

# Rectal neuroendocrine tumors: Can we predict their behavior?

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## Word Length

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Measures average word length

characters per word

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**25.6**

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# Rectal neuroendocrine tumors: Can we predict their behavior?

Rectal neuroendocrine tumors (r-NETs) are the second most common type of neuroendocrine tumor in the gastrointestinal tract [1]. In the last decades, their incidence has been rising, mainly as a result of improvements in colonoscopy techniques and the expanded use of colorectal cancer screening programs [2]. Endoscopically, r-NETs are typically round, small, and yellowish, often incidentally discovered during colonoscopies conducted for screening or other unrelated reasons. Histology usually reveals low-grade tumors, commonly classified as G1 or G2, with a low Ki-67 index [3-5]. Given their low risk of lymph node involvement or metastasis, current guidelines recommend endoscopic resection for small (<1 cm), low-grade, localized lesions (even though a recent French study demonstrated that up to 20% of r-NETs are not adequately recognized during endoscopies, resulting in inappropriate excision) [4,6]. Consequently, they tend to have a favorable prognosis with indolent behavior, often exhibiting some of the longest median overall survival rates in this tumor category (even exceeding 30 years) [2].

Several prognostic factors are used to assess the risk of lymph node and distant metastasis in r-NETs, including lesion size (typically with a cutoff of  $\geq 10$  mm), tumor grading, staging, and lymphovascular invasion [2,4,7].

Another area of interest is the clinical significance of incomplete endoscopic resection (with positive resection margins, or R1), which remains unclear but does not necessarily affect progression and recurrence outcomes [8].

Along with the WHO classification [3], the AJCC TNM staging system [9] and the European Neuroendocrine Tumor Society (ENETS) system [10] are used to

stratify patients. Tumor size, though important, should not be the sole factor in treatment planning, as grading and staging also play critical roles in determining outcomes [11].

In this context, the GATIS predicting score, proposed by Zang and colleagues [12], represents an innovative model designed to predict individualized survival outcomes for patients with rectal neuroendocrine tumors. This model analyzes the relationship between clinicopathological features and patients' prognoses. The authors identified tumor grade, T stage, tumor size, age, and prognostic nutritional index (PNI) as key prognostic factors, demonstrating that the GATIS Score provides a more accurate prognosis assessment compared to the WHO classification or the TNM staging system.

Notably, this study, in addition to considering grade, stage, and size, also accounts for clinical variables such as age and PNI. This highlights the growing importance of factors such as nutritional aspects, which are increasingly recognized as necessary in managing neuroendocrine tumors and other oncological diseases.

As demonstrated in other malignancies, malnutrition can significantly reduce the quality of life and the response to treatment—often underestimated aspects of patient care. This is also true for neuroendocrine tumors, although the data on this topic remain scarce and need further development [13].

As is well known, neuroendocrine tumors are rare and exhibit heterogeneous behavior. Their characteristic indolence makes it difficult to accurately determine their true nature, especially through retrospective studies with short follow-up periods.

Although a median follow-up of nearly three years (as in this study) may seem like a reasonable timeframe to assess the behavior of neoplastic disease, it may be insufficient for neuroendocrine tumors.

In such cases, even significantly longer follow-up periods (up to 13 years, as observed in other studies and for other primary sites [14]) may be inadequate for evaluating the behavior of these slow-growing conditions [15].

Moreover, in the context of prognostic factors and efforts to predict disease behavior, it is increasingly essential to recognize the growing importance of biomarkers and genetic/molecular markers. Their relevance in oncology has been rising steadily, especially in this tailored and personalized medicine era. While histopathological and molecular evaluations provide valuable prognostic insights, identifying biomarkers for NETs still needs to be explored, highlighting the need for further research [16,17]. We believe this is an important area that warrants further investigation, especially considering the heterogeneous nature of neuroendocrine tumors. Identifying valuable stratification factors would undoubtedly aid in guiding the management and follow-up of these patients.

Finally, although the effort to obtain such a large sample size is commendable, given the difficulty in acquiring it for a rare condition, it is important to note that the study is based on an Asian population. This may limit its applicability to other regions, such as the Western world, due to potential differences in genetic and environmental factors that could influence tumor outcomes.

In conclusion, the GATIS score is an innovative predictive model that can aid in stratifying patients with rectal neuroendocrine tumors.

Nevertheless, further larger prospective studies are essential, and the scientific community's efforts in this context should be directed toward developing international multicentric prospective studies, with the ultimate aim of accurately defining and understanding the behavior of these conditions.