Digestive and Liver Disease 51 (2019) 1725–1730

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Oncology

# The ENETS TNM staging and grading system accurately predict prognosis in patients with rectal NENs

Gabriele Capurso[a,b,*], Sebastien Gaujoux[c,d], Lorenzo Carlo Pescatori[a], Francesco Panzuto[a], Yves Panis[e,f], Emanuela Pilozzi[g], Benoit Terris[d,h], Louis de Mestier[f,i], Frederic Prat[d,j], Maria Rinzivillo[a], Romain Coriat[d,j], Anne Coulevard[f,j], Gianfranco Delle Fave[a], Philippe Ruszniewski[f,i]

[a] Digestive and Liver Disease Unit, S. Andrea Hospital, ENETs Center of Excellence, Rome, Italy
[b] Pancreato-biliary Endoscopy and EUS Division, Pancreas Translational and Clinical Research Center, ENETs Center of Excellence, San Raffaele Scientific Institute IRCCS, Milan, Italy
[c] Department of Pancreatic, Hepato-biliary and Endocrine Surgery, Cochin Hospital, APHP, Paris, France
[d] Faculté de Médecine Paris Descartes, Université Paris Descartes, Sorbonne Paris Cité, Paris, France
[e] Department of Colorectal Surgery, Beaujon Hospital, APHP, ENETs Center of Excellence, Clichy, France
[f] University Denis Diderot - Paris VII, Paris, France
[g] Pathology Unit, University Sapienza, S. Andrea Hospital, ENETs Center of Excellence, Rome, Italy
[h] Department of Pathology, Cochin Hospital, APHP, Paris, France
[i] Department of Gastroenterology and Pancreatology, Beaujon Hospital, APHP, ENETs Center of Excellence, Clichy, France
[j] Department of Gastroenterology, Cochin Hospital, APHP, Paris, France

ARTICLE INFO

*Article history:*
Received 1 April 2019
Accepted 17 July 2019
Available online 9 August 2019

*Keywords:*
Rectal
Carcinoid
Neuroendocrine
Staging
Grading

ABSTRACT

*Background:* Factors associated with rectal NENs prognosis are poorly investigated.
*Aim:* To evaluate the prognostic role of the ENETs staging and grading systems in rectal NENs.
*Methods:* Tertiary referral, multicenter, retrospective study. Factors associated with OS and PFS were investigated by Cox-regression analysis, with best size cut-offs calculated by ROC analysis.
*Results:* Of 100 patients (mean age 55, 45% male, mean size 16.2 mm) 62, 5, 10 and 23 were TNM stage 1 to 4, and 63, 15 and 22 were G1, G2 and G3. Primary treatment was endoscopic snare resection in 62%, endoscopic mucosal resection/endoscopic submucosal dissection in 10%, surgery in 20% and medical treatment in 8%. The best size cut-offs to predict OS and PFS were 10 and 12 mm. During a mean follow-up of 40.7 months 12% died and 26% progressed. The 5-year OS and PFS were 79.5% and 65.2%. Stage IV and G3 were associated with worse OS (HR 8.16; p = 0.002; HR 15.57; p = 0.0004) and PFS (HR 14.26 p < 0.0001; HR 6.42; p = 0.0007).
*Conclusion:* Both staging and grading accurately predict rectal NENs prognosis. Size alone has limited accuracy as 26% of patients with stage IV and 16% with G3 have a primary tumour ≤ 10 mm.


## 1. Background

The incidence of neuroendocrine neoplasms (NENs) has been steadily increasing over the past decades [1,2]. Among NENs arising in the digestive tract (dNENs), rectal ones are the commonest [2]. A significant increase in the diagnosis of rectal NENs has occurred, mainly due to incidental diagnosis during colonoscopy performed for other indications, including screening for colorectal cancer [3]. It has been estimated that the incidence of rectal NENs during screening colonoscopy is as high as 0.17% [4]. As most rectal NENs are small and localized lesions at the time of diagnosis, and only a small fraction presents with distant metastases, their prognosis is usually good, with a global 5-year survival rate above 75% [5].

Rectal NENs are classified by a specific TNM staging system based on tumour size and invasion of other structures or organs. On the other hand, the grading system developed by the *European Neuroendocrine Tumors Society* (ENETs) [6] is based on the proliferative index (see Supplementary Table S1). While an advanced stage at diagnosis with metastatic disease (stage IV) or spread to lymph-nodes has a clear negative association with prognosis, the role of

* Corresponding author at: Pancreato-Biliary Endoscopy and EUS Division, Pancreas Translational and Clinical Research Center, San Raffaele Scientific Institute IRCCS, Via Olgettina 60, Milan, 20132, Italy.
*E-mail address:* capurso.gabriele@hsr.it (G. Capurso).

https://doi.org/10.1016/j.dld.2019.07.011
1590-8658/

size of the lesion at diagnosis, which distinguish stages 1 and 2, seems a less reliable predictor of prognosis [7]. ENETS grading of rectal NENs is instead peculiarly based on evaluation of the proliferative capacity as assessed by Ki67% or by mitotic count [7]. In 2010 and 2017 the WHO introduced a change of the nomenclature and classification of dNENs based on grading, which defines neuroendocrine tumours (NETs) both G1 and G2 cases and neuroendocrine carcinomas (NEC) those with Ki67 > 20% (G3) [8].

While it has been clearly recognized that a small size, the absence of metastatic disease and a low proliferative activity are good prognostic factors [7], there are few studies specifically evaluating the respective role of staging and grading in predicting the prognosis of rectal NENs. Furthermore, those results are heterogeneous, as in patients with primary lesion in the colon and rectum were often pooled together [9,10], while the behavior of tumours from these two primary sites is usually very different. Other previous studies suffer from selection bias as they were almost limited to small rectal lesions incidentally diagnosed endoscopically and included a minority of patients with advanced disease at diagnosis who would instead present with symptoms or diagnosis made due to liver spread [11]. Furthermore, in many instances, data on grading were not available and histology was based on hospital records and not on evaluation from pathologists with a specific expertise on NENs [11,12]. Finally, while progression-free survival is an important surrogate outcome of tumour behavior in NENs, especially in these with a limited malignancy rate, most previous data only reported overall survival analyses which were based on registries.

The present study is aimed at evaluating the prognostic role of the ENETs staging and grading systems in predicting the clinical behavior in terms both of progression-free and overall survival, in a prospectively enrolled cohort of rectal NENS seen in 3 tertiary referral centers.

## 2. Methods

### 2.1. Study Design and Patients

A multicenter, retrospective study was conducted using institutional prospective databases of patients with histologically proven rectal NENs who received treatment and follow-up at 3 Centers. The study included all consecutive new patients who were diagnosed or referred with rectal NETs at the 3 participating Centers (Beaujon Hospital, Clichy and Cochin Hospital, Paris, France; Sant'Andrea Hospital, Rome, Italy) from January 2007 to December 2013. Inclusion criteria were: (i) a diagnosis of rectal NEN, as confirmed by histology (ii) information on tumour grade (iii) information on tumour stage and treatment (endoscopic, surgical, medical) available (iv) information on follow-up (at least one follow-up examination) available. As the study design was retrospective, therapeutic approaches were not standardized, and different treatments were applied at the participating centers depending on local expertise and time of enrollment. Similarly, follow-up was not standardized, but endoscopic and radiologic procedures were planned following guidelines of the ENETs [13], hence annual colonoscopies were usually performed alongside radiologic examination (either MRI or CT-scan). Histological specimens were examined by the referred experienced pathologist managing NENs at the participating Centers. Tumors were classified according to the TNM classification/ grading system [8]. The Ki67 proliferative index was expressed as a percentage based on the count of Ki67-positive cells per 2,000 tumor cells in areas of the highest level of immunostaining using the MIB1 antibody (DBA, Milan, Italy). TNM staging was performed on the current criteria accepted by the ENETS consensus conferences. Assessment of disease status was performed at each Center by local radiologists and clinicians. The research protocol has been approved by the ethics committee of the participating centers and full informed consent was obtained from all patients.

### 2.2. Data Analysis

All data were prospectively collected at the Center where the patient had been initially observed. A common computerized datasheet was created, and data regarding the main demographic, clinic, and pathological features were retrospectively analyzed. Continuous variables are expressed as mean (±SD) and were compared by means of t-test, while categorical variables were analyzed by Fisher test. Correlation between continuous variables was evaluated by means of Spearman correlation coefficient.

The outcome variables were overall survival (OS) and progression-free survival (PFS). PFS was defined as the interval between the diagnosis of rectal neuroendocrine neoplasm and the time of disease progression (DP), or patient death, if it occurred before documented radiological progression. According to RECIST criteria, DP was defined by the appearance of new lesions or recurrence after radical removal (either endoscopic or surgical) and/or increase in size of any measurable lesion as demonstrated by radiological procedures. OS was defined as the time between diagnosis and date of death. The PFS analysis was performed as follows: patients were censored in cases of no progression at the last adequate assessment, or if lost at follow-up. For survival analysis, data were censored if the patient was alive, or lost at follow-up (censoring date was the date of the last adequate tumor assessment). PFS, as well as OS analysis, were performed using the Kaplan-Meier method, and the results were compared by using a log-rank test. Risk factors were expressed as hazard ratio (95% confidence interval, CI). The analysis of risk factors for prediction of progression during follow-up was performed by univariate and multivariate analysis using a Cox proportional hazards regression model. The multivariate model was constructed by 'enter' method, after including all variables which had resulted significant at the univariate analysis. A receiver operating characteristics (ROC) curve was constructed to determine the optimal cutoff value of size of the primary lesion. ROC curve analyses were conducted for OS and PFS. P values were considered significant when <0.05. The statistical analysis was performed using dedicated software (Medcalc 12.1, Belgium).

## 3. Results

### 3.1. Study Population

During the study period 153 patients with rectal neuroendocrine neoplasm were evaluated. Of them, 53 were excluded from the present study as not meeting all inclusion criteria. Therefore, 100 patients were considered eligible for the study. As summarized in Table 1, mean age was 55 years (±12,89) and 45% were male. The primary tumour mean size was 16.2 mm (±18.48). Regarding the TNM stage at presentation, 62, 5, 10 and 23 were stage1 to 4, respectively. Grade (G) was G1, G2 and G3 in 63, 15 and 22 patients, respectively. Overall, 17 (17%) tumours were poorly differentiated, all of them being G3 cases. The primary treatment was endoscopic snare resection in 62% of cases, endoscopic mucosal resection or endoscopic submucosal dissection in 10%, surgery in 20% and medical treatment in 8%. Of the 8 patients being treated solely by medical treatments, four of them had G3 tumour and were treated with chemotherapy (etoposide + cisplatin); the remaining 4 patients with G2 tumours were treated with somatostatin analogues and with peptide receptor radionuclide therapy (PRRT) in 1 case.

The mean size of the rectal lesion at diagnosis was 5.9 mm (±3.60) in patients with stage 1, 25 mm (±23,86) in patients with

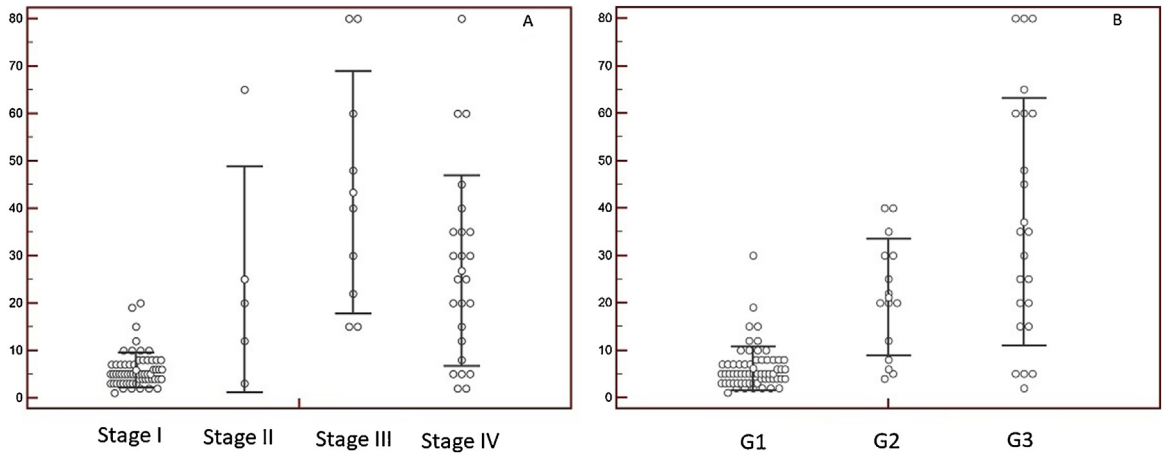


**Fig. 1.** Distribution of size of the primary rectal tumour according with stage (panel A) and grading (panel B). Dots represent size of individual lesions, the error bar represents mean ± SD.

**Table 1**
Study population.

| Patients' and Tumour Features (n = 100) | |
|---|---|
| Male / Female | 45 / 55 |
| Age (mean; SD) | 55 (±12.89) |
| Stage | |
| I | 62 (62%) |
| II | 5 (5%) |
| III | 10 (10%) |
| IV | 23 (23%) |
| Primary tumour size in mm (mean; SD) | 15.3 (±13.48) |
| Grade | |
| G1 | 63 (63%) |
| G2 | 15 (15%) |
| G3 | 22 (22%) |
| Ki67% (mean; SD) | 15.1 (±25.41) |
| Primary Treatment | |
| Snare Polypectomy | 62 (62%) |
| EMR / ESD | 10 (10%) |
| Surgery | 20 (20%) |
| Medical Treatment only | 8 (8%) |
| Follow-up months (mean ; SD) | 40.7 (±44.68) |

stage 2, 43.3 mm (±25.58) in stage 3, and 26.8 mm (±20.1) in stage IV patients (see Fig. 1). There was a significant difference in terms of size of the lesion between patients with stage 1 vs stage 2, 3 and 4 ($p < 0.0001$ for all comparisons), while the mean size of patients with stage 2 vs 3 ($p = 0.21$) 2 vs 4 ($p = 0.85$) and 3 vs 4 ($P = 0.06$) were not significantly different.

The mean size in patients with G1 tumours was 6.2 mm (±4.61) being smaller than in patients with a G2 (21.1 mm; ±12.30) and G3 (37.1 mm; ±20.09) tumours ($p < 0.0001$ for both comparisons) (Fig. 2). Also, G3 tumours were significantly larger compared with G2 ($p = 0.029$). There was a direct correlation between the TNM stage (1 to 4) and the grade (G1 to G3) ($r = 0.77$, 95% CI 0.68-0.84; $p < 0.0001$) and between the primary tumour size in mm and grade (G1 to G3) ($r = 0.63$, 95% CI 0.49-0.73; $p < 0.0001$).

### 3.2. Follow-up and Outcomes

The mean follow-up was of 40.7 months. During the period of observation 12 patients died: 10 were G3 and 2 were G2; 10 were stage 4 and 2 were stage 3; their median primary tumour size at diagnosis was 37.5 mm. During the same follow-up time, progression or recurrence of disease was recorded in 26 patients (26%). The 5-year overall survival estimate was 79.5% (see Fig. 3). The 5-year OS estimates for patients in stage I, II, III and IV were 96%, 100%, 77.8% and 41% respectively. The 5-year OS estimates for patients with G1, G2 and G3 tumours were 96%, 89% and 10% respectively. As far as regards progression-free survival, the 5-year PFS estimate was 65.2% (see Figure 4). The 5-year PFS estimates for patients in stage I, II, III and IV were 93%, 100%, 26.7% and 7.5% respectively. The 5-year survival rates for patients with G1, G2 and G3 tumours were 89.3%, 55.9% and 16.8% respectively.

As far as regards the 20 patients who were initially treated with surgery, 11 had positive nodes (N1) and 9 negative nodes (N0) at pathology examination. The mean disease-free survival (DFS) after surgery of the 11 N1 patients was 36.4 months compared to 60.7 months for the 9 N0 patients, with a significantly increased risk of recurrence (HR 8.7; 95% CI 2.3-32.4).

The ROC curve for OS with an area under the curve (AUC) of 0.702 identified a primary size of >12 mm as the optimal cut off for OS with a sensibility of 62.5 (95% CI 35.4-84.8), a specificity of 73.8% (95% CI 63.1 -82.8), a positive likelihood ratio of 2.11 and a negative likelihood ratio of 0.46. The ROC curve for PFS, with an AUC of 0.794, identified a primary size of >10 mm as the optimal cut off for PFS with a sensibility of 77.7 (95% CI 57.7-91.4), a specificity of 91.4 (95% CI 69.9-80.8), a positive likelihood ratio of 4.06 and a negative likelihood ratio of 0.27.

Factors associated with a reduced OS at Cox-regression analysis are shown in Table 2. At the multivariate analysis, independent predictors of worse OS were Stage IV of disease (HR 8.16; 95% CI 2.11-31.50; $p = 0.002$) and grade 3 lesion (ki67 > 5%) (HR 15.57; 95% CI 3.43-70.61; $p = 0.0004$), but not a primary tumour size> 12 mm. Similarly, independent predictors of worse PFS at the multivariate analysis (Table 3) were stage IV (HR 14.26; 9% CI 4.07-49.88; $p < 0.0001$) and grade 3 (HR 6.42; 95% CI 2.21-18.75; $p = 0.0007$), but not size and resection margins. In more detail, a positive resection margin (R1) was found in 20 cases, in 15 of them after endoscopic resection, with 6 of these 15 lesions being < 1 cm, and 14 of them being removed with snare polypectomy or endoscopic mucosal resection (EMR). We also separately analysed the Disease-free Survival (DFS) in 84 patients treated with surgery (20) or endoscopy (64) with an intention of radicality. In a multivariate logistic regression analysis, G3 (HR 5.5; 95% CI 1.3-22.7) and stage 4 (HR 10.3; 95% CI 2.6-40), but not R1 margins (HR 1.3; 95% CI 0.3-5.4) or size>10 mm (HR 1.3; 95% CI 0.3-5.5) were associated with the risk of recurrence in these 84 patients.

## 4. Discussion

The present study was aimed at evaluating the prognostic role of the ENETs staging and grading systems in predicting the clin-

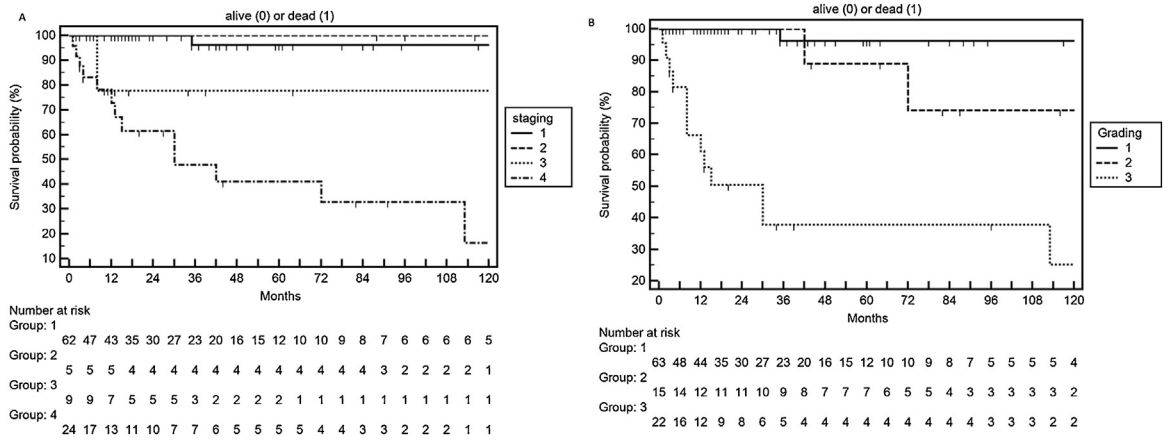


**Fig. 2.** Overall survival estimate according with primary rectal tumour stage (panel A) and grading (panel B).

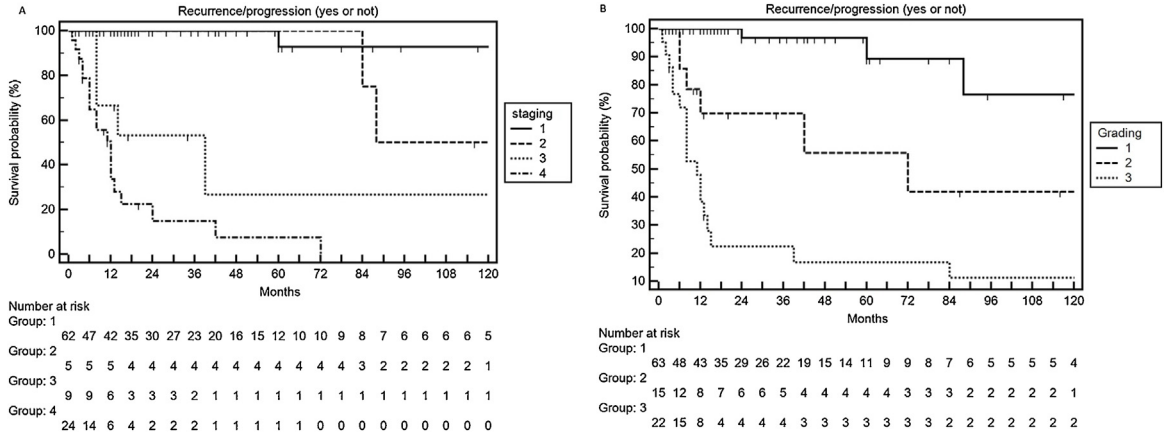


**Fig. 3.** Progression-free survival estimate according with primary rectal tumour stage (panel A) and grading (panel B).

**Table 2**
Cox-regression analysis of predictors of overall survival.

| Univariate | | | Multivariate | |
|---|---|---|---|---|
| | OR (95% CI) | p value | OR (95% CI) | p value |
| Initial multivariate analysis model | | | | |
| Age (per increasing year) | 1.01 (0.97-1.05) | 0.52 | - | - |
| Male Gender | 0.68 (0.25-1.88) | 0.46 | - | - |
| Size >12 mm | 2.85 (1.03-7.85) | 0.04 | 0.41 (0.12-1.31) | 0.13 |
| TNM Stage IV | 16.10 (4.61-56.24) | <0.0001 | 8.16 (2.11-31.50) | 0.002 |
| WHO G3 (Ki67>20%) | 18.79 (5.35-63.97) | <0.0001 | 15.57 (3.43-70.61) | 0.0004 |
| Ki67% (per increasing unit) | 1.03 (1.02-1.05) | <0.0001 | - | - |
| R1 resection | 2.02 (0.70-5.84) | 0.19 | - | - |
| Alternative multivariate analysis model with Ki67 as continuous variable | | | | |
| Size >12 mm | | | 0.76 (0.26-2.20) | 0.62 |
| TNM Stage IV | | | 8.46 (2.27-31.48) | 0.0015 |
| Ki67% (per increasing unit) | | | 1.03 (1.01-1.05) | 0.0002 |

ical behavior of rectal NENs in terms both of progression-free and overall survival. In this cohort of rectal NENs of all stages enrolled in 3 tertiary Centers, factors associated both with overall and progression-free survival were the presence of metastatic disease (stage IV) at diagnosis and the proliferative index as assessed by ki67% either as continuous variable or at high cut-off classifying the tumour as G3.

Rectal NENs are increasingly diagnosed, possibly due to increased use of colonoscopy for screening purpose. Hence, most studies on this tumour type are focused on small lesions treated endoscopically. Indeed, size is often considered a reliable predictor of tumour behavior. A recent evaluation of the SEER registry [14] evaluated 788 patients with rectal NENs < 2 cm and concluded that while tumours >1 cm have a small but not negligible risk of nodal metastasis, this risk is minimal in those <1 cm, thus suggesting that size is the most important prognostic factor, while grading was not evaluated. In our cohort, however, 26% of patients with stage IV disease at diagnosis had a primary tumour $\leq$ 10 mm (Fig. 1) and tumour size was not associated with prognosis (Tables 2 and 3). Similarly, 16% of G3 tumours had a primary tumour size <10 mm at diagnosis. The differences between the present results and those of previous studies might be due to the different included population. Shen and colleagues reported the outcome of 192 patients with colorectal NENs with findings suggesting that grading is more rel-

**Table 3**
Cox-regression analysis of predictors of progression-free survival.

| Univariate | | | Multivariate | |
|---|---|---|---|---|
| | OR (95% CI) | p value | OR (95% CI) | p value |
| Initial multivariate analysis model | | | | |
| Age (per increasing year) | 1.00 (0.98-1.03) | 0.52 | - | - |
| Male Gender | 0.99 (0.46-2.12) | 0.99 | - | - |
| Size > 10 mm | 5.96 (2.44-14.79) | 0.0001 | 1.39 (0.41-4.80) | 0.59 |
| TNM Stage IV | 20.04 (7.80-51.47) | <0.0003 | 14.26 (4.07-49.88) | <0.0001 |
| WHO G3 (ki67>5%) | 9.8 (4.38-21.91) | <0.0001 | 6.42 (2.21-18.75) | 0.0007 |
| Ki67 (per increasing unit) | 1.03 (1.02-1.04) | <0.0001 | - | - |
| R1 resection | 4.27 (1.80-10.12) | 0.001 | 1.75 (0.58-5.24) | 0.31 |
| Alternative multivariate analysis model with Ki67 as continuous variable | | | | |
| Size >10 mm | | | 1.69 (0.51-5.56) | 0.38 |
| TNM Stage IV | | | 15.94 (4.75-53.52) | 0<0001 |
| Ki67% (per increasing unit) | | | 1.02 (1.01-1.04) | 0.0004 |
| R1 resection | | | 2.25 (0.76-6.65) | 0.14 |

evant than staging in predicting the prognosis of such patients [9]. However, in that study patients with rectal and colonic primary tumour were pooled together, while these two sites are known to have a different clinical outcome, with colonic ones being far more aggressive [15]. Furthermore, in their series only 3% of all cases were diagnosed with Stage IV, which is the main reason for the reported poor reliability of staging. Our cohort is more homogeneously distributed across all disease stages, with about a quarter of patients with stage IV, as the patients were diagnosed or referred to tertiary Centers with specific expertise in NENs where not only patients with incidental diagnosis of small lesions, but also those with advanced disease could receive appropriate treatment. In another recent study by Weinstock and colleagues [12] the rate of patients with metastatic disease was 12%, and only 3% of cases had a G3 disease, thus limiting the possibility to evaluate the role of both staging and grading. Furthermore, information on the grade as assessed by Ki67 was missing in some 40% of cases and no data on recurrence-free survival were reported. To avoid that kind of bias, we included in the present study only patients for whom complete histologic information was obtained by pathologists with a specific expertise in NENs, and information on follow-up according with ENETs guidelines were available.

Another intriguing result of the present study regards the absence of prognostic significance of positive margins (R1) (Tables 2 and 3). Overall, a positive resection margin was found in 20 cases, in 15 of them after endoscopic resection. Notably, in 6 of these 15 cases the rectal lesions were < 1 cm, and in 14 of the 15 cases with R1 margins after endoscopic resection the polyp was removed with snare polypectomy or endoscopic mucosal resection (EMR), and only in 1 case by means of endoscopic submucosal dissection (ESD). These results are in line with previous reports on the superiority of ESD in this setting [16]. The common use of snare polypectomy in the present cohort is likely due to the relatively long time-span of the enrolment period, as ESD was less widely available in the first years of the study.

This study has some strengths, including the high number of cases with complete information and distribution across all stages and grades of disease and the record of recurrence or progression and not of survival only. Progression-free survival is considered an important surrogate marker of disease behaviour in the field of NENs where disease-related death is a relatively uncommon event, and it should be reported [17]. However, there are some limitations that need to be underlined. First, due to the retrospective nature and the relatively long time-span of enrolment, treatments, including endoscopic resection techniques, were not homogeneous and it is thus discussion on their effectiveness might be speculative. Also, these results were obtained in tertiary Centres and might not be generalizable in other settings.

In conclusion, the present results suggest that the specific staging and grading systems are able to predict PFS and OS in patients with rectal NENs, while size alone, even when the best-cut off is calculated, is a powerful prognostic tool, but should not be the only factor taken into account to plan treatment and follow-up strategy, as a quote of stage IV and G3 tumours present with small primary lesions.

Further prospective studies should be aimed at evaluating the real clinical significance of small rectal carcinoids that are incidentally detected, stratifying them depending on their grade, as it seems that even small lesions have potential to spread to distant sites.

## Conflict of interest

The authors have no conflicts of interest to disclose regarding this manuscript.

## Acknowledgment

GC receives research grant from the Associazione Italiana Ricerca sul Cancro, Italy (AIRC: IG 17177 GC).

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dld.2019.07.011.

## References

[1] Yao JC, Hassan M, Phan A, et al. One hundred years after 'carcinoid': epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the Unites States. J Clin Oncol 2008;26:3063–72.
[2] Dasari A, Shen C, Halperin D. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. JAMA Oncol 2017;3(October (10)):1335–42.
[3] Scherübl H. Rectal carcinoids are on the rise: early detection by screening endoscopy. Endoscopy 2009;41:162–5.
[4] Jung KS, Yun KE, Chang Y, et al. Risk Factors Associated with Rectal Neuroendocrine Tumors: A Cross-Sectional Study. Cancer Epidemiol Biomarkers Prev 2014;23:1406–13.
[5] Hauso O, Gustafsson BI, Kidd M, et al. Neuroendocrine tumor epidemiology: contrasting Norway and North America. Cancer 2008;113:2655–64.
[6] Rindi G, Klöppel G, Couvelard A, et al. TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. Virchows Arch 2007;451:757–62.
[7] Basuroy A, Haji A, Ramage JK, et al. Review article: the investigation and management of rectal neuroendocrine tumours. Aliment Pharmacol Ther 2016;44:332–45.
[8] Rindi G, Arnold R, Bosman F. Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: Bosman FT, Carneiro F, Hruban RH, editors. WHO classification of tumours of the digestive system. Lyon: IARC Press; 2010. p. 13–4.

[9] Shen C, Yin Y, Chen H, et al. Neuroendocrine tumors of colon and rectum: validation of clinical and prognostic values of the World Health Organization 2010 grading classifications and European Neuroendocrine Tumor Society staging systems. Oncotarget 2017;28(8):22123–34.
[10] Lee JL, Yu CS, Kim M, et al. Prognostic impact of diagnosing colorectal neuroendocrine carcinoma using the World Health Organization 2010 classification. Surgery 2014;155:650–8.
[11] Chi Y, Du F, Zhao H, et al. Characteristics and long-term prognosis of patients with rectal neuroendocrine tumors. World J Gastroenterol 2014;20:16252–7.
[12] Weinstock B, Ward SC, Harpaz N, Warner RR, Itzkowitz S, Kim MK. Clinical and prognostic features of rectal neuroendocrine tumors. Neuroendocrinology 2013;98:180–7.
[13] Ramage J, De Herder WW, Delle Fave G. Consensus guidelines update for colorectal neuroendocrine neoplasms (NEN). Neuroendocrinology 2016;103:139–43.
[14] Ngamruengphong S, Kamal A, Akshintala V, et al. Prevalence of Metastasis and Survival of 788 patients with T1 Rectal Carcinoid Tumors. Gastrointest Endosc 2019;89:602–6.
[15] Caplin M, Sundin A, Nillson, et al. ENETS Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Neoplasms: Colorectal Neuroendocrine Neoplasms. Neuroendocrinology 2012;95:88–97.
[16] Kaneko H, Hirasawa K, Koh R, et al. Treatment outcomes of endoscopic resection for rectal carcinoid tumors: an analysis of the resectability and long-term results from 46 consecutive cases. Scand J Gastroenterol 2016;51:1489–94.
[17] Ter-Minassian M, Zhang S, Brooks NV, et al. Association Between Tumor Progression Endpoints and Overall Survival in Patients with Advanced Neuroendocrine Tumors. Oncologist 2017;22:165–72.