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Directional Misclassification of WHO Neuroendocrine Differentiation in a CoC Registry: Implications for SEER and NCDB Outcomes Research

Sanjay Shankar[1,2], Joseph Watts[1,2], Harry Menon, DO[1,2], Katharine Thomas, MD[1,2]

[1]University of Nevada, Reno School of Medicine, Reno, NV; [2]Renown Health, Reno, NV

BACKGROUND

Accurate histologic grade coding is foundational to neuroendocrine neoplasm (NEN) registry-based research, as grade drives treatment selection, survival stratification, and external validity. Cancer registries use NAACCR-defined grade fields populated from pathology reports, which may not consistently capture WHO-recommended Ki-67-based grading for NEN. Systematic discordance would introduce non-random misclassification bias into SEER- and NCDB-based analyses relying on registry grade as the primary tumor characteristic.

METHODS

We conducted a single-institution analysis linking our CoC-accredited NEN registry (n=469) to WHO-aligned differentiation class chart-abstracted for 386 patients. Concordance was defined as agreement at the poorly versus well-differentiated level; within-class grade differences (e.g., G1 vs. G2 NET) were not counted as discordant. Of 386 chart-abstracted patients, 152 were analyzable (excluded: undetermined registry grade n=214, mixed differentiation class n=23). Directional asymmetry was tested with the binomial test.

RESULTS

Among 152 analyzable patients, concordance between registry-assigned grade and chart-abstracted WHO class was 95.4% (145/152). Discordance was identified in 7 patients (4.6%) and was entirely asymmetric: all 7 were under-coded (registry grade below WHO differentiation class; 7:0 ratio, binomial p=0.008). All discordant cases were NEC tumors assigned registry G1 (n=4) or G2 (n=3) rather than G3 — reflecting systematic failure to capture NEC in low registry-grade fields. Concordance was highest for NET G1 (97%, 121/125) and perfect for registry-assigned G3 (100%, 17/17 chart-confirmed NEC).

Table 1. Registry vs. WHO Grade Concordance (n=152)

Concordance Category	n	%	Note

Concordant	145	95.4	Agreement at poorly vs. well-differentiated level
Discordant — Total	7	4.6	7:0 ratio favoring under-coding (p=0.008)
— Under-coded	7	4.6	Registry G1 (n=4) or G2 (n=3); all chart-confirmed NEC
— Over-coded	0	0.0	None identified

152/469 included; excluded: undetermined registry grade (n=214 of 386 chart-abstracted), mixed differentiation (n=23), not chart-abstracted (n=83; some overlap). Binomial p=0.008. NEC=neuroendocrine carcinoma.

CONCLUSIONS

Registry grade under-coding in NEN is systematic: all 7 discordant cases were NEC tumors assigned registry G1 or G2, yielding a 7:0 directional ratio (p=0.008). Because NEC OS is measured in months vs. years for G3 NET, misclassification of NEC into low registry-grade fields attenuates grade-based survival differences in SEER and NCDB — producing upward bias in apparent low-grade survival. These findings underscore the need for WHO-aligned differentiation fields in prospective CoC registry updates and caution against use of registry grade as a WHO class surrogate in NEN outcomes research.

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