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The primary tumor location in colorectal cancer: A focused review on its impact on surgical management

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Abstract: The primary tumor location (PTL) has attracted increasing attention in recent years for colorectal cancer (CRC) patients. Although the underlying mechanisms for differences caused by PTL remain still unclear, right-sided colon (RCC) and left-sided colon (LCC) are now considered as distinct entities because of their different molecular profile and clinical response to surgery and chemotherapy. In this article, we review the influence of PTL particularly on surgical management of primary and metastatic CRC settings. For nonmetastatic CRC, RCC could be a slightly superior prognostic factor after curative resection in stage I-II CRC, while RCC could be an inferior prognostic factor in stage III CRC with worse survival after recurrence, suggesting the oncological aggressiveness of recurrent RCC. For metastatic CRC, RCC could be a predictor of worse survival after hepatectomy of liver metastases from CRC with aggressive recurrence pattern and lower chance of re-resection. In lung metastases from CRC, the role of PTL still remains uncertain because of the limited number of studies. As to the impact of PTL on survival outcome after cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy for peritoneal metastases from CRC, a discrepancy exists among studies and further investigation will be needed. The very simple clinical factor of PTL could provide important information for the prediction of the survival outcome after surgery in CRC. Further clinical and basic research will facilitate the clinical application of PTL in a more specified and personalized manner.

***Keywords*:** Primary tumor location, colorectal cancer, surgery

Introduction

Despite recent progress in therapeutic and diagnostic modalities, colorectal cancer (CRC) is a serious public health problem worldwide owing to its high incidence and cancer-related mortality. It accounts for approximately 10% of diagnosed cancers with almost 900000 cancer-related deaths annually (*1*).

In recent years, the concept of primary tumor location (PTL) in CRC has attracted attention as a surrogate marker for predicting therapeutic effect and prognosis both in localized and metastatic disease settings. Right-sided colon cancer (RCC) and left-sided colon cancer (LCC) can be regarded as clinically and molecularly distinct entities. The differences between RCC and LCC could be explained to some extent by the fact that the right-sided colon and left-sided colon are embryologically different; the cecum to proximal two-thirds of the transverse colon arises from the midgut which is supplied by the superior mesenteric artery, while the distal third of the transverse colon to the upper two-thirds of the anorectal canal arises from the hindgut which is supplied by the inferior mesenteric artery (*2*).

Many previous studies reported the clinical and biological differences between RCC and LCC. For example, from the perspective of epidemiology, RCC patients are predominantly in females and at an older age, while LCC patients are predominantly in males and at an early age with a frequency of occurrence more than that of RCC (*3*). RCC patients also tend to have advanced and larger tumors (*3,4*), which may be explained by the asymptomatic features of RCC and the resulting delay in diagnosis. Pathologically, the proportion of poorly differentiated adenocarcinoma and mucinous adenocarcinoma, which are regarded as biologically aggressive histological types, is higher in RCC than in LCC (*3*). Also, the genomic aspects of RCC and LCC are substantially different. RCC is more often microsatellite instability-high (MSI-high) and CIMP-high phenotype, while LCC is more often chromosomal instability-high (CIN-high) phenotype (*5*). The mutation profiles of key oncogenes and tumor suppressor genes are also different between RCC and LCC. KRAS mutation, which is associated with the effectiveness of anti-EGFR therapy, is more frequent in RCC than in LCC (*6*). BRAF mutation, an inferior prognostic factor in stage IV CRC, is more often in RCC (*2*), while APC and TP53 mutations are more often in LCC (*2*). Recent basic research further

reported other various differences between RCC and LCC such as plasma protein expression profile (*7*). In addition to these clinicopathological and molecular differences, metastatic patterns between RCC and LCC are also different. It is reported that peritoneal metastases are most frequent in RCC patients, while lung metastases are most frequent in rectal cancer patients (*8*). For bone metastases, RCC patients have the lowest incidence and rectal cancer patients have the highest (*9*). These multifactorial differences caused by PTL might eventually lead to the prognostic differences between RCC and LCC.

Although systemic chemotherapy with targeted agents for CRC has made remarkable advances, surgical resection is still the gold standard for the treatment of CRC. Recently, many studies have reported the influence of PTL on surgical outcome of CRC in various clinical settings. In this article, we review the impact of PTL particularly on surgical management of primary and metastatic CRC.

Definition of PTL

The definition of PTL differs among studies and clinical trials. In practical settings, most studies define CRC proximal to splenic flexure as "right-sided" and CRC at or distal to splenic flexure as "left-sided". However, the most confusing point is that some studies exclude the rectum from the left-sided colon, while some studies include the rectum with the left-sided colon. Besides, transverse colon is sometimes excluded from the analysis due to its mixed embryologic origin. In this article, in order to avoid confusion, we classified CRC into two groups: RCC (from cecum to splenic flexure) and LCC (from splenic flexure to rectum), unless otherwise specified.

PTL and surgical outcome in nonmetastatic stage I - III CRC

Surgical resection is the first-choice treatment for nonmetastatic stage I-III CRC, with adjuvant chemotherapy for high-risk stage II and stage III CRC to improve survival outcome. Current clinical practice guidelines in Japan (*10*), US (*11*) and Europe (*12,13*) on the principals for surgical management of primary CRC are summarized in Table 1. Interestingly, the effects of PTL on prognostic outcomes after surgery between early (stage I and II) and advanced (stage III and IV) CRC patients are considered to be opposite. For

Table 1. Summary of current clinical practice guidelines on the principals for surgical management of primary and metastatic colorectal cancer

Guideline	Primary colorectal caner	Metastatic colorectal caner
Japanese Society for Cancer of the Colon and Rectum guidelines 2019 (*10*)	The extent of lymph node dissection is determined based on the preoperative clinical findings and on the extent of lymph node metastasis and depth of tumor invasion. The extent of the pericolic/perirectal lymph node in colon cancer is defined by the positional relationship between the primary tumor and the feeding artery. Metastasis of the pericolic/perirectal lymph node at a distance of 10 cm or more from the tumor edge is rare.	If both the distant metastases and the primary tumor are resectable, curative resection of the primary tumor performed, and resection of the distant me-tastases is considered. If the distant metastases are resectable but the primary tumor is unresectable, in principle, resection of the primary tumor and distant metastases is not performed, and another treatment method is selected. If the distant metastases are unresectable but the primary tumor is resectable, the indication for the resection of the primary tumor is determined, based on the clinical symptoms of the primary tumor and the impact on the prognosis.
NCCN guidelines Version 4.2020 (*11*)	The recommended surgical procedure for resectable colon cancer is an en bloc resection and adequate lymphadenectomy. Adequate pathologic assessment of the resected lymph nodes is important with a goal of evaluating at least 12 nodes. Patients with resectable T4b tumors or with bulky nodal disease may be treated with neoadjuvant systemic therapy prior to colectomy.	Patients with metastatic disease in the liver or lung should be considered for surgical resection if they are candidates for surgery and if all original sites of disease are amenable to resection (R0) and/or ablation. Six months of perioperative systemic therapy should be administered to patients with synchronous or metachronous resectable metastatic disease. When a response to chemotherapy would likely convert a patient from an unresectable to a resectable state (*i.e.*, conversion therapy), this therapy should be initiated.
ESMO consensus guidelines (*12,13*)	The resection should include a segment of colon of at least 5 cm on either side of the tumor. At least 12 lymph nodes should be resected when feasible. En bloc resection of adjacent organ-invaded portions must be car-ried out in case of pT4b.	In patients with clearly resectable disease and favorable prognostic criteria, perioperative treatment may not be necessary and upfront resection is justi-fied. In patients with technically resectable disease where the prognosis is unclear or probably unfavorable, perioperative combination chemotherapy should be administered. In potentially resectable patients (if conversion is the goal), a regimen leading to high response rates and/or a large tumor size reduction is recommended.

ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network.

example, a retrospective study from US in 2008 using The Surveillance, Epidemiology, and End Results (SEER) database including 77,978 CRC patients who underwent surgical resection of primary CRC showed that RCC patients had lower hazard ratio (HR) in overall survival (OS) in stage II CRC (HR = 0.91, 95% confidence interval [CI] 0.88-0.95, $P < 0.001$), while RCC patients had higher HR in OS in stage III (HR = 1.06, 95% CI 1.02-1.11) and stage IV CRC (HR = 1.22, 95% CI 1.16-1.28). No difference in OS between RCC and LCC was observed in stage I CRC (*4*). A study from US in 2019 including 114,839 stage I-II and 71,024 stage III CRC patients, who underwent surgical resection, reported similar results. In stage I-II CRC, RCC patients had superior OS (HR = 1.13, 95% CI 1.09-1.17, $P < 0.001$). In stage III CRC, LCC patients had superior OS with chemotherapy (HR = 0.85, 95% CI 0.815-0.892, $P < 0.001$), while no difference in OS without chemotherapy (HR = 0.97, 95% CI 0.912-1.02, $P = 0.18$) (*14*). The tendency that early stage RCC patients had a survival benefit compared with early stage LCC patients may be partially explained by the greater prevalence of MSI-high in RCC, which predicts a good survival outcome (*15*).

In 2018, Ishihara *et al.* from Japan retrospectively investigated 5,664 stage II and III CRC patients who underwent curative resection. Although the 5-year recurrence free survival was slightly superior in RCC than in LCC (83.9% versus 81.1%, $P = 0.019$), the 5-year cancer-specific survival (CSS) after recurrence was significantly inferior in RCC than in LCC (30.6% versus 43.6%, $P = 0.016$), suggesting the oncologically aggressive nature of RCC after recurrence (*16*). The same tendency that the effect of PTL in stage II and III CRC might be related to survival outcome after recurrence rather than the recurrence risk after surgery with or without adjuvant chemotherapy was confirmed in several other studies. In 2016, Kerr *et al.* from UK analyzed the data from two randomized trials regarding adjuvant chemotherapy with 1,935 stage II and III CRC patients who received surgery, and reported that PTL had no significant effect on relapse-free survival, while RCC patients had significantly inferior survival after recurrence compared with LCC patients (HR 1.53, 95% CI 1.14-2.06, $P = 0.004$) (*17*). In 2019, Cascinu *et al.* from Italy analyzed data from three randomized trials including 5,239 stage II and III CRC patients who underwent surgical resection. In this study, the authors classified CRC into three groups: RCC (from the cecum to the hepatic flexure), transverse colon, and LCC. They found that there was no difference both in disease-free survival (DFS) and OS in stage II patients, while RCC patients had similar DFS but significantly inferior OS compared to LCC patients in stage III patients (HR = 1.35, 95% CI 1.14-1.62, $P < 0.001$) (*18*). A retrospective study from Japan in 2020 investigated 9,194 stage III CRC patients who received surgical resection. In this study, the authors classified the CRC patients into three groups: RCC, LCC (from the splenic flexure to sigmoid colon), and rectal cancer. They reported that rectal cancer was associated with worse relapse-free survival compared to LCC and RCC, while RCC had significantly shorter 5-year OS after recurrence compared to LCC and rectal cancer (RCC: 23.3%, LCC: 36.6%, rectal cancer: 31.6%, $P < 0.001$). They also reported the difference in recurrence pattern among PTL; 20% of RCC were peritoneal dissemination, 42% of LCC were liver metastases, and 33% of rectal cancer were local recurrence, which may influence survival outcomes after recurrence (*19*).

The results of large cohort studies on PTL and surgical outcomes after resection for stage I-III CRC are summarized in Table 2.

PTL and metastatic stage IV CRC

For resectable stage IV CRC patients, surgical resection of primary and metastatic lesions is actively considered aiming at long-term disease control and the possibility of cure. Current clinical practice guidelines in Japan (*10*), US (*11*) and Europe (*12,13*) on the principals for surgical management of metastatic CRC are summarized in Table 1. On the other hand, for the unresectable advanced stage IV CRC patients, systemic chemotherapy is the standard treatment while considering the possibility of resection of primary and metastatic disease in the case of sufficient tumor shrinkage. At the present time, with the combination of chemotherapy and targeted agents, the median OS in unresectable CRC patients has improved over time and now ranges from 25 to 30 months (*20*). In unresectable metastatic CRC, several studies have demonstrated that PTL could be both the prognostic marker for survival and the predictive marker for the therapeutic response to molecular targeted agents. The CALGB/SWOG 80,405 trial was a randomized clinical trial, which compared the effect of bevacizumab with cetuximab added to first-line FOLFOX or FOLFILI in metastatic CRC patients (*21*). The post-hoc study of this trial showed that the median OS of LCC patients was significantly superior to that of RCC (cecum to hepatic flexure, transverse colon was excluded in this study) patients (33.3 versus 19.4 months, $P < 0.0001$). Moreover, among KRAS wild-type metastatic CRC patients, RCC patients had longer OS from bevacizumab than cetuximab (HR 1.36, 95% CI 0.93-1.99, $P = 0.10$), whereas LCC patients had longer OS from cetuximab than bevacizumab (HR 0.77, CI 0.59-0.99, $P = 0.04$) (*21*). Similar results were reported in other randomized clinical trials such as CRYSTAL and FIRE-3 demonstrating that RAS wild-type metastatic RCC patients had limited benefit from first-line FOLFIRI plus cetuximab (*22*). The PRIME study also reported that the addition of panitumumab to FOLFOX improved the OS of LCC patients but not RCC patients (*23*). The current consensus is that RAS wild-type metastatic RCC patients

Table 2. Summary of large cohort studies on PTL and surgical outcomes after resection for Stage I - III CRC

Year	Reference	Study type	Study period	Number of patients	Survival analysis for RCC versus LCC
2008	Meguid *et al.* (*4*)	Retrospective (SEER database)	1988-2003	77,978	Stage I: no difference in OS Stage II: superior in OS (HR 0.91, 95% CI 0.88-0.95) Stage III: inferior in OS (HR 1.06, 95% CI 1.02-1.11)
2016	Kerr *et al.* (*17*)	Retrospective (Two trials)	2002-2004 2005-2010	1,935	Stage II-III: no difference in RFS, but inferior in OS after recurrence (HR 1.53, 95% CI 1.14-2.06)
2018	Ishihara *et al.* (*16*)	Retrospective (22 centers)	1997-2006	5,664	Stage II-III: superior in RFS, but inferior in 5-year CSS after recurrence (30.6% versus 43.6%)
2019	Turner *et al.* (*14*)	Retrospective (NCDB)	2006-2013	185,863	Stage I-II: superior in OS (HR 0.88, 95% CI 0.85-0.92) Stage III with chemotherapy: inferior in OS (HR 1.18, 95% CI 1.12-1.22) Stage III without chemotherapy: no difference in OS
2019	Cascinu *et al.* (*18*)	Retrospective (Three trials)	1989-1992 1992-1998 2007-2013	5,239	Stage II: no difference in DFS and OS Stage III: no difference in DFS, but inferior in OS (HR 1.35, 95% CI 1.14-1.62)
2020	Shida *et al.* (*19*)	Retrospective (24 centers)	1997-2012	9,194	Stage III: inferior in 5-year OS after recurrence (RCC: 23.3%, LCC: 36.6%, rectal cancer: 31.6%)

CI, confidence interval; CRC, colorectal cancer; CSS, cancer specific survival; DFS, disease free survival; HR, hazard ratio; LCC, left-sided colon cancer; NCDB, The National Cancer Database; OS, overall survival; PTL, primary tumor location; RCC, right-sided colon cancer; RFS, recurrence free survival; SEER, surveillance, epidemiology, and end results.

could have limited benefit from the anti-EGFR therapy. At present, in the NCCN guidelines version 4.2020, the anti-EGFR agents (cetuximab or panitumumab) in first-line therapy for advanced or metastatic CRC are recommended only for KRAS/NRAS/BRAF wild-type LCC (*11*).

PTL and surgical outcome in liver metastases from CRC

The liver is the most frequent site of distant metastases in CRC. Approximately 15% to 20% of CRC patients present with liver metastases at first diagnosis and more than 50% of CRC patients will develop liver metastasis during the course of the disease, accounting for two-thirds of CRC deaths (*24*). For resectable liver metastasis from CRC, surgical resection is the gold standard for prolonging progression-free survival (PFS) and potentially cure. At present, the reported 5-year OS after resection of liver metastasis from CRC approaches 40% to 50 % with the advent of effective chemotherapy regimen and advances in surgical techniques (*25-27*). In addition, the initially unresectable liver metastasis at the time of presentation could be down-staged and resected by conversion surgery with modern systemic chemotherapy including molecular target agents. For example, in a recent systemic review, the combination of fluorouracil, oxaliplatin, and irinotecan plus bevacizumab (FOLFOXIRI-Bev) achieved an overall surgical conversion rate of 39.1% and a R0 resection rate of 28.1% with median PFS and OS of 12.4 months and 30.2 months, respectively (*28*).

In recent years, many papers reported the effect of PTL on the prognosis after hepatectomy for liver metastases from CRC. A retrospective SEER database study from China in 2019 that investigated 1,508 CRC patients with synchronous liver metastases who underwent R0 surgical resection showed that RCC patients had significantly worse OS and CSS compared to LCC patients (OS, HR = 1.75, 95% CI 1.34-2.29; CSS, HR = 1.76, 95% CI 1.33-2.35) (*29*). Another retrospective SEER database study from US in 2020 demonstrated that both LCC (from the splenic flexure to rectosigmoid junction in this study) and rectal cancer patients with synchronous liver metastasis who underwent R0 surgical resection had significantly improved OS (HR = 0.72, 95% CI 0.62-0.83, $P < 0.001$) and disease-specific survival (HR = 0.73, 95% CI 0.58-0.92, $P = 0.008$) compared to RCC patients, while there was no survival difference between LCC and rectal cancer patients (*30*). This tendency that RCC is a poor prognostic factor has also been demonstrated in several systematic reviews. A meta-analysis from China in 2019 reviewing 12 studies with 6,387 CRC patients with liver metastases who underwent hepatic resection showed that RCC patients had worse 5-year OS (HR = 1.354, 95% CI 1.238-1.482) compared to LCC patients, but no significant difference in 5-year DFS (HR = 1.104, 95% CI 0.987-1.235) (*31*). Similarly, another meta-analysis from China in 2019 reviewing 45 study cohorts with 21,953 patients reported that RCC patients had significantly worse OS (HR = 1.39, 95% CI 1.28-1.51, $P < 0.001$) and DFS (HR = 1.18, 95% CI 1.06-1.32, $P = 0.004$) compared to LCC patients (*32*). For patients who need extensive liver resection, portal vein embolization (PVE) is widely used before surgery to promote the

growth of the future liver remnant (*33*). Although the number of patients was limited (N = 59), a retrospective study from Germany in 2020 reported that PTL was the only statistically significant predictor of intrahepatic PFS after PVE subsequent to major hepatic surgery on Cox regression analysis (HR = 2.242, 95% CI 1.125-4.465, P = 0.022), and RCC patients had significantly shorter intrahepatic PFS compared to LCC patients (median 4.0 months versus 10.2 months, P = 0.018) (*34*). Furthermore, the patterns of recurrence between RCC and LCC after resection of liver metastases may also be different. In 2020, Russolillo *et al.* from Italy reported that recurrence after hepatectomy in RCC patients was more often encephalic and at multiple sites, and RCC patients had a lower chance of re-resection compared to LCC patients (27.9% versus 37.5%, P = 0.024) (*35*). Overall, RCC could be an independent predictor of worse survival after surgical resection of liver metastases from CRC. Thus, the stratification based on PTL would be useful in clinical practice such as adding adjuvant chemotherapy and careful surveillance after hepatectomy of liver metastases from RCC.

PTL and surgical outcome in lung metastases from CRC

The lung is the second most frequent target organ of metastasis from CRC. A total of 5% to 15% of CRC patients will develop lung metastases. For unresectable lung metastases from CRC, systemic chemotherapy is considered, though the conversion rate is very low compared to liver metastases (*36*). Despite the lack of randomized controlled studies, in selected patients with resectable disease, pulmonary metastasectomy is widely considered for the treatment of lung metastases from CRC (*37*). According to a review that investigated 21 studies with 8,361 CRC patients with lung metastases who underwent surgical resection, the 5-years OS after first pulmonary metastasectomy were 24 to 82% and the median OS ranged from 35 to 70 months (*38*). Another meta-analysis investigated 15 studies with 1,669 CRC patients with lung metastases reported a mean 5-year OS of 49% (range 25-72%) after pulmonary metastasectomy (*39*). Various prognostic factors affecting survival outcomes after pulmonary metastasectomy have been reported. A best evidence topic review in 2016 reported that the prognostic factors in pulmonary metastasectomy for lung metastases from CRC include the size and number of metastases, intra-thoracic lymph node involvement, pre-thoracotomy CEA levels, and response to induction chemotherapy (*40*).

Regarding PTL, few studies investigated the effect of PTL on survival outcomes after pulmonary metastasectomy for lung metastases from CRC. One retrospective study from the US in 2020 with 194 CRC patients with lung metastases reported that LCC (from splenic flexure to sigmoid colon in this study) patients experienced prolonged 5-year OS after surgical resection on multivariate analysis compared to rectal cancer (HR = 0.31, 95% CI 0.10-0.93, P = 0.036), while no significant difference was observed between LCC and RCC (*41*). Further study with a large patient cohort will be needed to elucidate the impact of PTL on the outcome of surgical resection for lung metastases from CRC.

PTL and surgical outcome in peritoneal metastases from CRC

The peritoneum is the third most frequent site for metastases from CRC. About 4% to 5% of all CRC patients present with synchronous peritoneal metastases (*42,43*). Historically, peritoneal metastases from CRC had the worst outcome. However, with the advent of an aggressive surgical treatment in the form of complete cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC), the prognosis of CRC patients with peritoneal metastasis has been improved. At present, the expected median OS and 5-year survival obtained by CRS plus HIPEC at high volume centers are 19.2-34 months and 19-48%, respectively (*43*). Thus, in the selected patients with resectable peritoneal metastases from CRC, surgical resection particularly with CRS plus HIPEC is now actively attempted with potential for long-term survival and cure. On the other hand, the efficacy of HIPEC for peritoneal metastases from CTC still remains controversial according to the recent PRODIGE7 trial. The PRODIGE7 trial was the first randomized phase III trial that evaluated the effectiveness of HIPEC with oxaliplatin for the treatment of CRC patients with peritoneal metastases (*44*). This trial randomized 265 CRC patients with peritoneal metastases (peritoneal cancer index score ≤ 25) to CRS alone or CRS plus HIPEC with oxaliplatin. It reported excellent median OS of 41.7 months in non-HIPEC group and 41.7 months in HIPEC group, but there was no difference in OS between the groups (HR = 1.00, 95% CI 0.73-1.37, P = 0.995). The role of HIPEC for the treatment of peritoneal metastases from CRC should be studied further.

The well-known prognostic factors affecting survival after CRS plus HIPEC are peritoneal cancer index score and completeness of cytoreduction score. In addition to these factors, several studies investigated the prognostic role of PTL for peritoneal metastases from CRC. A retrospective population-based cohort study from the Netherlands in 2020 included 7930 CRC patients with synchronous peritoneal metastases. Of all 7,930 patients, 564 patients (7.1%) received CRS plus HIPEC. The overall analysis including all 7,930 CRC patients with peritoneal metastases showed that RCC was an independent prognostic factor in multivariate analysis and was significantly associated with worse OS compared to LCC (HR 1.11, 95% CI 1.03-1.19, P =

Table 3. Summary of studies on PTL and surgical outcomes after CRS plus HIPEC for peritoneal metastases from CRC

Year	Reference	Study type	Study period	Number of patients	Survival analysis for RCC versus LCC
2019	Kelly *et al.* (*48*)	Retrospective (Three centers)	1992-2016	115	Inferior in DFS (HR 2.27, 95% CI 1.09-4.76), inferior in OS (HR 2.57, 95% CI 1.13-5.84)
2019	Kotha *et al.* (*47*)	Retrospective (12 centers)	2000-2017	336	Inferior in DFS (HR 1.75, 95% CI 1.19-2.56), inferior in OS (HR 1.72, 95% CI 1.09-2.73)
2019	Péron *et al.* (*46*)	Retrospective (16 centers)	2004-2017	796	No difference in PFS (HR 1.02, 95% CI 0.85-1.23) and OS (HR 0.99, 95% CI 0.79-1.23).
2020	Blakely *et al.* (*49*)	Retrospective (CCR)	2004-2012	272	Inferior in DFS (median 21 versus 41 months, $P = 0.0011$) Inferior in OS (median 15.5 versus 34 months, $P = 0.0010$)
2020	de Boer *et al.* (*45*)	Retrospective (Population-based)	1995-2016	564	No difference in OS (median 30.3 versus 34.6 months, $P = 0.301$)

CCR, California Cancer Registry; CI, confidence interval; CRC, colorectal cancer; CRS, complete cytoreductive surgery; DFS, disease free survival; HIPEC, hyperthermic intraperitoneal chemotherapy; HR, hazard ratio; LCC, left-sided colon cancer; OS, overall survival; PFS, progression free survival; PTL, primary tumor location; RCC, right-sided colon cancer.

0.007). However, in the subgroup analysis limited to 564 patients who underwent CRS plus HIPEC, OS of RCC patients did not significantly differ from that of LCC patients (*45*). Another retrospective study from France in 2019 with 796 patients with peritoneal metastases from CRC who were treated with CRS plus HIPEC also reported the same tendency that there was no significant difference in OS or PFS between RCC and LCC (median OS 3.5 versus 4.0 years, HR = 0.99, 95% CI 3.5-4.4 years, $P = 0.90$) patients (*46*).

On the other hand, other retrospective studies with a smaller patient population reported worse prognosis of RCC after CRS plus HIPEC. A retrospective cohort study from the US in 2019 with 336 patients with peritoneal metastases from CRC reported a significantly shorter OS for RCC compared to LCC (median 30 months versus 45.4 months, $P = 0.028$), and RCC was an independent predictor of worse DFS and OS on multivariate analysis (*47*). A retrospective study from the US in 2019 with 115 patients with peritoneal metastases from CRC who underwent CRS plus HIPEC showed the same result of significantly inferior DFS (HR = 2.27, 95% CI 1.09-4.76, $P = 0.029$) and OS (HR = 2.57, 95% CI 1.13-5.84, $P = 0.021$) in RCC compared to LCC (*48*). Another retrospective study from US in 2020 with 272 patients with peritoneal metastases from CRC who underwent CRS plus HIPEC showed the same result of significantly shorter DFS and OS in RCC compared to LCC (15.5 months versus 34 months, $P = 0.0010$) (*49*).

The results of studies on PTL and surgical outcomes after CRS plus HIPEC for peritoneal metastases from CRC are summarized in Table 3. Given the differing results between these studies, it seems that the PTL may affect the prognosis of peritoneal metastases from CRC, and RCC patients have worse survival than LCC patients, while the impact of PTL on surgical outcome particularly with CRS plus HIPEC still remains controversial.

PTL and other distant metastases from CRC

Although not related to surgical management, a few studies reported the effect of PTL on other distant metastases such as brain or bone metastases. A recent retrospective SEER database study from China in 2020 investigated a total of 202,401 CRC patients. In this study, CRC was classified into three groups: RCC, LCC (from the splenic flexure and rectosigmoid junction), and rectal cancer. The reported overall incidence of brain or bone metastasis at initial diagnosis was 1.38% and 6.12% in metastatic CRC patients, respectively. PTL was associated with the incidence of bone metastasis with the lowest incidence for RCC (4.69%) and the highest incidence for rectal cancer (8.56%), while not associated with that of brain metastasis. As to prognosis, as with liver metastases, RCC patients had the shortest median survival in both brain (3 months) and bone metastasis (4 months) compared to LCC and rectal cancer patients (*9*).

Conclusion

Although the reason for the differences caused by PTL remains still unclear and probably multifactorial, the current understanding is that RCC is significantly associated with inferior survival after surgical resection compared to LCC in locally advanced CRC and liver metastases from CRC. In lung metastases from CRC, the role of PTL still remains uncertain because of the limited number of studies. Regarding peritoneal metastases from CRC, the role of PTL still seems controversial and needs further study to clarify the effect of PTL on surgical management. The very simple clinical factor of PTL in CRC could be an important biomarker for predicting the therapeutic outcome of surgical resection of primary and metastatic CRC. Further clinical and basic research will facilitate the clinical application of PTL in a more specified and personalized manner.

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