European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition
Annotations of colorectal lesions

Multidisciplinary, evidence-based guidelines for quality assurance in colorectal cancer screening and diagnosis have been developed by experts in a project coordinated by the International Agency for Research on Cancer. The full guideline document covers the entire process of population-based screening. It consists of 10 chapters and over 250 recommendations, graded according to the strength of the recommendation and the supporting evidence. The 450-page guidelines and the extensive evidence base have been published by the European Commission. The chapter on quality assurance in pathology was supplemented by an annex describing in greater detail some issues raised in the chapter, particularly details of special interest to pathologists. The content of the annex is presented here to promote international discussion and collaboration by making the issues discussed in the guidelines known to a wider professional and scientific community.

Methods ▼
The methods used are described in detail elsewhere in this supplement [34]. Briefly, a multidisciplinary group of authors and editors experienced in programme implementation and quality assurance in colorectal cancer screening and in guideline development collaborated with a literature group consisting of epidemiologists with special expertise in the field of CRC and in performing systematic literature reviews. The literature group systematically retrieved, evaluated and synthesized relevant publications according to defined clinical questions (modified Patient-Intervention-Comparison-Outcome-Study method). Bibliographic searches for most clinical questions were limited to the years 2000 to 2008 and were performed on Medline, and in many cases also on Embase and The Cochrane Library. Additional searches were conducted without date restrictions or starting before 2000 if the authors or editors who were experts in the field knew that there were relevant articles published before 2000. Articles of adequate quality recommended by authors because of their clinical relevance were also included.

Only scientific publications in English, Italian, French and Spanish were included. Priority was given to recently published, systematic reviews or clinical guidelines. If systematic reviews of high methodological quality were retrieved, the...
search for primary studies was limited to those published after the last search date of the most recently published systematic review, i.e. if the systematic review had searched primary studies until February 2006, primary studies published after February 2006 were sought. If no systematic reviews were found, a search for primary studies published since 2000 was performed. In selected cases references not identified by the above process were included in the evidence base, i.e. when authors of the chapters found relevant articles published after 2008 during the period when chapter manuscripts were drafted and revised prior to publication. The criteria for relevance were: articles concerning new and emerging technologies where the research grows rapidly, high-quality and updated systematic reviews, and large trials giving high contribution to the robustness of the results or allowing upgrading of the level of evidence.

The methodological quality of the retrieved publications was assessed using the criteria obtained from published and validated check lists. Evidence tables were prepared for the selected studies. The evidence tables, clinical questions and bibliographic literature searches are documented elsewhere [33].

### Results

#### 7A.1 Introduction

European Guidelines for quality assurance in pathology in colorectal cancer screening and diagnosis should provide multidisciplinary standards and best practice recommendations that can be implemented routinely across the EU. The authors therefore chose to limit the scope of the chapter on quality assurance in pathology [51] and to describe in greater detail in an annex some issues raised in the chapter, particularly details of special interest to pathologists. We also felt that an annex would be the appropriate place to point out new insights not yet widely adopted in Europe in routine practice that may be included in future updates of the Guidelines.

#### 7A.2 Grading of neoplasia

In the present Guidelines, a classification system for colorectal neoplasia has been recommended based on a modified version of the revised Vienna classification (Section 7A.3). For readers not yet familiar with the Vienna classification, it may be helpful to note that it is the first classification to include a clinical recommendation for each neoplastic category. Furthermore, the system was developed to improve diagnostic reproducibility in the interpretation of biopsy specimens and subsequent resection specimens [54–56]. Strictly speaking, the Vienna classification is only valid for biopsy specimens, since a clinical recommendation should follow. However, to avoid diagnostic inconsistencies, the Vienna classification can be used for resection specimens as well. In the Vienna classification and hence in the European Guidelines, the term neoplasia rather than dysplasia is used to refer to epithelial tumours associated with chronic inflammatory diseases. Whereas the Vienna classification differentiates between strictly intraepithelial lesions and those involving the lamina propria, the European Guidelines only refer to mucosal neoplasia that may or may not involve the lamina propria (see Section 7A.3). More importantly, the EU Guidelines recommend a two-tiered grading of mucosal neoplasia. The pathologist must decide whether a neoplastic mucosal lesion can be categorised as low or as high grade; for criteria, see Table 7A.1.

As always in neoplasia, the lesion should reach the mucosal surface (no epithelial maturation). Undermining edges of adjacent mucosa should be excluded. The criteria in Table 7A.1 can be weighted. The most important criteria for the diagnosis of carcinoma are the lateral expansion and the number of nuclear rows. In carcinoma, the number of nuclear rows should change within a single gland. High-grade neoplasia is diagnosed when the nuclear rows do not exceed 2–5 nuclei, and the glands do not show lateral expansion. Low-grade neoplasia is diagnosed when the nuclear rows do not exceed 2–3 nuclei [1,2,84].

In histopathology, the entity of carcinoma in situ is generally defined as carcinoma confined to the epithelial layer. In squamous epithelium such an entity can be readily diagnosed. In columnar epithelium, an analogous entity should theoretically also exist. However, to date there are no exact criteria that would permit diagnosis and that would enable the histopathologist to distinguish high-grade intraepithelial neoplasia from mucosal carcinoma that is invasive in the lamina propria. Therefore, throughout the entire gastrointestinal tract, use of the term carcinoma in situ is not recommended for respective lesions in columnar epithelium.

### Table 7A.1 Grading of gastrointestinal neoplasia

<table>
<thead>
<tr>
<th>Normal</th>
<th>Low-grade mucosal/ intraepithelial neoplasia (LGMN)</th>
<th>High-grade mucosal/ intraepithelial neoplasia (HGMN)</th>
<th>Invasive Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glands</td>
<td>non-branching</td>
<td>villous</td>
<td>branching, cribriform, irregular, solid</td>
</tr>
<tr>
<td>Expansion</td>
<td>up/down</td>
<td>villous</td>
<td>till surface</td>
</tr>
<tr>
<td>Epithelial differentiation</td>
<td>up/down</td>
<td>top-down and exceptional down-top</td>
<td>no maturation towards surface</td>
</tr>
<tr>
<td>Goblet cells</td>
<td>++</td>
<td>(+)</td>
<td>−/(+) retronuclear, atypical</td>
</tr>
<tr>
<td>Nuclear rows</td>
<td>1</td>
<td>2–3</td>
<td>2–5</td>
</tr>
<tr>
<td>Nuclear size</td>
<td>small, basal</td>
<td>palisading</td>
<td>enlarged</td>
</tr>
<tr>
<td>Chromatin</td>
<td>few</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Nucleoli</td>
<td>none</td>
<td>none</td>
<td>few small</td>
</tr>
</tbody>
</table>

Modified from [3,4,73].

**Vieth M et al. Annex Chapter 7 – Annotations of colorectal lesions... Endoscopy 2012; 44: SE131–SE139**
The term intramucosal carcinoma is widely introduced in the upper GI tract but not yet in the lower GI tract (see also Section 7A.4.5). We prefer the term mucosal neoplasia to intraepithelial neoplasia as high-grade dysplasia can contain epithelial neoplasia and invasion into the lamina propria according to the TNM classification.

7A. 3 Classification of serrated lesions

7A. 3. 1 Terminology

The terminology is still under discussion. Serrated lesions can be regarded as a continuous spectrum of colorectal lesions with increasingly more pronounced serrated morphology starting with a hyperplastic polyp and progressing to sessile serrated lesions (SSLs, sometimes referred to as sessile serrated adenomas or sessile serrated polyps), traditional serrated adenomas (TSA), and leading, finally, to adenocarcinoma. Not only the adenomatous component but also other alterations associated with more pronounced serrated morphology may potentially progresses to cancer (see Table 7A.2).

The situation involving sessile serrated lesions is complicated as these lesions only reveal complex structural abnormalities, not adenomatous changes. Therefore, these lesions are neither adenomatous nor are they neoplastic. This is why Kudo et al. [26] and Lambert et al. [27] recommended that these lesions no longer be called adenomas; instead they should be referred to as sessile serrated lesions (SSLs). Few of these lesions are reported to rapidly progress to invasive carcinoma [48]. Those few cases that do progress rapidly, particularly in the right colon, may be expected to appear more frequently as interval cancers. Traditional serrated adenomas (TSA), unlike SSLs, do contain adenomatous alterations, albeit sometimes quite subtle [31]; they are therefore termed correctly and treatment and surveillance should correspond to that of adenomas (see Chapters 8 and 9). Due to the continuous spectrum in the serrated pathway to colorectal cancer, lesions with combinations of serrated morphology and adenomatous cytology can be observed. If more than one histopathologic type in the serrated spectrum (HP, SSL, TSA) is discernible in a given lesion, or at least one type in combination with adenomatous tissue, such lesions are referred to as mixed polyps. The different histopathologic types (e.g., HP and SSL, SSL and TSA, adenoma and SSL, etc.) must be stated in the diagnosis.

7A. 3. 2 Hyperplastic polyp

Hyperplastic polyps (HPS) are composed of elongated crypts (no complex architecture) with serrated architecture in the upper half of the crypt. These polyps usually show some proliferation in the basal (non-serrated) part of the crypts (regular proliferation). Nuclei are small, regular, basal-orientated and lacking hyperchromasia, but with stratification of the upper (serrated) half of the crypts, and without cytological or structural signs of neoplasia. Differences in the appearance of the cytoplasm permit recognition of three types:

- Microvesicular type (MVHP);
- Goblet-cell-rich type (GCHP); and
- Mucin-poor type (MPHP)

The microvesicular variant greatly predominates, but distinction between types is subject to wide interobserver variation, especially in small lesions, and is not always possible. Currently, routine subclassification is therefore neither feasible, nor has it been shown to be beneficial.

At the molecular level the microvesicular variant of HP may be the precursor lesion for sessile serrated lesion, and a goblet-cell-rich HP may be the precursor lesion for a traditional serrated adenoma [40,41,66]. Routine distinction of these types is not necessary.

7A. 3. 3. Sessile serrated lesion

Sessile serrated lesions are described in the literature as “sessile serrated adenoma” and are often found in the right colon. This is a misnomer since sessile serrated lesions do not contain adenomatous changes [15,26,27]. To date, four synonymously used terms exist for these lesions: sessile serrated adenoma [67], superficial serrated adenoma [47], Type 1 serrated adenoma [19], and serrated polyp with abnormal proliferation [66]. We recommend using only the term sessile serrated lesion and avoiding use of any other terms for this entity. This recommendation is given in full awareness that sessile serrated lesions do not show histological signs of an adenoma, but, like adenomas, they should be excised if detected during an endoscopic examination. Currently even in the hands of expert GI pathologists the agreement on the sub-types of serrated lesions is only moderate [85]. The vast majority of SSLs will not progress to adenocarcinoma. Histological criteria of these sessile, usually larger lesions include an abnormal proliferation zone with structural distortion, usually most pronounced in dilatation of the crypts, particularly near the base. Abundant mucus production is usually also observed as pools of mucin in the lumen of the crypts and on the surface of the mucosa. SSLs are found mainly in the right colon and may be misdiagnosed as hyperplastic polyps. Clues to the correct diagnosis include location and large size. As discussed above, cytological signs of “neoplasia” are lacking, but structural abnormalities are present, i.e., glandular branching [15].

Sessile serrated lesions have an elevated serration index and serration in the basal half of crypts with basal dilation of crypts. The epithelium/stroma-ratio is believed to be >50% in SSL. There is crypt branching with horizontal growth (above muscularis mucosae; e.g. T- and L-shaped glands) and often pseudoinvasion into the submucosal layer, rectangular dilation of whole crypts with and without presence of mucus, increased number of goblet cells at the base of the crypts, vesicular nuclei with prominent nucleoli and proliferation zone in the middle of the crypts. Cur-

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Neoplasia</th>
<th>Risk of malignant transformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplastic polyp</td>
<td>no</td>
<td>minimal</td>
</tr>
<tr>
<td>Sessile serrated lesion</td>
<td>no</td>
<td>slightly increased but exact data are missing (rapid transformation may be possible in a short time)</td>
</tr>
<tr>
<td>Traditional serrated adenoma</td>
<td>yes</td>
<td>increased and suggested worse prognosis than carcinomas arising in sessile serrated lesions</td>
</tr>
<tr>
<td>Mixed polyp</td>
<td>yes</td>
<td>increased, but exact data are not available</td>
</tr>
<tr>
<td>Adenoma (tubular, villous)</td>
<td>yes</td>
<td>increased, 17 years on average</td>
</tr>
</tbody>
</table>

Table 7A.2 Continuous spectrum of serrated lesions and possible combinations of histopathologic types. Every lesion can give rise to adenocarcinoma. Most of the adenocarcinomas are believed to derive from adenomatous components.
Recently there is insufficient evidence available in the literature for weighting of these criteria. A well-oriented polypectomy is mandatory for the identification of such histological features. Correct assessment of the deepest portions of the mucosa is impossible in superficial or tangentially cut lesions [40,41]. Further criteria include an often asymmetrical expansion of the proliferation zone into the middle third of crypts. Often mild cytological atypia (slightly enlarged vesicular nuclei, nucleoli) is found without clear signs of neoplasia (dysplasia). BRAF-Mutations depend on the type and location of lesion (see Table 7A.3).

Other abnormalities include:

- The majority of SSL and TSA show CIMP and promoter methylation of hMLH1.
- BRAF mutations in 8 – 10% of all CRC (27 – 76% of CIMP and sporadic MSI-H CRC).
- BRAF mutations in the majority of SSL and TSA (also microvesicular variant of HP, especially proximal), but rarely (0 – 5%) in adenoma. [13,20,23,43 – 46,52,60,64,69,70].

The frequency of sessile serrated lesions in small retrospective series is estimated at 2 – 11% of all mucosal lesions in the colon [5,21]; between 8% and 23% are misdiagnosed as hyperplastic polyps with an interobserver variation of up to 40% [12,16,35,66].

The histological features separating HPs from SSLs constitute a continuous spectrum, and intermingled features can often be seen. This could explain the moderate interobserver concordance (k = 0.47) and the overlapping proliferative activity, and may justify establishing semi-quantitative criteria for diagnosis (e.g. >30% of undifferentiated cells) [9,53]. Only a few immunohistochemical markers (Ki67, Ki67+CK20, MUC6) have been tested for differentiation of HPs and SSAs, and their usefulness in colorectal screening and diagnosis remains to be validated [49,68]. At present, such an additional immunohistochemical analysis cannot be recommended (see Table 7A.4).

In all likelihood, lesions formerly interpreted as mixed hyperplastic and adenomatous polyp are, in fact, SSLs complicated by conventional neoplasia [61]. Special care must be taken in such cases to document the respective histopathologic components in such mixed polyps. Sometimes the conventional neoplastic part shows features other than in classical adenomas. The nuclei are prominent, less palisading and smaller than in classical adenomas. It is not clear whether this type of morphology is distinct for serrated lesions and whether any clinical implications can be drawn.

Prospective studies with risk stratification are needed to develop more precise methods of diagnosis and recommendations for classification. Sessile serrated lesions appear to take a long time (average age 17 years) to develop into an invasive carcinoma. In contrast, an ill-defined, small subsample of SSLs seems to rapidly progress [48,61]. Therefore, SSLs should be completely excised, particularly if they are located on the right side of the colon [39,41].

Diagnosis on a biopsy is not adequate to exclude SSL since the most severe histologic changes might only appear focally within a lesion that otherwise appears to be a hyperplastic polyp [58]. The German guidelines for colorectal cancer [57] recommend complete removal and follow-up of SSL similar to adenomas. An intensive surveillance protocol is recommended for sessile serrated lesions (surveillance colonoscopy after 3 – 5 years subsequent to complete excision of non-neoplastic SSL, after one year following excision of SSL HGIEN [57]. The UK guidelines [38,80 – 82] recommend complete excision but classify these lesions in the same risk category as hyperplastic polyps. The existing evidence base is not definitive as to the level of risk, and follow up decisions should be made locally until more evidence is forthcoming.

7A. 3. 4 Traditional serrated adenoma

Traditional serrated adenomas show neoplastic crypts with a serrated structure [79]. Compared to hyperplastic polyps, the most striking diagnostic feature of traditional serrated adenomas are the complex serrated morphology and the eosinophilic, “dysplastic” cytoplasm that still can be identified in cases with invasive adenocarcinoma. These lesions also frequently show BRAF mutations and CIMP with hMLH1 promoter methylation. Additionally, so-called intraepithelial microacini can be observed in the upper half of the mucosa (ectopic crypt formation). Often these lesions are located in the distal colon and can be found more frequently in elderly female individuals [15,31,68].

7A. 3. 5 Mixed polyp

A mixed polyp may contain partially hyperplastic, classical adenomatous or traditional serrated adenoma or sessile serrated lesion components. Rather than a continuous spectrum such lesions most probably represent several evolutionary lines, depending on the order of certain abnormalities in genes such as APC, BRAF and KRAS [40,41]. It has to be determined whether mixed polyps represent serrated lesions complicated by conventional neoplasia [62].

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Number (n = 414) (% of all lesions)</th>
<th>Proximal location (% of BRAF mutations)</th>
<th>Distal location (% of BRAF mutations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplastic polyp</td>
<td>120 (29%)</td>
<td>35 (29%)</td>
<td>85 (71%)</td>
</tr>
<tr>
<td>Sessile serrated lesion</td>
<td>36 (9%)</td>
<td>27 (75%)</td>
<td>9 (25%)</td>
</tr>
<tr>
<td>Trad. serrated adenoma</td>
<td>3 (1%)</td>
<td>2 (66%)</td>
<td>1 (33%)</td>
</tr>
<tr>
<td>Mixed polyp</td>
<td>7 (2%)</td>
<td>4 (57%)</td>
<td>1 (43%)</td>
</tr>
<tr>
<td>Tubular adenoma</td>
<td>237 (57%)</td>
<td>176 (74%)</td>
<td>61 (26%)</td>
</tr>
<tr>
<td>Villous adenoma</td>
<td>11 (3%)</td>
<td>8 (55%)</td>
<td>5 (45%)</td>
</tr>
</tbody>
</table>

Source: modified from [63].
Focal, hyperplastic-like narrowing of the basal region of a few crypts in SSL and the findings of flat sectors or ectopic crypt formation in SSL/TSA [68] are examples of combinations of serrated and adenomatous components. However, these features add no information of further diagnostic value; they probably result from the continuous developing nature of serrated lesions. We therefore recommend that the diagnosis of mixed polyp should be restricted to the definition given in Section 7A.3.1. Mixed polyps are serrated lesions in which more than one histopathologic type in the serrated spectrum (HP, SSL, TSA) is discernible in a given lesion or at least one type in combination with classical (unserrated) adenomatous tissue. The different histopathological types must be mentioned in the diagnosis, e.g. mixed polyp (HP and SSL, adenoma and SSL).

### Table 7A.5 Measurement of tumour budding. Source: modified from [6, 14, 25, 36, 37, 71, 74].

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>pT</th>
<th>Count</th>
<th>Magnif.</th>
<th>Object.</th>
<th>Area (mm²)</th>
<th>Classification</th>
<th>Cut-off</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ueno</td>
<td>2004</td>
<td>H&amp;E</td>
<td>20×</td>
<td>0.785</td>
<td>n.a.</td>
<td>negative/ positive</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ueno</td>
<td>2002</td>
<td>H&amp;E</td>
<td>25×</td>
<td>0.385</td>
<td>n.a.</td>
<td>&lt;10/10</td>
<td>10</td>
<td>degree of grading agreement</td>
<td></td>
</tr>
<tr>
<td>Shinto</td>
<td>2005</td>
<td>IHC: MNF 116</td>
<td>20×</td>
<td>low (&lt;10)/high (&gt;10) moderate (10–19), severe (&gt;20)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>score of cytoplasmic fragments</td>
<td></td>
</tr>
<tr>
<td>Shinto</td>
<td>2006</td>
<td>3</td>
<td>IHC: MNF 116</td>
<td>20×</td>
<td>low (&lt;10)/high (&gt;10) moderate (10–19), severe (&gt;20)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>scoring of cytoplasmic fragments called now podia</td>
</tr>
<tr>
<td>Okuyama</td>
<td>2002</td>
<td>1 and 2</td>
<td>H&amp;E</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>present/absent</td>
<td>1</td>
<td>endoscopically resected tumors were excluded</td>
</tr>
<tr>
<td>Okuyama</td>
<td>2003</td>
<td>3</td>
<td>H&amp;E</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>present/absent</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Okuyama</td>
<td>2003</td>
<td>3</td>
<td>H&amp;E</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>present/absent</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Prall</td>
<td>2005</td>
<td>IHC: MNF 116</td>
<td>250</td>
<td>0.785</td>
<td>low/high</td>
<td>25</td>
<td>ROC metastatic progression: 0–120 buds range; 14 median 20, 46 mean</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kazama</td>
<td>2006</td>
<td>1</td>
<td>IHC: CAM5.2 and AE1/AE3</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>present/absent</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Kanazawa</td>
<td>2007</td>
<td>H&amp;E</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>none/mild/moderate/marked</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nakamura</td>
<td>2008</td>
<td>H&amp;E</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>None/mild-low moderate/low high</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Choi</td>
<td>2007</td>
<td>2 or more</td>
<td>H&amp;E</td>
<td>20×</td>
<td>(0–3)/(4–5)/(6–10)/(11–38)</td>
<td>(0–3)/(4–5)/(6–10)/(11–38)</td>
<td>(0–3)/(4–5)/(6–10)/(11–38)</td>
<td>mean intensity: (+/−SD)6.6+/−5.6</td>
<td></td>
</tr>
<tr>
<td>Park</td>
<td>2005</td>
<td>2 or more</td>
<td>H&amp;E</td>
<td>20×</td>
<td>(0–3)/(4–5)/(6–9)/(10–38)</td>
<td>(0–3)/(4–5)/(6–9)/(10–38)</td>
<td>(0–3)/(4–5)/(6–9)/(10–38)</td>
<td>mean intensity: (+/−SD)6.6+/−5.6</td>
<td></td>
</tr>
<tr>
<td>Hoi</td>
<td>2005</td>
<td>200</td>
<td>0.05</td>
<td>5% of the horizontal length of the invasive front</td>
<td>0.05</td>
<td>5% of the horizontal length of the invasive front</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yasuda</td>
<td>2007</td>
<td>H&amp;E</td>
<td>present/absent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ishikawa</td>
<td>2008</td>
<td>IHC: MNF IIb</td>
<td>400</td>
<td>negative/ positive</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7A. 3. 6 Risk of progression
The vast majority of hyperplastic polyps and serrated lesions will not undergo malignant transformation. Only a fraction, especially in the group of sessile serrated lesions, may progress to rapidly aggressive carcinoma [5, 63]. Hyperplastic polyps rarely progress to carcinoma. A single case report can be found in the literature [78] and a second (unpublished) case has been reported in southern Germany. Interestingly, these carcinomas show features of gastric differentiation. Little evidence is available on which the risk of colorectal cancer associated with serrated lesions other than hyperplastic polyps could be reliably judged. The risk assessment for sessile serrated lesions is not yet defined, but a subset of these lesions appears to give rise to carcinoma often less than a few millimetres in size. In a series of 110 traditional serrated adenomas, 37% exhibited foci of significant neoplasia and 11% contained areas of intramucosal carcinoma [31]. Mixed polyps (e.g., HP/TSA/SSL or HP/adenoma) seem to have at least the same rate of progression to colorectal carcinoma as adenomas, and the risk might be higher [17, 28].

7A. 4 Assessment of T1 adenocarcinoma
Careful assessment in T1 adenocarcinoma is mandatory because a decision is required on local excision or a major operation.

7A. 4. 1 Size
Firstly, accurate measurement is very important, and measurement must be to the nearest mm (and not rounded-up to the nearest 5 or 10 mm). The maximum size of the lesion should be measured from the histological slide and if the lesion is disrupted or too large, from the formalin-fixed macroscopic specimen. If a biopsy is received it should be stated that size cannot be assessed.

7A. 4. 2 Tumour grade
Poorly differentiated carcinomas are identified by the presence of either irregularly folded, distorted and often small tubules, or the lack of any tubular formation and showing marked cytological pleomorphism. In the absence of good evidence, we recommend...
that a grade of poor differentiation should be applied in a \( \text{pT1} \)
cancer when ANY area of the lesion is considered to show poor
differentiation. It should be noted that this is not in accordance
with the WHO classification that recommends a certain propor-
tion of lesion showing poor differentiation before diagnosing a
lesion as G3. Poor differentiation includes undifferentiated and
poorly differentiated as defined by the WHO classification \([77, 79]\).

7A. 4. 3 Budding

Budding describes the biological behaviour of the tumour at the
front of invasion \([8]\). Budding or tumour cell dissociation \([11]\)
can be divided into slight, moderate and marked and is known from
the Japanese literature of the 1950s \([18]\) and 1990s \([24]\).
At this time, evidence is lacking concerning reproducibility of the
numerous methods for tumour budding measurement (see \( \text{Table 7A.5}\).
It is good practice but not mandatory to document the
presence or absence of single tumour cells at the front of inva-
sion, and we therefore recommend providing this additional in-
formation in the written report with an explanatory comment,
as budding has been suggested as a prognostic factor in colorectal
adenocarcinoma \([36, 42, 65]\).

7A. 4. 4 Site

The site of origin of each specimen should be individually identi-
ﬁed by the clinician and reported to the pathologist on the histo-
pathology request form. The pathologist should record this on the
proforma. This is important information because the risk of lymph
node metastasis from a T1 adenocarcinoma varies depending on the site and size of the lesion \((\text{rectum vs. other locations})\) \([50]\).

Definition of invasion

In columnar epithelium, it is difﬁcult to deﬁne the onset of inva-
sive carcinoma and reliably distinguish it from high-grade intra-
epithelial neoplasia. Criteria such as single tumour cells are more
likely to be seen in more advanced carcinomas, but not in early
carcinomas. Desmoplastic stromal reactions are also seldom
seen in very early carcinomas. However, basal membrane struc-
tures are frequently discernible in well-differentiated early carci-
nomas \([3, 4, 73]\), so that deﬁnitions using “invasion through the
basement membrane” are incorrect.

The WHO deﬁnition of adenocarcinoma in use when the EU
Guidelines were developed excluded diagnosis of intramuscosal
carcinoma in the colon or rectum, in contrast to the accepted
WHO deﬁnitions for the stomach, oesophagus and small bowel.
In the latter cases, a decision on surgical vs. local therapy is
made based on respective protocols. Comparable lesions in the
colon and rectum are reported as high-grade mucosal neoplasia
because a carcinoma in the colon is deﬁned by inﬁltration of the
submucosa according to the WHO classiﬁcation.

The discussion on this issue among the authors of the pathology
chapter in the EU Guidelines reﬂects, among other things, con-
cern about potential overtreatment of early T1 carcinomas which
are detected much more frequently in a screening setting. The
clinical management of a lesion where invasion of the lamina
propria has occurred is no different from that where high-grade
changes are conﬁned to the glands. This legitimate concern as to
increased morbidity and mortality due to miscommunication of
diagnostic criteria may be dealt with more effectively in the fu-
ture, as multidisciplinary management of lesions detected in
and outside of screening programmes advances. The authors
hope that such advances and their effective dissemination will
be stimulated by the publication of the new EU guidelines. This,
in turn, may lead to revision of the current WHO deﬁnition of
colorectal adenocarcinoma in a future revision of the WHO clas-
siﬁcation of gastrointestinal tumours. Pathologists should report
on what version of the WHO and TNM classiﬁcations their diag-
nosis is based.

In those cases in which intramuscosal colorectal cancer is suspect-
ed, and particularly in countries in which this diagnosis is docu-
mented in addition to the WHO terminology, explicit comments
by the pathologist are recommended. Based on the cytological
characteristics of the case, the pathologist should indicate
whether local endoscopic or surgical removal is recommended,
and the basis for this recommendation should be indicated. This
recommendation should be discussed in a multidisciplinary con-
ference prior to surgery. The Japanese criteria for such stratiﬁca-
tion have been published by Watanabe & Suda \([78]\). The updated
Paris classiﬁcation based on a workshop in February 2008 in Ky-
oto \([26]\) permits such subclassiﬁcation based on improved group-
ring and explains in detail the grading criteria \([27]\).

The use of the term colonic carcinoma in situ introduced by the
TNM system is inadequate because the criteria are too vague
and cannot be used for columnar epithelium.

A subclassiﬁcation of all carcinomas into low risk and high risk
based on risk of lymph node involvement should always be un-
dertaken. For exact criteria, please see Chapter 7 and the updated
Paris classiﬁcation \([26, 27]\).

Perineural invasion

Perineural invasion \((\text{PNI})\) was recently described as an indepen-
dent risk factor for colorectal cancer \([29, 50]\). PNI is signiﬁcantly
associated with high tumour stage, grade and metastases. Fur-
thermore, PNI serves as an independent predictor of disease-
free and cancer survival \([29, 50]\). Recently, an association with
other criteria indicating an aggressive course of disease, such as
lymphatic vessel permeation, venous invasion, tumour growth
pattern and budding \([22]\) were described by Poeschi et al. \([50]\).

Also, it was described that PNI-positive tumours are more likely
to be incompletely resected and more likely to progress after
Mayo regimen chemotherapy than PNI-negative tumours. Lately
Poeschl et al. were able to show that PNI is an additional indepen-
dent factor for local tumour relapse.

It is recommended to record PNI in routine sections of colorectal
cancer. According to recent studies \([29, 30, 32, 50]\) immunohisto-
chemistry or special stains are not necessary to detect PNI. Pro-
spective studies are needed to show the clinical relevance of
PNI, its relationship to other features such as lymphatic and vas-
cular invasion and the beneﬁt of alternative treatment for such
more aggressive tumours that are PNI positive.

Conclusions

Due to the unabated expansion of screening programmes in Eu-
rope in the coming years, pathologists will be dealing with an
increasing number of colorectal lesions that require more specia-
lized knowledge in order to provide the information needed by
clinicians to further improve patient outcomes. In addition to
other emerging topics, pathologists dealing with colorectal can-
cer screening should pay particular attention to continuing ad-
vances in grading of neoplasia, classiﬁcation of serrated lesions
and assessment of \( \text{pT1} \) cancers.
Disclaimer

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