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Neutrophil lymphocyte ratio and transarterial chemoembolization in neuroendocrine tumor metastases



Sean M. McDermott, BS,^a Neil D. Saunders, MD,^b Eric B. Schneider, PhD,^c
David Strosberg, MD,^a Jill Onesti, MD,^d Mary Dillhoff, MD,^a
Carl R. Schmidt, MD,^a and Lawrence A. Shirley, MD^{a,*}

^aThe Ohio State University Wexner Medical Center, Columbus, Ohio

^bEmory University School of Medicine, Division of General and GI Surgery, Atlanta, Georgia

^cUniversity of Virginia Department of Surgery, Charlottesville, Virginia

^dMercy Health, Department of Surgery, Grand Rapids, Michigan

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ABSTRACT

Background: The neutrophil-to-lymphocyte ratio (NLR) has been shown to be predictive of outcomes in various cancers, including neuroendocrine tumors (NETs), and cancer-related treatments, including transarterial chemoembolization (TACE). We hypothesized that NLR could be predictive of response to TACE in patients with metastatic NET.

Methods: We reviewed 262 patients who underwent TACE for metastatic NET at a single tertiary medical center from 2000 to 2016. NLR was calculated from blood work drawn 1 d before TACE, as well as 1 d, 1 wk, and 6 mo after treatment.

Results: The median post-TACE overall survival (OS) of the entire cohort was 30.1 mo. Median OS of patients with a pre-TACE NLR ≤ 4 was 33.3 mo versus 21.1 mo for patients with a pre-TACE NLR >4 ($P = 0.005$). At 6 mo, the median OS for patients with post-TACE NLR $>$ pre-TACE NLR was 21.4 mo versus 25.8 mo for patients with post-TACE NLR \leq pre-TACE NLR ($P = 0.007$). On multivariate analysis, both pre-TACE NLR and 6-mo post-TACE NLR were independent predictors of survival. NLR values from 1-d and 1-wk post-TACE did not correlate with outcome.

Conclusions: An elevated NLR pre-TACE and an NLR that has not returned to its pre-TACE value several months after TACE correlate with outcomes in patients with NET and liver metastases. This value can easily be calculated from laboratory results routinely obtained as part of preprocedural and postprocedural care, potential treatment strategies.

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* Corresponding author. The Ohio State University Wexner Medical Center, 410 W. 10th Ave., N-924 Doan Hall, Columbus, OH 43210-1228. Tel.: +(614) 293 0758; fax: +(614) 293 3465.

E-mail address: lawrence.shirley@osumc.edu (L.A. Shirley).

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Introduction

Neuroendocrine tumors (NETs) are malignant neoplasms that originate from the epithelium of organs with neuroendocrine differentiation. These neoplasms typically exhibit relatively indolent growth leading to prolonged survival.¹ Metastases involving the liver can be seen in 46%-93% of patients with NETs and often manifest diffusely throughout the liver before symptoms present, worsening the prognosis.² This often leads to synchronous diagnosis of primary tumor and liver metastases. Surgical intervention is limited in patients with diffuse bilobar hepatic metastases, making locoregional treatments such as transarterial chemoembolization (TACE) an optimal choice.³⁻⁵ TACE is often effective, controlling both the further progression of the tumor throughout the liver and the symptoms of excess hormone production.⁶⁻¹⁰

Although TACE is a standard-of-care procedure in these patients, the effectiveness of this treatment strategy in patients with significant hepatic involvement, where much of the liver parenchyma has been compromised, is incompletely understood. In addition, the selection criteria for patients with NETs to be treated with TACE, as opposed to other antineoplastic therapies, are poorly defined. As such, discovery of novel biomarkers would be valuable in this patient population.

The use of the NLR as a prognostic tool in cancer treatments has been consistently validated.¹¹⁻¹³ Elevated NLR has been shown to correlate with decreased survival in colorectal,^{14,15} gallbladder,¹⁶ hepatocellular,¹⁷⁻¹⁹ thymic,²⁰ lung,^{21,22} renal cell,^{23,24} esophageal squamous cell,²⁵ bladder,²⁶ adrenocortical,²⁷ pancreatic,²⁸ paranasal sinus,²⁹ gastric,³⁰ prostate,³¹ and breast³² carcinomas as well as osteosarcoma³³ and glioblastoma.³⁴ To better predict outcomes in patients with NETs and metastatic liver involvement who receive TACE, we hypothesized that a lower NLR pre-procedure, and postprocedure, would correlate with improved long-term outcomes.

Methods

After institutional review board review, the study was approved for waiver of consent and full waiver of Health Insurance Portability and Accountability Act research authorization. We reviewed the records of 262 patients at The Ohio State University Wexner Medical Center with metastatic neuroendocrine cancer who underwent TACE treatment between 2000 and 2016. Values collected included age at diagnosis, sex, race, primary tumor location and histology, presenting symptoms, the presence of carcinoid syndrome, whether the hepatic metastasis was diagnosed synchronously, tumor burden in the liver, whether primary tumor was resected, grade of tumor, presence of lymph node metastasis, presence of extrahepatic disease, tumor response to TACE on imaging, disease progression post-TACE, whether patients went on to hepatic resection, and survival. In addition, absolute neutrophil and lymphocyte values were collected from complete blood count (CBC) with differential drawn pre-TACE (the morning of the first procedure) and post-TACE (1 d, 1 wk,

and 6 mo after the completion of planned procedure course). The NLR was then calculated by dividing the neutrophil value by the lymphocyte value.

Response of the hepatic metastases to the TACE procedure was calculated using the Response Evaluation Criteria in Solid Tumors and the radiologist reports on the follow-up computed tomography or magnetic resonance imaging scans. Radiology reports were used from all computed tomography or magnetic resonance imaging scans taken after TACE to determine if and when progression of hepatic disease ensued.

When analyzing the entire cohort, at 36 mo, those patients alive had a median pre-TACE NLR of 3.3, while those who had died had a median pre-TACE NLR of 4.4. As such, the cohort was divided into two groups based on whether each patient's pre-TACE NLR was greater than or less than 4. The median NLR 1 d after TACE was 13.68 while the median NLR 1 wk after TACE was 9.12. For this reason, the cohort was then divided into two groups based on whether each patient's 1-d post-TACE NLR was greater than or less than 15, and then two additional groups based on whether each patient's 1-wk post-TACE NLR was greater than or less than 10. Finally, the cohort was divided into two groups based on whether each patient's 6-mo post-TACE NLR was greater than or less than the pre-TACE NLR. Comparisons were made between groups to investigate differences in median overall survival (OS) from the time of first TACE treatment. Of note, every patient received a periprocedural dose of 400 mg ciprofloxacin IV unless patient previously underwent a pancreaticoduodenectomy, in which case, they received 400 mg moxifloxacin per os for 5 d before the procedure and 21 d after the procedure.

Inclusion criteria were diagnosis of NET with metastatic disease to the liver, at least one TACE treatment used on the patient, and appropriate preprocedural and postprocedural data available. Categorical data were compared by chi-square or Fisher's exact test, and quantitative data by Student's *t* test or Mann-Whitney *U* test when appropriate. Survival curves were created using the Kaplan-Meier method, and comparisons made via log-rank test. Multivariate analysis was done using a Cox regression model and covariates of age, gender, race, type of primary tumor, whether the primary tumor was resected, tumor grade, presence of carcinoid syndrome, and if the diagnosis of liver metastasis was synchronous with the NET primary diagnosis. All statistics were analyzed using SPSS version 24 (IBM, Armonk NY).

Results

The cohort consisted of 262 patients who had a preTACE CBC drawn from which an NLR value could be calculated. Of these 262 patients, 260 had a CBC drawn 1 d after TACE, 224 had a CBC drawn 1-wk after TACE, and 205 had a CBC drawn 3 to 9 mo after TACE. The mean age at diagnosis of primary tumor was 57 y with small bowel being the most common primary site (35%). Thirty-one percent of the patients only had a single TACE procedure performed, 55% had only two procedures, 14% had three procedures, 8% had four procedures, and 2% had more than four procedures. There were 25 patients who experienced complications in the perioperative time period

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