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REVIEW

Pathologic research update of colorectal neuroendocrine tumors

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Abstract

Colorectal neuroendocrine tumors (NETs) originate from neuroendocrine cells in the intestinal tract, and represent a small area within oncology, but one which has provided increasing new data during the past years. Although the World Health Organization has determined clinical and histological features to predict prognosis for such tumors, they may not be valid on an individual basis. We aim to give an overview of the recent findings with regard to pathology, molecular genetics and diagnosis of NETs.

Key words: Neuroendocrine tumors; Carcinoid; Colorectal; World Health Organization classification; Tumor-node-metastases

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INTRODUCTION

Neuroendocrine (NE) cells are distributed throughout the human body, including the gastrointestinal (GI) tract, pancreas, lung, thyroid, adrenal gland and many other organs[1-4]. The GI tract has the largest population of NE cells[5]. However, neuroendocrine tumors (NETs) of the colon and rectum are rare. Results from analyses of the Surveillance, Epidemiology and End Results database demonstrated that the age-adjusted incidence of carcinoids of the small intestine and digestive system has increased by 460% and 720%, respectively, in the past 30 years due to, at least in part, the improvements in diagnostic technology such as endoscopy, as well as doctors' increased awareness[6]. In 2003, Modlin *et al*[7] reported that the incidence of NETs in the GI tract was 2.5-5 cases per 100 000 population annually. Males are more often affected than females, with a proportion of 1.8:1[8]. In the large intestine, NETs are more commonly found in the rectum (54%), then in the cecum (20%), sigmoid colon (7.5%), rectosigmoid colon (5.5%) and ascending colon (5%)[9].

Colon NETs usually appear as large tumors and often already have regional lymph nodes or liver metastasis at the time of diagnosis, therefore the prognosis is poor. On the other hand, NETs occurring in the rectum are often diagnosed incidentally during colonoscopy, therefore they are typically small, localized, non-functioning tumors with rare metastasis, probably as a result of early detection[6,8,10,11].

CLASSIFICATION

Colorectal NETs are traditionally classified as typical

Table 1 Classification of NETs of the colon and rectum[14,15]

Well-differentiated neuroendocrine tumor (carcinoid)
Benign: Non-functioning, confined to mucosa-submucosa, non-angioinvasive, < 1 cm in size (ileum) or ≤ 2 cm colon and rectum
Serotonin-producing tumor
Enteroglucagon-producing tumor
Benign or low-grade malignant (uncertain malignant potential): non-functioning, confined to mucosa-submucosa, angioinvasion, or < 1 cm in size (ileum) or ≤ 2 cm colon and rectum
Serotonin-producing tumor
Enteroglucagon-producing tumor
Well-differentiated neuroendocrine carcinoma (malignant carcinoid)
Low-grade malignant: invasion of the muscularis propria and beyond or metastases
Non-functioning or functioning serotonin-producing carcinoma (with carcinoid syndrome)
Non-functioning enteroglucagon-producing carcinoma
Poorly-differentiated neuroendocrine carcinoma
High-grade malignant

NETs: Neuroendocrine tumors.

carcinoid, atypical carcinoid and undifferentiated cancer according to the differentiation of the disease[12,13]. The term carcinoid can no longer characterize the entire morphologic and biologic spectrum of neoplasms of the disseminated NE cell system. The updated World Health Organization (WHO) classification of 2000 adopted the neutral and inclusive terms, tumor and carcinoma. In this classification, it is clearly explained how to characterize well-differentiated NETs (benign behavior or uncertain malignant potential), well-differentiated NE carcinoma (low-grade malignancy), and poorly-differentiated NE carcinoma of high-grade malignancy [small cell carcinomas (SCCs)][14,15]. The morphologic/biologic criteria including tumor size, angioinvasion, proliferative activity, histological differentiation, metastasis, invasion, and hormonal activity (association with clinical syndromes or diseases) have also been added (Table 1).

Well-differentiated NE tumor was referred to as typical carcinoid historically, and well-differentiated NE carcinomas were termed atypical carcinoid. Although this framework is helpful, lesions of uncertain behavior are poorly defined. In the WHO classification, SCC is synonymous with the term "poorly-differentiated NE carcinoma", but there is no clear differentiation between large cell NE carcinomas (LCNECs) and mixed endocrine-glandular neoplasms. No coincident repeat diagnosis could be made by different pathologists or by different institutions, although the WHO classification of colorectal NETs has been used for several years. The main reason is that the WHO classification has not been closely adhered to[1]. Pathological recognition of these tumors is critical, as the treatment strategy, particularly chemotherapy for a particular subtype, largely depends on the underlying pathology[16,17].

Well-differentiated NE tumor-carcinoid

Colorectal carcinoids account for approximately 6% of all GI NETs, often accompanied by chronic inflammatory disease such as ulcerative colitis or Crohn's disease. The tumors are usually multiple when complicated by these diseases[18]. In Crohn's disease, the incidence of carcinoids may increase, by a recent estimation of 15-fold[19,20]. In most instances, colorectal carcinoids present without obvious signs or symptoms and remain undetectable for years[8]. Most of the diagnoses are made incidentally at the time of surgery for other abdominal disorders. Their relatively high incidence in large autopsy series has provided evidence for this observation[21].

The tumors with NE differentiation have classical histological architecture of trabecular, insular, or ribbon-like cell clusters, and have no or minimal cellular pleomorphism and sparse mitoses[8,22,23]. Colorectal carcinoids display moderate neurofilament staining. They stain positive for chromogranin A (CgA) in more than 70% of cases, positive for neuron specific enolase (NSE) in more than 50% of cases, and prostatic acid phosphatase is expressed in 80%-100% of cases. However, the staining pattern is variable[8]. Other markers such as synaptophysin (Syn), somatostatin, 5-HT, or CD56 may be present as well. The Ki-67 index is higher in carcinoids of a size more than 5 mm, as compared to those sized less than 5 mm in diameter[24].

Rectal carcinoids are usually discovered incidentally during colonoscopy examinations. The tumors are usually small, non-functional and without regional or distant metastasis[25,26]. The 5-year overall survival rate of patients with rectal carcinoids is 88%. However, the prognosis of colon carcinoids is worse than that of its rectal counterpart[8,10,26,27]. There are data showing that there is a high frequency of combined adenocarcinoma and NETs in the proximal colon[28,29]. Perhaps this is one of the reasons explaining the worse prognosis in colon carcinoids than for their rectal counterpart.

Well-differentiated NE carcinoma-malignant carcinoid

Malignant carcinoid was termed as atypical carcinoid, historically. Only a few cases have been reported as malignant carcinoid of the large intestine due to uncertainty of its definition.

Well-differentiated NE carcinomas have histological features and a biological behavior that fall between well-differentiated NE tumors and poorly-differentiated NE carcinomas[8]. These are aggressive lesions and represent forms poorly differentiated from carcinoid with increased mitotic activity and presence of necrosis. Mitoses range from 1 to 10/10 high power field (hpf). The presence of necrosis serves as an important character of malignant carcinoid[8,30,31]. The cells range in appearance from uniform, large, polygonal, or fusiform types with abundant eosinophilic granular cytoplasm and round to oval nuclei similar to the cells seen in typical carcinoid, to pleomorphic cells with scanty cytoplasm and hyperchromatic variably sized and shaped nuclei[32]. The tumors are nonargentaffinic but strongly argyrophilic and they are

stained with the usual immunohistochemical markers of NE cell differentiation.

There are few reports of the clinical outcome of colorectal malignant carcinoids. It has been reported, however, that a patient with an atypical carcinoid of the lung has a significantly worse prognosis than those with typical carcinoids[33,34].

Poorly-differentiated NE carcinoma (small cell carcinoma)

Colorectal SCCs constitute 0.2%-0.8% of all colorectal tumors, mostly located in the right colon[1,35]. They are clinically aggressive; therefore have extremely poor prognosis, even when diagnosed at an early stage. Most patients present with overt distant metastases. Sometimes they are discovered in the background of colon inflammatory diseases, or in the background of NE cell proliferation[36,37].

Colorectal SCCs are identical to lung SCCs morphologically. These small blue cell tumors present the character of densely packed, small, and oval-, spindle-, fusiform-shaped anaplastic cells with minimal amounts of cytoplasm and granular nuclear chromatin. The size of the nuclei measures approximately twice the size of mature lymphocytes[38]. Solid sheets, nests, and rosettes as well as ribbon-like structures composed of small cells and intermediate cells form, which all exhibit more than 10/10 hpf mitoses[1].

In cases with classic histological features, it is unnecessary to demonstrate NE differentiation to establish the diagnosis. However, further analysis may be necessary in puzzling cases. SCCs typically express CgA, Syn, NSE, and CD56 by immunohistochemistry. Pan cytokeratin (AE1/AE3) and low molecular weight keratin are also reported to be positive in all SCCs[1,39]. Shida *et al*[40] reported that 70% of GI SCCs expressed human achaete-scute homologue gene-1 protein (hASH1), which is usually absent in normal GI NE cells, carcinoid and adenocarcinoma. The sensibility and specificity of hASH1 is better than other classic markers, such as CgA and Syn, and this protein may serve as a new biomarker for GI SCC diagnosis. There are also some reports demonstrating that cytokeratin is positive in these tumors and the Ki-67 index beyond 75% is often seen in SCCs[1].

As mentioned above, the prognosis of patients with GI SCCs is usually extremely poor. Most patients present with regional or overt distant metastases. Up to 80% of patients already have regional lymph nodes and/or distant metastases at the time of diagnosis[41]. When tumor size is larger than 5 cm, the median survival time for patients is usually less than 4 mo, and the median survival of those with smaller tumor is around 12 mo[1].

LCNEC

LCNECs are rare, poorly-differentiated NE carcinomas. LCNECs are amongst the worst studied group of colorectal NETs and their diagnostic criteria are briefly described in many standard texts[14]. The features of these tumors are similar to their counterpart in the lung[42]. They are malignant neoplasms composed of large cells structured in organoid, nested, trabecular, rosette-like, and palisading patterns that suggest NE differentiation. Compared to SCCs, LCNECs have more cytoplasm, nuclei are more vesicular, and nucleoli are prominent[42]. Focal necrosis is often observed. These tumors exist alone or associated with adjacent adenomas or conventional adenocarcinomas[43]. LCNECs are defined through both NE morphology and immunohistochemical positivity of NE markers.

CK20 is expressed in colorectal LCNECs; a generally acknowledged marker in adenocarcinoma which is rarely found in other NETs[44,45]. This phenomenon may indicate that there is some relationship between LCNECs and adenocarcinomas.

LCNECs have a similar prognosis to colorectal SCCs. Kumarasinghe *et al*[46] suggested that LCNECs should be included in the poorly-differentiated NE carcinoma category based on their poor prognosis.

Mixed endocrine-glandular neoplasm

Mixed endocrine-glandular neoplasms constitute a heterogeneous group of rare neoplasms. These tumors are composed of at least two distinct tumor populations, with the NE part containing at least 30% of obviously endocrine cells[14,47,48]. The degree of NE cell differentiation varies between tumors and between different tumor areas. The most common component is carcinoid, while poorly-differentiated NE type also exists, and another component can be adenocarcinoma or squamous carcinoma[14,15,49]. The NE component is usually well-differentiated, and easily recognized by its suggestive histological features; the NE nature of the tumor cells can be verified by the immunodetection of specific NE markers (such as CgA and Syn). Especially when the NE component is poorly differentiated, the demonstration of NE markers to confirm the diagnosis is needed[50]. More often, the diagnosis cannot be made until the tumors are stained with NE cell markers when the endocrine cells are inconspicuous and the quantity present is not obvious[1].

Because of their rarity and unusual presentation, the optimal strategy of management of mixed endocrine tumors is largely unknown. The more aggressive component of the mixed endocrine tumors must be taken into account when considering their treatment. Mixed tumors containing a well-differentiated NE component and an adenocarcinoma component are suggested to be treated as adenocarcinoma. Mixed tumors containing a poorly-differentiated NE component must be treated as poorly-differentiated NE carcinomas[50]. Some researchers report mixed NETs as having worse prognosis, thus the ascertainment of the NE component is important to predict the prognosis[48].

MOLECULAR GENETICS OF COLORECTAL NETs

The molecular mechanisms of NET tumorigenesis are

Table 2 Proposed staging system for rectal and colon NETs[62,63]

	Rectal	Colon
Depth of invasion and size		
T1	Up to and into muscularis propria, ≤ 1 cm	Any depth of invasion, ≤ 1 cm
	Up to muscularis propria, > 1 to ≤ 2 cm	Up to or including muscularis propria, > 1 to ≤ 4 cm
T2	Beyond muscularis propria, ≤ 1 cm	Beyond muscularis propria, > 1 to ≤ 4 cm
	Into muscularis propria, > 1 to ≤ 2 cm	Up to or including muscularis propria, > 4 cm
	Up to and into muscularis propria, > 2 cm	
T3	Invasion beyond muscularis propria, > 1 cm	Beyond muscularis propria, > 4 cm
Lymph node		
N0	No lymph node metastasis	
N1	Regional lymph node metastasis	
Distant metastasis		
M0	No distant metastasis	
M1	Distant metastasis	
Stage		
Ⅰ	T1; N0; M0	
Ⅱ	T1; N1; M0 or T2; Any N; M0	
Ⅲ	T3; N0; M0 or T3; N1; M0	
Ⅳ	Any T; Any N; M1	

unclear; however, these aspects have been focused on in many recent reports[51]. Increased knowledge of the molecular background for the development of NETs may improve the management of these tumors in the future. A number of genetic syndromes including multiple endocrine neoplasia syndrome-type 1 (MEN1), vov Hippel-Lindau syndrome, and neurofibromatosis-type 1 may be associated with intestinal NETs[8,52]. Some studies have demonstrated neither classic oncogenes (*scr*, *ras*, *myc*, *fos*, *jun*) nor suppressor genes (*P53*, *RB*) present in NETs[52,53]. However, there are reports of other gene site deletions. For example, *PDCD4* was found to be absent in NETs; this is a gene which is interrelated with cell proliferation, located at 11q13 close to *MEN1*[54].

The microsatellite instability (MSI) caused by mismatch repair (MMR) damage is an important cause of tumorigenesis in hereditary nonpolyposis colorectal cancer (HNPCC)[55-58]. Stelow *et al*[59] discovered the loss of *MMR* genes in colorectal SCCs, but not along with HNPCC. The chromosome instability caused by the loss of MMR genes possibly follows a different pathway from MSI in SCC tumorigenesis. Arnold *et al*[60] studied 34 poorly-differentiated colorectal NETs, 38 well-differentiated benign or malignant fore-/midgut NETs, and 150 sporadic colorectal cancers with known MSI status and found that 20/34 (59%) colorectal NETs *vs* 11/38 (29%) fore-/midgut NETs were CpG island methylator phenotype (CIMP) positive. The Ki-67 index was significantly higher in poorly-differentiated colorectal NETs compared with the less malignant fore-/mid-gut NETs. However the CIMP status did not correlate with survival.

Research in NET molecular genetics should target early detection, prognosis predicting, or treatment selection. Currently, new technologies should be used to find new sensitive and specific biochemical and tissue markers for colorectal NETs.

PROPOSED TNM STAGE AND RISK FACTORS

NETs are a challenging group of diseases, and the lack of a widely accepted staging system limits the clinician's ability to provide meaningful prognostic information to the patients. In October 2009, the 7th edition of the AJCC for the first time gave a detailed TNM description for NETs, classifying primary tumor (T), regional lymph nodes (N), and distant metastasis (M), respectively. However, no clarified TNM staging has been established for colon and rectal NETs[61].

In 2008, Landry *et al*[62,63] proposed a different staging system from that of conventional colorectal adenocarcinomas in the study of 4710 rectal NETs and 2459 colon NETs (Table 2). In their report[62], it was revealed that rectal NETs were the only primary malignancy in 82% of patients, 17% patients had one additional malignancy and 1% had two or more additional malignancies. The mean and median sizes of primary tumor were 1 and 0.6 cm, respectively. About 4.1% had regional lymph node metastases, and 2.4% presented with distant metastases at the time of diagnosis. The 5-year survival rates for patients with stages Ⅰ and Ⅱ disease were 97% and 84%, respectively. The 5-year survival rate for stage Ⅲ patients was 27% with a median survival time of 45 mo. The 5-year survival rate for stage Ⅳ patients was 20% with a median survival time of 31 mo. The 10-year survival rates of the disease for stages Ⅰ through Ⅳ were 91%, 56%, 14%, and 2.5%, respectively.

In another study[63] of colon NETs, the researchers demonstrated that there were regional lymph node metastases in 48% of patients, and distant metastases in 24% of patients at the time of diagnosis. The 5-year survival rates for stages Ⅰ and Ⅱ were 97% and 69%, respectively. Similarly, the 5-year survival rate for stage Ⅲ disease was 21%, with a median survival time of 27 mo.

The 5-year survival rate for stage Ⅳ disease was 17%, with a median survival time of 20 mo. The 10-year survival rates for stages Ⅰ through Ⅳ were 92%, 47%, 15%, and 5.4%, respectively.

Some studies have suggested some risk factors of colorectal NETs related to poor outcome, such as tumor size, depth of wall penetration, presence of lymphatic or venous invasion, and mitotic rate of metastasis in colorectal NETs[64-69]. The tumor size is related to prognosis. Most rectal NETs are less than 1 cm at the time of diagnosis[70,71]. The malignancy rate increases when the tumor grows larger than 1 cm. However, for small-sized tumors less than 1 cm at detection with predominant submucosal invasion there is usually a relatively high incidence of distant metastasis, about 1.7%-3.4%[71,72]. Some reports have shown that cancer-specific survival of patients with colorectal NETs without metastasis was better than that of those with adenocarcinomas. However, the survival rate is similar between carcinoid and adenocarcinoma if the tumors have lymph node or distant metastases[65]. On the other hand, colorectal NE carcinomas behave aggressively and are associated with a worse prognosis than that of conventional colorectal adenocarcinomas of the same stage[16,39].

CONCLUSION

The complexity, heterogeneity and scarcity of NETs, rare colorectal neoplasia, account for almost no improvement of survival rates in the past 30 years. The diagnosis for colorectal NETs mostly depends on pathology with the aid of immunohistochemistry. As we have summarized here, the 2000 WHO classification of colorectal NETs provides a solid basis for localization, biology and prognosis of individual NETs, but there are still some types of tumors not properly described. More studies will be needed with regard to diagnosis, treatment and prognosis.

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