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Stage IV Rectal Cancer with Liver Metastases: Is There a Benefit to Resection of the Primary Tumor?

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Abstract

Background Resection of primary and liver lesions is the optimal management of Stage IV rectal cancer with liver metastases. For patients with extensive liver metastases, FOLFOX and FOLFIRI have improved resection rates and survival. We compared survival outcomes in patients with Stage IV rectal cancer with liver metastases undergoing staged or synchronous resection with those undergoing primary rectal resection only or no resection at all.

Methods Patients with metastatic rectal cancer to liver were identified from a colorectal cancer database from 2002 to 2008. Patients received neoadjuvant chemoradiation and adjuvant FOLFOX or FOLFIRI therapy. The outcomes for patients who underwent synchronous resection, staged resection, resection of rectal tumor only, and no resection with chemotherapy only were compared. Statistical analysis was determined by ANOVA. Survival was determined using the Kaplan–Meier method.

Results Seventy-four patients were identified: 30 synchronous resections, 13 staged resections, 22 primary resection only, and 9 no resection. Median follow-up was 23 months (range = 4-58 months). Sixty-five percent of patients underwent liver resection with 26% rendered eligible for resection after adjuvant therapy. Those who underwent primary resection only had shorter median survival than those who underwent either staged or synchronous liver resection (31 vs. 47 vs. 46 months, respectively; $P = 0.17$). Survival was no different for synchronous versus staged resection ($P = 0.6$). Volume of liver disease predicted resectability ($P = 0.001$). Without liver resection, 2-year survival was approximately 60%. Palliative surgery was required in six of nine patients who did not undergo resection of their primary tumor.

Conclusions Current chemotherapeutic regimens lead to improved survival in patients with unresectable liver metastases. Upfront chemotherapy in the asymptomatic patient compared with resection of the primary tumor does not appear to significantly affect survival. However, given that 60% of patients were alive after 2 years, resection of the primary lesion for palliative reasons and local control must be considered.

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Introduction

Adenocarcinoma of the rectum is a highly treatable and often curable disease. Over half of patients diagnosed with colorectal cancer will develop liver metastases, of which 15-25% will have liver metastases at the time of primary diagnosis [1]. Of these patients only 10-25% are amenable to curative surgical resection [2]. Advances in chemotherapy with combinations of infusional fluorouracil/leucovorin (5-FU) with oxaliplatin or irinotecan (FOLFOX or FOLFIRI) with or without bevacizimab and/or cetuximab have dramatically increased overall survival [3–6], with many of these patients living beyond 2 years [6, 7]. In

addition, these advances in chemotherapy can downstage liver disease in as many as 40% of patients who initially were not candidates for curative resection [7–9]. As a result of these improvements from adjuvant therapy, the appropriate management of the local disease is becoming increasingly important.

For patients in whom a curative resection is not possible, resection of the primary lesion to manage symptoms such as obstruction, perforation, or bleeding is advocated. Patients with asymptomatic Stage IV rectal cancer with unresectable metastatic disease present a curious dilemma. Resection of the primary rectal tumor is advocated by some in order to prevent the need for urgent surgical procedures and the morbidity associated with tumor invasion into pelvic structures [10–13]. Others suggest deferring resection as many of these patients will succumb to progression of systemic disease rather than complications of the primary tumor [14, 15]. In retrospective series, survival has been found to be significantly better in patients with resection of their primary tumor than in those without resection, with median survival ranging from 11 to 16 months [12, 16, 17]. Presently, there are two treatment strategies: (1) initial resection of the asymptomatic lesion followed by adjuvant chemotherapy and (2) initial systemic chemotherapy with post-treatment assessment for further therapy. Both of these strategies are practiced without definitive evidence supporting one treatment option over the other.

Rectal cancer is unique in comparison to colon cancer in that the management of local disease is of greater importance and the timing of palliative or curative surgery in the era of improved chemotherapy is not standardized. With this study our aim was to compare survival outcomes in patients with Stage IV rectal cancer with liver metastases who underwent staged or synchronous resection with the outcomes of those who underwent primary rectal resection only or no resection at all in order to define the optimal management for these patients. We also sought to describe the incidence of tumor-related complications in patients who received initial chemotherapy without resection of their primary tumor.

Methods

A prospective database was queried for all patients diagnosed with Stage IV rectal cancer with liver metastases from 2002 to 2008. This time frame was chosen because since 2002 FOLFOX and FOLFIRI therapies have been the regimens of choice for Stage IV rectal cancer patients. Data collected from inpatient and outpatient records included age, location of tumor, metastatic sites, volume of liver disease, preoperative CEA levels, type and timing of primary tumor resection, timing of liver resection, administration of radiation and chemotherapy, and survival in months from time of diagnosis. Volume of liver disease was determined by review of preoperative radiological studies (CT, MRI, or PET scan) by a board-certified radiologist. Volume of hepatic involvement was divided into three subsets: <25% (mild), 25-75% (moderate), and >75% (extensive). Patients were grouped and analyzed based on the following treatment categories: Group 1, synchronous liver and primary tumor resection; Group 2, staged liver resection after primary tumor resection; Group 3, resection of primary tumor only; and Group 4, resection of neither primary nor liver tumor.

Survival analysis was performed using the Kaplan-Meier product limit method, and survival between groups was compared using the Mantel-Cox log-rank tests. Two patients (one from Group 1 and one from Group 3) were missing survival data and were eliminated from survival analysis. Survival times were calculated from time of diagnosis until most recent follow-up or death. A P value is given when two groups are compared. Statistical analysis was determined by ANOVA for continuous variables. The χ^2 test was used for analysis of categorical data. P values less than 0.05 were considered significant. Statistical calculations were performed using the commercially available software package GraphPad Prism 5.0 (GraphPad Software, San Diego, CA). Approval for this study was obtained from the Washington University School of Medicine's Human Studies Committee.

Results

Patient characteristics

One hundred twelve patients were identified with Stage IV rectal cancer. Thirty patients were excluded due to lack of liver metastases or pathology of primary tumor that was not consistent with adenocarcinoma. The remaining 83 patients had cancer metastatic to the liver either at presentation or during course of treatment. Eight patients were excluded due to incomplete medical records leaving 74 patients available for analysis (Fig. 1).

The median age was 55 years (range = 31-83 years). Patients were grouped into one of four categories depending on their treatment course, as described above (Fig. 1). Patient demographics and clinical and tumor characteristics are compared between groups (Table 1).

All 30 patients in Group 1 were deemed eligible for initial curative resection based on resectability of the liver lesions as determined by a hepatobiliary surgeon and performance status. Patients in Group 2 underwent staged primary resection followed by liver resection for the

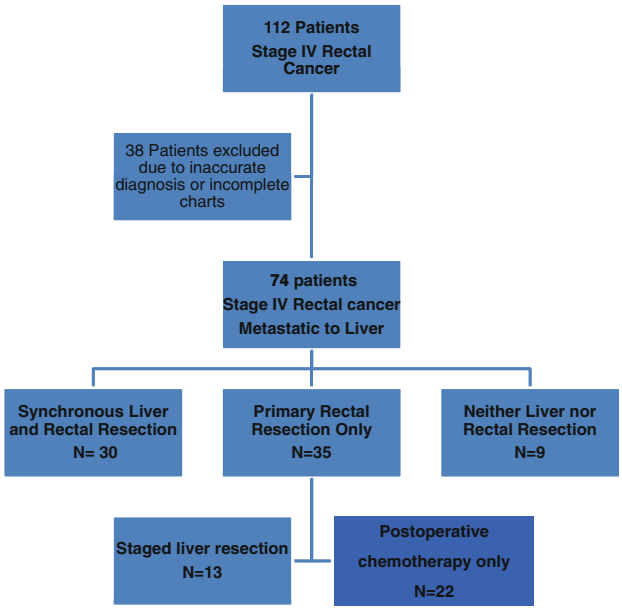

Fig. 1 Treatment course of patients presenting with Stage IV rectal cancer

following reasons: extensive liver disease burden that became resectable after postoperative chemotherapy (9 patients), liver disease discovered after surgery (1 patient), and comorbid medical conditions precluding initial synchronous resection (2 patients). In two patients it was unclear in the records as to why staged resection was performed. In Group 3 resection of the primary tumor only was performed due to symptoms of bleeding or obstruction (4 patients) or perforation during stent placement (2 patients). Thirteen patients had liver disease that was too extensive for initial combined resection and which ultimately did not respond to adjuvant treatment precluding staged resection. Two patients had comorbidities prohibiting initial liver resection with progression of disease during adjuvant therapy.

There were 9 patients who did not undergo surgery for either their rectal or liver tumor (Group 4). Eight patients had either locally advanced or unresectable primary disease precluding safe surgical resection. One patient had a near-complete response to neoadjuvant treatment but refused surgery and underwent endocavitary radiation instead. Another patient had a complete response of the rectal tumor but persistent liver metastases for which he continued chemotherapy. Six patients required creation of a diverting loop colostomy or end colostomy with mucous fistula during the course of their treatment due to the following reasons: obstructive symptoms (4 patients), development of a rectovaginal fistula requiring symptomatic control (1 patient), and colonic perforation (1 patient). At our institution, stenting of obstructing rectal lesions is not routinely performed because of the associated tenesmus and rectal pain from the stents themselves. Formal assessment of quality of life for Stage IV rectal cancer patients was not available. The median time to surgery from diagnosis in this group was 5.5 months.

In all patients studied, six had evidence of lung or peritoneal disease on presentation in addition to liver metastases (one in Group 1, one in Group 3, and four in Group

Table 1 Comparison of clinical and tumor characteristics of patients with Stage IV rectal cancer

	Group 1 (synchronous resection) ($N = 30$)	Group 2 (staged resection) ($N = 13$)	Group 3 (primary resection) ($N = 22$)	Group 4 (no resection) ($N = 9$)	P value
Male:Female	21:9	11:2	17:5	6:3	
Median age at diagnosis (years)	55	58	57	53	0.19
Median tumor distance from anal verge (cm)	8	9	10	4.5	0.12
Surgery performed					
LAR	22	11	13	0	–
APR	7	1	5	0	
Other	1	1	4	6 (all diverting colostomy)	
Volume of hepatic disease at diagnosis (%)					
<25%	28 (93)	12 (92)	14 (64)	3 (33)	0.0001
25-75%	2 (6)	1 (8)	7 (32)	1 (11)	
>75%	0	0	0	3 (33)	
Unknown	1	0	2	2	
Median preoperative CEA (ng/ml)	5.6	4.4	12	29.5	0.46

LAR low anterior resection, *APR* abdominoperineal resection, *CEA* carcinoembryonic antigen

4). The one patient in Group 1 had a lung resection after initial combined rectal and liver surgery. The one patient in Group 3 had a palliative colon resection in the setting of peritoneal disease. Nine patients had interval development of lung or pelvic spread of disease after initial surgery and initiation of chemotherapy (two in Group 1, two in Group 2, and five in Group 3).

Chemotherapy

The majority of patients (80%) in Groups 1-3 received standard preoperative 5-FU/external beam radiation treatment for rectal cancer (Table 2). Postoperatively, 76% of these patients received their full intended course of FOLFOX or FOLFIRI. The remaining 25% had incomplete treatment course due to medical comorbidities or patient noncompliance. Seven patients had unknown treatment courses.

In Group 4, seven of nine patients received external beam radiation during their treatment course. Four patients received multiple treatment lines of both FOLFOX and FOLFIRI. The treatment course of six patients included at least one biologic agent (bevacizumab or cetuximab).

Surgical mortality and survival

No patient who underwent curative or preemptive resection died within 30 days of operation. One patient in Group 4 died shortly after creation of colostomy due to respiratory distress. There were survival data for 96% of all patients available for analysis. The Kaplan-Meier curves depicting overall survival of all four groups are shown in Fig. 2. Median follow-up was 23 months (range = 4-58 months). Median overall survival for the entire cohort from time of diagnosis was 50 months. Although patients who ultimately underwent liver resection for cure tended to have longer median survival, this finding was not statistically significant (54, 50, 32, 37 months for Groups 1-4, respectively; $P = 0.1$).

Extent of hepatic disease was a significant predictor of resectability ($P < 0.001$). Patients in Group 1 had the least volume of hepatic involvement, while more than 50% of the liver was involved with tumor in patients in Groups 3 and 4. Neither the presence of extrahepatic metastatic disease or preoperative CEA levels was a significant predictor of resectability.

Discussion

The optimal treatment for the patient with Stage IV rectal cancer is complex and continues to evolve. The approach to treatment is generally determined by the extent of metastatic disease, the patient's performance status, and the presence of symptoms related to the primary tumor. The goals of therapy are to render the patient a candidate for

Table 2 Characteristics of preoperative and postoperative treatment received by patients with Stage IV rectal cancer

	Preoperative treatment	Postoperative treatment
Group 1 (synchronous resection) ($N = 30$)	27 received intended standard course of 5FU/XRT	23 received intended course of FOLFOX or FOLFIRI
	2 had no treatment as tumor initially thought to be sigmoid	
	1 patient did not complete full course	4 did not complete full course due to related comorbidities
Group 2 (staged resection) ($N = 13$)	9 received intended standard course of 5FU/XRT	11 received intended course of FOLFOX or FOLFIRI
	1 had no treatment as tumor initially thought to be sigmoid	
	2 had short-course radiation only	1 refused chemotherapy
	1 had chemotherapy only	1 unknown postoperative treatment course
Group 3 (primary resection) ($N = 22$)	16 received intended standard course of 5FU/XRT	15 received intended course of FOLFOX or FOLFIRI
	3 had no treatment as tumor initially thought to be sigmoid	
	2 had short-course radiation only	1 refused treatment
	1 stented as a bridge but required surgery for symptoms prior to initiation of treatment	1 had palliative XRT only
		5 unknown postoperative treatment course
Group 4 (no resection) ($N = 9$)	N/A	7 received intended course of FOLFOX or FOLFIRI
		6 received bevacuzumab or cetuximab
		1 unknown treatment course
		1 noncompliant with treatment

5FU 5-fluorouracil, *XRT* external beam radiation, *FOLFOX* fluorouracil, leucovorin, and oxaliplatin, *FOLFIRI* fluorouracil, leucovorin, and irinotecan

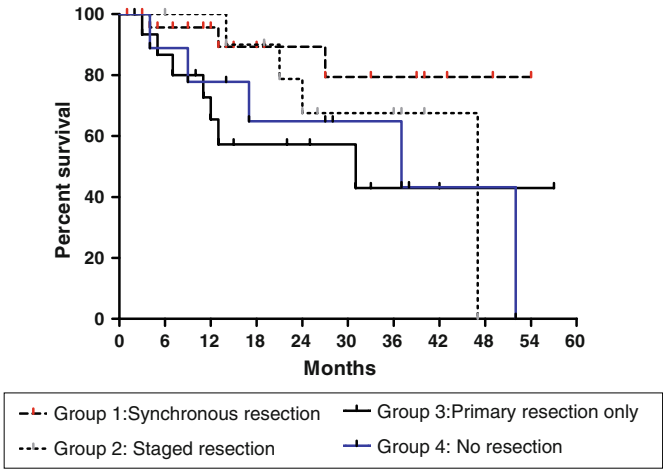

Fig. 2 Survival outcomes of patients with Stage IV rectal cancer. Overall median survival was 50 months. There was no statistically significant difference between groups although those with liver resection trended toward longer median survival times ($P = 0.19$)

curative resection or, if they are not a candidate for curative resection, to prolong survival and maintain quality of life.

Definitive management of the primary tumor in patients with unresectable liver metastasis can prove to be extremely challenging. The appropriate treatment is a balance between the potential of a "resectable" response to chemotherapy, the morbidity of surgical resection, and the potential for complications caused by a locally advanced rectal tumor in a population where quality of life is of the utmost importance. A multimodal approach to metastatic rectal cancer is necessary and includes a combination of chemotherapy, radiation therapy, and surgery for the primary tumor and metastatic sites [18]. Patients with liver metastases are potential candidates for either simultaneous or staged resection of the primary and liver tumors. A secondary intent of our study was to inquire whether there was any difference in survival between synchronous and staged resection. Thus, we limited our study to rectal cancer patients with liver metastases only. As in previous studies [19], we found that there was no statistically significant difference between synchronous and staged resection, with mean overall survival of 46 and 38 months, respectively ($P = 0.3$).

After resection of the primary lesion only, an additional 26% (9 of 35) of the Stage IV patients in this cohort were known to be able to undergo curative liver resection after adjuvant chemotherapy with either FOLFOX or FOLFIRI regimens. The most common reason for "unresectability" was bilateral disease that could not be resected with an anatomic resection. This "downstaging" is consistent with the published literature for FOLFOX and FOLFIRI protocols [7, 8]. A total of 65% of the patients in this study underwent liver resection with a curative intent. This finding demonstrates that the treatment algorithm of neoadjuvant chemoradiation, surgery, and adjuvant FOLFOX or FOLFIRI, ultimately followed by liver resection was able to produce equivalent survival compared to those patients who had synchronous resections. Limitations of this study include a small sample size, the retrospective study design, and the fact we are a tertiary care center where patients often receive their neoadjuvant and adjuvant therapy closer to home which contributes to incomplete data regarding number of treatment cycles, information on intent of duration or cessation of treatment or complications incurred.

The role of resection of the primary tumor in patients with unresectable liver metastases is debatable. The center of the issue is the benefit of surgical resection compared to the morbidity and mortality associated with surgery and the risk of the tumor causing a complication such as obstruction, bleeding, or invasion into pelvic structures resulting in pelvic pain or a fistula to the bladder or vagina if the primary is left in place. Further complicating this issue is the limited life expectancy of these patients and the treating physician's goal to maintain quality of life. Studies by Nash et al. [20], Al-Sanea et al. [21], and Law et al. [22] all demonstrated that palliative resection of the primary lesion in the setting of unresectable liver metastasis can be accomplished with acceptable morbidity and provides effective palliation. The group from Memorial Sloan-Kettering reported 15% morbidity with a 6% local recurrence rate and a median survival of 25 months [20]. Twenty percent of their patients required a colostomy. Law et al. and Al-Sanea et al. both reported similar morbidity, local recurrence rates, and cancer-specific survival. All three studies revealed that the extent of liver disease, response to chemotherapy, and absence of intraperitoneal disease were predictors of survival on multivariate analysis. In a meta-analysis by Scheer et al. [14], postoperative mortality was 2.7%, with 11.8 and 20.6% of patients experiencing major and minor postoperative morbidity, respectively. Therefore, resection of the primary lesions is safe, provides good local control, and allows the patient to proceed to adjuvant therapy in a timely fashion.

Other studies suggest a survival benefit to resection of the primary tumor in Stage IV rectal cancer. About 70% of patients diagnosed with Stage IV colorectal cancer in the USA during the last two decades underwent primary tumor resection as their initial treatment [23]. Retrospective data suggest that noncurative resection of asymptomatic colorectal primary tumors may prolong survival compared to nonresection [12, 16, 17]. Median survival in these studies was 11-16 months in resected groups and 2-9 months in unresected groups. Other studies, however, have not reported a survival benefit [14, 24]. Our study did not see a survival difference between resection of the primary tumor versus nonoperative management; however, our median survival for both groups was much higher than those of previous studies, likely reflecting the use of newer chemotherapeutic agents. This lack of difference in survival in our study also may be due to selection bias in our small number of patients in Group 4. In our institution, many patients will receive initial oncology consults but then opt for further treatments to be done by their local oncologists, leading to a number of patients lost to follow-up in our system. These nine patients in our study may reflect those with good response to treatment who continue to present to our institution, while those who did not respond may have had their palliative care transferred locally and are not reflected in our data. In addition, as stated in the Results section, six patients presented with lung or intraperitoneal metastases in addition to liver disease, while nine patients developed distant metastases other than liver after initial surgery and postoperative chemotherapy, introducing a potential bias in our survival numbers. This clearly underscores the importance of patient selection when deciding on the optimal treatment course.

There are very little published data on the morbidity and rate of development of symptoms associated with a locally advanced rectal cancer that has not been resected. The majority of studies on this topic do not specifically address rectal cancer, although in a systematic review of studies reporting the management of patients with asymptomatic colorectal cancer and synchronous irresectable metastases, more often left-sided tumors appeared to lead to significant symptoms [14]. Anecdotally, the majority of surgeons agree that dying from a complication such as obstruction or pain due to tumor invasion into pelvic structures is miserable for the patient leading many to recommend primary tumor resection despite the lack of data to supporting this practice. In a more current study by Poultsides et al. [25] reflective of today's modern chemotherapeutic regimens, 233 patients with synchronous Stage IV colorectal cancer who received up-front chemotherapy were retrospectively reviewed. Only 7% of the patients required surgical palliation for their intact primary tumor. Previous studies have noted a 9-29% risk of need for operative intervention due to tumor-related complications [12, 15, 26, 27]. The authors of the MSKCC study [25] did look at a subset of patients whose primary tumor was located in the rectum and found a 15% rate of need for emergent intervention, which in their opinion does not justify the routine use of prophylactic surgery in this setting. Median survival in their study was 18 months overall, while median survival after surgical or nonoperative intervention (such as stenting or palliative radiotherapy) was 6 months. In contrast, the majority of patients who underwent nonoperative management in our study did require palliative colostomy for obstruction or perforation at some point during their treatment course. In addition, median survival in our study was 37 months, including those who underwent palliative surgery. The reason for this difference in survival is unclear, although it again suggests the importance of patient selection. It is difficult to draw any conclusions from this small number of patients, but it is seen that many of these patients will require some form of palliation, especially since we show that 2-year survival exceeds 60%. Again, while our cohort is small, our data suggests that as patients live longer with their primary disease intact, there may be a greater chance of requiring a palliative procedure in the future.

In the era of improved chemotherapeutic agents and multimodality treatment, patients with metastatic rectal cancer are achieving significant improvements in outcomes. As a result, patients with metastatic disease can now be more widely treated with a curative intent. When metastatic disease is not resectable, up-front chemotherapy without resection of the primary lesion may be a reasonable approach. However, the risk of subsequent palliative surgery is not trivial and may be increased as patients live longer. In addition, the question of survival benefit from resection of the primary tumor was not sufficiently answered in our small cohort. Therefore, an aggressive approach to local control with neoadjuvant chemoradiation therapy and resection of the primary rectal cancer may provide substantial benefits to patients with Stage IV disease. The benefits include good local control of disease with the potential for synchronous resection or staged resection after adjuvant therapy. Future prospective trials that compare surgical and nonoperative management of these patients specifically looking at survival and quality of life are necessary before definitive recommendations are made.

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