

Patterns of Recurrence Following Liver Resection for Colorectal Metastases

Effect of Primary Rectal Tumor Site

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Hypothesis: Patients with rectal adenocarcinoma are at increased risk of locoregional recurrence compared with patients with colon cancer. This may affect the pattern of recurrence and survival rates following hepatic resection of liver metastases from rectal adenocarcinoma.

Design: Retrospective review of a prospectively collected cancer center database.

Patient and Methods: From April 1, 1984, to December 31, 2005, 582 patients with liver metastases from a primary colorectal adenocarcinoma underwent hepatic resection. Clinical and pathological factors were analyzed using Cox regression analyses and log-rank tests.

Results: Of 582 patients, 141 (24.2%) had liver metastases from a primary rectal tumor site. Treatment of the primary rectal tumor most frequently included chemoradiation therapy (59.6%) and low anterior resection (63.1%). Most rectal tumors were pathological stage T3/T4 (85.8%) and N1 (68.1%). Treatment directed at the hepatic metastases included resection only (81.5%), resec-

tion plus radiofrequency ablation (17.8%), or radiofrequency ablation only (0.7%). With a median follow-up time of 30.7 months, 80 of 141 patients (56.7%) developed recurrence; 23 patients (16.3%) developed recurrence in the pelvis. Of 23 patients with pelvic recurrence, 56.5% also developed recurrence in the liver. The 3- and 5-year survival rates for all patients were 62.4% and 36.4%, respectively. Of 80 patients who had a recurrence following hepatic metastectomy, 23 (28.8%) underwent another operation. Following repeat metastectomy, 3- and 5-year survival rates were 76.7% and 38.6%, respectively.

Conclusions: Following resection of hepatic rectal metastases, pelvic recurrence is relatively common, and most patients with pelvic recurrence will also develop recurrence in the liver. Surgery for recurrent disease following hepatic resection of rectal metastases is warranted among well-selected patients.

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EACH YEAR IN THE UNITED States, 150 000 patients¹ are diagnosed as having colorectal adenocarcinoma, approximately 40 000 of whom have a primary rectal tumor.² About 20% of patients with colorectal adenocarcinoma will have hepatic metastases that are limited to

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the liver at the time of diagnosis or will develop such metastases during their illness.³⁻⁵ Liver resection currently represents the best therapeutic option. Despite improvements in overall survival following liver resection to treat colorectal metastases,⁶⁻⁹ 50% to 60% of patients develop a recurrence of the disease.¹⁰⁻¹² In particular, primary rectal tumors are associated with an increased risk of locoregional recurrence compared with primary colon lesions. Specifically, the local

recurrence rate following rectal surgery ranges from 3% to 30%.^{13,14} Traditionally, the primary tumor site has not been associated with differences in survival rates.¹⁵ However, because patients with colorectal liver metastases now enjoy a much longer median survival time, more recently there has been concern that locoregional pelvic recurrence may adversely affect survival in patients with rectal cancer. Few, if any, studies have actually analyzed patterns of recurrence and outcome specifically in patients who present with rectal liver metastases.

The purpose of the current study was to determine the pattern of recurrence and the disease-free and overall survival rates of patients undergoing curative hepatic resection of liver metastases from rectal adenocarcinoma. We sought to examine how the primary rectal tumor site and the pattern of recurrence affected disease-free and overall survival rates following hepatic metastectomy.

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Table 1. Patient Clinicopathological Characteristics Stratified by Primary Tumor Site^a

Variable	Tumor Site		P Value
	Rectum (n=141)	Colon (n=441)	
Age, median, y	61	58	.007
Sex			
Female	51 (36.2)	147 (33.4)	.52
Male	90 (63.8)	294 (66.6)	
Preoperative CEA level, median, ng/mL	11	13	.89
T stage of primary tumor			
T1/T2	20 (14.2)	41 (9.3)	.09
T3/T3	121 (85.8)	400 (90.7)	
Nodal status of primary tumor			
Negative	45 (31.9)	150 (33.1)	.64
Positive	96 (68.1)	291 (65.9)	
No. of hepatic metastases, median	1	1	.95
Size of largest hepatic metastasis, median, cm	3.0	3.0	.83
Presentation			
Synchronous	57 (40.4)	218 (49.4)	.23
Metachronous	84 (59.6)	223 (50.6)	

Abbreviation: CEA, carcinoembryonic antigen.

SI conversion factor: To convert CEA to micrograms per liter, multiply by 1.0.

^aData are given as the number (percentage) of patients unless otherwise indicated.

METHODS

From April 1, 1984, to December 31, 2005, 582 consecutive patients who underwent hepatic resection for colorectal liver metastases at The Johns Hopkins Hospital were identified from our prospective institutional database. Only patients with colorectal liver metastases who were operated on with a curative intent were included in the study. Patients were deemed to have resectable hepatic disease only if it was anticipated that the metastasis could be completely resected, at least 2 adjacent liver segments could be spared, vascular inflow and outflow could be preserved, and the volume of the liver remaining after resection would be adequate.¹⁶ When applicable, radiofrequency ablation (RFA) was administered using the Starburst XLi or XLi-Enhanced device (Rita Medical Systems, Manchester, Georgia).

Standard demographic, clinicopathological, and tumor-specific data were collected for each patient. Specifically, data on carcinoembryonic antigen level, treatment-related variables, primary tumor location, American Joint Commission on Cancer stage (TNM classification), synchronous vs metachronous presentation, and hepatic metastasis number, size, and location were assessed. Following the surgical procedure, all patients were regularly followed up and prospectively monitored. Vital status and recurrence-related information were collected. With regard to recurrence, the sequence and overall pattern of recurrence were noted. *Pelvic recurrence* was defined as any locoregional (nodal, soft-tissue, or true mucosal) recurrence within the pelvis.

Summary statistics were obtained using established methods and presented as percentages or median values with the interquartile range. Time to recurrence and survival were estimated using the nonparametric product limit method (Kaplan-Meier).¹⁷ Differences in recurrence and survival were examined using the log-rank test. Factors associated with recurrence and survival were examined using univariate and multivariate Cox regression analy-

Table 2. Treatment Variables for Patients With Hepatic Metastasis From a Primary Rectal Tumor

Variable	No. (%) of Patients (n=141)
Therapy Directed at Primary Rectal Tumor	
Surgical procedure	
Low anterior resection	89 (63.1)
Abdominal perineal resection	52 (36.9)
Chemoradiation therapy	
Overall	84 (59.6)
Preoperative	38 (26.9)
Postoperative	46 (32.6)
Adjuvant chemotherapy	70 (49.6)
Therapy Directed at Hepatic Metastasis	
Surgical procedure	
Resection only	115 (81.5)
Resection and RFA	25 (17.8)
RFA only	1 (0.7)
Type of hepatic resection	
Wedge	45 (32.1)
Segmentectomy	43 (30.7)
Hemihepatectomy	40 (28.6)
Extended hepatectomy	12 (8.6)
Systemic chemotherapy	
Overall	137 (97.1)
Preoperative	45 (31.9)
Postoperative	81 (57.4)
Preoperative and postoperative	11 (7.8)

Abbreviation: RFA, radiofrequency ablation.

ses. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated, and $P < .05$ was considered significant. All statistical analyses were performed using SPSS statistical software, version 11.5 (SPSS Inc, Chicago, Illinois).

RESULTS

CLINICOPATHOLOGICAL CHARACTERISTICS

Of 582 patients who underwent metastectomy for colorectal liver metastasis, 441 (75.8%) had a primary colon tumor and 141 (24.2%) had a primary rectal lesion. Patients with colon and rectal tumors were similar with regard to most clinicopathological factors (**Table 1**).

Among the 141 patients with primary rectal tumors, most rectal tumors were treated with chemoradiation therapy (59.6%) and low anterior resection (63.1%) (**Table 2**). Following resection of the primary rectal tumor, pathological analysis revealed no evidence of macroscopic residual tumor in 8 patients (5.7%) (residual microscopic carcinoma only in 5 patients and complete pathological response with no microscopic evidence of carcinoma in 3). Surgical treatment for hepatic metastases was resection only in 115 patients (81.5%), RFA only for tumors in unresectable locations in 1 patient (0.7%), and resection of large or dominant lesions combined with RFA of smaller lesions in 25 patients (17.8%). Of 140 patients who underwent surgical resection, 95 (67.9%) had an anatomic resection and 45 (32.1%) had a nonanatomic resection. On final pathological analysis of the 141 patients with a primary rectal tumor who un-

Table 3. Treatment Variables Stratified by Synchronous vs Metachronous Presentation

Variable	Presentation, No. (%) of Patients		P Value
	Synchronous (n=57)	Metachronous (n=84)	
Simultaneous procedure	21 (36.8)	NA	.005
Rectal chemoradiation therapy	20 (35.1)	64 (76.2)	
Systemic chemotherapy			
Preoperative	14 (24.6)	4 (4.8)	.009
Preoperative or postoperative	35 (61.4)	64 (76.2)	.13
Rectal surgical procedure			
Low anterior resection	21 (36.8)	29 (34.5)	.85
Abdominal perineal resection	36 (63.2)	55 (65.5)	
Hepatic resection			
Minor (<3 segments)	42 (73.7)	47 (56.0)	.03
Major (≥3 segments)	15 (26.3)	37 (44.0)	

Abbreviation: NA, not applicable.

derwent metastectomy, no patient had a macroscopically positive margin (R2); the margin status was microscopically positive (R1) in 9 patients (6.4%) and microscopically negative (R0) in 132 (93.6%). Patients who underwent less than a hemihepatectomy were more likely to be treated by RFA (20.2%) than were patients who had a more extensive resection (2.1%) ($P < .001$).

Of patients with hepatic metastasis from a primary rectal tumor site, 45 (31.9%) received preoperative systemic chemotherapy before surgical treatment. Adjuvant postoperative therapy alone was administered to 81 patients (57.4%), whereas 11 (7.8%) received both preoperative and postoperative therapy. The type of chemotherapy varied; most patients received either oxaliplatin-based (FOLFOX) therapy (33 [31.7%]) or irinotecan-based (FOLFIRI) therapy (36 [34.6%]); a few (15 [14.4%]) were treated with fluorouracil-based monotherapy. In 20 patients (19.2%), the type of chemotherapy received was unknown.

We were particularly interested in looking at how the treatment of patients with rectal tumors differed based on whether they presented with metachronous or synchronous disease (**Table 3**). Of 57 patients with synchronous disease, 21 (36.8%) were treated with a simultaneous proctectomy and hepatectomy, whereas 36 (63.2%) underwent staged resections. Patients with synchronous disease were significantly less likely to have received chemoradiation therapy (synchronous, 20 [35.1%]; metachronous, 64 [76.2%]; $P = .005$) but were more likely to receive preoperative systemic chemotherapy (synchronous, 14 [24.6%]; metachronous, 4 [4.8%]; $P = .009$). Patients with synchronous disease were also less likely to have undergone a major hepatic resection (≥ 3 segments) (synchronous, 15 [26.3%]; metachronous, 37 [44.0%]; $P = .03$). In patients with metachronous disease ($n = 84$), the median interval from the time of diagnosis of primary rectal tumor to diagnosis of hepatic metastases was 16.8 months.

Following hepatic resection of rectal liver metastases, the perioperative complication rate was 19.9%. The

Table 4. Patterns of Recurrence Following Hepatic Resection of Rectal Metastases

Site of Recurrence	No. (%) of Patients (n=80)	
	First Site of Recurrence	Recurrence at Last Follow-up Visit
Pelvis only	8 (10.0)	6 (7.5)
Pelvis and liver	6 (7.5)	5 (6.3)
Pelvis and other site	4 (5.0)	4 (5.0)
Pelvis, liver, and other site	2 (2.5)	8 (10.0)
Liver only	27 (33.8)	22 (27.5)
Liver and other site	14 (17.5)	26 (32.5)
Other site only	19 (23.7)	9 (11.2)

median length of stay was 7 days (interquartile range, 5-9 days). Three patients died within 90 days of treatment, for a perioperative mortality rate of 2.1%.

PATTERNS OF RECURRENCE AND DISEASE-FREE SURVIVAL

With a median follow-up of 30.7 months, 80 of 141 patients (56.7%) developed a recurrence. Among 141 patients with hepatic metastases from a primary rectal tumor, 23 (16.3%) developed pelvic disease as a final component of recurrence. The sites of locoregional pelvic recurrence included lymph nodes ($n = 3$), soft tissue/pelvic side wall ($n = 16$), and the surgical anastomosis ($n = 4$). Most patients who developed a pelvic recurrence also had a recurrence outside of the pelvis, with the liver being the most common site of additional metastatic disease (**Table 4**). Of 23 patients who ultimately developed a pelvic recurrence, 13 (56.5%) also developed a recurrence in the liver. In total, 61 patients (43.3%) eventually developed a recurrence within the liver; 22 (36.1%) had liver-only recurrence, whereas 39 (48.9%) developed a recurrence within the liver plus an extrahepatic site. Stratifying recurrence by disease site, the 5-year overall risk of pelvic recurrence was 23.4% compared with 49.0% for hepatic recurrence (**Figure 1**).

Factors associated with increased risk of pelvic recurrence included a preoperative carcinoembryonic antigen level higher than 200 ng/mL (to convert to micrograms per liter, multiply by 1.0) (HR, 2.31; 95% CI, 0.68-7.78; $P = .18$) and a history of abdominoperineal resection (2.35; 0.82-6.79; $P = .11$). The date of rectal resection before 1994 also tended to be associated with an increased risk of pelvic recurrence (HR, 2.27; 95% CI, 0.98-5.26; $P = .06$). Chemoradiation therapy appeared to have a protective effect with regard to pelvic recurrence (HR, 0.37; 95% CI, 0.07-1.99; $P = .25$), although the finding was not statistically significant.

On univariate analysis, factors associated with the risk of hepatic recurrence included hepatic resection involving less than a hemihepatectomy (HR, 2.63; 95% CI, 1.33-5.15), positive margin status (2.5; 1.17-5.40), and history of RFA (3.0; 1.65-5.43) (all $P < .05$). On multivariate analysis, history of RFA treatment was the only factor independently associated with the risk of hepatic recur-

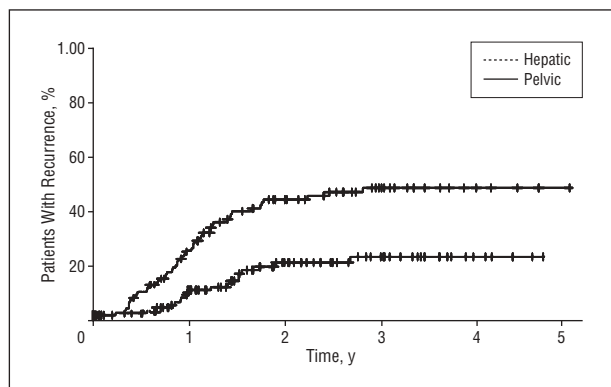


Figure 1. The 5-year risk of hepatic recurrence was 49.0% compared with 23.4% for pelvic recurrence. Of note, the risk of hepatic and pelvic recurrence appeared to plateau at about 3 years.

rence. Specifically, patients who were treated with RFA only or resection plus RFA had a higher 5-year recurrence rate than did patients who underwent resection alone (37.5% vs 10.4%, respectively; $P < .05$).

The 1-, 3-, and 5-year actuarial disease-free survival rates for patients with hepatic metastases from a primary rectal site were 68.4%, 34.5%, and 32.9%, respectively. Compared with patients who presented with a primary colon carcinoma site, patients with primary rectal tumors had similar disease-free survival following hepatic metastectomy (**Figure 2A**). Specifically, the 5-year disease-free survival rate was the same regardless of whether the primary tumor site was the colon or rectum (colon primary, 28.2%; rectal primary, 32.9%; $P = .63$).

Patients with rectal cancer who underwent resection of their primary lesion before 1994 ($n = 36$) had a worse median disease-free survival time (12.8 months) than did patients who underwent surgery for their primary tumor more recently (21.0 months) ($P = .02$). In contrast, patients who had a complete primary tumor pathological response following neoadjuvant rectal chemoradiation therapy had an improved median disease-free survival time (29.2 months; $P = .07$). Other liver-related factors associated with shorter disease-free survival following hepatic metastectomy included tumor size (HR, 1.69; 95% CI, 0.89-2.85), positive margin status (2.81; 1.42-5.56), and history of RFA (2.07; 1.19-3.59) (all $P < .05$).

OVERALL SURVIVAL

The median overall survival time following hepatic resection of metastases from a primary rectal tumor site was 42.1 months, and the 1-, 3-, and 5-year actuarial overall survival rates were 95.6%, 62.4%, and 36.4%, respectively. There was no difference in the overall survival rate between patients who had a primary colon vs primary rectal tumor site (5-year survival: primary colon, 40.3%; primary rectal, 36.4%; $P = .98$) (**Figure 2B**). Statistical analyses revealed several factors that were associated with poorer overall survival in patients with primary rectal tumors, including having a preoperative carcinoembryonic antigen level higher than 200 ng/mL (HR, 2.13; 95% CI, 1.18-3.83; $P = .01$) and N2 nodal disease (HR, 2.61;

95% CI, 1.49-4.58; $P = .001$). Although the trend was not statistically significant, patients who underwent resection of their primary rectal lesion before 1994 had a worse median overall survival time (35.6 months) compared with patients who underwent surgical treatment for their primary tumor more recently (47.9 months) ($P = .06$).

Another factor associated with overall survival in patients with metastatic rectal carcinoma following hepatic metastectomy was number of recurrent metastatic sites. That is, patients who developed recurrence at only 1 disease site (median survival time, 39.9 months) had significantly greater long-term survival time than did patients who developed recurrence at multiple anatomic sites (median survival time, 26.6 months) ($P = .004$) (**Figure 3A**). Whereas the number of recurrent sites had an important effect on survival time, the location of the recurrent disease did not seem to affect survival. Specifically, long-term survival was similar in those patients who developed a recurrence, regardless of whether the recurrence occurred in the pelvis, liver, or other anatomic site (**Figure 3B**).

SURGERY FOR RECURRENT DISEASE FOLLOWING HEPATIC METASTECTOMY

Of 80 patients who developed a recurrence following hepatic metastectomy, 35 patients (43.4%) underwent a repeat procedure, 23 (28.8%) of which were of curative intent. In these 23 patients, the site of recurrent disease following hepatic metastectomy included the pelvis only ($n = 6$), lungs only ($n = 5$), liver only ($n = 10$), liver and pelvis ($n = 1$), and liver and lungs ($n = 1$). For the 23 patients operated on with curative intent, repeat surgical treatment included abdominoperineal resection ($n = 1$), repeat low anterior resection ($n = 2$), pelvic exenteration ($n = 2$), pulmonary wedge resection ($n = 3$), pulmonary lobectomy ($n = 2$), hepatic wedge resection ($n = 5$), and hepatic hemihepatectomy ($n = 5$). Among those who required a repeat procedure, 1 patient underwent a staged partial hepatectomy combined with a low anterior resection, and 1 patient underwent a simultaneous repeated hepatic wedge resection combined with a right inferior pulmonary lobectomy. Of 23 patients who underwent a repeat operation with curative intent, the 3- and 5-year survival rates were 76.7% and 38.6%, respectively, after repeat liver resection.

COMMENT

The current study is, to our knowledge, the first specifically to examine the incidence and patterns of recurrence following hepatic resection of primary rectal carcinoma metastasis. Our data demonstrate that in a population of patients with metastatic rectal carcinoma to the liver, hepatic metastectomy resulted in a 5-year survival rate of 36.4%. However, most patients (67.1%) did develop a recurrence. Although the incidence of locoregional recurrence was higher in patients with a primary rectal tumor, the overall rate of recurrence was similar comparing patients with a primary colon (28.3%) vs a primary rectal (32.9%) tumor site ($P = .63$). For patients

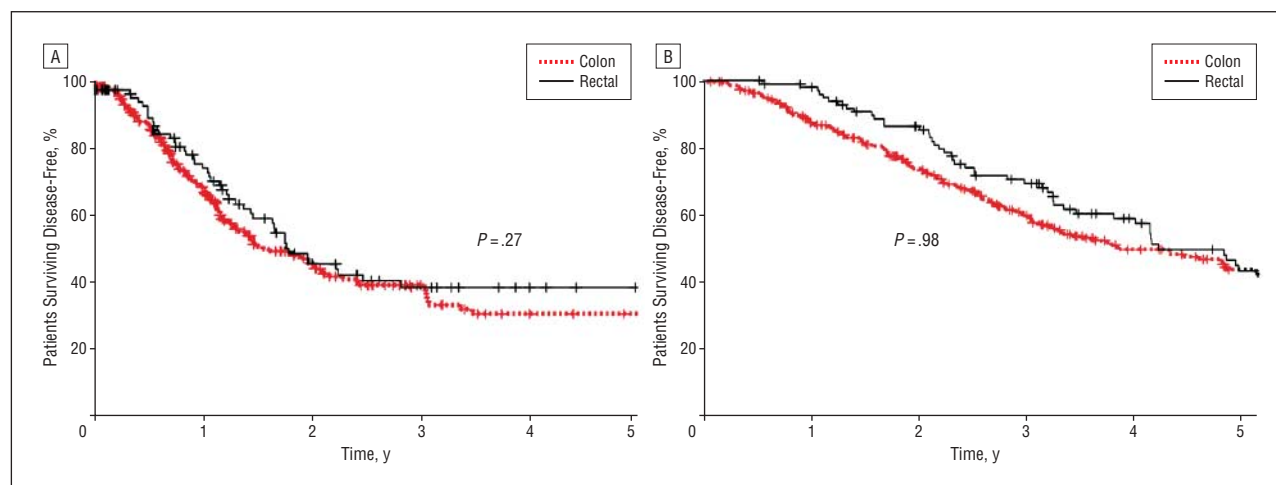


Figure 2. A, Compared with primary colon cancer, patients with primary rectal tumors had a similar disease-free survival rate. B, There was no significant difference in overall 5-year survival rate of patients who had primary colon vs rectal tumors.

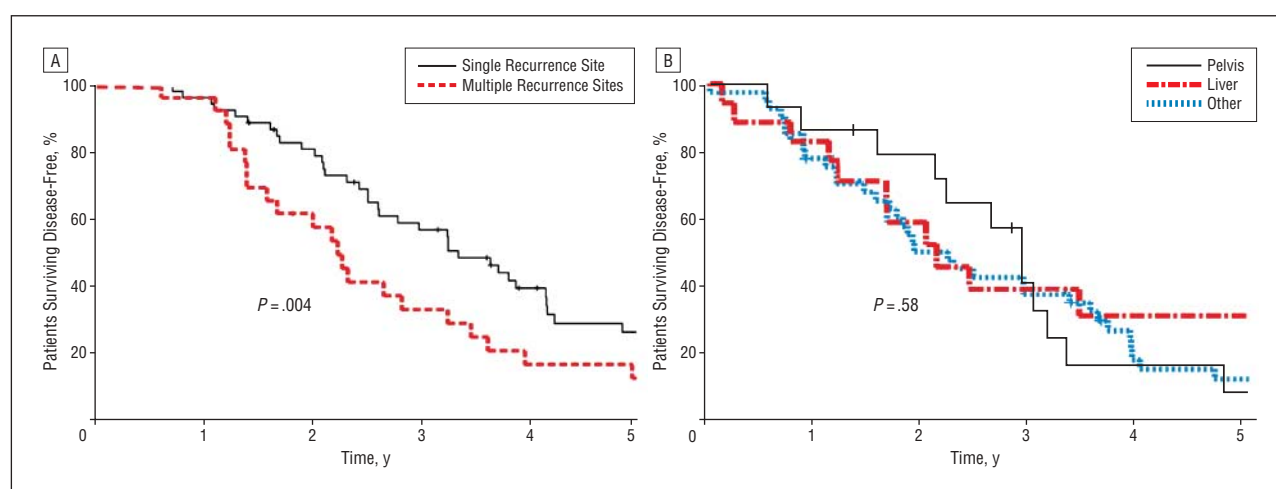


Figure 3. A, In patients with a primary rectal tumor, the number of recurrence sites was associated with survival following metastectomy. Patients who developed recurrence at only 1 disease site had a significantly better long-term survival rate compared with patients who developed recurrence at multiple anatomic sites. B, The location of the recurrent disease did not, however, affect outcome. Survival was similar among patients who developed recurrence, regardless of whether the site of recurrence was the pelvis, the liver, or another anatomic site.

with a primary rectal tumor, few (16.3%) had developed a recurrence within the pelvis at the time of last follow-up visit. The high rate of pelvic recurrence following hepatic resection has important implications because it emphasizes that adequate therapy of pelvic and hepatic disease is important and that close surveillance of the pelvis is necessary following resection of rectal liver metastases.

Before the adoption of the sharp total mesorectal excision (TME) technique, the locoregional recurrence rate following resection of rectal carcinoma was 20% to 30%,¹⁸⁻²⁰ with some studies even reporting recurrence rates as high as 50%.²¹ Blunt dissection to mobilize the rectum was believed to disrupt the mesorectal fascia and the adjacent tumor, leading to an increased risk of pelvic recurrence.²² Multiple controlled trials have shown that with the introduction of TME as the standard surgical technique for rectal carcinoma, the incidence of local recurrence has significantly decreased.²³⁻²⁶ As such, local recurrence rates more recently have been reported to be

in the range of 3% to 15%.²³⁻²⁷ In the current study, 16.3% of patients had developed a recurrence at the time of last follow-up visit; however, time-to-event analysis estimated that the 5-year actuarial pelvic recurrence rate was 23.4%. There are a number of possible reasons why the local recurrence rate in the current study was higher than other contemporary studies of localized rectal cancer. Local pelvic recurrence has been shown to be independently associated with the stage (T category, nodal status) and the location of the lesion within the rectum, as well as period of diagnosis (conventional surgery vs TME resection).²⁸ Our data support this latter finding; patients who underwent resection of their primary rectal lesion before 1994 (eg, before the widespread introduction of TME) had a worse median disease-free survival time and tended to have more pelvic recurrences. In addition, the overwhelming majority of patients in the current study also had rectal tumors with advanced T-stage (85.8%) and node-positive (65.1%) disease. More important, our study included more than 40% of patients

presenting with stage IV disease, who may have had tumors with more aggressive biological characteristics.

The National Institutes of Health Consensus Conference on rectal cancer has recommended postoperative chemoradiation for patients with transmural and/or node-positive rectal cancer.²⁹ These recommendations were largely based on data that showed decreased local recurrence rates with chemoradiation.³⁰ More recently, the German Rectal Cancer Study Group³¹ reported the results of a large, prospective, randomized trial that compared preoperative vs postoperative chemoradiation to treat clinical stage II and stage III disease. Although there was no difference in overall survival between the 2 groups, there was a significant reduction in the local recurrence rate (preoperative: 6% vs postoperative: 13%; $P = .006$) and treatment toxicity in the preoperative group. As such, the coordination of multimodality therapy is critical for successfully treating patients with primary rectal carcinoma. This can be particularly challenging in patients who present with synchronous local and systemic disease. In the current study, only 59.6% of patients received chemoradiation therapy—either preoperatively or postoperatively—despite the fact that the overwhelming majority of patients had T3/T4 (85.8%) and N1 (68.1%) disease. Perhaps even more significant was the finding that only 35.1% of patients with synchronous disease were treated with rectal chemoradiation therapy. Patients with synchronous disease instead were much more likely to be treated with preoperative systemic chemotherapy (Table 3). We did note that a history of chemoradiation therapy tended to have a protective effect on the risk of pelvic recurrence (HR, 0.37; 95% CI, 0.07-1.99; $P = .25$). This finding was not statistically significant, probably because the current study was underpowered. In the Dutch TME trial,²⁸ local recurrence was significantly higher when radiation therapy was excluded, suggesting that radiation therapy remains important in the era of TME. Whether the omission of chemoradiation in patients with a synchronous rectal tumor and hepatic metastasis leads to higher locoregional recurrence rates requires further study.

Another interesting finding of the current study was that most patients who developed recurrence in the pelvis also developed recurrence in the liver. In fact, the liver was the most common site of failure following hepatic metastectomy. Of 80 patients with rectal cancer who developed a recurrence, 25.0% had disease in the pelvis as a component of their first site of recurrence. In comparison, more than 50% of patients initially had recurrence in the liver (Table 4). Ultimately, 28.8% of patients developed recurrence in the pelvis, and 56.5% of these patients also developed recurrence in the liver. These pattern-of-recurrence data have important implications for postoperative surveillance purposes and in planning adjuvant therapy. Because most recurrences occur systemically, improvements in survival will likely depend on the use of systemic chemotherapy. In the current series, despite the high rate of R0 resection, virtually all patients (97.1%) received some form of systemic chemotherapy. Although evidence for the use of adjuvant systemic chemotherapy in the setting of an R0 hepatic resection is lacking, we strongly favor its use based on data extrapolated

from stage III colorectal disease as well as emerging data that specifically address stage IV disease.^{32,33}

Recurrence at disease sites such as the pelvis has traditionally been met with clinical nihilism. However, data from the current study suggest that the total number of recurrent sites, and not necessarily their location, was the most important prognostic factor. Specifically, patients who developed recurrence at only 1 disease site had a significantly better long-term survival duration than did patients who developed recurrence at multiple anatomic sites (Figure 3A). In contrast, the location of the recurrent disease did not seem to affect survival (Figure 3B). These data support previous work by Elias et al³⁴ that showed that the total number of metastases, inside or outside the liver, had a greater prognostic value than the location of the metastatic disease. In light of such data, a second resection should be strongly considered in patients with low volume recurrent locoregional or metastatic disease, regardless of the site. In the current series, of 80 patients who developed recurrence and underwent a repeat operation with curative intent, 3- and 5-year survival rates were 76.7% and 38.6%, respectively, not dissimilar to the 3- and 5-year overall survival rates following initial metastectomy. Our data, therefore, support the use of a second resection to treat locoregional and metastatic disease.

In conclusion, disease-free and overall survival duration were similar in patients undergoing hepatic resection regardless of whether the primary tumor site was the colon or rectum. Following liver resection of rectal metastases, local recurrence of pelvic disease was common, occurring in up to 25% of patients. In patients presenting with stage IV disease and potentially resectable liver metastases, adequate surgical resection of the primary tumor and prudent use of chemoradiation therapy should be considered. Furthermore, routine imaging of the pelvis following resection of rectal liver metastases is an important component in the surveillance of this cohort of patients. Finally, patients who develop recurrence in the pelvis also frequently develop recurrence in the liver. Overall survival is associated with the number of recurrent sites, but not necessarily the site of recurrence. Surgical treatment for recurrent disease following hepatic resection of rectal liver metastasis should be strongly considered because long-term survival can be achieved in well-selected patients.

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Author Contributions: Dr Pawlik had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Choti, Herman, and Pawlik. *Acquisition of data:* Gearhart and Pawlik. *Analysis and interpretation of data:* Assumpcao, Gleisner, Schulick, Swartz, and Pawlik. *Drafting of the manuscript:* Pawlik. *Critical revision of the manuscript for important intellectual content:* Assumpcao, Choti, Gleisner, Schulick, Swartz, Herman, Gearhart, and Pawlik. *Statistical analysis:* Herman

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REFERENCES

- Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. *CA Cancer J Clin*. 2005; 55(1):10-30.
- Burdy G, Panis Y, Alves A, Nemeth J, Lavergne-Slove A, Valleur P. Identifying patients with T3-T4 node-negative colon cancer at high risk of recurrence. *Dis Colon Rectum*. 2001;44(11):1682-1688.
- Bismuth H, Adam R, Levi F, et al. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. *Ann Surg*. 1996;224(4):509-522.
- Fong Y, Salo J. Surgical therapy of hepatic colorectal metastasis. *Semin Oncol*. 1999;26(5):514-523.
- Adson MA, van Heerden JA, Adson MH, Wagner JS, Ilstrup DM. Resection of hepatic metastases from colorectal cancer. *Arch Surg*. 1984;119(6):647-651.
- Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. *Ann Surg*. 2002;235(6):759-766.
- Pawlik TM, Scoggins CR, Zorzi D, et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. *Ann Surg*. 2005;241(5):715-724.
- Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Ann Surg*. 2004;239(6):818-827.
- Fernandez FG, Drebin JA, Linehan DC, Dehdashti F, Siegel BA, Strasberg SM. Five-year survival after resection of hepatic metastases from colorectal cancer in patients screened by positron emission tomography with F-18 fluorodeoxyglucose (FDG-PET). *Ann Surg*. 2004;240(3):438-450.
- Nordlinger B, Guiguet M, Vaillant JC, et al; Association Francaise de Chirurgie. Surgical resection of colorectal carcinoma metastases to the liver: a prognostic scoring system to improve case selection, based on 1568 patients. *Cancer*. 1996; 77(7):1254-1262.
- Adam R, Bismuth H, Castaing D, et al. Repeat hepatectomy for colorectal liver metastases. *Ann Surg*. 1997;225(1):51-62.
- Stone MD, Cady B, Jenkins RL, McDermott WV, Steele GD Jr. Surgical therapy for recurrent liver metastases from colorectal cancer. *Arch Surg*. 1990;125(6):718-722.
- Heald RJ, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal cancer: the Basinstoke experience of total mesorectal excision, 1978-1997. *Arch Surg*. 1998; 133(8):894-899.
- Minsky BD, Mies C, Recht A, Rich TA, Chaffey JT. Resectable adenocarcinoma of the rectosigmoid and rectum. I: patterns of failure and survival. *Cancer*. 1988; 61(7):1408-1416.
- Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg*. 1999;230(3):309-321.
- Clavien PA, Emond J, Vauthey JN, Belghiti J, Chari RS, Strasberg SM. Protection of the liver during hepatic surgery. *J Gastrointest Surg*. 2004;8(3):313-327.
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *Am Stat Assoc J*. 1958;53:457-480.
- Mollen RM, Damhuis RA, Coebergh JW. Local recurrence and survival in patients with rectal cancer, diagnosed 1981-86: a community hospital-based study in the south-east Netherlands. *Eur J Surg Oncol*. 1997;23(1):20-23.
- Kapiteijn E, Marijnen CA, Colenbrander AC, et al. Local recurrence in patients with rectal cancer diagnosed between 1988 and 1992: a population-based study in the west Netherlands. *Eur J Surg Oncol*. 1998;24(6):528-535.
- Manfredi S, Benhamiche AM, Meny B, Cheynel N, Rat P, Faivre J. Population-based study of factors influencing occurrence and prognosis of local recurrence after surgery for rectal cancer. *Br J Surg*. 2001;88(9):1221-1227.
- Rich T, Gunderson LL, Lew R, Galdibini JJ, Cohen AM, Donaldson G. Patterns of recurrence of rectal cancer after potentially curative surgery. *Cancer*. 1983; 52(7):1317-1329.
- Enker WE, Thaler HT, Cranor ML, Polyak T. Total mesorectal excision in the operative treatment of carcinoma of the rectum. *J Am Coll Surg*. 1995;181(4): 335-346.
- Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet*. 1986;1(8496):1479-1482.
- Swedish Rectal Cancer Trial Group. Improved survival with preoperative radiotherapy in resectable rectal cancer [published correction appears in *N Engl J Med*. 1997;336(21):1539]. *N Engl J Med*. 1997;336(14):980-987.
- Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med*. 2001;345(9):638-646.
- MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. *Lancet*. 1993;341(8843):457-460.
- Polglase AL, Grodski SF, Tremayne AB, Chee JB, Bhathal PS. Local recurrence following surgical treatment for carcinoma of the lower rectum. *ANZ J Surg*. 2004; 74(9):745-750.
- Visser O, Bakx R, Zoetmulder FA, et al. The influence of total mesorectal excision on local recurrence and survival in rectal cancer patients: a population-based study in greater Amsterdam. *J Surg Oncol*. 2004;95(6):447-454.
- NIH Consensus Conference: adjuvant therapy for patients with colon and rectal cancer. *JAMA*. 1990;264(11):1444-1450.
- Guillemin JG, Puig-La Calle J Jr, Akhurst T, et al. Prospective assessment of primary rectal cancer response to preoperative radiation and chemotherapy using 18-fluorodeoxyglucose positron emission tomography. *Dis Colon Rectum*. 2000; 43(1):18-24.
- Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med*. 2004;351(17):1731-1740.
- Portier G, Elias D, Bouche O, et al. Multicenter randomized trial of adjuvant fluorouracil and folinic acid compared with surgery alone after resection of colorectal liver metastases: FFCD ACHBTH AURC 9002 Trial. *J Clin Oncol*. 2006;24(31):4976-4982.
- Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomized controlled trial. *Lancet*. 2008;371(9617):1007-1016.
- Elias D, Liberale G, Vernerey D, et al. Hepatic and extrahepatic colorectal metastases: when resectable, their localization does not matter, but their total number has a prognostic effect. *Ann Surg Oncol*. 2005;12(11):900-909.

INVITED CRITIQUE

I read with interest the article by Assumpcao and colleagues, assessing outcomes for patients with hepatic metastases from rectal adenocarcinoma primary tumors. Rectal adenocarcinoma is often lumped with colon cancer; however, treatment, pattern of recur-

rence, and outcome can be quite different. Only 24% of hepatic resections in the current study were in patients with a primary rectal tumor site, whereas the rectum represents the primary site for nearly 33% of all colorectal cancer cases. This disparity has been demonstrated¹ and