

Synchronous and metachronous colorectal liver metastases: impact of primary tumor location on patterns of recurrence and survival after hepatic resection

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Abstract. *Background:* Considerable differences in terms of prognosis exist between the right-sided (RCC) and the left-sided colon cancer (LCC). *Aim of the work:* In this study, we evaluated prognostic implications of primary tumor location (PTL) among patients who underwent curative-intent hepatectomy for synchronous (SM) and metachronous (MM) colorectal liver metastases (CRLM). *Methods:* The study population included all consecutive patients affected by CRLM scheduled for first liver resection at three Italian oncological centers. *Results:* A total of 204 patients who underwent CRLM resection were included, 50% with RCC. Synchronous lesions were prevalent (n=133, 65%). Median OS was respectively 40.3 months for SM-RCC, 53.5 months for SM-LCC, 64.5 months for MM-RCC and 81.6 months for MM-LCC. Patients with MM-LCC showed an OS better than patients with SM-RCC (p=0.008) and SM-LCC (p=0.002). PTL had no influence on RFS. RCC group had less recurrences (75% vs 86.5%), though further surgery with curative-intent was possible more in LCC group (29.3% vs 32.5%). Cox proportional hazards model analysis showed that age and the presence of SM vs MM was associated with a significantly higher hazard ratio (HR) for death (HR=1.024; 95%CI=1.005-1.043; p=0.011 and HR=2.010; 95%CI=1.328-3.043; p=0.001, respectively). *Conclusions:* We confirmed that patients with CRLM and right-sided primary colon cancer experience worse survival after hepatic resection. The timing of metastasis has been revealed as important prognostic factor.

Keywords: colorectal cancer, liver metastases, hepatectomy, synchronous metastases, metachronous metastases, primary tumor, outcome.

Introduction

In Europe, colorectal carcinoma (CRC) is the second most commonly diagnosed cancer and a leading cause of death (1). Recently, many studies investigated the impact of primary tumor location (PTL) on the prognosis of patients affected by colorectal

cancer (CRC). Survival outcome of the right-sided colon cancer (RCC) is significantly worse than the left-sided colon cancer (LCC). Embryologically, the proximal two-thirds of the transverse colon and the caecum derives from the midgut, while the section of colon from the distal third of the transverse up to rectum arises from the hindgut (2). However, considering

that both of them derive from the endoderm, it does not seem that only the different embryological origin can explain a divergent clinical impact. It is well established that RCC and LCC display a different pattern of gene expression. RCC have been shown to be associated with an increase in RAS, BRAF and TGF β R2 mutations, CpG island methylator phenotype (CIMP), high microsatellite instability (MSI-high) (3–5). On contrary, mutations in the APC, KRAS, SMAD4 and TP53 genes, overexpression of the epidermal growth factor receptor (EGFR) ligands, epiregulin (EREG) and amphiregulin (AREG), and amplification of EGFR and human epidermal growth factor receptor 2 (HER2) occur more often in LCC (2,4,6,7). Another interesting factor are immunological differences. In fact, knowing that microbiome is largely varied in the entire gastrointestinal system, it has been suggested that also the immunological activity could be different in LCC and RCC. In the study of Kwak et al. (8), it has been demonstrated that the peripheral blood of patients affected by RCC was richer of mucosal-associated invariant T (MAIT) than LCC. MAIT cells are a T cell subset with tissue-homing properties. Importantly, the patients displaying a higher recruitment of MAIT cells in their tumor, as compared with the neighboring healthy tissue, showed a less favorable clinical outcome (9). Moreover, it has been reported that also the tumor-infiltrating lymphocytes (TILs) are more represented in the RCC (10). Furthermore, from a clinical point of view, these two entities show other differences: RCC are more often undifferentiated, are diagnosed in older women and with peritoneal metastases as compared to LCC, which, on the contrary, are frequently characterized by liver and lung metastasis (6).

Less is known about the outcome of patients who undergo curative-intent hepatectomy for synchronous (SM) and metachronous (MM) colorectal liver metastases (CRLM). Creasy et al. (11) reported that among patients undergoing resection of CRLM, LCC were associated with better median overall survival (OS). However, long-term survival and recurrence-free survival (RFS) were not significantly different stratified by primary location. On contrary, Sasaki et al. (12) showed that LCC had a worse RFS after CRLM, but a better OS than RCC. Furthermore, the prognostic

difference between synchronous (SM) and metachronous (MM) liver metastases exist. Synchronous liver metastases are detected either pre- or intra-operatively, or in a six month period postoperatively. In contrast, metachronous liver metastases were diagnosed at least six months after the primary tumor removal and are prognostically associated with better outcome (13). In patients with resectable or potentially resectable metastatic liver disease, a radical resection of the primary tumor and liver metastases may offer a chance of cure to some patients. Among patients eligible for surgery, different strategies have been developed: the “classical strategy” (primary colon cancer first), the “reverse strategy” (liver metastases first) and the “simultaneous” strategy (14). A recent meta-analysis showed similar long-term survival for simultaneous or delayed resection of SM (15).

In the present study, we evaluated the prognostic implications of primary tumor location among patients who underwent curative-intent hepatectomy for synchronous and metachronous colorectal liver metastases.

Materials and methods

Patients and follow-up

A total of 204 consecutive patients who underwent curative-intent surgery for CRLM between 2008 and 2017 in three Italian oncological centers (University Hospital of Parma, University Hospital of Modena, Sant’Orsola University Hospital of Bologna) were retrospectively reviewed using electronic medical records. RCC is derived from the embryologic midgut, including the proximal two-thirds of the transverse colon, ascending colon, and cecum. LCC is derived from the embryologic hindgut, which includes the distal third of the transverse colon, splenic flexure, descending colon, sigmoid colon, and rectum. We considered SM detected either pre- or intra-operatively, or in a six month period postoperatively. In contrast, MM were defined as those diagnosed six months after the operation for the primary lesion. The study protocol was approved by the ethics committee which was in accordance with the Declaration of Helsinki and Good Clinical Practice.

Statistical analysis

The patients were divided into groups, according to PTL (RCC vs LCC) and according to the presence of SM and MM CRLM. Clinicopathologic and long-term survival data were collected and reviewed to explore the prognostic implication of PTL in patients with SM and MM CRLM. OS was calculated from the date of colon cancer diagnosis to the date of death or date of the last follow-up. RFS was calculated from the date of liver surgery to the date of disease recurrence. Moreover, we calculated specifically also OS from the date of the liver surgery to the date of death or date of the last follow-up (OS-CRLM). RFS, OS and OS-CRLM curves were constructed using Kaplan-Meier method, and differences were analyzed using log-rank (Mantel-Cox) test. A Cox proportional hazards model analysis was performed to determine the joint association of several clinical factors investigated (sex, age at the diagnosis, primary tumor location and the presence of SM/MM). The p value was bilaterally tested, and values less than 0.05 were regarded as statistically significant.

Results

Study population, pattern of recurrence, surgery of recurrence

Of 204 patients who underwent a liver surgery for CRLM, 132 (64.7%) were males and 72 (35.3%) were females. 102 patients (50%) had a primary tumor located on the right-side and 133 patients (65.2%) patients presented at the diagnosis with SM. The median age for RCC-SM was 61 years (range 38 – 84 years), for LCC-SM 61.5 years (range 38 – 78 years), for RCC-MM 65.5 years (range 45 - 83 years) and LCC-MM 63 years (range 41 – 80 years). Clinicopathological characteristics of the 204 patients are detailed in Table 1.

The pattern of recurrence differ between the LCC and RCC group. 75 out of 100 RCC patients (75%) had a recurrence, compared to 83 out of 96 LCC patients (86.5%). In the right-sided group, the recurrence rate of 75 patients with extrahepatic, liver-limited and

Table 1. Clinico-pathological characteristics of the patients

Characteristics		n (%)
Sex	Male	64.7%
	Female	35.3%
Age (years) ^a	RS	62 (38-84)
	LS	60 (38-78)
	RM	64 (45-83)
	LM	62 (41-80)
Primary tumor location ^b	R	50%
	L	47.5%
KRAS mutant ^c	WT	36%
	Mutant	39%
NRAS mutant ^d	WT	57%
	Mutant	1%
BRAF mutant ^e	WT	35%
	Mutant	2%
Synchronous or metachronous metastases	S	65.2%
	M	34.8%
Right or left with synchronous or metachronous metastases	RS	35.3%
	LS	29.9%
	RM	17.2%
	LM	17.6%
Relapse after liver resection ^f	No relapse	18.6%
	Relapse	77.5%
Dead or alive ^g	Dead	54.9%
	Alive	41.2%

^a Age was available for 96.% of patients only

^b Primary tumor location was available for 97.5% of patients only

^c KRAS analysis was available for 75% of patients only ^d NRAS analysis was available for 58% of patients only ^e BRAF analysis was available for 37% of patients only

^f Relapse after liver resection was available for 96.1% of patients only

^g Dead or alive was available for 96.1% of patients only

widespread disease was (30.7%), (52%) and (17.3%), respectively. In the left-sided group, out of 83 patients, 25 patients (30.9%) had extrahepatic recurrence, 35 (43.2%) had intrahepatic recurrence and 21 (25.9%) both extrahepatic and intrahepatic one, in 2 patients this data are unknown. Further surgery with curative-intent was possible in the right-sided group in 22 patients (29.3%). In the left-sided group, in 26 patients (32.5%) further curative-intent surgery was possible.

Relapse-free survival, overall survival and overall survival after CRLM

Median RFS was not significantly different between the groups of RCC-SM, RCC-MM, LCC-SM and LCC-MM (Fig. 1). A trend toward statistical significant difference could be seen between LCC-SM and RCC-SM ($p=0.072$). Median RFS for the whole group was 12 months (95% CI 10.2 – 13.8). In particular, 15.1 months (95% CI 10.8 – 19.4) for RCC-SM, 9.2 months (95% CI 6 – 12.3) for LCC-SM, 11.9 months (95% CI 6.9 – 16.9) for RCC-MM and 13.3 months (95% CI 9.7 – 16.8) for LCC-MM.

Median OS for the whole group was 57.7 months (95% CI 48.3 – 67.1). In particular, 40.3 months (95% CI 35.8 – 71.2) for SM-RCC, 53.5 months (95% CI 35.8 – 71.2) for SM-LCC, 64.5 months (95% CI 44.9 – 83.9) for MM-RCC and 81.6 months (95% CI 58.7 – 104.3) for MM-LCC. Patients with MM-LCC showed an OS significantly better than patients with SM-RCC ($p=0.008$) and SM-LCC ($p=0.002$), as demonstrated in Fig. 2.

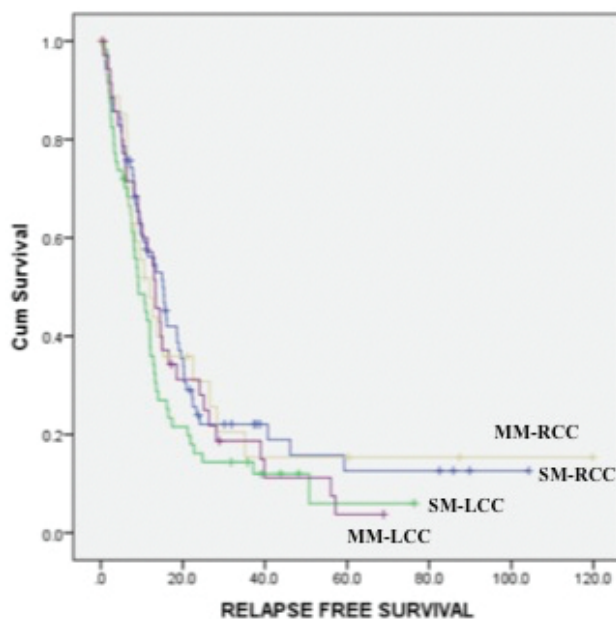


Figure 1. Relapse-free survival in patients after curative-intent surgery for liver metastases from colorectal cancer

Median RFS was not significantly different between the groups of RCC-SM, RCC-MM, LCC-SM and LCC-MM. A trend toward statistical significant difference could be seen between LCC-SM and RCC-SM ($p=0.072$).

Overall survival after the first liver surgery did not show statistically significant differences between the groups. Median OS for the whole group was months 43.7 (95% CI 38.2 – 49.1). In particular, 35.8 months (95% CI 21.2 – 50.5) for SM-RCC, 44.1 months (95% CI 34.3 – 53.9) for SM-LCC, 40.3 months (95% CI 27.3 – 53.2) for MM-RCC and 53.3 months (95% CI 40.7 – 65.8) for MM-LCC. No statistically significant differences were described between the groups (a. 3).

Prognostic factors of overall survival

On multivariate analyses, cox proportional hazards model analysis showed that age and the presence of SM vs MM was associated with a significantly higher hazard ratio (HR) for OS (HR=1.024; 95%CI=1.005-1.043; $p=0.011$ and HR=2.010; 95%CI=1.328-3.043; $p=0.001$, respectively).

Discussion

Our study showed that the patients' outcome after CRLM depends on PTL and the timing of metastasis.

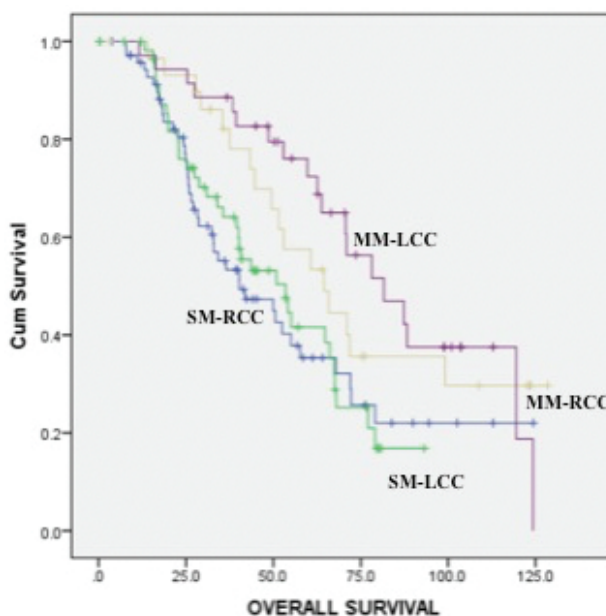


Figure 2. Overall survival

Patients with MM-LCC showed an OS significantly better than patients with SM-RCC ($p=0.008$) and SM-LCC ($p=0.002$).

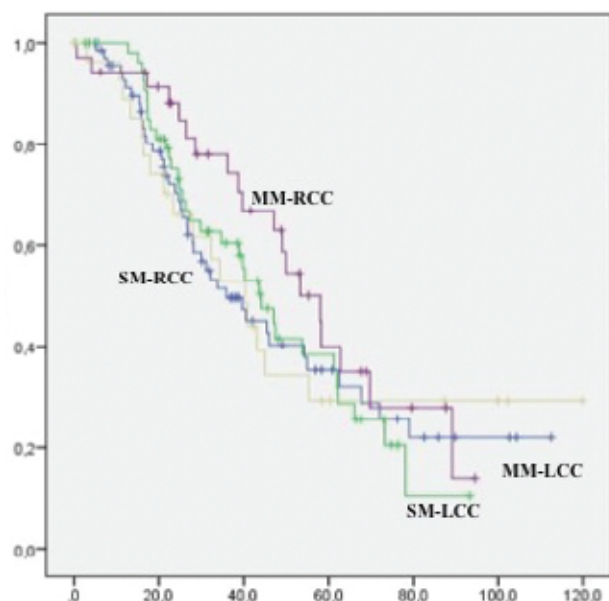


Figure 3. Overall survival in patients after curative-intent surgery for liver metastases from colorectal cancer

Overall survival after the first liver surgery did not show statistically significant differences between the groups.

The best outcome showed the patients with MM-LCC, followed by MM-RCC, SM-LCC and finally, the worse outcome experienced the patients with SM-RCC. The outcome of MM-LCC is doubled compared to SM-RCC. It has become widely accepted that CRC is no longer viewed as a unique pathological entity because of the considerable differences in terms of prognosis between the RCC and the LCC location. Survival outcome of RCC patients is significantly worse than LCC. Petrelli et al. (16) published a meta-analysis of 66 studies, including more than 1.000.000 patients. In this study, LCC were associated with a better OS compared to RCC, and this result was independent of stage, even if, results are conflicting for different tumor stages (17,18). Given that the RCC and LCC are embryologically distinct organs, different pathways may be involved in the neoplastic development of CRC based on anatomic location (12). Higher rate of BRAF and KRAS mutations, CpG island methylation and ERCC1 expression in RCC (19) might be responsible for less responsiveness to chemotherapy and targeted therapy (20). Moreover, RCC are more commonly characterized by high microsatellite

instability, high CpG island methylation (CIMP), which are also associated with poor response to chemotherapy (21). Infact, Yamashita et al. described worse PFS and worse OS after liver resection, whether they had pre-operative chemotherapy or not (22).

Liver is the most common site of CRC metastases. About one third of patients develop liver metastases, but only 10-30% are usually eligible to undergo liver resection due to the extent of the disease (23,24). Liver surgery remains the only potentially curative treatment for CRLM, with 10-year OS rates up to 16% (25). Unfortunately, around 75% of patients will develop disease recurrence within 2 years (26). Controversial data have been reported focusing on radically resected CRLM [11,22,27]. In several studies, patients with CRLM from RCC have been associated with worse OS, but conflicting results exist regarding RFS (11,22,23,28-30). Dupre' et al. (27) analysed prospectively collected data from 376 consecutive patients who underwent liver surgery for CRLM and compared the outcomes of patients with RCC and those with LCC. Median PFS was not significantly different between the two groups and median OS was shorter for patients with RCC (34.6 vs 45.3 months, $p = 0.035$). In concordance with our study, right-sided location of the primary tumor after CRLM is associated with worse OS, but seems to have no influence on PFS. These findings could suggest that the PTL should not change surgical decision-making. Similarly, Sasaki et al. (12) showed that after liver resection, the OS following recurrence was shorter in patients with RCC. In our study we described that the pattern of recurrence differs significantly between the LCC and RCC: RCC group had less recurrences (75% vs 86.5%), though further surgery with curative-intent was possible more frequently in LCC group (29.3% vs 32.5%). Similar results were published by Russolilo et al. (29). The authors conducted a study of 995 patients who undergo surgery for CRLM: in concordance with our study, the rate of re-resection was lower in RCC patients (27.9% vs. 37.5%). In fact, RCC seems to recur less frequently, but more aggressively.

Timing of metastasis is a controversial prognostic factor for patients with metastatic CRC. SM and MM liver metastases from CRC are characterized by a different gene expression signature (31).

Approximately 15-25% of patients with CRC are diagnosed with SM and another 10-20% develop MM (32,33). Colloca et al. (34) investigated the outcome of the patients by the timing of metastases and also different tumor characteristics associated with SM and MM. The patients with SM reported a poor prognosis (18.5 vs 62.5 months). The results from our study show similar data: the worse outcome experienced the patients with SM-RCC, followed by SM-LCC and MM-RCC and, finally, MM-LCC. Moreover, in our study, on multivariate analyses, the presence of SM were associated with worse patients' outcome. According to some authors, the role of chemotherapy seems to be more important in SM since they are more chemosensitive and chemo-naïve (34,35). This hypothesis is supported by the higher overall responses rates reported among patients with SM – CRLM (36). Considering different responsiveness to chemotherapy, PTL and timing of metastasis might be stratifying factor in trials evaluating peri-operative management of patients candidate to liver surgery for CRLM (27).

To the best of our knowledge, any previous study had evaluated the role of both PTL and the timing of metastasis. In our study, we confirmed the importance of both parameters for patients' prognosis. The median OS for SM-RCC remained the most severe and therefore these patients should be considered for different treatment approaches.

Our study has different limitations. As a retrospective analysis, it is subject to bias in selection, follow-up and missing data, even if we analysed prospectively reported consecutive patients who underwent surgery for CRLM. Furthermore, many pathological variables such as MSI status and KRAS/NRAS and BRAF status mutation are available for all patients, as well as tumor differentiation, lymphatic and venous invasion, histological subtypes as well clinical data are not available for all patients.

Conclusions

We confirmed that the patients with CRLM and right-sided primary colon cancer experience worse survival after hepatic resection than left-sided CRC

patients. Moreover, the timing of metastasis has been revealed as important prognostic factor, with special attention to SM-RCC who are characterized by the worse clinical outcome.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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