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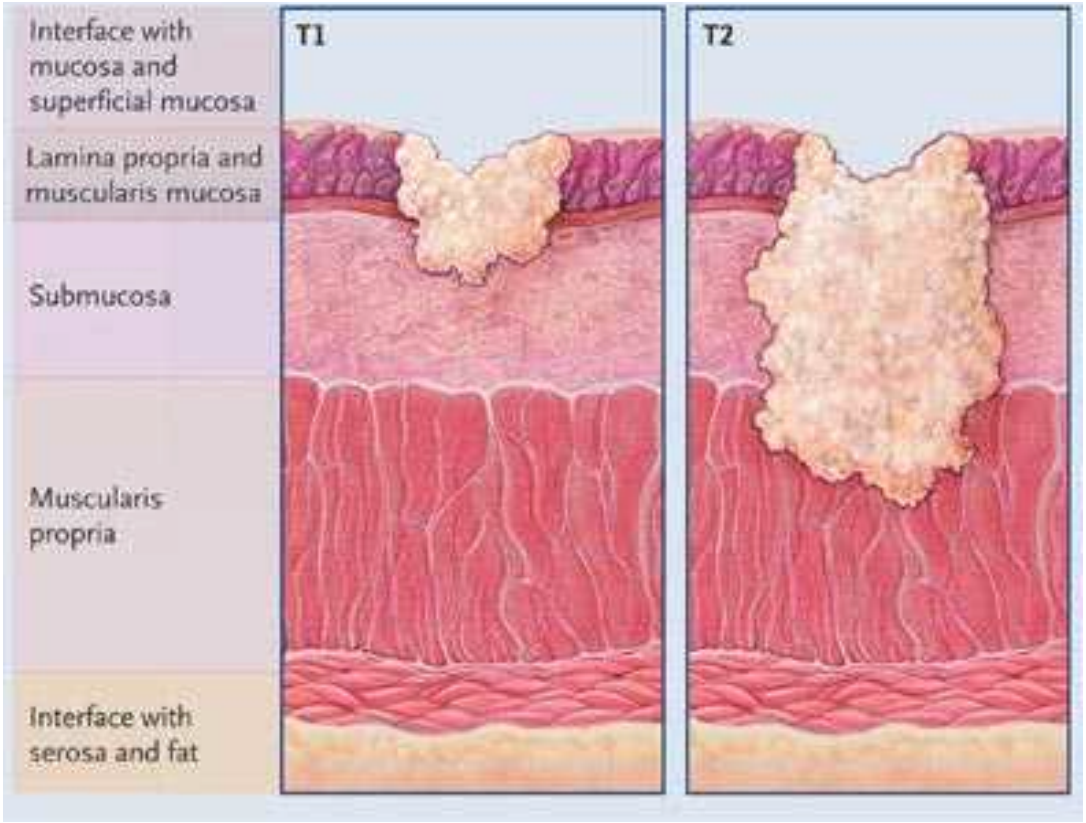
Rectal Cancer
Anatomo-pathological risk factors

C. Coimbra Marques

Early Rectal Cancer

Invasive adenocarcinoma spreading into, but not beyond the submucosa (T1)

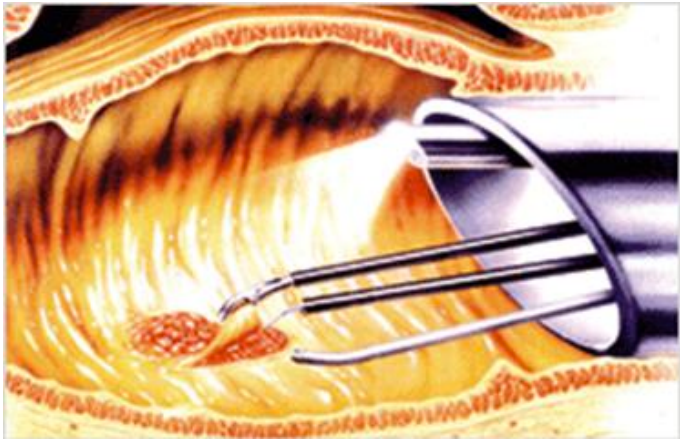


Polypoid carcinoma
Focus of malignancy within adenoma
Small ulcerating carcinoma

8-10% of resected rectal tumors

Local Surgery

Excellent results in morbidity
mortality
function



Mesorectum left in place

Nodal status is uncertain

Risk of leaving positive nodes

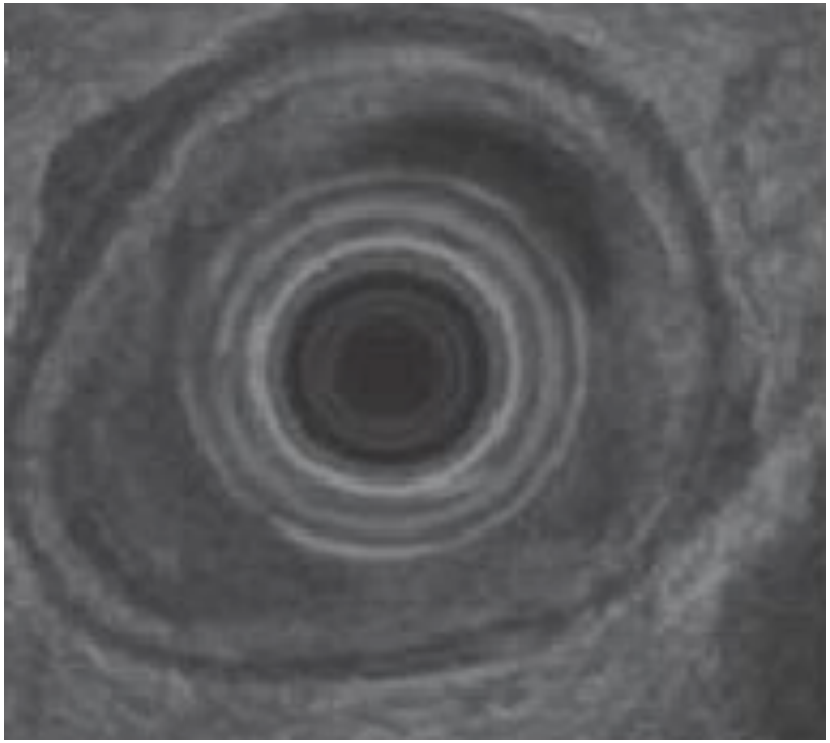
Lymph node metastases= pronostic factor

Risk of local and distal recurrences

Gennari et al. Hepatogastroenterlogy(2000)

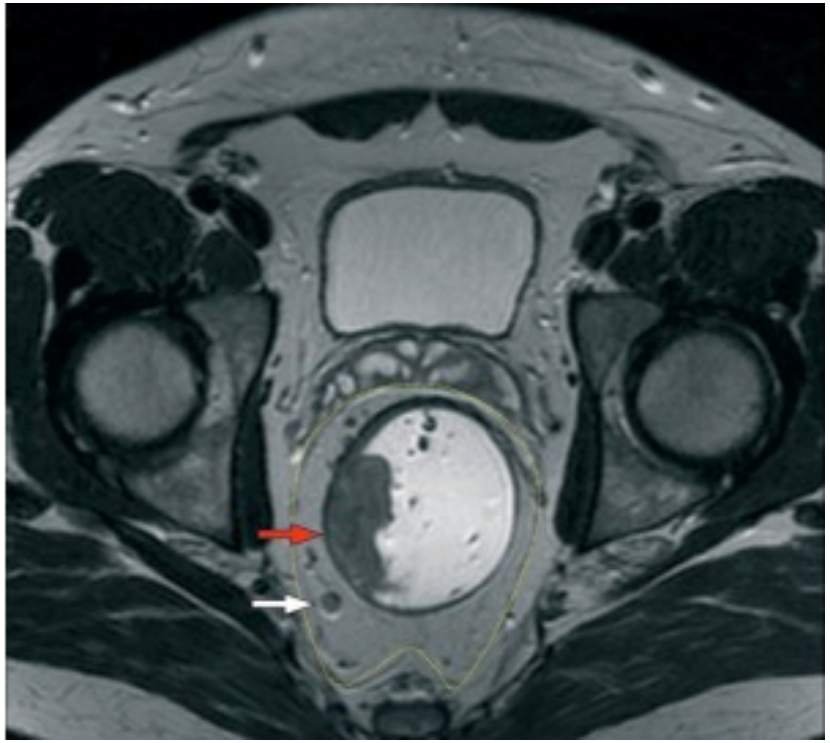
Staging

Endorectal ultrasonography



Accuracy of 89-94 %

Pelvic MRI



Accuracy of 92 %
USPIO

Histological Staging

Management of ERC ultimately depends on histo-pathological classifications

Specimens handled correctly

Pinned fresh

Relation between head-stalk

Fixed 24 hours

Sectionned in 3 mm slices

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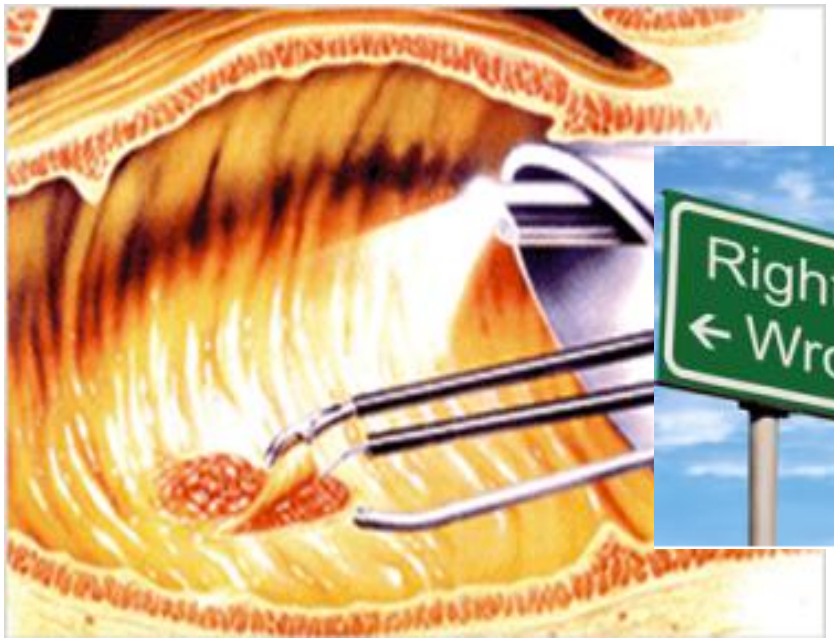
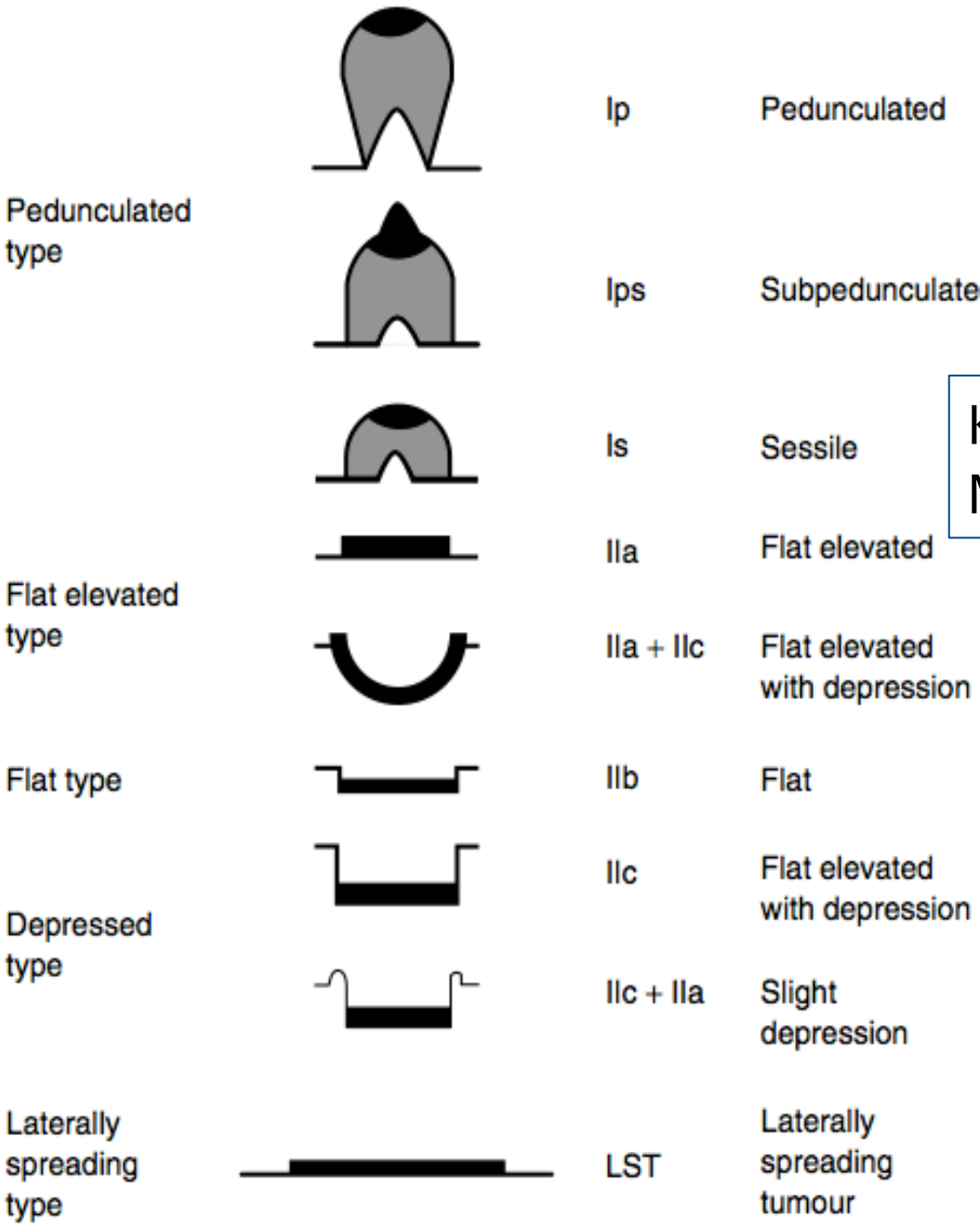
Assessing risk factors

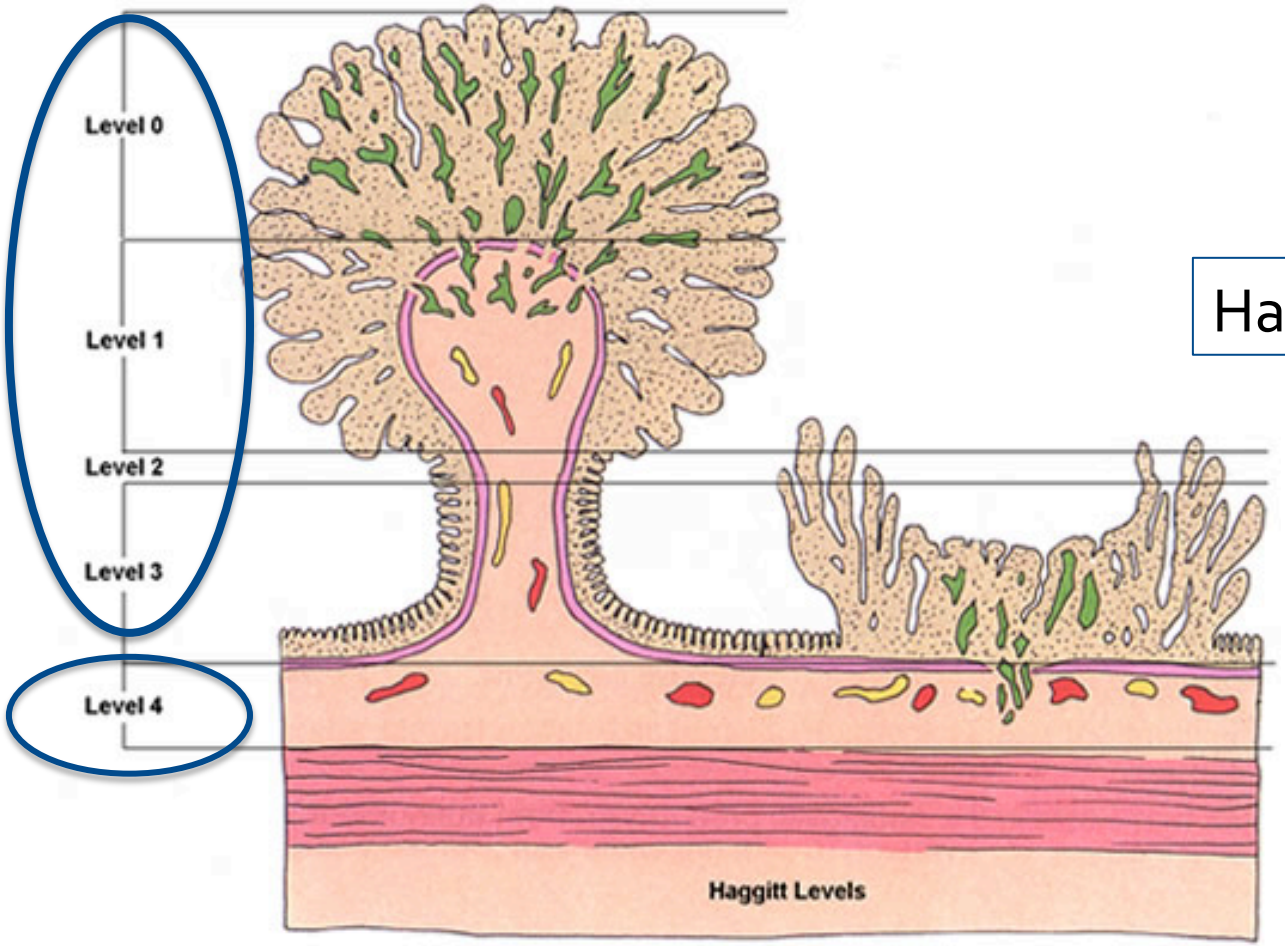
- Lymph node metastases
- Local recurrence





Kudo
Macroscopic classification

Kudo et al. Endoscopy (1993)



Haggitt classification

Haggitt et al. Gastroenterology (1993)

Sm1a
Less than a quarter of the width of the tumour invading the submucosa

Sm1b
Quarter to half the width of the tumour invading the submucosa

Sm1c
More than half the width of the tumour invading the submucosa

Sm2
Intermediate between Sm1 and Sm3

Sm3
Carcinoma invasion near to the muscularis propria

Invasion to a depth of 200–300 µm

Kikuchi (sm) classification

Kikuchi et al. Dis Colon Rectum (1995)

Sm1a
Less than a quarter of the width of the tumour invading the submucosa

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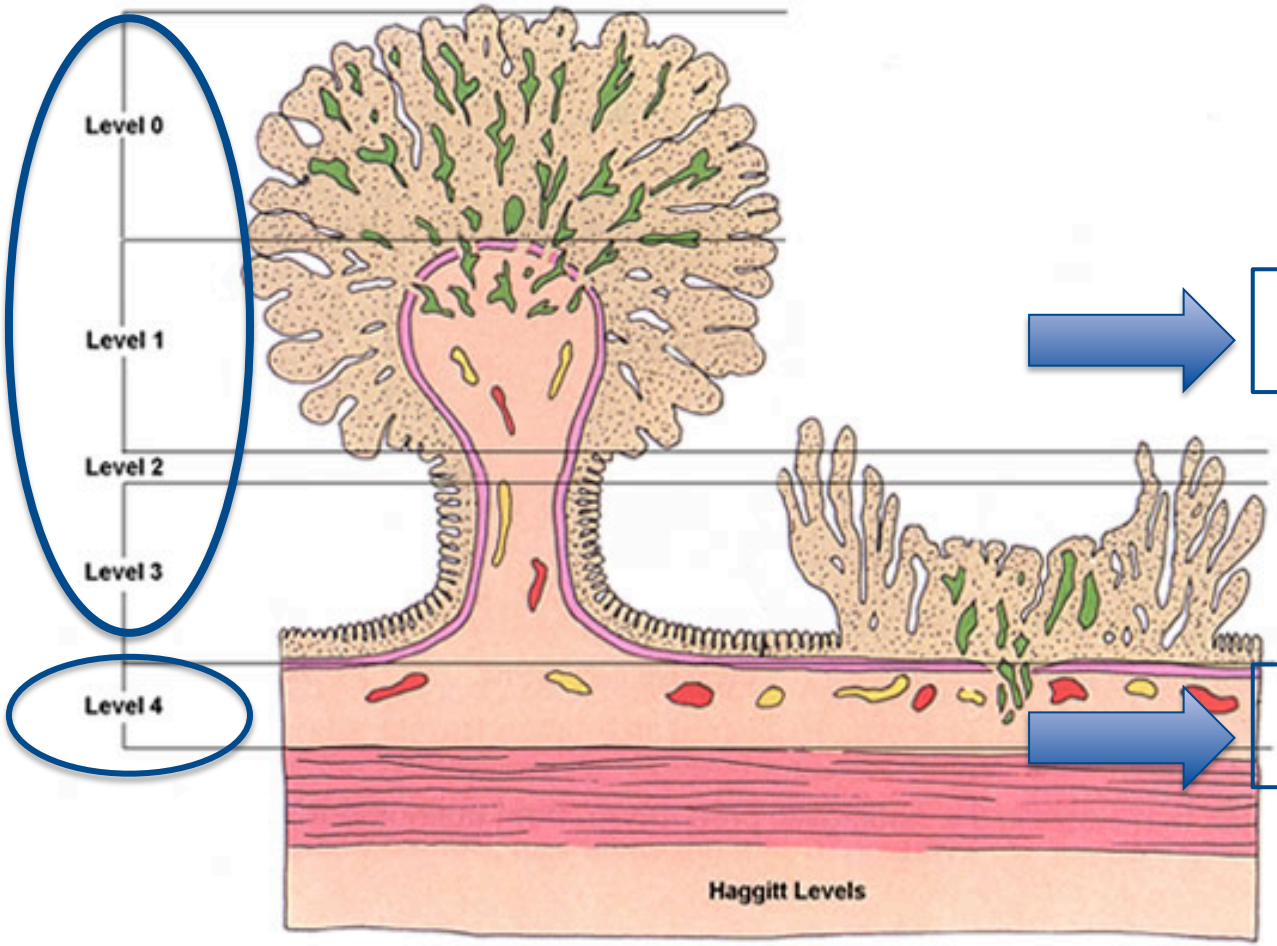

Kikuchi sm 1

Kikuchi sm 1-2-3

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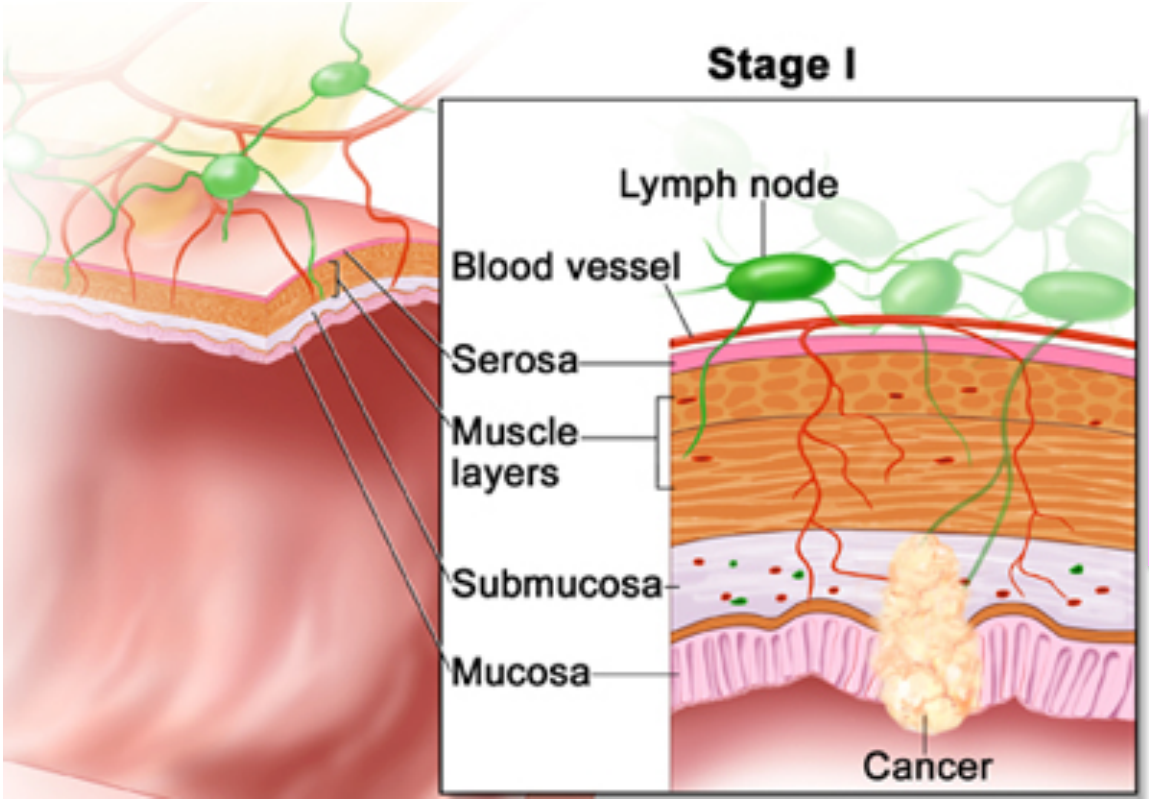
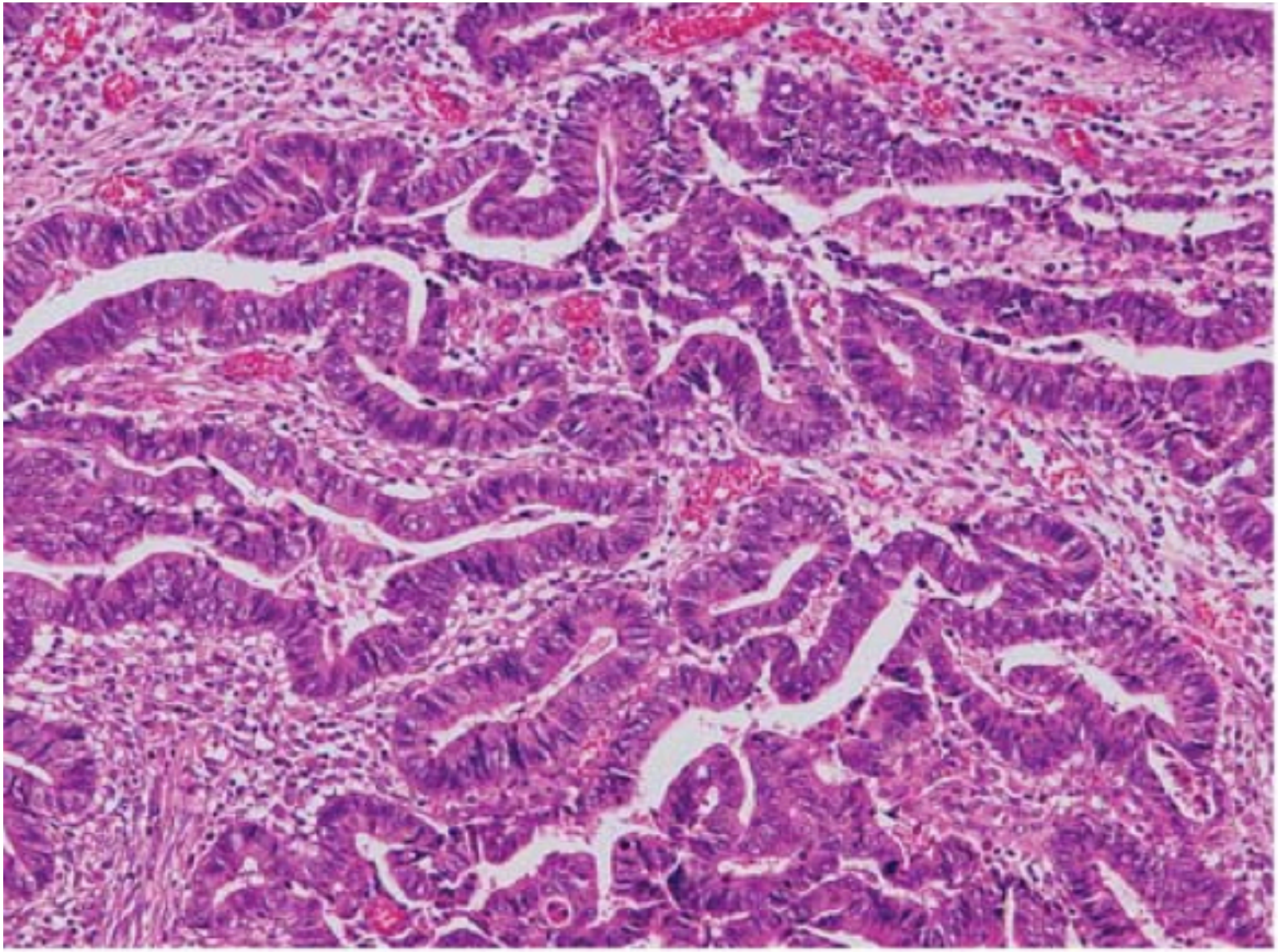
Can depth of tumour invasion predict lymph node positivity in patients undergoing resection for early rectal cancer?



Kikuchi (sm)	Lymph node +
Sm1	0-3%
Sm2	8-10%
Sm3	23-25%

Kikuchi et al. Dis Colon Rectum (1995)

Tytherleigh et al. British J Surgery (2008)



Well differentiated : simple tubular structure or « tree-like » branching

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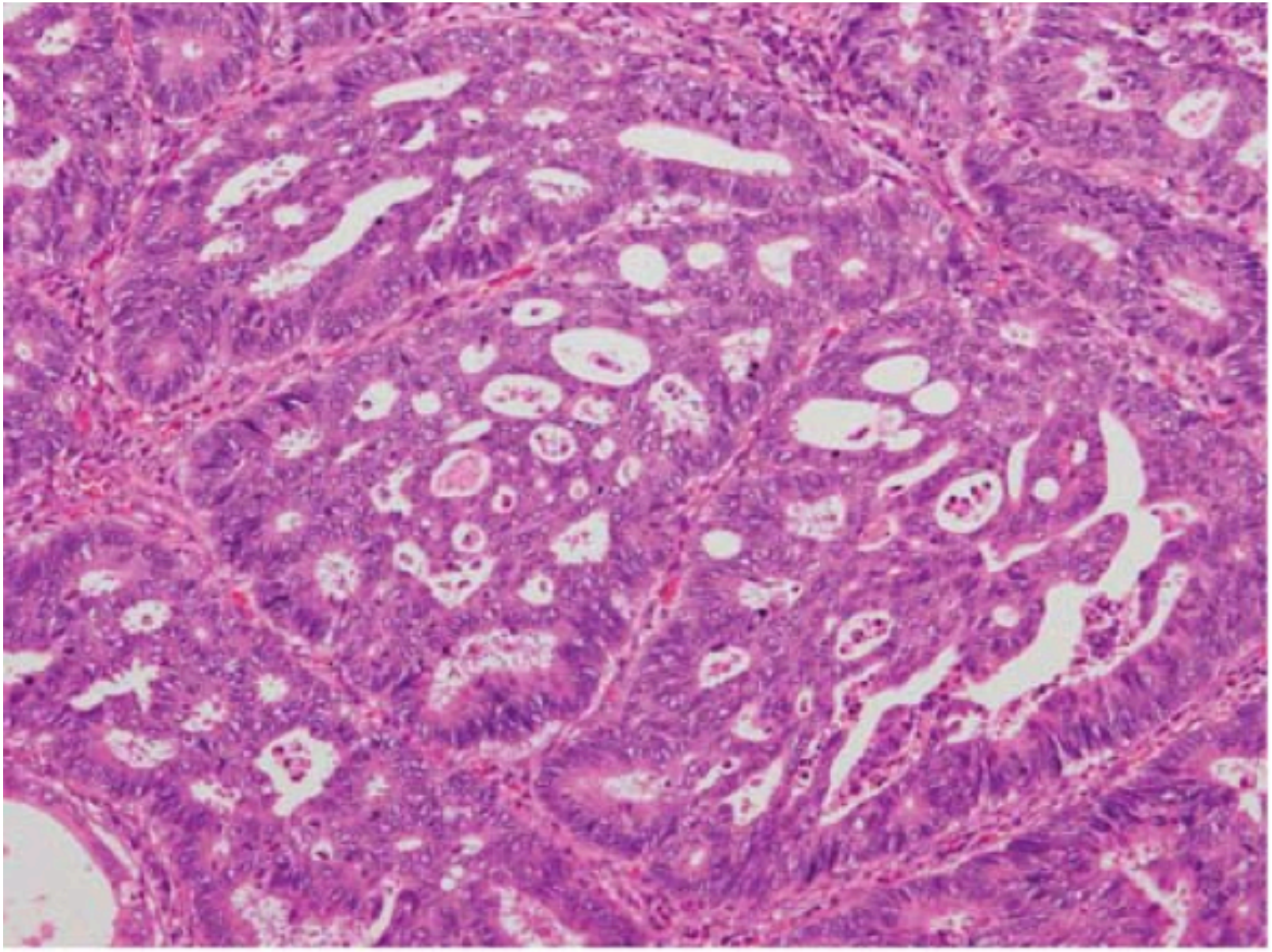

Moderate : cribriform pattern and a « sieve-like » branching

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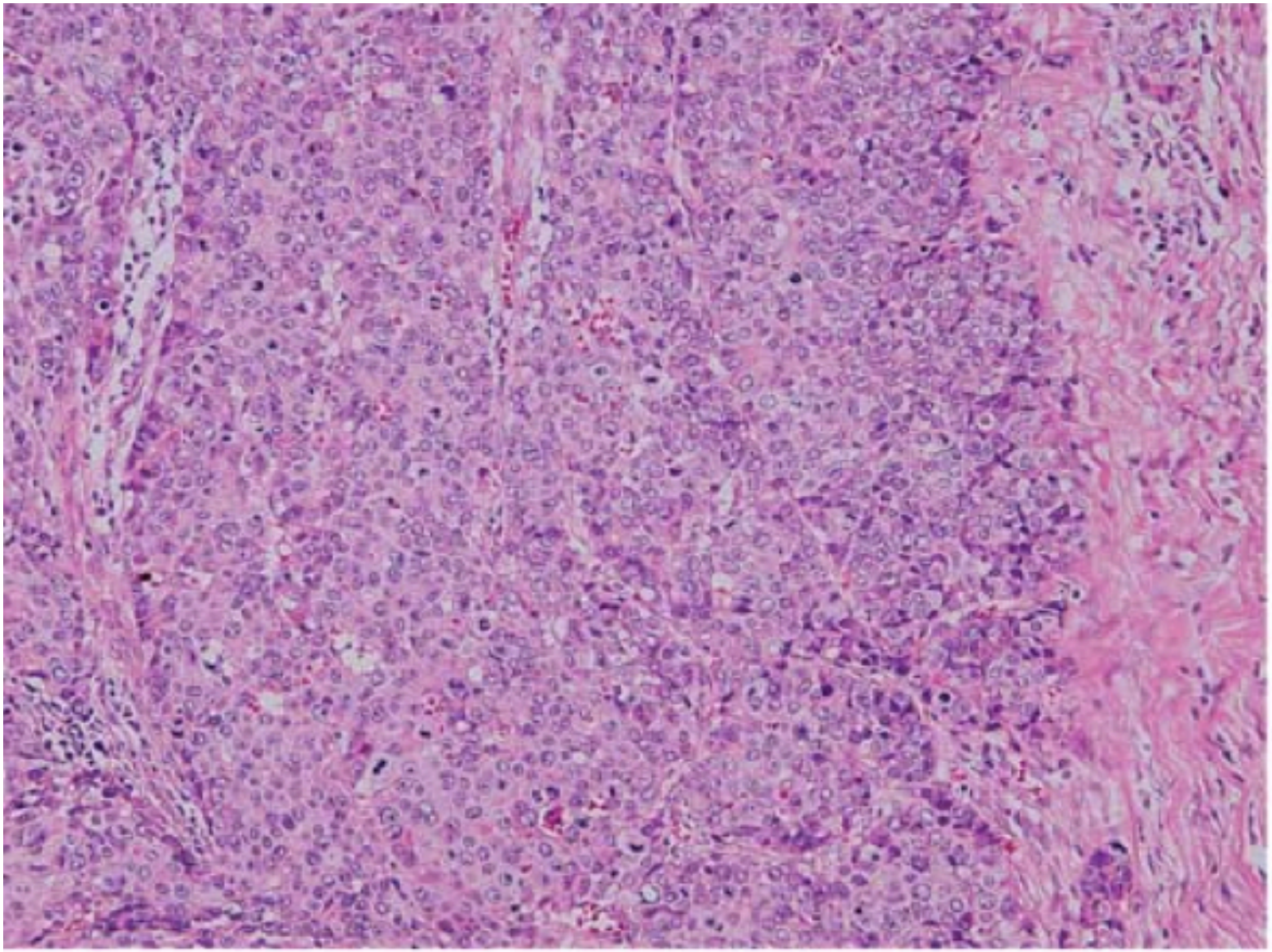
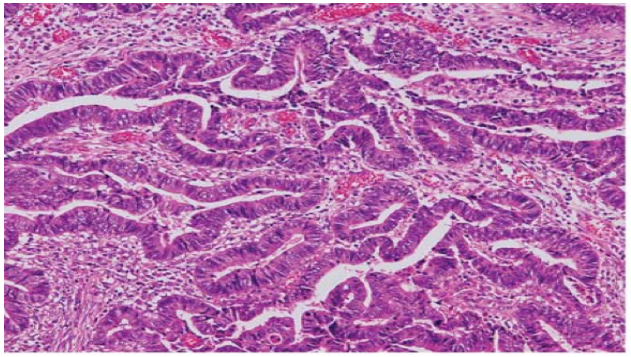
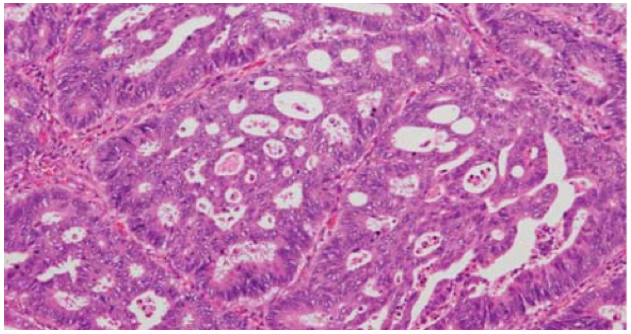


Poorly differentiated: lack of gland formation

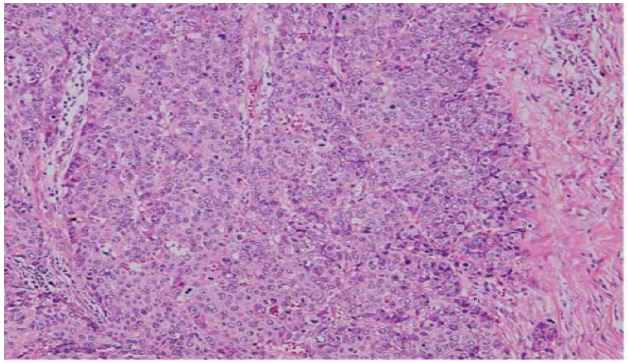




WHO categories :

- grade1 - 2 = well and moderately differentiated

→ Low risk of LN+



- grade 3: Poorly differentiated or mucinous carcinoma

→ high risk of LN+

Ueno et al. American J Surgical Pathology (2012)

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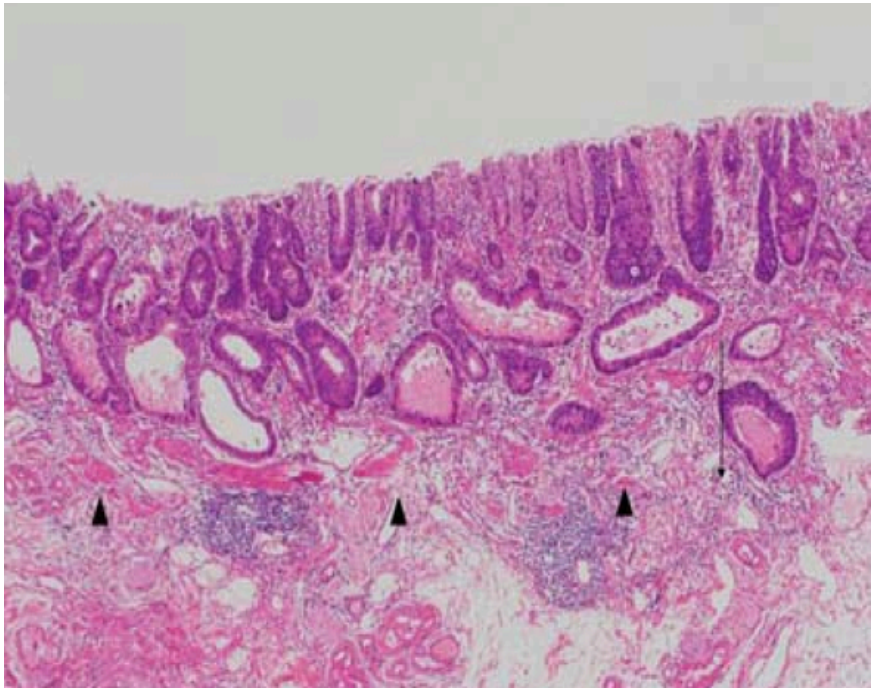
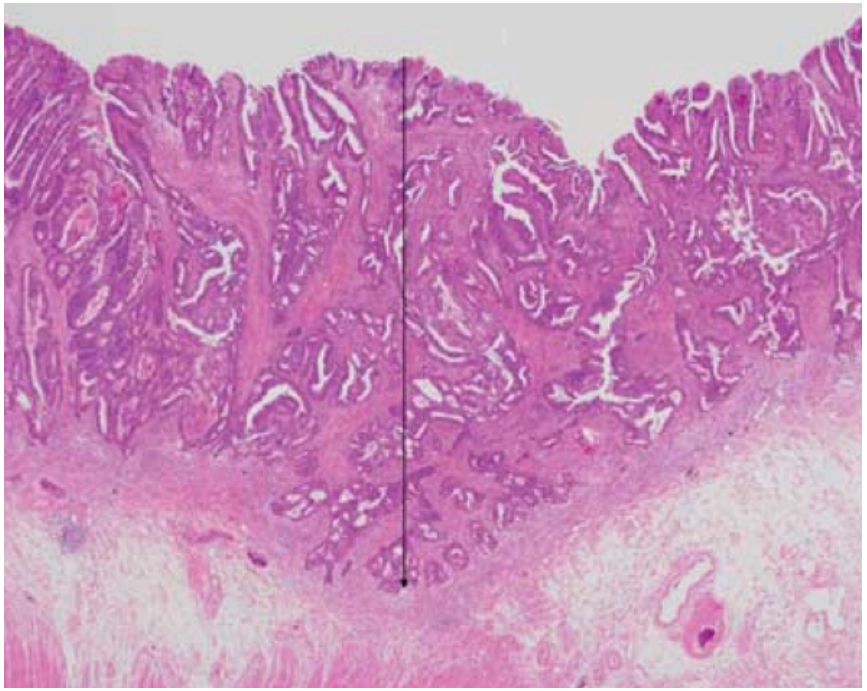
Disruption of the muscularis mucosa



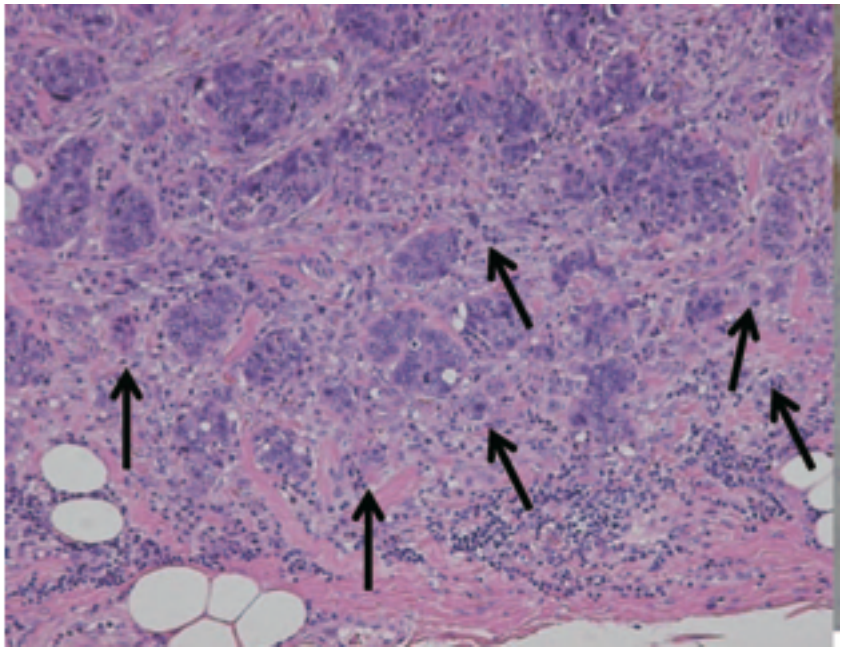
Type A = preserved muscularis mucosa

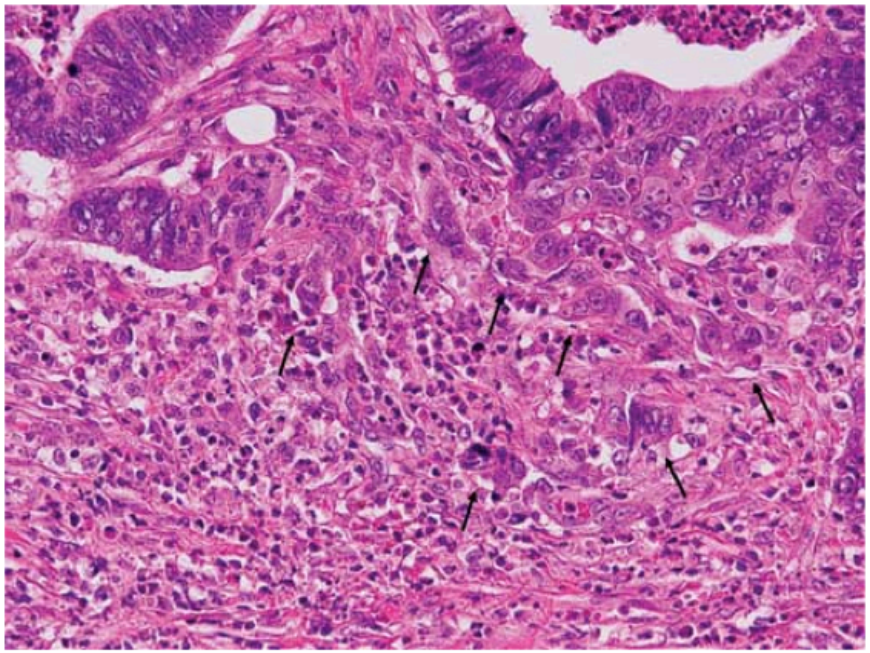


Type B = disrupted muscularis mucosa

Tumour budding

Single cancer cell or a cluster containing< 5 cancer cells at the invasive front of the tumour





Morodomi et al. Cancer(1989)

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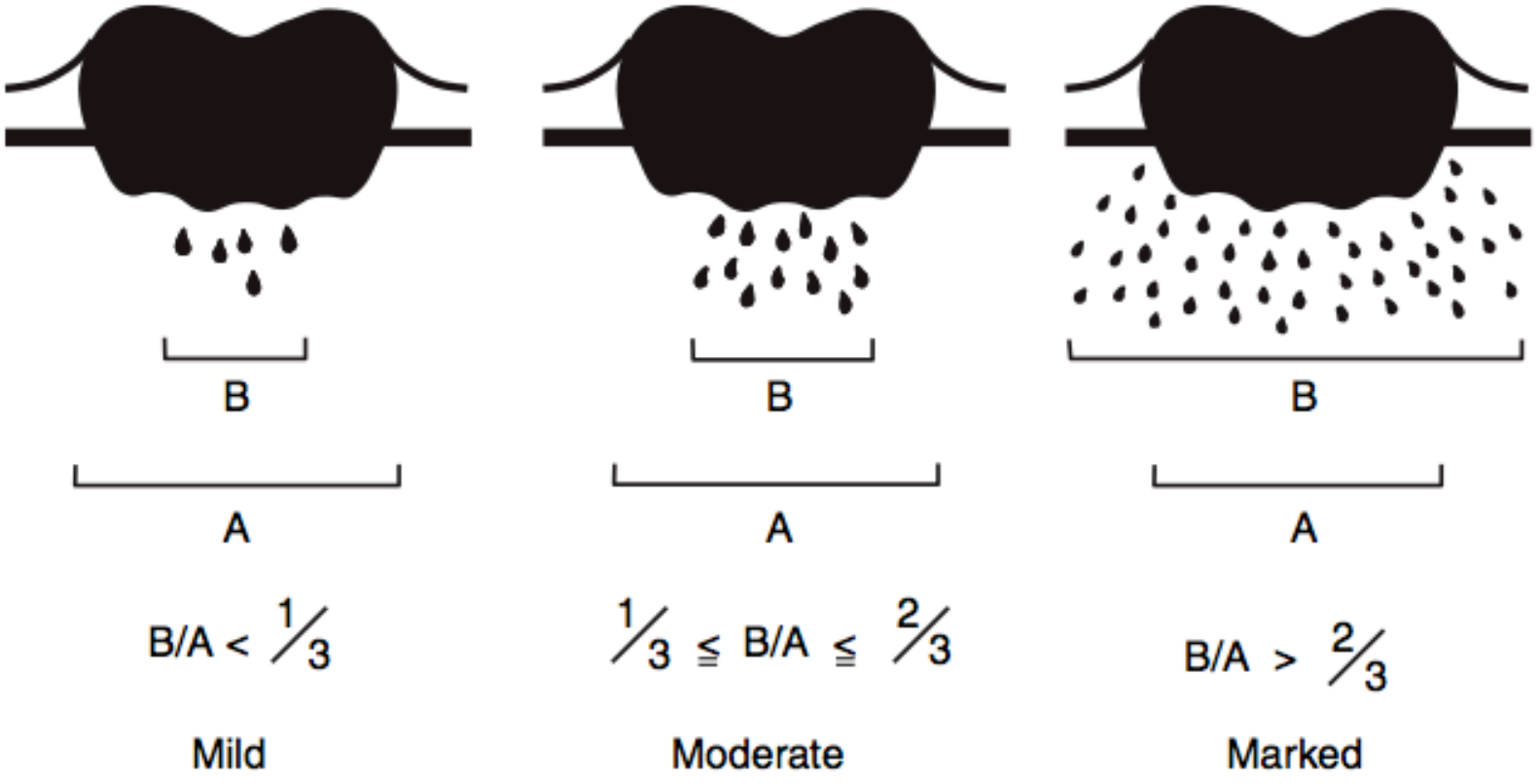
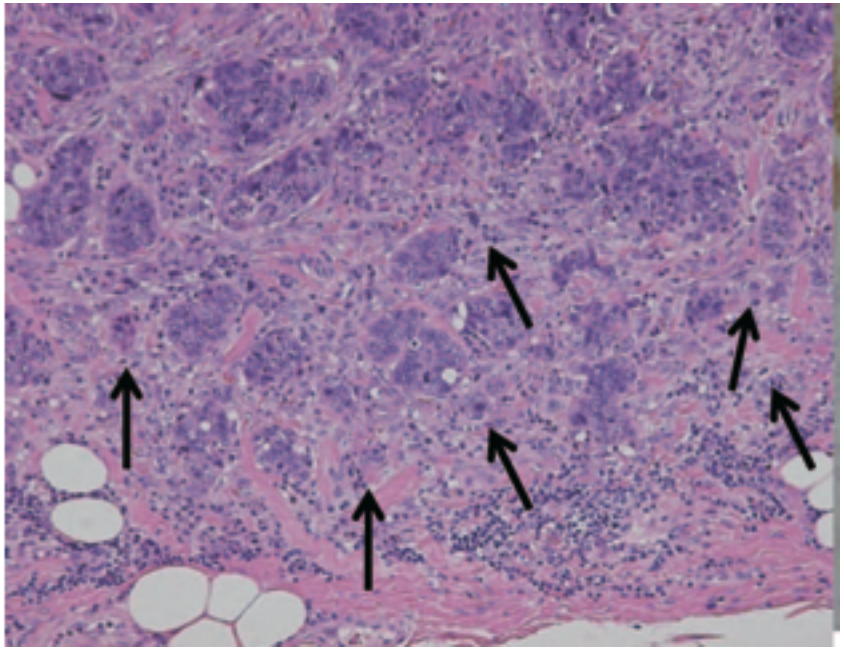
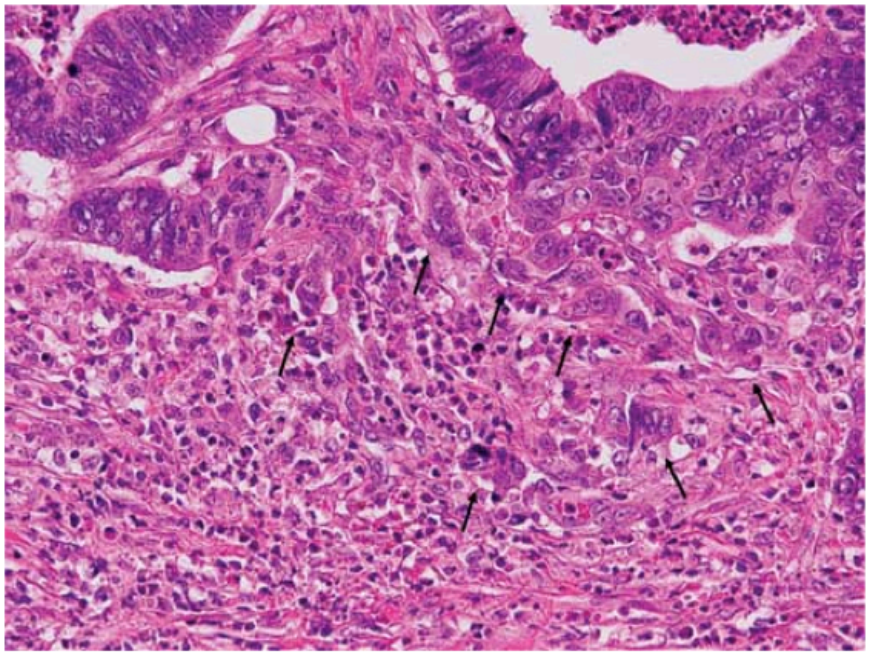
Tumor budding



Tumour budding

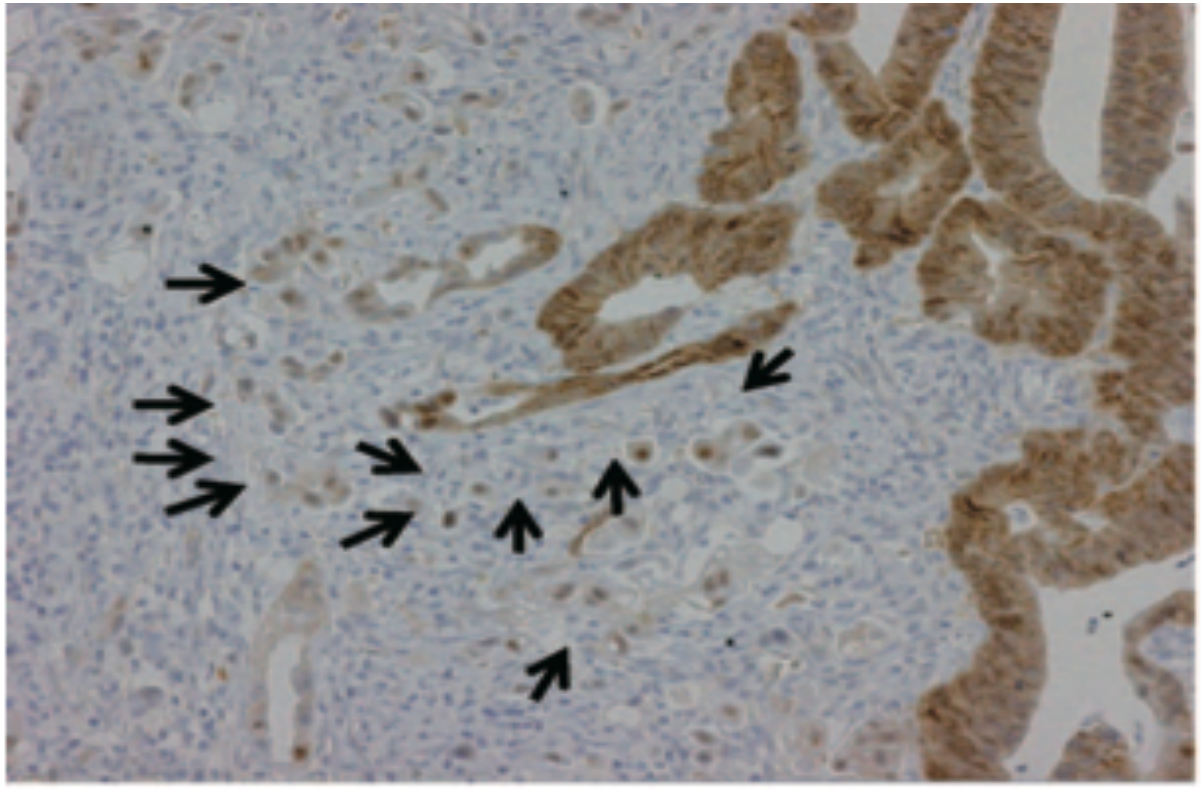
Hematoxylin-eosin (HE) staining difficult





β-catenin expression

- Wnt/β-catenin pathway is altered



Accumulation in the nucleus

Umemura et al. J of Experimental Medicine (2013)

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Tumor budding

Table 3. Multivariate analysis of risk factors affecting lymph node metastasis.

	Odds ratio	95% confidence interval	*P*
Gender	1.154	0.291 - 4.568	0.838
Mean age (years)	0.918	0.841 - 1.002	0.055
Budding (β-catenin, Grade2)	7.124	1.407 - 36.062	0.018
Budding (HE staining)	1.073	0.181 - 6.344	0.938
Depth of submucosal invasion (mean, μm)	1	1 - 1.001	0.033
Blood vessel invasion (HE staining)	< 0.001	< 0.001 - > 999.999	0.982
Lymphatic vessel invasion (HE)	0.742	0.024 - 22.701	0.864
Lymphatic vessel invasion (D2-40)	6.166	0.313 - 121.326	0.232

(Multivariate logistic model)

Umemura et al. J of Experimental Medicine (2013)

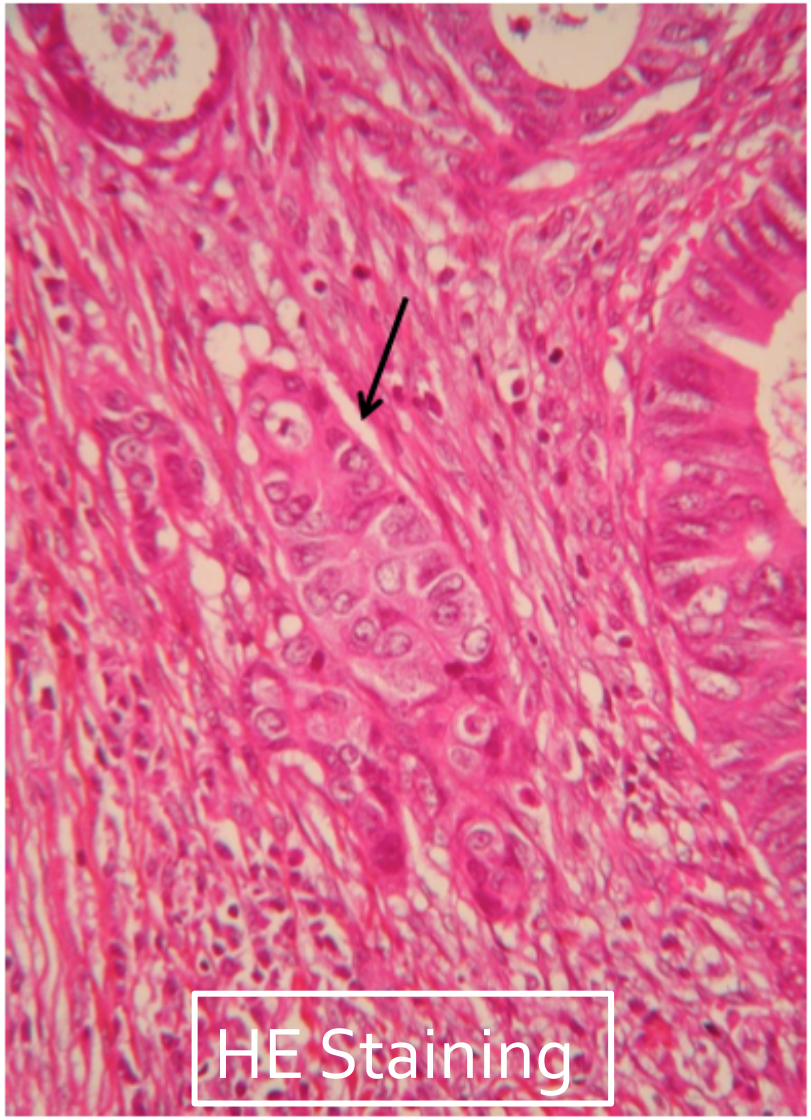
Tumour budding

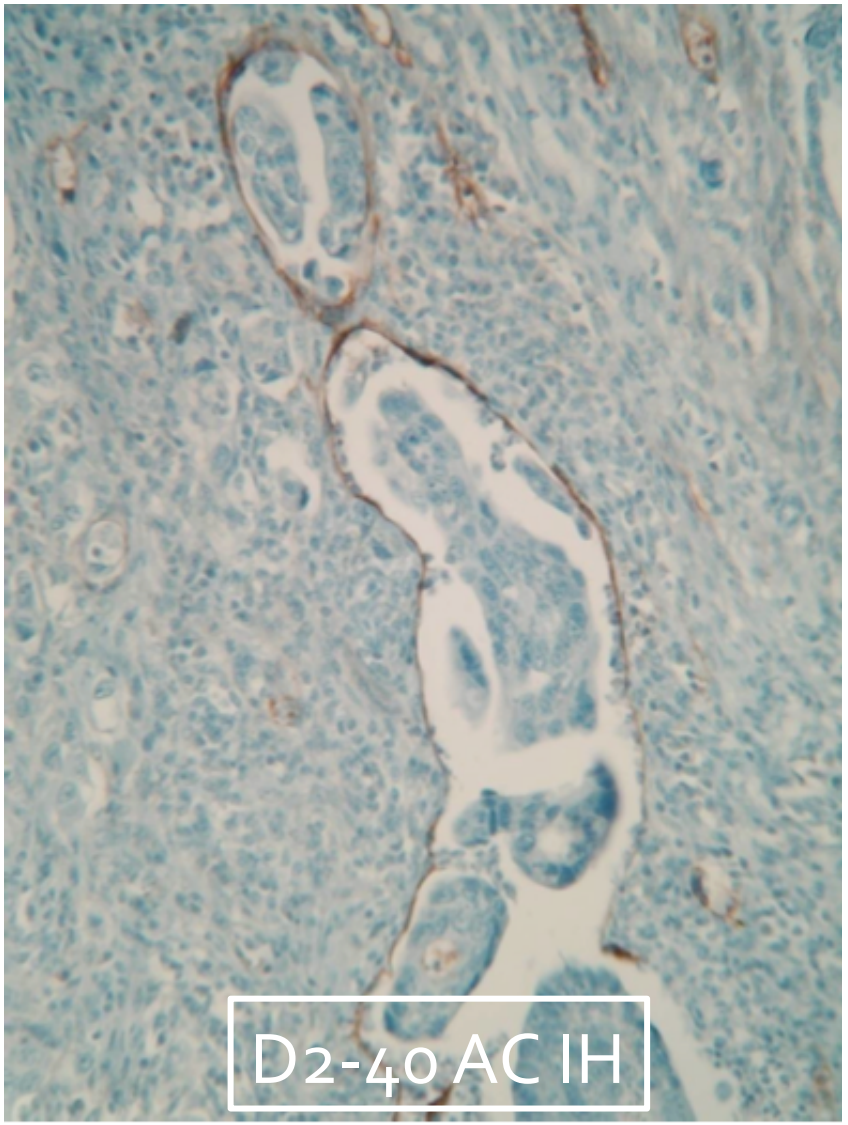
Correlation with

- Number of positive lymph nodes
- Development of extranodal tumour deposits
- Local recurrence

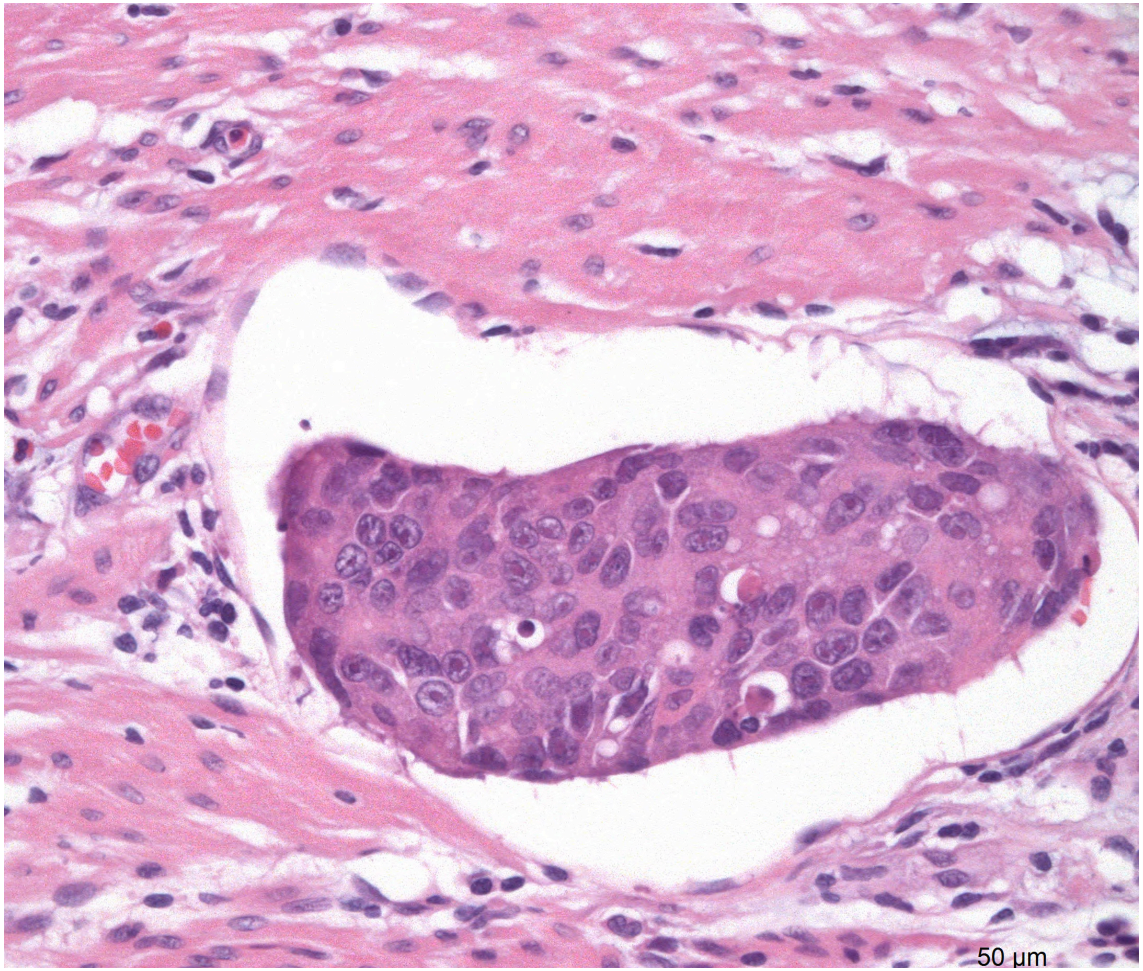
Ueno et al. Cancer (2002)

Lymphatic infiltration





Vascular invasion



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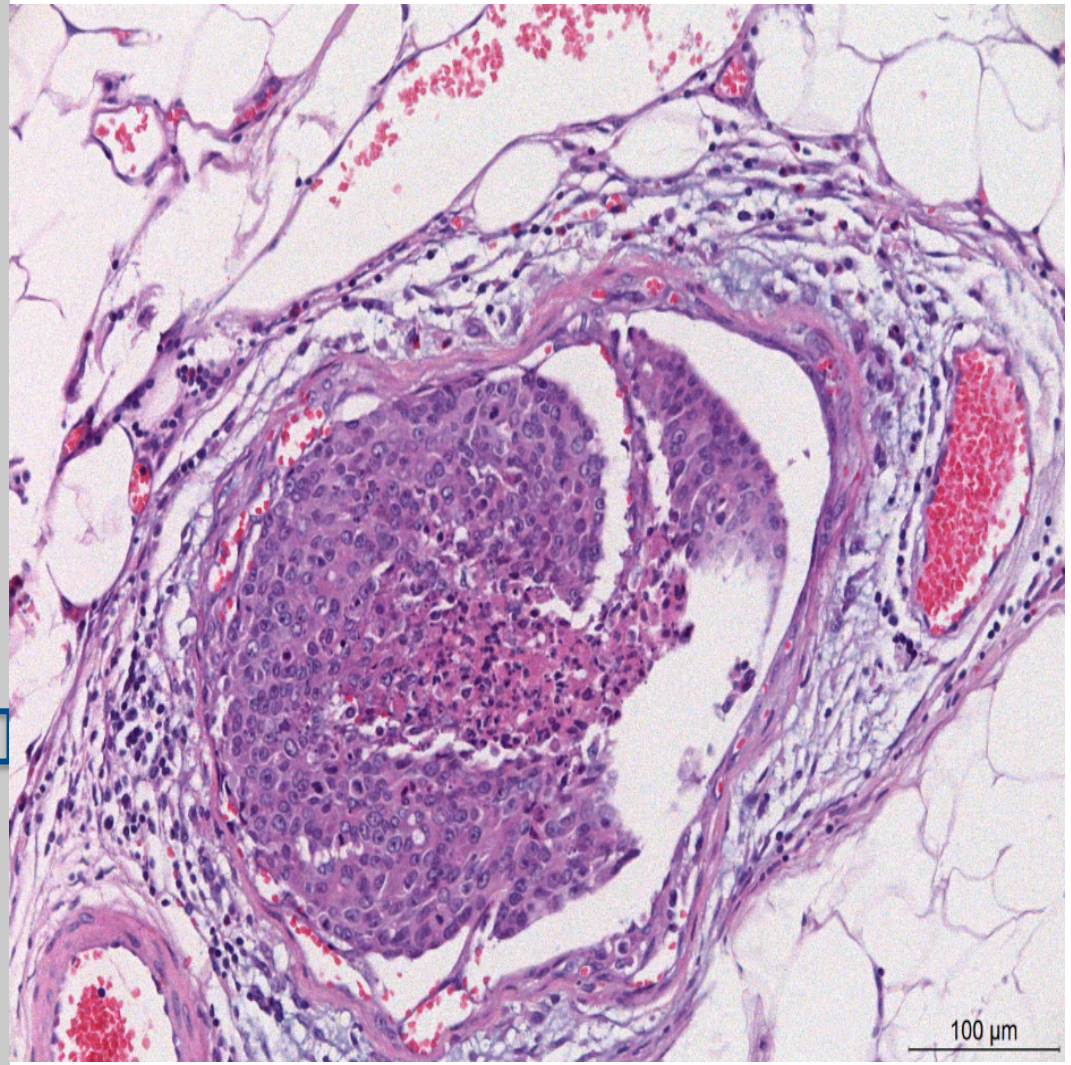
Vascular invasion

Variables	Number of patients	*P* values
Age (years)		0.18
< 50	4	
≥ 50	55	
Gender		1.0
Male	36	
Female	23	
Morphology		0.53
Sessile	51	
Pedunculated	8	
Histology		0.40
No pre-existing adenoma	11	
Tubular	16	
Tubulovillous	19	
Villous	13	
Degree of differentiation		0.64
Well	16	
Moderate	42	
Poor	1	
Degree of invasion		0.41
0	5	
1	2	
2	3	
3	0	
4	49	
Lymphatic invasion present	4	0.31
Venous invasion present	7	< 0.01
Desmoplastic reaction present	14	1.0
Lymphocytic infiltration		0.78
None	4	
Mild	31	
Moderate	8	
Severe	16	
Lymphoid follicles present	10	0.58
Margins		1.0
Pushing	14	
Infiltrating	45	



Bayar et al, Eur J Surg Oncol (2002)

	LYMPHATIC (LY) OR VASCULAR (v) INVASION
ABSENT	ly(0),v(0)
SLIGHT	ly(1),v(1)
MODERATE	ly(2),v(2)
MASSIVE	ly(4),v(4)

Japanese Society for Cancer of Colon and Rectum


WHICH
WAY
TO GO?

Swedish Rectal Cancer Registry

Distribution of T-stage and lymph node metastases.

T-stage	Distribution of T-stage (%)	Proportion with lymph node metastases (%)
T1, $n = 205$	13	12
T2, $n = 472$	29	22
T3, $n = 830$	51	46
T4, $n = 105$	7	65

Saraste et al.European Journal of Cancer (2013)

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Univariate analysis	Number	OR	95% CI	Multivariate analysis OR	95% CI
T-stage/sm-level					
Sm1	54	1	Ref		
Sm2	24	0.54	(0.06–5.12)		
Sm3	50	2.38	(0.67–8.46)		
Sm missing	77	2.08	(0.63–6.93)		
T2	472	3.45	(1.22–9.77)	1.97	(1.19–3.25)
Tumour differentiation					
High	114	1	Ref	1	Ref
Intermediate	498	1.98	(1.04–3.75)	1.72	(0.93–3.18)
Low	39	7.29	(3.06–17.4)	6.47	(2.71–15.4)
Differentiation missing	26	0.71	(0.15–3.38)		
Vascular infiltration					
Yes	61	4.81	(2.75–8.40)	4.34	(2.46–7.65)
No	492	1	Ref	1	Ref
Missing	124	0.96	(0.56–1.66)		
Perineural infiltration					
Yes	10	1.85	(0.46–7.31)		
No	458	1	Ref		
Missing	209	0.93	(0.61–1.42)		
Mucinous type					
Yes	52	1.87	(0.99–3.55)		
No	539	1	Ref		
Missing	86	0.97	(0.54–1.77)		
Tumour location (cm from anal verge)					
0–5 cm	118	1.03	(0.59–1.84)		
6–10 cm	259	1.23	(0.80–1.88)		
11–15 cm	300	1	Ref		
Gender					
Male	389	0.94	(0.63–1.39)		
Female	288	1	Ref		
Age[a]		0.99	(0.98–1.01)		

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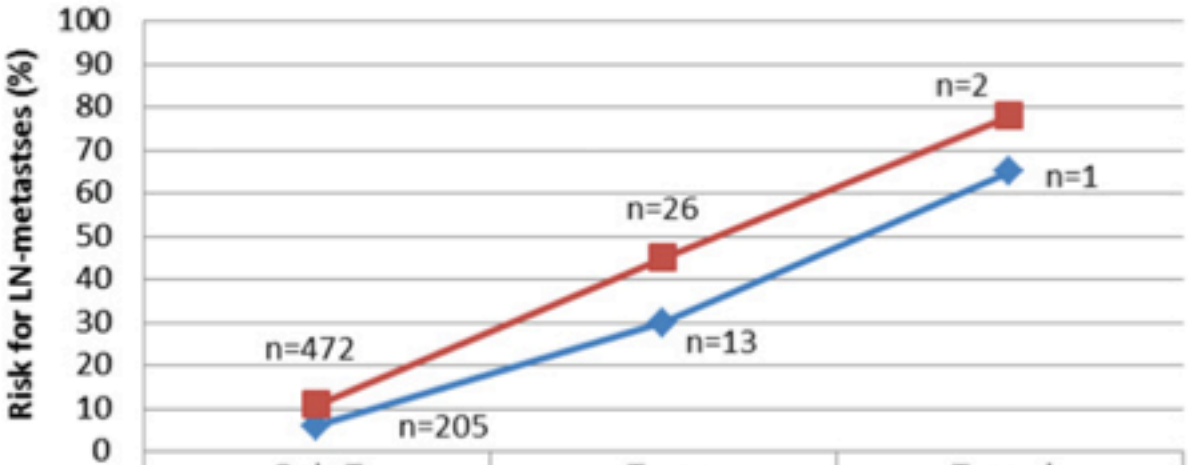
Risk stratification index



	Only T	T + a	T + a+ b
T1	6	30	65
T2	11	45	78

a= poor differentiation

b= vascular invasion

a = poor differentiation; b = vascular invasion.

The variables chosen for inclusion into the risk index are the variables with statistical significance in the multivariate analysis.

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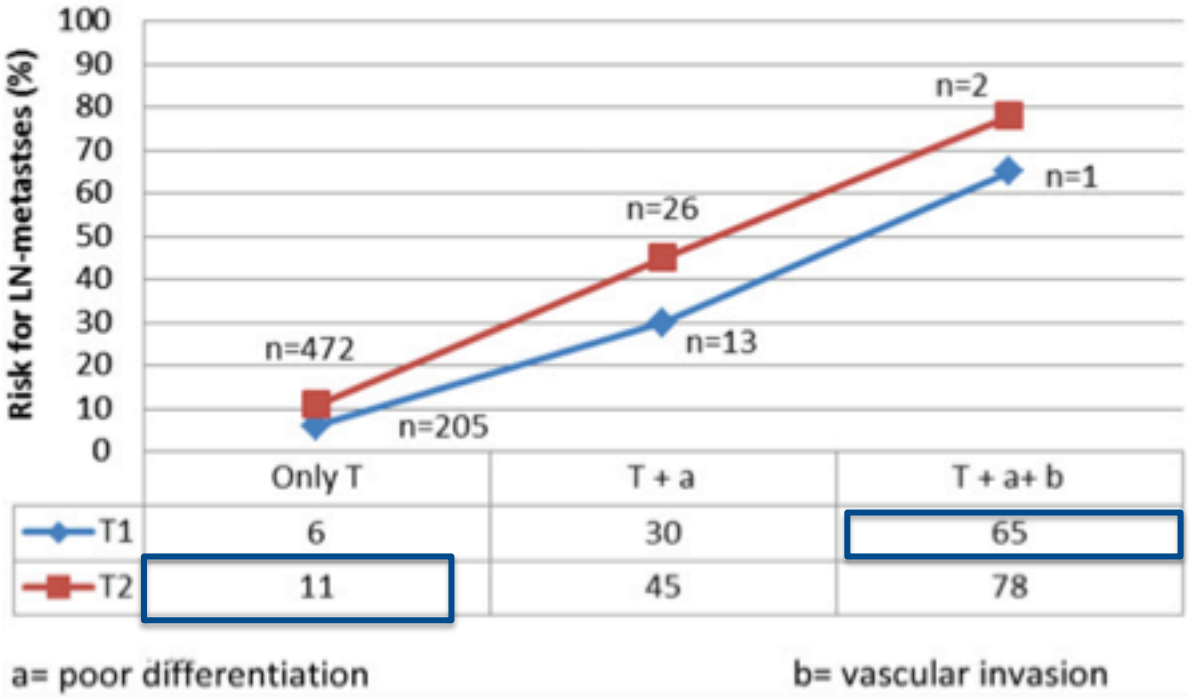
Risk stratification index



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a = poor differentiation; b = vascular invasion.
The variables chosen for inclusion into the risk index are the variables with statistical significance in the multivariate analysis.

Multivariate analysis of risk factors associated with lymph node metastasis in patients with early rectal cancer.

Risk factor	B	OR	95% CI	*P*-value
Depth of tumour penetration				
Sm1	0	1		
Sm2	−0.349	0.706	0.051–9.861	0.796
Sm3	−0.762	0.467	0.070–3.127	0.432
Muscularis propria (T_2)	−0.276	0.759	0.156–3.682	0.732
Tumour type				
Adenocarcinoma	0	1		
Mucinous/signet cell	0.302	1.352	0.386–4.733	0.637
Tumour grade				
Well differentiated	0	1		
Moderately differentiated	0.839	2.315	0.910–5.886	0.078
Poorly differentiated	2.459	11.696	3.262–41.945	**<0.001**
Vascular invasion				
Nil	0	1		
Intra-mural	0.399	1.490	0.630–3.523	0.363
Extra-mural	2.300	9.973	2.218–44.836	**0.003**

Rasheed et al.Colorectal Disease (2008)

	No. of patients with LNM (n = 46)	*No. of patients without LNM (n = 276)*	*Univariate P-value*
Status of the muscularis mucosa			
Type A[a]	1 (2%)	40 (98%)	0.02
Type B[b]	45 (16%)	236 (84%)	
Submucosal invasion depth (μm)			
<1000	1 (3%)	33 (97%)	0.05
>1000	45 (16%)	243 (84%)	
Tumor budding			
Positive	28 (26%)	78 (74%)	<0.01
Negative	18 (8%)	198 (92%)	
Tumor differentiation			
Well	23 (9%)	225 (91%)	<0.01
Moderate/poor	23 (31%)	51 (69%)	
Lymphatic invasion			
Positive	25 (33%)	51 (67%)	<0.01
Negative	21 (9%)	225 (91%)	
Venous invasion			
Positive	13 (29%)	32 (71%)	<0.01
Negative	33 (12%)	244 (88%)	

Tateishi et al. Modern Pathology (2010)

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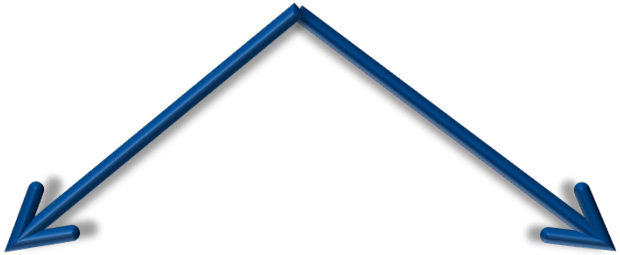
Multivariate analysis of risk factors for lymph node metastasis

Factors	*Odds ratio*	*95% CI*	P-*value*
Lymphatic invasion (+) *vs* lymphatic invasion (−)	3.19	0.22–0.94	<0.01
Well differentiation *vs* moderate/ poor differentiation	3.02	0.20–0.90	<0.01
Tumor budding (+) *vs* tumor budding (−)	2.59	0.12–0.83	<0.01

Tateishi et al. Modern Pathology (2010)

Patients with submucosal invasive cancer	322
Lymph node +	46 (14,3%)



40(87%)
Poor differentiation
Tumour budding
Lymphatic invasion

6(13%)
Disrupted muscularis mucosa

Tateishi et al. Modern Pathology (2010)

	Lymph node metastasis (including ITCs and micrometastasis)		Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
	Present	Absent				
Lymphatic invasion						
Present	6	1	37.5	97.5	85.7	79.6
Absent	10	39				
Tumour budding						
Present	16	26	100.0	65.0	38.1	100.0
Absent	0	14				
Lymphatic invasion or tumour budding						
Present	16	26	100.0	65.0	38.1	100.0
Absent	0	14				
Lymphatic invasion and tumour budding						
Present	7	0	43.7	100.0	100.0	81.6
Absent	9	40				

ITC = isolated tumour cells.

Kazama et al. British J of Cancer (2006)

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Clinicopathological studies addressing risk factors for synchronous regional lymph node metastases in early invasive colorectal carcinoma (pT1) by multivariate regression

Author	No.	Years of operation	Node positive of all (%)	Method of assessment	BUDhigh (%)	Node positive (%)‡	Risk factors by multivariate regression
Hase et al. (1995)	79	1970-1985	13.9	Scoring	55.7	25.0 / 0	Budding Depth of infiltration (SM), grading, lymphatic invasion
Ueno et al. (2004)	251	1980-2005	13.1	Counting H&E	15.1	42.1/7.9	Budding Depth of infiltration (> 500 lm), grading, lymphatic invasion
Wang et al. (2005)	159	1969-2002	10.1	Scoring	15.1	45.8/3.7	Budding Depth of infiltration (SM), grading, lymphatic invasion
Kazama et al (2006)	56	1990-2001	14.2	Scoring IHC†	75.0	38/0	Budding Lymphatic invasion
Sohn DK et al. (2007)	48	2000-2006	14.6	Counting H&E	20.8	60/2	Budding
Ishikawa Y et al. (2008)	71	1990-2006	39.0	Counting H&E	64.8	82/16	Budding Lymphatic invasion

Low-risk early rectal cancer

- Well or moderately differentiated adenocarcinoma and mucinous adenocarcinoma no
- No vascular or lymphatic invasion
- Kikuchi Sm1 and possibly Sm2
- Haggitt 1–3

Tytherleigh et al. British J Surgery (2008)

Low-risk early rectal cancer	High-risk early rectal cancer
Well or moderately differentiated adenocarcinoma and mucinous adenocarcinoma	Poorly differentiated adenocarcinoma and mucinous adenocarcinoma
	Signet ring and undifferentiated adenocarcinoma
No vascular or lymphatic invasion	Vascular or lymphatic invasion
Kikuchi Sm1 and possibly Sm2	Kikuchi Sm3 and possibly Sm2
Haggitt 1–3	Positive resection margin
	Relative factors Absence of lymphoid infiltration Tumour budding Poor demarcation at invasive front Poor differentiation at invasive front Cribriform-type structural atypia Position in distal third of rectum

no

Tytherleigh et al. British J Surgery (2008)

Feedback Form

June 16, 2013June 16, 2013

RiskPrediction.org.uk in association with:

Association of Coloproctology of GB&I

Cleveland Clinic Foundation

St Mark's Hospital

This model has been presented at the American Society of Colon and Rectal Surgeons (ASCRS) scientific meeting at Dallas Texas, May 2004.

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Calculate the St Mark's LNP Score

Choose a value in **each** category that matches your patient from the drop down lists describing the patient and histopathological criteria. Default values are shown for each category. Simply submitting the form as it is without changing the values (i.e. a young fit patient having s T1 well differentiated adenocarcinoma without any vascular or perineural invasion and conspicuous lymphocytic infiltration) still gives a % risk for lymph node metastases.

Questions? - contact Jason Smith or Paris Tekkis

Parameters	
Age	> 75 yrs old
Depth of invasion (T-stage)	T1
Differentiation	Well
Histological type	Adenocarcinoma / mucinous
Lymphocytic infiltration	Conspicuous infiltration
Vascular invasion	No invasion

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	> 75	> 75	> 75	> 75	> 75
Depth of invasion	T1	T1	T1	T1	T1
Differentiation	Well	Moderate	Poor	Well	Poor
Histological type	Adenoca	Adenoca	Adenoca	Adenoca	Adenoca
Lymphocytic infiltration	Yes	Yes	Yes	No	No
Vascular invasion	No	No	No	Yes	Yes
Perineural invasion	No	No	No	Yes	Yes
Positive lymph node probability (%)	3·7	7·2	24	27·8	75·9

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Decision making

Future perspectives

- Cancer biology

  p-27 (kip1) kinase inhibitor expression

  β-catenin expression

  E-cadferin expression

  DCC(deleted in colorectal cancer) protein

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Conclusions

Various factors have been identified as risk factors for lymph node metastases in early rectal cancer

The influence of each of these factors is still uncertain

Their detection on anatomo-pathology may be helpful in preoperative decision-making

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Conclusions

Clearer knowledge of the risk factors for lymph node metastases in histopathological analysis

Improvements in the diagnostic accuracy of radiology regarding lymph node metastases

→ Will improve the chances of local excision alone being sufficient for cure of early rectal cancer in selected patients

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