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

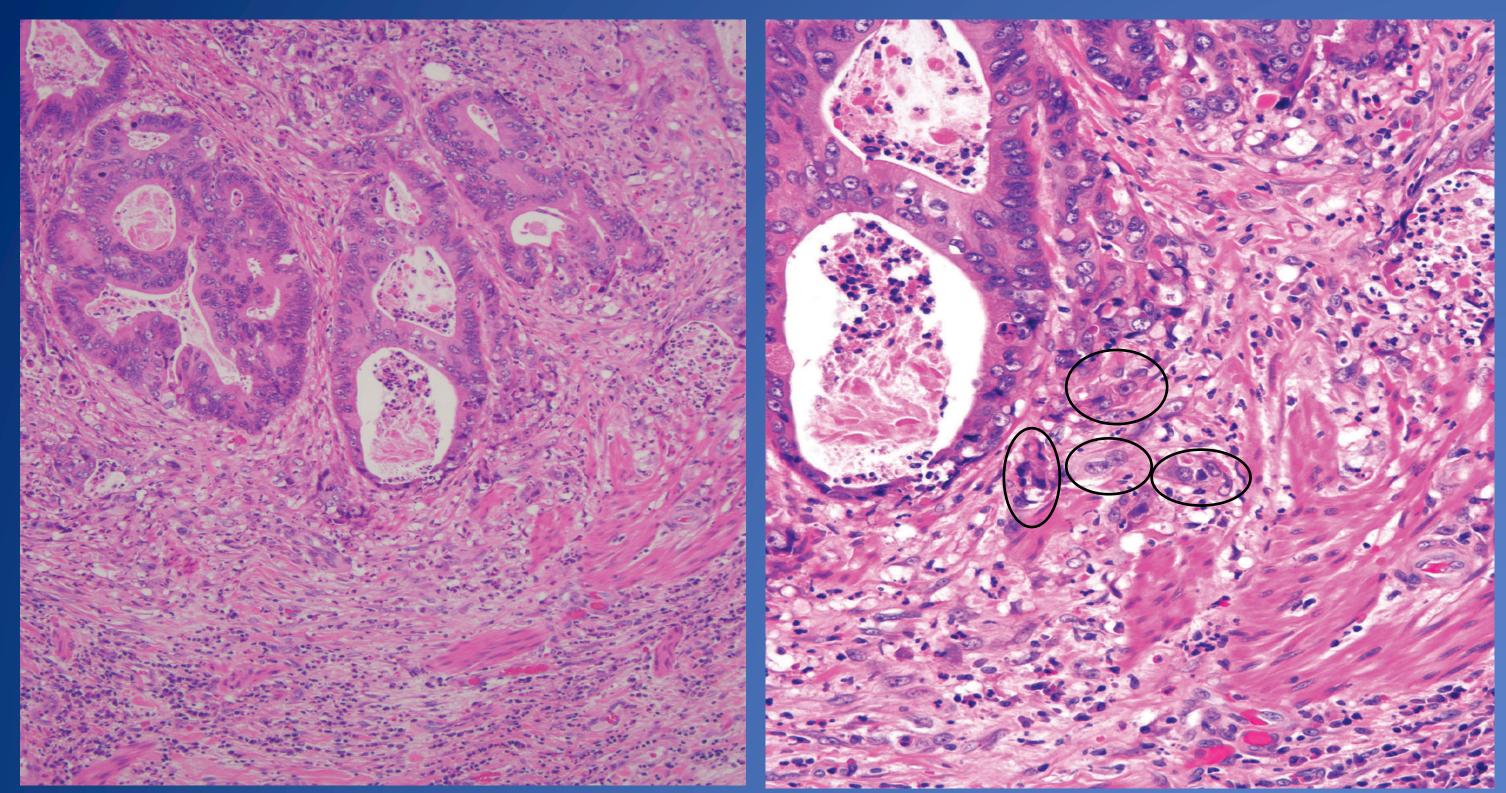
- Tumor budding should be evaluated in H&E stained sections •
- "Hotspot" selected after review of the advancing edge ightarrow
- Total number of buds in a 0.785mm² area (a 20x field on most microscopes) \bullet should be reported
- Cytokeratin may help, but grading should be done on H&E \bullet

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

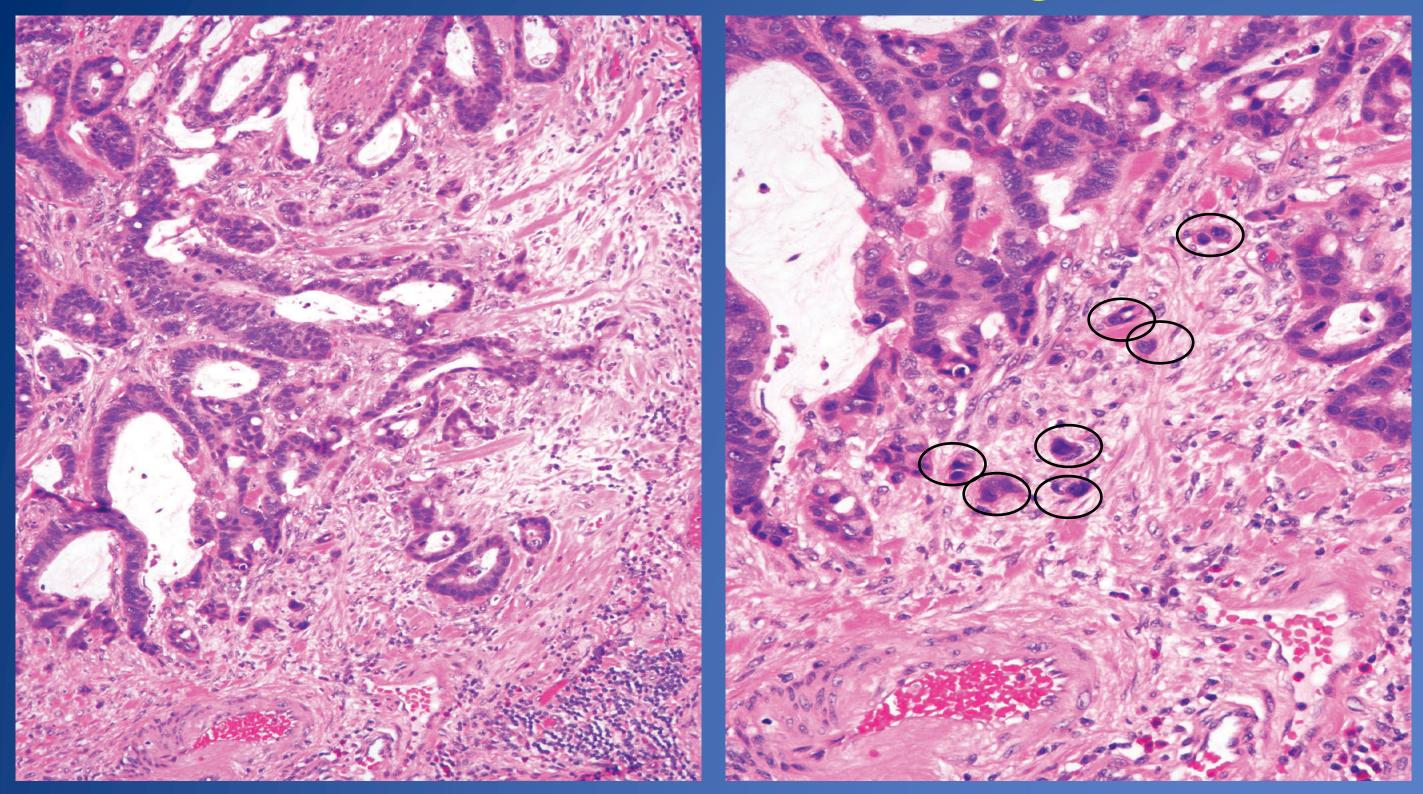
Lugli A, Kirsch R, Ajioka Y, et al. Mod Pathol. 2017 Sep;30(9):1299-1311.



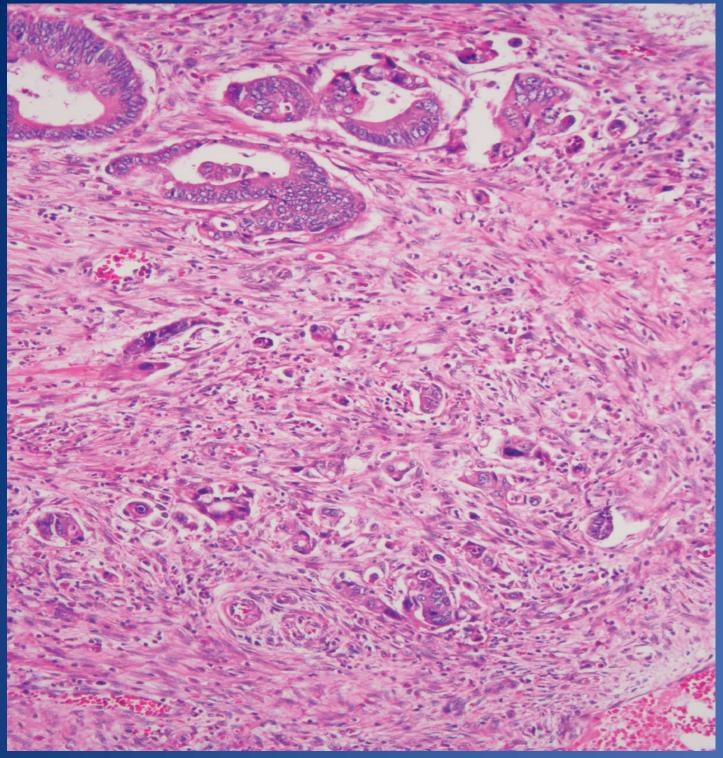
Low-Grade Budding

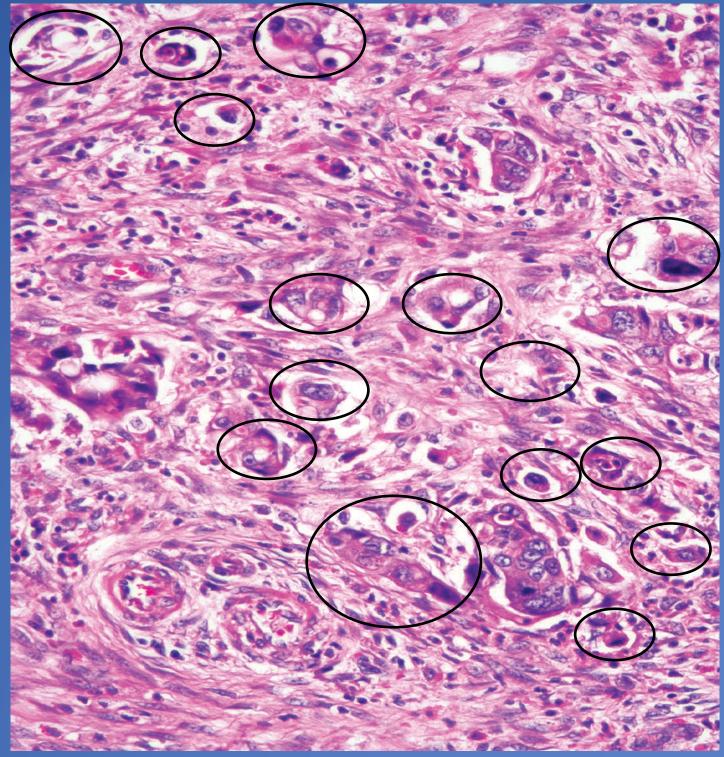


Intermediate-Grade Budding



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 l 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...

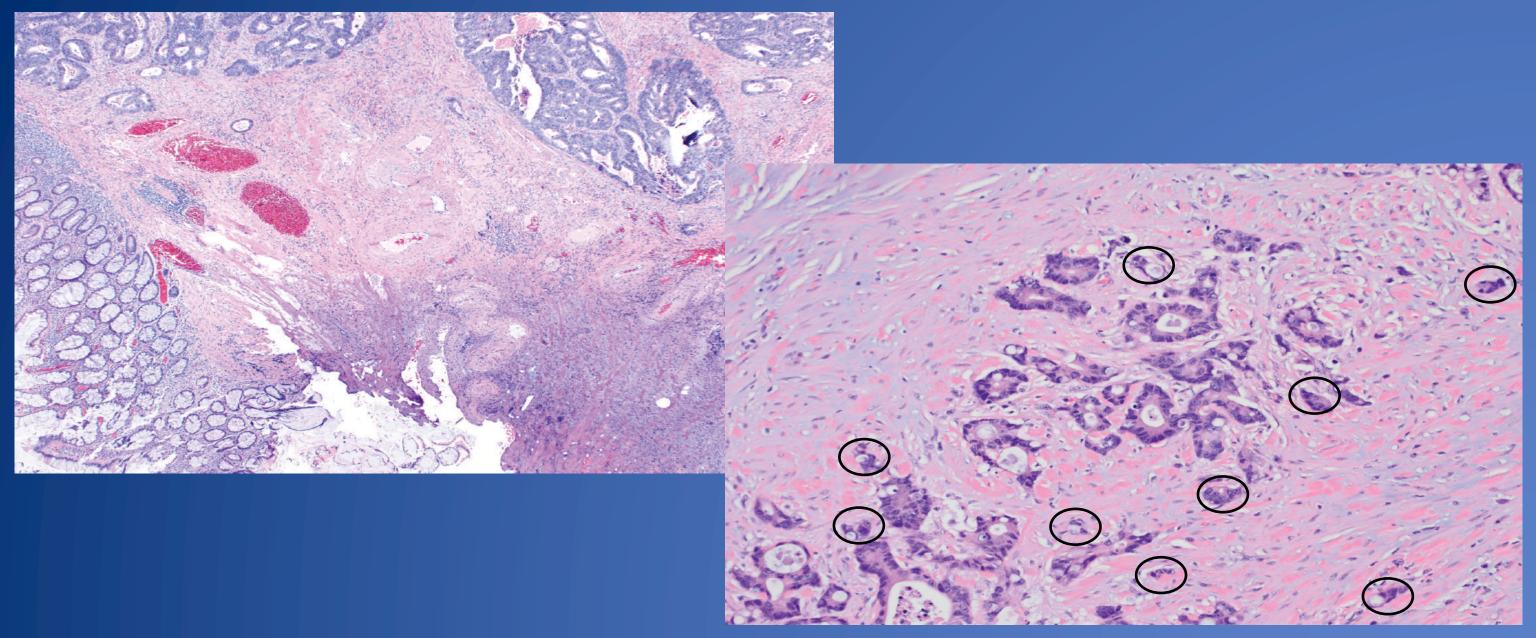
- When and how do you report tumor budding?
- Do you use cytokeratin?

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

Study name	Statistics for each study					Odds ratio a
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Akishima-Fukasawa Y, et al. 2011. Japan	1,969	0,559	6,934	1,054	0,292	_ I →
Asai K, et al. 2003 Japan	6,500	1,097	38,504	2,062	0,039	
Choi DH, et al. 2009. South Korea	16,200	1,390	188,843	2,223	0,026	
Choi PW, et al. 2008. South Korea	3,600	1,064	12,184	2,059	0,039	- I - I
Ishikawa Y, et al. 2008. Japan	5,014	1,041	24,155	2,010	0,044	
Kawachi H. 2015. Japan	3,140	1,901	5,186	4,470	0,000	
Lee SH, et al. 2014. South Korea	8,830	3,037	25,669	4,001	0,000	
Nishida T, et al. 2014. Japan	7,000	1,356	36,148	2,323	0,020	
Okamura T, et al. 2016. Japan	14,660	0,847	253,660	1,846	0,065	- 1 - +
Ryu HS, et al. 2014. South Korea	1,240	0,980	1,569	1,789	0,074	
Sohn DK, et al. 2007. South Korea	69,516	2,789	1732,743	2,585	0,010	
Suh JH, et al. 2012. South Korea	2,350	1,054	5,239	2,089	0,037	
Suh JP, et al. 2013. South Korea	9,500	1,524	59,226	2,411	0,016	
Sung HY, et al. 2010. South Korea	4,900	0,697	34,450	1,597	0,110	-
Tateishi Y, et al. 2010. Japan	2,590	1,961	3,420	6,710	0,000	
Ueno H, et al. 2010. Japan	3,600	1,311	9,884	2,486	0,013	
Ueno H, et al. 2014. Japan	3,800	3,036	4,756	11,656	0,000	
Umemura K, et al. 2013. Japan	1,073	0,181	6,352	0,078	0,938	
Wada H, et al. 2011. Japan	3,058	0,402	23,251	1,080	0,280	
Yamauchi H, et al. 2008. Japan	15,000	2,689	83,666	3,088	0,002	
Yasuda K, et al. 2007. Japan	11,112	0,846	146,031	1,832	0,067	1 4
	3,691	2,579	5,284	7,138	0,000	

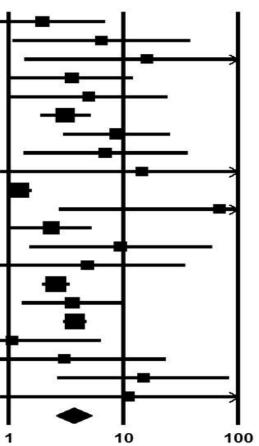
Budding -

0,1

0.01

Cappellesso 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.

and 95% CI



Budding +

You answered...

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

Importance of Tumor Budding in pT1 Adenocarcinoma

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

High-risk Features	Low-risk pT1	High-risk pT1	Miss
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)

sed metastases

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% \bullet

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 highrisk factors.

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

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

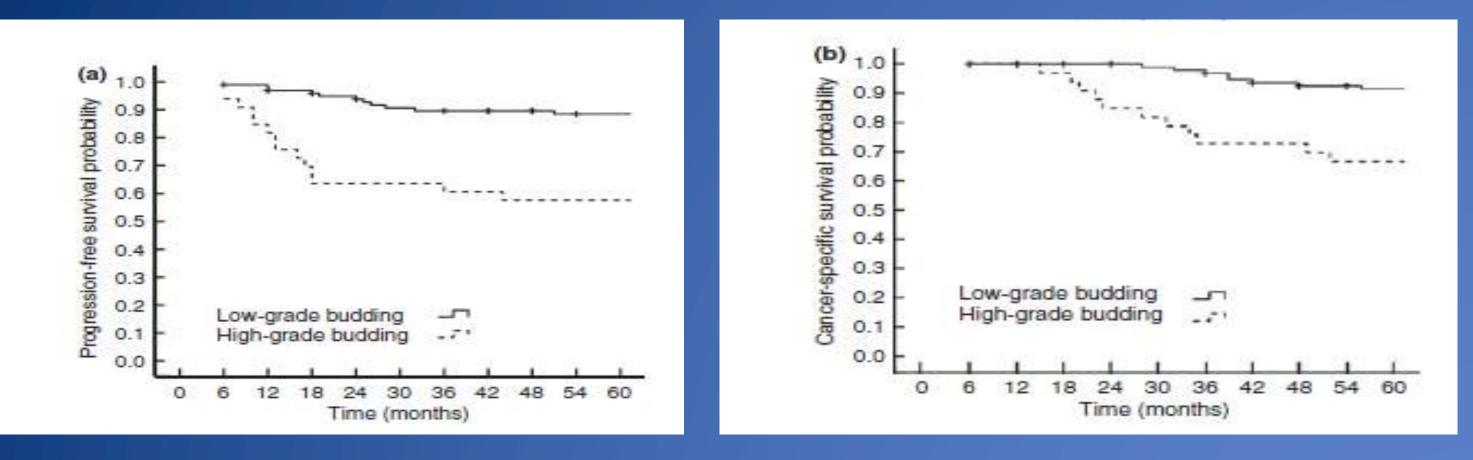
Significant differences in progression-free and cancer-specific survival in 120 patients igodolwith stage II disease

Time (months) Time (months)					
0 20 40 60 80 100 120	0 20 40 60 80 100 120				
0,1	0,1				
0.2	0.2				
0.3	0.3				
0.4	0.4				
Hazard Ratio: 4	Hazard Ratio: 6				
0.6	0.6				
0.7	0.7				
0.8	0.8				
0.9	0.9				
1.0 7 ~	1.0				
Progression-free survival probability	Cancer-specific survival probability				
84 n=36					
Low-grade budding	 High-grade budding 				

Betge J, Kornprat P, Pollheimer MJ, Lindtner RA, Schlemmer A, Rehak P, Vieth M, Langner C. Tumor budding is an independent predictor of outcome in AJCC/UICC stage II colorectal cancer. Ann Surg Oncol. 2012 Nov;19(12):3706-12

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 ullet



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 Recu Survival, Stage I	
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.



urrence-free

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

