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Proximal colon cancer and serrated adenomas – hunting the missing 10%

Pelvender Gill, Hannah Rafferty, David Munday, Adam Bailey, Lai Mun Wang, James E East, Runjan Chetty and Simon J Leedham

ABSTRACT – There is a 10% shortfall in the number of proximal colorectal cancer cases detected by the UK Bowel Cancer Screening Programme and the actual number of UK-registered proximal colorectal cancers. Sessile serrated adenomas/polyps (SSA/P) are common premalignant lesions in the proximal colon and are notoriously difficult to spot endoscopically. Missed or dismissed SSA/Ps might contribute to this UK proximal colon cancer detection disparity. In Oxfordshire, a service evaluation audit and histological review has shown a linear increase in the detection rate of these lesions over the past 4 years. This is the result of increased endoscopist and pathologist awareness of these lesions and improved interdisciplinary communication. This is the result of increased endoscopist and pathologist awareness of these lesions, together with improved interdisciplinary communication, and we predict that this will lead to a comparable detection increase nationwide. Ongoing surveillance of an increasing number of these premalignant lesions could become a significant endoscopic resource requirement once UK guidelines on serrated lesion follow up are established.

KEY WORDS: Colon cancer, serrated adenomas, bowel cancer screening, endoscopy

Introduction

Colorectal cancer is an ideal disease for population screening because it is common, has a well-recognised premalignant precursor lesion (the colorectal polyp) and treatment of the premalignant condition reduces the risk of cancer.[1] Endoscopy is an effective surveillance tool and the UK Bowel Cancer Screening Programme (BCSP), rolled out across England in 2009, is on track to meet the intended 16% reduction in overall bowel cancer mortality.[2] However, much of this mortality reduction relates to the detection of distal (left-sided) colonic tumours, because historically, full colonoscopic examination has been found to be ineffective at preventing proximal (right-sided) colonic tumours.[3,4] In the BCSP, faecal occult blood-triggered colonoscopy screening detects 22.8% of colorectal cancers proximal to, or at, the splenic flexure,[2] yet 33% of UK-registered colorectal tumours are located in the right hemicolon[5] – the missing 10%. This alarming gap in detection of a subset of colorectal cancers must be addressed to maximise the considerable health benefits of endoscopic population screening.

Part of this disparity is the result of reduced sensitivity of faecal occult blood testing for detecting proximal lesions; thus, patients with right sided polyps might not trigger BCSP colonoscopic examination.[6] However, the missing 10% also includes interval cancers, that is, tumours that present between screening examinations. Interval tumours result from missed or inadequately removed precursor lesions and/or accelerated tumour development, and are independently associated with a proximal colonic location.[7] Colonoscopic mucosal assessment of the proximal colon can be limited by bowel preparation or by incomplete examination[8] and, because it is a visual, operator-dependent procedure, there can be wide variation in polyp detection rates among colonoscopists.[9] Furthermore, there can be pronounced macroscopic, histological and molecular differences between the colonic precursor lesions predominantly found in the proximal and distal hemi-colons, indicating regional variation in the colonic microenvironment[10] and tumour biology.[11]

Colorectal carcinogenesis pathways

Over the past 20 years, meticulous phenotypic and molecular characterisation of colorectal cancer has led to the development of three main mechanistic pathways, defined by the underlying molecular pathogenesis and epitomised by an inherited polyposis syndrome.

Chromosomal instability

Chromosomal instability (CIN) is the most common cause of conventional adenomas that develop in all areas of the colorectum. This pathway arises from the sequential accumulation of genetic mutations in important tumour suppressor genes, usually initiated by a mutation in the gene encoding adenomatous polyposis coli *(APC)*. This is epitomised by germline mutation of *APC* in familial adenomatous polyposis (FAP)

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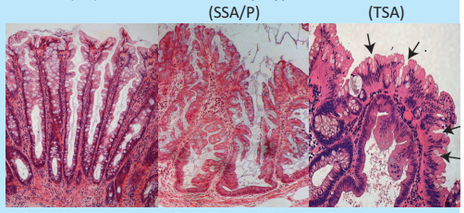
Oxford University Hospitals registered audit 2070

Table 1. Subdivision of serrated lesions based on histological criteria. Histological subclassification of serrated lesions into hyperplastic polyps, SSA/P and TSA. The different types of lesion have different regional colonic predilections and, importantly, have variable malignant potential.

	Hyperplastic polyp (HP)	Sessile serrated adenoma/polyp (SSA/P)	Traditional serrated adenoma (TSA)
Histological appearance			
Histological characteristics	• Serration present in uper (luminal part of crypts • Crypts are elongated but straight and narrow at the base • No cellular atypia	• Serration variably present throughout crypt length • Architectural disturbance at crypt base (inverted T or boot-shaped) • Dilated crypts with mature mucinous cells at base • Can occur with and without cellular atypia	• Prominent crypt serration throughout crypt length • Ectopic crypt formation (arrows) at right angles to main crypt axis contributes to serration • Can occur with and without cellular atypia
Common colonic location	Distal colon (recto-sigmoid)	Proximal colon	Distal (left) himicolon
Malignant potential	Benign	Pre-malignant	Pre-malignant

HP = hyperplastic polyps; SSA/P = sessile serrated adenomas/polyps; TSA = traditional serrated adenomas.

CpG island methylator phenotype

CpG island methylator phenotype (CIMP) tumours arise via the serrated neoplasia pathway and have a marked predilection for the proximal colon. Following an initiating genetic mutation in the genes encoding *BRAF* or *KRAS*, these lesions progress via epigenetic silencing of tumour suppressor and mismatch repair (MMR) genes by promoter methylation. This pathway is epitomised by serrated polyposis syndrome.

Microsatellite instability

Microsatellite instability (MSI) tumours are also more commonly located in the proximal colon. They arise from defective DNA repair through inactivation of mismatch repair genes, epitomised by the germline mutation of MMR genes seen in Lynch syndrome (hereditary non-polyposis coli [HNPCC]).

Although there can be considerable overlap between these pathways, sometimes even within an individual tumour, this molecular classification can help to distinguish important clinical characteristics, such as patient demographics, tumour distribution, response to therapy and prognosis.

Serrated lesions

Serrated lesions of the colorectum are characterised histologically by a saw-toothed appearance of the crypt epithelium. Formerly, all lesions exhibiting this characteristic morphology were called hyperplastic polyps and were thought to have no malignant potential.[12] However, more recently, serrated lesions have been characterised by their morphological and molecular profiles into different subsets that vary in their risk of malignant transformation (Table 1).

Sessile serrated adenomas/polyps (SSA/Ps) are the established precursor lesions to CIMP carcinomas, which are over-represented in interval tumours[7] and might account for up to one-third of all colorectal cancers.[13] SSA/Ps have a marked predilection for the right side of the colon and, although they progress indolently initially, they are believed to have an accelerated progression to cancer once sufficient epigenetic alterations have accumulated to initiate cellular atypia.[14] Furthermore, proximal serrated lesions are worryingly common, having been detected in as many as 1 in 5 screening colonoscopies of patients at average risk patients; they are also notoriously difficult to detect with standard white-light endoscopy.[16,17] It is likely that some missed, dismissed or undetected SSA/Ps eventually develop into CIMP tumours[18,19] and contribute to the UK proximal colon cancer detection disparity.

Clarifying diagnostic difficulties

Diagnosis of serrated lesions depends both on the endoscopist finding the polyp and the pathologist recognising the subtle morphological diagnostic criteria that distinguish SSA/Ps from common histological mimics, such as hyperplastic polyps, which carry little malignant potential.

Endoscopically, hyperplastic polyps are diminutive, pale lesions that are most commonly found in the distal colon. SSA/Ps are often flat areas of thickened mucosa, frequently draped over a fold, that can be indistinct from surrounding normal mucosa once the characteristic tenacious covering mucus cap has been washed off (Fig 1). The spraying of indigocarmine dye on the colonic mucosa (chromoendoscopy) or the use of narrowband imaging (NBI) can help to distinguish these lesions from surrounding normal tissue (Fig 1) and enhances serrated lesion endoscopic detection.[17]

Historically, the histopathological distinction of SSA/Ps from hyperplastic polyps has been beset by uncertainty surrounding confusing, inconsistent terminology and evolving diagnostic classification criteria leading to poor inter-observer agreement, even between specialist pathologists.[20] Recently, the publication of American consensus guidelines[21] has provided clarity, with SSA/P diagnosis dependent on the presence of just a single crypt with the characteristic architectural disturbances depicted in Table 1.

In the UK, there are currently no guidelines for surveillance of serrated lesions, but German,[22] Korean[23] and new American consensus guidelines[21] have recognised the malignant potential of these lesions and have recommended surveillance intervals comparable with conventional adenomas.

SSA/P detection in Oxfordshire

We hypothesised that improved endoscopic quality, endoscopist awareness and tightening of the SSA/P pathological diagnostic criteria would lead to large increases in the detection of SSAs in the UK. To assess this locally, we examined the pathology reporting trends for serrated lesions preceding and during the establishment of the BCSP. We performed a search of the computerised records of the Department of Cellular Pathology of the Oxford University Hospitals, for all lesions diagnosed as hyperplastic polyp (HP) proximal to the splenic flexure or SSA/Ps anywhere in the colon, from January 2009 to December 2012. Slides from 620 patients were reviewed and contentious cases were resolved by consensus of the three pathologists (PG, LMW and RC).

Surprisingly, our results showed that, the SSA/P was an unrecognised pathological entity in our hospitals until 2010, with all lesions before this classified as HPs. Reassessment of all proximal colonic HPs from 2009 to 2012 using the new diagnostic criteria led to the reclassification of a mean 42% of proximal HPs as SSA/Ps, indicating misinterpretation of the morphological criteria to distinguish these lesions. When reclassified HPs and correctly-diagnosed SSA/Ps were included, we demonstrated a linear increase in the prevalence of SSA/P detection since 2009, with 215 lesions diagnosed in 159 patients in 2012 (Fig 2a). This represents an increased detection rate of 62 polyps in 45 patients per year and, if this rate is continued, we will diagnose SSA/Ps in more than 200 patients in 2013 (Fig 2b).

Basing surveillance recommendations on the new American consensus guidelines,[21] we compared the endoscopic follow up arranged for patients with correctly identified SSA/Ps and the reclassified proximal HP cohort. Of these, 61% of patients with a formally diagnosed SSA/P were offered a repeat surveillance colonoscopy, whereas only 41% of those with an original diagnosis of HP had routinely arranged follow up (t-test, p=0.0027). This was usually dependent on the presence of concomitant pathology, such as conventional adenomas.

Dramatic increase in prevalence

SSAs are important precursor lesions to colorectal cancer and their detection is an essential part of early cancer prevention strategies. Their detection also depends on endoscopist identification of these frequently subtle lesions and the pathologist's application of updated diagnostic criteria to distinguish SSA/Ps from common histological mimics. Interdisciplinary communication is vital to ensure that pathologists and clinicians share relevant clinical information. With the establishment of the malignant potential of SSA/Ps, our gastrointestinal pathologists were less likely to dismiss an SSA/P as an HP, particularly if the endoscopist indicated that it was found in the proximal hemicolon. Poorly orientated or equivocal lesions often required serial sectioning to assist the search for crypts exhibiting characteristic SSA/P architectural disturbance. An ongoing lack of awareness of the new diagnostic criteria and subjectivity among pathologists were reflected by the misdiagnosis of a mean 42% of proximal colonic HPs; however, inhouse pathology education sessions and a move to gastrointestinal monospecialist reporting has seen a decrease in this rate over the past year.

After histologically reviewing and reclassifying serrated lesions over a 4-year period, we identified a dramatic and consistent increase in the prevalence of SSA/Ps. By controlling for pathological diagnostic variability, we showed that this linear increase is the consequence of improved endoscopic SSA/P detection resulting from increased endoscopist awareness of the appearance and significance of these lesions, the use of high-definition endoscopes and techniques, such as chromoendoscopy or NBI, to aid standard white-light endoscopy, as well as the establishment of endoscopic quality assurance measures with the local BCSP in 2010.

Implications of increased SSA/P detection

In Oxford, only 17.6% of premalignant serrated lesions were found on bowel cancer screening lists; thus, it is vital that all

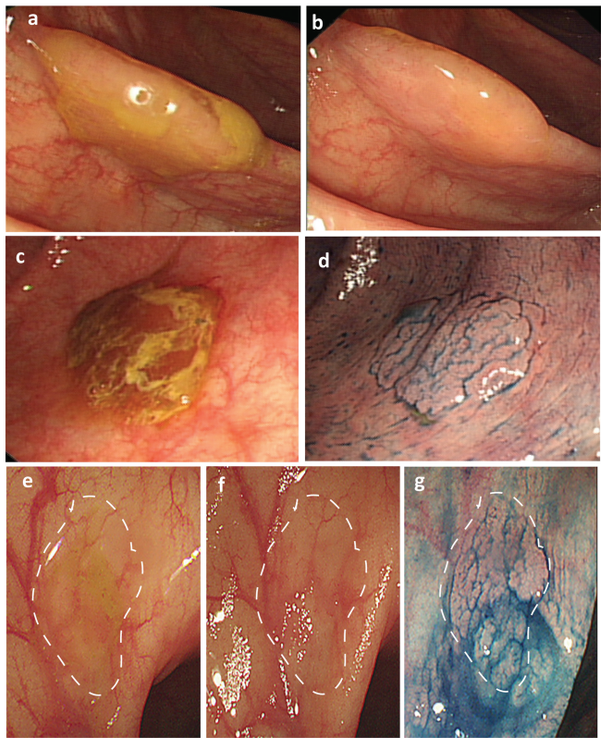


Fig 1. Endoscopic appearance. The characteristic appearance of an SSA/P draped over a colonic fold with (a) and without (b) the mucus cap. Indigocarmine dye spray can help to distinguish serrated lesions from the surrounding mucosa (c) once the mucus cap has been washed off (d). Sessile serrated adenomas can be difficult to detect with standard white-light endoscopy (e). A small mucus cap is the only clue to the underlying lesion (white dashed line). (f) When the cap is washed away, the lesion is indistinguishable from the surrounding mucosa (f) until indigocarmine dye is used to highlight the area in preparation for endoscopic resection (g). SSA/P = sessile serrated adenoma/polyp.

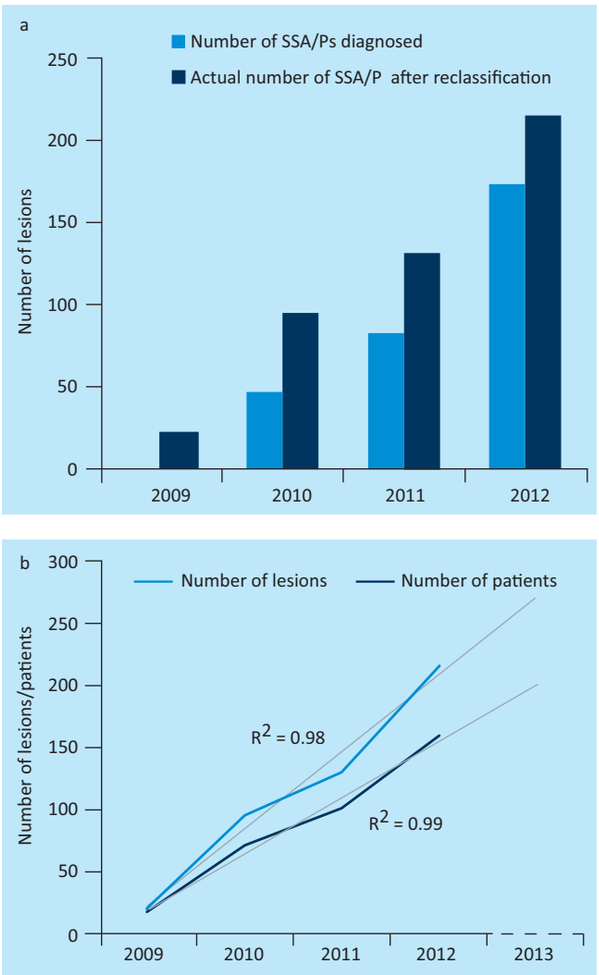


Fig 2. Premalignant serrated lesions detection in Oxfordshire since 2009. (a) We have seen a linear increase in the diagnosis rate (blue bars) and actual prevalence of premalignant serrated lesions after reassessment of all proximal hyperplastic polyps (dark blue bars) since 2009. The gap between the bars reflects a reducing pathologist misdiagnosis rate. (b) Extrapolation of these data shows that, at current rates, we are set to diagnose more than 260 premalignant serrated lesions (blue lines) in more than 200 patients (dark blue lines) during 2013. SSA/P = sessile serrated adenoma/polyp.

endoscopists, not only accredited bowel cancer-screening doctors, are trained and familiar with the identification and removal of these lesions. The linear increase in diagnosis of these lesions in Oxfordshire might reflect local specialist endoscopist and pathologist interest in serrated adenomas. However, we predict that the increasing awareness of these lesions among UK endoscopists and pathologists will lead to comparable large increases in SSA detection nationwide. It is important to know whether any improvement in endoscopic lesion detection will impact upon right-sided cancer diagnosis. For this, we must look to evidence from the USA and Germany; nations that established endoscopic bowel cancer screening in 2001 and 2002, respectively. Recently published data have demonstrated that high-quality colonoscopy is finally reducing right-sided colon cancer prevalence.[24,25]

The significant difference in the arranged follow up of patients with lesions labelled as 'serrated adenoma/polyp' or 'hyperplastic polyp' in the pathology report, underlines the crucial role of the pathologist in guiding clinician surveillance recommendations and highlights the importance of making every possible effort to make the pathological distinction between true SSA/Ps and their common histological mimics. There are no UK surveillance recommendations yet published for SSAs, but if the new American consensus guidelines had been applied, then a further 114 surveillance colonoscopies would have been required for our Oxfordshire SSA cohort. The surveillance of increasing numbers of these lesions might come to represent a significant future endoscopic resource requirement.

As with many assessments of endoscopic and pathological practice, the more you look, the more you find, and the time and resources required for the determined hunting of SSAs has to be balanced against an increasing demand for endoscopic and pathologist capacity. It is too early to say whether dramatic increases in SSA removal will have any impact on the detection of UK proximal colorectal cancer cases, but given their undoubted malignant potential and their endoscopic inconspicuousness, it is likely that missed SSAs contribute to the disparity in proximal colon cancer detection. With increased multidisciplinary awareness, evolving endoscopic technology and improved endoscopic training and quality assurance, there is real hope that improved endoscopic SSA/P detection will have an impact in reducing the missing 10%.

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Effectiveness of a geriatrician in the emergency department in facilitating safe admission prevention of older patients

Sally Jones and Peter Wallis

ABSTRACT – The decision to admit a frail older patient is rarely made by a geriatrician and often falls to staff in the emergency department (ED), who may not have the training to balance the risks, benefits and alternatives. We based a consultant geriatrician in the ED with the primary aim of facilitating admission prevention for older patients and this was achieved for 64% (543/848) of patients. A secondary aim was to facilitate direct admission to elderly care wards when admission was necessary, and this was achieved for 57% of admitted patients (174/305). The geriatrician was able to facilitate discharge from the ED for over half of potential 30-day readmissions seen. The overall 7-day ED re-attendance rate was 10.1%, but only 3.4% of patients were admitted with the same problem, indicating true admission prevention rather than admission delay. In conclusion, the placement of a consultant geriatrician in the ED is effective in facilitating admission prevention for older patients.

KEY WORDS: Geriatrician, emergency department, admission prevention, frail

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Introduction

Frail older patients constitute a large proportion of patients attending emergency departments (ED) in the UK, with 28,651 patients over the age of 75 attending the ED at the Heart of England Foundation Trust in 2012/13. The proportion of ED attendances resulting in an acute hospital admission rises with age,[1,2] and yet the risks associated with hospital admission – such as falls, delirium, hospital-acquired infection and de-conditioning – are greatest in the frail elderly. Older patients and those with multiple comorbidities have longer lengths of stay than younger patients,[3] thus increasing their exposure to the problems