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Hepatic resection of non-colorectal and non-neuroendocrine liver metastases – Survival benefit for patients with non-gastrointestinal primary cancers – A case-controlled study

Jan E. Slotta [a,b,*,c], Jochen Schuld [b,c], Sabrina Distler [b], Sven Richter [b], Martin K. Schilling [b], Otto Kollmar [a,b]

[a] Department of General, Visceral and Paediatric Surgery, University Medical Center Göttingen, Germany
[b] Department of General, Visceral, Vascular and Paediatric Surgery, Saarland University Medical Center, Homburg, Saar, Germany

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ABSTRACT

Purpose: Whereas resection of colorectal liver metastases is gold standard, there is an ongoing debate on benefit of resection of non-colorectal (NCRC) and non-neuroendocrine (NNEC) liver metastases.
Methods: The potential survival benefit of patients undergoing resection of NCRC or NNEC liver metastases was investigated. Data from a prospectively maintained database were reviewed over a 7-year period. Kaplan–Meier method was used for the evaluation of outcome following resection.
Results: 101 patients underwent 116 surgical procedures for synchronous and metachronous NCRC or NNEC liver metastases with a morbidity of 23% and a mortality of ~1%. 11 patients underwent repeated liver resection procedures. Overall 5-year survival after liver resection was 30% depending on primary tumour site. Median survival was significantly increased after resection of hepatic metastases from non-gastrointestinal primaries compared to gastrointestinal primaries. Resection of hepatic metastases from non-gastrointestinal primaries resulted in significantly increased median survival compared to exploration only. Patients with hepatic metastases from gastrointestinal primaries did not benefit from hepatic surgery.
Conclusion: Hepatic resection for liver metastases from NCRC or NNEC cancers is a save treatment procedure. However, the decision to perform surgery should depend on the primary cancer. Especially patients with liver metastases from non-gastrointestinal primaries profit from hepatic surgery.

1. Introduction

Liver resection for the treatment of distant cancer metastases is a well established therapy option which has been introduced in the middle of the past century.[1] As a result of improved knowledge of liver anatomy and physiology[2] as well as modern surgical techniques and intensive care treatment strategies, hepatic surgery for liver metastases has become a safe procedure with low mortality.[3,4] Whereas the prognosis of untreated liver metastases from colorectal cancer is very poor with a median survival of less than 12 months,[5] resection of colorectal liver metastases representing the only curative treatment option improves the prognosis to a 5-year survival rate of ~40%[6] and 10-year survival rates of up to 25%.[7,8] Furthermore, aggressive surgical therapy of neuroendocrine liver metastases has recently been demonstrated to improve clinical symptoms and increase survival rates up to 83% after 3–5 years.[9–12]

In contrast, there is an ongoing debate on the indication for resection of hepatic metastases from non-colorectal (NCRC) and non-neuroendocrine (NNEC) primary tumours. In such patients, metastases reach the liver via systemic circulation, and thus a systemic tumour spread has to be assumed. Therefore, systemic chemotherapy has been recommended for these patients in the past. Furthermore, the group of patients with isolated liver metastases from NCRC and NNEC is found to be small in number and very heterogeneous due to a large variety of underlying primary tumours. Consequently, there is a huge diversity of palliative chemotherapy regimes for the treatment of liver metastases from the different primaries, at least leading to a median survival of 24–27 months in slow-growing cancers, such as renal cell carcinomas

* Corresponding author. Department of General, Visceral and Paediatric Surgery, University Medical Center Göttingen, Germany. Tel.: +49 551 398700; fax: +49 551 39 14171.
E-mail address: jan.slotta@med.uni-goettingen.de (J.E. Slotta).
[c] These authors contributed equally to this work.

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or breast cancer.[13,14] In contrast, for pancreatic[15] or gastric cancers,[16] chemotherapy has shown to be ineffective as survival is only prolonged by a few weeks. The issue of liver metastases surgery for NCRC and NNEC is clinically important. In parallel to therapy of colorectal cancer, cryosurgery or radio frequency ablation have been discussed as minimally invasive local approaches in systemic NCRC or NNEC tumour disease,[17,18] but these therapies are not established as standard treatment options for NCRC or NNEC liver metastases yet. However, some recently published reports suggest that patients with liver metastases from NCRC and NNEC carcinoma might benefit from hepatic resection.[19–22] A recently published overview by Lehner et al. showed a 5-year survival rate of 27–39% in patients undergoing liver resection of NCRC and NNEC metastases.[4] Interestingly, there are diverging results showing a clear-cut impact of the localisation of the primary tumour on the respective survival rates.[4,20]

Thus, the aim of the present study was to analyse the benefit of liver resection for NCRC and NNEC hepatic metastases in the patient collective of our large hepatobiliary referral centre. Furthermore, the intent of the present study was to investigate if the surgical approach for resectable liver metastases of NCRC and NNEC origin is an effective strategy to prolong survival compared to palliative treatment regimes and to emphasize the value of surgery in multimodal therapy concepts.

2. Patients and methods

2.1. Data acquisition

Data from all patients undergoing hepatic surgery were prospectively entered in an i.s.h.-med database (GSD, Berlin, Germany) running on a SAP platform (SAP, St Leon-Rot, Germany). For this cohort study, data from patients undergoing liver resection for NCRC and NNEC metastases in a 6-year period were retrieved from that database and analysed retrospectively. Thus, for all patients all data for any variable were available.

2.2. Inclusion criteria for surgery

In all patients, resection of the primary cancer was categorized to be formally curative as defined by removal of all macroscopically detectable tumour and microscopically clear resection margins. Operations on the primary tumour were performed in combination with or without chemotherapy and radiotherapy using neoadjuvant and adjuvant protocols. Histological classification was performed according to international standards.[23] All patients undergoing liver resection had a standardised general anaesthesia including epidural analgesia, balanced volume status and prophylactic perioperative antibiotics. In our retrospective study, all patients presenting at our hepatobiliary centre for resection of hepatic metastases from NCRC or NNEC primaries were included. The decision on operability was based on patients' performance status, declared patients' will, and informed consent. Further, resectability as well as choice of the operative procedure – selected to ensure both adequate oncological resection margins and a maximal volume of functional hepatic parenchyma remnant – were based on preoperative diagnostics, i.e. CT scan or magnetic resonance tomography. Findings after laparotomy and intraoperative ultrasound were the final criteria for resection of hepatic metastases or exploration only in case of non-resectability. Criteria for non-resectability were infiltration of all three liver veins, diffuse liver metastases and non-resectable extrahepatic tumour manifestations, either detected in preoperative imaging or as intraoperative finding. Synchronous or metachronous state of the metastases as well as number, location (uni-lobular or bi-lobular) or size of the metastases were no exclusion criteria for surgical exploration.

2.3. Surgical procedures and postoperative follow-up

Partial hepatectomy was performed as anatomical resection according to Couinaud,[2] as non-anatomical or wedge resection and as a combination of anatomical and non-anatomical resections with or without Pringle's manoeuvre, selective vascular clamping or selective vascular occlusion. Major hepatectomy was defined as resection of three or more anatomical liver segments.[24] Tissue destruction within the parenchymal dissection line was usually performed by ultrasonic dissection and the resection margins of the remnant liver were coagulated by argon plasma beamer. Complete lymph node dissection of the hepatoduodenal ligament was performed when size and firmness of the lymph nodes were suspicious for malignant infiltration.

Data was recorded prospectively in our database including all demographic details, disease-related data, medical data and data from the peri-operative and postoperative course. Recurrence and follow-up information from the patients was determined from the medical records or was assessed retrospectively. Follow-up examinations included CT-scan or magnetic resonance tomography every 6 months after hepatic surgery for liver metastases.

2.4. Statistical analyses

Data is expressed as absolute numbers, percent, or mean ± standard error of the mean (SEM) unless indicated otherwise. The length of follow-up was calculated from the date of liver resection at our institution with a median of 18 months. Comparisons of categorical and continuous variables were performed using the χ^2-test, Fisher's exact test if applicable and the Wilcoxon rank-sum test. Differences between more than two groups were calculated by ANOVA followed by the recommended post-hoc test. To clarify and structure our data, patients with neoadjuvant treatment of liver metastases before liver surgery in our centre and loss of follow-up were excluded from univariate and survival analyses. Survival analyses were estimated according to the Kaplan–Meier method and compared with the long-rank test using the software package SPSS 14.0® (SPSS GmbH Software, Munich, Germany). Patients who died from unknown cause of death were also counted as an 'event' in the Kaplan–Meier analysis as well as other patients who died from tumour recurrence. P values of <0.05 were considered significant.

3. Results

3.1. Patient demographics

101 patients underwent a total of 116 surgical procedures for liver metastases from NCRC or NNEC primary cancers, including 24 explorations only. Our cohort comprised 57 female (56.4%) and 44 male (43.6%) patients with a mean age of 58.6 ± 1.1 years at time of liver surgery, among which 20.8% were older than 70 years (Table 1).

Regarding the primary tumour, T stages 1–3 were found in similar frequency, precise T staging could not be determined in 28 patients. 26.7% of the patients had synchronous hepatic metastases, defined as liver metastases occurring within 6 months after diagnosis of the primary tumour. 48 patients had adjuvant chemotherapy for the respective primary tumour, and 10 underwent chemotherapy even before liver surgery (Table 1).

Table 1
Patient demographics ($n = 101$) and histological classification of the primary non-colorectal and non-neuroendocrine tumour. Data are given as mean ± SEM or *n*.

Variable	Mean ± SEM or *n*
Gender [female/male]	57/44
ASA score	2.32 ± 0.06
Body mass index [BMI, kg/m^2]	25.44 ± 0.49
BMI > 30 kg/m^2	19
Age [years]	58.58 ± 1.14
Age >70 years	21
Hepatitis (B/C)	1/0
Diabetes	13
Chronic kidney disease	9
Chronic heart disease	14
Chronic pulmonary disease	9
Hypertension	62
Previous abdominal operation	94
T stages primary tumour[23]	
Tx	28
T1	24
T2	30
T3	28
T4	6
Synchronous liver metastases (M1)	27
Adjuvant chemotherapy for the primary tumour	48
Chemotherapy before liver resection	10
Time between surgery for primary tumour and first liver resection in our institution (months)	50.3 ± 6.4

3.2. Surgical procedures

Surgical procedures performed are listed in Table 2. Fourteen patients underwent major hepatectomies with resection of three or more liver segments (12.1%) and 78 patients underwent minor liver resections, mostly performed as combined resections of more than 2 hepatic sites. In 24 cases, only abdominal exploration was performed due to intraoperative finding of non-resectability of the hepatic metastases (20.7%).

Local ablative procedures were performed in 7 patients to achieve total tumour destruction at the resection margin. All 7 patients had a follow-up as described above and showed no difference from patients undergoing a resection procedure only (data not shown).

Table 2
Operative technique, operative parameters and morbidity and mortality of 101 patients undergoing 116 liver resection procedures for non-colorectal and non-neuroendocrine liver metastases. Repeated procedures were performed in 11 patients ranging from 2 to 4 procedures. Data are given as mean ± SEM or *n*.

Variable	Mean ± SEM or *n*
Exploration only	24
Repeated liver resection procedures ($n = 11$ patients)	26 (2–4/patient)
Major liver resection	
• Hemihepatectomy (right/left)	4/1
• Extended right/left resection	2/2
• Central resection	1
• >2 anatomical segments	4
Minor liver resection	
• Segmentectomy	9
• Bisegmentectomy	21
• Atypical/wedge resections	47
• Cryosurgery only	1
Simultaneous liver and primary tumour resection	15
Hepatoduodenal lymph node dissection	6
Additional cryosurgery of liver metastases	5
Cryosurgery of the resection margin	1
Radiofrequency of liver metastases	1
Operative time [min]	168.9 ± 7.4
Blood loss (ml)	518 ± 79
Postoperative hospital stay (days)	11.1 ± 0.7
ICU/intermediate care stay (days)	2.1 ± 0.3
Complications CTC grade 3[25]	10
Complications CTC grade 4[25]	2
Complications CTC grade 5[25]	1

3.3. Operative and perioperative data; morbidity and mortality

11 out of the 101 patients underwent 26 repeated liver resection procedures overall. The operative and perioperative data are shown in Table 2. Operative time was 169 ± 7 min with resection times of 19 ± 3 min. Mean blood loss was 518 ± 79 ml, whereas there was an average blood loss of 302 ± 77 ml associated with the resection procedure. The maximum diameter of the resection margin was 7.6 ± 0.5 cm. Volumetric analyses revealed a mean resection volume of 342 ± 61 cm^3.

Mortality of the 116 procedures was 0.9% because one patient died after extended liver resection due to liver insufficiency and subsequent multi organ failure (CTCAE grade 5,[25] Table 2). Overall rate of major and minor postoperative complications (CTCAE 2-3) was low. Complications with CTCAE grades 3 and 4 were mainly bleeding complications or bile leakages with subsequent surgical or radiological intervention (Table 2). Average postoperative hospital stay was 11.1 ± 0.7 days, and ICU/IMC stay was 2.1 ± 0.3 days.

3.4. Overall survival and tumour-free survival after liver resection

Table 3 shows anatomical associations of hepatic metastases to the respective primary cancer. As shown, main primary tumours were gynaecological, urogenital and gastrointestinal cancers. The overall 1, 3, and 5-year survival rates (Table 4) for the entire cohort of 101 patients were 66%, 43%, and 30% respectively, after the first occurrence of liver metastases. Overall recurrence-free 5-year survival rate was 25% after first liver resection and liver-related recurrence-free survival rate was 39%. Comparing gender differences in survival rates, there were no significant differences regarding survival rates after first occurrence/resection of liver metastases, overall tumour-free survival rate after first hepatic resection, and liver-related tumour-free survival rate (Table 4). Analysis of the primary tumour site revealed that patients with liver metastases from non-gastrointestinal primary tumours had a significantly longer survival than those with metastases of gastrointestinal primary tumours ($p < 0.05$; Fig. 1A, Table 4). However, these groups did not differ concerning recurrence-free survival (Table 4; Fig. 1B). Age at the time of resection as well as extent of hepatic resection had no further impact on patient's survival.

Subgroup analyses revealed that, in particular, those patients undergoing resection of hepatic metastases from gastrointestinal

Table 3
Site of the primary tumour grouped by anatomical association for 101 patients undergoing hepatic resection non-colorectal and non-neuroendocrine liver metastases with corresponding median survival after liver resection. Data are given as *n*.

Primary tumour site	*n*	Median survival [months]
Breast	24	38.20
Gastric	14	17.30
Pancreas	13	8.20
Urogenital	12	24.61
Melanoma	7	2.69
Uterus	6	20.98
Small intestine	6	57.16
Ovarian	5	15.84
Pulmonary	2	15.69
Oesophageal	2	12.48
Pharynx	2	6.00
Liposarcoma	1	40.20
Adrenal	1	13.05
Parotid	1	10.85
Thyroid	1	23.93
CUP	4	41.34

Table 4
Survival analyses of patients with non-colorectal and non-neuroendocrine liver metastases undergoing liver resection related to variables of the primary tumour. Data are expressed for survival rates (1, 3 and 5 years) after first occurrence/resection of liver metastases (Phx), for the overall tumour free survival rate after first Phx, and the liver-related tumour free survival rate. *$p < 0.05$.

Variable	n	Survival after Phx			Tumour-free survival after first Phx			Tumour-free survival after Phx (liver)		
		1 y	3 y	5 y	1 y	3 y	5 y	1 y	3 y	5 y
Overall	101	66	43	30	66	36	25	74	48	39
Gender										
Male	44	64	40	28	66	42	28	74	55	40
Female	57	68	44	31	66	33	24	74	44	38
Primary site										
Gastrointestinal	37	59	33	20*	58	35	26	68	57	47
Non-gastrointestinal	64	70	49	35	70	38	26	68	51	41
Age										
<70	80	70	46	31	64	33*	24	73	45	38
≥70	21	52	30	30	76	66	33	82	71	36
Temporal relationship										
Synchronous	27	52	31	22	66	58*	58*	66	58	58
Metachronous	74	71	47	33	66	32	21	77	47	37
Repeated liver resections										
Yes	11	100*	77*	60*	53	15*	15	59	22*	22
No	90	61	37	24	70	48	39	80	61	45

primary cancers had no survival benefit compared to exploration only (Fig. 1C). In contrast, patients with hepatic metastases from non-gastrointestinal had a significantly prolonged survival after resection compared to exploration only ($p < 0.05$; Fig. 1D). For further risk stratification, the impact of different non-gastrointestinal primary cancers on the overall survival was analysed. Resection of hepatic metastases from gynaecological and urogenital primary cancers resulted in a median survival of 27 months and 25 months, respectively, turning the disease in a chronic course.

Analysis of the temporal relationship between primary cancer and occurrence of hepatic metastases, i.e. synchronous vs. metachronous occurrence of hepatic metastases, showed no significant differences for 1, 3 and 5-year overall survival (Table 4).

3.5. Repeated liver resections

In 11 out of 101 patients, a total of 26 repeated liver resections were performed due to local recurrence, as indicated by ultrasound or CT-scan. Analysis of overall survival showed a significant survival benefit for patients undergoing repeated surgery ($p < 0.05$; Table 4). Tumour-free survival rates and liver-related tumour-free survival rates in patients with repeated hepatic resections were significantly reduced compared to patients with only one liver resection procedure ($p < 0.05$, Table 4).

With regard to prevention of hepatic metastases, we analysed the impact of chemotherapy for primary cancer on their occurrence. Interestingly, adjuvant chemotherapy was found to neither reduce overall survival rates, nor overall tumour-free, nor liver-related tumour-free survival rates significantly.

4. Discussion

4.1. Patient outcome with liver metastases from NCRC and NNEC primary cancer

A variety of possible explanations for improved outcome of patients undergoing hepatic surgery for non-colorectal and non-neuroendocrine liver metastases within the last few decades can be considered. Besides advantages in preoperative diagnostics, improved surgical techniques and novel postoperative intensive care therapy regimes may have led to increased survival rates after hepatic surgery, as also found after resection of colorectal liver metastases.[5,8] However, due to the generalized extent of their disease the prognosis of patients with hepatic metastases from NCRC and NNEC primary cancer is very poor. Although resection of hepatic metastases has been considered to be ineffective to prolong survival and to be a rather palliative approach, several recent publications demonstrated that hepatic surgery for metastases might be a promising tool to prolong patients' survival.[20,21] Among our 101 patients, we found survival rates in line with other recent publications.[20,26] Furthermore, the overall 5-year survival rate was even comparable to that after resection of liver metastases from colorectal cancer,[8,27] which in turn is a widely accepted therapy concept. Disease-free survival among our patients was comparable to data demonstrated recently elsewhere.[20,28] Thus, one can argue that resection of hepatic metastases of NCRC and NNEC primary cancers is a safe therapy option despite a systemic cancer disease. Interestingly, disease-free survival and overall survival rates were very similar in our cohort. This suggests that survival is strongly correlated to recurrence of metastases, which do not necessarily have to appear within the liver. This small difference between overall and disease-free survival is possibly a reflection of systemic tumour disease and different biological behaviour of the different tumour entities. Admittedly, this is a retrospective analysis of prospectively collected data, so our data concerning disease-free survival does not allow for any conclusion on tumour biology.

4.2. Surgery for liver metastases from NCRC and NNEC primary cancers

In the literature, striking differences with regard to survival rates after hepatic surgery for metastases depending on the origin of the primary tumour and the extent of metastatic dissemination are reported. For example, after resection of solitary hepatic metastases of renal cell carcinomas a 5-year survival of 25–35% is described,[29] whereas 5-year survival after hepatic resection of pancreatic metastases is only 8%.[4] These diverging survival rates demonstrate that a general recommendation for hepatic resection of liver metastases is not reasonable. With this background we analysed patients with liver metastases from gastrointestinal or non-gastrointestinal primary cancers. In line with others, we found a significant survival benefit for patients with liver metastases from non-gastrointestinal primaries, even though there was no difference regarding recurrence-free survival.[30,31] This difference in survival rates depending on different origins of primaries has been described to be more distinct by Schmelzle, as well as others, showing a 5-year survival of 0% in patients with liver metastases from gastrointestinal primary cancer.[21,31–33] However, we herein present for the first time a 5-year survival rate of 20% in patients within a median follow-up time of 18 months undergoing hepatic surgery for metastases from NCRC or NNEC gastrointestinal primaries. This surprisingly high survival rate might be due to an aggressive surgical treatment, including central hepatic resections or extended hepatic resections, which are surgical procedures not performed routinely in all surgical departments. Our data adds information on current consensus that hepatic surgery for liver metastases from NCRC or NNEC non-gastrointestinal primary cancers represents a promising therapy option and has even been proposed to be considered as a gold standard.[19,33] However data for hepatic resection of metastases from gastrointestinal primaries is still controversial and therefore liver resection for patients with pancreatic and upper-gastrointestinal cancers as well as melanoma metastases should not be recommended.

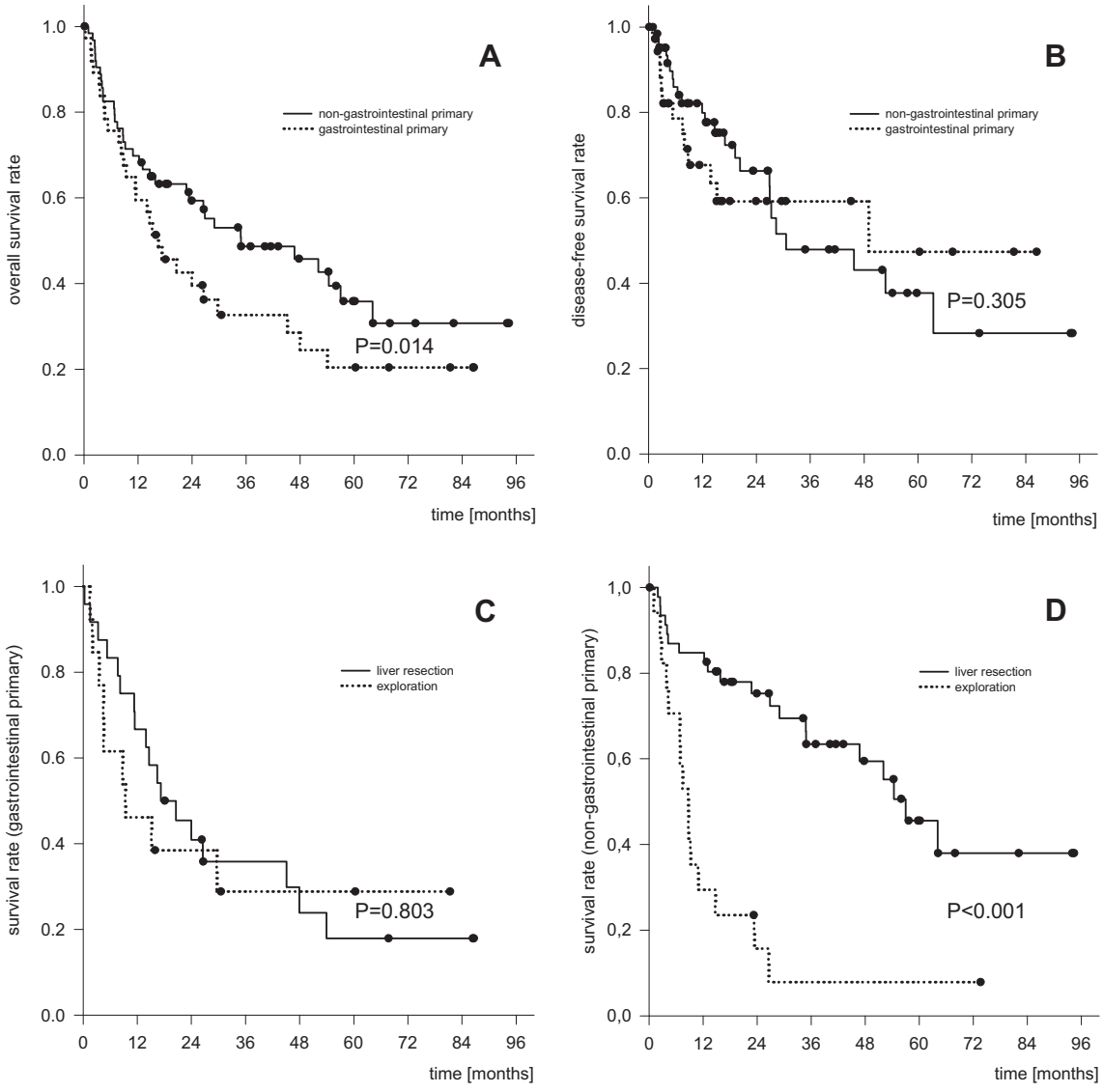

Fig. 1. Kaplan–Meier curves of patient overall survival (A) and recurrence free survival (B) after hepatic resection of liver metastases of non-colorectal and non-neuroendocrine non-gastrointestinal (solid line, $n = 64$) and gastrointestinal primary cancers (dotted line, $n = 37$). Panels C and D display Kaplan–Meier curves of patient survival after exploration only (dotted line) and after hepatic resection (solid line) of liver metastases of non-colorectal and non-neuroendocrine primary cancers for (C) gastrointestinal ($n = 37$) and (D) non-gastrointestinal ($n = 64$) primary cancers.

The influence of the primary tumour site on survival has also been demonstrated by Ercolani et al., showing worst survival rates for resected hepatic metastases from gastrointestinal non-colorectal and non-neuroendocrine primary cancers.[19] In line with the findings of Ercolani et al., we found a median survival of ~27 months for gynaecological and ~25 months for urogenital primary cancers, underlining the striking impact of primary tumour site on prognosis after hepatic surgery. Although we and others have demonstrated that surgery for hepatic metastases from NCRC or NNEC primaries is effective to prolong patients' survival depending on the primary cancer,[19] it is still to be discussed if surgery is superior to local ablative procedures, as shown for hepatic metastases of breast cancer[17,18,34] or systemic chemotherapy. This discussion is also complicated by the fact that a large variety of chemotherapy concepts for palliative treatment of liver metastases from NCRC or NNEC primaries were performed. Until now, most patients with liver metastases from NCRC and NNEC primary cancers receive only best medical support or, wherever possible, palliative chemotherapy. Palliative chemotherapy is considered to improve quality of life, but not necessarily prolong survival, as demonstrated in patients with liver metastases from gastric carcinomas.[16] In this context, the median survival of patients receiving palliative chemotherapy for liver metastases from pancreatic carcinoma or melanoma is only 4 weeks to 6 months.[35,36]

4.3. Repeated resections for liver metastases from NCRC and NNEC primary cancer

Repeated liver resections are established surgical procedures for colorectal metastases. The technique of parenchyma-sparing resection has reduced both morbidity and mortality. In the present study we could demonstrate that repeated liver resections are also a successful treatment option for patients with NCRC and NNEC liver metastases improving 3 and 5-year survival rates compared to single hepatic surgery, which is in line with findings by Adam and co-workers.[22] Consequently, in our patients, tumour-free survival rates and liver-related tumour-free survival rates were reduced when undergoing repeated hepatic surgery. However, atypical

resections were performed in most cases indicating a highly selected cohort with small liver metastases. The small extent of liver resection volume may explain both the low complication rate and the good survival rates, also indicating slow tumour growth or early detected liver metastases. Yet the small number of patients undergoing repeated resections of hepatic metastases does not allow a valid correlation of intrahepatic recurrence to a certain pattern of primaries.

4.4. Limitations

The study is limited by the fact that there is no reference cohort of patients who did not undergo surgery, but who only received systemic chemotherapy. Unfortunately, these data were not available. This would have been helpful to elucidate the "real" survival benefit of surgical approach for treatment of hepatic metastases.

5. Conclusion

Our data underline the current concept that hepatic resection of liver metastases from NCRC and NNEC primaries is a safe method. Patients with hepatic metastases from non-gastrointestinal cancer especially from gynaecological and urogenital primaries benefit from liver resection, whereas liver surgery for hepatic metastases from upper gastrointestinal primaries, pancreatic cancer or melanoma could not be recommended. For those tumour entities, therapy should be multimodal and interdisciplinary.

Ethical approval

There was no ethical application necessary for this retrospective, blinded data analysis.

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Author contribution

Jan E. Slotta: data analysis, manuscript preparation.
Jochen Schuld: statistical analyses.
Sabrina Distler: data acquisition.
Sven Richter: manuscript preparation.
Martin K. Schilling: study design.
Otto Kollmar: manuscript preparation.

Conflict of interest

All authors declare that they have no conflict of interest.

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