Chapter 20
Management of the Patient with Rectal Cancer Presenting with Synchronous Liver Metastasis

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Introduction

An estimated 39,610 new cases of rectal cancer (RC) are expected in the United States in 2015 [1]. Synchronous colorectal liver metastasis (SCRLM) occurs in 20 % of patients with locally advanced RC [2, 3]. Median overall survival (OS) for patients with SCRLM is 20–24 months without resection as opposed to 5-year OS of up to 50 % with R0 resection of metastatic disease [4]. Oncologic outcomes continue to improve with the development of new effective chemotherapy regimens and increased hepatectomy rates [5, 6]. Patients with SCRLM constitute a heterogeneous group with varying preoperative fitness, tumor biology, tumor resectability, and symptomatology related to the primary tumor. Potential cure is dependent on the ability to resect all disease, and requires a multidisciplinary approach. Locally advanced RC requires chemoradiation (CRT) with surgery, whereas SCRLM is initially addressed with chemotherapy. Surgery for symptomatic relief is reserved for select cases. The optimal sequence of multimodality treatment to address the primary tumor and associated metastatic disease is under active investigation.

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Search Strategy

An electronic search was conducted using the PubMed database for reports published in the English language between January 1990 and October 2015 using the key words rectal cancer in various combinations with liver metastasis(es), hepatic metastasis(es), staged resection, simultaneous resection, synchronous resection, combined resection, liver-first, chemotherapy, and radiation. Referenced studies from identified reports were reviewed if relevant. The "related articles" function was used to further expand the search. Only studies published between 2000 and 2015 clearly identifying at least 20 patients with RC and synchronous liver metastases were included in the tables summarizing the studies. If more than one study was reported from the same institution, the most recent study focusing on RC was included.

Patient population	Intervention	Comparator	Outcomes studied
Patients with RC and SCRLM	Staged rectum-first approach	Liver-first approach Simultaneous resections approach	Perioperative morbidity Disease free survival (DFS) OS

Results

Evaluation of the Patient with Rectal Cancer and Synchronous Hepatic Metastasis

The initial evaluation of patients with rectal cancer and SCRLM includes determination of symptomatology, colonoscopy, staging, determination of resectability from an oncologic standpoint, and evaluation of the future liver remnant based on imaging before and after multimodality treatment, as well as assessment of fitness for surgery. In addition to imaging of the primary tumor with magnetic resonance imaging (MRI) and endorectal ultrasound [7], computed tomography (CT) is useful to evaluate distant disease. Contrast-enhanced MRI can detect or further characterize small hepatic lesions and is superior to CT in the setting of post-chemotherapy hepatic steatosis [8]. Fluorodeoxyglucose-positron emission tomography (FDG-PET) can detect extrahepatic disease that would preclude curative resection and change management in up to 24 % of cases [9, 10]. Two randomized prospective trials reported conflicting results regarding the utility of FDG-PET [11, 12]. Ruers et al. demonstrated that non-curative surgery was avoided in one of six patients as a result of PET findings [11] whereas Moulton et al. failed to confirm these results [12]. Additional studies have supported the use of FDG-PET in patients with rectal cancer and SCRLM [13–20]. Sensitivity of PET after chemotherapy is reduced due to decreased metabolic activity of residual tumor [21–24].

Liver biopsy can be helpful in select cases with equivocal imaging findings but should not be performed routinely due to the risk of tract seeding [25–28].

Treatment Options

Following a diagnosis of rectal cancer with SCRLM, the treatment plan is formulated with the goal of prolonging survival and maximizing the prospects of a curative resection. Many studies combine both colon and rectal cancer and are compromised by selection bias; no prospective randomized data comparing treatment approaches exists to guide management decisions. Rectal cancer presents additional challenges compared to colon cancer with concerns for local recurrence, potential need for adjuvant or neoadjuvant radiation therapy, and complexity of pelvic surgery. The heterogeneity of scientific data pertaining to chemotherapy and radiation regimens, and the introduction of various drugs during the last two decades add to the challenges of data interpretation [29, 30].

Table 20.1 summarizes studies directly comparing the perioperative results of surgical approaches for colorectal cancer with SCRLM. Table 20.2 shows comparative oncologic outcomes of those studies. Table 20.3 presents outcomes of case series of the different surgical approaches.

Multimodality Treatment Although chemotherapy is generally included in the treatment plan of patients with SCRLM, there is no consensus on timing, benefit, and risk. The EORTC 40983 randomized trial demonstrated improvement in progression free survival but not overall survival when six cycles of neoadjuvant and six cycles of adjuvant FOLFOX were administered perioperatively, compared to surgery alone. Resection rates were equivalent in both groups showing that the window of resectability is not lost with neoadjuvant chemotherapy. Notably, the chemotherapy group had fewer nontherapeutic laparotomy rates (5 % versus 11 %) [76, 77]. Similarly, two meta-analyses comparing surgery with or without chemotherapy demonstrated the benefit of chemotherapy in disease free but not overall survival [78, 79].

Neoadjuvant chemotherapy allows early treatment of micrometastatic disease, and provides upfront information regarding tumor biology and response to adjuvant chemotherapy. Outcomes after hepatectomy are superior in patients with a positive tumor response to neoadjuvant chemotherapy as opposed to nonresponders [6, 80, 81]. This selects out patients with progression of disease on chemotherapy prior to surgery, who have significantly lower disease free and overall survival [82]. Neoadjuvant chemotherapy may also improve resectability in borderline resectable or initially unresectable SCRLM [83–85]. Disadvantages of upfront chemotherapy include the risk of progression of initially resectable disease [86], the dilemma of disappearing liver metastases, as well as liver injury prior to hepatectomy. There is conflicting evidence regarding the safety of neoadjuvant chemotherapy prior to liver surgery [87–92], and the response to treatment should typically be assessed every

Table 20.1 Studies comparing morbidity and mortality of surgical approaches for CRC with SCRLM

Author (year)	N (RC with SCRLM)	Follow-up (months)	Approach, N (RC with SCRLM)	Morbidity (%)	P value	Mortality (%)	P value	RC cases analyzed separately (Y/N)	Quality of Evidence
Weber (2003) [31]	97 (34)	30	SR, 35 (10)	23	0.326	0	NS	N	low
			RF, 62 (24)	32		0			
Chua (2004) [32]	96 (45)	NR	SR, 64 (32)	53	0.25	0	NS	N	low
			RF, 32 (13)	41		0			
Capusotti (2007) [33]	79 (27)	NR	SR, 31 (10)	33	0.037	1	0.392	N	low
			RF, 48 (17)	56		0			
Reddy (2007) [34]	610 (162)	NR	SR, 135 (54)	36	0.86	3	NR	N	low
			RF, 475 (108)	39		1			
Thelen (2007) [35]	219 (78)	70	SR, 40 (6),	18	0.166	10	0.012	N	low
			RF, 179 (72)	25		1.1			
Turrini (2007) [36]	119 (44)	66	SR, 57 (24)	21	0.07	3.5	0.09	N	low
			RF, 62 (20)	31		5			
Yan (2007) [37]	103 (42)	24	SR, 73 (27)	32	NR	0	NS	N	low
			RF, 30 (15)	43		0			
Assumpcao[a] (2008) [38]	141 (57)	31	SR, 21 (21)	20 (for liver resection)	–	2.1	–	Y (all RC)	low
			RF, 36 (36)						
Martin (2009) [39]	230 (53)	NR	SR, 70 (30)	56	0.24	2	NS	N	low
			RF, 160 (23)	55		2			
Moug (2009) [40]	64 (24)	NR	SR, 32 (12)	34	0.69	0	NS	N	low
			RF, 32 (12)	59		0			
Slupski (2009) [41]	89 (24)	NR	SR, 28 (10)	14	0.9	0	NR	N	low
			RF, 61 (14)	13		1			

Author (year)	N (RC with SCRLM)	Follow-up (months)	Approach, N (RC with SCRLM)	Morbidity (%)	P value	Mortality (%)	P value	RC cases analyzed separately (Y/N)	Quality of Evidence
Brouquet (2010) [42]	156 (81)	25	SR, 43 (18)	47	NS	5	NS	N	low
			RF, 72 (35)	51		3			
			LF, 27 (19)	37		0			
Cellini (2010) [43]	74 (74)	23	SR, 30 (30)	NR	–	0	NS	Y (all RC)	low
			RF, 13 (13)	NR		0			
De Haas (2010) [44]	228 (41)	41	SR, 55 (12)	11	0.015	0	0.557	N	low
			RF, 173 (29)	25		0.6			
Luo (2010) [45]	405 (206)	NR	SR, 129 (69)	47	>0.05	1.5	1.000	N	low
			RF, 276 (137)	54		2			
van der Pool (2010) [46]	57 (57)	34	SR, 8 (8)	25R[b], 25 L	0.59R 0.39 L	0	NS	Y (all RC)	low
		40	RF, 29 (29)	31R, 17 L		0			
		28	LF, 20 (20)	20R, 30 L		0			
Vigano (2011) [47]	36 (36)	39	SR, 32 (32)	31	NR	5	NR	Y (all low/ mid RC)	very low
			RF, 4 (4)	25		0			
Abbott (2012) [48]	144 (87)	36	SR, 60 (34)	38	NR	3.3	0.38	N	low
			RF, 84 (53)	41		1.2			
Dexiang (2012) [49]	1061 (357)	19	SR, NR	25	NS	2	NS	N	low
			RF, NR	21		2.4			

(continued)

Table 20.1 (continued)

Author (year)	N (RC with SCRLM)	Follow-up (months)	Approach, N (RC with SCRLM)	Morbidity (%)	P value	Mortality (%)	P value	RC cases analyzed separately (Y/N)	Quality of Evidence
Mayo (2013) [50]	1004 (276)	34	SR, 329 (91)	27	>0.05	2.7	>0.05	N	low
			RF, 647 (170)	25		3.2			
			LF, 28 (15)	39		0			
Slesser (2013) [51]	112 (49)	NR	SR, 36 (19)	25	0.161	6	0.241	N	low
			RF, 76 (30)	45		1.3			
van Dijk (2013) [52]	50 (50)	32	SR, 26 (26)	31	–	0	–	Y (all RC)	low
			RF, 12 (12)						
			LF, 7 (7)						
Fukami (2015) [53]	63 (28)	NR	SR, 41 (16)	22	0.758	0	NS	N	low
			RF, 22 (12)	27		0			
Sabbagh (2015) [54]	52 (52)	42	SR, 15 (15)	58R[b], 15 L	0.06R 0.9 L	0	NS	Y (all low/ mid RC)	low
			RF, 27 (27)	30R, 10 L		0			
			LF, 10 (10)	60R, 20 L		20			
She (2015) [55]	116 (32)	23	SR, 28 (13)	25	0.28	7.1	0.29	N	low
		28	RF, 88 (19)	16		1.1			
Silberhumer (2015) [56]	198 (198)	NR	SR, 145 (145)	41	0.30	0	NS	Y (all RC)	low
			RF, 53 (53)	47		0			

CRC colorectal cancer, *RC* rectal cancer, *SCRLM* synchronous colorectal liver metastasis, *NR* not reported, *NS* not significant, *DFS* disease free survival, *OS* overall survival, *SR* simultaneous resection approach, *RF* rectum-first approach, *LF* liver-first approach

[a] Study included both synchronous and metachronous metastatic disease and no separate analysis of synchronous disease was performed. This study was not focused on surgical outcomes

[b]Morbidity related to rectal resections (R) and liver resections (L) reported separately

Table 20.2 Studies comparing DFS and OS of surgical approaches for CRC with SCRLM

Author (year)	N (RC with SCRLM)	Follow-up (months)	Approach, N (RC with SCRLM)	DFS (% 5-year *or* months)	P value	OS (% 5-year *or* months)	P value	RC cases analyzed separately (Y/N)	Quality of Evidence
Weber (2003) [31]	97 (34)	30	SR, 35 (10)	NR	–	21 %	0.967	N	Low
			RF, 62 (24)	NR		22 %			
Chua (2004) [32]	96 (45)	NR	SR, 64 (32)	9 %	0.53	29 %	0.52	N	Low
			RF, 32 (13)	14 %		43 %			
Minagawa (2006) [57]	160 (76)	49	SR, 142 (72)	NR	–	37 months	0.95	N	Low
			RF, 18 (4)	NR		31 month			
Thelen (2007) [35]	219 (78)	70	SR, 40 (6),	NR	–	53 %	0.983	N	Low
			RF, 179 (72)	NR		39 %			
Turrini (2007) [36]	119 (44)	66	SR, 57 (24)	19 months	0.04	32 %	0.06	N	Low
			RF, 62 (20)	14 months		25 %			
Yan (2007) [37]	103 (42)	24	SR, 73 (27)	14 %	NS	36 %	0.9	N	Low
			RF, 30 (15)	14 %		37 %			
Assumpcao (2008) [38]	141 (57)	31	SR, 21 (21)	33 %	–	34 %	–	Y (all RC)	Low
			RF, 36 (36)						
Yoshidome (2008) [58]	137 (59)	NR	SR, 116 (49)	52 %[a]	0.003	NR	–	Y	Low
			RF, 21 (10)	87 %					
Moug (2009) [40]	64 (24)	NR	SR, 32 (12)	10 month	0.487	21 %	0.838	N	Low
			RF, 32 (12)	14 months		24 %			
Slupski (2009) [41]	89 (24)	NR	SR, 28 (10)	NR	–	45 %	0.006	N	Low
			RF, 61 (14)	NR		38 %			

(continued)

Table 20.2 (continued)

Author (year)	N (RC with SCRLM)	Follow-up (months)	Approach, N (RC with SCRLM)	DFS (% 5-year *or* months)	P value	OS (% 5-year *or* months)	P value	RC cases analyzed separately (Y/N)	Quality of Evidence
Brouquet (2010) [42]	156 (81)	25	SR, 43 (18)	11 month	NS	55 %	0.389	N	Low
			RF, 72 (35)	11 month		48 %			
			LF, 27 (19)	11 month		39 %			
Cellini (2010) [43]	74 (74)	23	SR, 30 (30)	NR	–	54 months	0.1	Y (all RC)	Low
			RF, 13 (13)	NR		50 month			
De Haas (2010) [44]	228 (41)	41	SR, 55 (12)	8 %[b]	0.005	74 %[b]	0.871	N	Low
			RF, 173 (29)	26 %		70 %			
van der Pool (2010) [46]	57 (57)	34	SR, 8 (8)	15 months	–	73 %	NR	Y (all RC)	Low
		40	RF, 29 (29)			28 %			
		28	LF, 20 (20)			67 %			
Vigano (2011) [47]	36 (36)	39	SR, 32 (32)	40 %	–	59 %	–	Y (all low/ mid RC)	Very low
			RF, 4 (4)						
Abbott (2012) [48]	144 (87)	36	SR, 60 (34)	18 months	0.95	66 months	0.62	N	Low
			RF, 84 (53)	18 months		66 months			
Andres (2012) [59]	787 (202)	NR	RF, 729 (169)	26 %	0.992	46 %	0.965	N	Low
			LF, 58 (33)	30 %		48 %			
Dexiang (2012) [49]	1061 (357)	19	SR, NR	NR	–	44 %	NS	N	Low
			RF, NR	NR		49 %			
Mayo (2013) [50]	1004 (276)	34	SR, 329 (91)	NR	–	42 %	0.526	N	Low
			RF, 647 (170)	NR		44 %			
			LF, 28 (15)	NR					

Author (year)	N (RC with SCRLM)	Follow-up (months)	Approach, N (RC with SCRLM)	DFS (% 5-year *or* months)	P value	OS (% 5-year *or* months)	P value	RC cases analyzed separately (Y/N)	Quality of Evidence
Slesser (2013) [51]	112 (49)	NR	SR, 36 (19)	33 %[b]	0.837	75 %[b]	0.379	N	Low
			RF, 76 (30)	32 %		64 %			
van Dijk (2013) [52]	50 (50)	32	SR, 26 (26)	36%[c]	–	80 % [c]	–	Y (all RC)	Low
			RF, 12 (12)						
			LF, 7 (7)						
Fukami (2015) [53]	63 (28)	NR	SR, 41 (16)	NR	–	66 %[b]	0.054	N	Low
			RF, 22 (12)	NR		67 %			
Sabbagh (2015) [54]	52 (52)	42	SR, 15 (15)	32 months	0.1	48 months	0.4	Y (all low/ mid RC)	Low
			RF, 27 (27)	31 month		60 month			
			LF, 10 (10)	8 months		38 months			
She (2015) [55]	116 (32)	23	SR, 28 (13)	28 %[b]	0.089	0	0.003	N	Low
		28	RF, 88 (19)	11 %		33 %			

CRC colorectal cancer, *RC* rectal cancer, *SCRLM* synchronous colorectal liver metastasis, *NR* not reported, *NS* not significant, *DFS* disease free survival, *OS* overall survival, *SR* simultaneous resection approach, *RF* rectum-first approach, *LF* liver-first approach

[a]Tweleve-month hepatic disease free survival reported

[b]Three-year survival rates reported

[c]Two-year survival rates reported

Table 20.3 Case series reporting outcomes of surgical approaches for CRC with SCRLM

Author (year)	Approach	N (RC)	Follow-up (months)	Morbidity (%)	Mortality (%)	DFS (% 5-year *or* months)	OS (% 5-year *or* months)	RC cases analyzed separately (Y/N)	Quality of Evidence
de Santibanes (2002) [60]	SR	71 (41)	29	21	0	9 %	38 %	N	Very low
Tsai (2007) [61]	SR	97 (21)	29	8	0	10 %	34 %	N	Very low
Huh (2010) [62]	SR	91 (50)	28	37	1.1	NR	27 %	N	Very low
van der Pool (2010) [63]	BF	105 (33)	26	17	2	25 %	34 %	N	Very low
Boostrom (2011) [64]	SR	45 (45)	60	57	0	28 %	32 %	Y (all RC)	Very low
An (2012) [65]	SR	108 (108)	48	NR	NR	18 months	62 months	Y (all RC)	Very low
Nakajima (2012) [66]	SR	86 (38)	73	64	0	NR	45 %	N	Very low
Roxburgh (2012) [67]	SR	46 (24)	37	33	0	NR	NR	Y	Very low
Ayez (2013) [68]	LF	42 (42)	31	24 L, 31R[a]	NR	40 %	67 %	Y (all RC)	Very low
De Rosa (2013) [69]	LF	37 (25)	NR	40 L, 25R[a]	0 L, 4.2R[a]	NR	30 %[b]	N	Very low
Hatwell (2013) [70]	SR	51 (20)	NR	55	0	NR	NR	Y	Very low
Yoshioka (2013) [71]	SR	127 (49)	45	61	0	17 %	65 %	N	Very low

Author (year)	Approach	N (RC)	Follow-up (months)	Morbidity (%)	Mortality (%)	DFS (% 5-year *or* months)	OS (% 5-year *or* months)	RC cases analyzed separately (Y/N)	Quality of Evidence
Gall (2014) [72]	BF	53 (53)	30	32[c]	NR	19 %	39 %	Y (all RC)	Very low
Lin (2014) [73]	SR	154 (47)	36	29.9	NR	35 %	46 %	N	Very low
Buchs (2015) [74]	LF	34 (34)	36	27	0	NR	53 %	Y (all RC)	Very low
Ferretti (2015) [75]	SR	142 (58)	29	31	2.1	63 %	72 %	N	Very low

CRC colorectal cancer, *RC* rectal cancer, *SCRLM* synchronous colorectal liver metastasis, *NR* not reported, *NS* not significant, *DFS* disease free survival, *OS* overall survival, *SR* simultaneous resection approach, *BF* bowel-first approach, *LF* liver-first approach

[a]Morbidity and mortality related to rectal resections (R) and liver resections (L) reported separately

[b]Three-year survival rates reported

[c]Morbidity only related to liver resection reported

2 months [93]. Some studies have demonstrated no survival advantage to using preoperative vs postoperative chemotherapy [94, 95]. Nevertheless, patients with rectal cancer and SCRLM are more likely to have a locally advanced primary tumor [38, 96], and strong consideration should be given to neoadjuvant therapy.

Targeted chemotherapy with agents such as Cetuximab, Panitumumab, and Bevacizumab has demonstrated improvements in response and resection rates [97–108]. Hepatic arterial infusion chemotherapy may improve resectability or reduce recurrence in experienced centers [109–113].

Combined modality treatment including FU-based chemotherapy plus pelvic radiation is well established for nonmetastatic locally advanced rectal cancer as it has been shown to reduce local recurrence. However, the precise role, necessity and timing of radiation has not been established in the setting of locally advanced rectal cancer in the setting of SCRLM. Of 185 patients who underwent complete resection of rectal cancer and SCRLM by Butte et al., only 4 % developed isolated pelvic recurrence. The majority of recurrences were distant and concomitant radiation therapy was not associated with a reduction in pelvic recurrences [114]. Others have reported similar results [65, 115]. Lee et al. showed that radiation reduced local recurrence only in patients with T4 tumors [116].

FU-based chemotherapy alone, as commonly used as a sensitizer during the administration of pelvic radiation, is probably suboptimal treatment for the synchronous liver disease [117], and more intensive chemotherapy is likely required [29, 118, 119]. Indeed, there is early evidence to suggest that chemotherapy alone without radiation may result in adequate local control. Schrag et al. showed that of 30 patients who completed 6 cycles of FOLFOX with bevicizumab without RT, all had tumor regression and underwent total mesorectal excision with a 25 % complete pathologic response and a 0 % 4-year LR rate [120]. This concept shows promise for patients with rectal cancer and SCRLM.

Classic Staged Resection: Rectum- First Approach The classic staged bowel-first approach addresses the primary tumor prior to liver resection. As such, local symptoms which may interrupt subsequent treatment can be avoided. Additionally, aggressive disease may reveal itself between the staged resections to avoid unnecessary hepatectomy. Gall and colleagues reported on 53 patients with rectal cancer and SCRLM who underwent the rectum-first approach. Chemotherapy followed by combined modality chemoradiation were administered based on locoregional staging of the primary tumor. Proctectomy was performed, followed by hepatectomy 6 weeks later with additional chemotherapy. No patients had progression of liver disease prior to second stage surgery, and all proceeded without a delay caused by complications from the proctectomy. Two patients had unresectable disease at the time of hepatectomy. Five-year DFS and OS were 19 % and 39 % respectively [72].

Yoshidome et al. noticed that 43 % of patients who underwent the staged bowel-first approach for colorectal cancer and SCRLM developed new liver lesions prior to hepatectomy, which changed the initial surgical plan. None developed extrahepatic disease and all were ultimately resectable. The majority of new lesions occurred elsewhere in the liver, suggesting the presence of occult micrometastasis undetect-

able at initial evaluation. Further, hepatic disease free survival was improved when delayed hepatectomy was performed as opposed to simultaneous resection [58]. Disease progression to unresectability between stages is usually related to the identification of new liver or extrahepatic metastases rather than growth of the preexisting liver lesions. This may spare 36 % of patients a nontherapeutic hepatectomy without affecting survival [121].

Staged Resection: Liver-First Approach In the liver-first approach to rectal cancer with SCRLM, 2–6 cycles of neoadjuvant chemotherapy are typically administered prior to liver resection. Chemoradiation followed by proctectomy is then performed [74, 122]. An advantage of the liver first approach is that it avoids the period of at least 3 months required to treat the primary tumor with neoadjuvant chemoradiation and proctectomy prior to addressing the SCRLM, which is the prognostic determinant [122, 123]. Postoperative complications after proctectomy delay timely treatment in up to 50 % of cases [124]. In fact, less than 30 % of patients undergoing bowel-first surgery proceed to the initially planned hepatectomy due to disease progression, whereas up to 80 % undergo liver resection with the liver first approach [59, 125]. Further, resection of the primary tumor as an initial step may result in a loss of inhibition, and progression of metastatic disease [126–130].

A liver first approach with preliminary chemotherapy allows for some responders with initially unresectable SCRLM to be resected. For those whose liver disease remains unresectable for cure, a nontherapeutic proctectomy may be avoided [131]. Complications related to the primary tumor are uncommon during chemotherapy [132–139], and symptoms of bleeding, pain, and mild obstruction at presentation usually resolve after 1–2 cycles of chemotherapy [140].

Mentha et al. first described the liver first approach [122]. They subsequently reported their experience of 33 patients with rectal cancer demonstrating a 5-year overall survival of 61 %, with 15 % developing a pelvic recurrence. Complications related to the primary tumor requiring emergency intervention occurred in two patients (6 %), both of which had R1 rectal resections and ultimately developed recurrences [74].

In the largest reported experience of 42 patients with locally advanced rectal cancer and SCRLM, 74 % of patients completed the entire protocol including resection of the rectal primary. The remaining patients developed metastatic disease prior to addressing the primary tumor, of which 91 % were spared needless rectal surgery. Notably, five patients received a diverting stoma at some point during the protocol to prevent obstruction. Five-year disease free and overall survival were 40 % and 67 % respectively [68]. de Jong et al. reported the option of “watchful waiting” of the primary tumor with this approach should there be a complete clinical response [141].

Simultaneous Resections With advances in perioperative care, anesthesia, surgical technique, and outcomes after liver surgery [4–6, 142, 143], this approach allows resection of both the primary tumor and SCRLM in one operation, but is not recommended during emergent surgery for complications secondary to the rectal tumor

[144]. There are reports of laparoscopic simultaneous resections performed safely [70, 75, 145–152]. Advantages of this approach include shorter cumulative hospital stay, as well as patient convenience of a single operation with less interruption of chemotherapy. The majority of reports describing this approach combines colon and rectal resections, and have significant selection bias towards less extensive SCRLM and liver resections [153].

Boostrom et al. reported the Mayo Clinic experience with 45 patients who underwent synchronous resection for rectal cancer with SCRLM. There were no mortalities and 16 % suffered severe complications, which did not differ amongst patients undergoing abdominoperineal resection or major liver resection (three or more segments). Five-year disease free and overall survival were 28 % and 32 % respectively [64]. Vigano et al. described combined resection for 34 patients with locally advanced mid or low rectal cancer and SCRLM after neoadjuvant chemotherapy, chemoradiation, or both. There was one mortality and a 36 % morbidity rate. Five-year disease free and overall survival were 40 % and 59 % respectively. Five patients had major liver resections [47].

Ferretti et al. studied 142 patients from 14 centers internationally who underwent laparoscopic synchronous resections of SCRLM, 41 % of whom had rectal primaries; only 12 % involved major liver resection. Overall morbidity was 31 % with a 5.6 % anastomotic leak rate, and a mortality rate of 2.1 %. The independent predictors of morbidity were ASA score more than or equal to three and operative time. Rectal primary and major liver resections were not predictors [75].

Utilizing the synchronous approach, there have been successful reports of two-stage hepatectomy for bilobar or advanced SCRLM. This approach allows for proctectomy with the less extensive first stage hepatectomy, followed by major second stage hepatectomy with diverting stoma reversal. Bilobar advanced SCRLM can be addressed while minimizing the number of operations and optimizing timing of chemotherapy delivery [154, 155].

There are reports of increased mortality when extensive liver resections are combined with colorectal resections [34, 156]. Factors shown to increase morbidity of this approach include the presence of a diverting stoma, a rectal primary, duration of surgery, blood loss, and transfusion need [66, 157], indicating that more extensive surgery may be associated with increased morbidity. Others have demonstrated preoperative patient fitness to be the significant predictor as represented by age, ASA grade, and POSSUM score [67]. Outcomes from some reports suggest that this approach may not be appropriate for elderly patients [35, 158], those with locally advanced rectal cancer [144], or those requiring major resections [34, 35]. These data suggest that patient selection is critical to the safety of this approach.

Comparison of Surgical Approaches There are no prospective randomized trials comparing surgical approaches, and most studies combine colon and rectal cancer without analyzing results pertaining to rectal cancer specifically. Comparison of approaches is difficult given the selection bias of staging more extensive SCRLM resections, and difficulty determining cumulative resection rates and morbidity from staged procedures [159, 160].

There are only two small retrospective studies comparing all three approaches for rectal cancer with SCRLM [46, 54]. Sabbagh et al. showed similar complete resection rates, overall complications, mortality, DFS, and OS between all three groups [54]. van der Pool et al. also showed similar morbidity and mortality between the groups. The simultaneous approach was associated with shorter hospital stay, but was applied to patients with early stage primaries and limited liver disease [46].

Silberhumer et al. compared 43 patients who underwent staged rectal first resection with 145 who underwent synchronous resections. The staged group included a larger number of major liver resections for larger liver lesions, and patients undergoing abdominoperineal resection. Morbidity and mortality rates were similar, even in a subgroup analysis of those undergoing major hepatectomy. Hospital stay was significantly shorter in the simultaneous group [56].

Mayo et al. performed the largest multi-institutional retrospective comparison of all 3 approaches including 1004 patients with colorectal cancer and SCRLM, of which 276 had rectal cancer. The liver first group was more likely to have a rectal primary, bilobar disease, and more hepatic lesions treated during liver surgery. Patients in the simultaneous group were less likely to undergo major hepatectomy. Morbidity and mortality rates were similar between groups, even in those undergoing major hepatectomy, although there was a nonsignificant trend towards increased mortality in patients undergoing extended hepatectomy in the simultaneous group. Five-year overall survival was similar among all three groups. Notably, a rectal primary was independently associated with worse survival [50]. Brouquet et al. reviewed the MD Anderson experience of 156 patients with colorectal cancer and SCRLM, 52 % of whom had rectal cancer. Morbidity, mortality, R0 resection rates, DFS, and OS were similar between all 3 approaches. Interestingly, 5 % of patients undergoing the liver first approach developed symptoms related to the primary tumor requiring colostomy, both of whom had nontraversable tumors on initial colonoscopy [42]. Similarly, a meta-analysis comparing all three approaches for CRC showed no difference in morbidity, mortality, or survival despite the tendency of patients with a larger burden of SCRLM to undergo a liver first approach. This suggests that the liver first approach may be appropriate for this group of patients [161].

Recommendations Based on the Data

Evaluation of the Rectal Cancer Patient with Synchronous Hepatic Metastasis

In addition to standard imaging for staging, contrast-enhanced MRI of the abdomen increases detection and further characterizes SCRLM, particularly after neoadjuvant chemotherapy (evidence moderate; weak recommendation). FDG-PET can detect extrahepatic disease prior to surgery; however sensitivity after chemotherapy is reduced (evidence moderate; weak recommendation).

Treatment Options: Multimodality Treatment

Patients with rectal cancer and SCRLM should receive perioperative chemotherapy (evidence high; strong recommendation), however there is no consensus on timing. Neoadjuvant chemotherapy can be recommended, particularly for patients with initially borderline resectable or unresectable SCRLM. Reassessment at 2–4 months from onset of therapy is recommended to minimize liver damage prior to hepatectomy (evidence low; weak recommendation). Radiation therapy may have a benefit in preventing morbid local complications in patients at high risk for pelvic recurrence (evidence low; weak recommendation). Priority should be given towards addressing more common and prognostically more significant distant disease. Isolated local recurrence is uncommon.

Treatment Options: Surgical Approach

All three approaches (rectum first, liver first and synchronous resection) are equivalent regarding safety and oncologic outcome. Patient selection and local expertise are important considerations (evidence low; weak recommendation). Fit patients undergoing surgery with low anticipated blood loss and operative time can safely undergo synchronous resection (evidence low; weak recommendation). Initially diverted, asymptomatic, or mildly symptomatic patients with a locally advanced primary tumor and/or advanced bilobar SCRLM are suitable for the liver first approach (evidence low; weak recommendation). Resectional surgery can be avoided in cases of disease progression. Non-diverted patients with significant symptoms secondary to the primary tumor who may not tolerate the simultaneous approach are well-suited for the rectum first approach (evidence low; weak recommendation.)

A Personal View of the Data

The summarized evidence regarding management of rectal cancer metastatic to the liver is heterogeneous. An individualized approach based on patient characteristics, disease factors, and degree of symptomatology is proposed in Fig. 20.1. In the absence of severe symptoms related to the primary tumor, the authors' approach is to initiate systemic chemotherapy in patients who are potentially resectable. Patients with diffuse bilobar metastatic disease or additional extrahepatic lesions can be palliated based on extent of disease, functional status, and degree of symptoms. Potentially resectable patients should be reassessed following systemic chemotherapy to select out nonresponders who can be palliated non-surgically. Patients who are resectable following chemotherapy can undergo synchronous resection if medically fit, R0 rectal resection is possible, and anticipated morbidity from liver

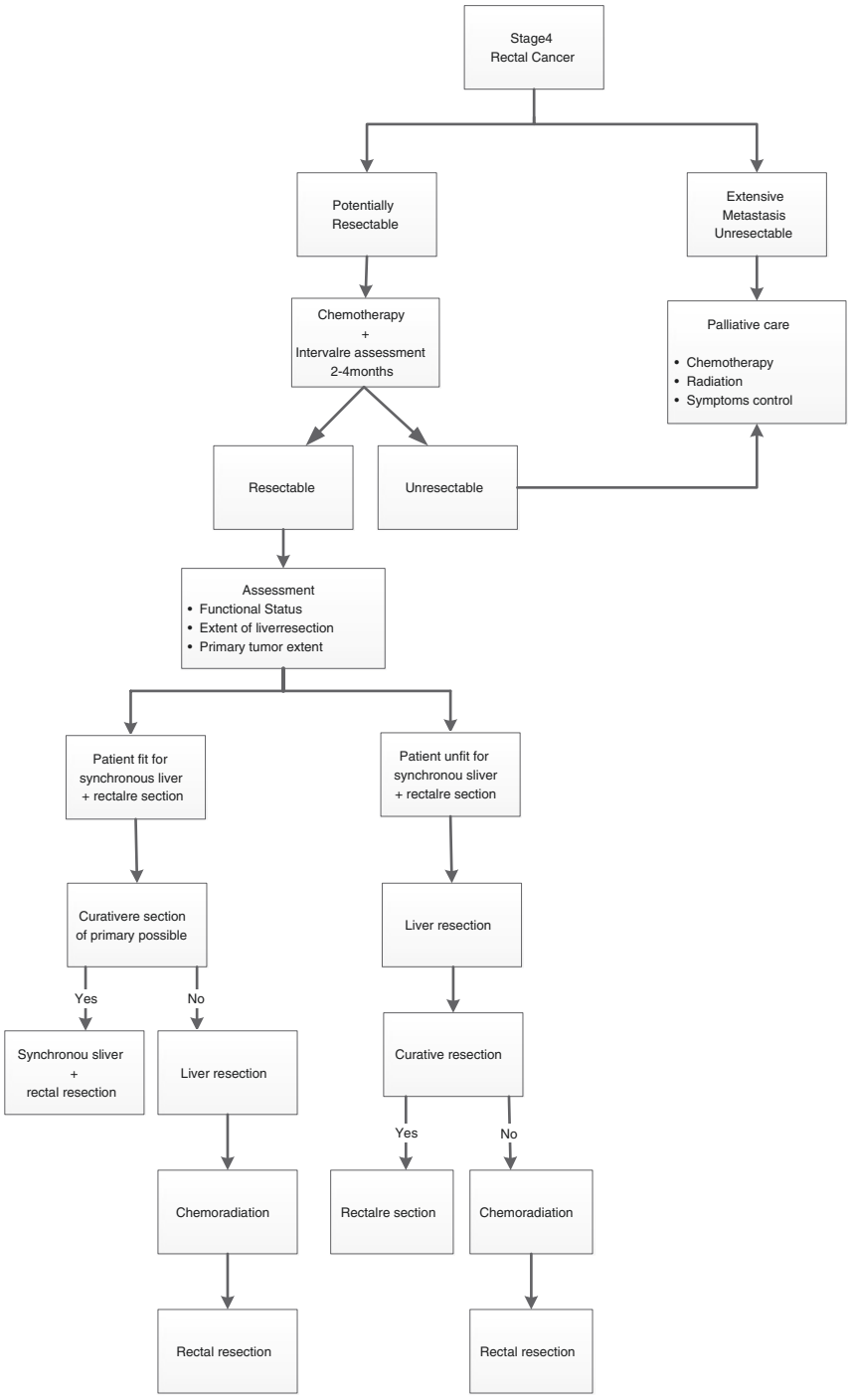

Fig. 20.1 Suggested algorithm for approach of patients with RC and SCRLM

resection based on extent of disease is minimal. Otherwise, a staged liver first approach is advisable, as systemic disease determines disease free and overall survival. Furthermore, complications of rectal resection may further delay treatment if the rectal tumor is resected first.

Following liver resection, proctectomy is performed if curative resection is possible. If radial and/or distal margins are threatened with a higher risk of pelvic recurrence, then chemoradiation precedes rectal resection. Not reflected in the provided algorithm is one additional variation. In healthy patients with extensive SCRLM requiring two-stage hepatectomy, the first stage (minor left-sided resection) is performed with rectal surgery. The second major hepatectomy can be performed with ileostomy reversal in diverted cases. Finally, these recommendations do not apply to patients who present with acute obstruction or profuse rectal bleeding. The former subgroup can be addressed by fecal diversion or in select cases endoluminal stenting, while the latter can benefit from resection of the primary tumor, endoluminal fulguration, or external beam radiation therapy.

Summary of Recommendations

1. In addition to standard imaging for staging, contrast-enhanced MRI of the abdomen increases detection and further characterizes SCRLM, particularly after NCT (evidence moderate; weak recommendation).
2. FDG-PET can detect extrahepatic disease prior to surgery, however sensitivity after chemotherapy is reduced (evidence moderate; weak recommendation).
3. Patients with rectal and SCRLM should receive perioperative chemotherapy (evidence high; strong recommendation), however there is no consensus on timing.
4. Neoadjuvant chemotherapy can be recommended, particularly for patients with initially borderline resectable or unresectable SCRLM. Reassessment at 2–4 month intervals is recommended to minimize liver damage prior to hepatectomy (evidence low; weak recommendation).
5. Radiation therapy may have a benefit in preventing morbid local recurrence in patients at high risk for local recurrence (evidence low; weak recommendation).
6. All three surgical approaches are equivalent regarding safety and oncologic outcome. Patient selection and local expertise are important considerations (evidence low; weak recommendation).
7. Fit patients undergoing surgery with low anticipated blood loss and operative time can safely undergo synchronous resection (evidence low; weak recommendation).
8. Initially diverted, asymptomatic, or mildly symptomatic patients with a locally advanced primary tumor and/or advanced bilobar SCRLM are suitable for the liver first approach (evidence low; weak recommendation).
9. Non-diverted patients with significant symptoms secondary to the primary tumor who may not tolerate the simultaneous approach are well-suited for the rectum first approach (evidence low; weak recommendation).

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