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ORIGINAL ARTICLE

Determinants of survival after liver resection for metastatic colorectal carcinoma

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Summary

Purpose: *Prognostic factors for survival after liver resection for metastatic colorectal cancer identified up to date are quite inconsistent with a great inter-study variability. In this study we aimed to identify predictors of outcome in our patient population.*

Methods: *A series of 70 consecutive patients from the oncological hepatobiliary database, who had undergone curative hepatic surgical resection for hepatic metastases of colorectal origin, operated between 2006 and 2011, were identified. At 44.6 months (range 13.7-73), 30 of 70 patients (42.85%) were alive. Patient demographics, primary tumor and liver tumor factors, operative factors, pathologic findings, recurrence patterns, disease-free survival (DFS), overall survival (OS) and cancer-specific survival (CSS) were analyzed. Clinicopathologic variables were tested using univariate and multivariate analyses.*

Results: *The 3-year CSS after first hepatic resection was 54%. Median CSS survival after first hepatic resection was 40.2 months. Median CSS after second hepatic resection was 24.2 months. The 3-year DFS after first hepatic resection was 14%. Median disease free survival after first hepatic resection was 18 months. The 3-year DFS after second hepatic resection was 27% and median DFS after second hepatic resection 12 months. The 30-day mortality and morbidity rate after first hepatic resection was 5.71% and 12.78%, respectively. In univariate analysis CSS was significantly reduced for the following factors: age >53 years, advanced T stage of primary tumor, moderately-poorly differentiated tumor, positive and narrow resection margin, preoperative CEA level >30 ng/ml, DFS <18 months. Perioperative chemotherapy related to metastasectomy showed a trend in improving CSS (p=0.07). Perioperative chemotherapy improved DFS in a statistically significant way (p=0.03). Perioperative chemotherapy and achievement of resection margins beyond 1 mm were the major determinants of both CSS and DFS after first liver resection in multivariate analysis.*

Conclusions: *In our series predictors of outcome in multivariate analysis were resection margins beyond 1mm and perioperative chemotherapy. Studies on larger population and analyses of additional clinicopathologic factors like genetic markers could contribute to development of clinical scoring models to assess the risk of relapse and survival.*

Key words: *colorectal cancer, hepatic metastases, liver resection, prognostic factors*

Introduction

Advances in both surgical techniques and development of efficient chemotherapy regimens and targeted therapies, and of course multidisciplinary approach, have led to unprecedented improvement of the long-term survival of patients with hepatic metastases of colorectal cancer. Barely used 20 years ago, surgical resection of hepatic metastases became a standard approach mainly in specialized centers, and up to 20% of patients benefit from hepatic resection [1].

Substantial improvements have been documented also in the median survival of metastatic colorectal cancer since 1957 when 5-Fluorouracil was the sole agent used and the median survival did not exceed 6-8 months, irrespective of the administration schedule. The introduction of novel

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agents such as irinotecan and oxaliplatin brought median survival to 17-21 months [2-6]. Then, targeted therapies consisting of bevacizumab, cetuximab, panitumumab, and lately regorafenib and aflibercept increased it to values exceeding 24 months. Unfortunately, despite of all these advances, cure cannot be obtained using drug therapy alone [7-12].

Hepatic surgery is of paramount importance to further increase the prognosis of these patients who previously benefited only from chemotherapy. Surgical resection of hepatic metastases led to historical rates of 30-40% of 5-year OS. There are also a number of studies which demonstrate long-term OS (22-24%) at 10 years [13-15].

Methods

A series of 70 consecutive patients from the oncological hepatobiliary database were identified, who had undergone curative hepatic surgical resection for hepatic metastases of colorectal origin. All patients underwent hepatic surgery between 2006 and 2011 at the Institute of Gastroenterology and Hepatology, Cluj-Napoca, Romania. All 70 patients had pathologic confirmation of colorectal liver metastasis. Preoperative imaging included thoracic and abdomino-pelvic computed tomography in all patients, with oral and intravenous contrast. Intraoperative ultrasound was used in 22 patients (31.4%). All patients underwent curative hepatic resection during open laparotomy by a hepatobiliary surgeon. In 20 patients (28.5%) the Habib 4X bipolar resection device (1500X RF Generator) was applied to assist hepatic resection, inducing intraoperative coagulation of tissue during the surgical procedure.

The primary colorectal cancer was staged using UICC/AJCC staging system for colorectal cancer [16].

Synchronous liver metastases were defined as those detected within 3 months of diagnosis of primary colorectal cancer. The size of the liver lesion was measured by the pathologist in centimeters before fixation of the specimen. The Broder's system was used to histologically grade metastases. Surgical margins were defined by histology as either cancer negative or positive. The margin of resection was measured in millimeters by the pathologist before fixation of the specimen. Postoperative mortality was defined as death occurring in the hospital or within 30 days of resection. The anatomic distribution of liver lesions was defined by the Couinaud nomenclature [17].

The Brisbane 2000 terminology of liver anatomy and resections was used. Briefly, extended right hepatectomy (resection of IV + V + VI + VII + VIII ± I segments), extended left hepatectomy (resection of II + III + IV + V + VIII ± I segments), right hepatectomy (resection of V + VI + VII + VIII ± I segments), left hepatectomy (resection of II + III + IV ± I segments), bisegmentectomy (resection of 2 adjacent segments), or segmentectomy (resection of a single segment) were performed [18].

Endpoints

The endpoints of this study were OS DFS and CSS, and recurrence at the most recent follow-up evaluation. OS was defined as the time interval between the date of hepatic resection and the date of death or most recent date of follow-up if the patient was alive. CSS was defined as the time from hepatic resection to death from primary cancer. Patients who died in the postoperative period or during hospitalization after the fist hepatic resection were excluded from the survival analysis. Recurrence was defined as the time from hepatic resection to first documented disease recurrence in the liver or other sites. The criterion for establishing recurrent disease was radiologic evidence of progression. Recurrence in the liver was defined as a new lesion detected in the liver more than 1 month after hepatic resection; other extrahepatic recurrences were labeled as distant. DFS was defined as the time from hepatic resection to hepatic or extrahepatic recurrence.

Statistics

Patients were enrolled prospectively but the statistical analyses were retrospective. Patient demographics, primary tumor and liver tumor factors, operative factors, pathologic findings, recurrence patterns, median DFS, OS and CSS were analyzed. Survival was estimated using Kaplan-Meier analysis; differences in survival were assessed using the log-rank test. Differences in tumor recurrence rates between treatment groups were analyzed using the Student's t-test, and Yates corrections or Fisher exact test depending on the number of patients [19].

Two-sided tests were applied. Differences were considered to be statistically significant when the p value was <0.05. Finally the Cox proportional hazard model [20] was used in univariate and multivariate analysis for OS, DFS, and CCS.

Results

Patient population

All 70 patients with hepatic metastasis of colorectal origin were operated (curative hepatic resection) and followed at the Institute of Gastroenterology and Hepatology of Cluj-Napoca, Romania between January 2006 and December 2011. Fifty-three percent of the patients were male. The median patient age for the whole group was 59 years (range 34-85).

Primary tumor characteristics

The primary cancer was located in the colon

in 70% of the patients (right 9; transverse 4; left including sigmoid 34, multiple primaries 2) and in the rectum in 30% of them. At the time of initial presentation, 4 (5.7%) patients had stage I and 12 (17.1%) stage II colon cancer. Stage III represented the largest group with 23 patients (32.85%), while 31 (44.28%) patients had stage IV disease (synchronous metastases). Sixteen patients (22.85%) had well differentiated colorectal tumors, 43 (61.42%) moderately differentiated tumors and 11 (15.71%) poorly differentiated tumors. Carcinoembryonic antigen (CEA) was elevated in 31.78% of the patients at the time of metastases diagnosis, normal in 13.95%, and was not elevated preoperatively in 54.26%.

Liver metastases

Of the metastases 68.5% were unilateral, 31.5% were bilateral and there were 2 diagnoses with missing data; 46.51% were single lesions, 19.37% were 2 concomitant lesions, 32.55% were ≥3 hepatic lesions, and 2 had missing data.

Surgical resections

Fifty three of 70 patients (76%) underwent one hepatic resection, while 17 (24%) patients underwent 2 hepatic resections. Initial resectability was assessed as possible in 69.35% of cases, while in 30.65% the hepatic lesions were characterized as non-resectable. In this patient population 86 hepatectomies were performed. Of these, 20.93% were major hepatectomies, involving more than 3 segments. All 86 hepatectomies were with curative intent. Although each patient had macroscopically complete resection of the metastases, in 25 (29.07%) resections microscopically positive pathologic surgical margins were observed. Resection margin between 1 and 2 mm was found in 13 (15.11%) hepatic resections and > 3 mm in 48 (55.82%). The median number of metastases resected per patient was 1 (range 1–8). Median metastatic size was 3 cm. From the total 86 resections, in 39 (45.34%) blood transfusion was necessary perioperatively, but the frequency of blood transfusions has decreased over time. The mean number of blood transfusion units needed was 0.82 (mean 0; range 0-6 units).

Surgical morbidity and mortality

The 30-day mortality was 5.71%. Of the 4 deaths, 1 patient had minor and 3 patients had major liver resection. Causes of death were abdominal sepsis (1 patient), hepatic failure (2 patients), and bleeding from liver parenchyma (1 patient). One patient died after the first adjuvant chemotherapy cycle (capecitabine monotherapy 2500 mg/m^2, days 1-14), due to grade 5 gastrointestinal toxicity (diarrhoea with dehydration). The 30-day morbidity was 12.78%. Of 9 patients with postoperative complications, 2 had bile leak, 2 had hepatic abcess, 1 had hepatic and general complications (sepsis) and 4 had general complications (sepsis, hepatic failure).

Chemotherapy regimens

Of 70 patients, 18 benefited from neoadjuvant chemotherapy before hepatic resection, mainly fluoropyrimidine-based, with addition of oxaliplatin (7 patients) or irinotecan (3 patients). Only 6 of 18 benefited from targeted therapy: bevacizumab (4 patients), cetuximab (2 patients) because financial restrictions limited the approval of usage of these agents in our country. A total of 90 cycles were administered to these 18 patients. The mean number of cycles of neoadjuvant chemotherapy was 5/patient. The response rate to neoadjuvant chemotherapy was 61% using the RECIST. The rate of complete response was 5.6% (1 patient), of partial response was 55.5% (10 patients), while 27.8% (5 patients) had stable disease and 11.1% (2 patients) had progressive disease under chemotherapy.

Of the population of 70 patients, taking into account both the preoperative and postoperative chemotherapy, the mean number of chemotherapy cycles was 14.1 cycles/patient, with a total of 859 cycles administered to all patients. Ten (14.3%) patients did not have chemotherapy at all (5 because of patient refusal, 3 because of 30-day postoperative death, and 2 because of medical contraindications). Twelve (17.1%) patients had 1-6 perioperative chemotherapy cycles, 17 (24.3%) had 7-12 perioperative chemotherapy cycles, 16 (22.8%) had 13-18 perioperative chemotherapy cycles, and 9 (12,8%) had 19-24 perioperative chemotherapy cycles (Table 1).

There were 6 (8.7%) patients heavily treated with more than 24 chemotherapy cycles. As for the number of chemotherapy lines, 26% had one chemotherapy line, 21% had 2, 29% had 3, 7% had 4 and 3% had more than 5 chemotherapy lines (Table 2).

With regard to chemotherapy combined with bevacizumab, 12 of 70 patients (17.1%) were treated with FOLFOX+bevacizumab, 11 patients (15.7%) with CapeOx+bevacizumab, 4 patients (5.7%) with capecitabine+bevacizumab, 1 patient (1.4%) was treated with LV5FU2+bevacizumab and 1 (1.4%) patient

Table 1. Number of chemotherapy cycles preceding/following hepatic resection

Chemotherapy cycles	*Patients, N*	*%*
0	10	14.3
1-6	12	17.1
7-12	17	24.3
13-18	16	22.8
19-24	9	12.8
>24	6	8.7
Total: 859 cycles		
Mean : 14.1 cycles/patient		

Table 2. Number of chemotherapy lines preceding/following hepatic resection

Lines	*Patients, N*	*%*
1 line	18	26
2 lines	15	21
3 lines	20	29
4 lines	4	7
5 lines	1	1.5
6 lines	1	1.5
No chemotherapy	10	14

with bevacizumab monotherapy. As for cetuximab, 2 (2.8%) patients were treated with FOLFOX+cetuximab, 5 patients (7.1%) with irinotecan+cetuximab and 7 patients (10%) with cetuximab monotherapy. Two (2.8%) patients benefited from FOFLFIRI+panitumumab and 1 (1.4%) patient was included in a clinical trial with FOLFIRI+ramucirumab (Table 3).

Regarding the chemotherapy not combined with targeted agents, the following schedules were used: FOLFOX4 in 30 (42.8%) patients, FOLFIRI in 17 (24.2%) patients, CapeOx in 12 (17.1%) patients, CapeIri in 7 (10.0%) patients, Capecitabine in 9 (12.8%) patients, Irinotecan in 4 (5.7%) patients, LV5FU2 in 3 (4.2%) patients, FuFol in 1 (1.4%) patient, and other regimens (MTX, MMC, UFT) in 4 (5.7%) patients (Table 3).

Survival and recurrence

The median follow-up period was 44.6 months (range 13.7-73). At the end of the follow-up, as of June 2013, 30 (42.85%) patients were alive, of which 11 (15.71%) disease-free, 7 (10%) had hepatic metastases and 5 (7.14%) had extrahepatic ± hepatic metastases. Forty (57.14%) patients died, of which 4 died postoperatively (5.71%), 1 (1.42%) died during first cycle of adjuvant chemotherapy, and 2 (2.85%) died of cardiovascular causes.

The 4-year OS and CSS after colectomy were

Table 3. Types of chemotherapy preceding/following hepatic resection

Types of chemotherapy	*Patients, N*	*%*
Chemotherapy without targeted agents		
FOLFOX4	30	42.8
FOLFIRI	17	24.2
CapeOx	12	17.1
CapeIri	7	10.0
Capecitabine	9	12.8
Irinotecan	4	5.7
LV5FU2	3	4.2
FuFol	1	1.4
Other (MTX, MMC, UFT)	4	5.7
Chemotherapy with targeted agents		
FOLFOX4+bevacizumab	12	17.1
CapeOx+bevacizumab	11	15.7
Capecitabine+bevacizumab	4	5.7
LV5FU2 +bevacizumab	1	1.4
Bevacizumab	1	1.4
FOLFOX4 + cetuximab	2	2.8
Irinotecan + cetuximab	5	7.1
Cetuximab	7	10.0
FOLFIRI + panitumumab	2	2.8
FOLFIRI+ ramucirumab	1	1.4

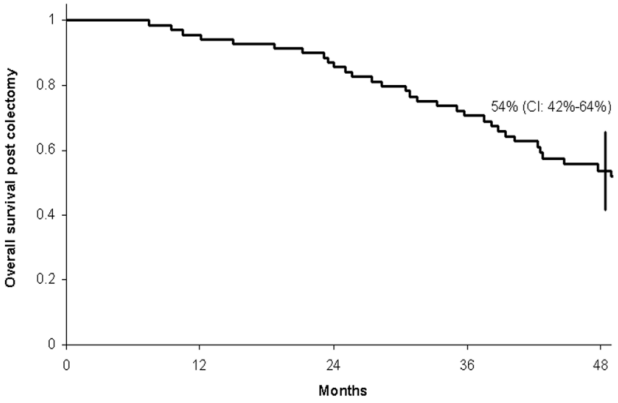

Figure 1. Overall survival of patients undergoing hepatic resection for colorectal metastases following colectomy.

54 and 60%, respectively (Figures 1 and 2).

The 3-year CSS after first hepatic resection was 54%. Median CSS after the first hepatic resection was 40.2 months (Figure 3).

Eighty six percent of patients developed liver recurrence or metastases located at other sites within 3 years of the first hepatic resection. The

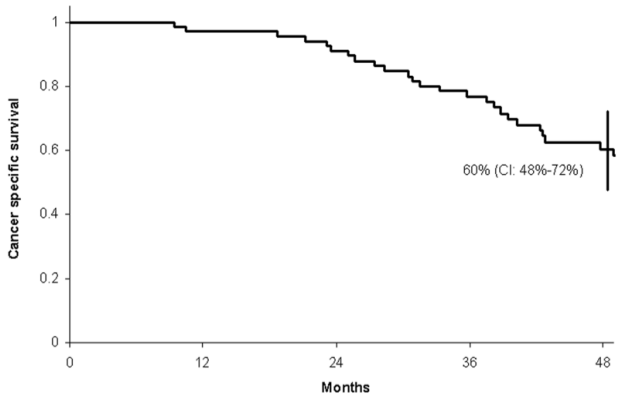

Figure 2. Cancer-specific survival of patients undergoing hepatic resection for colorectal metastases following colectomy

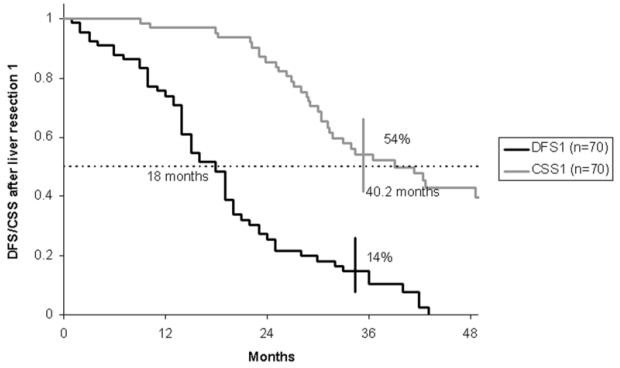

Figure 3. Median and 3-year disease-free survival (DFS) and cancer-specific survival (CSS) of patients undergoing hepatic resection for colorectal metastases after first hepatic resection.

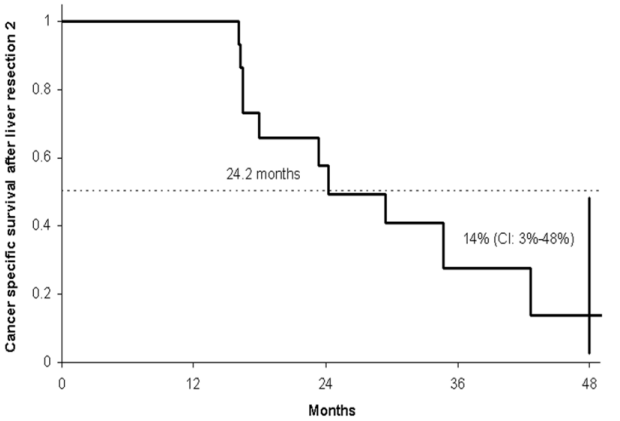

Figure 4. Median and 3-year disease-free survival and cancer-specific survival of patients undergoing hepatic resection for colorectal metastases after second hepatic resection.

Table 4. Risk factor analysis of clinical and pathologic factors of 3-year cancer-specific survival after first liver resection: Univariate analysis

Risk factors	*N*	*3-year CSS (%)*	*p value*
Gender			
Male	37	42	0.07
Female	33	66	
Age, years			
<53	17	68	0.04
≥53	53	49	
Primary tumor site			
Colon	49	50	0.44
Rectum	21	64	
Primary tumor stage			
I+II	16	67	
III	23	43	0.44
IV	31	56	
T stage			
T2	6	80	
T3	54	53	0.05
T4	10	38	
N stage			
N0	22	62	0.11
N+	48	51	
N ratio			
<30	42	58	0.07
≥30	28	50	
Tumor grade			
G1	16	67	0.05
G2-3	54	50	
Synchronous/metachronous metastases			
Synchronous	32	53	0.66
Metachronous	38	56	
Metastases' diameter (mm)			
<30	37	53	0.64
≥30	33	54	
Number of metastases			
Single	42	57	0.84
Multiple	28	51	
Positive resection margin (mm)			
0 mm	24	39	0.04
≥1mm	46	62	
Narrow resection margin (mm)			
0-1	44	36	<0.01
≥2	26	65	
Preoperative CEA level (ng/ml)			
<30	18	77	0.04
≥30	11	32	
Disease-free interval (months)			
<18	35	26	<0.01
≥18	35	82	
Perioperative chemotherapy			
Yes	56	60	0.07
No	14	23	

CSS: cancer specific survival

Table 5. Risk factor analysis of clinical and pathologic factors of disease-free survival after first liver resection: Univariate analysis

Risk factors	*N*	*3-year DFS (%)*	*p value*
Gender			
Male	37	7	0.11
Female	33	22	
Age, years			
<53	17	31	0.04
≥53	53	8	
Primary tumor site			
Colon	49	18	0.82
Rectum	21	13	
Primary tumor stage			
I+II	16	22	
III	23	11	0.82
IV	31	9	
T stage			
T2-3	60	17	0.36
T4	10	0	
N stage			
N0	22	15	0.98
N+	48	12	
N ratio			
<50	49	16	0.03
≥50	21	10	
Tumor grade			
G1-2	59	15	0.13
G3	11	10	
Synchronous/metachronous metastases			
Synchronous	31	11	0.54
Metachronous	39	17	
Metastases diameter (mm)			
<30	37	15	0.46
≥30	33	14	
Number of metastases			
Single	42	21	0.18
Multiple	28	5	
Narrow resection margin (mm)			
0-1	44	4	0.02
≥2	26	21	
Preoperative CEA level (ng/ml)			
<30	18	15	0.05
≥30	11	18	
Perioperative chemotherapy			
Yes	56	17	0.03
No	14	10	

DFS: disease free survival

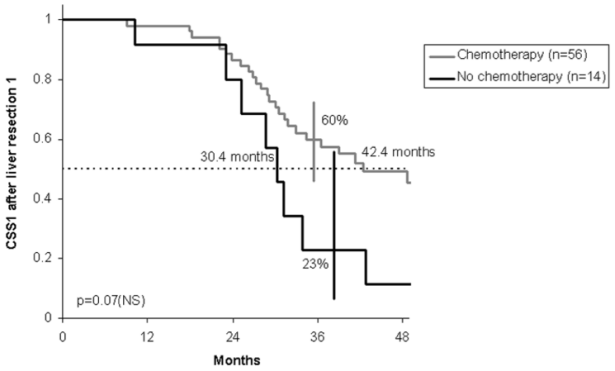

Figure 5. Cancer-specific survival after first liver resection with and without perioperative chemotherapy

distribution of site of recurrences or metastases was hepatic only in 33 (47.1%) patients, hepatic and extrahepatic in 13 (18.6%), and extrahepatic only in 14 (20%). Of the 33 hepatic relapses, 19 (57.57%) were resectable or were rendered to resectable using neoadjuvant chemotherapy. Of the 19 resectable patients, 2 refused repeat hepatic resection. In conclusion, 17 of 70 (24.28%) patients benefited of second hepatic resection. Extrahepatic recurrences were located in the peritoneum (12 patients; 17.14%), lung (9 patients; 12.85%), and other sites (7 patients; 10%). Four patients (5.71%) developed local recurrences or metachronous tumors located in the colon or rectum.

The CSS and DFS at 3 years following second liver resection was 35 and 27%, respectively. Median CSS and median DFS was 24 and 12 months, respectively (Figure 4).

Seventy three percent of patients developed recurrence within 3 years of the second hepatic resection. The distribution of sites of recurrence or metastases was in the liver only in 8 (47.05%) patients, hepatic and extrahepatic (retroperitoneal and cutaneous respectively) in 2 (11.77%) patients, and extrahepatic only (pulmonary) in 2 (11.77%) patients. Four patients (5.71%) remained disease-free at the end of the follow-up period.

Analysis of risk factors

All host and tumor factors were correlated to CSS and DFS (Tables 4 and 5). Patients who died postoperatively were excluded from risk analysis.

Univariate analysis

CSS was significantly reduced in connection with the following factors: age >53 years, T stage of the primary tumor, moderately-poorly differentiated tumor, positive and narrow resection margin (0-1 mm), preoperative CEA level > 30 ng/ml,

DFS <18 months (Table 4).

Perioperative chemotherapy improved CSS but not at a statistically significant level (p=0.07) (Figure 5).

Multivariate analysis

Multivariate analysis was performed on the factors correlating significantly to CSS and DFS in univariate analysis. Low DFS was significantly associated with narrow resection margins (0-1 mm) and lack of perioperative chemotherapy. The DFS hazard ratio was 4.82 in the presence of both these factors, 1.98 in the presence of narrow resection margin and 2.43 in the lack of perioperative chemotherapy. Low CSS was significantly associated with narrow resection margins (0-1mm) and lack of perioperative chemotherapy. The CSS hazard ratio was 7.11 in the presence of both these factors, 2.73 in the presence of narrow resection margin and 2.6 in the lack of perioperative chemotherapy.

Discussion

Herein we reported a single-institution experience on the hepatic resection of colorectal metastases with an average 44.6-month follow-up. Our study period spanned over 5 years. The actuarial 3-year CSS was 54%, which is consistent with the predicted survival of other large series [14-16,20-23].

Our study and numerous others have correlated a number of clinical, pathological, and interventional factors with OS, recurrence and DFS of patients with resected hepatic metastases from colorectal cancer by univariate and multivariable analyses [24-27].

Selection of patients for hepatic resection of colorectal metastases is likely to affect the consistency of the correlates to survival. There is a great variability between institutions and even in the same institution regarding the selection of patients for multidisciplinary approach. Selection criteria have broadened because now there is evidence supporting survival benefit for resection, perioperative risk has decreased, and the performance of imaging methods has improved. Nowadays surgery is a standard procedure and the only curative method of treatment. The decision to resect hepatic metastases is taken according to the definition of resectability which also has changed a great deal lately. Up-to-date criteria differ from center to center and require only preservation of a minimum 30% of functional liver tissue with adequate vascular supply and biliary drainage and 40% in case of cirrhosis [28]. Patients who have benefited from all therapeutic options have superior outcomes. Administration of preoperative chemotherapy allows also marginally resectable disease to be rendered resectable, and offering to patients the opportunity to attain long-term survival, response rate being correlated with resectability rate [29-31].

When chemotherapeutic agents are used (5 fluorouracil, oxaliplatin, irinotecan), response rate does not exceed 50% [32,33].

More intensive regimens which demonstrate a higher response rate are triplets like FOLFIRINOX (60%), and combinations of chemotherapeutic agents with targeted therapy (70%) [34-42].

Following hepatic resection, chemotherapy is used to improve DFS. There are few clinical trials conducted on patients with colorectal cancer following hepatic resection. Two trials were closed earlier due to poor accrual, two were negative and one was positive. The study conducted by Portier et al. [43] demonstrated a significant improvement in DFS, the one conducted by Langer et al. [44] failed to demonstrate such an effect, but the metaanalysis of both trials showed a trend to improved DFS and OS but without statistical significance (p=0.058). Multivariate analysis of the pooled data showed that chemotherapy is a statistically significant good prognostic factor [45]. Using multivariate analysis, our results show once again that chemotherapy is a significant prognostic factor for both CSS and DFS, as well as narrow resection margin.

Thus, there is no consensus about using adjuvant chemotherapy after curative hepatic resection and adjuvant chemotherapy is a treatment option after hepatic resection, especially in patients who did not receive preoperative chemotherapy. As for perioperative chemotherapy for resectable disease, the EORTC 40983 study compared perioperative chemotherapy (3 cycles of FOLFOX preoperatively and 3 cycles postoperatively) to surgery alone. The trial was negative in the intention-to-treat analysis with a strong trend to improved DFS (HR 0.79 [0.62-1.02], p=0.058). Using the common definition of progression-free survival for the patients actually resected, the results were positive, and the interpretation is that patients do benefit after perioperative chemotherapy [46].

Also a literature-based metaanalysis compared surgery alone with the combined approach consisting in any preoperative or postoperative

chemotherapy added to surgery and showed significant benefit for DFS, therefore it is considered that surgery alone is no longer acceptable even in case of resectable metastases [47].

For clarifying the aspect of neoadjuvant chemotherapy in resectable patients there are two trials going on: a NSABP (NCT01189227) and a German AIO study (NCT01266187) are randomizing resectable patients to perioperative vs postoperative chemotherapy; the first one uses FOLFOX-IRI/bevacizumab, the second FOLFOX/cetuximab.

Conclusion

Our univariate analysis identified a number of variables affecting outcome. Multivariate analysis showed that perioperative chemotherapy and the resection margin significantly affected survival. A major short-term objective in this field was the development of a generally accepted and validated scoring system with clinical utility to guide treatment decisions for physicians and assist them in patient counseling regarding prognosis and selection of postoperative chemotherapy schedules. An important fact is that after the introduction of perioperative chemotherapy different prognostic factors emerged. In the studies published up until now major differences in risk factors have been observed. This low concordance suggests that stratification of patients according to clinical and pathological factors alone is clinically unreliable. The most consistent finding of this study was that long-term survival is possible after curative liver resection and this is improved by perioperative chemotherapy and good quality surgery with negative resection margins.

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