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Analysis of prognostic factors after resection of solitary liver metastasis in colorectal cancer – a 22-years bicenter study

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In the last years, a large number of studies investigated predictors of outcome after hepatic resection for liver metastases of colorectal cancer. The results reported are very heterogeneous and sometimes discording. We focused on a homogeneous group of patients characterized by solitary colorectal liver metastasis treated with a curative (R0) resection. Between 1993 and 2014, 350 patients were recruited at the University Hospitals of Jena and Magdeburg. The 5- and 10-year overall survival rates were 47% and 28%, respectively. The 5- and 10-year disease-free survival rates were 30% and 20% respectively. The analysis of the prognostic factors revealed that pT category of primary tumor, size and grade of the metastasis and extension of the liver resection had no statistically significant impact on survival and recurrence rates.

The age of the patients, pN2 category of the primary tumor, synchronous metastases, neoadjuvant chemotherapy and extrahepatic tumor showed a negative influence on the prognosis. Moreover, patient with rectal cancer had lower intrahepatic recurrence rate but a higher extrahepatic recurrence rate. In multivariate analysis, age, status of lymph node metastases at the primary tumor, location of primary tumor, time of appearing of the metastasis, the use of preoperative chemotherapy and the presence of extrahepatic tumor proved to be independent statistically significant predictors for the prognosis.

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LIST OF ABBREVIATIONS

5-FU	5-Fluorouracil
5-FU/FA	5-Fluorouracil/folinic acid
ALPPS	Associating liver partition and portal vein ligation for staged hepatectomy
CLM	Colorectal liver metastases
CRC	Colorectal cancer
DFS	Disease free survival
EGFR	Epidermal growth factor receptor
FOLFIRI	Irinotecan in combination with 5-FU/FA
FOLFOX	Oxaliplatin in combination with 5-FU/FA
HAI	Hepatic arterial infusion chemotherapy
MD	Magdeburg
n.s.	Not significant
OS	Overall survival
RFA	Radio- frequency ablation
SIRT	Selective internal radiation therapy
TACE	Transarterial chemoembolization

1. INTRODUCTION

1.1 Epidemiology

Colorectal cancer (CRC) is the third most common tumor in men and the second in women, with an estimate of 1.4 million new cases annually resulting in approximately 694,000 deaths. An increasing incidence of CRC has been observed in countries where the overall risk of large bowel cancer was low, while in historically high-risk countries either a decrease (USA, Canada and New Zealand) or stabilization (Western Europe and Australia) has been reported (1).

Data from the "*Robert Koch-Institut, Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V (2016*)" show that Germany had 62.400 new diagnosis of CRC in 2013, thereof 28.400 were women. In the same year, approximately 25.700 patients died from CRC.

It is widely known that increased consumption of red and processed meat, alcoholic drinks, body and abdominal fatness as well as smoking all increase the risk for colorectal cancer. On the other hand, foods containing dietary fibre, regular physical activity and drugs such as statin and aspirin, reduce the risk of colon cancer (2).

The liver is the first major organ reached by venous blood draining from the gastrointestinal tract. Cancer cells traveling by hematogeneous spread, therefore, have a high likelihood of arriving and lodging within the sinusoids of the liver. This would explain the observation that the liver is the most common organ of distant metastases from colorectal cancer (3).

Hepatic metastases develop in approximately 50 % of colorectal cancer cases (4). The liver, in addition to being the most common site of metastases, is also the first and only area of spread in 30 % - 40 % of patients (5). The metastases are defined as synchronous if found at the time of presentation of the primary tumor or metachronous if identified at a later date. Approximately 20 % of patients with CRC already have metastases at diagnosis, and this figure has been stable over the last two decades (6).

1.2 Strategy of treatment

1.2.1 Surgery

Surgery is considered the gold standard treatment and the only potentially curative option for colorectal liver metastases (CLM). In the late 1990s, surgery was offered only to a high selected group of patients with liver-limited disease, confined to only one lobe. These patients should have no more than three metastases and the larger one should not be bigger than 5 cm. Moreover the resection had to be technically feasible with at least 1 cm tumor free margins (4). Following these criteria, for about 90 % of the patients the disease was considered unresectable and for these patients a 5-year survival was reported of merely 3.3 % and 6.1 % for synchronous or metachronous metastases, respectively (7). Later on, it became clear that the first option to improve overall survival was to expand surgery indications.

Nowadays, the absolute contraindications to resection with curative intent are unresectable extrahepatic disease, extensive liver involvement (that means more than six liver segments involved, 70 % liver invasion or all three hepatic veins involved), major liver insufficiency, Child B or C liver cirrhosis and patients unfit for or declining surgery (8). The presence of limited extrahepatic disease is no longer considered an absolute contraindication (5).

In patients with synchronous resectable metastases there are three operative options including staged resection with colon first strategy, staged resection with liver first strategy, or simultaneous resection of both primary tumor and metastases. A recent multicenter work found no significant difference in morbidity, mortality or long-term oncologic outcomes between the three options (9). The decision to do simultaneous resections should be based on the overall complexity of both procedures and the patient's comorbidities. In case of risk of primary tumor complications such as bleeding, obstruction or perforation, the colorectal-first approach should be favored. The liver-first sequence is most suited to rectal cancers so that the liver metastases are not left untreated during the radiation portion of treatment to the rectum. The priority in staged resections may be given to colorectal-first or liver-first strategies depending on possible complications related to the primary tumor or on the progression of CLM during the treatment of the primary tumor (10).

It is conventionally accepted that resection of up to 75 % of the total liver volume or six liver segments can be safely performed in patients with normal liver parenchyma. In the setting of steatosis, steatohepatitis or cirrhosis, the volume of liver that can safely be resected may have to be dramatically reduced to avoid the risk of postoperative hepatic failure.

In an attempt to improve the functional liver remnant, various techniques have been employed including portal vein embolization, two stage hepatectomy or portal vein ligation. In the portal vein embolization, after selective catheterization, one of two portal branches and its ramifications are occluded through the diffusion of embolizing agent. One month after the embolization, the hypertrophy of the remnant liver parenchyma should be evaluated through a 3-dimensional computed tomography and the surgical eligibility has to be redefined (11).

As a remarkable modification, the right-liver radioembolization based left-liver hypertrophy was proposed as an alternative since it was demonstrated that portal vein embolization carries a significant risk of postinterventional tumor progression (12). Unilateral radioembolization produces significantly less contralateral hypertrophy than portal vein embolization. However, the hypertrophy induced by radioembolization is substantial and it could be used to reach tumor response and prevent tumor progression in the embolized lobe (13).

The two stage hepatectomy is a strategy whose overall intention is curative; however, the first hepatic resection is intended to remove the highest possible number of metastases, but not all of them. The remnant liver hypertrophies and systemic chemotherapy limits the growth and spread of the remaining tumor deposits. The second hepatectomy is performed when adequate parenchymal hypertrophy has reduced the risk of postoperative liver failure (14).

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) was introduced as a procedure to induce a more rapid hypertrophy of the functional remnant liver. Briefly, ALPPS involves portal vein ligation of the to-be resected segments and in situ split of the liver during the first stage. The rapid hypertrophic response allows removal of the deportalized liver in the second stage when volume and/or function of the future remnant liver is sufficient, usually after 1 to 2 weeks. In a recent study, early oncologic outcomes of patients with

advanced liver metastases undergoing ALPPS, otherwise unresectable, appear not better than of matched patients receiving systemic treatment (15).

1.2.2 Chemotherapy

The first chemotherapeutic agent to be used with any success for metastatic colorectal cancer was the intravenous fluoropyrimidine 5-Fluorouracil (5-FU) in combination with folinic acid (5-FU/FA). 5FU inhibits thymidylate synthase which is a key enzyme in the synthesis of pyrimidines, thus reducing pyrimidines available for DNA replication. Folinic acid enhances the effect of 5-fluorouracil by inhibiting thymidylate synthase.

The development of the oral Capecitabine permitted to rise the tolerability of the chemotherapy. Capecitabine is a fluoropyrimidine carbamate precursor of 5FU. It is catalyzed by a number of enzymatic steps to 5FU. The enzyme involved in the final conversion to 5FU, thymidine phosphorylase, is found at higher levels in tumor cells than normal cells, thereby giving higher doses to the tumor and reducing systemic exposure to 5FU (16).

In the following years, the development of newer cytotoxic drugs such as oxaliplatin and irinotecan improved the response to chemotherapy. Oxaliplatin is a third-generation platinum compound that inhibits DNA replication and transcription and results in cell death. First, it was used as monotherapy for patients who did not respond to 5-FU/FA showing a 10 % of response (17). The next step was to use oxaliplatin in combination with 5-FU/FA. This combination has become widely known as “FOLFOX”. Several large phase-III trials have demonstrated that the addition of oxaliplatin to 5-FU/FA if compared with 5-FU/FA alone, results in a greater tumor objective response even if there is no meaningful improvement in overall survival. These findings have paved the way for the use of FOLFOX as a tool for down-staging CLM before resection (18).

In a similar way to oxaliplatin, irinotecan, a campothecin derivatives that works through the inhibition of topoisomerase I, is routinely used in combination with 5-FU/FA and is known by the acronym “FOLFIRI”. A major randomized study compared FOLFIRI with either 5-FU/FA alone or irinotecan alone and demonstrated an increase in overall survival, progression free survival and local tumor response. The results of this study were responsible for FOLFIRI becoming

established in the U.S. as the first line treatment option for metastatic colorectal cancer (19).

The obvious consequence was to confront FOLFOX and FOLFIRI. A randomized trial demonstrated that FOLFOX was superior to FOLFIRI in term of time of progression, response rate and overall survival (20). Moreover, it was demonstrated that FOLFOX has better result in down-staging unresectable disease (21). Therefore, the clinical standard in UK is to offer FOLFOX as first line followed by FOLFIRI at progression (16). Actually, the German Guidelines consider the two schemas as equivalent so that the decision should be founded on potentially side effects.

In the last years, the aim in drug development was to create targeted therapies in order to induce the maximal interference to tumor cell growth with minimal normal cell toxicity. One of the target used is the *epidermal growth factor receptor* (EGFR) that promotes transcription of genes involved in proliferation, metastases and angiogenesis. Cetuximab is a monoclonal antibody, which competitively binds to the extracellular domain of EGFR.

This monoclonal antibody has demonstrated to be effective in patients with KRAS wild-type metastatic CRC. Data from previous studies showed an ability of cetuximab to reverse resistance to irinotecan and obtain responses in patients who had previously progressed on irinotecan suggesting a potentially increased efficiency by combining both drugs (22).

An important and controversial question is the use or not of neoadjuvant or perioperative chemotherapy in case of resectable liver metastases. The german guidelines do not suggest to use neoadjuvant chemotherapy and recommend to prefer a near-term resection. A randomized phase-III trial of Nordlinger *et al*. showed that the combination of perioperative chemotherapy with FOLFOX and surgery increases progression-free survival compared with surgery alone (23). Nevertheless, they found no statistical difference in overall survival with the addition of perioperative chemotherapy (24).

Even the use of adjuvant chemotherapy is controversial. The first drug tested was 5-FU. It has been demonstrated that systemic adjuvant chemotherapy with a 5-FU-based regimen prolongs survival (25). In the following years, a lot of studies tried to demonstrate the effectiveness of newer chemotherapeutic agents.

FOLFOX seems to be the most promising drug protocol. FOLFIRI should not be recommended as adjuvant chemotherapy since in a phase-III trial showed no significant improvement in disease free survival in comparison with 5-FU/FA (26).

1.2.3 Local ablation strategy

For patients with unresectable disease or significant comorbidities precluding resection, there are several alternative therapies able to spare liver parenchyma. The thermal ablation of tumors utilizes image guidance to deliver extreme temperatures to a tumor and its surrounding tissue. The advantages include its adaptability to minimally invasive approaches, the ability to spare liver parenchyma and a low morbidity rate. Thermal ablation can be performed percutaneously, laparoscopically or at laparotomy (10).

Radio-frequency ablation (RFA) is the most commonly used form of thermal ablation in the treatment of liver tumors. In RFA, needles placed in and around the tumors deliver alternating electrical current in the radiofrequency range that generates heat. The limitation is that it is generally ineffective in tumors bigger than 3 cm and the rate of local recurrence is high. In addition, the heat generated by RFA can injure adjacent structures (10).

Another technique is the cryoablation that involves liquid nitrogen or argon gas being delivered into the liver tumor, guided by ultrasound. Ice crystal formation during rapid freezing causes destruction of cellular structure and kills the tumor cells. Cryoablation has fallen out of favor because of a higher complication rate and recurrence rate in comparison with RFA (27).

Colorectal liver metastases have been shown to depend heavily on the hepatic artery for most of their blood supply, whereas the normal liver parenchyma relies mainly on portal blood flow. Based on this concept, several techniques have been developed such as hepatic arterial infusion chemotherapy (HAI), transarterial chemoembolization (TACE) and selective internal radiation therapy (SIRT). HAI is a technique that introduce chemotherapy directly through a catheter placed in the gastroduodenal artery. A high concentration of antimetabolite substance reaches the tumor permitting a lower systemic toxicity. Floxuridine is the most commonly used chemotherapy (10). A recent study of Ammori *et al*. reached a 25 % of conversion to complete resection with a combination of HAI and systemic

chemotherapy. Moreover, 5-year survival was significantly better in the conversion group (28).

TACE is the administration of embolic particles mixed with chemotherapeutic drugs. It produces a shutdown of blood flow and the simultaneous release of high doses of the drug. The most used chemotherapy is irinotecan (27). A comparison of TACE versus systemic therapy showed that the first one prolonged the median survival and was associated with a greater tumor response in the liver. The regional approach was not inferior to FOLFIRI in preventing extrahepatic metastatic progression (29).

In the SIRT procedure, a single dose of 2.0–3.0 GBq of 90-yttrium microspheres is delivered into the hepatic artery that results in selective tumor uptake and radiation (30). There are three phase-III randomized controlled trial that test the efficacy and safety of FOLFOX plus minus SIRT in patients with metastatic CRC. The results failed to show an improvement in disease free survival or overall survival at any site with the addition of SIRT. On the other hand, the liver disease control was improved by the addition of SIRT (31).

1.3 Prognostic factors

The big challenge in the treatment of metastatic colorectal cancer is to predict accurately the likely outcome of treatment strategies. In the last years, a large number of studies investigated predictors of outcome after hepatic resection for liver metastases of colorectal cancer (32–39). The results reported are very heterogeneous and most of the risk factors described are still a subject of an ongoing debate. The most cited predictive factors are number of hepatic metastases, node-positive compared to node-negative primary, poorly differentiated compared to well or moderately differentiated primary, extrahepatic disease compared to liver-only disease, diameter of the liver metastases, preoperative carcinoembryonic antigen level, and positive compared to negative resection margins (4).

On the base of these findings, several investigators proposed prognostic scoring systems of varying complexity to improve patient selection to ensure that patients selected for surgery benefit from such an intervention in terms of cancer-specific

survival in comparison with alternative less invasive ablative therapies or adjuvant/additive therapy (40–46).

One of the most famous and studied risk score is the Fong´s clinical risk score. Fong created a clinical risk score to identify patients with a higher risk of recurrence and poorer survival. The score was founded on the 5 criteria that have shown to be independent predictors of outcome in the multivariate analysis of consecutive 1001 liver resection for colorectal metastases. The five criteria were nodal status of primary, disease-free interval from the primary to discovery of the liver metastases less than 12 months, number of tumors more than 1, preoperative carcinoembryonic antigen level more than 200 ng/ml and size of the largest tumor more than 5 cm. For each criteria one point was assigned, and the total score was compared with the clinical outcome of each patient after liver resection. The total score was found to be highly predictive for long-term outcome (3).

More recently, several authors confirmed the prognostic value of Fong´s clinical risk score and suggested the use of chemotherapy (neoadjuvant or adjuvant) in patients with resectable disease but high clinical risk score (47–49). This demonstrate that recognizing potential risk factors before surgery is extremely useful in order to change or complete the surgical therapy with other strategies.

1.4 The subgroup of solitary colorectal liver metastasis

There is a general consensus that patients with solitary colorectal liver metastasis have a significant better prognosis than patients with multiple metastases (50–52). As reported in Table 1, the overall 5-year survival reported in the literature for these group of patients ranges from 44 % to 71 % (3,53–61). Only one study of Aloia *et al*. reported a 5-year survival of 71 % (54). In most of the studies, about a half of the patients with solitary metastases survive at 5 years after surgery.

A recent meta-analysis summarized information of survival after liver resection for colorectal metastases of papers published between 1999 and 2010. The observed mean 5-year survival for all the patients (with solitary and multiple liver metastases) was 40.3 %. For solitary metastases, a 5-year survival of 47.4 % was reported (4). These results are not that excellent as expected. The survival

data of patients with solitary metastases are not that far from the data known for multiple liver metastases.

Table 1: Survival data for patients with solitary liver metastases

Author [Ref.-No.]	Year	No. of patients [*n*]	5-year overall survival
Fong (3)	1999	491	44 %
Oshowo (53)	2003	20	55 %
Aloia (54)	2006	150	71 %
White (55)	2007	30	58 %
Lee (56)	2008	116	66 %
Berber (57)	2008	90	48 %
Konopke (58)	2009	122	55 %
Merkel (59)	2009	303	52 %
Hur (60)	2009	42	50 %
McKay (61)	2009	37	48 %

The few studies that considered separately solitary liver metastases, are retrospective studies that confront liver resection and ablative technique in the treatment of the metastatic tumor (53,54,56,57,60). They all agree that surgery has lower rates of local recurrence than RFA. Three of five works showed a significant better disease-free and overall survival in patients treated with surgery demonstrating that hepatic resection is superior than RFA in the treatment of solitary colorectal liver metastases (54,57,60). RFA may be a safe alternative for hepatic treatment only for patients who are considered unsuitable for surgical treatment since this ablative technique offers a better prognosis than chemotherapy alone (52).

The next important question is to identify which are the factors that influence the prognosis of patients with solitary liver metastases. The literature is reach of works that try to define the predictive factor after surgery for colorectal liver metastases but none of them focused on patients with solitary liver disease.

1.5 Aim

The idea of this study is to concentrate the attention on a focused group of patients characterized by solitary liver metastasis treated with curative resection in order to have a more homogeneous population and to improve the reliability and applicability of the results.

The aim of this study is to answer the following key-question: which are the factors that influence the follow up of patients that underwent hepatic resection for solitary liver metastasis and how they influence the prognosis?

The identification of prognostic factors would assist in the choice of the treatment strategy and in the identification of those patients most likely to benefit from an intensification of the follow up or more aggressive (adjuvant or additive) therapy.

2. PATIENTS AND METHODS

2.1 Patients recruitment

At the University Hospitals of Jena and Magdeburg all the patients that underwent a primary liver resection because of a solitary colorectal metastasis were recruited from January 1993 to December 2014.

Following inclusion criteria were considered:

- singular liver metastasis of colorectal cancer,
- curative resections (R0 resection status) as confirmed by histological investigation,
- available follow-up data and a postoperative time period of at least 3 months,
- all the patients were more than 18 years old,
- patients with histologically proven colorectal carcinoma.

In addition, all patients with extrahepatic tumor manifestation were enrolled at the time of operation.

Exclusion criteria were the following:

- R1 resection in the histological examination,
- presence of more than one metastasis in the operative protocol or in the histological examination,
- patients that died within the first three months after liver resection.

The patients were all recovered for a planned resection. In the preoperative phase, all patients underwent an accurate anamnesis, a physical examination, laboratory tests and an abdominal ultrasound or a computed tomography scan examination.

All the operations were described in detail in the operative protocol. In all the cases where the result of the intraoperative exploration differed from the preoperative imaging, the examination of the liver was completed with an intraoperative ultrasound.

All the operations were performed by a surgeon with experience in hepatobiliary surgery. All kind of strategies were collected: liver-first, colorectal-first or simultaneous. All kind of resections were included: wedge resection, atypical resection, resection of one or more segments, right hepatectomy, left hepatectomy. All the surgical specimens were analyzed by the pathological

department of the responsible university. Size, weight, macroscopic and microscopic description and R status were always reported.

2.2 Data collection

The collection of information was retrospective both for the University Hospital of Magdeburg and for the University Hospital of Jena. Concerning the patients treated in Magdeburg, the necessary data such as personal data, age, gender, contact, diagnosis, history of treatment, site and size of tumor, preoperative imaging, operation details, histological results, postoperative complications, chemotherapy schema were collected from:

- tumor centrum of Magdeburg,
- medical clinical reports that were extracted from the general archive of the university hospital or from hospital software “Medico”.

The follow-up information was: date of recurrence, site of recurrence, kind of therapy for recurrence (surgical or systemic chemotherapy) and date of death. These follow-up data were collected by:

- municipalities of residence,
- questionnaires sent to family practitioners,
- questionnaires sent to oncologists responsible for the aftercare.

If the patients received the oncological aftercare at our institutions, the information was obtained from the clinical reports of the oncological department. All patients were observed until death or until July 2016.

All information of the two centers was combined into a unique database.

All the data were treated respecting the rights of personal privacy.

2.3 End points

To determine the long-term outcome, 4 endpoints were pursued:

- overall survival (OS): the end point was the date of death; the censored data was the date of last observation,
- disease-free survival (DFS): the end point was the date of death of any cause or the date of first recurrence. The censored data was the date of last disease-free observation,
- intrahepatic recurrence rate: the end point was the date of first hepatic recurrence or of any other recurrence. The censored data was the date of death or the date of last observation,
- extrahepatic recurrence rate: the end point was the date of first extrahepatic recurrence without hepatic recurrence. The censored data was the date of death or the date of last observation.

For each end point following characteristics were analyzed:

- age at the time of resection (age < or ≥ 70 years),
- hospital where the operation was performed (Jena or Magdeburg),
- localization of the primary tumor (colon or rectum),
- invasion of the primary tumor at the histological examination (pT1-2 *versus* pT3-4),
- degree of spread to regional lymph nodes (pN0-1 *versus* pN2) in the primary tumor,
- grading of the metastasis (grade 1/2 *versus* grade 3),
- time of diagnosis of liver metastasis (synchronous or metachronous metastasis),
- dimension of the metastasis (<-3 or > 3 cm),
- use or not of neoadjuvant chemotherapy before liver resection,
- presence or absence of extrahepatic tumor at the time of surgery,
- number of resected liver segments (less or more than 3).

2.4 Statistical analysis

Univariate analysis was performed through the chi-squared test to identify which parameter had a statistical significant influence on each endpoint. Cumulative survival rates and rates of recurrence were calculated with the Kaplan–Meier procedure and significance testing were performed with the log-rank test.

Multivariate analysis was performed using a Cox regression model to identify those risk factors independently associated with survival and recurrence that had been statistically significant in the univariate analysis. Differences were considered significant at $p<0.05$. For the analysis, IBM SPSS Statistics® (version 23.0; IBM Corp. in Armonk, NY, U.S.A.) software program was used.

2.5 Ethic approval

The study was performed according to the guidelines of the Declaration of Helsinki for Biomedical Research from 1964 and its further up-dates as well as according to the instructions of the institutional ethic committee. All patients signed an informed consent prior to their surgical intervention as well as for the permission of follow-up observations as appropriate. All patients gave their consent for registration in the tumor registry. We only used data from the clinical data registry.

3. RESULTS

3.1 Demographic data

From January 1993 to December 2014, 350 patients were enrolled in the study. At the University Hospital of Jena, 244 (69.7 %) patients were operated while 106 (30.3 %) were operated at the University Hospital of Magdeburg. We had a relative old patients group with 91 patients (26 %) of the total over 70 years (figure 1).

Of the entire group of patients, we had 213 male and 137 female patients resulting in a sex ratio of m : f = 1.55 : 1.

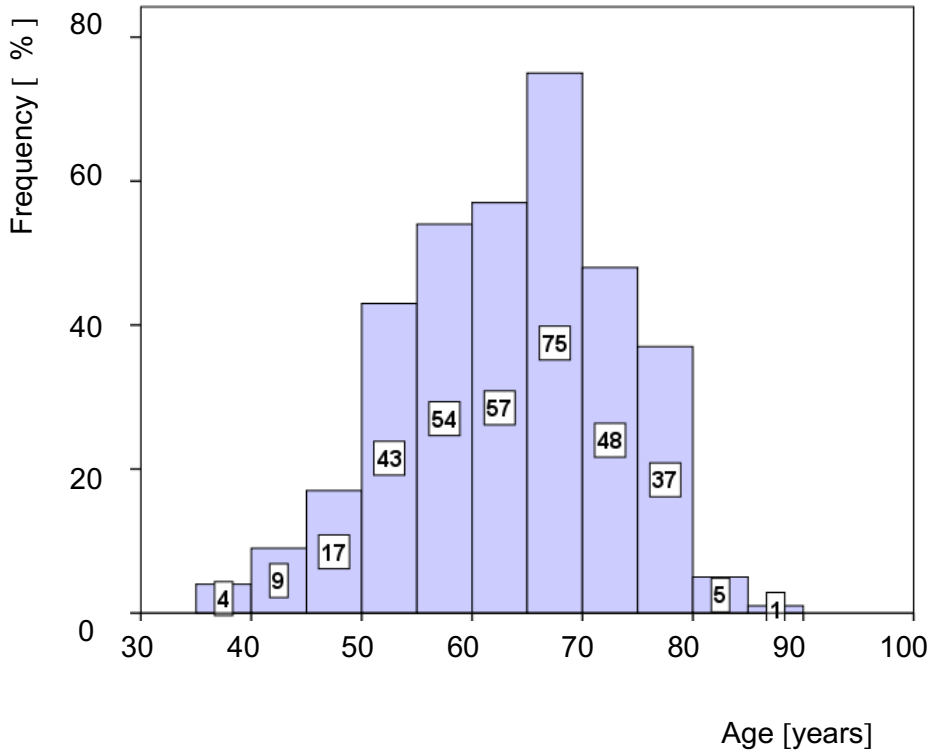

Figure 1: Distribution of various age groups of patients with liver resection for CLM

3.2 Primary tumor data

The primary tumor was localized in rectum in 142 cases (40.6 %) and in colon in 208 cases (59.4 %). Two hundred eighty five patients (81.4 %) had a pT-category 3 or 4 and 65 (18.6 %) had a pT-category 1 or 2. Of the total, 81 (23.1 %) patients had more than 3 lymph node metastases. Of the total, 247 patients had a tumor grade1/2, 53 patients had a tumor grade of 3 and in 50 cases the tumor grade was not reported.

Table 2: Characteristics of patients, primary tumors, metastases and therapy

		In total		Site of liver resection				*p*
				Jena		MD		
In total		350	100.0 %	244	69.7 %	106	30.3 %	--
Age	< 70 years	259	74.0 %	188	77.0 %	71	67.0 %	0.063
	≥ 70 years	91	26.0 %	56	23.0 %	35	33.0 %	
Site of primary	Colon	208	59.4 %	149	61.1 %	59	55.7 %	0.345
	Rectum	142	40.6 %	95	38.9 %	47	44.3 %	
pT category	PT1/pT2	65	18.6 %	46	18.9 %	19	17.9 %	0.882
	PT3 /pT4	285	81.4 %	198	81.1 %	87	82.1 %	
pN category	pN0/1	269	76.9 %	186	76.2 %	83	78.3 %	0.783
	pN2	81	23.1 %	58	23.8 %	23	21.7 %	
Grading	Grade 1/2	247	82.3 %	182	79.8 %	65	90.3 %	0.051
	Grade 3	53	17.7 %	46	20.2 %	7	9.7 %	
Diagnosis of metastasis	Synchronous	138	39.4 %	88	36.1 %	50	47.2 %	0.057
	Metachronous	212	60.6 %	156	63.9 %	56	52.8 %	
Interval primary to liver metastasis	≥ 12 months	183	52.3 %	131	53.7 %	52	49.1 %	0.485
	< 12 months	167	47.7 %	113	46.3 %	54	50.9 %	

Interval primary to liver metastasis	≥ 24 months	93	26.6 %	65	26.6 %	28	26.4 %	1.000
	< 24 months	257	73.4 %	179	73.4 %	78	73.6 %	
Extrahepatic tumor	None	313	89.4 %	214	87.7 %	99	93.4 %	0.132
	Present	37	10.6 %	30	12.3 %	7	6.6 %	
Diameter of metastasis	≤ 3 cm	138	39.4 %	91	37.3 %	47	44.3 %	0.235
	> 3 cm	212	60.6 %	153	62.7 %	59	55.7 %	
Type of resection	Local excision	58	16.6 %	25	10.2 %	33	31.1 %	<0.001
	< 3 segments	146	41.7 %	98	40.2 %	48	45.3 %	
	≥ 3 segments	146	41.7 %	121	49.6 %	25	23.6 %	

3.3 Liver resection data

The detection of the metastasis appeared simultaneous to the primary tumor in 138 (39.4 %) patients (synchronous metastasis). In 212 (60.6 %) cases, the liver metastasis was detected after the diagnosis of the primary (metachronous metastasis). In 212 patients, 60.6 % of cases, the diameter of the metastasis was bigger than 3 cm. In 204 cases (58.3 %), less than 3 liver segments were resected.

A total of 37 patients (10.6 %) had an extrahepatic tumor lesion at the time of liver resection. Of the total, only 51 patients (14.6 %) underwent a neoadjuvant chemotherapy before the liver resection. There was no perioperative mortality.

Considering the place where the patients were operated, all the features except one were similar in the two groups. The only one feature that differed in the two groups was the size of the liver resection: in Jena, there were more hemihepatectomies while in Magdeburg, there were more local excisions or minor resections.

3.4 Univariate survival analysis – Overall survival

At the end of the study, 215 patients had died, 135 were still alive. Median follow-up time of patients dead or alive were 37 months and 80 months, respectively. Estimated median survival time of all patients was 54 months.

The overall survival rates after 1, 3, 5, and 10 year(s) were 93 %, 67 %, 47 %, and 28 %, respectively (Figure 2).

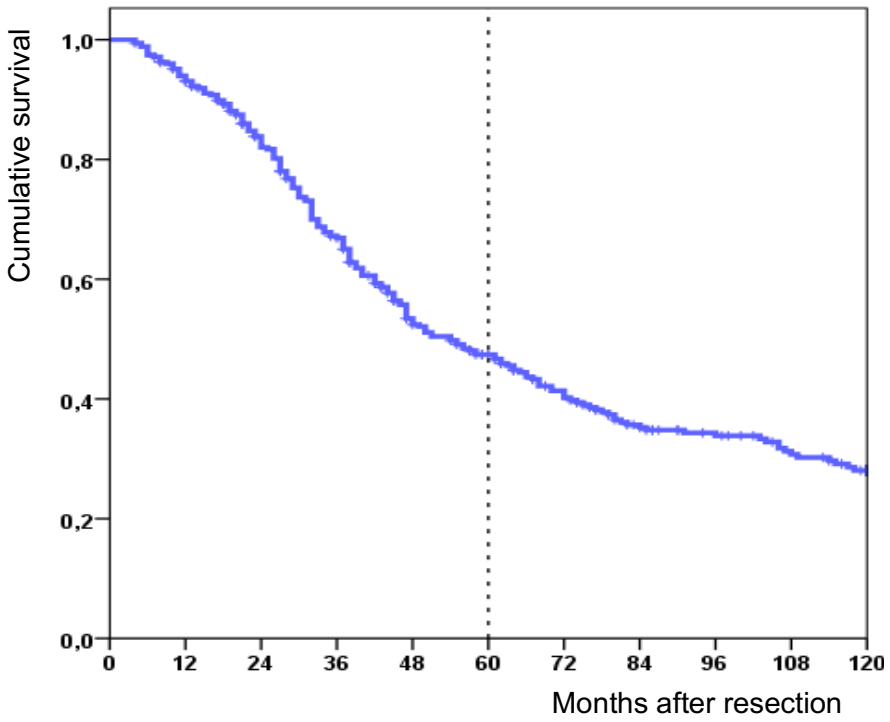

Figure 2: OS of all patients with liver resection for CLM over 10 years

3.4.1 Localization of the hospital

Estimated median survival times of patients who had liver resection in Jena and Magdeburg (MD) were 56 months and 47 months, respectively.

Estimated 5-, and 10-year survival rates of patients who had liver resection in Jena were 48 % and 31 %, respectively. For patients resected in Magdeburg, the figures were 45 % and 18 %, respectively (Figure 3).

The differences in survival rates did not reach statistical significance (p=0.117).

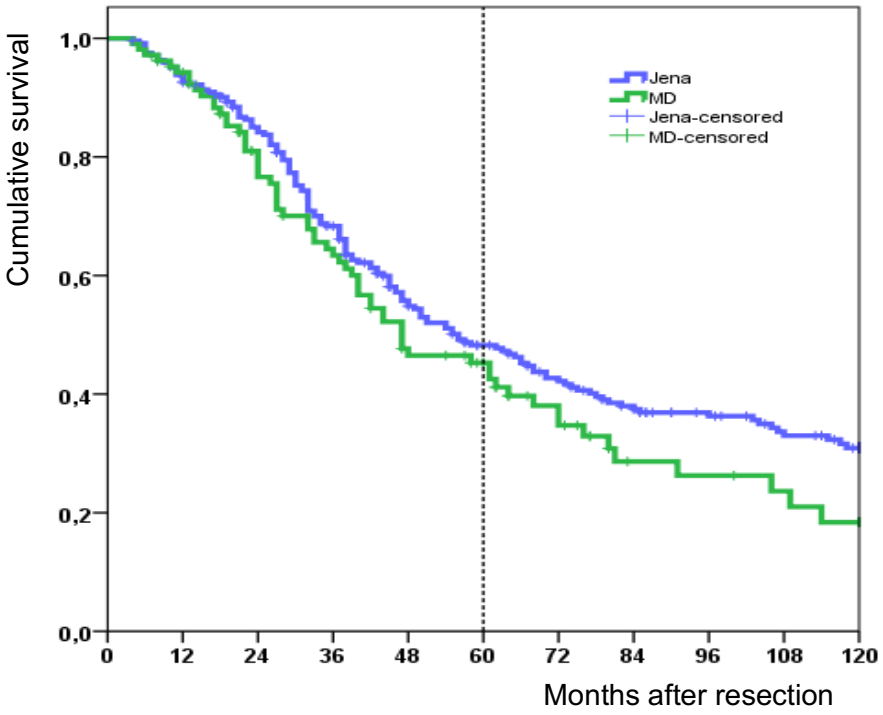

Figure 3: OS dependent on the hospital where liver resection was performed

3.4.2 Age of the patients

Estimated median survival times of 91 older and 259 younger patients were 40 months and 61 months, respectively.

Estimated 5-, and 10-year survival rates of younger patients were 50 % and 32 %, respectively. For older patients, the figures were 39 % and 13 %, respectively (Figure 4).

The differences in survival rates were statistically significant (p=0.007).

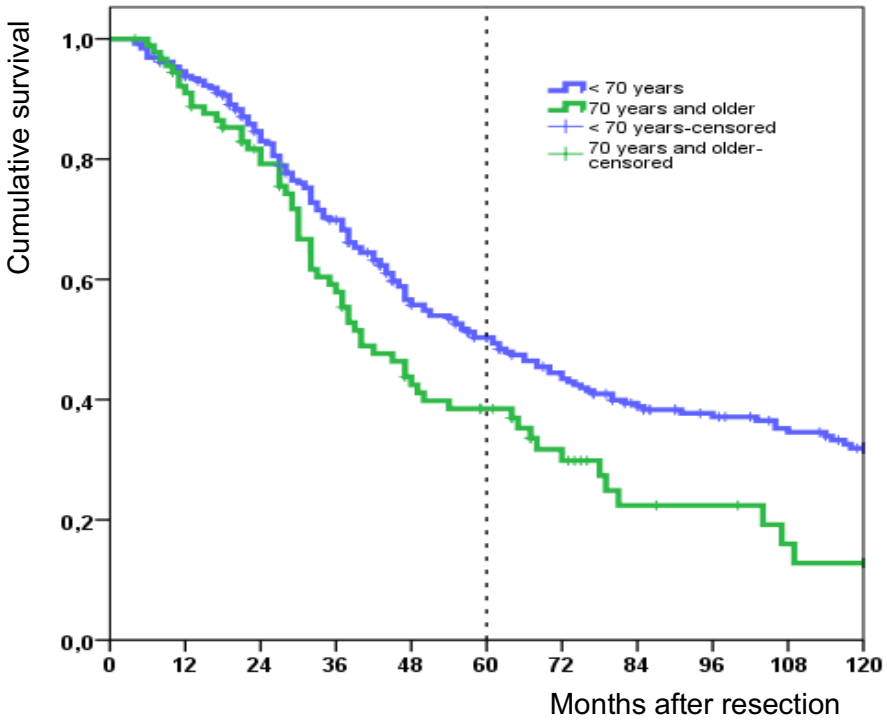

Figure 4: OS dependent on age of patients with CLM

3.4.3 pT category

Estimated median survival times of patients with primary tumour pT1/2 (65 patients) and pT3/4 (285 patients) were 72 months and 50 months, respectively. Estimated 5-, and 10-year survival rates of patients with pT1/2 category of primary tumor were 55 % and 30 %, respectively. For patients with pT3/4 category of primary tumor, the figures were 46 % and 28 %, respectively (Figure 5).

The differences in survival rates did not reach statistical significance (p=0.316).

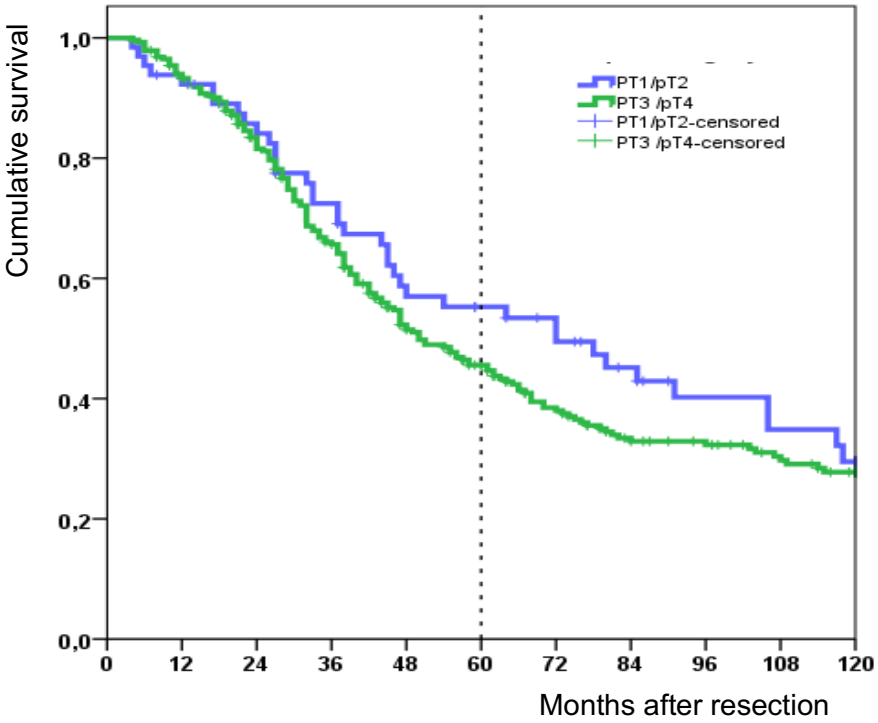

Figure 5: OS dependent on pT category of primary tumor

3.4.4 pN category

Estimated median survival times in cases with pN category pN0/1 (269 patients) or pN2 (81 patients) were 61 months and 42 months, respectively. Estimated 5-, and 10-year survival rates of tumor with pN category pN0/1 were 51 % and 30 %, respectively. For tumor with pN category 2, they were 36 % and 21 %, respectively (Figure 6).

The differences in survival rates were statistically significant (p=0.018).

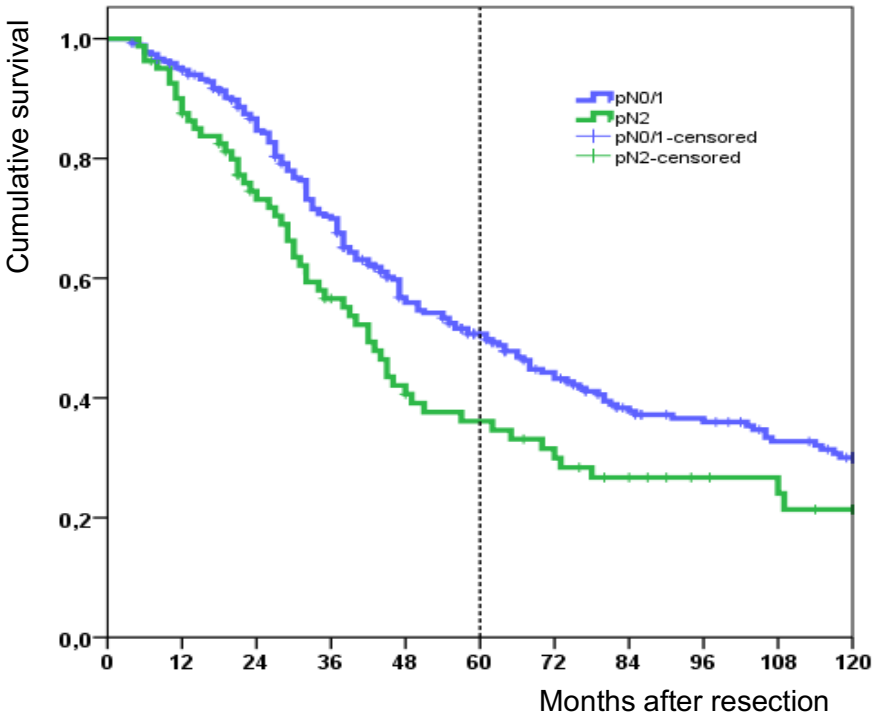

Figure 6: OS dependent on pN category of primary tumor

3.4.5 Tumor grading

Estimated median survival times in case of tumor grade 1/2 (247 patients) and grade 3 (53 patients) were 51 months and 39 months, respectively. Estimated 5-, and 10-year survival rates of patients with tumor grade 1/2 were 46 % and 28 %, respectively. For patients with tumor grade 3, they were 42 % and 29 %, respectively (Figure 7).

The differences in survival rates did not reach statistical significance (p=0.241).

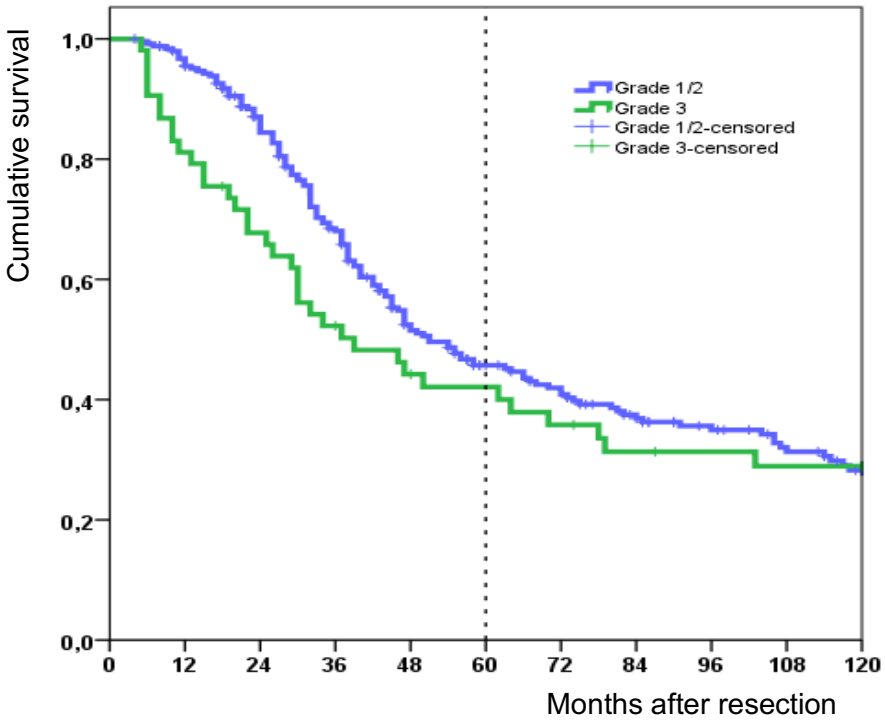

Figure 7: OS dependent on grading of the metastasis

3.4.6 Time of diagnosis of the metastasis

Estimated median survival times of patients with synchronous (138 patients) or metachronous (212 patients) metastases were 51 months and 56 months respectively. Estimated 5-, and 10-year survival rates of patients with synchronous metastases were 46 % and 26 %, respectively. For patients with metachronous metastases, they were 49 % and 30 %, respectively.

The differences in survival rates did not reach statistical significance (p=0.172). (Figure 8).

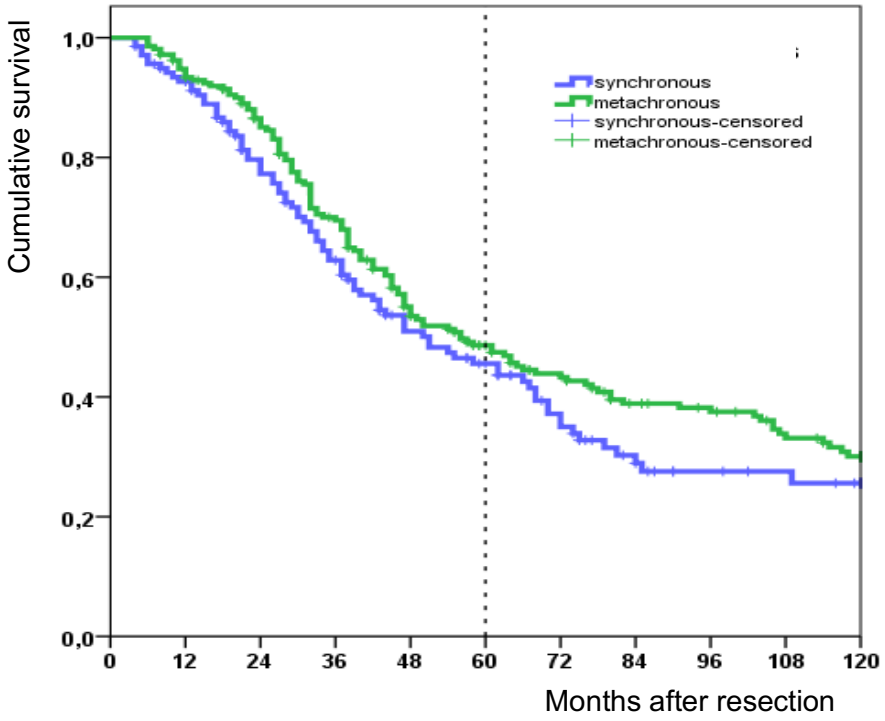

Figure 8: OS dependent on time of diagnosis of CLM

Estimated median survival times of patients that received the diagnosis of liver metastasis before (167 patients) or later than 12 months (183 patients) after diagnosis of primary tumor, were 51 months and 56 months, respectively. Estimated 5-, and 10-year survival rates of patients with a soon diagnosis of metastasis were 53 % and 25 %, respectively. For patients with later diagnosis of metastasis, they were 45 % and 29 %, respectively.

The differences in survival rates did not reach statistical significance (p=0.202).

The median survival time for patients who received the diagnosis before (257 patients) or after 24 months (93 patients) from the diagnosis of the primary tumor were 50 and 64 months, respectively. Estimated 5-, and 10-year survival rates of patients with a soon diagnosis were 49 % and 31 %, respectively. For patients with later diagnosis, they were 46 % and 26 %, respectively.
The differences in survival rates did not reach statistical significance (p=0.546).

3.4.7 Presence of extrahepatic tumor lesion

Estimated median survival times of patients without (313 patients) or with extrahepatic tumor lesion (37 patients) at the time of diagnosis of the liver metastasis were 58 months and 38 months, respectively. Estimated 5-, and 10-year survival rates of patients without extrahepatic tumor were 49 % and 30 %, respectively. For patients with extrahepatic tumor, the 5-, and 10-year survival rates were 31 % and 12 %, respectively (Figure 9).
The differences in survival rates were statistically significant (p=0.018).

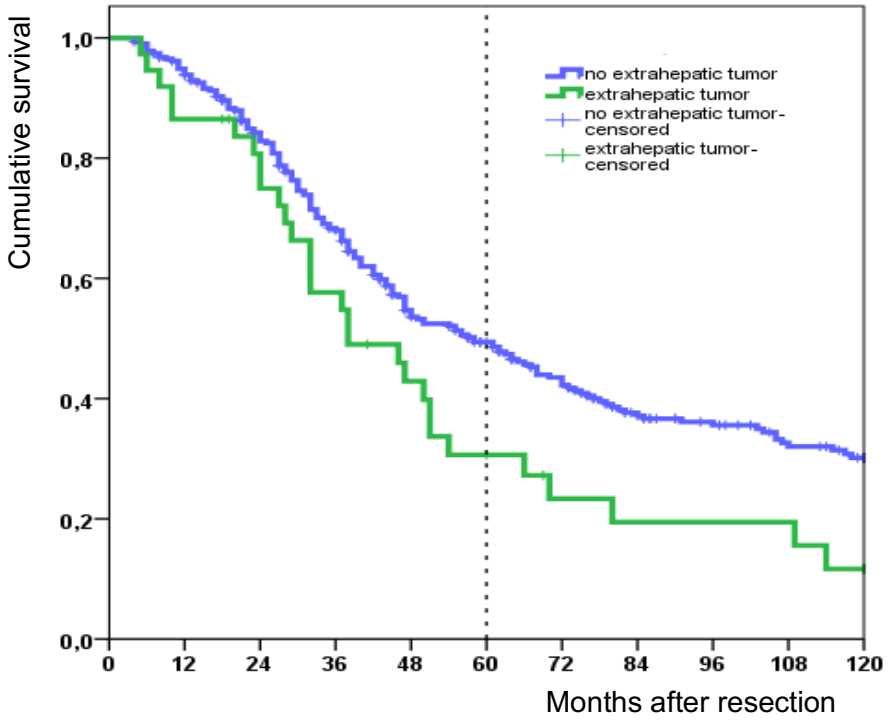

Figure 9: OS dependent on extrahepatic tumor lesion

3.4.8 Diameter of the metastasis

Estimated median survival times of patients with liver metastasis diameter less (138 patients) or more than 3 cm (212 patients) were 62 months and 48 months, respectively. Estimated 5-, and 10-year survival rates of patients with a small metastasis were 53 % and 33 %, respectively. For patients with a bigger metastasis, the 5-, and 10-year survival rates were 44 % and 25 %, respectively (Figure 10).

The differences in survival rates did not reach statistical significance (p=0.119).

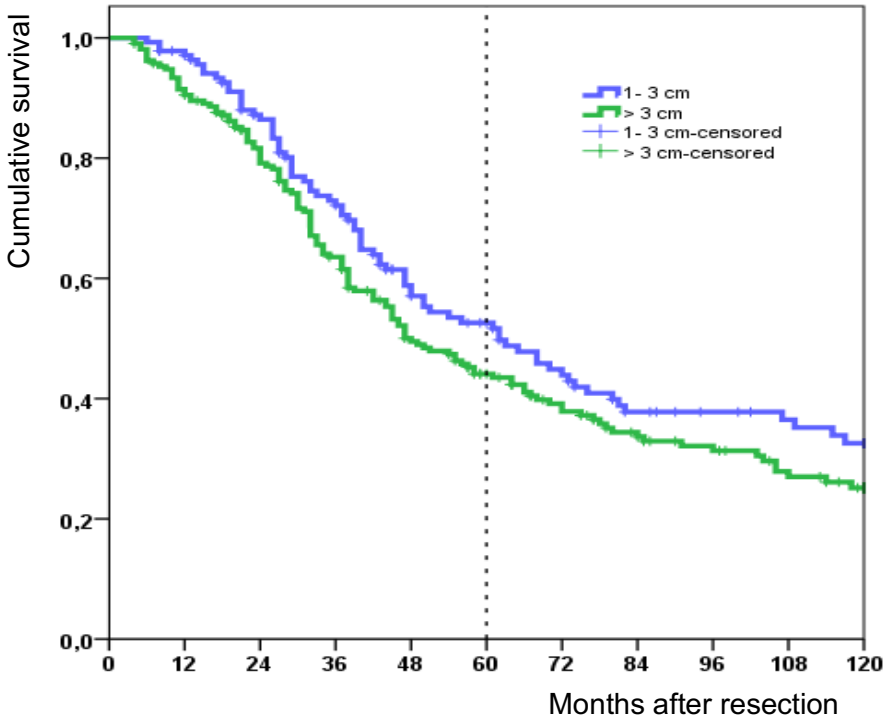

Figure 10: OS dependent on diameter of CLM

3.4.9 Type of liver resection

Estimated median survival times of patients who received an atypical resection (58 patients), resection of < 3 segments (146 patients) and resection of ≥ 3 segments (146 patients) were 48 months, 64 months and 46 months, respectively.

Estimated 5-, and 10-year survival rates of patients who received an atypical resection were 45 % and 19 %, respectively. Estimated 5-, and 10-year survival rates of patients with minor resection were 52 % and 32 %, respectively. For patients that received major resection, the estimated 5-, and 10-year survival rates were 45 % and 27 %, respectively (Figure 11). The differences in survival rates did not reach statistical significance (atypical *vs*. < 3 segments: p=0.139, atypical vs. ≥ 3 segments: p=0.808, < 3 segments *vs*. ≥ 3 segments: p=0.137).

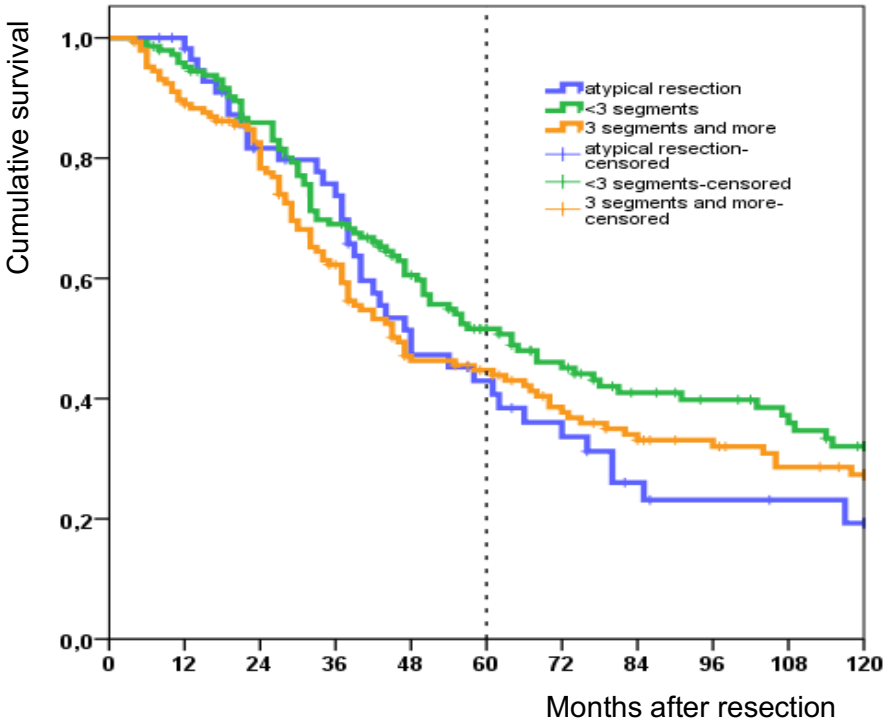

Figure 11: OS dependent on type of liver resection of CLM

3.4.10 Use of neoadjuvant chemotherapy

Patients that received neoadjuvant chemotherapy (51 patients, 14.6 %) had an estimated median survival time of 45 months. Patients who did not receive chemotherapy before liver resection (299 patients, 85.4 %) had an estimated median survival time of 55 months.

Estimated 5-, and 10-year survival rates of patients who received neoadjuvant chemotherapy were 42 % and 26 %, respectively. For patients who did not get chemotherapy before liver resection, the 5-, and 10-year survival rate were 48 % and 28 %, respectively (Figure 12). The differences in survival rates did not reach statistical significance (p=0.283).

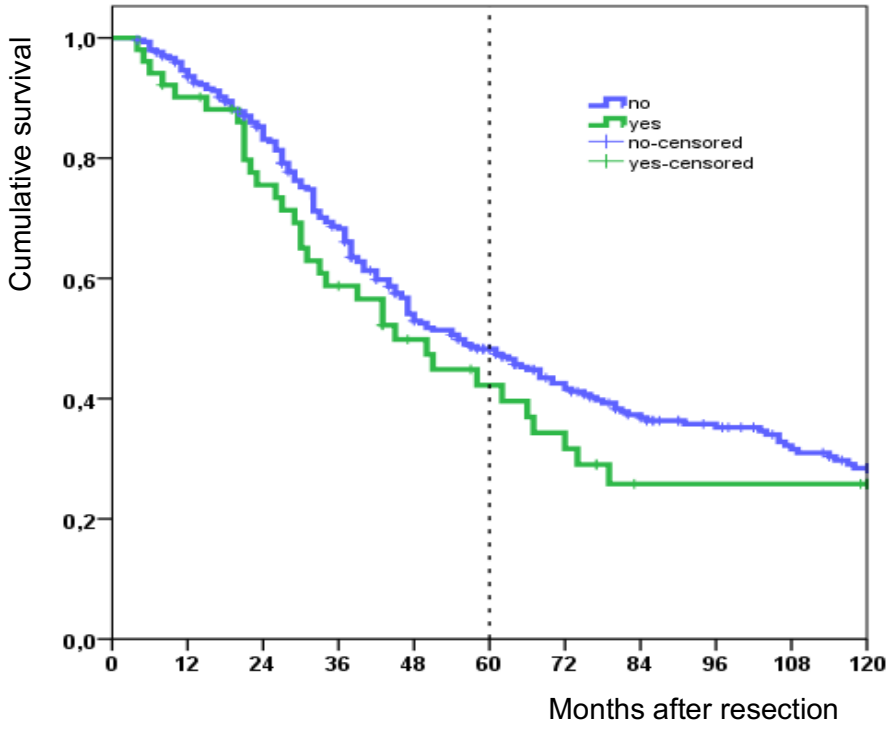

Figure 12: OS dependent on neoadjuvant chemotherapy before liver resection of CLM

3.5 Univariate survival analysis – Disease-free survival

The disease-free survival of all patients (DFS) after 5 and 10 years was 30 % and 20 %, respectively (Figure 13).

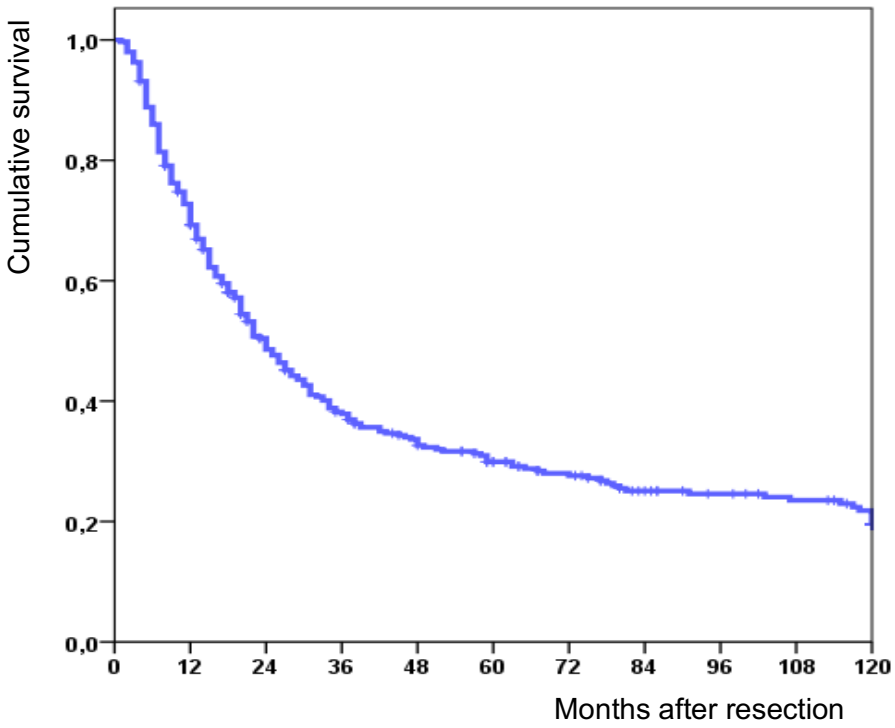

Figure 13: DFS of all patients with liver resection of CLM

3.5.1 Age of the patients

Estimated 5-, and 10-year disease-free survival rates for the 259 patients < 70 years of age were 31 % and 22 %, respectively. For the 91 patients ≥ 70 years of age, the figures were 26 % and 12 %, respectively (Figure 14).

Age at liver resection did not influence disease-free survival statistically significant (p=0.575).

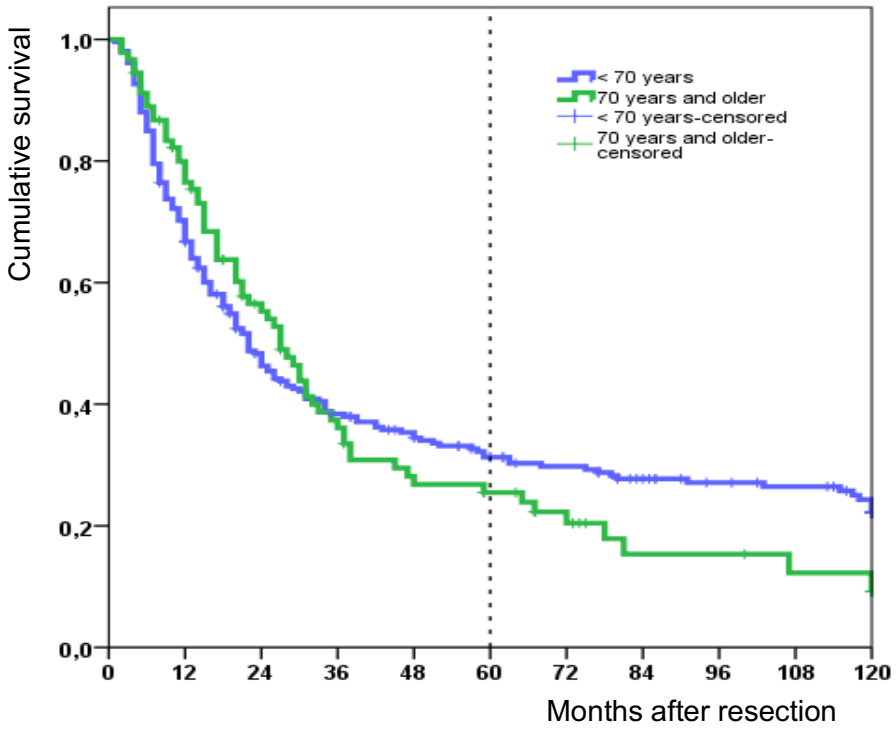

Figure 14: DFS dependent on age of patients with liver resection for CLM

3.5.2 pT category

Estimated 5-, and 10-year disease-free survival rates for the 65 patients with primary tumor category pT1/2 were 43 % and 28 %, respectively. For the 285 patients with primary tumor category pT3/4, the disease-free survival rates were 27 % and 20 % (Figure 15).

pT category of the primary tumor did not influence disease-free survival statistically significant (p=0.090).

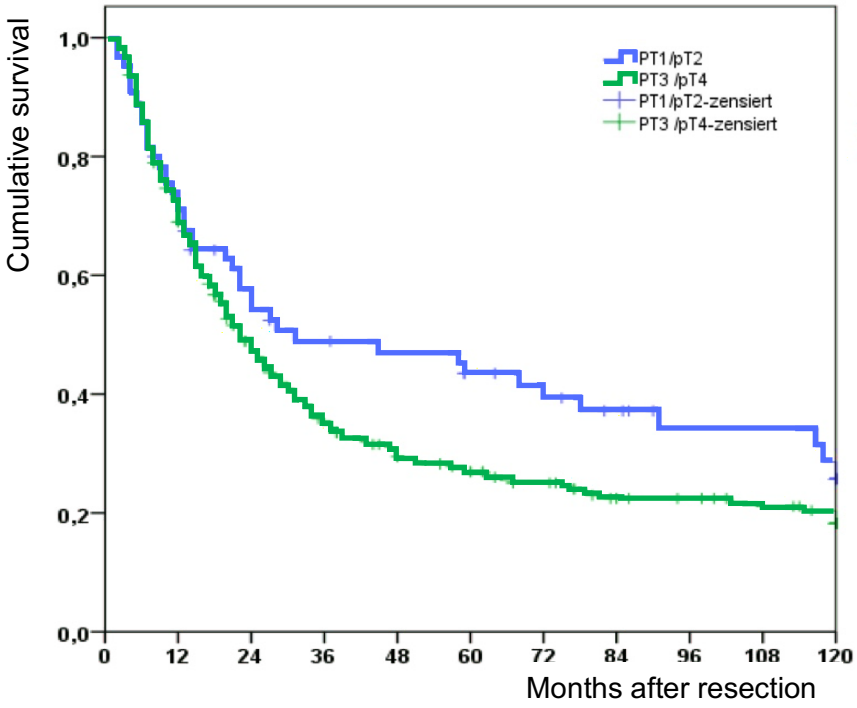

Figure 15: DFS dependent on pT category of primary tumor

3.5.3 pN category

Estimated 5-, and 10-year disease-free survival rates for the 269 patients with pN0/1 primary tumors were 34 % and 22 %, respectively. For the 81 patients with pN2 primary tumors, the figures were 18 % and 13 %, respectively (Figure 16). pN category of primary tumor influences disease-free survival statistically significant (p=0.006).

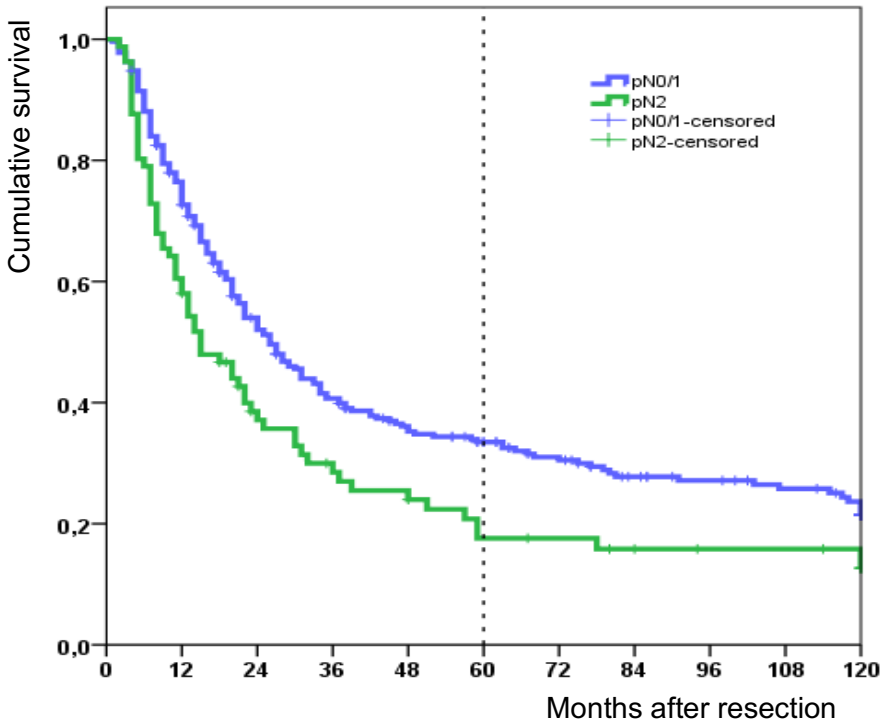

Figure 16: DFS dependent on pN category of primary tumor

3.5.4 Tumor grading

Estimated 5-, and 10-year disease-free survival rates for the 247 patients with grade 1 or grade 2 tumors were 31 % and 20 %, respectively. For the 53 patients with grade-3 tumors, the figures were 28 % and 21 %, respectively (Figure 17). Grading did not influence disease-free survival statistically significant (p=0.372).

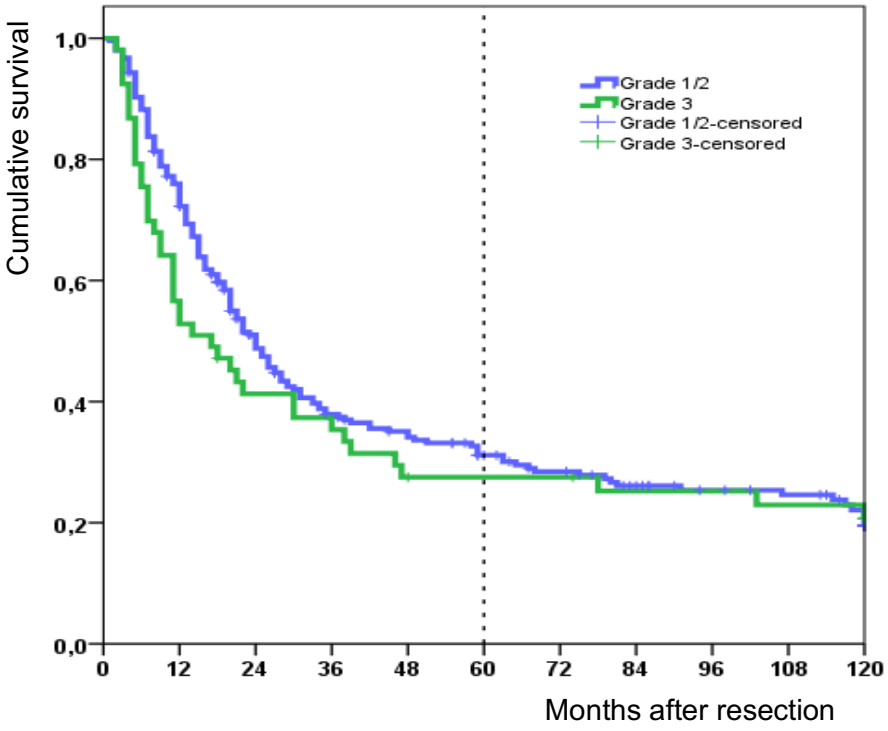

Figure 17: DFS dependent on grading of the metastasis

3.5.5 Time of diagnosis of the metastasis

Estimated 5-, and 10-year disease-free survival rates for the 138 patients with synchronous metastases were 23 % and 14 %, respectively. For the 212 patients with metachronous metastases the figures were 34 % and 23 %, respectively (Figure 18).

Timing of liver metastasis did influence disease-free survival statistically significant (p=0.021).

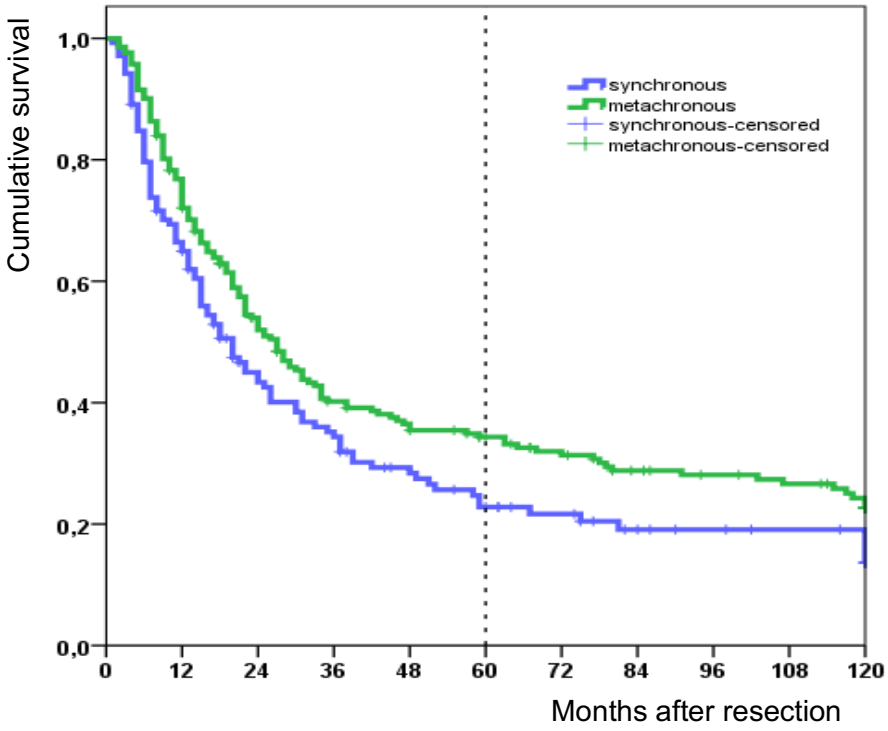

Figure 18: DFS dependent on time of diagnosis of the metastasis

3.5.6 Presence of extrahepatic tumor lesion

Estimated 5-, and 10-year disease-free survival rates for the 37 patients with extrahepatic tumor lesion were 12 % and 8 %, respectively. For the 313 patients without extrahepatic tumor, the figures were 32 % and 21 %, respectively (Figure 19).

Extrahepatic tumor lesion at the time of the operation did influence disease-free survival statistically significant (p=0.004).

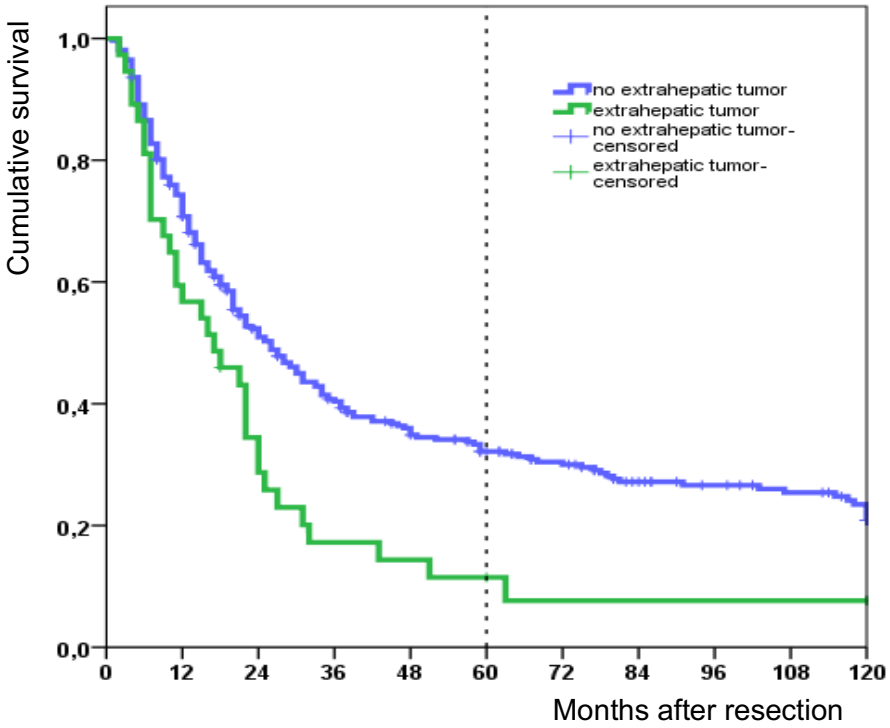

Figure 19: DFS dependent on extrahepatic tumor lesion

3.5.7 Diameter of the metastasis

Estimated 5-, and 10-year disease-free survival rates for the 138 patients with metastases $\leq$ 3 cm were 33 % and 24 %, respectively. For the 212 patients with metastases > 3 cm the figures were 28 % and 17 %, respectively (Figure 20). The diameter of the metastasis did not influence disease-free survival statistically significant (p=0.243).

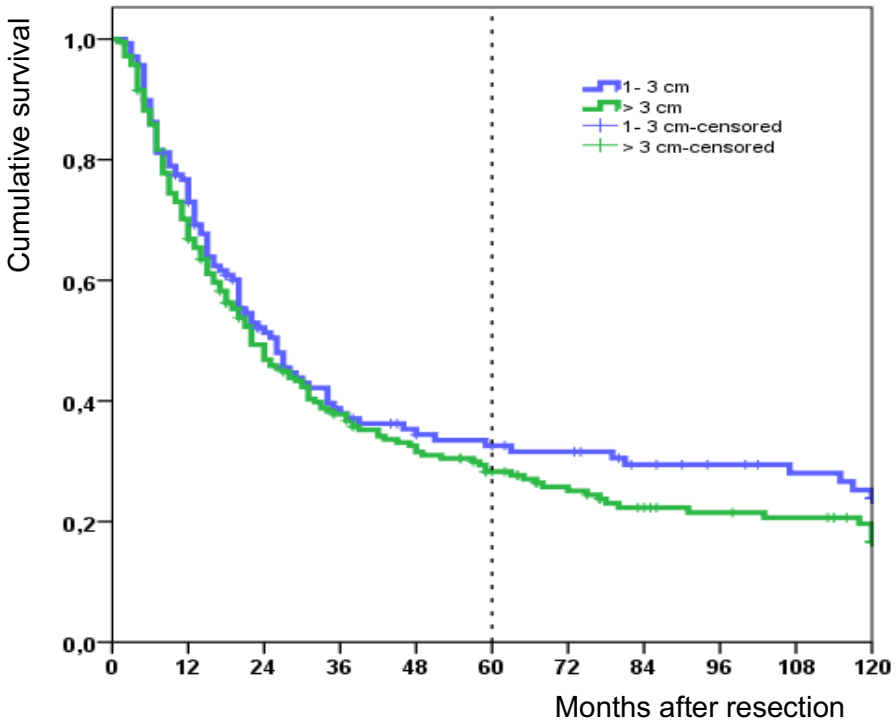

Figure 20: DFS dependent on diameter of the liver metastasis

3.5.8 Type of liver resection

Estimated 5-, and 10-year disease-free survival rates for the 58 patients with atypical resection were 16 % and 6 %, respectively. Estimated 5-, and 10-year disease-free survival rates for the 146 patients with < 3 segments resected were 33 % and 21 %, respectively. For the 146 patients with ≥ 3 segments resected the figures were 32 % and 22 %, respectively (Figure 21).

The size of the liver resection did not influence disease-free survival statistically significant (atypical *vs*. < 3 segments: p=0.071, atypical *vs*. ≥ 3 segments: p=0.425, < 3 segments *vs*. ≥ 3 segments: p=0.342).

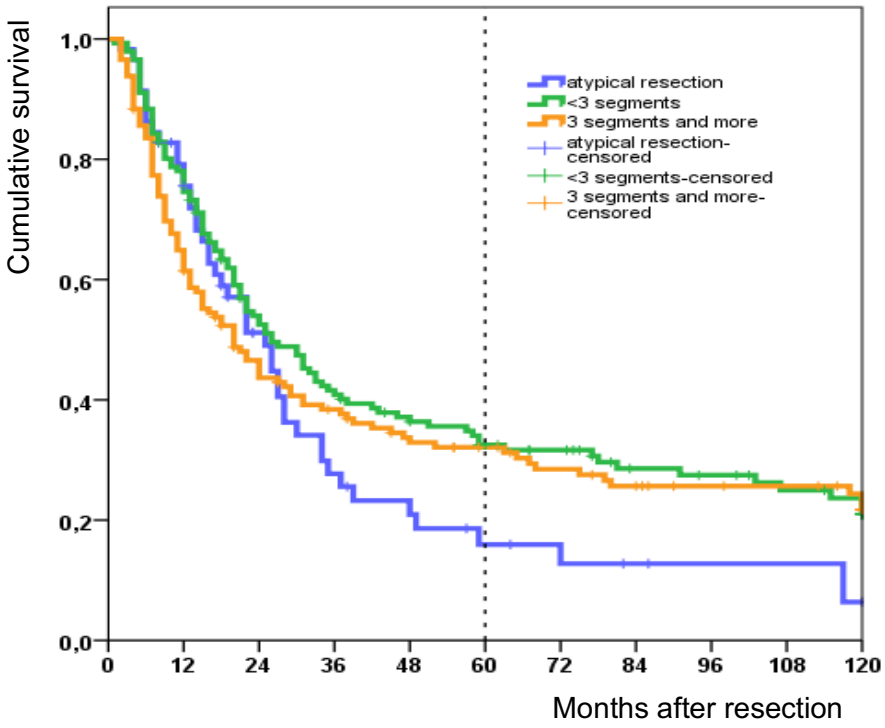

Figure 21: DFS dependent on type of liver resection for CLM

3.5.9 Use of neoadjuvant chemotherapy

Estimated 5-, and 10-year disease-free survival rates for the 51 patients with neoadjuvant chemotherapy before liver resection were 19 % and 11 %, respectively. For the 299 patients without neoadjuvant chemotherapy before liver resection the figures were 32 % and 21 %, respectively (Figure 22).

Neoadjuvant chemotherapy before liver resection did influence disease-free survival statistically significant (p=0.008).

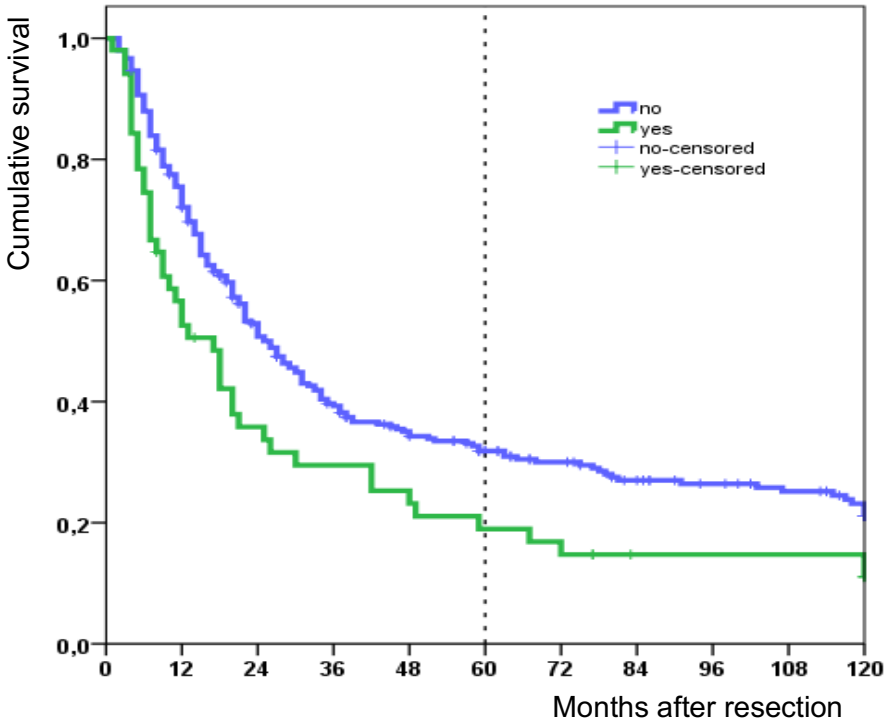

Figure 22: DFS dependent on neoadjuvant chemotherapy

3.6 Extrahepatic and intrahepatic recurrence

Till the end of the study, 146 patients did not show any signs of tumor recurrence. 204 patients had tumor recurrence (Table 3).

Table 3: Site of recurrence

Site of recurrence	**[*n*]**	
Liver only	93	Intrahepatic recurrence
Liver and other metastases	31	
Liver and other metastases and local recurrence	1	
Lung only	31	Extrahepatic recurrence
Local recurrence only	19	
Local recurrence and other metastases	3	
Other metastases	26	
In total	**204**	

The cumulative intrahepatic recurrence rate after 10 years was 41 % (Figure 23). Approximately half of these appeared within the first 12 postoperative months. The cumulative extrahepatic recurrence rate was lower than the intrahepatic recurrence (27 % after 10 years).

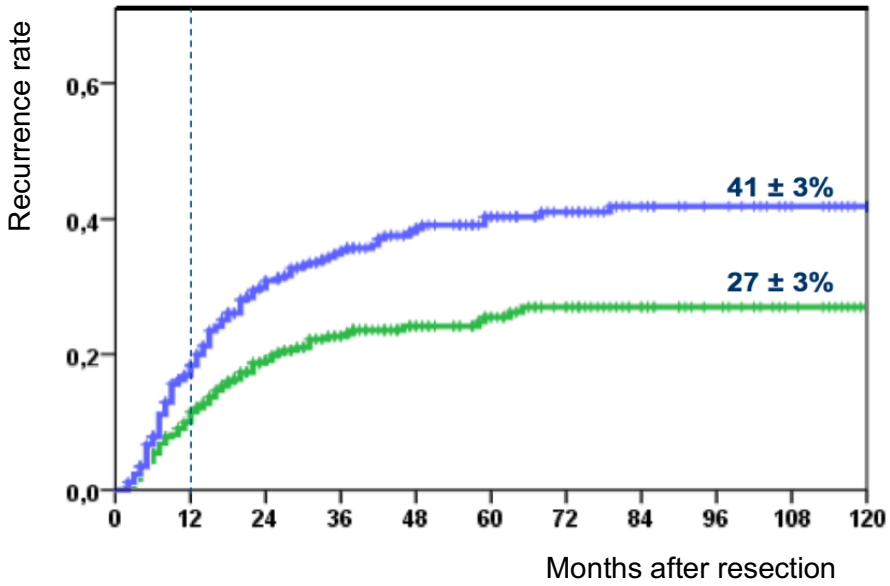

Figure 23: Cumulative intrahepatic (blue) and extrahepatic (green) recurrence rate

3.6.1 Localization of primary tumor

The site of primary tumor was correlated to the type of recurrent tumor: 10-year extrahepatic recurrence was 22 % for 208 colon cancers and 33 % for 142 rectal cancers (p=0.029). In contrast to that, 10-year intrahepatic recurrence was 46 % for colon cancer and 35 % for rectal cancer (p=0.032) (Figure 24).

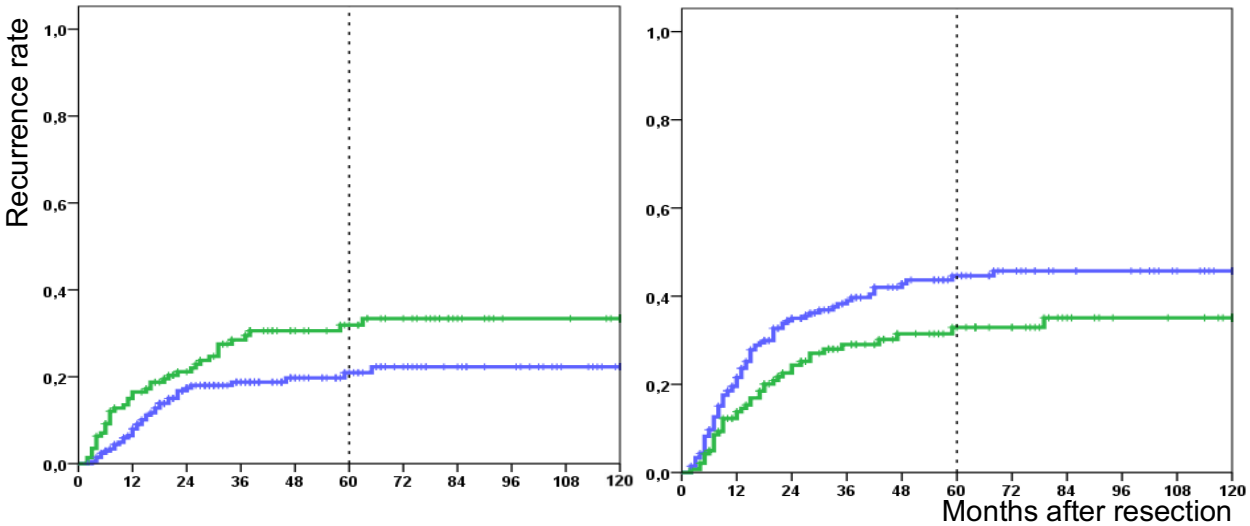

Figure 24: Extrahepatic (left) and intrahepatic (right) recurrence dependent on site of primary tumor (blue = colon, green = rectum)

3.6.2 pN category

The pN category of the primary tumor did not influence the cumulative rate of extrahepatic recurrence (p=0.805): 10-year extrahepatic recurrence was 27 % for 269 pN0/1 primary tumors and 27 % for 81 pN2 primary tumors. In contrast to that, in primary tumors with more than 3 lymph node metastases (pN2) the rate of intrahepatic recurrence was statistically significant higher than in pN0/1 primary tumors (p=0.012) (Figure 25). 10-year intrahepatic recurrence was 38 % and 54 % for pN0/1 and pN2 primary tumors, respectively.

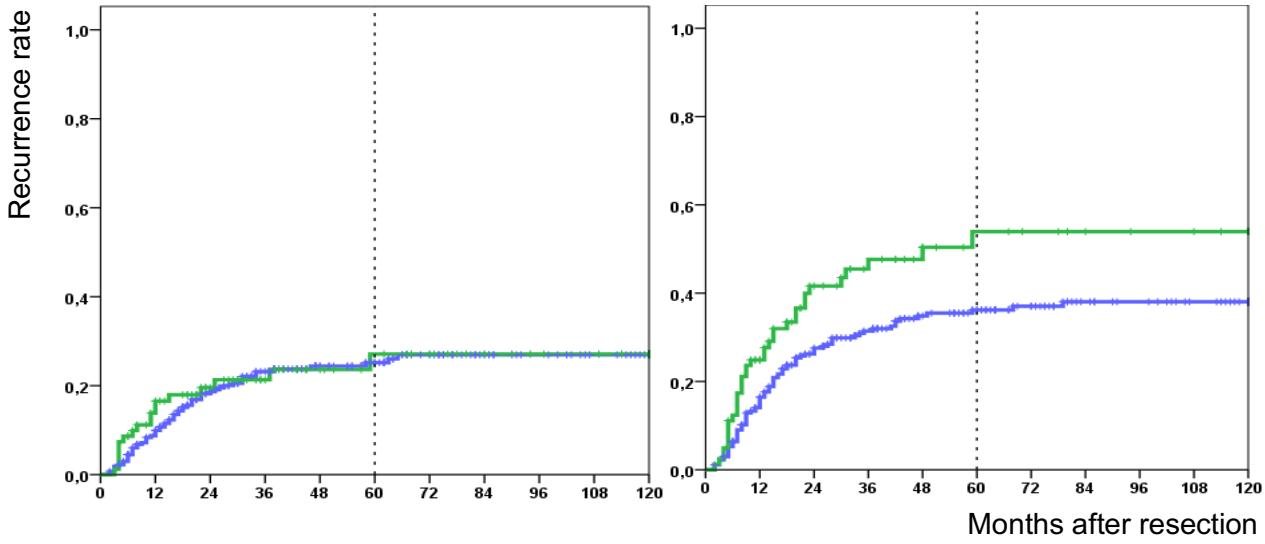

Figure 25: Extrahepatic (left) and intrahepatic (right) recurrence dependent on pN category (blue = pN0/1, green = pN2)

3.6.3 Use of neoadjuvant chemotherapy

Neoadjuvant chemotherapy (51 patients) before liver resection did not influence the extrahepatic recurrence rate statistically significant (p=0.811). The 10-year extrahepatic recurrence rate was 20 % for patients treated with neoadjuvant chemotherapy and 28 % for patients who did not received chemotherapy before surgery.

In contrast to that, the intrahepatic recurrence rate was increased statistically significant (p<0.001) (Figure 26). The 10-year intrahepatic recurrence rate was 64 % for patient who received neoadjuvant chemotherapy and 37 % for patients that did not receive chemotherapy before surgery.

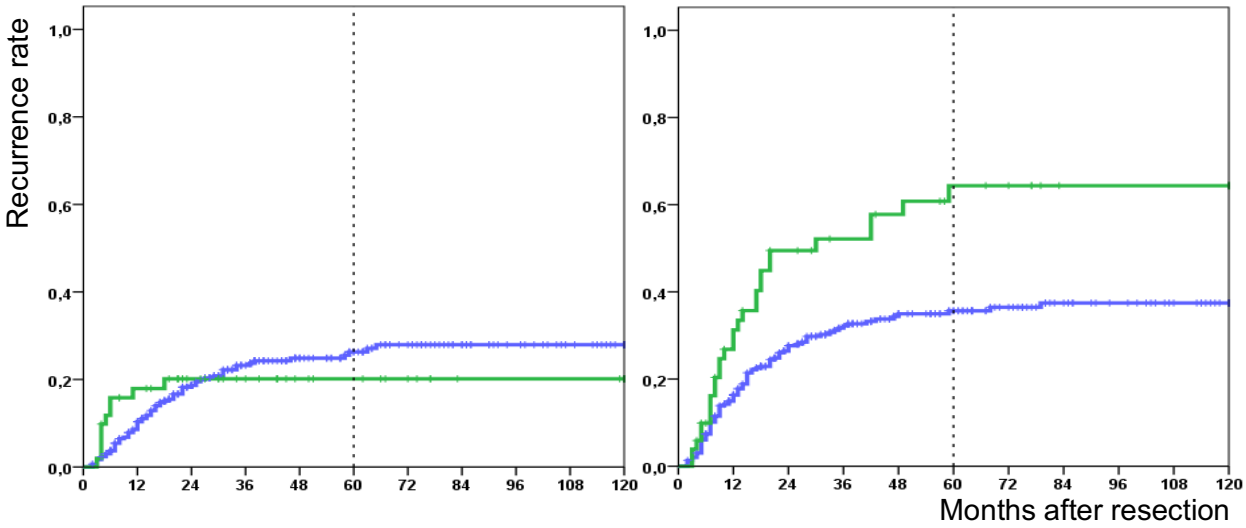

Figure 26: Extrahepatic (left) and intrahepatic recurrence (right) dependent on the use of neoadjuvant chemotherapy before liver resection (blue = no, green = yes)

3.6.4 Time of diagnosis of metastasis

Extrahepatic recurrence rates did not show any correlation to the time of diagnosis of the liver metastasis (p=0.400). The 10-year extrahepatic recurrence rates for patients with synchronous or metachronous metastases were 22 % and 29 %, respectively.

In contrast to that, synchronous metastases showed a higher intrahepatic recurrence rate than metachronous metastases (p=0.002). The 10-year intrahepatic recurrence rates for patients with synchronous and metachronous metastases were 52 % and 35 %, respectively (Figure 27).

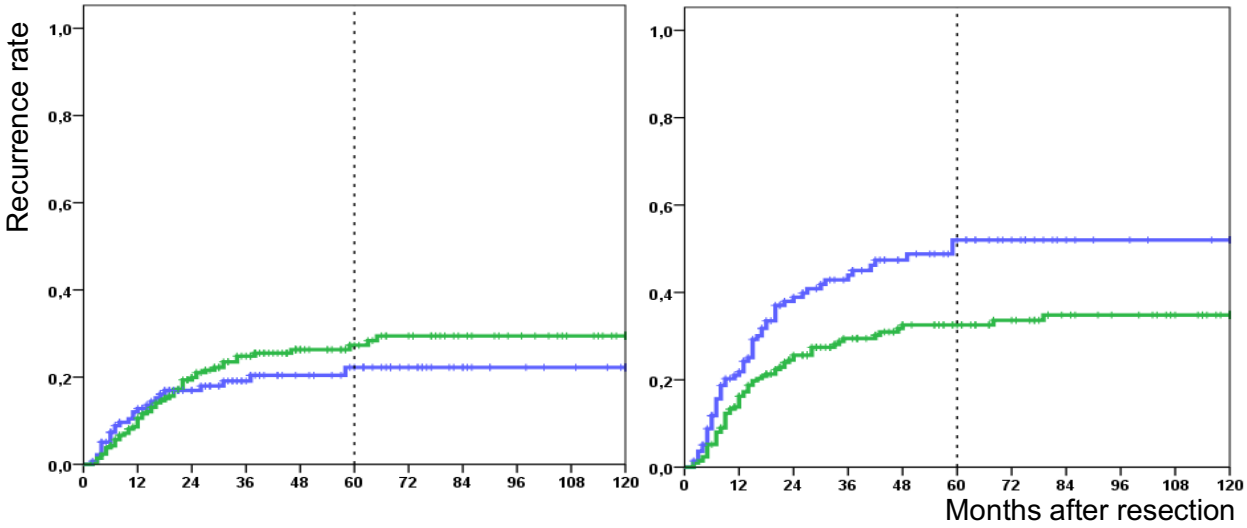

Figure 27: Extrahepatic (left) and intrahepatic recurrence (right) dependent on time of diagnosis of the metastasis (blue = synchronous, green = methachronous)

3.6.5 Presence of extrahepatic tumor lesion

The presence of extrahepatic tumor at the time of diagnosis of liver metastasis (37 patients) increased the rate of extrahepatic recurrence statistically significant (p=0.009). The 10-year extrahepatic recurrence rates for patients who had or not extrahepatic tumor were 48 % and 25 %, respectively.

In contrast to that, the rate of intrahepatic recurrence was not influenced statistically significant by extrahepatic tumor (p=0.417) (Figure 28). The 10-year intrahepatic recurrence rate for patients with or without extrahepatic tumor were 47 % and 41 %, respectively.

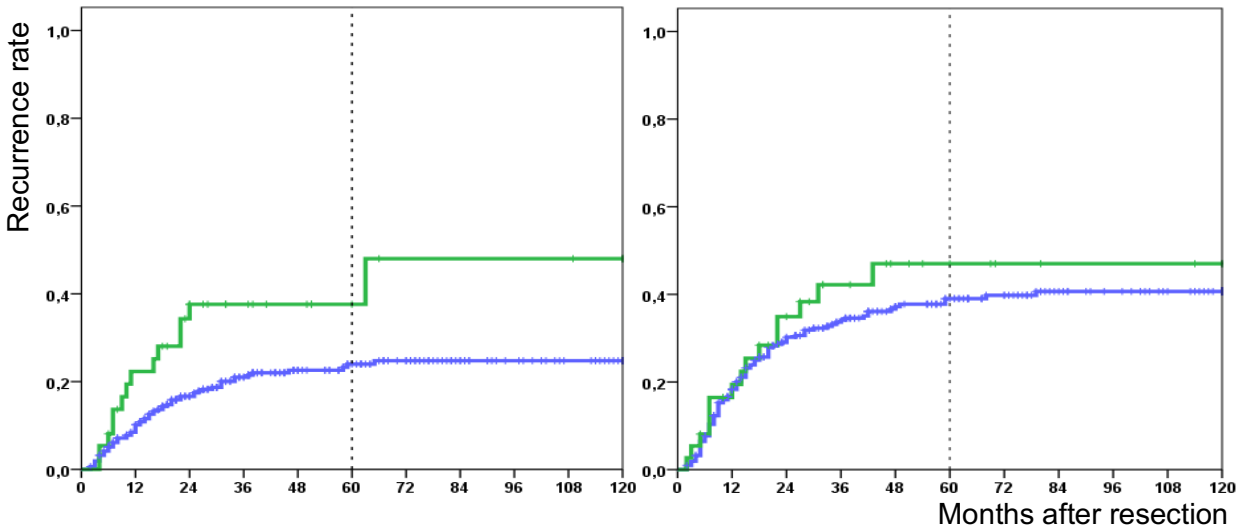

Figure 28: Extrahepatic (left) and intrahepatic recurrence (right) dependent on extrahepatic tumor at the time of liver resection for CLM (blue = absent, green = present)

Univariate analysis (Table 4) demonstrated that independently of the surgical department where the operation was performed,

- invasion of the primary tumor lesion (pT category),
- grade of malignancy of the metastasis,
- size of the metastasis (and)
- extend of the liver resection

had no statistically significant impact onto survival and recurrence rate.

Table 4: Summary of univariate analysis

	***p* OS**	***p* DFS**	***p* Intrahepatic recurrence**	***p* Extrahepatic recurrence**
Hospital	0.117	0.949	0.668	0.257
Age	**0.007**	0.575	0.301	0.790
Site of primary tumor	0.776	0.192	**0.032**	**0.029**
pT category	0.316	0.090	0.087	0.599
pN category	**0.018**	**0.006**	**0.012**	0.805
Grading	0.241	0.372	0.990	0.485
Time of metastasis	0.172	**0.021**	**0.002**	0.400
Neoadjuvant chemotherapy	0.283	**0.008**	**<0.001**	0.811
Size of metastasis	0.119	0.243	0.789	0.352
Extrahepatic tumor	**0.018**	**0.004**	0.417	**0.009**
Number of segments resected	0.650	0.663	0.402	0.592

3.7 Multivariate analysis

The multivariate analysis was performed with a Cox regression step wise forward. Factors were included if the *p* value was < 0.05 and excluded if the *p* value was > 0,10. The same model was used for all the endpoints.

Multivariate analysis (Table 4) confirmed all the results obtained with the univariate analysis. Age, status of lymph node metastases at the primary tumor, location of primary tumor, time of appearing of the metastasis, the use of preoperative chemotherapy and the presence of extrahepatic tumor can be considered as independent predictors for the prognosis.

Table 5: Summary of multivariate analysis

	***p* OS**	***p* DFS**	***p* Intrahep. recurrence**	***p* Extrahep. recurrence**
Age	**0.005**	n.s.	n.s.	n.s.
Site of primary tumor	n.s.	n.s.	**0.039**	**0.027**
pN category	**0.029**	**0.008**	**0.017**	n.s.
Time of metastasis	n.s.	n.s.	**0.037**	n.s.
Neoadjuvant chemotherapy	n.s.	**0.003**	**0.004**	n.s.
Extrahepatic tumor	**0.023**	**0.006**	n.s.	**0.009**

4. DISCUSSION

In the last years, a large number of studies investigated predictors of outcome after hepatic resection for CLM. Several factors were identified to influence the prognosis, however, the results reported are very heterogeneous and often discorded. Since the most study populations are very diversified comprehending every number of metastases, in this work we focused on a more homogeneous group of patients characterized by solitary CLM treated with a curative (R0) resection. The aim is to achieve more trustable results and to analyze a subgroup of patient until now considered as those having a considerable better prognosis. The surgical department where the operation was performed, had no statistically significant impact on the oncological outcome. Therefore, the combined analysis of the patients who underwent hepatic resection at the two centers is justified.

4.1 Survival rates for solitary metastases

The absence of perioperative mortality and the overall survival rate confirm the accepted concept that surgery is a safe procedure with the best long-term outcome if compared with other ablative or systemic therapy. In the literature, independently of the number of metastases, the median 5- and 10-year survival rates reported were 38 % and 26 %, respectively (4). In our subgroup of solitary metastases, we reached a 5- and 10-year survival rate of 47 % and 28 %. These results show that patients with solitary metastases does not benefit of such an excellent prognosis if compared with patients with multiple metastases.

The disease-free survival rate showed that a big part of the patients developed recurrence, especially in the first months after the liver resection. Therefore, a close-up and careful monitoring for patients treated with curative resection of a single metastasis, independently of the size of the metastasis, assume a crucial role in the follow up.

4.2 Tumor recurrence

According to other reports, we saw more intrahepatic than extrahepatic tumor recurrence (62,63). Interestingly, the half of intrahepatic tumor recurrence appeared within the first 12 postoperative months after surgery. This may indicate an underestimation of tumor burden due to undetected (occult) liver lesions at the

time of liver surgery. We assume these patients had multiple subclinical metastases thus small at the time of operation that they cannot be identified even with the most sensitive diagnostic tool, the intraoperative ultrasound. These metastases became clinically detectable a few months after liver resection. We suppose that in this subgroup of patients, we did not resect a solitary liver metastasis but rather the “first one” of multiple subsequently occurring liver metastases. A previous study demonstrated that immunohistochemically detected hepatic micrometastases were found in about a half of patients treated with curative liver resection. The presence of micrometastases was a predictive factor for increased risk of intrahepatic recurrence and was a poor prognostic indicators of survival (64).

The big challenge would be the detection of the patients that are classified as having a single metastasis but present undetectable micrometastases. To reveal the patients that suffer from a fast tumor progression, a “watch and wait” strategy in the first months after diagnosis could be taken into consideration. If during this time window the patients develop other metastases, it can be assumed that they were present as subclinical undetected micrometastases even at the time of diagnosis. In this group of patients, the strategy of treatment has to be discussed again in order to reach a complete surgical resection of the tumor or, in case of unresectable disease, another treatment strategy should be adopted such as local ablation, liver-parenchyma-sparing surgical technique or systemic therapy or a combination of the previous.

A study of Voskoboynik *et al*. analyzed the follow up of patients with newly diagnosed metastatic colorectal cancer that received an initial treatment in confront with patients who received a “watch and wait” strategy. It was demonstrated that the “watch and wait” approach does not compromise the survival rate of the patients. It was adopted in case of low bulk and asymptomatic disease, where progression at known sites of disease was considered unlikely to cause rapid clinical deterioration. The great majority (87.5 %) of watch and wait patients subsequently received treatment, at a median of 3.7 months due to tumor factors such as significant disease progression or the development of bulky or symptomatic disease or at patients’ discretion (65).

4.3 Negative prognostic factors

Our population was a relative elderly patient group since about one third of the patients was more than 70 years old. The age of the patients had a significant impact only on the overall survival. In fact, especially for this end point the age-related comorbidities play an important role that disappears in the other end points. This demonstrates that surgery is justified even in elderly patients, if the comorbidities allow to safely tackling the operation.

The data presented, according to several previous studies (39,43,66,67), shows that the regional lymph node involvement of the primary tumor lesion is one of the strongest prognostic factors. It was independently associated with a reduced survival and a worse tumor recurrence rate diminishing the whole postoperative outcome. This aspect may be related to the tumor biology and growing characteristics showing a particular aggressiveness of the disease.

The primary tumor site had an influence only on the incidence of intra- and extrahepatic tumor recurrence. In the presented groups, patients with rectal cancer had more extrahepatic recurrence than patients with colon cancer the latter one had a higher intrahepatic recurrence. On one side, this can be explained by the fact that patients with a primary rectal cancer had a higher loco-regional recurrence rate that is classified as an extrahepatic tumor site. On the other hand, the anatomical features may cause a different metastatic pattern since the venous blood and the lymphatic drainage from the lower rectum passes through the systemic venous pathway rather than the portal pathway. As support to this hypothesis, an analysis of the pattern of tumor recurrence published by Tan *et al*. revealed that pulmonary tumor recurrence occurs more frequently in rectal cancer whereas liver metastases are more frequent in colon cancer (68).

According to the literature (54,56), the presence of synchronous metastases was associated with a higher intrahepatic tumor recurrence and a worse disease-free survival. This can be intuitively explained with a late diagnosis of the disease or with a more aggressive character of the tumor such as a tendency of dissemination that leads to a worse prognosis.

In opposition to previous works (54,69,70), the size and the grade of the metastases did not influence survival. Further, the extend of liver resection did not influence outcome. It can be therefore assumed that – if a resection is

technically feasible – it should be always performed, even in cases of bigger metastases. On the other hand, if an R0 resection of the metastasis can be achieved with a wedge resection, there is no need to perform a larger resection.

4.4 Microscopic status

The importance of the microscopic status of the resection margin is largely described. Recent reports demonstrated that a microscopically positive R1 margin is strongly correlated with worse overall survival (71–74). Since the 1980s, there had been a general consensus that the optimal surgical margin during resection of CLM should measure ≥ 1 cm. In fact, some authors even suggested that inability to accommodate a 1-cm margin should perhaps preclude a patient from being considered for hepatic resection (46,75). More recently, however, multiple reports have demonstrated that margin width has any effect on outcome as long as a negative margin is achieved (71,73). This aspect increases the responsibility of the surgeon who should strive assiduously to achieve complete macro- and microscopic resection of CLM to ensure the best outcome for the patient.

4.5 Extrahepatic disease

As previously reported (76,77), the presence of extrahepatic tumor disease at the time of the operation significantly reduced the survival rate and increases the risk of recurrence of extrahepatic metastasis. No influence was seen on the intrahepatic tumor recurrence. This does not mean necessarily that the presence of extrahepatic tumor lesions should be considered as a contraindication to surgery as some authors reported. Recently, an increased number of authors demonstrate that the presence of limitedly resectable extrahepatic tumor disease should not be an absolute contraindication to resection, as a subset of patients may derive a long-term survival benefit (76–78). A recent review of Chua *et al*. showed that resection of colorectal liver metastases with extrahepatic disease is a safe surgical option with median mortality rate of less than 1 %. Moreover, when an R0 resection status in hepatic resection was achieved, the median 5-year survival reached 25 % (79). Taking into account that surgery of all resectable

disease is the best chance of long-term survival, whenever technically possible, it should be discussed.

4.6 Neoadjuvant chemotherapy

The use of neoadjuvant chemotherapy was first indicated for patients with unresectable liver metastases, where the purpose was to downstage the extent of metastases to technically facilitate a safe and feasible operation with preservation of an adequate remnant liver volume (80). Successively, the use of neoadjuvant chemotherapy was assessed even for resectable liver metastases. A big multicenter study of Adam *et al*. studied the effect on survival of preoperative chemotherapy in confront to upfront surgery for solitary methachronous liver metastases. In a group of 1,471 patients, the use of preoperative chemotherapy did not improve overall- or disease-free survival. Moreover the rate of postoperative complications was significantly higher in the group of patients that received chemotherapy before surgery (67). The European Organization for Research and Treatment of Cancer conducted the only randomised, controlled, phase-III trial that demonstrated that perioperative therapy with FOLFOX (before and after surgery) increases progression-free survival compared with surgery alone for patients with liver-only metastases but they could not report a statistically significant survival difference between the two groups (23,24).

In the same way, in our group there is no difference in overall survival between patients that received or not preoperative chemotherapy. Moreover, the use of preoperative chemotherapy revealed to be an independent negative predictor of outcome with a significant worse disease-free survival and higher intrahepatic tumor recurrence.

A large study of Adam *et al*. analyzed patients with CLM that underwent liver resection after systemic chemotherapy. Patients defined as “complete pathological responder” without any viable tumor cell at the pathological examination, had excellent survival outcomes, with 5-year overall survival and 5-year disease-free survival of both 76 %. Unfortunately, these results concern only a small minority of the total of patients resected in fact a complete pathological response was observed in only 4 % of patients (81).

A recent large review of Chua *et al*. analyzed the rates of radiological response and pathological response after neoadjuvant chemotherapy. It has been calculated that the overall objective radiological response was observed in 64 % of patients, with only a small proportion of patients (4 %) demonstrating complete pathological response (82).

In other words, the use of chemotherapy before surgery can lead to a complete radiological response which means that metastases disappear in preoperative imaging, nevertheless, it does not necessarily reflect a complete pathological response. In a study by Benoist *et al.*, the histopathologic examination of the sites where CLM disappeared, showed viable tumor cells in 80 % of the patients (83). Moreover, a recent review by Gaujoux *et al*. reported that if the disappearing metastases were left *in situ*, the tumor recurrence rate ranged from 38 to 74 % (84). On the basis of these findings, it can be supposed that the use of neoadjuvant chemotherapy in the presented group could have masked the presence of more subclinical metastases, in addition to the known solitary metastasis, that were not resected at the time of surgery. Probably, these micrometastases develop and spread only after liver resection, when the chemotherapy was interrupted, leading to a higher and earlier recurrence of the disease.

4.7 Conclusion

The peculiarity of this work is that it concentrates on a defined group of patients otherwise always included in a more heterogeneous population characterized by multiple liver metastases.

Patients with solitary metastases are mostly considered a subgroup of patient with excellent prognosis, however, we could not confirm these expectations. The survival and recurrence rate are not that far from the results of patients with multiple metastases. Liver resection remains the first choice of treatment, nevertheless it is a signal that a careful and close-up monitoring after surgery is definitely needed.

Furthermore, since we noted that a subgroup of the investigated patients quickly developed recurrence after surgery, we questioned if in these cases, we resected the “first one” of multiple liver metastases already present as undetected

micrometastases at the time of surgery. The next big challenge would be the preoperative identification of these patients in order to choose an appropriate strategy of treatment. In this regard, a “watch and wait” approach could be taken into discussion.

Through the high number of cases, we reached important and sometimes unexpected results. The long-term prognosis after resection of solitary hepatic metastases is influenced by multiple factors acting in different ways. In our group the use of neoadjuvant chemotherapy was not able to improve the long-term follow-up, indeed it has revealed itself as a negative predictor. The strongest factors were the involvement of regional lymph nodes of the primary tumor, the presence of extrahepatic tumor disease at the time of liver resection and the time of occurrence of the metastasis.

Through these informations, we are able to recognize in advance which patients would benefit from an intensification of the follow up, from a systemic therapy after surgery or from a reoperation. This would lead to the realization of a patient-specific treatment in order to improve the oncological outcome and the quality of life.

5. SUMMARY

In recently published studies about the outcome after hepatic resection for colorectal liver metastases, the results are very heterogeneous and sometimes discording. We focused on a homogeneous group of patients characterized by solitary colorectal liver metastases treated with a curative (R0) resection.

We recruited a total of 350 patients at the University Hospitals of Jena and Magdeburg who underwent curative liver resection between 1993 and 2014. All patients had follow-up until death or till summer 2016.The 5- and 10-year OS rates were 47 % and 28 %, respectively. The 5- and 10-year DFS rates were 30 % and 20 %, respectively. These results are not that excellent as expected. The analysis of the prognostic factors revealed that pT category of primary tumor, size and grade of the metastases and extension of the liver resection had no statistically significant impact on survival and recurrence rates.

The age of the patients, the involvement of more than three lymph node metastases by the primary tumor, synchronous metastases, the use of neoadjuvant chemotherapy and the presence of extrahepatic tumor showed a negative influence on the prognosis. Moreover, patient with rectal cancer had a significant lower intrahepatic recurrence rate but a higher extrahepatic recurrence rate. In the multivariate analysis these results proved to be independent statistically significant predictors for the prognosis showing that the long-term follow up of these kind of patients is multifactorial influenced. More than three lymph node metastases at the primary tumor and the presence of extrahepatic tumor demonstrated to be factors with the worst influence on the follow up. The use of chemotherapy before liver resection was not able to improve survival or tumor recurrence. This information can help the clinicians to stratify the patients and to recognize which patients would benefit from an intensification of the follow up, from a reoperation or from a systemic therapy or from a local-ablative treatment. This led to offer a patient-specific strategy of treatment in order to improve the oncologic outcome and the quality of life.

6. REFERENCES

1 Matias M, Casa-nova M, Faria M, Pires R, Tato-costa J, Ribeiro L, Costa L. Prognostic Factors after Liver Resection for Colorectal Liver Metastasis. *Acta Med Port* 2015; 28: 357–69.

2 van de Velde CJH, Boelens PG, Borras JM, Coebergh JW, Cervantes A, Blomqvist L. EURECCA colorectal: Multidisciplinary management: European consensus conference colon & rectum. *Eur J Cancer* 2014; 50: 1.e1-1.e34.

3 Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999; 230: 309–18.

4 Kanas GP, Taylor A, Primrose JN, Langeberg WJ, Kelsh MA, Mowat, FS, Alexander DD, Choti MA, Poston G. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. *Clin Epidemiol* 2012; 4: 283–301.

5 Hadden WJ, de Reuver PR, Brown K, Mittal A, Samra JS, Hugh TJ. Resection of colorectal liver metastases and extra-hepatic disease: a systematic review and proportional meta-analysis of survival outcomes. *HPB (Oxford)* 2016; 18: 209–20.

6 Riihimäki M, Hemminki A, Sundquist J, Hemminki, K. Patterns of metastasis in colon and rectal cancer. *Sci Rep* 2016; 6: 1–9.

7 Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier A-M. Epidemiology and management of liver metastases from colorectal cancer. *Ann Surg* 2006; 244: 254–9.

8 Poston GJ, Adam R, Alberts S, Curley S, Figueras J, Haller D, Kunstlinger F, Mentha G, Nordlinger B, Patt Y, Primrose J, Roh M, Rougier P, Ruers T, Schmoll HJ, Valls C, Vauthey NJN, Cornelis M, Kahan JP. OncoSurge: a strategy for improving resectability with curative intent in metastatic colorectal cancer. *J Clin Oncol* 2005; 23: 7125–34.

9 Mayo SC, Pulitano C, Marques H, Lamelas, J, Wolfgang CL, De Saussure W, Choti MA, Gindrat I, Aldrighetti L, Barrosso E, Mentha G, Pawlik TM. Surgical management of patients with synchronous colorectal liver metastasis: a multicenter international analysis. *J Am Coll Surg* 2013; 216: 707–16.

10 Abdalla EK, Bauer TW, Chun YS, D'Angelica M, Kooby DA, Jarnagin WR. Locoregional surgical and interventional therapies for advanced colorectal cancer liver metastases: expert consensus statements. *HPB (Oxford)* 2013; 15: 119–30.

11 Elias D, Ouellet J-F, de Baère T, Lasser P, Roche A. Preoperative selective portal vein embolization before hepatectomy for liver metastases: Long-term results and impact on survival. *Surgery* 2002; 131: 294–9.

12 Hoekstra LT, van Lienden KP, Doets A, Busch ORC, Gouma DJ, van Gulik TM. Tumor Progression After Preoperative Portal Vein Embolization. *Ann Surg* 2012; 256: 812–8.

13 Garlipp B, de Baere T, Damm R, Irmscher R, van Buskirk M, Stübs P, Deschamps F, Meyer F, Seidensticker R, Mohnike K, Pech M, Amthauer H, Lippert H, Ricke J, Seidensticker, M. Left-liver hypertrophy after therapeutic right-liver radioembolization is substantial but less than after portal vein embolization. *Hepatology* 2014; 59: 1864–73.

14 Adam R, Laurent A, Azoulay D, Castaing D, Bismuth H. Two-stage hepatectomy: A planned strategy to treat irresectable liver tumors. *Ann Surg* 2000; 232: 777–85.

15 Olthof PB, Huiskens J, Wicherts DA, Huespe PE, Ardiles V, Robles-Campos R, Adam R, Linecker M, Clavien PA, Koopman M, Verhoef C, Punt CJA, van Gulik TM, de Santibanes E. Survival after associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) for advanced colorectal liver metastases: A case-matched comparison with palliative systemic therapy. *Surgery* 2017; 161: 909–19.

16 Kelly C, Cassidy J. Chemotherapy in metastatic colorectal cancer. *Surg Oncol* 2007; 16: 65–70.

17 Levi F, Perpoint B, Garufi C, Focan C, Chollet P, Depres-Brummer P, Zidani R, Brienza S, Itzhaki M, Iacobelli S. Oxaliplatin activity against metastatic colorectal cancer. A phase II study of 5-day continuous venous infusion at circadian rhythm modulated rate. *Eur J Cancer* 1993; 29A: 1280–4.

18 Robinson S, Manas DM, Pedley I, Mann D, White SA. Systemic chemotherapy and its implications for resection of colorectal liver metastasis. *Surg Oncol* 2011; 20: 57–72.

19 Saltz LB, Cox J V, Blanke C, Rosen, Lee S, Fehrenbacher L, Moore MJ, Maroun JA, Ackland SP, Locker PK, Pirotta N, Elfring GL, Miller LL. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med* 2000; 343: 905–14.

20 Goldberg RM, Sargent DJ, Morton RF, Fuchs, Charles SR, Ramesh K, Williamson SK, Findlay BP, Pitot HC, Alberts SR. A Randomized Controlled Trial of Fluorouracil Plus Leucovorin, Irinotecan, and Oxaliplatin Combinations in Patients With Previously Untreated Metastatic Colorectal Cancer. *J Clin Oncol* 2003; 22: 23–30.

21 Tournigand C, André T, Achille E, Lledo, Gérard, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C, de Gramont A. FOLFIRI followed by FOLFOX6 or the reverse sequence in

advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004; 22: 229–37.

22 Jhonatan Sotelo M, García-Paredes B, Aguado C, Sastre J, Díaz-Rubio Miguel Jhonatan Sotelo E, Agua-do C, Díaz-Rubio E, Díaz-Rubio García E. Role of cetuximab in first-line treatment of metastatic colorectal cancer. *World J Gastroenterol* 2014; 20: 4208–19.

23 Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, Bechstein WO, Primrose JN, Walpole ET, Finch-Jones M, Jaeck D, Mirza D, Parks RW, Collette L, Praet M, Bethe U, Van Cutsem E, Scheithauer W, Gruenberger T. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet* 2008; 371: 1007–16.

24 Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, Bechstein WO, Primrose JN, Walpole ET, Finch-Jones M, Jaeck D, Mirza D, Parks RW, Mauer M, Tanis E, Van Cutsem E, Scheithauer W, Gruenberger T. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): Long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2013; 14: 1208–15.

25 Parks R, Gonen M, Kemeny N, Jarnagin W, D'Angelica M, DeMatteo R, Garden OJ, Blumgart LH, Fong Y. Adjuvant chemotherapy improves survival after resection of hepatic colorectal metastases: analysis of data from two continents. *J Am Coll Surg* 2007; 204: 753-61-3.

26 Zhang W, Song T. The progress in adjuvant therapy after curative resection of liver metastasis from colorectal cancer. *Drug Discov Ther* 2014; 8: 194–200.

27 Clark ME, Smith RR. Liver-directed therapies in metastatic colorectal cancer. *J Gastrointest Oncol* 2014; 5: 374–87.

28 Ammori JB, Kemeny NE, Fong Y, Cercek A, Dematteo RP, Allen PJ, Kingham TP, Gonen M, Paty PB, Jarnagin WR, D'Angelica MI. Conversion to Complete Resection and/or Ablation Using Hepatic Artery Infusional Chemotherapy in Patients with Unresectable Liver Metastases from Colorectal Cancer: A Decade of Experience at a Single Institution. *Ann Surg Oncol* 2013; 20: 2901–7.

29 Fiorentini G, Aliberti C, Tilli M, Mulazzani L, Graziano F, Giordani P, Mambrini A, Montagnani F, Alessandroni P, Catalano V, Coschiera P. Intra-arterial infusion of irinotecan-loaded drug-eluting beads (DEBIRI) versus intravenous therapy (FOLFIRI) for hepatic metastases from colorectal cancer: Final results of a phase III study. *Anticancer Res* 2012; 32: 1387–95.

30 Khatri VP, Chee KG, Petrelli NJ. Modern multimodality approach to hepatic colorectal metastases: Solutions and controversies. *Surg Oncol* 2007; 16: 71–83.

31 Peeters M, Wasan HS, Gibbs P, Sharma NK, Taieb J, Heinemann V, Ricke J, Peeters M, Findlay M, Weaver A, Mills J, Wilson C, Adams R, Francis A, Moschandreas J, Virdee PS, Dutton P, Love S, Gebski V, Gray A, Van Hazel G, Sharma RA. First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. *Lancet Oncol* 2017; 18: 1159–71.

32 Amano R, Yamada N, Nakata B, Kimura K, Yashiro M, Ohira M, Hirakawa K. Prognostic indicator for the resection of liver metastasis of colorectal cancer. *Surg Today* 2014; 44: 1287–92.

33 Iancu C, Mocan LC, Todea-Iancu D, Mocan T, Zaharie FV, Graur F, Puia IC, Munteanu D, Bala O, Agoşton-Coldea L, Mihăileanu F, Mitre C, Ionescu D, Vlad LE. Survival prognostic factors in patients with resection of liver metastasis from colorectal cancer. *Rom J Intern Med* 2008; 46: 229–237.

34 John SKP, Robinson SM, Rehman S, Harrison B, Vallance, A. French JJ, Jaques BC, Charnley RM, Manas DM, White SA. Prognostic factors and survival after resection of colorectal liver metastasis in the era of preoperative chemotherapy: An 11-year single-centre study. *Dig Surg* 2014; 30: 293–301.

35 Arru M, Aldrighetti L, Castoldi R, Di Palo S, Orsenigo E, Stella M, Pulitanò C, Gavazzi F, Ferla G, Di Carlo V, Staudacher C. Analysis of prognostic factors influencing long-term survival after hepatic resection for metastatic colorectal cancer. *World J Surg* 2008; 32: 93–103.

36 Choti M a, Sitzmann J V, Tiburi MF, Sumetchotimetha W, Rangsin R, Schulick RD, Lillemoe KD, Yeo CJ, Cameron, JL. Trends in long-term survival following liver resection for hepatic colorectal metastases. *Ann Surg* 2002; 235: 759–66.

37 Mutsaerts EL a R, van Ruth S, Zoetmulder F a N, Rutgers EJT, Hart A a M, van Coevorden F. Prognostic factors and evaluation of surgical management of hepatic metastases from colorectal origin: a 10-year single-institute experience. *J Gastrointest Surg* 2005; 9: 178–86.

38 Pulitanò C, Bodingbauer M, Aldrighetti L, Choti, M, Castillo F, Schulick RD, Gruenberger T, Pawlik TM. Colorectal Liver Metastasis in the Setting of Lymph Node Metastasis: Defining the Benefit of Surgical Resection. *Ann Surg Oncol* 2012; 19: 435–42.

39 Kuo I-M, Huang S-F, Chiang J-M, Yeh, C-Y, Chan K-M, Chen J-S, Yu, M-C. Clinical features and prognosis in hepatectomy for colorectal cancer with centrally located liver metastasis. *World J Surg Oncol* 2015; 13: 1–12.

40 Fong Y, Salo J. Surgical therapy of hepatic colorectal metastasis. *Semin Oncol* 1999; 26: 514–23.

41 Iwatsuki S, Dvorchik I, Madariaga JR, Marsh JW, Dodson F, Bonham AC, Geller DA, Gayowski TJ, Fung JJ, Starzl TE. Hepatic resection for metastatic colorectal adenocarcinoma: a proposal of a prognostic scoring system. *J Am Coll Surg* 1999; 189: 291–9.

42 Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K,Bachellier P, Jaeck D. Surgical resection of colorectal carcinoma metastases to the liver: A prognostic scoring system to improve case selection, based on 1568 patients. *Cancer* 1996; 77: 1254–62.

43 Rees M, Tekkis PP, Welsh FKS, O'Rourke T, John TG. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. *Ann Surg* 2008; 247: 125–35.

44 Schindl M, Wigmore SJ, Currie EJ, Laengle F, Garden OJ. Prognostic Scoring in Colorectal Cancer Liver Metastases. *Arch Surg* 2005; 140: 183.

45 Gayowski TJ, Iwatsuki S, Madariaga JR, Selby R, Todo S, Irish W, Starzl TE. Experience in hepatic resection for metastatic colorectal cancer: analysis of clinical and pathologic risk factors. *Surgery* 1994; 116: 703-11.

46 Cady B, Stone MD. The role of surgical resection of liver metastases in colorectal carcinoma. *Semin Oncol* 1991; 18: 399–406.

47 Shin SJ, Ahn JB, Choi JS, Choi GH, Lee KY, Baik SH, Min BS, Hur H, Roh JK, Kim NK. Implications of clinical risk score to predict outcomes of liver-confined metastasis of colorectal cancer. *Surg Oncol* 2012; 21: 6–11.

48 Ayez N, van der Stok EP, Grünhagen DJ, Rothbarth J, van Meerten E, Eggermont AM, Verhoef C. The use of neo-adjuvant chemotherapy in patients with resectable colorectal liver metastases: Clinical risk score as possible discriminator. *Eur J Surg Oncol* 2015; 41: 859–67.

49 Nakai T, Ishikawa H, Tokoro T, Okuno K. The Clinical Risk Score Predicts the Effectiveness of Adjuvant Chemotherapy for Colorectal Liver Metastasis. *World J Surg* 2015; 39: 1527–36.

50 Chan K-M, Wu T-H, Cheng C-H, Lee W-C, Chiang J-M, Chen J-S, Wang J-Y. Prognostic significance of the number of tumors and aggressive surgical approach in colorectal cancer hepatic metastasis. *World J Surg Oncol* 2014; 12: 1–8.

51 Brouquet A, Andreou A, Vauthey JN. The management of solitary colorectal liver metastases. *Surgeon* 2011; 9: 265–72.

52 Abdalla EK, Vauthey J-N, Ellis LM, Pollock R, Broglio KR, Hess K, Curley S. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Ann Surg* 2004; 239: 818–24.

53 Oshowo A, Gillams A, Harrison E, Lees WR, Taylor I. Comparison of resection and radiofrequency ablation for treatment of solitary colorectal liver metastases. *Br J Surg* 2003; 90: 1240–3.

54 Aloia TA, Vauthey JN, Loyer EM, Ribero D, Pawlik TM, Wei SH, Curley SA, Zorzi D AE. Solitary Colorectal Liver Metastasis. *Arch Surg* 2006; 141: 460–6.

55 White RR, Avital I, Sofocleous CT, Brown KT, Brody LA, Covey A, Getrajdman GI, Jarnagin WR, Dematteo RP, Fong Y, Blumgart LH, D'Angelica M. Rates and patterns of recurrence for percutaneous radiofrequency ablation and open wedge resection for solitary colorectal liver metastasis. *J Gastrointest Surg* 2007; 11: 256–63.

56 Lee WS, Yun SH, Chun HK, Lee WY, Kim SJ, Choi SH, Heo JS, Joh JW, Choi D, Kim SH, Rhim H, Lim HK. Clinical outcomes of hepatic resection and radiofrequency ablation in patients with solitary colorectal liver metastasis. *J Clin Gastroenterol* 2008; 42: 945–9.

57 Berber E, Siperstein A. Local recurrence after laparoscopic radiofrequency ablation of liver tumors: an analysis of 1032 tumors. *Ann Surg Oncol* 2008; 15: 2757–64.

58 Konopke R, Kersting S, Bunk A, Dietrich J, Denz A, Gastmeier J, Saeger HD. Colorectal liver metastasis surgery: Analysis of risk factors predicting postoperative complications in relation to the extent of resection. *Int J Colorectal Dis* 2009; 24: 687–97.

59 Merkel S, Bialecki D, Meyer T, Müller V, Papadopoulos T, Hohenberger W. Comparison of clinical risk scores predicting prognosis after resection of colorectal liver metastases. *J Surg Oncol* 2009; 100: 349–57.

60 Hur H, Taek Ko Y, Soh Min B, Sik Kim K, Sub Choi J, Kook Sohn S, Hwan Cho C, Kyu Ko H, Tai Lee J, Kyu Kim N. Clinical Surgery-International Comparative study of resection and radiofrequency ablation in the treatment of solitary colorectal liver metastases. *Am J Surg* 2009; 197: 728–36.

61 McKay A, Fradette K, Lipschitz J. Long-term outcomes following hepatic resection and radiofrequency ablation of colorectal liver metastases. *HPB Surg* 2009; 2009: 1-8.

62 D'Angelica M, Kornprat P, Gonen M, DeMatteo RP, Fong Y, Blumgart LH, Jarnagin WR. Effect on Outcome of Recurrence Patterns After Hepatectomy for Colorectal Metastases. *Ann Surg Oncol* 2011; 18: 1096–103.

63 de Jong MC, Pulitano C, Ribero D, Strub J, Mentha G, Schulick RD, Choti MA, Aldrighetti L, Capussotti L, Pawlik TM. Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1669 patients. *Ann Surg* 2009; 250: 440–8.

64 Yokoyama N, Shirai Y, Ajioka Y, Nagakura S, Suda T, Hatakeyama K. Immunohistochemically detected hepatic micrometastases predict a high risk of intrahepatic recurrence after resection of colorectal carcinoma liver metastases. *Cancer* 2002; 94: 1642–7.

65 Voskoboynik M, Bae S, Ananda S, Desai J, Kosmider S, Gibbs P. An initial watch and wait approach is a valid strategy for selected patients with newly diagnosed metastatic colorectal cancer. *Ann Oncol* 2012; 23: 2633–7.

66 Cardona K, Mastrodomenico P, D'Amico F, Shia J, Gönen M, Weiser MR, Paty PB, Kingham TP, Allen PJ, De Matteo RP, Fong Y, Jarnagin WR, D'Angelica MI. Detailed Pathologic Characteristics of the Primary Colorectal Tumor Independently Predict Outcome after Hepatectomy for Metastases. *Ann Surg Oncol* 2013; 20: 148–54.

67 Adam R, Bhangui P, Poston G, Mirza D, Nuzzo G, Barroso E, Ijzermans J, Hubert C, Ruers T, Capussotti L, Ouellet J-F, Laurent C, Cugat E, Colombo PE, Milicevic M. Is Perioperative Chemotherapy Useful for Solitary, Metachronous, Colorectal Liver Metastases? *Ann Surg* 2010; 252: 774–87.

68 Tan KK, Lopes Jr. G de L, Sim R. How Uncommon are Isolated Lung Metastases in Colorectal Cancer? A Review from Database of 754 Patients Over 4 Years. *J Gastrointest Surg* 2009; 13: 642–8.

69 de Ridder JAM, Knijn N, Wiering B, de Wilt JHW, Nagtegaal ID. Lymphatic Invasion is an Independent Adverse Prognostic Factor in Patients with Colorectal Liver Metastasis. *Ann Surg Oncol* 2015; 22: 638–45.

70 Saiura A, Yamamoto J, Koga R, Kokudo N, Seki M, Oya M, Ueno M, Kuroyanagi H, Fujimoto Y, Natori T, Yamaguchi T, Muto T. Outcome After Hepatic Resection of Solitary Liver Metastasis from Colorectal Cancer in the Caudate Lobe. *World J Surg* 2007; 31: 2378–83.

71 Altendorf-Hofmann A, Scheele J. A critical review of the major indicators of prognosis after resection of hepatic metastases from colorectal carcinoma. *Surg Oncol Clin N Am* 2003; 12: 165–92.

72 Pawlik TM, Scoggins CR, Zorzi D, Abdalla EK, Andres A, Eng C, Curley S, Loyer EM, Muratore A, Mentha G, Capussotti L, Vauthey J-N. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. *Ann Surg* 2005; 241: 715–22.

73 Poultsides GA, Schulick RD, Pawlik TM. Hepatic resection for colorectal metastases: the impact of surgical margin status on outcome. *HPB (Oxford)* 2010; 12: 43–9.

74 Tranchart H, Chirica M, Faron M, Balladur P, Lefevre LB, Svrcek M, de Gramont A, Tiret E, Paye F. Prognostic Impact of Positive Surgical Margins After Resection of Colorectal Cancer Liver Metastases: Reappraisal in the Era of Modern Chemotherapy. *World J Surg* 2013; 37: 2647–54.

75 Ekberg H, Tranberg KG, Andersson R, Lundstedt C, Hägerstrand I, Ranstam J, Bengmark S. Determinants of survival in liver resection for colorectal secondaries. *Br J Surg* 1986; 73: 727–31.

76 Pulitanò C, Bodingbauer M, Aldrighetti L, de Jong MC, Castillo F, Schulick RD, Parks RW, Choti MA, Wigmore SJ, Gruenberger T,Pawlik TM. Liver Resection for Colorectal Metastases in Presence of Extrahepatic Disease: Results from an International Multi-institutional Analysis. *Ann Surg Oncol* 2011; 18: 1380–8.

77 Carpizo DR, Are C, Jarnagin W, DeMatteo R, Fong Y, Gönen M, Blumgart L, D'Angelica M. Liver Resection for Metastatic Colorectal Cancer in Patients with Concurrent Extrahepatic Disease: Results in 127 Patients Treated at a Single Center. *Ann Surg Oncol* 2009; 16: 2138–46.

78 Elias D, Ouellet J-F, Bellon N, Pignon J-P, Pocard M, Lasser P. Extrahepatic disease does not contraindicate hepatectomy for colorectal liver metastases. *Br J Surg* 2003; 90: 567–74.

79 Chua TC, Saxena A, Liauw W, Chu F, Morris DL. Hepatectomy and resection of concomitant extrahepatic disease for colorectal liver metastases - A systematic review. *Eur J Cancer* 2012; 48: 1757–65.

80 Leonard GD, Brenner B, Kemeny NE. Neoadjuvant chemotherapy before liver resection for patients with unresectable liver metastases from colorectal carcinoma. *J Clin Oncol* 2005; 23: 2038–48.

81 Adam R, Wicherts DA, de Haas RJ, Aloia T, Lévi F, Paule B, Guettier C, Kunstlinger F, Delvart V, Azoulay D, Castaing D. Complete pathologic response after preoperative chemotherapy for colorectal liver metastases: myth or reality? *J Clin Oncol* 2008; 26: 1635–41.

82 Chua TC, Saxena A, Liauw W, Kokandi A, Morris DL. Systematic Review of Randomized and Nonrandomized Trials of the Clinical Response and Outcomes of Neoadjuvant Systemic Chemotherapy for Resectable Colorectal Liver Metastases. *Ann Surg Oncol* 2010; 17: 492–501.

83 Benoist S, Brouquet A, Penna C, Julie C, El Hajjam M, Chagnon S, Mitry E, Rougier P, Nordlinger B. Complete Response of Colorectal Liver Metastases After Chemotherapy: Does It Mean Cure? *J Clin Oncol* 2006; 24: 3939–45.

84 Gaujoux S, Goéré D, Dumont F, Souadka A, Dromain C, Ducreux M, Elias D. Complete radiological response of colorectal liver metastases after chemotherapy: what can we expect? *Dig Surg* 2011; 28: 114–20.

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CONFLICT OF INTEREST

I hereby declare that I have submitted the doctoral theses to the Otto-von-Guericke University Medical School at Magdeburg (Germany) entitled

"**Analysis of prognostic factors after resection of liver liver metastasis in colorectal cancer - a 22-year bicenter study**"

at the Department of General, Abdominal, Vascular and Transplant Surgery (Head Prof. Dr. R. S. Croner) with the support of Prof. Frank Meyer and Ms. Priv.-Doz. Altendorf-Hofmann without any other help and writing of the dissertation I used no other tools than the ones listed there.

During the writing of the dissertation rights of third parties were not violated.

So far, I have not submitted this dissertation to any German or foreign university for a doctorate. I transfer to the Faculty of Medicine the right to produce and distribute further copies of my dissertation.

Magdeburg, 26.March 2018

Signature

CURRICULUM VITAE

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ADDENDUM

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