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Tumour Review

Neuroendocrine neoplasms of rectum: A management update

Emilio Bertani[a,*], Davide Ravizza[b], Massimo Milione[c], Sara Massironi[d], Chiara Maria Grana[e], Dario Zerini[f], Alessandra Nella Piccioli[a], Giuseppe Spinoglio[a], Nicola Fazio[g]

[a] Division of Gastrointestinal Surgery, European Institute of Oncology, Milano, Italy
[b] Division of Endoscopy, European Institute of Oncology, Milano, Italy
[c] Department of Pathology and Laboratory Medicine, IRCCS Foundation National Cancer Institute, Milano, Italy
[d] Division of Gastroenterology, Ospedale Policlinico, Milano, Italy
[e] Division of Nuclear Medicine, European Institute of Oncology, Milano, Italy
[f] Division of Radiotherapy, European Institute of Oncology, Milano, Italy
[g] Division of Gastrointestinal Medical Oncology and Neuroendocrine Tumors, European Institute of Oncology, Milano, Italy

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ABSTRACT

The estimated annual incidence of R-NENs is 1.04 per 100,000 persons although the real incidence may be underestimated, as not all R-NEN are systematically reported in registers. Also the prevalence has increased substantially, reflecting the rising incidence and indolent nature of R-NENs, showing the highest prevalence increase among all site of origin of NENs. The size of the tumor reveals the behavior of R-NENs where the risk for metastatic spread increases for lesions > 10 mm. Applying the WHO 2010 grading system to whole NENs originating in the gastroenteropancreatic system, R-NENs are classified as Well-Differentiated Neuroendocrine Tumors (WD-NET), which contain NET G1 and NET G2, and Poorly-Differentiated Carcinomas (PD-NEC) enclosing only G3 neoplasms for which the term carcinoma is applied. The treatment is endoscopic resection in most cases: conventional polypectomy or endoscopic mucosal resection (EMR) for smaller lesions or endoscopic submucosal resection with a ligation device (ESMR-L), cap-assisted EMR (EMR-C) and endoscopic submucosal dissection (ESD). However it is important to know when the endoscopic treatment is not enough, and surgical treatment is indicated, or when the latter could be unnecessary. For PD-NECs, it has recently been demonstrated that chemoradiotherapy is associated with a similar long-term survival to that obtained with surgery. As well, new targeted-agents chemotherapy may be indicated for metastatic WD-NETs.

Introduction

Gastro-entero-pancreatic neuroendocrine neoplasms (GEP NENs) are heterogeneous malignancies, with significantly increased incidence and prevalence, as it has been well-documented over the last two decades [1–4]. Among all GEP NENs, rectal NEN (R-NENs) have exhibited the greatest increase in incidence in recent years. Even though there are conflicting data on the current prevalence and incidence of R-NENs, the major data emerging from both the US National Cancer Institute Surveillance, Epidemiology and End Results database (SEER) and national cancer registries in Western Europe, indicate that the greatest increase in incidence occurred for gastric and rectal NENs, while the smallest increase occurred for small intestine NENs [5]. A recent study from the Joint Cancer Registry showed that the small intestine was the most common site of GEP NEN with the largest absolute increase in incidence, although R-NEN exhibited the greatest relative increase [6]. Reflecting the rising incidence and indolent nature of R-NENs, also the prevalence increased substantially, showing the highest prevalence increase among all site of origin of NENs.

Methods

A literature search was conducted for original clinical studies and meta-analyses addressing the epidemiology, pathology, management, and prognostic factors of R-NENs using the MEDLINE database (from 2005) and relevant conference databases (from 2014). Search queries included the following terms: (neuroendocrine OR carcinoid) AND rectum OR hindgut. Abstracts of the last five years from major scientific congresses were also browsed. Guidelines from NEN international scientific societies and main oncological societies were also examined. Records were vetted to identify studies on epidemiology, pathology, treatment (in particular endoscopic treatment) and prognostic factors.

* Corresponding author at: Division of Gastrointestinal Surgery, European Institute of Oncology, Via G., Ripamonti, 43520141 Milano, Italy.
E-mail address: emilio.bertani@ieo.it (E. Bertani).

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Epidemiology

The rectum is the third most common site of gastrointestinal NENs [3]. Being 5.25/100.000 case/year the crude incidence of all GEP NENs estimated in the last decades, according to the last review of SEER, the estimated annual incidence of R-NENs is 1.04 per 100.000 persons [6]. However, the real incidence may be underestimated, as not all R-NENs are systematically reported in registers. Also the prevalence increased substantially, reflecting the rising incidence and indolent nature of R-NENs, showing the highest prevalence increase among all site of origin of NENs.

R-NENs are usually asymptomatic, even though they may be associated with rectal bleeding or change in bowel habits and pain [10].

With advances in diagnostic endoscopy, the detection of R-NENs has increased. Moreover, they are being increasingly identified possibly as a result of colorectal cancer screening programs. R-NENs represent 2% of all rectal neoplasia [11–14] and are reported in approximately 0.05%–0.07% of patients undergoing screening colonoscopy [15,16].

Screening colonoscopy lead to a shift to smaller-sized (< or = 13 mm) rectal carcinoids and earlier tumor stages at diagnosis. Accordingly, about 80% of rectal NENs are localized tumors < 1 cm in size that are very rarely accompanied with invasion or metastasis at the initial diagnosis. As a result, during the last 35 years, the overall 5-year survival of patients with rectal NENs has increased by almost 20% in the US [16].

The 5-year survival is estimated at 93% in patients presenting with localized disease and 86% overall [17].

R-NENs usually appear as solitary, yellowish, sessile, submucosal polypoid lesions (Fig. 1), whereas only rarely do they show irregular surfaces or are pedunculated or hyperemic or multiple [16–18]. As reported from a recent systematic review, approximately 80% of tumors are < 10 mm, 15% between 11 and 20 mm, and 5% > 20 mm and they are mainly localized to the submucosa [19].

Risk factors associated with rectal NENs are largely unexplored. They are difficult to identify because of the overall relatively low incidence rate of these tumors and the resulting difficulty in conducting large epidemiological studies. From a recent retrospective study [19], four factors were significantly associated with rectal NENs: higher levels of cholesterol [odds ratio (OR) = 1.007, p = 0.016], ferritin (OR = 1.502, p = 0.002), presence of metabolic syndrome (OR = 1.768, p = 0.026), and family history of cancer among first-degree relatives (OR = 1.664, p = 0.042).

Metastatic disease is infrequent (< 20%) with eight percent of patients presenting with regional lymph node metastases, and about 4% presenting with distant metastases. Tumor size > 10 mm, and muscular and lymphovascular invasion are independently associated with an increased risk of metastases [17,21]. Ki-67 labeling index and lymphatic/venous permeation were reported as independent risk factors for metastasis [22]. In their study, among several factors analyzed, Hyun et al. [23], suggested that in addition to the size, endoscopic atypical features were independent risk factors for lymph node metastasis.

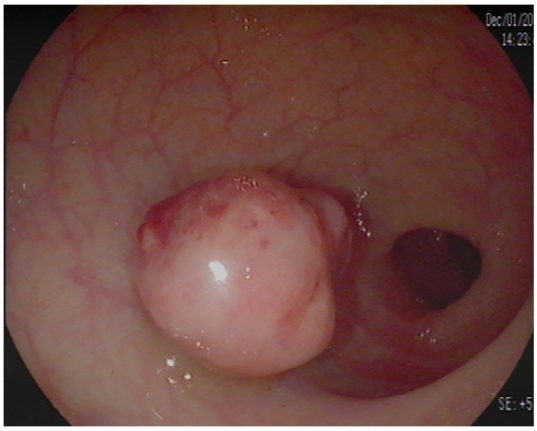

Fig. 1. Conventional endoscopic view showing a 15-mm polypoid type neuroendocrine tumor in the upper rectum.

However only few studies explored the long term clinical outcomes of endoscopically resected rectal NEN [23,24].

Rectal poorly-differentiated neuroendocrine carcinomas (R-PDNECs) represented 12% in a large series of poorly differentiated GEP NENs recently reported from the SEER database [25]. In this series for R-PDNECs median age at diagnosis was 64, stage at diagnosis was localized in 17%, regional in 25% and metastatic 57%. Finally, histotype was small cell in around 40% and large cell or other in the remaining 60% of R-PD-NECs.

Pathology

R-NENs are included into the WHO 2010 classification for GEP NENs, that comprises the following categories:

(1) Well-Differentiated Neuroendocrine Tumors (WD-NET), containing NET G1: mitoses < 2/10 HPF (High Power Field) and Ki-67 ≤ 2% and NET G2:mitoses 2-20/10 HPF and Ki-67 3–20%, tumors;
(2) Poorly-differentiated carcinomas (PD-NEC) enclosing only G3 neoplasms for which the term carcinoma is applied (NEC: mitoses > 20 HPF or Ki-67LI > 20%).
(3) Mixed adenoneuroendocrine carcinomas (MANECs)
(4) Hyperplastic lesions

(1) Rectal WD-NET (R-WD-NET) are frequently described at gross examination as being of 5 mm in maximum size, round, and without ulceration (Fig. 1). Of note, R-WD-NET was described as an incidental finding on prostatic needle core biopsy [18].

At morphological examination R-WD-NETs show: organoid architecture, ribbon or gyriform pattern, rare mucin secretion or anaplasia, absence of necrosis, neoplastic cells uniform for size, and abundant content of secretory granules responsible for intense and diffuse staining for general neuroendocrine markers (synaptophisin and chromogranins A-B). R-WD-NETs are very often constituted by L cells and so they express only Chromogranin B. Nuclear chromatin is regular with inconspicuous nucleoli, with no cell atypia. Mitoses are rare or uncommon. Among NETs originating in whole large bowel R-WD-NET is the most frequent with an annual incidence in the USA of 10 per million vs. 500 per million for adenocarcinoma [26]. R-WD-NET is rarely familial [27] its 5-year survival is 90% [15].

The following TNM items (Tables 1a and 1b), individually or considered together, are linked to lower survival: 2 cm in maximum size or

Table 1a
TNM classification of colorectal NETs.

T- Primary tumor
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
T1 Tumor invades lamina propria or submucosa and is no greater than 2 cm in size
T1a Tumor less than 1 cm in size
T1b Tumor 1–2 cm in size
T2 Tumor invades muscolaris propria or is greater than 2 cm in size
T3 Tumor invades subserosa, or non-peritonealized pericolic or perirectal tissues
T4 Tumor perforates peritoneum or invades other organs
N-Regional lymph nodes
NX Regional lymph nodes cannot be assessed
N0 No regional lymph-node metastasis
N1 Regional lymph-node metastasis
M- Distant metastasis
M0 No distant metastasis
M1 Distant metastasis

Adapted from Bosman et al. [41].