Short Communication

Rectal and anal canal neuroendocrine tumours

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Abstract: Neuroendocrine tumors (NETs) are rare, representing 0.5% of all newly diagnosed malignancies. Rectal and anal canal (AC) NETs account for less than 1% of all rectal and AC cancers. Review our institutional experience on NET of the rectum and AC, with emphasis on demographic, histological and treatment features and oncologic outcomes. The study group was identified from the Portuguese Regional South Oncological Registry. From 2000 to 2014, 22 patients with rectal or AC NETs were treated at our institution. Medical records were retrospectively reviewed. There were 12 males (54.5%) and 10 females (45.5%) and the median age at diagnosis was 59.5 years. The majority had rectal NET (81.8%). All 4 patients with AC NETs had neuroendocrine carcinoid (NEC) tumors. Of the patients with rectal NETs, 3 had NEC and 15 had NET, mainly G1. Different approaches to treatment were made according to histological and staging features. After an average follow-up of 39.1 months, 16 patients were alive and only one with evidence of disease. The median time to progression was 12.4 months and the liver was the most frequent site of metastasis. The European and North American Neuroendocrine Societies offer guidelines for the treatment of rectal NETs. However, for AC NETs there are only small series and not prospective studies due to their rarity, hence the importance to report institutional experience. Our practice demonstrated that primary excisional treatment, regardless the histology, provides a favorable prognosis and long survival.

Keywords: Neuroendocrine tumors (NETs); carcinoid tumor; rectum; anal canal (AC)

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Introduction

Neuroendocrine cells are present in a higher percentage in the gastrointestinal tract. Neuroendocrine tumors (NETs) are rare, representing about 0.5% of all newly diagnosed malignancies. Rectal (Rec) and anal canal (AC) NETs account for less than 1% of all Rec and AC cancers. The proportion of Rec NENs in Europe is less at 5–14% of all NETs (1-4). These tumors are often asymptomatic at diagnosis, being detected incidentally during routine lower gastrointestinal endoscopy. They present as small, sessile masses or thickened areas. The classic carcinoid symptoms occur in less than 10% of all patients and in most cases, requires hepatic metastatic disease (5). There are three histological groups: NETs, neuroendocrine carcinoid (NEC) tumors and mixed adenoneuroendocrine carcinoid tumors (MANEC). These are graded into three levels based on tumor cell proliferation: G1: Ki67 <3%; G2: Ki67 3–20%; G3: Ki67 >20%. NETs have well-differentiated with low cellular atypia—G1 or G2—and express neuroendocrine markers—chromogranin A, synaptophysin—and hormones. On the other hand, NEC is a poorly differentiated, high-grade malignant tumor with marked cellular atypia, frequent necrosis and high proliferative activity—G3 (6). The prognostic factors for metastatic disease are tumor size, depth on invasion and lymph node involvement (1,6,7).

Materials and methods

The study group was identified from the Portuguese Regional South Oncological Registry. From 2000 to 2014 twenty-two patients were identified with Rec and

AC NETs treated at our institution. Medical records were retrospectively reviewed. Demographic, histological treatment features and oncologic outcomes were analyzed. The staging was based on the World Health Organization (WHO) and the 2012 European Neuroendocrine Tumour Society (ENETS) proposal (7). It was studied the use of endoscopic and surgical procedures, conventional laparoscopic surgery and the use of chemotherapy (CT) and radiotherapy (RT).

Statistical analysis

Due to the low incidence and fewness of these tumors, it was made a descriptive analysis and survivals outcomes, although without any statistical significance. It was utilized the IBM SPSS Statistics® software version 20.

Results

Twenty-two patients were identified and treated at our institution over a period of fifteen years [2000–2014], 54.5% were males and 45.5% females, with a median age at diagnosis of 59 years (range, 34–89 years). Most patients had Rec tumors (81.8%), although all AC were NEC tumors. The histological and staging features are categorized on *Table 1*.

Patients with NEC tumors were treated with RT alone, simultaneous CT and RT followed by endoscopic excisional treatment, transanal excision, abdominoperineal (APR)/anterior rectum resection (ARR) when an R1 disease was present, ARR alone or Best Supportive Care. Patients with NETs were mostly treated with a resection approach either endoscopic or surgical.

According to our results (*Figure 1A*), patients with

Table 1 Demographic, histological, clinical and treatment characteristics

Variable	NETs (G1&G2)		NECs (G3)	
	N (relative %)	Total %	N (relative %)	Total %
All patients	14	63.6	8	36.4
Age, median (years)	57.5 [34–80]		70 [50–89]	
Gender				
Women	7 (50.0)	31.8	3 (37.5)	13.6
Men	7 (50.0)	31.8	5 (62.5)	22.7
Stage				
I	10 (71.4)	45.5	4 (50.0)	18.2
II	0	–	1 (12.5)	4.5
III	1 (7.1)	4.5	2 (25.0)	9.1
IV	3 (21.4)	13.6	1 (12.5)	4.5
Primary site				
Rectum	14 (100.0)	63.6	4 (50.0)	18.2
Anal canal	–	–	4 (50.0)	18.2
Treatment				
Endoscopic excision	6 (42.9)	27.3	2 (12.5)	9.1
Surgical excision	5 (35.7)	22.7	3 (37.5)*	13.6
Transanal excision	–	–	1 (12.5)	4.5
CT alone	1 (7.1)	4.5	1 (12.5)	4.5
RT alone	2 (14.3)	9.1	1 (12.5)	4.5
Simultaneous CT&RT	–	–	2 (25.0)	9.1
BSC	–	–	1 (12.5)	4.5

*, these three patients underwent to surgical excision as a secondary treatment, one after simultaneous CT & RT and the other two due to positive margins after the initial excisional approach. NET, neuroendocrine tumor; NEC, neuroendocrine carcinoid; CT, chemotherapy; RT, radiotherapy; BSC, best supportive care.

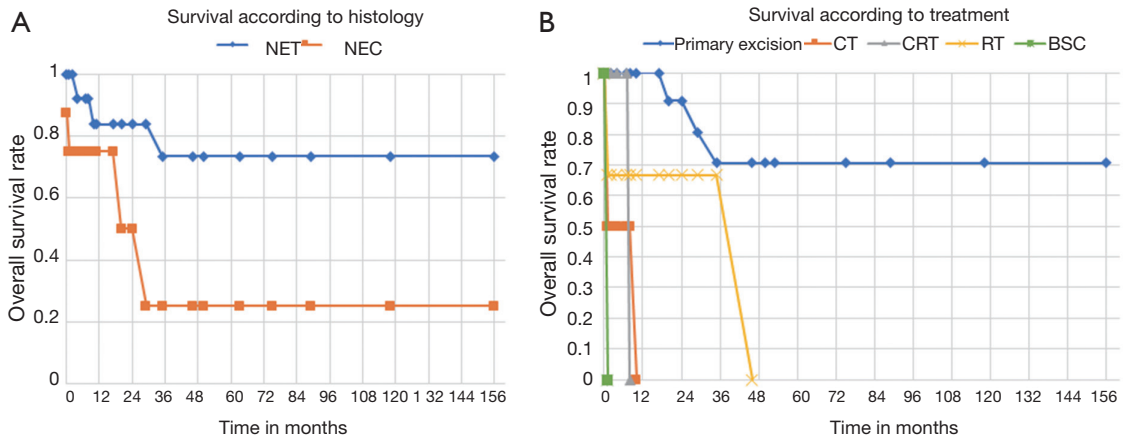

Figure 1 Survival analysis: (A) overall survival curves in patients with neuroendocrine tumor (NET) or neuroendocrine carcinoma (NEC); (B) overall survival curves according to the treatment that they underwent—primary excision, chemotherapy (CT), simultaneous chemotherapy and radiotherapy (CRT), radiotherapy (RT) or best supportive care (BSC).

NEC tend to have a poorer prognosis and lower survival, although we couldn't identify significant differences between histology (P=0.67). Patients with primary excision as initial treatment (*Figure 1B*), had longer overall survival (P<0.05). The median time to progression was 12.4 months and the most frequent site of metastasis was the liver. For metastatic disease, the core treatment was CT although with poor response.

Discussion

Even though our cohort has a small number of cases it is important to emphasize Rec and AC NECs account for less than 0.1% of all colorectal malignancies and they are consistently poorly differentiated and associated with a poor prognosis (1-4). Our results show that NECs tend to have lower overall survival when compared with NETs and surgical or endoscopic tumor removal has a major impact on overall survival (*Figure 1B*), regardless the histological characteristics.

The risk of metastatic disease of NETs increases with tumour size—2% when <1 cm, 10–15% 1–2 cm, 60–80% ≥2 cm—with no involvement of the *muscularis propria* (8). This reiterates the importance of endoscopy ultrasonography for proper staging in tumors have <2 cm. NETs are often localized—75–85%—and rarely have distant metastasis at diagnosis—2–8%. The management of metastatic NETs, in this case, Rec NETs, experience shows that these are often very aggressive. There are two approved drugs to be applied in this setting, lanreotide, and everolimus (8,9). Some phase II studies also show some evidence of activity for VEGF inhibitors (10).

In locoregional NECs, emerging data suggest that chemoradiation without surgery may be sufficient, although still controversial. This is an important consideration given that a radical surgery, such as APR, maybe required. In the scope of metastatic disease, second line regimens after platinum based therapy are unclear.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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