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Oncology

Does the site of primary colorectal cancer influence the outcome after resection of isolated liver metastases?

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ABSTRACT

Introduction: In unresectable patients with metastatic colorectal cancer (CRC), the site of the primary is a strong prognostic factor warranting major adjustments in palliative medical treatment. Initial results suggested that the site of CRC influences prognosis after curative resection of colorectal liver metastases (CLM). In this study, we evaluated outcome after resection of isolated CLM with regard to the location of the primary.
Methods: 221 patients with macroscopically complete resection of CLM and no known extrahepatic disease were identified. 63 patients had right-sided and 158 had left-sided CRC. Tumors of the transverse colon and rectum were excluded. Survival was evaluated using the Kaplan–Meier method.
Results: Characteristics of CLM, primary tumor stage and chemotherapeutic regimens were not significantly different between the two groups. Kaplan–Meier five-year survival was comparable (41%) in patients with right- or left-sided CRC ($p = 0.64$). Microscopic resection margin, number of liver metastases, age and nodal status but not the site of the primary tumor significantly influenced survival.
Conclusion: The site of the colorectal primary in this well-defined group of patients after resection of isolated CLM did not prove to be of significant prognostic value. Whether the primary tumor in CLM is located on the left side or the right should not preclude patients from surgery.
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1. Introduction

Surgical resection plays an important role in the management of colorectal liver metastases (CLM). Numerous clinical, pathological and molecular factors have been identified as influencing the prognosis not only of colorectal cancer (CRC) per se but also after resection of CLM. A potentially worse prognosis in patients with right-sided location of the primary in non-metastasized cases was already described several years ago [1–5]. However, the concept that right-sided and left-sided CRC may represent different diseases or disease phenotypes (e.g. differences in embryologic origin, pathogenesis, genetic and molecular features) is relatively new [6,7]. Different outcomes between right- and left-sided CRC have been clearly demonstrated in recent chemotherapy studies for metastasized CRC [8,9]. The question may be raised whether this prognostic influence of the site of the primary CRC may also be found after resection of CLM. Different overall survival rates after resection of CLM in patients with right-sided primary CRC were recently reported from American Cancer Centers [9–11]

In this paper, we evaluated the outcome after more than 220 curative liver resections performed for isolated CLM in our institution since the year 2000, all with clearly-defined location of the primary CRC in the left or right colon.

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2. Patients and methods

2.1. Selection of patients for the study

Patients were identified from our surgical CLM database. For our study, we included only patients with first liver resection for isolated CLM performed between 2000 and 2016, site of the primary in the right or left colon (see below) and sufficient postoperative follow-up. Patients with rectal cancer or primary tumors in the transverse colon were not considered for this study. Patients with extrahepatic disease, repeat liver resections, macroscopic residual disease (R2-resection) or unclear resection margins (Rx) were also excluded from this analysis in order to obtain optimal prognostic information regarding the site of the primary CRC.

2.2. Chemotherapy

For the purpose of this study, only chemotherapies given or finished within 6 months before hepatic metastasectomy, including oxaliplatin and irinotecan (±targeted therapy), were defined as neoadjuvant chemotherapy (neoCTX) as described earlier by our group [12]. After neoCTx, a treatment-free interval of 4–6 weeks was required before surgery in our patients. In addition, the total length of (any) chemotherapy given before resection was evaluated.

2.3. Surgical technique

Intraoperative ultrasound of the liver was routinely performed. Parenchymal transection was generally carried out using cavitron ultrasonic aspiration (CUSA EXcel, Integra, New Jersey, USA) and (irrigated) bipolar forceps. The Pringle maneuver was not routinely employed in our patients. Resected specimens were always sent for intraoperative frozen section examination. If positive resection margins were found, margin re-resection was performed during the same surgery, if technically/anatomically feasible.

2.4. Definition of CRC location and liver resection

The primary colorectal carcinoma (CRC) was classified as right-sided when located in the cecum, ascending colon or the right colic flexure. CRC located at the left colic flexure, the descending colon or the sigmoid colon was classified as left-sided. For further subgroup and risk factor analysis, the extent of liver resection was categorized as minor (wedge resection or segmental resection; bi-segmentectomy) or major (hemihepatectomy/four anatomical segments or more).

2.5. Complications

Morbidity was evaluated for all complications and for surgical complications (with or without the need for re-intervention) for both groups. In-hospital mortality was also evaluated.

2.6. Statistics

All patient-related perioperative data were taken from our prospective CLM surgery database. Following exploratory data analysis, comparisons between groups were performed using X^2 test, Fisher's exact test or Mann–Whitney *U* test, where applicable.

Survival status was obtained from the comprehensive cancer center registry at our institution and/or from the computerized hospital information system. Overall survival was analyzed using the Kaplan–Meier method, followed by a log-rank test for the comparison of subgroups. Multivariate survival analysis was performed with the Cox proportional hazard model (forward selection strategy using a likelihood ratio statistic; inclusion *p*-value = 0.1) including the report of relative risks and their 95% confidence interval.

All data analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY; IBM Corp.).

Table 1
Demographic, surgical, pathological and postoperative data of 221 patients with right- or left-sided colorectal cancer undergoing hepatic resection for isolated colorectal liver metastasis.

	Right-sided primary CRC n = 63	Left-sided primary CRC n = 158	*p*
Age, years (median; range)	65 [39–82]	64 [33–85]	0.27
Male sex (n;%)	33 [52%]	101 [64%]	0.11
Metachronous hepatic metastasis (n;%)	26 [41%]	75 [48%]	0.40
Extent of resection			
Major	32 [51%]	86 [54%]	0.63
Minor	31 [49%]	72 [46%]	
N-status primary CRC			
N0	15 [25%]	52 [34%]	0.35
N1	23 [39%]	59 [39%]	
N2	21 [36%]	41 [27%]	
Max. tumor size in mm			
(Median; range)	30 [2–195]	33 [3–160]	0.64
(Mean ± SD)	44 ± 40	41 ± 27	
No. of metastases			
(Median; range)	2 [1–11]	2 [1–12]	0.53
(Mean ± SD)	2.0 ± 1.6	2.4 ± 2.2	
No. liver metastases I			
One	24 [47%]	67 [46%]	0.86
>one	27 [53%]	80 [54%]	
No. liver metastases II			
1–4	49 [96%]	133 [90%]	0.20
>4	2 [4%]	14 [10%]	
Hepatic margin			
Positive	9 [14%]	14 [9%]	0.23
Negative	54 [86%]	144 [91%]	
Any chemotherapy before liver resection			
Yes	34 [54%]	83 [52.5%]	0.85
No	29 [46%]	75 [47.5%]	
Duration of any chemotherapy in months			
(Median; range)	4.0 [1–12]	6.0 [1–24]	0.013
(Mean ± SD)	4.53 ± 2.49	6.18 ± 3.92	
Neoadjuvant chemotherapy			
Yes	19 [30.2%]	49 [31%]	0.90
No	44 [69.8%]	109 [69%]	
Duration of neoadjuvant chemotherapy in months			
(Median; range)	3.0 [1–12]	6.0 [1–22]	0.036
(Mean ± SD)	4.09 ± 3.05	6.02 ± 4.04	
Mortality (in hospital)	1 [1.6%]	2 [1.3%]	0.85
Any complication			
Yes	44 [69.8%]	74 [46.8%]	0.002
No	19 [30.2%]	84 [53.2%]	
Surgical complication			
Yes	34 [54%]	64 [40.5%]	0.069
No	29 [46%]	94 [59.5%]	

3. Results

3.1. Basic demographic, oncological and perioperative data

Table 1 shows the basic demographic, operative and oncological data of patients undergoing liver resection for isolated colorectal liver metastases depending on the location of the primary (colonic) carcinoma. The subgroups of patients with right-sided or left-sided primary tumor showed no significant/relevant difference

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