Impact of primary tumor location on patterns of recurrence and survival of patients undergoing resection of liver metastases from colon cancer

IMPACT OF PRIMARY TUMOR LOCATION ON PATTERNS OF RECURRENCE AND SURVIVAL OF PATIENTS UNDERGOING RESECTION OF LIVER METASTASES FROM COLON CANCER

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Abstract

Background: Several studies have described a worse prognosis for right-sided colon cancer compared to left-sided. However, results are conflicting for different tumor stages. The aim of the study was to compare survival and patterns of recurrence following resection of liver metastases from right-sided colon cancer (RS-LM) versus left-sided (LS-LM).

Patients and Methods: Patients undergoing first resection for colon cancer LM between 2000 and 2017 were analyzed. Tumors of the cecum, ascending, and transverse colon were defined as right-sided; tumors of the sigmoid flexure, descending, and sigmoid colon were defined as left-sided. Rectal cancer, multiple primaries and unknown location were excluded.

Results: Out of 995 patients, 686 fulfilled inclusion criteria (RS-LM=322, LS-LM=364). RS colon cancer had higher prevalence of metastatic lymph nodes (67.4% vs. 57.1%; P =0.008). RS-LM were more often mucinous (16.8% vs. 8.5%, P=0.001) and poorly differentiated (58.3% vs. 48.9%, P=0.014). After a median follow-up of 81 months, 451 (65.7%) patients experienced recurrence (RS-LM 49.2% vs. LS-LM 50.8%). In RS-LM group, recurrence was more often encephalic (2.3% vs. 0%; P= 0.029) and at multiple sites (34.2% vs. 23.5%; P=0.012). The rate of re-resection was significantly lower in RS-LM patients (27.9% vs. 37.5%; P = 0.024), also considering only liver recurrences (22.9% vs. 37.6%, p=0.012). Multivariate analysis showed RS-LM to have lower rates of five-year overall (35.8% vs. 51.2%, P=0.002) and disease-free survival (26% vs. 43.6%, P=0.002).

Conclusions: RS-LM were more often mucinous and poorly differentiated compared with LS. RS-LM is associated with worse survival and aggressive rarely re-resectable recurrences.

INTRODUCTION

Over recent years, many studies investigated the impact of primary tumor location on the prognosis of patients affected by colon cancer (CC) showing that right-sided (RS) have worst prognosis in comparison with left-sided (LS) [1]. In 2017, Petrelli et al.[1] published a meta-analysis of 66 studies, including more than 1.000.000 patients. Regardless of the stage, LS colorectal cancers were associated with a mortality rate of less than 20% compared to RS colorectal cancer. However, results are conflicting for different tumor stages. Weiss et al.[2] showed that RS colorectal cancer have respectively lower mortality in stage II and higher mortality in stage III compared to LS. Similar results have been reported by Hutchins et al[3] and Zhang et al.[4]. These findings seem to be explained by different molecular features expressed in stage II and III. RS colorectal cancer in stage II have more commonly microsatellite instability that is associated to lower metastatic spread [5,6] and consequently better prognosis, compared to LS colorectal cancer. By contrast, in stage III, RS colorectal cancer have higher rates of BRAF mutations which significantly reduce overall survival (OS) rates[7]. Regarding stage IV, 2 recent studies[8,9], analyzed the results of 6 trials (CRYSTAL, FIRE-3, CALGB 80405, PRIME, PEAK e 20050181) including patients with unresectable KRAS wild-type liver metastases (LM) who underwent chemotherapy associated with monoclonal antibodies. The Authors stated that the negative impact of RS was maintained in the metastatic lesions. Furthermore, radiological response to preoperative chemotherapy appeared to be significantly lower in RS-LM[8,9]. The prognostic impact of the primary tumor site in patients undergoing liver resection for colorectal metastases, is largely unknown. Even if some Authors identified worsen OS and disease-free survival (DFS) in patients with resected RS-LM compared to LS-LM, these data were not confirmed, or only partially confirmed in other studies[10-13]. This study was designed to compare survival and pattern of recurrences of patients who underwent resection for liver metastases from RS versus LS colon cancers in a tertiary center.

PATIENTS AND METHODS

The study population included all consecutive patients affected by colorectal LM scheduled for first liver resection between 01/2000 and 12/2017. Tumors of the cecum, ascending, and transverse colon were defined as right-sided (RS); tumors of the sigmoid flexure, descending, and sigmoid colon were defined as left-sided (LS). Rectal cancer, multiple primaries and unknown location were excluded. Preoperative and intraoperative data, pathological findings, short and long-term outcomes were compared between the two groups, with special attention to pattern of recurrences.

Management of patients

The management of patients with colorectal liver metastases at our Institution has been previously reported[14-15]. Briefly, the preoperative staging for all patients included a total colonoscopy and thoraco-abdominal computed tomography (CT). Hepatic magnetic resonance imaging was regularly performed in patients receiving preoperative chemotherapy and in patients with uncertain diagnosis. Positron emission tomography (PET)-CT was performed in selected patients with multiple bilobar LM synchronous to the primary tumor, simultaneous extrahepatic disease, or uncertain extrahepatic lesions. In recent years, KRAS mutations at codons 12 and 13, NRAS and BRAF mutation were tested. Chemotherapy before liver resection was administered to initially unresectable patients (conversion therapy) and to selected resectable patients (neoadjuvant chemotherapy) if they met the following criteria: 4 or more CRLM, simultaneous extrahepatic disease or possibility to perform more conservative LR after tumor shrinkage. In such cases, a short treatment was scheduled (4–6 cycles) and surgery was planned at response. The treatment strategy was systematically planned by a multidisciplinary committee. Surgery was scheduled only if complete resection (R0/R1) was achievable. Portal vein occlusion (PVO) was performed if the estimated future remnant liver volume was ≤ 25 % in patients with a normal liver and ≤30 % in those with intensive preoperative chemotherapy[16,17]. CT-scan and CT liver volumetry were performed 4 weeks after PVO. Liver resection was performed afterword sufficient hypertrophy had occurred. PVO was performed at least 30 days after interruption of chemotherapy and 40 days after administration of the last dose of

bevacizumab. Intraoperative liver ultrasonography was routinely performed to stage the liver metastases and to guide liver resection.

Follow-up of all patients was performed every 3 months and included carcinoembryonic antigen levels, and abdominal ultrasonography or thoraco-abdominal CT. Follow-up was performed by outpatient clinics or by contacting the general practitioner of the patients, and it was updated to March 2017 or at the time of death.

Definitions

The radiological tumor response was classified according to the RECIST criteria[18]. Types of hepatectomies were classified according to the Brisbane 2000 terminology[19]. Major hepatectomy was defined as the resection of 3 or more Couinaud's segments. Morbidity included all postoperative complications and was graded according to the Dindo-Clavien classification[20]. Complications of grade III or higher were defined as major morbidity. Operative mortality was defined as death within 90 days after surgery or before discharge from the hospital. R1 resection was defined as surgical margin<1mm. The diagnosis of mucinous adenocarcinoma was based on the World Health Organization criteria, i.e., a mucinous component of more than 50%.[21]

Statistical Analysis

Patients were identified from a prospectively maintained database and retrospectively analyzed. All statistical analysis was performed with IBM SPSS Italy (v20.1). Categorical variables were compared using the chi square test or Fisher's exact test, as appropriate. Continuous variables were compared between groups using the unpaired t test or Mann-Whitney U test, as appropriate. The Kaplan-Meier method was used to estimate survival probabilities, which were compared using the log-rank test. Multivariate analysis was performed using a Cox proportional hazard model to identify independent prognostic factors of OS and DFS after LR. All P values were two-sided, and values of $P < 0.05$ were considered statistically significant.

Disease-free survival was measured from the date of hepatic resection until the date of radiographic detection of recurrence or last follow-up. Overall survival was measured from the date of hepatic resection until the date of death or last follow-up.

RESULTS

Overall, among 995 patients undergoing a first LR for colorectal LM (Figure 1) at the authors institution between 2000 and 2017, 686 fulfilled inclusion criteria: 322 patients with liver metastases from RS colon cancer (RS-LM group) and 364 patients with liver metastases from LS colon cancer (LS-LM group).

Patient characteristics and tumor details

Table 1 summarizes patient characteristics. The two groups were similar in terms of sex, BMI and ASA score. LS-LM was associated with younger median age (63 years vs. 66 years; p<0.001). RS-LM patients had higher prevalence of metastatic lymph nodes of primary tumor (67.4% vs. 57.1%; P =0.008) compared with LS-LM group. The mutational status was assessed respectively in 209 patients for KRAS (85 RS-LM vs. 124 LS-LM); 181 patients for BRAF (109 RS-LM vs. 72 LS-LM) and 188 patients for NRAS (111 RS-LM vs. 77 LS-LM). The rate of KRAS mutation was slightly higher in RS-LM group (52.94% vs. 39.51), but the difference was not statistical significant (p=0.055).

The median number of liver metastases were 2 and median size 3 cm in both groups. Almost half of patients had bilobar liver metastases, without differences in the two groups. The presence of synchronous extrahepatic diseases were diagnosed in a similar proportion of patients (RS-LM 21.4% vs. LS-LM 17.8%), mainly lung and distant lymph-nodes metastases.

Chemotherapy details (Table 2)

Perioperative chemotherapy was administered to 86.8 % of patients (n = 596), including patients who received chemotherapy preoperatively only (n = 178, 25.9%), postoperatively only (n = 167, 24.3%), and both (n = 251, 36.6%). No differences on administration of chemotherapy and type of preoperative chemotherapy were observed between the two groups. Progression disease while on

preoperative chemotherapy occurred slightly more common in RS-LM group (9.9% vs. 5.3%; P = 0.075).

Intraoperative details and pathological findings

Major hepatectomy was performed in 81 (25.2%) patients of RS-LM group and 81 (22.3%) patients of LS-LM group. One patient died in each group, in both cases because of severe postoperative liver failure. Overall morbidity and major morbidity were similar in the two groups (RS-LM 29.8% and 9.3% vs. LS-LM 32% and 6.9%). R1 resection was performed in a similar proportion of patients (RS-LM 14.1% vs. LS-LM 15.7%). Liver metastases from RS-LM were more often mucinous (16.8% vs. 8.5%, P=0.001) and poorly differentiated (58.3% vs. 48.9%, P=0.014). (Table 2)

Survival Analysis

After a median follow-up of 81 months, both the median OS (RS-LM 35.7 months; 95% IC 29.1-42.2 vs. LS-LM 63.3 months 95% IC 47.5-79.0) and median DFS (RS-LM 20.8 months 95% IC 17.2-24.4 vs. LS-LM 32.7 months 95% IC 16.9-48.5) were worsen in RS-LM group. Five- and ten-years OS (Figure 2) were 35.8% and 18.3 % for RS-LM and 51.2% and 35.1% for LS-LM ($p<0.001$), respectively. Three- and 5-year DFS (Figure 3) were respectively 36.8% and 26% in RS-LM patients and 49.6% and 43.6% in LS-LM patients ($p<0.001$). There were 202 patients treated between 01/2000 and 03/2008. 39 (19.3%) of them were disease free with a significant higher proportion in LS-LM group (26.3% vs. 12.6%, P=0.019).

Recurrence Site and Treatments

Table 3 summarizes pattern of recurrence in both groups. 451 (65.7%) patients experienced recurrence (RS-LM 49.2% vs. LS-LM 50.8%). In RS-LM patients, recurrence was more often encephalic (2.3% vs. 0%; P= 0.029) and at multiple sites (34.2% vs. 23.5%; P=0.012). The rate of re-resection was significantly lower in RS-LM patients (27.9% vs. 37.5%; P = 0.024). This finding was confirmed also considering liver-limited recurrences (22.9% vs. 37.6%, p=0.012).

Prognostic factors for overall survival and disease free survival

The differences in OS and DFS by primary location was adjusted for known prognostic clinicopathologic variables and the results of the multivariable model are in Table 4. Controlling for these factors, the HR for death and recurrence in patients with a RS-LM were 1.474 (1.154-1.883, p = 0.002) and 1.397 (1.125- 1.735, p=0.002) respectively, compared with the LS-LM group. Node-positive primary tumour (p=0.006), more than 3 metastases (p=0.001), positive margin for hepatectomy (p<0.001) and presence of resectable extrahepatic disease (p<0.001), had a negative impact as well on OS. The DFS was negatively affected also by node-positive primary tumour (p=0.029) and more than 3 metastases (p<0.001).

DISCUSSION

Several studies have described a worse prognosis for right-sided colon cancer compared to left-sided. [1-4,22] However, controversial data have been reported focusing on radically resected colorectal cancer liver metastases.[10–13] The aim of the study was to compare survival and pattern of recurrences of patients who underwent resection for liver metastases from RS versus LS colon cancers in a tertiary center. Our results showed that RS-LM were associated with lower OS (35.8% vs. 47.1%) and DFS (20.5% vs. 30.8%) at 5 years compared with LS-LM. In several studies, RS-LM have been associated with lower OS[10–12], but conflicting results exist regarding DFS [10–12]. In particular, Creasy et al.[11] showed similar DFS in contrary with our data and Yamashita et al [10]. The Authors[11] stated that these different results may be explained by the different follow-up time: 11 years in their study and almost 3 years in Yamashita et al[20]. Nevertheless, our results confirmed the negative impact of RS-LM on DFS, despite a follow-up of 7 years.

The worse survival of RS-LM patients could be related to greater aggressiveness of metastatic right-sided colic tumors, which is confirmed by the higher rate of lymph-node metastases of primitive tumors, a lesser degree of differentiation and a more common mucinous histology of liver metastases. All these characteristics impact negatively on OS and DFS. Lymph nodes involvement represents an important prognostic factor in patients with non-metastatic colon-rectal cancer[23]

Furthermore, recent studies confirmed these data also in patients with resected metastatic disease.[24,25] In particular, Ozawa et al [25] showed that lymph node metastases may influence the probability of survival, but also the extent of the metastatic liver disease and the rates of re-resection in case of recurrence. Our multivariate analysis confirmed the negative impact of lymph nodes metastasis on OS and DFS. In 2017 Fonseca et al.[26] showed that differentiation grade of liver metastases was associated with worst survival (both OS and DFS) and higher incidence of extrahepatic recurrences. The Authors reported that the highest degrees of differentiation were associated with a greater peri-tumoral inflammatory cell infiltration as well the absence of pseudocapsule. Both these histological features indicate a more aggressive and invasive tumoral phenotype.

In a previous case-control study conducted in our center[27], we compared the results of 102 patients surgically treated for mucinous LM with as many non-mucinous LM. Data showed that mucinous histology was associated with worst rates of OS (33.2% vs. 55.2%) and DFS (32.5% vs. 21.0%) at 5 years. Furthermore, the mucinous histology was more common in RS-LM, it was associated to reduced chemotherapy response and an increased expression of KRAS gene mutations. In our series, KRAS mutation had higher prevalence in RS-LM, but the difference did not reach statistical significance, probably due to the small number of patients with KRAS status assessed. Yamashita et al.[10] confirmed the higher prevalence of KRAS mutations in RS-LM in a series of 725 patients.

RS-LM recurrences not only occurred earlier, but more frequently involved multiple sites (34.2% vs. 23.5%). Brain metastases have been developed only in the RS-LM group who also presented a double chance of developing bone metastases, compared with LS-LM. These data justified the lower rate of redo-resection (27.9%) in comparison with LS-LM (37.5%). Similar results were also found considering only the patients with liver recurrences; only one fourth of RS-LM patients with liver recurrences underwent to radical resection against 38% of LS-LM patients. It is interesting to note that in the study of Creasy et al [11] the OS from the date of recurrence was significantly worse

in RS-LM patients, although DFS rate was similar. These data could probably be the consequence of the greater aggressiveness of RS-LM recurrences that we identified in our study.

The present study presents some limitations. First, it was a retrospective analysis, even if data were collected prospectively. KRAS and BRAF mutational status were only available in a small number of patients, conclusive data require a larger population analysis.

Furthermore, the population of resected CLM patients was extremely selected. Probably, an *intention-to-treat analysis* could highlight furthers differences between RS-LM and LS-LM patients.

In conclusion, our results showed that RS-LM were more frequently mucinous and poorly differentiated compared with LS-LM. RS-LM was associated with worse OS and DFS and aggressive recurrences. During the follow-up, patients with RS-LM have higher chances to develop multiple recurrences and recurrence located in rare sites (e.g. bones, brain). These findings show that RS-LM patients may need a tailored management, including an accurate preoperative selection, administration of adjuvant chemotherapy and an intensive follow-up protocol which may require the planning of PET in case of suspicious to early detect extrahepatic recurrences.

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Figure legend

Figure 1. Patient selection.

Figure 2. Overall survival after liver resection for right-sided and left-sided colon cancer. RS-LM liver metastases from right-sided colon cancer; LS-LM liver metastases from left-sided colon cancer;

Figure 3. Disease free survival after liver resection for right-sided and left-sided colon cancer. RS-LM liver metastases from right-sided colon cancer; LS-LM liver metastases from left-sided colon cancer;