

# Lesiones serradas: clasificación y seguimiento

**Dr. Antoni Castells**  
**Servicio de Gastroenterología**  
**Hospital Clínic, Barcelona**  
**([castells@clinic.cat](mailto:castells@clinic.cat))**



# Colorectal polyps

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- Non-neoplastic hyperplastic polyps (HPs)
- Neoplastic adenomas (tubular, tubulovillous, villous), cytologic dysplasia → **adenoma-carcinoma sequence**



Normal  
mucosa



Adenoma



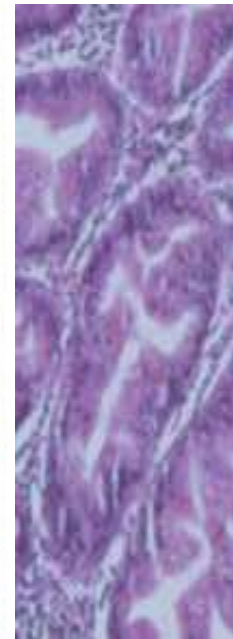
Carcinoma

- Jass (1983): relationship between HPs and CRC → **HP-carcinoma sequence**

# Serrated lesions

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- Heterogeneous group of polyps with serrated morphology
- Variable shape of CRC precursors → the word “lesion” is preferred
- Significant risk for neoplastic progression → 20-25% of sporadic or non-syndromic CRC (mainly proximal colon)



# Histologic classification of serrated lesions

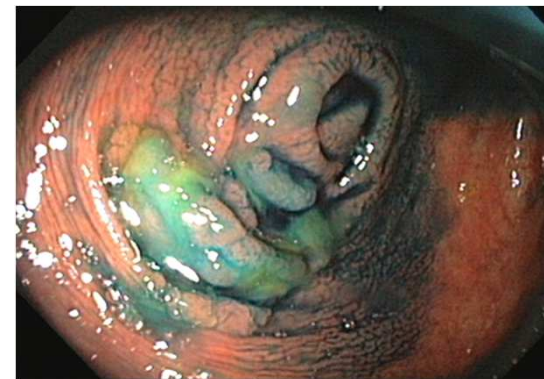
**TABLE 1. Comparison of 2 current histopathological classifications of serrated polyps/lesions according to Odze and Hornick<sup>28</sup> and Snover et al<sup>23</sup>**

Odze and Hornick 2009 <sup>28</sup> : type and synonym	Snover et al <sup>23</sup> : type and synonym
<b>I. Nondysplastic</b>	
<b>A. Normal architecture, normal proliferation</b>	
Hyperplastic polyps	Hyperplastic/metaplastic polyp
a. Goblet cell hyperplastic polyp	Microvesicular hyperplastic polyp
b. Microvesicular hyperplastic polyp	Goblet cell hyperplastic polyp
c. Mucin-poor hyperplastic polyp	
<b>B. Abnormal architecture, abnormal proliferation</b>	
Sessile serrated polyp	Sessile serrated adenoma/polyp serrated polyp with abnormal proliferation
<b>II. Dysplastic</b>	
A. Serrated adenoma (traditional)	Traditional serrated adenoma
B. Sessile serrated polyp with dysplasia mixed polyp, advanced sessile serrated polyp	serrated adenoma filiform serrated adenoma
C. Conventional adenoma with serrated architecture	Sessile serrated adenoma/polyp with dysplasia mixed hyperplastic-adenomatous polyp advanced sessile serrated adenoma/polyp
<b>III. Unclassifiable</b>	
Serrated polyp (either with or without dysplasia)	

# Clinical characteristics of serrated lesions

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- **Hyperplastic polyps (HP)**
  - 75% of serrated lesions
  - Sessile, pale-appearing, <5 mm
  - Common in rectosigmoid area → no malignant transformation
  - “High-risk” HPs: multiplicity(>20), >10 mm, proximal location, family history
- **Sessile serrated adenomas (SSA)**
  - 15-20% of serrated lesions
  - Sessile, pale-appearing lesion covered by mucus, >5 mm
  - Common in proximal colon
  - Female predominance, associated with aging



# Clinical characteristics of serrated lesions

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- **Traditional serrated adenomas (TSA)**
  - 1-6% of serrated lesions
  - Location: rectosigmoid (60%)
  - Pedunculated, >5 mm (>10 mm in the right colon)
  - Rate of malignant transformation similar to adenomas, and related to the size and location → large, proximal TSA may progress more rapidly

# Sessile serrated pathway

## Morphologic changes

Normal mucosa

↓  
ACF

↓  
MVHP

↓  
SSA

↓  
SSA-HGD

↓  
CRC

## Molecular changes

**BRAF** mutation

Apoptosis inhibition

*p16*, *IGFBP7*, others?  
methylation

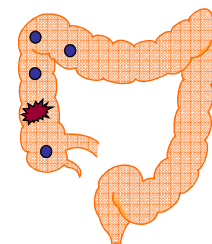
Neoplastic progression  
through CIMP-H

***MLH1***  
methylation

MSI-H tumors

*MCC / APC*  
methylation and/or  
*p53*, 18q LOH...

MSS tumors



- Proximal tumors
- Mutated *BRAF*
- CIMP-H
- MSI-H (MSS)
- *MLH1* loss

# Alternative serrated pathway

## Morphologic changes

Normal mucosa

↓  
ACF

↓  
HP

↓  
TSA/MP?

↓  
TSA-HGD?

↓  
CRC

## Molecular changes

*KRAS* mutation

Apoptosis inhibition

*p16*, *IGFBP7*, others?  
methylation

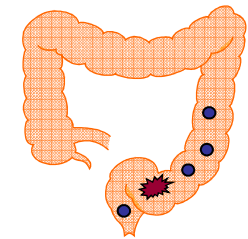
Neoplastic progression  
through CIMP-L

*MGMT*  
methylation

MSI-L tumors

*MCC / APC*  
methylation and/or  
*p53*, 18q LOH...

MSS tumors



- Distal tumors
- Mutated *KRAS*
- CIMP-L
- MSS / MSI-L



# Endoscopic detection of serrated lesions

## Detection rate of proximal serrated polyps in screening colonoscopy

Endoscopist	Number of colonoscopies	Patient age <sup>a</sup>	Male	≥1 Adenoma	≥1 Proximal serrated polyp	Adenoma detection rate per colonoscopy <sup>a</sup>	Proximal serrated polyp detection rate per colonoscopy <sup>a</sup>
1	3189	59.8 ± 8.0	52%	47%	18%	1.06 ± 1.79	0.26 ± 0.68
2	154	57.8 ± 8.0	45%	31%	10%	0.76 ± 1.59	0.14 ± 0.46
3	532	57.4 ± 7.3	45%	33%	6%	0.73 ± 1.57	0.08 ± 0.35
4	109	58.2 ± 7.0	46%	39%	11%	0.86 ± 1.46	0.18 ± 0.55
5	331	57.4 ± 6.9	48%	40%	13%	0.77 ± 1.36	0.18 ± 0.53
6	124	58.4 ± 6.9	44%	33%	8%	0.77 ± 1.66	0.11 ± 0.41
7	528	58.9 ± 7.7	41%	31%	11%	0.69 ± 1.47	0.16 ± 0.48
8	56	59.2 ± 7.6	50%	46%	13%	1.20 ± 1.86	0.14 ± 0.40
9	348	57.7 ± 7.5	37%	36%	12%	0.74 ± 1.48	0.17 ± 0.52
10	359	57.7 ± 7.3	53%	25%	3%	0.45 ± 1.05	0.04 ± 0.20
11	90	57.7 ± 6.7	52%	17%	1%	0.22 ± 0.56	0.01 ± 0.11
12	83	59.1 ± 8.3	52%	27%	2%	0.46 ± 0.98	0.02 ± 0.15
13	327	58.1 ± 7.8	60%	29%	11%	0.50 ± 0.95	0.15 ± 0.49
14	297	59.5 ± 8.2	50%	21%	4%	0.38 ± 1.07	0.06 ± 0.37
15	154	57.8 ± 8.0	45%	31%	10%	0.76 ± 1.59	0.14 ± 0.46
Combined	6681	58.9 ± 7.8	49%	38%	13%	0.84 ± 1.60	0.19 ± 0.57

<sup>a</sup>Mean ± SD.

# Endoscopic detection of serrated lesions

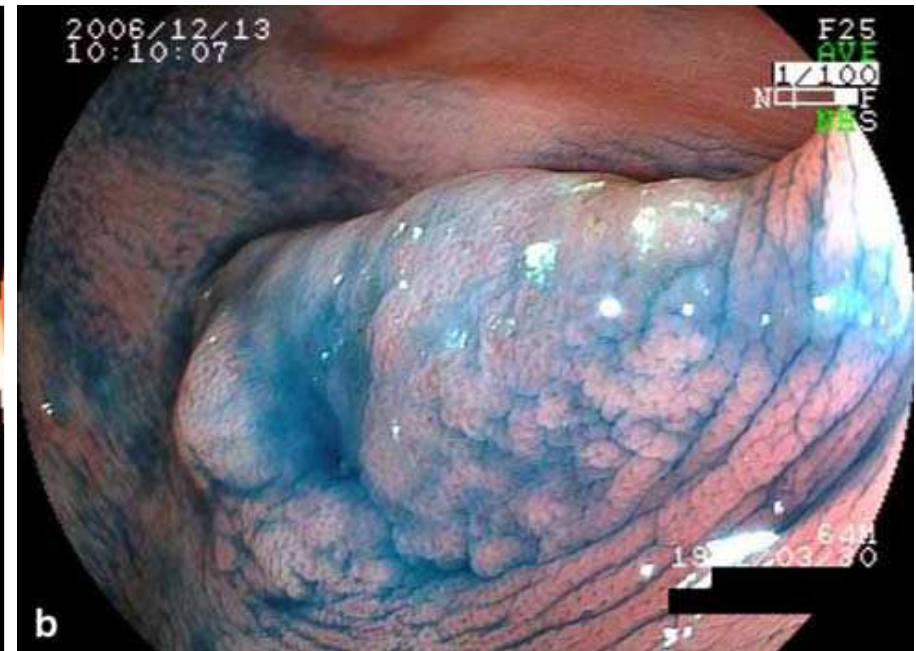
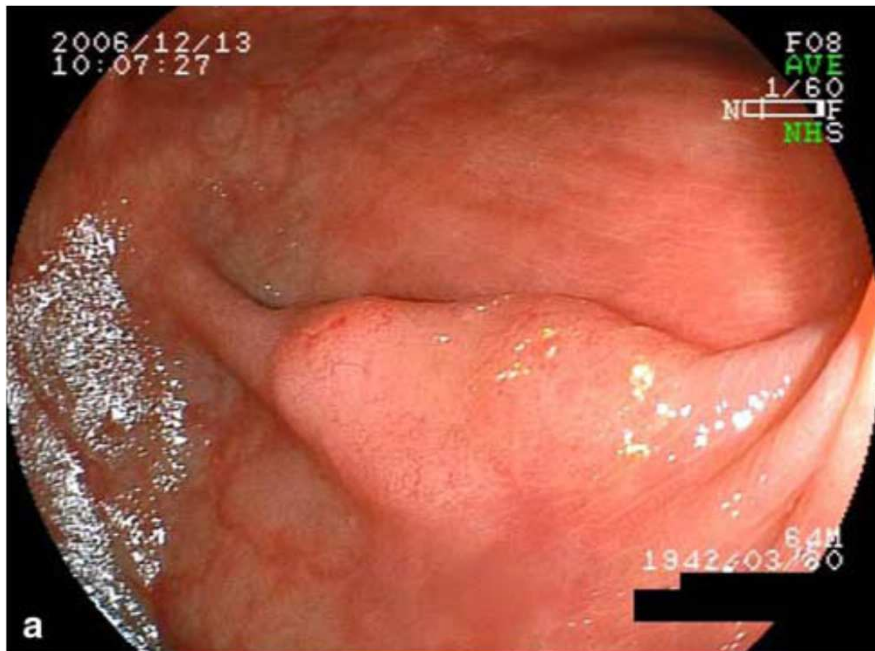
## Detection rate of proximal serrated polyps per endoscopist

Comparison (vs endoscopist 1)	Odds ratio (95% CI)	P value
Endoscopist 2	0.50 (0.29–0.85)	.0114
Endoscopist 3	0.31 (0.21–0.44)	<.0001
Endoscopist 4	0.57 (0.31–1.05)	.0701
Endoscopist 5	0.67 (0.48–0.94)	.0198
Endoscopist 6	0.40 (0.21–0.78)	.0066
Endoscopist 7	0.59 (0.45–0.79)	.0003
Endoscopist 8	0.66 (0.30–1.46)	.3055
Endoscopist 9	0.65 (0.47–0.91)	.0111
Endoscopist 10	0.16 (0.09–0.29)	<.0001
Endoscopist 11	0.05 (0.01–0.37)	.0033
Endoscopist 12	0.11 (0.03–0.46)	.0025
Endoscopist 13	0.57 (0.40–0.82)	.0021
Endoscopist 14	0.19 (0.11–0.35)	<.0001
Endoscopist 15	0.50 (0.29–0.85)	.0114

CI, confidence interval.

# Endoscopic appearance of serrated lesions

- Frequently flat or sessile
- Covered by mucus
- Overlooked during colonoscopy: missed lesions → **interval CRC**
  - Right sided
  - Microsatellite instability (MSI)
  - CIMP-H



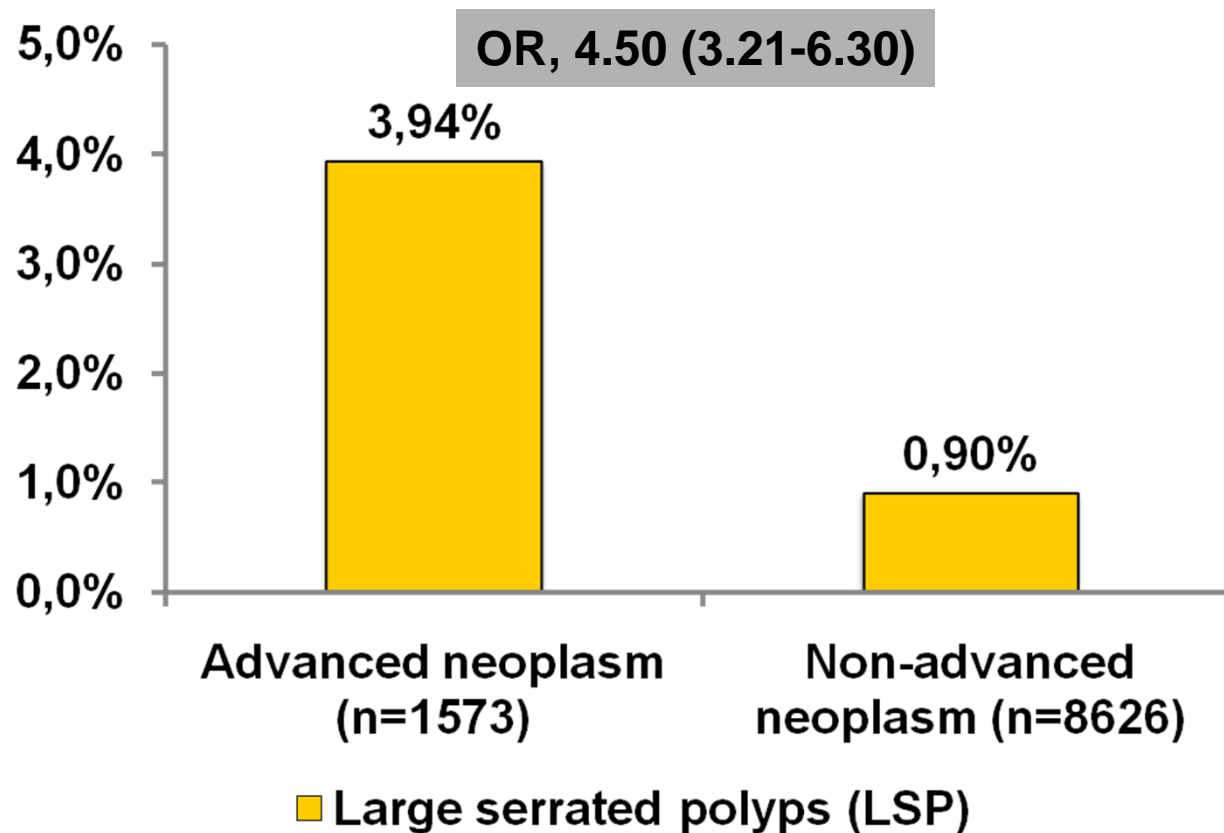
# Risk of malignant transformation

## Large serrated polyps (LSPs) as **predictive factors of advanced neoplasia**

	Subjects <u>without</u> advanced neoplasia (n = 8626)	Subjects <u>with</u> advanced neoplasia (n = 1573)	Univariate analysis, OR (95% CI)
Age	57.7 ± 15.1	65.2 ± 12.0	
<65 y	5487	730	1.00
≥65 y	3139	843	2.02 (1.81–2.25) <sup>b</sup>
Gender			
Female	4348	594	1.00
Male	4278	979	1.68 (1.50–1.87) <sup>b</sup>
Number of small adenomas <sup>a</sup>			
0–3	8537	1470	1.00
≥4	89	103	6.72 (5.03–8.97) <sup>b</sup>
LSPs			
No	8548	1511	1.00
Yes	78	62	4.50 (3.21–6.30) <sup>b</sup>

# Risk of malignant transformation (I)

Large serrated polyps (LSPs) as **predictive factor of advanced neoplasia**



Hiraoka *et al.* Gastroenterology 2010

# Risk of malignant transformation (I)

## Predictive factors of advanced neoplasia according to location (multivariate analysis)

Variables	<u>Distal advanced</u> neoplasia, OR (95% CI)	<u>Proximal advanced</u> neoplasia, OR (95% CI)
Age $\geq 65$	1.76 (1.55–2.00) <sup>b</sup>	2.05 (1.72–2.43) <sup>b</sup>
Male gender	1.72 (1.52–1.97) <sup>b</sup>	1.34 (1.13–1.60) <sup>c</sup>
Number of small ademonas $\geq 4$ <sup>a</sup>	3.74 (2.74–5.08) <sup>b</sup>	4.85 (3.41–6.79) <sup>b</sup>
LSPs	2.96 (2.01–4.29) <sup>b</sup>	3.63 (2.29–5.55) <sup>b</sup>

# Risk of malignant transformation (II)

## ColonPrev study (colonoscopy arm, 5,059 individuals)

Patients with serrated polyps <sup>‡</sup>	1054 (20.8)
No. of serrated polyps/patient	
1	588 (11.6)
2	223 (4.4)
3	110 (2.2)
4	48 (0.9)
≥5	85 (1.7)
Proximal <sup>§</sup> serrated polyps <sup>‡</sup>	329 (6.5)
Large <sup>  </sup> serrated polyps <sup>‡</sup>	90 (1.8)
Large serrated proximal polyps <sup>‡</sup>	36 (0.7)



# Risk of malignant transformation (II)

**TABLE 3. Predictive factors of advanced neoplasia according to location (multivariate analysis)**

<b>Variable</b>	<b>Proximal* advanced neoplasia† OR (95% CI)</b>	<b>Distal advanced neoplasia† OR (95% CI)</b>
Serrated polyps‡		
No		1
Yes		1.49 (1.15-1.95)
Large§ serrated polyps‡		
No	1	1
Yes	4.15 (1.69-10.15)	2.61 (1.48-4.58)



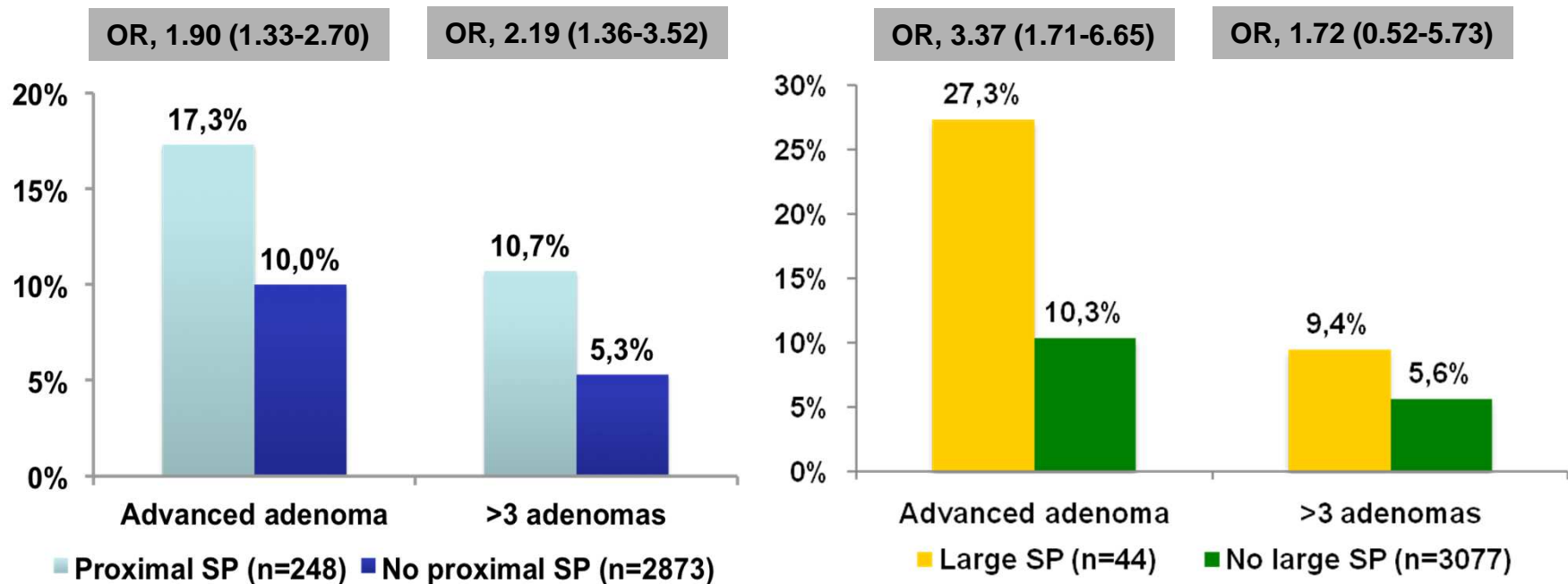
# Risk of malignant transformation (III)

Prevalence of advanced / multiple adenomas in patients with and without **proximal** and **large serrated polyps**

Baseline	Advanced adenoma	≥3 Tubular adenomas <sup>a</sup>
Proximal ND-SP (n = 248), %	17.3	10.7
No Proximal ND-SP (n = 2873), %	10.0	5.3
OR (95% CI)	1.90 (1.33–2.70)	2.19 (1.36–3.52)
Large ND-SP (n = 44), %	27.3	9.4
No Large ND-SP (n = 3077), %	10.3	5.6
OR (95% CI)	3.37 (1.71–6.65)	1.72 (0.52–5.73)

# Risk of malignant transformation (III)

Prevalence of advanced / multiple adenomas in patients with and without **proximal** and **large serrated polyps**



# Risk of malignant transformation (III)

## Proximal serrated polyps as a risk factor of advanced neoplasia on follow-up

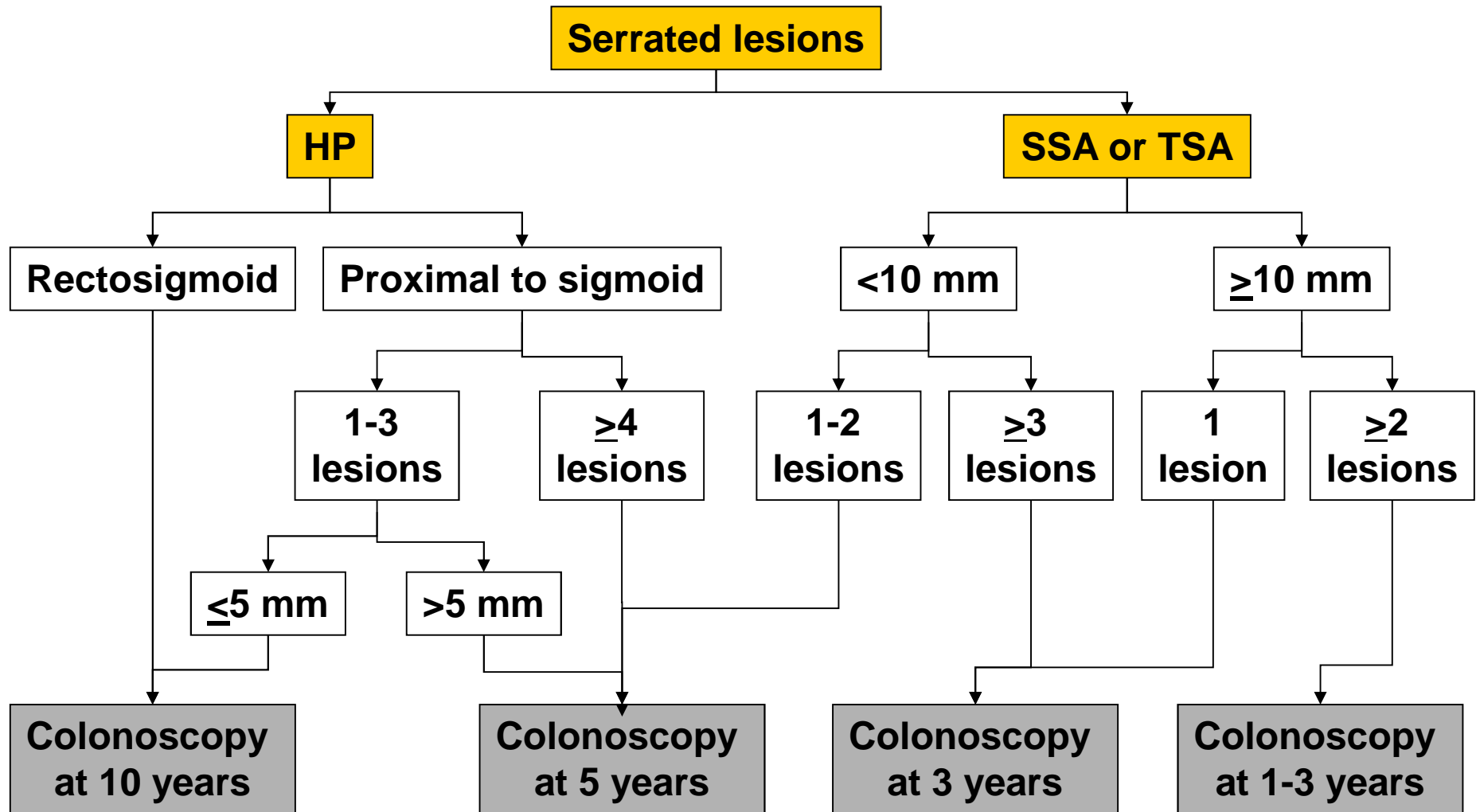
Findings on baseline CSP	Baseline CSP (n)	Subjects with follow-up CSP, n (%)	Advanced neoplasia on follow-up CSP, n (%)	OR (95% CI)
<u>No neoplasia</u>	1950	454		
With proximal ND-SP	118	39 (33.1)	2 (5.1)	2.09 (0.44–9.87)
Without proximal ND-SP	1832	415 (22.6)	11 (2.7)	
<u>Small tubular adenoma &lt;10 mm</u>	842	634		
With proximal ND-SP	87	63 (72.4)	5 (7.9)	1.23 (0.46–3.28)
Without proximal ND-SP	755	571 (75.6)	36 (6.3)	
<u>Advanced neoplasia</u>	329	283		
With proximal ND-SP	43	38 (88.4)	11 (28.9)	2.25 (1.02–4.96)
Without proximal ND-SP	286	245 (85.7)	36 (14.7)	

# Surveillance strategies in serrated lesions

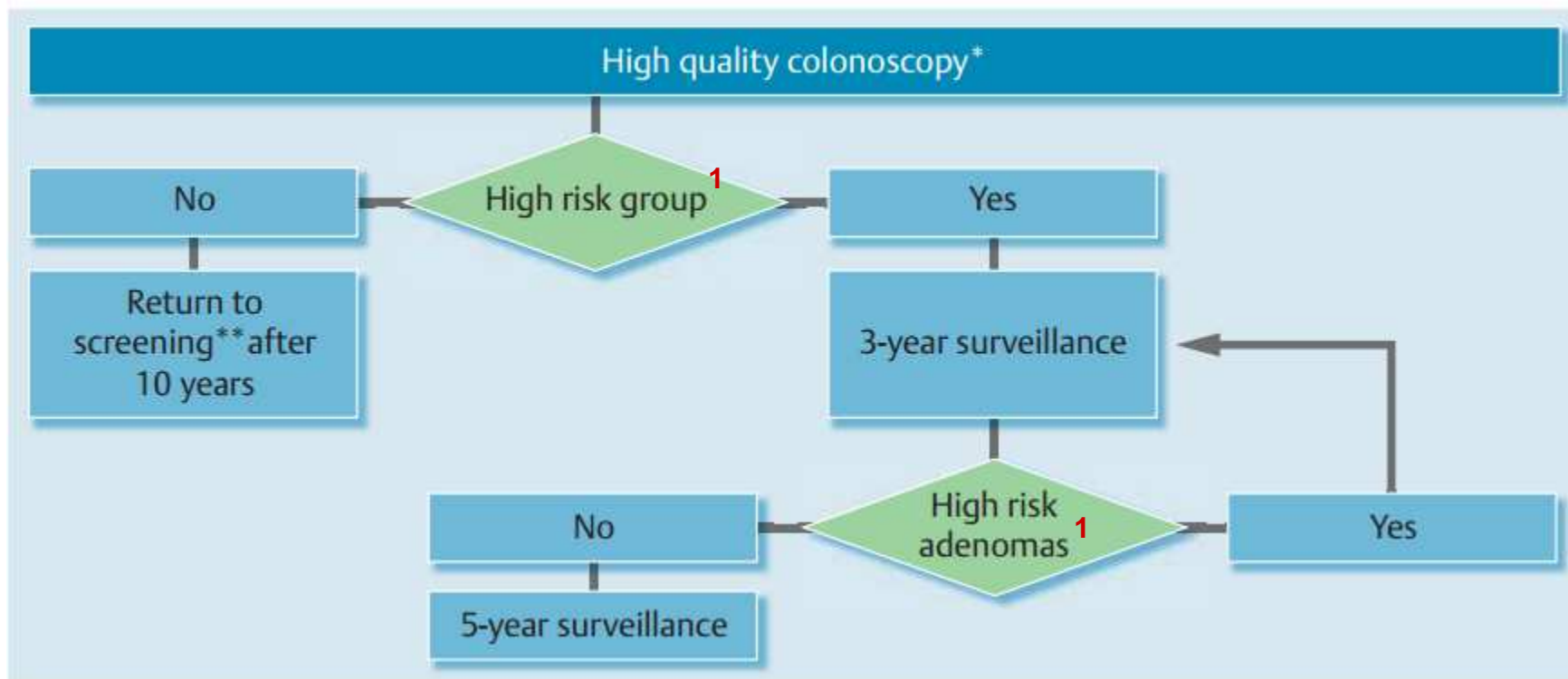
TABLE 3. Guidelines for colorectal carcinoma colonoscopy screening and surveillance after the removal of serrated lesions according to the European Union<sup>15</sup> and National Comprehensive Cancer Network<sup>72-74</sup> recommendations, and the risk of malignant transformation<sup>14</sup>

Diagnosis	Risk of colorectal carcinoma <sup>14</sup>	Interval for control <sup>*,†</sup>
Hyperplastic polyp	None	No indication for follow-up
Sessile serrated lesion	Slightly increased, but exact data are missing	5 or 3 or 1 y
Traditional serrated adenoma	Increased	5 or 3 or 1 y

# Surveillance strategies in serrated lesions (ASGE)



# Surveillance strategies in adenomas and serrated lesions (ESGE)



<sup>1</sup>High risk group: patients with an adenoma  $\geq 10$  mm; or with high-grade dysplasia; or a villous component; or  $\geq 3$  adenomas; and **patients with a serrated lesion  $\geq 10$ mm or with dysplasia.**



# Risk stratification of patients with colorectal adenomas **and/or** serrated polyps, and postpolypectomy surveillance

Risk stratum	Diagnostic criteria <sup>2</sup>	Surveillance strategy
No-risk lesions	Hyperplastic polyps < 10 mm limited to rectum and sigmoid colon	Return to the screening program
Low-risk lesions <sup>3</sup>	1 – 2 tubular adenomas < 10 mm with low-grade dysplasia, or 1 – 2 serrated polyps < 10 mm without dysplasia <sup>4, 5</sup>	Return to the screening program
Intermediate-risk lesions <sup>6</sup>	3 – 4 tubular adenomas < 10 mm with low-grade dysplasia, or 1 – 4 tubular adenomas 10 – 19 mm with low-grade dysplasia, or 1 – 4 adenomas < 20 mm with villous component, and/or high-grade dysplasia, and/or intramucosal carcinoma, or 3 – 4 serrated polyps < 10 mm without dysplasia <sup>4, 5</sup> , or 1 – 4 serrated polyps 10 – 19 mm without dysplasia <sup>4, 5</sup> , or 1 – 4 serrated polyps < 20 mm with dysplasia <sup>4, 5</sup>	Colonoscopy at 3 years
High-risk lesions	≥ 5 adenomas/serrated polyps <sup>4</sup> , or ≥ 1 adenoma/serrated polyp <sup>4</sup> ≥ 20 mm	Colonoscopy at 1 year <sup>7</sup>

# Summary

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- Serrated lesions are the **precursors of up to one-third of CRC**
- CRC arising in serrated lesions are usually in the **proximal colon**
- Serrated lesions should be classified in **HP, SSA** with and without dysplasia, and **TSA** (WHO criteria)
- Serrated lesions have a **distinct endoscopic appearance**, and they are more difficult to detect
- Recommendations for **postpolypectomy surveillance** are mostly based on features of serrated lesions associated with increased risk of advanced neoplasms.



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