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Contents

Monthly Volume 11 Number 5 May 24, 2020

REVIEW

- 250 Immunotherapy – new perspective in lung cancer
Pinheiro FD, Teixeira AF, de Brito BB, da Silva FAF, Santos MLC, de Melo FF
- 260 CITED2 and the modulation of the hypoxic response in cancer
Fernandes MT, Calado SM, Mendes-Silva L, Bragança J

MINIREVIEWS

- 275 Formulation strategies in immunotherapeutic pharmaceutical products
Zhang Y, Williams III RO, Tucker HO

ORIGINAL ARTICLE**Retrospective Cohort Study**

- 283 Human epidermal growth factor receptor 2 positive rates in invasive lobular breast carcinoma: The Singapore experience
Kee GJ, Tan RYC, Rehena S, Lee JJX, Zaw MWW, Lian WX, Yeong J, Tan SM, Lim SH, Tan BKT, Yap YS, Dent RA, Wong FY, Lee GE

SYSTEMATIC REVIEWS

- 294 Impact of primary tumour location on colorectal liver metastases: A systematic review
Bingham G, Shetye A, Suresh R, Mirnezami R

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Impact of primary tumour location on colorectal liver metastases: A systematic review

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Abstract

BACKGROUND

Colorectal cancer (CRC) is the third most common cause of cancer-related death worldwide. Despite significant advances in screening, surgical management and adjuvant therapies, average 5-year survival seldom exceeds 60% in most developed nations. Metastatic disease represents the primary cause of mortality in patients with CRC, and the liver is the most common location for distant tumour spread. Up to 25% of patients are found to have synchronous liver metastases at the time of diagnosis and a further 30%-40% will develop metachronous disease in the course of follow-up. It has been suggested that primary tumour location [right side versus left side, primary tumour location (PTL)] can influence oncological outcomes in this patient group and that this should be considered in prognostic models and therapeutic decision-making algorithms. This suggestion is not universally accepted and there have been conflicting reports in the literature to date.

AIM

To provide a comprehensive summary of the available evidence regarding the impact of PTL on oncological outcomes in patients with colorectal cancer liver metastases (CRCLM).

METHODS

MEDLINE, EMBASE and COCHRANE were searched for relevant publications using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses methodology. Data on oncological outcomes was then extracted from full text articles that met the predefined inclusion criteria.

RESULTS

A total of 41 studies were identified that met predefined inclusion criteria for this review. In 21 out of 38 studies that provided data on overall survival, a statistically significant improvement in overall survival was reported in patients

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with left sided primary tumours. These studies included a total of 13897 patients compared with 4306 patients in the studies that did not show a significant difference. Eight studies noted a similar trend towards improved disease-free or progression-free survival. Several authors observed distinct patterns of relapse after treatment of hepatic metastases according to PTL; for example hepatic recurrence after treatment of CRCLM appears to occur more aggressively with right-sided CRC.

CONCLUSION

Taken together, the findings of the present review indicate that PTL may have a role as an independent prognostic factor when determining treatment and disease surveillance strategies in CRC. The mechanisms responsible for this variation remain poorly understood, but are likely to relate to molecular, histological and embryological differences, as well as inherent differences in therapeutic sensitivity.

Key words: Liver metastasis; Colorectal cancer; Location; Primary tumour; Outcome

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Core tip: Primary tumour location is associated with differing oncological outcomes and patterns of hepatic metastatic behaviour in patients with colorectal cancer liver metastases. Specifically, this systematic review indicates that there is improved overall survival in patients undergoing treatment for colorectal cancer liver metastases with left-sided colorectal cancer (CRC), compared with right-sided CRC. These findings suggest that primary tumour location may have a role in developing more individually-tailored staging, treatment and surveillance strategies for patients with CRC in the future. Current chemotherapeutic regimens may require additional modification(s) to take into account the fundamental molecular and embryological differences that underpin primary tumour sidedness.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer subtype world-wide with over 1 million new cases diagnosed in 2018^[1]. Metastatic disease represents the primary cause of mortality in CRC, and up to 25% of patients are found to have synchronous metastases at the time of diagnosis. A further 40% will develop metachronous disease and approximately 25%-30% of patients will develop liver metastases in the course of follow-up^[2]. Indications for curative intent treatment of CRC liver metastases (CRCLM) have expanded rapidly over the last three decades, and several key factors have led to improvements in outcome, notably enhanced radiological detection, improved chemotherapeutic efficacy and more aggressive surgical treatment^[3]. With modern combined-modality treatment approaches, 5-year survival in excess of 50% has been reported in selected patients with CRCLM^[4]. Clinico-pathological factors believed to be associated with worse oncological outcome in CRCLM include the presence of synchronous metastases, bi-lobar liver involvement, metastases > 5 cm in size, and the presence of extra-hepatic disease^[4,5]. It has also been suggested by a number of authors that primary tumour location (PTL) - right side versus left side, can influence patterns of hepatic metastatic dissemination and survival^[6,7]. For example, a number of studies have demonstrated inferior oncological outcome in patients undergoing surgical resection of CRCLM with right-sided versus left-sided colonic primary tumours^[8-10]. This has not been a consistent observation, and others have shown no clear association^[11,12]. The aim of the present systematic review is to provide a summary of the available evidence on the impact of PTL on oncological outcomes in patients with CRCLM.

MATERIALS AND METHODS

Identification of studies

An electronic literature search was carried out using MEDLINE (1965 to March 2020), EMBASE (1980 to March 2020) and the Cochrane Library databases. The medical subject heading terms and key words used are as follows: “Colon” or “rectal cancer”, “liver metastasis” or “liver metastases” or “hepatic metastasis” or “hepatic metastases” and “left” and “Right”. Studies, abstracts and citations were scanned for relevance. The latest date of this search was 27 March 2020. The publications deemed relevant were read in full and assessed for inclusion and their references scanned to identify papers not identified in the initial search.

Inclusion criteria

The methodology was designed around the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” recommendations for improving the standard of systematic reviews^[13].

Studies meeting the following criteria were included for review: (1) Language: Full article accessible in English language only; Conference abstracts only were excluded. (2) Patient population: Studies reporting outcomes in ≥ 10 male/female patients aged ≥ 18 years with colorectal cancer and liver metastases. Where multiple publications were identified covering overlapping periods of time from the same institution/research group, the most recent and/or relevant data were selected for inclusion, and (3) Outcome measures: Studies were included if they reported oncological outcome data such as overall survival (OS), progression-free survival (PFS), recurrence-free survival (RFS) or disease-free survival (DFS). Studies reporting oncological outcomes for metastatic colorectal cancer were excluded if results were not reported for liver metastases specifically. Patients with metastases at multiple sites were included if one site was liver.

Data extraction

Three authors (Bingham G, Shetye A, Suresh R) independently extracted the following data from eligible studies: First author, year of publication, country of origin, study type, number of patients by gender, site of primary and age, primary study endpoint(s), secondary endpoint(s), extent and distribution of liver metastases, follow-up duration, adjuvant/neoadjuvant management, overall survival, progression-free survival, recurrence-free survival. Where there was uncertainty regarding inclusion a second author was consulted for consensus. All papers included were graded according to level of evidence using the system proposed by the Scottish Intercollegiate Guidelines Network^[14]. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow-diagram summarising the above search strategy is provided in [Figure 1](#).

RESULTS

A total of 4094 potentially relevant publications were initially identified through the search strategy summarised in [Figure 1](#). After screening of titles and abstracts, 3700 publications were withdrawn, leaving 394 articles for full text review. A reference search from these articles identified a further 26 studies of potential relevance. Of the 420 full text publications that were evaluated, 41 studies, including a total of 18426 patients, were found to meet our predefined inclusion criteria and were included in the review process. Study characteristics from these 41 studies are summarised in [Table 1](#). Study population in these studies ranged from 24 to 3125 patients. Studies comprised two cohort prospective studies^[15,16] (evidence level 2+) and 39 retrospective studies (evidence level 2+ - 2++)^[8-12,17-30], this included 6 papers with pooled analysis (evidence level 2+-2++)^[10,12,15,16,18,49]. There were no randomised controlled trials.

Overall survival

Data on the influence of PTL on OS in CRCLM was provided by 38 of the studies included for review, including a total of 18203 patients. In 21 of these studies (13897 patients -76.3% of the total patient population captured) a statistically significant trend was observed with improved OS in patients with left sided primary tumours undergoing treatment for CRCLM (*l*-CRCLM). For example, Wang *et al*^[17] in their study of 1508 patients receiving surgical treatment for synchronous CRCLM, of which 593 had right sided primary colorectal tumours (*r*-CRCLM), found a significant difference in 5-year OS between left and right sided primaries (*l*-CRCLM 40.1%, *r*-CRCLM 24.6%, $P < 0.001$). They also found that patients with *r*-CRCLM were more

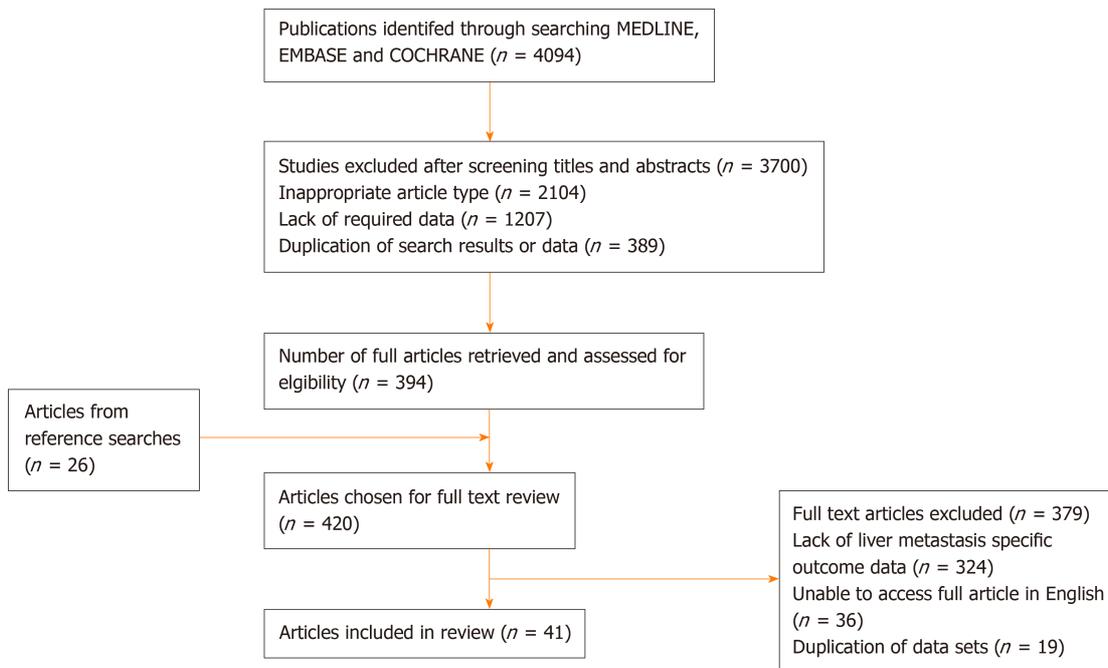


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram summarising study selection process.

likely to be T4 (31.3% *vs* 20.1%, $P < 0.001$) N2 (42.5% *vs* 31.8%, $P < 0.001$), and poorly differentiated (30.5% *vs* 15.1%, $P < 0.001$). Creasy *et al*^[9] in a similar cohort of 907 patients (36% with right sided primaries) undergoing hepatic resection found a median OS of 5.2 years in *l*-CRCLM compared with 3.6 years with in *r*-CRCLM ($P = 0.004$), with a hazard ratio (HR) of 1.22 ($P = 0.028$) on multivariate analysis. In their population database study of 3125 patients in Sweden Norén *et al*^[18] found that *l*-CRCLM extended median OS by 4 mo ($P = 0.02$) compared with *r*-CRCLM. In addition, the authors reported enhanced 5-year OS (45.8% *vs* 44.5% $P = 0.02$), with a HR of 0.75 for *l*-CRCLM ($P < 0.001$).

A further 17 studies with 4306 patients found no statistically significant difference in OS between the two groups, but there was a trend towards longer OS in patients with *l*-CRCLM on the whole. For example, Gasser *et al*^[12] found patients with a *l*-CRCLM had 22 mo longer median overall survival compared to *r*-CRCLM ($P = 0.051$). This contrasts with only 2 studies that showed lower OS in patients with *l*-CRCLM study, Dulundu *et al*^[19] and Viganò *et al*^[20], but neither with statistical significance ($P = 0.072$ and $P < 0.05$ respectively). These results are summarised in Table 2.

Disease-free survival

Benefit in DFS was also suggested, but not as convincingly as OS. This data was more sparsely provided, as some authors opted to alternatively provide PFS. Four studies including 3013 patients showed improved DFS in *l*-CRCLM. Russolillo *et al*^[21] found improved median DFS by almost 1 year (32.7 mo *vs* 20.8 mo, $P = 0.002$) in their 364 patients with *l*-CRCLM (*vs* 322 patients with *r*-CRCLM) when assessing patterns of recurrence and survival following resection of liver metastases. In 2017 Heise *et al*^[22] reported a DFS benefit in patients with *l*-CRCLM undergoing repeat hepatectomy after recurrence of colorectal cancer (HR: 0.19, $P = 0.001$). Liao *et al*^[10] studied 1442 patients with stage III CRC who went on to develop CRCLM, and found that patients with left-sided colon cancer had better 3-year DFS (70.9% *vs* 66.5%, $P = 0.033$) compared to those with *r*-CRCLM.

In contrast to these observations, only one study by Sasaki *et al*^[23] found significantly improved 3-year DFS in patients with *r*-CRCLM (28% *vs* 20.2%, $P = 0.001$) in their study of 426 patients who were undergoing curative intent hepatectomy.

Thirteen studies with 3423 patients showed no significant difference in DFS between *l*-CRCLM and *r*-CRCLM. These results are summarised in Table 3.

Progression-free survival

Only five publications provided data on PFS, and these data are summarised in Table 4. These studies including 2805 patients showed significantly improved PFS in *l*-CRCLM versus *r*-CRCLM. For example, de Haas *et al*^[24] showed in 726 patients

Table 1 Summary of characteristics of included studies

Ref.	Year	Country of study	Number of patients included	Median follow up (mo)	Primary tumour location (n)			Median age (yr)		
					L	R	Rectum	L	R	Rectum
Zhou <i>et al</i> ^[27]	2017	China	295	24	89	94	112	57	59	61
Zhang <i>et al</i> ^[30]	2017	China	194	12	144	50		60	55.5	
Makowiec <i>et al</i> ^[37]	2018	Germany	221		158	63		64	65	
Chafai <i>et al</i> ^[29]	2005	Australia	398	26.8	277	71				
Rougier <i>et al</i> ^[15]	1995	France	537		197	117	223			
Wang <i>et al</i> ^[38]	2018	China	420	26	334	86		57	58.5	
Gu <i>et al</i> ^[28]	2018	China	102		51	51		63	61.5	
Gasser <i>et al</i> ^[12]	2019	Austria	259	38.1	200	59		64	66	
de Haas <i>et al</i> ^[24]	2010	France	750	39	413	154	200			
Marques <i>et al</i> ^[11]	2018	Brazil	151	42	124	27		57	61	
Russolillo <i>et al</i> ^[21]	2019	Italy	686	81	364	322		63	66	
Umeda <i>et al</i> ^[34]	2013	Japan	100	36	40	23	37			
Zheng <i>et al</i> ^[31]	2018	China	318		233	85				
Mavros <i>et al</i> ^[39]	2013	United States	97	26.4	44	24	27			
Viganò <i>et al</i> ^[20]	2014	Italy	749	51.4	63	87	48			
Connor <i>et al</i> ^[40]	2016	Canada	63	31.5	27	10	21			
Eefsen <i>et al</i> ^[41]	2015	Denmark	254	44.6	125	51	78			
Schirripa <i>et al</i> ^[33]	2015	Italy	309	45.6	138	87	82			
Loosen <i>et al</i> ^[42]	2018	Germany	125		102	23				
Amikura <i>et al</i> ^[32]	2018	Japan	342	52.7	236	106				
Yamashita <i>et al</i> ^[26]	2018	United States	725	27/41	487	238		56	58	
Dulundu <i>et al</i> ^[19]	2017	Turkey	108		40	24	44	58.5	63.2	63.8
Creasy <i>et al</i> ^[9]	2016	United States	907	132	578	329		62.4	65.4	
Sasaki <i>et al</i> ^[23]	2016	United States	426	28.9	297	129				
Palkovics <i>et al</i> ^[43]	2018	Hungary	319		114	72	133			
Dupré <i>et al</i> ^[8]	2018	United Kingdom	364	41.8	290	74		65.1	68.6	
Heise <i>et al</i> ^[22]	2017	Germany	160	21	113	47				
Shigematsu <i>et al</i> ^[44]	2018	Japan	396	36.4	155	93	148			
Rhu <i>et al</i> ^[45]	2017	South Korea	410	30.5	289	121		58.41	59.56	
Lionti <i>et al</i> ^[25]	2018	Italy	63	40	22	23	18			
Wang <i>et al</i> ^[46]	2017	China	159		130	29				
Norén <i>et al</i> ^[18]	2015	Sweden	3125		1109	1092	924			
Berardi <i>et al</i> ^[47]	2018	Belgium	62	24	11	4	47			
Cremolini <i>et al</i> ^[16]	2018	Italy	159	42.1	40	64	52			
McCracken <i>et al</i> ^[48]	2019	United States	612		388	226		55	62	
McVey <i>et al</i> ^[49]	2019	United States	732	26.8	397	336		59	62	
Imai <i>et al</i> ^[35]	2019	Japan	163	38.8	127	36				
Koch <i>et al</i> ^[36]	2018	Germany	30		24	5	1			
Liao <i>et al</i> ^[10]	2018	Taiwan	1442	58.	888	554		62.4	64.6	
Adam <i>et al</i> ^[50]	2011	France	186	37	106	35	41			
Wang <i>et al</i> ^[17]	2019	China	1508		557	593	358			

De Haas *et al*^[24]: Transverse colon grouped with left rather than right sided primaries; Yamashita *et al*^[26]: Data for study and validation sets respectively, midgut *vs* hindgut not left *vs* right. L: Left; R: Right.

undergoing hepatic resection for CRCLM, that patients with *l*-CRCLM had a higher 5-year PFS (18% *vs* 16%, $P = 0.009$). No papers give significant evidence to the contrary and only one study with 63 patients showing no significant difference^[25].

Table 2 Overall survival data

Ref.	Year	Median OS (mo)				5 Year OS (%)				OS Hazard ratio			
		L	R	Rectum	P value	L	R	Rectum	P value	L	R	Rectum	P value
Zhou et al ^[27]	2017	35	33	32		27.5	23.1	23		0.85	1	1.02	
Zhang et al ^[30]	2017	22	12		0.012 ^a								
		14	10										
Makowiec et al ^[37]	2018					41	46						
Chafai et al ^[29]	2005					22.5	9.9		< 0.001 ^a	1	1.68		< 0.001 ^a
Rougier et al ^[15]	1995	8.2	4.5	7.6	< 0.001 ^a								
		6.8	3.8	6.6	< 0.001 ^a								
Wang et al ^[38]	2018					38.3	46.5			1	1.08		
Gu et al ^[28]	2018	40.3	29.4		0.042 ^a					1	6.2		< 0.001 ^a
Gasser et al ^[12]	2019	55.5	33.5	58.2						1	1.53		0.029 ^a
de Haas et al ^[24]	2010					54	36	48	0.001 ^a	1	1.5		
Marques et al ^[11]	2018									1	2.1		
Russolillo et al ^[21]	2019	63.3	35.7		0.002 ^a					0.82	1		< 0.001 ^a
Umeda et al ^[34]	2013									1.24	1	1.62	
Zheng et al ^[31]	2018	29.5	21.9		< 0.001 ^a					0.5	1		< 0.001 ^a
Mavros et al ^[39]	2013									1	1.09		
Viganò et al ^[20]	2014	41.3	58.3	47.4		43.1	44.7	41.3					
Connor et al ^[40]	2016									1	2.4		0.0321 ^a
Eefsen et al ^[41]	2015									0.63	1	0.57	0.045 ^a
Schirripa et al ^[33]	2015	57.3	35.5	61.1	0.017 ^a					1	1.59	0.95	0.017 ^a
Loosen et al ^[42]	2018									1	2.32		
Amikura et al ^[32]	2018					56.1	48.4			1	1.287		
Yamashita et al ^[26]	2018					52	32		< 0.0001 ^a	1	2.04		< 0.0001 ^a
						78	55		0.003 ^a	1	1.9		0.0009 ^a
Dulundu et al ^[19]	2017	30.43	46.38	40.86		52.5	54.1	59					
Creasy et al ^[9]	2016	62.4	43.2			50.4	38.5		0.028 ^a	1	1.22		0.028 ^a
Sasaki et al ^[23]	2016	55.3	44.1		0.033 ^a	53.7	41.5			0.76	1		0.033 ^a
Palkovics et al ^[43]	2018	39	36	40									
Dupré et al ^[8]	2018	45.3	34.6		0.035 ^a	37.5	25.4		0.010 ^a	1	1.429		0.036 ^a
Shigematsu et al ^[44]	2018									0.67	1	0.63	
Rhu et al ^[45]	2017									0.862	1		
Wang et al ^[46]	2017									0.75	1		
Norén et al ^[18]	2015	61	57	48	0.02 ^a	45.8	44.5	42.6	0.02 ^a	0.75	1	0.73	< 0.001 ^a
Cremolini et al ^[16]	2018									0.96	1		
McCracken et al ^[48]	2019	75.6	54		< 0.001 ^a					1	1.6		0.001 ^a
McVey et al ^[49]	2019	43	44.2							1.108	1		
		79.4	64.6		0.037 ^a					0.629	0.788		0.024 ^a
Imai et al ^[35]	2019					55.5	52.3			1	3.44		0.021 ^a
Koch et al ^[36]	2018									0.66	1		
Liao et al ^[10]	2018					75.2	61.7		0.005 ^a				
Adam et al ^[50]	2011					31	0	36	0.003 ^a	1	2.2		0.003 ^a
Wang et al ^[17]	2019					40.1	24.6		< 0.001 ^a	1	1.75		< 0.001 ^a

Zhang et al^[30]: Top group: Overall population, bottom row: Patients who did not receive chemotherapy; Rougier et al^[15]: Resection subgroup data presented in row above non-resection subgroup data; Yamashita et al^[26]: Data for study set displayed above data for validation set; McVey et al^[49]: R1 Resection data displayed over R0 Resection data. OS: Overall Survival.

^aP < 0.05. L: Left; R: Right.

DISCUSSION

The data summarised in this systematic review appear to support the suggestion that CRCLM arising from right-sided colorectal primary tumours are associated with

Table 3 Disease free survival data

Ref.	Year	Median DFS (mo)				3 yr DFS (%)				DFS HR			
		L	R	Rectum	P value	L	R	Rectum	P value	L	R	Rectum	P value
Wang <i>et al</i> ^[36]	2018					22.4	29.1						
Gasser <i>et al</i> ^[12]	2019	12.6	9.1	9.6									
Marques <i>et al</i> ^[11]	2018									1	1.1		
Russolillo <i>et al</i> ^[21]	2019	32.7	20.8		0.002 ^a								
Connor <i>et al</i> ^[40]										1	1.6		
Eefsen <i>et al</i> ^[41]										0.60	1	0.92	
Schirripa <i>et al</i> ^[33]	2015					12.0	10.7	12.6		1	1.23	1.04	
Amikura <i>et al</i> ^[32]	2018					35.4	32.3			1.09	1		
Yamashita <i>et al</i> ^[26]	2018					27	15		0.001 ^a	1	1.71		< 0.0001 ^a
						41	21		0.001 ^a	1	1.48		< 0.0001 ^a
Creasy <i>et al</i> ^[9]	2016					37	29				1.14		
Sasaki <i>et al</i> ^[23]	2016					20.2	28		0.001 ^a				
Heise <i>et al</i> ^[22]	2017									0.19	1		0.001 ^a
Shigematsu <i>et al</i> ^[44]	2018									0.85	1	0.97	
Wang <i>et al</i> ^[46]	2017									1.36	1		
Berardi <i>et al</i> ^[47]	2018									1.06	1	1.63	
Cremolini <i>et al</i> ^[16]	2018									0.81	1		
Imai <i>et al</i> ^[35]	2019	22.9	21.3										
Liao <i>et al</i> ^[10]	2018					70.9	66.5		0.033 ^a				

Yamashita *et al*^[26]: Data for study set above data for validation set, midgut *vs* hindgut, not left *vs* right; Imai *et al*^[35]: 5 Year DFS% not 3-year disease free survival.

^aP < 0.05. DFS: Disease free survival; L: Left; R: Right; HR: Hazard ratio.

inferior OS compared with those arising from the left-sided CRC. Specifically, 21 of the 38 studies that provided data on OS reported statistically significant inferior OS in patients with *r*-CRCLM. Liao *et al*^[10] for example demonstrated in their large study of 1442 patients that patients with *l*-CRCLM had better 5-year OS, 5-year cancer-specific survival, and 5-year RFS, all with statistical significance. In 2018 Yamashita *et al*^[26] similarly concluded in their cohort of 725 patients undergoing upfront hepatic resection, that there was a significant survival benefit to having *l*-CRCLM, but that this benefit was no longer evident after neoadjuvant chemotherapy. The relationship between primary site and DFS and PFS with CRCLM is less clear, though again there appears to be a trend towards improved oncological outcome in *l*-CRCLM. Explaining these variations in oncological outcome is likely to require a deeper understanding of the underlying molecular and embryological differences associated with primary tumour sidedness.

There are subtleties in regards to variable oncological outcome identified in this review that merit further discussion. For example, in terms of DFS, Sasaki *et al*^[23] reported interesting findings in terms of patterns of relapse with *l*-CRCLM compared with *r*-CRCLM. Specifically, in their study patients with *l*-CRCLM exhibited a shorter disease-free interval compared with patients who had undergone treatment for *r*-CRCLM ($P = 0.01$). However, irrespective of timing of relapse, and in spite of a longer disease-free interval, when patients with *r*-CRCLM did succumb to hepatic recurrence, it was consistently found to be with more advanced disease (> 4 recurrent lesions, $P < 0.01$). As a result, the authors found significantly reduced OS and significantly reduced survival after recurrence in *r*-CRCLM, compared with *l*-CRCLM. Thus it is conceivable, for reasons as yet unclear, that the liver is able to “hold off” recurrence of hepatic metastases arising from right-sided primaries for longer, but also that when this does finally occur, it is a more aggressive pattern of progression, leading to the paradoxical observation in some studies of seemingly favourable disease free interval, but ultimately inferior OS with *r*-CRCLM.

Previously the suggestion has been made that the typically more indolent course of presentation of right CRC, might in part be responsible for inferior outcome with resulting liver metastases^[10]. The notion here is that delayed diagnosis of primary tumour results in an increased risk of developing synchronous metastases which are then incurable^[51]. This would mean potentially fewer curative-intent resections offered

Table 4 Progression free survival data

Ref.	Year	Median PFS (mo)				5 yr PFS (%)				PFS HR			
		L	R	Rectum	P value	L	R	Rectum	P value	L	R	Rectum	P value
Zhou <i>et al</i> ^[27]	2017					12.5	7.1	11.5	0.012 ^a	0.67	1	0.85	0.012 ^a
de Haas <i>et al</i> ^[24]	2010					18	16	7	0.009 ^a				
Zheng <i>et al</i> ^[31]	2018	9.2	7.3		0.002 ^a					0.75	1		0.002 ^a
Lionti <i>et al</i> ^[25]	2018									0.5	1	1	
Liao <i>et al</i> ^[10]	2018					70.9	66.5		0.033 ^a				

^a $P < 0.05$. PFS: Progression free survival; L: Left; R: Right; HR: Hazard ratio.

to these patients, resulting in observed abbreviated survival. However, in this study we have also shown that there is evidence that PTL also has prognostic impact in patients with unresectable disease from the outset. For example, Zhou *et al*^[27] reported on outcomes in 295 patients with unresectable CRCLM undergoing palliative radio-frequency ablation, and found similar rates of OS, but that the PFS was significantly better in patients with *l*-CRCLM (HR: 0.67, $P = 0.012$). Gu *et al*^[28] also reported outcomes following palliative-intent radio-frequency ablation in patients with CRCLM, finding that patients with *l*-CRCLM had a significantly lower risk of recurrence outside of the ablation zone, with increased OS of 40.3 mo compared with 29.4 mo in *r*-CRCLM ($P = 0.042$). Multivariate analysis confirmed a HR of 6.2 ($P = 0.001$) for *r*-CRCLM predicting OS. This data is further supported by findings reported by Chafai *et al*^[29] in 2005, who studied patients with unresected synchronous liver metastases after resection of the primary tumour. They found a significantly shorter survival in palliative patients who had *r*-CRCLM compared with *l*-CRCLM (2 years survival 9.9% vs 22.2%, HR: 1.5 $P < 0.001$). In circumstances where palliative/debulking surgery is offered, differences continue to persist for *l*-CRCLM versus *r*-CRCLM. For example, in 2017 Zhang *et al*^[30] found that hepatic palliative resection prolonged median OS by 8 mo in patients with *l*-CRCLM (palliative resection vs no resection: 22 mo vs 14 mo, $P = 0.009$); however, by comparison no such improvement in OS was observed for patients with *r*-CRCLM undergoing palliative resection (12 mo vs 10 mo, $P = 0.910$).

With regards to defining putative mechanistic explanations for these differences, a number of factors should be considered. Firstly, there is considerable evidence that right sided CRCs are significantly more likely to harbor negative prognostic features; they tend to present at a more advanced stage, often in older patients, with a greater chance of synchronous metastatic disease, are more likely to carry unfavourable genetic mutation(s), and show poor differentiation^[18,21,27,31,52]. It could therefore follow that patients with right sided CRC simply present with more advanced and aggressive disease from the outset. This however was not a uniform finding across the studies included in this review. For example, Creasy *et al*^[9] found no such differences between right sided versus left sided CRC in terms of proportion of patients with the largest metastasis > 5 cm, proportion of patients with multiple metastases, or the proportion of patients with extra-hepatic disease. In spite of this relative equipoise, the authors reported significantly improved OS in patients with *l*-CRCLM and suggest that unique differences based on sidedness are likely to exist that extend beyond the aforementioned conventionally accepted differences.

From this perspective a number of mechanisms have emerged that could play a role in contributing to the inferior oncological outcome observed in patients with *r*-CRCLM. These broadly can be considered as: (1) Molecular differences; (2) Histopathological differences; (3) Therapeutic sensitivity differences; and (4) Embryological differences.

Molecular differences

There are well-established molecular differences between right- and left-sided CRC with the former more often exhibiting *KRAS* and/or *BRAF* mutation^[12,33,34,53]. RAS mutations have consistently been found to be associated with more aggressive tumour biology and are identified in up to 45% of patients with metastatic CRC. For example, the studies published by Amikura *et al*^[32] and Shindoh *et al*^[54] both demonstrate that RAS mutational status is associated with significantly worse survival in CRCLM (Amikura *et al*^[32]: 5-year OS: 42.4% vs 65.3%, $P = 0.0006$; Shindoh *et al*^[54]: 3-year DFS 59.9 vs 83.6% $P = 0.016$). Of note, it has also been reported that among patients put forward for curative intent resection of CRCLMs, the incidence of RAS

mutation is only around 10%-15%, indicating that underlying tumour biology, seemingly inseparably linked to PTL, exerts additional prognostic relevance as it appears to indirectly influence surgical candidacy^[53]. Goffredo *et al*^[56] evaluated outcomes in 2655 patients undergoing CRCLM resection. They observed a significant increase in likelihood of mutant KRAS with right-sided PTL, compared to left and correspondingly found reduced OS in patients with *r*-CRCLM. It is likely that additional molecular drivers are responsible for the variations seen according to PTL, and RAS/BRAF likely account for only part of the molecular landscape especially since only a limited proportion of these cases are put forward for resection^[54]. This notion is supported by Huang *et al*^[57] who found no significant association between KRAS/BRAF mutational status and prognosis in patients presenting with metachronous CRCLM.

The role of mismatch repair (MMR) status and microsatellite instability (MSI) in the context of PTL seems less certain. Right sided CRC is more frequently associated with deficient MMR and MSI^[7,56,58]. These tumours tend to be typified by poor differentiation, mucinous features and lymphocytic invasion. Evidence supports the suggestion that MSI is associated with improved oncological outcome^[59,60]. However, this is at odds with the findings of the present review, where *r*-CRCLM appears to have shortened survival. This may reflect fundamental differences in MMR status according to tumour stage. For example, Jernvall *et al*^[61] found MSI to be a more common finding in right sided Stage II CRC, but this was less frequently observed in stage IV disease. In this review molecular data were only available from a limited number of publications and subdivision of molecular phenotype according to PTL has not been provided in most cases. Hence, we are not able to draw any more definitive conclusions on the precise interplay between molecular factors and PTL. Considering these limitations, The Cancer Genome Atlas Network sought to evaluate a broader panel of genetic mutations and defined cases as “hypermutated” where a mutation rate of $> 12/10^6$ bases was found. Out of 276 samples analysed, the majority of hypermutated cases were right sided primary tumours. The group suggest that hypermutated phenotype is a significant negative prognostic feature, and this may in part account for inferior survival with *r*-CRCLM, as noted in the present review^[62].

Histological differences

Several investigators have evaluated tumour histopathological features in order to determine if the difference in sidedness outcomes and tumour aggressiveness can be explained by one or more of these. Desmoplastic growth behaviour, presence of poorly differentiated clusters and tumour budding have all been considered^[25,41,63]. Strong evidence, however, relates to the prevalence of mucinous elements. Viganò *et al*^[20] and Russolillo *et al*^[21] have both demonstrated mucinous adenocarcinoma to be more prevalent in right-sided CRC ($P = 0.002$ and $P = 0.001$, respectively). Viganò *et al*^[20] reported significantly shortened OS with *r*-CRCLM versus *l*-CRCLM. They observed that, when compared with non-mucinous carcinoma, mucinous carcinoma has a higher KRAS mutation rate 61.8% *vs* 36.4%; $P = 0.037$) and lower chemotherapy response rate (63.9% *vs* 85.2%; $P = 0.006$). Specifically, Viganò *et al*^[20] reported lower 5-year OS (33.2% *vs* 55.2%; $P = 0.010$) and DFS (32.5% *vs* 49.3%; $P = 0.037$) for mucinous tumours undergoing hepatic resection. One can extrapolate from these observations that inferior survival and right sided PTL are linked by an increased tendency for mucinous histology.

Therapeutic sensitivity differences

There are also suggestions in the literature that chemosensitivity is important in predicting survival, and that there may be a differing chemosensitivity profile according to PTL. In their meta-analysis of 16 first-line trials evaluating the efficacy of chemotherapy alone *vs* chemotherapy with targeted biologics in patients with unresectable metastatic CRC, You *et al*^[64] found survival of patients with right sided CRC was inferior to those with left in patients receiving chemotherapy alone, implying that right-sided tumours overall are less chemosensitive. This finding is supported by Yamashita *et al*^[26] found that *r*-CRCLM were independently associated with “minor pathological response” (defined as cancer cells accounting for $\geq 50\%$ of residual cells), and were thus less sensitive to chemotherapy with worse RFS and OS. Interestingly, Marques *et al*^[11] found that when selecting patients for CRCLM resection based on chemosensitivity, the survival disadvantage seen with *r*-CRCLM was eliminated. This suggests fundamental differences in tumour biology with the less chemosensitive phenotype more frequently seen with right-sided PTL and in turn associated with poorer survival.

This difference is maintained after the addition of well-established antiangiogenic biologics. You *et al*^[64] found inferior survival in patients with *r*-CRCLM receiving chemotherapy and bevacizumab compared with *l*-CRCLM. Zheng *et al*^[31] studied the

effect of cetuximab as an addition to chemotherapy in KRAS wild-type patients with initially unresectable hepatic metastases. They found a survival benefit to cetuximab in patients with both *r*-CRCLM and *l*-CRCLM, but importantly noted that this effect was more substantial in the latter, with higher rates of effective tumour downstaging and extended OS.

Embryological differences

In terms of embryology, Yamashita *et al*^[26] suggest that the mid-gut embryological origin of the right colon may be responsible for the variable responsiveness of *r*-CRCLM to chemotherapy and differing oncological outcomes. Specifically, in their study of outcomes in 725 patients, they found reduced responsiveness to chemotherapy, reduced RFS and reduced OS in patients with *r*-CRCLM. The authors reported that this difference was maintained irrespective of RAS mutational status, which is considered to be one of the key oncogenic differences between right- and left-sided colon cancers. It is possible however, that other factors centered around the distinct development of these regions of gut, including unique lymphatic and venous drainage basins, and exposures to unique types of bacterial flora, could be contributing to oncological variability. This is an area that requires further research.

Limitations

As a systematic review this paper has some inherent limitations, it is restricted by the quality of the literature available. However, all included papers were graded using the SIGN criteria with small studies excluded to mitigate this. Care was taken to perform a complete literature search, but studies and some work in progress may have been missed. Larger studies and well as future meta-analysis will be necessary to more clearly establish this trend and may provide a deeper understanding of the mechanisms at play.

In conclusion, the present review provides compelling data to support the notion that PTL significantly influences oncological outcome in patients with CRCLM. Overall, the data presented indicate that patients with *r*-CRCLM appear to have truncated overall, disease-free and progression-free survival. Some of these differences are likely to be accounted for by molecular heterogeneity, but other factors such as embryological origin and colonic microbial composition are areas that have received comparatively less attention in terms of research, and these may represent promising avenues to explore in the future. With the understanding that PTL could have prognostic relevance, comes the need to adjust treatment pipelines for patients accordingly. For example, patients with right-sided CRC may require abbreviated intervals between surveillance scans and tumour-marker assessment after primary tumour resection. In addition, given their more aggressive pattern of recurrence after hepatic resection/treatment, patients with *r*-CRCLM may benefit from a more radical first-line treatment of hepatic metastases. For example, the role of non-anatomical resection and the use of locally-ablative techniques in *r*-CRCLM may need more careful consideration.

ARTICLE HIGHLIGHTS

Research background

Colorectal cancer (CRC) is the third most common cause of cancer related death with liver being the most common metastatic site. It has been long suggested that left and right sided primary tumours exhibit different behaviour but relatively little has been written about how this relates specifically to outcomes in colorectal cancer with liver metastases (CRCLM).

Research motivation

To improve current understanding regarding the impact of PTL on CRCLM given the relative paucity of information in this area. This in turn could have a significant impact on patient morbidity and mortality.

Research objectives

To ascertain whether there is a significant difference in oncological outcome in patients with CRCLM depending on PTL and to present some hypotheses that may explain any differences found. This systematic review demonstrates a significant difference in outcomes based on PTL with inferior oncological outcome for patients with right-sided CRC. Further work is needed to better characterise the mechanisms responsible for this variation in order to inform clinical decision making.

Research methods

A systematic review of Medline, Cochrane and Embase using the Terms “The medical subject heading terms and key words used are as follows: “Colon” or “rectal cancer”, “liver metastasis” or “liver metastases” or “hepatic metastasis” or “hepatic metastases” and “left” and “Right”.

This search was combined with a bibliographic search to find the relevant publications and extract data from these papers. The methodology was based around the Preferred Reporting Items for Systematic Reviews and Meta-Analyses' recommendations for systematic reviews

Research results

Twenty-one studies with a total of 18203 patients showed a statistically significant trend of improved overall survival in patient with left sided primary tumours undergoing treatment for colorectal cancer liver metastases (*l*-CRCLM). Four studies including 3013 patients showed improved disease free survival (DFS) in *l*-CRCLM. Only five publications provided data on progression free survival (PFS). These studies including 2805 patients showed significantly improved PFS in *l*-CRCLM *vs* *r*-CRCLM. The findings of this review are congruent with the accepted premise of superior survival in left sided colorectal cancer, and uniquely show that this remains true in the context of metastatic liver disease. We highlight a number of factors that may contribute to this, including KRAS/BRAF mutational status, presence of mucinous elements, and impaired chemosensitivity –all which are shown to be associated with right-sided PTL. The exact interplay between these known factors, PTL, and the emerging new mutations and molecular markers is yet to be determined and work needs to be done to determine the importance of PTL within the conglomeration.

Research conclusions

The findings of this review indicate that PTL may have a role as an independent prognostic factor when determining treatment and disease surveillance strategies specifically in colorectal cancer that has metastasised to the liver. We find improved survival for both resected and unresectable *l*-CRCLM as well as a maintained trend after addition of biologics to established chemotherapy regimens. Hepatic recurrence after treatment of CRCLM appears to occur more aggressively with right-sided CRC, conferring significantly reduced survival. Explaining these variations in oncological outcome requires a deeper understanding of the underlying molecular and embryological differences associated with primary tumour sidedness. Microsatellite instability, interestingly, whilst more common in right-sided tumours, has been shown to be independently associated with improved survival – a finding somewhat incongruent with the overall picture of inferior survival in *r*-CRCLM. This suggests alternative mechanisms beyond MMR and microsatellite instability are likely to be involved. KRAS and BRAF mutational status, mucinous adenocarcinoma, and impaired chemosensitivity are all known to be significantly associated with right-sided CRC, and we show here that this association and the accompanying inferior survival persists in *r*-CRCLM. A better understanding of the role of PTL in the oncological outcomes of metastatic CRC may allow for improved risk stratification and redesigned patient pathways.

Research perspectives

There is a considerable amount of data available on the oncological outcomes of patients undergoing liver resection for CRCLM, as related to PTL. This shows with convincing evidence that outcomes are superior for patients with *l*-CRCLM. Future research should be focused on gathering associated molecular and genetic data as related to PTL to better understand the tumour biology of right-sided CRC. This may allow the determination of ideal molecular markers, both for risk stratification/prognostication, and that may be used as potential therapeutic targets.

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