Serum neuron-specific enolase level is an independent predictor of overall survival in patients with gastroenteropancreatic neuroendocrine tumors

Annals of Oncology Advance Access published December 27, 2015

Letter to the editor concerning 'Serum neuron-specific enolase level is an independent predictor of overall survival in patients with gastroenteropancreatic neuroendocrine tumors'

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Abbreviated title for page headings: NSE is an independent predictor for survival in GEP-NET patients

Key words: gastroenteropancreatic neuroendocrine tumors (GEP-NETs), neuron-specific enolase (NSE)

Serum neuron-specific enolase (NSE) is considered a tumor marker in patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs) [1]. It is elevated in 30-50% of GEP-NET patients and correlates with tumor size [2, 3]. NSE has a sensitivity of 38% and specificity of 73% for GEP-NET detection [2]. The prognostic role of serum NSE as a biomarker for GEP-NETs patients' survival is poorly studied [4].

We retrospectively studied 592 patients with sporadic (non-familial) ENETS TNM stage IV GEP-NETs. Median follow-up was 58.7 months (25^{th}-75^{th} percentile: 34.02-92.98). Serum NSE was measured at first consultation, using enzyme immunoassay (NSE Cobas E602, Roche Diagnostics, Mannheim, Germany).

Cut-off values for serum NSE were: NSE ≤1xULN (≤16.2 µg/l), NSE 1-3xULN (16.2-48.6 µg/l) and NSE >3xULN (48.6 µg/l).

Primary outcome was overall survival, calculated from date of diagnosis to date of death by any cause, or date of last follow-up. Using statistical software R version 3.1.3 "survival" package, overall survival was estimated with the Kaplan–Meier method. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated with Cox proportional hazards models including age at diagnosis, OctreoScan® (SRS) positivity (Krenning Scale ≥2 in all lesions), primary tumor site, sex, and bone metastases.

242 (41%) of GEP-NET patients had an elevated NSE (>1 x ULN). NSE >3x-ULN were seen in pancreatic NETs.

Median overall survival (mOS) across all groups was 103.9 months (95% CI: 92.8-137.1). mOS was 161.8 months in the NSE ≤1xULN group (95% confidence interval (CI): 130.7-not reached (NR)) and 72.5 months in the NSE 1-3xULN group (95% CI:

60.2-108.6; Cox proportional hazard-adjusted HR vs. NSE ≤1xULN: 1.96 [1.45-2.63], p<0.001). In the NSE >3xULN group, mOS was 27.8 months (95% CI: 15.2-44.7; HR vs. NSE ≤1xULN: 6.15 [4.36-8.69], p<0.001) (Fig. 1). Significant contributors to our model included: age at diagnosis (HR 1.03 [1.02-1.04], p<0.001) and SRS positivity (HR 0.48 [0.28-0.83], p<0.001)..

The ENETS/WHO grading system using Ki-67 staining was introduced in 2010 [5]. Therefore, we used SRS positivity as a surrogate marker for ENETS/WHO tumor grading, since SRS-positive GEP-NETs are generally well-differentiated, ENETS/WHO grade 1-2 tumors. However, the assumption that all SRS-positive could have ENETS/WHO grade 1-2 tumors could be considered a limitation of this study. We therefore studied the subpopulation of 367 patients with known ENETS/WHO 2010 grading (62% of all patients). In this population, the same Cox proportional hazard model with ENETS/WHO grade as an additional parameter was applied and showed that higher ENETS/WHO grade significantly contributed (p<0.001) to the model, but that NSE remained independently associated with overall survival (p<0.001). Multivariate analysis data is shown (Supplementary Table 1).

This study demonstrates that NSE is a biomarker for overall survival in ENETS TNM stage IV GEP-NET patients. Our study cohort had a median follow-up of almost 5 years and an mOS of over 8.5 years across all groups. Elevated NSE was found in over 40% of patients, confirming published data [2, 3]. Elevated serum NSE indicates a more aggressive disease course and determination of NSE at first consultation could, therefore, have prognostic implications.

disclosure

Roxanne van Adrichem: No relationship to disclose.

Kimberly Kamp: No relationship to disclose.

Timon Vandamme: Attends in advisory boards for and received speakers fees from Ipsen and Novartis.

Marc Peeters: Attends in advisory boards for and received speakers fees from Ipsen, Novartis and Amgen.

Richard Feelders: Attends in advisory boards for and received speakers fees from Ipsen and Novartis.

Wouter de Herder: Attends in advisory boards for and received speakers fees from Ipsen and Novartis.

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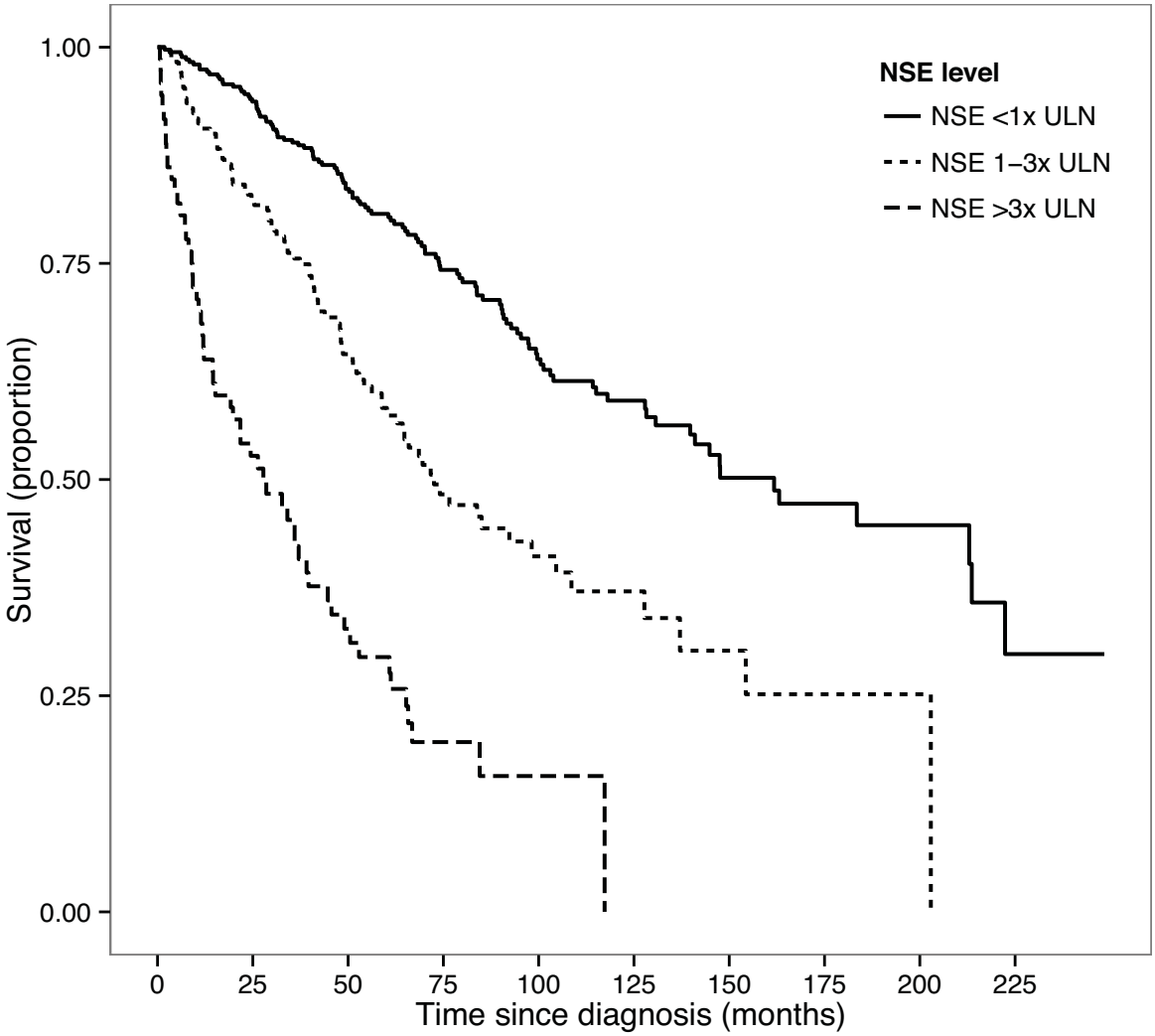
Legend to Figure 1.

Kaplan-Meier estimate of overall survival in a normal (≤1 x ULN, ▬), intermediate (1-3 x ULN, ▪▪▪) and, high (>3 x ULN, ▬ ▬) levels groups of first serum neuron-specific enolase measurement by referral (NSE).



Number of patients at risk

NSE <1x ULN	350	325	239	159	104	64	37	21	13	4
NSE 1–3x ULN	170	138	90	41	24	13	7	2	1	0
NSE >3x ULN	72	36	20	7	1	0	0	0	0	0