

When is it Important to Report Tumor Budding?

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When is it Important to Report Tumor Budding?

- Recommended to be reported in
 - pT1 cancers arising in polyps and other stage I carcinomas
 - Stage II cases

Tumor Budding

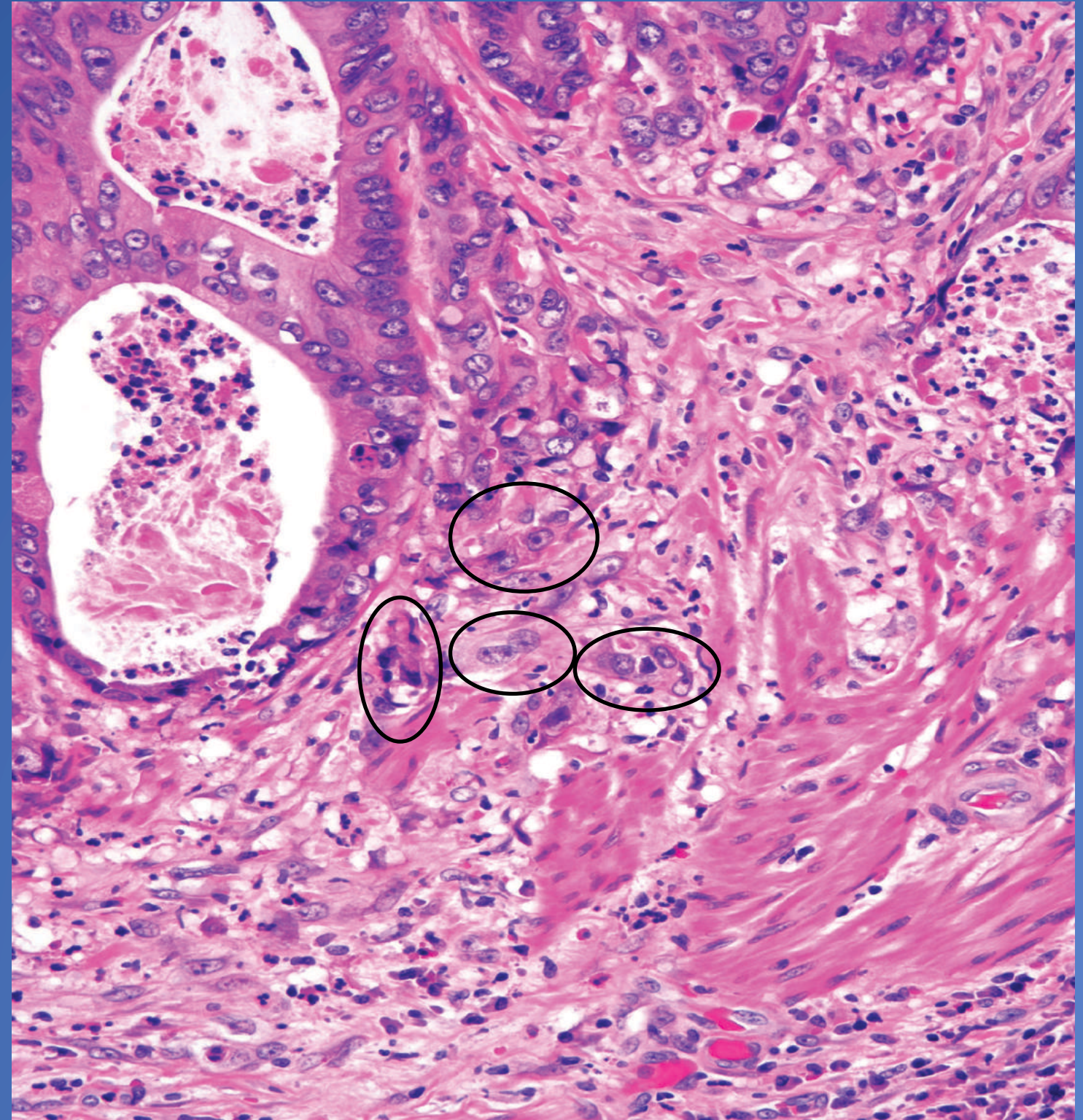
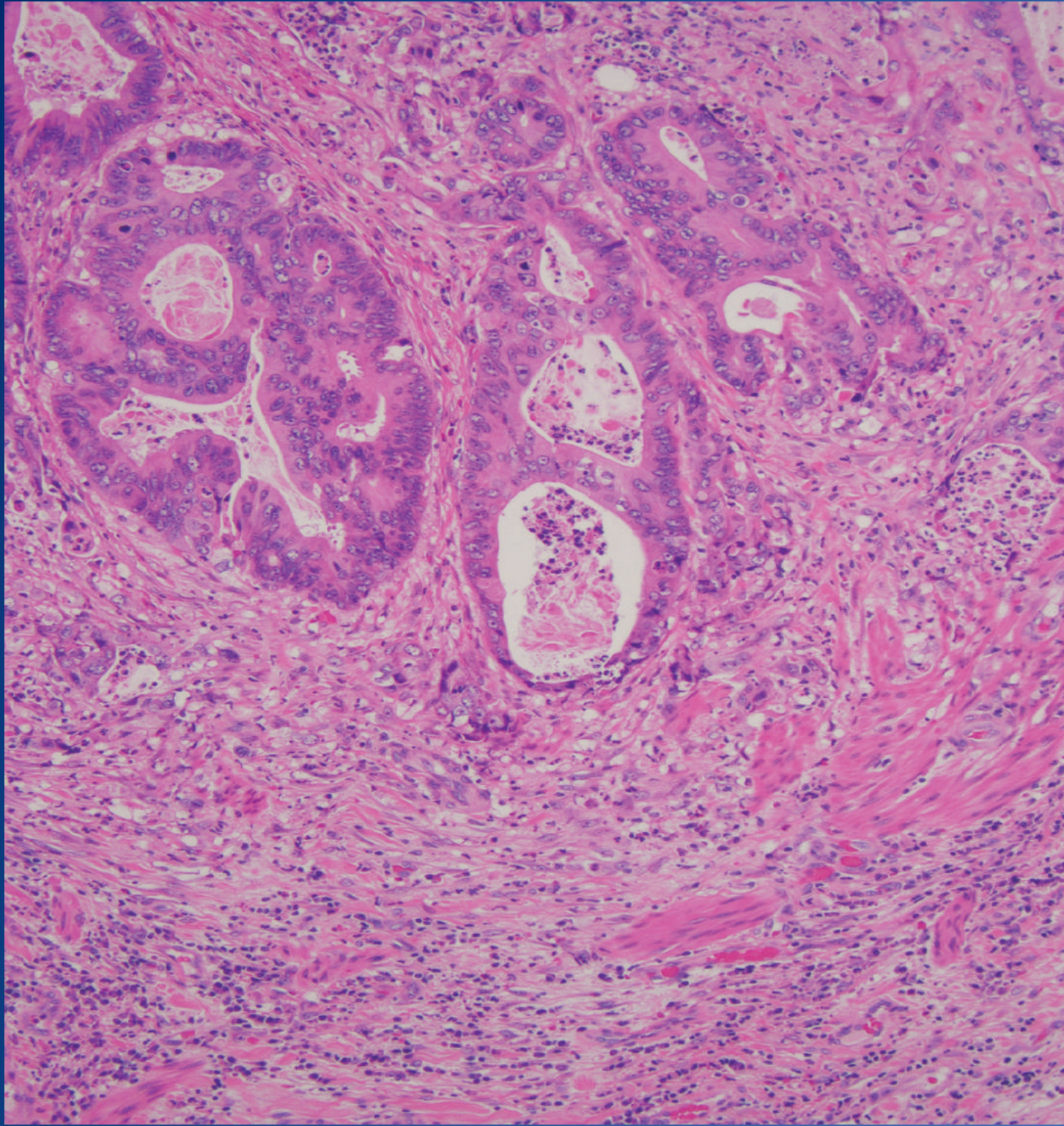
- Single cells or clusters of <5 cells at the advancing edge of a colorectal adenocarcinoma
- Thought to herald epithelial-mesenchymal transition
- Often observed in cancers with other histologic features of aggressive behavior, including advanced TNM stage, high tumor grade, lymphovascular and perineural invasion
- Independent adverse prognostic indicator

International Tumor Budding Consensus Conference (ITBCC), 2016

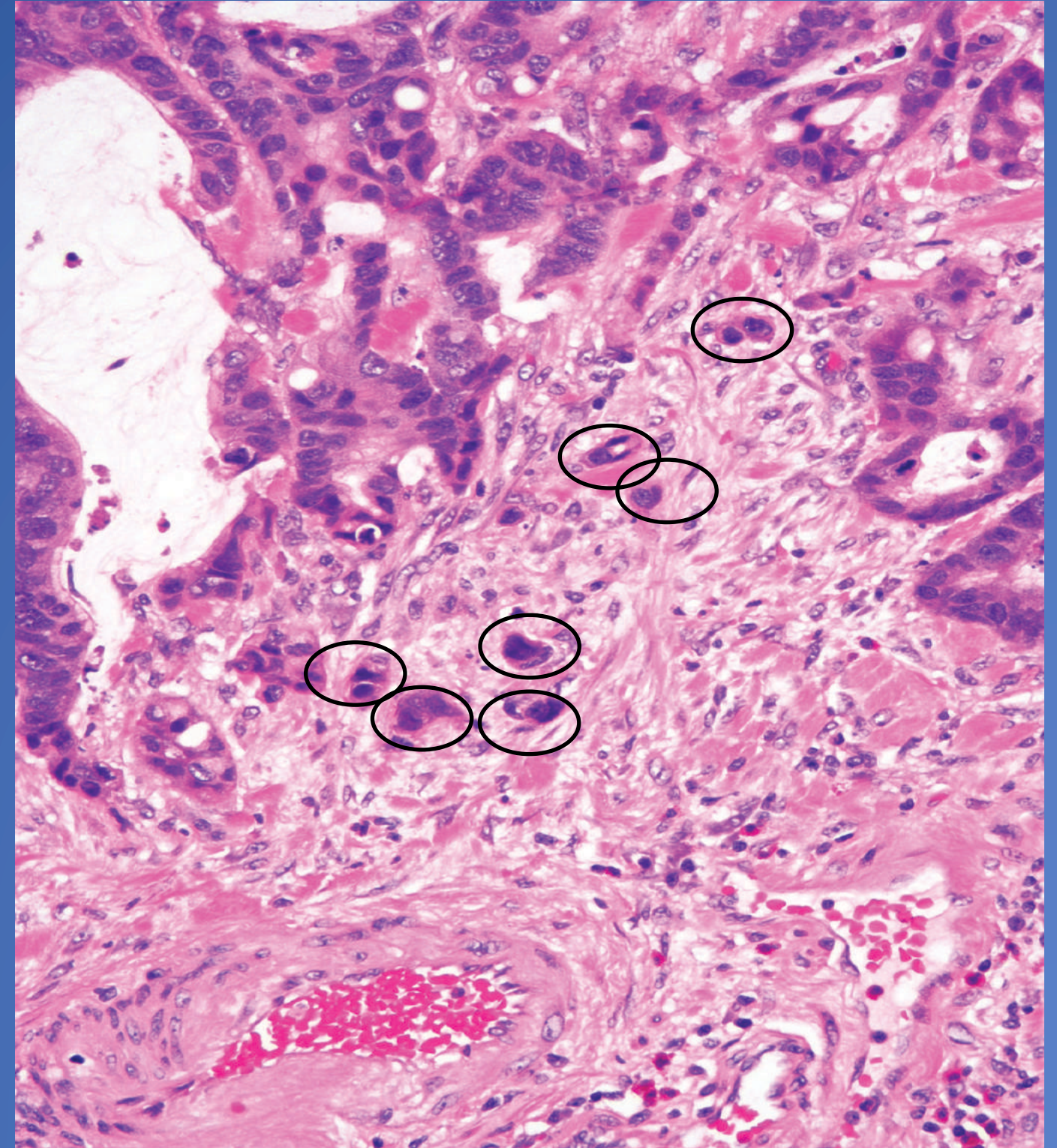
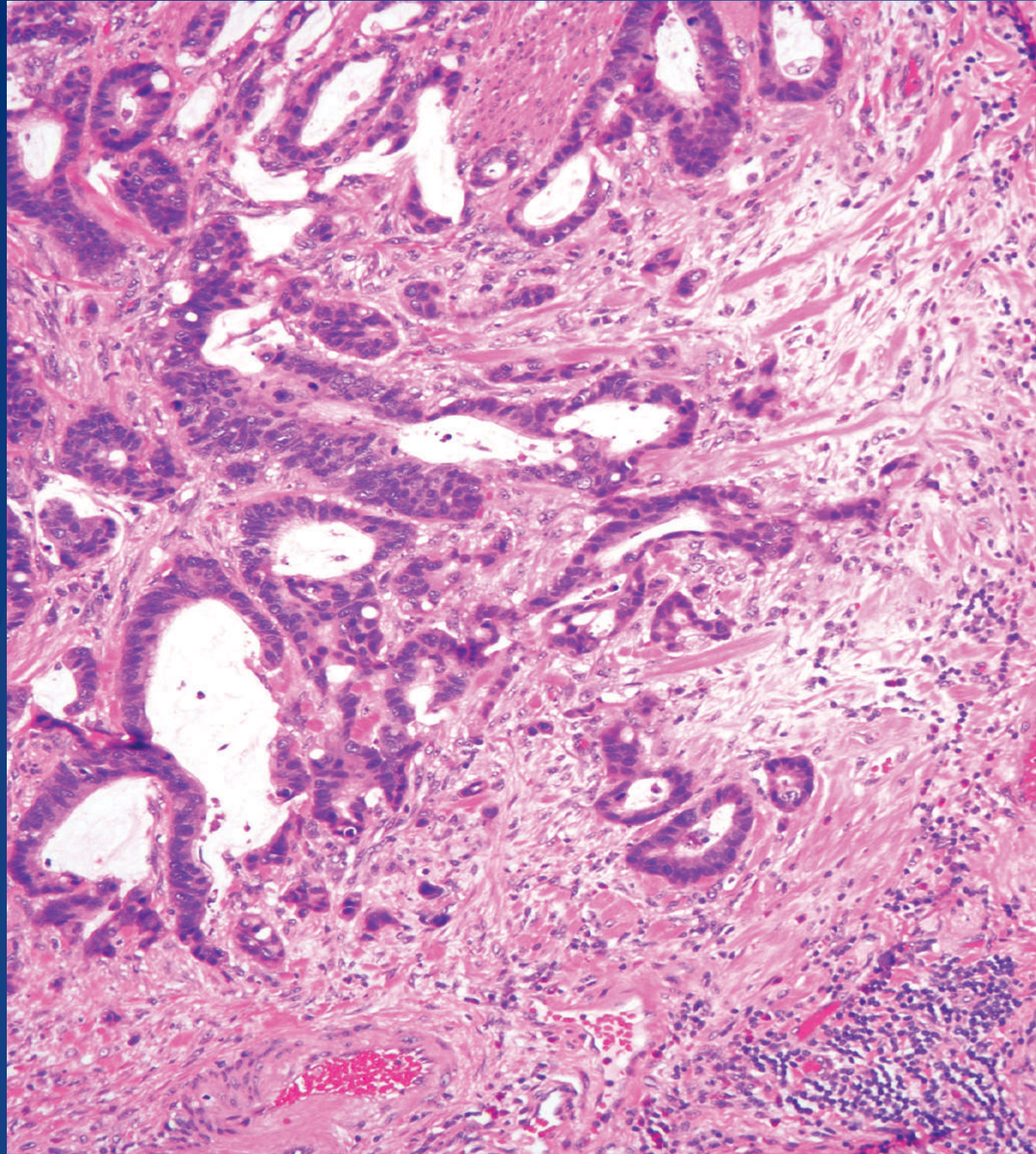
- Tumor budding should be evaluated in H&E stained sections
- “Hotspot” selected after review of the advancing edge
- Total number of buds in a 0.785mm² area (a 20x field on most microscopes) should be reported
- Cytokeratin may help, but grading should be done on H&E

Number of Tumor Buds in the Hotspot	Grade
0-4	Low
5-9	Intermediate
≥10	High

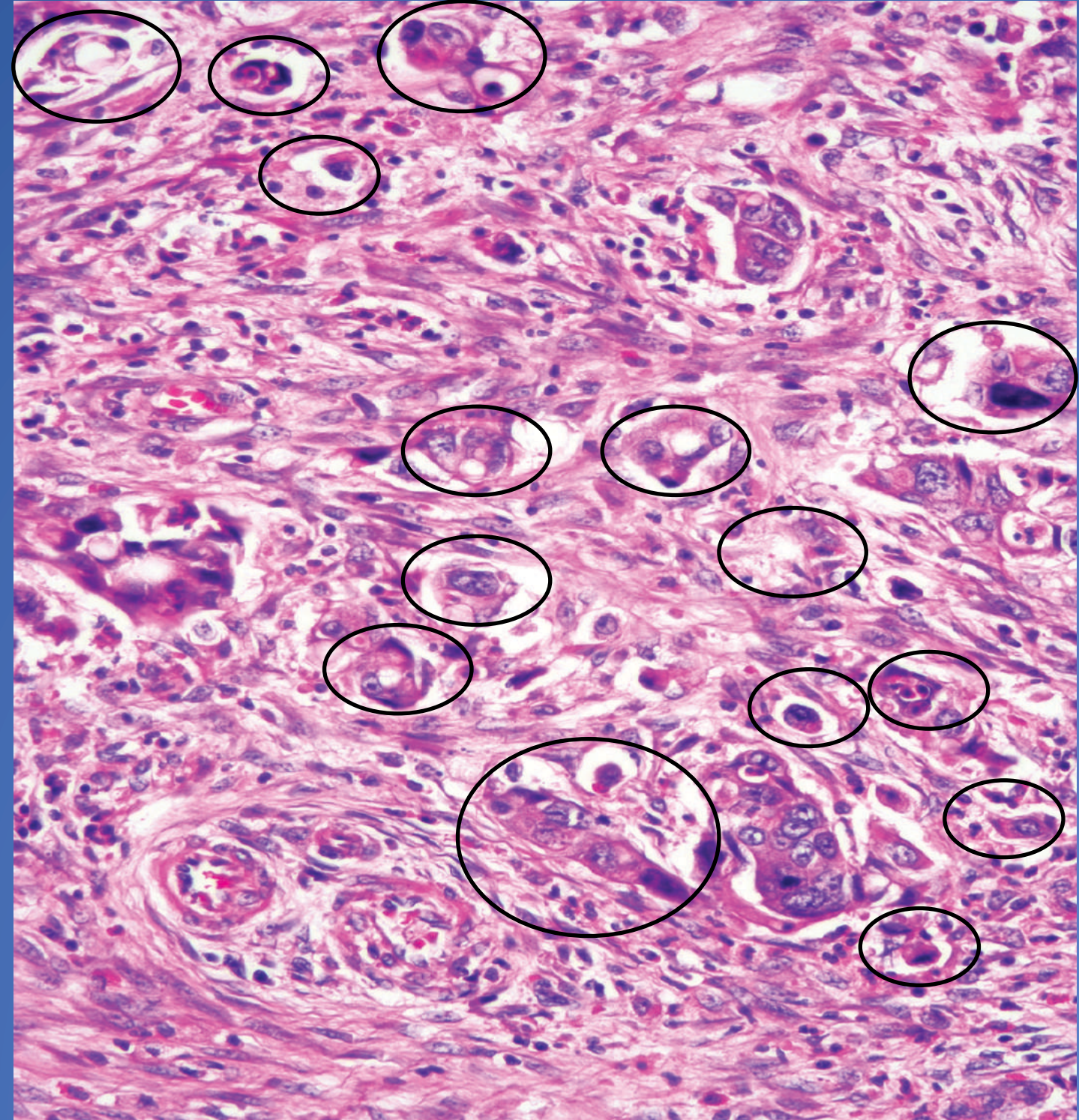
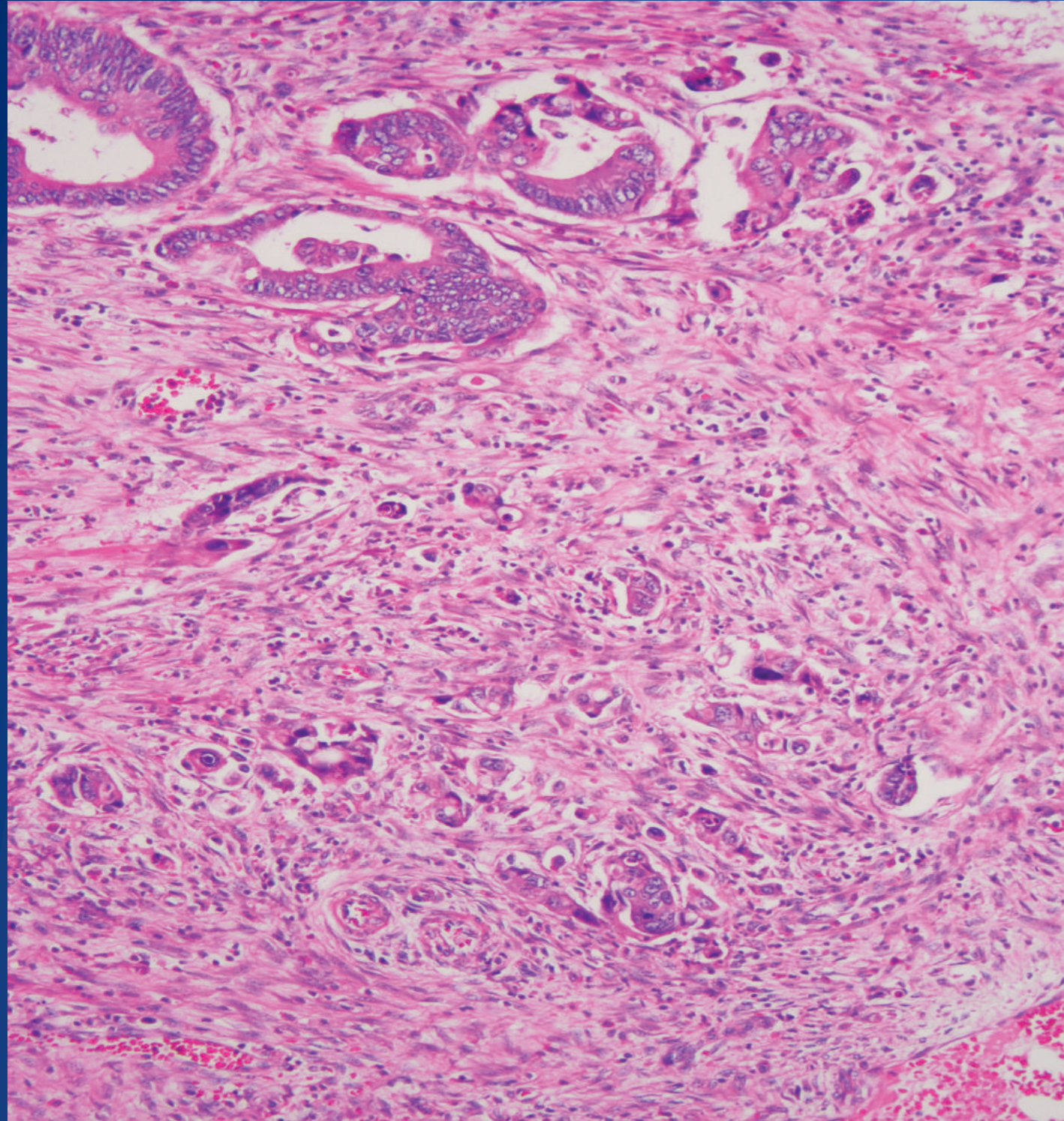
Low-Grade Budding



Intermediate-Grade Budding



High-Grade Budding



Tumor Budding is of Particular Importance in Low-Stage Colorectal Cancers

- *“This is not a required element, but it is recommended that this feature be reported for **cancers arising in polyps** as well as for **stage I and II cases.**” - CAP protocol, 2018*
- Predicts lymph node metastases in endoscopically resected pT1 colorectal cancers
 - Triage of patients for additional surgery
- Independent predictor of survival in stage II colorectal cancer
 - Shorter progression-free and cancer-specific survival seen in patients with high-grade tumor budding in numerous studies
 - Triage of patients for adjuvant therapy

We asked you...

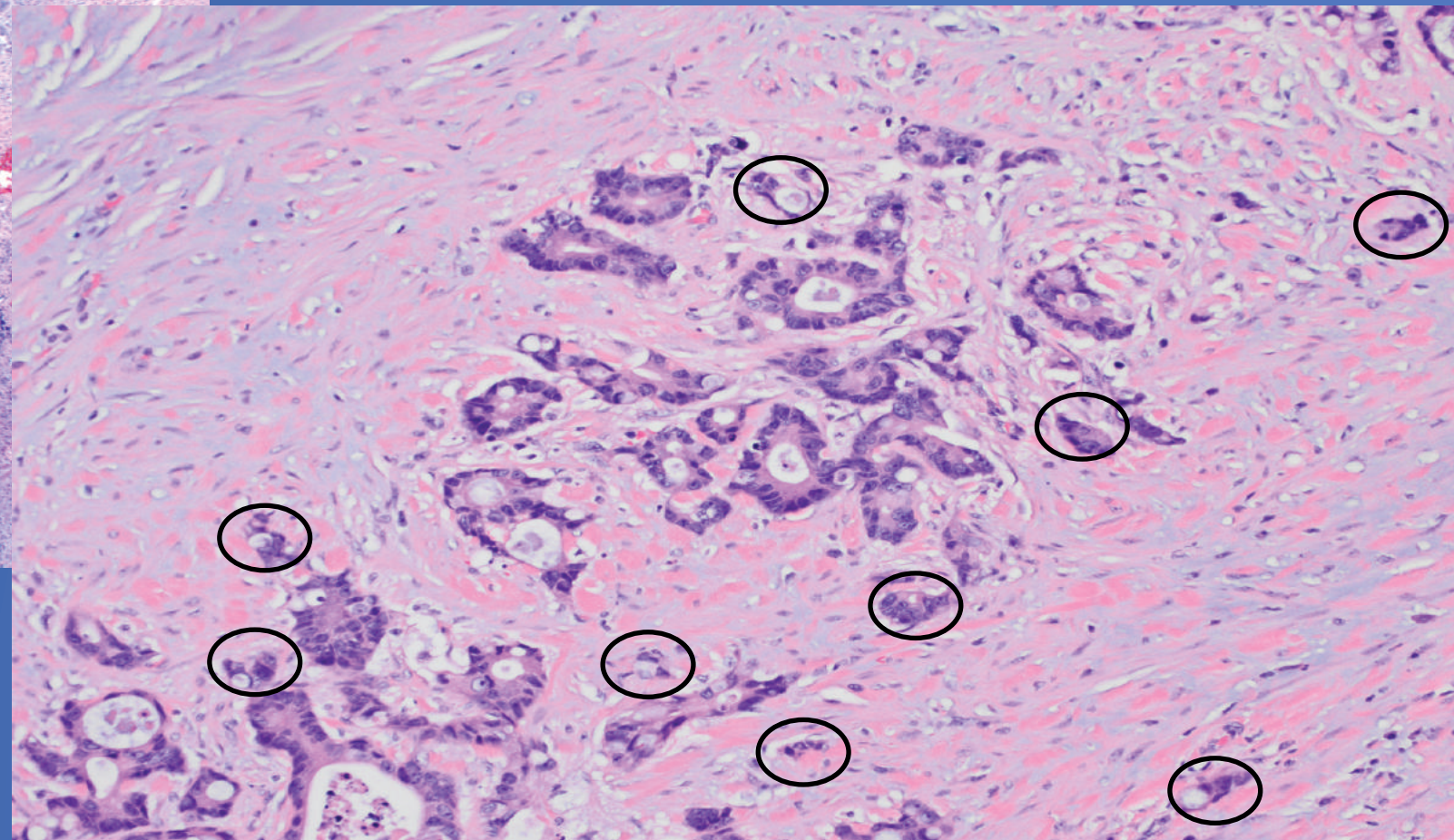
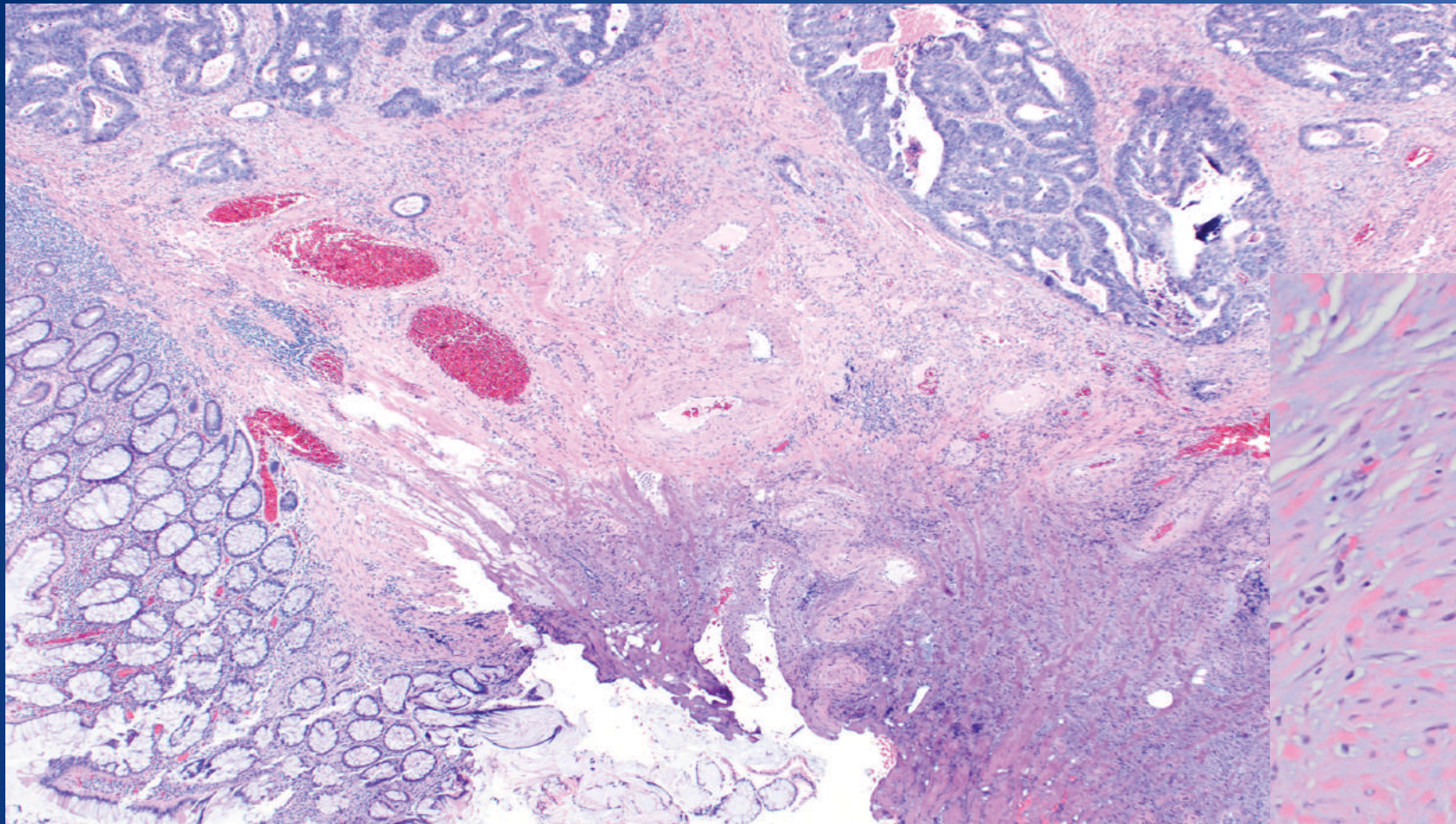
- When and how do you report tumor budding?
- Do you use cytokeratin?

You answered...

- I report tumor budding in
 - Every case (40%, n=22)
 - Stage I and II cases and pT1 cancer in a polypectomy (40%, n=22), *i.e.* as recommended, but not required, by CAP
 - I usually do not report tumor budding (20%, n=11)
- Most (69%) do not use cytokeratin stains to assess tumor budding

We asked you...

You are examining a colon polypectomy that contains pT1 adenocarcinoma with low-grade morphology, no lymphovascular invasion, and a clear margin. You also note a maximum of 9 tumor buds in the “hotspot” field. How do you comment on tumor budding?



You answered...

- I report intermediate-grade tumor budding with (35%) or without (53%) the specific number of buds in the “hotspot field”

Tumor Budding Predicts Lymph Node Metastases in pT1 Adenocarcinoma

Study	Budding Criteria	Total Case #	Lymph node metastases (#, %)	OR in Multivariate analysis
Ueno et al., 2004	>5	251	33 (13%)	3.7
Tateishi et al., 2010	any	322	46 (14%)	2.59
Nakadoi et al., 2012	>5	499	41 (8%)	5
Lee et al., 2018	>3.5	133	16 (12%)	10

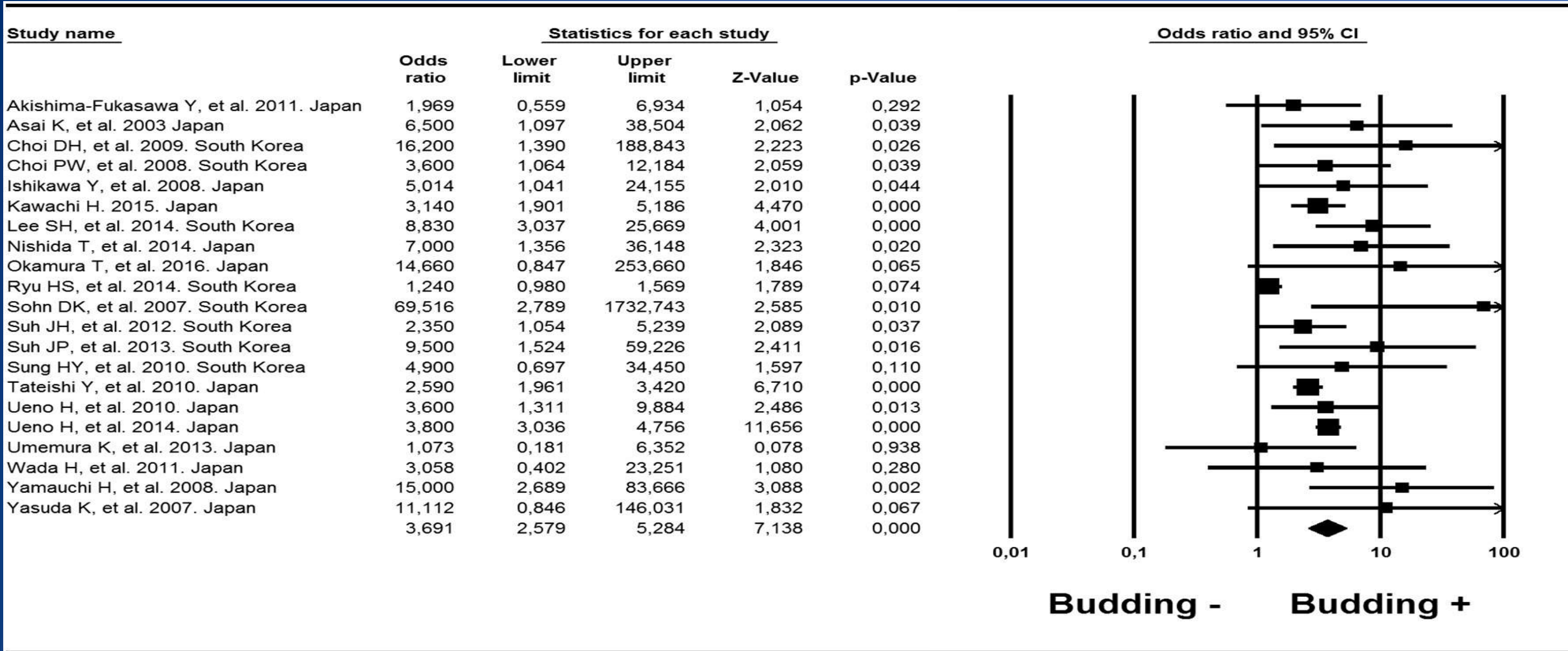
Ueno H, Mochizuki H, Hashiguchi Y, Shimazaki H, Aida S, Hase K, Matsukuma S, Kanai T, Kurihara H, Ozawa K, Yoshimura K, Bekku S. Gastroenterology. 2004 Aug;127(2):385-94.

Tateishi Y, Nakanishi Y, Taniguchi H, Shimoda T, Umemura S. Mod Pathol. 2010 Aug;23(8):1068-72

Nakadoi K, Tanaka S, Kanao H, Terasaki M, Takata S, Oka S, Yoshida S, Arihiro K, Chayama K. J Gastroenterol Hepatol. 2012 Jun;27(6):1057-62

Lee SJ, Kim A, Kim YK, Park WY, Kim HS, Jo HJ, Oh N, Song GA, Park DY. Hum Pathol. 2018 Aug;78:8-17.

Tumor Budding Predicts Lymph Node Metastases in pT1 Adenocarcinoma



Cappelleso R, Luchini C, Veronese N, Lo Mele M, Rosa-Rizzotto E, Guido E, De Lazzari F, Pilati P, Farinati F, Realdon S, Solmi M, Fassan M, Rugge M. Tumor budding as a risk factor for nodal metastasis in pT1 colorectal cancers: a meta-analysis. Hum Pathol. 2017 Jul;65:62-70.

You answered...

How can you justify commenting on intermediate- or high-grade tumor budding, yet classify a cancer in polypectomy as low-grade? How are you assessing cancer grade in polyps (i.e. does any amount of non-gland-forming cancer constitute a high-grade component)?

Importance of Tumor Budding in pT1 Adenocarcinoma

- Backes *et al.* studied 37 patients with pT1 adenocarcinomas in pedunculated adenomas and lymph node, intramural, or distant metastases

High-risk Features	Low-risk pT1	High-risk pT1	Missed metastases
Poor differentiation Lymphovascular invasion Haggitt level 4	43%	57%	1%
Poor differentiation Lymphovascular invasion Haggitt level 4 Tumor budding	35%	65%	1%

- Observed a negative association between tumor budding and metastasis
- Decreased specificity, but did not improve sensitivity
- Included tumor budding in a weighted algorithm that improved specificity, but combined it with other high-grade morphologic patterns (i.e. poorly-differentiated clusters)

Importance of Tumor Budding in pT1 Adenocarcinoma

Feature	Positive Lymph Nodes (n=12) #, (%)	Negative Lymph Nodes (n=227) #, (%)	OR	p value
Width of invasion >4mm	11 (92)	117 (52)	10	0.007
Depth of invasion >2mm	10 (83)	109 (48)	5	0.02
Poor differentiation	8 (67)	36 (16)	10	<0.001
Tumor budding	3 (25)	47 (20.7)	1	0.72
Lymphatic invasion	4 (33)	51 (23)	2	0.48
Venous invasion	0	21 (9)	1	0.61

Brown IS, Bettington ML, Bettington A, Miller G, Rosty C. J Clin Pathol. 2016 Apr;69(4):292-9.

Confounding Issues

- Difficult to assess importance of tumor budding versus areas with other types of high-grade histology in pT1 adenocarcinoma in polyps
- Clinical colleagues are not familiar with the concept and may not understand its importance in reports

What are your clinical colleagues doing with this information?

67% responded that their clinicians either have never mentioned tumor budding or probably don't know what it is.

How should we report on tumor budding at the invasive front of pT1 adenocarcinoma arising in pedunculated colorectal adenomas? Is it better stated as a high-grade component?

Let's Hear from the Forum



We asked you...

- You are examining a resection of high-grade colonic adenocarcinoma that invades the visceral serosa, but lymph node metastases are absent. A maximum of 17 tumor buds are present at the advancing edge. How do you document this in the report?

You answered...

- I document that tumor budding is present and give the highest number of buds in a 20x field: 47%
- I document that tumor budding is present: 29%
- I do not document it: 20%

What are Clinical Colleagues Doing with this Information?

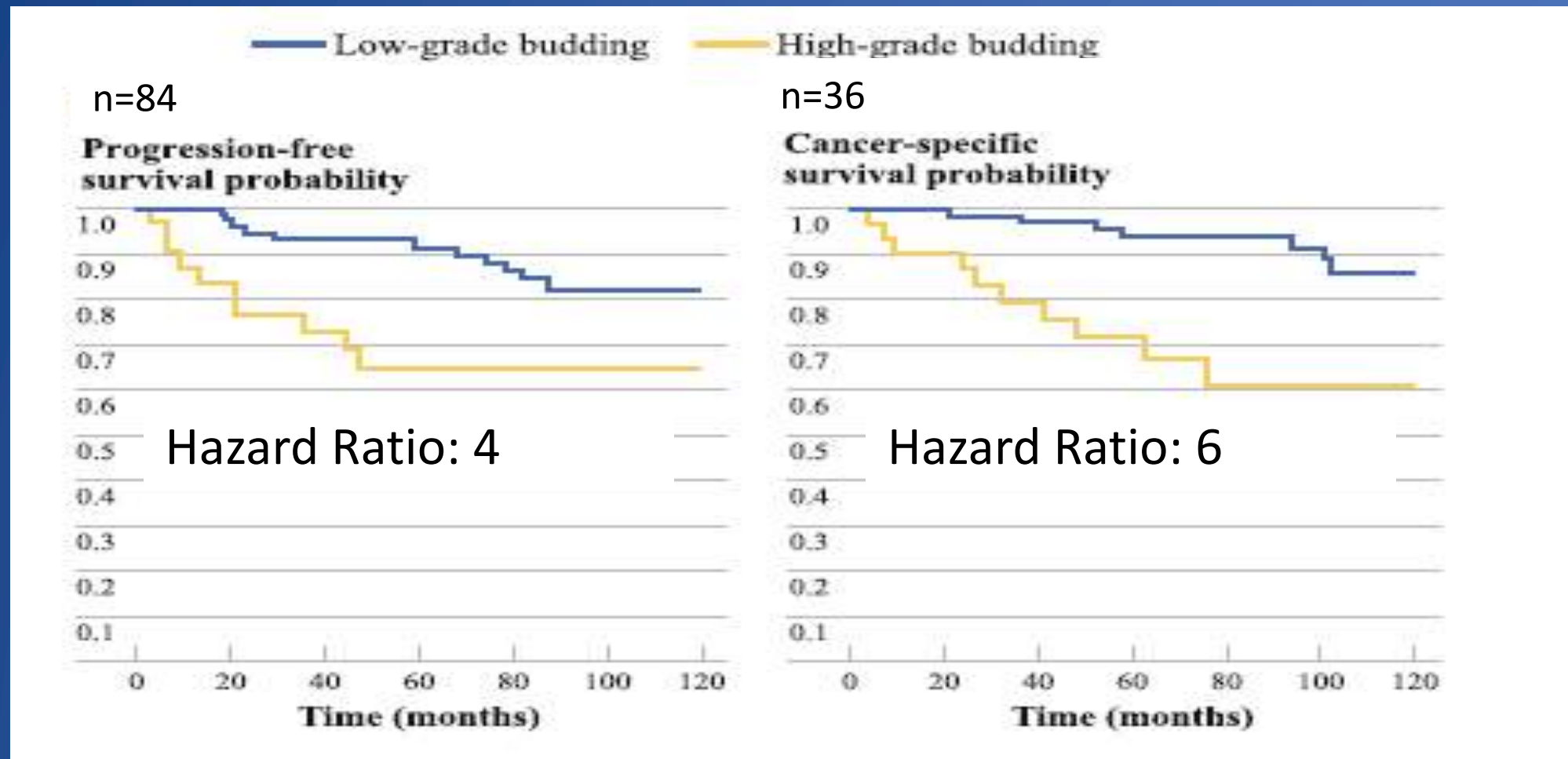
Our oncologists are very interested to know the tumor budding score and number in the stage II setting.

They are more comfortable making treatment decisions based on other high-risk factors.

- Tumor perforation, lymphovascular or perineural invasion, serosal involvement, poor differentiation

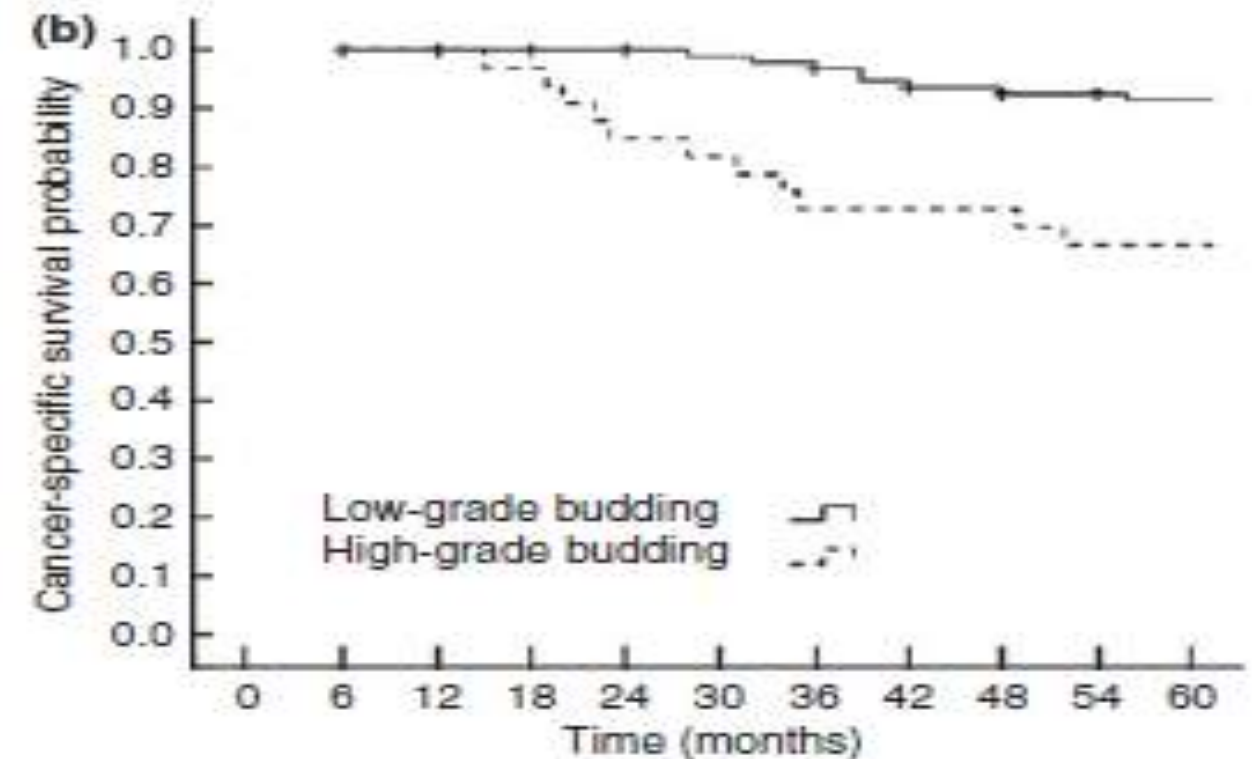
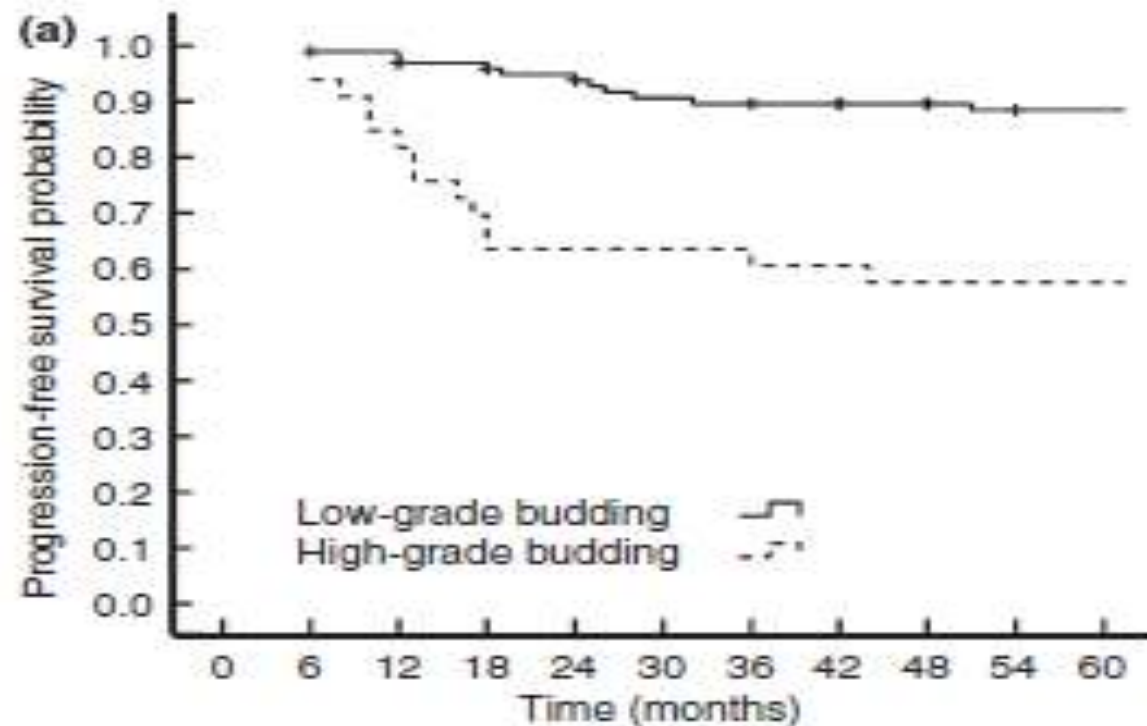
Effect of Tumor Budding on Outcomes in patients with Stage II Colorectal Cancer

- Significant differences in progression-free and cancer-specific survival in 120 patients with stage II disease



Effect of Tumor Budding on Outcomes in patients with Stage II Colorectal Cancer

- 135 patients: 99 with low-to-intermediate grade budding, 36 with high-grade budding



Lai YH, Wu LC, Li PS, Wu WH, Yang SB, Xia P, He XX, Xiao LB. Tumour budding is a reproducible index for risk stratification of patients with stage II colon cancer. *Colorectal Dis.* 2014 Apr;16(4):259-64.

Prognostic Importance of Tumor Budding

- Konishi *et al.* evaluated a variety of histologic features at the invasive front in 851 colorectal cancers including 350 stage II cases

Tumor Budding Grade	Three-year Recurrence-free Survival, Stage II	Three-year Recurrence-free Survival, Stage III
1	94%	89%
2	80%	74%
3	68%	60%

Konishi T, Shimada Y, Lee LH, Cavalcanti MS, Hsu M, Smith JJ, Nash GM, Temple LK, Guillem JG, Paty PB, Garcia-Aguilar J, Vakiani E, Gonen M, Shia J, Weiser MR. Poorly Differentiated Clusters Predict Colon Cancer Recurrence: An In-Depth Comparative Analysis of Invasive-Front Prognostic Markers. *Am J Surg Pathol.* 2018Jun;42(6):705-714.

Questions

- Prognostic relevance of high-grade tumor budding is established
- Is it worthwhile to report low-to-intermediate grade tumor budding?
- Is there added value to reporting tumor budding in cases with other factors that would triage a patient to adjuvant therapy or are we just muddying the waters?

Let's Hear from the Forum

