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Colorectal neuroendocrine neoplasms : areas of unmet need

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Colorectal Neuroendocrine Neoplasms – areas of unmet need

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Running Title | Unmet needs in colorectal NENs

Introduction

The subject of colorectal neuroendocrine neoplasms (NENs), subdivided into welldifferentiated NENs, termed neuroendocrine tumours (NETs; grade (G) 1 and 2), and poorlydifferentiated NENs, termed neuroendocrine carcinomas (NECs; G3) according to the 2010 World Health Organisation (WHO) classification, has arguably not had as much attention or study as NENs occurring in other sites. Colorectal NETs and NECs are however easier to study than many others since they are usually not difficult to remove and are increasingly detected because of intensified colorectal cancer screening and surveillance programs. Colorectal NETs and NECs show site-specific heterogeneity with variable behaviour and different therapeutic options; these various aspects provide unique challenges. Because of bowel cancer screening programs, colorectal NENs, like conventional adenocarcinomas, may be diagnosed at a stage that is associated with improved survival.

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In this article we intend to describe and define areas of unmet needs relating to the epidemiology, classification, pathology, diagnosis and therapy of colorectal NETs (including NETs G3), colorectal NECs, and finally, mixed adeno-neuroendocrine carcinomas (MANECs) by reviewing and discussing the relevant literature.

Epidemiology

In the most recent analysis of the Surveillance, Epidemiology, and End Results (SEER) Program [1] there has been an ongoing increase in NENs overall over the past 30 years. As to the rectal NENs this increase particularly concerns rectal NETs, while the proportion of patients with rectal NECs remains stable. There has also been a marked increase in caecal NECs (doubling over the past 10 years) although colonic NECs remain at a stable level.

Rectal NETs

1. Epidemiology:

Rectal NETs have been reviewed extensively in the literature recently [2][3] with data that does not needing repeating but it is noted that the incidence of rectal NET is rising and is higher in certain ethnic groups. These tumours are unlike any other NETs in that they are usually small, low-grade and can often be completely removed at endoscopy.

2. Molecular pathology

High immunohistochemical PROX1 expression was found to be associated with increased metastatic potential of rectal NETs, and CIMP (CpG island methylator phenotype) positivity as well as miR-885 expression seem to be related to lymphovascular invasion. [4][5] Specific expression of Notch homolog 1 (NOTCH-1) has been shown for rectal NETs (in 100%) and global gene expression of ISL, (Islet-1 transcription factor), LIM homeobox-1, cathepsin-B, glucagon, and tryptophan hydroxylase-1 genes differs in comparison with small intestinal NETs. [6]

The finding of neuroendocrine cells within an existing adenoma removed from the colon is well described [7], and the presence of the NET is associated with a more aggressive behaviour of the adenoma with increased beta-catenin nuclear staining. This is distinct from a mixed adeno-neuroendocrine carcinoma (MANEC) – see below. It is not clear why the presence of NET in the adenoma should be related to the adenoma-carcinoma sequence and this needs further investigation.

3. Diagnosis

Rectal NET Imaging

Many patients diagnosed with colorectal NETs do not require radiological or nuclear medicine imaging because the tumour is resected as a small polyp (<5mm), at the time of colonoscopy, when the tumour is at a very early stage. For those with a primary rectal NET, the cross-sectional imaging protocol would be similar to that in patients with rectal cancer.

Primary tumour staging is performed with magnetic resonance imaging (MRI), which is standard practice for T stage but may not be so accurate for N stage [2,8], although some centres prefer rectal ultrasound to assess the relation of the tumour to the different layers of the bowel wall. [9] The diagnosis of perirectal lymph node metastases may be difficult because of the limited penetration of the ultrasound which is insufficient to examine the whole extent of the perirectal space. Rectal MRI generally also includes contrast-enhanced imaging of the liver for detection of metastases.

Rectal G1 and G2 NETs, and sometimes also rectal NECs, show somatostatin receptor expression and are therefore suitable for somatostatin receptor imaging that should be performed by ⁶⁸Gallium (Ga)-DOTA-somatostatin analogue-positron emission tomography (PET)/computerised tomography (CT) rather than by somatostatin receptor scintigraphy because of the better spatial resolution and image contrast of PET. Preferably the CT performed at the time of the PET/CT is performed as a fully diagnostic CT, including intravenous contrast-enhancement. In general functional imaging as above would only be performed in cases where MRI/CT shows invasion of muscle layer, node or metastatic spread or in high-risk cases (G2/G3 and larger tumours).

Rectal NET Endoscopy -

Rectal NETs are often diagnosed endoscopically and, in the past, biopsy results have been needed before the diagnosis is suspected. More recently they can be suspected on their appearances at endoscopy with the advantage that a plan can be made for endoscopic resection at the first procedure. Rectal NETs appear as small yellowish, waxy-looking sessile or submucosal polyps and when they enlarge to 1cm they often have a depressed central area. Suspecting a NET can prevent some inappropriate resections that have been attempted in the past. Since local excision of a small rectal NET is often also the definitive and final treatment, endoscopic resection should be best performed radically. Knowledge of the difference between NETs and other lesions will allow careful planning of the resection, increasing the chance of radical resections. Unfortunately no statement was made on NET in the performance statements for endoscopists. [10]This emphasises that education of endoscopists about the possibility of NET is going to be important.

Training in lesion recognition of other lesions (e.g. Paris and Kudo classification of adenomatous polyps [11]) is well-advanced but recognition of a NET is in its infancy. In this

regard members of ENETS have proposed a training programme in NET recognition for colonoscopists, and such a development has started. Training for colonoscopists in NET recognition was recently started in the Netherlands. Based on patient histories combined with endoscopic images a self-directed training website was initiated. Questions and discussions concerning the preferred endoscopic approach were included. The pilot with this material was recently concluded and currently the training website is undergoing improvements before going online in the Netherlands. The most important feedback from the pilot was that more links were needed to existing guidelines and more images to improve recognition of NET lesions. The intention is that this, or a similar system, should be available in all countries.

Unmet need I Endoscopic training programmes should include NET recognition module

4. Treatment of localized disease

In general grade G1 NETs of the rectum measuring less than 10mm can be removed by local excision, but there continue to be isolated reports of some of these small tumours with invasion into the muscle layer and with lymph node (LN) metastases. [12] At 5mm and less, it is generally accepted that they are removed endoscopically and no recurrence occurs. From 10-20mm many can be removed endoscopically, but increasing numbers of cases with LN and distant metastases are reported. Attempts have been made to develop an algorithm including grade, size and lymphovascular (LV) invasion to predict LN and distant metastases but this has not been validated in a large cohort.

There is therefore uncertainty about the optimal management of rectal NETs measuring more than 5mm, and the tests required to exclude pathologically-enlarged pelvic LN are unclear. Currently ENETS guidelines suggest that all patients with rectal NETs undergo some investigation including those less than 5mm. [13][14] Kojima et al. suggest a cut-off of 1cm together with absence of LN invasion; others have taken 5mm as a cut-off. Imaging specifics are shown below.

Surgery vs endoscopic therapy for rectal NETs:

There are an increasing number of ways of removing these tumours, particularly when small. These include snare polypectomy, endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), Cap-assisted EMR, transanal endoscopic microsurgery (TEMS), and other newer techniques such as transanal minimally invasive surgery [15] for total mesorectal excision (TAMIS-TME). The exact role of these techniques in different grades and stages of rectal NETs remains to be defined. In particular there is interest in the fact that R1 resections (resections with an excision margin <1mm) can be performed but recurrence in many of these cases does not occur within the first 5 years of follow-up. [16][17–21] It is therefore hard to know if repeat resection is needed, or whether an observation protocol will suffice.

There is also a need to define indications for surgical resection strictly according to optimized outcome, particularly for G3-NECs. Whereas surgery contributed to improved outcome in non G3-NEC patients, it failed in G3 patients. [22][23] A few studies demonstrated that multimodal and neoadjuvant approaches might be beneficial for this specific group of patients. [24][25]

Unmet need I Define indications for surgical resection according to whether there is evidence for improved outcome, particularly for G3-NEC.

Unmet need II Define optimum follow up for R1 endoscopic resection cases.

Unmet need III Define algorithm for most appropriate therapy for 10-20mm NET.

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5. Treatment of advanced disease

Targeted drugs and chemotherapy unmet needs for advanced rectal NET are essentially the same as colonic NET and are discussed below.

Peptide Receptor Radionuclide Therapy (PRRT) for rectal NETs:

Patients with disseminated disease and high tumour somatostatin receptor expression (defined as greater or equal to uptake in the liver by somatostatin receptor scintigraphy) are generally suitable for peptide receptor radiotherapy (PRRT), which has shown favourable activity in small groups of patients. In 23 patients with TNM stage IV rectal NETs who

received 2 to 13 cycles with 7.4 GBq of ¹⁷⁷Lutetium (Lu)-DOTA-octreotate the median overall survival was 58 months (mean 46, range 9-98 months) after the start of PRRT. No patient achieved a radiological complete response (CR) in first line (0/9%), but after subsequent surgery / external beam radiation 2 patients had a CR; partial responses (PR) were observed in 13/23 patients (57%); stable disease (SD) in 6/23 (26%) and 2/23 (9%) patients progressed during therapy (PD). [26]

Colonic NETs

- 1 Epidemiology/pathology. Well-differentiated colonic NENs (i.e. colonic NETs) are extremely rare and outnumbered by poorly-differentiated NENs (i.e. colonic NECs). It is not clear if caecal NETs belong in the same category as colonic NET, or whether they are part of midgut NETs (as per the original classification accord to embryonic origin).
- **2 Diagnosis**: Most colonic NETs are diagnosed at colonoscopy and biopsy with staging by axial imaging and functional status by PET (FDG and Gallium Dotatate).

3 Treatment of localised disease:

Endoscopic resection of more proximal colonic NETs has rarely been described [27] with surgical resection being the main therapy. The finding of neuroendocrine hyperplasia within random colonic biopsies is described, and particularly the "microcarcinoids" found in inflammatory bowel disease [28][29] which are not thought to be aggressive and might be a response to inflammation.

4 Treatment of advanced disease:

PRRT

A subgroup of 16 patients with "hindgut" NETs out of a total of 1214 patients in the whole study [30] who were treated with ¹⁷⁷Lu-DOTA-octreotate up to a cumulative intended dose of 27.8–29.6 GBq achieved 0 (0%) CR, 4 (33%) PR, 6 (50%) SD, 1 (8%) PD and one patient was not evaluable. The median progression-free survival and median time to progression were both 29 months and overall survival was not reached.

Targeted therapies

Everolimus now has a European licence for treating GEPNET which includes Colorectal NET. The evidence in this group is not strong but the data on colorectal NET from the RADIANT-2 study was published [31] indicating an improved PFS due to everolimus in a small group of 39 patients.

In the RADIANT-4 trial [32] only 12% (25 patients) had a rectal NET and 2% (5) were colonic. Overall, there was an improved PFS in non-midgut NET, but this includes stomach, colon and rectum. There is an indication that mTOR inhibition is of benefit in colorectal NET but further evidence should be gathered in randomised trials. Post marketing surveillance of this group of patients will be important and this is an unmet need.

Somatostatin Receptor Agonists (SSRA) in colonic NET: in patients whose disease is SSRSpositive, treatment with SSRA is usually adopted. There is a lack of randomised data with only 16 colorectal NET patients randomised in the CLARINET Study. It seems unlikely that randomised trials will now be done but collection of data and response rates in postmarketing (phase 4) trials should be considered.

Unmet need I phase 4 data of colonic NET therapy with everolimus and SSRA.

Unmet need II define whether caecal NET should be classified with midgut or with colonic NET.

Colorectal NENs G3 (including NET and NEC)

1 Classification

According to the 2010 WHO classification, NENs that are poorly-differentiated and called NECs, have, until recently, been synonymous with a grade 3, defined by a Ki67 index >20%. A subgroup of patients with G3 NENs, however, were found to have retained a well-differentiated morphology, and these NENs appear to be biologically different in terms of their natural clinical behaviour, prognosis, uptake on peptide receptor imaging and response to chemotherapy from NECs. [33] In the study by Heetfield, [34] panNET G3 patients were likely to live longer (even though they did not respond as well to platinum etoposide chemotherapy with a 2% response rate). Of note however, these tumours are infrequent. In the colorectal group there were 0 and 3 patients with colonic and rectal NET G3, respectively (compared to 52 patients with colorectal NECs). Although the NEN classification and grading has only been updated for pancreatic NENs and not yet for colorectal NENs, it is already now

recommended to consider separately colorectal patients with NET G3 (Ki67 >20%) from patients with poorly-differentiated NEC G3. [35]

Unmet need | to clearly stratify colorectal NEN G3 patients into NET G3 and NEC patients

2 Treatment

Up to 85% of patients have metastases at the time of diagnosis (65% with distant metastases); therefore most patients are managed with systemic chemotherapy. Level 1 data are limited and most currently-used regimens are adopted from (small cell) pulmonary NECs. Studies of chemotherapy are not exclusive to patients with colorectal NECs, since most studies are of extra-pulmonary NECs with colorectal patients representing a subgroup (reviewed in Garcia-Carbonero). [36] In summary, platinum (cisplatin or carboplatin) and etoposide chemotherapy is the cornerstone of first-line chemotherapy achieving relatively high response rates (mean 45%; range 14%-75%) although the median OS is poor; approximately 1 year (range 6-23 months). Patients invariably relapse after first-line chemotherapy; a number of second-line regimens have been used based on retrospective series and small prospective studies (including FOLFOX (5-fluorouracil [5-FU] and oxaliplatin), FOLFIRI (5-fluorouracil and irinotecan), temozolomide +/- capecitabine). None is considered a standard regimen due to lack of level 1 evidence.

To illustrate this, in a large multicentre study [34] a total of 204 patients with grade 3 neuroendocrine neoplasms were identified; 25% of these were NEC of colonic (n=31) or rectal (n=21) origin. The median Ki67 in the NEC patients was 80% (range 25-100%). Only a minority (12%) of patients with NECs presented with non-metastatic disease; the median OS in all NEC patients was 17 months. The disease control rate (PR and SD) was 68% and median PFS 5.0 months with platinum/etoposide chemotherapy. Second- and third-line chemotherapy was given to 79 (48%) and 39 (23%) of patients with NECs, respectively; this was predominantly FOLFIRI or FOLFOX. Efficacy of such treatment was very modest (with response rates of 16% and 10%; and median PFS and OS 3.0 and 7.6 months in second line and 2.5 and 6.2 months in third line, respectively).

There were 82 of the 305 patients (27%) with colorectal primary tumours in the NORDIC NEC study [37] (colon n=61, rectal n=21); the median PFS and OS was 3 months (95%-Cl 2.1–3.9) and 8 months (95%-Cl 6.0–9.9), and 4 months (95%-Cl 3.1–4.9) and 10 months (95%-Cl 7.9–

12.1) for colon and rectal NECs, respectively. Overall 100 patients, received second-line chemotherapy (temozolomide-based or docetaxel-containing regimens). The response rate after first-line chemotherapy (all patients) was 31%; this reduced to 18% after second-line chemotherapy (in 84 evaluable patients).

An interesting observation from the NORDIC NEC study was the difference in radiological response rate between patients with a Ki67 of <55% (15%) compared with patients with a Ki- $67 \ge 55\%$ (42%, p<0.001). Conversely, patients with a lower Ki67 (<55%) had a better overall survival (14 versus 10 months, p<0.001) suggesting that these may constitute different patient populations. Of note, all patients in this study were selected by having G3 NENs, although a proportion of patients, especially with Ki67 <55% may have had well-differentiated tumours with a proliferation rate >20% and thus would fall in the new category of NET G3 patients. The median survival for all patients receiving chemotherapy was 11 months (95% confidence interval 9.4-12.6 months).

Unmet need | need to improve efficacy of first line treatment; identifying ways to induce durable responses which translate into improved overall survival.

Unmet need | need to identify new effective systemic therapy regimens post failure of platinum etoposide chemotherapy for advanced disease.

Unmet need | need to identify and validate biomarkers to select patient most likely (or unlikely) to benefit from systemic therapy.

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MANEC

1 Definition and pathology

Mixed adenoneuroendocrine carcinomas (MANECs) of the gastrointestinal tract are defined as heterogeneous neoplasms showing, according to the current 2010 WHO classification, exocrine and neuroendocrine components, each component corresponding to at least 30% of the whole tumour cell population. [38] The cells of these components either form monodifferentiated complexes that combine with each other in a collision/mosaic pattern or are intimately combined/intermingled and may even show amphicrine features. In the colon the two components usually display high grade malignant features, both adenocarcinoma and neuroendocrine carcinoma, and only occasionally may exhibit low grade malignant

ownloaded by: /ashington University 28.252.67.66 - 9/19/2018 8:57:09 AM features. [39,40] Publications report that their prognosis is worse than that of colonic adenocarcinomas. [41] In the near future MANECs may be called MiNENs, since this term has now been introduced in the recent new WHO classification of PanNENs and will probably also be used in the forthcoming 5th edition of the WHO classification of digestive tumors.

MANECs are particularly common in the colon. Recent publications broadened our knowledge on their immunoprofile, [39] and most importantly on their genetic features [42,43] and clinical course. [41] There is a need to get more insight into their site-specific distribution and relative frequency, their clinical presentation and behaviour, their mutational profiles regarding targeted therapies, and their response patterns to therapies. There is also a need for pathologists to clearly clarify a distinction between MANEC and presence of a small component of NE cells (<30% of tumour cell population) in conventional colonic adenocarcinomas. The distinction between NEC, MANEC and conventional adenocarcinoma (ADC) with a NE-cell component remains difficult in some cases because their definition is not well determined. Moreover, the NE staining can be detected in adenocarcinoma (ADC) without any characteristics of NE morphology such as rosettes, ribbons, cords or trabeculae. The staining pattern of NE markers also varies from case to case. Indeed, the NE staining can be diffuse (this has been reported to be more frequent in poorly-differentiated ADC, [44] or positive only in part of the tumour or in scattered cells. Suresh et al reported, in a retrospective series of colonic adenocarcinomas in which they performed a systematic immunostaining with synaptophysin and chromogranin A, a NE staining in more than 2% of cells in 33.9% of colon adenocarcinomas (39% in the sigmoid and rectum), including 11.3% of cases with a cut-off >30%, that could have been defined, with appropriate immunostaining, as MANEC according to WHO classification. In surgical samples, the 30% cut-off of NE cells is of help but in biopsy samples, this count it is not possible. In addition, the definition of the NE cell component is not clear. Indeed, if the WHO 2010 classification rules for NEN are respected, both chromogranin-A and synaptophysin must be co-expressed for the diagnosis of NE component. However, in many papers the expression of one of these markers is sufficient to describe a NE component. These problems of definitions may explain why studies on the frequency of NE differentiation in colonic ADC have produced conflicting results. [45][44][46]

Recent molecular data in colonic NECs and MANECs (which are paralleled by data from the pancreas and lung) [47–53] showed that there are two main signatures in NECs, one

characterized by RB1 and TP53 mutations and the other exhibiting KRAS, BRAF, ADM and occasionally MSI alterations, suggesting that some colonic NECs and MANECs may derive from cells that also give rise to conventional ADCs. It could also be that neoadjuvant treatment such as chemo-radiotherapy might change the phenotype of colonic ADCs, as has been described in prostatic adenocarcinomas. [54] In liver metastases of well-differentiated colorectal ADCs resected after systemic treatment, diffuse synaptophysin-positivity may be observed. Such data point to the difficulty in the morphological classification of poorly differentiated NENs and emphasize the need for including genetic data into new classifications.

2 **Treatment of advanced disease:** Currently MANEC tumours are treated using similar regimens to adenocarcinoma. There are no trials of different systemic therapies for MANEC and this is an unmet need.

Unmet need I Development of genetic markers for more accurate classification of MANEC.

Unmet need II Frequency and mapping of well-defined NECs and MANECs to colon and rectum.

Unmet need III Characterization of resected ADCs previously treated with chemoradiotherapy

Unmet need IV Develop trials of different systemic therapies in MANEC.

Screening and earlier recognition of colorectal NENs

Earlier diagnosis of colorectal NETs and NECs will lead to reduced mortality. Bowel cancer screening (BCS) programmes have reduced mortality in colon cancer and it is logical that population screening programmes may reduce mortality from colorectal NETs. Studies of the bowel cancer screening programme in UK are now published. [55] It is unlikely that occult blood testing (FOBT) will select out those with colorectal NENs for screening and it remains to be seen if faecal immunotesting (FiT) will do so. With the worldwide increase in colonic diagnostic investigation, it is likely that more NENs will be found at progressively earlier stages. In the UK bowel cancer screening programme between 2006 and 2014, 146 NET were identified of which 62 were rectal, 40 colonic and 24 terminal ileal.

Unmet need I There is a place for an audit of BCS Programmes for assessing whether patients were treated according to guidelines both for the initial endoscopy and the subsequent NET management.

Conclusions

Focusing on recent data regarding the epidemiology, classification, pathology, diagnosis and therapy of colorectal NENs we identified a number of unmet needs. The following is the summary of unmet needs derived from the review above with some possible solutions.

Rectal:

Unmet need I Endoscopic training programmes should include NET recognition module. Solution: Training module for use worldwide.

Unmet need I Define indications for surgical resection according to whether there is evidence for improved outcome, particularly for G3-NEC.

Solution: retrospective surgical data analysis.

Unmet need I Define optimum follow up for R1 endoscopic resection cases.

Solution: Analysis of long-term follow up of EMR and ESD cases.

Unmet need I Define algorithm for most appropriate therapy for 10-20mm NET.

Solution: Meta-analysis and modelling of factors associated with recurrence.

Colonic:

Unmet need I phase 4 data of colonic NET therapy with everolimus and SSRA. **Solution:** Phase 4 trials.

Unmet need I define whether caecal NET should be classified with midgut or with colonic NET.

Solution: Epidemiological studies of progression and survival.

Colon NEN G3:

Unmet need | need to clearly stratify colorectal NEN G3 patients into NET G3 and NEC patients.

Solution: define histological characteristics more closely

Unmet need | need to improve efficacy of first line treatment; identifying ways to induce durable responses which translate into improved overall survival.

Solution: Further prospective Trials of first line therapies.

Unmet need | need to identify new effective systemic therapy regimens post failure of platinum etoposide chemotherapy for advanced disease.

Solution: Trials of systemic therapies post platinum-etoposide

Unmet need | need to identify and validate biomarkers to select patient most likely (or unlikely) to benefit from systemic therapy.

Solution: Prospective biomarker studies

MANEC:

Unmet need I Development of genetic markers for more accurate classification of MANEC.

Solution: Pathology studies of genetic markers.

Unmet need I Frequency and mapping of well-defined NECs and MANECs to colon and rectum.

Solution: Retrospective international studies of frequency and site of MANEC

Unmet need I Characterization of resected ADCs previously treated with chemoradiotherapy.

Solution: Histopathological studies of resected ADC.

Unmet need I Develop trials of different systemic therapies in MANEC.

Solution: Prospective therapy trials of systemic chemotherapy regimens in MANEC.

Screening:

Unmet need I There is a place for an audit of BCS Programmes for assessing whether patients were treated according to guidelines both for the initial endoscopy and the subsequent NET management.

Solution: Audit of BCS programmes internationally.

The above solutions propose a large challenge to the international research community to advance our knowledge in these tumours.

Accepted manuscript

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