Abstract

BACKGROUND: The aim of this study was to analyze the feasibility and early outcomes of 2-stage liver resection for bilobar metastases.

METHODS: Data from 39 consecutive patients undergoing 2-stage hepatectomy between 2004 and 2010 were prospectively collected.

RESULTS: The median age was 59 years (range, 33–79 years), and the ratio of men to women was 1.8:1. Metastases were colorectal carcinoma (n = 33), neuroendocrine tumors (n = 3), gastrointestinal stromal tumor (n = 1), ocular melanoma (n = 1), and salivary gland carcinoma (n = 1). Perioperative chemotherapy was given to 32 patients (82%). Twenty-nine patients (74%) underwent portal venous embolization. Radiofrequency ablation was used in 8 patients (21%). Twenty-seven patients (69%) successfully completed clearance. For the 1st and 2nd stages, the median lengths of stay were 11 days (range, 6–53 days) and 13 days (range, 6–44 days), and morbidity rates were 23% and 56%. Liver insufficiency occurred in 2 (5%) and 6 (22%) patients. Overall mortality was 2.6%. For colorectal metastases, median survival in successes versus failures was 24 versus 10 months (P = .03), and 3-year survival was 30% versus 0%.

CONCLUSIONS: Two-stage hepatectomy is feasible, with 69% of patients achieving clearance with low mortality. Morbidity is significant, particularly transient hepatic insufficiency.

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KEYWORDS: Liver metastases; Colorectal carcinoma; Two-stage hepatectomy; Portal venous embolization

Surgery offers the only potential for long-term survival in patients with liver metastases from colorectal and several other cancers. 1,2 Although colorectal cancer accounts for most liver resections for metastatic disease, resections are also performed in selected patients for breast, neuroendocrine tumor, melanoma, salivary gland, gastrointestinal stromal tumor, and several other cancers that have metastasized to the liver.

Historically, extensive bilobar liver metastases precluded patients from potentially curative surgery. Over the past 2 decades, improvements in systemic chemotherapy, advances in surgical technique, and the complementary use of other techniques, such as portal vein embolization and radiofrequency ablation, have allowed a more aggressive approach to the treatment of liver metastases, with improvements in survival. 1 As a result, the criteria for resectability of hepatic metastatic disease have expanded considerably. 3 Rather than excluding patients from surgery on the basis of the number and size of metastases, we now consider all patients for resection when it is possible to resect all disease
while retaining a future liver remnant volume ≥5% of body weight with preserved vascular inflow and outflow and biliary drainage.

The major limitation in many patients has been the inability to clear all metastatic disease in 1 operation while preserving an adequate future liver remnant. For these patients a 2-stage hepatectomy approach has been advocated. Staged resection, with or without portal venous embolization, enables a period of regeneration of the future liver remnant between hepatectomies, thus increasing the volume of the future liver remnant and reducing the risk for post-hepatectomy liver insufficiency. The selected use of this approach has increased the number of patients able to achieve surgical clearance of metastatic disease.

Several studies of 2-stage hepatectomy have been published to date, with most including few patients (Table 1). The aim of this study was to assess the feasibility and outcomes of patients selected for this approach, with multiple bilobar liver metastases from malignancies in which liver resection has a role.

### Methods

A prospective database of liver resections performed by a single consultant hepatobiliary surgeon between 2004 and 2010 was collected and retrospectively analyzed. During this period, 349 consecutive patients underwent hepatectomy. Thirty-nine of these patients (11%) were selected for a 2-stage approach to surgical clearance of hepatic metastases. Sixty-six hepatectomies were performed in these 39 patients.

#### Two-stage hepatectomy therapeutic strategy

Patients were considered for the 2-stage approach when all hepatic disease could not be cleared with a single hepatectomy while preserving an adequate future liver remnant. The future liver remnant was measured by 3-dimensional computed tomographic volumetry and considered inadequate when it consisted of a volume < 0.5 mL/kg body weight.

In all cases, the 2-stage approach was planned before the 1st hepatectomy and was performed with curative intent (intent to resect all evident hepatic metastases). Treatment with perioperative chemotherapy was decided in a multidisciplinary setting, including both the surgeon and the medical oncologist.

At the 1st hepatectomy, the minor hepatectomy was generally performed, leaving the major hepatectomy for the 2nd stage. When possible, mobilization of the contralateral liver and dissection of the porta hepatis was avoided to minimize adhesions encountered at the 2nd hepatectomy.

Portal venous embolization or ligation was used in patients with inadequate future liver remnants. This was achieved by transhepatic percutaneous embolization by a hepatobiliary interventional radiologist in all except 1 patient, who had surgical portal venous ligation.

After restaging with computed tomography, a 2nd hepatectomy was planned when there was sufficient hypertrophy of the future liver remnant and no evidence of significant disease progression. The 2nd hepatectomy proceeded as soon as the patient had recovered from the 1st hepatectomy and had achieved an adequate future liver remnant volume, except when interval chemotherapy was indicated. The 2-stage approach was deemed successful when it achieved clearance of all evident macroscopic disease.

#### Data collection and statistical analysis

Standard patient demographic data comprising age and sex were collected. Tumor characteristics recorded were tumor type, the number and distribution of metastases, diameter of the largest metastasis, whether metastases were synchronous or metachronous, and the presence of extrahepatic disease. Operative data collected included resection type, the use of radiofrequency ablation, and concurrent surgical procedures. Other therapeutic data recorded were
treatment with chemotherapy and the use of portal venous embolization or ligation. Pathologic margin status for each resection was recorded as R0 or R1. Postoperative hospital stay and morbidity were recorded, and the Clavien grading system\textsuperscript{13} was used to score complication severity. Operative mortality was defined as postoperative death within 90 days of surgery. Date of last follow-up and the presence of known recurrent disease were also recorded.

Data between groups were compared using Fisher's exact test for categorical data and independent \( t \) tests for continuous data. Survival probability was estimated using the Kaplan-Meier method and compared using log-rank tests. Differences with \( P \) values \( \leq .05 \) were considered significant. MedCalc (MedCalc Software, Mariakerke, Belgium) was used to perform all statistical analysis.

## Results

### Patient and tumor characteristics

Table 2 shows the demographic and tumor data for the patient population in this study. The median age was 59 years (range, 33–79 years), and the ratio of men to women was 1.8:1. All patients had an Eastern Cooperative Oncology Group performance status of 1 or 2. Resection was performed for metastatic disease from colorectal carcinoma in 33 patients, neuroendocrine tumors in 3, gastrointestinal stromal tumor in 1, ocular melanoma in 1, and salivary gland carcinoma in 1. Metastatic disease was synchronous in 26 and metachronous in 13. The median number of hepatic metastases was 10 (range, 2–21), and the median largest metastasis was 46 mm (range, 4–200 mm). Concurrent extrahepatic metastatic disease was present in 6 patients before 1st hepatectomy: 1 with neuroendocrine carcinoma lymph node metastases, 3 with colorectal lung metastases, 1 with localized colorectal peritoneal metastases, and 1 with colorectal lymph node metastases. Two patients had local recurrence of their primary in situ tumors: salivary gland carcinoma in 1 patient and colorectal carcinoma in 1 patient. Ten patients had in situ colorectal primary tumors, 9 of which were resected at the 1st-stage hepatectomy; the 10th patient had the colonic tumor resected in a separate procedure after recovery from 2nd hepatectomy.

### Chemotherapy

Chemotherapy was given before the 1st stage in 29 patients (74%). For the 33 patients with metastases of colorectal origin, the majority (n = 28 [85%]) received chemotherapy before the 1st hepatectomy. Thirteen of these (46%) received conventional chemotherapy (5-fluorouracil based plus oxaliplatin or irinotecan), and the remainder received biologic agents (either cetuximab or bevacizumab) in addition to conventional chemotherapy. Six patients (15%; all with colorectal metastases) received interval chemotherapy before the 2nd stage. Every patient at the end of surgical clearance was referred back to the oncologist for consideration of further chemotherapy.

### Surgery and additional therapeutic procedures

In most patients (n = 29 [74%]), the less extensive of the planned hepatectomies was performed at the 1st stage. In 79% of patients (n = 31), the disease in the left lobe was cleared at the 1st hepatectomy. Nine 1st hepatectomies (23%) compared with 16 2nd hepatectomies (59%) were major resections (defined as \( \geq 3 \) segments; \( P = .062 \)).

Radiofrequency ablation was used as an adjunct to surgical resection in 8 patients (21%). Three patients underwent open radiofrequency ablation at 1st hepatectomy, 2 at 2nd hepatectomy, and 3 as a separate percutaneous procedure.

Concurrent procedures were performed in 12 patients (31%). Ten patients underwent synchronous colorectal resection (anterior resection in 9, abdominopereineal resection in 1), 1 patient underwent localized peritoneal clearance of colorectal metastases, and 1 patient with neuroendocrine carcinoma had a distal pancreatectomy. One patient who had an anterior resection also had a salpingo-ophorectomy, appendectomy, and lymph node clearance. All of these were performed at 1st hepatectomy.

Portal venous embolization or ligation was performed in 29 patients (74%). In 28 of these, portal venous embolization was performed percutaneously in the interval between hepatectomies. One patient underwent a surgical portal ve-

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**Table 2** Patient demographics and tumor characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>59 (33–79)</td>
</tr>
<tr>
<td>Men/women</td>
<td>1.8:1</td>
</tr>
<tr>
<td>Tumor type</td>
<td></td>
</tr>
<tr>
<td>Colorectal carcinoma</td>
<td>33</td>
</tr>
<tr>
<td>NET</td>
<td>3</td>
</tr>
<tr>
<td>GIST</td>
<td>1</td>
</tr>
<tr>
<td>Ocular melanoma</td>
<td>1</td>
</tr>
<tr>
<td>Salivary gland carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Metachronous</td>
<td>13</td>
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<tr>
<td>Synchronous</td>
<td>26</td>
</tr>
<tr>
<td>Tumor number</td>
<td>10 (2–21)</td>
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<tr>
<td>Size of largest tumor (mm)</td>
<td>46 (4–200)</td>
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<tr>
<td>EHMD</td>
<td>6</td>
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<tr>
<td>Lung</td>
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<tr>
<td>Peritoneal</td>
<td>1</td>
</tr>
<tr>
<td>Lymph node</td>
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</tr>
<tr>
<td>Local recurrence of primary tumor</td>
<td>2</td>
</tr>
<tr>
<td>Colon</td>
<td>1</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>1</td>
</tr>
<tr>
<td>In situ colorectal primary</td>
<td>10</td>
</tr>
</tbody>
</table>

Data are expressed as median (range) or as numbers. EHMD = extrahepatic metastatic disease; GIST = gastrointestinal stromal tumor; NET = neuroendocrine tumor.
nous ligation at the time of the planned 2nd stage, which was delayed because of insufficient future liver remnant volume. The median time between 1st and 2nd hepatectomies was 12 weeks (range, 6–28 weeks).

Feasibility

Twenty-seven patients (69%) successfully completed both stages, achieving clearance of disease. Twelve patients (31%) failed to complete surgical clearance, 11 because of disease progression (8 liver, 3 peritoneal) and 1 because of inadequate hypertrophy of the future liver remnant. Two of the 6 patients with colorectal liver metastases who received interval chemotherapy failed because of disease progression. Of the 11 with disease progression, 6 (55%) were deemed unresectable on restaging before 2nd laparotomy and the remainder at 2nd laparotomy.

The likelihood of successful clearance of disease by 2-stage surgery was not affected by age, gender, Eastern Cooperative Oncology Group performance status, tumor number, size of largest tumor, whether the liver metastases were synchronous or metachronous, the presence of extrahepatic metastatic disease, the use of portal venous embolization or ligation, or perioperative chemotherapy.

Overall, 15 patients (38%) completed both stages as per the preoperative surgical plan. Twelve (31%) completed both stages but required modifications of the plan.

Margins

Of all hepatectomies, 45 (68%) were R0 resections. Twenty-nine patients (74%) had R0 resections at the 1st hepatectomy and 16 patients (59%) at the 2nd hepatectomy (P = .692). Overall, 14 patients (36%) achieved complete disease clearance, with all margins R0.

Length of stay, morbidity, and mortality

For the 1st and 2nd stages, respectively, the median lengths of stay were 11 days (range, 6–53 days) and 13 days (range, 6–44 days) (P = .019).

Overall patient morbidity was 56% (n = 22): 8 from liver insufficiency (21%), 7 from bile leaks (18%), 2 from ascites (5%), 2 from abdominal sepsis (5%), 3 from wound complications (8%), 1 from a pancreatic leak (3%), 1 from chest sepsis (3%), and 1 from antibiotic anaphylaxis (3%). For 1st and 2nd hepatectomies, morbidity rates were 23% (n = 9) and 56% (n = 15) (P = .095). Table 3 shows morbidity for 1st and 2nd hepatectomies.

Eighteen percent of patients (n = 7) had ≥1 severe complication (Clavien grade 4 or 5). Thirty percent of complications were severe. There was no statistically significant difference in the number of severe complications between 1st-stage and 2nd-stage hepatectomy (2 vs 6; P = .128).

Bile leaks occurred in 2 patients (5%) after the 1st hepatectomy and in 5 patients (19%) after the 2nd hepatectomy (P = .228). Postoperative liver insufficiency occurred after 1st and 2nd hepatectomies in 2 (5%) and 6 (22%) patients, respectively (P = .128). All of those who developed liver insufficiency after the 2nd hepatectomy had undergone portal venous embolization. In 2 of these, the resultant hypertrophy was noted to be marginal; in all others, it was considered adequate.

Mortality rates after 1st and 2nd hepatectomies were 0% and 3.7% (P = .418), with 1 death occurring after 2nd-stage hepatectomy because of acute liver insufficiency. This patient had a reasonable hypertrophic response to portal venous embolization and a postembolization future liver remnant volume deemed to be marginal but sufficient. Mortality per hepatectomy was 1.5%. Overall patient mortality was 2.6%.

Survival of patients with colorectal liver metastases

Thirty-three patients planned for 2-stage hepatectomy had metastases of colorectal origin. Twenty-three of these completed 2-stage surgery. Ten failed to complete the 2nd stage, all because of disease progression.

Of those patients unable to complete 2nd-stage surgery, at last follow-up, only 1 was alive with disease (at 8 months after the 1st hepatectomy); the remainder were deceased, with none surviving beyond 32 months. Of patients successfully cleared of all known colorectal liver metastases, at last follow-up (median, 12 months), 8 were alive and recurrence free, 1 was alive and disease free after a further hepatectomy for recurrence, 1 was alive with liver-only disease recurrence, and 13 were deceased, including 1 postoperative mortality.

For those successfully completing 2-stage clearance of liver metastases, compared with those failing to complete

| Table 3 Morbidity and mortality and hospital stay for 1st and 2nd hepatectomies |
|-----------------------------------|------------------|------------------|
| Patients                          | First hepatectomy | Second hepatectomy |
|                                   | (n = 39)          | (n = 27)          |
| Hospital stay (d)                 | 11 (6–53)         | 13 (6–44)         |
| Mortality                         | 0 (0%)            | 1 (3.7%)          |
| Morbidity                         | 9 (23.1%)         | 15 (55.6%)        |
| Liver insufficiency               | 2 (5.1%)          | 6 (22.2%)         |
| Bile leak                         | 2 (5.1%)          | 5 (18.5%)         |
| Intra-abdominal sepsis            | 2 (5.1%)          | 1 (3.7%)          |
| Ascites                           | 1 (2.6%)          | 1 (3.7%)          |
| Wound complication                | 2 (5.1%)          | 1 (3.7%)          |
| Chest sepsis                     | 1 (2.6%)          | 1 (3.7%)          |
| Drug anaphylaxis                  | 1 (2.6%)          |                  |
| Pancreatic leak                   | 1 (2.6%)          |                  |

Data are expressed as median (range) or as number (percentage).
the 2nd stage, the median survival from time of diagnosis of liver metastases was 31 versus 23 months (95% confidence interval, 180–1.251; \(P = .061\); Figure 1), and the median survival from time of 1st hepatectomy was 24 versus 10 months (95% confidence interval, .153–1.138; \(P = .030\); Figure 2). Three-year survival for those achieving surgical clearance was 30% from 1st hepatectomy and 44% from the time of diagnosis of liver metastases. There were no 3-year survivors in those unable to complete 2nd-stage surgery.

From the time of diagnosis of liver metastases and the time of 1st hepatectomy, overall median survival was 29 and 16 months, and overall 3-year survival was 28% and 19%. For patients completing 2-stage resection of hepatic disease, median survival was 18 months from 1st hepatectomy when \(\geq 1\) surgical margin was R1, compared with 33 months when all surgical margins were R0 (95% confidence interval, .607–5.658; \(P = .251\), and 3-year survival was 13% versus 47% (Figure 3).

Of those with colorectal metastases who died, 1 patient died of post–radiofrequency ablation sepsis, 1 died secondary to liver failure after 2nd-stage liver resection, 1 died because of complications after subsequent resection of the colorectal primary tumor, and the remainder died of metastatic disease.

**Comments**

Two-stage hepatectomy for bilobar liver metastases in combination with selected use of portal venous embolization is feasible, with 69% of patients achieving macroscopic surgical clearance in this study. This is consistent with other reports showing feasibility rates of 69% to 100%.5–11,14

In patients who have inadequate future liver remnant to undergo disease clearance with a single hepatectomy, it offers the best chance of achieving adequate future liver remnant hypertrophy. Two-stage hepatectomy has been shown to result in greater hypertrophy of the future liver remnant than a strategy of portal venous embolization before a single hepatectomy.15

The surgical strategy must be individualized after careful assessment of disease distribution and relationship to key underlying vascular and biliary structures. Most patients in this study (76%) underwent minor hepatectomies at the 1st stage, with the major hepatectomy planned for the 2nd stage. Other authors have also preferred this approach with increasing experience.10

It is preferable to avoid mobilization of the contralateral liver or dissection of the porta hepatitis during the 1st hepatectomy to minimize adhesions encountered at the 2nd
stage. This is one of the arguments for performing the minor hepatectomy procedure first. Other considerations when deciding on operative strategy include which lesions are most likely to limit the chance of surgical success and whether concurrent procedures are required. It is preferable to deal with any concurrent disease to be resected at the 1st hepatectomy rather than at the 2nd, when the risk for postoperative liver insufficiency is greater. An added complication, such as anastomotic leak from colorectal resection, in the setting of liver insufficiency may have disastrous consequences. For the same reason, a minor hepatectomy when a concurrent procedure is planned at the 1st stage is preferable.

Achieving clearance often requires modification of the planned surgical strategy after assessment at laparotomy, as macroscopic and operative ultrasound assessment of tumor and underlying liver disease may differ from preoperative imaging findings.

Currently, there is no accurate means of determining the future liver remnant volume required in an individual patient. Minimal requirements estimated by patient weight, body surface area, or percentage of total liver volume measured by computed tomographic volumetry do not take into account the function of the liver parenchyma to be preserved. Underlying liver disease needs to be considered. In addition, the type and duration of chemotherapy administered before hepatectomy have been shown to correlate with severity of liver injury and surgical risk, and must be taken into account when deciding on the required future liver remnant volume. On the basis of experience in living related donor liver transplantation and historical portal venous embolization data, a minimum future liver remnant of 25% (in a healthy liver) is adequate, below which there is a high risk for liver insufficiency. We used a minimum volume of 5% body weight, which approximately corresponds to 25% of total liver volume as calculated by established formulas.

Portal venous embolization should be used selectively whenever the future liver remnant volume is deemed inadequate. All patients who developed liver insufficiency after the 2nd hepatectomy had undergone portal venous embolization; therefore, routine portal venous embolization would not have reduced the risk and cannot be recommended. Tumor growth may be stimulated by the same growth factors that induce regeneration after resection and portal venous embolization.

Mortality in these patients is most often related to liver failure secondary to an inadequate future liver remnant, as was the case in the single postoperative death in this series. With careful patient selection, low surgical mortality can be achieved. The overall surgical mortality rate of 2.6% in this series compares favorably with other series of 2-stage hepatectomy.

In this study, patients proceeded to the 2nd stage as soon as they had adequately recovered from the 1st hepatectomy and had achieved sufficient future liver remnant volume. The median interval was 12 weeks, shorter than that reported by other groups. For colorectal metastases, it is generally recommended that patients receive chemotherapy before embarking on 2-stage hepatectomy. Because progression on chemotherapy has been shown to indicate poor prognosis despite surgery, at least disease stabilization on chemotherapy should be required before proceeding. Interval chemotherapy between hepatectomies can also be considered, particularly when the ability to complete clearance is considered borderline. Chemotherapy does not appear to impair the regenerative response after portal venous embolization, but cumulative hepatic toxicity of chemotherapy must be considered in these patients who, because of the extent of resection required, are at risk for postoperative liver insufficiency. Decisions regarding chemotherapy timing and duration must be individualized and made by collaboration between the surgeon and the medical oncologist.

In patients requiring a 2-stage approach to clear hepatic metastatic disease, surgery is complex, often involving the use of radiofrequency ablation and concurrent procedures. The volume of the future liver remnant is often marginal, and many patients have undergone prolonged chemotherapy and have significant chemotherapy-associated liver injury. Consequently, morbidity is significant, particularly transient liver insufficiency after the 2nd hepatectomy. Overall patient morbidity in this series was 56%. Morbidity and postoperative length of stay were greater after the 2nd hepatectomy compared with the 1st hepatectomy, although this did not reach statistical significance. There was a trend toward more liver insufficiency after the 2nd hepatectomy (22% vs 5%). The lack of statistical significance may be due to small patient numbers in this study.

In this study, patients proceeded to the 2nd stage as soon as they had adequately recovered from the 1st hepatectomy and had achieved sufficient future liver remnant volume. The median interval was 12 weeks, shorter than that reported by other groups.

For colorectal liver metastases, survival in patients who undergo 2-stage hepatectomy is significantly greater than in those treated with best palliative chemotherapy, who rarely survive beyond 20 months. In this series, patients successfully achieving disease clearance had a median survival from the time of 1st hepatectomy of 31 months and a 3-year survival rate of 30%. Other studies have reported 3-year survival rates up to 58%, comparable with patients treated with single-stage hepatectomy. Many patients underwent neoadjuvant chemotherapy before hepatectomy. From the time of diagnosis of liver metastases, median and 3-year survival in patients achieving successful surgical clearance were 31 months and 44%. Although this is one of the largest
reported series, overall patient numbers are small, and median follow-up is relatively short, limiting the interpretation of oncologic outcomes in this study.

Ideally, all patients would achieve clearance with R0 resection margins. There is good evidence that margin status is a key predictor of survival after hepatectomy for colorectal metastases. In this series, patients who had ≥1 R1 resection had a reduced median survival time of 18 months compared with 33 months, although this failed to reach statistical significance, possibly because of small patient numbers. Patients undergoing 2-stage hepatectomy represent a cohort with advanced disease. In such extensive disease, the ability to achieve clear margins is frequently hampered by the proximity of metastases to vital inflow and outflow structures. As such, a significant proportion of patients may have ≥1 R1 margin (39% of those patients who completed 2 stages in this study). Two other studies have reported margins both smaller than this study (Table 1).

Conclusions

Two-stage hepatectomy for multiple bilobar liver metastases, in combination with selected use of radiofrequency ablation and portal venous embolization, is feasible, with 69% of patients achieving successful surgical clearance. Morbidity is significant with such an aggressive surgical approach, particularly transient hepatic insufficiency after the 2nd hepatectomy, but low surgical mortality can be achieved. Given the survival benefit compared with the poor prognosis in patients treated with best palliative chemotherapy alone, this approach can be justified in suitably selected patients.

References