Chapter 11
Colorectum: Mucosal Neoplasias

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11.1 Introduction

Most lesions (74%) detected on screening colonoscopy are *protruded-type polyps* (0-I), of which about a third are hyperplastic (non-neoplastic), and the remaining two thirds are neoplastic (i.e., adenomas or carcinomas). The other lesions (24%) are flat (0-II) or laterally spreading tumors (LSTs) [1]. The probability of detecting small and minute neoplasias is much higher for protruded lesions than for flat lesions [1–3], but 50% of colorectal carcinoma (CRC) originates from flat precursors [4].

The importance of flat- and depressed-type lesions, well known in Japan [2, 5], was first proven in Western patients in a prospective study of 1000 routine colonoscopies in Leeds, UK. Apart from 2.5% advanced carcinomas, a total of 327 neoplasias (including 6 early CRC) were detected with 62% polypoid, 36% flat (including 15% LST), and 1.2% depressed-type morphology. High-grade intraepithelial neoplasia (HGIN) or carcinomas were present in 8% of polypoid, 14% of flat, and 75% of depressed-type neoplasias [6]. Therefore, we must know the different lesions and their malignant potential.

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Furthermore, a recent meta-analysis has shown poor curative endoscopic resection rates outside East Asia, caused by frequent resection of deep submucosal (sm)-invasive early CRC [7]. For curative endoscopic resection, we must be able to distinguish superficial versus deep sm-invasive early CRC by gross morphology and magnifying endoscopic signs of surface and capillary structures.

11.2 Prevalence and Carcinoma Risk of Macroscopic Types of Colorectal Neoplasias

Prevalence of lesions and *risk of cancer* are shown for macroscopic types in Table 11.1a and for LSTs in Table 11.1b. The overall prevalence of these lesions compares well with the adenoma detection rate between 15% (women) and 25%

Table 11.1 (a) Prevalence and cancer risk of colonic mucosal neoplasms [2, 5, 6, 9, 10]

Superficial neoplastic lesion		Prevalence (%)	Cancer risk (%)	Recommended resection
Polypoid 0-Ip/Isp/Is		~15–20	1–15	Snaring
Elevated/flat 0-IIa/b		~5	4–6	EMR
Depressed 0-IIc		~0.5	30–75	→ En bloc

Table 11.1 (b) Prevalence and cancer risk of laterally spreading tumors [5, 9–13]

Superficial neoplastic lesion			Prevalence[a] (%)	Cancer risk[b] (%)	SMI risk[c] 95% CI	Recommended resection[d]
	% LST[c]					
LST-GH	35		~1.9	0.9	0.1–1.0	→ EMR
LST-GM	26		~1.4	40–45[b]	6–15	IEE → En bloc[d]
LST-NG	33		~1.8	20–29[b]	2–8	IEE → En bloc?
LST-NG-PD	5.5		~0.3	70–75[b]	20–43	→ En bloc[d]
All LST			5.4%[a]	37%[c]	8.5%[c]	

GH granular homogenous, *GM* granular, nodular-mixed, *HGD* high-grade dysplasia, *IEE* image-enhanced endoscopy, LST laterally spreading tumor, *NG* non-granular, flat-elevated, *NG-PD* non-granular, pseudo-depressed, *SMI* sm invasion

[a]Prevalence 5% and 5.84% in two CRC screenings [9, 10]; subtype prevalence = 0.054 × %LST

[b]Cancer risk according to Refs. [9, 12, 13]

[c]Data from recent meta-analysis (with unconvincing analysis for LST prevalence of 0.83%) [11]

[d]ESD for large size (>40 mm) LST-GM, for LST-NG, and LST-NG-PD according to [12]

(men), a *benchmark* for screening colonoscopy [8]. The prevalence of non-protruded neoplasias represents their predicted low detection rate—but it's important not to miss them, because of their considerable cancer risk.

11.3 Basic Structure of Colorectal Mucosa and Neoplasias

Colorectal mucosa shows (on standard WLI) smooth surface reflex (of mucin layer) and mildly reddish color with a branching (dendritic) submucosal vascular pattern of collecting venules (Fig. 11.1). Colonic mucosal glands are tubular structures, and the pit-like gland openings form a regular carpet of small round pits—normal *PP type I* [14] (Table 11.2b and Fig. 11.2). Inflammation causes edema and vascular erythema of the mucosal and sm layer, diminished surface reflex (by inhomogeneous mucin layer), and epithelial erosions or submucosal ulcers. Permeation of the dendritic sm vascular pattern is diminished or absent, but the surface shows normal round pits type I or, when chronic, regenerative hyperplasia with stellar pits type II (Fig. 11.2a, b).

Analysis of mucosal neoplasias uses magnifying NBI (M-NBI) and chromoendoscopy (M-CE) with indigo carmine or crystal violet. S. Kudo [14] had characterized on M-CE the surface structure of glands (*pit pattern, PP*) (Fig. 11.2), and Y. Sano [15] illustrated the alterations of capillary pattern (CP) in normal mucosa, hyperplastic and neoplastic mucosal lesions (Table 1.3). The Narrow-Band Imaging International Colorectal Endoscopic (NICE) Classification (Table 1.4) was developed to standardize optical diagnosis with non-magnifying NBI, according to color, vessels, and surface pattern. The NICE classification is a simple and accurate tool to differentiate hyperplastic and adenomatous polyps. However, it is difficult to differentiate HGIEN from submucosal invasive cancer. Therefore, the Japanese NBI Expert Team Classification (JNET) for M-NBI analysis was conceived to predict

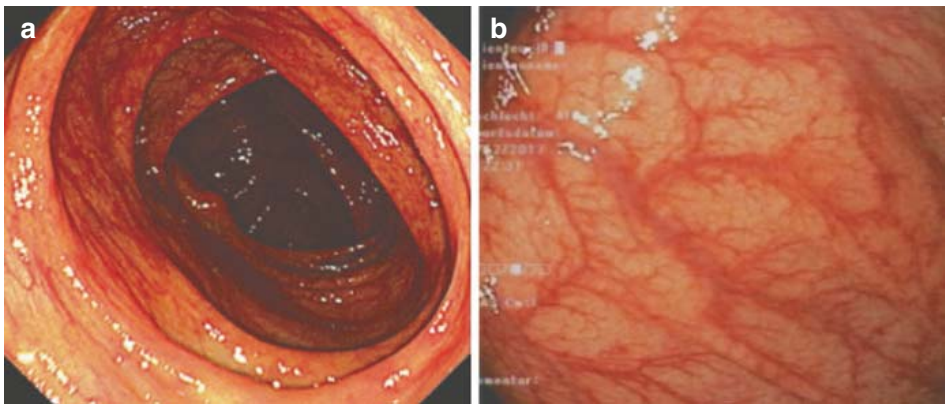
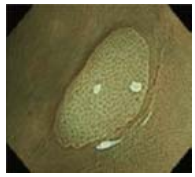
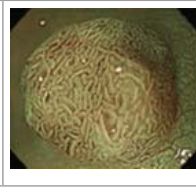


Fig. 11.1 (**a**) Normal ascending colon, WLI. (**b**) Normal ascending colonic mucosa, WLI

Table 11.2 (a) Magnifying NBI classification of colorectal neoplasias by Japan NBI Expert Team (JNET)

JNET	Type 1	Type 2A	Type 2B	Type 3
Vessel type	Invisible *1	Regular caliber Regular distribution (meshed/spiral) *2	Variable caliber Irregular distribution	Loose vessel areas Interruption of thick vessels
Surface type	Regular dark or white spots similar to normal mucosa	Regular (tubular/ branched/papillary)	Irregular or obscure	Amorphous areas
Likely histology	Hyperplastic polyp / SSA/P	LGIEN	HGIEN/Shallow sm- invasive cancer*3	Deep sm- invasive cancer
NBI				

Adapted from Sano [17], with permission of John Wiley and Sons
*1. If visible, the caliber in the lesion is similar to surrounding normal mucosa
*2. Micro-vessels are often distributed in a punctate pattern, and well-ordered reticular or spiral vessels may not be observed in depressed lesions
*3. Deep submucosal invasive cancer may be included
SSA/P sessile serrated adenoma/polyp

the T category of early neoplasias [16, 17] (Table 11.2a). JNET has renamed capillary pattern (CP I/II/IIIA/IIIB) to vessel pattern (V1/2A/2B/3). JNET classification includes vessel and surface pattern and consists of three types: In Type 1 lesions (hyperplastic polyp / SSA/P), the vessel pattern is barely visible (regular network) or invisible and the surface pattern is dark spots or white spots. Type 2 is subdivided into two subtypes: Type 2A lesions, indicating low-grade intraepithelial neoplasia (LGIEN), show regular vessel (caliber, distribution) and surface pattern. Type 2B lesions, indicating HGIEN or superficial submucosa (sm)-invasive cancer, show irregular vessel pattern, such as variable caliber and irregular distribution, and irregular or obscure surface pattern. Type 3 lesions show loose vessel areas, thick-caliber vessels, and amorphous surface, and suggest sm2–3 invasive cancer (specificity 85%) [17, 18].

NICE and *JNET* classifications belong to *minimal standard terminology (MST)* of the World Endoscopy Organization (WEO). However evaluated for sm-invasive cancer on still images, the NICE classification without any magnifying endoscopy yielded inadequate accuracy, and the JNET classification, without exact surface pattern (SP) on crystal violet M-CE, had only moderate accuracy [16, 18]. By contrast, combined vessel pattern (VP) and pit pattern (PP) classifications accurately discriminate mucosal *versus* sm-invasive cancer and educate for both SP and VP diagnosis [14, 15, 19–22]. Endoscopic diagnosis is then summarized as the JNET type. (Compare algorithm Fig. 11.10.)

Table 11.2 (b) Pit pattern type of colonic mucosa [14, 19]

	Type[a]	Description of pits	Histopathological correlates
	I	Round (uniform pits)	Normal or inflammatory mucosa
	II	Stellar or papillary	Hyperplastic mucosa (hyperplastic polyp or serrated adenoma)
	IIIs[b]	Small tubular, round	Adenoma or carcinoma (often depressed type)
	III_L	Large tubular or round	Adenoma (often classical polypoid adenoma)
	IV[a]	Branching or gyrus-like	Adenoma (often villous)
	V_I low-grade	Irregular pits with smooth margins	Adenoma (LGIN), early cancer (HGIN, T1 m, or T1 sml)
	V_I high-grade	Irregular, narrow pits with rough margins	sm-invasive cancer (80% ≥ sm2)
	V_N	Nonstructured	sm-invasive cancer (≥sm2)

[a]Patterns: normal (type I), hyperplastic or serrated (type II), neoplastic (types III–V)
[b]IIIs and V show amorphism (i.e., asymmetrical pits irregular in arrangement and sizes, in part destructed) and are highly predictive of malignancy. Type IIIs adenoma probably is the precursor lesion for flat and depressed superficial cancers and carries a high risk of minute mucosal cancer nests; type V areas (Vi high grade, V_N) indicate a high risk of submucosal invasion [5, 14, 19, 20]

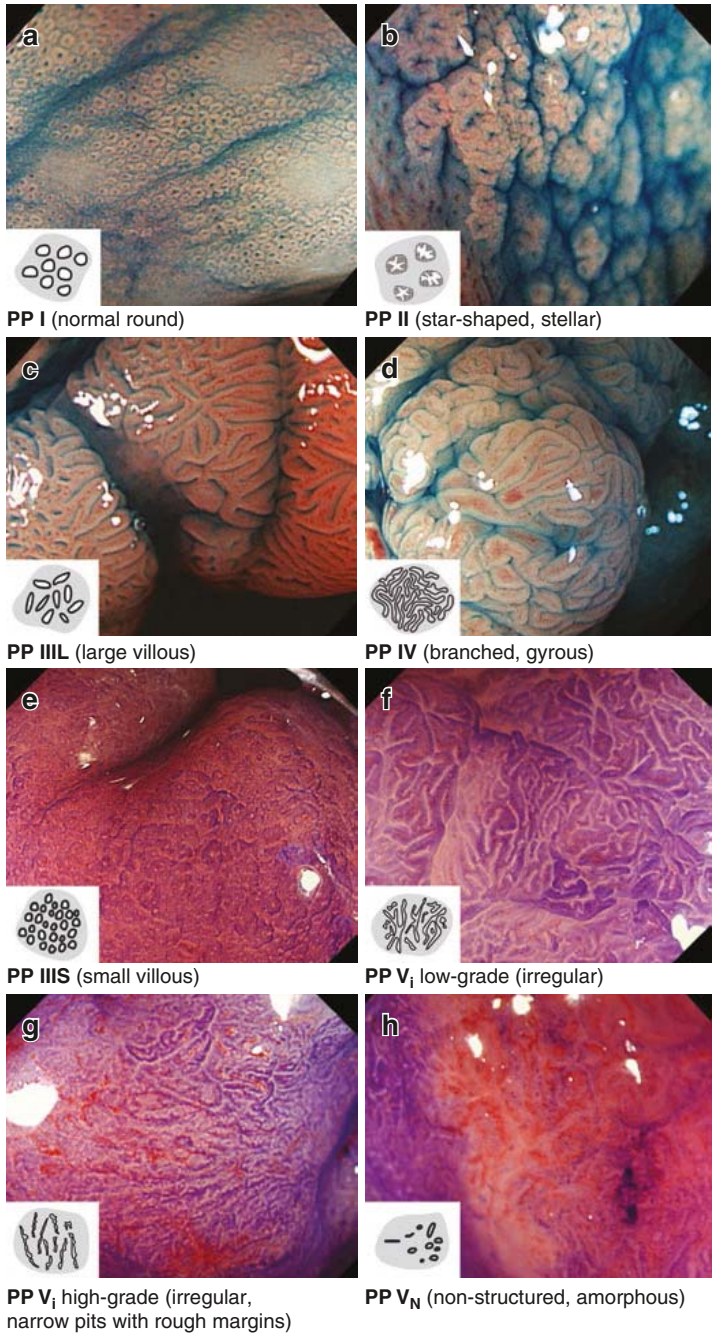


Fig. 11.2 Colonic pit pattern types I–V_N on magnified (~40–80-fold) chromoendoscopy ((**a**–**e**) indigo carmine; (**f**–**g**) crystal violet). (**a**) PP I (normal round). (**b**) PP II (star-shaped, stellar). (**c**) PP III_L (large villous). (**d**) PP IV (branched, gyrous). (**e**) PP IIIs (small villous). (**f**) PP V_I low-grade irregular. (**g**) PP V_I high-grade irregular (narrow pits with rough margins). (**h**) PP V_N (non-structured, amorphous). (According to Kudo [14, 19]). Compare Table 11.2a for explanation

11.4 Macroscopic Type and Appearance of Colorectal Lesions

11.4.1 Distinction of NICE Types on Standard WLI and CE

Mucosal neoplasias (adenoma, HGIN, adenocarcinoma) are lesions with clear *margins*, *disappearance* of *dendritic submucosal vessel pattern*, and the presence of *neoplastic pit patterns* (PP III–V) with indigo carmine CE or (in cases of serrated adenomas) variants of hyperplastic PP (Fig. 11.3). Delineation of the lateral margins of protruding or flat neoplasia is easy in normal colonic mucosa. A lack of clear margin in the presence of hyperplastic PP favors *hyperplastic* (non-neoplastic) *polyps* (*HP*), most of them in rectosigmoid colon as lesions 0-Is/Isp or 0-IIa (Fig. 11.4a, b). They must not be confused with serrated adenomas, which also exhibit hyperplastic PP, often in the right colon as lesions 0-Is or 0-IIa. (Compare Sect. 11.4.2, below). In addition, several similar protruding lesions (0-Isp, 0-Is, 0-IIa) present normal mucosal surface and submucosal vascular pattern, such as submucosal tumor (*SMT*), rare *hamartoma* (Peutz-Jeghers polyp, juvenile polyp), or *inverted diverticulum*, which is soft and pliable. Reddish or isochrome polypoid or sessile lesions with normal or hyperplastic surface pattern are typical of *inflammatory pseudopolyps* in ulcerative colitis or Crohn's disease (Fig. 11.4c, d), and rarely typical of sm-infiltrating lymphoma or secondary carcinoma originating from other sites or organs (peritoneum, ovary, metastatic cancer).

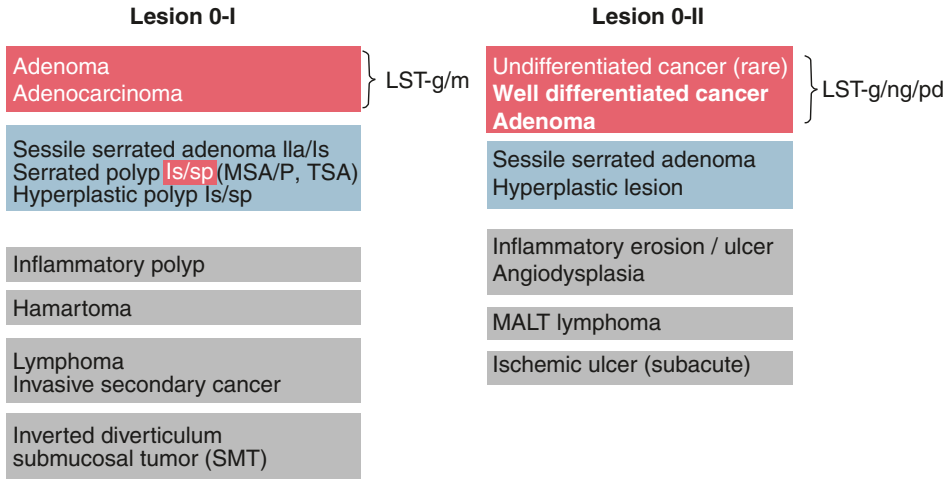


Fig. 11.3 Differential diagnosis of colorectal lesions according to pit pattern on *indigo carmine CE*: neoplastic (*red*), hyperplastic/serrated (*blue*), and normal pit pattern (*grey*). Mucosal neoplasias (adenomatous, serrated, and cancerous) exhibit distinct *sharp margins* on indigo carmine CE or magnifying NBI, in contrast to hyperplastic or inflammatory lesions or diffuse submucosa-infiltrative neoplasias. MSA/P—mixed serrated adenoma/polyp; TSA—traditional serrated adenoma

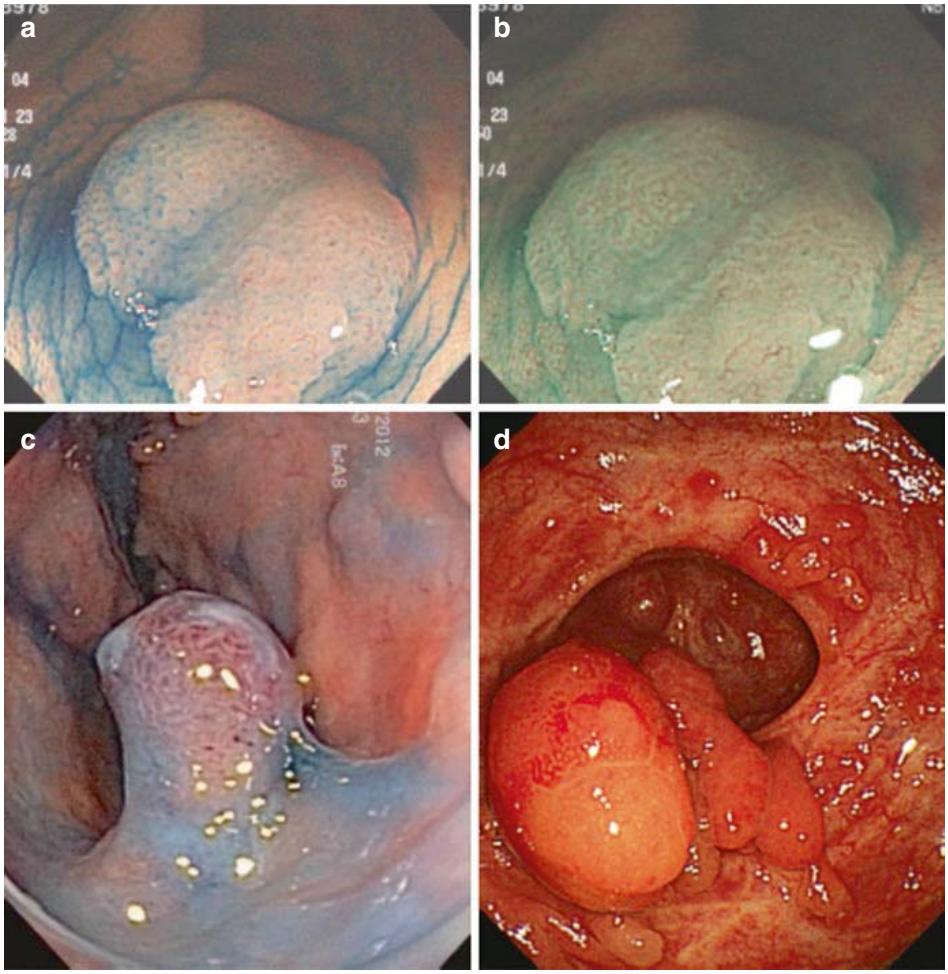


Fig. 11.4 (**a**, **b**) *Sessile hyperplastic polyp*, PP II (stellar) = SP 1 in cecum. (**a**) Indigo carmine CE. (**b**) VP 1 (faint mesh) in cecum, JNET type 1, M-NBI (40×). (**c**) *Nonneoplastic 0-Ip* (chronic inflammatory-regenerative lesion in moderately active ulcerative colitis, PP II), sigmoid colon indigo carmine CE. (**d**) *Nonneoplastic 0-Isp and 0-Is lesion* with unclear margin, in part visible VP 1, PP II (inflammatory-regenerative, moderately active Crohn's disease), sigmoid colon, JNET type 1, WLI

Flat or depressed lesions (*0-IIa–c*, often reddish) with key neoplastic signs (clear margins, neoplastic PP, and disappearance of dendritic sm vascular pattern) are *mucosal neoplasias*. Reddish hyperemic lesions with uncertain margins comprise inflammatory mucosal lesions, such as erosions and inflammatory ulcer (Fig. 11.5), ischemic ulcer, or angiodysplasia. Pale, flat lesions with nearly *normal PP* are typical for mucosal *MALT lymphoma* or subacute *ischemic ulcerations* that show pale or mildly red lesions, but they differ by having a bare proper muscle layer in the center surrounded by a margin of regular mucosa (lack of neoplastic PP) (Fig. 11.6). Pale, flat lesions with the disappearance of the sm vascular pattern and some unclear

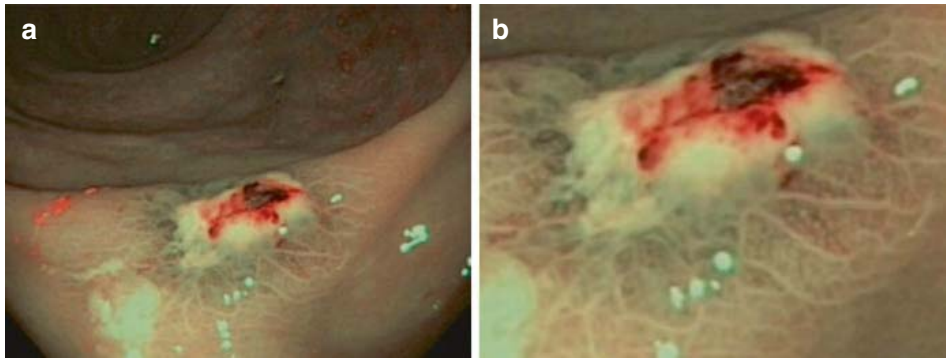


Fig. 11.5 (**a**) Solitary rectal ulcer in an 82-year-old man, on standard NBI. (**b**) VP type 1 (meshed), PP type I, and uncertain margin of fibrin covered ulcer, standard NBI

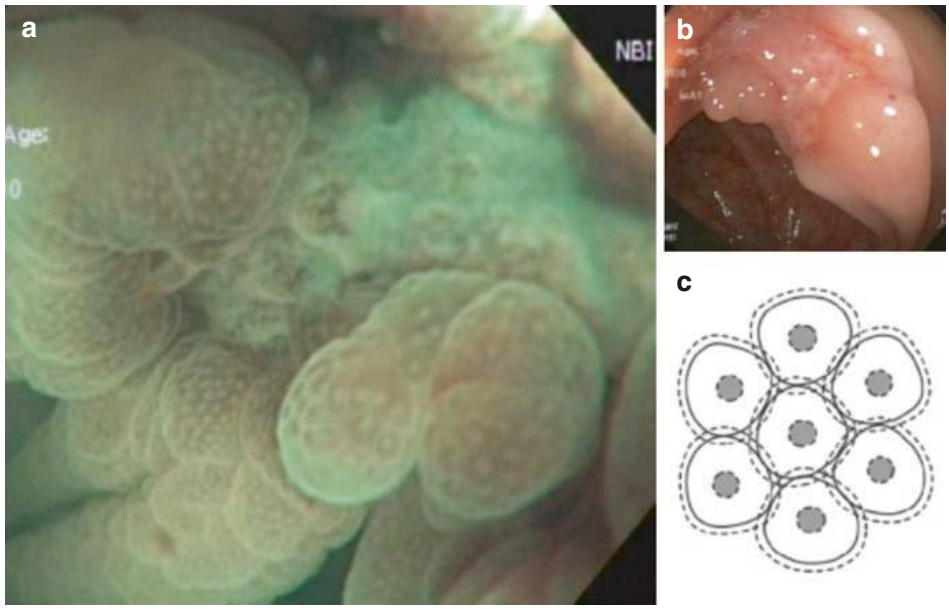


Fig. 11.6 Lesion type 0-III. One of the two ulcers on neighboring haustral folds in the left transverse colon in an 80-year-old woman. (**a**) Typical *subacute ischemic ulcer* with bare ground (proper muscle) and mucosal margins showing normal VP (meshed) and PP I. (**b**) Standard WLI aspect. **(c)** Schema of PP I and VP 1

margins are also compatible with *LST-NG*, but that shows *clear margins* on magnifying NBI.

Flat and *depressed neoplasias* including *LST-NG* and most *LST-granular* types, including *LST-GH*, *LST-GM*, and *LST-G-whole nodular,* show discolored, often pale, areas with clear margins and disappearance of normal sm vascular pattern (Fig. 11.7a–j). They are further distinguished in *classic adenoma*, *serrated adenomas, HNPCC-associated adenoma*, and *HGIN/intramucosal carcinoma* (*See* Sect. 11.5).

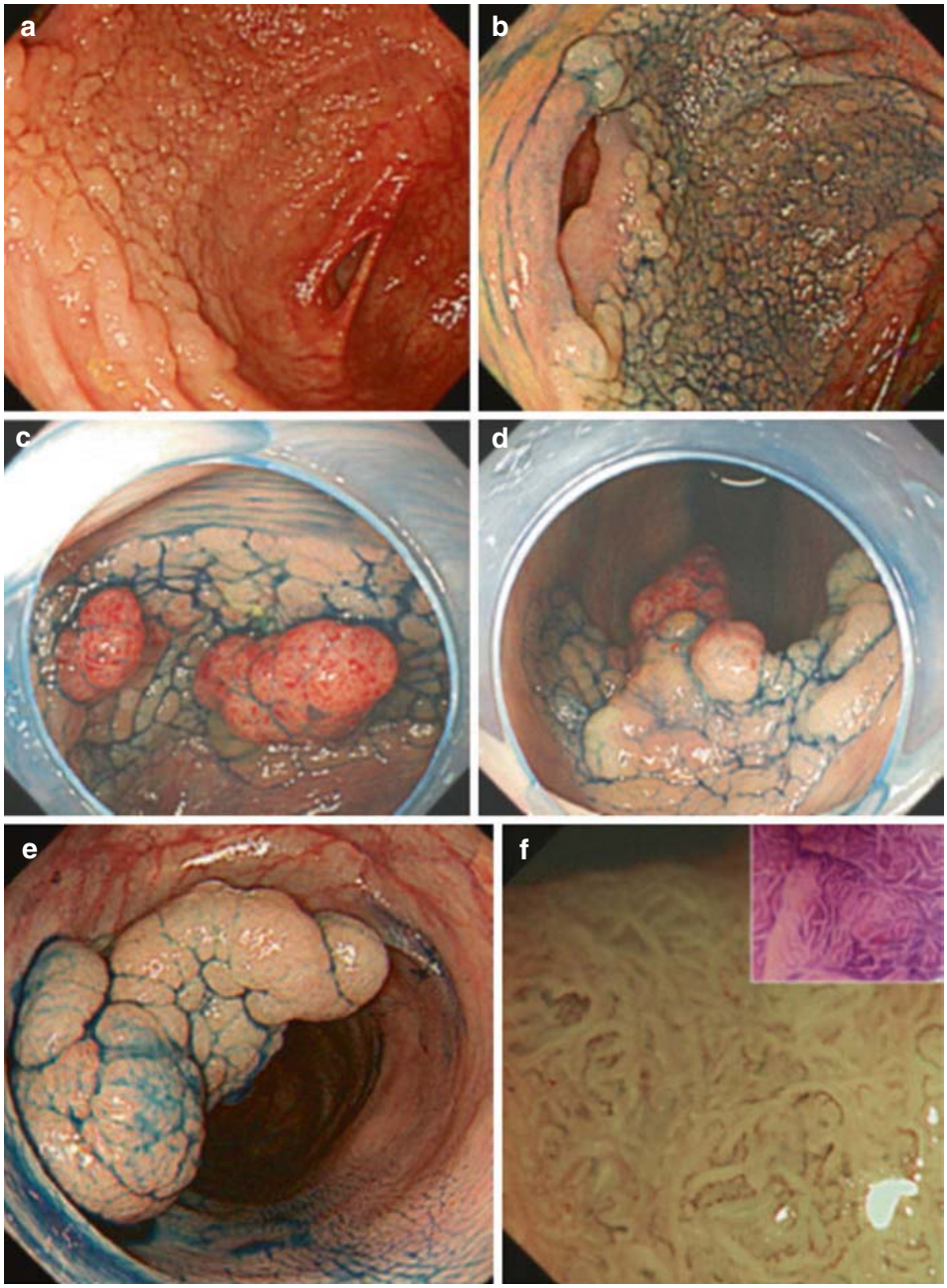


Fig. 11.7 *LST-G*. (**a**, **b**) LST-G granular homogenous type, cecum. (**a**) WLI; (**b**) indigo carmine CE. (**c**, **d**) Rectal LST-GM, granular mixed nodular type, indigo carmine CE, (**c**) prograde view; (**d**) retroflex view. (**e**) LST-G whole nodular. 0-Is + IIa, 30 mm in diameter, transverse colon, indigo carmine CE. (**f**) Same LST-GM as in (**e**) on M-NBI (80×): VP 2B (*insert* with crystal violet CE: PP type $V_{I\ low\ grade}$), *JNET type 2B*. ESD: tubular adenocarcinoma T1a (LPM)

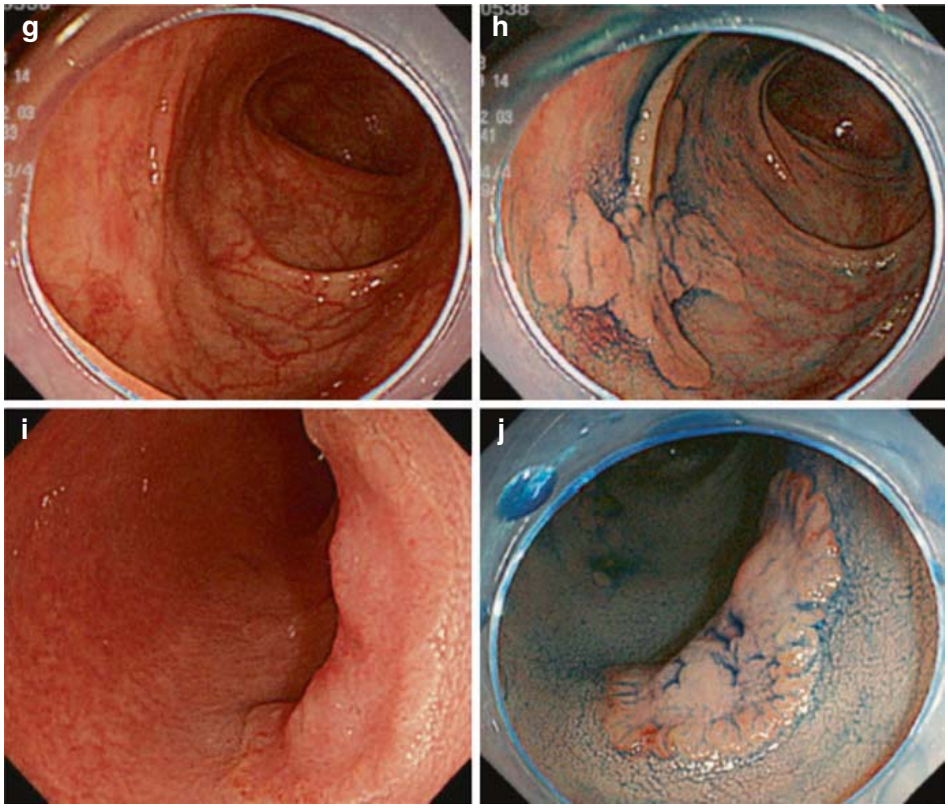


Fig. 11.7 (continued) ESD: tubular adenocarcinoma T1a (LPM) (**g**, **h**) LST-NG flat (0-IIa); WLI and indigo carmine; (**i**, **j**) LST-NGPD (0-IIa + IIc, central protrusion), WLI and indigo carmine CE

Early cancer with invasion into sml often presents mild (0-IIc) or marked (IIc + IIa) surface depression (Fig. 1.2). Depressed neoplasias type 0-IIc display *air-induced deformation* (*AID*) when infiltrating only muscularis mucosae (MM) or superficial sml submucosa layer. (*Compare* Fig. 11.14.)

Most *LST-NG* show normal color and *relatively ill-defined margins*; therefore, only larger LST-NG lesions are easily apparent on WLI endoscopy. LST-NG may be overlooked, unless you pay alert attention to convergent folds, loss of glossy surface reflex, and especially disappearance of dendritic sm vessel pattern. Indigo carmine CE demonstrates the distinct margins of the lesion (Fig. 11.7h, j). Prevalence of LST is highest in the right colon and the rectum. Risk of focal cancer in different LST types [13] is detailed in Table 11.3. The probability of *malignant transformation of LST* increases with *size* of the lesion, especially when >30 mm, and *type*, being high in *LST-GM* and *LST-NG*, and highest in pseudo-depressed *LST-NGPD* (Fig. 11.7i, j). Retrospective analysis (period 1998–2006) of LSTs ≥20 mm in size resected at the National Cancer Center, Tokyo, confirmed sm-invasive cancer in 0.9% of LST-GH, 16% of LST-GM, 23% of LST-NG, and 58% of LST-NGPD, but only in 5% of small size (d < 20 mm) LST-GM or LST-NG [12]. Hence, the NCC

Table 11.3 Characteristics of LST and Lesion 0-IIc (and IIa + c) treated with ESD [13]

		Mean		Percentage of lesion type			
	Lesion	*n*	Size (mm)	Adenoma (%)	T1a[b] (%)	Ca sml (%)	Ca ≥sm2[a] (%)
	LST-G(H)	57	32	58	42	0	0
	LST-G(M)	86	39	40	42	14	5
	LST-NG(F)	77	22	60	30	7	3
	LST-NG(PD)	25	20	28	24	44	4
	IIc and IIa + IIc	6	17	0	33	0	67[c]

[a]All lesions were chosen suitable for ESD (leading to selection bias, because LST with endoscopic criteria of massively sm-invasive cancer had a priori been excluded). Note the high percentage of HGIN/mucosal cancer in larger LST
[b]Intramucosal HGIN/cancer only, no sm-invasive cancer
[c]4 of 6 cases

and JGES guidelines recommend resection en bloc for LST-NG of size ≥20 mm, LST-GM ≥40 mm, and LST-NGPD [12, 23].

11.4.2 Distinction of NICE Type 2 (Adenomatous) Versus *Type 1 (Serrated) Lesions*

Serrated lesions (SL) presumably give rise to 15% of all colorectal carcinomas (CRC) and 25–30% of proximal CRC; they lately have raised endoscopic and histologic attention [24]. The four subtypes of SL exhibit a wide range of CRC potential (see Table 2.6):

- Hyperplastic polyps (HP), nearly none (considered non-neoplastic)
- Serrated sessile adenoma/polyps without dysplasia (SSA/P), moderate CRC potential (13% in 7 years)
- SSA/P with dysplasia (i.e. mixed serrated adenoma, MSA) and traditional serrated adenoma (TSA), high CRC potential (approximately 50% in 5 years) [24].

Serrated adenomas are located predominantly in the rectosigmoid (especially types Ip and Isp, TSA) and in the right colon (especially types 0-II, SSA/P and MSA). On *non-magnifying* NBI, the WASP classification (Workgroup serrAted polypS and Polyposis) accurately (87%) distinguished *type 2 lesions* (brown color, brown vessels, and branched or tubular SP) from *type 1 lesions* (SSA/P, MSA) using two positives of four discriminators (clouded surface [=mucus], vague border,

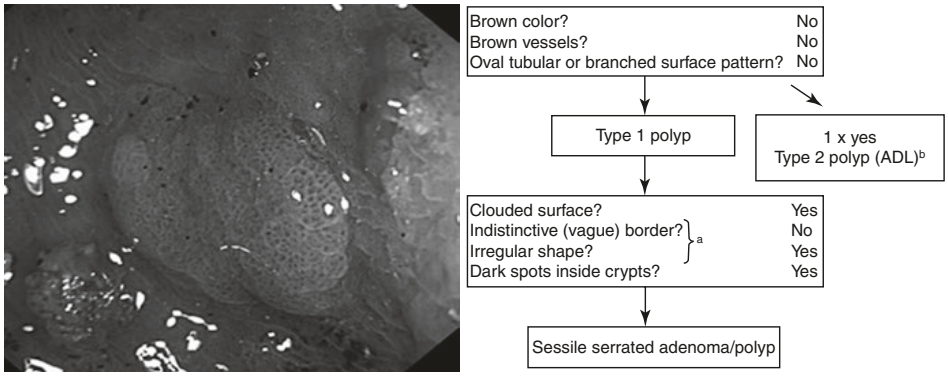


Fig. 11.8 Representative: NBI image of sessile serrated adenoma/polyp (SSA/P) with decision pathway for WASP classification. [a]Indistinct border, irregular shape: Criterion was derived from standard WLI/NBI still images (non-magnified, non-CE), and is not maintained when using magnifying indigo carmine CE or magnifying NBI. [b]ADL—adenomatous/cancerous lesion. (From Ijspeert et al. [26], with permission of John Wiley and Sons Inc)

irregular shape, dark spots inside crypts) (Fig. 11.8) [25, 26]. However, two discriminators, indistinct margins and irregular shape, no longer hold true when using M-NBI or indigo carmine CE. Based on the WASP classification, large European cohorts on screening colonoscopy yielded a prevalence of 30% for HP, 3–8% for SSA/P, less than 1% each for MSA and TSA, and 0.5% for serrated polyposis syndrome (SPS) [27] (*see* Table 2.6). Accurate distinction among NICE type 1 lesions would provide cost-saving policies for HP ("resect and discard" and "resect or leave in") and select serrated neoplasias for endoscopic resection. (*See* Sect. 11.5.3.)

11.5 Differential Diagnosis of Lesions on Magnifying Endoscopy

The basic strategy to analyze VP with M-NBI and then PP with M-CE allows accurate endoscopic differential diagnosis to predict histologic type and tumor category of early neoplasias [19].

Note *Magnified NBI (≥60×)* and often *crystal violet M-CE* is required to accurately (>90%) differentiate with VP (CP) and SP (PP) [5, 16, 19–22]:

- Adenoma *versus* carcinoma
- Intramucosal *versus* submucosal deeply invasive carcinoma
- Hyperplastic lesion *versus* adenoma and serrated neoplasias (The latter distinction is less accurate; *see* Sect. 11.5.3.)

11.5.1 Differential Diagnosis of JNET Type 2 Lesions (Adenoma/Superficial Adenocarcinoma)

Classic adenomas consist of transformed colonocytes with enhanced nucleus/cytoplasm ratio, loss of polar orientation of cell nuclei, enhanced clonal proliferation of colonocytes, and formation of regular pseudoglandular structures *without* goblet cells. By definition, adenomas lack invasive or metastatic potential, and the process of cell-cell adhesion is preserved. Therefore, the lesion forms single-layered, glandular marginal epithelium, seen as *surface pattern* (*SP*) using NBI and CE with magnification (Fig. 11.2). The enhanced proliferation of pseudoglandular structures creates patterns of different surface shapes visualized as *PP* type *III*L or *IV,* rarely *IIIs* or *Virregular* (Fig. 11.2c–f), and regular, dense vessel pattern (VP) *2A, lesion JNET type 2A* (Figs. 11.9 and 11.12b, c). The margin of adenoma is

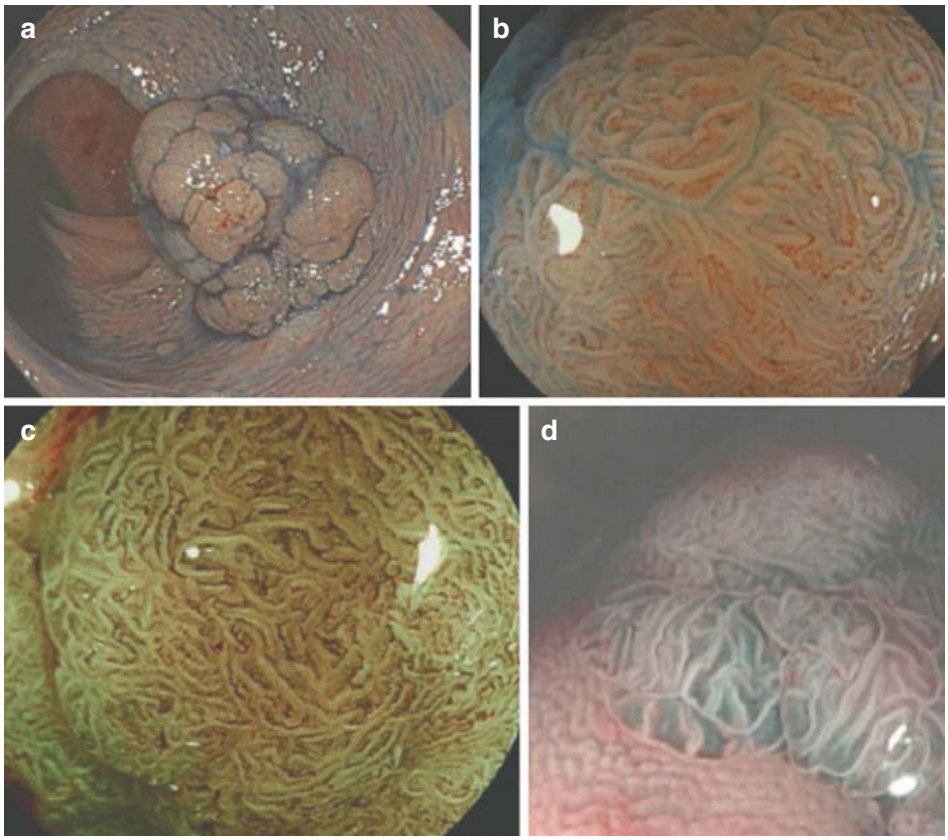


Fig. 11.9 (**a**–**d**) *Protruding neoplasia 0-Isp*, 25 mm in diameter. (**a**) WLI indigo carmine CE. (**b**) With magnification. (**c**) M-NBI (80-fold): JNET type 2A (VP 2A, PP IV). Histology: *tubulovillous adenoma* with focal HGIN. (**d**) *Protruding adenoma 0-Isp*, 15 mm in size, clear margin without demarcation of relief, JNET type 2A with even surface marginal crypt epithelium (PP IIIL, VP 2A); M-NBI 60-fold). EMR *tubular adenoma* with LGIN

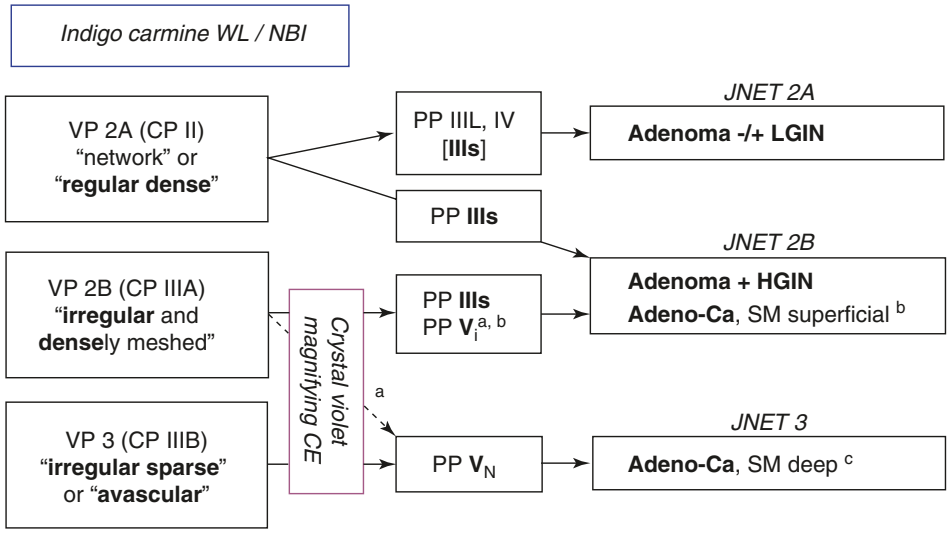


Fig. 11.10 *Analysis of colorectal adenomatous/cancerous lesions* with magnifying NBI/CE, to distinguish malignancy and grade of invasiveness by vessel *VP* and pit pattern *PP* [19], for JNET types 2 and 3. [a] PP type V_I high grade with encroachment of margins signals deep sm invasion. [b] Superficial sm invasion <1000 µm. [c] Deep sm invasion ≥1000 µm

clearly visible on WLI (and M-NBI) by change of SP type, but without encroachment of surface relief (Fig. 11.9d, *compare* Fig. 1.6). The regular epithelial structure of adenomas is well visualized as evenly marginal epithelium (MCE) on M-NBI. The basic diagnostic strategy is very accurate (>90%) [14, 19, 22, 28]; see the algorithm in Fig. 11.10.

Flat HNPCC neoplasias in hereditary nonpolyposis colorectal cancer syndrome (Fig. 11.11a–c) show distinctive 0-IIa/b/c type lesions, mainly *pale* with *clear margins* after indigo carmine enhancement or on magnifying NBI. The overall number of lesions in the colon is *not* significantly increased in HNPCC as compared with sporadic adenoma carriers, but *flat adenomas with pale components* (70–80% mucinous villous) and *CRC* occur at an earlier age (mean 35–40 years) and predominantly (~70%) in the *right hemicolon* [29]. A high proportion (40–80%) contains *HGIN* or *carcinoma*, mainly with mucinous differentiation [29–31]. M-NBI shows VP 2A or 2B and PP IIIL, IV, or V_I/V_N. Indigo carmine-CE is recommended for HNPCC surveillance improving detection rate (0.3 → 0.7 lesions per patient).

Key Points

Adenoma (JNET type 2A) shows typical findings on WLI and indigo carmine:

- Disappearance of submucosal vascular pattern
- Clear lateral margins of the lesion (without encroachment)
- Reddish color, with lobulation on the lesion surface
- Regular pit pattern, tubular (IIIL, sometimes IIIs) or branched (IV)
- Even distension of flat-type adenomas on insufflation/desufflation

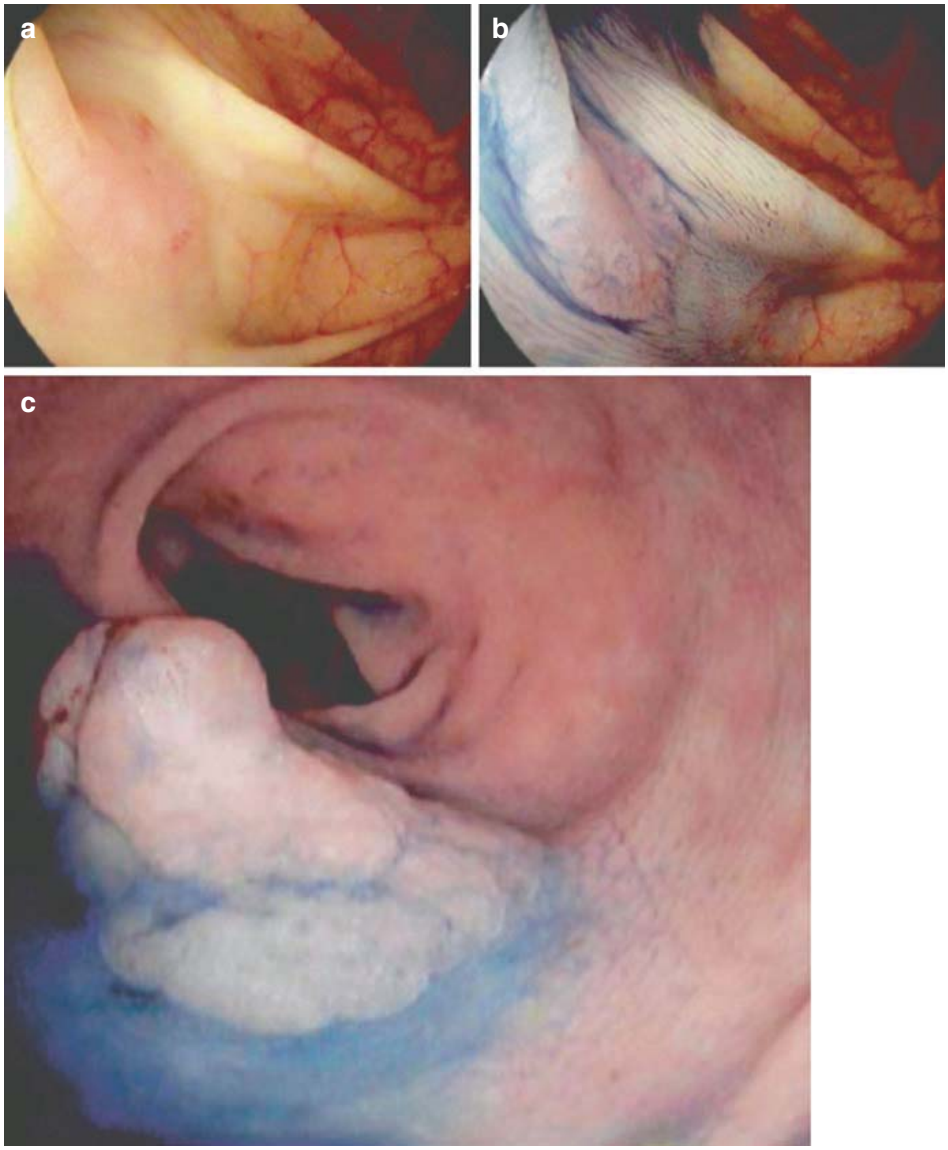


Fig. 11.11 (**a**) LST-NG (0-IIa) isochrome, ascending colon, in a 41-year-old man with HNPCC (*MLH-1* mutation). (**b**) Indigo carmine shows enhanced margins of the neoplasia. (**c**) LST-GM (0-Is + IIa), isochrome, 15 mm, in a 32-year-old woman with HNPCC (*MLH-1* negative), detected at surveillance 24 months after negative colonoscopy, with indigo carmine. (Pan-)chromoendoscopy enhances detection of flat neoplasias in HNPCC. (From Rondagh et al. [29], with permission of Thieme)

Typical structural findings on magnifying NBI:

- Even surface pattern (even white zone = marginal crypt epithelium)
- Regular network vessel pattern (VP 2A)

Differentiated adenocarcinoma (G1, G2) exhibits irregularities in thickness and shape of cancerous marginal crypt cell layers (*irregular SP*) and irregular pseudogland structure (irregular pit pattern *PP type* V_I or V_N on crystal violet M-CE) (Figs. 11.2f–h and 11.7f, Sect. 11.8, case no. 1). Absorptive staining of epithelial cells with *crystal violet* best demonstrates irregular or destroyed pseudoglandular structure (*PP* V_I *or* V_N) (Fig. 11.2f–h). Coherently growing cancer cell clusters exhibit sharp margins with a "*demarcation line*" and *encroachment of surface relief* towards surrounding adenomatous or normal epithelium. Angiogenesis creates an irregular, dense vessel pattern *VP 2B* [16, 17, 19] (Figs. 11.7f and 11.12c).

Undifferentiated carcinoma (G3) is rare (<5%) in the colorectum, and its endoscopic distinction from differentiated cancer is not yet evidence-based.

Key Points
Hallmarks of *superficial differentiated adenocarcinoma* (G1 or G2), *JNET type 2B*:

- Irregular SP (uneven thickness of cancerous epithelium)
- Irregular pit pattern PP III_S or PP V_I
- Irregular vessels VP 2B
- Demarcation of relief (DL and encroachment) at lateral margin towards adenoma/mucosa
- Air-induced deformation (AID) of type 0-II cancer (Fig.11.14a–c).

11.5.2 *Diagnosis of Superficial AC* Versus *Deep sm-Invasive AC (JNET Type 2B* Versus *Type 3)*

The estimated *vertical depth of invasion* guides the decision for or against endoscopic resection of early cancer. Other risk factors for lymph node metastasis, such as lymphovascular invasion and tumor cell budding, are not predictable from endoscopic signs; targeted biopsy is necessary to exclude poorly differentiated CRC G3 (prevalence <5% in CRC).

Protruded-type early colon cancer is highly suspicious for *sm2–3 invasion* in the presence of a small, thick pedicle (*fullness of stalk*), a small nodule on polypoid neoplasia (*Buddha sign*), or an expansive nodule with *loss of lobulation* (Fig. 11.13b). Further evidence is friability, central depression with PP V_N or ulcer-

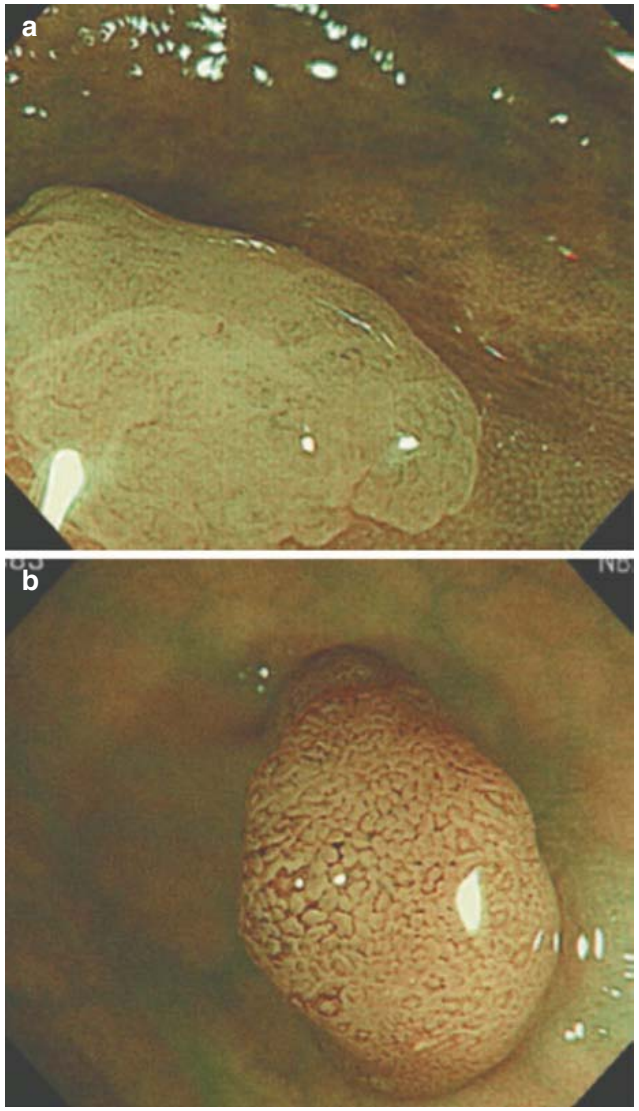


Fig. 11.12 Vessel pattern (VP) types (m-NBI, 100×). (**a**) *VP 1* meshed is faintly visible (−) in hyperplastic lesion 0-IIa *JNET type 1* (with PP type II), as compared with VP type 1 (+), visible in adjacent normal mucosa (*right side*). (**b**) *VP 2A*, regularly meshed, in lesion 0-Is *JNET type 2A* is typical for adenoma (probable PP IIIL)

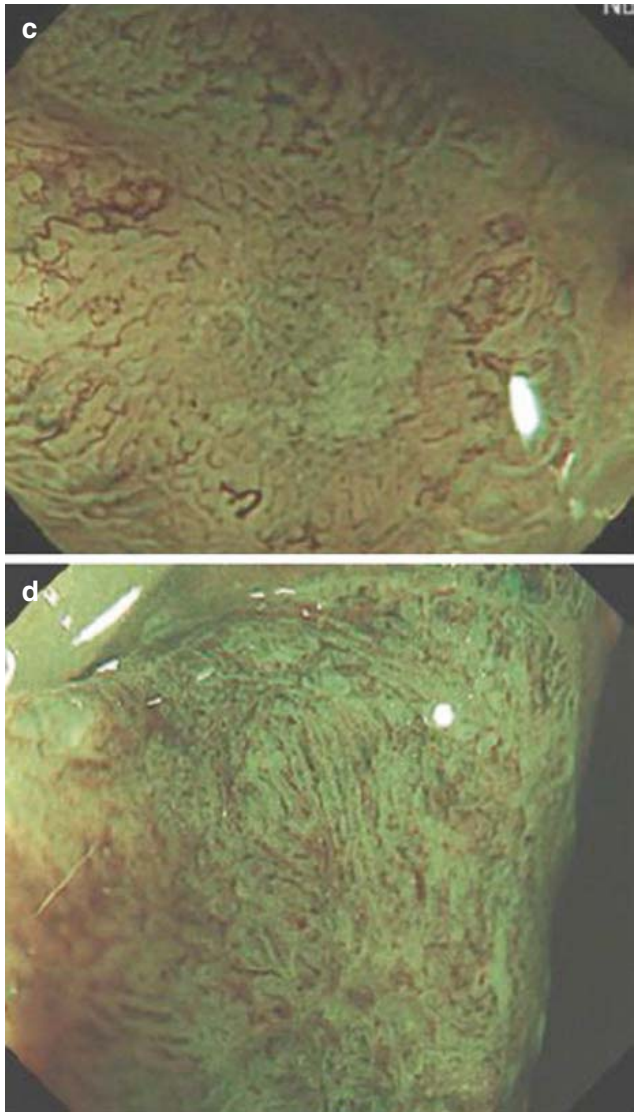


Fig. 11.12 (continued) (**c**) *VP 2B*, irregularly meshed, *dense* vessel pattern, in flat lesion compatible with adenoma and HGIN or intramucosal (or superficially sm-invasive) differentiated cancer. Crystal violet CE is recommended for evaluation of pit pattern, probably lesion JNET type 2B. (**d**) *VP 3*, loosely irregular, and in part *sparse* vessels suggesting sm-invasive early cancer (≥sm2). Crystal violet CE is required to categorize the corresponding pit pattern type V (e.g., high-grade irregular or nonstructured) and diagnose lesion JNET type 3

ation, or fixed deformation of protruding neoplasia upon insufflation/desufflation (Figs. 1.2b, 11.13, and 11.14d–f). *Deep sm-invasive cancer* destroys (at least in part) pseudogland structure and microcapillaries and causes a destructive, amorphous pit pattern (*PP* V_I *high grade*, V_N) and irregular, sparse vessels *VP 3* with varying thick caliber (Figs. 11.2g–h and 11.12d). Typical images are shown in Figs. 11.14e, f and 11.15f.

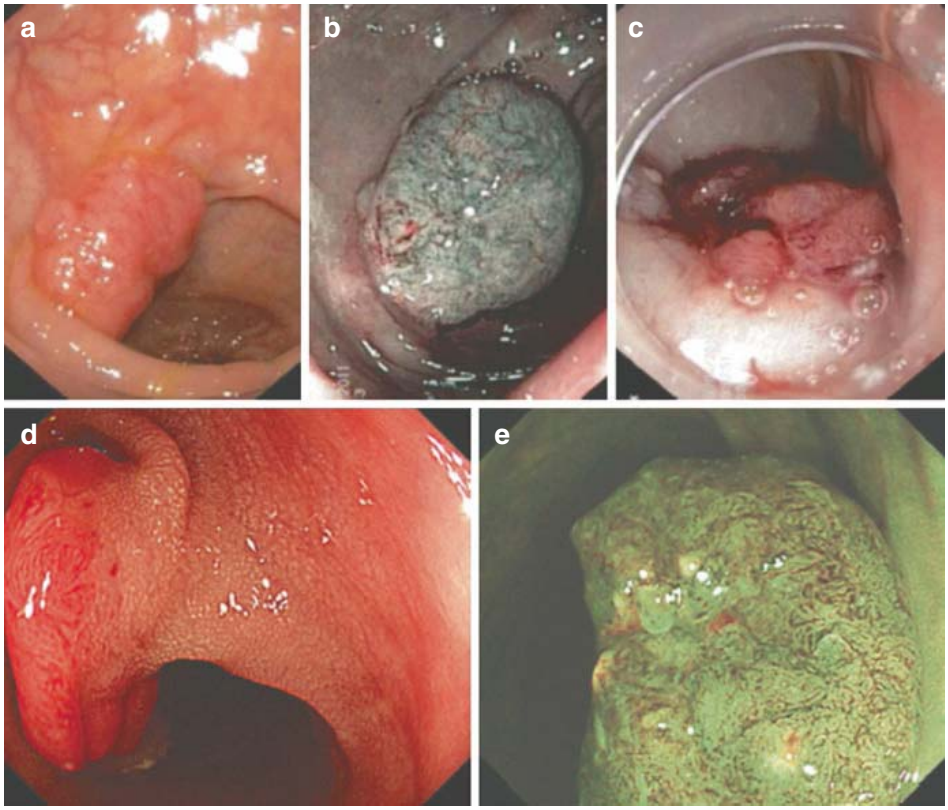


Fig. 11.13 (**a**, **b**) *Nodular neoplasia type 0-Is* with aboral pseudodepression (0-Is + c), friability, and VP 3. (**c**) *Complete non-lifting* on sm injection (3 × 5 mL) in descending colon. Laparoscopic resection disclosed tubulovillous adenoma and f*ocal adenocarcinoma G2, sm3*. (**d**, **e**) *Polypoid lesion type 0-Ip* in sigmoid colon. **(d)** Short pedestal with "fullness of stalk" (WLI), and **(e)** VP type 3 and PP type Vi high grade (M-NBI). Histology: well-differentiated *adenocarcinoma (G2)*, *sm2*, and lymphovascular invasion (−)

Key Points

Deep submucosal invasion sm ≥ 2 of early CRC 0-IIa may be diagnosed from various findings [5, 16, 20–22, 28, 32, 33]:

- Expansive nodule with *loss of lobulation* in LST-GM
- Central depression or ulcer with PP V_N
- Expansive protrusion or nodule in depression 0-IIc
- *Fixed deformity* of CRC lesion (e.g., constant swollen convergence of folds −/+fusion) (Fig. 11.14d, e).

Typical signs are shown in Figs. 11.13, 11.14, 11.15 and 11.16e, f.

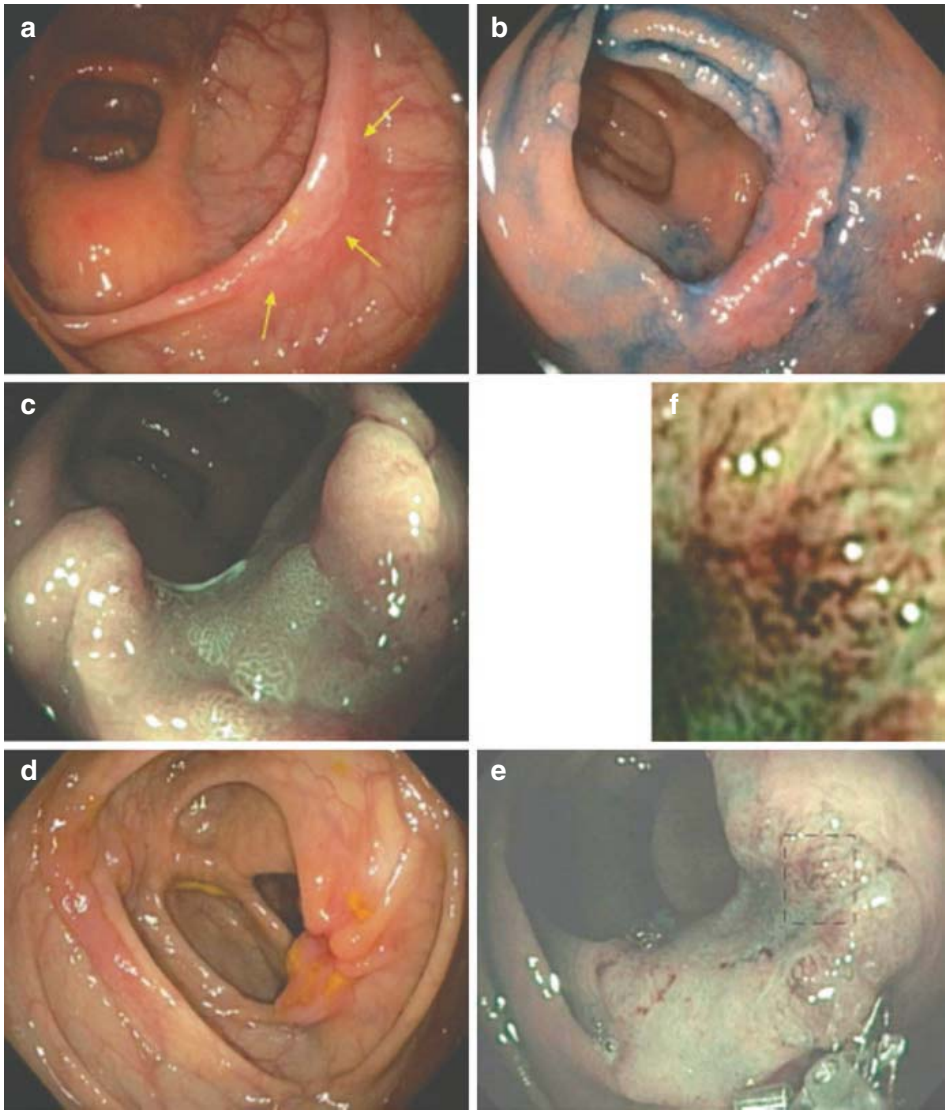


Fig. 11.14 (**a–c**) LST NGPD (0-IIa + c) in ascending colon with *marked air-induced deformation (AID)*: (**a**) Insufflation with adherent mucus; *yellow arrows* mark the margin of the lesion. (**b**) Indigo carmine. (**c**) Desufflation (cleaned). (**d**, **e**) Neoplasia 0-IIc + IIa with *fixed shape* and folds during insufflation/desufflation, transverse colon, WLI. (**f**) VP 3, lesion JNET type 3, NBI 80×. Hemicolectomy: adenocarcinoma G2 (mucoid differentiated), pT1b (sm3), Ly0, V0, N0 (0/9), and sm fibrosis

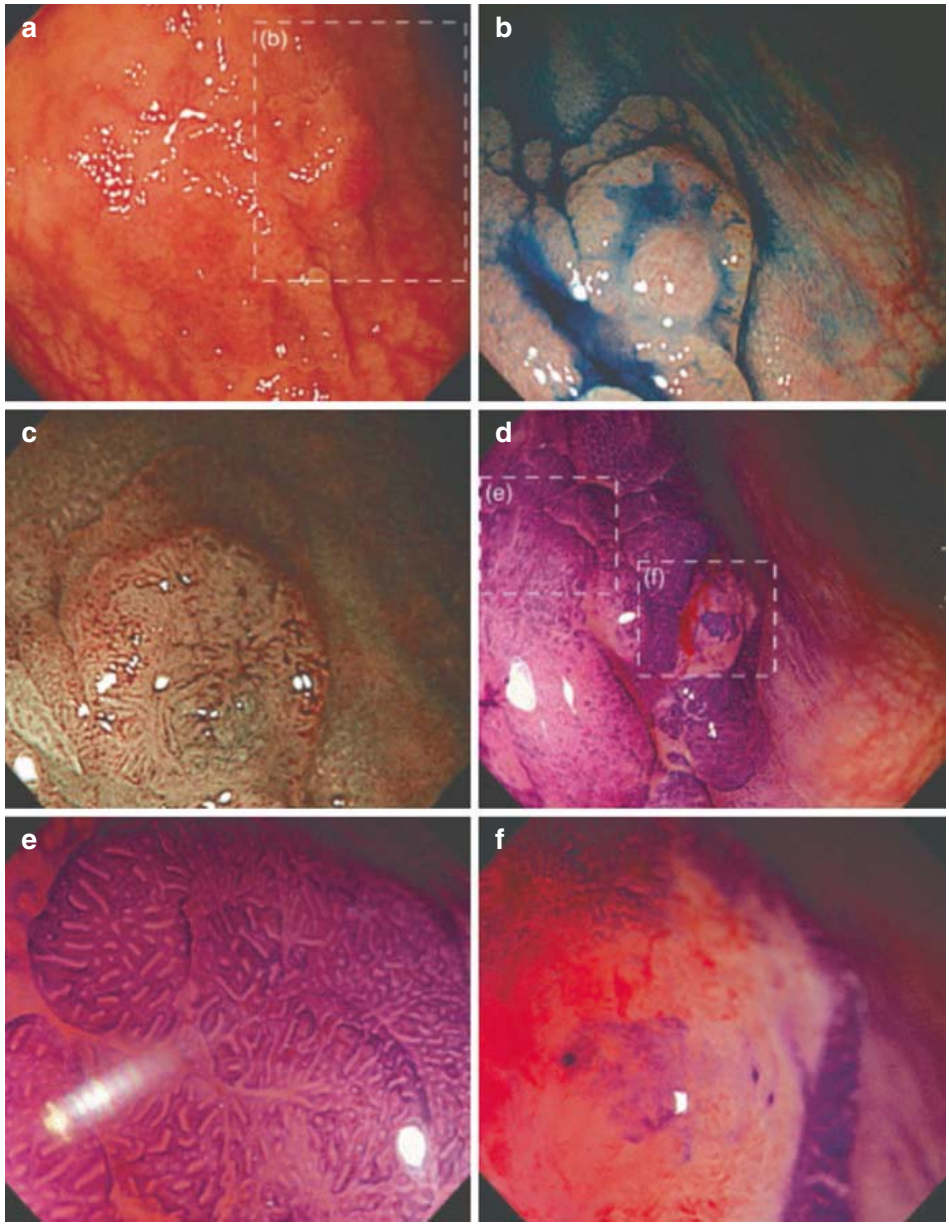


Fig. 11.15 Early CRC 0-IIa + IIc (>sm2 invasive), in sigmoid colon of a 59-year-old man. (**a**) Lesion on WLI. (**b**) Right margin of lesion with protuberance in depression, indigo carmine. (**c**) Protuberance on NBI (V 2B = CP IIIA in center). (**d**) Crystal violet, showing location of (**e**) and (**f**). (**e**) PP IIIL, magnified (80×). (**f**) Tiny area of amorphous PP Vn, magnified (80×). ESD using dual knife → adenocarcinoma G1, psm1 (990 μm), 29 × 20 mm, ly0 v0; curative R0

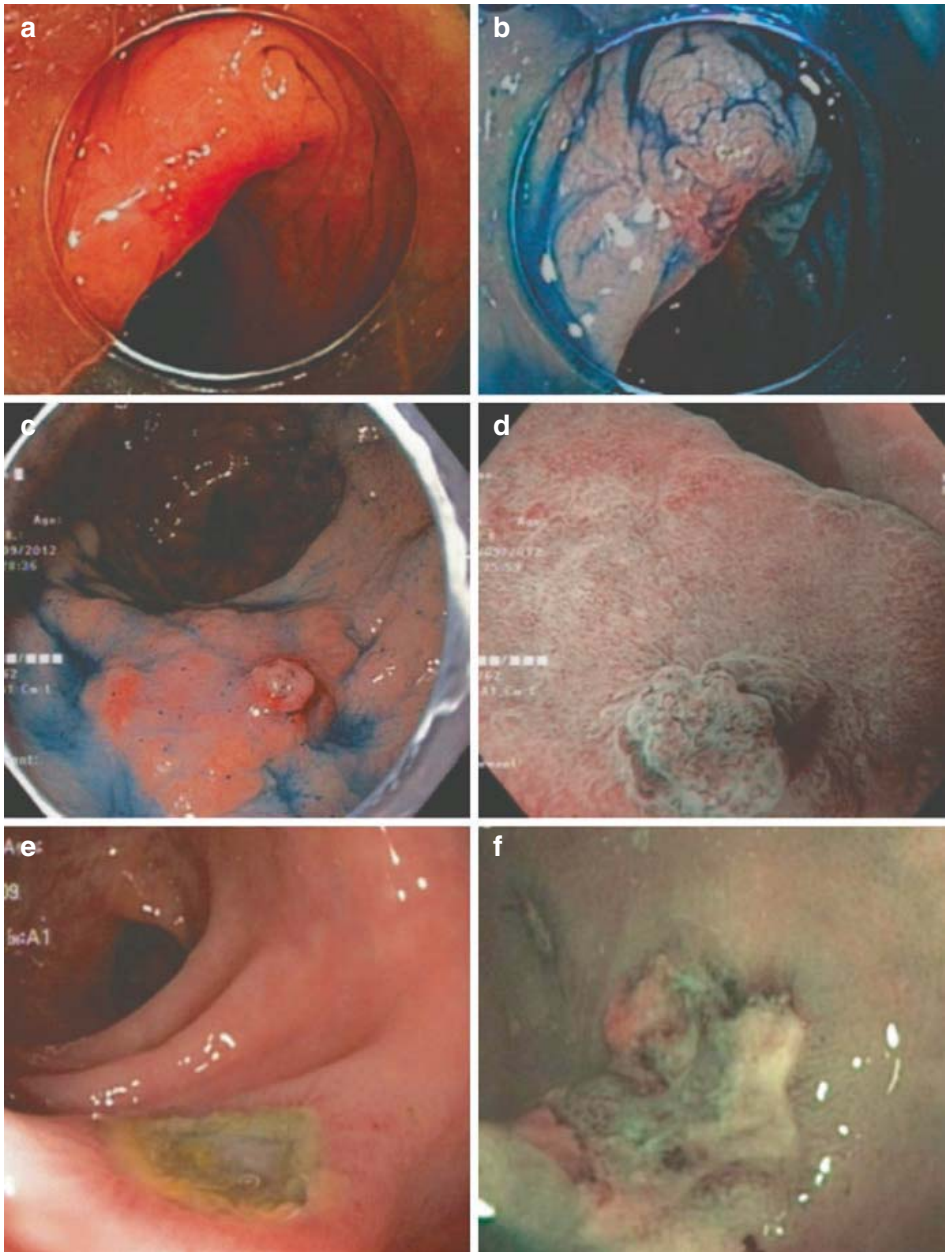


Fig. 11.16 Signs (a–d) suspicious for sm invasion. (**a**, **b**) Early cancer 0-IIa + c, with *constant folds and fusion of folds* (JNET type 2B/3), transverse colon. Laparoscopic hemicolectomy: adenocarcinoma G2, pTis (M), N0 (0/20), ly0, v0; R0. (**c**, **d**) LST-NG (0-IIb, VP 2A, PP IIIs) with polyp (*0-Isp, VP 2B, PP* V_I): lesion JNET type 2B. ESD: adenocarcinoma G2, pTis (M) and tubular adenoma with LGIN and HGIN. (**e**, **f**) *Lesion 0-III*, transverse colon, 18 mm (VP 3, probably PP V_N): lesion JNET type 3. Surgery: *advanced adenocarcinoma* G2, *pT2*

Key Points
Three clues indicate ≥sm2-invasion (JNET type 3) of early CRC [16, 17, 19, 32, 33]:

- *Shape and rigidity* of neoplastic lesion and folds (lack of AID)
- *Highly irregular/amorphous PP* [VI/V_N] and *sparse VP 3*
- *Poor lifting or non-lifting* of neoplasia upon submucosal injection

Predilection sites of sm-invasive carcinomatous foci in LSTs have been analyzed in a series of 511 large, en bloc–resected LSTs of different subtypes [33] (Fig. 11.17). Such predilection sites must be assessed for signs of invasive cancer, such as bleeding sites, sclerous wall change (lack of AID), irregular or sparse VP 2B/VP 3, and amorphous PP V_N. Large nodules (>10 mm) in LST-granular mixed types most likely harbor mucosal or even sm-invasive carcinomatous foci, as do depressed areas in homogenous LST-GH, granular-mixed LST-GM, or non-granular LST-NG. Multiple sm-invasive cancer foci in LST-NG are hardly predictable on endoscopy; the lesion requires resection en bloc.

Key Points
Deep submucosal invasion of early cancer is suspected in the presence of:

- Laterally spreading tumors (LST, Fig. 11.17) with
  - Large nodule >10 mm with PP V_N in LST-GM
  - LST-GM of whole large-nodular type with PP V_I or V_N
  - LST-GM >30 mm size with pit pattern V_I or V_N
  - LST-G with depressed area IIc + IIa and PP V_N
  - LST-NG(PD) >20 mm size with PP V_N
  - Protrusion or ulcer in LST-NG
- Non-lifting upon submucosal injection of any of the above lesions

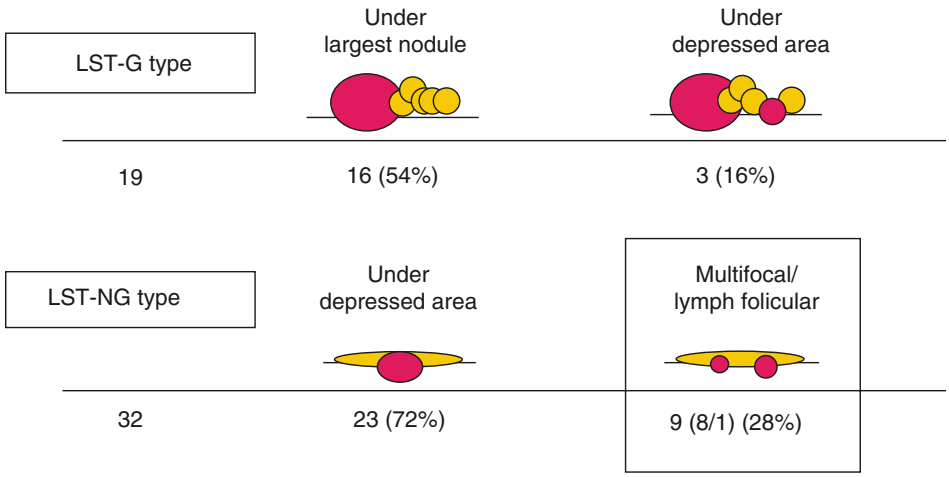


Fig. 11.17 Predilection site (*red nodule*) of *sm-invasive* carcinomatous foci in different types of LST. Parts that are probably non-invasive are shown in *yellow*. (Adapted from Uraoka et al. [33], with permission of John Wiley & Sons Inc)

11.5.3 Tentative Distinction of Serrated Lesions, JNET Type 1

Among JNET type 1 serrated lesions (SL), hyperplastic polyps HP are frequently seen in the rectosigmoid as lesions 0-Is or IIa with indistinct margins, stellate PP II and scanty VP 1 (Fig. 11.4a, b). By contrast, *sessile serrated adenoma/polyp* (SSA/P) differs from HP by distinct margins, and neoplastic variants of hyperplastic pit pattern (PP II-O and III_H) and *varicose microvessels* (VMV) (Fig. 11.18a), whereas *SSA/P with dysplasia* (MSA) in addition shows adenomatous PP IV (Fig. 11.18b, lower right). And *traditional serrated adenoma* (TSA) 0-Ip/s shows stellar PP II combined with adenomatous PP III_L and IV (Fig. 11.18b, upper row). Based on these features, the algorithm in Fig. 11.19 tentatively distinguishes SSA/P (Fig. 11.20a–f) from HP (Fig. 11.21), and from MSA (Fig. 11.22c–f) and TSA (Fig. 11.22a, b). *Focal early serrated adenocarcinoma* (SAC) is identified within a serrated lesion by areals of irregular or amorphous PP Vi or Vn and irregular VP 2B or 3 (Fig. 11.19). However, this analysis has not yet been prospectively validated.

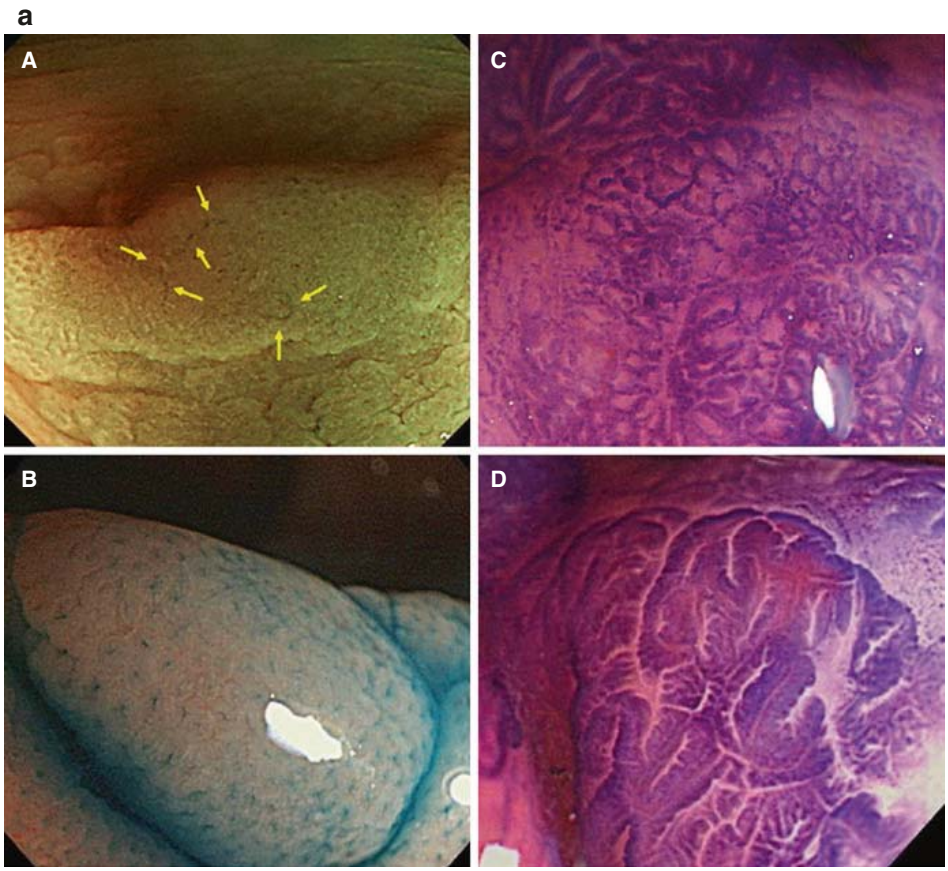


Fig. 11.18 (**a**) ***Surface patterns of serrated neoplasias***. (***A***) Granular surface pattern with 0-II-D appearance and presence of single "*varicose microvessels*" (VMV) (*arrows*) extending beyond periglandular vessels (M-NBI, 40-fold). (***B***) Kudo PP type II (*stellar*) (indigo carmine CE, 60-fold). (***C***) Dilated PP type II-D = II-O. (***D***) Fuji type IIIH pit pattern is wider and more rounded; the dilatation of the crypts produces a "fern-like" appearance. (***C, D***, Crystal violet m-CE, 60-fold.) (From Uraoka et al. [36], with permission of SPRINGER)

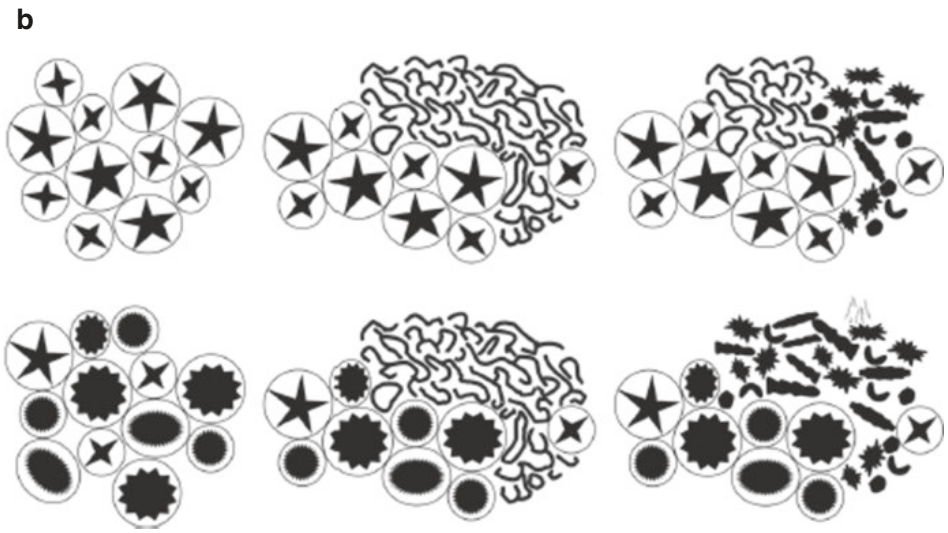


Fig. 11.18 (continued) (**b**) **Traditional serrated adenomas (TSA)** *(upper row)* show stellar PP type II (*left*) alternating or mixed with adenomatous type III (*middle*) or branched type IV (*right*). ***Sessile serrated adenomas (SSA)*** *(lower row)* exhibit wide-open oval or stellar-like crypt orifices, termed PP type II-O ("open") (*lower left*), which may alternate with or progress to a type IV adenomatous surface pattern (*middle*) or type V invasive surface pattern (*right*). (Modified from [34])

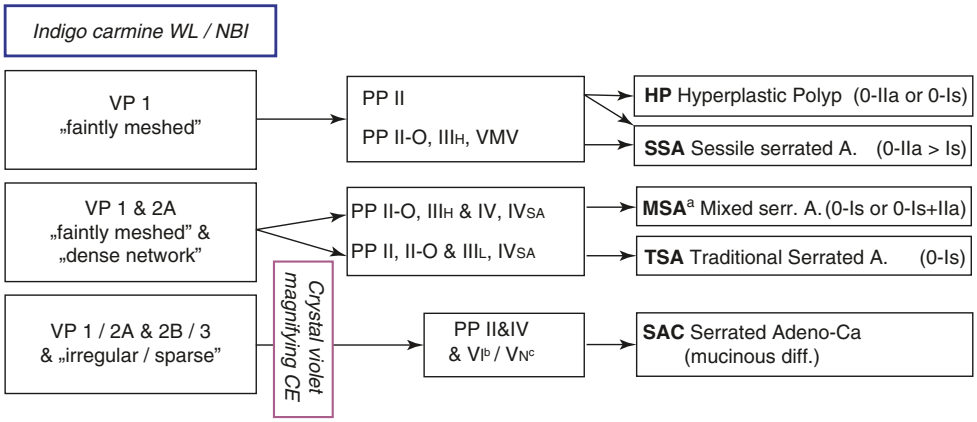


Fig. 11.19 Tentative endoscopic distinction of hyperplastic lesion versus serrated lesions by VP and PP. [a] MSA = SSA/P with dysplasia (according to WHO). [b] Indicating superficial sm invasion <1000 µm. [c] Indicating deep sm invasion ≥1000 µm. PP II-O—II-open (or also: PP III_H—fern-like); PP IV_{SA}—pinecone-like

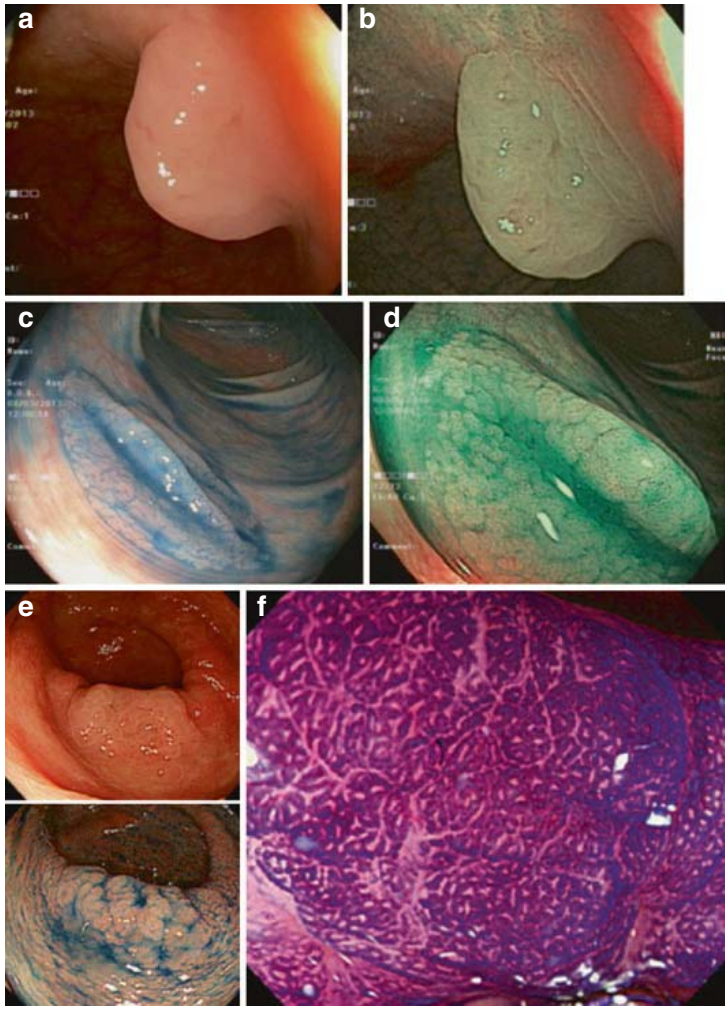


Fig. 11.20 *Sessile serrated adenomas* (confirmed by histology). (**a**, **b**) Pale lesion 0-Is, 15 mm, PP II and VP I(−) ascending colon, WLI and NBI. (**c**, **d**) Pale LST-NG (0-IIa), PP II and II-O, transverse colon, indigo carmine, WLI and NBI. (**e**) Pale LST-GH (0-IIa), ascending colon. WLI (*top*), indigo carmine (*bottom*). (**f**) PP type II-O, crystal violet m-CE (80×)

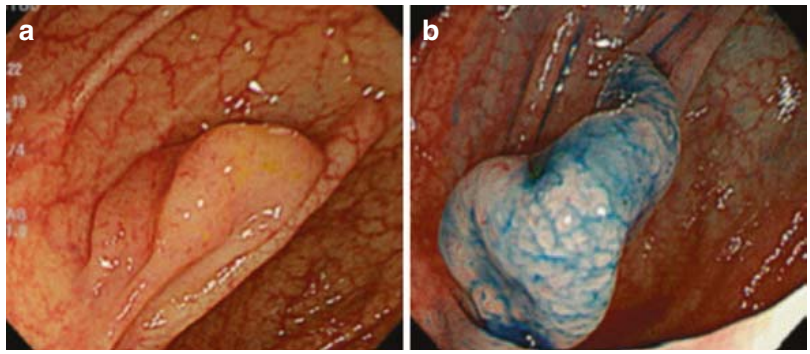


Fig. 11.21 (**a**, **b**) *Hyperplastic polyp 0-Ip*, pale PP II (stellar). WLI and indigo carmine

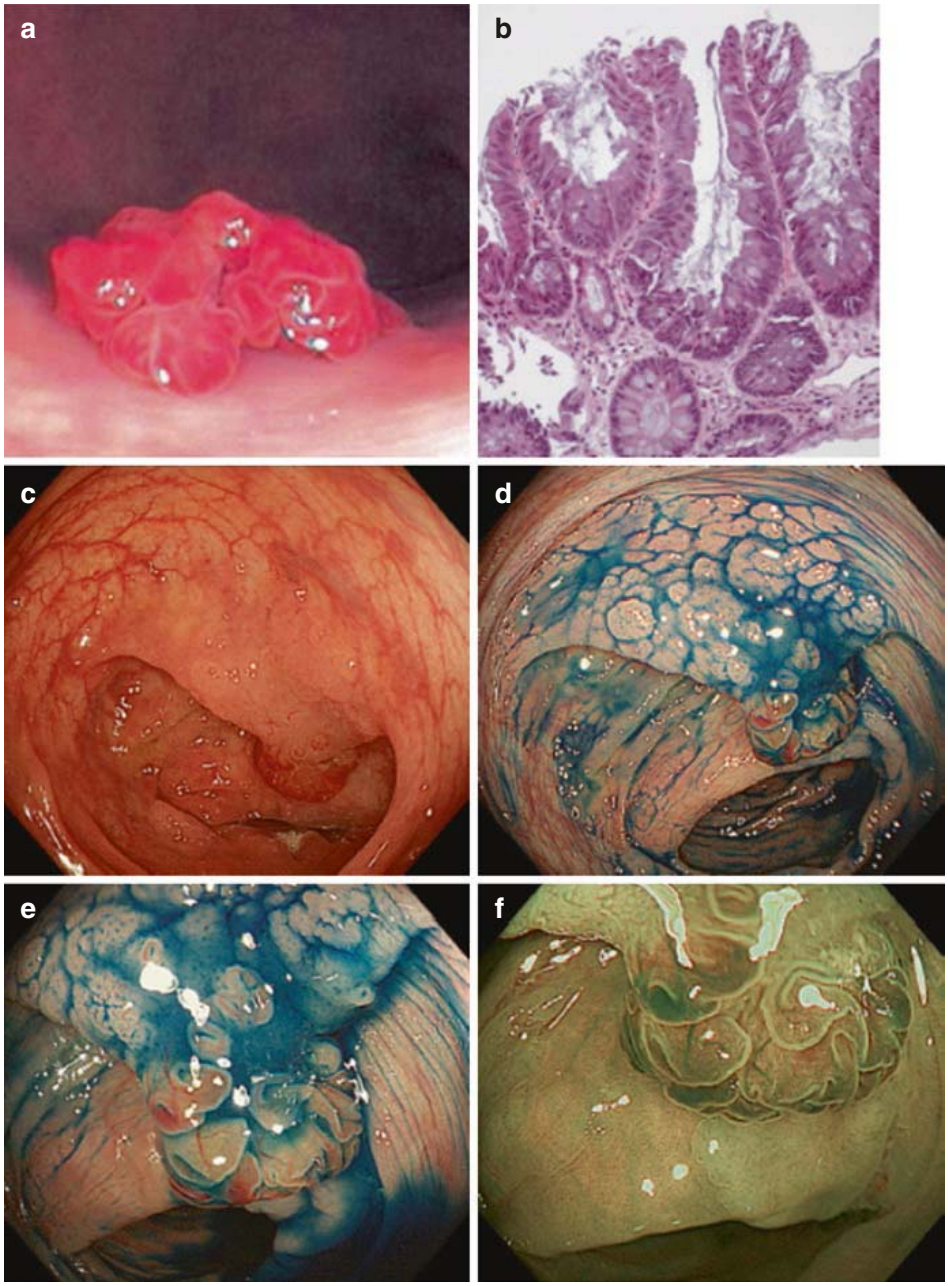


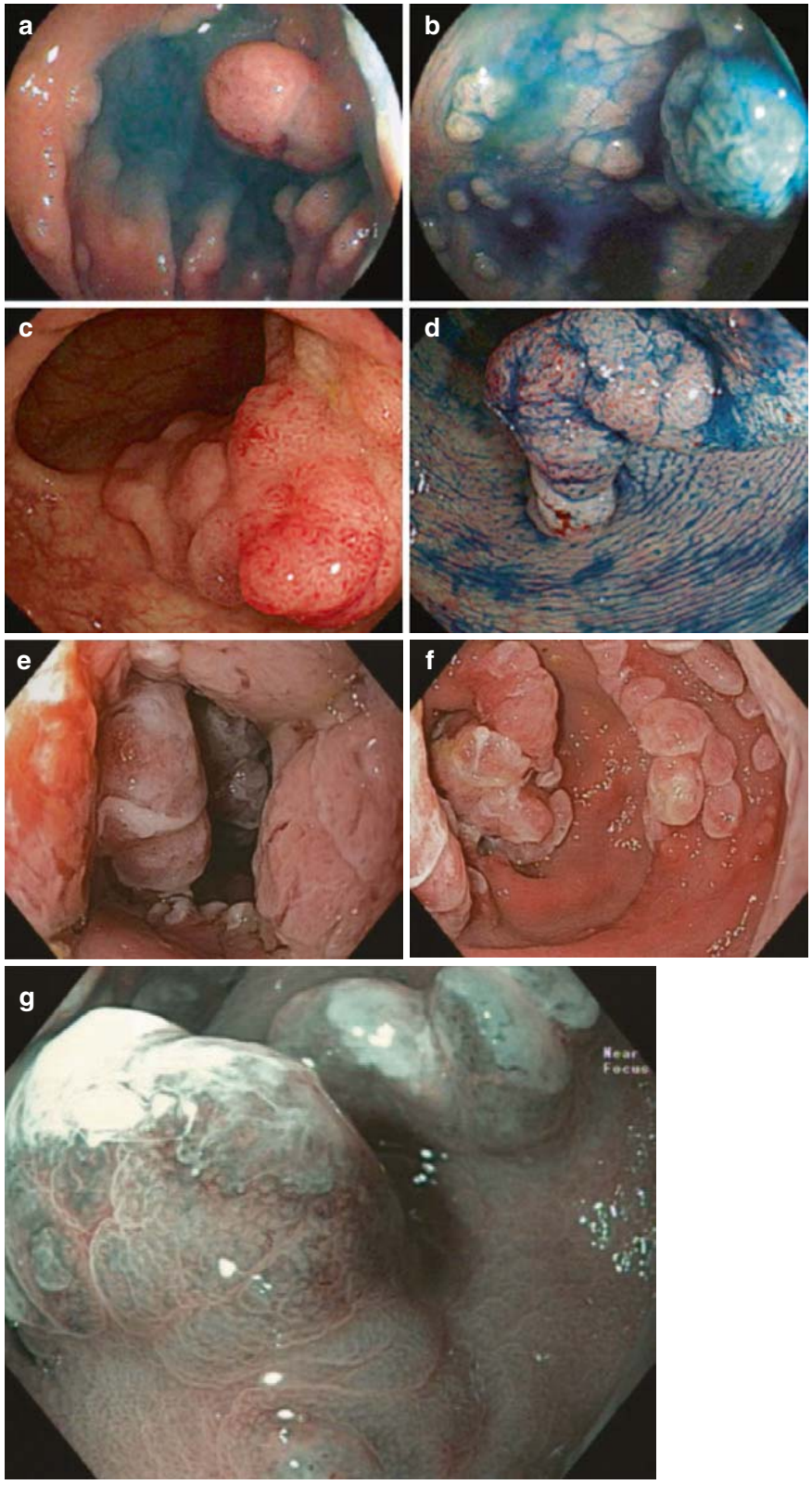
Fig. 11.22 Serrated adenoma (SA) (**a**, **b**, polypoid; **c–f**, mixed type). (**a**) Polypoid serrated adenoma (*TSA*) 0-Isp, colon descendens: PP type IV_{SA} (pinecone-like), WLI. (From Morita et al. [35], with permission of Thieme.) (**b**) SA, H&E stain: serrated crypts with goblet cells and mucin and glandular and cellular atypia. (**c–f**) LST-G mixed, isochrome, located in ascending colon. (**c**) WLI. (**d**) Indigo carmine. (**e**) PP IVSA (gyrous, *right*) and II and II-O (*left*); indigo carmine m-CE 80×. (**f**) VP 2A (irregular meshed and dense, *right*) and VP 1 (*left, top): mixed JNET types 2A & 1;* m-NBI 80×. Histology for (**c–f**): mixed-type SA (sessile serrated adenoma/polyp with dysplasia)

Sessile serrated adenomas (*SSA*) (Figs. 11.20a–f and 11.22c–f), without or with dysplasia, present types 0-IIa more often than 0-Is, occur mainly in the right colon, and have high carcinogenic potential with rapid malignant transformation [24, 34–37]. They are often covered with sticky, adherent mucus that requires tenacious flushing with a water jet to clean the mucosal surface; it tends to cover mucosal pathology such as a flat serrated adenoma or even serrated adenocarcinoma, whereas mucus adherent to normal mucosa is easily washed off. On histology, the adenoma contains goblet cells and mucin, often in dilated and serrated crypts (Fig. 11.22b) that are the structural basis for altered pit appearance on imaging. Compared with the normal stellar type II pit pattern, the surface pattern typically shows wider and more rounded pit orifices with serrated margins (Fig. 11.18a(A,C,D) and 11.18b, lower row), named pit pattern *type II-O (open shape)* or *II-D (dilated)* (Fig. 11.19a and 11.20f); these may alternate with adenoma-like pattern *type IV* or pinecone-like *type* IV_{SA} (Fig. 11.22e, f) [34, 35]. SSA/P typically show scant VP 1 with varicose microvessels (VMV) *extending beyond* periglandular vessels (Fig 11.18a(A)). *Mixed-type serrated adenoma*, *MSA*, is a variant harboring both *flat hyperplastic* parts (stellar PP II) and *sessile adenoma-like* parts (PP II-O, III_H, IV, and IV_{SA}) named *SSA/P with dysplasia* [34, 36, 37] (Fig. 11.22c–f).

Polypoid 0-Ip (traditional) serrated adenomas (*TSA)*, are often reddish due to adenomatous parts with PP type III or IV (Fig. 11.22a, b). TSA show a mixed pattern (Fig. 11.18b, upper row) alternating with areas of stellar pits type II and neoplastic pits *PP type II-O* and *type IV* or variant *PP* IV_{SA} [34–37] (Fig. 11.22a).

Serrated polyposis syndrome (*SPS)*, formerly called hyperplastic polyposis syndrome, is characterized by multiple serrated polyps (typically SSA/P and/or HP) spread throughout the colon. This rare syndrome is associated with multiple SSAs, HPs, conventional adenomas, and increased risk for colon cancer (serrated adenocarcinoma); it requires surveillance and removal of all hyperplastic or serrated lesions [24, 27, 38] (Fig. 11.23a–d). By contrast, true *hyperplastic polyposis* may be seen in *rectal prolapse syndrome* (*RPS*) as a consequence of chronic mechanical stress causing mucosal and fibromuscular hyperplasia of the distal rectal submucosa and mucosa (Fig. 11.23e–g). This condition is treatable with laparoscopic rectopexia.

Fig. 11.23 (**a**–**d**) *Serrated polyposis syndrome (SPS)* with multiple serrated adenomas, and 20-mm traditional serrated adenoma (pinecone-like aspect) in ascending colon (>30 hyperplastic/serrated polyps in colorectum). (**a**, **b**) *TSA and SSA in SPS*, WLI and indigo carmine CE. (**c**, **d**) Serrated adenocarcinoma (*SAC*) in SPS patient. WLI and indigo carmine. (From Miwata et al. [38], with permission of John Wiley & Sons). (**e**–**g**) *Hyperplastic polyposis with rectal prolapse syndrome*. (**e**, **f**) Mucous and fibrin pseudomembranes on hyperplastic polyps (WLI). (**g**) Note entirely normal PP I and II, VP 1 (meshed) (NBI 60×)



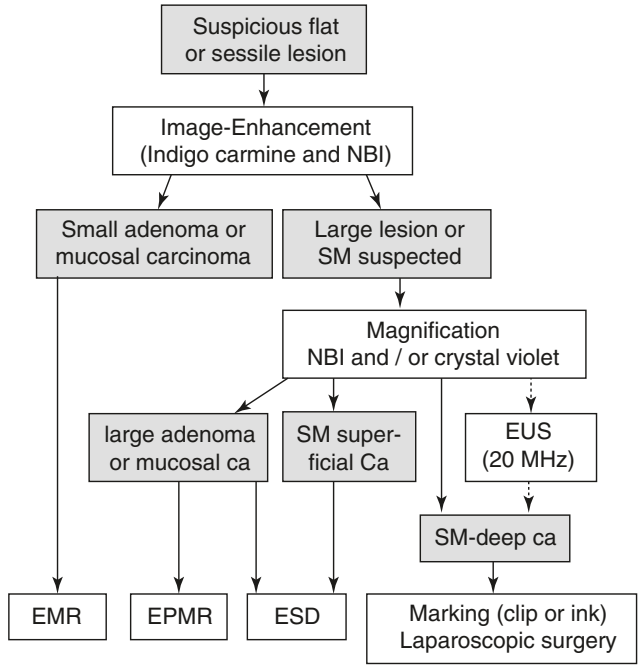


Fig. 11.24 Recommended colonoscopic approach for suspicious flat or sessile lesions. Endoscopic mucosal resection with snaring (*EMR*) removes small mucosal neoplasias en bloc, and large noninvasive adenoma (−/+HGIN) in piecemeal fashion (*EPMR*). NBI with at least 50-fold magnification should be available for analysis. We recommend crystal violet stain to assess for a pit pattern (PP V) characteristic of sm invasion. High-resolution endoscopic ultrasound (Hr-EUS, 20 MHz) is helpful when available, but is not standard

11.6 Endoscopic Resection of Mucosal Neoplasias

Endoscopic analysis on WLI, M-CE, and M-NBI of macroscopic lesion type, pit pattern, and vessel pattern according to the JNET classification is superior to high-resolution endoscopic ultrasound (Hr-EUS) (*see* Chap. 5) for the diagnosis of *superficial versus deep sm-invasive* cancer. The decision on the presence of superficial or deep sm invasion is challenging but is key for resective strategy (Fig. 11.24).

All colonic polyps (0-I lesions), including diminutive polyps, are indications for *endoscopic resection*. Removal of hyperplastic polyps smaller than 5 mm (especially multiple hyperplastic polyps in the rectum) is not generally necessary [23, 39].

Note: All hyperplastic lesions proximal to the sigmoid colon and hyperplastic lesions in the rectosigmoid larger than 5 mm in size, as well as all serrated adenomas/polyps, must be completely removed [23, 39, 40].

11.6.1 Snaring Resection Techniques

Snare polypectomy (without sm injection under the polyp) is the preferred ablation

procedure for semipedunculated, pedunculated, or sessile polyps (adenomas −/+ focal mucosal carcinomas). *Endoscopic mucosa resection (EMR)* with sm injection under the lesion removes slightly larger sessile or flat neoplasias (diameter 10–20 mm) en bloc with free margins. EMR of flat lesions using the cold snaring technique (en bloc and EPMR) yields superior specimens for histology and probably a lower recurrence rate [40].

EMR has limitations such as piecemeal resection for flat lesions larger than 20 mm, resection of lesions involving the dentate line or the ileocecal valve, and resection of lesions with a non-lifting sign. Piecemeal resection results in less accurate histological assessment and often leads to local recurrence. Nevertheless, LSTs suspicious for malignant foci and neoplasias 0-IIc require endoscopic or surgical resection en bloc [23, 39].

Note *Indications for EMR* [23, 39]:

- Adenomas type 0-IIa/IIb (PP type IIIL, IV, [IIIs]), diameter ≤20 mm
- Neoplasias type 0-IIc (PP IIIs) of size ≤15 mm with lifting sign upon sm injection
- LST of homogenous granular type (LST-GH) without signs of submucosal invasion (piecemeal EPMR)

Limitations of large-sized EMR [23, 39, 41–43]:

- Lesions exceeding 2 cm diameter are not resectable en bloc
- Submucosal fibrosis (e.g., in chronic inflammatory disease or often in LST-NG)
- Technical limitations for snaring (e.g., mucosal folds, colonic angulation, small rectal carcinoid tumors)
- High rate of local recurrence (up to 30%) after EPMR of large lesions (HGIN or T1a cancer, diameter >3 cm) [42].

Complications of EMR [39–42]:

- Perforation (risk 4–5%, higher in cases with technical limitations)
- *Post-polypectomy coagulation syndrome* (risk 0.5–1.2%; high risk of delayed perforation and severe peritonitis)
- *Recurrent or late bleeding* (risk ~5%) at the EMR site

11.6.2 Endoscopic Submucosal Dissection (ESD)

Colonic endoscopic submucosal dissection (ESD) is more difficult but is standard in experienced centers [7, 43–45]. In Japan, ESD is standard for early malignant or difficult-to-snare flat neoplastic lesions (complex lesions) (Table 11.4). The basic principles for en bloc resection of flat neoplasias have been accepted in the British Guideline: En bloc resection is mandatory for neoplasias suspicious for malignant foci or for complex flat lesions with high risk of incomplete or complicated endoscopic snaring. These patients should be referred to specialized interdisciplinary centers [39]. Many Western guidelines still accept EPMR for such lesions, however. Depending on national guidelines, LST-GM may also be resected in piecemeal fashion, with the larger nodule

resected first [33]. The outcome of ESD is discussed in Chap. 3.

Note Mucosal or submucosal (sm1)-invasive cancer (G1 or G2, Ly0 V0, without tumor cell budding) seldom recurs (<2%) when it is resected en bloc with free margins (R0). The risk of lymph node metastasis is near zero if the depth of submucosal invasion is <1000 μm [23, 46].

Table 11.4 Indications of ESD for Colorectal Tumors[a] (JGES Guideline 2015 [23])

Lesions for which endoscopic en bloc resection is required:
1. Lesions for which en bloc resection with snare EMR is difficult to apply
LST-NG, particularly LST-NGPD
Lesions showing a V_I type pit pattern
Carcinoma with shallow T1 (SM) invasion
Large depressed-type tumors (0-IIc)
Large protruded-type lesions (0-Is/Isp) suspected to be carcinoma[b]
2. Mucosal tumors with submucosal fibrosis [c]
3. Sporadic localized tumors in conditions of chronic inflammation such as ulcerative colitis
4. Local residual or recurrent early carcinomas after endoscopic resection

[a]Partially modified from the draft proposed by the Colorectal ESD Standardization Implementation Working Group
[b]Including LST-G, nodular-mixed type
[c]As a result of a previous biopsy or prolapse caused by peristalsis of the intestine

Surgery is indicated *after ESD* for any of the following conditions:

- Vertical (deep) margin that is tumor-positive (R1)
- Deep submucosal invasion (>1000 μm below MM)
- Lympho−/ vascular tumor infiltration is positive (Ly 1 or V 1)
- Cancer grading is poorly differentiated or undifferentiated (G3, G4)
- Tumor budding Bd 2 or Bd 3 at the deepest front of invasion (differentiated AC)

Indication for *a priori surgical resection:*

- Signs of deep submucosal invasion of proven carcinoma [23, 47]

11.7 Lesions of the Anal Canal

The *surgical anal canal* extends for 4–5 cm from the rostral end of the inner sphincter (oral end of the contracted anal canal) down to the anal verge, which corresponds to the end of the outer anal sphincter. The inner 3 cm with anal papillae all around (median 8 [6–11]) and crypts are covered with columnar epithelium, and the anoderm (1.5–2 cm transition zone aboral to the dentate line) has stratified squamous epithelium down to the end of the intersphincteric groove, where, on the anal verge (~1 cm), the keratinized anal skin starts. Somatic sensation (pudendus nerve branches) starts at the dentate line.

Using standard endoscopes (with M-WLI and M-NBI), most of the anal canal and anoderm (distended by insufflation) is well visualized on retroflex view from the rectum. On NBI, the dentate line is displayed as a sharp border between brownish columnar rectum epithelium and greenish-white squamous epithelial anoderm (Figs. 11.26d and 11.33a).

Anal lesions, in the anoderm, show some similarities to squamous epithelial lesions in the esophagus. Condylomata acuminata (wart-like lesions type 0-Is/p or II-a) are caused by human papillomavirus (HPV) infection and show many elongated regular-caliber capillaries in squamous epithelium (similar to esophageal papillomas) on M-WLI and M-NBI. Most neoplastic anal lesions (dysplasia and early squamous cell cancer) are triggered by infection with HPV subtypes, especially in high-risk individuals with anal intercourse or extensive condylomata acuminata [48]. *Anal neoplasias* display irregular alterations in capillary and surface architecture similar to squamous epithelial neoplasias in esophagus. *High-grade anal dysplasias* (*AIN III*) are Lugol-voiding [49] (*see* Case 10 and Fig. 11.33 in Sect. 11.8). Retroflex inspection of the anal canal and anoderm with high-definition magnifying WLI/NBI endoscope allows excellent diagnostic imaging. We recommend an interdisciplinary diagnostic and therapeutic work-up of such lesions, involving dermatology, anorectal surgery, and gastroenterology [49].

11.8 Cases: Adenomas, Dysplasia, and Early Colorectal Cancer

Case 1: Small Lesion 0-Is + 0-IIc Located at the Sigmoid Colon

A small lesion 0-IIc with central bulging (0-Is), 8 mm in diameter, was detected on

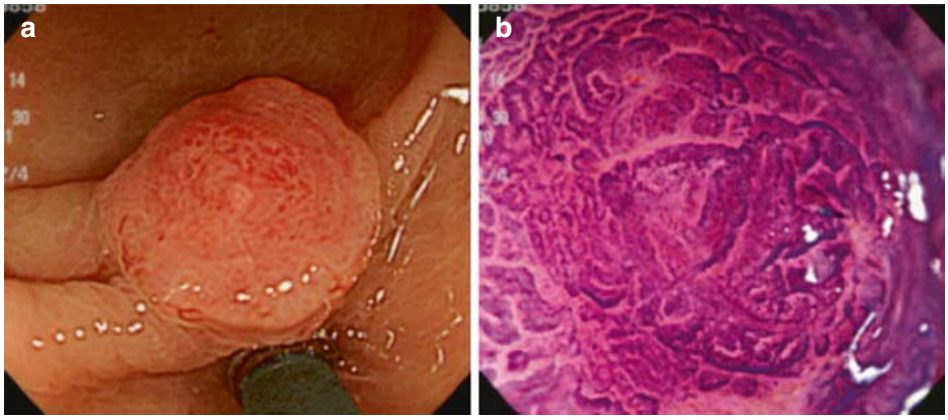


Fig. 11.25 (**a–d**) *Lesion 0-Is + IIc* (d 4 cm, *bulging in IIc*) on haustral fold in sigmoid colon. (**a**) WLI. (**b**) Crystal violet CE (WLI, 80×), PP type V_I *high grade*

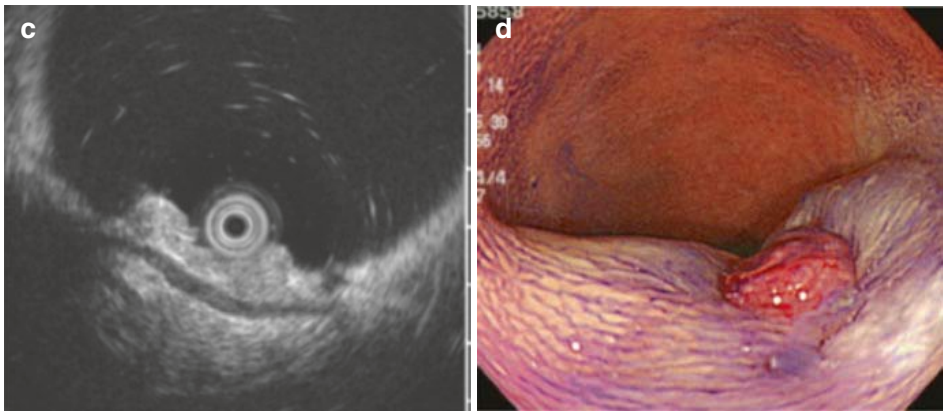


Fig. 11.25 (continued) (**c**) Radial Hr-EUS shows a 4-mm-wide *break in sm echo layer*. (**d**) Complete *non-lifting sign* after sm injection of 3 × 2 mL fluid. *Diagnosis*: Deeply sm-invasive early CRC. *Surgery*: well-differentiated AC, pT1b, *deeply sm invasive* (2000 μm), ly 1 v 0

a haustral fold in sigmoid colon. Magnifying view (80×) with crystal violet staining revealed a highly irregular-type Vi pit pattern, and Hr-EUS (20 MHz) disclosed a 4-mm-wide break in the sm echo band. Both findings supported deeply sm-invasive cancer, a diagnosis further strengthened by complete non-lifting sign upon sm injection. The patient underwent curative laparoscopic resection: adenoca (tub2), pT1bsm (2000 μm), ly1, v0, pPM0, pDM0, pRM0, and 0-Is + IIc (Fig. 11.25).

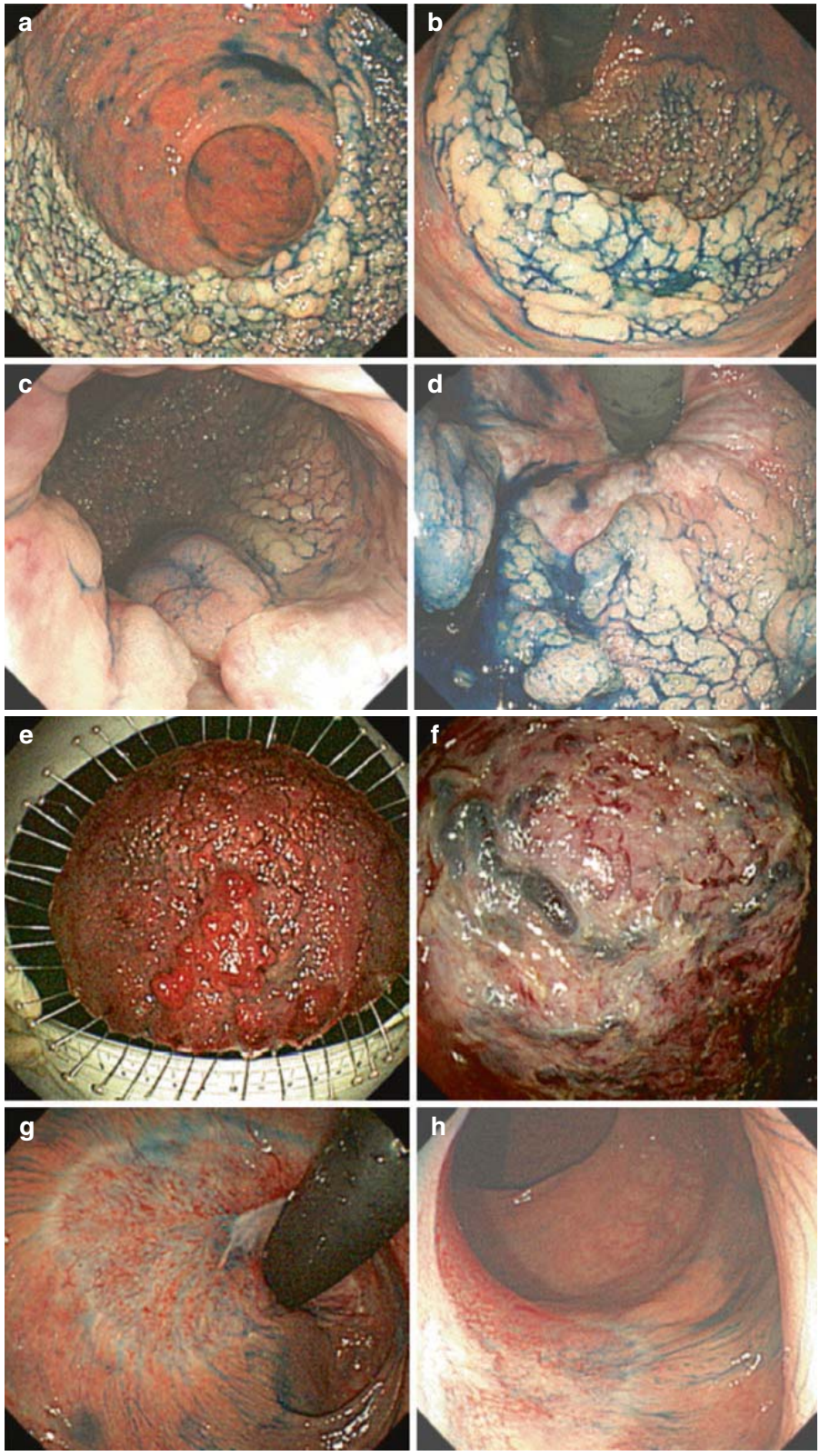
Note All four signs of sm invasiveness (macroscopic/PP/EUS/non-lifting), when combined, allow highly accurate diagnosis.

Case 2: Large Rectal LST-G Mixed Type Invading Anal Canal

Rectal LST-G mixed type (0-IIa + Is) consisting of homogenous granular parts and one triangular-shaped sessile lesion (4 × 3 cm, 1 cm elevated) was diagnosed in a woman in her mid-40s. CE showed PP type IIIL and IV (Fig. 11.26) and on the sessile part some PP type IIIs but no ulcerations or friability. Surgical full-wall resection would certainly have interfered with anal function and fecal continence. Therefore, the patient favored diagnostic ESD en bloc. Circular dissection of the anal margin and anal channel in prograde fashion, followed by stepwise partial circumferential incision and submucosal dissection in retroflex fashion, allowed en bloc resection of the entire lesion including the sm vascular plexus.

Note ESD en bloc of advanced adenoma or mucosal cancer of the anorectum can provide cure and preserve normal anorectal function.

Fig. 11.26 (**a**–**d**) Large LST-G mixed type (0-IIa + Is), extending about 9 cm from squamocolumnar junction (= dentate line, shown on top of panel **d**) (**c**, **d**; 70% circumferential) at the posterior wall over the Houston fold (**a**, **b**) into the rectum (WLI, indigo carmine CE). (**e**) Specimen was resected by dual knife with safety margin and (**f**) intact sm vascular stratum (sml-2); submucosal view of specimen → *histopathology*: *focal differentiated adenocarcinoma, depth M*, in tubulovillous adenoma 130 × 103 mm, ly0, v0, pLM0, pVM0; curative resection R0. (**g**, **h**) Follow-up after 6 months showed a scar after ESD with regenerative mucosa and no narrowing of the anal channel



Case 3: Small Lesion 0-IIa + c at the Sigmoid Colon

Screening colonoscopy in a 77-year-old woman showed a small (d 1 cm) lesion type 0-IIa + c with PP type IIIs (on biopsy HGIN) at the inner curve of the rectosigmoid flexure (Fig. 11.27). Hybrid-ESD with snaring of final sm bridge resected the lesion en bloc, without thermal damage to resection bed or to the specimen, which revealed tubular adenoma with HGIN, resected R0.

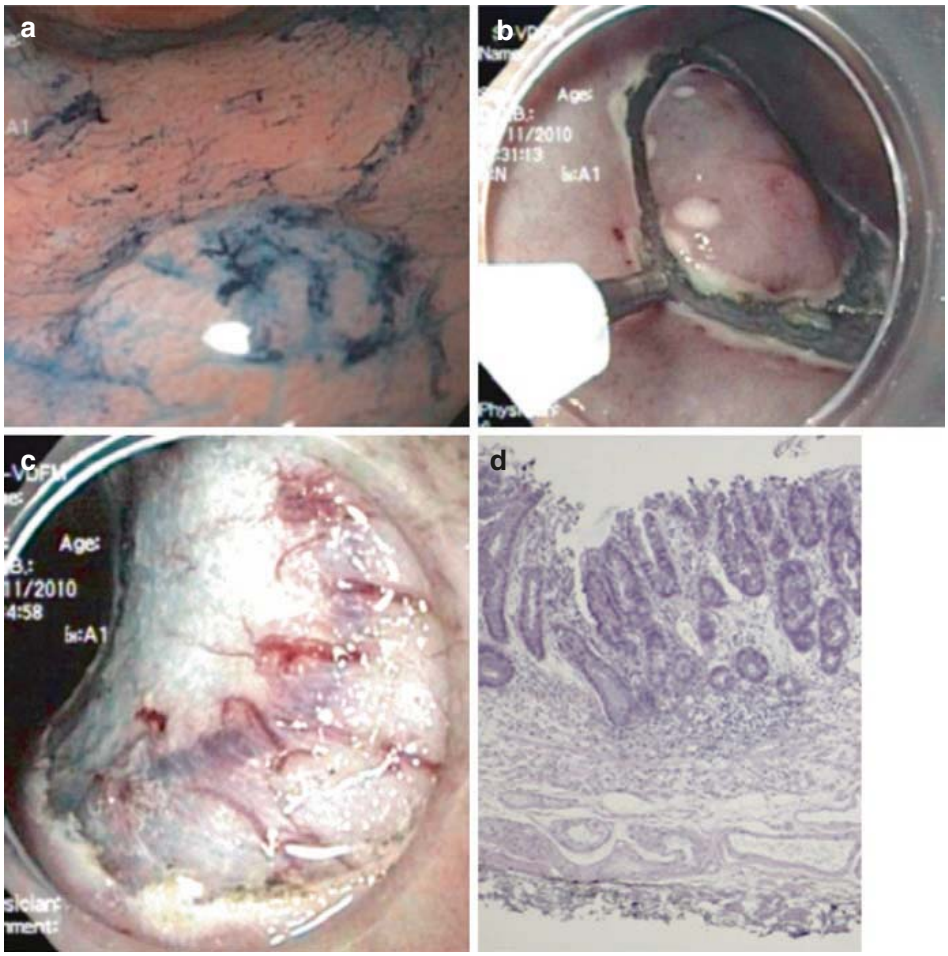


Fig. 11.27 (**a**) Small lesion type 0-IIa + c with PP IIIs on M-CE (40×) using indigo carmine. Previous targeted biopsy: HGIN. (**b**) Simplified ESD with final snaring. (**c**) Bare resection bed. (**d**) Cross section of the specimen, showing tubular adenoma with focal HGIN and no thermal damage at the deep margin

Note Simplified hybrid-ESD (with low-power snaring) has advantages:

- Shorter procedure time (during the ESD learning curve)
- High-quality ESD specimen for histology, without thermal artifacts

Case 4: LST-G Whole Nodular Type (0-Is + Isp), Sigmoid Colon
A polypoid lesion, LST-GN-whole nodular, in sigmoid colon showed signs of deep sm invasion (Fig. 11.28), a contraindication for snaring polypectomy.

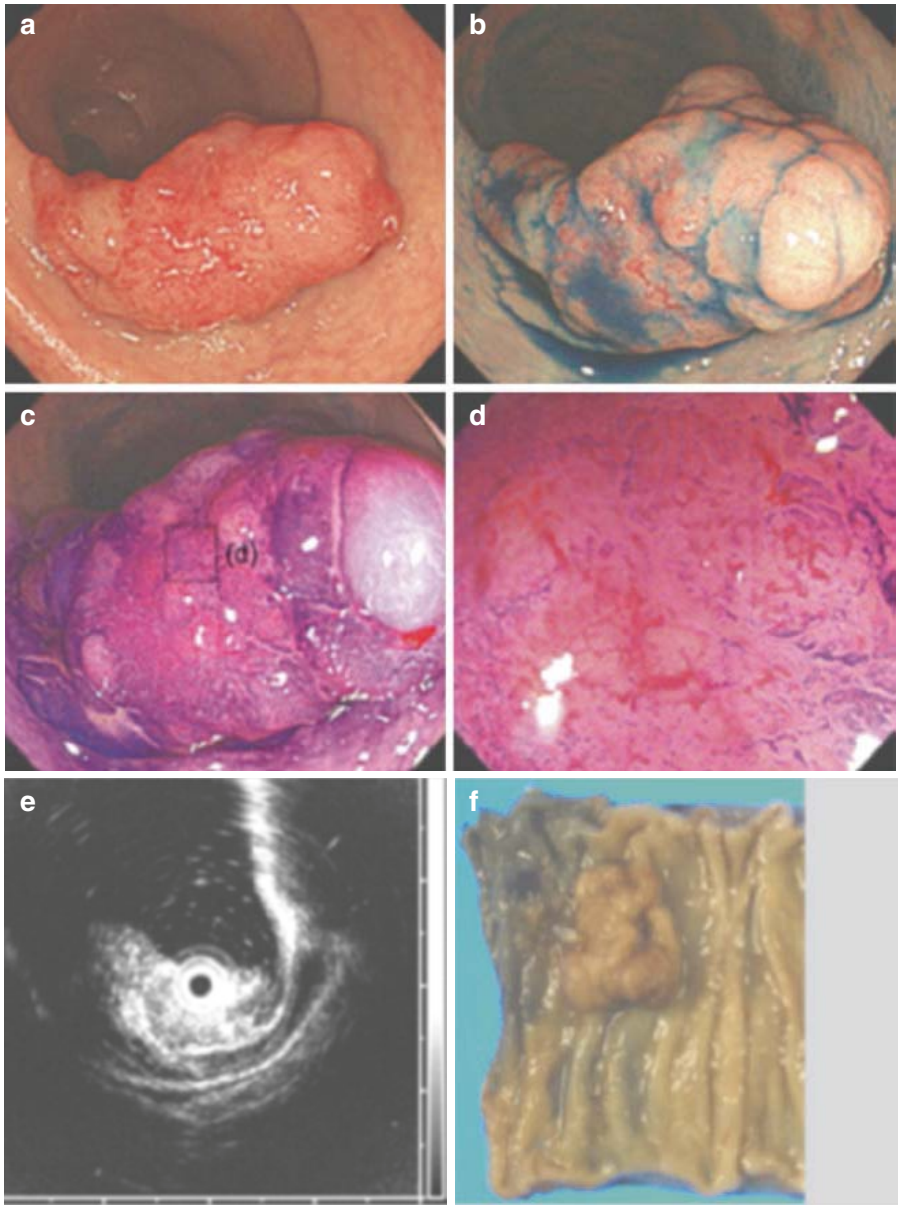


Fig. 11.28 LST-GN whole nodular type (0-Is + Isp), 20 mm in diameter. (**a**) WLI. (**b**) Indigo carmine. (**c**) Crystal violet CE, which disclosed (**d**) focal areas with *PP type V$_I$ high grade*. (**e**) Hr-EUS (20 MHz) showed a *break of sm echo band* beneath the lesion. (**f**) Specimen of laparoscopic resection: adenocarcinoma G1, pT1b*sm2, ly1, v1*, pN0

Note Accurate endoscopic analysis of neoplastic polyps prevents polypectomy (R2 resection) on deeply sm-invasive cancer type 0-Is/p.

Case 5: Relatively Large Cecal Lesion LST-G Whole Nodular (0-Is)
On complete colonoscopy performed for a positive fecal occult blood test, a lesion 0-Is, whole nodular, 5 × 3 cm in size, was found located on the last lateral haustral fold of the cecum. Detailed endoscopic analysis was performed and ESD was conducted for diagnostic and possibly curative intention (Fig. 11.29).

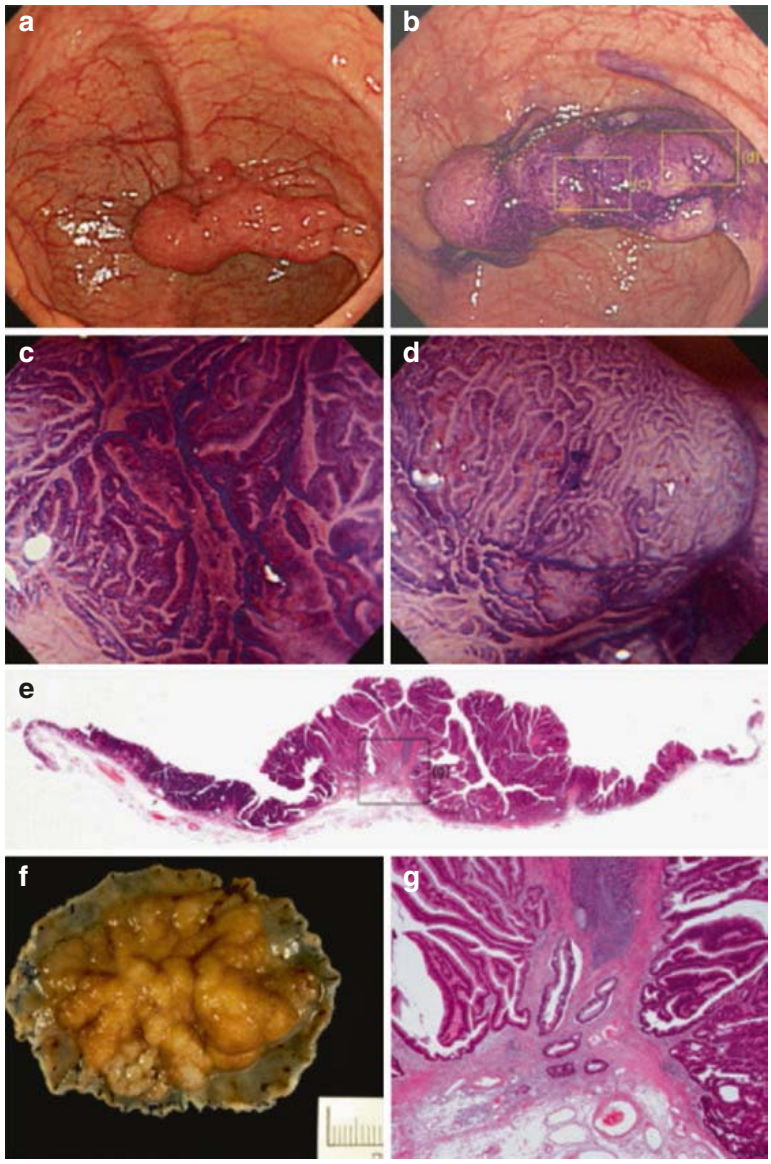


Fig. 11.29 (**a**) A lesion 0-Is, whole nodular, 5 × 3 cm in size, on the last lateral haustral fold of the cecum. (**b**) On crystal violet CE, the lesion showed PP type IIIL and IV and irregular PP V in small depressed areas (*insert* **c, d**), which revealed on M-CE (80×) (**c**) PP type Vi low grade and (**d**) PP type Vi high grade. (**f**) ESD en bloc performed for diagnostic purpose yielded a single specimen of the entire lesion with safety margins. (**e**) Sequential transverse sections showed lateral and vertical margins negative. (**g**) *Histology*: adenocarcinoma, tub1, size 50 × 35 mm (specimen 55 × 40 mm), sm1 (500 μm), ly0, *v1*. Laparoscopic hemicolectomy with lymph node dissection was recommended

Case 6: LST-NG Located at the Sigmoid Colon

Screening colonoscopy showed a LST-NG, (d 4 cm) with slight pseudodepression extending over a haustral fold (Fig. 11.30). Analysis suggested *intramucosal cancer*. ESD en bloc was performed.

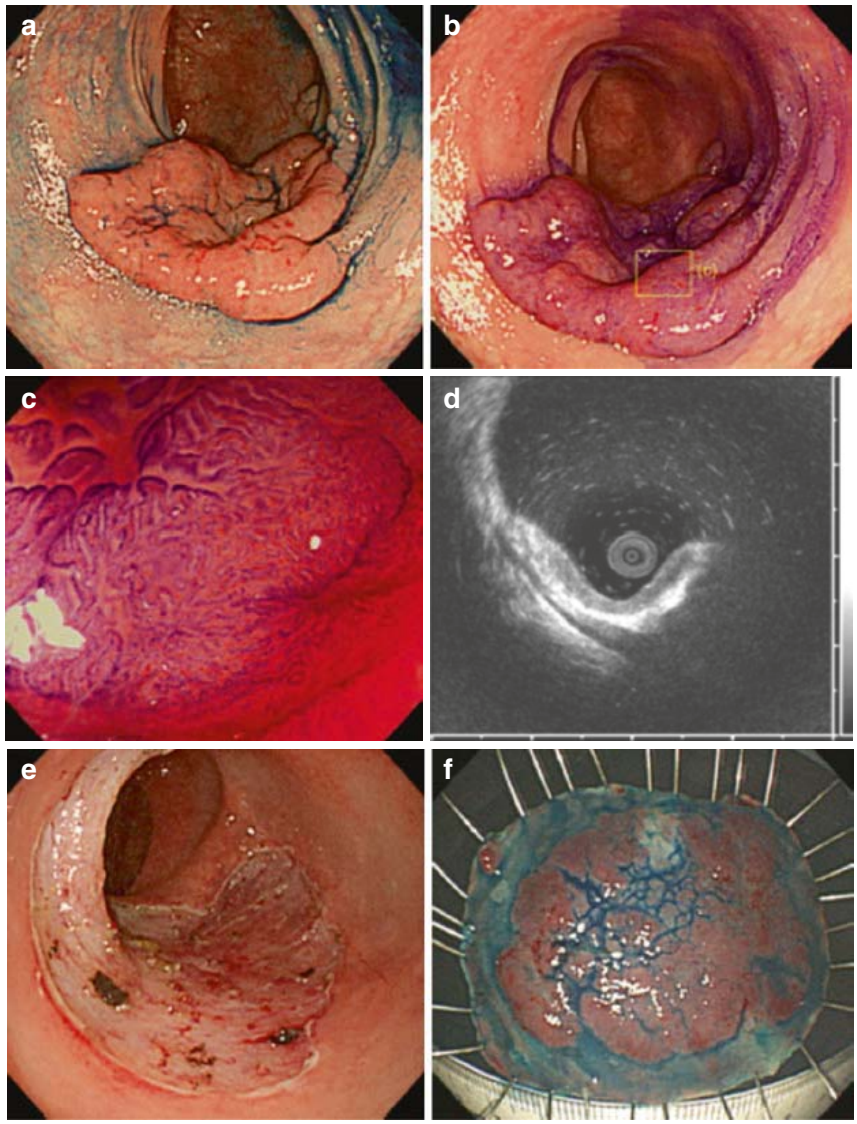


Fig. 11.30 (**a–f**) *LST-NGPD* (d 4 cm) in sigmoid colon. (**a**) Indigo carmine CE. (**b**) Crystal violet CE. (**c**) M-CE (80×) with crystal violet stain: PP type V_I *low grade*. (**d**) Radial Hr-EUS shows *intact sm echo layer* (white echo band). (**e**) Resection bed. (**f**) ESD specimen (indigo carmine). Histology: adenocarcinoma, pT1b *sm1* (990 µm), tub1, ly0, v0, HM0, VM0

Note Attempt ESD for cure on LST-NGPD, unless signs of *deep* sm invasion.

Case 7: LST-NG (Sized ~5 cm) Located at the Transverse Colon

In this 76-year-old man on anticoagulant therapy, colonoscopy for anemia showed mucosal irregularity at transverse colon (Fig. 11.31).

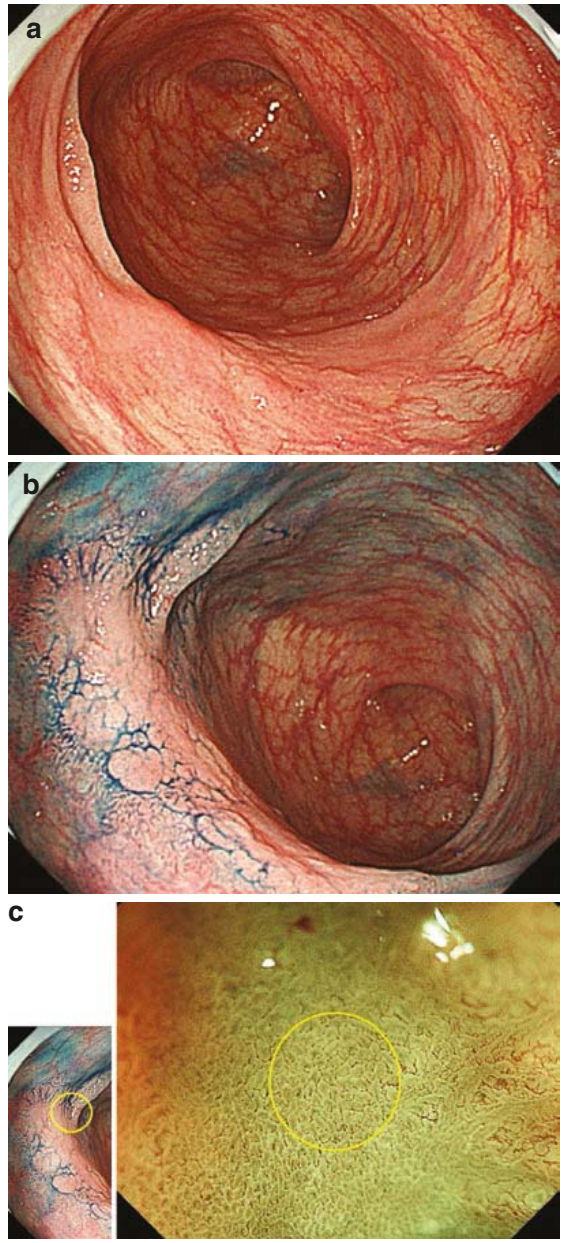


Fig. 11.31 (**a**) Reddish surface irregularity with loss of sm vascular pattern (*bottom*). (**b**) Indigo carmine spraying revealed a flat lesion 0-IIb, further analyzed by magnifying imaging (80×) using (**c**) NBI (VP 2B)

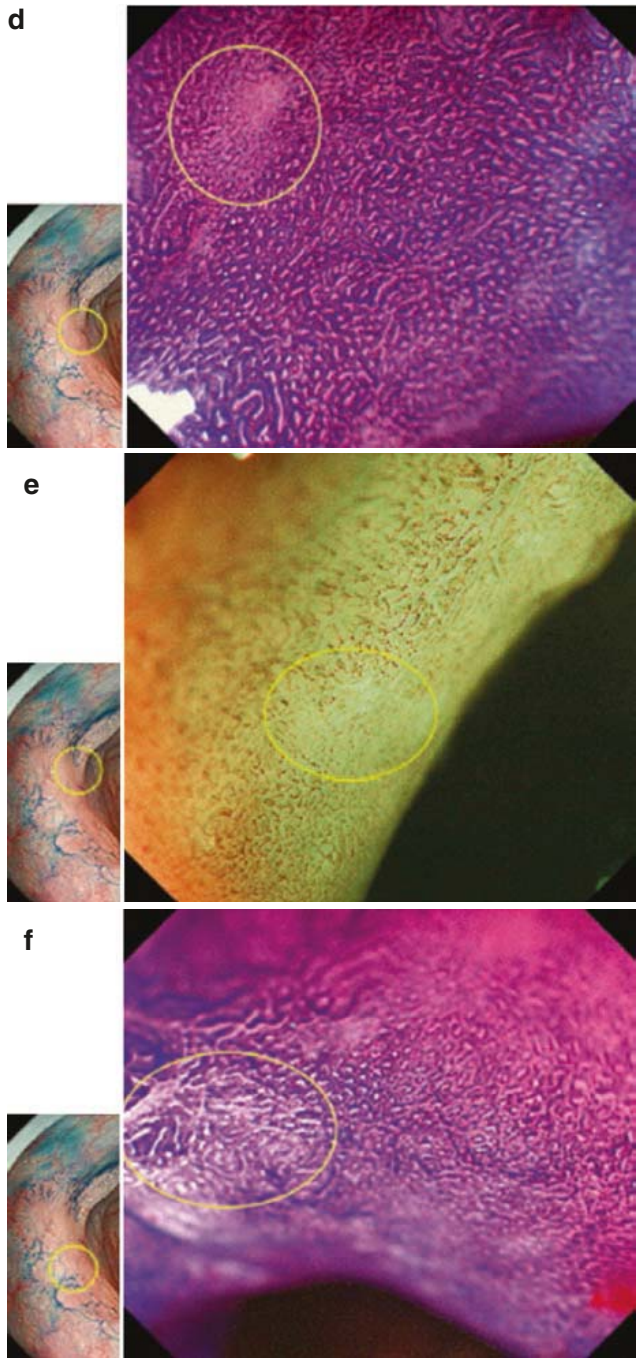


Fig. 11.31 (continued) (**d**) crystal violet (PP Vi low grade). One tiny spot showed (**e**) VP 3 on m-NBI and (**f**) PP V_I high grade on crystal violet m-CE. *Clinical diagnosis*: LST-NG JNET type 2B and focal type 3 suspicious for sm-invasive, differentiated adenocarcinoma, diameter nearly 5 cm. ESD was recommended (for diagnostic purpose)

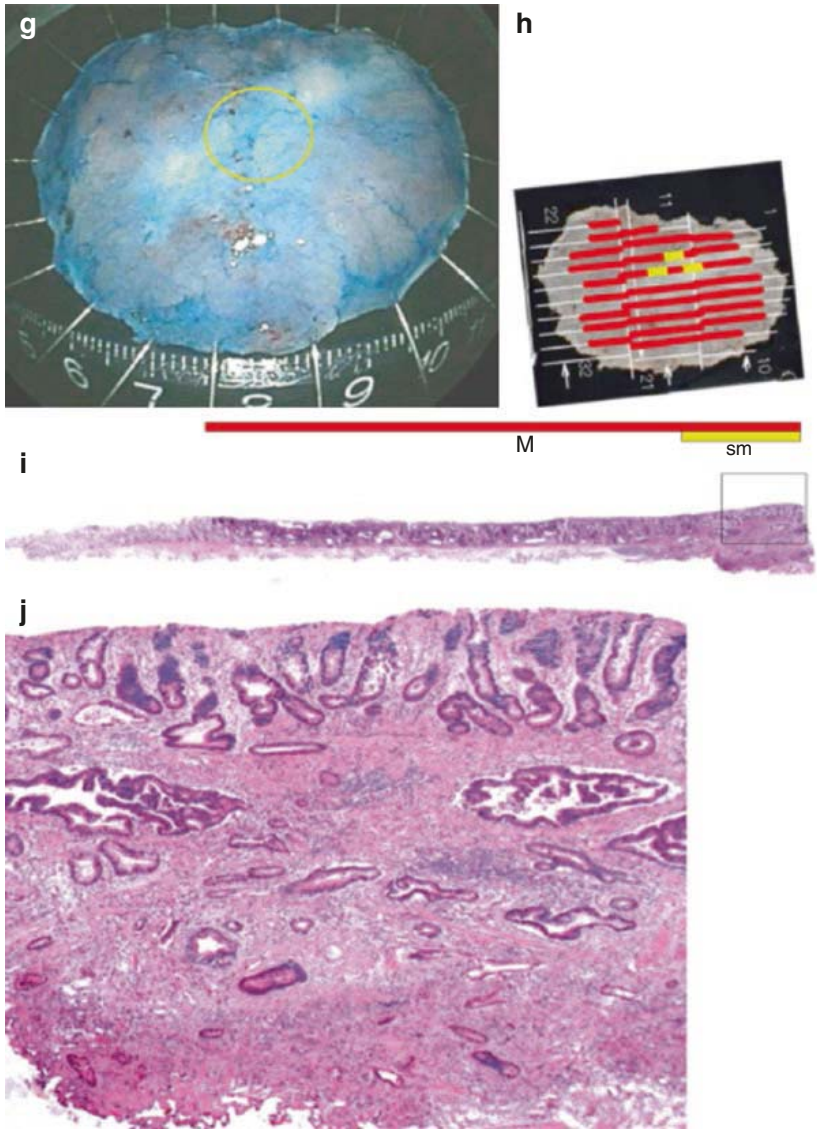


Fig. 11.31 (continued) (**g**) The specimen with safety margin was pinned and documented (*suspicious area marked*). (**h**) Specimen sections mapped for intramucosal (*red*) and sm-invasive (*yellow*) cancer. (**i**) Section (H&E stain) with maximum sm invasion (**j**). (**j**) H&E stain 100-fold. *Histopathology*: adenocarcinoma, tub1 > tub2, 48 × 37 mm, p*sm* > *3000 µm*, ly0, v0, HM0, *VM1*. Hemicolectomy with lymph node dissection was recommended

Note:

- ESD can provide precise histological information, especially when the pathologist is informed about suspicious areas.
- Histology may change the clinical strategy for cancer therapy.

Case 8: Rectal LST-G (Size ~5 cm)

Total colonoscopy was performed for a positive fecal occult blood test in this 48-year-old woman. A large rectal lesion (~5 cm) was pointed out (Fig. 11.32).

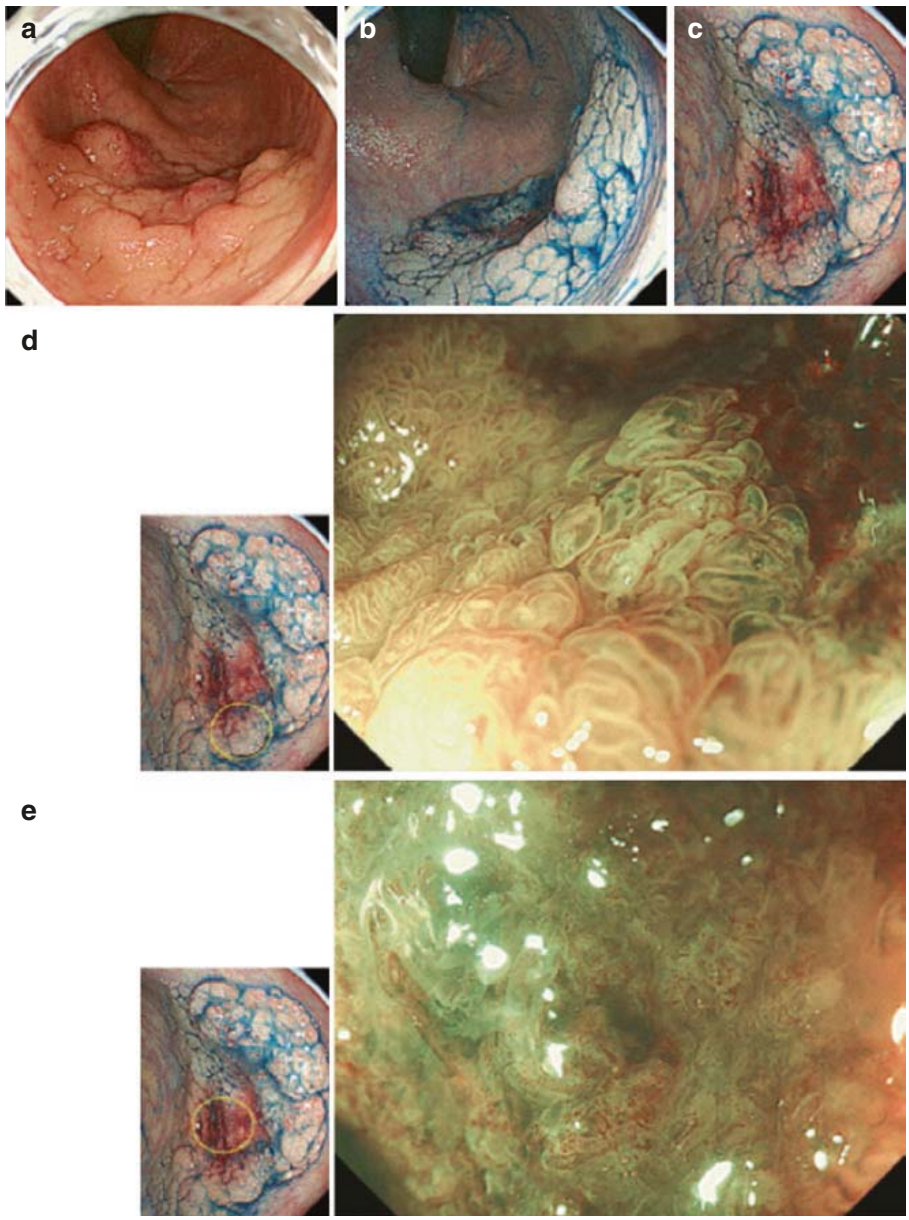


Fig. 11.32 (**a**) Rectal *LST-G (0-IIa + c)*, d ~5 cm, on WLI and (**b**, **c**) indigo carmine CE. (**d**) Vessels VP 2A (in 0-IIa margin, *left*) and (**e**) VP 2B (in 0-IIc lesion, *left*): Lesion JNET type 2B, on m-NBI (80×)

Note Preoperative endoscopic diagnosis is not always perfect.
Consider diagnostic ESD before recommending major surgery (especially anorectal surgery)

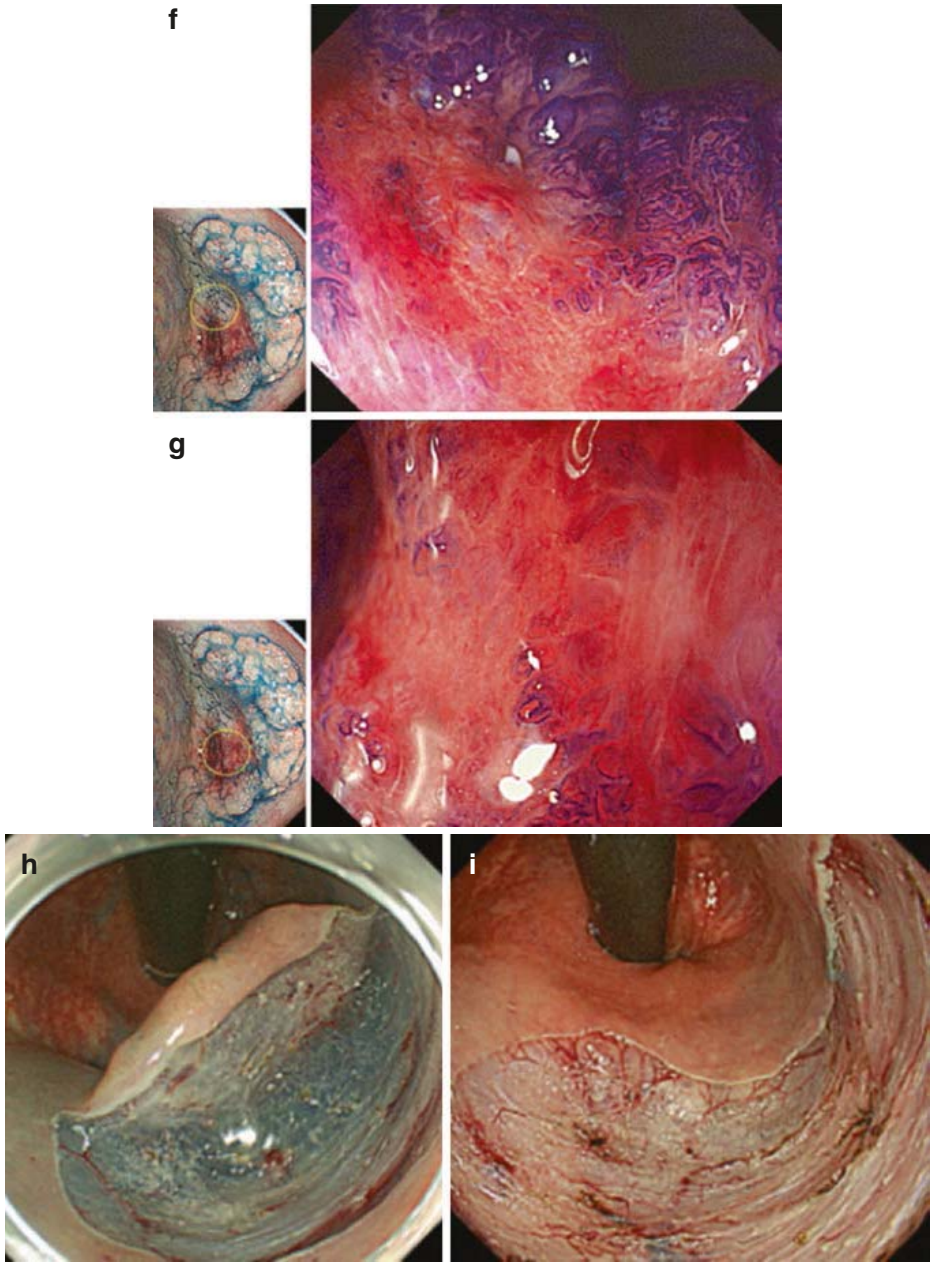


Fig. 11.32 (continued) Crystal violet stain (with little sticky mucus) shows (**f**) PP type IIIL in 0-IIa and (**g**) PP type Vn in 0-IIc part. *Clinical diagnosis*: *LST-G with deeply sm-invasive cancer (focal JNET type 3)*, sized 5 cm. (**h**, **i**) ESD was attempted for diagnostic purpose

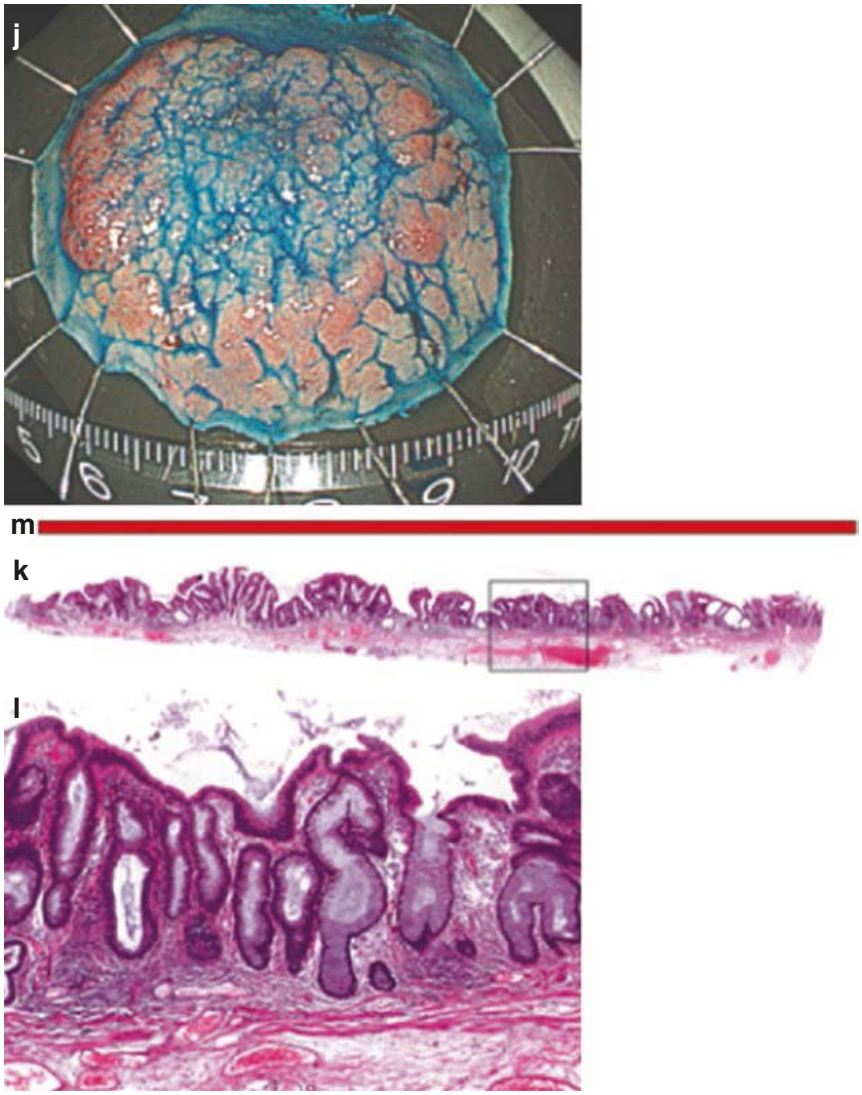


Fig. 11.32 (continued) (**j**) ESD specimen (indigo carmine): the surface structure of the neoplasia was slightly irregular after clearance of mucus. *Histology*: (**k**) Noninvasive (*m, red line = entirely mucosal*) tubulovillous adenoma (H&E stain, box **l**) with (**l**) focal high-grade dysplasia (H&E stain, 100-fold)

Case 9: Anal Squamous Cell Lesion 0-IIb-G (Size ~10 mm)

A 39-year-old woman had experienced painful anal itching and occasional minor contact bleeding for 2 months. Ano-/rectoscopy with magnifying (60-fold) colonoscope displayed in retroflex view a reddish, velvety lesion 0-IIb (10 × 10 mm) in the anoderm between the dentate line and anal verge at the left lateral side. Diagnostic biopsy was performed, and later curative ESD (Fig. 11.33).

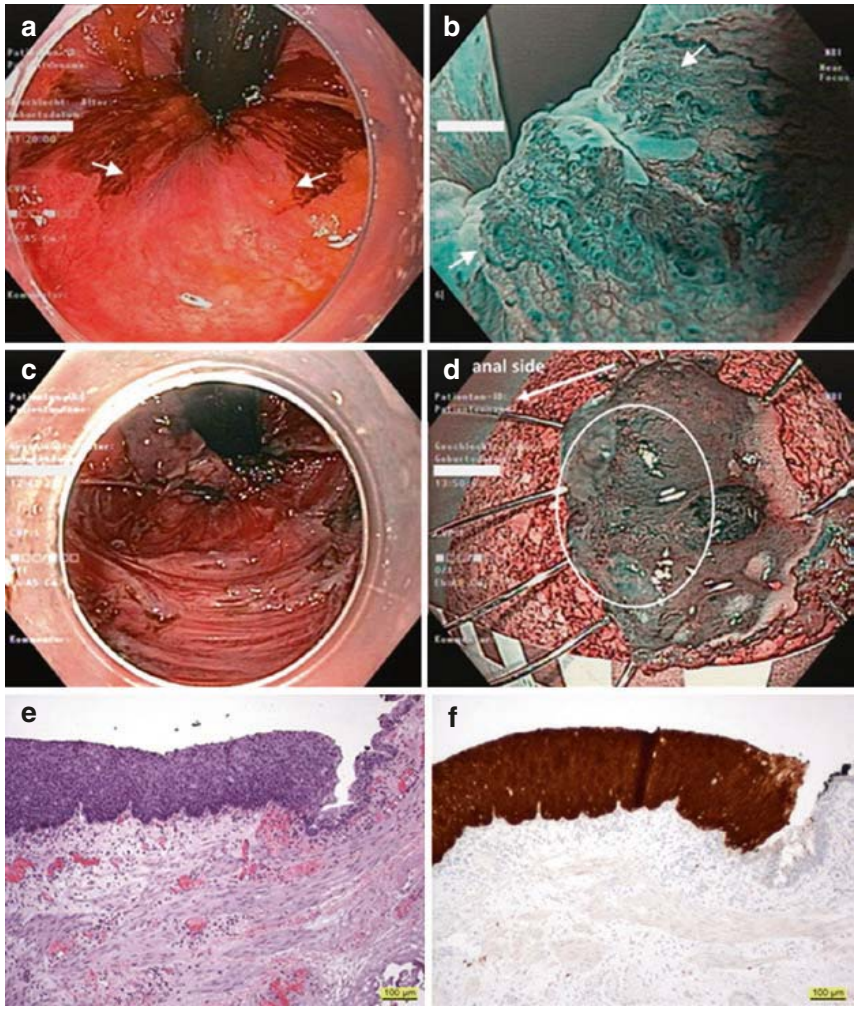


Fig. 11.33 (**a**) Lugol-voiding reddish lesion 0-IIb with clear margin (*arrows*) to Lugol-staining anoderm that also contrasts to columnar mucosa (squamocolumnar junction = dentate line), seen on WLI. (**b**) M-NBI (60×) showed a brownish-greenish discolored area (dense irregular MV) with irregular surface relief, loss of permeation of sm veins, and clear margins to non-keratinized anoderm, suspect for anodermal neoplasia. *Biopsy:* High-grade dysplasia (HGD), positive for HPV-16. (**c**) Resection bed after ESD en bloc. (**d**) ESD specimen (2.5 × 1.7 cm, with complete markings of safety margin). (**e**) Histology (H&E stain, 100×): *High-grade intraepithelial dysplasia,* free resection margins (*AIN III, R0*). (**f**) Immunohistochemistry (IHC) strongly positive for p16 protein (confirming AIN III). Not shown: In-situ hybridization ++ for high-risk HPV-16 in AIN (negative in anoderm). Follow-up after 9 months: Complete remission of the HPV-16–induced AIN (Modified from Wagner et al. [49] with permission of Thieme)

Note ESD can be considered for cure of intraepithelial neoplasias in anoderm, preferably in cooperation with dermatologist and proctologic surgeon.

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