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PREFACE

These guidelines have been produced by the Bowel Cancer Screening Programme Pathology Group. Members of the panel were:

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These guidelines have been endorsed by the Association of Clinical Pathologists and the Association of Colproctologists of Great Britain and Northern Ireland.

A version of these guidelines with additional examples can also be found at www.virtualpathology.leeds.ac.uk/nbcs/guidelines.php.

Please send comments/suggestions/feedback to patpq@leeds.ac.uk for consideration for the revision of these guidelines.

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1. INTRODUCTION

1.1 Background

The NHS Bowel Cancer Screening Programme (NHS BCSP) will, in due course, become the largest programme for bowel cancer screening in the world. It offers a unique opportunity to improve survival in this condition as well as clarifying the importance of current diagnostic criteria and identifying the biological potential of precursors of colorectal cancer.

These guidelines are produced under the auspices of the NHS BCSP. They have been derived to answer many of the questions that have arisen within the pilot screening centres in England and Scotland, to ensure that key data are collected in a consistent manner and to enable further recommendations to be made to provide the best possible evidence base for routine practice. We welcome feedback and will develop these guidelines as the evidence base improves. We are striving to ensure consistency across the UK and between the published recommendations of concerned professional organisations such as the Royal College of Pathologists, the British Society of Gastroenterology and the Association of Coloproctology of Great Britain and Ireland. We have also built on the pathology work undertaken during the Cancer Research UK (CRUK) flexisigmoidoscopy trial by adopting many of the definitions we developed for that trial. These guidelines are consistent with the dataset produced by the Royal College of Pathologists for reporting colorectal cancer (including local excision specimens) and will be developed closely with them in the future.

1.2 General issues

Dysplasia is divided into low and high grade to improve interobserver agreement, with ‘high grade dysplasia’ equating to ‘severe dysplasia’ in older systems. The term hyperplastic rather than metaplastic polyp is recommended; neither is a good name, but adding a third only confuses matters further. The reasons for recommending the term hyperplastic are that, firstly, it has been used in both pilot centres; secondly, true metaplasia (e.g. squamous islands) can rarely occur in dysplastic adenomas; and, thirdly, the term metaplastic is defined as a change in epithelial type from one mature epithelial type to another. Although the epithelium of a hyperplastic lesion is abnormal, it is not of a different epithelial type. Different antigenic patterns have been demonstrated in hyperplastic polyps, but are not those of another mature epithelial type. Polyps have been broadly subclassified into classical, hyperplastic serrated spectrum and other types of lesion. We have concentrated on early invasive lesions as these have proved challenging within the pilot screening centres, the evidence base is currently poor and the national screening programme will generate many of these difficult lesions. We have also sought to identify the serrated spectrum to allow further investigation in this area.

The target for histopathology reporting is that 90% of lesions should be reported within 7 days. This will allow patients who have had a polyp removed at colonoscopy to be given an appointment to be seen the following week in the follow-up clinic.

Pathologists must complete either the screening programme proforma or its computerised version. These are to be returned to the screening centre administrator for pathology data to be entered onto the bowel cancer screening system (BCSS). Pathologists may also wish to provide a free text report directly to the clinician.

A copy of the latest version of the proforma can be found at www.virtualpathology.leeds.ac.uk/nbcs/nbcs.php.
2. DISSECTION OF SUBMITTED LESIONS

The material received will be either a biopsy of a lesion, an excision of a polyp or a submucosal resection of a sessile lesion or a larger resection that is either a transendoscopic mucosal excision (TEM) or a full surgical excision. If only a biopsy is received, the size of the lesion and completeness of excision will not be assessable by the pathologist and these should be recorded as not assessable (n/a).

Although the principles of pathological reporting are the same as in major resections, a number of features require special attention in local excisions of (presumed) early cancers with curative intent because they are used to determine the necessity for more radical surgery. In addition to the assessment of completeness of excision, these include recording parameters that predict the presence of lymph node metastasis in early tumours, namely tumour size, poor differentiation, the depth of invasion into the submucosa and the presence of submucosal lymphovascular invasion.\textsuperscript{2–7} However, there is only limited evidence and no consensus in the published literature on exactly how some these parameters should be assessed, especially the depth of submucosal invasion. We hope to improve this situation from data derived from the bowel cancer screening programme.

Local excisions are undertaken endoscopically or, in the case of early rectal tumours, under direct vision. The majority of carcinomas arise within pre-existing adenomas that may be polypoid, sessile or flat, and the best pathological information is derived when lesions are excised in their entirety to include both the invasive and preinvasive components.\textsuperscript{8} Polypoid lesions on a narrow stalk can be fixed intact, whereas sessile lesions should be pinned out, mucosal surface upwards, on a small piece of cork or other suitable material, taking pains to identify the narrow rim of surrounding normal tissue before fixing intact. Piecemeal removal of tumours, which is entirely acceptable for palliative resections, should be avoided because it precludes a reliable assessment of completeness of excision.

After fixation, polypoid lesions may be bisected through the stalk if they measure $< 10$ mm; larger polyps are trimmed to leave a central section containing the intact stalk, and all fragments are embedded for histology. It is recommended that at least three sections are taken from blocks containing the stalk. The margins of larger, sessile lesions should be identified with appropriate coloured markers (inks or gelatine), and the whole of the specimen transversely sectioned into $3$ mm slices and submitted for histology in sequentially labelled cassettes. When the margin of normal tissue is less than $3$ mm, a $10$ mm slice containing the relevant margin should be made and further sectioned at right angles.
3. KEY DIAGNOSTIC FEATURES

3.1 Site

The site of origin of each specimen should be individually identified by the clinician and provided to the pathologist on the request form. The pathologist should record this on the pathology proforma. This is important information because the risk of lymph node metastases from a T1 adenocarcinoma varies depending on the site of the lesion.7

3.2 Type

Three broad groups of lesion are reported, namely classical adenomas, serrated lesions and other polyps. Classical adenomas are divided into tubular, tubulovillous or villous types. The spectrum of lesions with a serrated growth pattern is subdivided into hyperplastic polyps, mixed dysplastic/hyperplastic adenomas and serrated adenomas. Other types of polyp include inflammatory polyps, juvenile polyps, Peutz–Jeghers or other types which are included under not otherwise specified and described in free text.

3.3 Classical adenomas

By definition, adenomas must show dysplasia. They can be of tubular, tubulovillous or villous types, and demarcation between the three is based on the relative proportions of tubular and villous components according to the ‘20% rule’ described in the WHO classification.8 At least 20% of the estimated volume of an adenoma should be villous to classify a polyp as tubulovillous, and 80% villous to be defined as a villous adenoma. All other lesions are classified as tubular.

The 20% rule applies only to wholly excised polyps and to intact sections of those lesions that are large enough to provide reliable proportions. For small fragmented lesions or superficial polyp biopsies, the presence of at least one clearly identifiable villus merits classification as ‘at least tubulovillous’.

3.4 Villousness

Although it is accepted that a neoplastic villus almost defies definition, the following descriptions have been developed to help recognize ‘villousness’.

Villous structures may take different forms that, in themselves, are not known to have any particular significance but may assist observer reproducibility. These include:

- ‘Classical’ villi, which are composed of long, slender, upgrowths of epithelium on a thin delicate stromal core that branches little. These usually have parallel sides (although sometimes a bulbous tip), and often appear to extend right down to the muscularis mucosae.
- ‘Palmate’ villi, which are composed of clustered, broader, branching, leaf-like structures with a hand-like configuration. Tubular glands may be present at the base of these structures, and sometimes may even be present within the stromal core of villi.
- ‘Foreshortened’ villi, which are composed of slender non-branching outgrowths with a thin stromal core that clearly protrude beyond the overall surface contour of an otherwise well developed tubular lesion.
Figure 1 A fragmented biopsy showing a villous component.

Figure 2 An example of classical villi, which should provide little difficulty to a pathologist. The bulbous tip that can be seen is well demonstrated.
Most diagnostic difficulties will arise with foreshortened villi, particularly in distinguishing ‘true’ villi from exaggerated, axially sectioned, neoplastic crypts with distended luminal openings. In these situations, it is better to err on the side of underdiagnosis of villous change, especially in small (< 1 cm) adenomas, and to restrict the term to lesions only for those with convincing outgrowths.

Villous structures with low grade dysplasia not infrequently show a characteristic quality to the epithelium, with rows of regular tall columnar cells with large conspicuous apical mucin vacuoles that are reminiscent of the surface epithelium of the stomach. This is in contrast to the typical goblet cells interspersed with eosinophilic colonocytes containing sparse or no obvious mucin that are characteristic of tubular adenomas. The presence of such a ‘mucinous’ epithelium should sway the diagnosis in favour of villous histology if it is conspicuous in an otherwise indeterminate lesion.

3.5 Hyperplastic polyps: serrated adenoma spectrum

The pathology of serrated lesions is currently an active area of research, and there is a limited evidence base for the relative importance of some of the phenotypes that have been described in the literature. In light of this, the current guidelines identify practical categories that may be studied further and subcategorised in future when more evidence is available. In the spectrum are non-dysplastic hyperplastic polyps, dysplastic lesions with a serrated architecture, called here serrated adenomas, and mixed hyperplastic/adenomatous polyps.

3.6 Hyperplastic polyps

The architecture of the glands can vary from normal to grossly distorted. Usually, in the case of hyperplastic polyps, the glands demonstrate elongated crypts with an excess of columnar absorptive cells leading to a tufted, crenated appearance towards the surface. A variable degree of epithelial proliferation can be seen in the base of the crypts. The cells are cytologically regular with no dysplasia present.
Figure 4  Examples of tubulovillous adenomas.
3.7 **Serrated adenomas**

These lesions have the morphology of hyperplastic polyps, namely a serrated epithelial surface with abundant eosinophilic cytoplasm, but they show definite dysplasia throughout the lesion.

3.8 **Mixed hyperplastic/adenomatous polyps**

These lesions have both non-dysplastic hyperplastic type epithelium showing a serrated glandular architecture and areas of adenomatous dysplastic epithelium. The two phenotypes are morphologically distinct, and, although they may intermingle, individual glandular structures showing both patterns are not present.

3.9 **Other types**

3.9.1 **Inflammatory polyps**

Experience from NHS BCSP pilot sites has shown that inflammatory type polyps are relatively common. Although they are most usually seen as a complication of chronic inflammatory bowel disease, particularly ulcerative colitis, they are also seen in association with diverticulosis, mucosal prolapse and at the site of ureterosigmoidostomy. Furthermore, sporadic single inflammatory type polyps are well described in the colorectum. As the reporting pathologist may not know the true context of such polyps, we recommend that all such polyps are classified as ‘inflammatory polyp’.

3.9.2 **Juvenile polyps**

Classical juvenile polyps are spherical in shape, show an excess of lamina propria and have cystically dilated glands. The expanded lamina propria shows oedema and mixed inflammatory cells. Experience from the NHS BCSP pilot sites suggests that occasional juvenile type polyps are identified, even in the screening age group. Juvenile polyps are, of course, most common in children, but occasionally examples are seen in adults. It remains uncertain whether the juvenile type polyps identified in the screening population are true classical juvenile polyps or whether they represent inflammatory type polyps with mimicry of classical juvenile polyps. We advise that any polyp showing juvenile polyp type features should be classified as a ‘juvenile polyp’ for the purposes of diagnostic reporting in the NHS BCSP. In classical juvenile polyps, there is often epithelial hyperplasia but dysplasia is very rare, with only a handful of case reports in the literature.  

So-called ‘atypical juvenile polyps’ show different morphological features, with a multilobated architecture, intact surface mucosa (usually) and a much more pronounced epithelial component. They are a characteristic feature of juvenile polyposis. It would seem most unlikely, given the rarity of juvenile polyposis and the age of the screening population, that such polyps might be seen in the NHS BCSP. Such a polyp should be recorded as representing ‘juvenile polyp’. They are much more likely to harbour epithelial dysplasia.

3.9.3 **Peutz–Jeghers polyps**

Although these polyps are usually seen in Peutz–Jeghers syndrome, occasional examples are demonstrated as single sporadic polyps in the colon. There remains uncertainty as to whether ‘inflammatory myoglandular polyp’ represents a similar entity. As with juvenile polyposis, it would seem most unlikely, given the rarity of the syndrome and the age of the screening population, that Peutz–Jeghers syndrome would be diagnosed as part of the NHS BCSP. Although Peutz–Jeghers polyps are classified as hamartomas, they have a very organised structure. They have a central core of smooth muscle with conspicuous branching, each branch being covered by colorectal
type mucosa that appears hyperplastic but not dysplastic. As with sporadic juvenile polyps, solitary Peutz–Jeghers type polyps are most unlikely to demonstrate foci of dysplasia.

3.9.4 Cronkhite–Canada syndrome

We believe that it is most unlikely such cases will present via the NHS BCSP, and the true diagnosis may not be recognised by pathological assessment. Such polyps are probably best regarded as being of inflammatory type.

3.10 Other polyps, including carcinoids and stromal polyps

Small rectal mucosal nodules, showing the characteristic features of hind gut carcinoids, are not uncommon. For pathological reporting as part of the NHS BCSP, we recommend that these are recorded as ‘other polyp’ and that their true nature is recorded in free text. Furthermore, there are a number of stromal tumours that can also present as polyps. Lipomas and leiomyomas of the muscularis mucosae are probably the most likely to be seen in the NHS BCSP, and we recommend that these are recorded as ‘other polyp’ and that their true nature is recorded in free text. North American experience with bowel cancer screening indicates that, rarely, other unusual forms of stromal tumour can present as polypoid nodules in the screening programme. Such stromal lesions include ganglioneuroma, neurofibroma, gastrointestinal stromal tumour (GIST), various forms of vascular tumour, perineurioma, fibroblastic polyp and epithelioid nerve sheath tumour.

3.11 Shape

The NHS BCSP is not designed to detect flat adenomas because it does not mandate magnifying endoscopy or chromoendoscopy. Flat adenomas have not been separately identified at this stage, but this area will be revisited in the future when more experience has been gained. The pilot sites saw these lesions only rarely in their material.

3.12 Size

An accurate measurement is very important and must be to the nearest millimetre (and not ‘rounded up’ to the nearest 5 or 10 mm). This will be audited. If possible, the maximum size of the lesion should be measured from the formalin fixed macroscopic specimen. For small lesions (5 mm or less) that fit on one section in their entirety, it is acceptable to measure their dimensions from the glass slide. If a biopsy is received, then n/a should be entered in the size box.

3.13 Dysplasia

We recommend that high grade dysplasia and low grade dysplasia are used instead of mild, moderate and severe dysplasia. This will increase the interobserver agreement and allow pathologists to concentrate on the important diagnostic criteria.

3.14 High grade dysplasia

The changes of high grade dysplasia should usually involve more than just one or two glands (except in tiny biopsies of polyps), sufficient to be identified at low power examination. Caution should be exercised in overinterpreting isolated surface changes that may be due to trauma, erosion or prolapse.

High grade dysplasia is diagnosed on architecture, supplemented by an appropriate cytology. Hence, its presence is nearly always suspected by the appearance under low power of complex
architectural abnormalities in structures whose epithelium looks thick, blue, disorganised and ‘dirty’. The architectural features are:

- complex glandular crowding and irregularity (note that the word ‘complex’ is important and excludes simple crowding of regular tubules that might result from crushing)
- prominent budding (note that the word ‘prominent’ is important; there is probably some degree of glandular budding, by definition, in all tubular adenomas)
- a cribriform appearance and ‘back to back’ glands
- prominent intraluminal papillary tufting.

Figure 5  (A) High grade dysplasia showing architectural changes. (B) Another area of high grade dysplasia from the same case showing a lesser degree of architectural abnormalities.
Figure 6  (A) and (B) The changes shown here are not those of high grade but are of low grade dysplasia because of the architectural changes. The cytology is less worrying.
Although many of these features often coexist in high grade dysplasia, individually they are neither necessary nor usually sufficient. Indeed, they may occasionally occur in lower grades of dysplasia, which is why it is necessary to go on to scrutinise the cytological features for signs of high grade dysplasia. The **cytological** features are:

- loss of cell polarity or nuclear stratification to the extent that the nuclei are approximately equally, though haphazardly, distributed within all three thirds of the height of the epithelium
- markedly enlarged nuclei, often with a dispersed chromatin pattern and a prominent nucleolus
- atypical mitotic figures
- prominent apoptosis, giving the lesional epithelium a ‘dirty’ appearance.

Again, these features usually coexist in high grade dysplasia, and caution must be exercised in using just one. It should be emphasised again that they should **occur in a background of complex architectural abnormality**. Marked loss of polarity and nuclear stratification sometimes occurs on the surface of small, architecturally regular, tubular adenomas that otherwise have a lower grade of dysplasia, probably as a result of trauma, and must not be used to classify a lesion as high grade. The only exception to the rule is when the specimen consists of just a small biopsy from a polyp, ie when there is insufficient tissue to assess the architecture properly. In this situation, it is permissible to label florid cytological abnormalities alone as high grade dysplasia, but this will usually lead to re-excision of the whole polyp, when it will be possible to assess the whole lesion properly.
4. ADENOCARCINOMA

4.1 Definition of invasion

The recommended definition of an adenocarcinoma is the one that is in everyday use within the UK of invasion of neoplastic cells through the muscularis mucosae into the submucosa of the bowel wall.

This definition does not allow for the diagnosis of intramucosal carcinoma, and such cases should be considered to be high grade dysplasia. Also, the definition does not allow comparison with Japanese series, in which a diagnosis of carcinoma can be made on cases of high grade dysplasia without invasion, but it is compatible with US and European literature.

The TNM classification of colorectal tumours is given in Appendix 1, and the relevant SNOMED codes are given in Appendix 2.

4.2 Epithelial misplacement

Epithelial misplacement of adenomatous epithelium into the submucosa of a polyp is a well recognised phenomenon. It is commonly seen in prolapsing polyps in the sigmoid colon. Experience from the pilot sites suggests that this will be one of the most difficult areas of pathological diagnostic practice in the NHS BCSP. These sigmoid colonic polyps are particularly prone to inflammation and ulceration, features which tend to enhance the dysplastic changes present. When associated with epithelial misplacement, the potential for misdiagnosis of early carcinoma and the overall diagnostic difficulties become much greater.

4.3 Early adenocarcinomas (pT1)

Tumours that invade the muscularis propria (pT2) usually require further surgery and should be staged according to the cancer minimum dataset.

pT1 tumours will provide many difficulties in the programme, and the current evidence base for their management is poor. Thus as a priority we have chosen to concentrate on generating a firm evidence base for management. This will require a limited number of extra assessments that we will then refine on the basis of the data emerging from the pilot sites and the programme. In particular, substaging and differentiation grading are addressed.

4.4 Substaging

In pT1 tumours, the frequency of lymph node metastasis in sessile tumours that involve the superficial, middle and deep thirds of the submucosa (so-called Kikuchi levels sm1, sm2 and sm3 respectively⁶) has been reported to be 2%, 8% and 23% respectively.⁷

In polypoid lesions, Haggitt et al⁵ identified the level of invasion into the stalk of the polyp as being important in predicting outcome and found that ‘level 4’ invasion, in which tumour extended beyond the stalk of the polyp into the submucosa but did not invade the muscularis propria, was an adverse factor.
However, neither the Kikuchi (for sessile tumours) nor the Haggitt (for polypoid tumours) system is easy to use in practice, especially if there is fragmentation or suboptimal orientation of the tissue; one study found lymph node metastases in 6 out of 24 Haggitt level 3 lesions. More recently, Ueno et al\textsuperscript{14} proposed that the depth of invasion measured in microns beyond the muscularis mucosae provides a more objective measure, and this system has been adopted in Japan. Each classification has advantages and disadvantages. The Kikuchi system cannot be used if there is no muscularis propria; the Haggitt system is of no value in sessile lesions; and measurement depends on a recognisable submucosa from which to measure. In view of the uncertainty and lack of consensus, a firm recommendation for one method of assessing local invasion cannot be made, and all three approaches should be filled in on the template proforma so that a future analysis can compare the value of these substaging methods.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure7a.png}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure7b.png}
\caption{Haggitt levels of invasion in polypoid carcinomas. Reproduced with permission from Mainprize KS, Mortensen NJM, Warren BF. Early colorectal cancer: recognition, classification and treatment. \textit{British Journal of Surgery}, 1998, 85: 469–476. Copyright British Journal of Surgery Society Ltd. Permission is granted by John Wiley \& Sons Ltd on behalf of the BJSS Ltd.}
\end{figure}
4.5 Tumour grade

Poorly differentiated carcinomas are identified either by the presence of irregularly folded, distorted and often small tubules or by the lack of any tubular formation. In the absence of good evidence, we recommend that a grade of poor differentiation should be applied to a polyp cancer when any area of the lesion is considered to show poor differentiation. This differs from the recommendation for major colorectal cancer resections in the Royal College of Pathologists’ dataset, in which grade is determined on the predominant area. Applying the ‘worst area’ criterion will allow all potentially poorly differentiated tumours to be identified for research into which of the two approaches is better for identifying T1 cancers at increased risk of lymph node metastases for major resection without exposing such patients to the possibility of undertreatment. An early review of poorly differentiated pT1 cases will be undertaken.

4.6 Lymphovascular invasion

Definite invasion of endothelium lined vascular spaces in the submucosa is generally regarded as a significant risk for lymph node or distant metastasis. Sometimes, retraction artefacts around tumour aggregates can make assessment uncertain, in which case this uncertainty should be recorded and the observation interpreted by the multidisciplinary team in light of any other adverse histological features.

4.7 Margin involvement

It is important to record whether the deep (intramural) resection margin is involved by invasive tumour (which may be an indication for further surgery) and whether the mucosal resection margin is involved by carcinoma or pre-existing adenoma (in which case a further local excision may be attempted).

There has been considerable discussion and controversy in the literature over the degree of clearance that might be regarded as acceptable in tumours which extend close to the deep submucosal margin. It is important that this is measured and recorded in the report. It is likely that most would regard a clearance of < 1 mm as an indication for further therapy. However, some would use < 2 mm and a few < 5 mm.
REFERENCES

APPENDIX A: TNM CLASSIFICATION OF COLORECTAL TUMOURS

pT  Primary tumour
pTX  Primary tumour cannot be assessed
pT0  No evidence of primary tumour
pT1  Tumour invades submucosa
pT2  Tumour invades muscularis propria
pT3  Tumour invades through muscularis propria into subserosa or non-peritonealised pericolic or perirectal tissues
pT4  Tumour directly invades other organs (pT4a) and/or involves the visceral peritoneum (pT4b)

pN  Regional lymph nodes
pNX  Regional lymph nodes cannot be assessed
pN0  No regional lymph node metastasis
pN1  Metastasis in 1–3 regional lymph nodes
pN2  Metastasis in four or more regional lymph nodes

pM  Distant metastasis
pMX  Distant metastasis cannot be assessed
pM0  No distant metastasis
pM1  Distant metastasis

APPENDIX B: SNOMED CODES FOR COLORECTAL TUMOURS

T codes
T-66000  Appendix
T-67000  Colon
T-68000  Rectum

M codes
M-81400  Adenoma
M-74000  Dysplasia
M-80103  Carcinoma
M-81403  Adenocarcinoma
M-80703  Mucinous adenocarcinoma
M-84903  Signet ring cell adenocarcinoma
M-85603  Adenosquamous carcinoma
M-80703  Squamous cell carcinoma
M-80413  Small cell carcinoma
M-80203  Undifferentiated carcinoma
M-82433  Adenocarcinoid/goblet cell carcinoid tumour