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%), resection 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 patients are diagnosed as having colorectal adenocarcinoma, approximately 40,000 of whom have a primary rectal tumor. About 20% of patients with colorectal adenocarcinoma will have hepatic metastases that are limited to the liver at the time of diagnosis or will develop such metastases during their illness. Liver resection currently represents the best therapeutic option. Despite improvements in overall survival following liver resection to treat colorectal metastases, 50% to 60% of patients develop a recurrence of the disease. 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%. Traditionally, the primary tumor site has not been associated with differences in survival rates. 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.
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 (63.2%) (Table 2). Following resection of the primary rectal tumor, pathological analysis revealed no evidence of microscopic 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-

Abbreviation: CEA, carcinoembryonic antigen.

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

Abbreviation: RFA, radiofrequency ablation.

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 analysis.
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 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 extralhepatic 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 abdominoperi- neal 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-

![Table 3. Treatment Variables Stratified by Synchronous vs Metachronous Presentation](image1.png)

![Table 4. Patterns of Recurrence Following Hepatic Resection of Rectal Metastases](image2.png)
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 (3-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 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.

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 1](http://example.com/f1.png)  
**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.
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 (e.g., 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

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.
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.29 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—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—either preoperatively or postoperatively—despite the fact that the overwhelming majority of patients had T3/T4 (85.8%) and N1 (68.1%) disease.

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 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.

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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.
REFERENCES


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 recurrence, 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 demonstrated and...