大腸癌取扱い規約（英語版第2版）
［大腸癌取扱い規約第7版補訂版準拠］

Japanese Classification of Colorectal Carcinoma

Japanese Society for Cancer of the Colon and Rectum

Second English Edition

Kanehara & Co., Ltd., Tokyo

Japanese Classification

of

Colorectal Carcinoma

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Preface

Thirty-five years have passed since the Japanese Society for Cancer of the Colon and Rectum (JSCCR) was first established in 1973. During this period, the incidence of colorectal cancer has increased 4.5 fold in Japan. Consequently, Japan has one of the highest incidences of colorectal cancer in the world. The first edition of the General Rules of Japanese Classification of Colorectal Carcinoma (JCCRC) was published in Japanese in 1977 and the latest edition (7th edition) in 2006. Our classification system and treatment strategy of colorectal cancer differ in some respects from those of western countries; particularly, in grouping and grading of regional lymph nodes, grading of lymph node dissection and management of early cancer. Over a period of 35 years, our treatment strategies have undergone substantial development with advances in diagnostic imaging and an accumulation of experience based on analysis of the database of JSCCR, which has been reflected in each new edition.

In the 7th Japanese edition, considerable changes have been made to enhance consistency both with TNM classification and with Japanese classifications of other gastrointestinal cancers. In addition, the part relating to treatment strategies has been excluded from the 7th edition as the JSCCR guidelines for the treatment of colorectal cancer were published in 2005. All histopathologic micrographs of various types of tumors have been renewed and macroscopic and colonoscopic photographs of tumors of each macroscopic type have been updated in an attempt to help share uniform pictures of the classification of tumor appearances.

As more than 10 years have passed since the first English edition was translated from the 5th Japanese edition, we have decided to publish the English version of the latest edition. The current edition of JCCRC is intended to clarify for foreign clinicians and pathologists the underlying principles of the current Japanese classification system and how they are being continuously developed upon to further improve quality of diagnosis and prognosis of colorectal cancer.

January 2009

Kenichi Sugihara
President,
Japanese Society for Cancer of the Colon and Rectum

Preface of the First English Edition

In 1977, the Japanese Society for Cancer of the Colon and Rectum published the first Japanese edition of the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus. Goals of the General Rules were to contribute to the continuing investigation and treatments of these cancers by applying common rules of clinical and pathological descriptions. Since the TNM classification by the UICC was not yet established at the time, the General Rules were prepared based on the Dukes classification and other general rules by Japanese societies, such as the Japanese Research Society for Gastric Cancer, the Japanese Society for Breast Cancer, the Japanese Society for Esophageal Diseases, and etc. However, the need for details and accurate descriptions in the General Rules impressed to be a high-level science but a complex practice. We believe that they have been achieving their intended goal and that they are indispensable.

The General Rules have always tried to meet three requirements: 1) to be simple, universally applicable, and useful; 2) to be adequate for statistical studies; and 3) to be internationally acceptable. Furthermore, we thought that the General Rules, which should be theoretical and systematic as a manual, would not be of much benefit unless their concepts became diffused. According to this policy, part of the 3rd edition was translated into English in the Japanese Journal of Surgery (1983), which has been well received and utilized.

The General Rules repeated corrections and revisions cover classifications of clinical and histopathological aspects, including aspects of surgical treatments, endoscopy, radiotherapy, and chemotherapy. In particular, regional lymph nodes have been grouped, according to anatomical distance from the tumor, for the advancement of surgical treatments. This seemingly complex concept is presumed to be useful for understanding tumor invasion and lymph node dissection. In addition, improvement of the curability of distant metastases to the liver and lungs is expected to result from surgical resections. The categories of regional lymph nodes and the curability are also included in the General Rules.

Now, we present the first English edition of the Japanese Classification of Colorectal Carcinoma, with full illustrations and detailed descriptions. This English edition is based on the 5th Japanese edition of the General Rules.

I sincerely hope that this English edition will be widely accepted, and that it will contribute to treatments of colorectal cancer.

October 1997

Masayuki Yasutomi
President,
Japanese Society for Cancer of the Colon and Rectum

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Guidelines for classification

Explanatory notes

Guidelines for classification

1 Aims and subjects

1.1 Aims

This classification is intended to help to improve the treatment outcome of patients with colorectal cancer and to define common guidelines for clinical and pathological description and statistical reporting.

1.2 Subjects

This classification applies to primary carcinomas of the colon, rectum and anus and does not apply to recurrence or metastasis. It is recommended that the findings of any primary colorectal tumor other than carcinomas are also recorded according to this classification. Clinical, surgical and pathological findings are recorded separately.

2 General principles (refer to p. 34)

Findings are recorded by using upper case letters for depth of invasion (M, SM, MP, SS, SE, SI, A, AI), lymph node metastasis (N), liver metastasis (H), peritoneal metastasis (P) and other distant metastasis (M). The extent of each finding, except the depth, is recorded in Arabic numerals following designated letter. "X" is used when the finding is unknown. Four categories of findings, namely clinical, surgical, pathological, and final findings, are identified by placing the lower case letters "c", "s", "p", and "f", respectively, in front of each upper case letter. The "f" for final findings may be omitted.

Clinical and surgical findings are recorded in the following order: tumor location, macroscopic type, tumor size, depth of invasion, N, H, P, M and staging.

e.g.: S, type 2, 50×40 mm, pSS, pN0 (0/14), sH0, cP0, cM0, fStage II

Table 1 General principles in recording the findings

Clinical findings (c)	Surgical findings (s)	Pathological findings (p)	Final findngs (f)
Physical examination Diagnostic imaging X rays, endoscopy, ultrasonography, CT scan, MRI Biopsy and cytology Biochemical and/or immunological examination Others (*e.g.* genetic studies)	Intraoperaive findings Intraoperative diagnostic imaging Intraoperative cytology Frozen sections	Pathological examination of specimens obtained by endoscopic resection or surgical resection	Comprehensive summary based on clinical, surgical, and pathological findings.

Pathological findings are recorded in the following order: macroscopic type, tumor size, histological type, depth of invasion, cancer/stroma ratio, invasive growth pattern, lymphatic invasion, vascular invasion, lymph node metastasis and surgical resection margins.

e.g.: type 2, 50×30 mm, tub1, pSS, med, INFb, ly1, v2, pN1 (2/13), pPM0 (80 mm), pDM0 (40 mm), pRM0 (20 mm)

3 Recording of findings

3.1 Primary tumors

3.1.1 Number and size of the lesions and proportion of the tumor in relation to the circumference of the bowel (refer to p. 34)

The two greatest dimensions of the tumor and the ratio and percentage of the tumor to the circumference of the bowel are recorded. All the diagnostic modalities used (barium enema study, colonoscopy, CT scan, MRI, ultrasonography, digital examination, etc.) are recorded.

Note: If the number and size of the tumors cannot be assessed, it is recorded as "unknown".

3.1.2 Tumor location (refer to p. 34)

3.1.2.1 Definition of large intestine

Large intestine consists of cecum, colon, rectosigmoid and rectum. In this classification, it also includes vermiform appendix and anal canal.

3.1.2.2 Anatomical divisions of large intestine

Large intestine is divided into the following eight anatomical divisions.

C: Cecum
  V: Vermiform appendix
A: Ascending colon
T: Transverse colon
D: Descending colon
S: Sigmoid colon
RS: Rectosigmoid
R: Rectum
  Ra: Upper rectum
  Rb: Lower rectum
P: Anal canal (Proctos)
  E: External skin

Note 1: If more than one division is involved, each division involved is recorded in the order of degree of involvement starting with the division in which the bulk of the tumor is

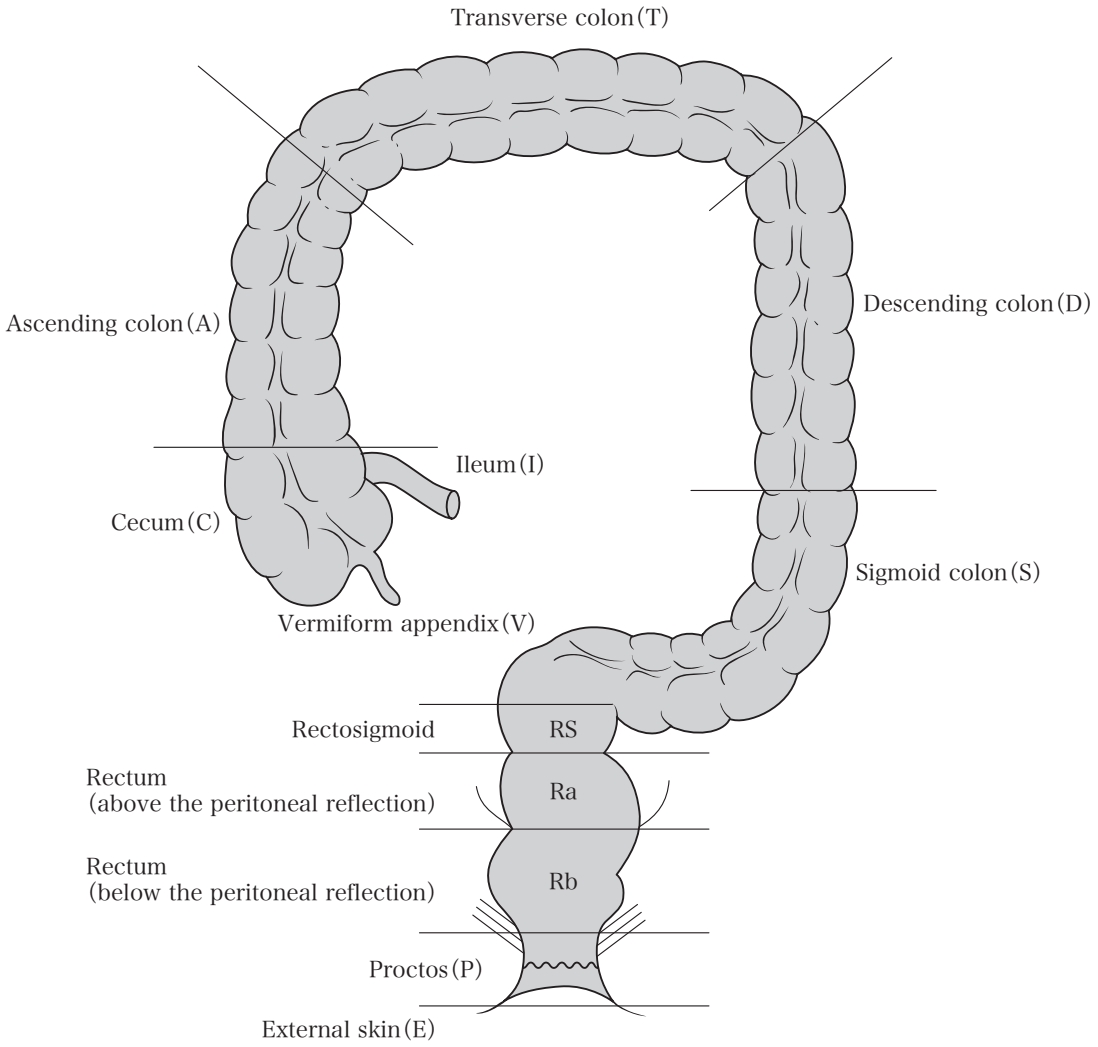


Fig. 1 Anatomical divisions of large intestine

I : **I**leum	RS: **R**ecto**s**igmoid
V: **V**ermiform appendix	R : **R**ectum
C: **C**ecum	Ra: **R**ectum (**a**bove the peritoneal reflection)
A: **A**scending colon	Rb: **R**ectum (**b**elow the peritoneal reflection)
T: **T**ransverse colon	P : **P**roctos
D: **D**escending colon	E : **E**xternal skin
S: **S**igmoid colon	

located.

e.g.: RS-Ra

Note 2: For rectal cancer, the distance between the lower edge of the tumor and the anal verge or dentate line is recorded.

3.1.2.3 Circumferential divisions of the wall of large intestine

The cross-section of the wall of the rectosigmoid, rectum and anal canal is anatomically divided into four equal divisions: anterior (ant), posterior (post), left (lt) and right (rt). Circumferential tumors are recorded as "circ".

Note: If more than one quadrant of the bowel wall is involved, each part involved is recorded in the order of degree of involvement.

e.g.: ant-lt

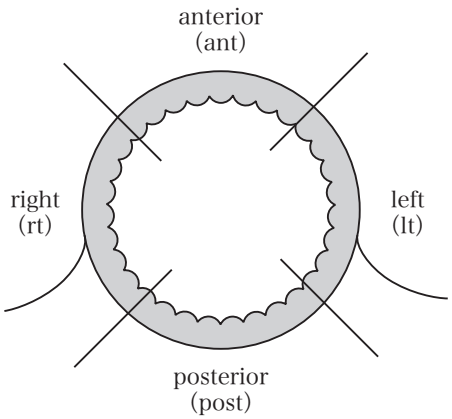


Fig. 2 Four quadrants of the wall of the rectosigmoid and rectum

3.1.3 Macroscopic types (refer to p. 35)

3.1.3.1 Main macroscopic types

Type 0: Superficial type

Type 1: Polypoid type

Type 2: Ulcerated type with clear margin

Type 3: Ulcerated type with infiltration

Type 4: Diffusely infiltrating type

Type 5: Unclassified type

3.1.3.2 Subtypes of macroscopic type 0

Type 0 applies to an 'early' cancer, defined as a tumor whose depth of invasion is

assumed or confirmed to be “M” or “SM”.

Type Ⅰ: Protruded type

Ip: Pedunculated type

Isp: Subpedunculated type

Is: Sessile type

Type Ⅱ: Superficial type

Ⅱa: Elevated type

Ⅱb: Flat type

Ⅱc: Depressed type

Note 1: Anal canal tumors that originate from mucosa are defined as ‘intra-canal’ type and are classified as either type 0, 1, 2, 3, or 4. Anal canal tumors that originate from anal glands or ducts and predominantly occupy the muscular layer or beyond are defined as ‘extra-canal type’ and they will generally be classified as type 5.

Note 2: If the tumor is composed of two different types, the type occupying the largest area is recorded first, followed by ‘+’ and the other type.

e.g.: Ⅱc+Ⅱa

Note 3: The macroscopic types before chemotherapy or radiotherapy as well as after the therapy are recorded.

3.1.4 Depth of tumor invasion (refer to p. 37)

M: Invasion confined to mucosa

SM: Invasion to submucosa

MP: Invasion to muscularis propria

For parts of intestine that have serosa/visceral peritoneum

SS: Invasion to subserosa

SE: Invasion penetrating serosa

SI: Direct invasion to adjacent organs or structures

For parts of intestine that do not have serosa/visceral peritoneum

A: Invasion through muscularis propria into pericolic or perirectal tissues

AI: Direct invasion to adjacent organs or structures

Note 1: An ‘early cancer’ refers to a tumor whose depth of invasion is M or SM.

Note 2: When depth of invasion is SM, the depth of submucosal invasion is measured and recorded. (refer to p. 37)

e.g.: pSM (800 μm)

Note 3: When depth of invasion is A, it is recommended the depth of invasion from the outer border of the muscularis propria is measured and recorded. (refer to p. 39)

e.g.: pA (2 mm)

Note 4: If the tumor is located in both parts of intestine, with and without serosa, the part with the deepest invasion is recorded first followed by the other part.
e.g.: SE-A

Note 5: When depth of invasion is SI or AI, the name(s) of the organ(s) or structure(s) invaded is recorded.
e.g.: AI (prostate)

3.2 Metastatic lesions

3.2.1 Lymph node metastasis (refer to p. 40)

3.2.1.1 Lymph node groups and station numbers (refer to p. 40)

Lymph nodes of the colon, rectum and anus are classified and numbered according to their anatomy in relation to arteries as described in Tables 2 and 3 and Figure 3.

3.2.1.2 Lymph nodes subject to lymphadenectomy (Regional lymph nodes)

Regional lymph nodes consist of three groups; pericolic/perirectal, intermediate and main lymph nodes. In addition, lateral pelvic nodes are included as a fourth group in the rectum. The extent of regional lymph nodes can vary according to the anatomical location of the tumor in relation to its feeding artery/arteries. (refer to p. 41, Fig. 15, 16 & 17)

3.2.1.3 Lymph node metastasis (N) (refer to p. 43)

NX: Lymph node metastasis cannot be assessed

N0: No evidence of lymph node metastasis

N1: Metastasis in 1 to 3 pericolic/perirectal or intermediate lymph nodes

N2: Metastasis in 4 or more pericolic/perirectal or intermediate lymph nodes

N3: Metastasis in main or lateral lymph nodes

Note 1: The extent of pericolic/perirectal lymph nodes to be dissected is determined by the location of the tumor and its feeding arteries. (refer to p. 42-46) (Fig. 15, 16 & 17)

Note 2: The ratio of the number of metastatic nodes to the total number of lymph nodes retrieved is recorded.
e.g.: sN0 (0/14), sN1 (2/18), pN2 (5/16), pN3 (6/20)
This ratio is also recorded according to the groups: pericolic/perirectal, intermediate, main, and lateral.
e.g.: pN1 (3/15): pericolic (2/8), intermediate (1/4), main (0/3)
e.g.: pN2 (6/21): perirectal (4/10), intermediate (2/5), main (0/3), lateral (0/3)

Note 3: Lateral lymph nodes refer to lymph nodes 263D, 263P, 273, 283 and 293.

Note 4: When lymph nodes 260, 270, or 280 are dissected, it is recorded.

Note 5: In an anal canal cancer, lymph nodes 292 are classified as intermediate nodes.

Note 6: Lymph node metastasis beyond the regional lymph nodes is classified as M1.

Note 7: If cancer deposit is found in pericolic/perirectal fat tissue with no evidence of residual lymph node, this is recorded. (refer to p. 43)

Table 2 Lymph node groups

	Superior mesenteric artery	Inferior mesenteric artery	Iliac artery
a Pericolic/perirectal lymph nodes	Lymph nodes along the marginal arteries and vasa recta of the colon (Pericolic nodes)	Lymph nodes along the marginal arteries and vasa recta of the colon (Pericolic nodes) Lymph nodes along the terminal sigmoid artery (Pericolic nodes) Lymph nodes in the mesorectum along the superior rectal artery (Perirectal nodes)	Lymph nodes medial to the pelvic nerve plexus along the middle rectal artery (Perirectal nodes)
b Intermediate lymph nodes	Lymph nodes along the colic arteries (Ileocolic nodes) (Right colic nodes) (Right middle colic nodes) (Left middle colic nodes)	Lymph nodes along the left colic and sigmoid arteries (Left colic nodes) (Sigmoid colic nodes) Lymph nodes along the inferior mesenteric artery between the origin of the left colic artery and the origin of the terminal sigmoid artery (Inferior mesenteric trunk nodes)	
c Main lymph nodes (Lateral lymph nodes)	Lymph nodes at the origin of each colic artery (Ileocolic root nodes) (Right colic root nodes) (Middle colic root nodes)	Lymph nodes along the inferior mesenteric artery proximal to the origin of the left colic artery (Inferior mesenteric trunk nodes)	Lymph nodes along the internal iliac arteries (Distal internal iliac nodes) (Proximal internal iliac nodes) Lymph nodes along the common iliac arteries (Common iliac nodes) Lymph nodes along the obturator vessels and nerves (Obturator nodes) Lymph nodes along the external iliac arteries (External iliac nodes)
d Lymph nodes proximal to the Main lymph nodes	Lymph nodes along the superior mesenteric artery (Superior mesenteric nodes) Lymph nodes around the abdominal aorta and the inferior vena cava (Para-aortic nodes)	Lymph nodes around the abdominal aorta and the inferior vena cava (Para-aortic nodes)	Lymph nodes around the abdominal aorta and the inferior vena cava (Para-aortic nodes)
e Other lymph nodes	Infrapyloric lymph nodes (Infrapyloric nodes) Lymph nodes along the gastroepiploic vessels (Gastroepiploic nodes) Lymph nodes at splenic hilum (Splenic hilum nodes)		Lymph nodes around aortic bifurcation (Aortic bifurcation nodes) Presacral lymph nodes (Median sacral nodes) (Lateral sacral nodes) Lymph nodes in the inguinal area (Inguinal nodes)

Table 3 Lymph node station numbers

	Pericolic/perirectal lymph nodes	Intermediate lymph nodes	Main lymph nodes (Lateral lymph nodes)	Lymph nodes proximal to the Main lymph nodes	Other lymph nodes
Superior mesenteric artery					
Ileocolic arteries	201 (Pericolic nodes)	202 (Ileocolic nodes)	203 (Ileocolic root nodes)		
Right colic artery	211 (Pericolic nodes)	212 (Right colic nodes)	213 (Right colic root nodes)	214 (Superior mesenteric nodes)	
Right middle colic artery	221 (Pericolic nodes)	222-rt (Right middle colic nodes)		216 (Para-aortic nodes)	
Left middle colic artery	221 (Pericolic nodes)	222-lt (Left middle colic nodes)	223 (Middle colic root nodes)		206 (Infrapyloric nodes)
Inferior mesenteric artery					204 (Gastroepiploic nodes)
Left colic artery	231 (Pericolic nodes)	232 (Left colic nodes)			210 (Splenic hilum nodes)
Sigmoid artery					
First	241-1 (Pericolic nodes)	242-1 (First sigmoid colic nodes)	253 (Inferior mesenteric nodes)	216 (Para-aortic nodes)	
Second	241-2 (Pericolic nodes)	242-2 (Second sigmoid colic nodes)			
Terminal sigmoid artery	241-t (Pericolic nodes)				
Superior rectal artery	251 (Perirectal nodes)	252 (Inferior mesenteric trunk nodes)			
Iliac artery					
Middle rectal artery	251 (Perirectal nodes)				
Internal iliac artery			263D (rt・lt) (Distal internal iliac nodes) 263P (rt・lt) (Proximal internal iliac nodes)		
Common iliac artery			273 (rt・lt) (Common iliac nodes)	216 (Para-aortic nodes)	260 (rt・lt) (Lateral sacral nodes)
Obturator vessels			283 (rt・lt) (Obturator nodes)		270 (Median sacral nodes)
					280 (Aortic bifurcation nodes)
External iliac artery			293 (rt・lt) (External iliac nodes)		292 (rt・lt) (Inguinal nodes)

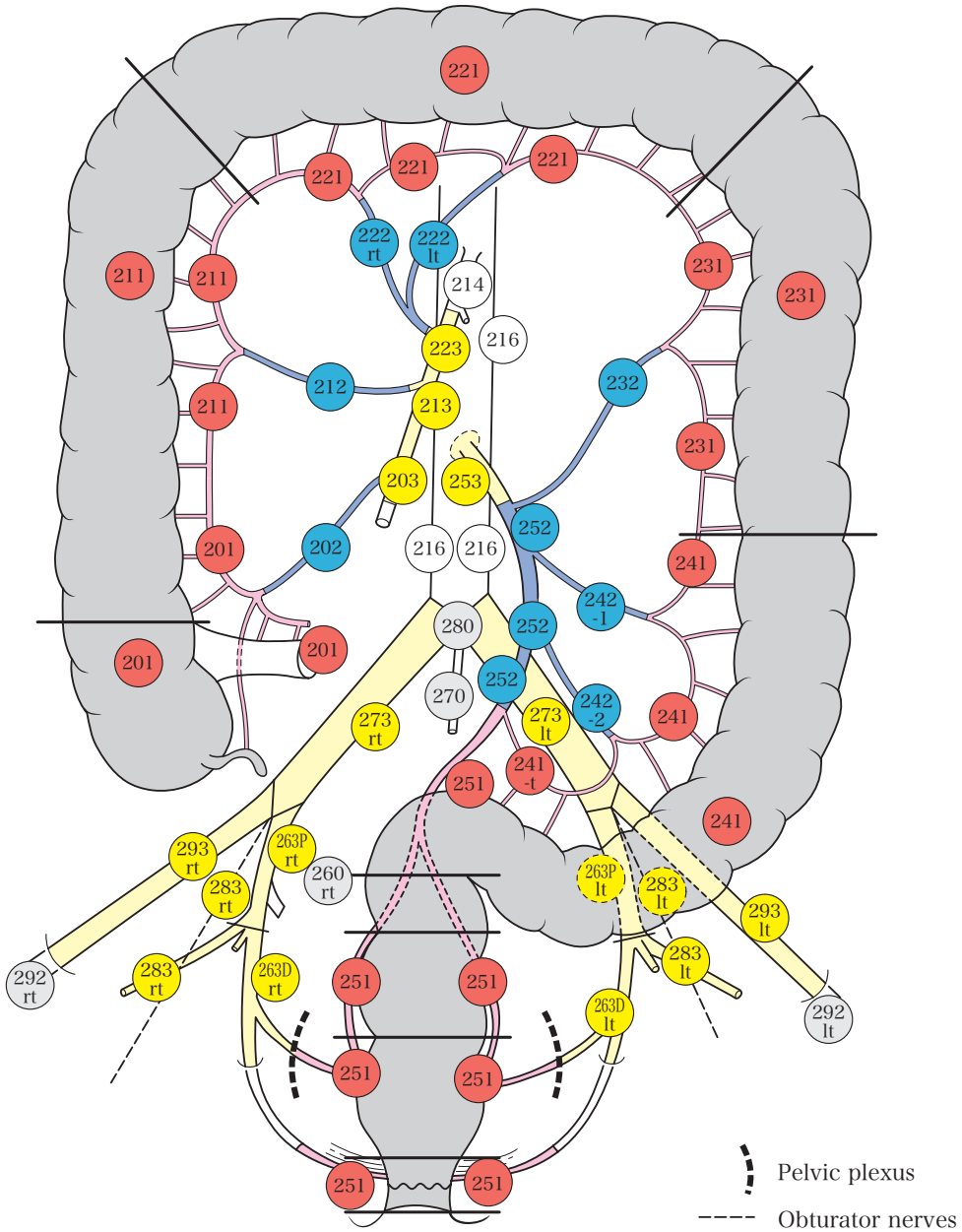


Fig. 3 Lymph node groups and station numbers

●: Pericolic/perirectal lymph nodes
●: Intermediate lymph nodes
●: Main lymph nodes (Lateral lymph nodes)
○: Lymph nodes proximal to the Main lymph nodes
●: Other lymph nodes

3.2.2 Liver metastasis (H) (refer to p. 47)

HX: Liver metastasis cannot be assessed

H0: No liver metastasis

H1: One to 4 metastatic tumors all of which are 5 cm or less in maximum diameter

H2: Other than H1 or H3.

H3: Five or more metastatic tumors at least one of which is more than 5 cm in maximum diameter

Table 4 Grading of liver metastasis

<table>
<tr><th></th><th>H1</th><th>H2</th><th>H3</th></tr>
<tr><td>N0
N1</td><td>A</td><td>B</td><td rowspan="2"></td></tr>
<tr><td>N2</td><td>B</td><td rowspan="2">C</td></tr>
<tr><td>N3
M1</td><td colspan="2"></td></tr>
</table>

Note 1: 'N' refers to the grade of lymph node metastasis of the primary lesion.

Note 2: 'H' and 'Grade' are recorded together.

e.g.: H1 (Grade A)

Note 3: Metastasis to lymph nodes in the hepatic hilum is recorded as HN1 and HN0 if not present.

3.2.3 Peritoneal metastasis (P) (refer to p. 47)

PX: Peritoneal metastasis cannot be assessed

P0: No peritoneal metastasis

P1: Metastasis localized to adjacent peritoneum

P2: Limited metastasis to distant peritoneum

P3: Diffuse metastasis to distant peritoneum

Note 1: When metastasis is limited to the ovaries, it is classified as P2.

Note 2: When ascites is present, cytological examination is recommended. Negative results of cytological examination are represented as Cy0 and positive results as Cy1.

Note 3: The clinical significance of cytological examination of peritoneal lavage fluid has yet to be determined. If the examination is proved to be positive, the result is recorded as such, but not as Cy1.

3.2.4 Extrahepatic distant metastasis (M)

MX: Distant metastasis other than liver and/or peritoneum cannot be assessed

M0: No distant metastasis other than liver and/or peritoneum

M1: Distant metastasis other than liver and/or peritoneum

Note 1: Lymph node metastasis beyond the regional lymph nodes is classified as M1.

Note 2: In M1, the metastatic organs or structures are recorded.

e.g.: M1 (lung)

e.g.: M1 (No216)

Note 3: Lung metastasis is further classified as follows:

LMX: Lung metastasis cannot be assessed

LM0: No lung metastasis

LM1: Metastasis limited to one lobe

LM2: Metastasis to more than one lobe in one side of lung

LM3: Metastasis to both sides of lungs or presence of lymphangitis carcinomatosis, pleuritis carcinomatosis or hilar node metastasis

Note: The site of metastatisis is indicated by recording the side (rt, lt), lobe (U, M, L), trachea (Tr), main, secondary and tertiary (B1-10) bronchi, and segment (S1-10).

3.3 Staging

Table 5 Stage grouping

<table>
<tr><td rowspan="2"></td><td colspan="3">H0, M0, P0</td><td>H1, H2, H3, M1,
P1, P2, P3</td></tr>
<tr><td>N0</td><td>N1</td><td>N2, N3</td><td>M1 (lymph nodes)</td></tr>
<tr><td>M</td><td>0</td><td colspan="3"></td></tr>
<tr><td>SM
MP</td><td>Ⅰ</td><td rowspan="2">Ⅲa</td><td rowspan="2">Ⅲb</td><td rowspan="2">Ⅳ</td></tr>
<tr><td>SS, A
SE
SI, Al</td><td>Ⅱ</td></tr>
</table>

3.4 Multicentric colorectal cancers, multiple primary cancers and multiple cancers (refer to p. 48)

In multicentric colorectal cancers, the number of the lesions is recorded.

In multiple primary cancers, the organs involved are recorded.

Note 1: When there are multicentric mucosal cancers, it is recorded.

Note 2: Whether the cancers are synchronous or metachronous is recorded.

3.5 Family history and hereditary diseases (refer to p. 48)

The occurrence of all cancers in the first degree relatives (parents, children, siblings) of the

patient is recorded. Diagnosis, relationship to the patient, sex, and age at the time of diagnosis are recorded.

Either construction of a pedigree chart or recording of the number of siblings and children is recommended.

If a diagnosis of FAP or HNPCC has been made, it is recorded.

4 Treatment

4.1 Endoscopic treatment

Snare polypectomy

Endoscopic mucosal resection (EMR)

Endoscopic submucosal dissection (ESD)

Note 1: Any other therapeutic procedures, if performed, are recorded.

Note 2: Whether the resection has been performed en bloc or by piecemeal are recorded.

4.2 Surgical treatment (refer to p. 49)

4.2.1 Approach to the lesion

Transanal

Laparoscopic or laparoscopically assisted

Open

Others

4.2.2 Surgical procedures (refer to p. 49)

Polypectomy

Excision of tumor

Local excision

Appendectomy

Ileocecal resection

Limited colectomy

Right hemicolectomy

Left hemicolectomy

Sigmoidectomy

Subtotal colectomy

Total colectomy

Proctocolectomy

High anterior resection

Low anterior resection

Hartmann procedure

Abdominoperineal resection
Total pelvic exenteration
Others

Bypass surgery
Colostomy, ileostomy
Exploratory laparotomy
Other palliative procedures

Note 1: In limited colectomy, the part of the colon resected is recorded.
e.g.: limited colectomy (ascending colon), limited colectomy (transverse colon), limited colectomy (splenic flexure)

Note 2: High or low anterior resection is only used for rectosigmoid or rectal cancer. They are not used for sigmoid colon cancer even if the anastomosis is near the peritoneal reflection.

4.2.3 Extent of lymph node dissection (D)

DX: The extent of lymph node dissection cannot be assessed
D0: Incomplete dissection of pericolic/perirectal lymph nodes
D1: Complete dissection of pericolic/perirectal lymph nodes
D2: Complete dissection of pericolic/perirectal and intermediate lymph nodes
D3: Complete dissection of all regional lymph nodes

Note 1: In rectal cancer, lymph node dissection along the superior rectal or inferior mesenteric artery is recorded as "prx" while lateral lymph node dissection as "lat".

Note 2: In rectal cancer, D3 represents lymph node dissection along the superior rectal and inferior mesenteric arteries and bilateral lateral lymph node dissection. Lateral lymph node dissection requires dissection of lymph nodes 263D, 263P and 283.

Note 3: When lateral lymph node dissection is not performed in rectal cancer despite lymph node dissection along the superior rectal and inferior mesenteric arteries, it is recorded as D2 (prxD3).

Note 4: When lateral lymph node dissection is performed only on one side in rectal cancer, it is represented as D2 and the side of lateral node dissection performed is recorded.
e.g.: D2 (prxD3+rt.lat), D2 (prxD2+lt.lat)

Note 5: When main lymph nodes along the inferior mesenteric artery are not dissected despite bilateral lateral lymph node dissection, it is recorded as D2 (prxD2+lat).

Note 6: It is desirable to retrieve 12 or more lymph nodes.

4.2.4 Anastomosis

4.2.4.1 Types of anastomosis

End-to-end anastomosis

Side-to-end anastomosis
End-to-side anastomosis
Side-to-side anastomosis
Functional end-to-end anastomosis

Note: When an ileal or colonic pouch is constructed, it is recorded.

4.2.4.2 Methods of anastomosis

Hand-sewn anastomosis
single layer
two layers
Stapled anastomosis
single stapling
double stapling
functional end-to-end

4.2.5 Combined resection of adjacent organs and structures

All organs or structures resected because of cancer invasion are recorded.

Note: Whether the organ was resected totally or partially is recorded.

4.2.6 Preservation of autonomic nerves (AN) (refer to p. 50)

Grade of preservation of autonomic nerves is recorded in rectal cancer.

ANX: Preservation of autonomic nerves cannot be assessed
AN0: Autonomic nerves are all removed
AN1: Pelvic plexus on one side is preserved. Pelvic plexus on the other side and superior hypogastric plexus are removed
AN2: Pelvic plexuses on both sides are preserved. Superior hypogastric plexus is removed
AN3: Pelvic plexus on one side and superior hypogastric plexus are preserved. Pelvic plexus on the other side is removed
AN4: All autonomic nerves are preserved

Note 1: In AN1 and AN3, the side of the autonomic nerves preserved is recorded.
e.g.: AN3 rt, AN1 lt
Note 2: When partial preservation of pelvic plexus is performed, it is recorded.
e.g.: resection of the 3rd pelvic splanchnic nerve (S3).

4.2.7 Cancer involvement at resection margins

Note: Tumor status at resection margins are confirmed by pathological examination.

4.2.7.1 Specimens obtained by endoscopic resection

4.2.7.1.1 Horizontal margin (lateral/mucosal margin) (HM)

HMX: Tumor involvement of the lateral margin cannot be assessed

HM0: No tumor identified at the lateral margin

HM1: Tumor identified at the lateral margin

Note: In HM0, the margin of clearance is measured and recorded.

4.2.7.1.2 Vertical margin (deep/intramural margin) (VM)

VMX: Tumor involvement of the deep margin cannot be assessed

VM0: No tumor identified at the deep margin

VM1: Tumor identified at the deep margin

Note 1: In VM0, the margin of clearance is measured and recorded.

Note 2: When an adenoma gland duct alone extends to the margin in a lesion that contains both carcinoma and an adenoma component, record as HM0 (adenoma component positive).

Note 3: Specify the margin even when the lesion consists of adenoma alone.

4.2.7.2 Specimens obtained by surgical resection

4.2.7.2.1 Proximal margin (PM)

PMX: Tumor involvement of the proximal margin cannot be assessed

PM0: No tumor identified at the proximal margin

PM1: Tumor identified at the proximal margin

4.2.7.2.2 Distal margin (DM)

DMX: Tumor involvement of the distal margin cannot be assessed

DM0: No tumor identified at the distal margin

DM1: Tumor identified at the distal margin

4.2.7.2.3 Radial margin (circumferential resection margin) (RM)

RMX: Tumor involvement of the radial margin cannot be assessed

RM0: No tumor identified at the radial margin

RM1: Tumor identified at the radial margin

Note 1: In PM0, DM0 and RM0, the margins of clearance are measured and recorded.

Note 2: HRM0 represents liver resection where tumor is not identified at the resection margin while HRM1 indicates that tumor is identified at the margin.

4.2.8 Residual tumor (R) (refer to p. 50)

RX: Residual tumor status cannot be assessed

R0: No residual tumor

R1: No residual tumor, however, tumor is suspected at the resection margin

R2: Macroscopic residual tumor

Note 1: When metastatic lesions are removed without residual tumor, it is recorded as R0.

Note 2: When primary and metastatic tumors are removed at the same time, R status is evaluated on each tumor and the greater degree of R is recorded as the final R.

e.g.: When primary tumor is R0 and metastatic liver tumor is R1, final R is recorded as R1.

Note 3: R status is confirmed by histological examination.

4.2.9 Curability (Cur)

4.2.9.1 Endoscopic resection

Curability EA (Cur EA): HM0 and VM0

Curability EC (Cur EC): HM1 or VM1

4.2.9.2 Surgical resection

Curability A (Cur A): R0 in Stage 0, Ⅰ, Ⅱ, or Ⅲ

Curability B (Cur B): R0 in Stage Ⅳ or R1 in any Stage

Curability C (Cur C): R2 in any Stage

Note: Curability B consists of heterogeneous groups in terms of prognosis; one with good prognosis and the other with poor prognosis. For example, the prognosis of patients with Stage Ⅳ R0 and those with R1 is different. In analysis of Curability B, stages and residual tumor status is clearly demonstrated.

4.3 Chemotherapy and radiotherapy

4.3.1 Chemotherapy (refer to p. 50)

Name(s) of drug(s): Drug(s) used as combination therapy is described.

Route of administration: Intravenous, oral, intra-arterial, or others

Method of administration: bolus infusion, intravenous drip infusion, or others

Dosage: Dose per unit body surface area and total dose

Administration schedule: Interval between treatment cycles, frequency of administration.

In neoadjuvant therapy, the interval between completion of treatment and surgery is recorded.

In adjuvant therapy, the interval between surgery and start of chemotherapy is recorded.

Duration: Starting date and completed date of treatment

Total dosage: Total dose of chemotherapy given during the course

Reasons for withdrawal: Progression of the disease, adverse events, refusal, or others

Performance status (PS): PS is sequentially recorded on the ECOG grade scale. (Refer to p. 55)

Note: Response to chemotherapy is evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST).

4.3.2 Radiotherapy

4.3.2.1 Aims of radiotherapy

Curative

Adjuvant: preoperative, intraoperative, postoperative, and combination

Palliative

4.3.2.2 Methods of radiotherapy

Equipment (source)

Radiation quality

Energy

Radiation technique: stationary radiation, moving beam radiation, etc., number of beams, treatment position

Field size

Dose per fraction (Gy)

Fractionation: number of fractions per day and number of fractions per week

Treatment period

Total dose (Gy)

Other therapy combined: *e.g.* chemotherapy

4.3.2.3 Radiation field

Note: Response to radiotherapy is evaluated histologically on the resected specimen. (Refer to p. 27)

5 Handling of resected specimens

5.1 Macroscopic examination and handling of surgically resected specimens

The macroscopic appearances of tumors at different stages of fixation (fresh, incomplete fixation [fixation for about 10 minutes] and complete fixation [fixation for 1 or 2 days]) are recorded.

Note: Fresh specimens are suitable for observing the color and vascular pattern of tumors and completely fixed specimens are suitable for observing the surface appearance of tumors.

1) Fresh specimens of resected colon and rectum are examined by macroscopic inspection and palpation for the presence of serosal and mesenteric invasion and lymph node metastasis. If present, their location, distance from surgical margins, and manner of invasion should be recorded.

2) (a) After macroscopic examination, rectal specimens are opened on the anterior side and along the long axis of the rectum.

(b) Specimens from other parts of the intestine are opened on the antimesenteric side.

(c) If a tumor is located on the line of intended dissection, the intestine should be opened elsewherer.

3) The opened intestine is placed on a flat board with the mucosal side up and the edges of the intestine are pinned to the board with stainless steel pins. It is recommended that the intestine is stretched to a point that reproduces its original endoscopic appearance. The specimen is photographed with a scale immediately. Sketches should be prepared, and measurements should be recorded.

4) Measurements (Fig. 4)

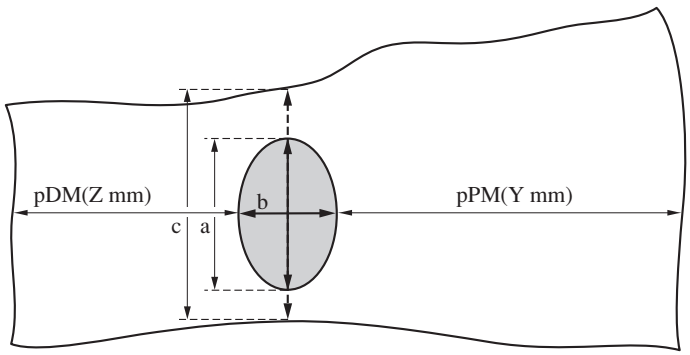
(a) The distances between the tumor edge and both the proximal and distal cut ends are measured. If the tumor is a rectal tumor, the distance between the dentate line and the lowest part of the tumor and the distance between the anal verge and the lowest part of the tumor are measured.

(b) The greatest dimension of the tumor and the dimension perpendicular to it are measured. Recording method: Tumor size is recorded as maximum tumor diameter × diameter at right angles to it × height of the tumor.

(c) The percentage of the inner circumference of the intestine occupied by the tumor (circumferential ratio of the tumor), is calculated by using the formula: (maximum transverse diameter of the tumor/transverse diameter of the intestine measured in the open resected specimen) × 100 (%).

(d) If a distinct ulcer or intramucosal component of the tumor is present, it is recorded.

(e) If the tumor is protruded type (type Ⅰ), the following items are recorded: maximum diameter, maximum diameter at right angles to it, height of the head of the tumor and length of the non-neoplastic stalk of the tumor. The surface appearance, firmness



Measurement of the tumor size: a × b (mm)
Assessment of circumferential ratio of the tumor: a/c × 100 (%)

Fig. 4 Measurement of the resected specimen

and cross-sectional features of the tumor are also described.

5) The pinned-out intestine is then completely immersed in a container of formalin solution with its mucosal side down.

Note: In order to obtain satisfactory specimens for immunohistochemistry and genetic analysis, it is recommended that fixation is started immediately after the macroscopic examination and should last preferably 1 or 2 days but no longer than 3 days.

6) Sectioning of the formalin-fixed specimen

(1) The specimen is photographed with a scale. Sketches are prepared and measurements are recorded.

(2) Section lines are made to determine the deepest level of tumor invasion.

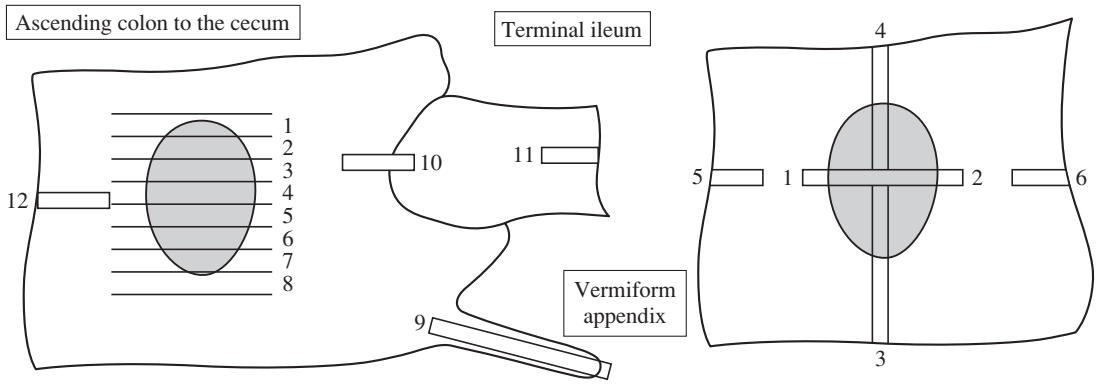
(3) In principle, section lines are made along the long axis of the intestine. Additional sections perpendicular to the long axis of the intestine may be useful to demonstrate the site of deepest invasion by the tumor. The vermiform appendix may be sectioned either longitudinally or transversely (Fig. 5).

Note: The location of a diverticulum in relation to the mesentery can be clearly demonstrated on transverse sections.

If the tumor is thought to be an early carcinoma, the entire tumor is sectioned at 2 to 4 mm intervals.

Note 1: If the tumor is small (<20 mm) or submucosal invasion is suspected, the specimen is sectioned at 2 mm intervals. If the tumor is 20 mm or larger in size, it is sectioned at 3 to 4 mm intervals.

Note 2: In order to reconstruct the histological distribution of the tumor on the photograph, it is important to take a gross photograph showing the shallow section lines in the muco-



a. early carcinoma b. advanced carcinoma

Fig. 5 Sectioning of the resected specimen

sal surface of the tumor.

In principle, the entire tumor is sectioned at 4 to 5 mm intervals even in advanced carcinomas and the cross sections are examined macroscopically to determine the depth of invasion and to find out whether the tumor has invaded the serosa, adventitia, mesentery or adjacent organs. In addition, the clearances from surgical margins are measured on cross sections.

Note 1: Sectioning may be performed either longitudinally (Fig. 5-a, #1-8), perpendicularly to the long axis of the intestine (Fig. 5-b), or along the greatest axis of the tumor.

Note 2: Representative sections for histological examinations are selected by careful macroscopic examination of the specimen.

(4) Cross sections of the tumor are photographed or sketched and macroscopic features are recorded.

Note: In principle, the specimen is placed with its mucosal side facing up and the distal (caudal) end to the left.

7) Examination of resected lymph nodes

(1) Formalin-fixed lymph nodes are cut at 2 mm intervals along their largest diameter that passes through the hilus and examined macroscopically for the presence of metastasis which is often detectable as a grayish white area.

(2) When metastasis is present macroscopically, the sections containing the metastasis and the largest cut section that passes through the hilus are selected for histological examination.

(3) When metastasis is not present macroscopically, the largest cut section that passes through the hilus is selected for histological examination.

5.2 Macroscopic examination and handling of endoscopically resected specimens

Specimens obtained by complete endoscopic excision (en bloc excision) are handled as follows. Whenever possible, specimens obtained by partial excision should be handled as those obtained by complete endoscopic excision.

(1) Stretching and fixation

When the lesion is sessile-type or superficial-type, the specimen is stretched lightly, pinned with the mucosal side up to a flat board with stainless steel pins, and then completely immersed with the mucosal side down in a container of formalin solution. Polyps are immersed in formalin solution immediately.

(2) Macroscopic examination

The size of the resected specimen and the following features of the tumor are recorded: size, macroscopic type, length of the stalk, surface appearance, color, and distances from horizontal/lateral and vertical/deep margins.

Note: It is recommended that the resection margins are marked with ink immediately after endoscopic excision.

(3) Sectioning (Fig. 6)

Pedunculated polyps with a thick stalk (2 mm or more in diameter):

The first cut is made 1 mm from the center of the stalk and the polyp is sectioned at 2 mm intervals.

Note: The entire polyp is sectioned and examined histologically.

Pedunculated polyps with a thin stalk (less than 2 mm in diameter):

The stalk is totally embedded in paraffin and thin sections of the paraffin block are cut for examination.

Sessile lesions and superficial-type lesions:

The specimen is cut at 2 mm intervals to determine the margins of clearance.

Note 1: Stereomicroscopic examination can be useful for identifying the extent of the lesion and for proper sectioning.

Note 2: In principle, all section lines are made in the same direction. However, sectioning in different directions is permissible when necessary.

Note 3: If submucosal invasion is suspected, then the first cut should be made in longitudinal axis 1 mm from site of suspected deepest invasion.

(4) Photography

Photography is performed before and after sectioning.

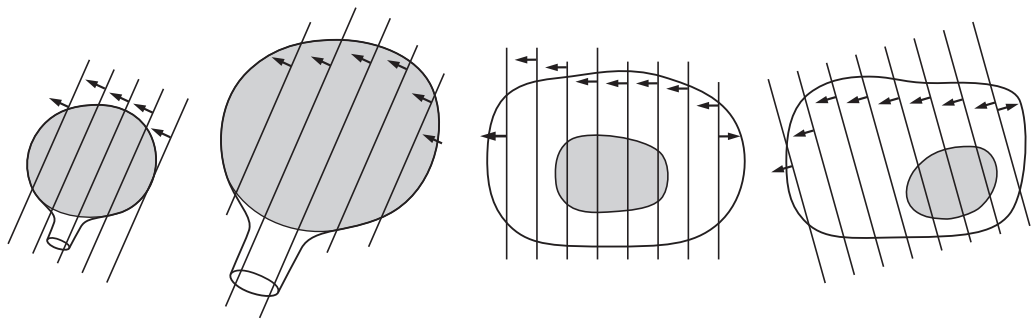


Fig. 6 Sectioning of a resected specimen obtained by endoscopy
Arrows indicate the line of sectioning of the block.

Note 1: To make a histological map of the tumor, it is essential to photograph the tumor with section lines.

Note 2: Shallow section lines in the mucosal surface are recommended for photography.

5.3 Macroscopic findings

5.3.1 Tumor location (refer to p. 3, 34)

5.3.2 Macroscopic types (refer to p. 5, 35)

5.3.3 Serosal and mesenteric invasion

5.3.4 Lymph node metastasis and location

5.3.5 Distance from resection margins

5.3.6 Mode and extent of tumor invasion and metastasis

5.3.7 Tumor size

The maximum diameter, the maximum diameter perpendicular to it and the height of the tumor are recorded.

5.3.8 Proportion of the tumor in relation to circumference of the bowel

Note: The percentage of the inner circumference of the intestine occupied by the tumor is calculated by using the formula: (maximum transverse diameter of the tumor/transverse diameter of the intestine measured in the open resected specimen)×100(%).

5.3.9 Size of ulcerated area

5.3.10 Size of the intramucosal component of the tumor

5.3.11 Protruded tumors

The following are recorded:

Whether pedunculated or sessile

Maximum diameter, maximum diameter at right angles to it, height of the head of the tumor and length of the non-neoplastic stalk of the tumor

Surface appearance, and features of the tumor in cross-section

Length of the non-neoplastic stalk of the tumor

Note 1: Macroscopic features of the tumor on the mucosal and serosal sides and on cross sections are recorded.

Note 2: Macroscopic observations, measurements, description and photograph with a scale included in the field of view are made.

Note 3: It is recommended that the macroscopic and histological findings are compared by creating histological mapping onto a photograph of the tumor with section lines.

5.4 Histological findings

5.4.1 Histological types (refer to p. 56)

a Large intestine (excluding vermiform appendix and anal canal)

1 Benign epithelial tumors

1.1 Adenoma

1.1.1 Tubular adenoma

1.1.2 Tubulovillous adenoma

1.1.3 Villous adenoma

1.1.4 Serrated adenoma

1.2 Familial adenomatous polyposis coli

2 Malignant epithelial tumors

2.1 Adenocarcinoma

2.1.1 Papillary adenocarcinoma (pap)

2.1.2 Tubular adenocarcinoma (tub)

2.1.2.1 Well differentiated type (tub1)

2.1.2.2 Moderately differentiated type (tub2)

2.1.3 Poorly differentiated type

2.1.3.1 Solid type (por1)

2.1.3.2 Non-solid type (por2)

2.1.4 Mucinous adenocarcinoma (mud)

2.1.5 Signet-ring cell carcinoma (sig)

2.2 Endocrine cell carcinoma (ecc)

2.3 Adenosquamous carcinoma (asc)

2.4 Squamous cell carcinoma (scc)

2.5 Miscellaneous carcinomas

3 Carcinoid tumors

4 Non-epithelial tumors

4.1 Myogenic tumor

4.2 Neurogenic tumor

4.3 GIST (Gastrointestinal stromal tumor)

4.4 Lipoma and lipomatosis

4.5 Vascular tumor

4.6 Miscellaneous non-epithelial tumor

5 Lymphomas

5.1 B-cell lymphoma

5.1.1 MALT lymphoma

5.1.2 Follicular lymphoma
5.1.3 Mantle cell lymphoma
5.1.4 Diffuse large B-cell lymphoma
5.1.5 Burkitt lymphoma
5.1.6 Others B-cell lymphomas
5.2 T-cell lymphoma
5.3 Hodgkin lymphoma
6 Unclassified tumors
7 Metastatic tumors
8 Tumor-like lesions
8.1 Hyperplastic (metaplastic) polyp and polyposis
8.2 Hyperplastic nodule
8.3 Juvenile polyp and polyposis
8.4 Peutz-Jeghers polyp and Peutz-Jeghers-type polyp
8.5 Cronkhite-Canada syndrome, Cronkhite-Canada polyp
8.6 Cowden syndrome (disease), Cowden polyp
8.7 Benign lymphoid polyp and polyposis
8.8 Inflammatory polyp and polyposis
8.9 Mucosal prolapse syndrome
8.10 Cap polyposis
8.11 Endometriosis
8.12 Pseudolipoma (micropneumatosis)
8.13 Inflammatory fibroid polyp
8.14 Others (Heterotopic gastric mucosa, etc)

b Vermiform appendix
1 Benign epithelial tumors
1.1 Adenoma
1.2 Mucinous cystadenoma
2 Malignant epithelial tumors
2.1 Adenocarcinoma
2.2 Mucinous cystadenocarcinoma
2.3 Others malignant epithelial tumors
3 Carcinoid tumors
4 Non-epithelial tumors
5 Lymphomas
6 Unclassified tumors

7 Metastatic tumors
8 Tumor-like lesions
8.1 Hyperplastic (metaplastic) polyp and hyperplastic nodule
8.2 Mucocele
8.3 Peutz-Jeghers polyp and Peutz-Jeghers-type polyp
8.4 Others tumor-like lesions

c Anal canal
1 Benign epithelial tumors
2 Malignant epithelial tumors
2.1 Adenocarcinoma
2.1.1 Rectal type
2.1.2 Anal gland origin
2.1.3 Associated with anal fistula
2.1.4 Other extracanal types of adenocarcinoma
2.2 Squamous cell carcinoma (scc)
2.3 Adenosquamous carcinoma (asc)
2.4 Basaloid carcinoma
2.5 Miscellaneous types of carcinoma
3 Extramammary Paget disease
4 Malignant melanoma
5 Non-epithelial tumors
6 Tumor-like lesions
6.1 Fibrovascular polyp (fibrous polyp)
7 Others

5.4.2 Depth of tumor invasion (refer to p. 37, 39)

Note 1: For SM carcinoma, the depth of submucosal invasion is recorded.
e.g.: pSM (800 μm)

Note 2: For tumors that have invaded beyond the muscularis propria in a portion of intestine without serosa, it is recommended that the depth of extramural invasion is recorded.
e.g.: pA (2 mm)

5.4.3 Amount of fibrous stroma

Medullary type (med): There is little fibrous stroma within the tumor.

Note: Carcinoma that contains stroma rich in inflammatory cells is included in this type.

Intermediate type (int): Intermediate between the medullary type and the scirrhous type.

Scirrhous type (sci): There is abundance of fibrous stroma within the tumor.

5.4.4 Invasive growth pattern (INF)

INF a (expansive type): Macroscopically, the tumor shows expansive growth and there is a distinct boundary between the tumor and the surrounding tissue.

INF b (intermediate type): Intermediate between INF a and INF c

INF c (infiltrative type): Macroscopically, the tumor exhibits infiltrative growth and the boundary with the surrounding normal tissue is indistinct.

5.4.5 Invasion of the vessels

5.4.5.1 Lymphatic invasion (ly)

ly0: No invasion

ly1: Minimal invasion

ly2: Moderate invasion

ly3: Severe invasion

5.4.5.2 Venous invasion (v)

v0: No invasion

v1: Minimal invasion

v2: Moderate invasion

v3: Severe invasion

Note 1: Invasion of the vascular system is assessed in the largest cross section of the tumor.

Note 2: If immunostaining is used to examine for lymphatic invasion, it should be stated.
e.g.: ly1(D2-40)

Note 3: If Elastica staining is used to examine for venous invasion, it should be stated.
e.g.: v1(VB) by Victoria blue staining, v2(EVG) by Elastica van Gieson staining

Note 4: If the results of the examination for lymphatic or venous invasion are unclear, they should be recorded as ly/v.

Note 5: The level of deepest venous invasion should be recorded.
e.g.: v1(SS)(EVG)

5.4.6 Lymph node metastasis

Lymph node ratio is represented as number of positive nodes/number of resected nodes and is recorded for each group and for the total resected nodes.

5.5 Histological criteria for assessment of response to neoadjuvant therapy

Grade 0 (No effect): No tumor cell necrosis or degeneration in response to treatment is seen.

Grade 1 (Mild effect)

(a) Minimal effect: Tumor cell necrosis or degeneration is present in less than 1/3 of the entire lesion.

(b) Mild effect: Tumor cell necrosis, degeneration and/or lytic change is present in more than 1/3 but less than 2/3 of the entire lesion.

Grade 2 (Moderate effect): Prominent tumor cell necrosis, degeneration, lytic change, and/or disappearance is present in more than 2/3 of the entire lesion but viable tumor cells remain.

Grade 3 (Marked effect): Necrosis and/or lytic change is present throughout the entire lesion and it is replaced by fibrosis with or without granulomatous change. No viable tumor cells are observed.

5.6 Histological assessment of biopsy specimens (Group classification)

(refer to p. 64)

Group X: Inadequate material for histological diagnosis

Group 1: Normal tissue and a non-neoplastic lesion

Group 2: Lesions in which it is difficult to determine whether the lesion is tumorous or non-tumorous

Group 3: Adenoma (benign neoplasm)

Group 4: Neoplastic lesion suspected of being carcinoma

Group 5: Carcinoma

6 Outcome survey

The following data are recorded for statistical analysis.

6.1 Number of patients

Total number of outpatients with colorectal cancer

Total number of inpatients with colorectal cancer

6.2 Multicentric colorectal cancers, multiple primary cancers and multiple cancers

6.3 Modalities of treatment and adjuvant therapy

Endoscopic treatment

Surgical treatment

Chemotherapy

Radiotherapy

Other non-invasive treatment

No treatment

Note: Refer to section 4.2 (surgical treatment) when documenting surgical procedures.

6.4 Total number of patients who had any treatment for colorectal cancers

The number and proportion of patients who had each treatment are recorded.

6.4.1 Resection rate

Resection rate＝number of patients who had surgical resection/total number of surgical patients

Number and proportion of patients who had surgical resection with respect to each curability (A, B and C).

Note: Patients who had surgical resection include those who had polypectomy, excision of tumor or local excision.

6.4.2 Endoscopic treatment

Patients treated by endoscopic procedure alone are distinguished from those who had surgical resection.

6.4.3 Chemotherapy and radiotherapy

Number and proportion of patients who had chemotherapy and/or radiotherapy are recorded according to the response criteria. (refer to p. 52)

6.5 Number and rate of operative mortality

Note 1: Operative mortality is defined as death within 30 days after surgery irrespective of whether the patient was in the hospital or not.

Note 2: Rate of operative mortality is defined as the ratio of the number of operative death to the total number of patients who had surgery.

6.6 Number and rate of hospital mortality following surgery

Note 1: Hospital mortality is defined as death while in hospital following any surgical treatment.

Note 2: Rate of hospital mortality is defined as the ratio of the number of hospital death to the total number of patients who had surgical treatment.

6.7 Follow-up survey

The following data are recorded for survival analysis.

6.7.1 Survival

Alive: The most recent date of follow-up is recorded.

Dead: The date of death is recorded.

Unknown (lost to follow-up): The final date of follow-up is recorded.

Cause of death

Treatment-related death

Death due to colorectal cancer

Death due to other malignancy: the name of the malignancy is recorded

Death due to other disease: the name of the disease is recorded

Death due to accidents including suicide

Death due to unknown cause.

6.7.2 Recurrence/Metastasis; site(s) and mode

Presence or absence of recurrence

Date when recurrence is confirmed

Site(s) and mode of recurrence

Note: Site(s) and mode of each recurrence are recorded in the order in which they were confirmed.

Local recurrence

Anastomotic recurrence

Recurrence in regional lymph nodes

Other type of local recurrence

Lymph node metastasis (recurrence in non-regional lymph nodes)

Liver metastasis

Lung metastasis

Hematogenous metastasis (other than liver and lung metastases)

Peritoneal metastasis

Recurrence or metastasis at unspecified sites

Note: Sites of recurrence/metastasis are recorded by using abbreviation as in TNM classification.

Liver: HEP, Lung: PUL, Peritoneum: PER, Lymph nodes: LYM, Bone: OSS, Brain: BRA, Adrenal gland: ADR, Skin: SKI, Others: OTH

6.8 Long-term outcome

The following data are recorded for statistical analysis

Target population (i.e. patients who had endoscopic treatment, surgical treatment, etc.)

Methods of estimating survival

Actuarial survival rate

Direct method

Cumulative survival rate: Life-table method, Kaplan-Meier method

Relative survival rate

Test of significance for survival rates

Proportion of patients lost in follow-up

Note: Refer to 'The general guidelines for cancer treatment' published by the Japanese Society for Clinical Oncology (Kanehara & Co., Ltd., 1991) when calculating survival rates and test of significance.

6.9 Assessment of response to chemotherapy and radiotherapy

Response to chemotherapy and radiotherapy is evaluated according to the classification in Response Evaluation Criteria in Solid Tumors (RECIST) (refer to p. 52)

Supplement; TNM Classification

Primary Tumor (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis Carcinoma in situ: intraepithelial or invasion of lamina propria

T1 Tumor invades submucosa

T2 Tumor invades muscularis propria

T3 Tumor invades through the muscularis propria into the subserosa, or into non-peritonealized pericolic or perirectal tissues

T4 Tumor directly invades other organs or structures, and/or perforates visceral peritoneum

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in 1 to 3 regional lymph nodes

N2 Metastasis in 4 or more regional lymph nodes

Distant Metastasis (M)

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

STAGE GROUPING

STAGE	T	N	M	Dukes	MAC	Japanese Classification
0	Tis	N0	M0	*	*	0
I	T1	N0	M0	A	A	I
	T2	N0	M0	A	B1	
ⅡA	T3	N0	M0	B	B2	Ⅱ
ⅡB	T4	N0	M0	B	B3	
ⅢA	T1-T2	N1	M0	C	C1	Ⅲa
ⅢB	T3-T4	N1	M0	C	C2/C3	
ⅢC	Any T	N2	M0	C	C1/C2/C3	Ⅲb
Ⅳ	Any T	Any N	M1	*	D	Ⅳ

MAC (modified Astler-Caller)

Explanatory notes

2 General principles (refer to p. 2)

Once pathological findings have been obtained, final findings are recorded. The "f" referring to final findings can be omitted.

e.g.: S, Type 2, 50×40 mm, SS, N0, H0, P0, M0, Stage II

Clinical findings should be distinguished from pathological findings.

e.g.: Clinical findings were cMP, cN0, cH0, cP0, cM0 but pathological findings were pSS, pN1.

3 Recording of findings

3.1 Primary tumors

3.1.1 Number and size of the lesions and proportion of the tumor in relation to the circumference of the bowel (refer to p. 3)

In synchronous primary colorectal cancers, the location, size, percentage of the circumference of the bowel occupied by tumor, macroscopic type and depth of invasion are recorded for each tumor. The tumor with the greatest depth of invasion is considered to be the main primary tumor. If two or more tumors with the same depth of invasion are present, the tumor with the greatest diameter is considered to be the main primary tumor.

3.1.2 Tumor location (refer to p. 3)

3.1.2.2 Anatomical divisions of the colon, rectum and anus

C: Cecum

The blind pouch that lies distal to the upper lip of the ileocecal valve.

A: Ascending colon

The portion of large intestine that extends from the cecum to the hepatic flexure.

T: Transverse colon

The portion of large intestine that extends between the hepatic and splenic flexures.

D: Descending colon

The portion of large intestine that extends from the splenic flexure to the origin of the sigmoid colon (usually at the level of the iliac crest).

S: Sigmoid colon

The portion of large intestine that locates between the iliac crest and the promontory.

RS: Rectosigmoid

The portion of large intestine that locates between the promontory and the inferior border of the second sacral vertebra.

R: Rectum

Ra: Upper rectum

The portion of large intestine that locates between the inferior border of the sec-

ond sacral vertebra and the level of the peritoneal reflection.

Rb: Lower rectum

The portion of large intestine that locates between the peritoneal reflection and the superior border of the puborectal muscle

P: Anal canal (Proctos)

The tubular portion that extends from the superior border of the puborectal muscle to the anal verge

Note 1: The tubular sphincter that forms the ileocecal valve lies between the ileum (I) and the cecum (C) and it is included in the cecum in this classification.

Note 2: The portion of large intestine that extends from the level of the promontory to the inferior border of the second sacral vertebra is anatomically a part of the sigmoid colon; however, surgically it is defined as the rectosigmoid (RS).

Note 3: The level of the peritoneal reflection can be approximated by the level of Kohlrausch's fold (middle Houston's valve).

Note 4: The UICC (TNM classification 6th edition) defines that "the anal canal extends from rectum to perianal skin (to the junction with hair-bearing skin). It is lined by the mucous membrane overlying the internal sphincter, including the transitional epithelium and dentate line."

3.1.3 Macroscopic types (Fig. 8-13) (refer to p. 5)

Subtypes of type 0 are classified similarly to the classification of early gastric cancer as published by the Japanese Endoscopy Society. However, type III is omitted as this does not exist in colorectal cancer.

Since early colorectal cancers are usually very small, the macroscopic type of the tumor is determined by its endoscopic appearance, irrespective of its histology. If the pathological

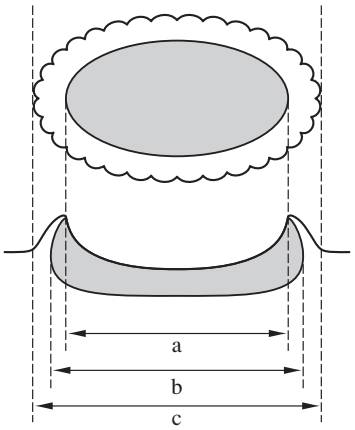


Fig. 7 Measurement of superficial type

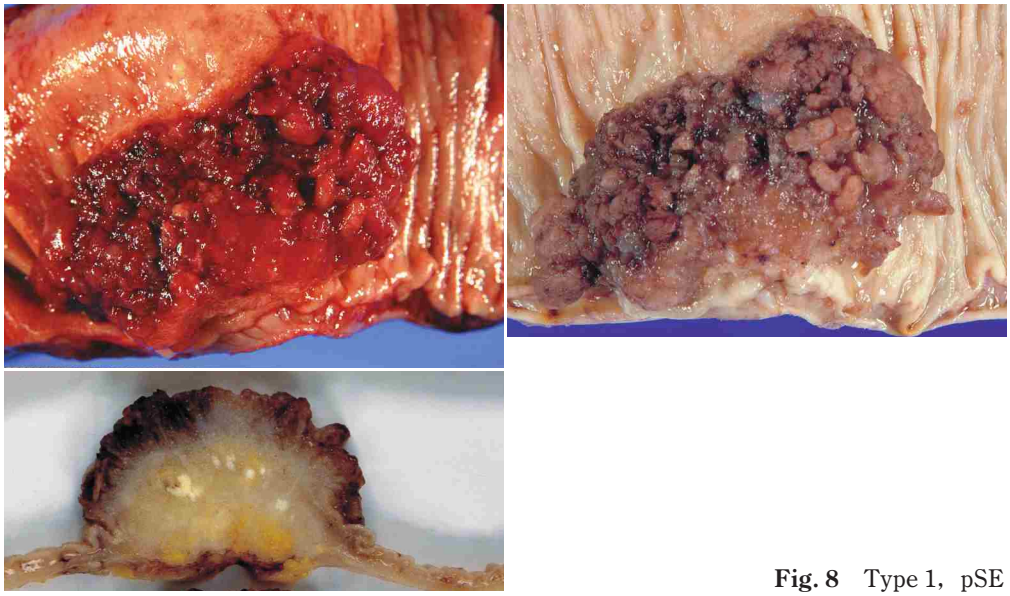


Fig. 8 Type 1, pSE

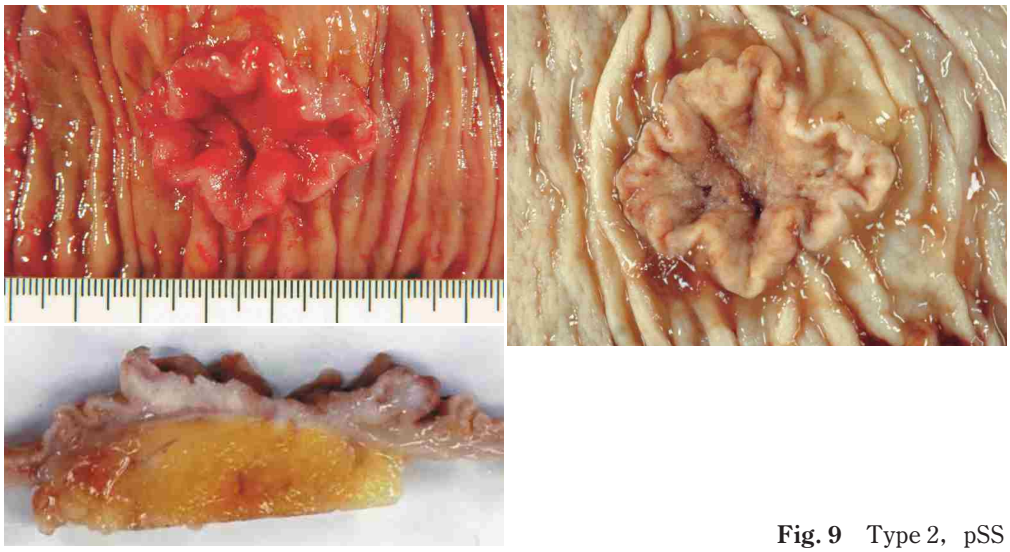


Fig. 9 Type 2, pSS

examination reveals the tumor is advanced, the original macroscopic type should not be changed.

The size of the malignant lesion exposed on the surface is represented as 'a' (mm), the size of the lesion determined by histology as 'b' (mm), and the overall size as 'c' (mm). The size is recorded as 'c' mm ('b' mm) (Fig. 7).

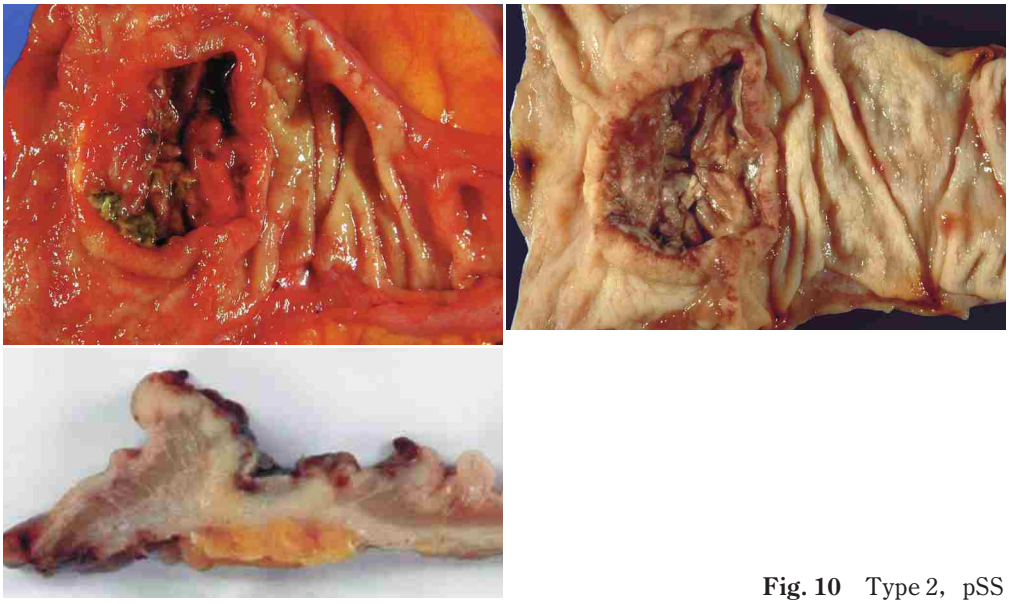


Fig. 10 Type 2, pSS

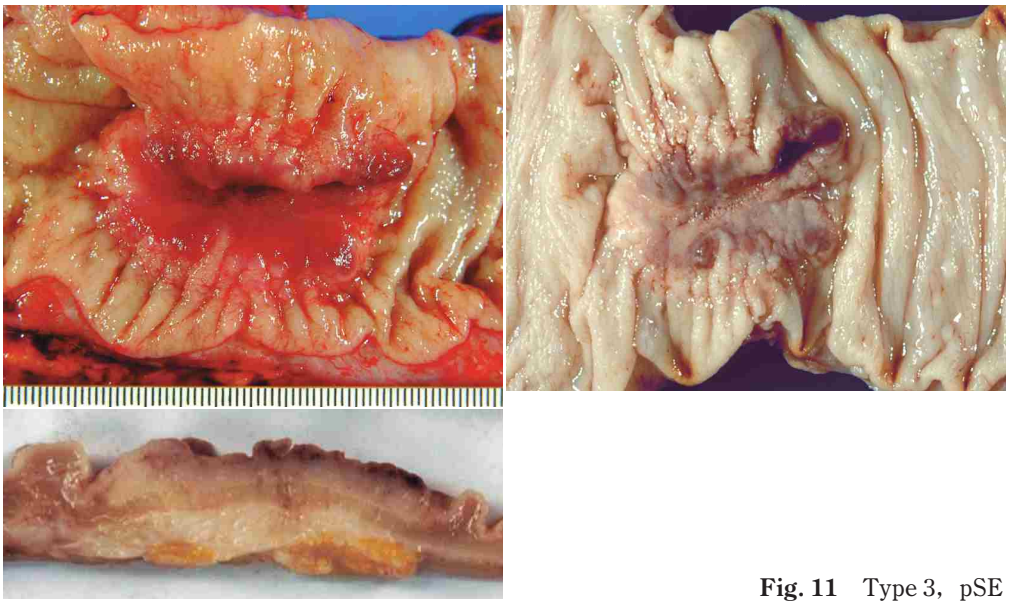


Fig. 11 Type 3, pSE

3.1.4 Depth of tumor invasion (refer to p. 6)

Depth of submucosal invasion in SM cancers (Fig. 14)

1. When it is possible to identify the muscularis mucosae, the depth of submucosal invasion is the distance between the deeper edge of the muscularis mucosae and the deepest invasion.
2. When it is not possible to identify the muscularis mucosae, the depth of submucosal inva-

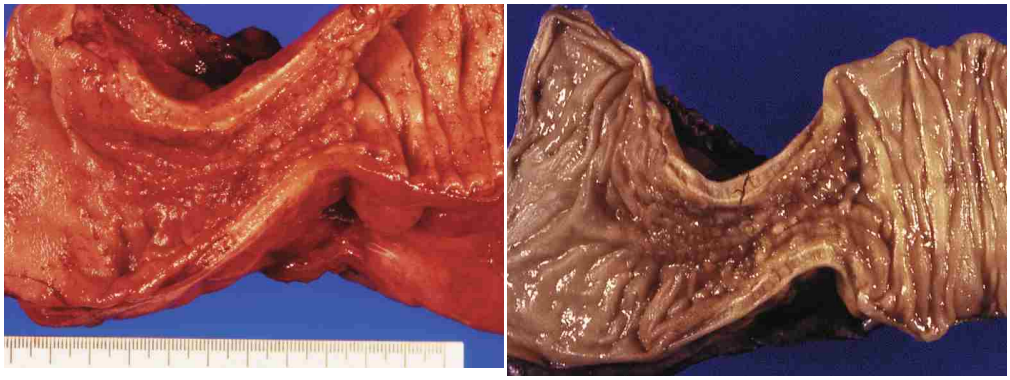
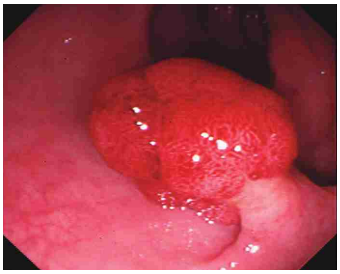
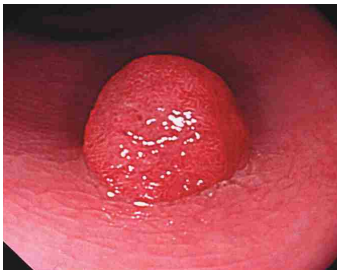


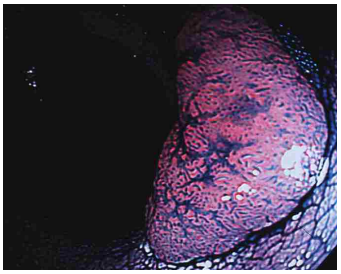
Fig. 12 Type 4, pSE



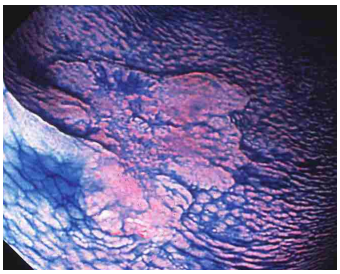
1. Ⅰp



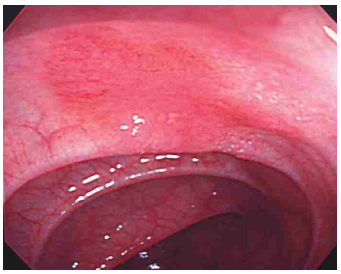
2. Ⅰsp



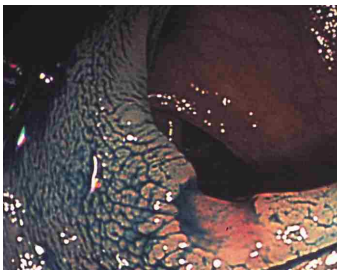
3. Ⅰs



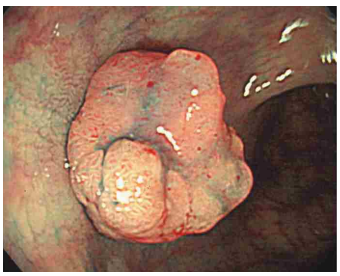
4. Ⅱa



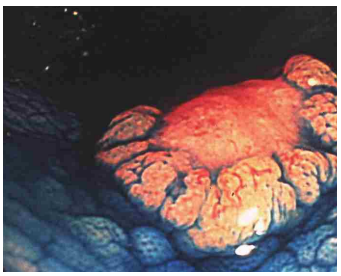
5. Ⅱb



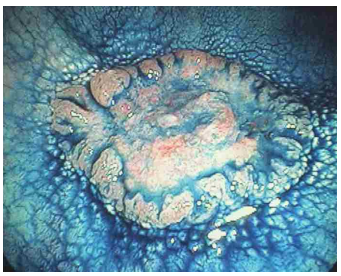
6. Ⅱc



7. Ⅰs+Ⅱc



8. Ⅱa+Ⅱc



9. Ⅱc+Ⅱa

Fig. 13 Subtypes of type 0

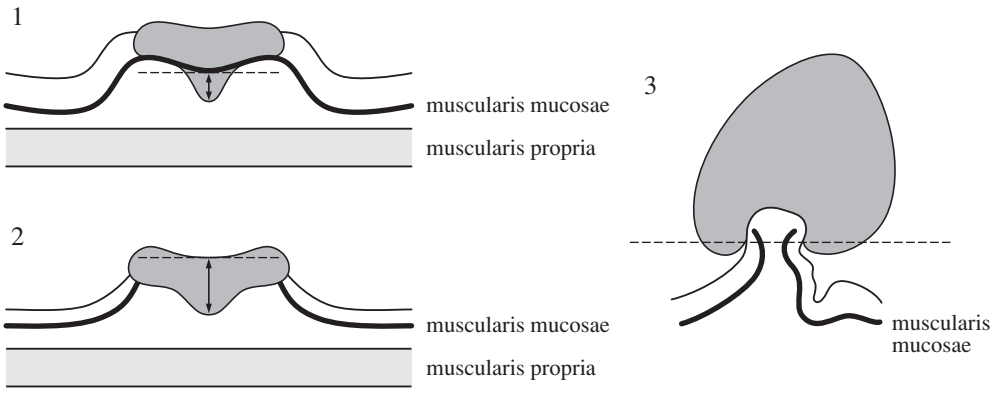


Fig. 14 Depth of submucosal invasion in SM cancers

sion is the distance between the surface of the tumor and the deepest invasion.

3. In polypoid tumor (Ip) with disrupted muscularis mucosae, the depth of submucosal invasion is the distance between the deepest invasion and the reference line being defined as the boundary between the tumor head and the pedicle.

When cancer does not invade beyond the reference line, it is defined as head invasion.

Migration of adenomatous glands (pseudocarcinomatous invasion or submucosal misplacement) should be differentiated from true submucosal invasion (Fig. 26).

Depth of extramural invasion in tumors that extend beyond the muscularis propria in a portion of intestine without serosa

1: When it is possible to identify the muscularis propria, the depth of extramural invasion is the distance between the lower edge of the muscularis propria and the deepest invasion.

2: When it is not possible to identify the muscularis propria within the tumor, the depth of extramural invasion is the distance between the lower edge of the muscularis propria in the adjacent tissue and the deepest invasion.

Note: Lymphatic invasion, venous invasion, and perineural invasion not in continuity with the primary tumor are not considered in depth of tumor invasion and therefore not included.

Direct extension to other intestine, mesentery or omentum via serosa or mesentery is classified as SI or AI.

Invasion of the external sphincter is classified as AI.

3.2 Metastatic lesions

3.2.1 Lymph node metastasis (refer to p. 7)

There have been a few amendments to the names and station numbers of lymph nodes. (Tables 2 and 3, Fig. 3)

3.2.1.1 Lymph node groups and station numbers (Tables 2 and 3, Fig. 3) (refer to p. 7)

Pericolic/perirectal lymph nodes

Lymph nodes along the marginal arteries and vasa recta of the colon (Pericolic nodes)

Lymph nodes along the terminal sigmoid artery (Pericolic nodes)

Lymph nodes in the mesorectum along the superior rectal artery (Perirectal nodes)

Lymph nodes medial to the pelvic nerve plexus along the middle rectal artery (Perirectal nodes)

Intermediate lymph nodes

Lymph nodes along the branches of the superior mesenteric artery

Ileocolic, right colic and middle colic arteries (Ileocolic nodes, Right colic nodes, Right middle colic nodes and Left middle colic nodes, respectively)

Lymph nodes along the branches of the inferior mesenteric artery

Left colic and sigmoid arteries (Left colic nodes and Sigmoid colic nodes, respectively)

Lymph nodes along the inferior mesenteric artery between the origin of the left colic artery and the origin of the terminal sigmoid artery (Inferior mesenteric trunk nodes)

Main lymph nodes

Related to the superior mesenteric artery

Lymph nodes at the origin of each colic artery (Ileocolic root nodes, Right colic root nodes and Middle colic root nodes)

Related to the inferior mesenteric artery

Lymph nodes along the inferior mesenteric artery proximal to the origin of the left colic artery (Inferior mesenteric nodes)

Lateral lymph nodes

Lymph nodes along the internal iliac arteries (Distal internal iliac nodes and Proximal internal iliac nodes)

Lymph nodes along the obturator arteries (Obturator nodes)

Lymph nodes along the common iliac arteries (Common iliac nodes)

Lymph nodes along the external iliac arteries (External iliac nodes)

Lymph nodes proximal to the Main lymph nodes

Lymph nodes along the superior mesenteric artery proximal to the origin of the middle colic artery (Superior mesenteric nodes)

Lymph nodes around the abdominal aorta and the inferior vena cava (Para-aortic nodes)

Other lymph nodes

1) Lateral sacral nodes, Median sacral nodes and Aortic bifurcation nodes

2) Lymph nodes in the inguinal area (Inguinal nodes)

3) Infrapyloric nodes, Gastroepiploic nodes and Splenic hilum nodes

Note 1: The inferior mesenteric artery originates from the aorta and after giving off the terminal sigmoid it continues as the superior rectal artery.

Note 2: The internal iliac artery is arbitrarily divided into a proximal part and a distal part related to the origin of the superior vesical artery.

3.2.1.2. Lymph nodes subject to lymphadenectomy (Regional lymph nodes) (refer to p. 7)

3.2.1.2.1 Station number coding (Table 3, Fig. 3)

The station numbers for lymph nodes associated with the large intestine are coded with three-digit numbers starting only with 200's.

The last digit in the numbers assigned to lymph nodes represents the group of nodes

1: pericolic/perirectal lymph nodes

2: intermediate lymph nodes

3: main lymph nodes

The second digit represents major arterial branches

0: ileocolic artery

1: right colic artery

2: middle colic artery

3: left colic artery

4: sigmoid arteries

5: inferior mesenteric and superior rectal arteries

For lymph nodes relating to iliac arteries, 3 is used for the last digit of the number. The proximal internal iliac nodes are represented by letter P and the distal internal iliac nodes by letter D. The station number may be followed by 'rt' (right) or 'lt' (left) to represent the respective side where necessary.

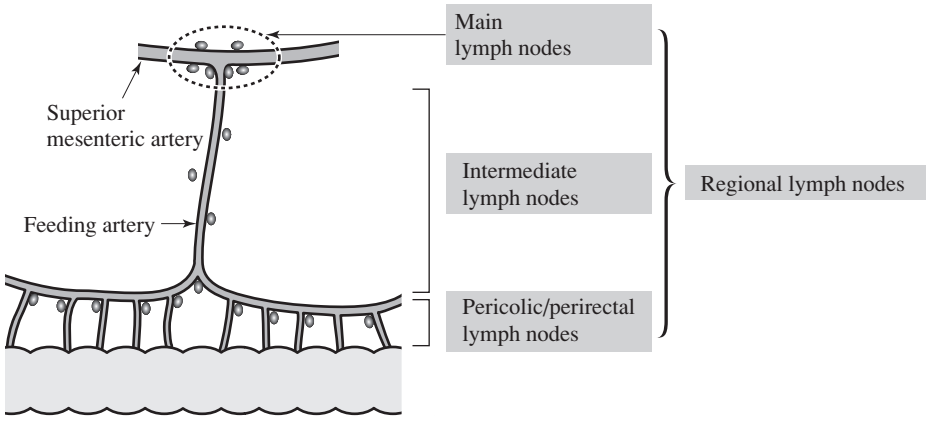
0 is used as the last digit for Presacral lymph nodes and 2 is used as the last digit for Inguinal nodes. The latter are classified as Intermediate nodes for anal cancer.

Superior mesenteric nodes, para-aortic nodes, infrapyloric nodes, gastroepiploic nodes

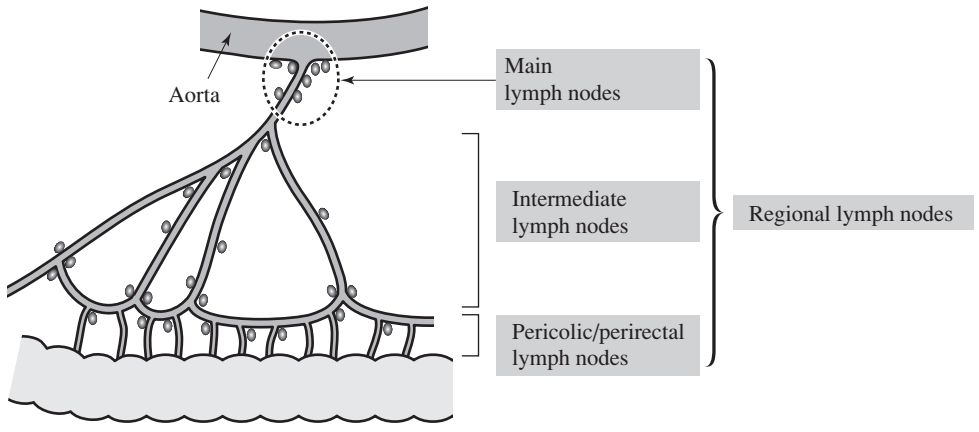
	Pericolic: 1	Intermediate: 2	Main: 3
Ileocolic: 0	201	202	203
Right colic: 1	211	212	213
Middele colic: 2	221	222	223
Left colic: 3	231	232	
Sigmoid: 4	241	242	
Superior rectal and inferior mesenteric: 5	251	252	253

and splenic hilum nodes are represented as 214, 216, 206, 204, and 210, respectively, consistent with the numbering in Japanese Classification of Gastric Carcinoma.

3.2.1.2.2 Lymph node grouping (Fig. 15)



a. Superior mesenteric artery



b. Inferior mesenteric artery

Fig. 15 Basic principles of lymph node grouping

3.2.1.2.3 Pericolic lymph nodes (Fig. 16)

The arteries supplying the colon include the ileocolic, right colic, middle colic (right and left branches), left colic and sigmoid arteries. The pericolic lymph nodes that are subject to lymphadenectomy for a tumor of the colon are classified into four patterns based on the location of the tumor and its feeding artery.

Pericolic lymph nodes are:

a. Lymph nodes within 10 cm from the tumor on either side when the feeding artery is in close proximity to the tumor
b. Lymph nodes between 5 cm from the entry point of the artery and 10 cm away from the tumor on the opposite side when there is only one feeding artery within 10 cm from the tumor
c. Lymph nodes 5 cm away from the entry point of each artery on either side when there are two feeding arteries within 10 cm from the tumor
d. Lymph nodes located between 5 cm away from the entry point of the nearest artery and 10 cm away from the tumor on the opposite side when there is no feeding artery within 10 cm from the tumor

3.2.1.2.4 Perirectal lymph nodes (Fig. 17)

Proximal perirectal lymph nodes that are subject to lymphadenectomy for a tumor of the rectosigmoid and rectum are lymph nodes that lie proximally between the tumor and the entry point of the terminal sigmoid artery. If the distance between the tumor and the entry point of the terminal sigmoid artery is less than 10 cm, lymph nodes that lie proximally within a 10 cm of the tumor are perirectal lymph nodes.

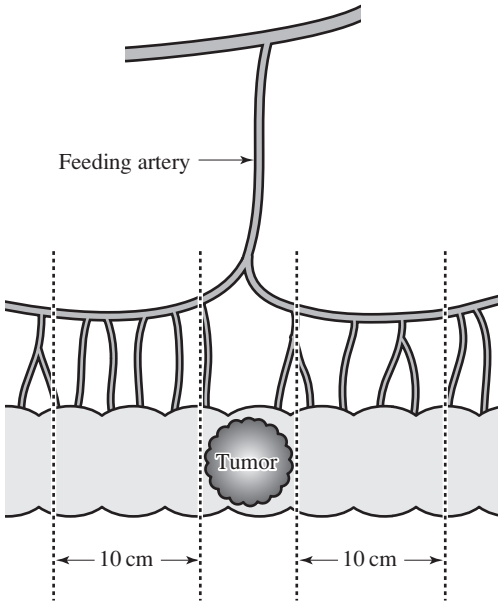
For a tumor of the rectosigmoid (RS) and upper rectum (Ra), the distal perirectal lymph nodes are those that lie distally within 3 cm of the tumor. For a tumor of the lower rectum (Rb), lymph nodes within 2 cm of the tumor are perirectal lymph nodes.

Note: Lymph nodes subjects to lymphadenectomy (regional lymph nodes) are: 1) pericolic/perirectal lymph nodes that are defined according to the location of the tumor and its feeding artery, 2) intermediate lymph nodes along the feeding artery and 3) the main nodes.

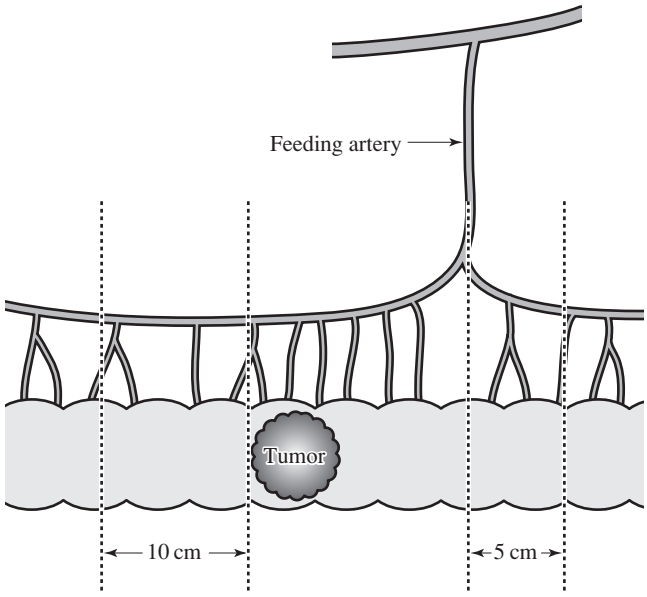
3.2.1.3 Lymph node metastasis (N) (refer to p. 7)

Note 7: A tumor nodule in the pericolic or perirectal fat tissue without histological evidence of residual lymph node in the nodule, if present, should be recorded as such.

As shown in Figure 18, tumor nodules in the pericolic or perirectal fat tissue without histological eviedence of residual lymph node may be classified into 1) scattered microscopic lesion, 2) lymphovascular invasion, 3) perineural invasion or 4) macroscopic lesion.

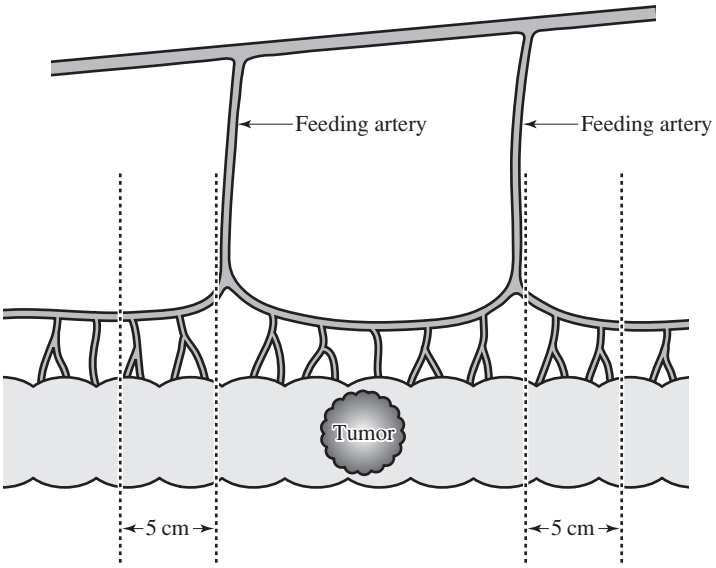


a. When there is a feeding artery in close proximity to the tumor

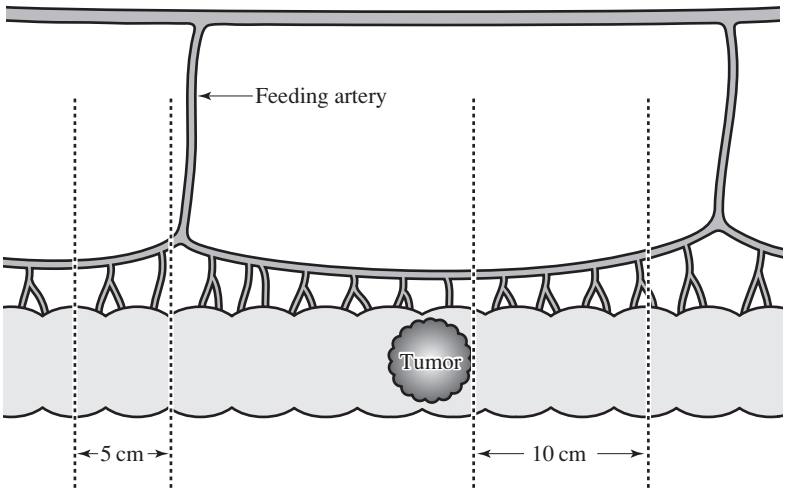


b. When there is only one feeding artery within 10 cm from the tumor

Fig. 16-1 Pericolic lymph nodes that are subject to lymphadenectomy (regional lymph nodes) for a tumor of the colon

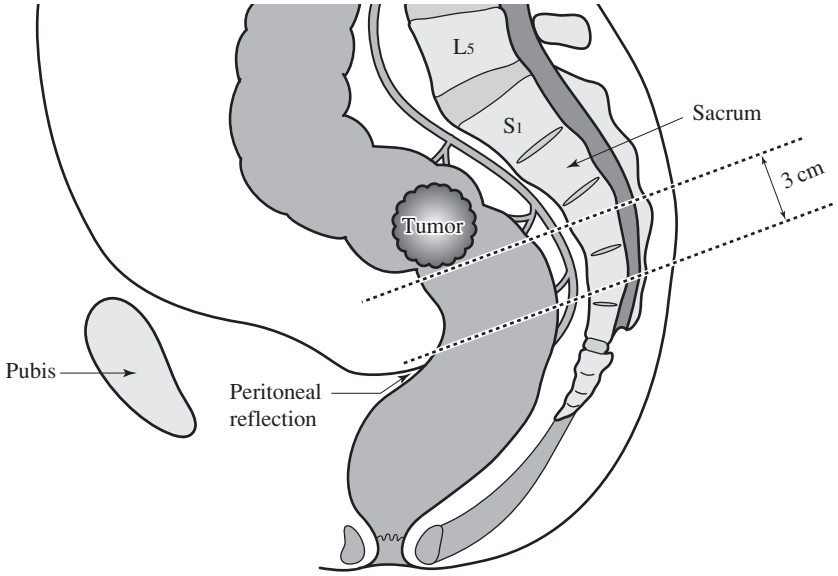


c. When there are two feeding arteries within 10 cm from the tumor

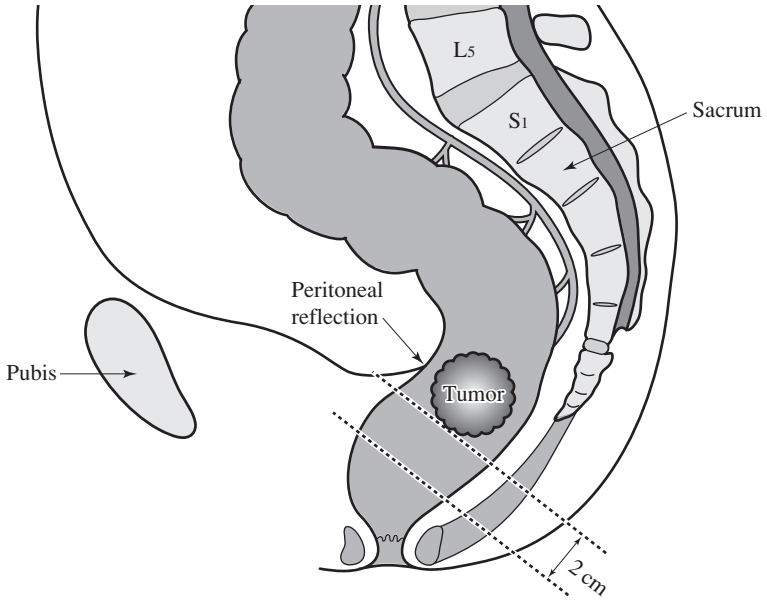


d. When there is no feeding artery within 10 cm from the tumor, the artery closest to the tumor is regarded as its feeding artery.

Fig. 16-2 Pericolic lymph nodes that are subject to lymphadenectomy (regional lymph nodes) for a tumor of the colon



a. When the tumor is located above the peritoneal reflection



b. When the distal edge of the tumor is located below the level of the peritoneal reflection

Fig. 17 Perirectal lymph nodes that are subject to lymphadenectomy for a tumor of the rectosigmoid and rectum

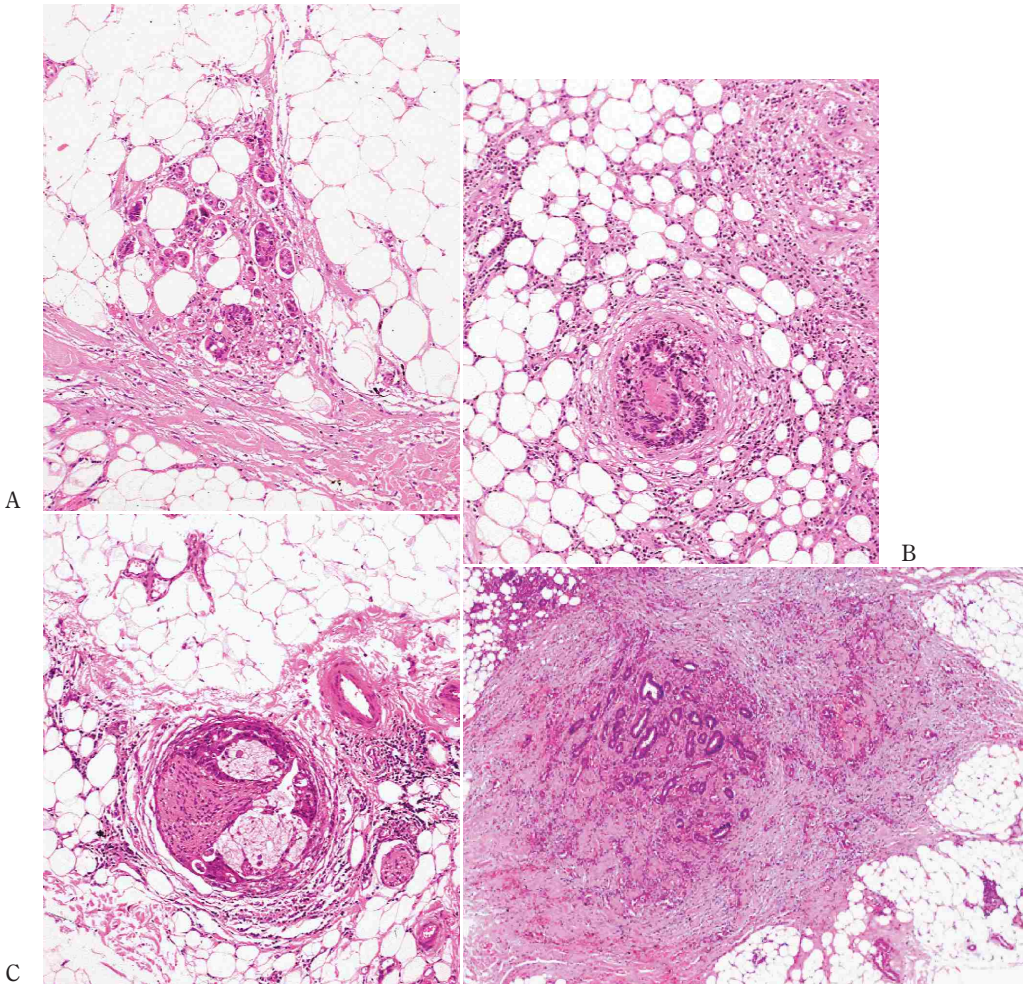


Fig. 18 Tumor nodules in the pericolic or perirectal fat tissue without histological evidence of residual lymph node

A. scattered microscopic lesion
B. lymphovascular invasion
C. perineural invasion
D. macroscopic lesions

3.2.2 Liver metastasis (H) (refer to p. 11)

Grade of liver metastasis is determined according to the number and the maximum diameter of the metastatic lesion(s) and the grade of lymph node metastasis of the primary tumor.

3.2.3 Peritoneal metastasis (P) (refer to p. 11)

When cancer cells are detected in ascitic fluid by cytological examination, it is recorded as Cy1.

Note: Since the prognostic significance of Cy1 is currently unknown, Cy1 does not affect the staging.

3.3 Staging (refer to p. 12)

Stage Ⅲ represents the disease where metastasis is present in regional lymph nodes. Thus, SI/AI N0 disease, previously classified as Stage Ⅲ, is included in Stage Ⅱ in the current version of the classification.

3.4 Multicentric colorectal cancers, multiple primary cancers and multiple cancers (refer to p. 12)

Multicentric colorectal cancers are defined as presence of two or more primary cancers in the large bowel.

Multiple primary cancers are defined as presence of primary cancer in other organ(s) in addition to colorectal cancer.

Multiple cancers entail multicentric colorectal cancers and multiple primary cancers.

Synchronous cancers and metachronous cancers:

When two or more primary cancers are diagnosed within a year, they are referred to as synchronous cancers.

When two or more primary cancers are diagnosed over the period of a year or longer, they are referred to as metachronous cancers.

3.5 Family history and hereditary diseases (refer to p. 12)

3.5.1 Familial adenomatous polyposis (FAP)

The diagnosis of FAP is made when any one of the following criteria is met:

1) More than 100 adenomas in the colon and rectum

Note: It is regardless whether there is a family history of FAP.

2) Fewer than 100 adenomas in the colon and rectum with a family history of FAP

Note: Fewer than 100 adenomas with no family history of FAP are referred to as multiple adenomas.

3) A mutant *APC* gene in germ-line cells

Note: If any other cause of multiple colorectal adenomas, *e.g.* a mutant *MYH* gene is found, it should be specifically stated.

Any extracolonic disease should be recorded, if present.

Note: Diseases known to be associated with FAP include osteomas desmoid tumors, soft tis-

sue tumors, gastric fundic gland polyps, duodenal polyps and thyroid cancer.

3.5.2 Hereditary non-polyposis colorectal cancer (HNPCC)

It is recommended that the Amsterdam Criteria Ⅱ (Revised Amsterdam Criteria) is used for the diagnosis of HNPCC.

Amsterdam Criteria Ⅱ (Revised Amsterdam Criteria) (1999)

Three or more relatives with HNPCC-associated cancer and all of the following criteria must be met:

1) One affected patient should be a first-degree relative of the other two.

2) Two or more successive generations should be affected.

3) Cancer in one or more affected relatives should be diagnosed before the age of 50 years.

4) Familial adenomatous polyposis should be excluded in any cases of colorectal cancer.

5) Tumors should be verified by pathological examination.

Note: HNPCC-associated cancer refers to colorectal cancer, endometrial cancer, small bowel cancer, ureteral cancer and cancer of the renal pelvis.

4 Treatment

4.2 Surgical treatment (refer to p. 13)

Approach to the lesion, operative procedure, grade of lymph node dissection, method of anastomosis and adjacent structures resected are recorded.

Type and technique of anastomosis are also recorded.

4.2.2 Surgical procedures (refer to p. 13)

Polypectomy refers to removal of a polyp from its base, whereas excision of tumor refers to removal of a tumor with full-thickness of the bowel wall.

Local excision refers to either submucosal resection or full-thickness resection.

Right hemicolectomy refers to resection of the terminal ileum, cecum, ascending colon and the right one third of transverse colon, including ileocolic vessels, right colic vessels and the right branch of middle colic vessels.

Left hemicolectomy refers to resection of the left one third of transverse colon, descending colon and sigmoid colon, including the left branch of middle colic vessels, left colic vessels and sigmoid vessels.

Colectomy (colonic resection) other than ileocecal resection, right hemicolectomy, left hemicolectomy, sigmoidectomy, subtotal colectomy and total colectomy is recorded as limited colectomy and the colon resected is recorded in parentheses.

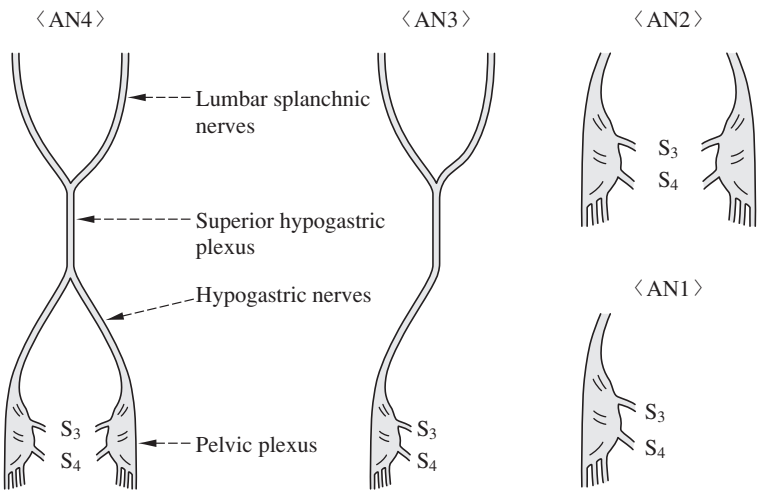


Fig. 19 Preservation of autonomic nerves

4.2.6 Preservation of autonomic nerves (refer to p. 15)

The autonomic nerves that require close attention during operations for rectal cancer include lumbar splanchnic nerves, superior hypogastric plexus, hypogastric nerves, pelvic plexuses and pelvic splanchnic nerves.

Lumbar splanchnic nerves, superior hypogastric plexus and hypogastric nerves belong to the sympathetic nerves, while pelvic splanchnic nerves belong to the parasympathetic nerves.

4.2.8 Residual tumor status (R) (refer to p. 16)

Residual tumor status based on intraoperative macroscopic findings is recorded as sR0, sR1, or sR2.

Residual tumor status based on pathological findings is recorded as pR0, pR1, or pR2.

If cancer tissue appears to be exposed at the resection margins without any macroscopic residual tumor, the residual tumor status should be recorded as sR1.

If cancer tissue is demonstrated at the resection margins microscopically, the residual tumor status should be recorded as pR1.

Pathological grading supersedes surgical (macroscopical) grading for the final assessment of residual tumor.

4.3 Chemotherapy and radiotherapy

4.3.1 Chemotherapy (refer to p. 17)

Evaluation of tumor response to treatment described in the "Response Evaluation Criteria

in Solid Tumors (RECIST)" is as follows:

4.3.1.1 Definition of lesions for evaluation

In phase Ⅱ trials where tumor response is used as a prospective endpoint, the lesions to be evaluated should be clearly defined. Although definitions are not always used in phase Ⅲ trials, the lesions are examined to evaluate tumor progression status.

4.3.1.1.1 Measurable lesions

Measurable lesions are as follows: 1) tumor lesion whose longest diameter is 20 mm or more when measured by CT or MRI with a section of 10 mm or less; 2) tumor lesion whose longest diameter is 10 mm or more when measured by CT or MRI with a section of 5 mm or less; 3) tumor lesion whose longest diameter is 20 mm or more when measured on plain chest X-rays being surrounded by aerated lung (not abutting the mediastinum or thoracic wall) and 4) superficial lesion with its longest diameter 20 mm or more that can be documented by color photography with a ruler (*e.g.* metastatic skin lesions).

4.3.1.1.2 Non-measurable lesions

Non-measurable lesions are lesions other than those defined in section 4.3.1.1.1.

The following are considered non-measurable lesions regardless of the size or examination method.

Bone lesions
Leptomeningeal disease
Ascites
Pleural/pericardial effusion
Lymphangitis cutis/pulmonis
Abdominal masses that are not confirmed or monitored by imaging
Cystic lesions

4.3.1.2 Selection of target/non-target lesions and baseline documentation

No more than 10 measurable lesions that have been identified before treatment are selected as target lesions in the order of maximum dimensions. Site of the lesion, investigation employed, date of examination and its maximum dimension are documented as baseline values according to the target lesion selected. In addition, the sum of the maximum dimensions of all target lesions is calculated and recorded.

All other lesions that have not been selected as target lesions are designated as non-target lesions regardless of their measurability. The sites, investigations employed and date of examination of these no-target lesions are recorded.

4.3.1.3 Assessment of tumor response

At the end of each treatment course, both target and non-target lesions are evaluated by

the same investigations as those employed at the baseline. Maximum dimensions of the target lesions and whether the non-target lesions have responded or progressed are recorded. Tumor response to radiotherapy is evaluated in 0, 4 and 12 weeks after completion of the therapy. In case of neoadjuvant long-course radiotherapy, it is recommended that tumor response is evaluated in 3-5 weeks after completion of the therapy.

4.3.1.4 Tumor response criteria

Tumor response is evaluated according to the RECIST guideline at the end of every 2 courses of the treatment. Tumor response for each individual is represented by their best response along the period. Tumor response should be monitored continuously. Additional recording is required only when either complete response (CR) or obvious progression of the disease is identified during the follow-up period.

All eligible patients must be assessed for tumor response to the treatment. Patients whose tumor response cannot be evaluated are represented as not evaluable (NE) and they should be included in the response evaluation.

4.3.1.4.1 Response criteria for target lesions

Complete response (CR):

Disappearance of all target lesions

Partial response (PR):

30% or more decrease in the sum of maximum dimensions of the target lesions compared to those at the baseline

Progressive disease (PD):

20% or more increase in the sum of maximum dimensions of the target lesions compared to the smallest sum maximum dimensions recorded since the treatment started

Stable disease (SD):

Less shrinkage/response than PR and less progression than PD

Not evaluable (NE):

Unable to investigate the target lesions or to evaluate tumor response for some reasons

4.3.1.4.2 Response criteria for non-target lesions

Complete response (CR):

Disappearance of all non-target lesions with normal tumor markers

Incomplete response/Stable disease (IR/SD):

Persistence of one or more non-target lesions and/or raised tumor markers

Progressive disease (PD):

Unequivocal progression of existing non-target lesions

Not evaluable (NE):

Unable to investigate the target lesions or to evaluate tumor response for some reasons

4.3.1.4.3 Overall response

Overall response is evaluated following each course of treatment based on a combination of tumor response in target and non-target lesions as shown in the table below. If tumor response cannot be assessed (NE) either in target or non-target lesions, overall response is recorded as NE. Appearance of new lesions is evaluated separately from response in target lesions or response in non-target lesions.

The duration of response for 4 weeks is no longer required to evaluate overall response as CR or PR, which used to be a requisite in WHO criteria. The date when the overall response is evaluated as CR or PR should be recorded.

Table Overall response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	IR/SD	No	PR
PR	Not PD	No	PR
SD	Not PD	No	SD
PD	Any	Yes/No	PD
Any	PD	Yes/No	PD
Any	Any	Yes	PD

4.3.1.4.4 Best overall response: confirmation required

The best overall response is, in geneal, the best response during the course of the treatment. CR is the highest grade of response and is followed in descending order by PR, SD, PD, and NE. An overall response of SD requires the maintenance of the condition from the start of treatment to the end of the second course. (When the response to the first course of treatment is SD but it turns out to be PD after the second course, the best overall response is recorded as PD).

If tumor response cannot be assessed by imaging because of unequivocal disease progression or death due to disease progression before evaluation of the first treatment course, it is recorded as PD. If tumor response is unavailable because of the cease of treatment due to toxicity or patients' refusal, it is recorded as NE.

Best overall response

CR: where complete response (CR) has been assigned as overall response on two con-

secutive assessments that have been performed with an interval of no less than 4 weeks.

PR: where either partial response (PR) or complete response (CR) has been assigned as overall response on two consecutive assessments that have been performed with an interval of no less than 4 weeks and does not meet the criteria for CR as best overall response.

SD: where stable disease (SD) has been assigned as overall response on one or more assessment and progressive disease (PD) has not been assigned either on the first or the second assessment and does not meet the criteria for either CR or PR as best overall response.

PD: where PD has been assigned as overall response and does not meet the criteria for any of CR, PR and SD.

NE: where NE (not evaluable) has been assigned on every assessment.

Table Criteria for best overall response of SD and PD

Overall response after 1st course	Overall response after 2nd course	Overall response after 3rd course	Best overall response
SD	SD	PD	SD
NE	SD	PD	SD
SD	NE	PD	PD
NE	NE	PD	PD
SD, PR, or CR	PD	—	PD
PR or CR	NE	PD	PD

4.3.1.5 Response rate

Only CR and PR are considered to have responded to treatment and used to calculate the response rate. All patients who meet the eligibility criteria including those assigned NE should be included in analysis of the response rate.

4.3.1.6 Overall survival (OS), Progression-free survival (PFS), Relapse-free survival (RFS), Disease-free survival (DFS), Time to treatment failure (TTF)

There are a number of endpoints other than response rates as listed in the table below. All eligible patients should be included in analysis. The date of registration is the starting date.

Table Endpoints and events to be counted

Endpoints	Events (the earliest event is counted)		
Overall survival (OS)	All-cause death		
Progression-free survival (PFS)	All-cause death	Disease progression/ Relapse	
Relapse-free survival (RFS)	All-cause death	Relapse	
Disease-free survival (DFS)	All-cause death	Relapse	Secondary cancer
Time to treatment failure (TTF)	All-cause death	Disease progression/ Relapse	Withdrawal of treatment

4.3.1.7 Adverse events (CTC-AE)

Adverse events are recorded with respect to each treatment. This includes type, incidence rate, grade, time of occurrence, duration and reversibility. It is recommended that they are recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.

The following serious adverse events are summarized separately:

Any death during the treatment or within 30 days after completion of the treatment

Death beyond 30 days after completion of the treatment where there is a possibility that the death is related to the treatment

Grade 4 non-hematological toxicity

Note: ECOG Performance Status

Grade	Performance status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, *e.g.* light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

(Oken MM, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5: 649-655, 1982.)

5 Handling of resected specimens

5.4 Histological findings

5.4.1 Histological types (refer to p. 24)

a. Large intestine (excluding vermiform appendix and anal canal)

1 Benign epithelial tumors

1.1 Adenoma

Most adenomas in the large intestine are circumscribed elevated lesions (protruded type or superficial type).

Their surface is usually granular, lobulated or gyrus-like, but papillary or villous structure is sometimes seen.

Based on their microscopic architecture, adenomas are classified as tubular, villous, tubulovillous or serrated.

1.1.1 Tubular adenoma

Tubular adenomas are mainly composed of tubular structures. In general, high proliferative activity is seen in the upper portion of the glands (Fig. 20-22).

1.1.2 Tubulovillous adenoma

Tubulovillous adenoma is an intermediate type and consists of a mixture of tubular and villous components (Fig. 23).

1.1.3 Villous adenoma

Villous adenomas are composed of leaf- or finger-like processes having a narrow core of lamina propria and no branching. In general, high proliferative activity is seen in the upper portion of the glands but may be seen throughout their entire length (Fig. 24).

1.1.4 Serrated adenoma

Serrated adenomas have serrated glandular architecture reminiscent of that of hyperplastic polyps. Unlike hyperplastic polyps, they have cytological features such as pseudostratified and enlarged nuclei, surface mitosis, incomplete mucinous differentiation and eosinophilic cytoplasm (indicating their neoplastic nature) (Fig. 25).

Adenomas are classified according to their degree of architectural and cytological atypia into low grade (equivalent to adenomas with mild and moderate atypia), high grade (equivalent to adenomas with severe atypia) and a mixture of low grade and high grade.

Note 1: The term “polyp” can be defined macroscopically as a circumscribed and elevated lesion in the mucosa irrespective of its histological characteristics.

Note 2: The term “adenomatous polyp” should not be used to describe an adenoma, except in the term “familial adenomatous polyposis” when used as a synonym for familial adenomatosis.

Note 3: The term "papillary adenoma" should not be used to describe any adenomas.

Note 4: Serrated adenomas resemble hyperplastic polyps because the epithelium has a serrated morphology in the upper half of the duct. But in contrast nuclear swelling, pseudostratification and mitotic figures are visible in the superficial part. It is a benign tumor (adenoma) that exhibits a reduced number of goblet cells, eosinophilic cytoplasm, etc.

Note 5: Adenomas with replacement of the submucosa, i.e. pseudocarcinomatous invasion, should not be diagnosed as carcinoma that has invaded the submucosa (Fig. 26).

1.2 Familial adenomatosis

Familial adenomatosis is diagnosed when at least 100 colorectal adenomas are found or if fewer than 100, when there is a family history of familial adenomatosis.

Adenomas may be found in the stomach, duodenum, jejunum, and ileum. Sometimes more than 100 fundic gland polyps (fundic gland polyposis) are seen in the stomach.

2 Malignant epithelial tumors (carcinoma)

Histological types of carcinoma of the colon and rectum can be classified as follows.

Tumors that contain more than one histological type of carcinoma are classified besed on the predominant histological type.

Note 1: When a tumor contains more than one histological type of carcinoma, all the histological types should be described, and it is recommended that the proportion of each type is stated.

Note 2: The presence of the most poorly differentiated histological type and the presence of sprouting at the invasive front of the carcinoma are considered to correlate with the prognosis. The methods of describing these features are now under investigation.

Note 3: When both carcinoma and an adenoma component are present in the same lesion, record as "carcinoma with adenoma". Carcinoma with adenoma is classified into the following two types according to the proportions of the tumor occupied by the carcinoma component and the adenoma component:

a. Carcinoma in adenoma: Carcinoma with adenoma in which the carcinoma component is smaller than the adenoma component.

b. Carcinoma with adenoma component: Carcinoma with adenoma in which the carcinoma component is the same size or larger than the adenoma component.

2.1 Adenocarcinoma

Adenocarcinoma is characterized by malignant glandular epithelium having a tubular or papillary architecture or that producing mucus.

2.1.1 Papillary adenocarcinoma (Fig. 27)

Papillary adenocarcinomas have a papillary glandular structure composed of columnar or cuboidal cells. Carcinoma with a villous or serrated architecture is also included in this type.

2.1.2 Tubular adenocarcinoma; well differentiated type (Fig. 28-31) and moderately differentiated type (Fig. 32)

Well differentiated tubular adenocarcinoma is characterized by distinct and large gland formation and moderately differentiated tubular adenocarcinoma is composed of medium to small glands with a cribriform structure.

2.1.3 Poorly differentiated adenocarcinoma (Fig. 33, 34)

Poorly differentiated adenocarcinoma has little tendency to form glands or tubules but intracellular mucus production is seen. The tumor displays a solid or non-solid growth pattern.

Note 1: Solid type is composed of cancer cells that have formed a solid or sheet-like structure and exhibits expansive growth (Fig. 33). Non-solid type is composed of cancer cells with small glands, in small cluster or trabecular structure, or composed of isolated cancer cells. It exhibits infiltrative growth (Fig. 34).

Note 2: Carcinoma with lymphoid stroma is classified as non-solid type.

2.1.4 Mucinous adenocarcinoma (Fig. 35, 36)

Mucinous adenocarcinoma is composed of cells that produce substantial amount of mucus outside the cells forming mucus nodules or lakes. It comprises well differentiated mucinous adenocarcinoma originating from well differentiated type adenocarcinoma (papillary adenocarcinoma, well and moderately differentiated tubular adenocarcinoma) and poorly differentiated mucinous adenocarcinoma originating from poorly differentiated type adenocarcinoma (non-solid type, signet-ring cell carcinoma).

2.1.5 Signet-ring cell carcinoma (Fig. 37)

Tumor cells in signet-ring cell carcinoma contain various amounts of mucus. They have signet-ring cells, and have little tendency to form glands or tubules.

The signet-ring cells resemble intestinal goblet cells both histochemically and electron-microscopically.

2.2 Endocrine cell carcinoma (Fig. 38)

Endocrine cell carcinomas are composed of rather uniformly small or medium sized cancer cells containing little cytoplasm and forming a sheet-like or large solid structure. They have highly vascular stroma.

The nuclei of the cancer cells are larger and more hyperchromatic than the nuclei of carcinoid tumors.

The nucleoli are not conspicuous but mitotic figures are frequently seen.

Note 1: Histological diagnosis of endocrine cell carcinoma requires a demonstration of the presence of neuroendocrine granules either by immunohistochemistry or under an electron-microscope.

Note 2: In general, endocrine cell carcinoma is characterized by a high rate of vessel invasion and hepatic or lymph node metastasis.

Note 3: Endocrine cell carcinoma that consists of small cells is usually referred to as small cell carcinoma.

Note 4: Endocrine cell carcinoma of the gastrointestinal tract is usually associated with adenocarcinoma (adenoendocrine cell carcinoma), and it is thought to be derived from adenocarcinoma.

2.3 Adenosquamous carcinoma (Fig. 39)

Adenosquamous carcinoma consists of a mixture of adenocarcinoma and squamous cell carcinoma. The two histological components may be intermingled, or there may be a clear boundary between them.

2.4 Squamous cell carcinoma

Squamous cell carcinoma is rare in the large intestine.

Note: Squamous cell carcinoma arising from the epithelium of the anal canal is classified as squamous cell carcinoma of the anal canal.

2.5 Miscellaneous carcinomas

Miscellaneous carcinomas comprise choriocarcinoma, α-fetoprotein-producing adenocarcinoma, undifferentiated carcinoma, etc.

Undifferentiated carcinoma is composed of small or large malignant cells forming a sheet-like or large solid structure. It lacks a glandular structure and no mucus secretion or neuroendocrine granules are demonstrated by immunohistochemical or other methods.

3 Carcinoid tumor (Fig. 40)

Carcinoid tumors arise from immature endocrine cells located within the proliferative zone of the digestive tract glands and have low grade malignant potential. They are composed of uniform small cells and have a ribbon-like, nest-like, trabecular, rossette-like or glandular structure, and highly vascular stroma. In the colon and rectum, the carcinoid tumors usually stain positive with argyrophil stain, whereas carcinoid tumors in the vermiform appendix usually stain positive with argentaffin stain. H & E staining reveals brownish serotonin granules in the peri- or sub-nuclear area. In the early stage of their development, carcinonoid tumors are located in the deep portion of the mucosa but the main site of the tumors grow gradually into the submucosa. Prevalent sites in the large intestine are the lower rectum and the vermiform appendix.

Note 1: Although goblet cell carcinoid in the vermiform appendix has been classified as a subtype of carcinoid tumor, many investigators now think that it should be classified as poorly differentiated adenocarcinoma (non-solid type) because of its distinct patterns of growth and metastasis from typical carcinoid tumor and the similarity of its mucus

production and Paneth cell differentiation to adenocarcinoma.

Note 2: Eighty percent of typical carcinoid tumors of the vermiform appendix produce serotonin and 20% produce peptide PYY. On the other hand, 90% of typical carcinoid tumors of the rectum produce peptide PP and PYY and 10% produce serotonin.

4 Non-epithelial tumors

4.1 Myogenic tumors

Myogenic tumors arise from the muscularis mucosae or muscularis propria and may show nuclear palisading. Myogenic tumors that have low cellularity and lack mitotic figures are leiomyomas and those with high cellularity and numerous mitotic figures are leiomyosarcomas.

Myogenic tumors are immunostain positive for α-smooth muscle actin, muscle-specific actin and desmin, and stain negative for KIT (CD117).

4.2 Neurogenic tumors

Neurilemoma is the most common neurogenic tumor and multiple neurilemomas are seen in patients with von Recklinghausen disease. Most neurilemomas arise between the outer and inner layer of the muscularis propria.

Granular cell tumors mainly arise in the submucosa.

Note: Schwann cell hyperplasia and neurilemomas are sometimes seen in the mucosa.

4.3 GISTs (Gastrointestinal stromal tumors)

The majority of GISTs are immunostain positive for KIT but a few are immunostain negative for KIT and myogenic and neurogenic tumor markers. In addition, 80% of GISTs are immunostain positive for CD34. Differentiation between GISTs and myogenic tumors is sometimes difficult by H & E staining alone. GISTs may consist of spindle cells or epithelioid cells.

Note: Myogenic tumors and GISTs are considered to have high malignant potential when the tumor exceeds 50 mm in size or its MIB-1 (Ki-67) labeling index is greater than 10%. Although the mitotic index is usually used as a means of assessing the malignant potential of tumors, the MIB-1 labeling index is recommended because of its higher reproducibility than the mitotic index. Tumors associated with necrosis are suspected of being highly malignant regardless of the size.

5 Lymphoma

Lymphoma is classified, according to WHO classification, into B-cell lymphoma (MALT lymphoma, follicular lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, Burkitt lymphoma, others), T-cell lymphoma and Hodgkin lymphoma. For details, see WHO Classification: "Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues".

8 Tumor-like lesions

8.1 Hyperplastic polyps and polyposis (Fig. 41)

Hyperplastic polyps and polyposis are characterized by elongation and dilatation of the tubules and luminal serration. The epithelial cells do not exhibit neoplastic atypia and they contain abundant and faintly eosinophilic cytoplasm throughout the entire length of the tubules. High proliferative activity is seen in the lower half of the tubules.

Note: Non-neoplastic tubules may show misplacement to the submucosal layer.

8.2 Hyperplastic nodules (Fig. 42)

The macroscopic appearance of hyperplastic nodules is similar to that of hyperplastic polyps but they lack luminal serration.

8.3 Juvenile polyps and polyposis (Fig. 43)

Juvenile polyps consist of epithelial tubules, which may be dilated or cystic, embedded in an excess of lamina propria. The superficial portion of the lamina propria is edematous and composed of proliferating and dilated capillaries, proliferating fibroblasts and fibrous tissue, and chronic inflammatory cell infiltrates. They may be complicated by hemorrhage or erosion.

Juvenile polyps appear as reddish edematous elevations with necrotic tissue at the surface and may be sessile or pedunculated. They are seen in both children and adults.

Note: A condition characterized by numerous juvenile polyps confined to the large intestine is called colorectal juvenile polyposis and when juvenile polyps are also present in the stomach and small intestine, this condition is called gastrointestinal juvenile polyposis.

8.4 Peutz-Jeghers syndrome and Peutz-Jeghers-type polyps (Fig. 44)

Peutz-Jeghers syndrome is a hereditary syndrome characterized by polyposis of the gastrointestinal tract and abnormal pigmentation in of the skin and mucous membranes. Polyps develop in the stomach and the small and large intestine. The polyps are composed of epithelial hyperplasia with various degrees of gland dilatation and accompanied by tree-like branching of the muscularis mucosae.

They are non-neoplastic lesions.

Note: Solitary polyps with histological features identical to those of the polyps in Peutz-Jeghers syndrome are called Peutz-Jeghers-type polyps.

8.5 Cronkhite-Canada syndrome and Cronkhite-Canada polyps (Fig. 45)

Cronkhite-Canada syndrome is manifested by gastrointestinal polyposis, alopecia (generalized loss of hair), skin pigmentation, nail atrophy and protein-losing gastroenteropathy. Multiple polyps are detected throughout the digestive tract and the polyps are composed of enlarged cystic glands containing eosinophilic material and edematous stroma.

The mucosa between the polyps also contains edematous stroma and cystic glands.

8.6 Cowden syndrome (disease) and Cowden polyps

Cowden syndrome is a hereditary disease characterized by multiple polyps throughout the digestive tract and is very often accompanied by various benign skin lesions and carcinoma of the breast and thyroid gland.

The polyps in the large intestine are similar to juvenile polyp histologically.

8.7 Benign lymphoid polyps and polyposis

Benign lymphoid polyps are polypoid lesions that consist of circumscribed areas of hyperplasia of lymphoid follicles. The polyps are usually up to several millimeters in diameter. The most prevalent sites are the cecum and the rectum and a condition in which multiple lesions are present is called polyposis. Multiple polyps are usually of uniform size and less than 5 mm in diameter.

8.8 Inflammatory polyps and polyposis

Inflammatory polyps are non-neoplastic polyps that develop in association with inflammation. They consist of pseudo-polyps and regenerative polyps.

8.9 Mucosal prolapse syndrome (Fig. 52)

Mucosal prolapse syndrome is a condition characterized by capillary proliferation and dilatation and chronic inflammatory cell infiltrates, especially in the superficial layer of the mucosa propria and fibromusculosis. Macroscopically they are flat, elevated, ulcerative or colitis cystica profunda types. The elevated type is composed of dilated and proliferating glands and is usually accompanied by surface erosion and conspicuous granulation tissue.

8.10 Cap polyposis

The macroscopic and histological features of cap polyposis are reminiscent of those of the elevated type of mucosal prolapse syndrome. However, cap polyposis is characterized by a wide range of localizations from the sigmoid colon to the rectum (occasionally extending to the right side of the colon), whereas the mucosal prolapse syndrome is confined to the rectum.

b. Vermiform appendix

1 Benign epithelial tumors

1.1 Adenoma

The classification of adenomas of the vermiform appendix is identical to adenomas of the large intestine.

1.2 Mucinous cystadenoma

Mucinous cystadenomas are benign cystic tumors lined by neoplastic tall columnar epithelium with abundant mucus production and the lumen of the vermiform appendix is filled with mucus.

2 Malignant epithelial tumors

2.1 Adenocarcinoma

The classification of adenocarcinoma of the appendix is identical to adenocarcinoma of the large intestine.

2.2 Mucinous cystadenocarcinoma (Fig. 46)

Mucinous cystadenocarcinomas are cyst-forming carcinomas that consist of papillary, well or moderately differentiated adenocarcinoma with abundant mucus production. There is usually little cytological atypia.

Note: Mucinous cystadenocarcinomas sometimes exhibit the structure of pseudomyxoma peritoneum.

3 Carcinoid tumor

See the section on the large intestine.

c. Anal canal

In this guideline, the definition of the anal canal is made primarily at the stage of macroscopic examination of the specimens.

The area between the superior border of the internal sphincter and the boundary of the perianal skin is defined as the anal canal on the resected specimens.

The anal canal is divided into three different parts: an area lined by 1) glandular epithelium (similar to rectum), 2) transitional zone epithelium or transitional epithelium (consisting of stratified cuboidal or columnar cells) and 3) anal epithelium (stratified squamous epithelium lacking the appendages of the skin).

The anal glands are seen in the submucosal layer and in the sphincter muscle layer of the anal canal with their openings into the anal crypts.

1 Benign epithelial tumors

Adenomas arising in the mucous epithelium of the rectal type are classified in the same way as adenomas of the large intestine. Cystadenomas, squamous papillomas, etc. are sometimes seen in other parts of the anal canal.

2 Malignant epithelial tumors

2.1 Adenocarcinoma

2.1.1 Rectal-type adenocarcinoma

Rectal-type adenocarcinoma implies adenocarcinoma or mucinous carcinoma arising from the

rectal mucosa of the anal canal.

Note: Internationally rectal-type adenocarcinoma of the anal canal is included in ordinary rectal adenocarcinoma.

2.1.2 Adenocarcinoma of anal gland origin

Adenocarcinoma of anal gland origin is extremely rare. The tumors are located in the wall of the anal canal and carcinomatous components are often undetectable in the mucosa.

2.1.3 Adenocarcinoma associated with anal fistula

Adenocarcinoma associated with anal fistula occurs in patients with a long history of anal fistula. The tumors are often mucinous carcinoma and seen in the wall of the anal canal.

Note: Squamous cell carcinoma of anal gland origin or associated with an anal fistula is sometimes seen.

2.2 Squamous cell carcinoma

Squamous cell carcinoma originates in transitional or squamous epithelium.

3 Extramammary Paget disease (Fig. 47)

Extramammary Paget disease lesions are characterized by the presence of large abnormal pale-staining cells (Paget cells) within the epidermis.

4 Malignant melanoma (Fig. 48)

Malignant melanoma develops in the vicinity of the dentate line and forms an elevated lesion. Usually the lesions contain melanin pigment but they are occasionally amelanotic.

7 Tumor-like lesions

Condyloma acuminatum, squamous papillomas, retention cysts of anal glands, submucosal abscesses, internal hemorrhoids and fibrovascular polyps are tumor-like lesions that are seen in the anal canal.

5.6 Histological assessment of biopsy specimens (Group classification) (refer to p. 28)

5.6.1 Principles

The classification applies only to colorectal biopsy specimens, including hot biopsy specimens, that have been obtained endoscopically and it does not apply to polypectomy, mucosal resection or surgical specimens. It also applies only to epithelial lesions. This Group classification is intended to clarify the diagnostic (disease) category of lesions, and, in principle, when the diagnosis is made by biopsy, the diagnostic term is recorded, and the Group classifi-

cation is recorded along with it.

5.6.2 Criteria for grouping

Group X: Inadequate material for histological diagnosis

No epithelial component is included in the biopsy specimen or the specimen is inadequate as a result of being severely damaged by the biopsy procedure.

Group 1: Normal tissue and non-neoplastic lesion

Normal mucosa and inflamed or hyperplastic mucosa (Fig. 51, 52).

Group 2: Lesions in which it is difficult to determine whether the lesion is tumorous or non-tumorous

Lesions in which it is difficult to determine whether the lesion is tumorous (adenoma, adenocarcinoma) or non-tumorous based on cell atypia, structural atypia, etc., are included in this group. Lesions in which differentiating between serrated adenoma and a hyperplastic polyp is a problem, atypical gland ducts that appear in association with mucosal prolapse syndrome, etc., correspond to such lesions (Fig. 53, 54).

Group 3: Adenoma (benign neoplasia)

A range of lesions in terms of cellular atypia or structural atypia is included in this group (Fig. 55-57), and lesions that have been judged to be benign neoplasia belong to this group.

Group 4: Neoplastic lesion suspected of being carcinoma

(1) A sufficient amount of tumor tissue is biopsied but a definite diagnosis of carcinoma cannot be made on the basis of architectural and cytological atypia (Fig. 58).

(2) Carcinoma is suspected but the biopsy specimen is too small to make a definite diagnosis.

(3) Carcinoma is suspected but the biopsy specimen is too severely damaged to make a definite diagnosis.

Group 5: Carcinoma

The lesion is definitely diagnosed as carcinoma on the basis of its nuclear atypia (enlarged, irregularly contoured, hyperchromatic nuclei, loss of nuclear polarity, large nucleoli) or cytoplasmic abnormalities (marked mucus depletion, basophilic cytoplasm), and on abnormal duct structure (irregular branching, tortuosity, fusion, etc.) (Fig. 59-61).

Note 1: When group classification is difficult because the amount of tissue that has been collected IS small, etc., it is important not to force a classification, but to record only the

tissue findings (tissue diagnosis) and inform the clinician of the need for a repeat biopsy, etc.

Note 2: Sometimes atypical epithelium appears against a background of chronic inflammation in ulcerative colitis or another inflammatory bowel disease (IBD) in which it is difficult to differentiate between tumorous and non-tumorous, but when the presence of IBD is clear clinically and pathologically, it is preferable to record the class of degree of atypia according to the Histopathological Evaluation Criteria for the Atypical Epithelium that Occurs in Ulcerative Colitis* and not to use the Group classification. Nevertheless, even when this type of atypical epithelium is present, when the presence of IBD is not clear at the time of biopsy, the diagnosis is sometimes made by using the group classification (especially Group 2). In such instances, the class of degree of atypia can by recorded later, at the stage when a definite diagnosis of IBD has been made.

In addition, ordinary adenomas and carcinomas sometimes also develop in patients with IBD, and when they do, the group classification is used.

*Ministry of Health and Welfare Special-Disease Intractable Inflammatory Bowel Disorder Survey Study Group: Histopathological Evaluation Criteria for the Atypical Epithelium that Occurs in Ulcerative Colitis: Proposal for New Evaluation Criteria Designed for Application to Surveillance Colonoscopy. J Jpn Soc Colo-proctol, 47: 547-551, 1994.

Note 3: Since Group 2 includes tissue in which it is difficult to differentiate between tumorous tissue and non-tumorous tissue, consider the need to collect detailed clinical information or perform a repeat biopsy.

Ref: Vienna classification of gastrointestinal epithelial neoplasia

The Vienna classification applies to the diagnosis of both biopsy specimens and resected specimens. Epithelial neoplastic lesions associated with inflammatory bowel disease can also be classified by this classification.

Category 1	Negative for neoplasia/dysplasia
Category 2	Indefinite for neoplasia/dysplasia
Category 3	Non-invasive low-grade neoplasia (low-grade adenoma/dysplasia)
Category 4	Non-invasive high-grade neoplasia
	4.1 High-grade adenoma/dysplasia
	4.2 Non-invasive carcinoma (carcinoma in situ)*
	4.3 Suspicion of invasive carcinoma
Category 5	Invasive neoplasia (carcinoma)
	5.1 Intramucosal carcinoma**
	5.2 Submucosal carcinoma or beyond

*Non-invasive indicates no distinct evidence of invasion

**Neoplasia which shows invasion to the lamina propria or muscularis mucosae

By WHO classification, "non-invasive neoplasia" is termed as "intraepithelial neoplasia (dysplasia)".

(Schlemper RJ, et al. The Vienna classification of gastrointestinal epithelial neoplasia. Gut 47: 251-255, 2000.)

Histological photographs

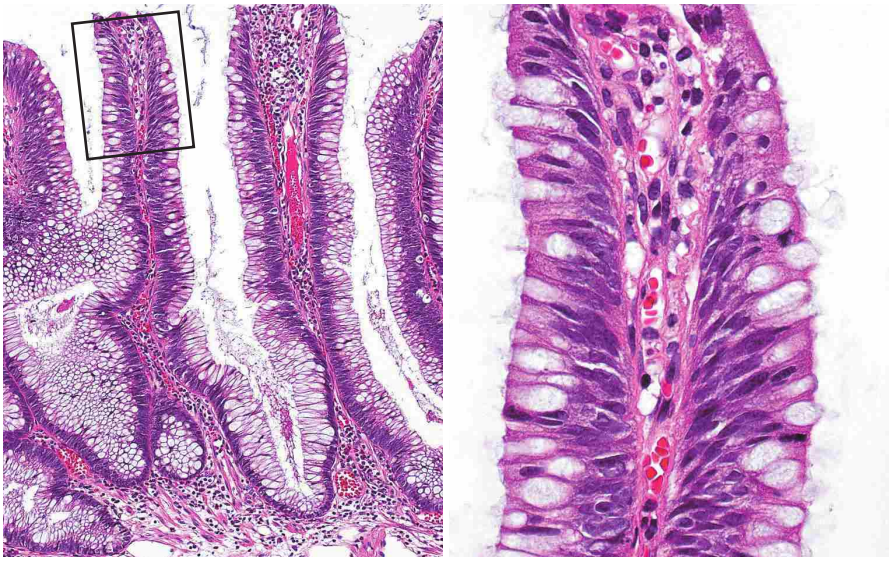


Fig. 20 Tubular adenoma (low grade)

Low-grade tubular adenoma with abundant mucus production. High proliferative activity is seen in the upper portion of the glands and neoplastic cells are migrating toward the bottom with differentiation (left). Pseudostratification of spindle-shaped nuclei is seen in the area of high proliferative activity but their polarity is maintained (right).

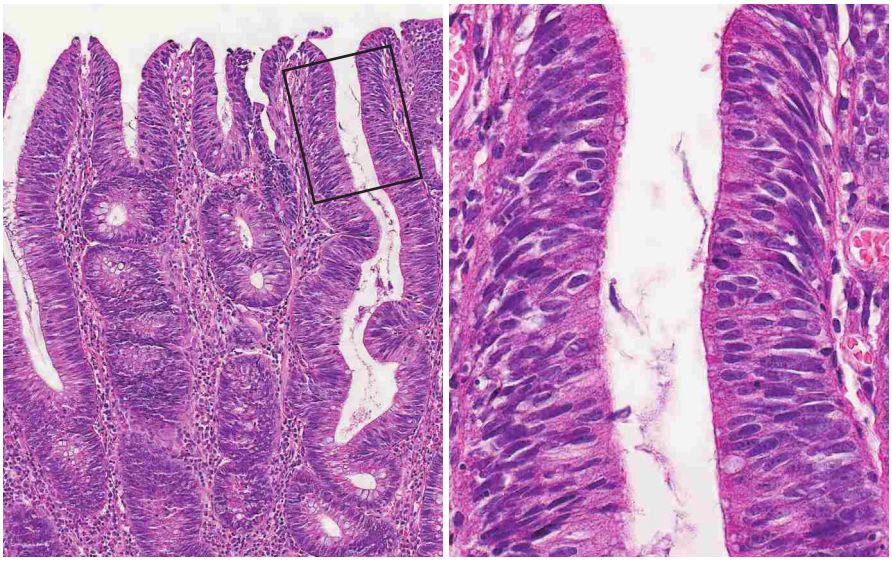


Fig. 21 Tubular adenoma (low grade)

Low-grade tubular adenoma with scanty mucus production. High proliferative activity is seen in the upper portion of the glands and neoplastic cells are migrating toward the bottom with differentiation (left). The spindle-shaped nuclei in the area of high proliferative activity are pseudostratified (right) but in the lower portion they are arranged regularly in the basal half of the gland lumen (left).

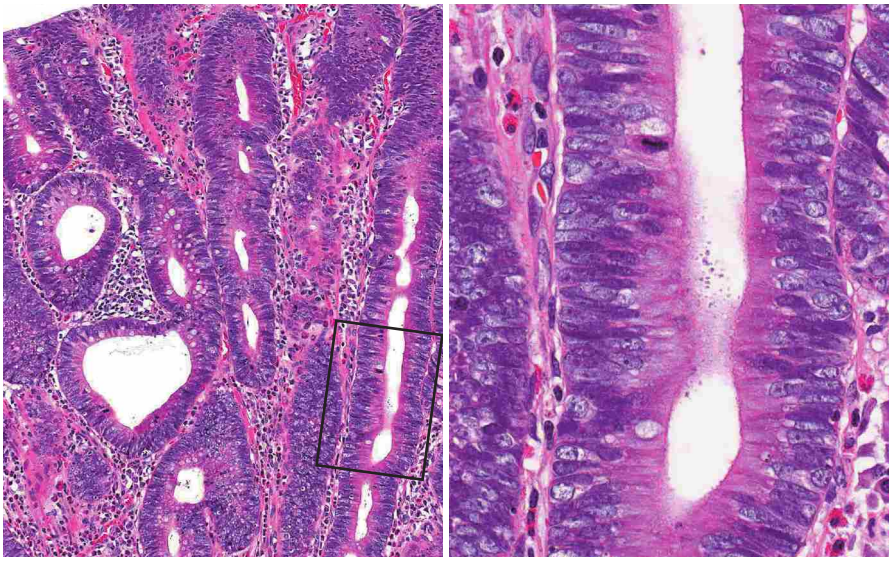


Fig. 22 Tubular adenoma (high grade)
High-grade tubular adenoma with scanty mucus production. Neoplastic glands are dilated and tortuous. High proliferative activity is seen in the upper portion of the glands, where prominent nuclear pseudostratification and numerous mitotic figures are seen (left). Mitotic figures are also found in area with low proliferative activity (right). Degree of nuclear pseudostratification is extended to the basal half of the glandular lumen. Neoplastic cells have round to oval nuclei with a clear chromatin pattern and small basophilic nucleoli and the Golgi apparatus in the cytoplasm is inconspicuous.

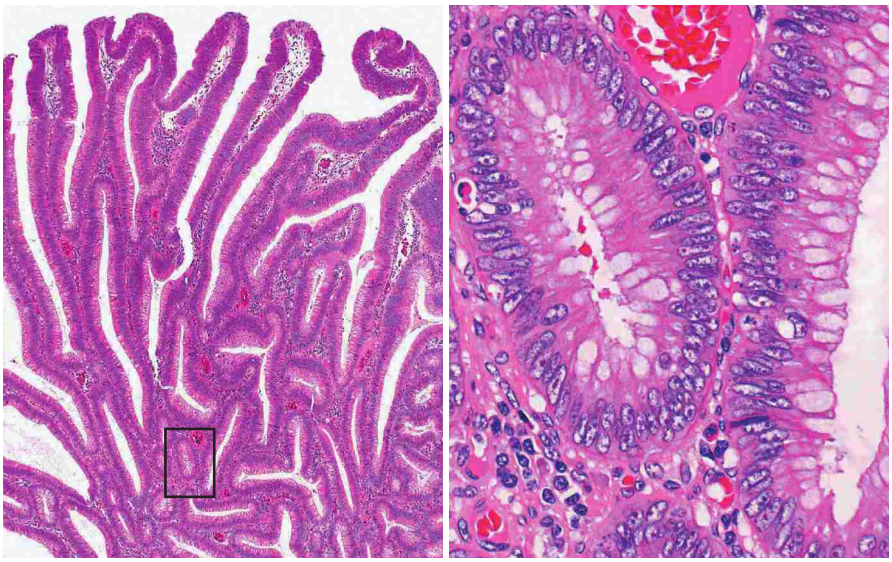


Fig. 23 Tubulovillous adenoma (low grade)
Left: Low-grade tubulovillous adenoma with moderate mucus production. High proliferative activity is seen in the upper portion of the glands, where the nuclei exhibit pseudostratification (left). In area with low proliferative activity (right), the nuclei of the neoplastic cells have a clear chromatin pattern and small basophilic nucleoli and the cells are arranged regularly in the basal half of the glandular lumen. The Golgi apparatus is clearly visible in the supranuclear area of the cytoplasm.

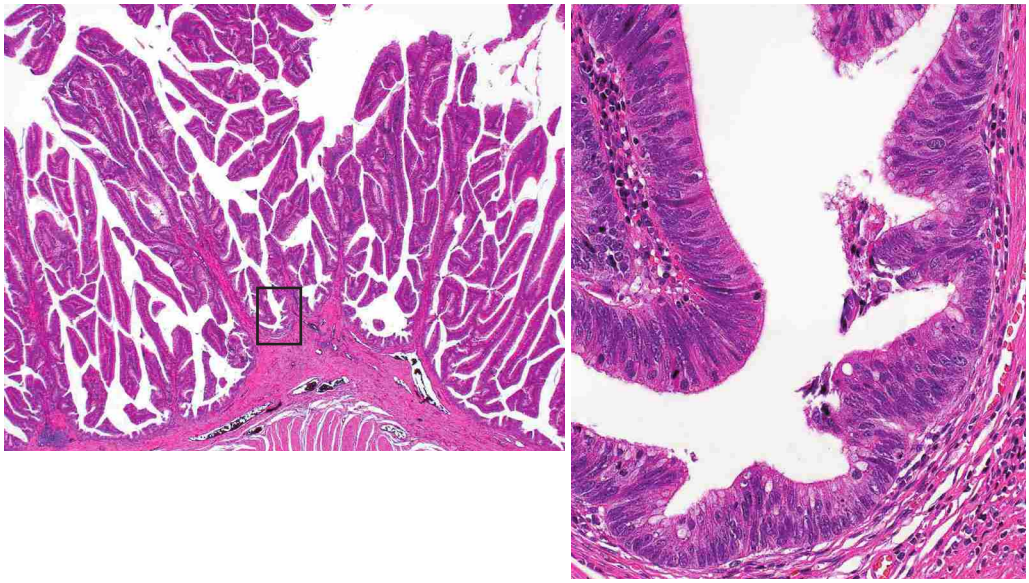


Fig. 24 Villous adenoma (high grade)
Neoplastic tubules show villous or papillary architecture with a narrow core of lamina propria (left). The entire length of the tubules shows high-grade atypia with prominent nuclear stratification and numerous mitotic figures (right). Mucus production is not conspicuous.

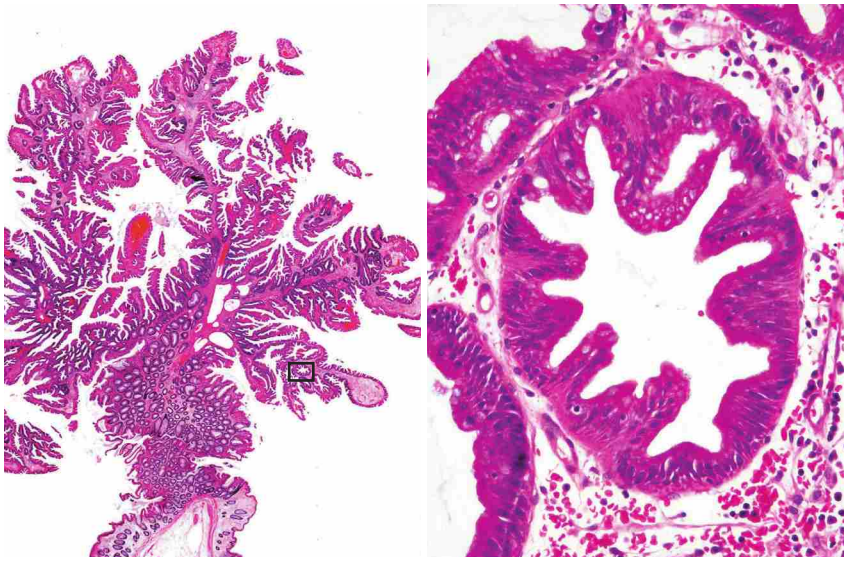


Fig. 25 Serrated adenoma (low grade)
A pedunculated polyp with papillary growth by neoplastic glands. Luminal serration is seen even at low-power magnification (right). Neoplastic glands consist of eosinophilic cells and a small number of goblet cells. A high nuclear population and nuclear pseudostratification are present, in contrast to hyperplastic polyps.

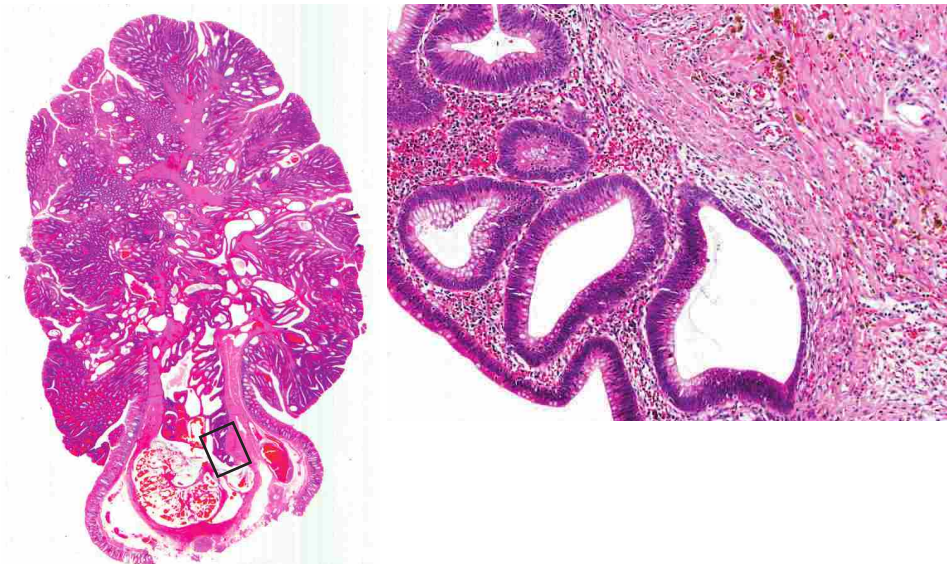


Fig. 26 Pseudocarcinomatous invasion by low-grade tubular adenoma
Low-grade tubular adenoma showing pseudoinvasion of the submucosa (left). A layer of lamina propria is present in atypical glands with pseudoinvasion. Hemosiderin deposition can be seen in the interstitium (right).

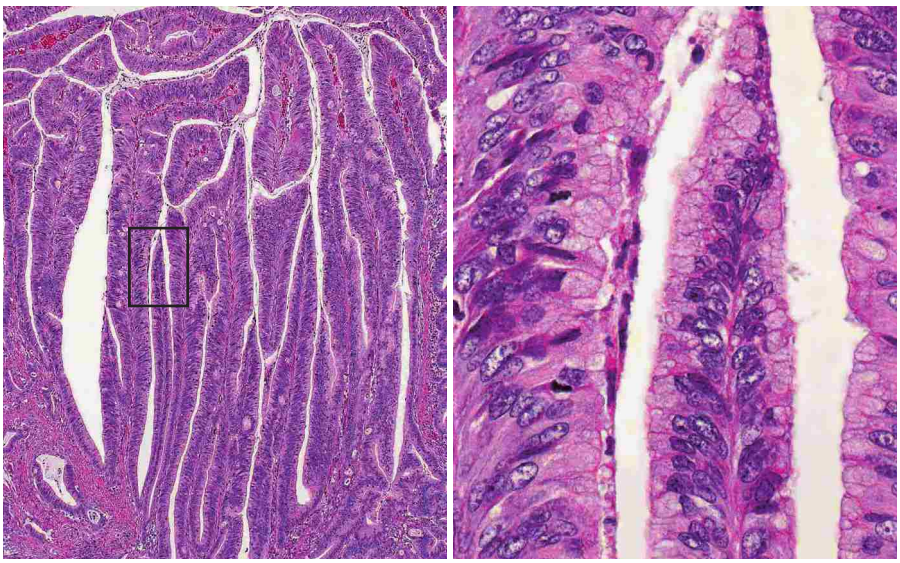


Fig. 27 Papillary adenocarcinoma
Papillary adenocarcinoma consists of neoplastic glands having papillary or villous architecture (left). Enlarged round or oval nuclei with pseudostratification are seen. Mucus droplets are seen at the luminal side of the columnar cells (right).

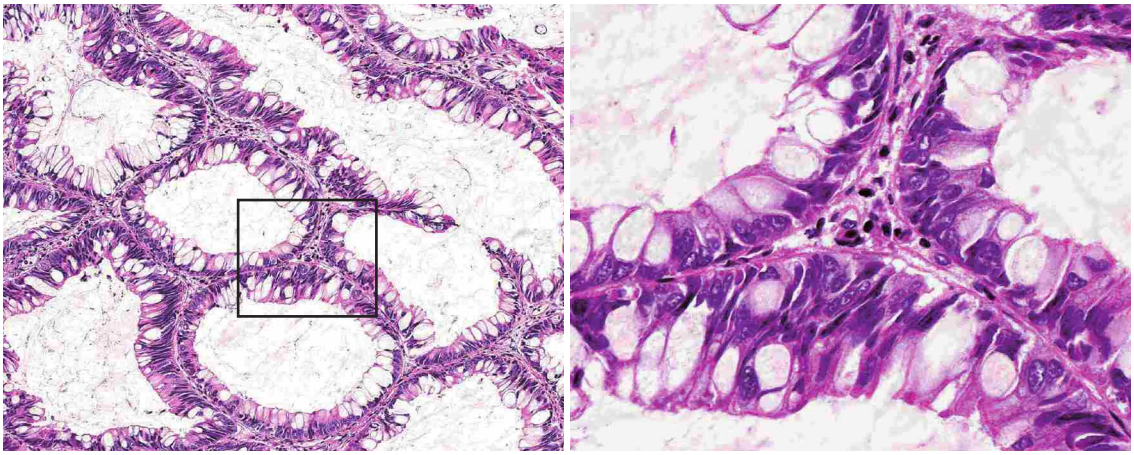


Fig. 28 Well differentiated tubular adenocarcinoma

Well differentiated type tubular adenocarcinoma with abundant mucus production (left) (Glands with similar histological features have invaded the submucosa). The nuclei are hyperchromatic and pleomorphic with loss of nuclear polarity. The level of the nuclear pseudostratification is uneven and the Golgi apparatus in the cytoplasm is obscure (right).

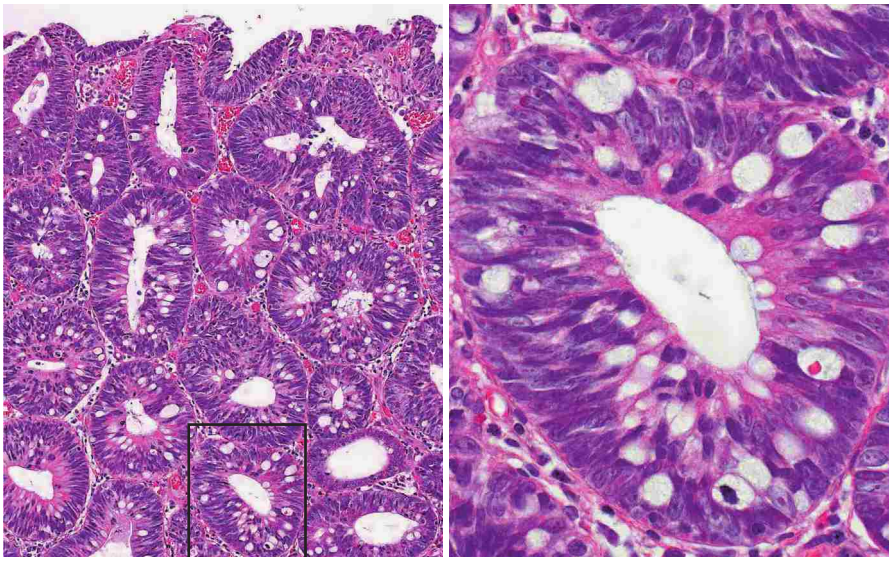


Fig. 29 Well differentiated tubular adenocarcinoma

The tumor with a distinct tubular structure (left). Nuclei are oval or spindle-shaped and they show severe pseudostratification throughout the tubules. Enlarged basophilic or eosinophilic nucleoli are seen (right).

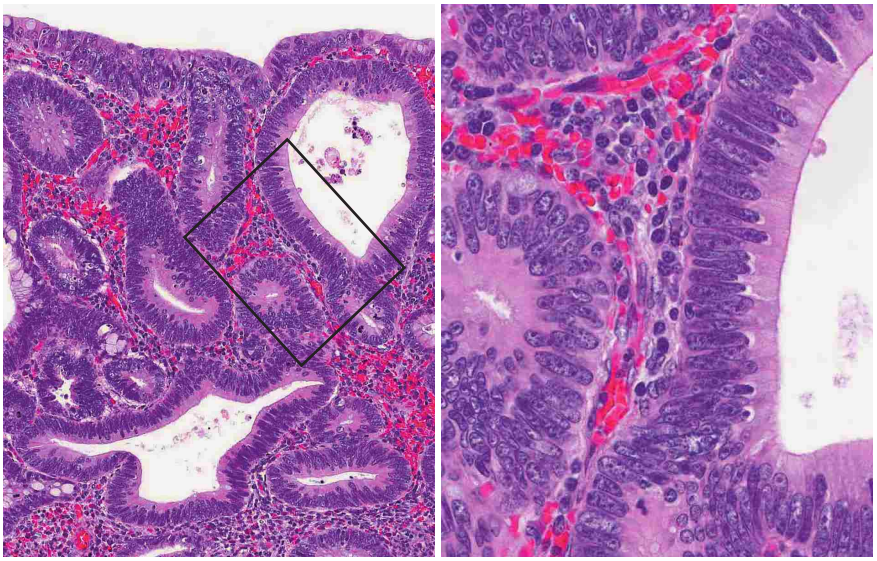


Fig. 30 Well differentiated tubular adenocarcinoma
Cancerous tubules are dilated and tortuous (left). Nuclear stratification is seen up to half the height of the epithelial glands. Cancer cells have enlarged hyperchromatic nuclei with prominent nucleoli, and eosinophilic cytoplasm with scanty mucus production. They also have an indistinct Golgi apparatus.

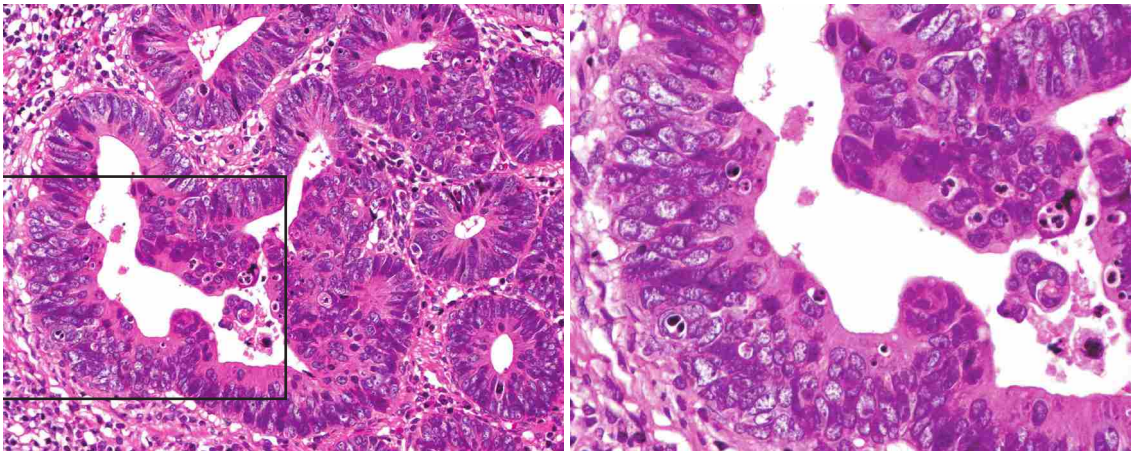


Fig. 31 Well differentiated tubular adenocarcinoma
Well differentiated type tubular adenocarcinoma with high-grade cellular atypia. Mucus production is scarcely seen. Round or oval nuclei show severe pseudostratification.

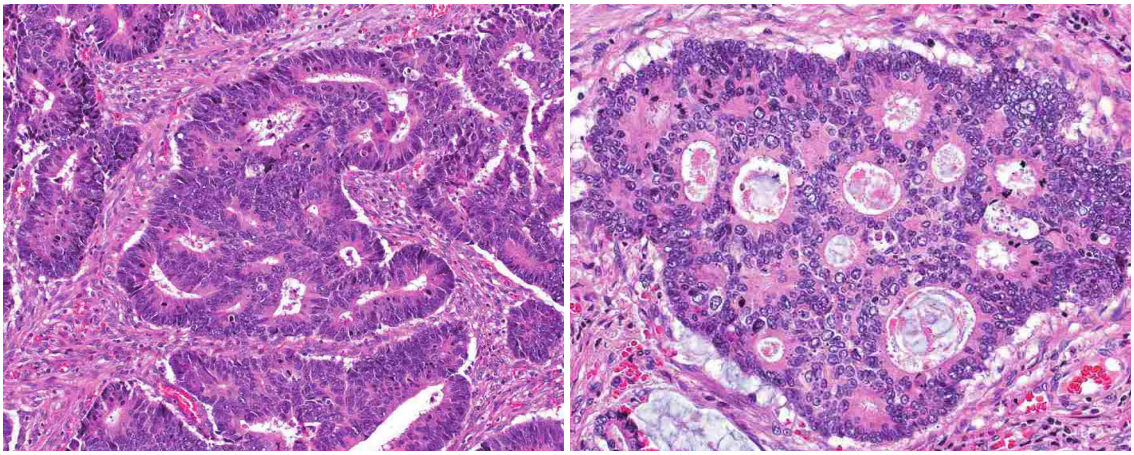


Fig. 32 Moderately differentiated tubular adenocarcinoma
A tubular structure is present at in the periphery and a cribriform pattern in the central area (left). Typical cribriform pattern glands are seen. (right: submucosal invasive part of an advanced carcinoma)

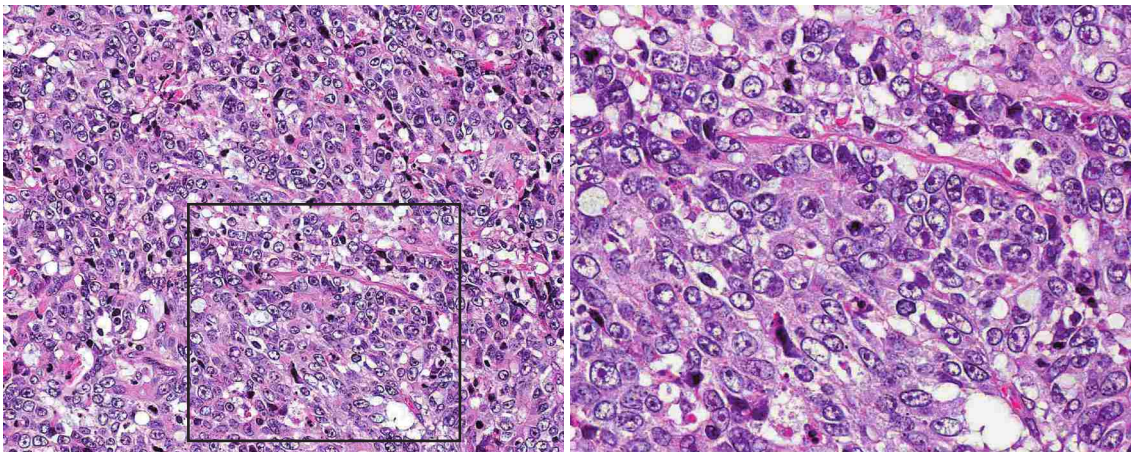


Fig. 33 Poorly differentiated adenocarcinoma: solid type (por1)
Cancer cells show solid growth and there is little stroma (por1). The majority of nuclei are round or oval in shape.

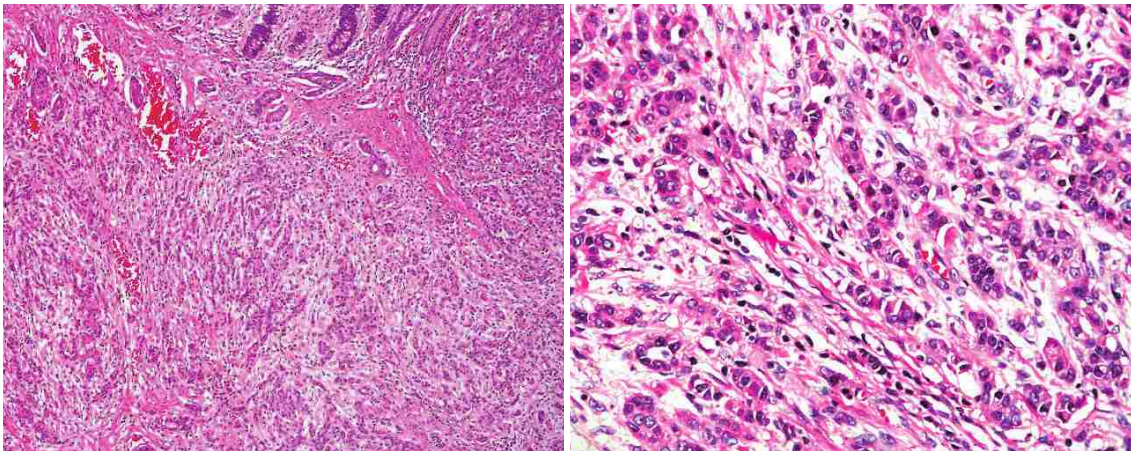


Fig. 34 Poorly differentiated adenocarcinoma: non-solid type (por2)
Cancer cells form a predominantly trabecular structure and show less formation of tubules but are rich in fibrous stroma (por2). Hardly any mucus production is seen.

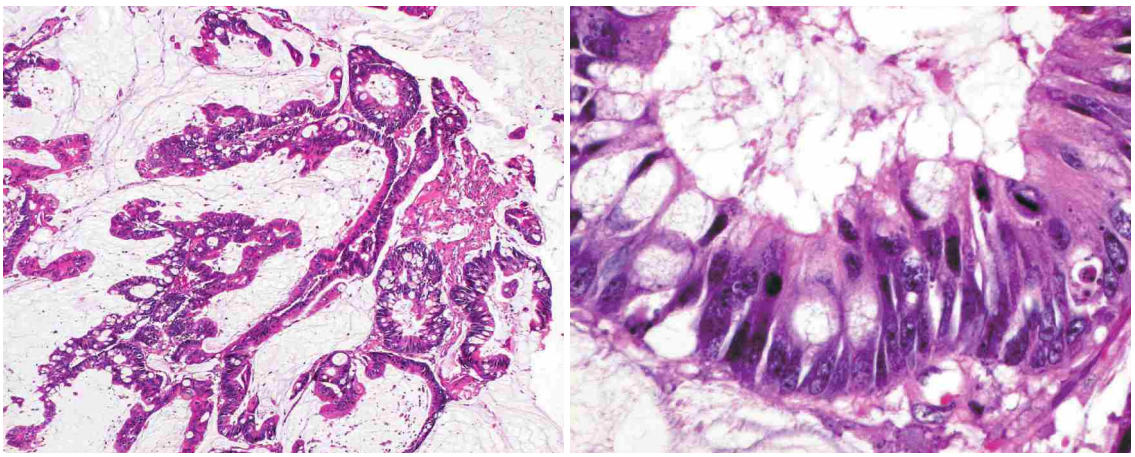


Fig. 35 Mucinous adenocarcinoma: well differentiated type
Mucinous tumor consists of well differentiated type tubular adenocarcinoma with low-grade atypia (Submucosal invasive part).

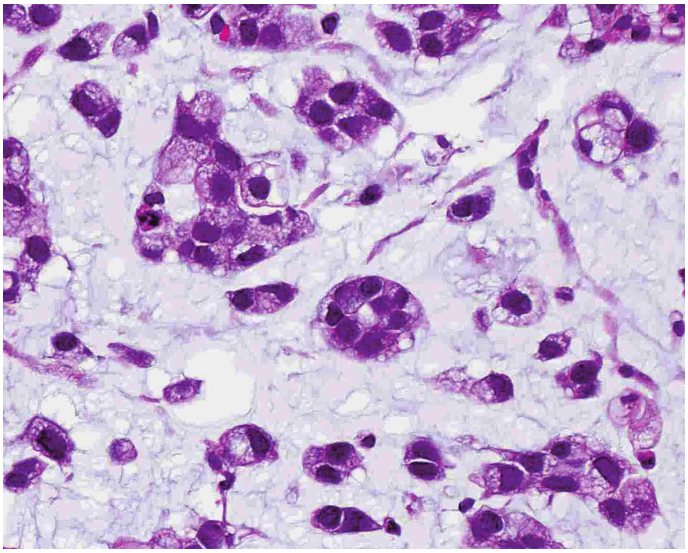


Fig. 36 Mucinous adenocarcinoma: poorly differentiated type

Mucinous tumor consists of poorly differentiated type tubular adenocarcinoma and/or signet-ring cell carcinoma with marked extracellular mucus secretion.

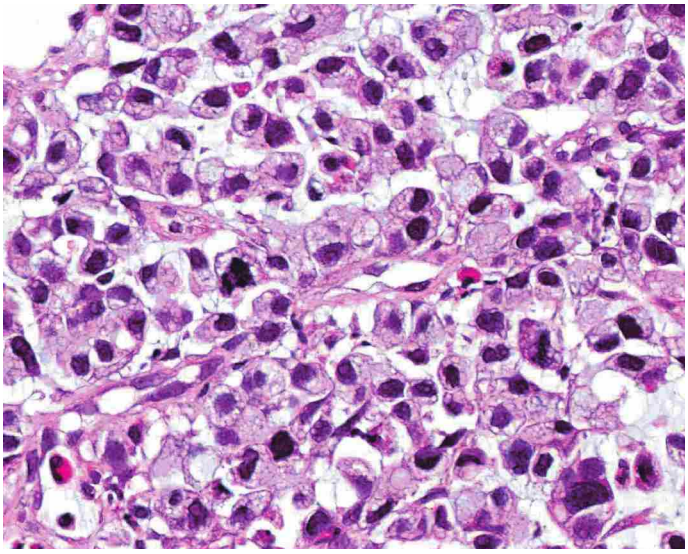


Fig. 37 Signet-ring cell carcinoma

Cancer cells containing abundant intracellular mucus are seen.

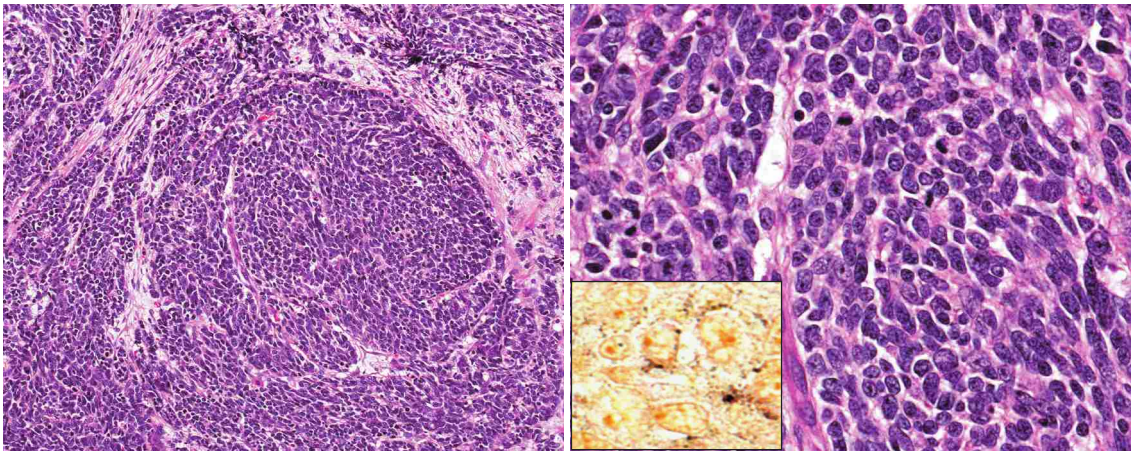


Fig. 38 Endocrine cell carcinoma
The tumor is composed of rather uniform small or medium sized cancer cells, containing scanty cytoplasm, that have formed a sheet-like or large solid structure and contains a highly vascular stroma (right and left). In general, the cancer cell nuclei are larger and more hyperchromatic than those of carcinoid tumor. Although the nucleoli are not conspicuous, there are numerous mitotic figures (insert).

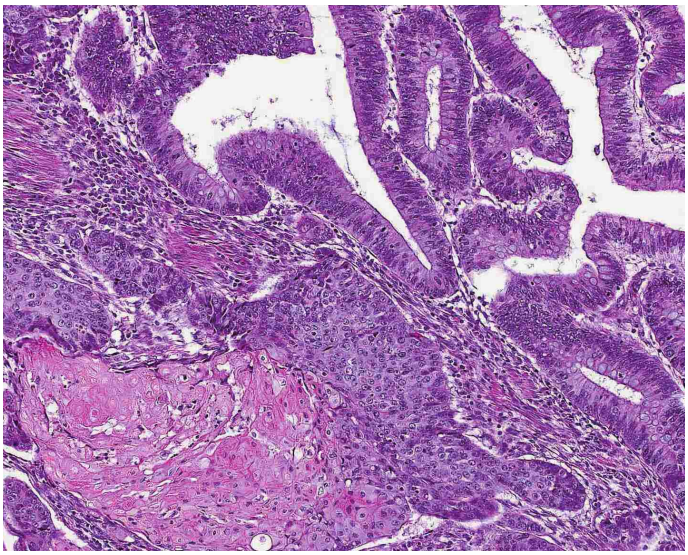


Fig. 39 Adenosquamous carcinoma
Tubular adenocarcinoma (well-differentiated type) and squamous cell carcinoma (well-differentiated type) are both present.

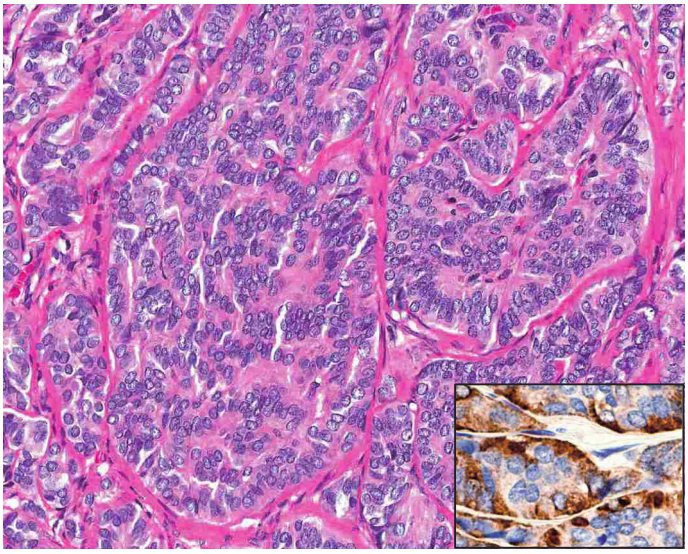


Fig. 40 Carcinoid tumor
Carcinoid tumor of the rectum (shows submucosal compornent). It is composed of uniform small cells with round or oval nuclei forming ribbon-like and trabecular structures with a highly vascular stroma. In general, mitotic figures are infrequent. The tumor contains numerous chromogranin A-positive cells (insert).

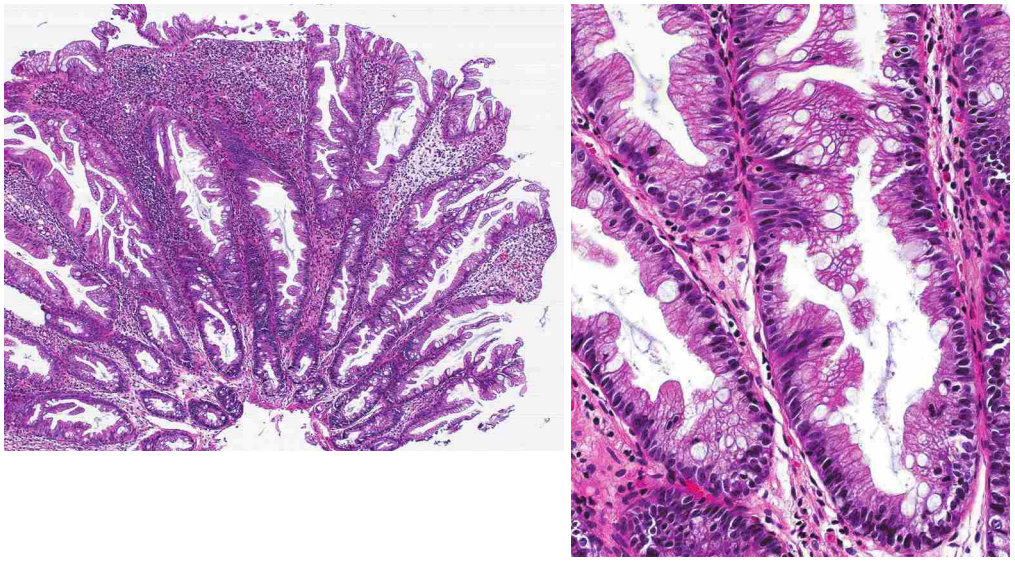


Fig. 41 Hyperplastic polyp
This elevated lesion consists of tubules and exhibits luminal serration. The epithelial cells do not exhibit neoplastic atypia and they contain faintly eosinophilic cytoplasm. High proliferative activity is seen in the lower portion of the tubules.

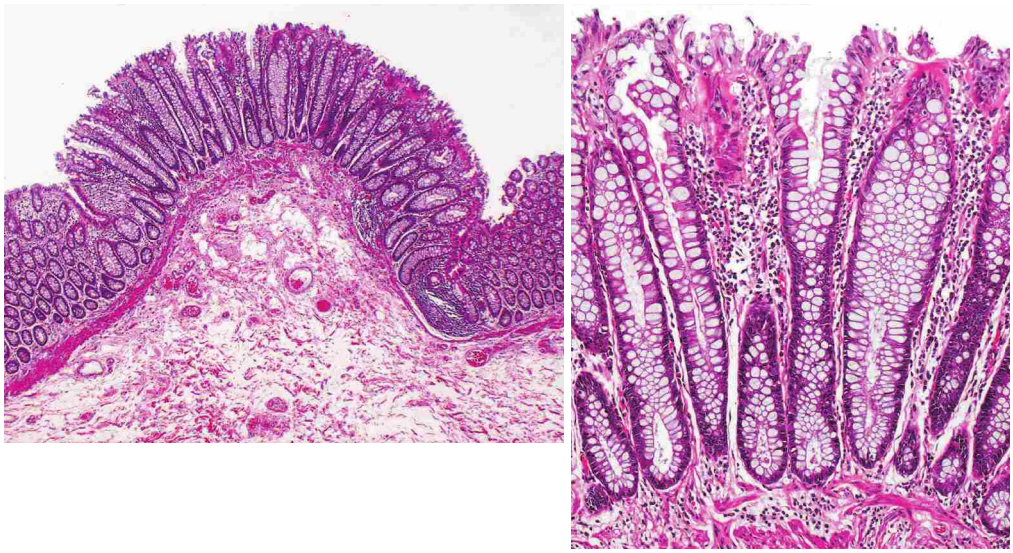


Fig. 42 Hyperplastic nodule
A localized area consisting of hyperplastic glands without luminal serration is seen.

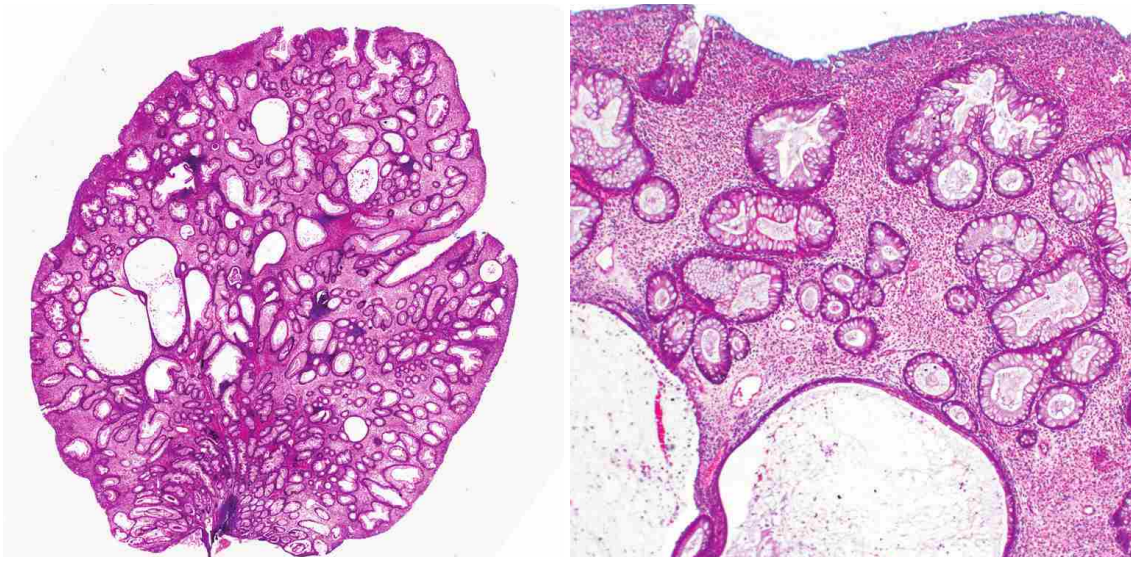


Fig. 43 Juvenile polyp
The polyp consists of a large amount of stroma and dilated tubules (left). The superficial lamina propria is expanded by proliferation and dilatation of capillaries, fibroblast and fibrous tissue and contains rich stromal cells as a result of chronic inflammatory cell infiltrates. Mild cystic dilatation of tubules is seen.

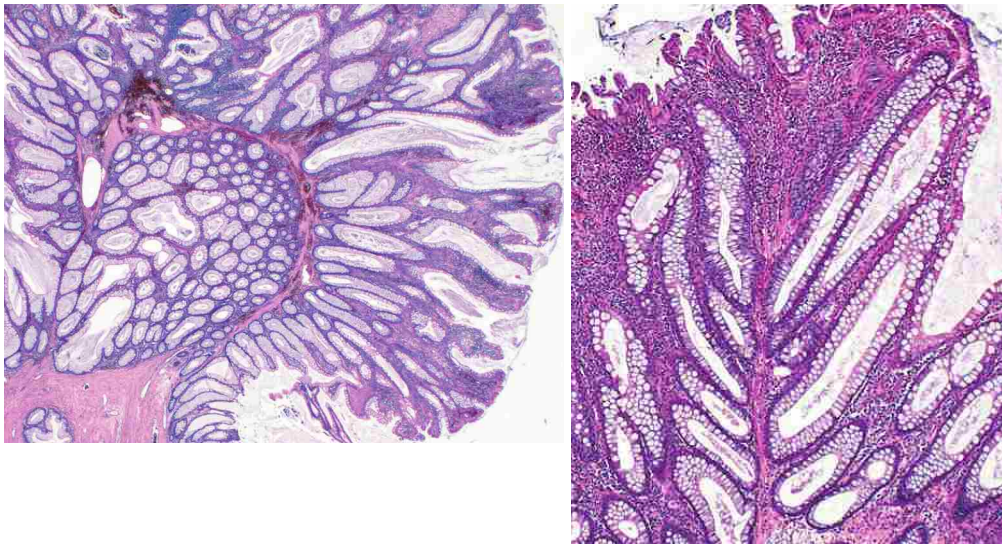


Fig. 44 Peutz-Jeghers polyp
The polyp is composed of hyperplastic epithelial cells with dilated tubules accompanied by tree-like branching of the muscularis mucosa.

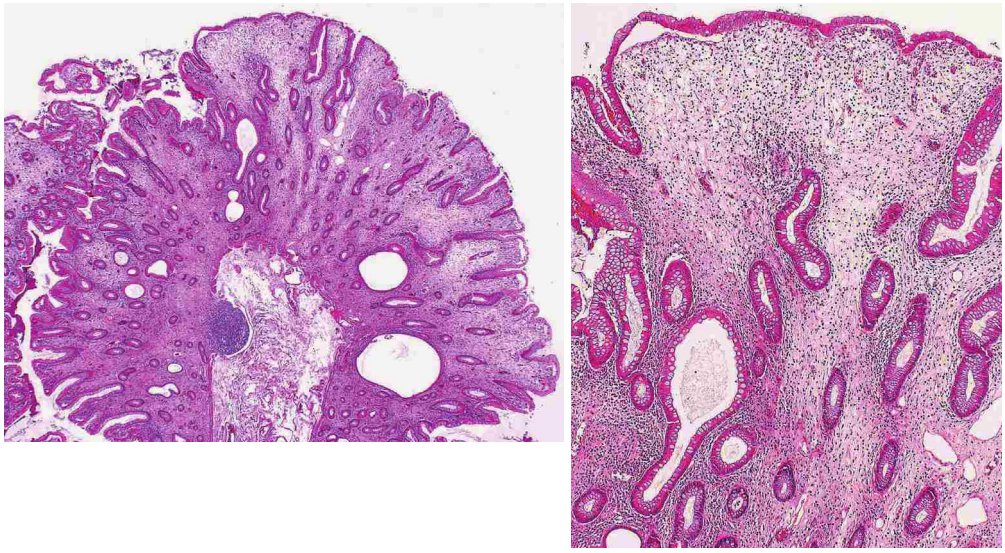


Fig. 45 Cronkhite-Canada syndrome
The lamina propria is highly edematous and contains mild to moderate chronic inflammatory infiltrates. Elongation and dilatation of glands are also seen, causing diffuse marked thickening of the mucosa. The thickening is severest at the top of the semilunar folds and it usually appears as a polypoid lesion.

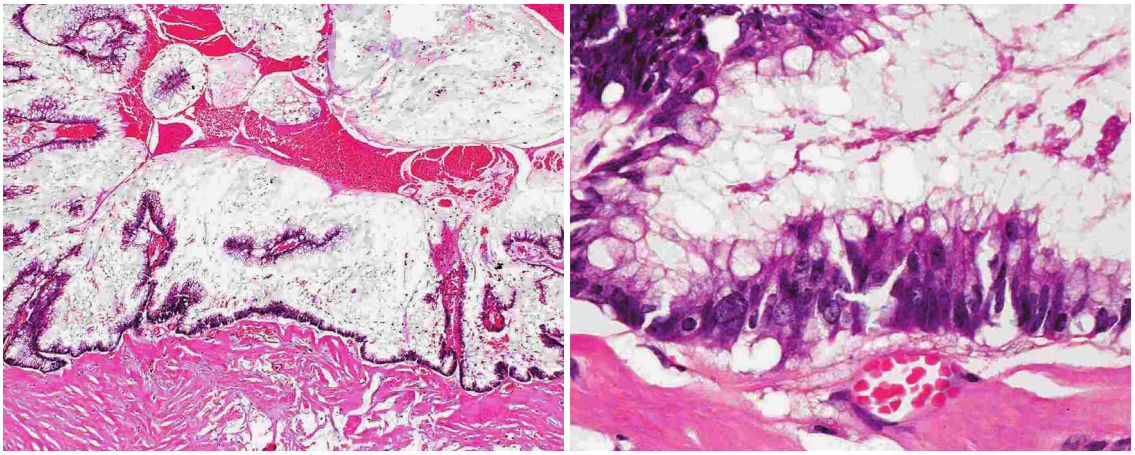


Fig. 46 Mucinous cystadenocarcinoma of the vermiform appendix
Papillary adenocarcinoma that has formed cystic lesions and produced abundant mucus. The nucleus to cytoplasm ratio (N/C ratio) of the cancer cells is low but nuclear pseudostratification and anisonucleosis/anisokaryosis are seen. The Golgi apparatus in the cytoplasm is obscure.

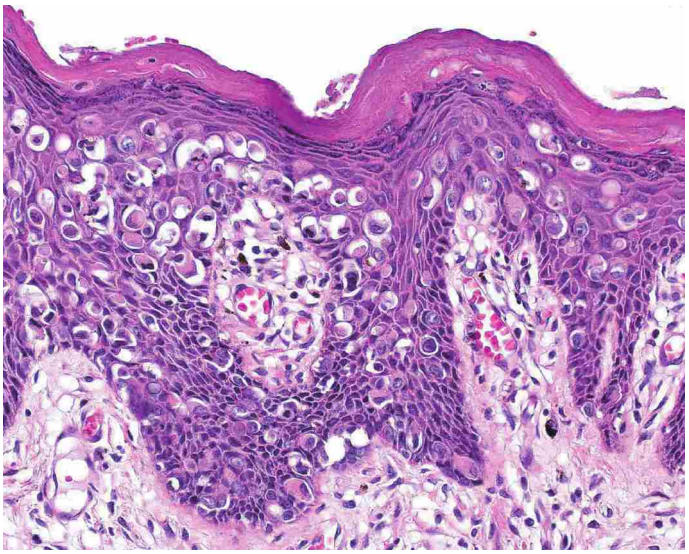


Fig. 47 Extramammary Paget disease
Numerous Paget cells (round to oval cells with abundant faintly eosinophilic cytoplasm and enlarged nuclei) are seen in the epidermis.

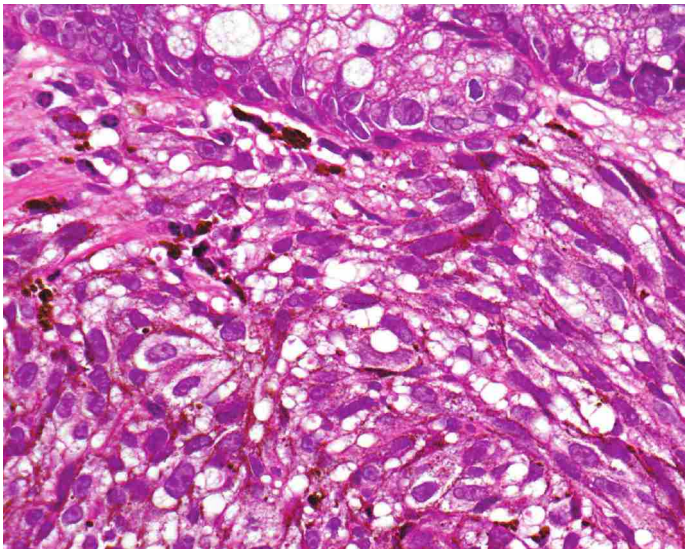


Fig. 48 Malignant melanoma
Melanin pigments are present in the tumor cells. The nuclei are oval or spindle-shaped and contain distinct nucleoli.

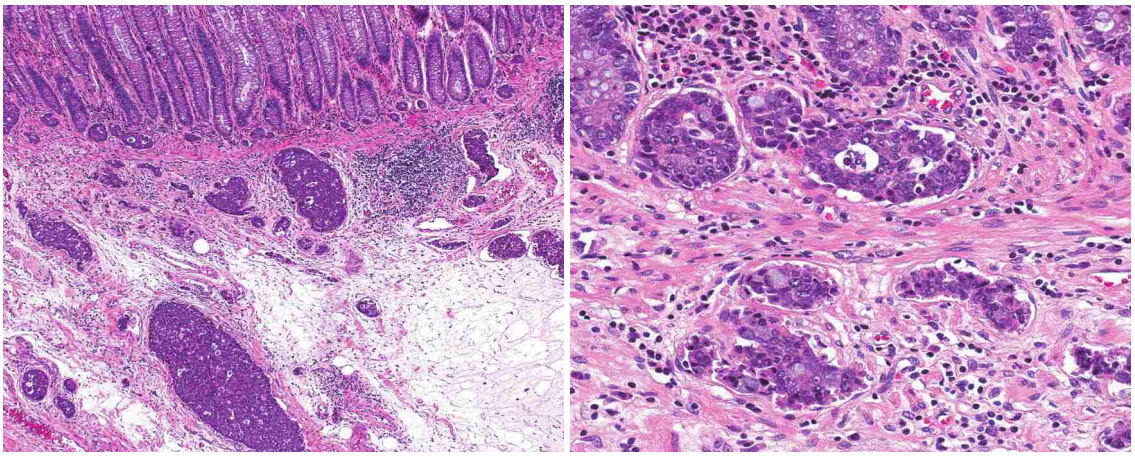


Fig. 49 Lymphatic invasion (ly3)
Cancer nests of various sizes are seen above and beneath the muscularis mucosae (left). The cancer nests are located in lymphatic channels lined by flat endothelial cells. A few lymphocytes and a small amount of lymphatic fluid are present in the channels but few red blood cells are seen. The walls of the lymphatic channels lack smooth muscle (right).

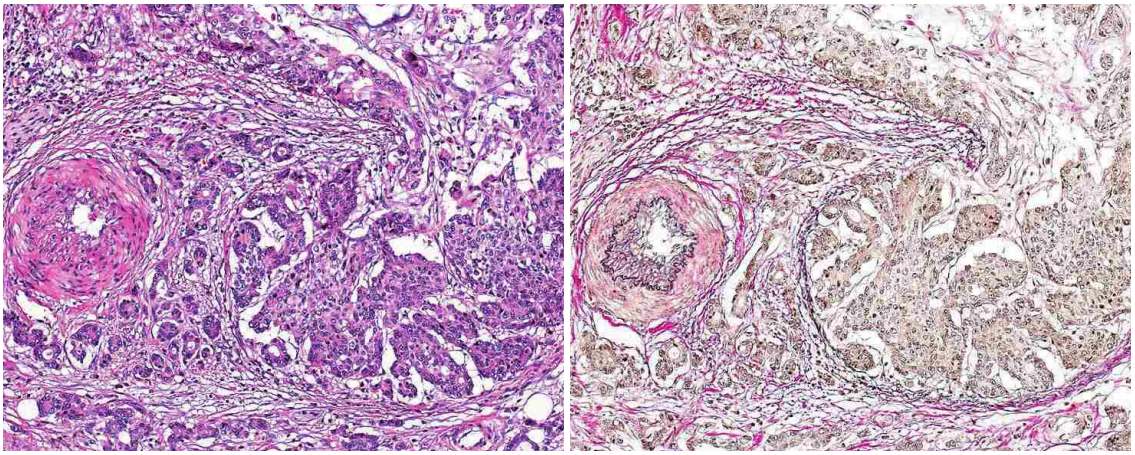


Fig. 50 Venous invasion
Occasionally, it is difficult to detect venous invasion by hematoxylin and eosin (H & E) staining (left). Elastica van Gieson (EVG) staining is useful for detecting venous invasion (visible to the right of the artery) (right).

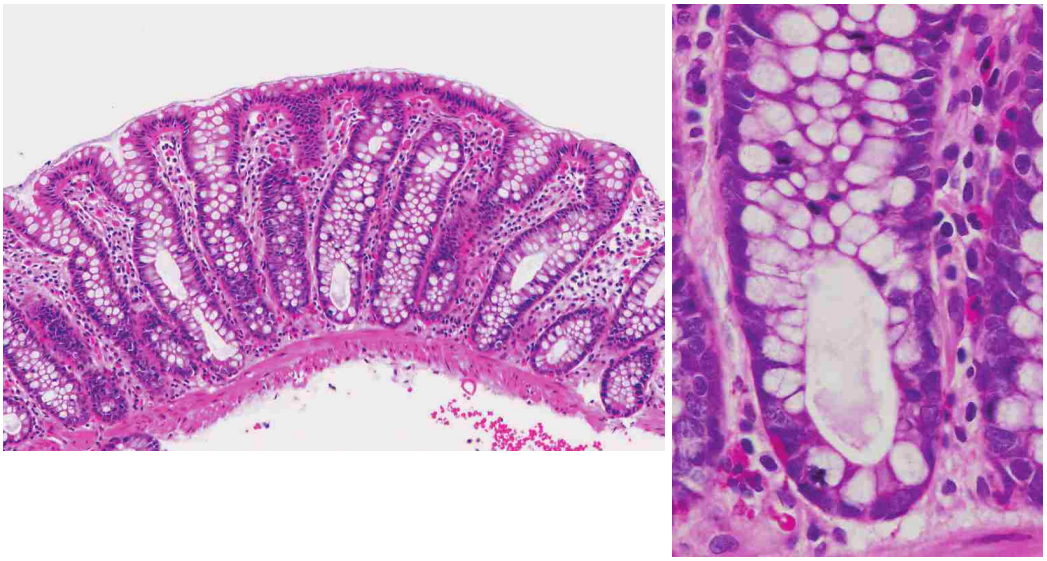


Fig. 51 Group 1
The degree of chronic inflammatory cell infiltrates in the mucosa is within the normal range. The colonic mucosa consists of uniform tubular glands and the epithelial cells do not show neoplastic atypia. The proliferative zone is located in the lower half of the gland (normal mucosa).

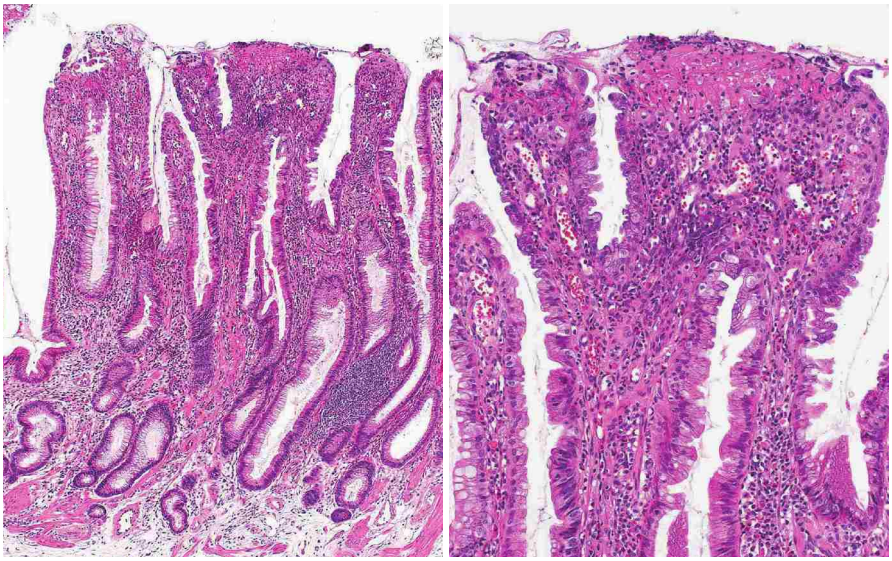


Fig. 52 Group 1 (mucosal prolapse syndrome)
The mucosa contains elongated gland ducts and there is active erosion at the surface associated with capillary proliferation and dilatation. Prominent inflammatory infiltrates and fibromuscular hyperplasia are seen in the stroma. Although the epithelial cells are immature and mucus production has decreased, they show a smooth transition to more maturer cells. When only the superficial portion has been sampled by the biopsy and differentiation from tumor is difficult, classify in Group 2.

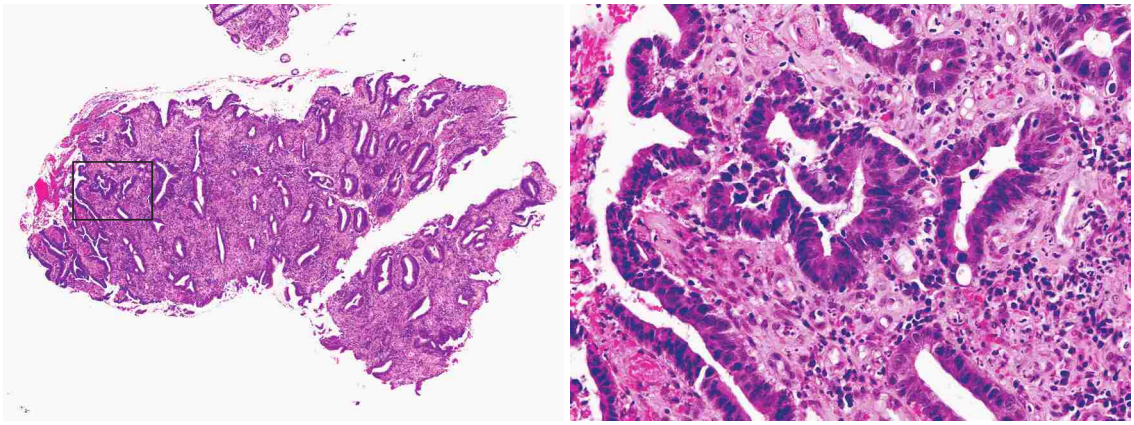


Fig. 53 Group 2
Low magnification (left): Distal mucosal biopsy of a narrowed segment of descending colon. Sporadic gland ducts exhibiting different degrees of differentiation accompanied by superficial erosion are observed. The overall picture suggests regenerative atypia.
High magnification (right): Portion exhibiting severe atypia. Gland duct density is low, but pseudostratification is seen in the nuclei. Differentiation from tumor was difficult only in the examination of this portion, and it was determined to be Group 2.

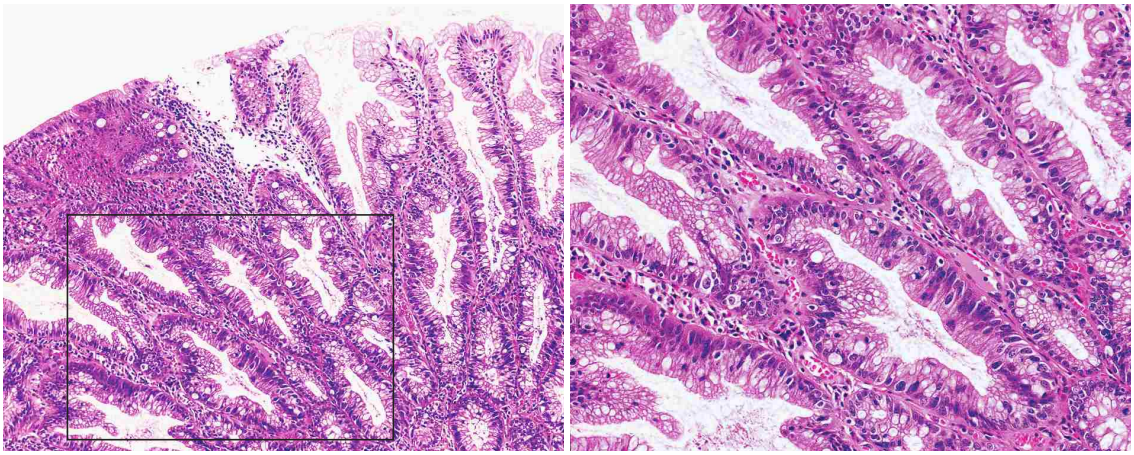


Fig. 54 Group 2

Lesion in which differentiation between serrated adenocarcinoma and a hyperplastic polyp is a problem.
Low magnification (left): The overall picture suggests a hyperplastic polyp composed of serrated gland ducts.
High magnification (right): The nuclei of part of the epithelium are enlarged and exhibit atypia, and when it is possible to suspect a tumor lesion, diagnose as Group 2.

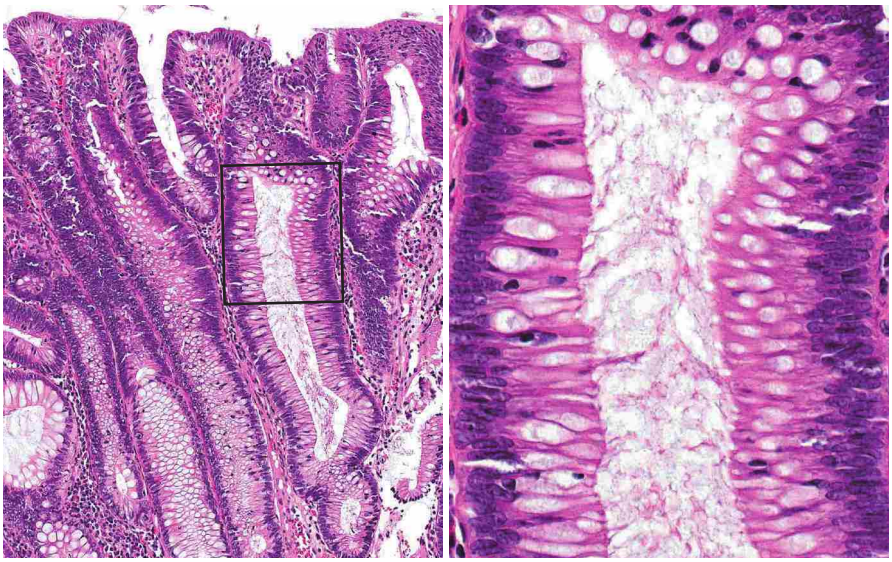


Fig. 55 Group 3

High proliferative activity is seen in the upper portion of the glands. High nuclear population with pseudostratification and mitotic figures are suggestive of a neoplastic lesion. Most of the cells contain basal spindle-shaped nuclei that are arranged at the basal membrane and nuclear pseudostratification is seen not higher than half the height of the glands. Differentiated cells containing abundant mucus are seen in the lower portion of the glands (low-grade tubular adenoma; equivalent to adenoma with mild atypia).

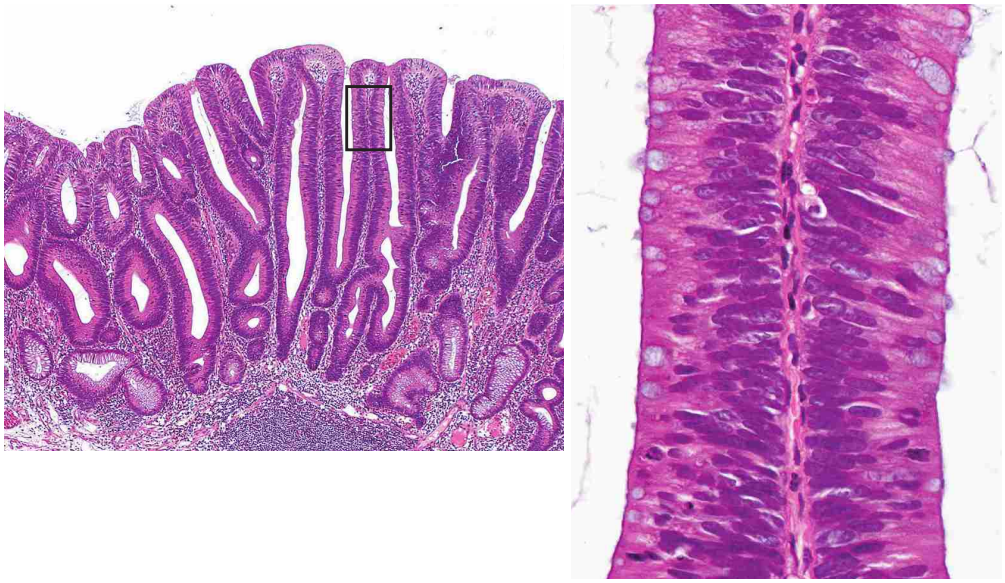


Fig. 56 Group 3
Nuclear pseudostratification limited in the area with high proliferative activity (left). The nuclei are spindle-shaped and their polarity is maintained. Nuclear pseudostratification is seen up to half the height of the epithelial glands. The epithelial cells show mucus depletion. The Golgi apparatus is conspicuous (low-grade tubular adenoma; equivalent to adenoma with moderate atypia).

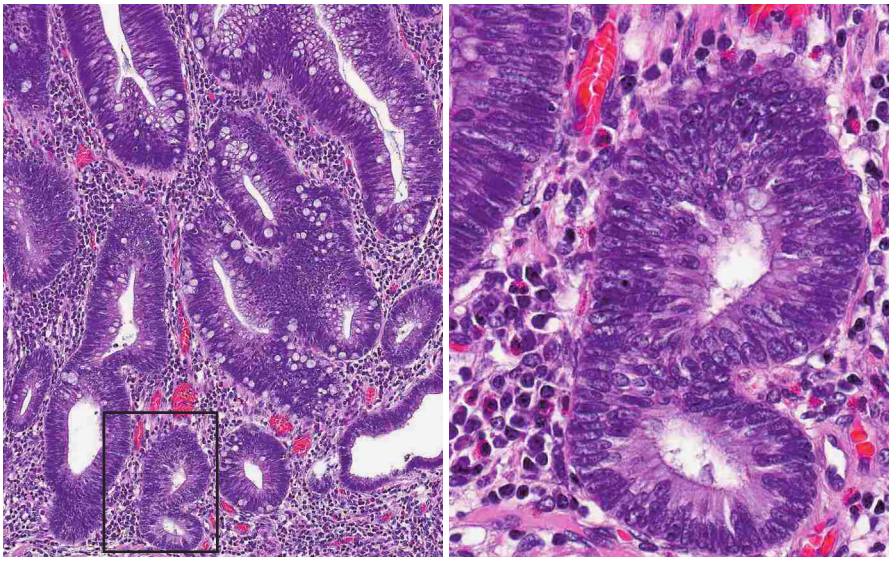


Fig. 57 Group 3
Branching and confluence of tubular glands is seen. Even in the lower portion of the glands nuclear pseudostratification is seen up to half the height of the epithelium but the nuclei are enlarged and round or oval in shape (left). The Golgi apparatus is inconspicuous. The nuclei are hyperchromatic. Nucleoli are visible, but they are not markedly enlarged (right). (high-grade tubular adenoma; equivalent to adenoma with severe atypia as formerly termed).

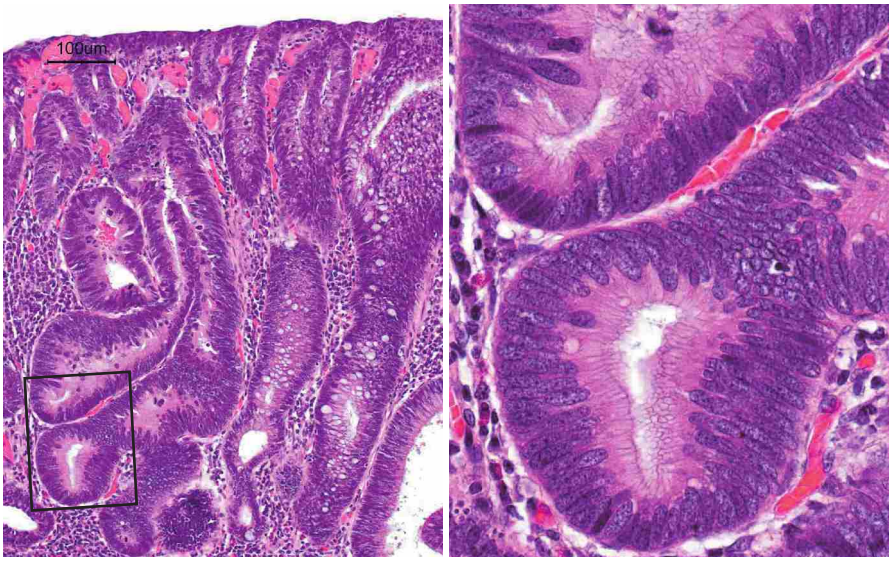


Fig. 58 Group 4

The right half of the left figure shows a low-grade tubular adenoma but the left half shows a high degree of atypia with conspicuously branched and tortuous neoplastic glands. The glands consist of cells with a high N/C ratio and uniformly enlarged nuclei with dense chromatin. The Golgi apparatus in the cytoplasm is inconspicuous (right). These features are suggestive of well differentiated tubular adenocarcinoma with low-grade atypia (well differentiated type low-grade adenocarcinoma).

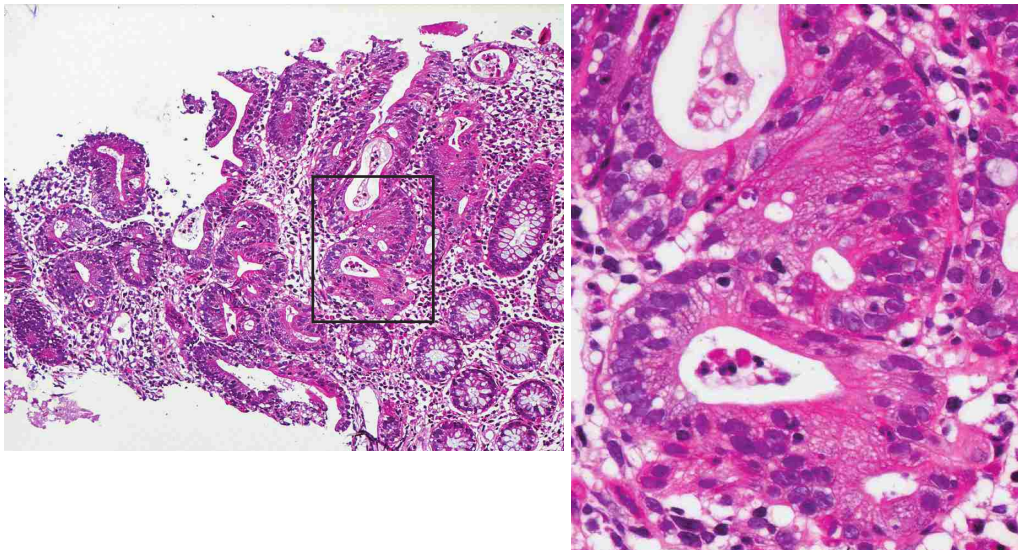


Fig. 59 Group 5

The neoplastic glands are rather small but of various sizes. Branching and tortuousity are marked. The nuclei are small but round or oval in shape and their polarity has been lost. Enlarged nucleoli are seen in some cells (well to moderately differentiated tubular adenocarcinoma).

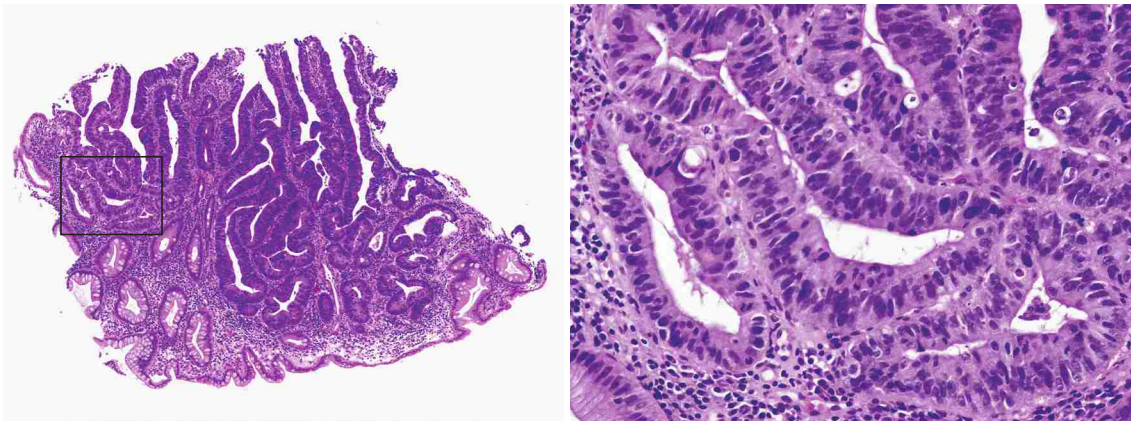


Fig. 60 Group 5

The neoplastic glands show regular tubular architecture. They consist of cells with hyperchromatic nuclei. The nuclei are spindle-shaped or elliptical and arranged basally but they are enlarged and exhibit prominent pseudostratification (well differentiated tubular adenocarcinoma).

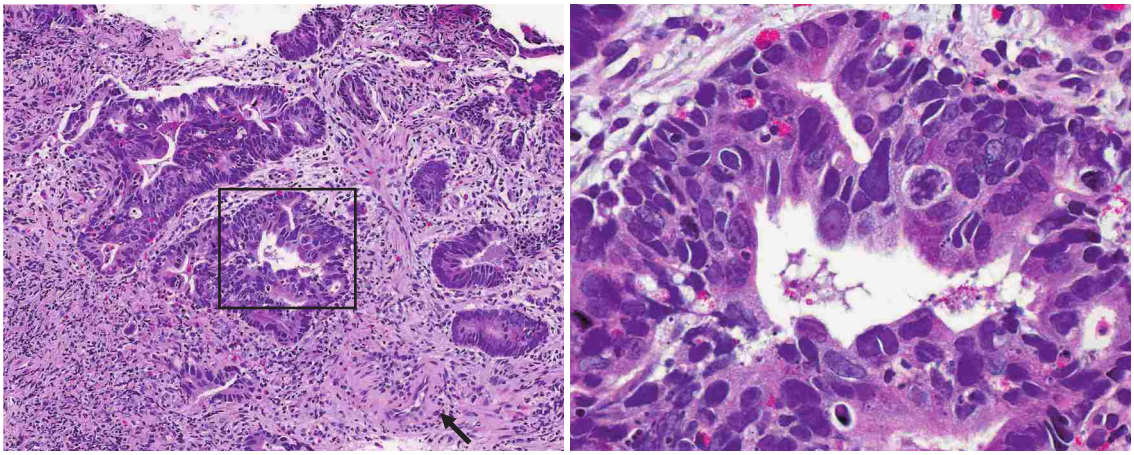


Fig. 61 Group 5

Carcinoma with high-grade atypia. A histological diagnosis of submucosal invasion is based on the desmoplastic reaction and presence of a small artery nearby (arrow) (moderately differentiated type high-grade tubular adenocarcinoma).

Abbreviations

A	ascending colon [p.3]
A	tumor invasion through muscularis propria into pericolic or perirectal tissues (for parts of intestine that do not have serosa/visceral peritoneum) [p.6]
AI	direct tumor invasion to adjacent organs or structures (for parts of intestine that do not have serosa/visceral peritoneum) [p.6]
AN	autonomic nerve [p.15]
ant	anterior [p.5]
C	cecum [p.3]
c	clinical findings [p.2]
circ	circular [p.5]
CR	complete response [p.52, 53]
Cur	curability, surgical resection [p.17]
Cur E	curability, endoscopic resection [p.17]
Cy	cytology [p.11]
D	descending colon [p.3]
D	extent of lymph node dissection [p.14]
DM	distal margin [p.16]
E	external skin [p.3]
EMR	endoscopic mucosal resection [p.13]
ESD	endoscopic submucosal dissection [p.13]
f	final findings [p.2]
H	hepatic metastasis [p.11]
HM	horizontal margin [p.16]
HN	hepatic node metastasis [p.11]
HRM	hepatic radial margin [p.16]
I	ileum [p.4]
INF	infiltration [p.27]
int	intermediate type [p.26]
IR/SD	incomplete response/stable disease [p.52]
LM	lung metastasis [p.12]
lt	left [p.5]
ly	lymphatic invasion [p.27]
M	mucosa (tumor invasion confined to mucosa) [p.6]
M	extrahepatic distant metastasis [p.11]
MP	muscularis propria (tumor invasion to muscularis propria) [p.6]
med	medullary type [p.26]
N	lymph node metastasis [p.7]
NE	not evaluable [p.53, 54]
P	anal canal (proctos) [p.3]
P	peritoneal metastasis [p.11]
p	pathological findings [p.2]
PD	progressive disease [p.52, 54]

PM	proximal margin [p.16]
post	posterior [p.5]
PR	partial response [p.52, 54]
PS	performance status [p.17, 55]
R	rectum [p.3]
R	residual tumor [p.16]
Ra	upper rectum (above peritoneal reflection) [p.3]
Rb	lower rectum (below peritoneal reflection) [p.3]
RM	radial margin [p.16]
RS	rectosigmoid [p.3]
rt	right [p.5]
S	sigmoid colon [p.3]
s	surgical findings [p.2]
sci	scirrhous type [p.27]
SD	stable disease [p.52, 54]
SE	serosa (tumor invasion penetrating serosa) [p.6]
SI	direct tumor invasion to adjacent organs or structures (for parts of intestine that have serosa/visceral peritoneum) [p.6]
SM	submucosa (tumor invasion to submucosa) [p.6]
SS	subserosa (tumor invasion to subserosa) [p.6]
T	transverse colon [p.3]
V	vermiform appendix [p.3]
v	venous invasion [p.27]
VM	vertical margin [p.16]
X	cannot be assessed [p.2]

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