Title

Synchronous metastatic colon cancer and the importance of primary tumor laterality - A National Cancer Database analysis of right- versus left-sided colon cancer.

Journal

American journal of surgery, 220(2)

ISSN

0002-9610

Authors

Zhao, Beiqun
Lopez, Nicole E
Eisenstein, Samuel
et al.

Publication Date

2020-08-01

DOI

10.1016/j.amjsurg.2019.12.002

Peer reviewed

HHS Public Access

Author manuscript

Am J Surg. Author manuscript; available in PMC 2021 August 01.

Published in final edited form as:

Am J Surg. 2020 August ; 220(2): 408–414. doi:10.1016/j.amjsurg.2019.12.002.

Synchronous metastatic colon cancer and the importance of primary tumor laterality – A National Cancer Database analysis of right- versus left-sided colon cancer

Beiqun Zhao[*], **Nicole E. Lopez**, **Samuel Eisenstein**, **Gabriel T. Schnickel**, **Jason K. Sicklick**, **Sonia L. Ramamoorthy**, **Bryan M. Clary**

Department of Surgery, University of California, San Diego, United States

Abstract

Background—The role of laterality for patients with synchronous metastatic colon cancer (SMCC) is not well-defined.

Methods—Using the National Cancer Database (2010–2015), we compared patients with metastatic right- (RCC) versus left-sided colon cancer (LCC). We performed Kaplan-Meier analysis to compare overall survival (OS) for each metastatic site and utilized adjusted Cox proportional hazard analysis to identify predictors of OS.

Results—Patients with RCCs were more likely to be older, female, and have more comorbidities. LCCs were more likely to metastasize to liver and lung, whereas RCCs were more likely to metastasize to peritoneum and brain. There was equal likelihood to metastasize to bone. OS was significantly longer for LCCs for all metastatic sites. After controlling for multiple variables, RCC (HR 1.426, $p < 0.001$) remained an independent predictor of worse OS compared to LCC.

Conclusions—Laterality of the primary tumor plays an important role in outcomes for patients with SMCC.

Keywords

Colon cancer; Metastatic; Laterality; NCDB; Outcomes

Introduction

Colorectal cancer is the fourth most common cancer diagnosis in the United States, resulting in approximately 50,000 deaths annually.[1] Of the patients with newly diagnosed colorectal cancer, up to 25% will present with metastatic disease, and up to 50% will develop metastatic disease in the future.[2,3] Until recently, metastatic disease has been considered incurable and associated with poor overall survival.[1] However, while overall survival for these patients continue to be far shorter than for patients without metastatic disease, it has improved in recent years due to both advances in chemotherapy and shifting paradigms in the indications for metastastectomy.[4–6] Therefore, it has become increasingly important to identify patients with metastatic disease who would benefit from more aggressive treatment.

[*] Corresponding author. 9300 Campus Point Drive, MC 7220, La Jolla, CA, 92037, United States. markzhao@ucsd.ed (B. Zhao).

In recent years, it has also been recognized that not all colon cancers are the same. One key distinguishing feature may be laterality (e.g. right-sided versus left-sided). This distinction is based on both the differential embryologic origin (the right colon arising from the midgut, while the left colon arising from the hindgut) and vascular supply (the right colon is supplied by the superior mesenteric artery while the left colon is supplied by the inferior mesenteric artery) of the right and left colon. In addition, other studies have demonstrated a variety of notable genetic and histologic differences between right and left colon cancers.[7–10]

Given these differences, one would expect unequivocal evidence showing disparities in outcomes based on laterality, with right-sided tumors having worse survival. However, previous literature in non-metastatic colon cancer has shown conflicting results. In patients with non-metastatic colon cancer, some population-based studies have suggested no difference or better survival for right-sided tumors.[11–13] Conversely, two meta-analyses showed that survival is worse for patients with right-sided colon cancer.[14,15] For patients with synchronous metastatic colon cancer (SMCC), the role of laterality in patient outcomes is also not well-defined, with most studies limited to single-institution experiences and showing conflicting results.[16–18] In this study, we aim to compare the patient, disease, and treatment factors between synchronous metastatic right-sided and left-sided colon cancer using a large national database. We hypothesize that patients with right-sided SMCC will have worse overall survival compared to patients with left-sided tumors.

Materials and methods

Patients were identified in the National Cancer Database (NCDB), a national oncology outcomes database that is jointly sponsored by the American College of Surgeons' Commissions on Cancer (CoC) and the American Cancer Society. The NCDB contains clinical oncology data sourced from over 1,500 CoC-accredited centers and represents >70% of newly diagnosed cancer cases nationwide. Using the NCDB, all patients with synchronous metastatic colon adenocarcinoma diagnosed from 2010 to 2015 were identified. Because the NCDB only contains de-identified patient information, this study was exempt from institution review board approval.

The primary tumor was identified as adenocarcinoma by International Classification of Disease for Oncology histology codes (8140–8145, 8210, 8211, 8220, 8221, 8255, 8261–8263, 8310, 8323, 8330–8332, 8480, 8481, 8490, 8525, 8530, 8570–8574). The right colon was defined as cecum through transverse colon, and the left colon was defined as splenic flexure through sigmoid colon. The location of the split was based on embryologic origin, vascular supply, and the convention used by previous studies comparing laterality in colon cancer.[3,10,16,17,19]

Variables were selected due to clinical significance and availability within NCDB. Survival time was defined as the number of months from diagnosis. As per NCDB, patient age was defined as the age of the patient at the time of diagnosis. Charlson-Deyo Comorbidity Score was reported as 0, 1, or ≥2. Primary tumor grade was dichotomized into low-grade (i.e. well-differentiated, moderately-differentiated) versus high-grade (poorly-differentiated, undifferentiated/anaplastic). Signet ring and mucinous histology of the primary tumor was

identified. In addition, the presence of KRAS mutation or microsatellite instability of the primary tumor was also identified. Treating center type was dichotomized into academic versus non-academic centers (e.g. community cancer program, comprehensive community cancer program, integrated network cancer program). The number of lymph nodes examined was dichotomized into <12 lymph nodes versus ≥12 lymph nodes, as per current treatment guidelines.[20] The presence of positive lymph nodes was also identified. Patients receiving any type of chemotherapy was identified. Patients who underwent resection of their primary tumor was identified. Patients who underwent resection of a distant secondary tumor site, excluding those who had lymph nodes resected, were considered as receiving surgery of their metastatic site. Lastly, patients with synchronous liver, lung, peritoneum, bone and brain metastasis at the time of diagnosis was identified.

Statistical analysis

Comparison of primary right-colon cancer (RCC) versus left-colon cancer (LCC) was organized into patient-related factors, disease-related factors, and treatment-related factors. We tested for significance by the Mann-Whitney U and Fisher's exact tests for numerical and categorical variables, respectively. Kaplan-Meier with log-rank testing was performed to compare the median overall survival of patients stratified by metastatic site. We performed an unadjusted Cox proportional hazard analysis with all clinically relevant predictors except for resection margin status, as this variable requires the primary tumor to be resected. In addition, unknown categories were included for tumor grade, KRAS mutation, and microsatellite instability variables. In order to identify independent predictors of overall survival (OS), we performed Cox regression analysis. Predictors that are potential confounders of OS and with clinical significance were selected for unadjusted analysis. An adjusted model was then constructed from the unadjusted model with inclusion criteria set at p-value <0.20. All metastatic sites were forced into the adjusted model. Kaplan-Meier analysis and Cox regression analysis was also performed for a subset of patients who underwent surgery of the primary sites, surgery of the non-primary site, and received chemotherapy. Patients with missing data were excluded from statistical analysis. All statistical analyses were performed using SPSS (IBM Corp, Version 24, Armonk, NY). All statistical tests were two-sided, and level of statistical significance was set at 0.05 for all analyses.

Results

A total of 356,628 patients with RCC and LCC were identified. Of these, 57,663 (16.2%) patients had SMCC. Table 1 shows a comparison of patient-related, disease-related, and treatment-related factors between RCC versus LCC. Compared to RCC, patients with LCC were significantly younger ($p < 0.001$) and less likely female ($p < 0.001$, OR = 0.83). There were also a higher proportion of Asian and Pacific Islander patients with LCC (RCC = 2.2%, LCC = 4.1%), while there were more black patients with RCC (RCC = 17.3%, LCC = 15.2%). In addition, there were more patients with Charlson/Deyo Score of 1 or ≥2 in the RCC group.

Of the 220,514 patients with RCC, 33,080 (15.0%) had SMCC. Of the 136,114 patients with LCC, 24,553 (18.0%) had SMCC. Patients with LCC were significantly more likely to have any metastasis compared to patients with RCC (OR = 1.25, $p < 0.001$). Specifically, of patients with SMCC, patients with LCC were more likely than RCC to metastasize to the liver and lung (OR = 1.21 and OR = 1.15, respectively; $p < 0.001$ for both). Conversely, patients with LCC were less likely to metastasize to the peritoneum and brain (OR = 0.84 and OR = 0.84; $p < 0.001$ and $p = 0.014$, respectively). There was no significant difference in metastasis to bone (OR = 0.996, $p = 0.929$). Patients with LCC were significantly less likely to have signet ring histology (OR = 0.47, $p < 0.001$), mucinous histology (OR = 0.62, $p < 0.001$), KRAS mutation ($p < 0.001$, OR = 0.55), microsatellite instability ($p = 0.68$ $p < 0.001$), high-grade tumor (OR = 0.53 $p < 0.001$), and to be pathologic stage T4 (OR = 0.82 $p < 0.001$).

Patients with LCC were more likely to be treated at an academic center (OR = 1.09 $p < 0.001$) and to receive chemotherapy (OR = 1.42 $p < 0.001$). Patients with LCC were less likely to have their primary tumor resection (OR = 0.91 $p < 0.001$), but there was no significant difference in the resection rate of the metastasis (OR = 1.040, $p = 0.056$). Patients with LCC were also less likely to have ≥12 lymph nodes examined (OR = 0.77, $p < 0.001$) and to have positive lymph nodes (OR = 0.75, $p < 0.001$). There were no significant differences in negative resection margin status (OR = 1.037, $p = 0.165$).

Fig. 1 shows the Kaplan-Meier survival curves of the different metastatic sites stratified by primary tumor laterality. Median OS for patients with primary LCC was significantly longer than patients with RCC for liver metastases (21.9 months, 95% CI 21.4–22.4 versus 13.0 months, 95% CI 12.7–13.3; $p < 0.001$), lung metastases (16.3 months, 95% CI 15.5–17.1 versus 10.4 months, 95% CI 9.9–10.9; $p < 0.001$), peritoneal metastases (15.9 months, 95% CI 15.2–16.5 versus 11.4 months, 95% CI 11.0–11.8; $p < 0.001$), bone metastases (8.3 months, 95% CI 7.0–9.6 versus 5.4 months, 95% CI 4.9–5.9; $p < 0.001$), and brain metastases (5.8 months, 95% CI 4.0–7.5 versus 4.6 months, 95% CI 3.9–5.3; $p = 0.044$). Unadjusted and adjusted Cox proportional hazard analysis is shown in Table 2. A total of 12,664 (22.0%) patients were excluded from the adjusted analysis due to missing data. In the adjusted analysis, we found that despite controlling for multiple predictors, RCCs continued to be associated with worse OS compared to LCCs (HR = 1.257, 95% CI 1.229–1.286, $p < 0.001$).

In patients who underwent primary site resection, metastasectomy, and chemotherapy, the median OS for patients with primary LCC continued to be significantly longer than patients with RCC for liver metastases (43.5 months, 95% CI 41.6–45.4 versus 30.1 months, 95% CI 28.6–31.6; $p < 0.001$), lung metastases (32.9 months, 95% CI 29.5—36.4 versus 21.6 months, 95% CI 19.6–23.5; $p < 0.001$), and peritoneal metastases (30.7 months, 95% CI 28.5–32.9 versus 23.0 months, 95% CI 21.7–24.2; $p < 0.001$). There was no difference in survival for bone metastases (13.9 months, 95% CI 4.9–22.8 versus 11.6 months, 95% CI 8.5–14.7; $p = 0.831$) and brain metastases (15.7 months, 95% CI 1.2–30.1 versus 16.8 months, 95% CI 10.8–22.8; $p = 0.592$). However, this analysis maybe limited by the low number of patients (115 patients with bone metastases and 68 patients with brain

metastases). In adjusted Cox regression analysis (Table 3), RCCs continued to be associated with worse OS compared to LCCs (HR = 1.375, 95% CI 1.282–1.475, p < 0.001).

Discussion

To our knowledge, this study represents the largest modern series of patients with SMCC in the United States. In this analysis, we find that there are marked differences between patients who present with synchronous metastasis from right-versus left-colon tumors. Patients with synchronous metastatic RCCs tend to be older, female, and have higher Charlson/Deyo comorbidity scores. They are also more likely to metastasize to the peritoneum and brain, while patients with synchronous metastatic LCCs are more likely to metastasize to the liver and lung. Patients with synchronous metastatic RCCs were more likely to have signet ring and mucinous histology, KRAS mutation, microsatellite instability, and high-grade tumors. Patients with synchronous metastatic RCCs were less likely to be treated at an academic center but were more likely to have their primary tumor resected. In addition, patients with RCCs were more likely to have ≥12 lymph nodes examined but were more likely to have positive lymph nodes. Despite having more adverse prognostic factors, patients with synchronous metastatic RCCs were less likely to receive chemotherapy (at a surprisingly low rate of 67.6%) and radiation therapy. For each metastatic site analyzed, patients with RCC had significantly shorter OS compared to patients with LCC. In addition, after controlling for multiple predictors, RCC continued to be associated with worse OS, suggesting that there remain additional contributors to its poor prognosis. These findings were consistent when analyzing a subset of patients received aggressive therapy, including resection of the primary site, resection of the non-primary site, and receiving chemotherapy.

Our findings are consistent with previous studies, which utilized national and international databases, that show patients with RCC tend to be older, female, have more comorbidities, and exhibit histologic and genetic features associated with poor prognosis (i.e. signet ring histology, KRAS mutation).[9,11,21–23] However, in contrast to previous studies, our study also outlines the metastatic patterns of RCC versus LCC. We found that patients with LCC are more likely to metastasize overall, and specifically, more likely to metastasize to the liver and lung, which are the two most common sites of metastasis for colon cancer.[3] This finding may be explained by the pathologic differences between RCC and LCC, in which LCCs are more likely to be infiltrating and phenotypically more aggressive.[21,24] In contrast, RCCs are more likely to metastasize to the peritoneum. This may be partially explained by the increased prevalence of mucinous and signet ring histology, both of which have been implicated to increase the risk for peritoneal metastasis.[25,26] In addition, given the current understanding of the pathophysiology of peritoneal metastasis, patients with deep tumor invasion (i.e. pathologic stage T4 tumors), have a higher risk of developing peritoneal metastasis.[27] In our study, patients with RCC were significantly more likely to have pT4 disease. The pathophysiology for these differential metastatic properties by laterality is beyond the scope of the current study, but likely represents tumor biology considerations and not anatomical issues.

In our study, we found that no matter the metastatic site, overall survival was significantly worse for patients with RCC compared to LCC. This finding suggests the need to consider

more aggressive utilization of systemic therapy to prevent the development of metastatic disease in patients with right-sided colon cancer, though previous studies have suggested that RCCs are more resistant to conventional systemic therapy.[28] Alternatively, because LCCs are more likely to metastasize overall, it may be prudent to more aggressively surveil these patients in order to detect metastatic disease earlier. Lastly, these differential outcomes may play a role in how we treat patients with SMCC, especially in patients with peritoneal metastases who are under consideration for cytoreductive surgery.[29]

There were also some notable differences in the treatment of SMCC. LCCs were significantly more likely to be treated at an academic center compared to RCCs. The differences in referral patterns of patients with RCC and LCCs are not well-defined and may warrant further research. However, a previous study has suggested that high-volume centers, which tend to be academic centers, have higher rates of metastastectomy and chemotherapy utilization.[30] However, the role of hospital volume in survival for patients with SMCC is not well-defined.

In addition, it was also surprising that while approximately 60% of synchronous RCC and LCC patients had their primary tumors resected, only approximately 20% had a metastasectomy. There are several potential explanations for this apparent discrepancy. A significant proportion of these patients likely underwent palliative resection of their primary site, which some have suggested may lead to improved outcomes.[31] Alternatively, a certain proportion of patients may have had a planned “colon-first” approach, but never completed the liver resection. However, the actual proportion of patients that fit this scenario is not well-defined in the literature.

Surprisingly, in our analysis, only 67.6% of patients with RCC, and only 74.8% of patients with LCC, received any chemotherapy. While this unexpectedly low rate of utilization may be due to data-reporting errors, this rate is consistent with previous studies using both the NCDB and the Surveillance, Epidemiology, and End Results databases.[30,32] Alternatively, this low utilization rate may be due to the fact that patients with RCC, compared to LCC, tend to present with more advanced oncologic disease[9] and more comorbidities.[11,21] In addition, as previously mentioned, the belief that metastatic RCCs are more resistant to conventional chemotherapy than LCCs may further discourage patients and clinicians to utilize chemotherapy for metastatic RCCs.[28] While these factors may have contributed to the lower rate of chemotherapy in the RCC group compared to the LCC group, it should be noted that the chemotherapy rate in the LCC group was still surprisingly low at about 75%. Studies to further elucidate the reason behind the low utilization rate of chemotherapy in patients with SMCC is needed.

Patients with RCC were more likely to have positive lymph nodes than patients with LCC. While this may be because RCCs are often diagnosed at more advanced T stages and/or its predilection for lymphovascular invasion,[9] it may also be because patients with RCCs are more likely to have at least 12 lymph nodes examined and are, therefore, more often properly staged compared to patients with LCCs. This finding, a phenomenon seen in previous studies,[33,34] is not fully understood but may be related to the higher concentration of lymph nodes in the ileocolic region.[34] Alternatively, another explanation may be that

patients with LCCs are at higher risk for obstruction, which may necessitate emergency surgery where an adequate lymph node dissection is not a priority (especially in patients with known metastatic disease).

In our adjusted, it was unsurprising that increasing age, increasing comorbidity, high-grade tumor, signet ring or mucinous histology, and positive lymph nodes were all associated with worse overall survival. However, positive KRAS mutation was associated with statistically significant worse OS than negative KRAS mutation, its effect size was small, underlying the need to better define the role of KRAS testing and targeting in the treatment of patients with metastatic colon cancer.[35,36] The role of microsatellite instability is also controversial in patients with metastatic disease.[37,38] In our adjusted analysis, it was not a significant predictor of overall survival. Of the metastatic sites, bone metastasis had the highest hazard ratio, signifying its poor prognosis as seen in other studies.[39] Lung metastasis had the lowest hazard ratio among the metastatic sites. This phenomenon has been seen in other studies, in which the presence of lung metastasis or lung metastasis-associated variables were not prognostic for overall survival.[19] This may be due to improvements in the treatment of patients with pulmonary metastasis from colon cancer.[40] It was surprising to find that the presence of positive lymph nodes was associated with *improved* OS on unadjusted analysis. This may have been because patients with positive lymph nodes were more likely to receive more aggressive therapies, leading to improved OS. However, once other factors were controlled for in adjusted analysis, the presence of positive lymph nodes became associated with worse OS. This finding emphasizes the importance of adjusted analysis in retrospective analyses. Lastly, despite controlling for multiple variables, the presence of right-sided primary SMCC was still associated with worse overall survival. This finding suggests that there are still other factors that are contributing to the worse overall survival in these patients which are not accounted for in this model.

Our findings confirmed our hypothesis that patients with synchronous metastatic RCCs have significantly worse prognosis compared to patients with LCCs. When compared to LCC patients, the characteristics of RCC patients with synchronous metastatic disease are similar to those in non-metastatic patients. However, the importance of laterality in the non-metastatic patient population has been controversial, with some studies suggesting no difference or better survival in RCC patients.[11–13] A potential explanation is that the role of laterality becomes more pronounced as the disease advances, resulting in little or no difference in early-stage disease, and large differences in late-stage disease. This finding has been suggested in previous studies,[16] and would explain why the evidence for poorer outcomes are much stronger in metastatic RCCs than for non-metastatic RCCs. In addition, a single-institution study consisting of only patient with liver metastases found no difference in OS between RCC and LCC.[18] However, this study is limited by its sample size and generalizability. In our study, RCCs continued to be associated with worse OS despite controlling for the presence of liver metastasis. Further research is warranted to further define the role of laterality in patients with specific metastatic sites.

Limitations

Limitations to this study includes its retrospective nature. We are limited by the data collected in the NCDB, which restricted our ability to test other potential predictors in metastatic colon cancer (i.e. BRAF mutations). Disease-specific survival and recurrence data are also not currently available in the NCDB. We excluded patients with missing values. While statistical techniques such as imputation can be used to combat missing data, we expect the large sample sizes in our cohorts to provide reliable statistical interpretations. The retrospective nature of our study also does not allow us to evaluate the complex decision-making process that takes place in the treatment of these complicated patients. Therefore, treatment bias of may have affected outcomes, though we attempted to control for this by including treatment variables in our adjusted analysis. Given the use of neoadjuvant systemic therapy for patients with colon metastases, it is possible that some patients were still undergoing neoadjuvant systemic therapy with a planned metastasectomy in the future. However, it is not known if the proportion of these patients differ by laterality of the primary site. Lastly, the NCDB only contains patients treated at CoC-accredited centers. While data in the NCDB contains >70% of all cancer diagnosis in the United States, the results of this analysis may not be generalizable to non-CoC-accredited centers.

Conclusions

In conclusion, right-sided and left-sided SMCC are distinct entities. In terms of patient, disease, and treatment factors, patients with right-sided colon tumors are more often associated with predictors of worse prognosis. While these factors likely contribute to the worse overall survival seen in patients with right-sided colon tumors, our adjusted analysis suggest that there are other factors that may also play a role in the affecting the overall survival for these patients. The findings of this study further advocate for taking into account laterality in not only the design of clinical trials in colon cancer, but also in the treatment and surveillance of patients with colon cancer.

Acknowledgements

Dr. Beiqun Zhao is supported by the National Library of Medicine Training Grant [NIH Grant: T15LM011271]. Dr. Eisenstein is a consultant for Auris Health. All other authors have no relevant disclosures.

References

1. Cancer Facts & Figures. American Cancer Society; 2018.
2. Qiu M, Hu J, Yang D, Cosgrove DP, Xu R. Pattern of distant metastases in colorectal cancer: a SEER based study. Oncotarget 2015;6(36):38658–38666. [PubMed: 26484417]
3. Riihimaki M, Hemminki A, Sundquist J, Hemminki K. Patterns of metastasis in colon and rectal cancer. Sci Rep 2016;6:1–9. 10.1038/srep29765. [PubMed: 28442746]
4. Pawlik TM, Scoggins CR, Zorzi D, et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. Ann Surg 2005;241(5):715–724. 10.1097/01.sla.0000160703.75808.7d. [PubMed: 15849507]
5. Aloia T, Sebagh M, Plasse M, et al. Liver histology and surgical outcomes after preoperative chemotherapy with fluorouracil plus oxaliplatin in colorectal cancer liver metastases. J Clin Oncol 2006;24(31):4983–4990. 10.1200/jco.2006.05.8156. [PubMed: 17075116]

6. Kopetz S, Chang GJ, Overman MJ, et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol 2009;27(22):3677–3683. 10.1200/JCO.2008.20.5278. [PubMed: 19470929]
7. Soong R, Powell B, Elsaleh H, et al. Prognostic significance of TP53 gene mutation in 995 cases of colorectal carcinoma influence of tumour site, stage, adjuvant chemotherapy and type of mutation. Eur J Cancer 2000;36(16): 2053–2060. 10.1016/S0959-8049(00)00285-9. [PubMed: 11044641]
8. Kirby JA, Bone M, Robertson H, Hudson M, Jones DEJ. The number of intraepithelial T cells decreases from ascending colon to rectum [1]. J Clin Pathol 2003;56(2):158 10.1136/jcp.56.2.158.
9. Nawa T, Kato J, Kawamoto H, et al. Differences between right- and left-sided colon cancer in patient characteristics, cancer morphology and histology. J Gastroenterol Hepatol 2008;23(3):418–423. 10.1111/j.1440-1746.2007.04923.x. [PubMed: 17532785]
10. Lee MS, Menter DG, Kopetz S. Right versus left colon cancer biology: integrating the consensus molecular subtypes. J Natl Compr Cancer Netw 2017;15(3):411–419. 10.6004/jnccn.2017.0038.
11. Karim S, Brennan K, Nanji S, Berry SR, Booth CM. Association between prognosis and tumor laterality in early-stage colon cancer. JAMA Oncol 2017;3(10): 1386–1392. 10.1001/jamaoncol.2017.1016. [PubMed: 28594974]
12. Weiss JM, Pfau PR, O'Connor ES, et al. Mortality by stage for right- versus left-sided colon cancer: analysis of surveillance, epidemiology, and end results-medicare data. J Clin Oncol 2011;29(33):4401–4409. 10.1200/JCO.2011.36.4414. [PubMed: 21969498]
13. Warschkow R, Sulz MC, Marti L, et al. Better survival in right-sided versus left-sided stage I - III colon cancer patients. BMC Canc 2016;16(1):6–13. 10.1186/s12885-016-2412-0.
14. Yahagi M, Okabayashi K, Hasegawa H, Tsuruta M, Kitagawa Y. The worse prognosis of right-sided compared with left-sided colon cancers: a systematic review and meta-analysis. J Gastrointest Surg 2016;20(3):648–655. 10.1007/s11605-015-3026-6. [PubMed: 26573851]
15. Petrelli F, Tomasello G, Borgonovo K, et al. Prognostic survival associated with left-sided vs right-sided colon cancer a systematic review and meta-analysis. JAMA Oncol 2017;3(2):211–219. 10.1001/jamaoncol.2016.4227. [PubMed: 27787550]
16. Sasaki K, Andreatos N, Margonis GA, et al. The prognostic implications of primary colorectal tumor location on recurrence and overall survival in patients undergoing resection for colorectal liver metastasis. J Surg Oncol 2016;114(7): 803–809. 10.1002/jso.24425. [PubMed: 27792291]
17. Yamashita S, Brudvik KW, Kopetz SE, et al. Embryonic origin of primary colon cancer predicts pathologic response and survival in patients undergoing resection for colon cancer liver metastasis. Ann Surg 2018;267(3):514–520. 10.1007/s10741-014-9462-7 (Natural). [PubMed: 28002060]
18. Wang K, Xu D, Yan XL, Poston G, Xing BC. The impact of primary tumour location in patients undergoing hepatic resection for colorectal liver metastasis. Eur J Surg Oncol 2018;44(6):771–777. 10.1016/j.ejso.2018.02.210. [PubMed: 29580735]
19. Engstrand J, Nilsson H, Stromberg C, Jonas E, Freedman J. Colorectal cancer liver metastases - a population-based study on incidence, management and survival. BMC Canc 2018;18(1):1–11. 10.1186/s12885-017-3925-x.
20. NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. 2008 10.1007/978-1-4020-6754-9_3356.
21. Benedix F, Kube R, Meyer F, Schmidt U, Gastinger I, Lippert H. Comparison of 17,641 patients with right- and left-sided colon cancer: differences in epidemiology, perioperative course, histology, and survival. Dis Colon Rectum 2010;53(1):57–64. 10.1007/DCR.0b013e3181c703a4. [PubMed: 20010352]
22. Li P, Xiao Z, Braciak TA, Ou Q, Chen G, Oduncu FS. A relationship to survival is seen by combining the factors of mismatch repair status, tumor location and age of onset in colorectal cancer patients. PLoS One. 2017;12(3):1–11. 10.1371/journal.pone.0172799.
23. Price TJ, Beeke C, Ullah S, et al. Does the primary site of colorectal cancer impact outcomes for patients with metastatic disease? Cancer. 2015;121(6):830–835. 10.1002/cncr.29129. [PubMed: 25377235]
24. Elnatan J, Goh HS, Smith DR. C-KI-RAS activation and the biological behaviour of proximal and distal colonic adenocarcinomas. Eur J Cancer 1996;32(3): 491–497. 10.1016/0959-8049(95)00567-6.

25. Hugen N, Van de Velde CJH, De Wilt JHW, Nagtegaal ID. Metastatic pattern in colorectal cancer is strongly influenced by histological subtype. Ann Oncol 2014;25(3):651–657. 10.1093/annonc/mdt591. [PubMed: 24504447]
26. Kermanshahi TR, Magge D, Choudry H, et al. Mucinous and signet ring cell differentiation affect patterns of metastasis in colorectal carcinoma and influence survival. Int J Surg Pathol 2017;25(2):108–117. 10.1177/1066896916664990. [PubMed: 27571790]
27. Lemoine L, Sugarbaker P, Van Der Speeten K. Pathophysiology of colorectal peritoneal carcinomatosis: role of the peritoneum. World J Gastroenterol 2016;22(34):7692–7707. 10.3748/wjg.v22.i34.7692. [PubMed: 27678351]
28. Baran B, Mert Ozupek N, Yerli Tetik N, Acar E, Bekcioglu O, Baskin Y. Difference between left-sided and right-sided colorectal cancer: a focused review of literature. Gastroenterol Res 2018;11(4):264–273. 10.14740/gr1062w.
29. Kotha NV, Baumgartner JM, Veerapong J, et al. Primary tumor sidedness is predictive of survival in colon cancer patients treated with cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy: a US HIPEC collaborative study. Ann Surg Oncol 2019;26(7):2234–2240. 10.1245/s10434-019-07373-0. [PubMed: 31016486]
30. Krell R, Regenbogen S, Wong S. Variation in hospital treatment patterns for metastatic colorectal cancer. Cancer. 2015;121(11):1755–1761. 10.1002/cncr.27633.Percutaneous. [PubMed: 25640016]
31. Park JH, Kim TY, Lee KH, et al. The beneficial effect of palliative resection in metastatic colorectal cancer. Br J Canc 2013;108(7):1425–1431. 10.1038/bjc.2013.94.
32. Vargas G, Sheffield K, Parmar A, et al. Trends in treatment and sruvival in older patients presenting with stage IV colorectal cancer. J Gastrointest Surg 2014;18(2):369–377. 10.1371/journal.pone.0178059. [PubMed: 24234244]
33. Rhoads KF, Ackerson LK, Ngo JV, Hazard FKG, Subramanian SV, Dudley RA. Adequacy of lymph node examination in colorectal surgery: contribution of the hospital versus the surgeon. Med Care 2013;51(12). 10.1097/MLR.0b013e3182a53d72.Adequacy.
34. Shen SS, Haupt BX, Ro JY, Zhu J, Bailey HR, Schwartz MR. Number of lymph nodes examined and associated clinicopathologic factors in colorectal carcinoma. Arch Pathol Lab Med 2009;133(5):781–786. [PubMed: 19415953]
35. Kim HS, Heo JS, Lee J, et al. The impact of KRAS mutations on prognosis in surgically resected colorectal cancer patients with liver and lung metastases: a retrospective analysis. BMC Canc 2016;16(1):1–8. 10.1186/s12885-016-2141-4.
36. Lee DW, Kim KJ, Han SW, et al. KRAS mutation is associated with worse prognosis in stage III or high-risk stage II colon cancer patients treated with adjuvant FOLFOX. Ann Surg Oncol 2015;22(1):187–194. 10.1245/s10434-014-3826-z. [PubMed: 24889488]
37. Fujiyoshi K, Yamamoto G, Takenoya T, et al. Metastatic pattern of stage IV colorectal cancer with high-frequency microsatellite instability as a prognostic factor. Anticancer Res 2017;37(1):239–248. 10.21873/anticanres.11313. [PubMed: 28011498]
38. Yim KL. Microsatellite instability in metastatic colorectal cancer: a review of pathology, response to chemotherapy and clinical outcome. Med Oncol 2012;29(3):1796–1801. 10.1007/s12032-011-0050-6. [PubMed: 21901450]
39. Baek SJ, Hur H, Min BS, Baik SH, Lee KY, Kim NK. The characteristics of bone metastasis in patients with colorectal cancer: a long-term report from a single institution. World J Surg 2016;40(4):982–986. 10.1007/s00268-015-3296-x. [PubMed: 26541868]
40. Pfannschmidt J, Dienemann H, Hoffmann H. Surgical resection of pulmonary metastases from colorectal cancer: a systematic review of published series. Ann Thorac Surg 2007;84(1):324–338. 10.1016/j.athoracsur.2007.02.093. [PubMed: 17588454]

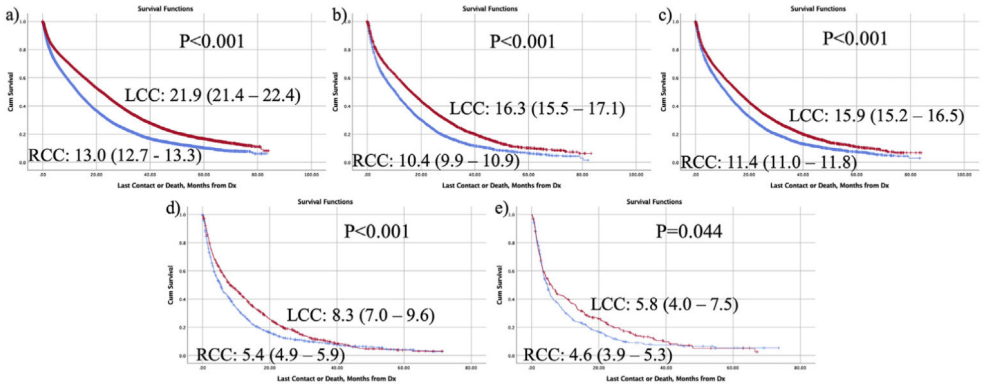

Fig. 1.

Kaplan-Meier survival curves, stratified by primary tumor site, for liver (a), lung (b), peritoneum (c), bone (d), and brain (e) metastases.

Table 1

Comparison of patient-related, disease-related, and treatment-related factors for patients with right-versus left-sided metastatic colon cancer. RCC = right-sided colon cancer; LCC = left-sided colon cancer.

	RCC (%)	LCC (%)	P-value (OR)	95% CI
Patient Factors				
Age (median)	67	62	<0.001	-
Race			<0.001	-
White	26107 (78.9)	19286 (78.5)		
Black	5714 (17.3)	3725 (15.2)		
American Indian	93 (0.3)	91 (0.4)		
Asian/Pacific Islander	737 (2.2)	1018 (4.1)		
Other/Unknown	429 (1.3)	433 (1.8)		
Female Sex	16871 (51.0)	10518 (42.8)	<0.001 (0.720)	0.696–0.744
Charlson/Deyo Score			<0.001	-
0	23412 (70.8)	18428 (75.1)		
1	6914 (20.9)	4549 (18.5)		
≥2	2754 (8.3)	1576 (6.4)		
Disease Factors				
Any Metastasis	33080	24553		
Liver Metastasis	26663 (80.6)	20473 (83.4)	<0.001 (1.208)	1.157–1.261
Lung Metastasis	6807 (20.6)	5641 (23.0)	<0.001 (1.151)	1.106–1.198
Peritoneum Metastasis	11953 (36.1)	7881 (32.1)	<0.001 (0.836)	0.807–0.865
Bone Metastasis	1556 (4.7)	1151 (4.7)	0.929	-
Brain Metastasis	504 (1.5)	314 (1.3)	0.014 (0.837)	0.727–0.965
Signet Ring Histology	902 (2.7)	320 (1.3)	<0.001 (0.471)	0.414–0.536
Mucinous Histology	3063 (9.3)	1463 (6.0)	<0.001 (0.621)	0.582–0.662
KRAS Mutation	6037 (51.5)	3474 (36.8)	<0.001 (0.548)	0.518–0.579
Microsatellite Instability	1262 (21.2)	698 (15.5)	<0.001 (0.681)	0.615–0.754
High-Grade Tumor	9280 (34.8)	4319 (22.0)	<0.001 (0.528)	0.506–0.551
Pathologic T4	7891 (26.3)	5210 (22.6)	<0.001 (0.817)	0.785–0.851
Treatment Factors				

	RCC (%)	LCC (%)	P-value (OR)	95% CI
Academic Center	10003 (30.2)	7885 (32.1)	<0.001 (1.091)	1.053–1.131
Primary Tumor Resected	20961 (63.4)	14987 (61.2)	<0.001 (0.907)	0.877–0.939
Metastasis Resected	6959 (21.1)	5324 (21.7)	0.057	-
≥12 lymph Nodes Examined	17669 (54.5)	11526 (48.0)	<0.001 (0.771)	0.745–0.797
Positive Lymph Nodes	17178 (52.5)	11018 (45.5)	<0.001 (0.754)	0.730–0.780
Chemotherapy	21593 (67.6)	17771 (74.8)	<0.001 (1.421)	1.369–1.476
Negative Margins	15775 (77.6)	11276 (78.2)	0.169	-

Table 2

Unadjusted and adjusted Cox regression analysis.

	Unadjusted			Adjusted		
	HR	**95% CI**	**p-Value**	**HR**	**95% CI**	**p-Value**
Age	1.027	1.026–1.028	<0.001	1.013	1.012–1.014	<0.001
Female Sex	1.011	0.990–1.032	0.319	-	-	-
Race						
White	Ref.	-	<0.001	Ref.	-	<0.001
Black	1.020	0.992–1.050	0.165	1.044	1.013–1.075	0.005
American Indian	1.010	0.842–1.212	0.914	1.107	0.919–1.332	0.285
Asian/Pacific Islander	0.851	0.798–0.907	<0.001	0.930	0.870–0.993	0.031
Other/Unknown	0.794	0.723–0.873	<0.001	0.829	0.752–0.914	<0.001
Charlson-Deyo Comorbidity Score						
0	Ref.	-	<0.001	Ref.	-	<0.001
1	1.225	1.194–1.257	<0.001	1.095	1.066–1.125	<0.001
2	1.562	1.492–1.635	<0.001	1.226	1.170–1.285	<0.001
≥3	1.924	1.802–2.053	<0.001	1.373	1.284–1.469	<0.001
Treatment at Academic Center	0.811	0.792–0.829	<0.001	0.847	0.827–0.867	<0.001
Liver Metastasis[a]	1.008	0.981–1.036	0.564	1.350	1.310–1.392	<0.001
Lung Metastasis	1.302	1.270–1.335	<0.001	1.064	1.036–1.094	<0.001
Peritoneal Metastasis	1.331	1.303–1.360	<0.001	1.298	1.266–1.330	<0.001
Bone Metastasis	1.898	1.813–1.988	<0.001	1.445	1.377–1.517	<0.001
Brain Metastasis	1.936	1.785–2.099	<0.001	1.379	1.267–1.501	<0.001
Signet Ring/Mucinous Histology	1.142	1.104–1.181	<0.001	1.155	1.113–1.197	<0.001
Tumor Grade Differentiation						
Well/Moderate	Ref.	-	<0.001	Ref.	-	<0.001
Poor/Anaplastic	1.556	1.518–1.596	<0.001	1.487	1.448–1.526	<0.001
Unknown	1.740	1.693–1.787	<0.001	1.151	1.116–1.188	<0.001
KRAS Mutation						
Negative	Ref.	-	<0.001	Ref.	-	0.004
Positive	1.080	1.043–1.120	<0.001	1.039	1.002–1.078	0.039

	Unadjusted			Adjusted		
	HR	**95% CI**	**p-Value**	**HR**	**95% CI**	**p-Value**
Unknown	1.397	1.359–1.435	<0.001	1.051	1.021–1.082	0.001
Microsatellite						
Any Instability	Ref.	-	<0.001	Ref.	-	<0.001
No Instability	1.180	1.103–1.262	<0.001	1.065	0.994–0.141	0.073
Unknown Instability	1.491	1.443–1.539	<0.001	1.083	1.047–1.121	<0.001
Pathologic T4 Stage	0.998	0.973–1.023	0.852	-	-	-
Primary Tumor Resected	0.484	0.474–0.495	<0.001	0.515	0.493–0.539	<0.001
Metastasis Resected	0.566	0.551–0.582	<0.001	0.821	0.797–0.846	<0.001
≥12 Lymph Nodes Examined	0.518	0.507–0.529	<0.001	0.695	0.672–0.720	<0.001
Positive Lymph Nodes	0.725	0.710–0.740	<0.001	1.477	1.426–1.529	<0.001
Any Chemotherapy	0.303	0.296–0.310	<0.001	0.354	0.345–0.363	<0.001
Right-Side Primary Tumor	1.419	1.389–1.450	<0.001	1.257	1.229–1.286	<0.001

[a]Forced into the adjusted model.

Table 3

Unadjusted and adjusted Cox regression analysis in patients who underwent metastasectomy and chemotherapy.

	Unadjusted			Adjusted		
	HR	**95% CI**	**p-Value**	**HR**	**95% CI**	**p-Value**
Age	1.018	1.016–1.021	<0.001	1.016	1.013–1.019	<0.001
Female Sex	0.981	0.923–1.043	0.373	-	-	-
Race						
White	Ref.	-	0.008	Ref.	-	0.236
Black	1.005	0.921–1.098	0.903	1.060	0.963–1.166	0.238
American Indian	1.434	0.877–2.343	0.151	1.502	0.886–2.545	0.131
Asian/Pacific Islander	0.730	0.595–0.896	0.003	0.868	0.699–1.078	0.200
Other/Unknown	0.776	0.574–1.048	0.098	0.960	0.691–1.335	0.809
Charlson-Deyo Comorbidity Score						
0	Ref.	-	<0.001	Ref.	-	<0.001
1	1.216	1.126–1.313	<0.001	1.136	1.045–1.235	0.003
2	1.572	1.344–1.838	<0.001	1.315	1.110–1.559	0.002
≥3	1.658	1.275–2.154	<0.001	1.419	1.062–1.897	0.018
Treatment at Academic Center	0.656	0.615–0.700	<0.001	0.685	0.638–0.736	<0.001
Liver Metastasis	0.830	0.769–0.896	<0.001	1.411	1.275–1.560	<0.001
Lung Metastasis	1.441	1.315–1.579	<0.001	1.224	1.104–1.357	<0.001
Peritoneal Metastasis	1.677	1.575–1.786	<0.001	1.340	1.234–1455	<0.001
Bone Metastasis	2.824	2.309–3.455	<0.001	2.011	1.603–2.522	<0.001
Brain Metastasis	2.179	1.661–2.857	<0.001	1.498	1.114–2.014	<0.001
Signet Ring/Mucinous Histology	1.423	1.306–1.551	<0.001	1.219	0.980–1.515	0.076
Tumor Grade Differentiation						
Well/Moderate	Ref.	-	<0.001	Ref.	-	<0.001
Poor/Anaplastic	1.832	1.712–1.961	<0.001	1.624	1.504–1.754	<0.001
Unknown	0.924	0.809–1.057	0.249	1.043	0.894–1.217	0.591
KRAS Mutation						
Negative	Ref.	-	<0.001	Ref.	-	<0.001
Positive	1.143	1.048–1.246	0.002	1.112	1.012–1.223	0.028

	Unadjusted			Adjusted		
	HR	**95% CI**	**p-Value**	**HR**	**95% CI**	**p-Value**
Unknown	0.952	0.885–1.025	0.191	0.926	0.855–1.003	0.058
Microsatellite						
Any Instability	Ref.	-	<0.001	Ref.	-	<0.001
No Instability	1.406	1.212–1.630	<0.001	1.367	1.155–1.618	<0.001
Unknown Instability	1.190	1.103–1.284	<0.001	1.123	1.033–1.220	0.006
Pathologic T4 Stage	1.757	1.645–1.877	<0.001	1.508	1.406–1.618	<0.001
≥12 Lymph Nodes Examined	0.696	0.642–0.752	<0.001	0.656	0.602–716	<0.001
Positive Lymph Nodes	1.619	1.496–1.752	<0.001	1.505	1.379–1.642	<0.001
Right-Side Primary Tumor	1.547	1.453–1.646	<0.001	1.375	1.282–1.475	<0.001