Hindgut Neuroendocrine Neoplasia

James D. Smith¹ · Govind Nandakumar²

Received: 18 May 2015 / Accepted: 13 October 2015 / Published online: 26 October 2015
© Indian Association of Surgical Oncology 2015

Abstract Neuroendocrine neoplasias (NENs) consist of a spectrum of tumors which can originate throughout the body, behave in a variety of different ways but are characterized by a similar histological appearance. This article reviews the classification, staging, diagnosis and treatment of Hindgut Neuroendocrine Neoplasias.

Keywords Hindgut · Neuroendocrine · Carcinoid · Rectum · Colon

Introduction

Neuroendocrine neoplasias (NENs) consist of a spectrum of tumors which can originate throughout the body, behave in a variety of different ways but are characterized by a similar histological appearance.[1] They are thought to originate from enterochromaffin cells however recent genetic studies have postulated, particularly in the case of high grade neuroendocrine carcinomas (NEC) they may be a transformation of poorly differentiated carcinomas.[2] They are of a group of “small blue cell tumors,” consisting of uniform cells which have a round to oval stippled nucleus and scant, pink granular cytoplasm. The cells may align variously in islands, glands or sheets and high power examination shows bland cytopathology. They are

characterized immunohistochemically by staining for chromogranins & synaptophysin.[3] The cells of NEN often contain special secretory granules which produce biogenic amines and polypeptide hormones. This leads to these tumors being associated with symptoms corresponding to the secretory amines & hormones. [4]

The most common site for NEN is the gastrointestinal tract and pancreas (GEP). Grossly GEP NENs are often small, yellow or tan masses, frequently located in the submucosa or more deeply intramurally. They can be very firm due to an accompanying intense desmoplastic reaction. As they are often located intramurally, the overlying mucosa may be either intact or ulcerated. GEP NENs are classically divided along the embryological origins of the GI tract, foregut, midgut and hindgut; corresponding to the arterial supply to the respective portion of the GI tract. For the purposes of this review we will concentrate on hindgut neuroendocrine neoplasia which includes tumors located in the left colon, rectum and anus.

Classification & Staging

GEP NEN classification and staging has changed significantly in the past decade. The traditionally used terms such as carcinoid, atypical carcinoid and small/large cell carcinoma have been superseded by the terms well differentiated neuroendocrine tumors (NET) and poorly differentiated neuroendocrine carcinomas (NEC). This differentiates between the slow growing neuroendocrine tumors (previously called carcinoids) with the more aggressive neuroendocrine cancers (small or large cell carcinomas). The cut off between the 2 tumor types has been defined by both the World Health Organization (WHO) and the European Neuroendocrine Tumor Society. This has been identified as a Ki 67 staining on immunohistochemistry of greater than 20 % or a mitotic index within the tumor of 20 mitoses per

✉ Govind Nandakumar
doctorgovind@gmail.com

¹ Surgery Weill Cornell Medical College, 525 East 68th Street, New York, NY 10021, USA

² Courtesy Faculty at Weill Cornell Medical College, 20 Ali Asker Road, 560052 Bangalore, India

10 high powered fields (HPF). Within the well differentiated NET, there is a sub-classification between low grade NET (Ki67 index <3 % or 2 mitoses per 10 HPF) and intermediated grade NET (Ki67 index 3–20 or 2–20 mitoses per 10 HPF).[5, 6] (Fig. 1)

As WDNET and HGNEC behave differently there are staged as difference diseases. The more common WDNET can be staged with the TNM system however there are 2 widely used classifications that can be used the American Joint Committee on Cancer (AJCC) and European Neuroendocrine Tumor Society staging systems. They only differ slightly and have been shown to demonstrate no difference with respect to prognostic value.[7] (Table 1) As HGNECs behave in a more aggressive fashion they are staged according to the AJCC staging system for colorectal cancer. Unfortunately HGNEC generally presents with metastatic disease.[8] As WDNET and HGNEC behave in very different ways with differing prognosis and treatment they will be dealt with separately for purposes of this paper.

Hind Gut Well Differentiated Neuroendocrine Tumors (WDNET)

Diagnosis

The majority of hindgut WDNETs are diagnosed incidentally on colonoscopy and are located mainly in the rectum. With the increasing use of screening colonoscopy the incidence is also increasing. Along with HGNEC they account for approximately 1 % of hindgut tumors. They tend to be small at presentation. Generally located submucosally, they can ulcerate and present with rectal bleeding or hematochezia. Potentially if the tumor becomes large they may develop symptoms of mass effect such as tenesmus or altered bowel habits. Hindgut WDNET tend not to secrete amines or hormones and as such do not present with paraneoplastic effects. As the majority of hindgut tumors present incidentally they tend to be small with less than 10 % having metastatic disease.[9]

Once a diagnosis of WDNET has been made pathologically, local staging of rectal can be achieved using EndoRectal

Ultrasound (ERUS) or Magnetic Resonance Imaging (MRI) of the pelvis. The purpose of these investigations is to identify the size of the tumor and to assess regional lymph nodes. Distant staging can be obtained by Computerized Tomography (CT) of the abdomen, pelvis and chest. Somatostatin receptor scintigraphy (octreotide scanning) has been described to look for distant disease however a good quality CT or MRI scanning with contrast is just as beneficial in identifying metastatic disease. [10] As lymph node and metastatic disease for rectal WDNET less than 1 cm is rare distant staging is often not necessary. For left colon WDNET local staging with MRI pelvis or ERUS is not beneficial and CT is the most beneficial staging investigation. All patients should have chromogranin A levels checked at baseline as these can be used as a tumor marker for response to treatment and as a marker for recurrence. Hindgut WDNETs rarely secrete serotonin and as such assessment of Urine 5-HIAA can be considered but is not necessary.[11]

Management

The primary treatment for localized rectal WDNETs is resection with negative margins. When the tumor is less than 1 cm in diameter the incidence of lymph node metastases is rare and local excision of the tumor with negative margins is acceptable. This can be achieved endoscopically either by polypectomy, endoscopic mucosal resection or endoscopic submucosal dissection.[12] If this is not possible the tumors can be removed surgically via the anal canal either by Trans-Anal Excision (TAE), Transanal Endoscopic MicroSurgery (TEMs) of Trans-Anal Minimally Invasive Surgery (TAMIS). For tumors that are greater than 2 cm patients should undergo a rectal resection with a Total Mesorectal Excision (TME) either by anterior resection or abdomino-perineal resection. Tumors between 1 and 2 cms have been traditionally treated by local excision, however recent evidence suggest that tumor size greater than 1 cm along with lympho-vascular invasion and involvement of the muscularis propria is associated with tumor metastases and recurrence.[13, 14] Consideration for rectal resection with TME should therefore be given for tumors between 1–2 cms, particularly if other adverse features

Fig. 1 Pathological classification of hindgut neuroendocrine neoplasia

Table 1 The American Joint Committee on Cancer (AJCC) and European Neuroendocrine Tumor Society staging systems for well differentiated neuroendocrine tumors

AJCC					ENETS				
Stage	Primary Tumor (T)				T-Primary Tumor				
Tx	Primary tumor cannot be assessed				Primary tumor cannot be assessed				
T0	No evidence of primary tumor				No evidence of primary tumor				
T1	Tumor invades lamina propria or submucosa and size ≤ 2 cm				Tumor invades mucosa or submucosa				
T1a	Tumor size <1 cm in greatest dimension				Size <1 cm				
T1b	Tumor size 1–2 cm in greatest dimension				Size 1–2 cm				
T2	Tumor invades muscularis propria or size >2 cm with invasion of lamina propria or submucosa				Tumor invades muscularis propria of size >2 cm				
T3	Tumor invades through muscularis propria into subserosa or into nonperitonealized pericolic or perirectal tissue				Tumor invades subserosa/pericolic/perirectal fat				
T4	Tumor invades peritonum or other organs				Tumor directly invades other organs/structures and/or perforates visceral peritonum				
	Regional Lymph Nodes (N)				Regional Lymph Nodes				
NX	Regional lymph nodes cannot be assessed				Regional lymph nodes cannot be assessed				
N0	No regional lymph node metastases				No regional lymph node metastases				
N1	Regional lymph node metastases				Regional lymph node metastases				
	Distant Metastases (M)				M-Distant Metastases (Subspecifications as in Small Bowel)				
M0	No Distant Metastases				No Distant Metastases				
M1	Distant Metastases				Distant Metastases				
Stage	T	N	M		Stage	T	N	M	
I	T1	N0	M0		IA	T1a	N0	M0	
IIA	T2	N0	M0		IB	T1b	N0	M0	
IIB	T3	N0	M0		IIA	T2	N0	M0	
IIIA	T3	N0	M0		IIB	T3	N0	M0	
IIIB	AnyT	N1	M0		IIIA	T4	N0	M0	
IV	AnyT	AnyT	M1		IIIB	AnyT	N1	M0	
					IV	AnyT	AnyT	M1	

such as LVI, muscularis involvement or intermediate NET are present.[15]

For left colon WDNET, as these tumors are rare, there is little evidence to identify patients that are LN negative and therefore could be excised endoscopically. Again if the tumor can be removed by polypectomy or EMR with negative margins and is less than 1 cm this would seem a reasonable treatment option. If the margins are positive, the tumor is greater than 1 cm or there are high risk features such as intermediate grade NET or LVI, a standard left hemi-colectomy should be performed according to oncologic principles.[15]

Patients with hindgut WDNET rarely present distant metastatic disease with series reporting the incidence ranging between 5 and 10 %. (Table 2) The size of the tumor is the greatest factor associated with metastatic disease.[12] As metastatic hindgut WNET tumors are rare treatment is extrapolated from metastatic disease of the more common midgut and foregut metastatic WDNET. The most common site of metastatic disease is the liver with other sites including the lung and retroperitoneal lymph nodes.[15] Surgical resection can be considered for sites of respectable disease however recurrence

rates are high.[15] The mainstay of systemic treatment is somatostatin analogues such as octreotide both for limiting progression of disease and in the management of the symptoms of carcinoid syndrome. Surgical debulking of metastatic disease can also be considered for cases of severe carcinoid syndrome. Other liver directed therapies such as radio-frequency ablation and hepatic arterial embolization of the blood supply to the tumor may also offer some treatment benefit. Systemic cytotoxic chemotherapy has not shown to be of any benefit in metastatic WDNET outside of pancreatic WDNETs.[11] Peptide receptor radionuclide therapy using radiolabeled somatostatin analogs has shown some benefit in metastatic unresectable WDNET however is not currently offered in the US outside of clinical trials.[20]

Prognosis & Follow up

As most hindgut WDNET present as localized disease the prognosis is excellent with 5 year survival rates over 90 %. (Table 3) As recurrence are infrequent, particularly in tumors less than 1 cm in diameter an argument can be made for no

Table 2 Published reports of Hindgut WDNETs

Paper	Percentage Rectal WDNET	Number of cases	LN positive <10 mm	LN positive 1–2 cm	LN positive >2 cm	Percentage Stage 1 on presentation	5 year Survival
Lee et al. [16]	97.3 %	514	1.95 %	23.5 %	50 %	93.8 %	N/A
Lin et al. [17]	90 %	63	0%	10 %	53 %	79.4 %	92.1 %
Yoon et al. [18]	100 %	203	1.7 %	15 %	50 %	93.6 %	94 %
Gleeson et al. [12]	100 %	87	3 %	66 %	73 %	N/A	60 %
Kang et al. [9]	73.7 %	2565	N/A	N/A	N/A	80.7 %	91.3 %
Landry et al. [13]	100 %	4086	1 %	26 %	54 %	83 %	N/A
Shields et al. [19]	100 %	202	8 %	31 %	59 %	73 %	100 %
McDermott et al. [14]	100 %	4575	2.07 %	N/A	N/A	89 %	86 %

N/A not available

follow up at all.[15] For those lesions greater than 1 cm follow up can consist of yearly cross sectional imaging with either CT or MRI. Colonoscopy 1 year after resection with a further colonoscopy 4 years later would also seem to be a reasonable follow up protocol. Checking chromogranin A levels can be considered particularly if they were elevated pre-operatively. [11]

The prognosis for patients presenting with metastatic hindgut WDNETs is better than that for metastatic hindgut adenocarcinoma. Although rarely curable WDNET are slow growing and as such patients often live with the disease for some time. The reported 5 year survival rates for metastatic disease range from 17 to 20 %.[13, 24]

High Grade Neuroendocrine Carcinomas

Compared to WDNET, HGNEC is essentially an entirely different disease. It occurs much less frequently however behaves much more aggressively much more like the pulmonary equivalent, small cell carcinoma.[8] It more commonly presents as metastatic disease particularly in the colon as local symptoms are not as apparent. Hindgut HGNECs present in the same manner as adenocarcinomas with rectal bleeding, change of bowel habit and tenesmus being the most common symptoms.[22] Diagnosis is again made by colonoscopy and biopsy. Often HGNEC can occur in conjunction with colorectal adenocarcinomas. Where <1/3 of the tumor is adenocarcinoma, this is considered a HGNEC, where <1/3 is neuroendocrine it is considered an adenocarcinoma and where there

are similar amounts of both histological variants they are classified as a collision tumor.[25] There is some evidence that collision tumors, particularly if localized have an improved prognosis.[22] Histologically HGNEC can also be either the small cell type or large cell type with some reports that large cell HGNEC may have a better prognosis.[23]

Staging for localized and metastatic disease is the same as that for colorectal adenocarcinoma. CT chest abdomen and pelvis should be performed for distant staging. The most common sites of metastases are liver and lung. Local staging of rectal HGNEC can be performed using pelvic MRI or endorectal ultrasound. There is no role for octreotide scanning or checking for serum chromogranin A levels in HGNEC. HGNEC are PET avid however this modality may only offer benefit over CT scanning for indeterminate lesions.[8]

Management

The management of HGNEC follows more closely that of adenocarcinoma rather than that of HGNEC. For localized disease, even with radical surgical resection, recurrence is common and as such adjuvant or neoadjuvant systemic chemotherapy should be used. For localized colon HGNEC surgical resection followed by adjuvant chemotherapy should be performed. For rectal HGNEC, similar to rectal adenocarcinomas, management should start with neoadjuvant chemoradiotherapy as HGNEC appear to be radiosensitive.[22] As these tumors have a high systemic recurrence consideration should be given to follow on with systemic chemotherapy without

Table 3 Published reports of hindgut HGNECs

Study	Percentage Rectal HGNEC	Number of cases	Percentage metastatic disease	Median survival
Aytac et al. [21]	64 %	25	36 %	15 months
Smith et al. [22]	48 %	128	67 %	13.2 months
Shafqat et al. [23]	27 %	1367	58 %	7.1 months

surgery, particularly if there is a good response to radiotherapy. The reason for this is surgery; particularly major surgery like a rectal resection may delay systemic treatment, which is the patients' best way of preventing systemic recurrence. In fact although the numbers are small in the largest series of colorectal HGNEC, resection of colorectal HGNEC did not appear to influence survival.[22]

As hindgut HGNEC are uncommon with evidence limited to case series, chemotherapeutic treatment are derived from the management of the more frequent pulmonary HGNEC. Platinum based chemotherapy is therefore the treatment of choice. Published regimens include cisplatin with etoposide or irinotecan.[8] The most significant prognostic feature for localized disease appears to be an adenocarcinoma component included with the tumor (collision tumor). In this scenario the standard adjuvant treatment for colorectal cancer, 5-fluorouracil with oxaliplatin (FOLFOX) can be used as oxaliplatin has been shown to have a response in HGNEC also.[22]

For metastatic disease, unlike in adenocarcinoma, surgical resection does not appear to offer any survival benefit.[22] Surgical management should therefore be reserved for emergency situations such as obstruction or bleeding. The optimal surgical option should be one which leads to the patient starting systemic chemotherapy as soon as possible, such as a diverting ostomy or colonic stent in the case of obstruction. Response to chemotherapy has been shown to be the most significant prognostic factor in this disease. Again platinum based chemotherapy is the treatment of choice.[8]

Prognosis

The prognosis for patients with HGNEC is extremely poor in both localized and metastatic disease. The median survival has been reported as 10 months for metastatic disease and 27 months for localized disease. The most significant prognostic factor in metastatic disease is response to chemotherapy and the presence of a collision tumor. [22]

Follow up for patients with localized disease after resection and adjuvant treatment again is the same as that for adenocarcinoma and consists of yearly CTs with a colonoscopy at 1 year.

Conclusion

Hindgut neuroendocrine neoplasia consists of a spectrum of diseases from the benign acting rectal WDNET to the highly aggressive rapidly fatal metastatic HGNEC. Tumor grade is the key distinguishing factor with management and prognosis dependent on this.

References

1. Yang Z, Tang LH, Klimstra DS (2013) Gastroenteropancreatic neuroendocrine neoplasms: historical context and current issues. *Semin Diagn Pathol* 30(3):186–196
2. Karkouche R et al (2012) Colorectal neuroendocrine carcinomas and adenocarcinomas share oncogenic pathways. A clinicopathologic study of 12 cases. *Eur J Gastroenterol Hepatol* 24(12):1430–1437
3. Klimstra DS et al (2010) Pathology reporting of neuroendocrine tumors: application of the Delphic consensus process to the development of a minimum pathology data set. *Am J Surg Pathol* 34(3):300–313
4. Kamp K et al (2014) Parathyroid hormone-related peptide (PTHrP) secretion by gastroenteropancreatic neuroendocrine tumors (GEP-NETs): clinical features, diagnosis, management, and follow-up. *J Clin Endocrinol Metab* 99(9):3060–3069
5. Rindi G et al (2007) TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* 451(4):757–762
6. Klimstra DS et al (2010) The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. *Pancreas* 39(6):707–712
7. Chagpar R et al (2013) Neuroendocrine tumors of the colon and rectum: prognostic relevance and comparative performance of current staging systems. *Ann Surg Oncol* 20(4):1170–1178
8. Smith J, Reidy-Lagunes D (2013) The management of extrapulmonary poorly differentiated (high-grade) neuroendocrine carcinomas. *Semin Oncol* 40(1):100–108
9. Kang H et al (2007) Rare tumors of the colon and rectum: a national review. *Int J Colorectal Dis* 22(2):183–189
10. Reidy-Lagunes DL, Gollub MJ, Saltz LB (2011) Addition of octreotide functional imaging to cross-sectional computed tomography or magnetic resonance imaging for the detection of neuroendocrine tumors: added value or an anachronism? *J Clin Oncol* 29(3):e74–e75
11. Kunz PL et al (2013) Consensus guidelines for the management and treatment of neuroendocrine tumors. *Pancreas* 42(4):557–577
12. Gleeson FC et al (2014) Endoscopically identified well-differentiated rectal carcinoid tumors: impact of tumor size on the natural history and outcomes. *Gastrointest Endosc* 80(1):144–151
13. Landry CS et al (2008) A proposed staging system for rectal carcinoid tumors based on an analysis of 4701 patients. *Surgery* 144(3):460–466
14. McDermott FD et al (2014) Rectal carcinoids: a systematic review. *Surg Endosc* 28(7):2020–2026
15. Anthony LB et al (2010) The NANETS consensus guidelines for the diagnosis and management of gastrointestinal neuroendocrine tumors (nets): well-differentiated nets of the distal colon and rectum. *Pancreas* 39(6):767–774
16. Colonoscopy Study Group of Korean Society of, C (2011) Clinical characteristics of colorectal carcinoid tumors. *J Korean Soc Coloproctol* 27(1):17–20
17. Lin HH et al (2014) Clinicopathological analysis of colorectal carcinoid tumors and patient outcomes. *World J Surg Oncol* 12:366
18. Yoon SN et al (2010) Clinicopathological characteristics of rectal carcinoids. *Int J Colorectal Dis* 25(9):1087–1092
19. Shields CJ et al (2010) Carcinoid tumors of the rectum: a multi-institutional international collaboration. *Ann Surg* 252(5):750–755
20. Bison SM et al (2014) Peptide receptor radionuclide therapy using radiolabeled somatostatin analogs: focus on future developments. *Clin Transl Imaging* 2:55–66
21. Aytac E, Ozdemir Y, Ozuner G (2014) Long term outcomes of neuroendocrine carcinomas (high-grade neuroendocrine tumors) of the colon, rectum, and anal canal. *J Visc Surg* 151(1):3–7

22. Smith JD et al (2014) A retrospective review of 126 high-grade neuroendocrine carcinomas of the colon and rectum. *Ann Surg Oncol* 21(9):2956–2962
23. Shafqat H et al (2015) Survival of patients with neuroendocrine carcinoma of the colon and rectum: a population-based analysis. *Dis Colon Rectum* 58(3):294–303
24. Landry CS et al (2008) Proposed staging system for colon carcinoid tumors based on an analysis of 2,459 patients. *J Am Coll Surg* 207(6):874–881
25. Shia J et al (2008) Is non-small cell type high-grade neuroendocrine carcinoma of the tubular gastrointestinal tract a distinct disease entity? *Am J Surg Pathol* 32(5):719–731