# Hepatectomy for Noncolorectal Non-Neuroendocrine Metastatic Cancer: A Multi-Institutional Analysis

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**BACKGROUND:** Although hepatic metastasectomy is well established for colorectal and neuroendocrine cancer, the approach to hepatic metastases from other sites is not well defined. We sought to examine the management of noncolorectal non-neuroendocrine liver metastases.

**STUDY DESIGN:** A retrospective review from 4 major liver centers identified patients who underwent liver resection for noncolorectal non-neuroendocrine metastases between 1990 and 2009. The Kaplan-Meier method was used to analyze survival, and Cox regression models were used to examine prognostic variables.

**RESULTS:** There were 420 patients available for analysis. Breast cancer (n = 115; 27%) was the most common primary malignancy, followed by sarcoma (n = 98; 23%), and genitourinary cancers (n = 92; 22%). Crude postoperative morbidity and mortality rates were 20% and 2%, respectively. Overall median survival was 49 months, and 1, 3, and 5-year Kaplan-Meier survival rates were 73%, 50%, and 31%. Survival was not significantly different between the various primary tumor types. Recurrent disease was found after hepatectomy in 66% of patients. In multivariable models, lymphovascular invasion ($p = 0.05$) and metastases ≥5 cm ($p = 0.04$) were independent predictors of poorer survival. Median survival was shorter for resections performed between 1990 and 1999 (n = 101, 32 months) when compared with resections between 2000 and 2009 (n = 319, 66 months; $p = 0.003$).

**CONCLUSIONS:** Hepatic metastasectomy for noncolorectal non-neuroendocrine cancers is safe and feasible in selected patients. Lymphovascular invasion and metastases ≥5 cm were found to be associated with poorer survival. Patients undergoing metastasectomy in more recent years appear to be surviving longer, however, the reasons for this are not conclusively determined. (J Am Coll Surg 2012;214:769–777. © 2012 by the American College of Surgeons)

The liver is a primary site of metastasis for tumors originating at many sites. Metastatic colorectal cancer is the most common entity, with the portal circulation and lymphatic channels acting as the conduit for spread. Better understanding of tumor biology, improved techniques for liver resection,[1,2] and multidisciplinary treatments have led to new algorithms for managing metastatic disease in the liver. For selected patients, surgical resection of colorectal liver metastases has shown 5-year survival rates as high as 40% to 71%.[3-7] Numerous studies have shown that surgical resection is also a safe and appropriate intervention for hepatic neuroendocrine metastases.[8-11] Approaches and outcomes for hepatectomy in patients with liver metastases from noncolorectal non-neuroendocrine tumors, however, are not well defined.

Recent publications have suggested that hepatectomy for noncolorectal non-neuroendocrine liver metastases (NCNNLM) is feasible and safe.[12-18] Reports to date are largely confined to single-center studies. A better under-

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**Abbreviations and Acronyms**

DFS = disease-free survival
LVI = lymphovascular invasion
NCNNLM = noncolorectal non-neuroendocrine liver metastases
OS = overall survival

standing of the potential benefit of surgical resection for these tumors is needed. Our objective was to assess the safety and outcomes of patients undergoing liver resection for NCNNLM at high-volume hepatobiliary centers.

## METHODS

We examined patients who underwent liver resection between 1990 and 2009 for NCNNLM at 4 major hepatobiliary centers in the United States (Duke University Medical Center, Durham, NC; Johns Hopkins Hospital, Baltimore, MD; MD Anderson Cancer Center, Houston, TX; University of Pittsburgh Medical Center, Pittsburgh, PA). This study was approved by the Institutional Review Boards of the respective institutions. Patients with direct hepatic invasion by an extrahepatic primary tumor were excluded from analysis. Patients were evaluated by a multidisciplinary team and preoperative and/or postoperative systemic therapy was uniformly considered. Patients who showed progression of disease during preoperative systemic therapy were typically not offered hepatectomy. Resectable liver lesions are those for which complete resection is anticipated based on preoperative imaging, adequate vascular flow and biliary drainage are spared, and the size of the future liver remnant will be adequate (≥20% of total estimated liver volume).

Standard demographic and clinicopathologic data were collected for each patient, including sex, age, and race. Information about the original cancer diagnosis and adjuvant therapy was also collected, along with preoperative serum tumor markers. The number, size, and laterality of hepatic metastases were assessed. Perioperative details included use of laparoscopy, extent of hepatic resection, use of Pringle maneuver, operative time, blood loss, and mortality. The resected specimen was pathologically examined for margin status, lymph nodes, and lymphovascular invasion (LVI). For those patients in whom recurrent disease developed, disease-free intervals were calculated. If a liver metastasis occurred within 6 months of primary tumor resection, it was categorized as synchronous. Resection of ≥4 segments was considered a major hepatectomy.[19] Complications were reported based on the Clavien criteria.[20] Grade II or higher complications were included for analysis. Hepatectomy-specific complications included bleeding, bile leak, abscess, wound infections, and liver failure.

Patients who had residual disease after liver resection (R1 or R2 resections) were excluded from disease-free survival (DFS) analysis. Intraoperative mortality cases were excluded from overall survival (OS) and DFS analyses. Aside from that exception, OS reflects death from any cause. Deaths were ascertained by clinic and hospital records, public records, and the Social Security Death Index. Lengths of OS and DFS were calculated from the date of liver resection.

Variables that might be associated with survival outcomes in our cohort (based on previous literature) were identified for inclusion in the analysis a priori. These included age, sex, primary tumor type, major resection, synchronous lesions, additional extrahepatic metastatic disease, number of metastases, size of largest metastasis, margin status, lymphovascular invasion, use of adjuvant therapies, and the decade the resection was performed (1990−1999 vs 2000−2009). Descriptive statistics were calculated for all variables and the normality of the data examined. Chi-square and Mann-Whitney *U*-tests were used to test between-group differences on demographic and clinicopathologic parameters by primary tumor site. Multiple comparisons were accounted for by Bonferroni correction. Survival curves were generated using the Kaplan-Meier method.[21] Variables with univariate significance at a level of $p \leq 0.20$ were entered into a Cox regression multivariable analysis. Significance was set at $\alpha = 0.05$. Statistical analyses were performed using PASW statistical software (version 18; PASW Inc.).

## RESULTS

### Patient, tumor, and operative characteristics

We identified 420 consecutive patients who had undergone liver resection for NCNNLM, of whom 303 (72.1%) were female. Median age at time of liver resection was 55 (interquartile range 45 to 64) years. The number of operations performed annually is shown in Figure 1. There were 101 hepatectomies performed between 1990 and 1999, and there were 319 hepatectomies performed between 2000 and 2009. Breast cancer was the most common malignant pathology. The other primary tumor types and selected characteristics are shown in Table 1. Primary tumors were resected in 399 of 420 (95.0%) patients. The remaining 21 patients had complete responses to chemoradiation of their primary tumors and did not require resection.

Liver metastases were synchronous in 109 of 419 (26.0%) patients, and unilateral in 134 of 192 (70.0%) patients. Patients with melanoma were more likely to have metachronous development of liver metastases (93.5%) as

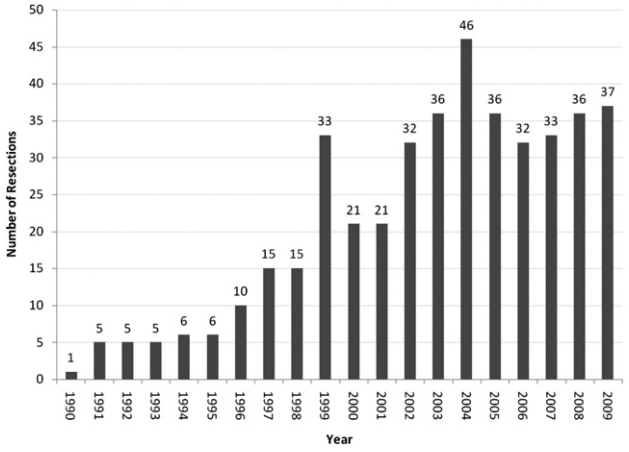


**Figure 1.** Annual number of liver resections for noncolorectal non-neuroendocrine liver metastases at 4 major hepatobiliary centers in the United States from 1990 to 2009 (n = 420).

compared with other histologies (72.4%; p = 0.01). Extrahepatic metastases were resected in 77 of 362 (21.3%) patients. R0 liver resections were achieved in 340 of 391 (87.0%) patients. Radiofrequency ablation was performed on additional liver metastases in 36 of 339 (10.6%) patients. In 57 of 396 (14.4%) patients, liver metastases were diagnosed before resection of the primary tumor. For the remaining patients, the mean time between resection of the primary tumor and diagnosis of liver metastases was 43 months (range 0 to 312 months). This includes 42 patients who had liver metastases diagnosed during surgery for their primary cancer. Twenty of the 101 patients in the 1990−1999 cohort had liver metastases diagnosed intraoperatively during surgery for their primary cancer, for a rate of 19.8%. In the 2000−2009 cohort, there were only 22 such intraoperative diagnoses among 319 patients, for a rate of 6.9%.

The vast majority of operations were open resections. Only 13 cases were completed laparoscopically, and 4 of these were hand assisted. Major hepatectomies were performed in 204 of 419 (48.7%) patients, and were more commonly performed for breast and melanoma compared with other primaries. In total, 326 patients were treated with chemotherapy: 275 of 414 (66.4%) received chemotherapy before hepatectomy and 208 of 399 (52.1%) received chemotherapy after hepatectomy. Transarterial chemoembolization was performed preoperatively in 1 patient and postoperatively in 2 patients. Radiation therapy was performed in 15 of 405 (3.7%) patients after hepatectomy. Eight patients underwent multiple liver resections for recurrent hepatic disease.

## Outcomes

Complications occurred in 84 of 420 (20.0%) patients. Eight (1.9%) patients died within 60 days, 4 of which were intraoperative deaths. Postoperative bleeding occurred in 6 (1.4%) patients, bile leak in 6 (1.4%), liver failure in 1 (0.2%), intra-abdominal abscess in 11 (2.6%), and wound infections in 5 (1.2%).

Table 2 summarizes long-term patient follow-up and outcomes. Median follow-up for all patients was 30 months. Median OS and DFS were 49 months and 23 months, respectively. Figure 2 displays corresponding survival curves. At the time of analysis, 211 (50.2%) patients were still alive and 93 (22.1%) had no evidence of recurrent disease.

Table 3 shows the results of our univariate Kaplan-Meier survival analysis. In unadjusted models, both LVI and size of the largest metastasis were associated with poorer survival (Fig. 3). In a multivariable analysis controlling for age, synchronicity, R0 resections, and use of adjuvant chemotherapy; LVI (hazard ratio = 1.81; p = 0.05) and metastases ≥5 cm (hazard ratio = 1.39, p = 0.04) remained significant predictors of poorer survival (Table 4).

Patients who underwent hepatectomy from 1990 to 1999 had a median survival of 32 months, and patients with resections from 2000 to 2009 had a median sur-

**Table 1.** Characteristics of 420 Patients Undergoing Hepatic Metastasectomy from 1990 to 2009

| | Breast | | Sarcoma | | Genitourinary* | | Melanoma | | Other† | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
| Patients | 115 | 27 | 98 | 23 | 92 | 22 | 31 | 7 | 84 | 20 |
| Preoperative chemotherapy | 100/114 | 88 | 54/97 | 56 | 62/90 | 69 | 14/31 | 45 | 45/82 | 55 |
| Postoperative chemotherapy | 71/109 | 65 | 55/94 | 59 | 43/89 | 48 | 8/30 | 27 | 31/77 | 40 |
| Synchronous | 24/114 | 21 | 25/98 | 26 | 23/92 | 25 | 2/31 | 6 | 35/84 | 42 |
| Major resection | 68/114 | 60 | 45/98 | 46 | 36/92 | 39 | 17/31 | 55 | 38/84 | 45 |
| R0 resection | 92/107 | 86 | 80/87 | 92 | 73/85 | 86 | 28/29 | 97 | 67/83 | 81 |

*There were 26 patients with renal cell carcinoma included in this category.
†This category includes 24 squamous cell carcinomas, 14 gastrointestinal stromal tumors, 13 gastroesophageal adenocarcinomas, 11 pancreaticobiliary cancers, 8 lung cancers, 5 adrenocortical carcinomas, 2 adenocarcinomas of unknown primary, a medullary thyroid cancer, a Hürthle cell cancer, a perivascular epithelioid cell tumor, a primary peritoneal cancer, a mesothelioma, a thymoma, and a paraganglionoma.

**Table 2.** Recurrence and Kaplan-Meier Survival Analyses after Metastasectomy

| | Breast (n = 115) | Sarcoma (n = 98) | GU (n = 92) | Melanoma (n = 31) | Other (n = 84) | Overall (n = 420) |
|---|---|---|---|---|---|---|
| Median follow-up, mo | 31 | 32 | 23 | 35 | 24 | 30 |
| Median OS, mo | 52 | 72 | 46 | 39 | 39 | 49 |
| 1-year OS, % | 79 | 82 | 66 | 57 | 69 | 73 |
| 3-year OS, % | 52 | 60 | 48 | 36 | 46 | 50 |
| 5-year OS, % | 27 | 32 | 32 | 36 | 30 | 31 |
| Median DFS, mo | 22 | 31 | 28 | 12 | 19 | 23 |
| Recurrence,* n (%) | 66/103 (64) | 55/89 (62) | 47/77 (61) | 21/29 (72) | 53/66 (80) | 242/364 (66) |
| Local/regional | 43/103 (42) | 32/89 (36) | 26/77 (34) | 9/29 (31) | 32/66 (48) | 142/364 (39) |
| Distant | 48/103 (47) | 42/89 (47) | 41/77 (53) | 17/29 (59) | 35/66 (53) | 183/364 (50) |

*Some patients had both local/regional recurrence and distant recurrence.
DFS, disease-free survival; GU, genitourinary; OS, overall survival.

vival of 66 months (p = 0.003). The respective 1, 3, and 5-year survivals were 61%, 39%, and 18% for those resections in the earlier decade, and 77%, 55%, and 38% in the latter decade. A post hoc comparison (using Bonferroni corrections) of demographic and clinical variables was performed to study this difference in survival between decades. These decade cohorts were similar with respect to age, sex, race, primary tumor type, synchronicity, tumor size, number of metastases, extrahepatic disease, LVI, and margin status. Operations from 2000 to 2009 involved less blood loss (median 250 mL; interquartile range 100 to 500 mL) as compared with operations from 1990 to 1999 (median 500 mL; interquartile range 200 to 800 mL; p = 0.01). In the latter decade, more patients were treated with preoperative chemotherapy (227 of 314 [72%] vs 48 of 100 [48%]; p = 0.001) and postoperative chemotherapy (178 of 305 [58%] vs 30 of 94 [32%]; p = 0.001).

After hepatectomy, recurrence occurred in 242 of 364 (66.5%) patients. Isolated hepatic recurrence occurred in 59 (16.2%) patients and isolated distant recurrence occurred in 100 (27.5%). Both distant and hepatic recurrence developed in 83 (22.8%) patients. Recurrence by primary tumor type is shown in Table 5. The various primary tumor types did not show significant differences in their overall recurrence rates, hepatic recurrences, bone metastases, or lung metastases. Brain metastases were more common in the breast cancer cohort.

### Observations on patients undergoing multiple liver resections

After their first hepatectomy, recurrent disease in the liver developed in 142 of 364 (39.0%) patients. Seven of these patients underwent a second liver resection for subsequent hepatic recurrence, and another patient underwent a total of 3 liver resections for multiple hepatic recurrences. The range of time between these hepatectomies was 5 to 55 months (median 35 months). The timing of each resection for these 8 patients is summarized in Table 6. Interestingly, each of these 8 patients was still alive at the end of the study period, with a median follow-up of 6 years after their last hepatectomy.

## DISCUSSION

Hepatic resection for colorectal liver metastases has been established as a safe practice with favorable outcomes in carefully selected patients. Because these metastases presumably spread to the liver via portal circulation and/or abdominal lymphatic channels, the extent of malignancy is often confined to the abdomen, making hepatectomy intuitively more effective for controlling the extent of disease. Likewise, liver metastases from neuroendocrine tumors can be resected safely with favorable outcomes. For cancers of other primary sites (eg, breast cancer), spread to the liver seems only possible through systemic hematogenous dissemination. Historically, there has been concern that hepatectomy is less beneficial for these patients, but this notion has been challenged by several publications during the last 2 decades. Because of the lack of data supporting other treatment modalities, the improved capabilities in preoperative workup, and the modern safety of liver surgery at tertiary centers, hepatectomy for NCNNLM is gaining enthusiasm.

Most published studies of hepatectomy for NCNNLM have only a small number of patients, which can limit the power of the observations and conclusions drawn from them. Other studies include patients from low-volume centers, which can also influence outcomes. The present study includes 420 patients from only high-volume liver centers in the United States. Table 7 shows our study in comparison with other publications specifically addressing hepatectomy for NCNNLM. When reported in the larger studies, the median survival ranged from 27 to 44 months.[15,18,22-24] Median survival in this series was 49 months, which is the longest among the published series of >100 patients.

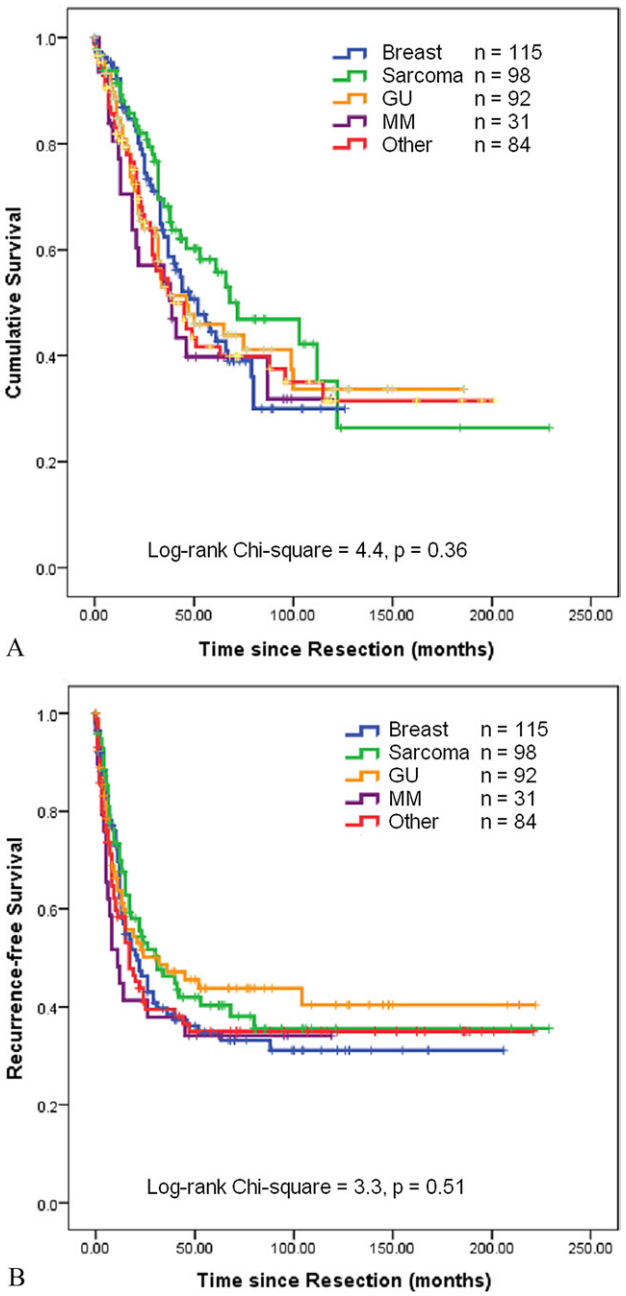


**Figure 2.** (A) Overall survival by primary tumor type. (B) Disease-free survival by primary tumor type. GU, genitourinary; MM, melanoma.

Hepatic resection for breast cancer metastases has been associated with median and 5-year survivals of 25 to 57 months and 18% to 61%, respectively.[25] Other reports have shown favorable survival for metastasectomy of breast and genitourinary cancers, which were well represented in our cohort.[15,22,23,26] Median survivals of our breast and genitourinary cohorts were 52 and 46 months, respectively. Our subset of sarcoma patients had median, 1, 3, and 5-year survivals of 72 months, 82%, 60%, and 32%, respectively. Comparably, 56 patients underwent sarcoma metastasectomy reported by DeMatteo and colleagues[27] with median, 1, 3, and 5-year survivals of 39 months, 88%,

**Table 3.** Univariate Analysis of Factors Associated with Survival after Liver Resection of Noncolorectal Non-Neuroendocrine Metastases

| Variable | Median OS (mo) | 95% CI | Log rank chi-square | p Value |
|---|---|---|---|---|
| Age, y | | | 3.5 | 0.06 |
| Younger than 65 | 52 | 38–66 | | |
| 65 or older | 44 | 31–57 | | |
| Sex | | | 0.04 | 0.85 |
| Female | 49 | 34–64 | | |
| Male | 46 | 21–71 | | |
| Tumor type | | | 4.04 | 0.40 |
| Breast | 52 | 36–68 | | |
| Sarcoma | 72 | 30–114 | | |
| Genitourinary | 46 | 18–74 | | |
| Melanoma | 39 | 14–74 | | |
| Other | 39 | 22–56 | | |
| Major resection | | | 0.90 | 0.34 |
| Yes | 46 | 35–57 | | |
| No | 50 | 26–74 | | |
| Synchronous | | | 2.43 | 0.12 |
| Yes | 61 | — | | |
| No | 122 | 96–148 | | |
| Extrahepatic metastatic disease | | | 0.03 | 0.88 |
| Yes | 48 | 24–72 | | |
| No | 49 | 35–63 | | |
| No. of metastases | | | 0.023 | 0.88 |
| 1 | 51 | 33–69 | | |
| ≥2 | 46 | 31–62 | | |
| Size of largest metastasis, cm | | | 9.2 | 0.002 |
| <5 | 66 | 46–86 | | |
| ≥5 | 37 | 29–46 | | |
| R0 resection | | | 2.42 | 0.12 |
| Yes | 52 | 38–66 | | |
| No | 37 | 30–44 | | |
| Lymphovascular invasion | | | 4.37 | 0.04 |
| Yes | 25 | 12–37 | | |
| No | 52 | 39–65 | | |
| Neoadjuvant chemotherapy | | | 0.75 | 0.39 |
| Yes | 52 | 36–68 | | |
| No | 46 | 27–65 | | |
| Adjuvant chemotherapy | | | 2.68 | 0.10 |
| Yes | 58 | 39–77 | | |
| No | 43 | 30–56 | | |

OS, overall survival.

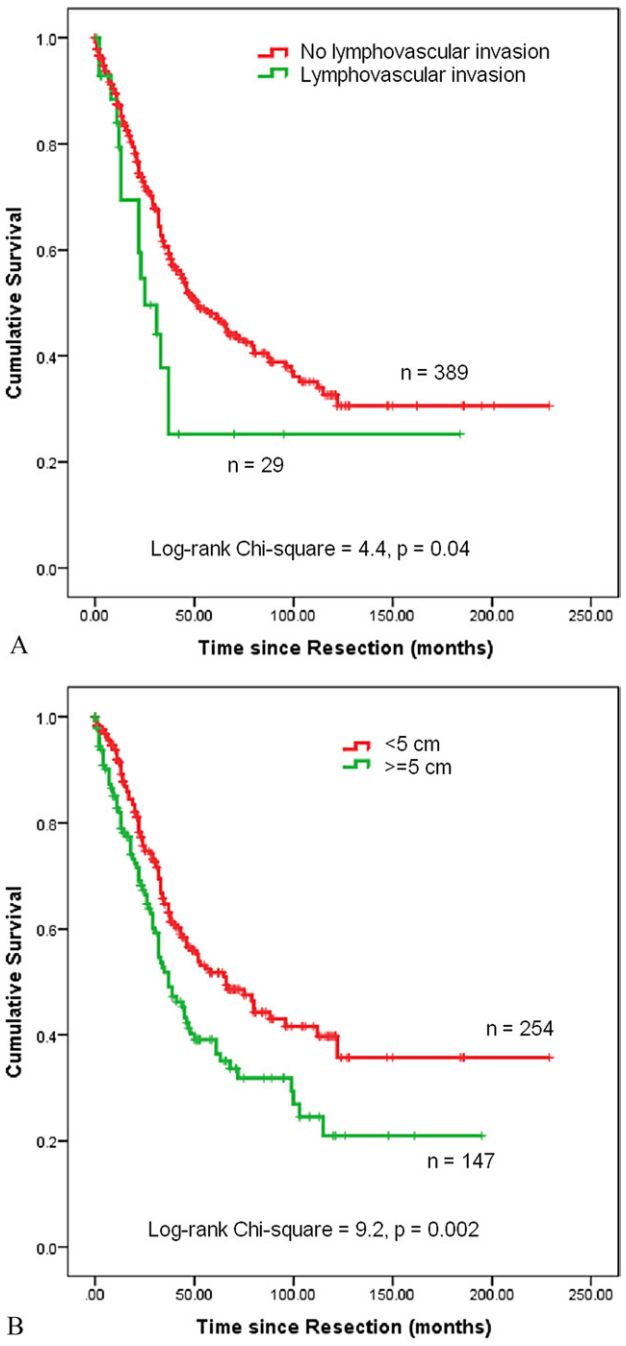


**Figure 3.** (A) Overall survival by presence of lymphovascular invasion. (B) Overall survival by size of largest metastasis.

50%, and 30%, respectively. Mariani and colleagues[28] study of 255 patients who underwent hepatic metastasectomy for melanoma showed a median survival of only 14 months compared with the median survival of 39 months in our series of 31 patients.

Patient selection is critical to improving long-term outcomes for hepatic metastasectomy. The body of literature

**Table 4.** Cox Proportional Hazards Regression Analysis of Factors Associated with Survival after Liver Resection of Noncolorectal Non-Neuroendocrine Metastases

| Variable | Hazard ratio | 95% CI | p Value |
|---|---|---|---|
| Age, y | | | 0.12 |
| Younger than 65 | 1 | — | |
| 65 or older | 1.33 | 0.93−1.89 | |
| Synchronous | | | 0.79 |
| No | 1 | — | |
| Yes | 1.05 | 0.67−1.36 | |
| Size of largest metastasis, cm | | | 0.04 |
| <5 | 1 | — | |
| ≥5 | 1.39 | 1.02−1.91 | |
| R0 resection | | | 0.17 |
| No | 1 | — | |
| Yes | 0.75 | 0.49−1.14 | |
| Lymphovascular invasion | | | 0.05 |
| No | 1 | — | |
| Yes | 1.81 | 1.01−3.29 | |
| Adjuvant chemotherapy | | | 0.18 |
| No | 1 | — | |
| Yes | 0.81 | 0.60−1.10 | |

on this topic is growing and, despite its heterogeneity, certain trends are emerging. Several authors' works have suggested a worse prognosis for esophageal and gastric adenocarcinoma metastases.[17,22,29,30] Our series included only 13 (3.1%) such patients, with similar results. OS of our entire cohort likely benefits from the conscious exclusion of these types of cancers by our multidisciplinary teams. Although a longer interval between resection of the primary tumor and development of metastases is sometimes considered a surrogate for favorable tumor biology,[16,22,23,30-32] our study did not find a survival benefit for longer intervals. R0 resection[23,30,31] and the presence of extrahepatic nodes[24] have also been implicated in survival for resection of NCNNLM. In our study, neither of these factors impacted survival to a statistically significant degree. Our cohort showed that LVI was associated with shorter survival, which has not been reported previously. Other publications have found that metastasectomy for larger lesions is associated with a poorer prognosis, and our data support this finding.[24,30]

Although stage IV adrenocortical cancer is associated with a dismal prognosis (≤15% 5-year survival),[33] our series of 5 patients who underwent resections for adrenocortical metastases had acceptable outcomes. Three patients died at approximately 3, 5, and 10 years after their liver resections. There are 2 patients still alive 9 and 13 years after their metastasectomies. Adam and colleagues[22] reported 28 cases of liver resection for adrenocortical metas-

**Table 5.** Percentage of Patients in Whom Recurrence Develops after Metastasectomy, by Primary Tumor Type*

| | Primary cancer histology | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Breast (n = 103) | | Sarcoma (n = 89) | | Genitourinary (n = 77) | | Melanoma (n = 29) | | Other (n = 66) | |
| | n | % | n | % | n | % | n | % | n | % |
| Any recurrence | 66 | 64 | 55 | 62 | 47 | 61 | 21 | 72 | 53 | 80 |
| Site of recurrence | | | | | | | | | | |
| Liver | 43 | 42 | 32 | 36 | 26 | 34 | 9 | 31 | 32 | 48 |
| Lung | 19 | 18 | 20 | 22 | 13 | 17 | 10 | 34 | 21 | 32 |
| Bone | 15 | 15 | 6 | 7 | 6 | 8 | 2 | 7 | 4 | 6 |
| Brain | 11 | 11 | 2 | 2 | 1 | 1 | 0 | | 1 | 2 |
| Abdominal | 13 | 13 | 23 | 26 | 27 | 35 | 7 | 24 | 11 | 17 |
| Other site | 4 | 4 | 5 | 6 | 5 | 6 | 2 | 7 | 3 | 4 |

*Many patients recurred in more than one site. Percentages shown represent the frequency of recurrence in a given site, not the proportion of recurrences that occur in those sites, so columns do not add to 100%.

tases with a 5-year survival of 66%. Patients with adrenocortical liver metastases who appear to have favorable tumor biology should be given careful consideration for hepatic resection.

A multidisciplinary approach provides an important tool for cancer patients. Neoadjuvant or adjuvant therapies were used in 338 (80.5%) of our study population, with many patients receiving more than one type of therapy. Patients who received any chemotherapy after hepatectomy lived longer, although this did not reach statistical significance. A weakness of such a binary analysis is that it includes patients who did not complete what might be considered a full course of therapy. This would cause us to underestimate the potential impact that a completed course of therapy might have on recurrence or survival. This study was not designed to evaluate the effectiveness of other liver-directed therapies, such as ablation. Previous reports about colorectal liver metastases showed that outcomes for ablated lesions are inferior to outcomes for surgical resection.[3]

Our patients who underwent repeat hepatectomy represent an intriguing group. All 8 patients were alive at the end of the study, some more than 9 years out from their first liver resection. Although recurrence typically portends a worse prognosis, these patients again highlight the importance of thoughtful selectivity and advances in the surgical techniques of liver resection. Other authors have also noted that repeat hepatectomy for NCNNLM is associated with improved survival.[22] Given these findings, patients with resectable hepatic recurrence should be considered for repeat hepatectomy.

There are several limitations of this retrospective review. We lack a control group and cannot make conclusions about the effectiveness of surgery in comparison with other treatments. Our cohort is also heterogeneous, composed of patients with metastases from several different primary tumors. Although some cancers are well represented, their malignant behavior might not be generalizable to less common primaries. We included patients during a 19-year span, and certainly during those years there have been substantial changes to adjuvant therapies, operative techniques, and cross-sectional imaging. Operative blood loss decreased over time in our study. As chemotherapeutic regimens evolve for cancers that metastasize to the liver, they

**Table 6.** Eight Patients Who Underwent Multiple Hepatectomies for Recurrent Disease in the Liver

| Patient | Primary tumor histology | Primary tumor diagnosed | Primary tumor resected | First liver metastasis diagnosed | First liver metastasis resected | Second liver metastasis diagnosed | Second liver metastasis resected | Last follow-up |
|---|---|---|---|---|---|---|---|---|
| A* | Breast | Dec 1994 | Jan 1995 | Aug 1996 | Feb 2001 | Apr 2004 | Jun 2004 | Aug 2008 |
| B | Melanoma | Jan 1995 | Jan 1995 | Nov 2003 | Apr 2004 | Sep 2004 | Sep 2004 | Oct 2009 |
| C | Sarcoma | Feb 1997 | Feb 1997 | Aug 2000 | Dec 2002 | Aug 2003 | Jun 2004 | Jun 2009 |
| D | GIST | May 1998 | May 1998 | Oct 1999 | Oct 1999 | Jan 2000 | Jun 2002 | Nov 2008 |
| E | Sarcoma | Sep 1999 | Sep 1999 | Feb 2004 | Oct 2004 | Feb 2008 | May 2009 | Jul 2009 |
| F | Adrenal | Jun 2000 | Aug 2000 | Jun 2000 | Sep 2000 | Dec 2002 | Oct 2004 | Sep 2009 |
| G | Sarcoma | Feb 2002 | Aug 2002 | Jan 2002 | Jun 2004 | — | Sep 2007 | Jun 2009 |
| H | Breast | Jun 2005 | Jun 2005 | Jun 2005 | Apr 2006 | Nov 2008 | Mar 2009 | Jul 2009 |

*Patient A was diagnosed with a third hepatic tumor in July 2005 and underwent resection the same month. She is still alive.
GIST, gastrointestinal stromal tumor.

**Table 7.** Publications Describing Patients Undergoing Resection for Noncolorectal Non-Neuroendocrine Liver Metastases

| First author | Year | n | Operative mortality, % | Operative morbidity, % | 5-year survival, % |
|---|---|---|---|---|---|
| Harrison[40] | 1997 | 96 | 0 | NR | 37 |
| Hemming[41] | 2000 | 37 | 0 | NR | 45 |
| Laurent[42] | 2001 | 39 | 0 | 8 | 35 |
| Takada[43] | 2001 | 14 | 7 | NR | NR |
| Yamada[44] | 2001 | 33 | 9 | 21 | 12 |
| Karavias[45] | 2002 | 18 | 0 | 11 | NR |
| Cordera[29] | 2005 | 64 | 2 | 7 | 30 |
| Ercolani[15] | 2005 | 142 | 0 | 21 | 34 |
| Weitz[16] | 2005 | 141 | 0 | 33 | NR |
| Adam[22] | 2006 | 1452 | 2 | 22 | 36 |
| Teo[46] | 2006 | 18 | 0 | 0 | NR |
| Lendoire[23] | 2007 | 106 | 2 | NR | 19 |
| Reddy[18] | 2007 | 82* | 4 | 30 | 37 |
| O'Rourke[24] | 2008 | 102 | 1 | 21 | 39 |
| Ercolani[30] | 2009 | 134 | 3 | 23 | 40 |
| Lehner[26] | 2009 | 242 | 2 | 21 | 28 |
| Groeschl† | 2011 | 420 | 2 | 20 | 31 |

*These 82 patients represent the NCNNLM subset of the entire study cohort.
†Represents the current article.
NR, not reported.

are affording patients longer survival.[34-36] In the past 2 decades, there has also been an increase in diagnostic accuracy for liver tumors with multidetector CT and MRI.[37,38] This higher quality cross-sectional imaging, along with other diagnostic tools, such as positron emission tomography, might have allowed for better patient selection in the later decade. In many ways, the longer survival in our 2000-2009 cohort mimics the recent improvement noted with patients undergoing resection for colorectal liver metastases.[39]

## CONCLUSIONS

In summary, NCNNLM represent an advanced stage of cancer that, when appropriately selected, can be resected safely and with reasonable survival outcomes. Hepatectomy should be considered as a tool within the broader scope of a multidisciplinary approach, especially for metastases <5 cm. Judicious use of chemotherapy in conjunction with surgery can further improve survival. In addition to the multiple prognostic factors that have already been identified in the literature, we found that microscopic evidence of LVI was associated with poorer outcomes. More investigation into this field is warranted to find the comparative benefit of surgery, chemotherapy, chemoembolization, radiation, and other adjunct therapies.

### Author Contributions

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