# Rates and Patterns of Recurrence Following Curative Intent Surgery for Colorectal Liver Metastasis

## *An International Multi-Institutional Analysis of 1669 Patients*

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**Objective(s):** To investigate rates and patterns of recurrence in patients following curative intent surgery for colorectal liver metastasis.

**Background:** Outcomes following surgical management of colorectal liver metastasis have largely focused on overall survival. Contemporary data on rates and patterns of recurrence following surgery for colorectal liver metastasis are limited.

**Methods:** One thousand six hundred sixty-nine patients treated with surgery (resection ± radiofrequency ablation [RFA]) for colorectal liver metastasis between 1982 and 2008 were identified from an international multi-institutional database. Clinicopathologic data, recurrence patterns, and recurrence-free survival (RFS) were analyzed.

**Results:** At the time of the initial liver-directed surgery, surgical treatment was resection only (90.2%), resection plus RFA (8.0%), or RFA alone (1.8%). While 5-year overall survival was 47.3%, 947 (56.7%) patients recurred with a median RFS time of 16.3 months. First recurrence site was intrahepatic only (43.2%), extrahepatic only (35.8%), intra- and extrahepatic (21.0%). There was no difference in RFS based on site of recurrence (intrahepatic: 16.9 months; extrahepatic: 16.6 months; intra- and extrahepatic: 16.2 month; $P > 0.05$). Receipt of adjuvant chemotherapy was associated with overall recurrence risk (hazard ratio [HR] = 0.56), while history of RFA (HR = 2.39, $P = 0.001$) and R1 margin status (HR = 1.36) were predictive of intrahepatic recurrence. Pattern of recurrence and RFS remained similar following repeat surgery for recurrent disease.

**Conclusions:** While 5-year survival following surgery for colorectal liver metastasis approaches 50%, over one-half of patients develop recurrence within 2 years. The pattern of failure is distributed relatively equally among intrahepatic, extrahepatic, and intra- plus extrahepatic sites. Patients undergoing repeat surgery for recurrent metastasis have similar patterns of recurrence and RFS time.

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Colorectal cancer is the third most common cancer worldwide, with a cumulative lifetime risk of approximately 5%.[1,2] In the United States, each year approximately 150,000 patients present with colorectal cancer and over 55,000 deaths are attributed to this disease, making it the second most common cause of cancer-related deaths in the United States.[3] Up to 10% to 20% of patients with colorectal adenocarcinoma have hepatic metastasis at the time of presentation,[4] while another 20% to 25% patients will develop metastasis during the course of their illness.[5–7] Without treatment, the prognosis of colorectal metastasis is poor and the 5-year survival rate is less than 5%. Liver resection represents the best curative therapeutic option[8] with ablative techniques being largely reserved for patients with metastatic disease who otherwise would be inoperable.[9]

In the 1980s and 1990s, the 5-year survival following hepatic resection of colorectal liver metastasis was reported to be about 30% to 35%.[6,7,10,11] With the introduction of improved patient selection, better surgical techniques, and more effective cytotoxic chemotherapy agents, 5-year survival following curative intent surgery of colorectal metastasis now approaches 45% to 60%.[12–15] Although advances in surgical and medical oncology have resulted in prolongation of survival for patients with colorectal liver metastasis, many patients still develop recurrent disease. Data on rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis are limited, however. In fact, most studies reporting on outcome following surgical management of colorectal metastasis have focused solely on overall survival rather than recurrence.[6,10,12,16] To date, most series on the topic of pattern of recurrence for colorectal metastasis have been limited by small sample sizes.[17–23] In addition, prior studies were largely single-institution and were published in an era prior to more effective systemic chemotherapy. Because patients with colorectal liver metastasis now enjoy a much longer overall survival following curative intent surgery, information on rates and pattern of recurrence are critical. In the current study, we sought to determine the rates of recurrence following surgery for colorectal liver metastasis. Specifically, we examine the pattern of recurrence of patients who were managed with curative intent resection and/or ablation. In addition, we identify those factors predictive of overall recurrence, as well as specific patterns of recurrence.

## METHODS

Between October 1982 and October 2008, 1669 patients treated with curative intent surgery for colorectal liver metastasis were identified from 4 major hepatobiliary centers in the United States (Johns Hopkins School of Medicine, Baltimore, MD) and Europe (Hôpitaux Universitaires de Genève, Geneva, Switzerland; Ospedale San Raffaele, Milan, Italy; Ospedale Mauriziano Umberto I, Turin, Italy). The study was approved by the Institutional Review Boards of the respective institutions. Only patients with colorectal liver metastasis who were operated on with curative intent were included in the study. Curative intent surgery included resection,

radiofrequency ablation (RFA), or combined resection plus ablation. 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.[8,24] RFA was considered curative in intent when under intraoperative ultrasound guidance, the probe could be optimally positioned to achieve complete destruction of the tumor and at least a 1 cm zone of normal liver parenchyma. In general, postoperative cross-sectional imaging was obtained following any surgery that involved an ablation to ensure adequate ablation, as well as, to establish a new baseline image for future follow-up. Only RFA treatments that were performed at the time of surgery were included; patients who underwent percutaneous RFA were excluded.

Before surgery, all patients were evaluated with a baseline history and physical examination, serum laboratory tests, and appropriate imaging studies (eg, computed tomography or magnetic resonance imaging scan of the abdomen and pelvis and chest radiography or a chest computed tomography) at the discretion of the treating physician. Following surgery, all patients were regularly followed and prospectively monitored for recurrence by serum carcinoembryonic antigen (CEA) levels, a computed tomography or magnetic resonance imaging scan of the abdomen and a chest radiograph every 3 to 4 months up to 2 years, and then every 6 months thereafter.

## Data Collection

Standard demographic and clinicopathologic data were collected on each patient including sex, age, CEA level, as well as treatment related variables including history of chemotherapy. Data were also collected on tumor characteristics. Specifically, data was collected on primary tumor location, American Joint Commission on Cancer stage (T, N, M), and presentation (synchronous vs. metachronous). The number, size, and distribution of the hepatic metastasis were also recorded. Resection was classified as less than a hemihepatectomy (eg, segmentectomy or subsegmentectomy), hemihepatectomy, or extended hepatectomy ($\geq$5 liver segments).[25] Date of last follow-up, vital status, and recurrence-related information were collected on all patients. With regard to recurrence, both the sequence and overall pattern of recurrence were noted. Recurrence was defined as a lesion that was biopsy proven recurrent adenocarcinoma or a lesion that was deemed suspicious on cross-sectional imaging in the setting of an elevated CEA level. Information regarding the location and number of lesions, as well as the disease-free interval from the date of initial operation to the development of recurrent disease was recorded. For the cohort of patients who developed repeat recurrences, data on the pattern and time interval between subsequent recurrences were also noted. Although the specific site of all recurrences were collected, for the purposes of analyses, recurrences were classified as intrahepatic only, extrahepatic only, or intra- and extrahepatic. As the objective of this study was not to evaluate the local efficacy of RFA, true local recurrences on a per-lesion ablation basis were not evaluated.

## Statistical Analyses

Summary statistics were obtained using established methods and presented as percentages or median values. Time to recurrence and survival were estimated using the nonparametric product limit method (Kaplan and Meier).[26] 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 analyses. The hazard ratio and the 95% confidence intervals (CI) were estimated and a *P* value less than 0.05 was considered significant. All statistical analyses were performed using SPSS Version 16.0 (Chicago, IL).

# RESULTS

## Patient and Tumor Characteristics

Table 1 shows the clinicopathologic features of the 1669 patients in the study. The median patient age was 61 years (range: 13–90 years) and most of the patients were male (n = 1009; 60.5%). Most patients who underwent liver-directed surgery for colorectal liver metastasis had a primary colon tumor (n = 1220; 73.1%), while 449 (26.9%) had a primary rectal lesion. Most primary colorectal tumors were staged as T3/T4 (n = 1266; 75.6%), while a minority of patients (n = 183; 11.0%) had T1/T2 disease. Primary tumor T stage was unknown in 220 (13.2%) patients. Among the 1449 patients who had primary tumor data available, the majority of patients had colorectal primaries that were associated with lymph node metastasis (n = 950; 65.6%). The median CEA level was 15 mg/mL. Synchronous (n = 808; 48.4%) versus metachronous (n = 861; 51.6%) presentation of liver metastasis was roughly equivalent. Some patients (n = 223; 13.3%) received perioperative systemic chemotherapy (eg, pre- and postsurgery), whereas other patients were treated solely with adjuvant chemotherapy (n = 716; 42.9%). Of the 728 cases in which the chemotherapy regimen was known, some patients were treated with 5-flurouracil-based monotherapy (n = 279; 38.3%); other patients received either oxaliplatin-based (FOLFOX) (n = 313; 43.0%) or irinotecan-based (FOLFIRI) (n = 136; 18.7%) therapy. Looking at the entire cohort, the median number of treated hepatic metastasis per patient was 1 (range: 1–15) and the median size of the largest lesion was 3.4 cm (range: 2 mm–24.0 cm). Most patients had disease confined to only one hemi-liver (n = 1257; 75.3%). The majority of patients had a clinical risk score[6] $\geq$2 (n = 880; 52.7%).

At the time of the initial liver-directed surgery, surgical treatment was resection only (n = 1506; 90.2%), resection plus RFA (n = 134; 8.0%), or RFA alone (n = 29; 1.8%). Of the 1506 procedures in which resection alone was undertaken, the extent of

**TABLE 1.** Patient Clinicopathologic Characteristics

| Variable | Number (%) |
|---|---|
| Patient characteristics | |
| Age (median) | 61 yr |
| Gender (male) | 1009 (60.4) |
| Preoperative factors | |
| CEA (median) | 15 mg/dL |
| Disease-free interval <12 mo | 1038 (62.2) |
| Clinical risk score >2 points | 221 (13.0) |
| Receipt of chemotherapy | 1155 (67.9) |
| Primary tumor characteristics | |
| Primary tumor site (colon) | 1220 (73.1) |
| T3/T4 disease | 1266 (75.6) |
| N-positive disease | 950 (65.6) |
| Hepatic metastasis characteristics | |
| Tumor number (median) | 1 |
| Size of largest hepatic lesion | 3.4 cm |
| Bilateral disease | 412 (24.7) |
| Details of surgical procedure | |
| Resection only | 1506 (90.2%) |
| Ablation only | 29 (1.8%) |
| Resection plus ablation | 134 (8.0%) |

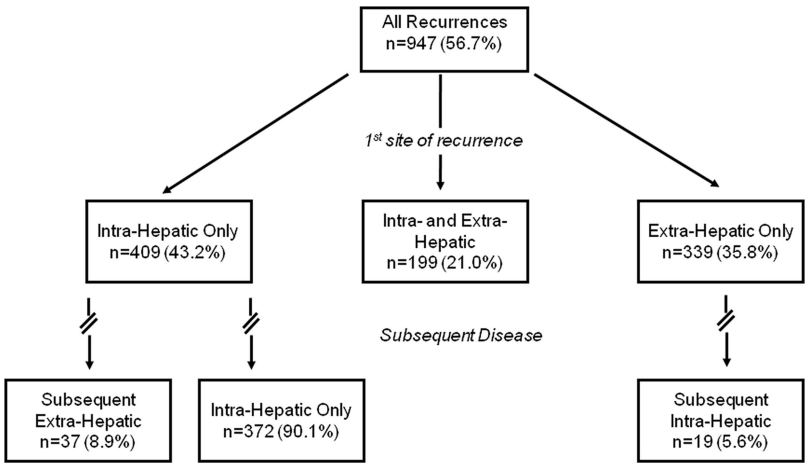



**FIGURE 1.** First pattern of recurrence. At a median follow-up of 30 months, 947 (56.7%) of 1669 patients developed a recurrence. Among all patients, 339 developed extrahepatic only disease as a first site of recurrence. In contrast, 608 patients presented with intrahepatic disease as a component as their first pattern of recurrence; 409 patients had only intrahepatic disease.

**TABLE 2.** Patterns of Recurrence Following Curative Intent Surgery of Colorectal Metastasis (n = 947)

| Site of Recurrence | First Site of Recurrence n (%) | First + Subsequent Recurrence Sites n (%) |
|---|---|---|
| Intrahepatic only | 409 (43.2) | 372 (39.3) |
| Intrahepatic + lung | 110 (11.6) | 152 (16.1) |
| Intrahepatic + other extrahepatic site | 89 (9.4) | 103 (10.8) |
| Extrahepatic only | 339 (35.8) | 320 (33.8) |
| Site of extrahepatic disease | n = 538 | n = 575 |
| Lung | 182 | 197 |
| Locoregional lymph nodes | 8 | 9 |
| Peritoneum | 34 | 35 |
| Bone | 23 | 25 |
| Periaortic/caval lymph nodes | 46 | 60 |
| Hilar lymph nodes | 24 | 32 |
| Brain | 16 | 22 |
| Adrenal | 5 | 7 |
| Pelvis | 31 | 36 |
| Ovary | 6 | 6 |
| Other | 20 | 23 |

hepatic resection was less than a hemihepatectomy in 829 (55.0%), a hemihepatectomy in 519 (34.5%), and an extended hepatectomy in 158 (10.5%). Patients who underwent RFA plus resection were less likely to undergo either a hemihepatectomy (n = 26; 19.4%) or an extended hepatic resection (n = 12; 9.0%) (both $P < 0.05$). Those patients who underwent resection plus RFA had a higher median number of treated hepatic metastasis (n = 5; range: 1–19) compared with patients who underwent either resection (n = 1; range: 1–20) or RFA (n = 1; range: 1–3) alone. On final pathologic analysis, no patient had a macroscopically positive margin (R2); the margin status was microscopically positive (R1) in 149 (8.9%) patients and microscopically negative (R0) in 1391 (83.3%) patients. Margin status was unknown in 132 (7.8%) patients. Tumor size, tumor number, and the extent of surgical resection did not predict margin status (all $P > 0.05$).

## Patterns of Recurrence

With a median follow-up of 30 months, 947 (56.7%) of 1669 patients developed a recurrence. Among all patients, 339 (20.3%) developed extrahepatic only disease as a first site of recurrence; 19 of these patients (5.6%) later developed intrahepatic disease as a second site of failure. In contrast, 608 patients (36.4%) developed intrahepatic disease as a component of the first site of recurrence; 199 of these patients (32.7%) initially experienced recurrence with synchronous extrahepatic disease (eg, intra- and extrahepatic recurrence). In contrast, 409 (67.3%) patients presented with intrahepatic disease only as their first pattern of recurrence (Fig. 1). Of the 409 patients who initially experienced recurrence with intrahepatic disease only, 37 (8.9%) subsequently had failure with distant metastasis, whereas 372 (90.1%) remained free of distant disease.

Of the 538 patients who developed an extrahepatic recurrence, the lung, peri-aortic/caval lymph nodes, and peritoneum were the most frequent sites of initial extrahepatic recurrence (Table 2). Specifically, 292 (54.3%), 46 (8.6%), and 35 (6.5%) patients, respectively, failed in the lung, peri-aortic/caval lymph nodes, or peritoneum as a first site of recurrence. In examining the overall final pattern of recurrence of the entire cohort (n = 1669), the overall rate of pulmonary, peri-aortic/caval lymph nodes, and peritoneal disease were 20.9% (n = 349), 3.6% (n = 60), and 2.1% (n = 35), respectively. Of 349 patients who failed in the lung, 92 (26.4%) had this as their only location of recurrence at the time of last follow-up.

## Predictors of Recurrence

The median overall survival following curative intent surgery of colorectal liver metastasis was 36 months and the 5-year actuarial overall survival rates was 47.3%. Median recurrence-free survival (RFS) was 23.0 months (95% CI: 21.1–24.9 months) with 1-, 3-, and 5-year actuarial disease-free survival rates of 69.2%, 37.7%, and 30.0%, respectively (Fig. 2). Several clinicopathologic factors were associated with any-site recurrence. Factors associated with overall shorter any-site RFS included rectum as the primary tumor site ($P = 0.03$), primary tumor lymph node metastasis ($P = 0.001$), synchronous presentation of primary tumor with hepatic metastasis ($P = 0.02$), history of RFA ($P < 0.001$), and receipt of chemotherapy ($P = 0.002$). The clinical risk score was also associated with risk of recurrence ($P < 0.001$). Other factors including tumor size >5 cm, preoperative CEA level, and final surgical margin status were not associated with overall RFS. On multivariate analysis, rectal primary tumor site (hazard ratio [HR] = 2.14, 95% CI: 1.60–2.87; $P < 0.001$), disease-free interval <12 months (HR = 1.43, 95% CI: 1.21–1.95; $P = 0.003$), history of RFA (HR = 2.14, 95% CI: 1.60–2.87; $P < 0.001$), receipt of chemotherapy (HR = 0.56, 95% CI: 0.33–0.65), as well as the clinical risk score (HR = 2.03, 95% CI: 1.55–2.98) each remained associated with overall RFS.

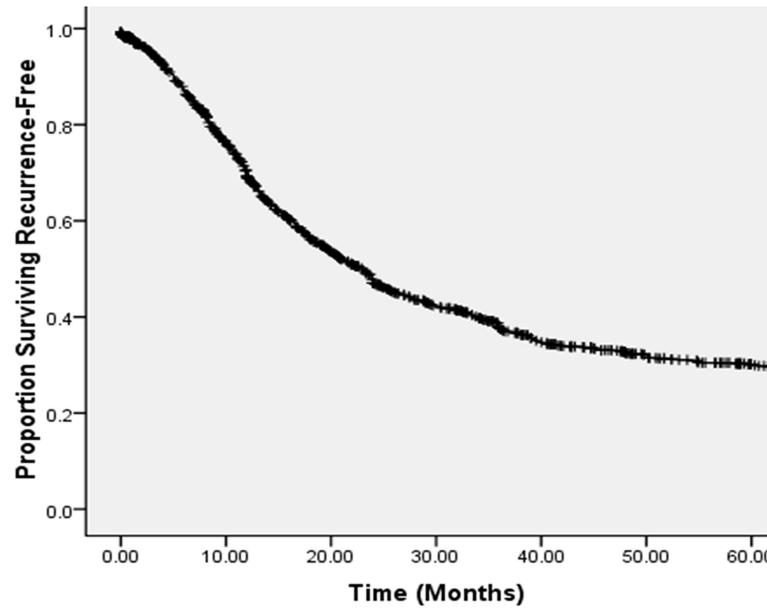



**FIGURE 2.** Although the 5-year actuarial overall survival was 47.3%, median recurrence-free survival was 23.0 months (95% CI: 21.1–24.9 months) with 1-, 3-, and 5-year actuarial disease-free survival rates of 69.2%, 37.7%, and 30.0%, respectively.

**TABLE 3.** Prognostic Factors Associated With First Site Pattern of Recurrence

| | Intrahepatic | | | Extrahepatic | | |
|---|---|---|---|---|---|---|
| Prognostic Factor | Hazard Ratio | 95% CI | *P* | Hazard Ratio | 95% CI | *P* |
| Rectal primary tumor | 1.01 | 0.84–1.21 | 0.90 | 1.38 | 1.15–1.65 | 0.001 |
| Primary LN metastasis | 1.25 | 1.04–1.50 | 0.02 | 1.36 | 1.12–1.67 | 0.002 |
| Synchronous metastasis | 1.29 | 1.10–1.54 | 0.002 | 1.17 | 0.98–1.38 | 0.08 |
| CEA 200 ng/mL | 1.24 | 0.90–1.66 | 0.20 | 1.22 | 0.88–1.67 | 0.24 |
| Hepatic lesion >5 cm | 0.99 | 0.81–1.22 | 0.94 | 1.26 | 1.02–1.53 | 0.03 |
| Hepatic lesions >4 | 1.15 | 0.80–1.64 | 0.46 | 1.73 | 1.21–2.50 | 0.003 |
| R1 resection | 1.36 | 1.11–1.69 | 0.01 | 1.06 | 0.81–1.39 | 0.68 |
| Receipt of chemotherapy | 0.73 | 0.61–0.88 | 0.001 | 0.78 | 0.64–0.93 | 0.009 |
| Receipt of RFA | 1.76 | 1.38–2.24 | 0.001 | 1.29 | 0.97–1.71 | 0.09 |

CI indicates confidence interval; LN, lymph node; CEA, carcinoembryonic antigen.

### RFS Based on the First Site of Recurrence

Among the entire cohort of patients who had disease recurrence (n = 947), the median RFS was 16.3 months (95% CI: 15.4–17.2 months). Of note, there was no difference in the median RFS based on the initial site of recurrence (intrahepatic only: 16.9 months vs. extrahepatic only: 16.6 months vs. intra- and extrahepatic: 16.2 months; $P > 0.05$).

Several factors were associated with an increased risk of intrahepatic disease as the first site of recurrence (Table 3). Patients with a synchronous presentation of the primary tumor and hepatic metastasis (HR = 1.29), receipt of chemotherapy (HR = 0.73), R1 margin status (HR = 1.36), and history of RFA (HR = 1.76) were associated with an increased risk of an intrahepatic recurrence as the initial site of failure (All $P < 0.05$) (Table 3). On multivariate analysis, R1 margin status (HR = 1.27) and history of RFA (HR = 2.39, $P = 0.001$) remained associated with intrahepatic recurrence. When extrahepatic disease as the first pattern of recurrence was analyzed primary rectal tumor site (HR = 1.38), primary tumor lymph node metastasis (HR = 1.36), hepatic tumor size >5 cm (HR = 1.26), and hepatic tumor number >4 (HR = 1.73), as well as receipt of chemotherapy (HR = 0.78) were each associated with an increased risk of extrahepatic recurrence. On multivariate analysis, rectal primary tumor site (HR = 1.65, $P = 0.004$) and tumor number >4 (HR = 1.68, $P = 0.01$) each remained associated with the risk of first site extrahepatic recurrence.

### Final Pattern of Recurrence

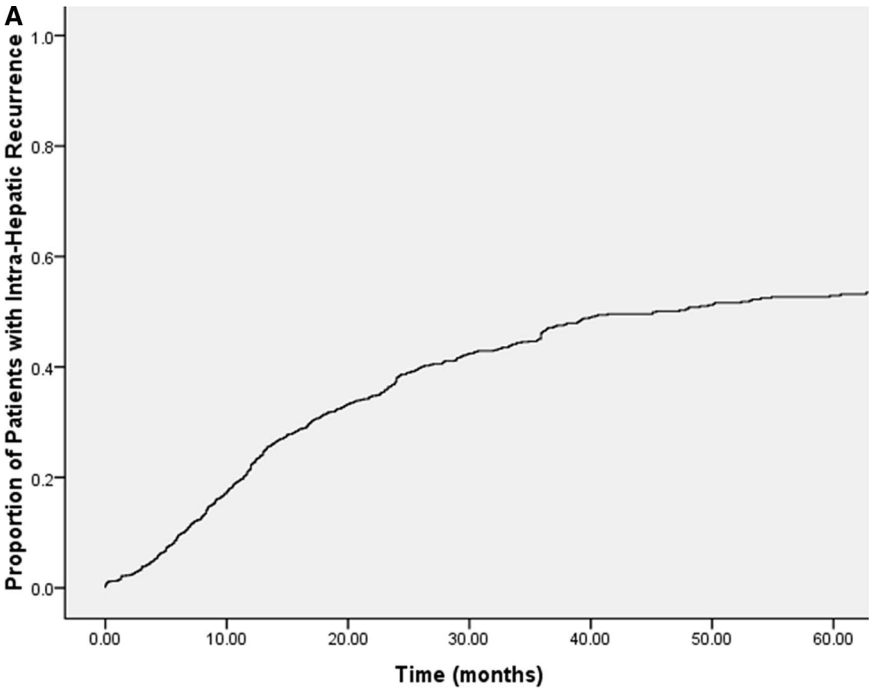
In examining the entire cohort of 1669 patients, the distribution of initial plus late sites of recurrence was intrahepatic only in 372 (22.3%) compared with extrahepatic only in 320 (19.2%) of patients. Stratifying by site of disease, the 5-year overall risk of intrahepatic recurrence was 52.3% compared with 59.9% for extrahepatic disease (Fig. 3).

Of the 947 patients who did recur, 359 (37.9%) patients had multiple different anatomic sites of recurrence when analyzing both the initial plus late sites of recurrence (Fig. 4). Specifically, 255 (15.3%) patients had recurred at both a liver plus an extrahepatic site. Of those patients with extrahepatic recurrence, 209 (38.8%) had at least 2 different anatomic extrahepatic sites as part of their final pattern of recurrence. Of note, 372 (22.3%) patients had isolated liver-only recurrence as their overall final pattern of recurrence.

Of the 947 patients who recurred, 197 (20.8%) patients underwent repeat curative intent surgery. Among these 197 patients, 52 and 9 patients had a third and fourth surgery, respectively, with curative intent. The overall pattern of recurrence remained similar with regard to intrahepatic versus extrahepatic versus intraplus extrahepatic disease following repeat curative intent surgery ($P = 0.91$) (Table 4). In addition, the median interval between recurrences following repeat curative intent surgery was similar (second recurrence: 15.6 months vs. third recurrence: 14.9 months vs. fourth recurrence: 13.6 months; $P = 0.63$).

## DISCUSSION

The goal of hepatic surgery for colorectal liver metastasis should be to resect or completely ablate all lesions within the liver to provide the patient with the best chance at long-term cure. Traditionally, most studies that have reported on curative intent surgery for colorectal metastasis have focused on overall survival.[6,10,12–16] In these studies, there has been a marked improvement in overall survival, with a near doubling of the historical 5-year survival rate of 30% to 35%[6,7,10,11] to the currently cited 5-year



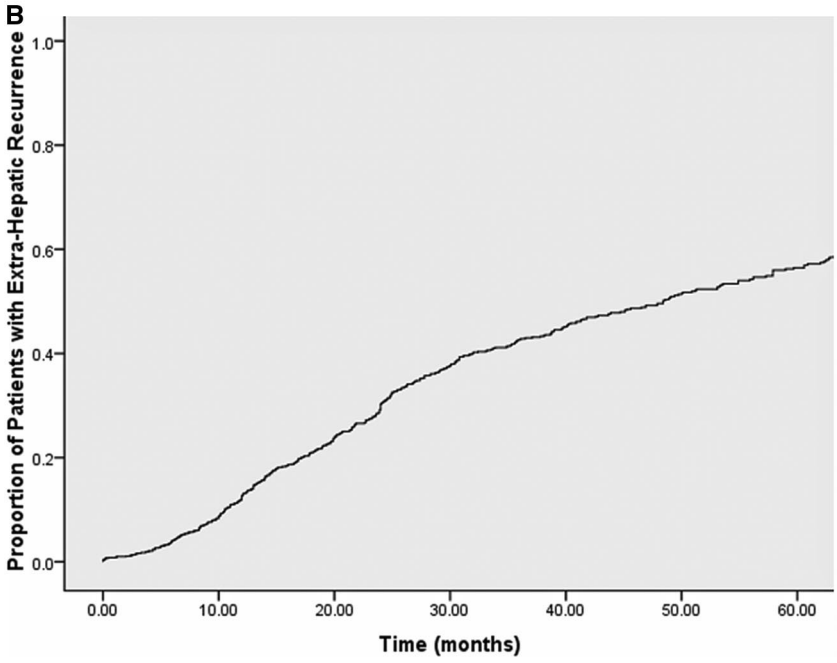




**FIGURE 3.** Stratifying by site of disease, the 5-year overall risk of intrahepatic recurrence was 52.3% (A) compared with 59.9% for extrahepatic disease (B).

survival rate of 45% to 60%.[12–15] These improvements in overall survival have occurred despite an expansion in the criteria of resectability for colorectal liver metastasis at many major hepatobiliary centers.[8] Specifically, the number of metastasis, size of tumor lesion, and a mandatory 1 cm margin of resection are no longer considered absolute criteria for a curative surgical approach. However, as the criteria for surgery of colorectal metastasis expand and patients with more extensive disease are considered for curative intent liver-directed surgery, the incidence and pattern of recurrence following liver surgery may be impacted. To date, the issue of recurrence following curative intent liver surgery of colorectal liver metastasis has largely been relegated to investigations concerned with RFA[9,14,27] or surgical margin status.[13,28,29] While more general data on rates and patterns of recurrence have been published, these data have been limited.[17–23] Previous studies that specifically addressed recurrence mostly included data from single institutions and most included fewer than 100 patients. As such, these series are limited by their small sample size and potentially lack generalizability. The current study is important because it defines the rate and pattern of recurrence following curative intent surgery for colorectal liver metastasis in a large, multinational, multi-institutional cohort of patients. We found, in spite of an overall 5-year survival approaching 50%, over one-half of patients developed recurrence within 2 years. When patients initially recurred, the pattern of failure was

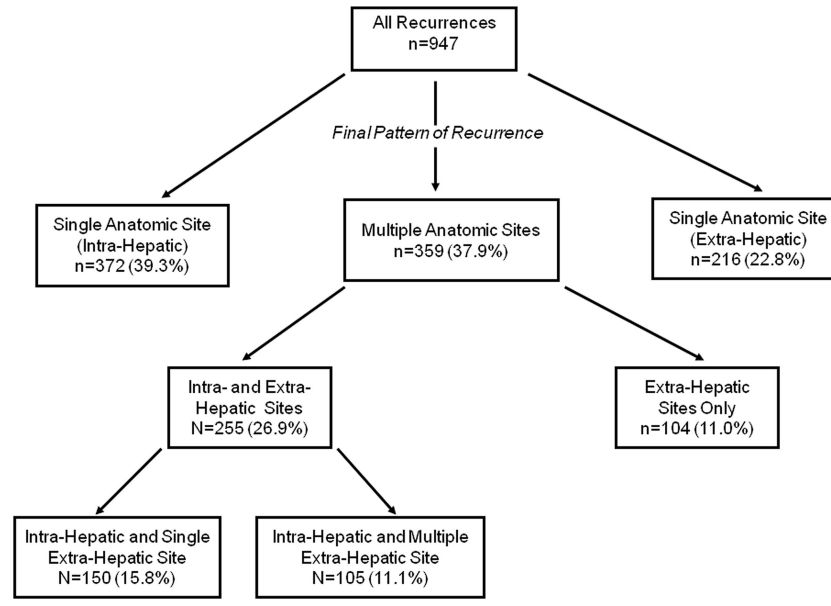



**FIGURE 4.** Overall final pattern of recurrence. At time of last follow-up, 372 patients had developed recurrence at only an intrahepatic site. In contrast, 359 patients had developed recurrence at multiple anatomic sites.

**TABLE 4.** Patterns of Recurrence Following Subsequent Curative Intent Surgical Interventions

| | Second Recurrence (n = 197) | Third Recurrence (n = 52) | Fourth Recurrence (n = 9) | *P* |
|---|---|---|---|---|
| Pattern of recurrence, % | | | | |
| Intrahepatic only | 35 | 38 | 33 | 0.91 |
| Extrahepatic only | 34 | 29 | 33 | |
| Both intra- and extrahepatic | 31 | 33 | 34 | |
| Time between recurrences, mo | 15.6 | 14.9 | 13.6 | 0.63 |

distributed relatively equally among intrahepatic, extrahepatic, and intra- plus extrahepatic sites.

At the time of last follow-up, we found that 947 of 1669 (56.7%) patients had developed a recurrence. In analyzing the entire cohort, RFS was 69.2% at 1 year; at 5-years following curative intent surgery, the RFS was only 30.0% (Fig. 2). The overall incidence of recurrence reported in the current study was therefore similar to the 60% to 85% overall recurrence rate reported previously.[17,19,22,23,30] However, unlike previous studies[18,22,30] that had investigated recurrence, the median time to any-site recurrence was demonstrably longer than historical controls. Specifically, in the current study, the overall median RFS was 23.0 months compared with previously reported RFS durations of 9 to 15.6 months.[18,22,30] Although the reasons for the prolongation in RFS are probably multifactorial, the use of modern chemotherapy regimens is clearly a key determinant. While chemotherapy alone is rarely, if ever, associated with durable survival, modern chemotherapy now results in median survival of up to 21 months in patients with unresectable disease.[31] The combination of modern chemotherapy with advances in surgical techniques has resulted in improvements in overall survival and increased hopes for actual "cure." Data from the current study, however, would suggest that "cure" remains an elusive goal. Instead, our data demonstrate that the actual overall rate of recurrence following curative intent surgery remains high (~60% to 70%) and is virtually no different than recurrence rates reported 2 decades ago.[11,22,30] Rather than decreasing recurrence rates, modern era multimodality curative intent therapy for colorectal liver metastasis appears to simply prolong the time to recurrence.

To a variable degree, the determinants of overall risk of recurrence have been previously examined in the literature. In the current study, factors associated with an overall shorter any-site RFS included rectum as the primary tumor site, primary tumor lymph node metastasis, and synchronous presentation of primary tumor with hepatic metastasis. Yamada et al[18] and Jatzko et al[32] had previously reported that recurrence after hepatectomy was influenced more by factors associated with the primary colorectal cancer than factors associated with the first liver metastasis. Fong et al[6] subsequently proposed a clinical risk score for predicting recurrence after hepatic resection that combine primary tumor factors (eg, nodal status of primary, disease-free interval <12 months) with metastasis-specific factors (CEA level, >200 ng/mL; number of tumors, >1; size of largest liver lesion, >5 cm). Interestingly, while the score was proposed as a prediction tool for recurrence, the main outcome of the original study was overall survival—not recurrence.[6] However, when the clinical risk score was applied to data in the current series, the aggregate score was indeed associated with risk of overall recurrence. In contrast, in examining initial sites of metastatic disease, the clinical risk score was not predictive of a particular pattern of recurrence.

In examining initial sites of recurrence, of the 947 patients who recurred, 409 (43.1%) patients had liver only disease, whereas 199 (21.0%) had recurrences in the liver plus other extrahepatic sites. Therefore, at the time of last follow-up, 608 of 1669 (36.4%) patients had the liver as part of their initial recurrence pattern. These data are consistent with previously reported case series that noted liver recurrence rates of 30% to 40%.[10,20,33] Unlike previous studies,[34,35] we did not find that number of hepatic metastasis nor size of the largest hepatic lesion had an effect on hepatic recurrence. In contrast, surgical margin status was associated with an increased risk of intrahepatic recurrence. de Hass al[36] had also noted that R1 resection was associated with increased risk of intrahepatic recurrences compared with R0 resection. Similarly, we, as well as others,[9,14,27] noted an increased risk of intrahepatic recurrence with the use of RFA. Irrespective of any single risk factor, the cumulative risk of liver recurrence was 52.3% at 5-years. Of note, the risk appeared to be highest over the first 3 years following surgery, with the risk subsequently reaching a plateau (Fig. 3A). In addition to clinic-morphologic and treatment-related factors, the phenotypic

patterns of recurrence may also be associated with potential genotypic differences.[37,38] Thorstensen et al[37] noted that the loss of the distal part of chromosome arm 1p was significantly different in local recurrences versus metastasis. In a separate study, Varghese et al[38] reported that different phenotypic metastatic sites have distinct gene expression.

As patients undergo surgery for more extensive metastatic liver disease, there has been a concern that the incidence of extrahepatic metastatic recurrence may increase. In the current series, 575 of 1669 (34.5%) patients ultimately developed extrahepatic recurrence. Certain cohorts of patients, however, were identified as having a particularly high risk of extrahepatic recurrence. Specifically, patients with more aggressive biologic factors such as primary tumor lymph node metastasis, hepatic metastasis greater than 4 in number, and hepatic metastasis tumor size >5 cm, each conferred a 25% to 75% increased risk of extrahepatic recurrences (Table 3). Our findings corroborate the notion that patients with hepatic metastasis characterized by certain aggressive biologic phenotypical traits are at an even greater risk of extrahepatic failure. While such clinical and morphologic factors should not dictate whether a patient is resectable, these data help to inform providers about the risk of systemic recurrence. Interestingly, unlike the risk of intrahepatic recurrence, the cumulative risk of systemic recurrence continued to increase over time without a discernable leveling off of the risk (Fig. 3B).

Although several institutions have reported on survival outcome following repeat hepatectomy,[39–41] data on the rate and pattern of recurrence following repeat curative intent surgery are lacking. Repeat curative intent surgery for recurrence is being increasingly performed with associated survival rates of 30% to 41%.[39–41] The rationale behind repeat liver-directed surgery for recurrent disease is supported in part by a belief that the liver is often the sole site of recurrent metastasis. We report on a subset of patients who underwent 2, 3, or 4 attempts at curative intent surgery for recurrent colorectal metastasis. Importantly, we found that the overall pattern of recurrence remained similar with regard to intrahepatic versus extrahepatic versus intra- plus extrahepatic disease (Table 4). Of note, following each attempt at curative intent surgery roughly two-thirds of patients had an extrahepatic metastasis as a component of disease failure. Perhaps more importantly, we also noted that the recurrence-free benefit of repeat curative intent surgery was similar regardless of the number of times previous surgery had been performed. Specifically, the median interval between recurrences following repeat curative intent surgery was 15.6, 14.9, and 13.9 months following the second, third, and fourth curative intent surgery, respectively. Repeat curative intent surgery should therefore be considered for subsequent recurrences, but only after careful clinical consideration that involves the same criteria of resectability established for the initial disease (eg, R0 resection, adequate hepatic reserve, etc).

The current study had several limitations. Because our study is retrospective in nature, there may have been selection/detection bias in our ascertainment of the pattern of recurrence. Although all participating centers queried institution-wide databases for information on recurrence, it is conceivable that the extent of extrahepatic recurrences may be under-represented due to the surgical nature of the databases used in the current study. These short-comings are inherent, however, in nearly all retrospective analyses of data on recurrence.

In conclusion, although 5-year survival following curative intent surgery for colorectal liver metastasis now approaches 50%, the problem of recurrence remains a serious clinical challenge. Despite a near doubling of overall survival, the risk of recurrence remains high (~65%–70%). In fact, while the overall RFS now approaches 2 years, the 5-year cumulative risk of intrahepatic and extrahepatic recurrence was over 50%. Factors associated with intrahepatic recurrence included margin status and RFA, while risk of extrahepatic recurrence was associated with a more aggressive tumor phenotype (eg, multiple, large metastasis). Although 5-year survival following curative intent surgery has improved,[8] the current study serves to emphasize that our ability to prevent recurrences is more sobering. We can only hope that future progress in the multidisciplinary care of patients with colorectal liver metastasis will lead to decreasing rates of recurrence that parallel the successes achieved in improving overall survival.

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# Discussions

DR. DAVID M. NAGORNEY (ROCHESTER, MINNESOTA): The clinical importance of recognizing patterns of recurrence is 2-fold: First, it reveals the limitations of the incident cancer operation and second, it provides direction for adjuvant treatment strategies in the future after resection. In that regard I have several questions. First, you attributed delays in recurrence primarily to adjuvant chemotherapy. This treatment is very easy to measure, but I think it shortchanges the impact of operative factors and imaging, which may be equally important but much more difficult to measure. Given the period of study, it would be interesting to determine whether intraoperative ultrasound, staged resections, multimodality imaging studies of the liver, and positron emission tomography (PET) scanning may have influenced the completeness of the original liver operation. Could you extract these data from your database and then correlate them to recurrent status? Second, although RFA was used in few patients, it strongly correlated with recurrence. Although there are likely to be many causes for this, it certainly raises a cautionary flag regarding its use. Does this finding about RFA mean that we should follow these patients differently? Should they receive a different adjuvant treatment program? Or should we just learn how to perform RFA better? Third, only 3 of the predictors of recurrence, that is, R stage, RFA and chemotherapy, are factors that we can influence. This expanded group of patients requires that we think about other areas we should address. Do you have any suggestions? Finally, the findings that subsequent recurrences remain predominantly at the site of the initial recurrence should influence adjuvant therapy. Because the liver remains the site of recurrence in more than 60% of the patients, the obvious question is, should we revisit the issue of hepatic arterial chemotherapy?

DR. TIMOTHY M. PAWLIK (BALTIMORE, MARYLAND): I think that your point with regards to chemotherapy is well taken. Although in the current series we did not specifically look at other factors such as cross-sectional imaging or PET scan, in some previously published data we reported that PET is actually a very important factor with regards to increasing the overall rate of nontherapeutic laparotomy and actually may affect overall patterns of recurrence. Although traditionally we give all the credit to chemotherapy, I think that better patient selection and better rational use of preoperative and intraoperative imaging may also, in part, contribute to the improvement in overall survival. With regards to RFA, I share a cautionary note. It is our standard of practice that when a lesion is resectable, we resect the lesion and only use ablation in those patients who for some reason are not candidates for resection. That being said, I think it is not fair to compare overall survival directly between RFA and resection. Since it is our standard to resect, only those patients with extensive disease received resection plus RFA; as such, patients who underwent RFA, in general, had liver disease that would not otherwise have been considered amenable to curative intent surgery. We are trying to use RFA to expand the eligibility of patients who may potentially be curable. I do not think that it will necessarily change the adjuvant therapy we use, but I think it may change the surveillance. I know that when I have ablated someone, I follow them perhaps even more closely than my resected patients. I also think there is significant heterogeneity in ablation when it is performed. Our group, as well as others, have proposed that we should stratify ablation as A0, A1, A2, as we do with resection (eg, R0, R1, R2). I think we all would agree that when we ablate we often feel that we achieved a really good "A0" ablation, but other times it may be more of a suboptimal ablation. With regards to the hepatic artery pump, I think it is a half empty/half full conversation. Some proponents of the pump may look at these data and say, well, if two-third of the patients are failing within the liver, this is good justification for using locoregional therapy such as the pump. Opponents of the pump may look at these data and say, well, roughly two-third of the patients fail outside the liver and we have good systemic chemotherapy, so why use the locoregional approach? I think that, in large part, the jury is still out. We do not routinely, however, employ putting pumps in an adjuvant setting.

DR. SEAN J. MULVIHILL (SALT LAKE CITY, UTAH): It would be useful to describe in the manuscript the use of adjuvant chemotherapy and stratify the patients according to their recurrence status according to that factor, and also the use of preoperative PET scanning, because there may be differences in patterns related to those maneuvers. My question is whether your database was detailed enough to assign margin status within the bounds of the current

controversy as to whether a 10 millimeter margin is equivalent to a 1 mm margin and different from a 0 mm or sub 1 mm microscopic margin.

Dr. Timothy M. Pawlik (Baltimore, Maryland): Again, we did not specifically look at the use of PET in this study. We did look at chemotherapy, and you are right. The use of chemotherapy was significantly protective with regards to both intra- and extrahepatic recurrence. We did stratify the perioperative chemotherapy pre- and postoperative versus purely postoperative and did not see a difference, although the numbers were small. With regards to the margin question, 2 points: One, we did not specifically look at that; and 2, I am somewhat biased because a few years ago our group published a paper in Annals of Surgery indicating that width of the R0 margin does not affect pattern of recurrence or overall survival. I tend to believe our data in that an R0 margin is an R0 margin whether it is 2 millimeters or 10 millimeters. Although, obviously, we should strive not to do minimal margin surgery, I do not think that there should be a "1 cm" rule used as an absolute nor even a relative contraindication for considering someone for surgery.

Dr. Anton J. Bilchik (Santa Monica, California): As you mentioned, a large reason for the improvement in survival after resection is systemic therapy. Since your study takes place over a 26-year period and since some of the countries with which you collaborated had access to oxaliplatin, about 8 years before the United States, can you comment on whether there was a difference in patterns of recurrence between countries?

Dr. Timothy M. Pawlik (Baltimore, Maryland): We did look at the data from about 1990 forward, and from 1990 back. Although there was a difference in the overall survival rate, the overall rate of recurrence was not different.

Dr. Steven A. Curley (Houston, Texas): Did you break down survival? Some of the patients early in the study would not have undergone state of the art imaging, would not necessarily have undergone intraoperative ultrasound. Was there a clear break point in the timing of the operations of these patients, ie, are patients operated on more recently, experiencing a better survival rate than those earlier in your series? Second, did you have enough patients in your study to look at the role of any neoadjuvant therapy, ie, the treatment response, and could that correlate with a prediction of survival or a better recurrence free survival? Ultimately, as you and I both know, the "so what" question in all of this is, what do we do with the data? Do we somehow stratify patients if they have some of these negative prognostic, pathologic, or clinical findings? Do we then use that to design clinical trials that will answer the question, should they receive prolonged chemotherapy? Should they, like some of our colleagues in medical oncology, receive some sort of biologic therapy for a period of several years?

Dr. Timothy M. Pawlik (Baltimore, Maryland): We did not specifically look at trends in overall survival. We chose an arbitrary break point of around 1990 and looked at survival before and after that point. With regards to your point of looking at neoadjuvant chemotherapy, we did not look at that vis a vis a pathologic response. However, some of the collaborators on the article, specifically Professor Mentha looked at the question of pathologic response to preoperative chemotherapy in a previously published report. I think you are exactly right. Ultimately, the goal would be to identify those patients who may benefit the most from treatment with neoadjuvant/preoperative chemotherapy. I think this is a question that still has not been answered and requires further attention.