Original article

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Ileocolonic neuroendocrine tumours identified in the English bowel cancer screening programme

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Abstract

Aim Ileocolonic neuroendocrine tumours (NETs) are diagnosed as part of bowel cancer screening programmes (BCSPs). The aim of this study was to identify and characterize NETs diagnosed within the English BCSP, a double-screen programme that uses guaic faecal occult blood test (gFOBT) screening and colonoscopy, by interrogating the national colorectal screening database and validating the findings with individual BCSP centres.

Method The Exeter database was interrogated by running queries to identify participants with coded NETs (from the start of the programme in July 2006 – 1 December 2014). A written proforma was sent to the responsible BCSP clinician for validation and characterization.

Results During this period, 13 061 716 participants were adequately screened using gFOBTs, and 259 765 participants had definitively abnormal results. There were 146 unique participants with NET-related codes from 216 707 BCSP colonoscopies. The diagnosis rates per 100 000 colonoscopies were 29 rectal, 18 colonic and 11 ileal NETs. The majority of rectal NETs had Grade 1 (80%) and Stage T1 (85.1%) disease. Over half of ileal NETs (53.6%) in this study had invasive disease, with 85.2% having nodal and 36.1% having metastatic disease.

Conclusion The current study highlights the rate of colorectal NETs diagnosed in the English BCSP. These data highlight a higher-than-anticipated incidence, and the potential additional benefit of BCSPs in identifying occult NETs.

Keywords Neuroendocrine, tumour, NET, bowel cancer screening, colorectal cancer, faecal occult blood

What does this paper add to the literature?
The paper is the first analysis of neuroendocrine tumours identified through a bowel cancer screening programme that uses double screening with faecal occult blood testing and colonoscopy. The diagnostic rates and characteristics of colonic, rectal and ileal NETs are described for the first time.

Introduction

Neuroendocrine tumours (NETs) are uncommon heterogenous tumours that commonly affect the gastroenteropancreatic tract. There is a delay in the diagnosis of all types of NETs, which can be longer than 5 years from the onset of symptoms [1]. The survival, epidemiology and end results (SEER) database highlighted the incidence of NETs that may potentially be diagnosed through colonoscopy, namely those of colorectal, appendiceal or small bowel origin. The incidence of both rectal and small bowel NETs in the SEER database was approximately 0.9 per 100 000 population per year [2,3]. NETs of the rectum and small bowel represent 34% of all NETs diagnosed. Primary NETs from other colonic sites are of much lower incidence – approximately 0.4 per 100 000 population per year – with little clinical data available [4]. The incidence of colorectal NETs has increased rapidly and this may be partly related to improved endoscopy and histological reporting [2,5–7]. There are limited data on the sites and stages of NETs diagnosed through bowel cancer screening programmes (BCSPs).

Rectal NETs diagnosed through BCSPs are smaller and at an earlier stage than those diagnosed through nonscreening endoscopy [8–10]. They are invariably ≤ 10 mm and of low grade (G1). There are few epidemiological data on rectal NETs diagnosed through

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BCSPs. In a Polish BCSP cohort of 50 148 participants, a prevalence of rectal NETs of 0.05–0.07%, or 50–70, per 100 000 colonoscopies performed was reported [8]. The increased numbers of rectal NETs diagnosed in this cohort compared with the SEER data (0.9 per 100 000 population) is likely to reflect its underlying age-specific prevalence, as participants in this single-screen BCSP cohort were unselected and asymptomatic at endoscopy. There are no clear data on the differences in incidence of rectal NETs with different BCSP strategies: direct to endoscopy (single screen) *vs* primary faecal occult blood test (FOBT) with secondary endoscopy (double screen). There are no published data on small bowel NETs identified during colonoscopy performed as part of the BCSP. This may partly relate to the fact that terminal ileum intubation and distal ileal endoscopic examination is not a routine requirement in BCSPs and so may contribute to under-reporting.

In the English BCSP roll-out period, 10% of participants attending for colonoscopy with an abnormal guaic FOBT (gFOBT) result were diagnosed with colorectal cancer (CRC) [11]. Screening with colonoscopy in those with abnormal gFOBT results has been reported to reduce CRC mortality by 25% in targeted populations that complete screening [12–15]. There are no data on the incidence or characteristics (including staging) of ileocolonic NETs that may be incidentally diagnosed during double screening for CRC. This study aimed to establish if asymptomatic participants in the English BCSP were incidentally diagnosed with ileocolonic NETs, which may support double screening with gFOBT and colonoscopy as a strategy to reduce delays in the diagnosis of NETs.

Method

English BCSP

The English BCSP uses primary screening FOBT and invitations to attend for secondary screening colonoscopy if the FOBT result is abnormal. Three postal kits for gFOBT are sent to invited participants and returned for analysis. Participants are invited to attend for the secondary screening test with colonoscopy if the primary screening gFOBTs are abnormal. From the start of the programme in July 2006 until 1 December 2014, 23 405 057 invitations were sent to subjects asking them to participate in the English BCSP. Of these invitations, 13 061 716 participants were adequately screened with three gFOBTs, equivalent to a 55.8% uptake for the primary screening test. Approximately 2% (259 765) of adequately screened participants had definitively abnormal gFOBT results. There was an 83.42% uptake for secondary screening with colonoscopy in participants (216 707) with an abnormal gFOBT result, equivalent to 1.66% of the total number of participants who were adequately screened.

BCSP (Exeter) database search

The English bowel cancer colonoscopy database (Exeter) was queried to capture potential NET-related search terms across relevant data tables. The 'polyp architecture', 'SNOMED' and 'lesion type' data tables were identified as relevant to NET-related colonoscopy findings. SNOMED is a systematically organized collection of clinical terms that is a core terminology for electronic health records [16]. Queries using the terms outlined in Table 1 were run for each data table to identify BCSP participants attending for colonoscopy with NET-related coding from the programme commencing in July 2006 to 1 December 2014. Goblet cell endocrine tumours and mixed endocrine tumour/adenocarcinomas were included in the 'lesion type' search as they are routinely discussed in NET multidisciplinary meetings. Participation data at primary screening and secondary screening were requested. The anatomical sites for the NET-related findings were categorized into colorectal, ileal, appendiceal and unknown sites. Colorectal NETs were subcategorized into colonic and rectal anatomical sites. There was no coding in the Exeter database for size, histological features and staging for noncolorectal pathology, such as NETs.

Data validation proforma

A written proforma was sent to the responsible BCSP clinician for all participants identified from the NET queries of the Exeter database to characterize the cases identified from the database queries. The proforma

Table 1 Queries used to search the Exeter database across the polyp architecture, SNOMED (a core clinical terminology for electronic health records [16]) and lesion type tables for participants with neuroendocrine tumours (NETs).

Polyp architecture	SNOMED	Lesion type
Endocrine tumour (carcinoid)	Endocrine carcinoma	Endocrine carcinoma
	Malignant carcinoid	Goblet cell endocrine tumour Malignant carcinoid Mixed endocrine tumour/Adenocarcinoma

contained validation questions as well as questions on tumour characterization (size, histological features and staging) and diagnostic and therapeutic modalities (endoscopic and surgical resection). Nonidentifiable clinical reports were reviewed if provided as supplementary data. Histological grading was classified according to the mitotic index and from the expression of Ki-67, a tumour proliferation marker [17,18]. No independent histopathological review of tissue specimens was performed. TNM staging of NETs was reported in line with European Neuroendocrine Tumor Society (ENETS) guidelines, with subclassification of T1 stage rectal NETs according to size (T1a <1 cm, T1b 1–2 cm), if provided on the written proforma or sufficiently described in the supplementary reports [19]. Metastatic disease was judged if present on radiological imaging, functional imaging or on EUS in line with ENETS guidance.

Data analysis

Data coding and analysis were performed using Microsoft® Excel® for Mac (2011). Coding rates per 100 000 colonoscopies performed were calculated and reported also according to anatomical site. Statistical testing was not performed given the lack of relevant comparative data for NETs identified in BCSPs. Data are presented as median with range and as percentage with absolute number (%, identified number/total number) for groupings identified during the analyses.

Results

BCSP (Exeter) database search

One-hundred and forty-six unique BCSP participants with NET-related codes were identified across the three database tables during the time period of this study (Table 2). The BCSP became fully established in 2010 (with colonoscopy volumes greater than 30 000 per year) and from this time onwards approximately 26 participants with NET-related codes were identified per year. Over half of participants with NET codes were male (59.6%, 87/146), a similar proportion to those who attended for colonoscopy screening. The overall coding rate for NETs was 67 per 100 000 colonoscopies per year, with the rates for rectal, colonic and ileal NETs being 29, 18 and 11 per 100 000 colonoscopies per year respectively (Table 2).

Data validation proforma

Proformas were distributed to BCSP sites for each of the 146 participants coded in the Exeter database search. There was an 82% return rate for proformas (119 proformas) from BCSP sites for analysis. Nine cases were validated as adenocarcinomas and were excluded from the analysis as being incorrectly coded as a NET. The incorrect coding reduced the overall NET coding rate by 4.2 per 100 000 colonoscopies per year. The effect on diagnosis rates according to anatomical

Table 2 Numbers of colonoscopies performed per year in participants with abnormal guaic faecal occult blood test (gFOBT) results.

Year	Colonoscopy	Total NETs	Female NETs	Male NETs	Colonic NETs	Rectal NETs	Ileal NETs	Appendiceal NETs	Unknown
2006	341	0	0	0	0	0	0	0	0
2007	5340	0	0	0	0	0	0	0	0
2008	15 419	8	2	6	3	3	1	0	1
2009	23 011	14	6	8	5	5	2	0	2
2010	33 491	23	8	15	7	10	5	0	1
2011	37 104	30	13	17	10	10	6	0	4
2012	35 556	26	11	15	4	13	2	2	5
2013	34 196	24	10	14	3	12	6	0	3
2014	32 249	21	9	12	8	9	2	0	2
Total	216 707	146	59	87	40	62	24	2	18
% of total		100	40	60	27	42	16	1	12
Average	24 079	16.2	6.6	9.7	4.4	6.9	2.7	0.2	2.0
Exclude 2006/2007	30 147	20.9	8.4	12.4	5.71	8.86	3.43	0.29	2.57
Coding rate		67	27	40	18	29	11	1	8

Participants (total, female and male) were identified using neuroendocrine tumour (NET)-related codes and were categorized, according to anatomical site, in the Exeter bowel cancer screening programme (BCSP) database. The average number of participants categorized according to gender and anatomical site per year (overall and excluding the 2006–2007 roll-out period), as well as the respective coding rates per 100 000 colonoscopies per year, are presented at the bottom of the table. NETs where the anatomical site was not coded are presented as Unknown.

site was not established given the uncertain effect of the proforma return rate on any calculation.

The majority of validated NET lesions were well differentiated (85%, 94/110) with only a minority reported as poorly differentiated (8%, 9/110). There were two goblet cell carcinoids of the appendix and two mixed adenoneuroendocrine carcinomas (MANECs) of the ascending colon (Table 3).

Almost half of the validated NETs were rectal (49%, 54/110) with the remaining in the ileum (27%, 30/110), colon (16%, 17/110) or appendix (7%, 8/110) (Table 4). The number of validated ileal NETs (30/110) was higher than those coded in the database (24/146). The number of validated appendiceal NETs (8/110) was also higher than those coded in the database (2/146). In contrast, there were fewer validated colonic NETs (17/110) than expected from the database (40/146). This suggests that the anatomical site coding in the BCSP Exeter database for proximal lesions identified at BCSP colonoscopy may be inaccurate or recorded as unknown site. An accurate anatomical site may not be coded when identified from a later surgical resection specimen because of CRC co-pathology. For example, seven appendiceal NETs were identified incidentally at surgery or on histology following a right hemicolectomy for CRC. These changes in validated numbers for anatomical sites have an uncertain effect on the anatomical site incidence and ratio calculations for NETs. In particular, the incidences and ratios for appendiceal and ileal NETs would increase, as the numbers in the validated cohort are higher than those in the database-coded cohort.

Table 3 Differentiation and histological appearance of neuroendocrine tumours (NETs) identified in bowel cancer screening programme (BCSP) participants.

Type of tumour	Total
Well-differentiated NET	94
Poorly differentiated NEC (small cell)	4
Poorly differentiated endocrine carcinoma	3
Poorly differentiated NEC (large cell)	2
Goblet cell carcinoid	2
Mixed adenoneuroendocrine carcinoma	2
Other/–	3
Total	110

The data presented in the table represent the results from surveys sent to BCSP sites for 146 participants identified in the Exeter BCSP database. Neuroendocrine carcinomas (NEC) are high grade and poorly differentiated tumours divided into small- or large-cell carcinomas.
–, no data available.

Histological grade was available for 98/110 participants; the majority were reported as Grade 1 (85% 83/98) with 8% (8/98) as Grade 2 and 7% (7/98) as Grade 3 (Table 4). Grade data were available for the majority of rectal NETs (47/54), ileal NETs (26/30) and colonic NETs (16/17). For rectal NETs, 91% (43/47) were reported as Grade 1, 2% (1/47) as Grade 2 and 6% (3/47) as Grade 3; for ileal NETs, 96% (25/26) were reported as Grade 1 and 4% (1/26) as Grade 2; and for colonic NETs, 56% (9/16) were reported as Grade 1, 19% (3/16) as Grade 2 and 25% (4/16) as Grade 3.

Data on the presence of metastatic disease were available for 86% (95/110) of cases of NETs. Metastases were present in 24% (23/95) of cases with the majority of these arising in participants with colonic (10/17) or ileal (9/27) NETs. Data on TNM staging for rectal and ileal NETs are discussed in more depth below.

Rectal NETs

Rectal NETs were reported as being small with a median size of 5 mm and an interquartile range of 3–6.75 mm (Table 4). The majority of rectal NETs (85%) were reported as being < 10 mm in size (46/54) with 11% being 10–20 mm (6/54) and only 4% being > 20 mm (2/54).

Rectal NETs were early stage (T1; 85.1%, 40/47) where data were available, with only a small proportion that invaded the muscularis propria or beyond (T2, 4.3%, 2/47; T3, 10.6%, 5/47). The overwhelming majority of rectal NETs of < 10 mm in size were stage T1a (97.4%, 38/39) with only one staged as T2 (2.6%, 1/39). Two-thirds of those of 10–20 mm (4/6) invaded the muscularis propria or beyond. Both rectal NETs of > 20 mm were Stage 3.

Data on N stage was available for 34% (18/54) of cases of rectal NET with a large percentage not assessed (29/54) or unknown (7/54). All (12/12) rectal NETs of < 10 mm did not have nodal disease where data were available or assessed. Half (2/4) of rectal NETs of 10–20 mm had nodal disease where available and assessed. Both rectal NETs that were > 20 mm had nodal disease. Data on M stage was available for 26% (14/54) of cases of rectal NET, which relates to endoscopy being the predominant resection modality for small lesions. No (11/11) rectal NETs of < 10 mm had evidence of metastatic disease (where data were available or assessed). Half (2/4; where available and assessed) of 10–20 mm rectal NETs had metastatic disease. Metastases were present in the one rectal NET that was > 20 mm (where data were available or assessed). Free text data for the sites of metastatic disease were limited and not used for analysis.

Table 4 Characteristics (anatomical site, size and histological grade) of neuroendocrine tumours (NETs) identified in bowel cancer screening programme (BCSP) participants.

Site	Number	Median size (mm) (IQR)	Grade 1	Grade 2	Grade 3	Grade unknown
Rectal	54	5 (3–6.75)	43	1	3	7
Colonic	17	31 (19.5–40)	9	3	4	1
Ileal	30	15 (11.75–25.25)	25	1	0	4
Appendiceal	8	15 (13–21.5)	6	2	0	
Unknown	1	–	–	–	–	–
Total	110	8	83	8	7	12

IQR, interquartile range.
–, no data available.

Ileal NETs

Data on T stage were available for 93% (28/30) of ileal NET cases. Of those with T-stage data, 46.4% (13/28) of ileal NETs did not invade beyond the muscularis propria (stage T1 or T2). Over half (53.6%) of ileal NETs were reported to have invaded into the subserosa or beyond into the visceral peritoneum (Stage T3 or T4). Data on N stage were available for 90% (27/30) of cases of ileal NET. Of those with N-stage data, 85.2% (23/27) of ileal NETs were reported to have nodal disease (N1). Data on M stage were available for 37% (11/30) of cases of ileal NET. Of those with M-stage data, 36.4% (4/11) of ileal NETs were reported to have metastases. Almost half (44.4%, 4/9) of participants with nodal disease also had metastatic disease. Free text data for the sites for metastatic disease were limited and not suitable for analysis.

Other findings

Colorectal cancer was a co-malignancy in 9% (8/91, data available) of participants. The NET was an incidental finding in 75% (6/8) of these cases. Appendiceal NETs were associated with CRC as a co-malignancy in five of six (83%) instances. Invariably the appendiceal NET was an incidental post-resection histological finding following hemicolectomy for a CRC identified during the colonoscopy. The two other instances of CRC were with rectal and ascending colon NETs. Adenomas were identified at BCSP colonoscopy in 55% (48/87, data available) of participants and were present in 74% (32/43) of rectal, 43% (3/7) of appendiceal and 35% (8/23) of ileal NETs. Reporting of the numbers of adenomas identified in participants was limited and not suitable for analysis.

Treatment at diagnosis

Therapy was attempted at the index BCSP colonoscopy in 83% (45/54) of rectal NETs with polypectomy in 73% (33/45) and EMR in 27% (12/45) instances. All participants with ileal and appendiceal NETs had surgery following the index BCSP endoscopy. The median number of lymph nodes involved on surgical resection was 2 with an interquartile range of 1–6. Therapies on metastases were performed on seven participants, ranging from the use of somatostatin analogues to hepatic resections for metastases and systemic chemotherapy.

Discussion

This study adds to the published data on NETs identified through BCSPs. NETs were identified with a higher ratio in the English double-screen BCSP than in the SEER population database (28 times greater) [4]. However, this BCSP screening to population cancer ratio was lower than that reported for CRC (55 times greater) [11,20]. The largest ratio was for colonic NETs (45 times greater), followed by rectal NETs (32 times greater). The ratios for ileal and appendiceal NETs were lower, at 12.2 and 5 times greater, respectively. This suggests that colonoscopy in participants with an abnormal gFOBT result may not be as effective for diagnosing NETs, in particular rectal NETs, when compared to diagnosing CRC. Importantly, the SEER data, used as the population incidence, is not age-specific, with the true age-specific incidence in 60- to 74-year-old subjects likely to be higher, leading to an overestimate of the ratio in this study. This fact further limits the effect of the double-screen BCSP strategy for identifying NET lesions. However, there may be benefit for participants with colonic and ileal NETs from the use of gFOBT screening in the BCSP. The ratio of colonic NETs in this double-screen BCSP approximates that of CRC. The possible diagnostic rate of ileal NETs may be higher than reported given that the terminal ileum is not routinely visualized during a BCSP colonoscopy. The role of gFOBT screening for ileal NETs is uncertain without additional data on BCSP terminal ileal intubation rates.

Data from the single-screen Polish BCSP reported rectal NET incidence of approximately 48 per 100 000 colonoscopies compared with 29 per 100 000 colonoscopies per year in this study [8]. This suggests that the use of endoscopy as an investigation is the most useful component for diagnosing rectal NETs. The English BCSP colonoscopy is only offered to participants who have an abnormal gFOBT result (2%). Analysis of single-screen bowel cancer programmes, including those limited to examination of the distal colon, would help identify the age-specific incidence of rectal NETs in the UK.

The study was limited by the two-stage approach to identify coded NETs and separate proforma to characterize, without independent histopathological review, tissue samples. There was no specific code for 'neuroendocrine tumour' in the database and the terms used were thought to be the most suitable for capturing NETs. Non-CRC and nonadenomatous lesions were not mandatory lesions for coding in the English BCSP. Factors such as endoscopic and histological reporting practices for non-CRC nonadenomatous lesions during a BCSP colonoscopy may additionally lead to under-reporting. The completion of the proforma, particularly the staging section, may have been inconsistent as there was no central review performed. However, there appears to be no difference in rectal NET characteristics between this study and the Polish study. The stage of rectal NETs reported is similar to that described in published non-BCSP data, with the majority limited to the submucosa (T1, 89%). Reassuringly, the majority of rectal NETs have T1 disease that can be managed with endoscopic resection alone with low risk of nodal and metastatic disease. Surgical resection modalities are available for more advanced rectal NET disease [3].

Future insights into the role of FOBT and endoscopy in identifying NETs, through screening of asymptomatic populations, may come through changes in the English BCSP. The recent introduction of a single-screen flexible sigmoidoscopy ('bowel scope') BCSP at the age of 55 years, in addition to the existing double-screen BCSP for subjects 60–75 years of age, is hypothesized to prevent colorectal adenocarcinoma cases and deaths [21]. This may help to quantify the effect of endoscopy itself in identifying rectal NETs and the true underlying age-specific incidence in unselected participants.

There are no published data on the role of FOBTs, either gFOBTs or faecal immunochemical tests (FITs), for aiding the diagnosis of gastrointestinal NETs. This study highlighted a 9% CRC co-malignancy rate. However, ileal NETS identified in this study were not associated with CRC but had advanced disease. This suggests that FOBTs may play a role in identifying asymptomatic ileal NETs. These luminal lesions can often have an ulcerated appearance that may lead to occult blood loss and FOBT positivity. The current gFOBT assay will be replaced by the quantitative FIT, which is specific for human blood, easier to process and more acceptable for participants to use [22]. A recent trial of the FIT against the gFOBT in the English BCSP demonstrated an increase in uptake of 7%, to 66.4%, particularly from previous non-responders, men and those from more deprived populations [23]. This change in primary screening test led to a twofold increase in diagnoses for CRC and a fivefold increase in diagnoses for advanced adenomas. The role of FIT in diagnosing colorectal and small bowel NETs is not clear and requires evaluation.

The number of incidental NETs diagnosed through population screening for CRC appears to have a limited impact on services, with an average of 26 participants identified per year in the English BCSP. It is not clear if bowel 'scope flexible sigmoidoscopy will result in far greater numbers of participants with rectal NETs requiring specialist input, such as advanced endoscopy services (for EUS and endoscopic submucosal dissection) and NET centres. It is also unclear whether bowel cancer screening programmes will have a significant positive impact on rectal NET morbidity and mortality, as has been demonstrated with CRC mortality [24,25]. The natural history of the disease and the tumour biology of small incidental colorectal NETs, such as rectal NETs, has not been characterized. However, the ileal NETs identified in this programme were more advanced with nodal and metastatic disease, which suggests a possible benefit of terminal ileal intubation in participants for whom no colorectal cause for a positive gFOBT has been identified.

Author contributions

The following 46 Bowel Cancer Screening Centres contributed to this study: Bedfordshire, Berkshire, Bradford & Airedale, Bristol & Weston, Calderdale, Kirklees & Wakefield, Cambridge, Cheshire, County Durham & Darlington, Coventry & Warwickshire, Cumbria & Morecombe Bay, Dorset, East & North Hertfordshire, Exeter, Mid, East & North Devon, Gloucestershire, Hampshire, Heart of England, Herefordshire & Worcestershire, Humber & Yorkshire Coast, Leicester, Liverpool & Wirral, Merseyside & North Cheshire, Milton Keynes & Buckinghamshire, North Derbyshire, North East London, North Essex, North of Tyne, Norwich, Oxfordshire, Pennine, Peterborough & Hinchingbrooke, Sandwell & West Birmingham, Shropshire, Solent, Somerset, South Derbyshire, South Devon, South East London, South Essex, South Yorkshire, St. Mark's, Surrey, SW London (St. Georges), Tees,

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Conflicts of interest

No authors have personal interests to declare for this paper.

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