

## ORIGINAL ARTICLE

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

Aslam Ejaz<sup>1</sup>, Bradley N. Reames<sup>1</sup>, Shishir Maithel<sup>2</sup>, George A. Poultsides<sup>3</sup>, Todd W. Bauer<sup>4</sup>, Ryan C. Fields<sup>5</sup>, Matthew J. Weiss<sup>1</sup>, Hugo P. Marques<sup>6</sup>, Luca Aldrighetti<sup>7</sup> & Timothy M. Pawlik<sup>8</sup>

<sup>1</sup>Department of Surgery, Johns Hopkins Hospital, Baltimore, MD, <sup>2</sup>Department of Surgery, Emory University, Atlanta, GA, <sup>3</sup>Department of Surgery, Stanford University, School of Medicine, Stanford, CA, <sup>4</sup>Department of Surgery, University of Virginia, Charlottesville, VA, <sup>5</sup>Department of Surgery, Washington University, School of Medicine, St Louis, MO, USA, <sup>6</sup>Department of Surgery, Curry Cabral Hospital, Lisbon, Portugal, <sup>7</sup>Department of Surgery, Liver Unit, Scientific Institute San Raffaele, Vita-Salute San Raffaele University, Milan, Italy, and <sup>8</sup>Division of Surgical Oncology, The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA

## 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.

Received 11 July 2017; accepted 31 August 2017

## Correspondence

Timothy M. Pawlik, Department of Surgery, Health Services Management and Policy, The Ohio State University, Wexner Medical Center, 395 W. 12th Ave., Suite 670, Columbus, OH 43210, USA.

## 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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup> 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

We have no financial or commercial interests to disclose.

Presented at the Annual Americas Hepato-Pancreato-Biliary Association Meeting, Miami, FL 2017.

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

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.<sup>5</sup> 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.<sup>6,7</sup> 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.<sup>8–13</sup> 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.<sup>14</sup> 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.<sup>15</sup> 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  $\geq 80\%$  of all visible disease was resected. Outcomes were stratified according to curative (R0/R1) versus non-curative  $\geq 80\%$  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,

Download English Version:

<https://daneshyari.com/en/article/8722795>

Download Persian Version:

<https://daneshyari.com/article/8722795>

[Daneshyari.com](https://daneshyari.com)