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Colorectal Excisional Biopsy (Polypectomy) Histopathology Reporting Guide

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are CORE. Elements in **grey text** are NON-CORE.

☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

CLINICAL INFORMATION (select all that apply) (Note 1)

- ◯ Information not provided
- ☐ Screening colonoscopy
- ☐ Known polyposis syndrome
  - ☐ Familial adenomatous polyposis (FAP)
  - ☐ *MUTYH*-associated polyposis (MAP)
  - ☐ Serrated polyposis
  - ☐ Other, *specify*
- ☐ Lynch syndrome
- ☐ Chronic inflammatory bowel disease
  - ☐ Ulcerative colitis
  - ☐ Crohn disease
- ☐ Previous polyp(s)
- ☐ Previous colorectal cancer
- ☐ Other, *specify*

ENDOSCOPIC PROCEDURE (select all that apply) (Note 2)

- ◯ Not specified
- ☐ Polypectomy/Endoscopic mucosal resection (EMR)
  - ☐ Cautery
    - ◯ Not specifed
    - ◯ Used
    - ◯ Not used
  - ☐ Submucosal injection
    - ◯ Not specifed
    - ◯ Used (EMR)
    - ◯ Not used
  - ☐ Resection type
    - ◯ Not specifed
    - ◯ En bloc
    - ◯ Piecemeal
- ☐ Endoscopic submucosal dissection (ESD)
- ☐ Transanal endoscopic microsurgery (TEMS)
- ☐ Transanal minimally invasive surgery (TAMIS)
- ☐ Endoscopic full thickness resection (EFTR)
- ☐ Other, *specify*

POLYP NUMBER[a] (Note 3)

(Per container)

◯ Not specified

OR ◯ Multiple (with no specific number given)

SPECIMEN SITE(S)[a] (select all that apply) (Note 4)

- ◯ Not specified
- ☐ Caecum
- ☐ Ileocaecal valve
- ☐ Appendiceal orifice
- ☐ Ascending colon
- ☐ Hepatic flexure
- ☐ Transverse colon
- ☐ Splenic flexure
- ☐ Descending colon
- ☐ Sigmoid colon
- ☐ Rectosigmoid junction
- ☐ Rectum
- ☐ Anorectal junction

mm from the anal verge

- ☐ Other, *specify*

ENDOSCOPIC POLYP SIZE AND CLASSIFICATION[a] (Note 5)

Size (mm)

◯ Not specified

mm

OR

Size range mm to mm

OR

Size category

◯ Diminutive ◯ Small ◯ Large

[a] *As indicated on the container label, pathology request form or colonoscopy report.*

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Classification (select all that apply)

- ◯ Not given
- ☐ Paris classification, *specify*
- ☐ Lateral spreading tumour classification, *specify*
- ☐ Optical diagnosis, *specify*

SPECIMEN DIMENSIONS (select all that apply) (Note 6)

Maximum dimensions of intact specimen

mm x mm

Maximum dimension of intact polyp

mm

Aggregated dimensions for fragmented polyps

mm x mm

Maximum dimension of largest piece for fragmented polyps

mm

HISTOLOGICAL TYPE OF POLYP (select all that apply) (Note 7)

(Value list from the World Health Organization (WHO) Classification of Tumours of the Digestive System (2019))

- ◯ No polyp identified (normal mucosa)
- ☐ Tubular adenoma
- ☐ Tubular adenoma, high grade
- ☐ Tubulovillous adenoma
- ☐ Tubulovillous adenoma, high grade
- ☐ Villous adenoma
- ☐ Villous adenoma, high grade
- ☐ Hyperplastic polyp
- ☐ Sessile serrated lesion
- ☐ Sessile serrated lesion with dysplasia
- ☐ Traditional serrated adenoma
- ☐ Traditional serrated adenoma, high grade
- ☐ Serrated adenoma unclassified
- ☐ Suspicious for adenocarcinoma
- ☐ Adenocarcinoma[b]
- ☐ Neuroendocrine tumour
  - ◯ Grade 1
  - ◯ Grade 2
  - ◯ Grade 3
- ☐ Neuroendocrine carcinoma
  - ◯ Small cell type
  - ◯ Large cell type
- ☐ Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN)

[b] *For adenocarcinoma, refer to HISTOLOGICAL TUMOUR TYPE describing all histological subtypes of adenocarcinomas.*

- ☐ Hamartomatous polyp
- ☐ Inflammatory polyp
- ☐ Mucosal prolapse polyp
- ☐ Other, *specify*

Additional features

For neuroendocrine neoplasms only

- ◯ Not applicable

Mitotic count /2 mm^2

AND/OR

Ki-67 proliferation index %

- ☐ Adenoma with epithelial misplacement
- ☐ Other, *specify*

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HISTOLOGICAL TUMOUR TYPE[c] (Note 8)

(Value list from the WHO Classification of Tumours of the Digestive System (2019))

- ◯ Not applicable
- ◯ No evidence of residual tumour
- ◯ Adenocarcinoma not otherwise specified (NOS)
- ◯ Mucinous adenocarcinoma
- ◯ Signet-ring cell adenocarcinoma
- ◯ Medullary carcinoma
- ◯ Serrated adenocarcinoma
- ◯ Micropapillary adenocarcinoma
- ◯ Adenoma-like adenocarcinoma
- ◯ Neuroendocrine carcinoma
  - ◯ Small cell type
  - ◯ Large cell type
- ◯ Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN)
- ◯ Other, *specify*

Precursor polyp/lesion

- ◯ Absent
- ◯ Present, *specify type*[d]

[c] *To complete this and all following elements ONLY if an adenocarcinoma, neuroendocrine carcinoma or MiNEN is present. If multiple primary carcinomas are present, separate datasets should be used to record this and all following elements for each primary carcinoma.*

[d] *Refer to HISTOLOGICAL TYPE OF POLYP.*

HISTOLOGICAL GRADE OF ADENOCARCINOMA (Note 9)

(Only adenocarcinoma NOS and mucinous adenocarcinoma should be graded)

- ◯ Not applicable
- ◯ Low grade (formerly well to moderately differentiated)
- ◯ High grade (formerly poorly differentiated)

EXTENT OF INVASION (Note 10)

- ◯ Non-invasive neoplasia/high grade dysplasia
- ◯ Invasion into submucosa
- ◯ Invasion into muscularis propria
- ◯ Invasion through the muscularis propria into pericolorectal connective tissue
- ◯ Invasion onto the surface of the visceral peritoneum
- ◯ Invasion into adjacent structure(s)/organ(s), *specify*

INVASIVE CARCINOMA DIMENSIONS (Note 11)

- ◯ Cannot be assessed

Maximum depth of invasion ____ mm

- ◯ Cannot be assessed

Maximum width of invasion ____ mm

LYMPHATIC AND VENOUS INVASION (Note 12)

- ◯ Not identified
- ◯ Present
  - ◯ Small vessel (lymphatic, capillary or venular)
  - ◯ Large vessel (venous)
    - ◯ Intramural
    - ◯ Extramural

TUMOUR BUDDING (Note 13)

(Should only be reported in non-mucinous and non-signet ring cell adenocarcinoma areas)

- ◯ Cannot be assessed

Number of tumour buds[e] ____

Tumour budding score

- ◯ Bd1 - low budding (0-4 buds)
- ◯ Bd2 - intermediate budding (5-9 buds)
- ◯ Bd3 - high budding (≥10 buds)

[e] *After scanning 10 fields on a 20x objective lens, the hotspot field normalised to represent a field of 0.785 mm².*

PERINEURAL INVASION (Note 14)

- ◯ Not identified
- ◯ Present

MARGIN STATUS (Note 15)

Deep margin

- ◯ Cannot be assessed
- ◯ Involved
- ◯ Not involved

Distance to invasive carcinoma ____ mm

Lateral margin

- ◯ Cannot be assessed
- ◯ Involved, *specify*
- ◯ Not involved

Distance to neoplasia ____ mm

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ANCILLARY STUDIES (Note 16)

For neuroendocrine neoplasms only

- ◯ Not applicable
- ◯ Neuroendocrine markers, *specify result(s) if available*

AND

Ki-67 proliferation index ____ %

Mismatch repair (MMR) immunohistochemistry

- ◯ Not tested
- ◯ Not interpretable
- ◯ MMR proficient
- ◯ MMR deficient
  - ◯ *MLH1/PMS2* loss
  - ◯ *MSH2/MSH6* loss
  - ◯ *MSH6* loss
  - ◯ *PMS2* loss
  - ◯ Other, *specify*

MMR status by microsatellite instability (MSI) testing

- ◯ Not tested
- ◯ Test failed
- ◯ MSI-high
- ◯ MSI-low
- ◯ MS-stable

***BRAF* V600E mutation testing**

- ◯ Not tested
- ◯ Test failed
- ◯ Mutated
- ◯ Wild type

***MLH1* promoter methylation testing**

- ◯ Not tested
- ◯ Test failed
- ◯ Methylated
- ◯ Not methylated
- ◯ Inconclusive

Other, *specify*

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Definitions

CORE elements

CORE elements are those which are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level III-2 or above (based on prognostic factors in the National Health and Medical Research Council levels of evidence[1]). In rare circumstances, where level III-2 evidence is not available an element may be made a CORE element where there is unanimous agreement in the expert committee. An appropriate staging system e.g., Pathological TNM staging would normally be included as a CORE element.

The summation of all CORE elements is considered to be the minimum reporting standard for a specific cancer.

NON-CORE elements

NON-CORE elements are those which are unanimously agreed should be included in the dataset but are not supported by level III-2 evidence. These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.

Key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion e.g., macroscopic tumour details, may be included as either CORE or NON-CORE elements by consensus of the Dataset Authoring Committee.

Scope

The dataset has been developed for the reporting of local excision specimens from the colon and rectum, including polypectomies, endoscopic mucosal resections (EMR), endoscopic submucosal dissections (ESD), endoscopic full thickness resections (EFTR), transanal submucosal excisions, transanal minimally invasive surgery (TAMIS) and transanal endoscopic microsurgery (TEMS) specimens.

Surgical resection specimens from patients with primary carcinoma of the colon and rectum, including neuroendocrine carcinomas (NECs) and mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs), are dealt with in a separate dataset.

The dataset is recommended for the reporting of neuroendocrine neoplasms (neuroendocrine tumours (NETs) and (NECs)) diagnosed from local excision specimens and thus differs from the dataset for the reporting of primary carcinoma of the colon and rectum in surgical resection specimens from which NETs are excluded.

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Note 1 – Clinical information (Non-core)

Clinical information can be provided by the clinician on the endoscopy report or the pathology request form. Pathologists could search for additional information from possible previous pathology reports.

The presence of a known polyposis syndrome, Lynch syndrome, chronic inflammatory bowel disease (IBD) or any other relevant gastrointestinal disorder should be recorded and provided to the pathologist as awareness of such underlying conditions may influence histological interpretation.

The diagnosis of conventional adenoma or advanced serrated polyp in a patient with IBD raises the possibility of IBD-associated dysplasia in the involved segment.

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Note 2 – Endoscopic procedure (Core and Non-core)

The type of endoscopic procedure is important as it may affect histological analysis, including the evaluation of resection margins.

Polypectomy removes polyps using a snare without or with submucosal injection of a solution to lift the lesion (EMR). Diminutive (1-5 millimetres (mm)) polyps and small (6-9 mm) sessile polyps are usually removed by cold snare or sometimes hot snare (mechanical transection without or with electrocautery). Hot snare polypectomy may be used for larger (10-19 mm) sessile polyps and pedunculated polyps. Depending on polyp size and configuration, en bloc or piecemeal removal is performed.[2]

Endoscopic submucosal dissection (ESD) consists of en bloc resection of superficial lesions of any size after submucosal injection of a solution, using specialised endoscopic knives. It is more commonly used in the upper gastrointestinal tract and sometimes performed in the large bowel for suspected superficial invasive carcinomas. One of the main advantages of ESD compared with EMR is an accurate evaluation of resection margins.

Transanal endoscopic microsurgery (TEMS) is a minimally invasive surgical procedure for en bloc removal of large rectal lesions and early rectal carcinomas not amenable to colonoscopic resection. For malignant lesions, the muscular layer of the rectum is removed with the specimen.

Transanal minimally invasive surgery (TAMIS) is a crossover procedure between laparoscopic surgery and TEMS for resection of benign and early-stage malignant lesions in the lower and mid rectum. The TAMIS technique can also be used for non-curative intent surgery of more advanced lesions in patients who are not candidates for radical surgery.

Endoscopic full thickness resection (EFTR) is a recent minimally invasive endoscopic technique that can be performed in the large bowel resulting in the full transection of all layers of the bowel. EFTR can be used for the management of challenging epithelial and subepithelial lesions that are not amenable to conventional endoscopic resection methods and previously required a surgical approach.

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Note 3 – Polyp number (Core)

Polyp number is an essential component used in bowel screening registries and for surveillance guidelines. Preferably, the endoscopist should submit tissue piece(s) from each polyp resection in a separate container, so that each specimen jar will contain only one polyp sample for histological evaluation.

When multiple polyps or an unknown number of polyps are received in a specimen container, this may preclude accurate assessment of i) the number of polyps received; ii) polyp classification; iii) the number of positive polyps if carcinoma is present in more than one fragment. As polyps are often resected in multiple fragments (piecemeal resection), the number of fragments does not necessarily reflect the number of polyps removed.

In the event that fragments are received from multiple polyps in a specimen container from multiple sites, the ability to accurately record polyp features corresponding to the polyp site of origin may be compromised. This may have impacts for bowel screening registry follow up.

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Note 4 – Specimen site(s) (Core)

Determination of specimen site is based on clinical information provided on the container label, the pathology request form or the endoscopy report. Any discrepancy should be discussed with the endoscopist.

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Note 5 – Endoscopic polyp size and classification (Non-core)

Polyp size is associated with risk of metachronous polyp and colorectal carcinoma, and is used to determine colonoscopy surveillance intervals. Conventional adenomas <10 mm are considered as low-risk lesions while conventional adenomas ≥10 mm are classified as advanced lesions. Polyps <10 mm in size are further divided into small (6-9 mm) and diminutive (1-5 mm) lesions. The size of conventional adenoma correlates with other advanced histologic features (villosity >25% of the polyp and high-grade dysplasia). Sessile serrated lesions (formerly known as sessile serrated adenoma/polyp) and hyperplastic polyps ≥10 mm are considered advanced lesions.

Information on endoscopic appearances of polyps should be recorded for endoscopy/histology correlation. This may be helpful to pathologists who may request deeper levels in tissue blocks when the first histologic impression does not match the endoscopic appearance (optical diagnosis).

Superficial and early neoplasms of the gastrointestinal tract can be assessed on the basis of their endoscopic appearance. Various classifications are used.

Using the Paris classification, type 0 neoplastic lesions are classified as polypoid (Ip and Is), non-polypoid (IIa, IIb and IIc), and non-polypoid and excavated (III) (Figure 1).[3]

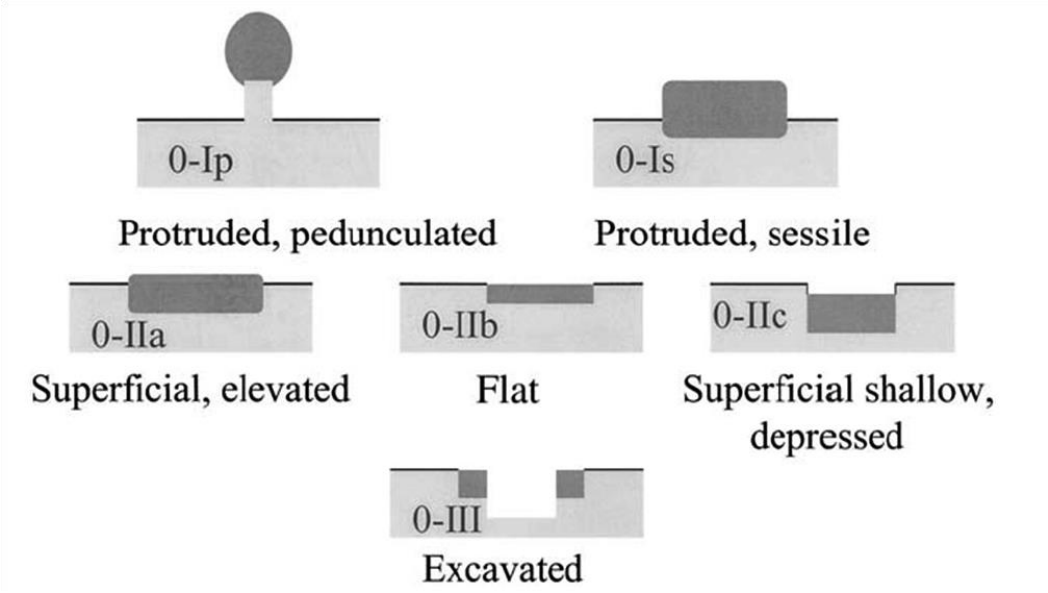

Figure 1: Schematic representation of the major variants of type 0 neoplastic lesions of the digestive tract: polypoid (Ip and Is), non-polypoid (IIa, IIb, and IIc), non-polypoid and excavated (III).
Terminology as proposed in a consensus macroscopic description of superficial neoplastic lesions. Reproduced with permission from Paris workshop participants (2003). The Paris endoscopic classification of superficial neoplastic lesions: oesophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 58(6 Suppl):S3-43.[3]

Lateral spreading tumours (LSTs) are a subgroup of the type IIa lesions, larger than 10 mm in diameter, and classified into 2 groups: granular and non-granular LSTs.[4] Granular LSTs are subclassified into homogenous and nodular mixed types. Non-granular LSTs have a higher malignant potential than the granular LST and are subclassified into flat, elevated and pseudo-depressed types.

For direct optical diagnosis of colorectal lesions, usually both high-definition white light as well as image-enhanced endoscopy, are becoming increasingly used. Various strategies and classifications exist, including the Narrow-band imaging (NBI) International Colorectal Endoscopic (NICE), the Japanese NBI Expert Team (JNET) and the Workgroup serrAted polypS and Polyposis (WASP) classifications.[5-7] The endoscopist's optical diagnosis can be reported as a specific type of the classification used or as histologic category: serrated lesions/polyps (hyperplastic polyp, sessile serrated lesion, sessile serrated adenoma with dysplasia), adenoma, early adenocarcinoma, advanced adenocarcinoma, submucosal lesion, others.

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Note 6 – Specimen dimensions (Core and Non-core)

The dimensions of large en bloc resection specimens (large EMR, ESD, TEMS, TAMIS, EFTR) need to be recorded. If possible, a photograph should be taken and recorded. When the specimen contains normal tissue and the polyp is macroscopically clearly visible, the maximum diameter of the polyp (without the stalk if pedunculated) should be given.

For polyps resected in piecemeal fashion, a measurement of the aggregated tissue fragments with a dimension of the largest piece of tissue can be given to provide some information about the amount of tissue submitted.

Resection specimens of sessile polyps usually include various amounts of normal surrounding colonic mucosa. The dimension of these specimens does not reflect the actual size of the polyp. The microscopic size may be more appropriate for these cases.

Various studies demonstrated some discordance between polyp sizes determined by endoscopy and pathology, with a tendency for larger endoscopy than pathology sizing.[8] For all polyps resected in piecemeal fashion, the endoscopic size is used for determining surveillance intervals. For en bloc resection specimens, the pathology size may be more accurate; however, these lesions are often large with little impact of size differences for determining colonoscopy surveillance intervals.

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Note 7 – Histological type of polyp (Core)

Each polyp should be classified according to the World Health Organization (WHO) Classification of Tumours of the Digestive System 5th edition, 2019.[9]

Conventional adenomas are divided based on the proportion of villous component: tubular adenoma (villous component <25% of the polyp), villous adenoma (villous component >75% of the polyp) and tubulovillous adenoma for all other cases. Conventional adenomas with a significant villous component (>25%) are advanced lesions. The presence of high grade dysplasia is reported. Conventional adenomas with high grade dysplasia are regarded as advanced lesions in colonoscopy surveillance guidelines. High grade dysplasia is characterised by marked architectural changes visible at low magnification (complex crowding, irregularity of glands, cribriform architecture, intraluminal necrosis), associated with cytological features (loss of cell polarity, enlarged nuclei with prominent nucleoli, often with atypical mitotic figures). Epithelial misplacement of adenomatous glands into the head or stalk of the polyp can be present in usually large pedunculated polyps. This should be recorded as a separate value in addition to the main histological subtype of polyp.

Dysplasia in sessile serrated lesion (SSLD), formerly known as sessile serrated adenoma/polyp, shows greater morphological heterogeneity than conventional adenoma. The dysplasia should not be graded because biologically advanced SSLDs may show mild morphological changes.[10]

Traditional serrated adenoma is considered as a low-grade dysplastic lesion with different morphology than the usual dysplasia in conventional adenomas. However, superimposed dysplasia can develop as these lesions progress. Only when high grade dysplasia is present, this be should recorded as traditional serrated adenoma (TSA), high grade.

Serrated adenoma unclassified can be used for lesions that are difficult to classify as either TSA or SSLD, not for SSL versus hyperplastic polyp.

Some advanced conventional adenomas or serrated lesions/polyps may demonstrate histological features suspicious but not definite for the diagnosis of adenocarcinoma. This can be due to limited amount of tissue, cautery artefact or cases difficult to distinguish between epithelial misplacement of adenomatous glands and invasive adenocarcinoma. Such cases should be recorded as an additional value "Suspicious for adenocarcinoma". The clinical behaviour of these lesions is not clear. The pathologist should comment in the report when an invasive carcinoma cannot be excluded but should not complete the elements for adenocarcinoma if the diagnosis of adenocarcinoma is not definite.

Neuroendocrine neoplasms are classified into NETs, NECs and MiNENs. NETs are graded 1-3 using the mitotic count and Ki-67 proliferation index (Table 1).[11] If the two proliferation indicators suggest different grades, the higher grade is assigned. Most NETs of the gastrointestinal tract are grade 1 or 2.

Table 1: Classification and grading for neuroendocrine neoplasms.

Terminology	Differentiation	Grade	Mitotic count (mitoses/2 mm^2)	Ki-67 index
NET, grade 1	Well differentiated	Low	<2	<3%
NET, grade 2		Intermediate	2-20	3-20%
NET, grade 3		High	>20	>20%
NEC, small cell type	Poorly differentiated	High	>20	>20%
NEC, large cell type			>20	>20%
MiNEN	Well or poorly differentiated	Variable	Variable	Variable

Reproduced with permission from Klimstra DS et al (2019). Classification of neuroendocrine neoplasms of the digestive system. In: *World Health Organization Classification of Digestive System Tumours. 5th ed.* IARC Press, Lyon. © World Health Organization/International Agency for Research on Cancer[12]

For adenocarcinoma in a polyp, NEC or MiNEN, refer to additional elements specific to malignant polyps (see **Note 8 HISTOLOGICAL TUMOUR TYPE**).

Other benign polyps (hamartomatous polyps, inflammatory polyps) do not have dysplasia. If superimposed dysplasia is identified in a hamartomatous polyp or if a particular subtype of hamartomatous polyp is identified (e.g., juvenile polyp, Peutz-Jeghers polyp), it should be recorded as an additional feature. Dysplasia arising in an inflammatory polyp raises the possibility of IBD-associated dysplasia.

Various types of mesenchymal polyp can be identified in polypectomy specimens, including perineurioma, Schwann cell hamartoma, schwannoma, neurofibroma, ganglioneuroma, lipoma, granular cell tumour, inflammatory fibroid polyp or gastrointestinal tumour. This should be recorded under the "other" category.

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Note 8 – Histological tumour type (Core and Non-core)

Colorectal cancers should be typed according to the WHO Classification of Tumours of the Digestive System, 5th edition, 2019.[9] This applies only in the setting of a malignant polyp and not of an endoscopic biopsy specimen. If identified, the precursor polyp/lesion from which the adenocarcinoma arose should be recorded. Some endoscopic resection specimens following a large biopsy or neoadjuvant therapy may only show a scar but no residual tumour.

Most colorectal adenocarcinomas are of no specific type (not otherwise specified (NOS)) but some subtypes of adenocarcinoma are defined as follows:

Mucinous adenocarcinoma classification requires greater than 50% of the tumour to comprise pools of extracellular mucin containing malignant glands or individual tumour cells. Microsatellite instability is present in a higher proportion compared to adenocarcinoma NOS. Tumours with less than 50% mucinous content are described as having a mucinous component.

Signet-ring cell adenocarcinoma classification requires greater than 50% of the tumour to demonstrate single malignant cells with intracytoplasmic mucin, displacing and typically indenting the nuclei, imparting signet-ring cell morphology. Signet-ring cell adenocarcinoma has stage-independent adverse prognostic significance relative to adenocarcinoma NOS.[13] There is a strong association with microsatellite instability and with Lynch syndrome.[14] Tumours with less than 50% signet-ring cell content are described as having a signet-ring cell component.

Medullary carcinoma is characterised by sheets of malignant cells with indistinct cell boundaries, vesicular nuclei, prominent nucleoli, abundant eosinophilic cytoplasm and prominent intratumoural lymphocytes and neutrophils. These tumours almost invariably demonstrate microsatellite instability and are associated with a good prognosis.[15]

Serrated adenocarcinoma shares morphological similarities with precursor serrated polyps, demonstrating glandular serrations, which are often slit-like, abundant eosinophilic or clear cytoplasm, minimal necrosis and sometimes areas of mucinous differentiation.[16]

Micropapillary adenocarcinoma is characterised by small, rounded clusters of tumour cells lying within stromal spaces mimicking vascular channels. At least 5% of the tumour should demonstrate this feature to classify as micropapillary adenocarcinoma. This pattern is most frequently encountered alongside adenocarcinoma NOS. There is a strong association with adverse pathological features including a high risk of lymph node metastatic disease.[17]

Adenoma-like adenocarcinoma is defined as an invasive adenocarcinoma in which at least 50% of the invasive tumour has an adenoma-like appearance with villous architecture, low grade cytology, a pushing growth pattern and minimal desmoplastic stromal reaction.[18] Diagnosis of adenocarcinoma on endoscopic biopsy is exceedingly difficult. This variant is associated with a good prognosis.

Neuroendocrine carcinomas (NECs) show marked cytological atypia, brisk mitotic activity, and are subclassified into small cell and large cell subtypes. NECs are considered high-grade by definition. A Ki-67 proliferation index <55% is associated with better overall survival.[19] MiNENs are usually composed of a poorly differentiated NEC component and an adenocarcinoma component. If a pure or mixed NEC is suspected on morphology, immunohistochemistry is required to confirm neuroendocrine differentiation, usually applying synaptophysin and chromogranin A as a minimum.

Other epithelial tumours rarely encountered include adenosquamous carcinoma, carcinoma with sarcomatoid components, undifferentiated carcinoma, squamous cell carcinoma and non-signet-ring cell poorly cohesive adenocarcinoma. Many of these are extremely rare.

If multiple primary tumours are present, separate datasets should be used to record histological tumour type and all following elements for each primary tumour.

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Note 9 – Histological grade of adenocarcinoma (Core)

Grading applies only to malignant polyps not to endoscopic biopsy specimens. Despite low level of interobserver agreement,[20] histological grade is associated with nodal status and is an independent prognostic factor used in risk assessment models for colorectal carcinoma.[21-23]

Various grading systems have been used over the years. A two-tiered grading system is more reproducible and more prognostically relevant than a four-tiered grading system. For consistency with the latest WHO classification,[9] grading should be based on gland formation: low grade (formerly well to moderately differentiated) and high grade (formerly poorly differentiated). Grading is based on the least differentiated component of the tumour, although there is no good evidence to support this stance and a minimum area of high grade tumour required for this classification has not been defined. Grading may not be applicable if the adenocarcinoma is very small.

Tumour buds or poorly differentiated clusters, most commonly seen at the invasive tumour front, should not be considered in the evaluation of grade. Emerging data suggests that grading based on poorly differentiated clusters is superior to conventional grading with respect to both prognostic value and reproducibility.[24,25]

Only adenocarcinoma NOS and mucinous adenocarcinoma should be graded. Grading is not applicable to other subtypes of adenocarcinoma, as grading by gland formation is difficult to apply to subtypes and most of these are associated with their own clinical prognosis e.g., bad for signet-ring cell adenocarcinoma, micropapillary adenocarcinoma, serrated adenocarcinoma and good for medullary carcinoma and adenoma-like adenocarcinoma. Mucinous adenocarcinoma should be graded on gland formation and epithelial maturation.[9] Tumour mismatch repair (MMR) status is likely to influence clinical behaviour of some histological tumour types, including mucinous adenocarcinoma, but some studies have found morphological grading superior to MMR status for prognostication of mucinous adenocarcinomas.[26,27] A cribriform pattern of invasive adenocarcinoma is associated with greater risk of nodal metastasis in malignant polyps.[28]

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Note 10 – Extent of invasion (Core)

The anatomic extent of tumour invasion, based on a combination of macroscopic and microscopic assessment of an excision specimen, is the most important prognostic factor in colorectal cancer. pT classification indicates the extent of invasion of the primary tumour in the absence of application of neoadjuvant therapy. Criteria of the Union for International Cancer Control (UICC)[29] and American Joint Committee on Cancer (AJCC)[30] 8th editions are applied, with the exception that pT in situ is not recognised. Rare cases of colorectal neoplasia confined to invasion of the lamina propria (intramucosal

carcinoma) are acknowledged but, given the negligible metastatic potential of such neoplasms, including those with a poorly differentiated morphology,[31,32] these should be classified under high grade dysplasia/non-invasive neoplasia.

Some rare polyps will remain difficult to classify as either invasive or non-invasive neoplasia, in particular when epithelial misplacement is present. Some adenomas may involve submucosal lymphoglandular complexes, mimicking invasive carcinoma,[33] but the distinction with an adenocarcinoma invading the submucosa can be challenging. In other cases, signet-ring cells limited to the mucosa may be identified in an adenoma.[34] The clinical behaviour of such lesions is not clear. The pathologist should comment in the report when an invasive carcinoma cannot be excluded or for rare cases with unknown clinical behaviour.

For endoscopic resection of early colorectal carcinoma, tumours are usually invading no deeper than into the submucosa (pT1). For rectal carcinoma removed by TEMS/TAMIS, invasion into the muscularis propria (pT2) or the perirectal fat tissue (pT3) can be present. Further consideration of colorectal carcinoma invading beyond the submucosa is provided in a separate surgical resection dataset.

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Note 11 – Invasive carcinoma dimensions (Core and Non-core)

Depth of invasion is one of the main histological risk factors associated with clinical outcome and used for patient management.[35,36] Submucosal invasion ≥1 mm is associated with an increased risk of lymph node metastasis.[37-39] Depth of invasion is the maximum thickness of invasive carcinoma, measured in mm, from the deepest aspect of the invasive tumour in the submucosa to either the overlying muscularis mucosae or the surface of the polyp, if the carcinoma is ulcerated or has overgrown the precursor polyp. This requires well-oriented sections perpendicular to the surface. If the resection is piecemeal, the maximum depth of invasion in any fragment is used.

A semi-quantitative evaluation of the depth of invasion into 3 or 4 levels may still be used in some parts of the world as follows:

- Haggitt levels 1 (head), 2 (neck), 3 (stalk) and 4 (beyond stalk) for pedunculated polyps, with significant increased risk of lymph metastasis for level 4 polyps.[36,40] This requires intact polyp with well-oriented sections from the head to the base.
- Kikuchi levels sm1 (superficial submucosa), sm2 (mid submucosa) and sm3 (deep submucosa) for sessile polyps, with significant increased risk of nodal metastasis for sm3 polyps.[41,42] This requires the presence of the muscularis propria to define the deep boundary of the submucosa, which is often absent in endoscopic resection specimens. The Kikuchi system can be more reliably applied in TEMS, TAMIS and EFTR specimens.

The maximum width of invasive carcinoma can also be recorded. Tumours with an invasive component ≥4 mm are more likely to be associated with lymph node metastasis.[28,43] If the resection is piecemeal, the maximum width of invasion in any fragment is used.

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Note 12 – Lymphatic and venous invasion (Core)

For colorectal cancer, it is important to report the presence or absence of lymphovascular invasion and to classify this further according to the type of vessels involved and, for veins, their intramural or extramural location, as these features may have different clinical and prognostic implications.

Small vessel invasion should be reported separately from venous (large vessel) invasion. Small vessel invasion is defined as tumour involvement of thin-walled structures lined by endothelium, without an identifiable smooth muscle layer or elastic lamina. Small vessels may represent lymphatics, capillaries or post-capillary venules. Lymphatics and venules may be distinguished by D2-40 immuno-histochemistry, which only stains lymphatic endothelial cells, not venular, but this is not routinely recommended in reporting polypectomy specimens. All forms of small vessel invasion are considered under the 'L' classification under UICC/AJCC TNM 8th editions.[29,30] Small vessel invasion is associated with lymph node metastatic disease and has been shown to be an independent indicator of adverse outcome in several studies.[44-46] A higher prognostic significance of extramural small vessel invasion has been suggested, but the importance of anatomic location in small vessel invasion is not well established.[45] In malignant polyps, lymphatic invasion is associated with an increased risk of lymph node metastasis.[38,47]

Venous invasion is defined as tumour present within an endothelium-lined space that is either surrounded by a rim of muscle or contains red blood cells.[48] It should be suspected in the presence of a rounded or elongated deposit of tumour beside an artery. Interpretation of such features is subjective and can be improved by the application of immunohistochemical and histochemical stains, in particular elastic staining to identify venous elastic lamina.[49,50] A circumscribed tumour nodule surrounded by a smooth muscle wall or an identifiable elastic lamina, evident on haematoxylin & eosin (H&E) or elastic stains, is considered sufficient to classify as venous invasion. Examination of multiple levels in blocks showing features suspicious of venous invasion can also be helpful in borderline cases.

Extramural (beyond muscularis propria) venous invasion has been demonstrated by multivariate analysis in multiple studies to be a stage independent adverse prognostic factor for colonic and rectal cancer.[45,51] However, it would only be identified in TAMIS or EFTR specimens. There is also evidence from several studies that intramural (intramuscular or submucosal) venous spread is also of prognostic importance but the evidence is much weaker than for extramural venous invasion.[52]

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Note 13 – Tumour budding (Non-core)

Tumour budding is defined as single cells or clusters of up to 4 tumour cells at the invasive front of invasive carcinomas. It is considered to be the morphological manifestation of epithelial mesenchymal transition.[53] Tumour budding is different from tumour grade (based on gland formation) and poorly differentiated clusters (≥5 cells).

There is increasing evidence that tumour budding is an independent adverse prognostic factor in colorectal carcinoma. Several studies have shown that pT1 colorectal carcinomas, including malignant polyps, with tumour budding score Bd2 and Bd3 (≥5 buds) are associated with an increased risk of lymph node metastasis.[38,39,54-56] For stage II colorectal carcinomas, tumour budding score Bd3 is associated with increased risk of recurrence and mortality.[57-59]

Tumour budding is reported as the number of buds and scored using a three-tiered system. According to the recommendations from a consensus conference on tumour budding,[60] the number of tumour buds is the highest count after scanning 10 separate fields (20x objective lens) along the invasive front of the tumour or the entire lesion for malignant polyps ('hotspot' approach). The count of tumour buds is only performed in non-mucinous, non-signet-ring cell adenocarcinoma areas. The number of tumour buds is counted on H&E. If the invasive front of the tumour is obscured by inflammatory cells, immunohistochemistry using pan-cytokeratin can be used to help identifying the buds, but the final count is performed on H&E. Depending on the eyepiece field number diameter of the microscope, the number of buds may need to be normalised to represent the number for a field of 0.785 mm^2 (objective lens 20x with eyepiece diameter of 20 mm).

Tumour budding should only be reported in non-mucinous and non-signet-ring cell adenocarcinoma areas.

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Note 14 – Perineural invasion (Core)

Multiple independent studies and one meta-analysis have demonstrated the adverse prognostic implication of perineural invasion in colorectal cancer, particularly in stage II disease.[61,62] One large multicentre study reported adverse prognostic significance of both intramural and extramural perineural invasion.[61] However, the importance of anatomic location in perineural invasion is not well established.

In malignant polyps, perineural invasion is extremely rare. It can sometimes be found in endoscopic resection or TEMS/TAMIS for early rectal carcinomas.

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Note 15 – Margin status (Core)

The margin status is an essential component of the histological examination. Assessment of margins can only be done for en bloc polypectomy, ESD, EFTR, TAMIS and TEMS specimens. Margins cannot be reliably assessed for specimens resected in piecemeal fashion.

An involved (positive) deep resection margin is a predictor for adverse outcome.[63] However, if no other adverse histological features are present, an involved deep margin is associated with a risk of local recurrence but not lymph node or distant metastasis. Various cut-offs have been used to define an involved deep margin. Most studies have shown that a clearance of <1 mm should be regarded as a positive margin.[64,65] Pathologists should report the deep margin as either involved if carcinoma cells are present directly at the margin, or record the clearance distance to nearest 0.1 mm between the deep margin and the closest invasive carcinoma. If the invasive carcinoma is within a diathermy zone, the distance between the outer aspect of the diathermy zone and the closest carcinoma should be reported if possible. In cases for which extensive diathermy artefacts obscure the presence of possible carcinoma at the margin, immunohistochemistry for CDX2 or pancytokeratin may be helpful in this assessment. If measurement is not possible, the margin status should be reported as non-assessable.

Lateral margin is less critical for patient management but needs to be recorded. A positive lateral margin does not influence local recurrence rate.[66] The status of the lateral margin should be recorded as either involved or by measuring the distance to nearest 0.1 mm between the closest lateral margin and the neoplasm (dysplasia or carcinoma). If possible, the component of the malignant polyp present at the margin (carcinoma or benign precursor polyp/lesion) should be specified. However, this distinction is not always possible.

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Note 16 – Ancillary studies (Core and Non-core)

If a pure or mixed neuroendocrine neoplasm is suspected on morphology, immunohistochemistry is required to confirm neuroendocrine differentiation, usually applying synaptophysin and chromogranin A as a minimum. As with other gastrointestinal tract and pancreatic neuroendocrine neoplasms, assessment of proliferation index by Ki-67 immunohistochemistry is fundamental to grading of the neuroendocrine component. A Ki-67 proliferation index <55% is associated with better overall survival in NECs.[19]

Testing colorectal carcinoma for MMR protein deficiency is standard of care for Lynch syndrome screening and provides therapeutic decision information for patient management.[67] MMR deficiency is associated with good prognosis, poor response to 5-Fluorouracil and predicts response to immune checkpoint blockage therapy.[68,69]

BRAF mutation testing and *MLH1* promoter methylation analysis are performed to help distinguish sporadic MLH1-deficient colorectal carcinomas from Lynch syndrome associated tumours, caused by constitutional *MLH1* mutation. The presence of either *BRAF* V600E mutation or *MLH1* promoter methylation effectively excludes Lynch syndrome. *BRAF* mutation status may also have predictive/therapeutic value.

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