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**Challenging diagnostic issues in adenomatous polyps with epithelial  
misplacement in bowel cancer screening: five years' experience of the BCSP  
Expert Board**

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**ABSTRACT**

The diagnostic difficulties of differentiating epithelial misplacement from invasive cancer in colorectal adenomatous polyps have been recognised for many years. Nevertheless, the introduction of population screening in the UK has provided extraordinary diagnostic problems. Larger sigmoid colonic adenomatous polyps, those most likely to show epithelial misplacement, are specifically selected into such screening programmes because these polyps are likely to bleed and screening is based on the detection of occult blood. The diagnostic challenges associated with this particular phenomenon have necessitated the institution of an “Expert Board”: this is a review of the first five years of its practice, **during which time 256 polyps from 249 patients have been assessed**. Indeed, the constitution of the Board has been with three pathologists because those pathologists do not necessary agree and a consensus diagnosis is required to drive appropriate patient management. However, this study has shown substantial levels of agreement between the three **Expert Board** pathologists **whereby** the ultimate diagnosis has been changed, from that of the original referral diagnosis, by the Board in half of **all the polyps, in the substantial majority from malignant to benign**. In 3% of **polyp cases**, the **Expert Board** consensus has been the dual diagnosis of both epithelial misplacement and adenocarcinoma, further **illustrating** the diagnostic difficulties. The Expert Board of the Bowel Cancer Screening Programme in the UK represents a unique and successful development for an extraordinary diagnostic conundrum created by the particular characteristics of bowel cancer screening.

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## INTRODUCTION

The NHS Bowel Cancer Screening Programme (BCSP), in England, was initiated in 2006 and was fully rolled out across the country by 2011. It offers universal population screening, by faecal occult blood testing, to those aged between 60 and 69 years old with age extension to 75 now fully rolled out.<sup>1,2</sup> As such, England is the first country, with a population over 50 million, to fully establish population screening for colorectal cancer in the world. The outcome of the first million tests was reported in 2011 with a 55-60% uptake of the stool guaiac faecal occult blood test (gFOBT) testing kits with 83% of those with a positive test undergoing colonoscopy.<sup>3</sup> Similar, but not identical, programmes have also been rolled out in the other countries that make up the British Isles, namely Scotland, Wales, Northern Ireland and the Republic of Ireland.

Initially it was the view of specialist pathologists in the UK that the introduction of the bowel cancer screening programme would cause few diagnostic or logistical problems with a relatively modest increase in workload, largely generated by adenomatous and hyperplastic polyps removed at colonoscopy and a manageable increase in the number of colorectal cancer resection specimens. Given the NHS experience of cancer screening, relatively strict quality assurance procedures were put in place,<sup>4</sup> with a specific BCSP External Quality Assurance (EQA) scheme,<sup>5</sup> but few would have anticipated the major diagnostic issues, faced by BCSP pathologists. The major pathological challenges were, and are, the biopsy diagnosis of colorectal cancer, serrated polyp pathology, the diagnosis and management of polyp cancer and, finally, epithelial misplacement in adenomatous polyps, especially of the sigmoid colon.<sup>6,7,8</sup>

There is no doubt that the challenges imposed by epithelial misplacement in adenomatous polyps of the sigmoid colon have proved the most difficult in terms of pathological diagnosis in BCSP.<sup>9</sup> In particular such adenomatous polyps, because of the narrowness of the sigmoid colon, its motility and the association with diverticular disease (or, at least, pre-diverticular disease) in the majority of patients of this age, are subject to pronounced mechanical trauma and this accounts for the high frequency of mucosal prolapse changes and epithelial misplacement that characterises these polyps.<sup>10</sup> Further, larger polyps, subject to mechanical trauma, inflammatory changes and ulceration, often bleed and

this accounts for their specific selection into bowel screening programmes which are dependent on the detection of occult blood.<sup>11</sup>

So, adenomatous polyps of the colon, especially of the sigmoid colon, can show epithelial misplacement into the submucosa and this can closely mimic invasive adenocarcinoma, leading to significant diagnostic conundra.<sup>9</sup> Epithelial misplacement, the preferred terminology in the UK, or 'pseudoinvasion', the preferred North American terminology, has long been recognised to mimic early polyp cancer.<sup>12</sup> It was first described by Muto and his colleagues in 1972.<sup>13</sup> They outlined the characteristic histological appearances, in which accompaniment by lamina propria, haemosiderin deposition, a lack of a desmoplastic reaction and similar cytology to the surface adenomatous polyp are the most characteristic features.<sup>13,14</sup> Nevertheless it is recognised that the differentiation from cancer can be very difficult<sup>15</sup> and immunohistochemistry has been promoted as a means of differentiating the two conditions,<sup>16-19</sup> although subsequent evidence and experience suggest that difficult cases are not aided by such immunohistochemical analysis.<sup>6,9</sup>

Very early in the establishment of the BCSP, it became apparent that the programme was generating very significant numbers of polyps with ambiguous histological features, leading to divergent diagnostic opinions amongst pathologists.<sup>20</sup> There was also a view that the over-diagnosis of polyp cancer and the poor understanding of the important prognostic features of polyp cancers could threaten the efficacy of BCSP due to over-treatment, especially by radical surgery. So, the BCSP National Pathology Committee, chaired by one of us (PQ), determined that a national pathology 'Expert Board' (EB) should be convened to assess all such difficult cases and provide a consensus diagnosis to ensure optimal patient management. Initially the Board consisted of three internationally recognised gastrointestinal pathologists (NAS, BFW & GTW), with the latter two being replaced in 2011 & 2012 by MRN and DSAS, when the two original members died/retired respectively. At all times, the Board consisted only of three pathologists, even during those transition periods.

This paper provides a five year review of this unique pathological diagnostic service and highlights key diagnostic features encountered in the differential diagnosis of epithelial misplacement and polyp cancer.

## MATERIALS AND METHODS

### Case referral and review:

The BCSP Expert Board comprises three experienced gastrointestinal pathologists, selected by their experience in the assessment of complex colorectal polyp pathology. The Board offers BCSP Centre pathologists the opportunity of a consensus diagnosis for any cases where there is particular diagnostic difficulty or divergent diagnostic opinions locally. The service is advertised through BCSP national, regional and local networks and cases have originated from all Centres and Regions providing a BCSP service in England. Indeed cases have also been reviewed from the separate national screening programmes that exist in Scotland, Wales, Northern Ireland, the Republic of Ireland, the Netherlands and Slovenia, although polyps from these countries make up only a small proportion of the total number. All of these countries' programmes have similar, but not identical, screening policies and practices. It should be emphasised that the service is specifically established to address the one diagnostic issue of the differentiation of epithelial misplacement from polyp cancer. Any other referrals to the coordinating pathologist are dealt with in the same way as referrals by that pathologist's 'routine' second opinion practice.

### Logistics:

All polyps assessed by the EB should have been processed standardly according to BCSP protocols and standards.<sup>5</sup> All representative histological slides, those that the Centre Pathologist has assessed, are sent by the Centre Pathologist to the Lead EB Pathologist (NAS) who reviews the slides and produces a report which is securely e-mailed to the Centre Pathologist. The slides are then posted to each of the other two EB Pathologists who each review the slides blinded to the diagnoses of the other EB pathologists and who each produce a report, which is securely e-mailed to the Centre Pathologist. The third EB Pathologist (MRN) reviews the three EB members' diagnoses and provides a consensus diagnosis for the Centre Pathologist. Relevant slides are then sent to the University of Leeds and posted on their website<sup>21</sup> so that interested parties can review all the EB cases initially blinded to the diagnoses of the originating

pathologist(s) and the Expert Board. Thus each EB pathologist provides an independent opinion on each case. The date of issue of each EB report is recorded in the database to assess any turnaround time issues. In occasional cases (less than 20 in total), the EB pathologists have made a recommendation that further deeper levels should be cut through the block(s) but additional immunohistochemistry has not been requested by the EB in any case.

An anonymised spreadsheet records individual cases referred to the EB to include polyp site, size, shape, type and grade of dysplasia and Centre Pathologist versus EB opinion. The EB pathologists independently assess each case as either benign/epithelial misplacement; malignant/suspicious; equivocal features (although EB pathologists are exhorted to make this diagnosis as little as possible) and finally the dual diagnosis of both epithelial misplacement and malignancy in the same polyp. The database is thus able to compare individual and consensus diagnoses of the EB with the diagnosis of the originating pathologist(s) and assess the degree of diagnostic consensus between members of the EB and the levels of diagnostic agreement or disparity between the EB consensus diagnosis and that of the referring screening centre.

#### **Statistical analysis:**

Statistical analysis utilised the methodology of Fleiss' generalised weighted kappa statistics (22) to assess the reliability of diagnostic agreement between multiple raters (the three EB pathologists) using a freely downloadable modified Excel type spreadsheet (<http://www.ccit.bcm.tmc.edu/jking/homepage/>). Fleiss' generalised weighted kappa statistics can be used as a statistical measure for assessing the reliability of agreement between the three 'raters' to a fixed number of items.



## RESULTS

A total of 256 polyps from 249 patients (there were two polyps in seven patients) were referred to the EB over a five year period from January 2009 to January 2014. 20 referrals to the EB were made in 2009 with a year-on-year increase to 72 referrals in 2013, a 260% increase over the five year period (Table 1). 72.3% of the patients were male. The age range was, inevitably, restricted to 60-75 as all patients were within the BCSP screening programme. All polyps were adenomatous in type and the large majority were from the sigmoid colon or the recto-sigmoid junction (78.9%). 12.2% were from the rectum and 3.7% from the descending colon. Sites in the proximal colon accounted for the remaining 5.2% of referrals, although there were no caecal polyps in the series. The polyps ranged from 5mm to 81mm in size and 85.2% were described as pedunculated. The majority were tubulovillous adenomas (74.6%) whilst tubular adenomas accounted for only 21.6% and villous adenomas just 3.8%. 32.6% of the adenomatous polyps showed low grade dysplasia only whilst 67.4% showed areas of high grade dysplasia, the latter adding to the diagnostic difficulties in epithelial misplacement polyps and emphasising the selected nature of the cases involved, as there is a BCSP national performance indicator that polyps with high grade dysplasia should not constitute more than 10% of adenomas.

Of the 256 polyps, there was a three-way agreement of the EB for the ultimate diagnosis, using the diagnostic categories described above, in 200 polyps, presenting 80.3% of the total case number. One EB pathologist did not use the equivocal category for any case and thus this category was excluded from the analysis. The expected chance agreement for a three-way diagnostic accord is 40.9%. Kappa is the excess agreement over that expected by chance and this was 0.667, representing a level of substantial agreement (0.6 to 0.8). Thus these results demonstrate substantial diagnostic agreement between the three experts in what is a highly selected and difficult diagnostic area.

To assess the levels of agreement and disagreement between the EB and the originating pathologist(s), it was appropriate to use only the subset of polyp cases where the three experts agreed and where a definitive diagnosis was submitted by the referring hospital, a total of 193 polyps. The comparison between the referring pathologist(s)

diagnosis and the EB consensus diagnosis is shown in Table 2 and Figure 1. The expected level of agreement was 30.4% and the observed level was 36.3% with a kappa of just 0.085, representing a level of 'agreement' only slightly better than chance.

In the 193 polyps where a diagnosis was given by the originating pathologist(s) and the three EB pathologists agreed amongst themselves, the 62 "equivocal" diagnoses made by the originating pathologist(s) were assessed as benign in 50 (81%), malignant in 11 (18%) and the dual diagnosis in just one (1%) by the EB. The 59 "benign" diagnoses made by the originating pathologist(s) were confirmed by the EB in 53 cases (90%); the other six were considered to be malignant. Of the 61 "malignant" diagnoses made by the originating pathologist(s), 42 (69%) were regarded by the EB as benign and just 17 (29%) were confirmed as malignant, although an additional two cases (3%) were regarded by the EB as representing the dual diagnosis of both epithelial misplacement and adenocarcinoma. There were 11 cases where the originating pathologist(s) had made the dual diagnosis but ten of these were considered to represent epithelial misplacement only by the EB. Overall, of the 131 diagnoses submitted by the originating pathologist(s), excluding equivocal cases, in 65 (50%) of cases the diagnosis was revised by the EB. In the 49 cases where there was no three-way consensus EB diagnosis, there were 11 cases where an "equivocal" diagnosis had been made by one EB member and, on four occasions, two had made an equivocal diagnosis. In these four cases, the EB could provide no consensus diagnosis, emphasising the especial diagnostic difficulties in these cases and the lack of a definitive diagnosis for those patients.

In general turn-around times have been very good, although in the early years there were two complaints about the time taken for clear management guidance to be given. This was ameliorated by ensuring secure e-mail transmission of reports and turn-around times since have been entirely satisfactory. Since that time, all cases have been seen and reported by two pathologists within two weeks, assuring a consensus diagnosis, in that timescale, in the great majority of cases. As the Board results rely on a consensus diagnosis, if the first two EB pathologists agree, then an effective diagnosis, for management purposes, is achieved after two EB pathologists have seen the case.

Whilst the Expert Board's pathologists and administrator request that originating pathologists provide all follow-up information available, too little time has elapsed to allow an accurate assessment of the overall diagnostic accuracy of the Expert Board. The levels of agreement between the three pathologists are reassuring but, nevertheless, we are aware of two cases where, at the same site in the sigmoid colon as the polyp in question, a cancer has been subsequently demonstrated. In both of these cases, on review, we accept that the pathology almost certainly represents the dual diagnosis of epithelial misplacement and adenocarcinoma, rather than just epithelial misplacement, the consensus diagnosis of the Expert Board. Thus these two cases serve to emphasise the extraordinary diagnostic difficulties that may be encountered in such adenomatous polyps of the sigmoid colon. **We have been unable to detect any significant changes in EB diagnostic performance through the five years in question and the change in personnel in the EB also has made no detectable difference to the overall diagnostic performance.**

Although we could have provided illustrative examples of some of the more difficult cases that this review encompasses, in this submission, we believe it more useful to direct the interested reader to the Virtual Pathology website of the University of Leeds, accessed at <http://www.virtualpathology.leeds.ac.uk/eqa/specialist/nbcs/> as that website holds all the cases from this series and indicates the originating pathologist(s) and the Expert Board diagnoses. Interrogation of that website undoubtedly provides a much more useful illustration of the diagnostic difficulties associated with these cases rather than providing a restricted number of illustrations here. **Good examples where the diagnosis of the originating pathologist(s) was downgraded to epithelial misplacement by all three EB members are cases 100, 114, 198 and 211. Illustrative examples of cases providing especial diagnostic difficulties for all are 106, 197 and 243.**

## DISCUSSION

The phenomenon of epithelial misplacement in larger, predominantly sigmoid colonic, adenomatous polyps within bowel cancer screening programmes is unique in the practice of gastrointestinal pathology. Perhaps, in pathology as a whole, the diagnostic conundra are rivalled only by difficult cutaneous melanocytic lesions in their ability to produce diagnostic disagreement between specialist, and often expert, pathologists. The diagnostic difficulties have been so profound as to require the establishment of the unique diagnostic service, the Expert Board, described here. The very constitution of the EB is with three pathologists because absolute agreement between expert pathologists is, by no means, guaranteed and a consensus diagnosis amongst three pathologists aims to ensure that there is a working diagnosis to allow further management to be enacted, although even this is not always entirely possible as demonstrated by the four cases in which there was no consensus diagnosis in the EB.

It is reassuring, however, that the EB pathologists have demonstrated substantial diagnostic agreement amongst themselves. Certainly the lack of perfect agreement between experts is to be expected, given the diagnostic difficulties and uncertainties. The relatively high “equivocal” diagnosis rates from referring pathologists are a reminder that the cases are not a random selection but rather a subset of cases likely to be more diagnostically difficult and therefore preferentially submitted for expert assessment. It is notable that there were only a relatively small proportion of cases (10%) where the diagnosis was ‘upgraded’ by the EB from the originating pathologist(s) benign diagnosis to a malignant one. Indeed it was much more likely (in 69% of cases) for the pathology to be ‘downgraded’ from adenocarcinoma to epithelial misplacement by the EB. Perhaps this reflects the experience of the EB in recognising the particular pathological features of epithelial misplacement versus the relative inexperience of non-specialist pathologists, not used to seeing the florid changes of epithelial misplacement in their routine practice. The diagnostic difficulties are also compounded by the presence of cases where there is the dual diagnosis of both epithelial misplacement and adenocarcinoma in an adenomatous polyp. The EB made this diagnosis less often than referring pathologist(s) and the dual diagnosis made by originating pathologist(s) was, in the great majority of cases, considered by the EB to represent epithelial misplacement only.

The increase in referrals to the EB each year since its inception likely reflects more widespread knowledge of the referral service but is also likely driven by the increasing number of cases generated by the BCSP each year and the greater understanding, amongst BCSP pathologists, of the diagnostic difficulties and issues.<sup>9</sup> Overall this review has shown that the BCSP EB provides an efficient and effective referral service for the most difficult of diagnoses, without which potential polyp cancer cases would be missed and, perhaps more importantly, there would be cancer over-calls, resulting in inappropriate treatment, including major surgery and insurance implications. The lack of long-term comprehensive patient follow-up is deemed a handicap and there has been little opportunity for the three EB pathologists to learn and modify diagnostic behaviour. This is offset by the low risks of metastatic disease in this situation of very early disease without adverse prognostic features (otherwise the diagnosis of cancer would be very easy). Some might maintain that many EB cases merely represent an academic exercise that does not change management. Against this is the argument that avoiding a costly colorectal cancer resection (with an overall cost in excess of £15,000) by the frequent identification by the EB of benign epithelial misplacement more than justifies the establishment and cost of the Expert Board.

Diagnostic pathologists are fortunate because, usually, they have the use of a battery of adjunctive tests to refine and embellish the diagnostic process. It is notable, and disappointing, therefore, to report that few such adjunctive tests have been shown to have any value in the assessment of these difficult adenomatous polyp cases.<sup>6,9</sup> Indeed we would argue that the most useful further 'test' is to ensure that the entire polyp has been adequately sampled for histological assessment, by assuring that the polyp has been submitted for histology in its entirety, and, critically, that levels have been cut right through each of the blocks. In our experience the latter is the most useful 'adjunctive test' to aid in the diagnostic process. Immunohistochemistry has been promoted, with the use of antibodies to assess, in particular, cell adhesion and basement membrane integrity.<sup>16</sup> However, such immunohistochemistry is effective in cases where the diagnosis is not much in doubt but has been shown to be of little value in difficult and equivocal cases.<sup>6,9</sup>

The diagnostic difficulties are certainly compounded by the recent recognition of so-called adenoma-like adenocarcinoma.<sup>23</sup> The pathology in these cases may show a striking resemblance to florid epithelial misplacement but it would be hard to argue against a diagnosis of adenocarcinoma in cases where the neoplastic epithelium has penetrated the muscularis propria and/or is present in the mesorectal/subserosal tissues. Nevertheless, especially in biopsy material, it may be extremely difficult to differentiate epithelial misplacement from adenoma-like adenocarcinoma.<sup>23</sup> Further, we recognise that previous intervention, both endoscopic and surgical, can itself cause epithelial misplacement,<sup>24</sup> underpinning the importance of endoscopists and surgeons ensuring, wherever possible, minimal intervention before the removal of (hopefully intact) large and potentially diagnostically difficult adenomatous polyps of the colorectum.

Currently the Board relies on the postal transmission of histological slides to three EB pathologists. In these days of tele-pathology, there is potential for remote reviewing and reporting of these cases. Indeed, currently, the BCSP EQA scheme is entirely digitised and pathologists review cases from the Leeds Virtual Pathology website. In the future, the Expert Board may be simplified and made even more efficient by digitisation of images, although such technology may provide further challenges in diagnostically exacting cases.

The establishment of bowel cancer population screening has, then, been responsible for the introduction of a unique pathological diagnostic conundrum, whereby the florid changes of epithelial misplacement cause very close mimicry of adenocarcinoma. Indeed it is apparent that many of the pathological features used to differentiate the two conditions lack specificity, perhaps best exemplified by Table 2 in a review, in this journal, of bowel cancer screening pathology, in which ten parameters are stated to be only 'usually' useful in the great majority of categories.<sup>6</sup> Further, features characteristically associated with malignancy, such as budding, glandular isolation and lymphovascular invasion, have all been seen, or closely mimicked, in epithelial misplacement cases, the former two when there are secondary inflammatory changes and the latter as an artefact. From this review, there seems little doubt that the establishment of this unique diagnostic service, the Expert Board, has aided the diagnostic process and has ensured, we think and hope, the appropriate patient management in the great majority of cases.

## REFERENCES

1. Etzioni R, Urban N, Ramsey S, McIntosh M, Schwartz S, Reid B, et al. The case for early detection. *Nat. Rev. Cancer*. 2003; **3**: 243–52.
2. Geboes K, Ectors N, Geboes KP. Pathology of early lower GI cancer. *Best. Pract. Res. Clin. Gastroenterol*. 2005; **19**: 963–78.
3. Logan RFA, Patnick J, Nickerson C, et al. Outcomes of the Bowel Cancer Screening Programme (BCSP) in England after the first 1 million tests. *Gut*. 2012; **61**: 1439–46.
4. Loughrey MB, Quirke P, Shepherd NA. Standards and datasets for reporting cancers: Dataset for colorectal cancer histopathology reports. Royal College of Pathologists, July 2014; accessed 30.06.16 at: <https://www.rcpath.org/resourceLibrary/dataset-for-colorectal-cancer-histopathology-reports--3rd-edition-.html>
5. Carey F, Newbold M, Quirke P, Shepherd N, Warren B, Williams G. Reporting lesions in the NHS Bowel Cancer Screening Programme: Guidelines from the Bowel Cancer Screening Programme Pathology Group. NHS Cancer Screening Programmes; 2007. accessed 30.06.16 at: <https://www.gov.uk/government/publications/bowel-cancer-screening-reporting-lesions>
6. Loughrey MB, Shepherd NA. The pathology of bowel cancer screening. *Histopathology*. 2015; **66** : 66–77.
7. Clouston AD, Walker NI. Polyps and tumour-like lesions of the large intestine. In: Shepherd NA, Warren BF, Williams GT, Greenson JK, Lauwers GY, Novelli MR, eds. *Morson & Dawson's Gastrointestinal Pathology*. Oxford: Wiley -Blackwell, 2013: pp 652–3.

8. Wong NACS, Hunt LP, Novelli MR, Shepherd NA, Warren BF. Observer agreement in the diagnosis of serrated polyps of the large bowel. *Histopathology*. 2009; **55**: 63–6.
  
9. Shepherd N, Griggs R. Bowel cancer screening-generated diagnostic conundrum of the century: pseudo-invasion in sigmoid colonic polyps. *Mod. Pathol*. 2015; **28**: S88–94.
  
10. Shepherd NA. Polyps of the large intestine. In: Haboubi N, Geboes K, Shepherd N, Talbot I, eds. *Gastrointestinal Polyps*. Cambridge: Cambridge University Press, 2002. pp 95–122.
  
11. St-John D, Young G, Alexeyeff M, et al. Evaluation of new occult blood tests for detection of colorectal neoplasia. *Gastroenterology*. 1993; **104**: 1661–8.
  
12. Pascal R, Hertzler G, Hunter S, Goldschmid S. Pseudoinvasion with high-grade dysplasia in a colonic adenoma. Distinction from adenocarcinoma. *Am. J. Surg. Pathol*. 1990; **14**: 694–7.
  
13. Muto T, Bussey HJ, Morson BC. Pseudo-carcinomatous invasion in adenomatous polyps of colon and rectum. *J. Clin. Pathol*. 1973; **26**: 25–31.
  
14. Muto T, Bussey HJ, Morson BC. The evolution of cancer of the colon and rectum. *Cancer*. 1975; **36**: 2251–70.
  
15. Haggitt RC, Glotzbach RE, Soffer EE, Wruble LD. Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polypectomy. *Gastroenterology*. 1985; **89**: 328-36.
  
16. Yantiss R, Bosenberg M, Antonioli D, Odze R. Utility of MMP-1, p53, E-cadherin, and collagen IV immunohistochemical stains in the differential diagnosis of adenomas with misplaced epithelium versus adenomas with invasive adenocarcinoma. *Am. J. Surg. Pathol*. 2002; **26**: 206–15.



17. Yantiss RK, Goldman H, Odze RD. Hyperplastic polyp with epithelial misplacement (inverted hyperplastic polyp): a clinicopathologic and immunohistochemical study of 19 cases. *Mod. Pathol.* 2001; **14**: 869–75.
18. Mueller J, Mueller E, Arras E, Bethke B, Stolte M. Stromelysin-3 expression in early (pT1) carcinomas and pseudoinvasive lesions of the colorectum. *Virchows. Arch.* 1997; **430**: 213-9.
19. Hansen TP, Fenger C, Kronborg O. The expression of p53, Ki-67 and urokinase plasminogen activator receptor in colorectal adenomas with true invasion and pseudoinvasion. *APMIS.* 1999; **107**: 689–94.
20. Turner JK, Williams GT, Morgan M, Wright M, Dolwani S. Interobserver agreement in the reporting of colorectal polyp pathology among bowel cancer screening pathologists. *Histopathology.* 2013; **62**: 916–24.
21. Virtual Pathology at the University of Leeds. Accessed 02.08.16 at:  
<http://www.virtualpathology.leeds.ac.uk/eqa/specialist/nbcs/>
22. McHugh ML. Interrater reliability: the kappa statistic. *Biochem. Medica.* 2012; **22**: 276–82.
23. Gonzalez R, Cates J, Washington M, Beauchamp R, Coffey R, Shi C. Adenoma-like adenocarcinoma: a subtype of colorectal carcinoma with good prognosis, deceptive appearance on biopsy and frequent KRAS mutation. *Histopathology.* 2016; **68**: 183–90.
24. Panarelli N, Somarathna T, Samowitz W, et al. Diagnostic challenges caused by endoscopic biopsy of colonic polyps: a systematic evaluation of epithelial misplacement with review of problematic polyps from the Bowel Cancer Screening Program, United Kingdom. *Am. J. Surg. Pathol.* 2016; **40**: 1075-83.