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EJSO
the Journal of Cancer Surgery
ELSEVIER
EJSO 33 (2007) 174–182
www.ejso.com

Selective resection of colorectal liver metastases

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Accepted 6 September 2006
Available online 12 October 2006

Abstract

Aims: Safety of liver surgery for colorectal cancer liver metastases after neoadjuvant chemotherapy has to be re-evaluated.
Patients and methods: Two hundred Patients were prospectively analyzed after surgery for colorectal cancer liver metastases between 2001 and 2004 at our institution. Special emphasis was given to perioperative morbidity and mortality under modern perioperative care.
Results: There was no in-hospital mortality and the perioperative morbidity was 10% (20/200). Four patients had to be reoperated due to bile leak or intraabdominal abscess. The remainder either had infectious complications or pleural effusion and/or ascites requiring tapping. Variables strongly associated with decreased survival were T, N, G and UICC (International Union against cancer) classification of the primary, hepatic lesions > 5 cm and elevated tumour markers. Short disease free interval and neoadjuvant chemotherapy without response predicted impaired recurrence free survival (RFS). Multivariate analysis revealed lymph node status and differentiation of the primary, presence of extrahepatic tumour and gender as factors associated with decreased survival. Administration of neoadjuvant chemotherapy was not associated with higher postoperative morbidity or prolonged hospital stay.
Conclusions: Modern dissection techniques and improved perioperative care contributed to a very low rate of surgery-related morbidity (10%) and a zero percent mortality which was also observed in patients pretreated with neoadjuvant chemotherapy prior to resection. Liver resection in experienced hands has become a safe part in the potentially curative attempt of treating patients with metastatic colorectal cancer.

Keywords: Liver resection; Colorectal cancer liver metastases; Neoadjuvant chemotherapy; Morbidity and mortality; Perioperative care

Introduction

Hepatic resection for metastatic colorectal cancer confined to the liver has been established as a safe and feasible treatment, prolonging patient survival unlike any other therapy in this population.[1–4] Up to 75% of patients present with non-resectable metastases – their survival is grossly compromised compared to patients undergoing potentially curative surgery.[5,6] Therefore the frontiers to extend surgery in order to completely clear visible tumour get constantly expanded.[7] Neoadjuvant chemotherapy is now considered a necessary addition to conventional surgical therapy, increasing recurrence free survival and rendering initially non-resectable patients eligible for surgery. Response to neoadjuvant treatment has already been established as a prognostic factor in predicting recurrence of disease.[8,9] However, there have been several reports in the current literature that safety of surgery may be compromised by the combination of neoadjuvant chemotherapy and extended resections.[10,11]

Perioperative morbidity and mortality in the recent literature range from 19 to 33% and 0.5 to 9% , respectively.[8,12–14] It has been shown that postoperative morbidity is associated with adverse outcome,[15] hence the patient does not only benefit from a low rate of complications in the short-term but also in the long-term. Very recently surgical techniques as well as perioperative care have substantially improved and

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0748-7983/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejso.2006.09.008

liver resection in experienced hands has a risk profile comparable to colorectal surgery or other standardized intraabdominal procedures. Only a few studies have analyzed the time period after 2000, hence little data are available about the current evolution of surgery for colorectal cancer liver metastases (CRCLM) under the aspect of neoadjuvant chemotherapy.[12,16]

The aim of our study was a prospective evaluation of the impact of neoadjuvant chemotherapy on morbidity and mortality in a single-centre series of 200 limited liver resections for CRCLM.

Materials and methods

We prospectively analyzed data from 200 patients who have undergone liver resection for colorectal cancer liver metastases at our institution from January 2001 to December 2004.

The database was built up using records available from the Vienna General Hospital Patient Information System (KIS) together with hospital and outpatient clinic charts and personal interviews. Follow-up was either through personal contact during routine clinic visits, through relatives or other treating institutions. Thirteen patients could not be contacted by these means, so their follow-up status was checked via municipal authorities.

The following data were extracted: demographics (date of birth, sex); site and pathology of primary colorectal cancer; adjuvant and neoadjuvant chemotherapies; presentation, distribution and pathology of liver metastases; surgical details; perioperative data including length of hospital stay and morbidity; and follow-up including disease recurrence or death. Postoperative morbidity was defined as any surgery-related condition which required either a surgical intervention, other invasive treatments (e.g. pleural effusion or ascites requiring tapping, intraabdominal abscess, bile leakage or wound infection requiring operative revision or interventional drainage) or any medical problems which delayed postoperative recovery and prolonged hospital stay (e.g. myocardial infarction, pulmonary embolism, etc.). Infections were regarded as contributing to morbidity if the postoperative stay was prolonged due to the infection and/or an intervention was necessary.

The 2000 IHPBA Brisbane Terminology of Liver Anatomy & Resections was used to classify liver resections.[17]

Standard preoperative workup routinely consisted of either 3-phase CT scans or MRI of the liver together with a CT scan of the abdomen and chest to rule out extrahepatic disease. Intraoperative ultrasound was used throughout the study period. Patients considered to have a high medical risk were additionally evaluated in cooperation with our attending anaesthesiologist, and diagnostic procedures like echocardiography or spirometry were done if necessary.

Surgery

Surgery was always performed or assisted by a senior surgeon with extensive experience in liver surgery. Sufficient exposition of the liver was achieved by bicostal incision combined with complete mobilisation of the liver from its suspending ligaments. If applicable, metastases were removed by the most parenchyma-sparing procedure possible (anatomical or non-anatomical segmental resection). Inflow control was not routinely used; however, in 20 cases it had to be established (12 complete, 8 selective), mainly because of increased tissue vulnerability after chemotherapy (15 out of 20 cases). Resection was always performed using Cavitron ultrasonic surgical aspirator (CUSA; Valleylab, Boulder, CO) and bipolar forceps in a two-surgeon technique. A hemostyptic fleece was applied on the resection edge after most resections, drains were not routinely used.

Anaesthesia

Patients were allowed to drink until midnight and received 1000 mL Ringer lactate solution overnight. Thirty minutes before skin incision, patients were given prophylactic intravenous single shot antibiotic therapy (metronidazole 1.5 g and cefuroxim 1.5 g). Anaesthesia was induced with fentanyl (1–3 μg/kg), propofol (2–3 mg/kg), and rocuronium (0.6 mg/kg) intravenously. It was then maintained with sevoflurane adjusted to keep arterial blood pressure within 20% of the pre-induction value. After induction of anaesthesia, a central venous catheter and an arterial line were inserted. Subsequently, saline solution was infused at a rate to keep central venous pressure (CVP) at levels lower than 5 mmHg during liver resection. Blood loss was replaced with colloids (Voluven®, HES 130/0.4, 6%; Fresenius Kabi GmbH, Graz, Austria) and crystalloids at a 1–2:1 ratio. After resection supplemental fluid was given to render patients to an euvolemic volume status and to maintain urine output of at least 1 mL kg^{-1} h^{-1}.

Target minimum hematocrit was determined prospectively based on the patient's age and cardiovascular status. The target hematocrit was 26% in patients aged < 65 years without significant cardiovascular disease; 28% in patients either aged ≥ 65 years or with significant cardiovascular disease; and $\geq$30% in patients aged ≥ 65 years with significant cardiovascular disease. Patients were kept normothermic using forced-air and intravenous fluid warmings.

Statistics

Statistical analysis was performed using SPSS 10.5 for Windows (SPSS Inc., Chicago, IL). Analysis of overall and recurrence free survival rates was performed using the Kaplan–Meier method, differences between survival rates were calculated with the log-rank test. p-Values < 0.05 were considered statistically significant. Variables showing significant influence on univariate analysis were further investigated using a multivariate stepwise Cox regression model. To compare different subgroups of patients (e.g. in regard to response to chemotherapy), a Chi-square test was used.

Results

Surgery

Two hundred hepatic resections were performed in the observed 4-year time period. Data on the type and extent of liver resections are illustrated in Table 1. The median number of liver lesions was 2 (range 1–10), the median tumour size of the largest CRCLM was 2.9 cm (range 0.3–15.0), which is comparable to other series published.[1,10,18,15] At our institution, an approach to maximally spare remaining liver tissue is traditionally favoured, hence non-anatomical resections were performed whenever possible and technically feasible.

The median operative time was 240 min (range 85–520). In 12 cases total inflow occlusion (Pringle manoeuvre) was used, during 8 resections selective Pringle was necessary. Fifty-five patients required transfusion of packed red cells perioperatively (median 2, range 1–13). Blood transfusions had no influence on both parameters of survival but there was a trend towards shorter OS and RFS if more than 2 packed red cells were applied intraoperatively (data not shown, $p = 0.056$ and 0.073, respectively). A large resection involving 5 or 6 segments and a tumour size larger than 5 cm predicted shorter overall and recurrence free survival compared to smaller resections and tumours (Table 4).

Table 1
Liver operations and secondary procedures

	Resection		Secondary procedure	
	Primary No. of patients	Secondary No. of patients		No. of patients
Trisectionectomy				
Left	1		Cholecystectomy	106
Right	5		Biliodigestive procedure	7
Hemihepatectomy			Splenectomy	2
Left	8		Other abdominal	29
Right	10		Intraarterial infusion pump	25
Sectionectomy			None	65
Left lateral	7	1		
Right posterior	7			
Right anterior	2			
Bisegmentectomies	9	2		
Segmentectomies	67	22		
Non-anatomical		51		
Multiple	46			
Solitary	38			
Total	200	76		234
Segments resected	Median (range) 2 (1–6)			

For nomenclature of resections refer to Ref.[17]

Postoperative course and survival

Most patients were admitted to the ICU postoperatively overnight (median 1, range 0–24 days). The median length of postoperative hospital stay was 9 days (range 4–47). Twenty patients (10.0%) experienced a postoperative morbidity during their stay. Four Patients were reoperated within 14 days: 1 patient had a major dehiscence of the subcutaneous wound, 1 a biliary leak, 1 patient developed a subphrenic abscess formation which could not be treated through percutaneous drainage and 1 patient had a complication concerning a central venous catheter, and had to undergo endovascular intervention postoperatively. Other complications included infectious problems (pneumonia, wound infection, intraabdominal abscess or haematoma requiring drainage), postoperative bowel paralysis or bile leakage requiring intervention. One patient developed severe rhabdomyolysis and had to be treated with venovenous hemofiltration for 1 day. In 1 patient, splenectomy was required because of a bleeding complication, which did not influence postoperative recovery. He was discharged on the 6th postoperative day. One patient required prolonged ventilator support and stayed in the ICU for 14 days. Developing a postoperative morbidity was not associated with higher risk of recurrence or shorter survival on univariate analysis ($p = 0.109$ and 0.417, respectively), however, patients whose admission time exceeded 14 days had shorter OS and RFS (Table 4). There was no in-hospital mortality.

Data on chemotherapy

Adjuvant chemotherapy after removal of the primary was administered if the primary cancer was at least UICC stage III or had a low differentiation on histological examination, which applied to 141 patients. The regimen routinely contained 5-flurouracil, a combination with oxaliplatin or irinotecan was used recently. One hundred and twelve patients received neoadjuvant chemotherapy after diagnosis of colorectal cancer liver metastases, for further analysis they were divided into either (1) 5-FU only (Mayo Clinic regimen), (2) 5-FU/oxaliplatin (FOLFOX4 ''DeGramont''/XELOX ''Cassidy''), (3) 5-FU/irinotecan (FOLFIRI ''Douillard''), (4) other (TOMOX, mitomycin-C + 5-FU), or (5) none (remaining 88 patients) (Table 2). 5-FU was either administered intravenously (56/105) or as an oral agent (capecitabine, 49/105). No patient in this collective received bevacizumab or cetuximab. Surgery was performed three to five weeks after the last administration of chemotherapy. One hundred and fifty patients received adjuvant chemotherapy after liver resection, using heterogeneous regimens.

Regimens containing oxaliplatin exhibited a significantly higher response rate than other therapies (Table 2). Patients who did not respond appropriately to chemotherapy (progressive disease (PD) or stable disease (SD)) had a higher risk of developing early recurrence on univariate analysis

Table 2
Data on neoadjuvant chemotherapy

Regimen	No. of patients	Response rate (PR or SD) (%)	χ^2 test
5-FU	15	20.0	$p < 0.001$
5-FU/oxaliplatin	72	70.8	
5-FU/irinotecan	11	27.3	
Other	14	35.7	
None	88		
Total	200		

Response rate of patients treated with neoadjuvant chemotherapy. PR, partial; SD, stable disease.

as compared to patients who had at least a partial response (PR); overall survival was not influenced (Table 4).

Neoadjuvant chemotherapy did not affect safety of surgery. Patients receiving chemotherapy did not have an increased risk of postoperative complications as compared to patients without neoadjuvant treatment. Postoperative length of stay was similar whether patients had chemotherapy or not, the administered regimen also had no impact on recovery. The amount of intraoperative blood loss and operation time were also not different if patients were pretreated with chemotherapy or not (Table 3).

Primary tumours and liver metastases − validation of the cohort

To evaluate, if the patients included in our cohort were comparable to those in other, larger series, we performed an analysis of well-established risk factors. Data on overall

Table 3
Safety of surgery after neoadjuvant chemotherapy

Regimen	Postoperative morbidity		χ^2 test	Length of stay (range)	χ^2 test
	No. of patients				
	No	Yes			
5-FU	12	3	NS	8 (4–28)	NS
5-FU/oxaliplatin	66	6	NS	8 (5–29)	NS
5-FU/irinotecan	10	1	NS	9 (6–47)	NS
Other	13	1	NS	10 (6–15)	NS
None	79	9		9 (5–16)	
Number of segments resected (patients with neo CHT)					
1–2	75	8	NS		
3–4	19	2	NS		
5–6	7	1	NS		
Intraoperative blood loss (packed red cells, mean ± SD)					
No chemotherapy	0.7 ± 1.4		NS		
Chemotherapy	1.2 ± 2.3				
Operation time (minutes, mean ± SD)					
No chemotherapy	242.7 ± 77.8		NS		
Chemotherapy	261.7 ± 86.1				

NS, not significant; CHT, chemotherapy; and SD, standard deviation.

(OS) and recurrence free survival (RFS) are illustrated in Table 4. Median follow-up for RFS was 27.2 months.

Sixty-four (32.0%) patients were women and 136 (68.0%) were men. Twenty (10.0%) patients underwent multiple procedures at different time points for recurrence of disease. The median age of the patients was 63.1 (range 28.5–83) years. There was no significant association between OS or RFS and age ($p = 0.438$ and 0.439, data not shown). Interestingly, males had a shorter overall survival compared to females, while RFS was not different (Table 4).

Positive primary nodal status, undifferentiated primary (G3) and UICC stages III and IV were predictive for lower overall survival. However, M1 status and synchronous spread to the liver, 2 very similar distributed subgroups, showed a trend towards adverse outcome, yet not being statistically significant for overall survival. For recurrence free survival, N, M and UICC stages as well as synchronous metastases and a disease free interval of less than 12 months, if metachronous, were highly predictive. Differentiation of the primary had no effect on early recurrence in our patients.

Patients with tumours larger than 5 cm had a shorter overall and recurrence free survival, whereas the number of metastases (1, 2–4 and more than 4) was only predictive for RFS. Distribution of lesions (uni/bilobar) had no influence on both parameters of survival ($p = 0.562$ and 0.094, respectively). Eighteen Patients underwent liver resection with known extrahepatic lesions secondary to colorectal cancer, most of them being pulmonary metastases. As expected, these patients had a drastically decreased overall survival although palliative chemotherapy and/or surgical approaches to reduce tumour burden were undertaken at a later time point. A positive resection margin on histological workup (R1) did not influence overall survival (39.1 vs 37.9 months, $p = 0.734$).

Increased tumour load represented through elevated tumour markers (CEA and CA 19-9) predicted shorter overall and recurrence free survival. Interestingly, levels of alkaline phosphatase (aP) higher than 150 U/l (normal < 129 U/l) and gamma glutamyl transferase (γGT) levels beyond 80 U/l (=2× upper limit of normal, ULN) were also highly associated with shorter OS and RFS, respectively. This applied mainly to patients who underwent neoadjuvant chemotherapy, because the incidence of increased aP or γGT was 4 times higher in this group (35 vs 10). Elevation of aP or γGT was less pronounced in responding patients, although this was not statistically significant ($p = 0.099$, Chi-square test).

Multivariate analysis of variables affecting OS and RFS

Parameters with significant influence on overall and recurrence free survival during univariate analysis were further investigated using a stepwise multivariate Cox regression model. For overall survival, the presence of extrahepatic tumour, alkaline phosphatase levels above 150 U/l at the time of liver resection, positive primary nodal

Table 4
Analysis of overall and recurrence free survival

Features	No. of patients	Mean OS	*p*-Value	Median RFS	*p*-Value
Sex					
Female	64	44.8 [40.2–49.4]	0.024	10.9 [2.9–19.0]	0.460
Male	136	37.0 [33.2–40.9]		12.1 [8.0–16.2]	
T status					
T1, 2	35	45.8 [41.4–50.2]	0.007	17.6 [10.5–24.8]	0.053
T3, 4	162	37.5 [33.8–41.1]		10.8 [8.0–13.6]	
N status					
N0	72	46.0 [42.2–49.7]	<0.001	17.2 [10.3–24.2]	0.016
N > 0	128	34.0 [29.6–38.4]		10.8 [7.9–13.7]	
M status					
M0	80	41.9 [37.7–46.0]	0.073	18.6 [11.3–25.9]	0.012
M1	120	37.3 [32.8–41.7]		10.5 [7.7–13.3]	
G status					
G1, 2	176	41.9 [38.6–45.1]	<0.001	12.4 [8.3–16.5]	0.570
G3	24	23.2 [17.5–29.0]		9.9 [1.1–18.8]	
UICC stage					
I, II	37	48.1 [43.9–52,4]	0.003	19.3 [6.2–32.4]	0.033
III, IV	160	36.8 [33.1–40.6]		10.9 [8.4–13.5]	
Diagnosis of metastases					
Synchronous	119	37.2 [32.7–41.7]	0.066	9.9 [7.1–12.7]	0.008
Metachronous	81	41.9 [37.8–46.1]		18.6 [12.2–25.0]	
Disease free interval					
<12 Months	24	35.4 [29.1–41.6]	0.730	8.2 [4.1–12.3]	<0.001
12–24 Months	29	42.2 [35.0–49.4]		18.3 [7.4–29.3]	
>24 Months	28	42.2 [36.9–47.4]		35.1 [27.8–42.5]	
Number of metastases					
1	85	40.7 [36.1–45.3]	0.387	14.7 [8.6–20.8]	0.030
2–4	77	35.8 [32.0–39.6]		13.6 [6.8–20.4]	
>4	33	32.7 [25.4–39.9]		5.1 [1.5–8.7]	
Largest tumour					
≤5 cm	146	41.0 [37.3–44.6]	0.009	13.6 [8.8–18.4]	0.007
>5 cm	46	30.4 [24.7–36.0]		6.1 [3.2–9.1]	
Number of segments resected					
1–2	154	42.2 [38.7–45.7]	0.003	13.0 [8.9–17.2]	0.012
3–4	34	32.9 [25.7–40.0]		11.7 [0.0–23.7]	
5–6	11	26.2 [16.6–35.8]		3.0 [2.3–3.8]	
Response to neoadjuvant chemotherapy					
PR	49	38.6 [34.2–43.1]	0.063	17.3 [14.2–20.3]	0.006
SD	13	27.4 [20.3–34.5]		8.4 [5.1–11.8]	
PD	31	29.4 [22.7–36.2]		5.3 [2.1–8.5]	
Unknown	19				
Extrahepatic tumour					
No	182	41.0 [37.8–44.3]	<0.001		
Yes	18	23.6 [16.9–30.2]			
CEA (μg/l)					
≤5 (normal)	63	43.0 [38.2–47.7]	0.013	13.6 [8.7–18.5]	0.005
>5	98	34.0 [30.0–38.0]		4.6 [0.4–8.7]	
CA 19-9 (kU/l)					
≤100	103	41.6 [37.8–45.4]	<0.001	13.6 [7.9–19.3]	0.001
>100	29	25.2 [18.6–31.8]		4.6 [0.2–9.0]	
Alk. phosphatase (U/l)					
≤150	145	40.5 [36.9–44.1]	<0.001	13.0 [8.9–17.2]	<0.001
>150	25	21.7 [14.4–29.0]		3.0 [1.2–4.9]	

Table 4 (*continued*)

Features	No. of patients	Mean OS	*p*-Value	Median RFS	*p*-Value
γGT (U/l)					
≤ 80	134	39.8 [36.1–43.6]	0.004	14.7 [10.7–18.7]	<0.001
> 80	36	30.7 [24.0–37.4]		3.0 [0.6–5.5]	
Length of stay					
≤14 Days	180	40.9 [37.7–44.2]	0.040	13.0 [8.8–17.3]	0.030
>14 Days	17	26.7 [19.8–33.7]		9.6 [6.4–12.7]	

Overall (OS) and recurrence free survival (RFS) in months [95% confidence interval]. *p*-Value: Kaplan–Meier Log-rank test. PR, partial response; SD, stable disease; PD, progressive disease; CEA, carcinoembryonic antigen; and γGT, gamma glutamyl transferase.

status, poor differentiation of the primary and sex all predicted adverse outcome. For recurrence, elevated CA 19-9 beyond 100 U/l prolonged postoperative stay and positive node status of the primary was predictive.

Discussion

It is now widely accepted that surgical resection for metastatic colorectal cancer confined to the liver is the standard of care providing the best overall and disease free survival rates[1–3,5,19] compared to other therapies.[4] From January 2001 to December 2004, 200 hepatic resections were performed at our institution for colorectal cancer liver metastases. Most series published contain a large number of patients and describe the advancement of safe surgery for CRCLM over the last decade.[1–3,20] However, to our knowledge, there is no recent paper dealing with patients exclusively treated after the year 2000.

Neoadjuvant chemotherapy becomes increasingly important in the treatment of patients with metastatic CRC, in order to prolong recurrence free survival, to render initially unresectable lesions resectable[21] and to decrease the extent of resections. Lack of response to chemotherapy is a reliable marker of early recurrence.[8]

Under this aspect Hepatobiliary surgeons are nowadays more likely to be confronted with patients pretreated with systemic chemotherapy. Reports have recently been dealt with the potential dangers of liver resections after neoadjuvant therapies. We were able to demonstrate that modern surgical techniques and perioperative management lead to a zero percent in-hospital mortality and 9 out of 10 patients can be treated without any surgery-related morbidity, even after neoadjuvant chemotherapy.

Safety of surgery after neoadjuvant chemotherapy

The study recently published by Karoui et al.[11] described a series of 214 resections in a 5-year time period with no postoperative mortality and a morbidity rate comparable to our data. However, this study's intent was to analyze a subgroup of 67 patients with major resections (≥3 segments) ± neoadjuvant chemotherapy. Patients who received neoadjuvant chemotherapy were more likely to develop postoperative complications – this was correlated with the number of chemotherapy cycles applied (e.g. 19% <6 cycles vs 61.5% >11 cycles). In our patients, there was no association between preoperative chemotherapy and development of complications, even in the subgroup with 3 or more segments resected (Table 3). This might at least be in part due to the fact that neoadjuvant protocols at our institution consist of a shorter number of total courses compared to the group of Karoui et al. (median 6 cycles, range 3–29). Another contributing factor might be the fact that large resections were undertaken using total vascular exclusion techniques in the report by Karoui et al.,[11] which may also contribute to morbidity. Development of modern dissection techniques (e.g. CUSA) enables the surgeon to perform increasingly safe and tissue sparing liver surgery with almost or even no postoperative mortality and a low rate of morbidity.[22–24] Nevertheless only few studies report a zero percent mortality.[19,25,26]

In the recently published study by Vauthey et al.,[10] the 90-day mortality was linked to steatohepatitis which was most likely to occur after administration of irinotecan-containing regimens, however, postoperative morbidity was not different between the treatment groups. This trial was very well designed and is an important contribution to our understanding of how neoadjuvant chemotherapy affects operative outcome. Nevertheless 2 concerns can be raised: patient acquisition in this study reaches back to 1992 and improvements in operative technique and perioperative care have changed substantially since then. Secondly, the rate of large resections (hemihepatectomy or more) in this cohort was 67.7%, although the characteristics of the liver tumours would probably have allowed more limited surgery (solitary tumours, 50.7%; median size 3.5 cm (range 1.1–9.4), median number 2 (range 1–12).

This concept has already been investigated in the pre-chemotherapy era by Kokudo et al.[27] They found no difference in overall and recurrence free survival if the cohort of patients was analyzed towards type of resection (anatomical vs non-anatomical). Furthermore, it was described, that in more than 80% of cases a major, anatomical hepatectomy was unnecessary and a smaller, non-anatomical resection would have been technically possible. Keeping these data in mind it should be reconsidered that in the age of sometimes extensive neoadjuvant chemotherapy, smaller, even non-anatomical resections might be favourable over traditional large hepatectomies.

Impact of postoperative morbidity on patient outcome

It has been shown in 2003 that acquiring postoperative morbidity decreases overall and recurrence free survival in patients resected for colorectal cancer liver metastases.[15] In Laurent's study, 311 patients have been treated within a 15-year time frame. Postoperative mortality and morbidity were 3 and 30%, respectively. Patients who developed a postoperative morbidity had a significantly shorter overall and recurrence free survival at 5 years (21 vs 42%, $p < 0.001$ and 12 vs 28%, $p = 0.001$, respectively). In our data, postoperative morbidity did not have an influence on either mode of survival, although a prolonged postoperative stay of more than 14 days (median 9 days) was correlated with adverse outcome both in univariate (OS and RFS, $p = 0.04$ and $p = 0.025$) and multivariate (RFS $p = 0.021$) analyses. Of these 17 patients, 9 (52.9%) had a longer hospital stay due to postoperative morbidity. Other reasons for prolonged postoperative stay were non-surgical issues like recurrent (but previously known) seizures, polyneuropathy after chemotherapy or start of warfarin therapy. One patient underwent transurethral prostatectomy 10 days after liver surgery due to previously not evident benign prostate hyperplasia which caused postvesical obstruction.

Risk factors influencing long-term outcome – triggers for neoadjuvant chemotherapy

Very concise work has been done on risk factor analysis and their application in recent years.[1,19,28–30] In our collective data set a considerable number of patients have been treated very recently and we were able to confirm known risk factors – most important for us because we aimed to validate our collective data set against previously published international series.

In almost every series of hepatic resection in the literature, the effect of sex and age is routinely analyzed for survival and risk of recurrence. Some illustrate that advanced age beyond 70 years is correlated with shorter survival and earlier recurrence,[2,26] while some do not.[1,19] In 2 recent papers, Zacharias et al.[18] and Nagano et al.[12] have answered this question and proved that elderly patients do benefit from surgical therapy without increased mortality even in repeated resections. In our collective almost one-third (60/200) of the patients were older than 70 and had the same OS and RFS as their younger counterparts. Interestingly, overall survival was significantly longer in women compared to men in our cohort, which was also evident in multivariate analysis. We are unable to explain this phenomenon, since the female cohort is in all parameters without statistical difference to the male and treatment quality was the same for every patient.

Properties of the primary tumour like T stage, nodal status, site (colon/rectum) and stage (Dukes or UICC) correlate with a shorter survival time.[1–3,19] Of these, only T and N stages were predictive in our univariate analysis. A low differentiation of the primary tumour (G3) was significantly associated with shorter overall, but not with recurrence free survival. In the multivariate analysis positive nodal status also predicted shorter OS (RR = 3.06) and RFS (RR = 1.88), but poor differentiation only had an influence on OS (RR = 2.49, Table 5). Similar results were described by Jatzko et al. in 1995.[31]

One hundred and twelve patients received neoadjuvant chemotherapy prior to resection of their hepatic metastases as described above. The response rates are depicted in Table 2. Progression or even stable disease after chemotherapy was predictive for early recurrence; there was a trend towards shorter overall survival, which currently did not reach statistical significance (Table 4). Resembling results have been reported by Adam et al.,[8] showing 5-year survival rates of 37% (PR), 30% (SD) and 8% (PD). However, overall survival is still superior to patients who have unresectable metastases; nevertheless it is increasingly important to re-evaluate the policy of surgical therapy depending on response to neoadjuvant chemotherapy.

We believe that patients at high risk for early recurrence (positive nodal status, tumours > 5 cm, high CEA, more than 1 lesion and disease free interval < 12 months) should receive neoadjuvant chemotherapy regardless of initial resectability due to the fact that phase II data recently presented at the 2005 ASCO meeting demonstrated a prolonged recurrence free survival in these patients.[32] Additional evidence will hopefully become available from the EORTC 40983 trial evaluating exactly this question, where RFS data will be presented early 2007.

Extrahepatic disease, resection margin

Eighteen patients (9.0%) had undergone liver resection with known extrahepatic disease, mainly lung metastases. In these patients, the extrahepatic lesions either responded very well to chemotherapy or efforts to resect the lesion were undertaken. Since the presence of extrahepatic

Table 5
Multivariate analysis

Feature	Favourable vs not favourable	RR	95% CI	*p*-Value
Overall survival				
Extrahepatic tumour	No vs yes	4.60	[2.21–9.56]	<0.001
Preoperative alkaline phosphatase (U/l)	≤150 vs >150	3.43	[1.81–6.48]	<0.001
N status primary	N0 vs >N0	3.06	[1.46–6.44]	0.003
G status primary	G1 or G2 vs G3	2.49	[1.30–4.75]	0.006
Sex	Female vs male	2.63	[1.23–5.61]	0.012
Recurrence free survival				
Preoperative CA 19-9 (kU/l)	≤100 vs >100	2.32	[1.32–4.06]	0.003
Length of stay (days)	≤14 vs >14	1.81	[1.09–3.01]	0.021
N status primary	N0 vs >N0	1.88	[1.04–3.40]	0.037

RR, relative risk; 95% CI, 95% confidence interval; and γGT, gamma glutamyl transferase.

disease, if resectable, is nowadays no contraindication for resection of liver metastases,[33] we included these patients as ''non curative resections'' in our analysis. In 11 patients, the histological workup categorized the surgical margin as being tumour involved (R1), so this group was analyzed separately. Interestingly, R1 at the resection edge was not a risk factor for shorter overall survival, yet extrahepatic disease strongly predicted adverse outcome. Our current institutional data do not support the idea that histologically positive margin does influence long-term survival as long as liver resection is performed using a dissection device which vaporises normal liver tissue surrounding liver metastases during transaction (data not shown).

Conclusion

In conclusion we were able to demonstrate that surgical therapy for colorectal cancer liver metastases has become a safe procedure in experienced hands and does no longer have to be recalled a hazardous procedure requiring numerous blood transfusions and a prolonged hospital stay. Despite the increasing number of patients treated with neoadjuvant chemotherapy, morbidity and mortality rates were not influenced by this essential therapy in our series. We credit this to the high number of ''limited'' (non-anatomical) resections which are traditionally preferred at our institution. Since our collective is well comparable to previously published international series in regard to tumour number and size as well as risk factor analysis, we believe that this approach is a feasible alternative in the era of neoadjuvant chemotherapy. Nevertheless a multidisciplinary approach is mandatory for the optimal outcome strategy in our main goal to cure metastatic colorectal cancer patients.

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