperative outcome after hepatic resection of colorectal metastases?
Regenerative nodular hyperplasia of the liver related to chemotherapy increases the risk of postoperative morbidity after resection of colorectal metastases, however, it may disappear during follow-up, providing an opportunity for future research to reduce its long-term consequences.

What is the effect of preoperative bevacizumab treatment on functional recovery and histology of the liver after resection of colorectal metastases?
Preoperative treatment with bevacizumab increases tumor necrosis but does not affect functional recovery of the liver after resection of colorectal metastases. Bevacizumab may also have a protective effect on the evolution of vascular lesions.

What is the value of a complete pathologic response of colorectal liver metastases in achieving long-term survival after hepatic resection?
Complete pathologic response results in exceptional survival rates after resection of colorectal liver metastases. The possibility of complete pathologic response is increased in the presence of small metastases with a high degree of chemoresponsiveness.

Is there a possibility of cure for patients with advanced colorectal liver metastases treated by a combination of chemotherapy and surgery?
Cure is possible for selected patients with advanced metastatic disease and is related to the initial tumor burden as well as tumor chemoresponsiveness. Five-year survival without tumor recurrence is an appropriate and practical definition of cure.

DISCUSSION AND FUTURE PERSPECTIVES

The studies reported in this thesis demonstrate the possibility of long-term survival for patients with advanced metastatic disease following a multimodal treatment strategy in a specialized liver surgery center combining chemotherapy and partial hepatectomy. Nevertheless, treatment protocols are aggressive and are accompanied by a substantial risk of complications related to massive chemotherapy and extensive (repeated) surgery. To optimize patient outcome, future research should focus on methods to improve individual therapeutic strategies and to reduce associated risks.

As noted before, chemotherapy is crucial in the achievement of systemic tumor clearance. Various regimens are currently available, but the best option is yet to be defined. Selection of the most optimal first-line treatment for individual patients generally occurs at the discretion of the medical oncologist. However, the degree of tumor burden and potential of surgery should not be denied. For initially unresectable metastases, high response rates to achieve significant tumor shrinkage is the main goal. Appropriate second-line treatment in case of tumor unresponsiveness is another challenge.[1] Accordingly, close collaboration between medical oncologists and surgeons is warranted.

Resectability of colorectal liver metastases is obviously related to chemotherapy efficacy and tumor response.[2] The administration of highly efficient first-line multidrug therapy is preferable for patients with advanced metastatic disease. Nevertheless, preoperative chemotherapy can induce nontumoral liver injury, increasing the risks of liver surgery.[3] Optimal duration and timing of chemotherapy treatment in relation with tumor response and operative risks is a key parameter for patient outcome and should be taken into account in each decision-making process. Interestingly, bevacizumab is suggested to have a protective effect on the development of vascular toxicity.[4,5] This observation, together with the availability of new agents, may help to reduce the risks of preoperative chemotherapy treatment.

An important issue remains the preoperative detection of the presence and degree of nontumoral liver damage. We, and also others, have found that elevated levels of serum markers are predictive of specific liver injury.[6] More sensitive tools will, however, be required. Possibly, advanced preoperative imaging modalities will be able to provide more detailed information of the nontumoral liver in the near future. In case of suggested liver injury, special techniques such as portal vein embolization should be used to minimize the risk of postoperative morbidity.

With the availability of biological agents, biomarker evaluation has gained increasing interest. For example, *K-ras* gene status has been shown to influence the efficacy of cetuximab, which targets EGFR.[7] Mutated *K-ras* status prevents inactivation of the EGFR signaling pathway, hereby blocking the effect of cetux-

imab.[8,9] Other biomarkers predictive of chemotherapy response (*B-raf*, *p*53) are currently under investigation. Furthermore, the search for new agents targeting specific pathways involved in tumor growth continues in preclinical studies. By this way, gene signatures could more accurately differentiate patients with regard to chemoresponsiveness, subsequently improving individual therapy, tumor response, and long-term outcome.

For patients with upfront resectable liver metastases, the administration of pre- and postoperative chemotherapy remains a matter of discussion. A recently published prospective randomized trial conducted by EORTC reported increased progression-free survival (9% benefit at 3 years) for resected patients treated by perioperative chemotherapy including oxaliplatin.[10] However, different aspects still need to be clarified before standardizing perioperative chemotherapy treatment for patients with resectable liver metastases.[11] Differences between synchronous and metachronous metastases, single and multiple metastases, as well as the value of pre- and postoperative chemotherapy remain largely unclear. In addition, resectable metastases may progress during preoperative chemotherapy treatment, reducing the possibility of radical resection. However, progression on chemotherapy is generally considered a contraindication for surgery, suggesting that a small number of chemotherapy cycles may be appropriate to assess chemoresponsiveness.[12] In our opinion, the combination of chemotherapy and surgery can offer the only chance of long-term disease-free survival for a systemic disease.

Concerning the delivery of chemotherapy, hepatic arterial infusion has been investigated for patients with advanced metastases predominantly affecting the liver. Response rates as high as 60% in first- and second-line have been reported.[13,14] Recently, a 5-year survival rate of 56% was demonstrated after secondary surgery following hepatic arterial infusion for massive colorectal liver metastases.[15] However, this appraoach is associated with a technical failure rate related to its invasiveness as well as increased hepatotoxicity owing to a high local drug concentration. Therefore, its true value opposed to currently available effective systemic chemotherapy is still under scrutiny.

When addressing long-term outcome of patients with colorectal metastases, the value of postoperative chemotherapy and the so-called liver-first approach are other aspects currently under investigation to reduce the risk of disease recurrence and improve survival. Some have reported a trend towards a benefit of postoperative fluorouracil-based chemotherapy regarding disease-free survival.[16] However, clear evidence does not exist. Concerning the liver-first approach, resection of liver metastases before resection of the primary tumor may theoretically avoid the risk of metastatic progression during treatment of the colorectal

tumor.[17] Initial results are promising, but confirmation needs to follow in further trials. Similarly, combined resection of the primary tumor and limited synchronous liver metastases is proposed.[18] The impact of this approach on (progression-free) survival also remains to be clarified in longer follow-up studies.

In conclusion, many progress has been made in recent years regarding the treatment of colorectal liver metastases. With multiple treatment options currently available, individual analysis of patient and tumor characteristics is essential. When curative surgery is considered, upfront maximum tumor response is a prerequisite condition to offer a chance of long-term survival. Clinical recommendations regarding most optimal pre- and postoperative chemotherapy regimens remain subject of further research. In all cases, optimal individual treatment strategies are the key goal, necessitating frequent discussion in multidisciplinary sessions including both surgeons and medical oncologists. Only in this way, outcome for patients with colorectal liver metastases can be further improved in the near future.

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Chapter 12

Samenvatting in het Nederlands (summary in Dutch)

Dikkedarmkanker (colorectaal carcinoom) is momenteel één van de meest voorkomende oorzaken van kanker-gerelateerde sterfte in de westerse wereld. Bijna 1 miljoen nieuwe gevallen worden jaarlijks wereldwijd gediagnosticeerd en uitzaaiingen naar de lever (levermetastasen) treden op in 50% van deze patiënten. In 25% van de gevallen zijn er reeds levermetastasen ten tijde van de diagnose van de primaire tumor. Dit proefschrift richt zich op nieuwe, gecombineerde behandelingsmethoden (combinatie van chirurgie en chemotherapie) voor patiënten met uitgebreide colorectale levermetastasen.

Chirurgische aspecten

In het geval van colorectale levermetastasen biedt een operatieve verwijdering (resectie) van de metastasen de enige kans op lange termijn overleving. Vijf jaar na de operatie is ongeveer 30% tot 40% van deze patiënten nog in leven. Echter, tot op heden kwam slechts een beperkt aantal patiënten met colorectale levermetastasen (10% tot 20%) in aanmerking voor chirurgische behandeling. De overige patiënten werden behandeld met chemotherapie, met een mediane overleving van slechts 6 tot 12 maanden.

Tot recent was resectie van colorectale levermetastasen slechts geïndiceerd voor patiënten met een beperkte uitbreiding van de ziekte. Patiënten met meer dan 4 metastasen, metastasen groter dan 5 centimeter of metastasen verspreid over beide leverkwabben kwamen niet in aanmerking voor chirurgie. De algemene gedachte was dat de risico's van een dergelijke operatie niet in verhouding stonden tot de eventuele overlevingswinst. Recente studies hebben echter laten zien dat ook voor deze groep patiënten een complete resectie van de metastasen kan resulteren in een significant langere overleving in vergelijking met niet-gereseceerde patiënten. De technische mogelijkheid tot een complete resectie van alle metastasen is daarom momenteel de enige beperkende factor voor een chirurgische behandeling van deze patiënten. Dit heeft geleid tot een aantal belangrijke ontwikkelingen op het gebied van de leverchirurgie.

Ontwikkelingen in de leverchirurgie

Een complete resectie van colorectale levermetastasen is mogelijk zolang 30% van het normaal functionerende leverweefsel overblijft na de operatie. Verschillende chirurgische technieken en strategieën zijn nu beschikbaar om deze situatie in meer patiënten te bereiken.

Het principe van vena portae embolisatie (PVE) berust op atrofie van het aangedane leverweefsel en hypertrofie van de toekomstige restlever. Afhankelijk van de lokalisatie van de colorectale metastasen (linker of rechter leverkwab) wordt besloten tot embolisatie van één van beide takken van de vena portae. PVE kan percutaan (echo-geleid) of tijdens resectie van de primaire tumor verricht

worden. In 4 tot 6 weken vindt vervolgens voldoende hypertrofie plaats van het toekomstige leverweefsel waardoor een uitgebreide leverresectie mogelijk wordt met reductie van het risico op postoperatieve leverinsufficiëntie. In *hoofdstuk 3* hebben wij de rol van PVE in de behandeling van patiënten met uitgebreide colorectale levermetastasen geanalyseerd. In 18% van alle patiënten die een uitgebreide (drie of meer anatomische segmenten) leverresectie ondergingen was PVE noodzakelijk om een resectabele situatie te bereiken. De lange termijn overleving (3-jaars overleving 44%) voor deze patiëntengroep was significant beter dan voor patiënten die geen leverresectie ondergingen. De intensiteit van de totale behandeling leidde wel tot een grotere kans op postoperatieve complicaties. Echter, zonder de beschikbaarheid van PVE zou deze groep patiënten met uitgebreide metastasen geen mogelijkheid hebben voor partiële leverresectie, resulterend in een zeer slechte prognose.

Een andere ontwikkeling die zich heeft voorgedaan is de zogenaamde twee-stappen operatie (two-stage hepatectomy). Deze strategie is voorbehouden aan patiënten met multipele metastasen in beide leverkwabben welke niet met een enkele operatie verwijderd kunnen worden, zelfs niet na toepassing van PVE. Het concept van de twee-stappen operatie is voor het eerst beschreven in het jaar 2000. De procedure berust op twee sequentiële leverresecties waarbij uiteindelijk alle metastasen worden verwijderd. Na de eerste resectie, vaak gecombineerd met PVE, treedt hypertrofie op van de toekomstige restlever, waardoor een tweede resectie na een aantal weken mogelijk wordt. Chemotherapie heeft hierbij een belangrijk aanvullende waarde om de tumorgroei te controleren. Tot op heden waren er echter slechts beperkte resultaten beschikbaar omtrent de twee-stappen operatie. In *hoofdstuk 4* hebben wij een 3- en 5-jaars overleving van 60% en 42% gerapporteerd voor patiënten die de totale procedure doorlopen (69% van de totale groep geselecteerde patiënten). De overleving voor deze patiëntengroep was vergelijkbaar met die van patiënten welke met één operatie een complete tumorresectie hadden bereikt. Deze resultaten bevestigen dat een twee-stappen operatie een kans op overleving kan bieden voor patiënten met multipele metastasen in beide leverkwabben. Selectie van de meest geschikte patiënten voor deze strategie is echter essentieel gezien de verhoogde kans op complicaties. Een slechte reactie van de tumor op chemotherapie en de aanwezigheid van extrahepatische ziekte spelen hierbij een belangrijke rol.

Bij sommige patiënten zijn de metastasen centraal in de lever gelokaliseerd. Vaak gaat dit gepaard met een nauwe relatie tot grote vasculaire of biliaire structuren, waardoor een extended hemihepatectomie links noodzakelijk is voor een complete tumor resectie. Vanwege de technische moeilijkheid van een dergelijke procedure, waarbij soms vasculaire resectie en reconstructie nodig is, wordt vaak gedacht dat deze ingreep gepaard gaat met een onacceptabel hoog

risico op complicaties. Om deze vraag te verhelderen hebben wij de korte- en lange termijn resultaten van deze procedure geanalyseerd in *hoofdstuk 5*. Opvallend genoeg wordt een extended hemihepatectomie links de laatste jaren in toenemende mate verricht. Postoperatieve complicaties vonden plaats in 55% van de patiënten zonder gevallen van mortaliteit. Een relatief hoog percentage patiënten had een R1 resectie (geen microscopisch tumorvrij resectievlak) (39%) en 87% van de patiënten presenteerde zich gedurende de follow-up met een recidief. Echter, door een gecombineerde behandeling met perioperatieve chemotherapie en resectie van recidief ziekte kon lange termijn overleving in een significant aantal patiënten worden bereikt (5-jaars overleving 27%). Deze resultaten rechtvaardigen daarom de toepassing van een extended hemihepatectomie links voor patiënten met centraal gelokaliseerde colorectale metastasen in een gespecialiseerd leverchirurgisch centrum.

Oncologische aspecten

Met de introductie van 5-fluorouracil (5-FU) en leucovorin (LV) is de mediane overleving van niet-gereseceerde patiënten gestegen tot ongeveer 12 maanden. Een gecombineerde toediening van 5-FU en LV met oxaliplatin of irinotecan heeft vervolgens geleid tot een overleving van meer dan 20 maanden. De toegenomen tumorrespons die gepaard ging met de betere effectiviteit van deze chemotherapeutica stimuleerde de ontwikkeling van een nieuwe behandelstrategie voor patiënten met initieel irresectabele colorectale levermetastasen. In 1996 beschreven Bismuth et al. de mogelijkheid van secundaire tumorresectie na behandeling met chemotherapie die had geresulteerd in een aanzienlijke vermindering van het volume van de metastasen. Met deze strategie werd een 5-jaars overleving van 40% bereikt, wat in latere studies werd bevestigd. Met de recente ontwikkeling van monoklonale antilichamen (cetuximab en bevacizumab) is de effectiviteit van chemotherapie nog meer toegenomen, waardoor voor meer patiënten resectie van de metastasen mogelijk wordt.

Ontwikkelingen op het gebied van chemotherapie

Hoewel de effectiviteit van nieuwe chemotherapeutica heeft geleid tot een toegenomen tumorrespons, hebben deze middelen ook effect op het nontumorale leverweefsel. Zowel steatose als sinusoïdale veranderingen ten gevolge van chemotherapie zijn in het verleden beschreven. Steatotische levers hebben een typisch gele kleur en leiden mogelijk tot een verhoogde kans op postoperatieve morbiditeit. Steatohepatitis, met name gerelateerd aan het gebruik van irinotecan, resulteerde in één studie zelfs tot een toename van de kans op mortaliteit. Vasculaire lesies, gekenmerkt door een typisch blauwe verkleuring van het leveroppervlak, zijn gerelateerd aan een verhoogde kans op bloedtransfusie

tijdens de operatie en een toegenomen risico op postoperatieve leverinsufficiëntie. De invloed van specifieke vasculaire lesies op het operatierisico is echter nog niet goed bekend.

In *hoofdstuk 6* hebben wij de gevolgen van regeneratieve nodulaire hyperplasie (RNH) met betrekking tot de postoperatieve uitkomst na resectie van colorectale levermetastasen geanalyseerd. RNH was gerelateerd aan een preoperatieve behandeling met oxaliplatin en ging gepaard met een verhoogd risico op postoperatieve complicaties. Preoperatief verhoogde concentraties van gamma-glutamyltransferase en totaal bilirubine waren voorspellende factoren voor de aanwezigheid van RNH. Tevens werd bij een aantal patiënten ten tijde van een tweede leverresectie geen RNH meer teruggevonden. Deze observatie biedt mogelijkheden voor toekomstig onderzoek om de negatieve gevolgen van RNH op de lange termijn te kunnen verminderen. Tevens dient nader te worden onderzocht wat de invloed is van onze bevindingen op de meest ideale perioperatieve chemotherapeutische behandeling. In ieder geval zullen voor patiënten met een verhoogde kans op RNH maatregelen genomen moeten worden om de risico's van een operatie zoveel mogelijk te beperken.

De toegenomen kennis omtrent tumorbiologie heeft geleid tot de ontwikkeling van specifieke middelen om de verschillende processen van tumorgroei te blokkeren. Cetuximab richt zich tegen de receptor van epidermale groeifactor. Bevacizumab, een monoklonaal antilichaam gericht tegen vasculair endotheliale groeifactor, remt het proces van angiogenese. In combinatie met irinotecan kan bevacizumab zowel de totale als progressievrije overleving van patiënten verlengen. Echter, recente studies hebben gesuggereerd dat bevacizumab de regeneratie van de lever na resectie van colorectale metastasen kan beperken. In *hoofdstuk 7* hebben wij daarom de invloed van bevacizumab op het functionele herstel van de lever na een partiële hepatectomie onderzocht. Tevens zijn de histologische effecten geanalyseerd. Het functionele herstel van de lever bleek in onze studie vergelijkbaar met de groep patiënten die niet met bevacizumab waren behandeld. Het percentage tumornecrose was echter significant hoger in de bevacizumab groep met een trend naar minder ernstige vasculaire lesies in de nontumorale lever. Deze resultaten, in combinatie met een hoge tumorrespons, zijn veelbelovend voor het gebruik van bevacizumab in de eerstelijnsbehandeling van patiënten met colorectale levermetastasen.

Resultaten multidisciplinaire behandeling

Momenteel is in een aanzienlijk aantal studies de mogelijkheid van lange termijn overleving voor patiënten met colorectale levermetastasen beschreven. Echter, de kans op daadwerkelijke genezing wordt nog vaak in twijfel getrokken, met name voor patiënten met uitgebreide metastasen in de lever. Dit is gebaseerd op de

gedachte dat genezing voor een kwaadaardige systemische ziekte in het algemeen zeer onwaarschijnlijk is.

De toegenomen effectiviteit van de huidige chemotherapeutica heeft geleid tot een betere tumorrespons en een hogere mate van tumornecrose. Een zogenaamde complete pathologische respons (100% tumornecrose) blijft echter zeldzaam. In onze ervaring komt deze situatie voor in 4% van alle gereseceerde patiënten die behandeld zijn met preoperatieve chemotherapie. In *hoofdstuk 8* hebben wij het belang van een complete pathologische respons voor lange termijn overleving onderzocht. De 5-jaars overleving voor deze groep patiënten was uitzonderlijk hoog (76%). Een beperkte grootte van de metastasen en een hoge gevoeligheid voor chemotherapie waren belangrijke factoren om de kans op een complete pathologische respons te vergroten. Een interessante bevinding was tevens dat een complete pathologische respons niet per definitie betekent dat de metastasen ook op de preoperatieve beeldvorming verdwenen zijn. Dit belangrijke resultaat benadrukt dat patiënten in een vroege fase doorverwezen dienen te worden voor chirurgie, voordat resterende metastasen niet meer teruggevonden kunnen worden. In een dergelijke situatie bestaat het risico dat niet alle tumorcellen gereseceerd worden en zodoende geen complete tumorresectie wordt bereikt.

Het belang van een complete pathologische respons voor de overleving van patiënten met colorectale levermetastasen werd bevestigd in *hoofdstuk 9*. In dit hoofdstuk hebben wij genezing gedefinieerd als een 5-jaar ziektevrije overleving na de laatste resectie van intra- of extrahepatische metastasen. Deze hypothese was gebaseerd op het feit dat recidieven met name optreden binnen 5 jaar na resectie. In deze studie vonden wij dat 16% van de patiënten met initieel irresectabele metastasen kon worden genezen door een combinatie van chemotherapie en partiële leverresectie. Een complete pathologische respons was een sterke voorspellende factor voor het bereiken van genezing. Het is aannemelijk dat chemotherapie van groot belang is voor een totale tumordestructie in het geval van een systemische ziekte. Naar ons idee zal de toepassing van chemotherapie daarom ook essentieel zijn voor het bereiken van genezing voor patiënten met meer beperkte levermetastasen (initieel resectabele patiënten). De mate van effectiviteit van chemotherapie en de hieraan gerelateerde tumorrespons zal zeer belangrijk blijven.

De toekomst

De studies beschreven in dit proefschrift laten zien dat lange termijn overleving mogelijk is voor patiënten met uitgebreide colorectale levermetastasen door een gecombineerde behandeling met chemotherapie en chirurgie. De beschreven behandelstrategieën zijn echter agressief en gaan gepaard met een aanzienlijk

risico op complicaties. Om deze resultaten te verbeteren zal toekomstig onderzoek zich met name moeten richten op methoden om individuele behandelingen te verbeteren en geassocieerde risico's te verminderen.

Het bereiken van resectie van colorectale levermetastasen is het belangrijkste doel in de behandeling van deze patiënten. Een grote effectiviteit van chemotherapie is hiervoor van groot belang. Behandeling met chemotherapie kan echter ook schade toebrengen aan de nontumorale lever met een verhoogd risico op complicaties na leverchirurgie. Een optimale timing en duur van de behandeling met chemotherapie in relatie met de mate van tumorrespons is dus van groot belang. Bij de ontwikkeling van nieuwe chemotherapeutische middelen zal de nadruk moeten liggen op het optimaliseren van de tumorrespons met zo min mogelijk kans op nontumorale schade.

De aanwezigheid van schade aan de nontumorale lever kan momenteel nog onvoldoende worden voorspeld voorafgaand aan een operatie. Bepaalde serum markers blijken in verschillende studies een voorspellende waarde te hebben. Sensitievere methoden zullen echter nodig zijn, waarbij met name gedacht moet worden aan geavanceerde beeldvormende technieken. Voor patiënten met een verhoogd risico op complicaties kunnen speciale technieken zoals PVE gebruikt worden om de kans op morbiditeit en mortaliteit te verminderen.

Met de toenemende kennis omtrent tumorbiologie zal de beschikbaarheid van monoklonale antilichamen zich steeds verder uitbreiden. Daarnaast zullen meer genetische markers bekend worden waarmee de respons op chemotherapie voorspeld kan worden. Het gemuteerde *K-ras* gen, bijvoorbeeld, blokkeert de werking van cetuximab. *B-raf* en *p*53 zijn nieuwe markers die momenteel onderzocht worden. In een optimale situatie zal voor individuele patiënten een genetische handtekening beschikbaar zijn, waarmee per individu de meest ideale chemotherapeutische behandeling bepaald kan worden.

Omtrent de toepassing van perioperatieve chemotherapie voor patiënten met beperkte, resectabele metastasen bestaat nog veel discussie. Een recente studie suggereert dat chemotherapie voor deze groep patiënten de progressievrije overleving kan verbeteren. Verschillende aspecten, zoals het verschil tussen synchrone en metachrone metastasen, enkele of meerdere metastasen en pre- of postoperatieve chemotherapie dienen nog verder onderzocht te worden. Daarnaast bestaat er tevens het risico op tumorprogressie gedurende de behandeling met chemotherapie, waardoor metastasen irresectabel kunnen worden. Chemotherapie zal echter toch belangrijk blijven om genezing van een systemische ziekte te kunnen bewerkstelligen.

Verschillende strategieën worden verder momenteel geanalyseerd om de overleving van patiënten met colorectale levermetastasen nog verder te verbeteren. Intra-arteriële chemotherapie wordt onderzocht voor patiënten met zeer

diffuse levermetastasen. Deze procedure gaat echter veelvuldig gepaard met technisch falen en heeft een hoge toxiciteit. De meerwaarde ten opzichte van systemische chemotherapie is daarom nog onduidelijk. De waarde van postoperatieve chemotherapie wordt onderzocht in gerandomiseerde studies. Andere strategieën zoals de 'liver-first approach' tonen veelbelovende resultaten met betrekking tot patiëntenoverleving. Hierbij worden in eerste instantie de levermetastasen gereseceerd, waarna op een volgend moment de primaire tumor wordt verwijderd. De waarde van deze strategie moet echter in grotere series met voldoende follow-up nader onderzocht worden.

Concluderend kan gezegd worden dat de laatste jaren veel progressie is geboekt in de behandeling van patiënten met colorectale levermetastasen. Een individuele aanpak is van groot belang, waarbij de juiste behandelstrategie in relatie tot de tumorkarakteristieken en risico's voor de patiënt bepaald dient te worden. Frequent multidisciplinair overleg tussen chirurgen en oncologen is hierbij essentieel. Alleen op deze manier zal de overleving van patiënten met colorectale levermetastasen in de toekomst verder verbeterd kunnen worden.

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Curriculum vitae

Dennis Wicherts was born on May 23rd 1981 in Soest, The Netherlands. In 1999 he graduated from Het Baarnsch Lyceum in Baarn and started Medical School at the University of Utrecht, The Netherlands. Since 2004 he performed research activities at the Department of Surgery of the University Medical Center Utrecht under the guidance of prof.dr. R. van Hillegersberg and prof.dr. I.H.M. Borel Rinkes. In January 2006 he graduated from Medical School.

From May 2006 until May 2008 he worked as a PhD student in the Centre Hépato-Biliaire (Assistance Publique - Hôpitaux de Paris, Hôpital Paul Brousse) in Paris, France (prof.dr. R. Adam). During this period he performed the work described in this thesis, which was presented at multiple international conferences.

His first clinical experience as a surgical resident was gained in the Meander Medical Center in Amersfoort, The Netherlands (dr. A.J. van Overbeeke) and in July 2009 he officially started his surgical training in the Albert Schweitzer Hospital in Dordrecht, The Netherlands (dr. R.J. Oostenbroek and dr. P.W. Plaisier). At the end of 2011 he will work for three months in the Antoni van Leeuwenhoek Hospital in Amsterdam (prof.dr. E.J.Th. Rutgers). His training will be finished in 2015 at the Academic Medical Center in Amsterdam (prof.dr. O.R.C. Busch).