**HPB**

## ORIGINAL ARTICLE

# Cytoreductive debulking surgery among patients with neuroendocrine liver metastasis: a multi-institutional analysis

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## Abstract

**Background:** Management of neuroendocrine liver metastasis (NELM) in the setting of unresectable disease is poorly defined and the role of debulking remains controversial. The objective of the current study was to define outcomes following non-curative intent liver-directed therapy (debulking) among patients with NELM.

**Methods:** 612 patients were identified who underwent liver-directed therapy of NELM from a multi-institutional database. Outcomes were stratified according to curative (R0/R1) versus non-curative $\geq$ 80% debulking (R2).

**Results:** 179 (29.2%) patients had an R2/debulking procedure. Patients undergoing debulking more commonly had more aggressive high-grade tumors (R0/R1: 12.8% vs. R2: 35.0%; $P < 0.001$) or liver disease burden that was bilateral (R0/R1: 52.8% vs. R2: 75.6%; $P < 0.001$). After a median follow-up of 51 months, median (R0/R1: not reached vs. R2: 87 months; $P < 0.001$) and 5-year survival (R0/R1: 85.2% vs. R2: 60.7%; $P < 0.001$) was higher among patients who underwent an R0/R1 resection compared with patients who underwent a debulking operation. Among patients with $\geq$50% NELM liver involvement, median and 5-year survival following debulking was 55.4 months and 40.6%, respectively.

**Conclusion:** Debulking operations for NELM provided reasonable long-term survival. Hepatic debulking for patients with NELM is a reasonable therapeutic option for patients with grossly unresectable disease that may provide a survival benefit.

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## Introduction

Despite the often indolent nature of neuroendocrine tumors, neuroendocrine liver metastases (NELM) are common. In fact, up to 60−90% of neuroendocrine tumors metastasize to the liver during the course of the disease.[1] The presence of NELM

can lead to decreased quality of life, constitutional symptoms, liver failure, and death. Perhaps not surprisingly, patients with untreated NELM have a worse overall survival compared with patients without NELM.[2] In addition, patients who have NELM treated with liver-directed therapy, especially when the total burden of liver disease is treated, have an overall survival benefit.[3] However, given the potential for widespread disease, many patients with NELM are unable to undergo complete resection of all visible disease (R0/R1). In fact, it has been

estimated that only 20% of patients with NELM are eligible for curative-intent resection due to the preponderance of multiple, bilateral hepatic metastases.[4]

Despite the inability to perform a curative resection, debulking of NELM tumors (R2 resection) has been advocated. Specifically, in one of the earliest reports, McEntee *et al.* proposed cytoreductive hepatic surgery for NELM.[5] Other studies have suggested that debulking of neuroendocrine disease in the presence of liver metastasis may confer a survival benefit, particularly in patients with symptomatic disease.[6,7] The majority of these studies, however, have been limited and included cohorts with a small number of patients and were based on single center experiences.[8–13] As such, management of neuroendocrine liver metastasis (NELM) in the setting of unresectable disease remains poorly defined and the role of debulking remains controversial. The objective of the current study was to define outcomes following non-curative intent liver-directed therapy (debulking) among patients with NELM using a large multi-institutional international cohort of patients.

## Methods

### Patient selection and data collection

All patients who underwent liver-directed therapy for NELM between January 1990 and December 2014 were identified from an international multi-institutional database. This multi-institutional database included patients treated at eight major hepatobiliary institutions (The Ohio State University Comprehensive Cancer Center, Columbus, OH; Johns Hopkins Hospital, Baltimore, MD; Stanford University, Stanford, CA; Washington University School of Medicine, St Louis, MO; University of Virginia, Charlottesville, VA; Scientific Institute San Raffaele, Vita-Salute San Raffaele University, Milan, Italy; Curry Cabral Hospital, Lisbon, Portugal; Winship Cancer Institute, Emory University, Atlanta, GA) as previously described.[14] Patients who underwent liver-directed therapy including liver resection (n = 471, 77.0%), ablation (n = 15, 2.4%), or a combined approach (n = 126, 20.6%) were included. The Institutional Review Board of the participating institutions approved the study.

Standard demographic and clinicopathologic data were collected including age, gender, race, type of surgery, and tumor-specific characteristics of both the primary NET and the liver metastases. Tumor-specific characteristics of the primary NET included location, histology, functional status, grade of differentiation, and presence or absence of lymph node metastases. Grade of tumor differentiation was defined according to the 2010 WHO grading system: G1, well differentiated; G2, moderately differentiated; G3, poorly differentiated.[15] Data on treatment-related variables, such as type of liver surgery and receipt of intraoperative ablation of unresected tumors, resection margin and rate of liver involvement were collected. An R0 resection was defined as a microscopically negative margin on final pathology,

an R1 resection was defined as a microscopically positive margin on final pathology without any known gross residual disease, and an R2 margin (debulking) was defined as resection or ablation with known residual gross disease. An operation was considered as a debulking operation if ≥80% of all visible disease was resected. Outcomes were stratified according to curative (R0/R1) versus non-curative ≥80% debulking (R2) as determined at the conclusion of the operation by the attending surgeon. Patients who underwent <80% debulking were excluded. The primary outcome of interest was overall survival (OS) defined as the time interval between the date of liver-directed therapy and the date of death.

### Statistical analysis

Discrete variables were reported as medians with interquartile range (IQR); categorical variables were reported as totals and frequencies. Univariable comparisons were assessed using the chi-squared or Wilcoxon-rank sum test as appropriate. Overall survival time was calculated from the date of initial liver-directed therapy. Survival adjusted for censoring was calculated using the Kaplan–Meier method and median values were compared using the log-rank test. The impact of various clinicopathological factors on OS was assessed using a Cox proportional hazards model. All analyses were carried out with STATA version 13.0 (StataCorp, College Station, TX) and a P-value of <0.05 (two-tailed) was considered statistically significant.

## Results

612 patients who underwent liver-directed therapy for NELM and met the inclusion criteria were included in the analytic cohort. Median patient age was 57 years (IQR: 49, 65) (Table 1). Most patients were Caucasian (n = 539, 88.1%) and male (n = 326, 53.3%). Among the patients with a known primary tumor location, most tumors originated in the pancreas (n = 254, 41.6%), with the small (n = 188, 30.8%) and large (n = 42, 6.9%) intestine being other common primary tumor locations. Synchronous liver metastases were found in 379 patients (61.9%). 45 patients (7.4%) received chemotherapy prior to liver-directed therapy. At the time of liver-directed therapy, patients underwent either liver resection alone (n = 471, 77.0%), ablation alone (n = 15, 2.4%), or combined resection/ablation (n = 126, 20.6%). Bilateral liver disease was present in a slight majority of patients (n = 329, 59.9%), however most patients had an estimated <50% liver involvement (n = 440, 79.4%).

Among the entire cohort, 179 patients (29.2%) underwent a debulking operation. Several clinicopathologic characteristics differed among patients who underwent a curative-intent versus debulking operation. Patients who underwent a debulking operation had a higher median age (debulking: 59 years, IQR: 52, 67 vs. curative-intent: 56 years, IQR: 48, 65; P = 0.02) and were more commonly male (debulking: n = 107,

Table 1 Clinicopathological characteristics of patients who underwent resection for neuroendocrine liver metastasis

| | All patients (N = 612) | Curative-intent R0/R1 resection (N = 433) | Debulking R2 operation (N = 179) | P-value |
|---|---|---|---|---|
| Age, years (IQR) | 57 (49, 65) | 56 (48, 65) | 59 (52, 67) | 0.02 |
| Male sex | 326 (53.3) | 219 (50.6) | 107 (59.8) | 0.04 |
| Ethnicity | | | | 0.26 |
| Caucasian | 539 (88.1) | 377 (87.1) | 162 (90.5) | |
| Black | 38 (6.2) | 31 (7.2) | 7 (3.9) | |
| Other | 35 (5.7) | 25 (5.8) | 10 (5.6) | |
| Location of primary tumor | | | | 0.25 |
| Pancreas | 254 (41.6) | 184 (42.6) | 70 (39.1) | |
| Small intestine | 188 (30.8) | 128 (29.6) | 60 (33.5) | |
| Large intestine | 42 (6.9) | 26 (6.0) | 16 (8.9) | |
| Symptomatic disease | 408 (66.7) | 274 (63.3) | 134 (74.9) | 0.006 |
| Primary tumor grade (N = 406) | | | | <0.001 |
| Low | 227 (55.9) | 176 (60.9) | 51 (43.6) | |
| Intermediate | 101 (24.9) | 76 (26.3) | 25 (21.4) | |
| High | 78 (19.2) | 37 (12.8) | 41 (35.0) | |
| Lymph node metastasis (N = 518) | 301 (58.1) | 196 (52.4) | 105 (72.9) | <0.001 |
| Synchronous liver metastasis | 379 (61.9) | 254 (58.7) | 125 (69.8) | 0.01 |
| Bilateral liver metastases | 329 (59.9) | 199 (52.8) | 130 (75.6) | <0.001 |
| Estimated liver involvement | | | | 0.06 |
| <50% | 498 (81.4) | 344 (79.5) | 154 (86.0) | |
| ≥50% | 114 (18.6) | 89 (20.6) | 25 (14.0) | |
| Type of liver operation | | | | 0.004 |
| Resection | 471 (77.0) | 348 (80.4) | 123 (68.7) | |
| Ablation | 15 (2.5) | 11 (2.5) | 4 (2.2) | |
| Resection + ablation | 126 (20.6) | 74 (17.1) | 52 (29.1) | |
| Extrahepatic disease | 70 (11.4) | 36 (8.3) | 34 (19.0) | <0.001 |

59.8% vs. curative-intent: n = 219, 50.6%; P = 0.04). Patients who underwent a debulking operation also more often had symptomatic disease (debulking: n = 134, 74.9% vs. curative-intent: n = 274, 63.3%; P = 0.006), high grade tumors (debulking: n = 41, 35.0% vs. curative-intent: n = 37, 12.8%; P < 0.001), synchronous disease (debulking: n = 125, 69.8% vs. curative-intent: n = 254, 58.7%; P = 0.01), and lymph node metastasis (debulking: n = 105, 72.9% vs. curative-intent: n = 196, 52.4%; P < 0.001). With regard to extent of disease, patients undergoing a debulking operation more commonly had bilateral liver metastases (debulking: n = 130, 75.6% vs. curative-intent: n = 199, 52.8%; P < 0.001) and extrahepatic disease (debulking: n = 34, 19.0% vs. curative-intent: n = 36, 8.3%; P < 0.001).

## Overall survival

After a median follow-up of 51 months, 174 patients (28.4%) in the entire cohort had died. The 1-, 3-, and 5-year overall survival

(OS) was 96.3%, 86.9%, and 78.3%, respectively. Several factors were associated with worse median OS (Table 2). Patient factors associated with worse median OS included age over 65 years (age <65 years: not reached vs. age ≥65 years: 123 months; P = 0.009). Pathologic factors associated with worse OS included high-grade tumors (low grade: not reached vs. intermediate-high grade: 89 months; P < 0.001) and lymph node metastasis (no lymph node metastasis: not reached vs. lymph node metastasis: 123 months; P < 0.001). Furthermore, patients with synchronous disease (no synchronous disease: not reached vs. synchronous disease: 124 months; P = 0.002) or extrahepatic disease (no extrahepatic disease: 169 months vs. extrahepatic disease: 87 months; P < 0.001) had a worse long-term outcome. Of note, patients who underwent a debulking operation had a worse median OS compared with patients who underwent a R0/R1 operation (R0/R1: not reached vs. R2/debulking: 87 months; P < 0.001) (Fig. 1). When stratified by the presence of symptoms, patients who underwent a R0/R1 resection had a better OS versus patients who

**Table 2** Hazard regression analysis of factors associated with overall survival

| Variables | Median Survival (Months) | P value | Multivariate Survival Analysis | | |
| --- | --- | --- | --- | --- | --- |
| | | | Hazard Ratio | 95% CI | P value |
| Age | | 0.009 | | | |
|   <65 years | Not reached | | Ref | | |
|   ≥65 years | 122.27 | | 1.28 | 0.75–2.18 | 0.36 |
| Race | | 0.99 | | | |
|   White | 140.41 | | | | |
|   Black | 168.99 | | | | |
|   Other | Not reached | | | | |
| Gender | | 0.48 | | | |
|   Male | 132.85 | | | | |
|   Female | 154.60 | | | | |
| Location of primary tumor | | 0.16 | | | |
|   Pancreas | 132.13 | | Ref | – | |
|   Small intestine | Not reached | | 0.39 | 0.19–0.76 | 0.006 |
|   Large intestine | Not reached | | 0.70 | 0.30–1.61 | 0.40 |
| Symptomatic disease | 137.88 | 0.29 | 0.76 | 0.42–1.39 | 0.38 |
| Primary tumor grade | | <0.001 | | | |
|   Low | Not reached | | Ref | – | |
|   Intermediate | 126.51 | | 1.92 | 1.04–3.56 | 0.04 |
|   High | 89.22 | | 1.55 | 0.73–3.29 | 0.25 |
| Lymph node status | | <0.001 | | | |
|   No lymph node metastasis | Not reached | | Ref | – | |
|   Lymph node metastasis | 123.26 | | 1.95 | 1.01–3.76 | 0.05 |
| Liver disease presentation | | 0.002 | | | |
|   No synchronous disease | Not reached | | Ref | – | |
|   Synchronous disease | 124.38 | | 1.27 | 0.68–2.83 | 0.35 |
| Liver metastasis location | | 0.62 | | | |
|   Unilateral metastases | 132.85 | | | | |
|   Bilateral metastases | 123.26 | | | | |
| Estimated liver involvement | | 0.08 | | | |
|   <50% | 127.60 | | Ref | – | |
|   ≥50% | Not reached | | 1.40 | 0.69–2.83 | 0.94 |
| Type of liver operation | | 0.08 | | | |
|   Resection | 169.0 | | Ref | – | |
|   Ablation | Not reached | | 0.94 | 0.12–7.44 | 0.96 |
|   Resection + ablation | 108.25 | | 0.98 | 0.49–1.96 | 0.96 |
| No extrahepatic disease | 168.99 | <0.001 | Ref | – | |
| Extrahepatic disease | 87.02 | | 1.93 | 0.92–4.07 | 0.08 |
| Intent of resection | | <0.001 | | | |
|   Curative-intent (R0/R1) | Not reached | | | | |
|   Debulking (R2) | 87.02 | | 2.92 | 1.65–5.17 | <0.001 |

underwent a R2 debulking operation (P < 0.001) (Fig. 2); in addition, 5-year OS was higher among patients who underwent a R0/R1 curative-intent resection (85.2%) versus patients who underwent a debulking operation (60.7%) (P < 0.001).

On cox proportional hazard regression analysis, intermediate-poor tumor grade was independently associated with an increased risk of death (HR 1.92, 95%CI 1.04–3.56; P = 0.04). Furthermore, patients undergoing a debulking operation had
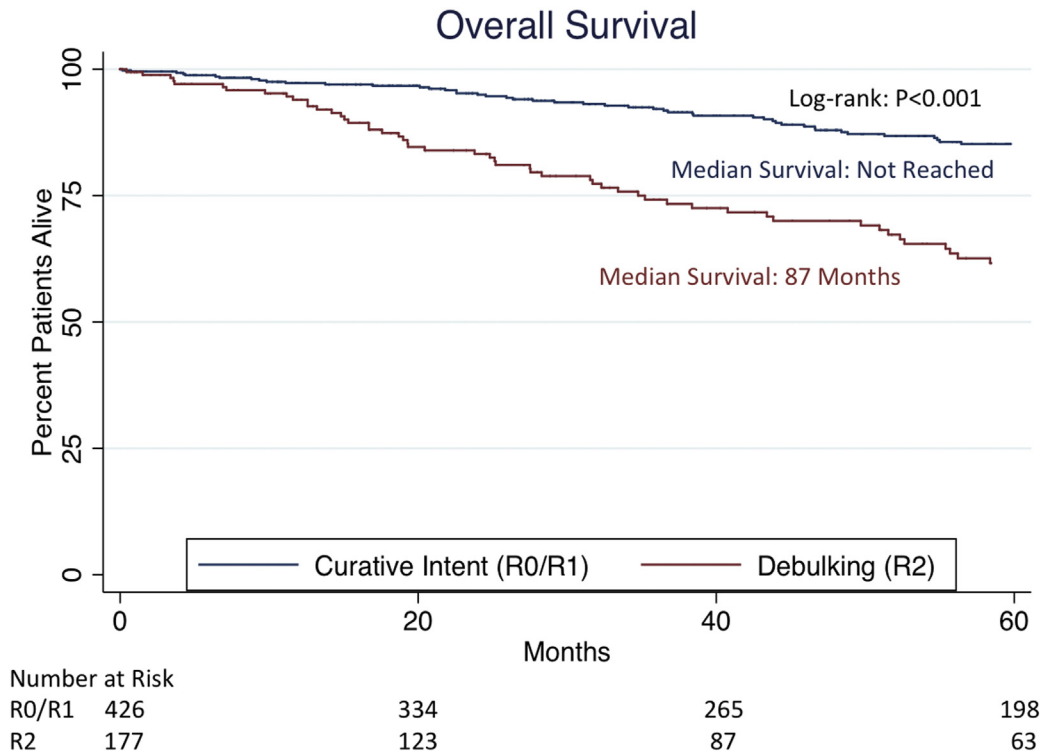
**Figure 1** - Kaplan–Meier overall survival curve among patients who underwent liver-directed therapy stratified by type of operation (KM graph truncated at 60 months)
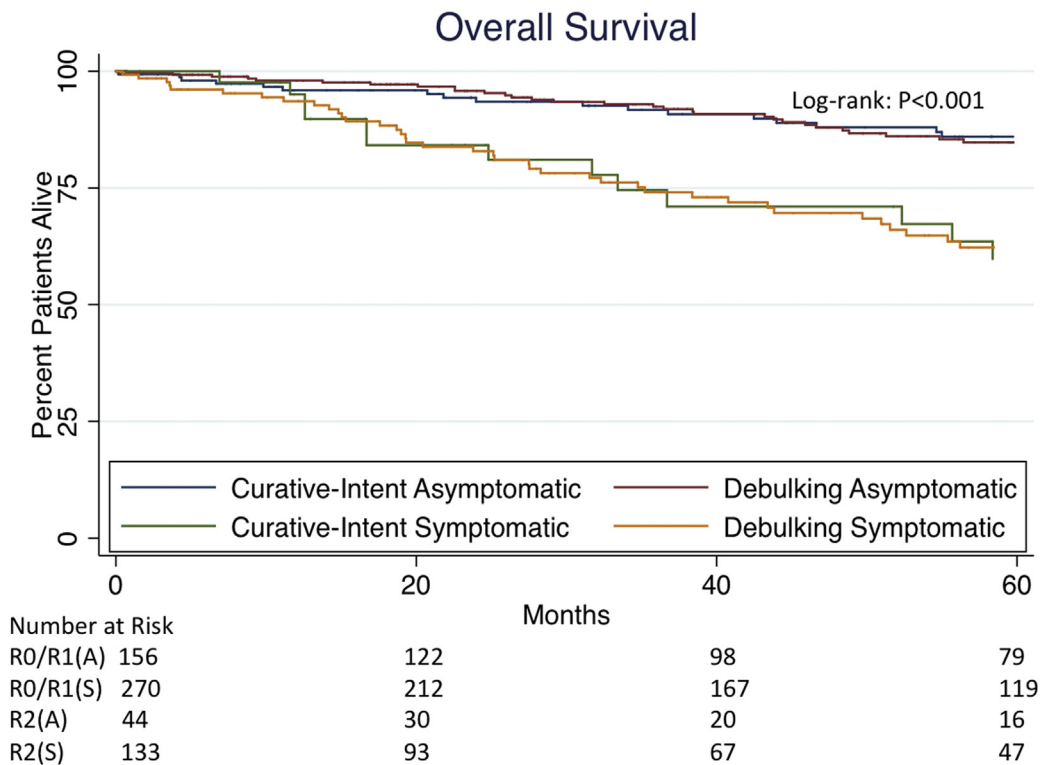


**Figure 2** - Kaplan–Meier overall survival curve among patients who underwent liver-directed therapy stratified by type of operation and presence of neuroendocrine tumor symptoms (KM graph truncated at 60 months)

nearly a 3 times increased risk of death (HR 2.92, 95%CI 1.65–5.17; P < 0.001) compared with patients who underwent a curative-intent operation. In a subset analysis of only patients who only underwent a debulking operation, patients with intermediate-poor grade disease and patients with synchronous disease were at higher risk of death long-term compared with patients who underwent debulking for well-differentiated or metachronous disease (both P < 0.05).

Patients were subsequently stratified based on extent of liver involvement. Median survival was longer among patients with <50% hepatic involvement versus patients with ≥50% hepatic involvement (<50%: not reached vs. ≥50%: 128 months; P < 0.001). Among patients with a high-burden of liver disease (≥50%), 5-year median OS remained higher among patients who underwent a curative-intent operation versus a debulking operation (R0/R1 curative intent: not reached vs. R2 debulking: 55 months; P < 0.001) (Fig. 3). Among patients who only underwent a debulking operation, patients who had <50% and underwent a debulking operation tended to have a longer median OS versus patients with ≥50% liver involvement (89 months vs. 55 months) (P = 0.14).

## Discussion

Among patients with NELM, liver-directed therapy provides a survival benefit in appropriately selected patient.[3] However,

approximately only 1 in 5 patients with NELM are eligible for curative-intent resection at the time of presentation due to the extent of disease. As such, debulking operations have been advocated to control symptoms and minimize the burden of disease. Previous studies have suggested a survival benefit from debulking or cytoreductive operations in patients with NELM.[5–7] In the current study, we present one of the largest cohorts of patients with NELM who underwent a debulking operation. In fact, among the over 600 patients included in the study, nearly 1 in 3 patients underwent a debulking operation. Perhaps not surprising, patients who underwent debulking had more extensive and aggressive disease characterized by a higher incidence of lymph node metastasis, worse tumor grade, and greater liver involvement. Despite having these more aggressive features, patients with NELM who underwent a debulking operation had a reasonable long-term median OS of almost 7.5 years. Furthermore, even among patients with a high burden of with ≥50% liver involvement, median OS was still almost 5 years.

For patients with NELM, the best hope for long-term survival is complete surgical excision of all visible primary and metastatic disease. Among patients with high tumor burden or tumors in anatomically challenging locations, curative-intent resection may not be possible. In the current cohort of 612 patients who underwent liver-directed therapy, 179 patients were unable to undergo a curative-intent operation and a
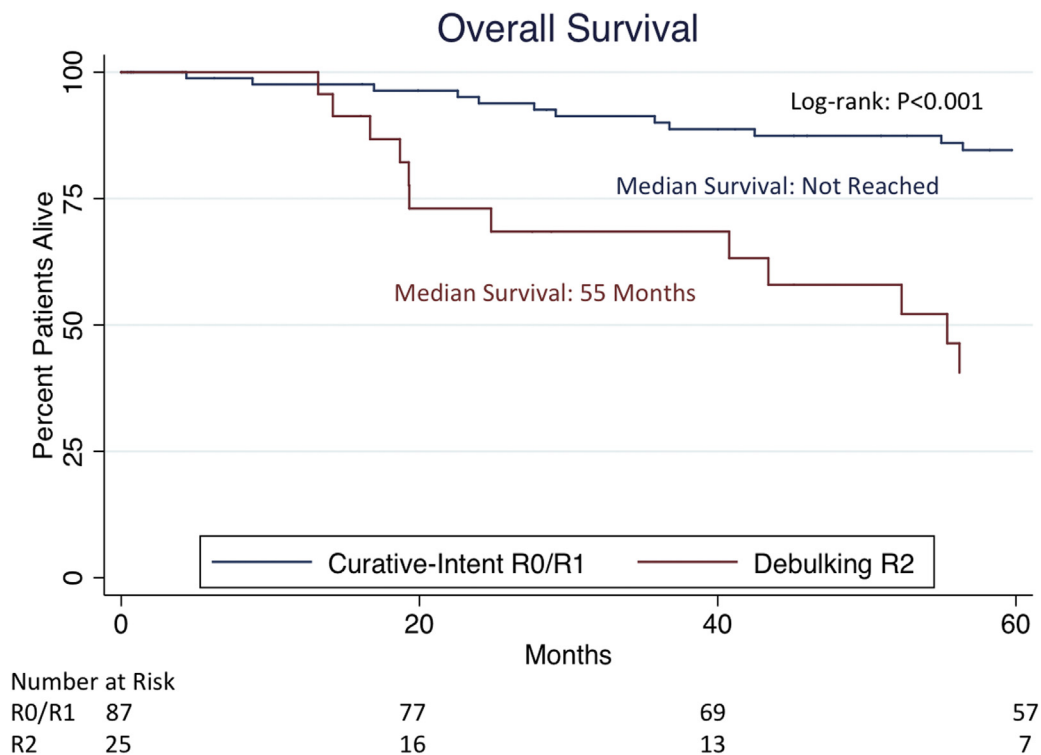


Figure 3 - Kaplan–Meier overall survival curve among patients who underwent liver-directed therapy with ≥50% hepatic involvement stratified by type of operation (KM graph truncated at 60 months)

debulking operation was performed instead. Of note, patients who underwent a debulking operation had higher rates of intermediate or high-grade tumors as well as the presence of primary tumor lymph node metastasis. Despite the increased presence of these negative prognostic factors, patients who underwent a debulking operation had a median OS of over 7 years. These data were similar to survival data reported by Glazer *et al.* in a smaller cohort of patients who underwent curative-intent resection for NELM.[7] In a different study by Graff-Baker *et al.* of 52 patients who underwent a debulking operation for carcinoid liver metastasis, 5-year disease-specific survival was 90% and median progression-free survival was 72 months.[16] These authors used a debulking threshold of 70% and performed debulking operations even in the presence of extrahepatic disease. Previous studies have advocated that >90% of disease as a threshold in performing a debulking operation.[5,6] In the current study, R2 resection/debulking was defined as removal of at least 80% of hepatic disease. Similar to Graff-Baker *et al.*, extrahepatic disease did not preclude a debulking operation among patients included in the current cohort. In fact, 20% of patients who underwent a debulking operation had extrahepatic disease. For further comparison, patients with NELM who received capecitabine and temozolomide in the large CAPTEM study by Fine *et al.* had a median OS of 83 months (28−140 months) from the diagnosis of liver metastases. Taken together, these data collectively show that despite a more aggressive tumor profile, debulking operations should be considered among patients with NELM.

Previous studies have attempted to identify patients who may benefit the most from a debulking operation, specifically suggesting that patients with symptomatic disease may benefit the most.[6,7] In the current study, patients who underwent a debulking operation more commonly presented with symptomatic disease (P = 0.006). However, in the cox-regression survival analysis, the presence or absence of NELM symptoms did not impact survival following liver-directed therapy (P = 0.29) (Fig. 2). Even when only patients who underwent a debulking operation were analyzed, median OS was comparable among patients who presented with asymptomatic or symptomatic disease (P = 0.79). In addition to symptomatic disease, high tumor burden has previously been proposed as an indication for debulking. After stratifying by extent of liver disease, patients with <50% hepatic involvement who underwent a debulking operation tended to have a longer median OS versus patients with ≥50% liver involvement (89 months vs. 55 months) (P = 0.14). On cox proportional hazard regression analysis, intermediate-poor tumor grade was also independently associated with an increased risk of death (HR 1.92, 95%CI 1.04−3.56; P = 0.04). As such, patients with <50% NELM involvement and those patients with well-differentiated tumors benefited the most from debulking.

The current study had several limitations. As with all retrospective studies, selection bias was a possibility. Patients in the current cohort were also treated at high-volume international

hepatobiliary centers, which may limit the generalizability of the results. Finally, certain clinicopathologic data (e.g. Ki-67, approximate percentage of residual tumor) and post-operative data (e.g. complications) were not collected and therefore these variables could not be assessed.

In conclusion, debulking operations for NELM provided reasonable long-term survival. When feasible, curative-intent resection provides the best hope for long-term survival. Cytoreductive debulking operations for patients with NELM is, however, a reasonable therapeutic option for patients with grossly unresectable disease especially among patients with <50% liver involvement and well-differentiated tumors.

## Conflict of interest

None declared.

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