ORIGINAL ARTICLE

Outcomes of extended versus limited indications for patients undergoing a liver resection for colorectal cancer liver metastases

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Abstract

Background: Currently, resection criteria for colorectal cancer liver metastases (CRCLM) are only limited by remnant liver function. Morbidity and survival after a partial hepatectomy with limited or extended indication criteria were compared.

Methods/Design: Between 1991 and 2010, patients undergoing a liver resection for CRCLM with limited ($n = 169$) or extended indication criteria ($n = 129$) were retrospectively identified in a prospectively collected single-centre database. Limited indication criteria were defined as less than three unilateral, not centrally located liver metastases in the absence of extra hepatic metastases. The extended criteria were only limited by predicted remnant liver volume and patients fitness. Data on co-morbidity, resection margin, short- and long-term morbidity, disease-free (DFS) and overall survival were compared.

Results: Patients with limited indications had less major complications (19.5% vs. 33.1%, $P < 0.01$), longer overall survival of 68.8 months [confidence interval (CI) 46.5–91.1] vs. 41.4 months (CI 33.4–49.0, $P \leq 0.001$) and longer median DFS of 22.0 months [confidence interval (CI) 15.8–28.2] vs 10.2 months (CI 8.4–11.9, $P < 0.001$) compared with the extended indication group. Cure rates, defined as 10-year DFS, were 35.5% and 15.8%, respectively. Fewer patients in the extended indication group underwent an R0 resection (92.9% vs. 77.5%, $P < 0.001$). Only 17% of all R1 resected patients had recurrences at the transection plane.

Conclusion: A partial hepatectomy for CRCLM with extended indications seems justified but is associated with higher complication rates, earlier recurrence and lower overall survival compared with limited indications. However, the median 5-year survival was substantial and a cure was achieved in 15.8% of patients.

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Introduction

During the last decade, the limited criteria for a partial liver resection have been replaced by more extended indication criteria.

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Improvements in surgical technique, optimization of peri-operative care, improvements in diagnostic imaging, pre-operative liver remnant volume modulation and effectiveness of modern chemotherapy regimens have boosted the widening of resectability criteria. Traditionally, only patients with a maximum of three colorectal cancer liver metastases, located peripherally at one side of the liver with an anticipated resection margin greater than 10 mm and without signs of extrahepatic disease were considered eligible for a partial liver resection.[1–4] Based on these limited

criteria, only 10–20% of patients with colorectal cancer metastases were eligible for a resection. Recent studies have shown that a liver resection in patients with multiple and/or bilateral colorectal liver metastases results in overall 5-years survival rates between 23% and 51%.[3,5] Moreover, centrally located liver metastases are no longer a contraindication for liver surgery. In patients with a normal functioning liver, extended hemihepatectomies can be performed safely and mesohepatectomy or a central liver resection is an alternative for an extended hemihepatectomy when parenchymal loss needs to be minimized.[6] If resectable extrahepatic metastases are present, a resection can be offered with 5-year overall survival rates up to 28%.[6,7] Thus, liver resection criteria for colorectal cancer liver metastases (CRCLM) are at present only limited by an anticipated R0 status and an adequate functional liver remnant. Patients in good general health, with technically resectable metastatic disease limited to the liver, regional lymph nodes or/and lungs, are considered for resection regardless of associated clinical predictive factors.[8–10]

Parallel to the expanding indications for a liver resection new strategies to improve resectability have also been popularized.[11–13] A liver resection combined with ablation of metastases[14–16] and/or induction chemotherapy to reduce the hepatic tumour size or tumour load may render unresectable metastases resectable or may help reduce the extent of liver resections.[17] Staged resections, with or without portal vein embolization/ligation, can be used for a two-step clearance of liver metastases, to increase future remnant liver volume and to achieve a definitive R0 status.

Expanding the indications and application of the aforementioned strategies has increased the number of patients becoming resectable.[18] The objective of the present study was to evaluate the post-operative clinical outcome and long-term survival in patients undergoing a liver resection for colorectal cancer liver metastases based on limited compared with extended indications.

Material and methods

Patients

A prospective database became operational in the Maastricht University Medical Centre HPB unit in 2001. All patients that underwent liver surgery before this date were included retrospectively. Patients undergoing liver surgery for CRCLM between 1991 and 2010 were included in the present study and assigned to a group with limited indication criteria or a group with extended indication criteria for resection. Patients were staged using a four-phase contrast enhanced abdominal CT scan. All patients with either primary or secondary liver tumours were discussed at a multidisciplinary liver meeting. Patient-specific co-morbidities and diagnostic procedures were assessed and the definitive treatment strategy was decided in consensus. Induction chemotherapy in irresectable patients, a liver resection combined with tumour ablation, pre-operative portal vein embolization, liver first policy in rectal cancer and a repeat hepatectomy were all among potential surgical strategies. Obviously some of these strategies became available only in more recent years. Vascular reconstructions were

Table 1 Indication criteria for resection of colorectal liver metastases

Limited indication criteria	Extended indication criteria
1. Three or less liver metastases	1. Four or more liver metastases
2. Located at one side of liver only	2. Bilateral metastases
3. No signs of extra hepatic metastases	3. Presence of resectable extra hepatic metastases
4. Anticipated resection margin more than 10 mm.	4. Centrally located metastases

occasionally used. In recent years, patients not undergoing liver surgery were assigned to stereotactic radiotherapy, percutaneous tumour ablation, Y^{90}- selective internal radiotherapy or palliative chemotherapy.

Study groups

Pre-operative CT-, MRI- or PET-CT-scans were used to determine the number and location of liver metastases. Operation notes gave insight in the specific type of resection, relation of metastases to the transection line, duration of surgery, the amount of blood loss and complications during surgery. Patients were, using predefined criteria, retrospectively assigned to either the extended indications group or to the limited indications group. Criteria for limited and extended indications are depicted in Table 1. Only patients with colorectal cancer liver metastases and a follow-up of at least 6 months were included in the present study.

Liver resections

All liver resections were classified in accordance with the IHPBA Brisbane nomenclature (Table 2).[19] A liver resection was performed as described previously.[20] To determine the definitive extent of hepatic metastases and transection line, intra-operative ultrasound was used routinely.

Peri-operative care

In February 2005, the Enhanced Recovery After Surgery (ERAS®) fast track peri-operative care programme was introduced in liver surgery at our centre. This programme enhances post-operative recovery and as a consequence reduces hospital length of stay (LOS).[21] Before the introduction of the ERAS programme there was no standard peri-operative care protocol.

Oncological follow-up

Follow-up consisted of outpatient visits with plasma carcinoembryonic antigen levels, every 3 months, and liver imaging twice in the first 2 years and annually up to 5 years after surgery. The median follow-up was 33 months (range, 0–235). In case of recurrence, patients were assessed with PET-CT and the indication for repeat liver or lung surgery was discussed in the multidisciplinary oncology meeting.

Table 2 Clinical characteristics

Variables	No. of patients			P
	All patients N = 298	**Limited indication criteria** N = 169	**Extended Indication criteria** N = 129	
Patient characteristics				
Median age [range], y	64 [24–88]	64 [28–88]	64 [24–82]	0.183
Gender, male (%)	177 (59.4)	110 (65.1)	67 (51.9)	0.022
Co-morbidities, present (%)	100 (33.6)	56 (33.1)	44 (34.1)	0.860
ASA classification				
Percentage with ASA 1	12.9	11.2	14.8	0.488
Percentage with ASA 2	60.8	59.2	62.5	0.604
Percentage with ASA 3	26.3	29.6	22.7	0.270
Primary tumour				
Location, colon (%)	177 (59.4)	98 (58.0)	79 (61.2)	0.571
AJCC T-stage, T3/T4 disease (%)	87.9	84.8	92.0	0.082
Nodal status, positive nodes (%)	65.9	64.6	67.6	0.618
Hepatic metastases				
Median size of largest lesion [range], cm	3.0 [0.0–20.0]	3.0 [0.4–13.0]	3.0 [0.0–20.0]	0.877
Larger than 5 cm (%)	18.7	17.6	20.2	0.622
Median number [range]	2 [1–12]	1 [1–3]	4 [1–12]	<0.001
Bilateral metastases (%)	74 (24.8)	0	74 (57.4)	–
Concomitant extrahepatic disease (%)	30 (10.1)	0	30 (23.3)	–
Pre-operative management				
Pre-operative chemotherapy (%)	42.1	34.5	52.0	0.003
Operative details				
Two-stage procedure planned	14	0	14	–
PVE during first stage	9	0	9	–
Second stage performed	10	0	10	–
Combined procedure (%)	13 (4.2)	7 (4.1)	6 (4.3)	0.940
Liver first procedure (%)	26 (8.4)	11 (6.5)	15 (10.8)	0.573
Type of liver resection (%)				
Major (> 3 segments)	174 (56.5)	81 (47.9)	97 (69.8)	<0.001
Left hemihepatectomy	18 (5.8)	9 (5.3)	9 (6.5)	0.669
Right hemihepatectomy	103 (33.4)	55 (32.5)	48 (34.5)	0.713
Left extended hemihepatectomy	4 (1.3)	0 (0.0)	4 (2.9)	–
Right ext. hemihepatectomy	12 (3.9)	2 (1.2)	10 (7.2)	0.007
Central liver resection	15 (4.9)	0 (0.0)	15 (10.8)	–
≤1 segmentectomy or (multi) metastasectomy	91 (29.5)	65 (38.5)	26 (18.7)	<0.001
Multisegmentectomies (≥ 2)	64 (20.8)	38 (22.5)	26 (18.7)	0.416
Only PVE	1 (0.3)	0 (0.0)	1 (0.7)	–
Concomitant local ablation* (%)	10 (3.2)	1 (0.6)	9 (6.7)	0.004
Post-operative management				
Percentage with post-operative chemotherapy	37.2	36.6	37.8	0.841

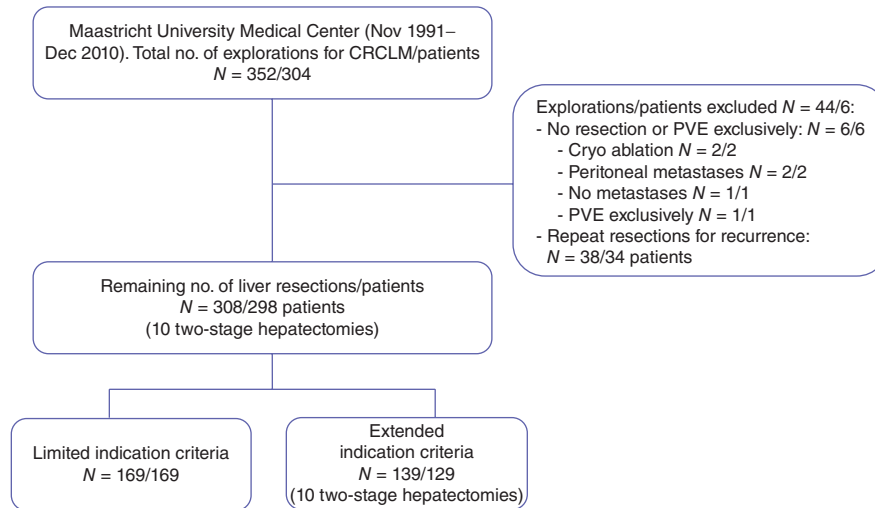ASA, American Society of Anesthesiologists; PVE, portal vein embolization.

Figure 1 Flowchart study population. PVE, portal vein embolization

Outcome parameters

The primary endpoint of the study was overall survival. Secondary endpoints were all complications: a liver surgery-specific composite endpoint,[22] readmissions, post-operative mortality, hospital LOS and disease-free survival (DFS). Complications were registered daily using National Surgical Adverse Event Registration (LHCR) software[23] of the Dutch Association of General Surgery before 2009 and in the hospital information system (SAP, Walldorf, Germany) thereafter. The post-operative course of all discharged patients was discussed at the surgeons' morning meeting and the Clavien–Dindo classification was used to grade complications after surgery.[24] Complications with a Clavien–Dindo score ≤2 were considered minor complications whereas complications ≥3a were considered major complications. Patient demographics were also registered and information on co-morbidity, location and TNM stage of the primary tumour and moment of occurrence of liver metastases were retrieved from patient charts. Size of the metastases and the resection margins were retrieved from pathology reports. R0 resections were defined as resections with a tumour-free resection surface. If invasion in the resection surface was present, the resection was considered R1. R1 resections with metastases reaching the resection surface were analysed separately for local recurrences and survival.

Overall survival (OS) and DFS after a liver resection were registered in months and calculated in percentages. Overall survival was calculated as the time period between the date of diagnosis and death. In the case of two-stage hepatectomies, DFS was calculated as the time period between the first stage operation and the recurrence of metastases after the second stage operation.

Statistical analysis

Data were analysed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Data are expressed as median and percentages or survival in months [95% confidence interval (CI)]. The chi-square test was used to analyse categorical data whereas continuous data were analysed using the t-test U-test. The time to recurrence and OS were calculated with the Kaplan–Meier (sensored) method using the date of liver surgery and date of diagnosis, respectively, as a reference date. A level of $P < 0.05$ was considered to be statistically significant.

Results

Patients

In total, 298 patients who underwent 308 liver resections for CRCLM between 1991 and 2010 were included. Ten patients had a two-stage strategy. Explorations with irresectable disease at laparotomy ($n = 6$) were excluded from further analysis (Fig. 1). In all patients with repeat resections for recurrent CRCLM ($n = 41$) results were analysed with the initial resection as a reference. The median age was 65 years (range 24–88). A total of 169 patients were included in the limited indications group compared with 129 patients in the extended indications group. Patient demographics, pre-operative characteristics, intra-operative details and pathology details are presented in Tables 2 and 3. Co-morbidities were present in 33.6% of patients, predominantly cardiovascular disease (28.2%), diabetes mellitus (7.7%) and pulmonary disease (4.0%). As expected through the allocation of patients, patients with extended indications had a more extensive spread of metastatic disease as is evidenced by the number of metastases, number of patients with bilateral disease and with concomitant extrahepatic disease. These patients underwent extended hepatectomies more often compared with the limited indications group (10.1% vs. 1.2%, $P < 0.001$). Surgical procedures are depicted in Table 2.

Pathological analysis

The percentage of R0 resections was 92.9% in the limited indications group and 77.5% in the extended indications group ($P < 0.001$).

Table 3 Comparison of surgical details, pathological details and hospital length of stay (LOS)

Variables	No. of resections / patients			P
	All resections / patients	Limited indication criteria	Extended indication criteria	
	N = 308 / 298	N = 169 / 169	N = 139 / 129	
Operative details				
Median estimated blood loss [range], ml	800 [10–11600]	775 [10–10000]	800 [50–11600]	0.592
Median duration of operation [range], min	217 [75–660]	204.5 [75–660]	240 [85–660]	<0.001
Pathology				
Resection margin,				
Patients with R0 resections	257 (86.2)	157 (92.9)	100 (77.5)	<0.001
Patients with R1 resections	41 (13.8)	12 (7.1)	29 (22.5)	<0.001
Patients with R2 resections	0.0	0.0	0.0	–
Hospital LOS				
Median LOS [range], days	8 [2–120]	8 [3–92]	8 [2–120]	0.579
Readmissions				
Number of patients readmitted (%)	30 (9.7)	14 (8.3)	16 (11.5)	0.342
Repeat resections				
Number of patients undergoing repeat resections for recurrence (%)	33 (11.1)	21 (12.4)	12 (9.3)	0.190
Number of patients with recurrence without resections (%)	122 (40.6)	62 (36.7)	60 (46.5)	0.190

Surgical outcome

There were no significant differences in blood loss during surgery, length of hospital stay and number of readmissions between both the groups. However, there was a significant difference in the median operation time 205 [75–660] min in the limited indications group compared with 240 [85–660] min in the extended indications group ($P < 0.001$; Table 3). Major complications occurred in 19.5% of the patients with limited indications compared with 33.1% of the patients with extended indications ($P = 0.007$). The 90-day post-operative mortality rate was 3.6% in the limited indication group compared with 5.0% in the extended indications group ($P = 0.519$; Table 4).

Overall survival

The median OS for all patients was 55.9 months (CI 48.5–63.3) with a 5-year OS rate of 48.3%. Patients in the limited indications group had a median OS of 68.8 months (CI 46.5–91.1) with a 5-year OS rate of 60.5%. Patients in the extended indications criteria group had a median OS of 41.2 months (CI 33.4–49.0) and a 5-year survival of 33.2% ($P < 0.001$). Ten-year OS rates in the limited indications group and the extended indications group were 35.5% and 15.8%, respectively.

365-day mortality

During the first post-operative year a steep drop in survival was observed in the Kaplan–Meier curve (Fig. 2) in both groups. We selected a group of all patients that died within 1 year after a partial hepatectomy and compared multiple patient characteristics with a group of all patients that survived at least 1 year. The only significant difference between the group that died within 1 year and the group that survived at least 1 year was age (median 67.7 [28.6–86.1] years and 63.7 [24.2–88.2], respectively and $P = 0.025$). Three more factors were borderline significant: combined oncological procedures, primary tumour positive lymph nodes and an American Society of Anesthesiologists' (ASA) score of 3. 9.5% of the patients that died within 1 year had a liver resection combined with a resection of the primary tumour compared with 3.6% of the patients that survived more than 1 year, $P = 0.077$. Moreover, 77.5% of the patients that died within 1 year had primary colorectal positive lymph nodes compared with 63.7% of the patients surviving more than 1 year, $P = 0.091$. Finally, 44.4% of the patients that died within 1 year were considered ASA 3 whereas only 24.6% of the patients that survived more than 1 year were considered as ASA 3, $P = 0.069$.

Disease-free survival

The median DFS for all patients was 15.7 months (CI 12.8–18.7) with a 5-year DFS rate of 23.7%. Patients in the limited indications group had a median DFS of 22.0 months (CI 15.8–28.2) and a 5-year DFS rate of 30.5%. Patients in the extended indications group had a median DFS of 10.2 months (CI 8.4–11.9) and a 5-year DFS rate of 14.2% ($P < 0.001$). Kaplan–Meier curves of both OS and DFS are presented in Figs 2 and 3.

Thirty-three patients with a hepatic recurrence underwent a repeat liver resection. 14% of these patients did not suffer a recurrence during follow-up. 86% of patients, 82% in the limited indications group and 92% in the extended group, developed a second recurrence. The median time from the repeat resection to the

Table 4 Complications

| Variables	No. of resections / patients			P
	All resections / patients	Limited indication criteria	Extended indication criteria	
	N = 308 / 298	N = 169 / 169	N = 139 / 129	
Complications				
Complications present	113 (36.7)	54 (32.0)	59 (42.4)	0.057
Minor complications present	34 (11.0)	21 (12.4)	13 (9.4)	0.392
Clavien–Dindo grade I	10 (3.2)	5 (3.0)	5 (3.6)	0.753
Clavien–Dindo grade II	24 (7.8)	16 (9.5)	8 (5.8)	0.227
Major complications present	79 (25.6)	33 (19.5)	46 (33.1)	0.007
Clavien–Dindo grade IIIa	48 (15.6)	20 (11.8)	28 (20.1)	0.045
Clavien–Dindo grade IIIb	8 (2.6)	2 (1.2)	6 (4.3)	0.085
Clavien–Dindo grade Iva	10 (3.2)	5 (3.0)	5 (3.6)	0.753
Clavien–Dindo grade Ivb	0 (0.0)	0 (0.0)	0 (0.0)	–
Clavien–Dindo grade V	13 (4.2)	6 (3.6)	7 (5.0)	0.519
Liver surgery specific composite endpoint (CEP)				
Liver surgery-specific CEP	67 (21.8)	29 (17.2)	38 (27.3)	0.031
Ascites	8 (2.6)	2 (1.2)	6 (4.3)	0.085
Post-resectional liver failure	11 (3.6)	4 (2.4)	7 (5.0)	0.209
Bile leakage	16 (5.2)	5 (3.0)	11 (7.9)	0.051
Intra-abdominal haemorrhage	9 (2.9)	4 (2.4)	5 (3.6)	0.524
Intra-abdominal abscess	35 (11.4)	19 (11.2)	16 (11.5)	0.941
90-day post-operative mortality	13 (4.2)	6 (3.6)	7 (5.0)	0.519
Other liver-related complications				
Hepatic encephalopathy	5 (1.6)	2 (1.2)	3 (2.2)	–
Liver dysfunction	2 (0.6)	0 (0.0)	2 (1.4)	–
Cholangitis	2 (0.6)	1 (0.6)	1 (0.7)	–
Other complications				
Sepsis	9 (2.9)	5 (3.0)	4 (2.9)	0.943
Cardiovascular	13 (4.2)	8 (4.7)	5 (3.6)	0.719
Pulmonary	28 (9.1)	17 (10.1)	11 (7.9)	0.653
Renal / urine tract	12 (3.9)	8 (4.7)	4 (2.9)	0.477
Gastro-intestinal	18 (5.8)	7 (4.1)	11 (7.9)	0.115
Haematological	1 (0.3)	0 (0.0)	1 (0.7)	–
Neurological	9 (2.9)	1 (0.6)	8 (5.8)	–
Wound infection	7 (2.3)	3 (1.8)	4 (2.9)	–

second recurrence was 8.7 [0.0–18.9] months and 6.9 [1.9–11.9] months (P = 0.390) in both groups, respectively.

Recurrence after R1 liver resections
On histological examination, the resection specimen of 41 patients (13.3%) showed a microscopically positive resection margin (R1 resection). In these patients, recurrence of metastases in any location (i.e. liver and elsewhere) occurred in 23 (56%) out of 41 patients. Thirteen (32%) of these patients developed hepatic recurrence of which 3 (7%) had both intra- and extrahepatic recurrence. Only seven (17%) of patients with an R1 resection

recurred at the former R1 resection surface: one patient in the limited indications group and six in the extended indications group. Ten (24%) patients showed extra hepatic recurrence only. Eighteen (44%) patients with an R1 resection stayed disease free during the follow-up period (median follow-up was 33.3 [0.2–165.9] months) (figure 4).
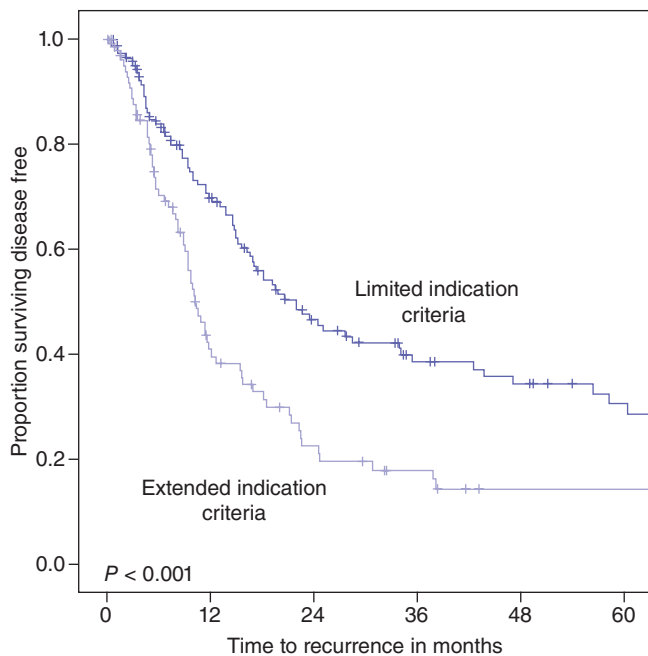
Overall survival in all patients with an R0 resection was 60.0 [53.0–67.0] months with a 5-year survival rate of 50.4%. Patients with an R1 resection showed a median OS of 44.3 [26.3–62.4] months and a 5-year survival rate of 34.9% (P = 0.040). Disease-free survival in all patients with an R0 resection was 16.9 [13.9–
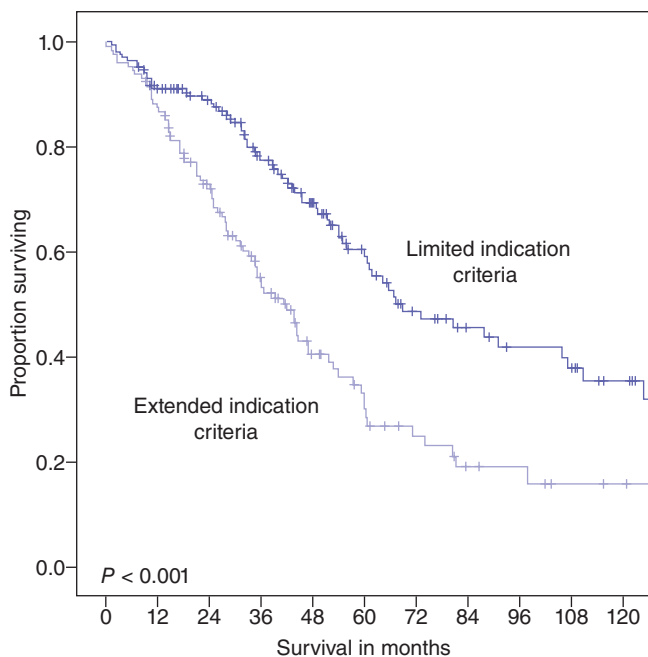
Figure 2 Overall survival

Figure 3 Disease-free survival

19.9] months (5-year DFS rate 25.2%) versus 9.4 [3.9–15.0] months (5-year DFS rate 17.4%) in patients with an R1 resection ($P = 0.091$).

Discussion

In this study, short- and long-term outcomes in patients undergoing a liver resection for colorectal cancer liver metastases with extended indications were assessed and compared with a group of patients operated according to limited indications criteria. We showed in the extended indications group a 5-year survival of 33.2% equivalent to a median OS of 41 months. In patients undergoing a liver resection according to the limited indications, a 5-year OS of 60.5% was observed, equivalent to a median OS of 69 months. In the latter group, 5-year DFS was 30.5% equivalent to a median DFS of 22 months. In patients with extended indications, 5-year DFS was 14.2% equivalent to a median DFS of 10 months, which is significantly lower than in patients with limited indications. When patients underwent a repeat liver resection for recurrence, the median DFS was prolonged by 8 months. Although the outcome was worse in the extended indication group, cure of a cure, defined as DFS longer than 10 years, was observed in 15.8% of patients.

Recently, short- and long-term outcomes in patients undergoing a liver resection for colorectal cancer liver metastases before and after 2000 have been published.[25] In that study, two time periods with mixed indication criteria were compared. Although extended indication criteria were used in the patient groups before and after 2000, most patients operated after 2000 were still treated within the limited indication criteria. This may explain the relatively small difference observed in a 5-year OS of 47% and 58% between the two groups, respectively, in that study. Outcome results regarding patients undergoing a liver resection for colorectal cancer liver metastases within extended indication criteria are scarce. Recent publications report on the influence on outcome of only one single component of the former contraindications, e.g. number of metastases, resection margin or extra hepatic disease.[3,5,7,26]

The results of this study are in line with recent publications and are slightly better than the results of a recently published meta-analysis of studies on a liver resection for colorectal cancer liver metastases before 2007.[9,25,27,28] From most published series, it transpires that over time survival after a liver resection of CRCLM improves probably as a consequence of improved effectiveness of modern chemotherapy regimens, improved peri-operative care, better patient selection and more aggressive resections. The OS of 56 months in this study may also be influenced by the long timeframe or modern chemotherapy regimens as well as additional treatment strategies in both patient groups with limited and extended indication criteria and seems to support an aggressive strategy towards CRCLM. From clinical practice, we observe that extending the indications for liver resection of colorectal cancer liver metastases renders more patients eligible. Our data show that
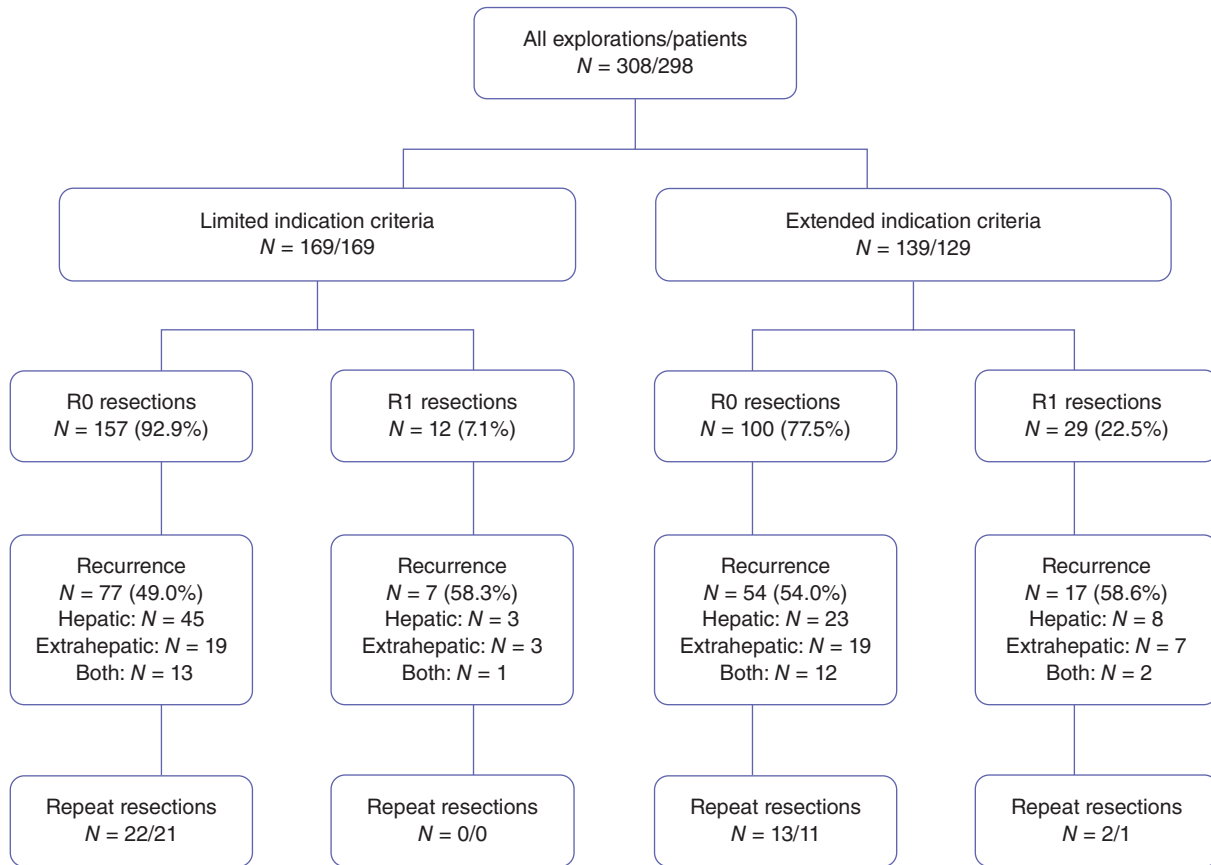
Figure 4 R1 resections, recurrence and repeat resections

extending the indications has its consequences for patients. It leads to more major complications, a shorter OS and a shorter DFS compared with patients with less extensive metastases. Major complications often require surgical, endoscopic, or radiological interventions. Although it may not be entirely legitimate to compare the median OS of 41 months in patients eligible for liver resection within extended indications to the median survival of 18–22 months in patients treated with chemotherapy alone, survival after a liver resection probably is substantially longer.[29–32] The increase in OS of approximately one and a half years compared with the available literature data on outcome after palliative chemotherapy alone, seems to justify the acceptance of a higher complication rate after a resection.

Wiering *et al.*[33] showed that quality of life recovered to baseline within 3 months in patients undergoing a potentially curative liver resection whereas a persistent decline in quality of life was demonstrated in patients immediately treated with palliative chemotherapy alone. If patients turned out to be irresectable at laparotomy, the quality of life was worst.[34] It can therefore be hypothesized that the occurrence of complications after liver surgery with curative intent is an acceptable phenomenon for patients. Futile laparotomies should be avoided by using optimal pre-operative patient selection.

The morbidity and mortality results in the present study are consistent with other recently published series,[25,35] although comparison is hampered to some extent as definitions used for severe or major morbidity vary across studies. In addition to standardized definitions of complications, the use of a composite endpoint for liver surgery-specific complications could enhance comparability of published series.[22]

Strikingly, the occurrence of more severe complications did not prolong the hospital LOS and did not lead to more readmissions. It can be hypothesized that the expected prolonged hospital LOS as a consequence of a higher percentage of major morbidity was compensated by the introduction of the Enhanced Recovery after Surgery (ERAS®) programme in our unit in 2005. A substantial proportion of patients deceased in the first year after a partial liver resection in both the extended indications and the limited indications group. In this study, high age, a ASA score of 3 and combined liver and colon resections proved to be risk factors for a high 365-day mortality. Hence, it should be possible to reduce post-operative mortality with better pre-operative patient selection. Unfortunately, our data, as well as other published data, did not show predictive factors usable to select patients who were at risk for mortality and consequently did not benefit from surgery.[36,37]

Compared with patients with limited indications, patients with extended indications more often underwent an R1 resection. In this series this did not lead to more repeat resections in the latter group. Moreover, we showed that only 17% of the patients with a R1 resection recurred at the level of the pathologically irradical resection surface. This might be a result of the use of the CUSA device (Integra LifeSiences, Plainsboro, NJ, USA), which does not allow the pathologist to evaluate the actual resection surface, as approximately 1 to 3 mm of hepatocytes disintegrate with the use of this device. The consequence of this observation might be that a close relation of metastases to vascular structures that cannot be resected is not an absolute contraindication for resection. Moreover, an R0 resection rate of 77.5% and a median survival of 41 months as well as the cure percentage of 15.8% seems to justify the use of extended indication criteria. As others have provided data to suggest these patients have a good quality of life, it also seems justified to be creative in future strategies to increase the resection rate in patients with colorectal cancer liver metastases. Suggestions might be to combine different treatment modalities that aim to remove or destroy metastases while functional liver capacity is maintained or enhanced. Open- or laparoscopic-resections combined with ablation, irreversible electroporation, peri-operative stereotactic radiotherapy or selective Internal Radio Therapy (SIRT) with Ytrium-bound microspheres,[38] may help to increase the R0 resection rate and further improve survival with an acceptable quality of life.

The new technique of *in situ* liver partition and portal vein ligation for a two-stage hepatectomy with a short interval (ISLT or ALPPS) seems promising but the current morbidity and mortality of this procedure is still too high[39–41]

Strong points of this study are the selection of a series of patients with extended indication criteria and a standardized complication registration. Limitations are the relatively small sample size owing to the single-centre study design, the large time period during which the patients were included, the different peri-operative neo-adjuvant or adjuvant chemotherapy strategies and the retrospective analysis of prospectively collected outcome data.

Conclusion

Liver resection for colorectal cancer liver metastases with extended indication criteria seems justified. An R0 resection rate of 77%, median 5-year overall survival of over 33% and cure in 16% of patients was achieved with acceptable post-operative mortality and morbidity.

Conflicts of interest
None declared.

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