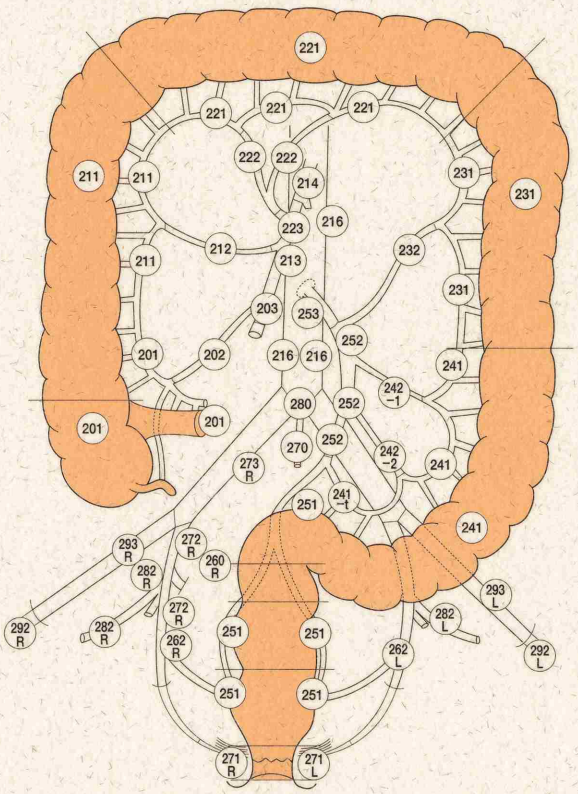
大腸癌取扱い規約（英語版）

Japanese Classification of Colorectal Carcinoma

Japanese Society for Cancer of the Colon and Rectum

First English Edition



KANEHARA & CO., LTD., TOKYO

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Preface

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

Contents

Part IV Response Assessment of Nonsurgical Treatments for Colorectal Carcinoma

Part I

Clinicopathological Findings

Principles

1. This classification should be applied only to primary carcinomas of the colon, rectum, and anus.
2. To provide more practical and theoretical rules, the following findings were adopted.

Clinical Findings	Any findings before surgical treatment and histological exploration. These findings should be recorded using capital letters with a prime, " ′ , " such as "MP′."
Surgical Findings	Any findings during surgery, including findings based on histopathological explorations. Clinical Findings can also be referred to. These findings should be recorded using capital letters without the prime.
Histological Findings	Histological findings should be recorded using small letters.

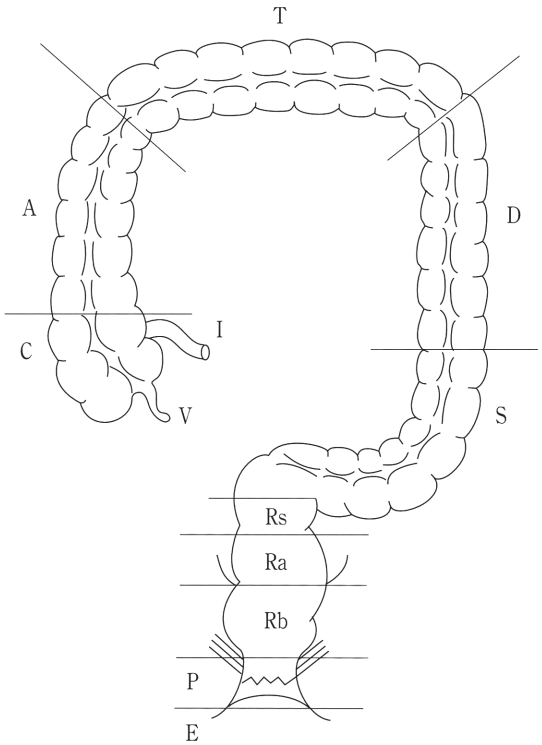
3. All histological findings should be those obtained by methods shown in the Handling of Resected Specimen (Part II).
4. Any findings once established must remain unchanged.
5. The word "unknown" should be applied to any uncertain findings.

A. Clinicopathological Findings

1 Tumor Location

The colon, rectum, and anus are anatomically divided into the following portions (Fig. 1).
If more than one portion or part is involved, all involved portions or parts should be recorded in order of involvement, first indicating the portion or part in which the bulk of the tumor is mainly situated.

Fig. 1. Portions of colon, rectum, and anus



I : Ileum
V : Appendix (Processus vermiformis)
C : Cecum
A : Ascending colon
T : Transverse colon
D : Descending colon
S : Sigmoid colon

R : Rectum
Rs : Rectosigmoid
Ra : Upper rectum
Rb : Lower rectum
P : Proctos/Anal Canal
E : External skin

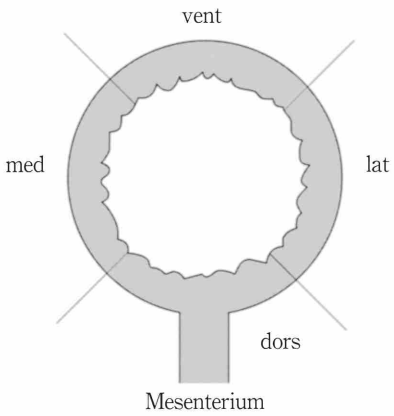
The rectosigmoid surgically is classified as "Rs," which is defined as the bowel at the level between the promontorium and the lower margin of the second sacral vertebra.

The border between Ra and Rb is defined as the bowel at the level of the peritoneal reflection, which approximately corresponds to the level of the middle Houston valve (Kohlrausch valve).

Proctos (P), the anal canal, is defined as the portion between the upper edge of the puborectal muscle and the anal verge. Skin around the anal verge is defined as External skin (E).

In the rectum and anal canal, the cross-sectional circumference of the bowel anatomically is divided into four equal parts: anterior (ant), posterior (post), left (lt), and right (rt) walls (Fig. 2).

Fig. 2. Four equal parts of circumferential divisions of the wall of large intestine



dors : Mesenteric side
vent : Side opposite to the mesenterium
lat : Lateral side
med : Medial side

2 Tumor Size

The greatest dimension of the tumor, and/or the extent of the tumor located in the cross-sectional circumference of the intestine, should be recorded.

3 Macroscopic Types

Type 0	Superficial, flat tumors with or without minimal elevation or depression
Type 0 I	Protruded type
Ip	Pedunculated type
Isp	Semipedunculated type
Is	Sessile type
Type 0 II	Superficial type
IIa	Superficial elevated type
IIb	Superficial flat type
IIc	Superficial depressed type
Type 0 III	Excavated type

Type 1	Protuberant type
Type 2	Ulcerated type with clear margin
Type 3	Ulcerated type with infiltration
Type 4	Diffusely infiltrating type
Type 5	Unclassified type

In this manual, Type 0 should be applied to an early cancer, which can be defined as a tumor whose "Depth of Invasion" may be limited to "M," or "SM."

Strictured type (str), mucinous type (muc), scirrhous type (sc), and villous type (v), can be appended.

4 Depth of Tumor Invasion

4.1 Intestine with serosa

M	Tumor invasion of mucosa
SM	Tumor invasion of submucosa
MP	Tumor invasion of muscularis propria
SS	Tumor invasion of subserosa
SE	Tumor invasion of serosa
Si	Direct tumor invasion of other organs or structures

In the "Si," the invaded organs or structures should be appended.

4.2 Intestine without Serosa

M Tumor invasion of mucosa

SM Tumor invasion of submucosa

MP Tumor invasion of muscularis propria

A1 Tumor invasion through muscularis propria into non-peritonealized part

A2 Tumor invasion of non-peritonealized, pericolic, or perirectal tissues

Ai Direct tumor invasion of other organs or structures

In the "Ai," the invaded organs or structures should be appended.

5 Lymph Nodes

5.1 Coding of Station Numbers

The station numbers should be coded as a three-digit number.

The first-digit number, 2, is assigned to the colon and rectum.

The second-digit number is assigned to the following regional arteries.

0 Ileocolic artery

1 Right colic artery

2 Middle colic artery

3 Left colic artery

4 Sigmoid artery

5 Inferior mesenteric artery and superior rectal artery

6 Middle rectal artery and lateral sacral artery

7 Iliac artery

8 Obturator artery

9 External iliac artery

The third-digit number is assigned as follows:

1 Epicolic/Paracolic lymph nodes, and Pararectal/Inferior rectal lymph nodes

2 Intermediate lymph nodes, and lymph nodes corresponding to intermediate nodes

3 Main lymph nodes, and lymph nodes corresponding to main nodes

0, 4, and 6 Others

5.2 Lymph Node Station Numbers

201 Lymph nodes along the peripheral arcade and vasa recta of ileocolic artery (Paracolic and Epicolic nodes)

202 Lymph nodes along ileocolic artery (Ileocolic nodes)

203 Lymph nodes at the root of ileocolic artery (Ileocolic Root nodes)

211 Lymph nodes along peripheral arcade and vasa recta of right colic artery (Paracolic and Epicolic nodes)

212 Lymph nodes along right colic artery (Right Colic nodes)

213 Lymph nodes at the root of right colic artery (Right Colic Root nodes)

221 Lymph nodes along peripheral arcade and vasa recta of middle colic artery (Paracolic and Epicolic nodes)

222 Lymph nodes along middle colic artery (Middle Colic nodes)

222–R Right branch (Middle Colic nodes, Right)

222–L Left branch (Middle Colic nodes, Left)

223 Lymph nodes at the root of middle colic artery (Middle Colic Root nodes)

231 Lymph nodes along peripheral arcade and vasa recta of left colic artery (Paracolic and Epicolic nodes)

232 Lymph nodes along left colic artery (Left Colic nodes)

241 Lymph nodes along peripheral arcade and vasa recta of sigmoid artery (Paracolic and Epicolic nodes)

241–1 First Sigmoid artery

241–2 Second Sigmoid artery

241–t Terminal Sigmoid artery

242 Lymph nodes along sigmoid artery (Sigmoid Colic nodes)

242–1 First Sigmoid nodes

242–2 Second Sigmoid nodes

251 Lymph nodes along superior rectal artery (Pararectal nodes)

252 Lymph nodes along inferior mesenteric artery distal to the origin of left colic artery (Inferior Mesenteric Trunk nodes)

253 Lymph nodes along inferior mesenteric artery central to the origin of left colic artery (Inferior Mesenteric Root nodes)

262 Lymph nodes along middle rectal artery located lateral to pelvic nerve plexus (Middle Rectal Root nodes)

262–R Right

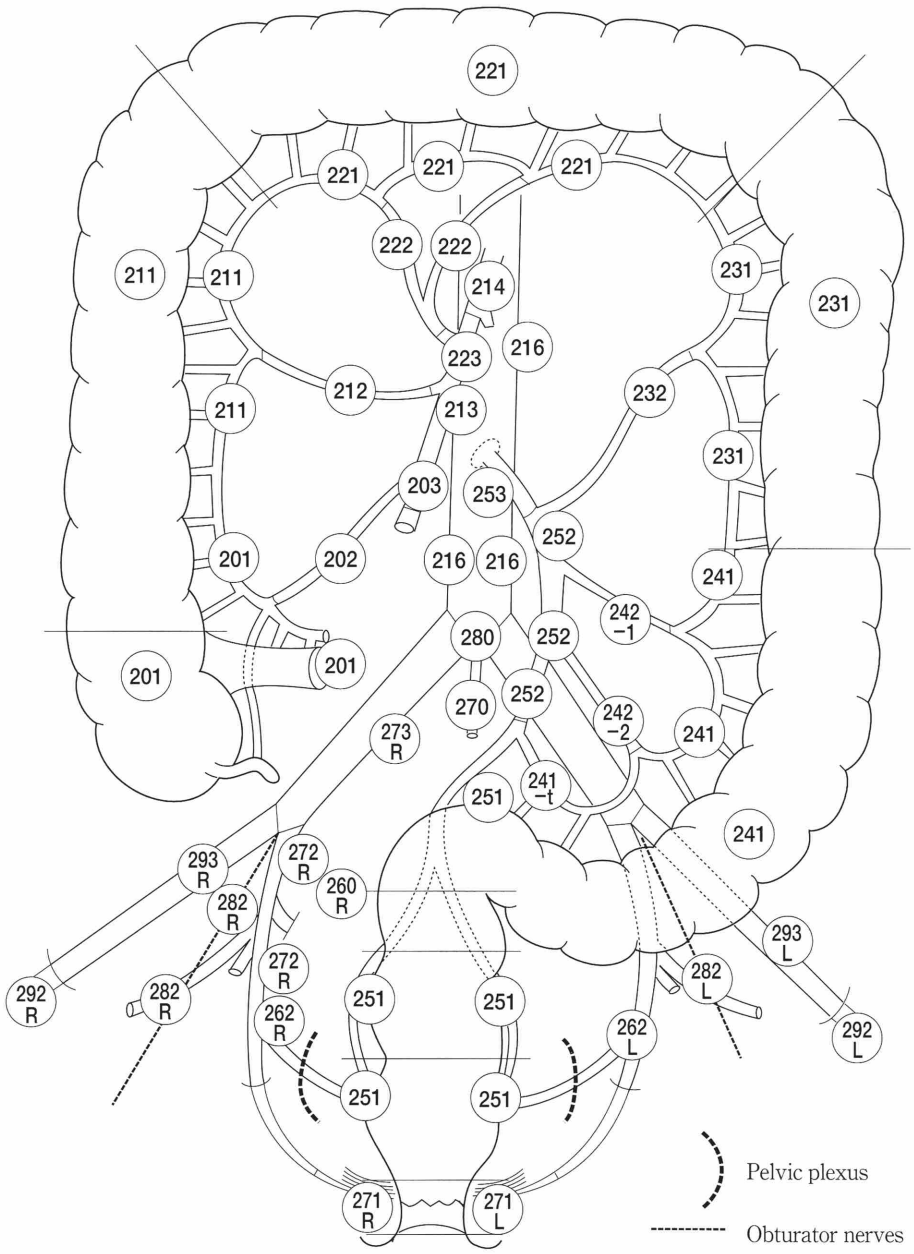
262–L Left

271 Lymph nodes along inferior rectal artery (Inferior Rectal nodes)
271–R Right
271–L Left
272 Lymph nodes along internal iliac artery (Internal Iliac nodes)
272–R Right
272–L Left
273 Lymph nodes along common iliac artery (Common Iliac nodes)
273–R Right
273–L Left
282 Lymph nodes along obturator nerve, artery, and vein (Obturator nodes)
282–R Right
282–L Left
292 Lymph nodes in inguinal area (Inguinal nodes)
292–R Right
292–L Left
293 Lymph nodes along external iliac artery (External Iliac nodes)
293–R Right
293–L Left

260 Lymph nodes along lateral sacral artery (Lateral Sacral nodes)
260–R Right
260–L Left
270 Lymph nodes on median sacral artery (Median Sacral nodes)
280 Lymph nodes around aortic bifurcation (Aortic Bifurcation nodes)

204 Lymph nodes along the gastroepiploic vessels (Gastroepiploic nodes)
206 Infrapyloric lymph nodes (Infrapyloric nodes)
210 Lymph nodes at splenic hilum (Splenic hilum nodes)
214 Lymph nodes along superior mesenteric artery central to the origin of middle colic artery (Superior Mesenteric nodes)
216 Lymph nodes around abdominal aorta (Para-aortic nodes)

Fig. 3. Lymph node station numbers



5.3 Lymph Node Groups

Lymph nodes are grouped according to the independent lymphatic spread. In the colon, two modes of lymphatic drainage are accompanied; lymphatic drainage along to the intestine (Paraintestinal drainage) and toward the mesenteric main lymph node (Mesenteric drainage). In the rectum, three modes of lymphatic drainage are accompanied; lymphatic drainage along to the intestine, toward the mesenteric main lymph node, and toward the pelvic wall (Lateral drainage).

For lymph node groups, refer to Tables 1–2 and Figs. 4–13.

Table 1. Lymph node groups of colon

	Lymph Drainage	Location				
		C	A	T	D	S
Group 1	Paraintestinal	201	211	221	231	241(1) 251(1)
Group 2	Paraintestinal	201	211	221	231	241(2) 251(2)
	Mesenteric	202	212	222	232	242(3) 252(3)
Group 3	Mesenteric	203	213 [206]	223 [204]	253(4) [210]	
Group 4		214		216		

(1) Epicolic/Paracolic lymph nodes located 5 cm or less in width on both of the proximal and distal sides of the tumor, including the tumor size

(2) Epicolic/Paracolic lymph nodes located more than 5 cm but no more than 10 cm in width on both of the proximal and distal sides of the tumor

(3) Intermediate lymph nodes along the artery of the tumor bearing segment

(4) Main lymph nodes at the root of the artery of the tumor bearing segment

[ ] Optional lymph nodes in Group 3.

Fig. 4. Location C

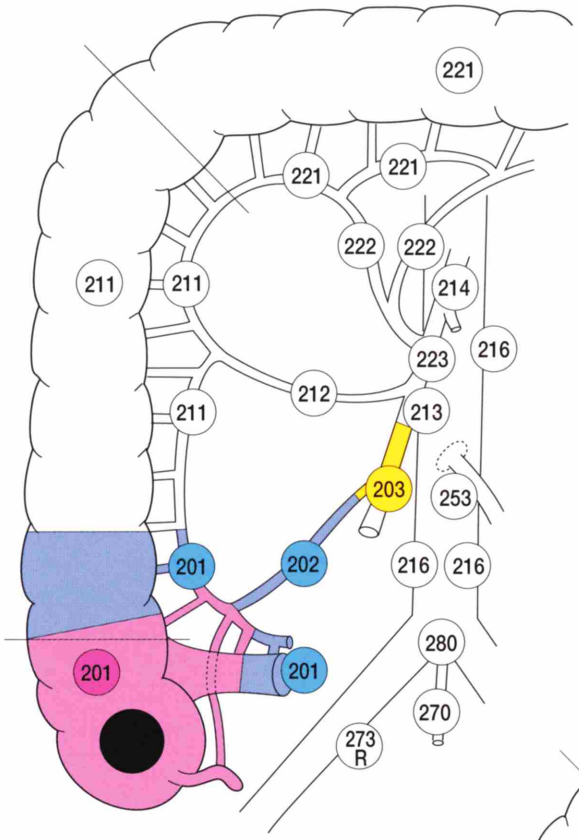
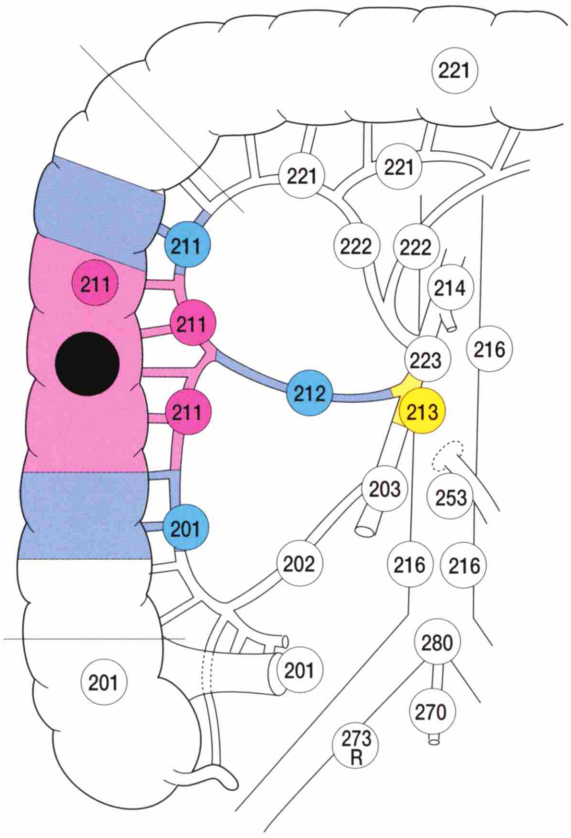


Fig. 5. Location A



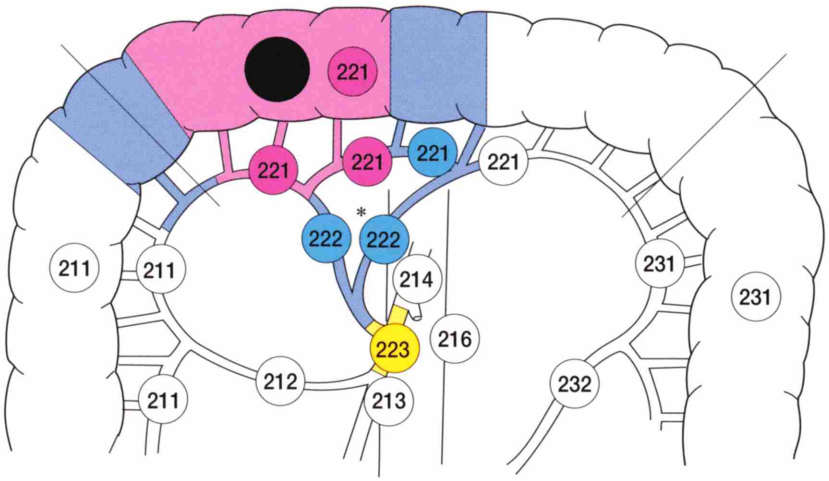
: Epicolic/Paracolic lymph nodes (Group 1)

: Epicolic/Paracolic, and/or Intermediate lymph nodes (Group 2)

: Main lymph nodes (Group 3)

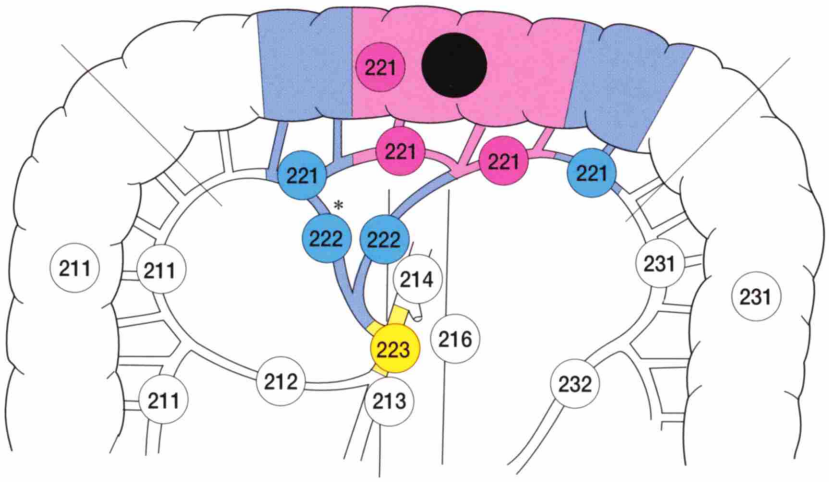
: Lymph nodes beyond Group 3 (Group 4)

Fig. 6a. Location T (Right)



* : The lymph node is dissected optionally.

Fig. 6b. Location T (Left)



* : The lymph node is dissected optionally.

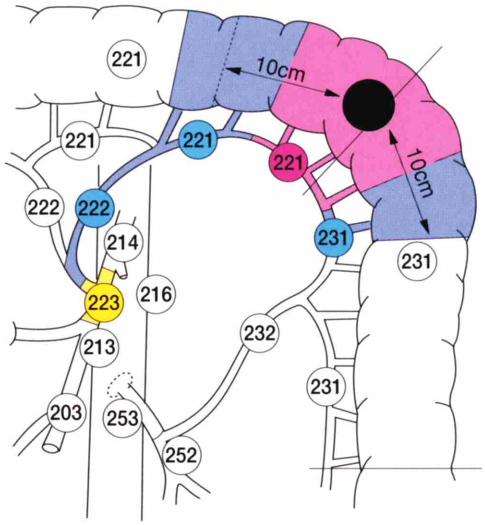
: Epicolic/Paracolic lymph nodes (Group 1)

: Epicolic/Paracolic, and/or Intermediate lymph nodes (Group 2)

: Main lymph nodes (Group 3)

: Lymph nodes beyond Group 3 (Group 4)

Fig. 7. Splenic flexure of colon



When inflow of the colic artery cannot be found 10 cm or less in width from the edge of the tumor, Epicolic/Paracolic lymph nodes in Group 2 have the extending portion to the nearest colic artery.

Fig. 8. Location D

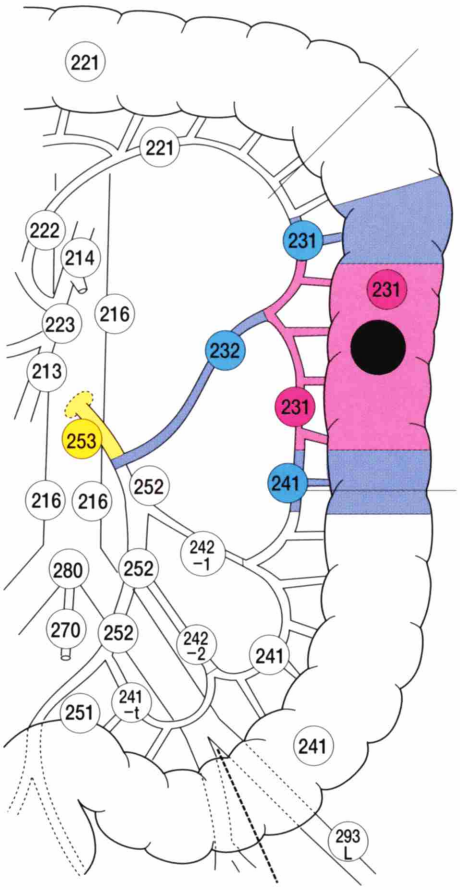
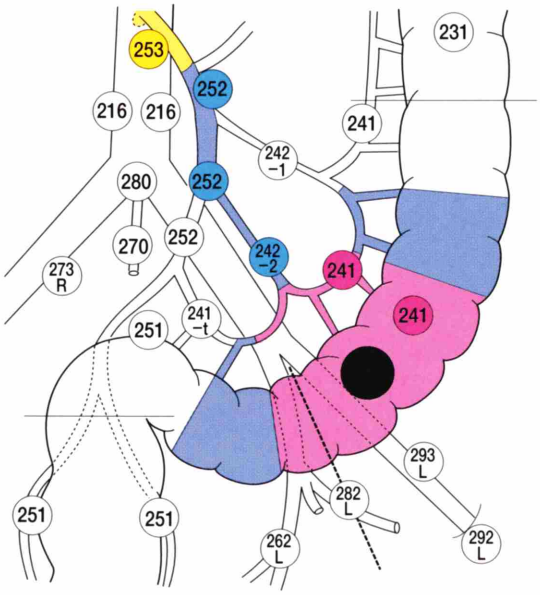


Fig. 9. Location S



: Epicolic/Paracolic lymph nodes (Group 1)

: Epicolic/Paracolic, and/or Intermediate lymph nodes (Group 2)

: Main lymph nodes (Group 3)

: Lymph nodes beyond Group 3 (Group 4)

Table 2. Lymph node groups of rectum and anus

	Lymph Drainage	Location			
		Rs	Ra	Rb	P
Group 1	Paraintestinal	251(2)	241(1) 251(1) 251(3)	271(3)	
Group 2	Paraintestinal	251(5)	241(4) 251(4) 251(6)	271(6)	
	Mesenteric	242	252		
	Lateral			262	272 [292]
Group 3	Mesenteric	253			
	Lateral		273 262 272	282 [260] [270] [280] [293]	
Group 4		216			

(1) Pararectal/Inferior rectal and/or Epicolic/Paracolic lymph nodes located 5 cm or less in width on the proximal side of the tumor, including the tumor size

(2) Pararectal lymph nodes located 3 cm or less in width on the distal side of the tumor

(3) Pararectal lymph nodes located 2 cm or less in width on the distal side of the tumor

(4) Pararectal/Inferior rectal and/or Epicolic/Paracolic lymph nodes located more than 5 cm but no more than 10 cm in width on the proximal side of the tumor

(5) Pararectal lymph nodes located more than 3 cm but no more than 6 cm in width on the distal side of the tumor

(6) Pararectal/Inferior rectal lymph nodes located more than 2 cm but no more than 4 cm in width on the distal side of the tumor

[ ] Optional lymph nodes in Group 3.

Fig. 10. Location Rs

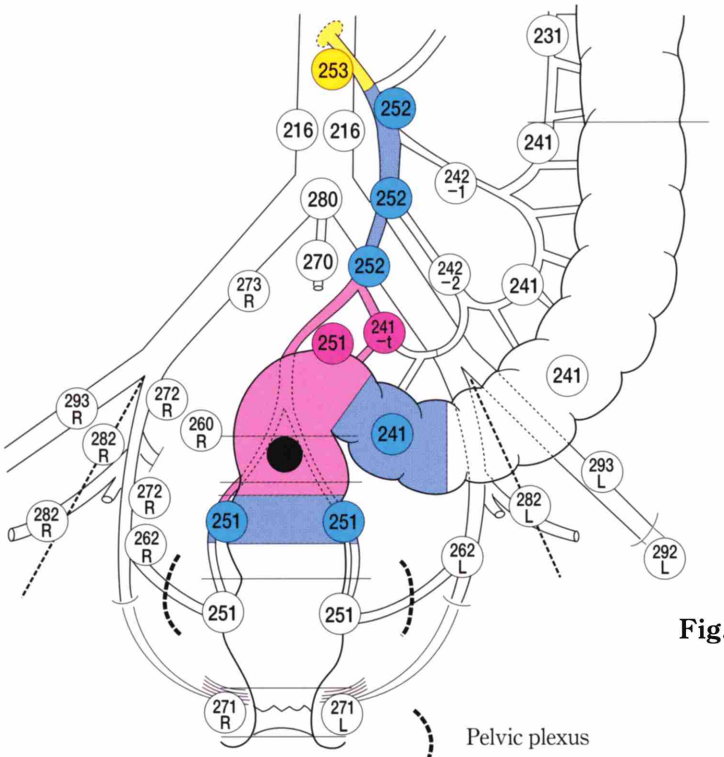
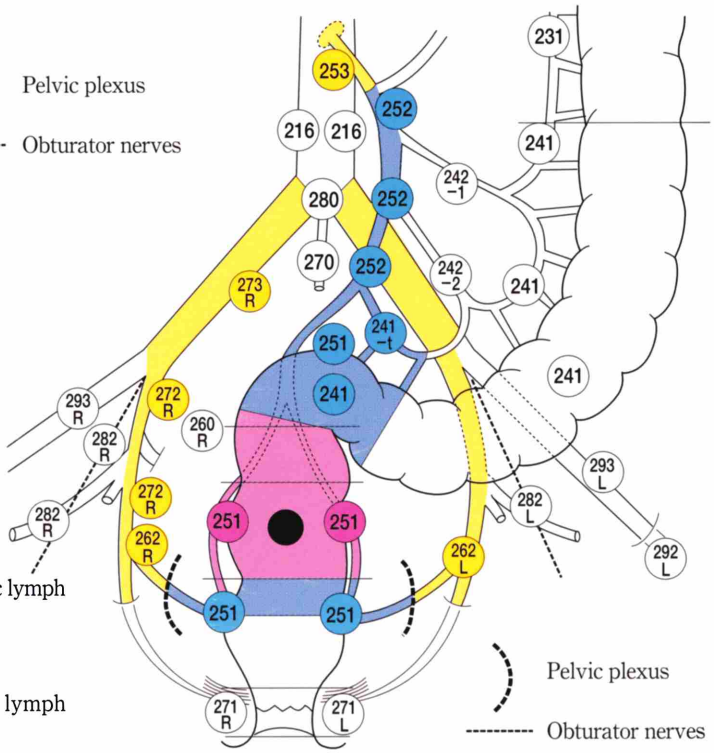


Fig. 11. Location Ra



: Pararectal, and/or Epicolic/Paracolic lymph nodes (Group 1)

: Pararectal, and/or Intermediate lymph nodes (Group 2)

: Main lymph nodes (Group 3)

: Lymph nodes beyond Group 3 (Group 4)

Fig. 12. Location Rb

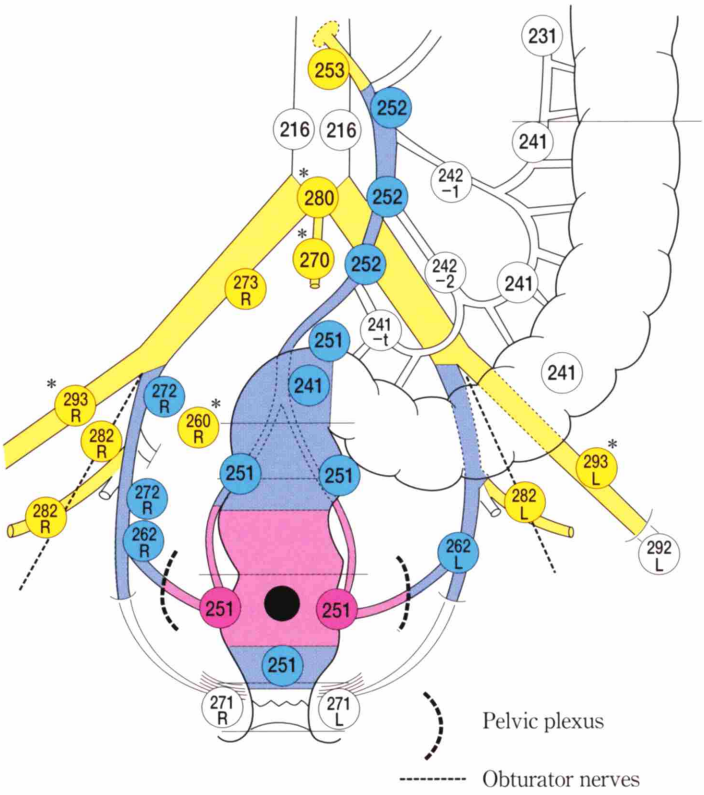
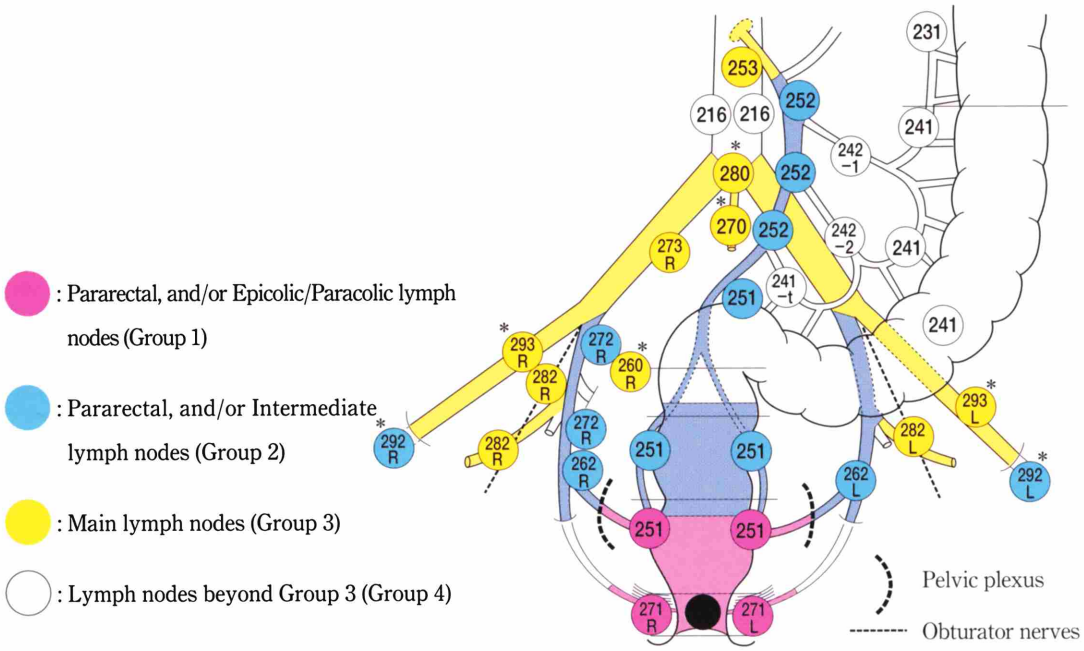


Fig. 13. Location P



5.4 Lymph Node Metastasis

N0 No lymph node metastasis
N1 Metastasis to Group 1
N2 Metastasis to Group 2
N3 Metastasis to Group 3
N4 Metastasis to Group 4

6 Peritoneal Metastasis

P0 No peritoneal metastasis
P1 Metastases only to adjacent peritoneum, which are removal by a combined resection
P2 A few metastases to distant peritoneum
P3 Numerous metastases to distant peritoneum

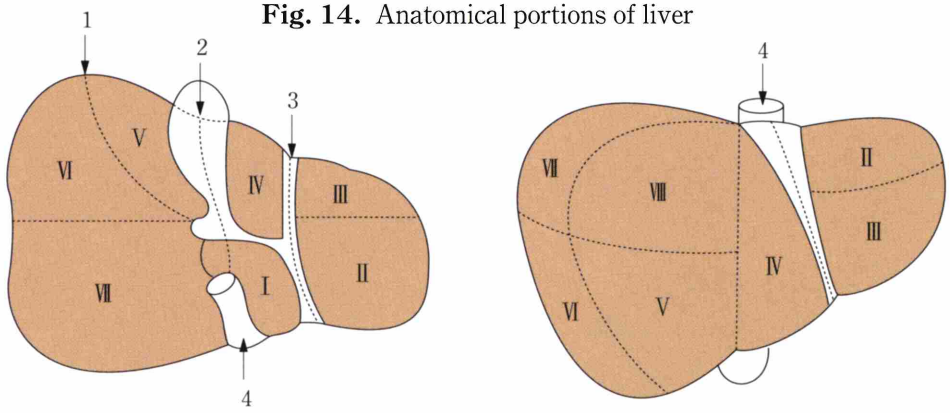
Ovarian metastasis without peritoneal dissemination should be classified as "P2."
In the cytological or histological examination, a positive result should be appended as "p(+)."

7 Liver Metastasis

H0 No liver metastasis
H1 Metastasis limited to one lobe
H2 Some metastases to both lobes (4 lesions or less)
H3 Numerous metastases to both lobes (5 lesions or more)

Tumor locations in the liver should be recorded according to the following figure.

Fig. 14. Anatomical portions of liver



a : Inferior aspect (facies visceralis)

b : Superior aspect (pars superior facies diaphragmatic hepatis)

1 : Right hepatic vein 2 : Cantlie's line 3 : Ligamentum teres hepatis 4 : Inferior vena cava

8 Pulmonary Metastasis

This classification should be appended in the "M(+)."

LM0 No pulmonary metastasis
LM1 Metastasis limited to one lobe
LM2 Metastases to multiple lobes but not meeting "LM3"
LM3 Numerous metastases to bilateral lungs, lymphangitis carcinomatosa, pleuritis carcinomatosa, or metastasis to hilar lymph nodes

9 Distant Metastasis

M(–) No distant metastasis
M(+) Distant metastasis, excluding peritoneal and/or liver metastasis.

In the "M(+)," metastatic organs or structures should be appended.

10 Invasion of Vascular Systems

The vascular systems should histologically be examined on the largest cross-sectional plane with the deepest tumor invasion.

10.1 Lymphatic Invasion

ly0 No invasion
ly1 Minimal invasion
ly2 Moderate invasion
ly3 Severe invasion

10.2 Venous Invasion

v0 No invasion
v1 Minimal invasion
v2 Moderate invasion
v3 Severe invasion

11 Stage Grouping

Tumor extension should be recorded according to the following stage grouping.

Table 3. Clinical and surgical stage grouping

Stage	Depth of Invasion	Metastases			
		Lymph Nodes	Peritoneum	Liver	Distant*
0	M	N0	P0	H0	M(–)
I	SM, MP	N0	P0	H0	M(–)
II	SS, SE, A1, A2	N0	P0	H0	M(–)
IIIa	Si, Ai	N1	P0	H0	M(–)
IIIb	Any	N2, N3	P0	H0	M(–)
IV	Any	N4	P1,2,3	H1,2,3	M(+)

* Refer to 9 Distant Metastasis.

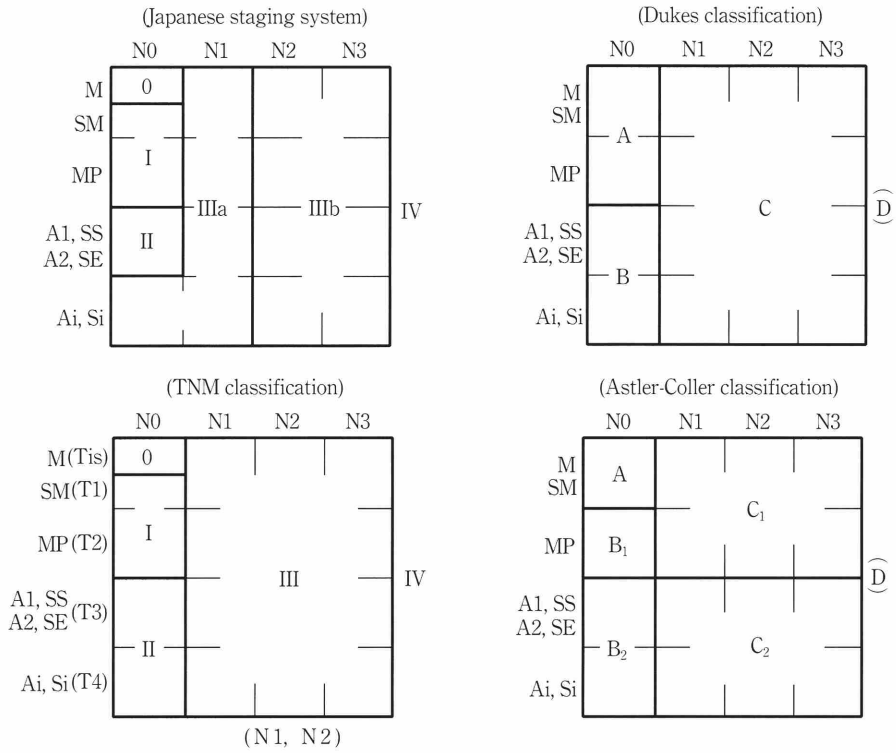
Table 4. Histological stage grouping

Stage	Depth of Invasion	Metastases			
		Lymph Nodes	Peritoneum	Liver	Distant*
0	m	n0	P0	H0	M(–)
I	sm, mp	n0	P0	H0	M(–)
II	ss, se, a1, a2	n0	P0	H0	M(–)
IIIa	si, ai	n1	P0	H0	M(–)
IIIb	any	n2, n3	P0	H0	M(–)
IV	any	n4	P1,2,3	H1,2,3	M(+)

* Refer to 9 Distant Metastasis.

The carcinoma with “m” or “sm” in the Depth of Invasion should be defined as an early cancer, regardless of presence or absence of lymph node metastases.

Fig. 15. Comparison of staging classification



Colon and Rectal Carcinoma

JS CCR	UICC * (TNM)	Dukes
0	0	
I	I	A
II	II	B
IIIa**		
IIIb	III	C
IV	IV	(D)
IIIa — Si	T4 II	B
IIIa — N1	N1 1-3 nodes → III	C
IIIb — N2	N2 ≥ 4 nodes → III	C
IIIb — N3	N2 ≥ 4 nodes → III	C

* A tumor nodule up to 3 mm in perirectal or pericolic adipose tissue is classified as T3 but not as N1 or N2.
** A case of Si and N(−) belongs to II of the TNM or B of the Dukes, but to IIIa of Japanese stage grouping.

Anal Carcinoma

JS CCR	UICC (TNM)
0	0
I	I
II	II
IIIa***	IIIA
IIIb	IIIB
IV	IV

M = Tis
SM, MP — T1 ≤2cm
A1 — T2 2-5cm
A2 — T3 >5cm
*** IIIa { Ai = T4 → IIIA; N1 = N1 → IIIB }
IIIb : N2 = N2, N3

*** A case of Ai and N1(+) belongs to IIIB of the TNM , but to IIIa of Japanese stage grouping.

B. Operative Procedures

1 Surgical Treatments

Resection of intestine

Local resection of intestine

Polypectomy, excluding endoscopic polypectomy

Bypass and colostomy

Exploratory laparotomy*

* Exploratory laparotomy with radiotherapy and/or chemotherapy should also be included in this category.

2 Combined Resection

All structures resected together with the main tumor, and the resected extension, should be recorded.

3 Tumor Invasion of Surgical Margins

The classification should be recorded for evaluation of "Curability of Surgical Resection."

3.1 Proximal Cut End

OW(–) No tumor invasion

OW(+) Tumor invasion

3.2 Distal Cut End

AW(–) No tumor invasion

AW(+) Tumor invasion

3.3 Surgical Cut End

EW(–) No tumor invasion

EW(+) Tumor invasion

In the histological finding, "ew(–)," the distance between the tumor and the cut end of the surgical surface should be recorded.

4 Lymph Node Dissection

D0 No dissection or incomplete dissection of Group 1 lymph nodes

D1 Dissection of Group 1 lymph nodes

D2 Dissection of Groups 1 and 2 lymph nodes

D3 Dissection of Groups 1, 2, and 3 lymph nodes

Lymph node dissection should be based on the independent lymphatic spread: lymphatic drainage along to the intestine, toward the mesenteric main lymph node, and toward the pelvic wall.

5 Curability of Surgical Resection

Curability of surgical resection should be evaluated both macroscopically and microscopically.

Curability A (Cur A) No residual tumors

Curability B (Cur B) No residual tumors but not evaluable as "Curability A"

Curability C (Cur C) Definite residual tumors

Table 5. Macroscopic curability of surgical resection

	M	P	H	D : N	EW	OW, AW
Cur A	M(–)	P0	H0	D≧N	(–)	(–)
	No residual tumors					
Cur B	M(+)(Excision)	P1,2(Excision)	H1,2(Excision)	D<N	(+)	(+)
	No residual tumors					
Cur C	M(+)	P(+)	H(+)	D<N	(+)	(+)
	Residual tumors					

The "D" and "N" numbers should be counted and evaluated according to the independent lymphatic spread: lymphatic drainage along to the intestine and toward the mesenteric main lymph node in the colon; lymphatic drainage along to the intestine, toward the mesenteric main lymph node, and toward the pelvic wall in the rectum.

Table 6. Microscopic curability of surgical resection

	M	P	H	D : n	ew	ow, aw
Cur A	M(–)	P0	H0	D≧n	(–)	(–)
	No residual tumors					
Cur B	M(+)(excised)	P1,2(excised)	H1,2(excised)	D<n	(+)	(+)
	No residual tumors					
Cur C	M(+)	P(+)	H(+)	D<n	(+)	(+)
	Residual tumors					

The “D” and “n” numbers should be counted and evaluated according to the independent lymphatic spread: lymphatic drainage along to the intestine and toward the mesenteric main lymph node in the colon; lymphatic drainage along to the intestine, toward the mesenteric main lymph node, and toward the pelvic wall in the rectum.

C. Surgical Results

For statistical analyses, the following figures should be recorded.

Total number of patients with colorectal carcinoma, who were seen at the institute

Total number of inpatients with colorectal carcinoma in the department of surgery

Total number of operations

Total number of operative deaths

Total number of hospital deaths

Operative death is defined as death within 30 postoperative days, regardless of the place of death.

The following information, if applicable, should be appended for each patient.

Treatments prior to the surgery

Chemotherapy

Radiotherapy

Endoscopic treatments

Other therapies

Previous resections

For survival analyses, the following items should be recorded.

Vital status

Surviving The latest date of follow-up

Deceased The date of death

Unknown (Lost to follow-up) The last date of follow-up

Causes of death

Operation-related death

Death due to the disease

Death due to other malignancy

Death due to other diseases

Death from accidents, including suicides

Death due to unknown causes

Part II

Histological Findings

Principles

This part composes 1) Criteria for Histological Classification, 2) Group Classification of Colorectal Biopsy Specimen, and 3) Handling of Resected Specimen.

1) In the Criteria for Histological Classification, carcinomas should be differentiated from tumors, epithelial and non-epithelial lesions, and tumor-like lesions.
   Histological type and grade of the tumors should be diagnosed through the methods shown in the Handling of Resected Specimen.
   In classifying and/or grading the carcinoma, the predominant pattern is adopted as its representative histological type and grade. For example, for a tumor consisting mainly of well-differentiated carcinoma with a part of moderately differentiated carcinoma, a diagnosis of "well-differentiated carcinoma" should be made. However, if an unnegligible amount of minor component exists, and, further, be a lesion related to poor prognosis, the component should be appended to a major diagnosis.
2) The purpose of Group Classification is to differentiate carcinomas from other lesions in biopsy specimens by colonoscopy and to express concisely the histological interpretation. Therefore, the classification should not be used for non-epithelial tumors. Furthermore, it should not be applied to express variable histological types within the same tumor resected.
3) In the Handling of Resected Specimen, standard methods of handling the surgically and endoscopically resected specimens are shown, and all the histological findings [indicated in Parts I, II, III, and IV] are recommended to be taken through these methods.

A. Criteria for Histological Classification

1 Histological Typing

- Large intestine
  - Benign epithelial tumors
    - Adenoma
      - Tubular adenoma
      - Tubulovillous adenoma
      - Villous adenoma
    - Adenomatosis
  - Malignant epithelial tumors
    - Adenocarcinoma
      - Well-differentiated adenocarcinoma
      - Moderately differentiated adenocarcinoma
      - Poorly differentiated adenocarcinoma
    - Signet-ring cell carcinoma
    - Mucinous adenocarcinoma
    - Adenosquamous carcinoma
    - Squamous cell carcinoma
    - Other carcinomas
  - Carcinoid tumor
  - Non-epithelial tumors (other than Lymphoma)
    - Benign non-epithelial tumors
      - Leiomyoma
      - Neurilemoma and Neurofibroma
      - Lipoma and Lipomatosis
      - Others
    - Malignant non-epithelial tumors
      - Leiomyoblastoma
      - Leiomyosarcoma
      - Others

- Lymphoma
  - Non-Hodgkin lymphoma
    - Follicular type
    - Diffuse type
  - Hodgkin disease
  - Others
- Unclassified tumors
- Metastatic tumors
- Tumor-like lesions
  - Peutz-Jeghers syndrome
  - Cronkhite-Canada syndrome
  - Cowden disease
  - Juvenile polyp and polyposis
  - Benign lymphoid polyp and polyposis
  - Hyperplastic polyp and polyposis
  - Hyperplastic nodule
  - Inflammatory polyp and polyposis
  - Colitis cystica profunda
  - Endometriosis
  - Heterotopic gastric mucosa
  - Others

Vermiform appendix

- Benign epithelial tumors
  - Mucinous cystadenoma
  - Adenoma and adenomatosis
- Malignant epithelial tumors
  - Mucinous cystadenocarcinoma
  - Adenocarcinoma
  - Others
- Carcinoid tumor
- Non-epithelial tumors (other than Lymphoma)
- Lymphoma
- Unclassified tumors
- Metastatic tumors

- Tumor-like lesions
  - Peutz-Jeghers syndrome
  - Hyperplastic polyp
  - Endometriosis
  - Others

- Anal canal
  - Benign epithelial tumors
    - Cystadenoma
    - Papilloma
  - Malignant epithelial tumors
    - Adenocarcinoma and Mucinous adenocarcinoma
      - Rectal type
      - Of anal gland origin
      - With anal fistula
      - Other extracanal type
    - Adenosquamous carcinoma
    - Squamous cell carcinoma
    - Basaloid carcinoma
    - Others
  - Malignant melanoma
  - Non-epithelial tumors
  - Tumor-like lesions
    - Condyloma acuminatum
    - Hypertrophied anal papillae
    - Retention cyst of anal glands
    - Submucosal abscess
    - Internal hemorrhoids
    - Others

- External Skin
  - Classification of skin tumors is applied.

2 Tumors and Tumor-like Lesions of Large Intestine

Adenoma

Most of adenomas in the large intestine show a circumscribed elevated lesion, frequently forming pedunculated or sessile polyps. Though relatively rare, flat lesions, including a depressed type, are also encountered, particularly in case of small size. The surface is usually smooth, but papillary or villous structures can also be seen. Epithelial cells show various degrees of atypia. These cells with low- or high-grade atypia can be difficult to differentiate from similar epithelial cells of non-neoplastic lesions or carcinoma. Furthermore, adenoma-like lesions with replacement of the submucosa, "pseudocarcinomatous invasion," can be encountered.

1. Tubular adenoma

   This adenoma is composed mainly of tubular structures (Figs. 1–3).

2. Tubulovillous adenoma

   This adenoma is composed of tubular as well as villous structures (Figs. 4 and 5).

3. Villous adenoma

   This adenoma is composed of leaf- or finger-like processes with a narrow core of the lamina propria (Fig. 6).

Note 1: Serrated adenoma, to which much attention has been given recently, is a type of adenoma characterized by serrated epithelium with cellular (nuclear) atypism of variable degree. However, since the histological criterion is not yet established well in Japan, the type is not recognized as independent in the classification of adenoma. The term should be applied only to a lesion with unequivocally characteristic histologies.

Note 2: The term polyp can be defined macroscopically as a circumscribed and elevated lesion in the mucosa, irrespective of its histological characteristics.

Adenomatosis

Adenomatosis is characterized by the presence of at least 100 colorectal adenomas. Polypoid lesions may be encountered in the stomach and small intestine, in addition to the large intestine.

Familial (occasionally unfamilial) polyposis coli and Gardner syndrome (gastrointestinal polyposis with osteoma and soft tissue tumors) are major candidates of this category.

Adenocarcinoma

Adenocarcinoma is characterized by malignant glandular epithelium composed mainly of tubular structures. Furthermore, it can be classified according to the grade of differentiation, and by the predominant pattern of differentiation.

1. Well-differentiated adenocarcinoma
   The tumor shows distinct and large gland formation composed of columnar epithelial cells (Figs. 7–9).
2. Moderately differentiated adenocarcinoma
   The predominant pattern of tumor is intermediate between well-differentiated and poorly differentiated adenocarcinoma (Fig. 10).
3. Poorly differentiated adenocarcinoma
   The tumor shows indistinct gland formation composed of cuboidal epithelial cells (Figs. 11 and 12).

Signet-ring cell carcinoma

The tumor cells, in which various amounts of mucin are retained, have a signet-ring shape, and little tendency to form glands or tubules. These cells resemble intestinal goblet cells histochemically and electron-microscopically (Fig. 13).

Mucinous adenocarcinoma (Colloid carcinoma)

Mucinous adenocarcinoma is composed of cells that produce a substantial amount of mucin outside of the cells, in which mucous nodules/lakes (muconodular type) are formed. Incomplete gland formation and/or signet-ring cells in the mucous lakes can be seen (Figs. 14 and 15).

Adenosquamous carcinoma

A mixture of neoplastic glandular and squamous components can be seen in the same tumor (Fig. 16).

Squamous cell carcinoma

Squamous cell carcinoma in the anal canal can be seen in the transitional zone and anal epithelium.

Other carcinomas

1. Small-cell carcinoma (Endocrine cell carcinoma)
   The solid tumor consisting of rather uniform cells with high nucleocytoplasmic (N/C) ratio and hyperchromatic nuclei is called "small-cell carcinoma" or "endocrine cell carcinoma," because of presence of endocrine granules in the cytoplasm or resemblance to the lung tumor of the same name (Fig. 17). This tumor usually shows high frequency of mitosis and vessel permeation.
2. Undifferentiated carcinoma
   This type of carcinoma is very rare. This category must be carefully distinguished from poorly differentiated adenocarcinoma, small-cell carcinoma, malignant melanoma, and malignant lymphomas.

Carcinoid tumor

This tumor, which probably arises from endocrine cells of the digestive tract, shows malignant behavior. In principle, uniform cells with small nuclei, and trabecular (ribbon-like) or compact (nest-like) patterns, can be seen, which are distinguished from characteristics of adenocarcinoma. Rarely differentiation of mucin production is encountered in the tumor cells. Since this tumor can be negative for both argentaffin and argyrophil stains, it is recommended to identify the presence of endocrine granules using electron-microscope (Fig. 18).

The tumor of the vermiform appendix is usually for both argyrophil and argentaffin stains.

Leiomyoma

Leiomyoma arises mainly from the muscularis propria, and may show palisading.

Neurilemoma and Neurofibroma	Multiple tumors may be encountered in patients with von Recklinghausen disease, which tumors can be seen in the intestine.
Vascular tumors	Lymphangioma, hemangioma, glomus tumor, and vascular leiomyoma can be classified in this category.
Leiomyoblastoma	Leiomyoblastoma is a special type of tumor consisting of clear and polygonal cells with abundant cytoplasm. These cells are arranged in an epithelial fashion (epithelioid leiomyoma). Differing from leiomyosarcomas, slow growth and infrequent metastases can be observed. In principle, the tumor can be classified as a low grade malignancy, and it should be differentiated from other mesenchymal tumors.
Leiomyosarcoma	This tumor shows various degrees of cellular atypia. The distinction between leiomyoma and leiomyosarcoma is difficult to make according to cellular atypia alone; however the respective mitotic figures are the most important indicator of malignancy.
Lymphoma	The classification of lymphoma is currently being modified. In the meantime, usage of the conventional classification should be continued. In others of this category, plasmacytoma, histiocytosis, etc. are included.
Peutz-Jeghers syndrome	This hereditary syndrome shows polyposis in the gastrointestinal tract and pigmentation in the skin and mucous membranes. Polyps lining (tree-like) branching of the muscularis mucosae diffusely occur and grow in the stomach and the small and large intestine. The epithelial cells show no atypia; however, they produce abundant mucus (Figs. 19 and 20).

Cronkhite-Canada syndrome

This syndrome shows gastrointestinal polyposis, alopecia (generalized loss of hair), skin pigmentation, nail atrophy, and protein-losing gastroenteropathy. Multiple polyps are detectable in the whole digestive tract, which polyps are composed of enlarged glands and edematous stroma.

Cowden disease (Multiple hamartomatous syndrome)

This rare hereditary disease shows multiple polyps throughout the digestive tract and is accompanied very often with skin and oral mucosal tumors, breast tumors (fibrocystic and carcinomatous), and thyroid tumors (adenomatous and carcinomatous). The intestinal polyp is histologically similar to juvenile or inflammatory polyp.

Juvenile polyps and polyposis

Juvenile polyps, which are non-neoplastic lesions, can be encountered in children, and occasionally in adults. These polyps show pedunculated types with a red surface, macroscopically, and glands with cystic enlargement with no cellular atypia are detected microscopically. Furthermore, edematous and abundant stromata, with occasional bleeding and erosion, can be recognized. Juvenile polyposis is rare (Figs. 21 and 22).

Benign lymphoid polyp and polyposis

These polypoid lesions consist of circumscribed hyperplasia of lymphoid follicles, and follicles covered by colonic mucosa. The polyp size ranges from several to 20-30 mm in diameter. Single polyps can occasionally be seen in the rectum, whereas polyposis can be seen in the whole large intestine.

Hyperplastic polyp and polyposis

This lesion is non-neoplastic; the polyps are usually less than 5 mm in diameter, with a pale and smooth surface. The polyps characteristically show small breaches in the muscularis mucosae, elongation of the tubules with dilatation of the lumen, and serrated epithelium. The epithelial cells, with no atypia, are clear or eosinophilic, and goblet cells are remarkably reduced (Fig. 23).

The lesion should be carefully differentiated from what is called serrated adenoma, particularly that with slight atypia (refer to Note 2, p. 33). The adenoma shows budding or tubular proliferation of variable degree and the epithelial cells (nuclei) are variably atypical, whereas the hyperplastic polyp consists of much simpler tubular structures with no or less cellular atypia than serrated adenoma.
Hyperplastic polyposis is characterized by progressive development of numerous hyperplastic polyps and is often accompanied by true adenomas such as serrated adenoma.

Hyperplastic nodule

This lesion consists of circumscribed and epithelial hyperplasia, in which tiny pale polyps can be recognized, without characteristics of hyperplastic polyps, and with no change of the muscularis mucosae.

Inflammatory polyp and polyposis

These lesions can be encountered in ulcerative colitis, and occasionally in other inflammatory diseases of the large intestine (Fig. 24).

Colitis cystica profunda

The lesion shows a polyp-like mucosal elevation resulting from erosion and ulceration; and the lesion can be classified into regional or diffuse type. The regional type is closely related to a solitary ulcer in the rectum, and the diffuse type is closely related to diffuse inflammation in the colonic canal.

Endometriosis

Ectopic endometrial tissues can be seen in the intestinal wall.

Others

There are tumor-like lesions difficult to be classified into any of above categories. Severe lymphoid hyperplasia developed in erosion or ulcer edge may be included here because of its unknown nature.

3 Tumors of Vermiform Appendix

Mucinous cystadenoma

Mucinous cystadenoma in the appendix is a benign cystic tumor lined by tall columnar cells, and the lumen of the appendix is filled with mucin.

Mucinous cystadenocarcinoma

Mucinous cystadenocarcinoma in the appendix, a cyst-forming carcinoma producing mucin, frequently shows well-differentiation and invasion of the appendix wall. The structure of pseudomyxoma peritoneum may be encountered (Fig. 25).

4 Tumors of Anal Canal

Malignant epithelial tumors

Definition of the anal canal at macroscopic level is shown in Part I, 1.1 Tumor Location. The histological indication of the area implies an area from the upper margin of the internal sphincter to the lower margin of the anal epithelium (squamous mucous membrane). The mucosa lining the anal canal can be divided into three different types: mucous epithelium of rectal type, transitional zone epithelium or transitional epithelium (consisting of stratified cuboidal or columnar cells), and anal epithelium (stratified squamous epithelium lacking skin appendages). Anal glands in the submucosal layer and sphincter muscle layer open into the anal crypt.

1. Rectal type

   The category implies adenocarcinoma or mucinous carcinoma arising from the rectal mucosa of the anal canal.

2. Adenocarcinoma (or mucinous adenocarcinoma) of anal gland origin

   This type is an extremely rare adenocarcinoma (or mucinous adenocarcinoma), whose tumor is located in the wall of the anal canal, and carcinomatous components are often undetectable in the mucosa (Figs. 26 and 27).

3. Adenocarcinoma (or mucinous adenocarcinoma) arising from anal fistula

These carcinomas can be recognized in patients with a long history of anal fistulae, whose tumor is seen in the wall of the anal canal, with occasional mucin production (Fig. 28).

Basaloid carcinoma

This special type of tumor histologically resembles basal cell carcinoma of the skin (Fig. 29).

Malignant melanoma

This melanoma is located in the vicinity of the dentate line, and produces melanin pigments, though occasionally exists, as a part of or entire tumor, an amelanotic tumor (Fig. 30).

B. Group Classification of Colorectal Biopsy Specimens

The epithelial element present in colorectal biopsy specimens is classified as any one of the following five groups, according to its highest atypia. The classification is applicable only to colorectal biopsy specimens through endoscopy, not to polypectomy, mucosal resection, and surgical specimens.

Group 1 Mucosa with no atypia

Normal mucosa (Fig. 31), and inflammatory or hyperplastic mucosa without atypia (Fig. 32)

Group 2 Non-neoplastic lesion with atypia

Hyperplastic or regenerative mucosa with atypia, and inflammatory (Figs. 33 and 34) or hyperplastic mucosa with atypia (Figs. 35 and 36)

Group 3 Neoplastic lesion with low-grade atypia

Adenoma with mild (Figs. 37 and 38) ormoderate (Figs. 39–42) atypia, and lesions difficult to diagnose as neoplastic or non-neoplastic ones (Figs. 43 and 44)

Group 4 Neoplastic lesion with high-grade atypia

Adenoma with severe atypia (Figs. 45 and 46), borderline lesions between benign and malignant one, and adenocarcinoma of highly well-differentiated type (Figs. 47–52)

Group 5 Definite carcinoma

It is recommended to append the histological type and degree of differentiation (Figs. 53–58).

Note 1: It is recommended to append histological diagnosis to the group classification.

Note 2: Small biopsy specimens do not always represent the entire lesion.

Note 3: If the biopsy specimens are too small or severely damaged, the group classification cannot be applied. These specimens should be diagnosed as "insufficient materials."

Histological Photographs

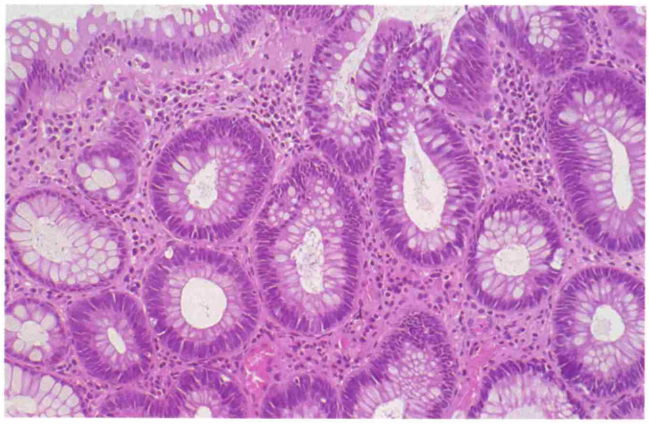


Fig. 1. Tubular adenoma (Slight atypia)

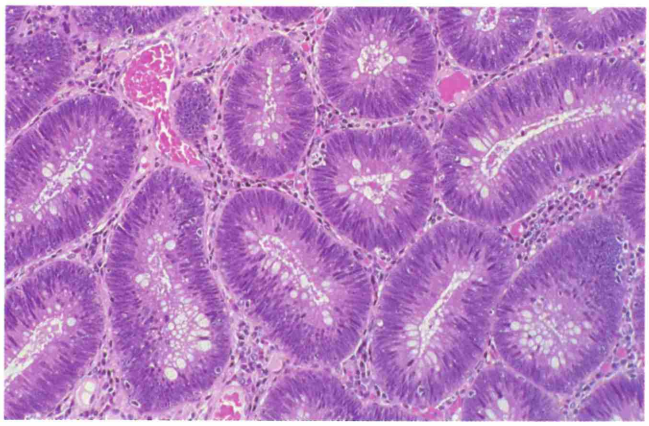


Fig. 2. Tubular adenoma (Moderate atypia)

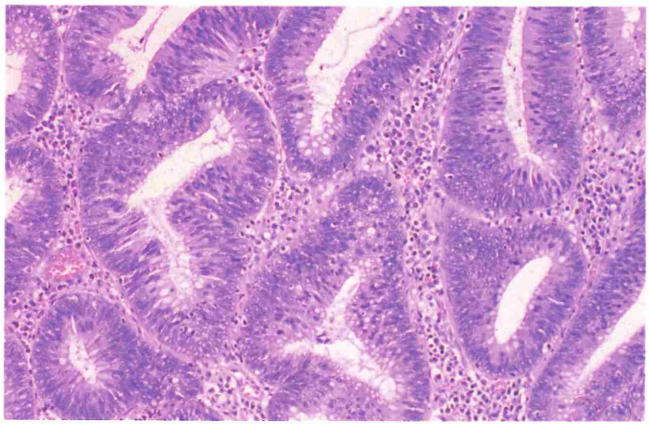


Fig. 3. Tubular adenoma (Severe atypia)

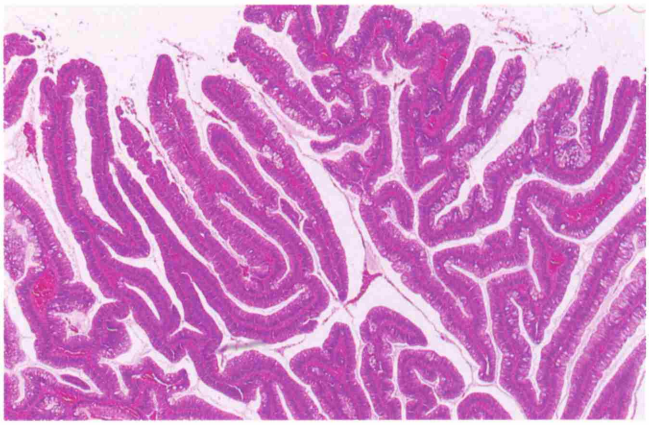


Fig. 4. Tubulovillous adenoma

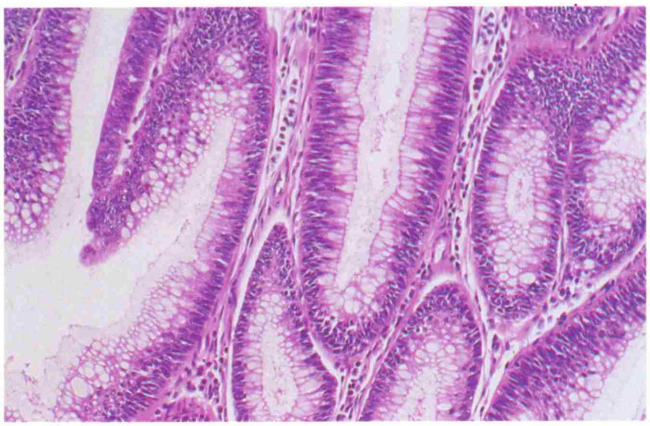


Fig. 5. Tubulovillous adenoma

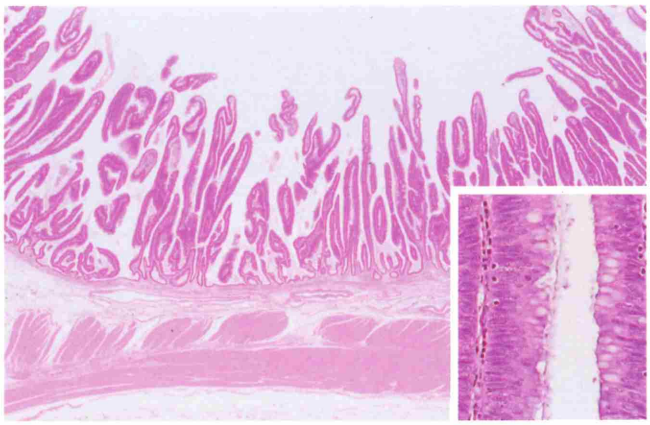


Fig. 6. Villous adenoma
Inset : High-power view

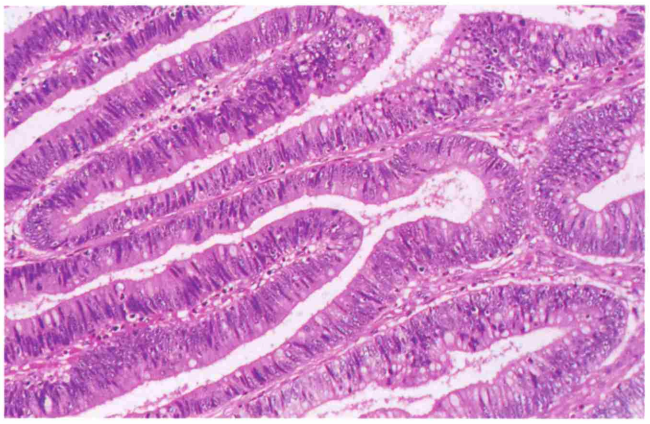


Fig. 7. Well-differentiated adenocarcinoma

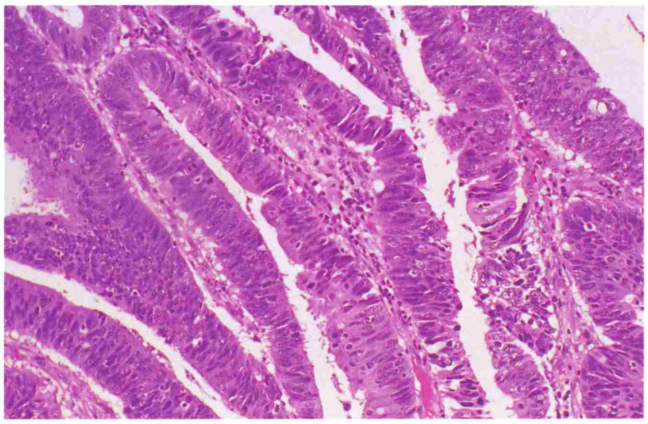


Fig. 8. Well-differentiated adenocarcinoma

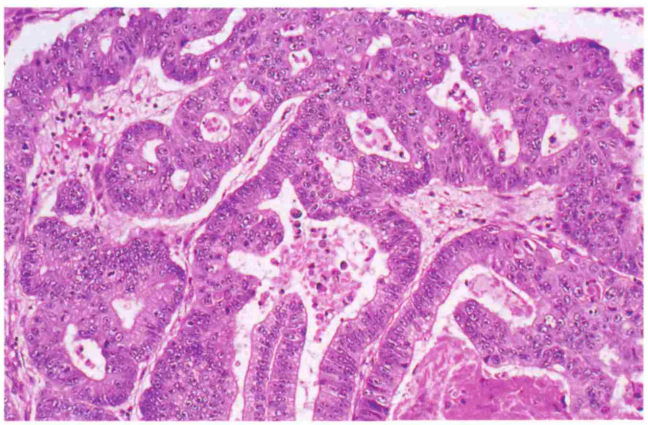


Fig. 9. Well-differentiated adenocarcinoma

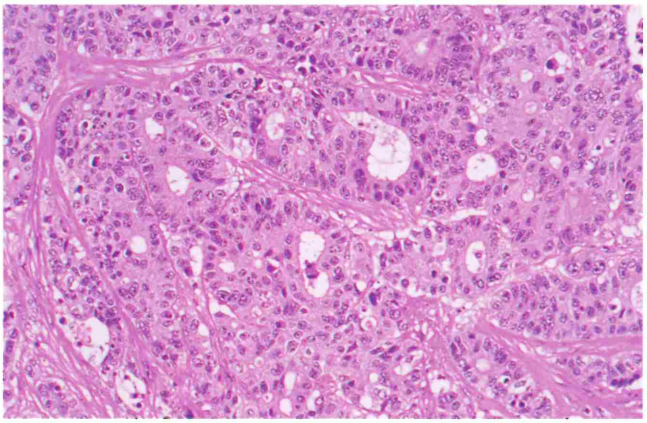


Fig. 10. Moderately differentiated adenocarcinoma

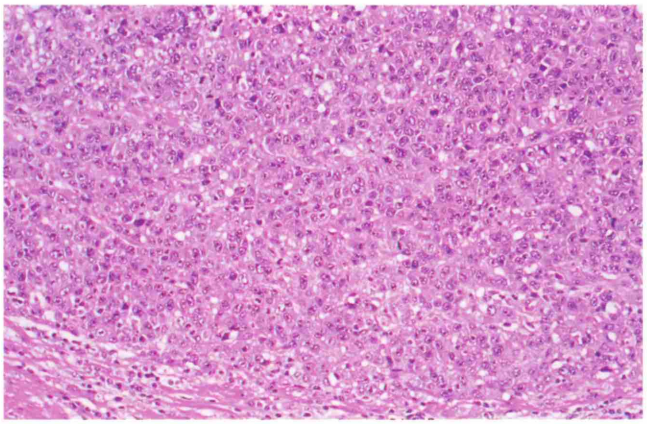


Fig. 11. Poorly differentiated adenocarcinoma

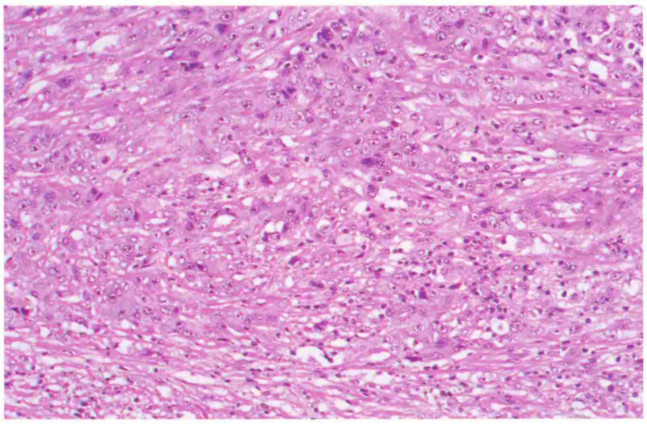


Fig. 12. Poorly differentiated adenocarcinoma

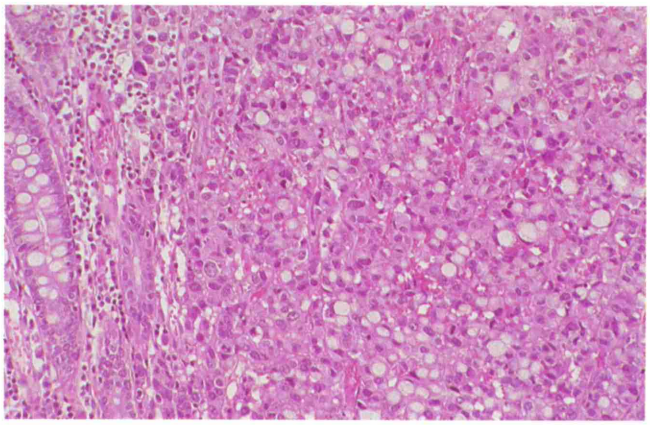


Fig. 13. Signet-ring cell carcinoma

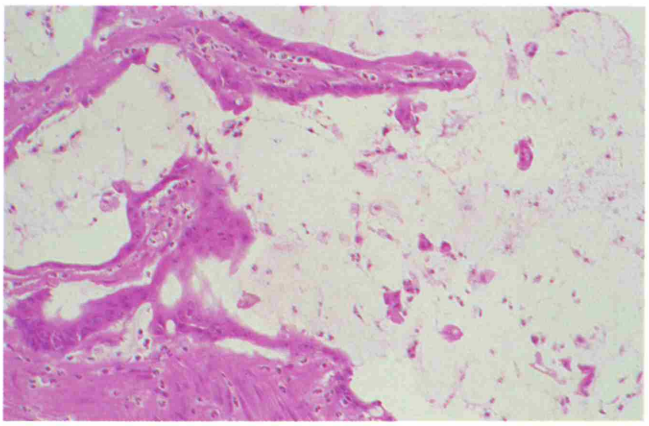


Fig. 14. Mucinous adenocarcinoma

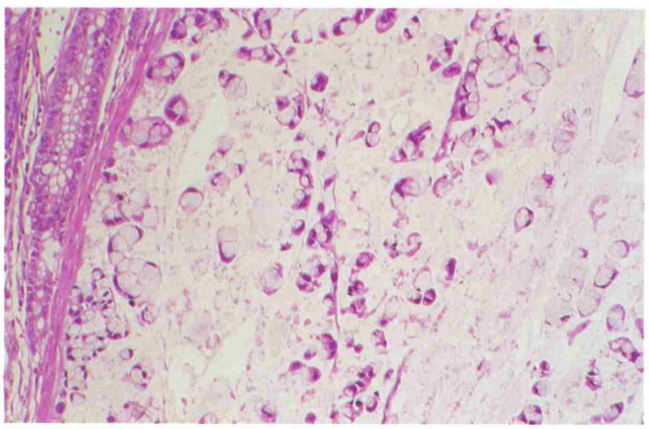


Fig. 15. Mucinous adenocarcinoma

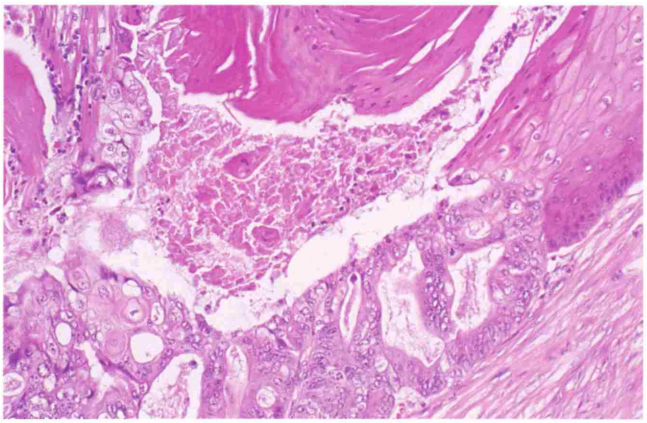


Fig. 16. Adenosquamous carcinoma

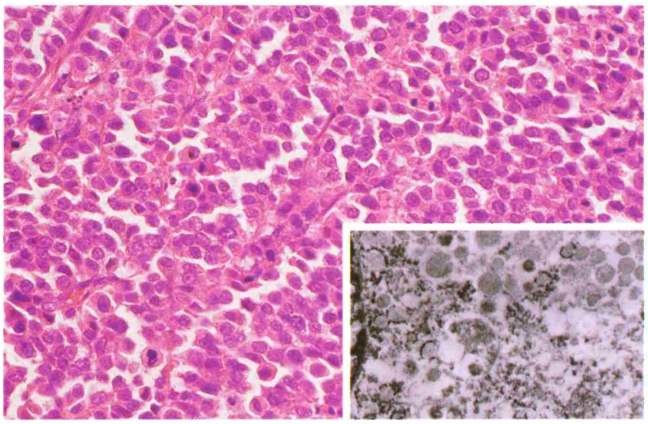


Fig. 17. Small-cell carcinoma/Endocrine cell carcinoma
Inset : Electron microscopic view of endocrine granules

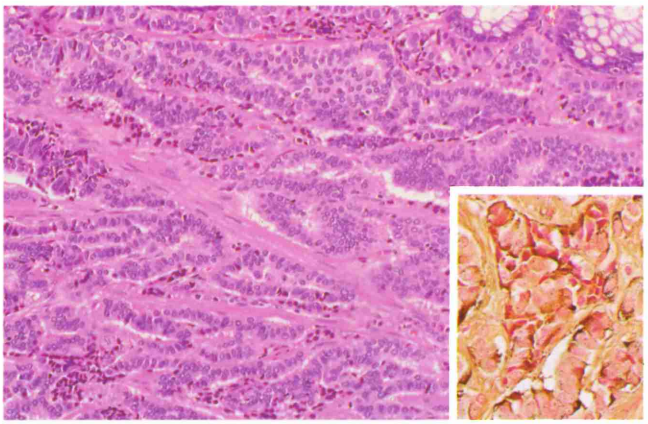


Fig. 18. Carcinoid tumor in rectum
Inset : Grimelius argyrophil stain

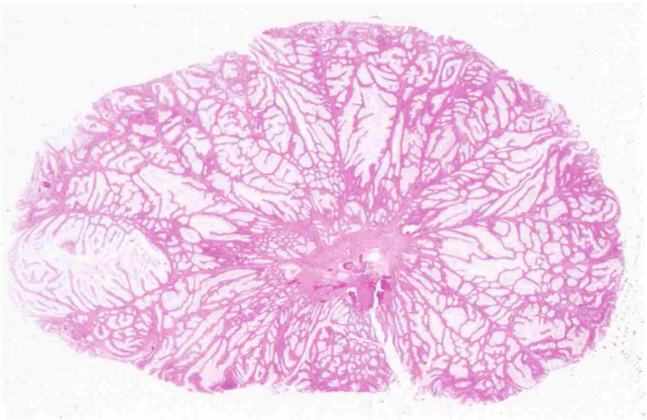


Fig. 19. Peutz-Jeghers syndrome

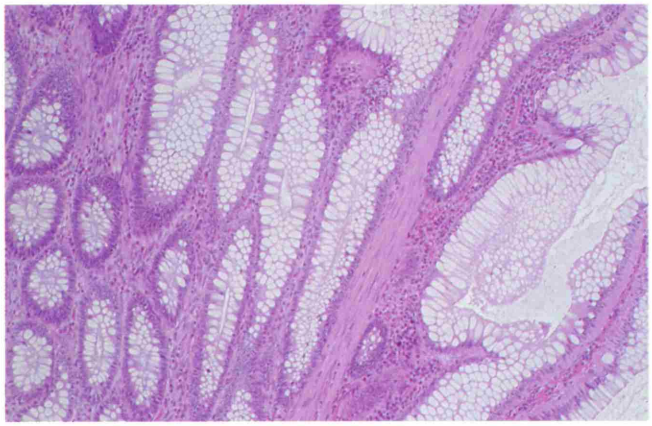


Fig. 20. Peutz-Jeghers syndrome

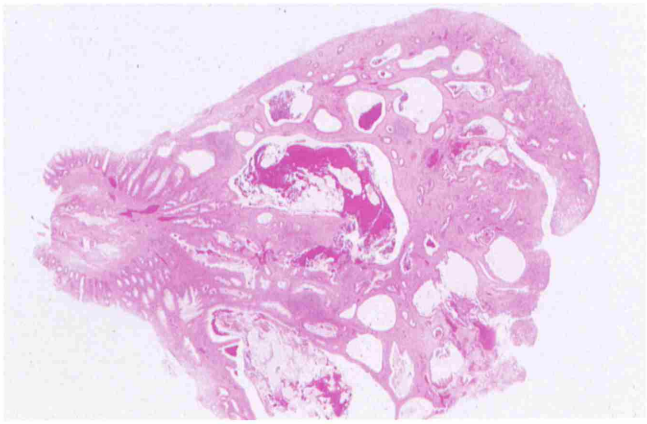


Fig. 21. Juvenile polyp

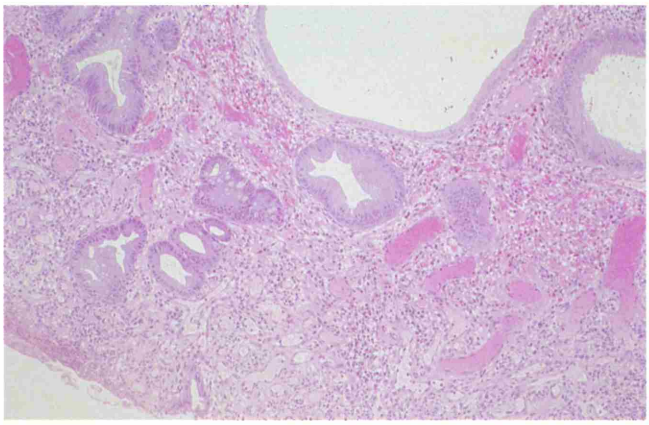


Fig. 22. Juvenile polyp

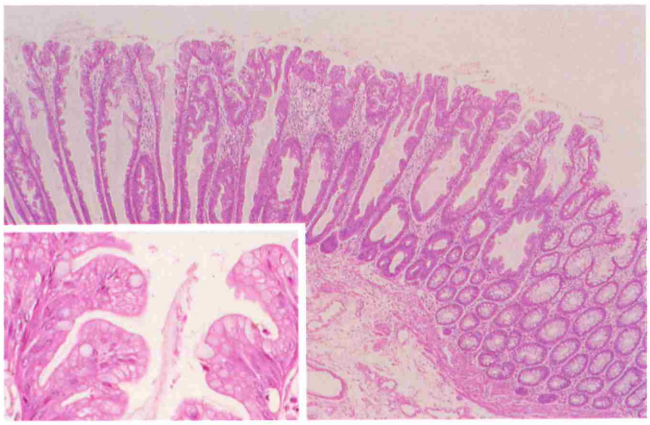


Fig. 23. Hyperplastic polyp
Inset : High-power view

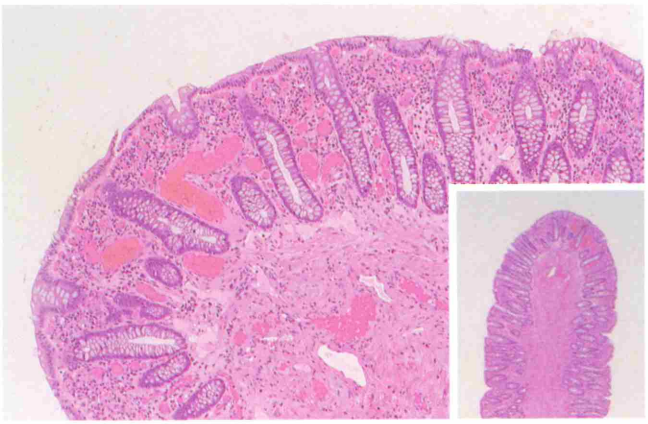


Fig. 24. Inflammatory polyp
Inset : Low-power view

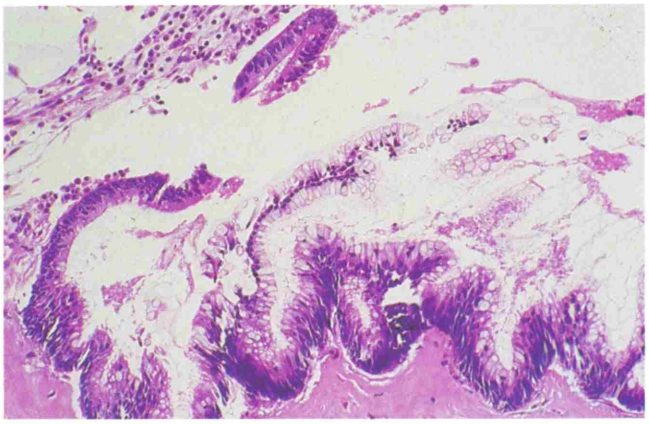


Fig. 25. Mucinous cystadenocarcinoma in the appendix

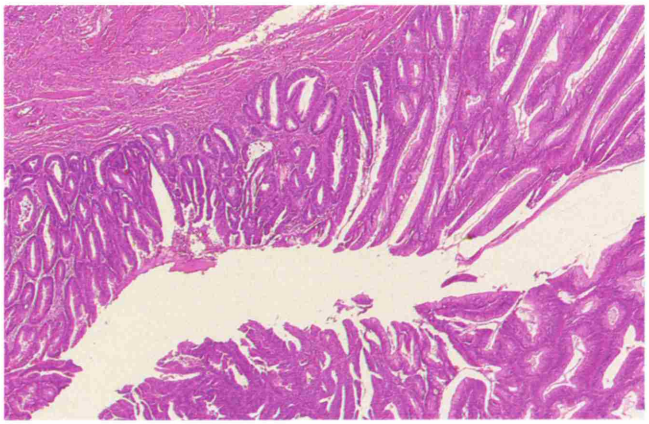


Fig. 26. Adenocarcinoma of anal gland origin

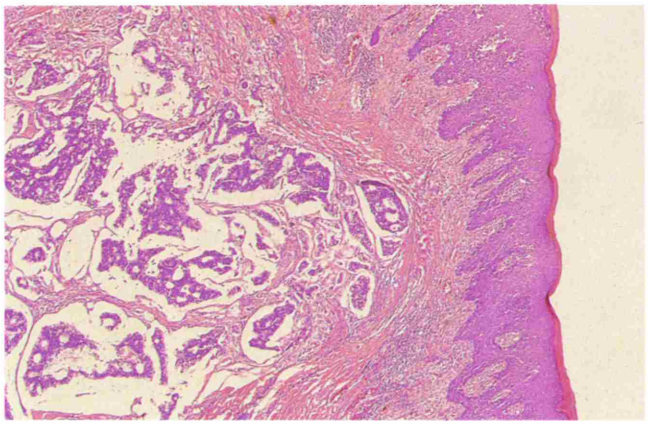


Fig. 27. Adenocarcinoma of anal gland origin

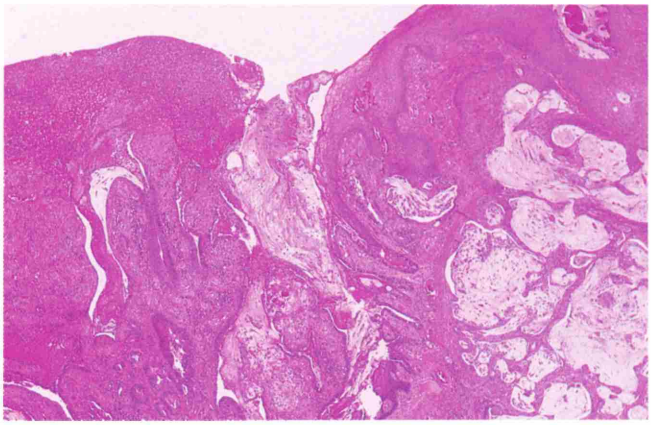


Fig. 28. Adenocarcinoma arising from anal fistula

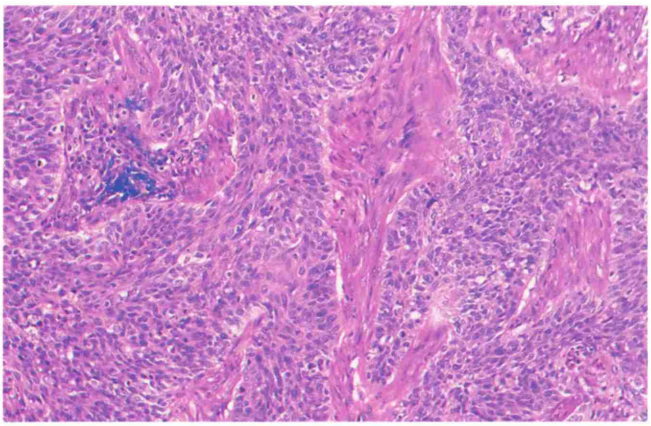


Fig. 29. Basaloid carcinoma in anal canal

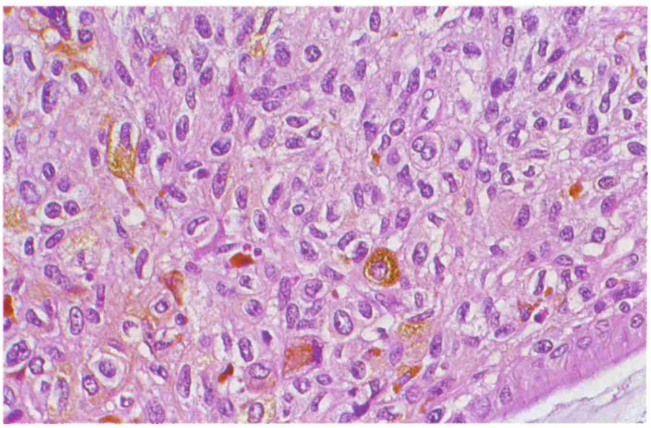


Fig. 30. Malignant melanoma in anal canal

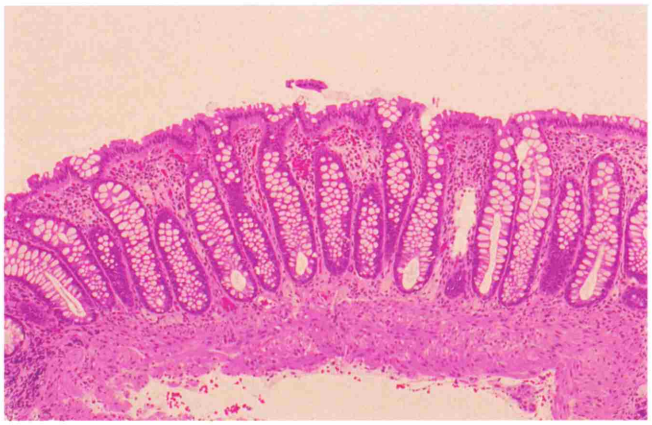


Fig. 31. Group 1
Normal mucosa

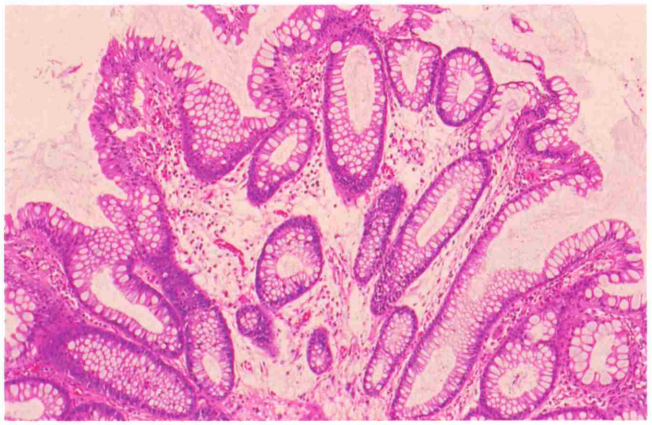


Fig. 32. Group 1
Hyperplastic mucosa without atypia

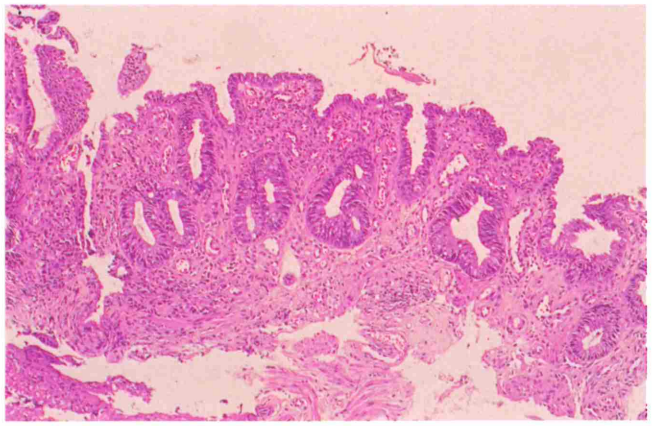


Fig. 33. Group 2
Regenerative or inflammatory mucosa with atypia (Mucosal prolapse syndrome)

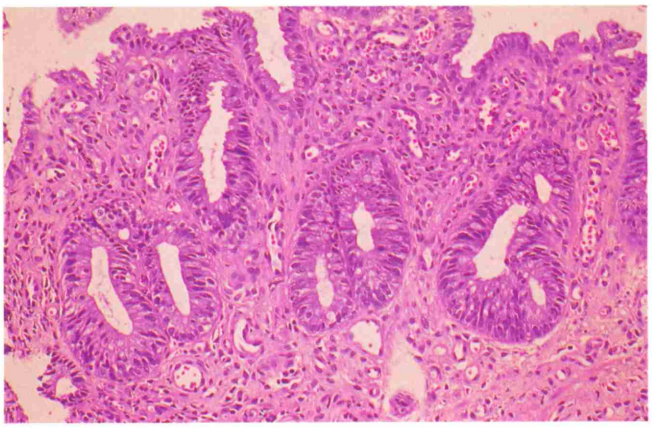


Fig. 34. Group 2
High-power view of Fig. 33

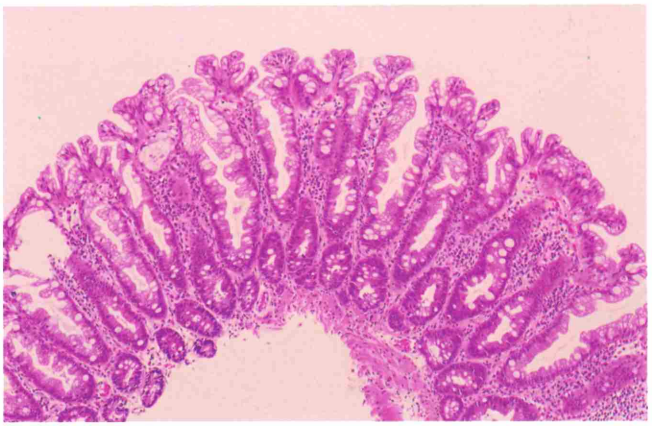


Fig. 35. Group 2
Hyperplastic polyp with mild atypia

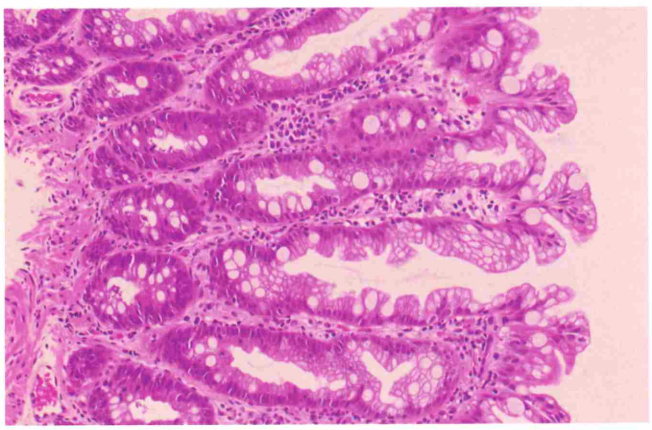


Fig. 36. Group 2
High-power view of Fig. 35

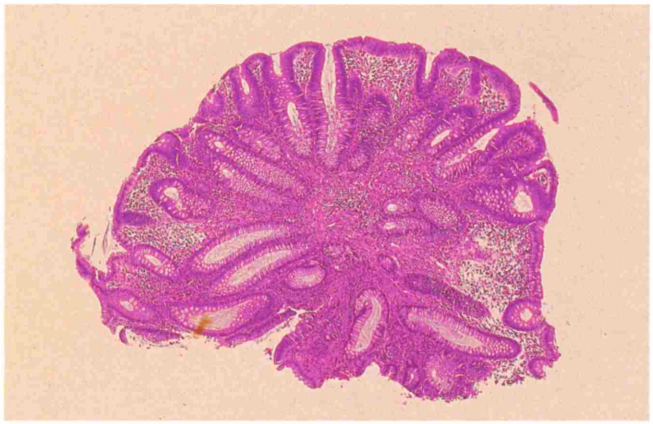


Fig. 37. Group 3
Tubular adenoma with mild atypia

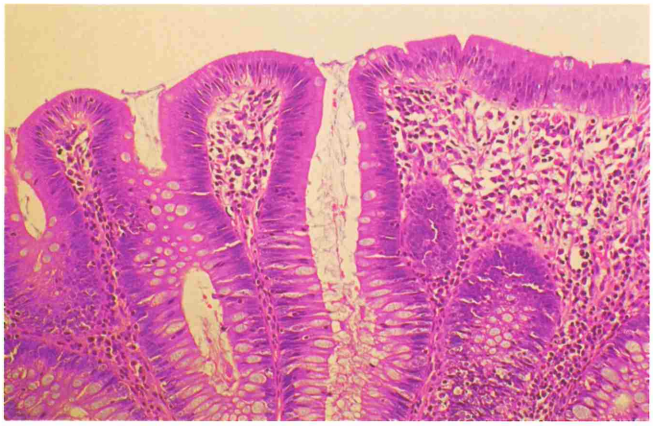


Fig. 38. Group 3
High-power view of Fig. 37

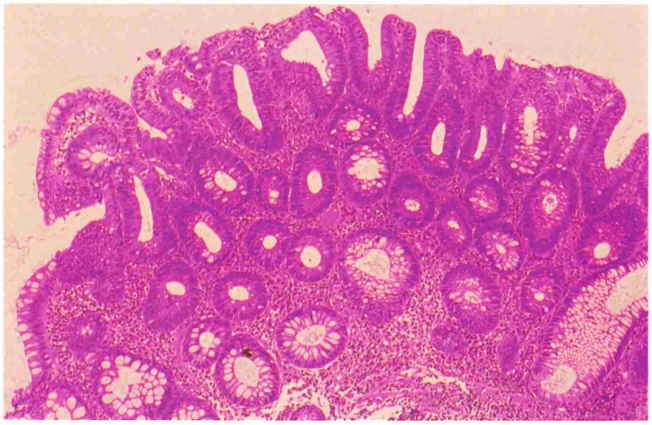


Fig. 39. Group 3
Tubular adenoma with moderate atypia

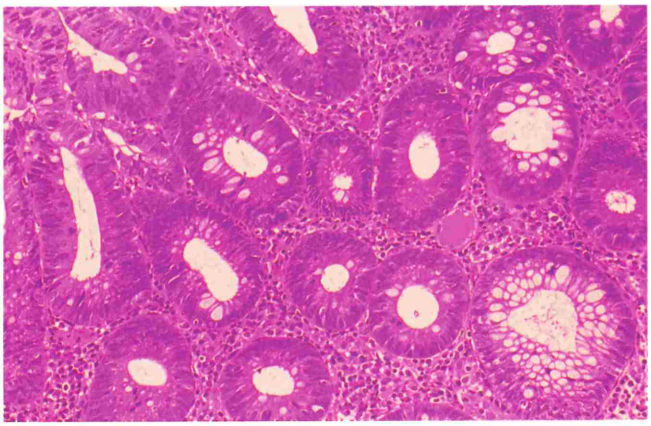


Fig. 40. Group 3
High-power view of Fig. 39

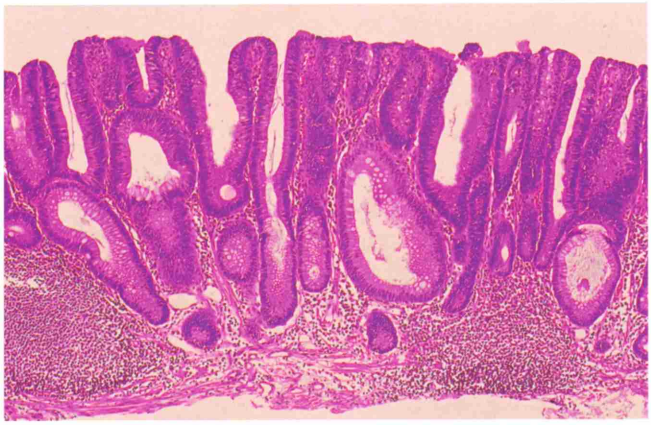


Fig. 41. Group 3
Tubular adenoma with moderate atypia

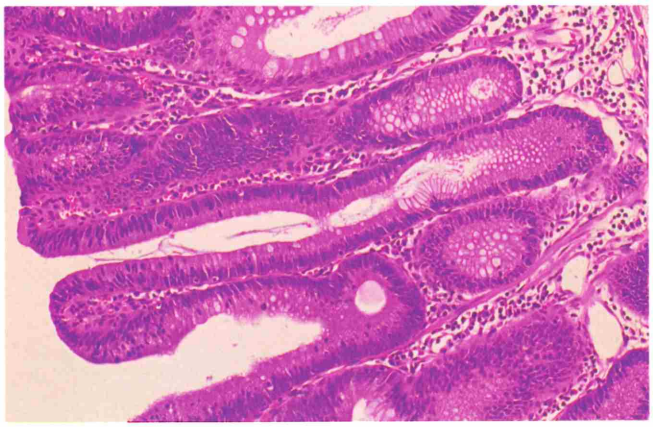


Fig. 42. Group 3
High-power view of Fig. 41

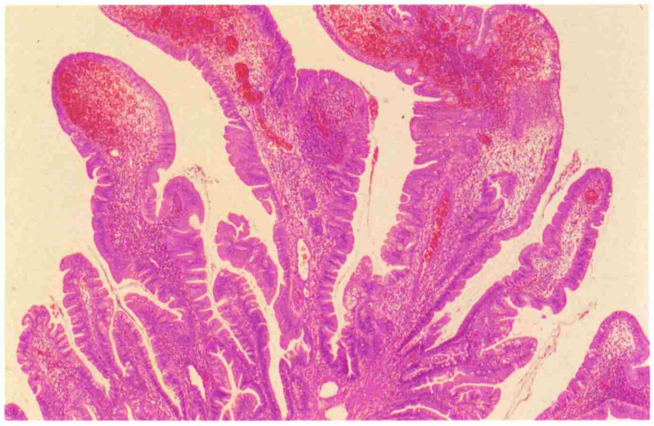


Fig. 43. Group 3
Serrated adenoma

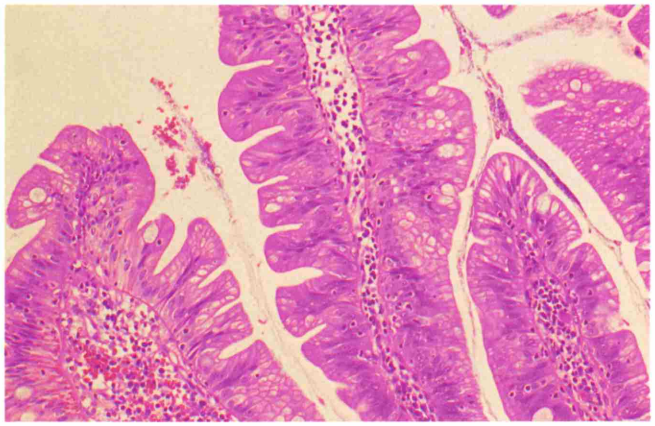


Fig. 44. Group 3
High-power view of Fig. 43

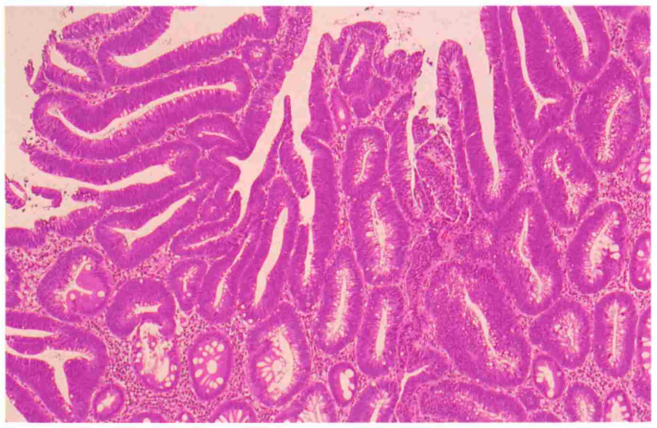


Fig. 45. Group 4
Tubular adenoma with severe atypia

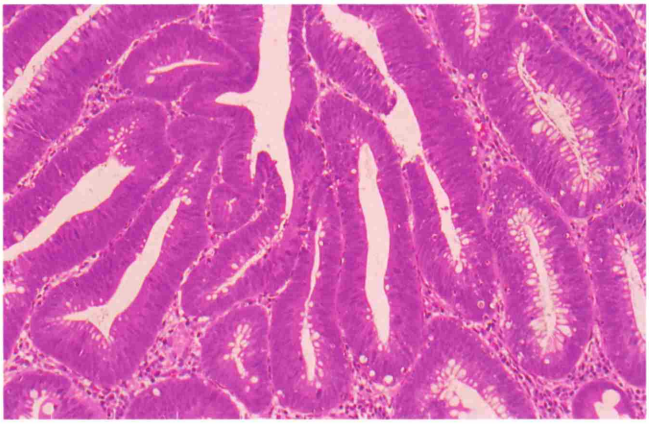


Fig. 46. Group 4
High-power view of Fig. 45

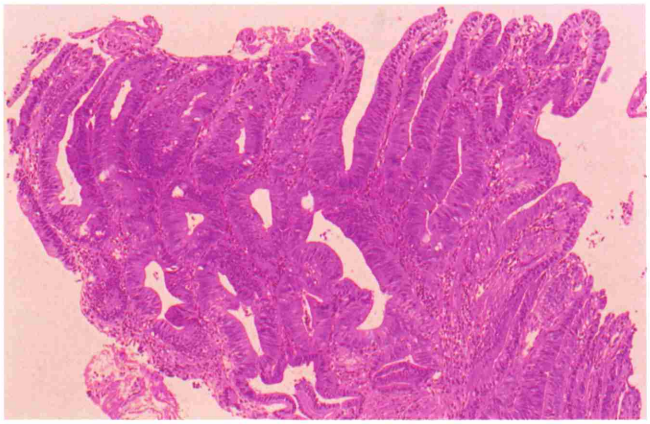


Fig. 47. Group 4
Lesion diagnosed as adenoma with severe atypia or adenocarcinoma of the highly well-differentiated type

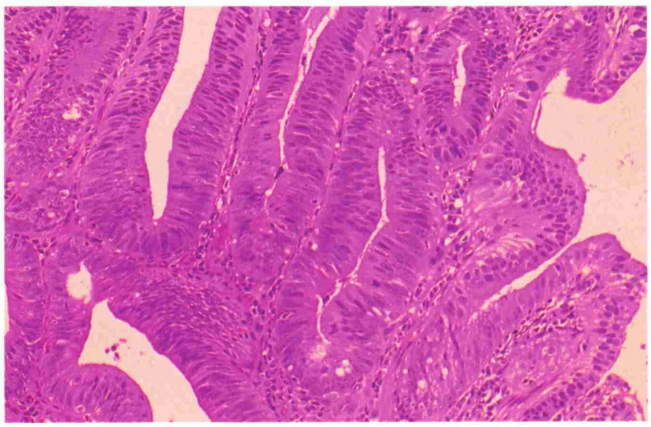


Fig. 48. Group 4
High-power view of Fig. 47

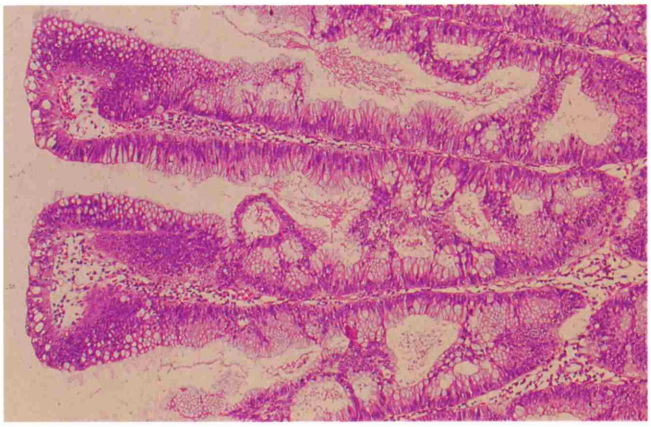


Fig. 49. Group 4
Adenocarcinoma of the highly well-differentiated type

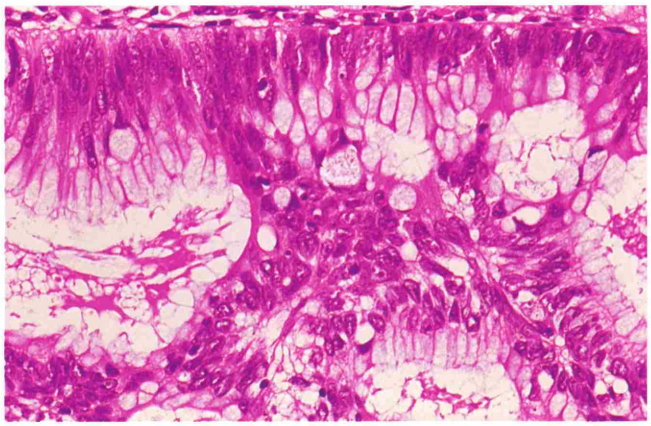


Fig. 50. Group 4
High-power view of Fig. 49

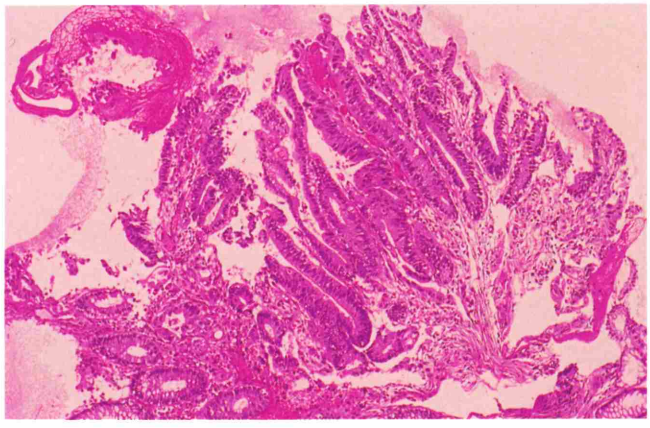


Fig. 51. Group 4
Adenocarcinoma of the highly well-defferentiated type

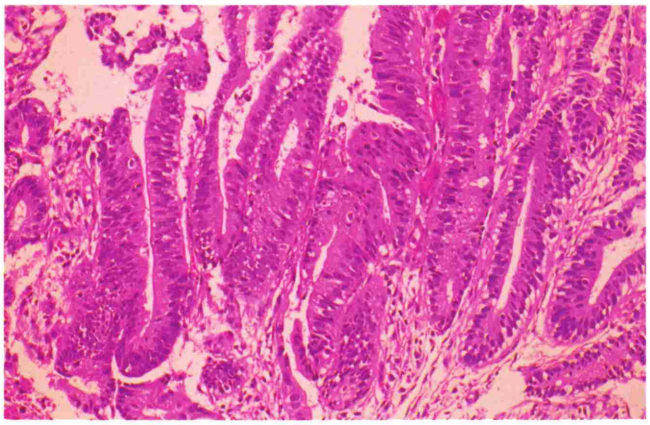


Fig. 52. Group 4
High-power view of Fig. 51

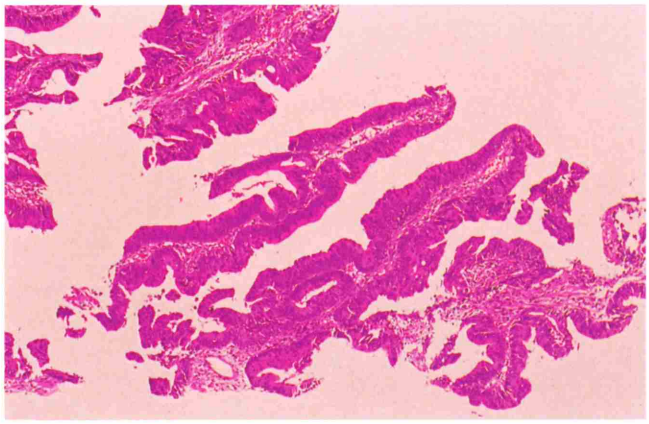


Fig. 53. Group 5
Adenocarcinoma of the well-differentiated type (Villous tumor)

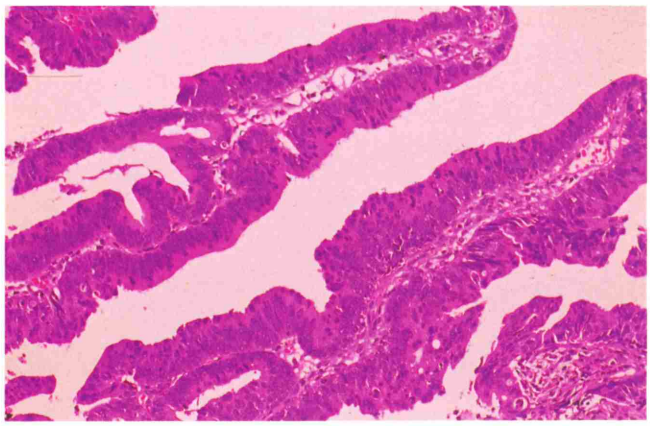


Fig. 54. Group 5
High-power view of Fig. 53

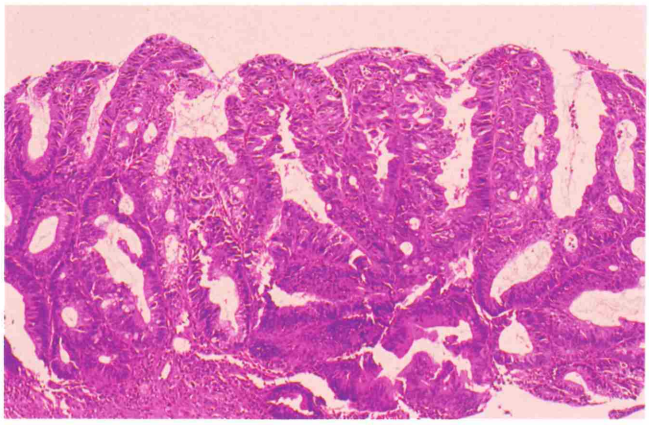


Fig. 55. Group 5
Adenocarcinoma of the well-differentiated type

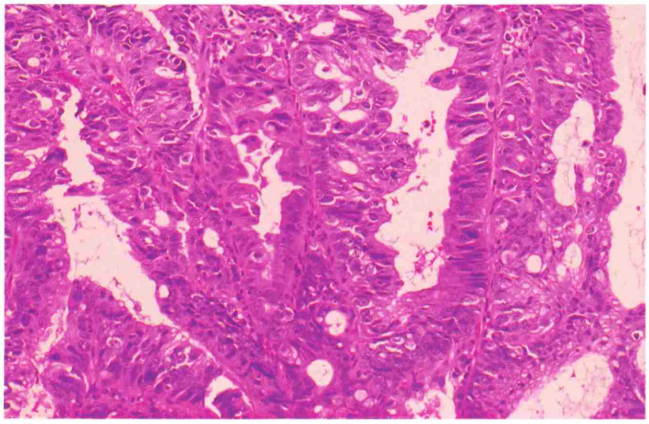


Fig. 56. Group 5
High-power view of Fig. 55

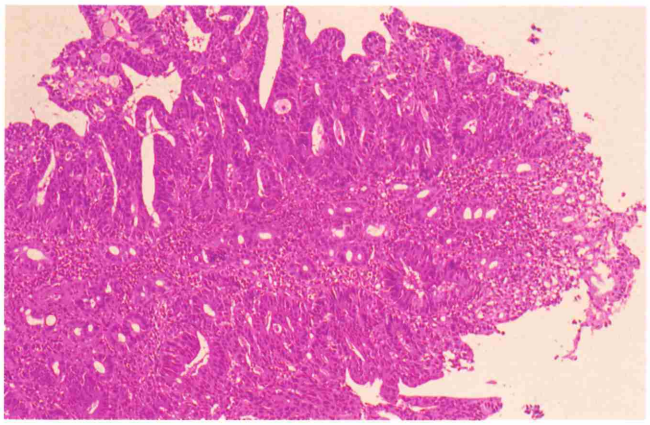


Fig. 57. Group 5
Adenocarcinoma of the moderately differentiated type

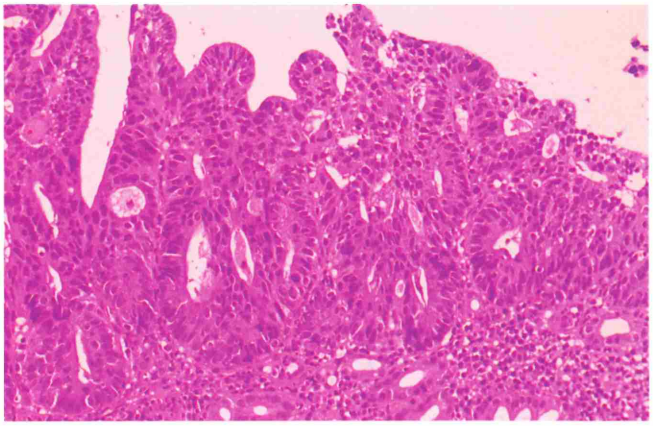


Fig. 58. Group 5
High-power view of Fig. 57

C. Handling of Resected Specimen

1 Before Fixation

1) A fresh specimen of the resected rectum should be opened on the anterior side and along the long axis of the rectum. Other intestinal specimens should be opened on the antimesenteric side. If a tumor is located on the cutting line, the intestine should be opened in some other way.

2) The opened intestine should be placed on a flat board with the mucosal side up, and should be explored macroscopically. The distances between the tumor edge and both the proximal and distal cut ends, and the greatest dimension and/or the largest circumferential length of the tumor, should be recorded. The ratio of the largest length of the tumor perpendicular to the canal long axis to the circumference of the canal circle should also be recorded.

   In the presence of a distinct ulcer, the above-mentioned measurements should also be recorded for the ulcer.

3) In the case of a protruded-type tumor and an endoscopically resected tumor specimen, the following items should be described: the size and shape of the tumor, and characteristics of the lesion, such as color, hardness, and cross-sectional features.

   Note : The cut end of specimens with no stalk or an extremely short stalk should be marked with Indian ink.

4) The lymph nodes are dissected according to the figures shown in Figs. 4–13.

5) Photography of the specimen, with a scale, and/or sketches, should be performed before and after fixation.

2 Fixation

1) The opened intestine should be placed on a flat board with the mucosal side up, and the edge of the intestine should be pinned to a board with stainless steel pins.

2) The pinned-out intestine should then be completely immersed in a container of formalin solution, for fixation.

3) Pedunculated polyps can be completely immersed in such a way that they hang down in the formalin solution from a floating board.

4) Complete immersion of the specimen for 72 hours is recommended.

3 Sectioning

1) In principle, several section lines should be made along the long axis of the intestine, to include the center of the tumor.
2) For demonstration of the deepest invasion of the tumor, sections perpendicular to the long axis of the intestine can be added.
3) Before and after this procedure, photographs and/or sketches of the intestinal mucosa should be made, for mapping of the lesion.
4) The resected specimen obtained by endoscopy should be sectioned as follows:

   In semipedunculated and pedunculated lesions, the section should be made to include both the head and stalk of the lesion (Figs. 59a–59c).

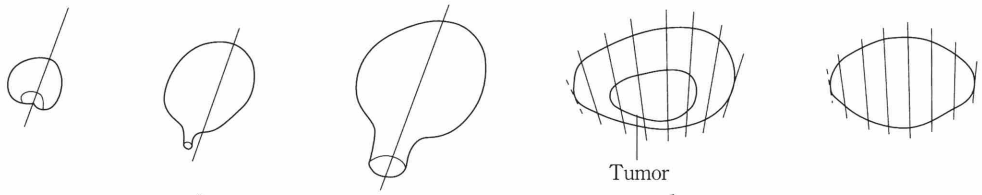
   For a specimen with a thin stalk (less than 2 mm in diameter), the stalk should be totally embedded, for examination by thin-sectioning of the paraffin block.

   For sessile or superficial-type lesions, the specimen should be cut at 2-mm intervals, to explore the cut ends and invasion depth.

   Though superficial-type tumors with a distinct margin should be cut to present the shortest distance from the tumor to the cut end (Fig. 59d).

   For tumors with an indistinct margin, it is recommended to make sections perpendicular to the long axis of the specimen (Fig. 59e).

Fig. 59. Sectioning of the resected specimen obtained by endoscopy



Part III

Endoscopic Findings and Management

Principles

Any tumor, benign or malignant, may be subjected to evaluation by colorectal endoscopy. Only endoscopic resection with electric cautery should be classified according to this manual. Procedures of endoscopic resection involve single or double snare polypectomy, piecemeal polypectomy and preinjectic mucosal resection (endoscopic mucosal resection, EMR). Diathermy biopsy (hot biopsy) can be included in endoscopic treatments, but it should not be included in resection cases.

Note : Surgery after endoscopic treatments should be classified into operative treatments.

A. Clinical Criteria

1 Clinical Findings

X-ray findings should be referred to.

1.1 Location and Size

These categories should be classified according to Clinicopathologic Findings.

1.2 Gross Appearance

Gross appearances of the lesion should be recorded as follows, and the word "like" should also be appended. After histological confirmation, the word "like" for carcinoma should be omitted.

Example:

Protruded type	
Pedunculated type	Ip like
Semipedunculated type	Isp like
Sessile type	Is like
Superficial type	
Superficial elevated type	IIa like, IIa+IIc like
Superficial flat type	IIb like
Superficial depressed type	IIc like, IIc+IIa like

The gross appearance of villous patterns should be recorded as "Is-v like."

Note : The excavated type, III like, should be excluded from endoscopic resection.

2 Evaluation of Endoscopic Excision

Excision

- Complete
- Incomplete
- Indefinite

Specimens

- Complete
- Incomplete
- Not retrieved

B. Histological Criteria

1 Histological Findings

Location, size, and gross appearance of the lesion should be classified according to Clinical Criteria.

2 Histological Classification

Tumor diagnosis

- Adenoma
- Carcinoma
- Carcinoma in adenoma
- Carcinoma with adenomatous component
- Carcinoma without adenomatous component

Note : Histological type of adenoma and carcinoma should be recorded according to Histological Typing (Part II).

Tumor invasion

- Cut end/Cut margin
- Submucosa
- Lymph vessels and/or veins

Note 1: The cut end of the resected specimen should be anatomically divided into the mucosal one (m-ce) and submucosal one (sm-ce). A tumor-free margin of <0.5 mm in width from the cut end should be classified as positive.

Note 2: The depth of tumor invasion of the submucosa can be classified according to a reference depth, i.e. 200-300 μm depth from the muscularis mucosae. The words "greater depth" or "lesser depth" than the reference depth should be appended.

Note 3: The tumor invasion should be distinguished from pseudo-carcinomatous invasion.

C. Evaluation of Colorectal Endoscopy

cur A	Adenoma, intramucosal carcinoma, and "lesser depth," with complete resection confirmed histologically.
Positive m-ce	Endoscopic resection should be added.
Positive sm-ce	Intestinal resection should be added.
Negative sm-ce with "greater depth"	Intestinal resection with lymph node dissection should cautiously be made because of potential lymph node metastasis.

Note : Hitherto additional surgical resection with lymph node dissection after endoscopic resection has been made according to the following factors:

Distinct invasion of lymph vessels and/or veins

Poorly differentiated adenocarcinoma or undifferentiated carcinoma

Massive invasion of the submucosa

However, the most problematic factor is the third one in the routine examination of endoscopically resected specimens and from which level of invasion of the submucosa should be categorized as massive one comes to a matter of discussion. In this book, for the moment, the massive one corresponds to "greater depth" as described above.

Endoscopic Photographs

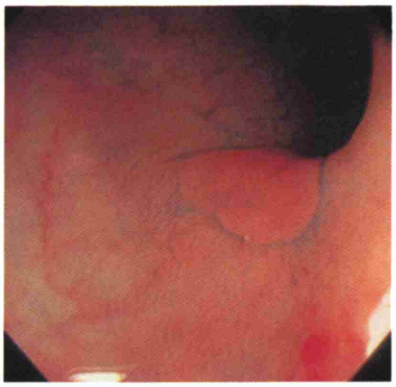


Fig. 1. IIa

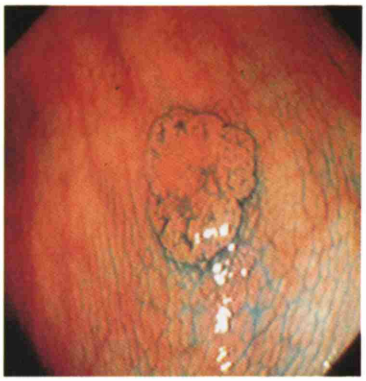


Fig. 2. IIa

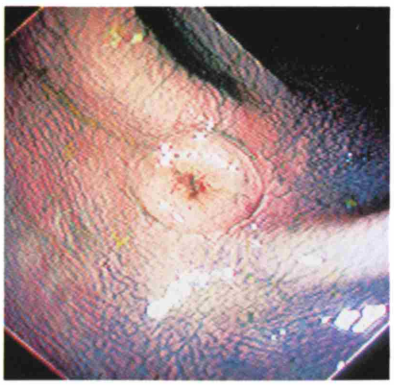


Fig. 3. IIa + IIc

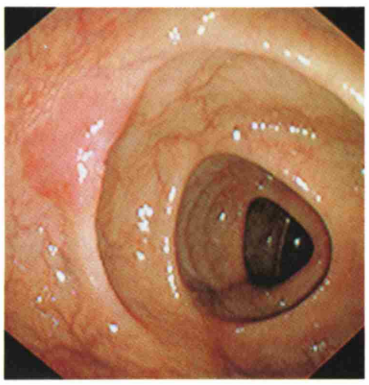


Fig. 4. IIb

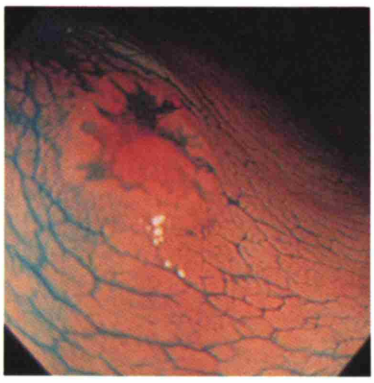


Fig. 5. IIc

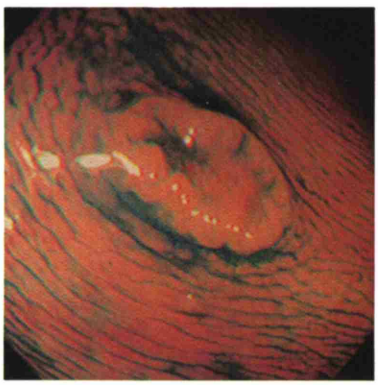


Fig. 6. IIc + IIa

Part IV

Response Assessment of Nonsurgical Treatments for Colorectal Carcinoma

A. Clinical Criteria

Foreword

The WHO criteria ("Reporting Results of Cancer Treatment" in the WHO Handbook, 1979) have been the standard for response assessment of cancer treatment. In 1986, the Japan Society for Cancer Therapy also established Criteria for Evaluation of the Effects of Solid Cancer Chemotherapy. In accordance with these criteria, the Japanese Research Society for Cancer of the Colon and Rectum has recommended application of the Response Assessment of Nonsurgical Treatments for Colorectal Carcinoma. Characteristics of the Response Assessment are as follows:

1. Nonsurgical treatments include radiotherapy, chemotherapy, immunotherapy, and thermotherapy; however, adjuvant chemotherapy is excluded from these treatments.
2. Diagnostic imaging of X-rays, endoscopy, ultrasound, CT, and MRI, as well as physical findings, can be applied to assess colorectal lesions.
3. Primary and metastatic lesions should be classified. Primary lesions can be classified into measurable lesions and evaluable but not measurable lesions.
   Measurable lesions can be measured bidimensionally (two directions) or unidimensionally (one direction or linear measurement).

1 Response Criteria for Primary Lesion

1.1 Measurable Lesion

Complete response (CR)

Complete disappearance on assessable examination, whose response continues for more than 4 weeks.

Partial response (PR)

i. For bidimensional measurements (e.g., A, B) with diagnostic imaging, the product (A x B) is more than 50% decrease in the tumor size. The response continues for more than 4 weeks. In addition there can be no appearance of new lesions or progression of any lesions.

ii. For unidimensional measurements with diagnostic imaging, the linear measurement is more than 30% decrease in the tumor size. The response continues for more than 4 weeks. In addition there can be no appearance of new lesions or progression of any lesions.

No change (NC)

The bidimensional product with diagnostic imaging is less than 50% decrease, or the linear measurement is less than 30% decrease in the tumor size. Furthermore, minimal enlargement of the tumor size is less than 25% in the bidimensional product or in the linear measurement. The response continues for more than 4 weeks. In addition there can be no appearance of new lesions or progression of any lesions.

The following responses can be subclassified as Minor Response (MR)

i. The bidimensional product with diagnostic imaging is more than 50% decrease, or the linear measurement is more than 30% decrease in the tumor size. However, the response continues for less than 4 weeks.
ii. The bidimensional product is more than 25% decrease but no more than 50% decrease. The response continues for more than 4 weeks.

Progressive diseases (PD)

The bidimensional product, or the linear measurement is more than 25% enlargement. The appearance of new lesion(s), or progression of any lesions can be found.

1.2 Evaluable but Not Measurable Lesion

Complete response (CR)

Complete disappearance on assessable examination, whose response continues for more than 4 weeks.

Partial response (PR)

Findings of assessable examination clearly differ from pretreatment findings, e.g., showing marked decreases, or significant regression. The responses continue for more than 4 weeks. In addition there can be no appearance of new lesions or progression of any lesions.

No change (NC)

Findings of assessable examination show no responses defined as "CR" or "PR," which continue for at least more than 4 weeks. In addition there can be no appearance of new lesions or progression of any lesions.

The following responses can be subclassified as Minor Response (MR)

i. Findings of assessable examination show "PR" responses, however, the responses continue for less than 4 weeks.

ii. Findings of assessable examination show slight regression and flattening of elevated or ulcerated lesions. The responses cannot be recognized as "PR" definition, however, they continue for more than 4 weeks.

Progressive disease (PD)

Findings of assessable examination show progression, or new-lesions appearance.

2 Response Criteria for Metastatic Lesion

2.1 Metastatic Lesion

These criteria closely meet the WHO criteria.

In various sites of lesions, priority should be given to appropriate diagnostic imaging for making assessments. Each method of assessment should be appended.

2.2 Carcinomatous Fluid

While neoplastic effusions or ascites should be recorded, volume changes cannot truly reflect alterations in tumor burden. Therefore, volume changes alone are not used to assess response.

Complete response of carcinomatous fluids

Effusion or ascites completely disappear, and washings or samples of any body fluids contain no carcinomatous cells. The findings continue for more than 4 weeks.

Partial response of carcinomatous fluids

The volume of effusion or ascites distinguishably decreases, and no increases; and washings or samples of any body fluids contain no carcinomatous cells. The findings continue for more than 4 weeks.

No response of carcinomatous fluids

Failure to meet the above criteria.

3 Determination of Overall Response in Lesion

The criteria meet the WHO criteria.

4 Rate of Response

"CR" and "PR," as defined according to the above, are the determinants of overall response.

Overall response should be calculated using the following ratios.

Overall response of eligible cases = "CR" cases + "PR" cases／A total number of eligible cases

Overall complete response of eligible cases = "CR" cases／A total number of eligible cases

5 Duration of Response

The following items should be recorded using dates.

A Date of initiation of treatment

B Date when tumor regression is first observed

C Date of observation documenting 50% regression

D Date of observation documenting complete disappearance of detectable neoplasm

E Date when new lesions are observed, or date of observable regrowth

Duration of response should be defined as follows:

Period of Complete Response (CR)	D – E
Period of Partial Response (PR)	C – E
Total period of Response	A – E

6 Extramural Review

Independent review of response and of its duration is recommended.

B. Histological Criteria

Principles

In nonsurgical treatments, various histological changes occur in the tumor tissue, not only at the cell level but also at the glandular structure or tissue level. To evaluate the therapeutic effects on tumors, it is important to determine the quantity of these changes, particularly of necrosis or disappearance of the tumor, in the whole lesion. The largest cross-sectional plane of the lesion should at least be explored, and it is recommended to compare its histological appearance with that of pretreatment biopsy specimens, by referring to the clinical findings. Furthermore, information about methods of treatment and periods from final administration to resection or autopsy should be attached, since such parameters may influence the histological findings.

Response assessment using biopsy specimens may be limited to a reference because of limitation of the material and heterogeneity of the changes.

1 Histological Changes

According to the amount of necrosis or disappearance of the tumor in the estimated total amount of the lesion, four major gradings, and two minor gradings for Grade 1, should be performed.

Grade 0 No change

Neither necrosis nor cellular or structural change can be seen throughout the lesion.

Grade 1 Mild change

1a Necrosis or disappearance of the tumor is present in less than 1/3 of the whole lesion, or only cellular or structural changes are visible in variable amounts.

1b Necrosis or disappearance of the tumor is present in less than 2/3 of the whole lesion.

Grade 2 Moderate change

Necrosis or disappearance of the tumor is present in more than 2/3 of the whole lesion, but viable tumor cells still remain.

Grade 3 Severe change

The whole lesion falls into necrosis and/or is replaced by fibrosis, with or without granulomatous changes. No viable tumor cells are observed.

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