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Title

Significant polyps and early colorectal cancer: the importance of high quality standardised histopathology.

Authors

[1]West NP	PhD FRCPath	Consultant histopathologist
[2]Langman G	FRCPath	Consultant histopathologist
[3]Haboubi N	FRCPath	Consultant histopathologist
[4]Carey F	FRCPath	Professor of Pathology
[5]Henry J	FRCPath	Consultant histopathologist
[6]Morgan M	FRCPath	Consultant histopathologist
[7]Sheahan K	FRCPath	Professor of Pathology

Author institutions

[1]Pathology and Tumour Biology, Leeds Institute of Medical Research at St. James's, University of Leeds, Leeds, UK

[2]Department of Cellular Pathology, Birmingham Heartlands Hospital, Birmingham, UK

[3]Department of Pathology, Spire Hospital, Manchester, UK

[4]Department of Pathology, Ninewells Hospital and University of Dundee, Dundee, UK

[5]Department of Cellular Pathology, South of Tyne and Wear Clinical Pathology Services, Queen Elizabeth Hospital, Gateshead, UK

[6]Department of Cellular Pathology, University Hospital of Wales, Cardiff, UK

[7]Department of Pathology, St. Vincent's University Hospital, Dublin & University College Dublin, Republic of Ireland

Corresponding author

Dr. Nick West

Pathology & Tumour Biology

Wellcome Trust Brenner Building

St. James's University Hospital

Beckett Street
Leeds,
LS9 7TF
n.p.west@leeds.ac.uk

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Conflict of interests

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Abstract

Significant polyps and early colorectal cancers (SPECC) require meticulous pathological handling and reporting to ensure that the presence or absence of high risk features is accurately determined. There are significant diagnostic difficulties in a proportion of cases with the possibility of submucosal invasion being overcalled, potentially exposing patients to the risks associated with major resectional surgery. Many of the high risk features in the Royal College of Pathologists minimum dataset for local excision of colorectal cancer are subjective with poor reproducibility, even among experienced gastrointestinal pathologists. This review will discuss the optimal methods for determining high risk lesions and introduce some of the novel markers that may facilitate this assessment.

Introduction

Pathologists play an important role in the management of patients with significant polyps and early colorectal cancers (SPECC). National standards are followed when dissecting and reporting polypectomy/local excision specimens in both the NHS bowel cancer screening programme (BCSP) and in routine non-screening practice. Early cancers should be reported according to the Royal College of Pathologists dataset for histopathological reporting of colorectal cancer [1], and proforma/synoptic reporting is strongly encouraged to ensure all important prognostic features in the dataset for local excision specimens are recorded.

When reporting SPECC lesions, the pathologist must in the first instance determine whether it shows evidence of submucosal invasion. There are a significant number of difficult cases that can be misinterpreted by the unwary, and displacement of adenomatous epithelium into the submucosa (pseudoinvasion) is particularly problematic. In a review of difficult cases in the NHS BCSP, 69% of lesions originally reported as malignant were downgraded to benign on expert review [2]. For this reason the NHS BCSP pathology committee have recommended that all cancers diagnosed in the programme are reported by two independent pathologists to reduce the risk of over treatment [3]. Occasionally it can be difficult to reach a consensus decision within a department, even across a group of specialist gastrointestinal pathologists. The NHS BCSP supports an expert board of three nationally recognised specialist gastrointestinal pathologists who will review such difficult cases and provide a consensus opinion. The results from the first five years of this process were published last year [2]. Some groups have proposed the use of immunohistochemistry for MMP-9 and type IV collagen to facilitate a diagnosis of invasion [4], although these techniques have not been validated across multiple centres and are not routinely recommended.

When reporting early (pT1) cancers, there are a number of high risk features that should be assessed and reported as standard. It is critical that pathologists correctly report these features, and the presence of any may indicate the need for full resectional surgery, with a significant risk of morbidity and mortality [5]. Clearly failure to identify such features may lead to undertreatment and increase the risk of tumour recurrence or distant spread. Commonly accepted high risk features include

diameter of the cancer greater than 30 mm, margin involvement (defined as tumour at or less than 1 mm from the margin), poor differentiation, lymphatic channel involvement, venous invasion and depth of invasion into or beyond SM3. This review will focus on the optimal histopathological examination of SPECC lesions and some novel markers that may facilitate more accurate estimation of risk.

Macroscopic examination

It is always preferable to receive polypectomy/local excision specimens intact, to facilitate accurate diagnosis, assessment of the resection margins and measurement of the lesion. Piecemeal excisions preclude this assessment. If the lesion is polypoid the specimen can generally be fixed intact. If the lesion is sessile, it should be fixed by either pinning to a polystyrene/cork board or placing between two foam inserts in a plastic cassette to ensure it stays flat. Larger specimens can be dealt with the same way in a large (mega block) cassette. Careful dialogue is required between the endoscopic and histopathological teams to ensure that the specimen pathway enables optimum reporting.

Polypoid lesions are initially classified based on shape. Pedunculated polyps protrude for more than twice the thickness of the adjacent mucosa and have a base less than one third of the diameter of the head of the lesion. Sessile lesions have a base and top of the lesion that are essentially the same width. Subpedunculated polyps are intermediate broad based lesions that are dealt with as for sessile lesions. Both pedunculated and sessile lesions can be bisected if small (< 10 mm) and serially sliced at 3 mm intervals if larger. For pedunculated lesions it is important that the stalk is embedded and examined at multiple levels. The tissue should be embedded in such a way as to facilitate measurement of the maximum size of the lesion on the glass slide (if possible) whilst maximising assessment of the margins.

Microscopic reporting of adenomas

Whist optimal macroscopic handling is very important to facilitate optimal histology, the diagnosis and most of the high risk features will be determined microscopically.

In standard adenomas, the proportion of villousness will determine whether a lesion is tubular (<25% villous), tubulovillous (25-75% villous) or villous (>75%). Increasing

villousness is known to be a high risk feature. Around the boundaries there is clearly significant interobserver variation. The degree of dysplasia should be classed as low grade or high grade primarily based on architecture.

Within the UK, serrated lesions should be classified according to national guidance, with particular care taken to recognise and report sessile serrated lesions, which have an association with the serrated neoplasia pathway [6]. There are some differences of opinion internationally around the nomenclature and definition of sessile serrated lesions. UK guidance supports using the WHO criteria of three crypts or two adjacent crypts showing at least one of the characteristic features [7], whereas US guidance recommends a diagnosis based on changes in a single crypt [8]. Using the US criteria has been shown to increase the diagnoses of sessile serrated lesions by up to 7% [9].

Adenomas ≥ 10 mm carry greater risk and are managed differently [10]. For this reason it is important that the assessment of size is standardised. The original St. Marks data was generated on formalin-fixed, paraffin embedded pathology specimens therefore measurement on the glass slides remains the gold standard where possible. Studies have shown significant differences between endoscopic estimates and glass slide measurements, with endoscopy tending to overestimate size potentially leading to unnecessary additional follow up [11]. Pathologists have also been shown to have a tendency to “round up” macroscopic measurements, so it is important that an accurate glass slide measurement of the adenoma size is given.

It is important to recognise that biopsy or partial polyp removal is not always sufficient to exclude a diagnosis of malignancy in colorectal polyps. Studies have shown a false negative rate of up to 18.5% if the entire lesion is not sampled [12]. This should be recognised in the text of the pathology report and clinicopathological correlation recommended to determine whether further investigation is required.

Microscopic reporting of early colorectal cancers removed by local techniques

Increasing diameter of the invasive component is associated with a greater risk of tumour recurrence, with an 18% increased risk per centimetre [13]. The maximum size of the lesion should therefore be accurately documented as for major

resections. Cancers measuring 30 mm or more are not usually resected by local excision.

Poor differentiation is a recognised adverse prognostic feature, however, this is highly subjective. Some studies have shown poor agreement (kappa 0.07) between even experienced gastrointestinal pathologists [14]. A two tier classification is recommended in the UK with any poorly differentiated focus defining poorly differentiation, and all other tumours being classed as well/moderately differentiated. This differs from the assessment method used in major resections where differentiation is based on the predominant area [1]. However, it is recognised that poor differentiation in the context of mismatch repair deficiency is common and is associated with a good prognosis. Recent NICE guidance states that all colorectal cancers should be tested for mismatch repair deficiency at the point of diagnosis to screen for Lynch syndrome, although this is not yet routine in many centres due to the lack of an established funding pathway [15]. If not performed in all cases, it is highly recommended to undertake testing of poorly differentiated cancers to allow accurate interpretation of risk.

Depth of invasion in pT1 cancers is related to the risk of lymph node metastases and can be assessed in pedunculated lesions by Haggitt levels and in sessile lesions by Kikuchi levels. Whilst these systems appear simple in textbook diagrams, their application in practice is often rather challenging. Pedunculated lesions can show significant distortion and unless the polyp has been well embedded it can be difficult to assess the microanatomy. Sessile lesions require the full thickness of the submucosa to assess, so can only be done if at least part of the muscularis propria is present at the base of the lesion. Even then, variability in the thickness of the submucosa and ulceration/destruction of the muscularis mucosae often make accurate assessment of submucosal thirds difficult. The agreement in Haggitt and Kikuchi staging has been shown to be ‘poor’ and ‘fair’ respectively with kappa values of 0.15 and 0.36 between four experienced gastrointestinal pathologists [14]. In Japan, the absolute depth of invasion beyond the muscularis mucosae has been shown to be predictive of nodal disease [16]. This is likely to be more practical as it does not require the full thickness of the submucosa to be present, however, destruction of the muscularis mucosae can still make this assessment subjective.

Cancer at or within 1 mm of the resection margin is classed as an involved margin in the same way as for major resections. However, there is some evidence that less than 1 mm of clearance is safe for early tumours undergoing local excision, but this has not been adopted in the 2nd edition of the NHS BCSP pathology reporting guidelines due for release shortly. The distance to both the lateral and deep margins should be assessed and the shortest distance reported. For adenomas, usually only the lateral margin applies if the resection plane is adequate, and adenoma must extend all the way to the margin to be involved. Further guidance on the assessment of margins is provided through the NHS BCSP [17]. Care should be taken to look for the diathermised plane of resection, which may retract back into the stalk of a polyp. Deeper levels may help to reveal the relevant margin. Care should be taken to account for the three dimensional configuration of polyps. In cases with doubt, a conservative approach should be adopted and only margins that can be confidently assessed should be reported. It is worth remembering that cancer or adenoma at the margin does not necessarily imply incomplete resection. Correlation with endoscopy is required to determine this.

Lymphatic and venous invasion are also recognised to be high risk. Both are now required to be reported under TNM8 along with perineural invasion. All three methods of spread can be difficult to report in practice with only fair agreement (kappa 0.35) for lymphovascular invasion between experienced gastrointestinal pathologists [14]. Lymphatic invasion can be overcalled in cases with retraction artefact and can also be easily missed. In cases with doubt, immunohistochemistry with a lymphatic marker such as D2-40 can be helpful. For venous invasion, destruction of the vessel wall can make assessment difficult. Looking for signs of an adjacent similar sized artery can be helpful, as can the use of elastin stains and immunohistochemistry.

Novel markers for assessing high risk

Recent work from the University of Leeds has shown that lymphatic and blood vessels are present in greater numbers in the superficial third of the submucosa than in the deeper layers [18]. SM3 had statistically smaller vessel circumference and area compared to SM1/SM2, which appears in contrast to the observation that SM3

involvement by carcinoma carries a greater risk in pT1 disease. Such digital pathological analysis facilitates the assessment of novel quantitative biomarkers including area. Further study by the Leeds group has shown a strong correlation between with area of submucosal invasion and the risk of nodal metastases [19]. Taken together with the distribution of lymphatic channels in the submucosa, this suggests that it is not necessarily the depth of submucosal invasion that infers risk, but the overall volume of disease in SM1. By definition, SM3 invasion generally implies a greater volume of disease in SM1/SM2 and therefore access to the greatest concentration of vascular structures.

Finally, tumour budding is well recognised to be a poor prognostic factor but is not routinely reported internationally. This is partly due to concerns over reproducibility and the wide variety of scoring systems available. Studies have shown only moderate agreement (kappa 0.44) when experienced gastrointestinal pathologists assess budding [14]. Recently an international consensus meeting has now agreed the optimal system to be used [20]. This consists of assessment on haematoxylin and eosin stained sections in one hotspot area at the invasive front using a three tier system. The new edition of the Royal College dataset lists budding as a non-core item, recognising the international consensus classification but requesting more evidence before its routine adoption in the UK [1]. However, in the US the College of American Pathologists has now recommended the routine reporting of tumour budding [21].

Summary

Pathologists play a major role in the treatment of SPECC lesions and it is essential that dissection and reporting is standardised to ensure that all of the high risk features are optimally assessed. Many of the high risk features are subjective but digital pathology facilitates the introduction of novel objective markers which give further insight into tumour behaviour.

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