VII Curso de Patología Digital

Hospital Universitario Puerta del Mar

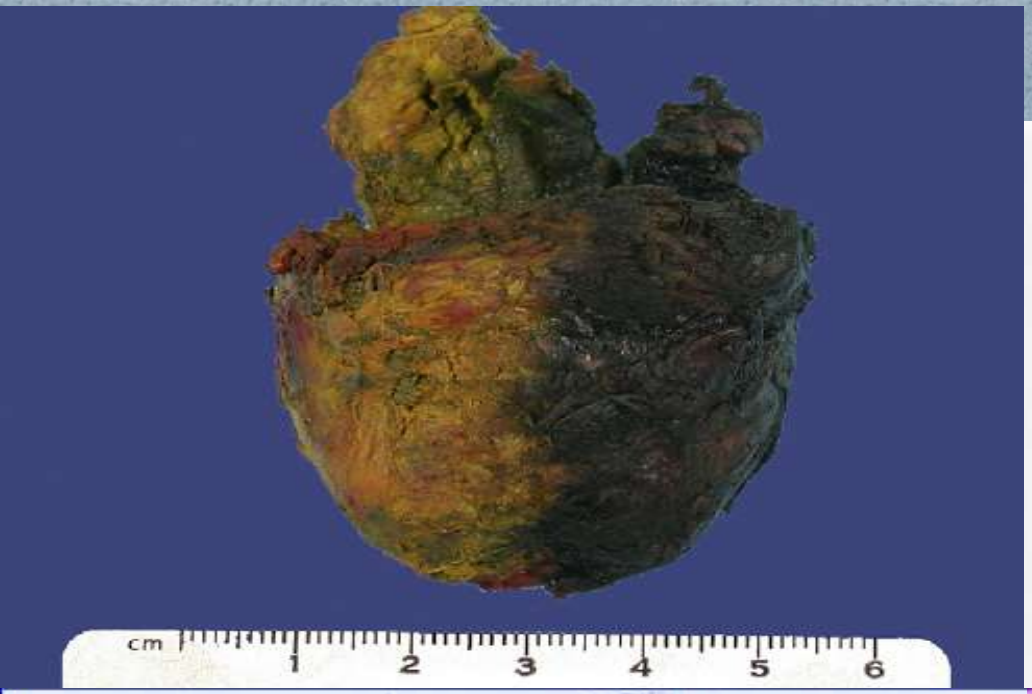
Cádiz

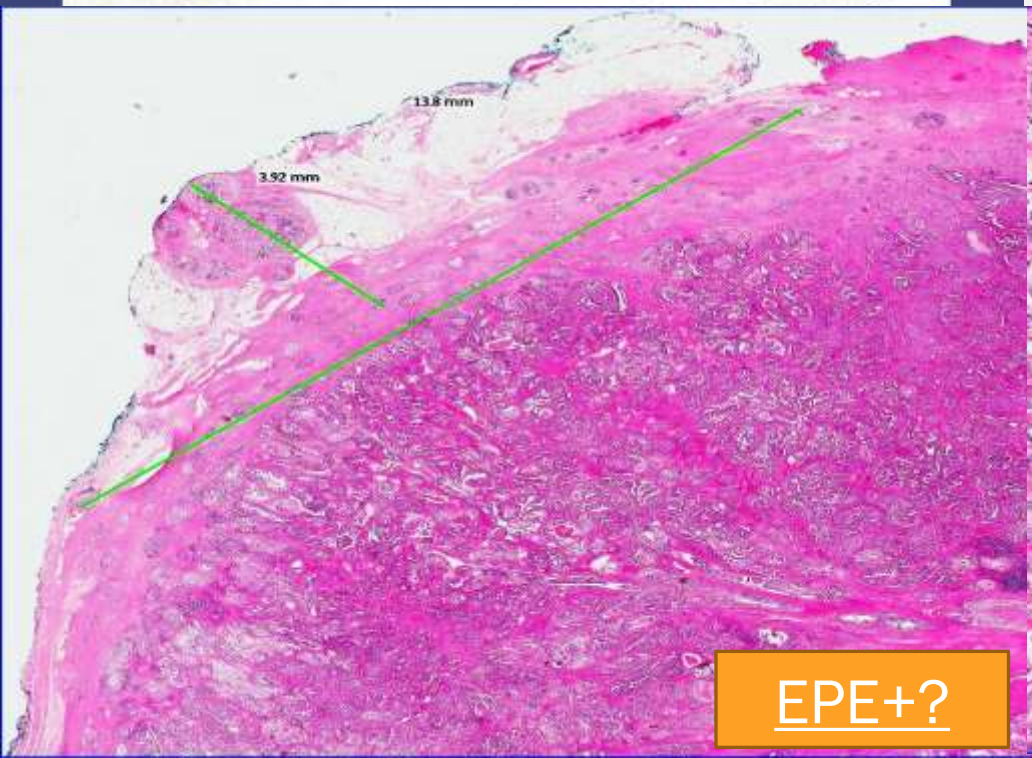
15 a 17 de octubre de 2018

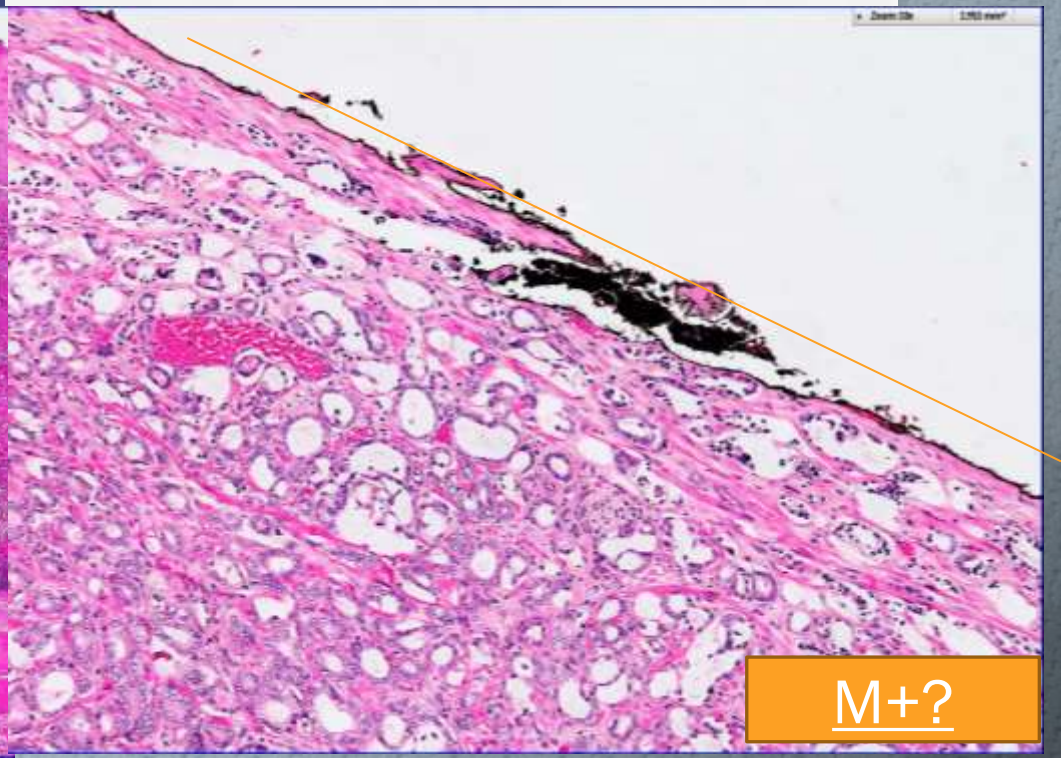
Patología digital en la evaluación de margen quirúrgico y extensión extraprostática en prostatectomía radical.

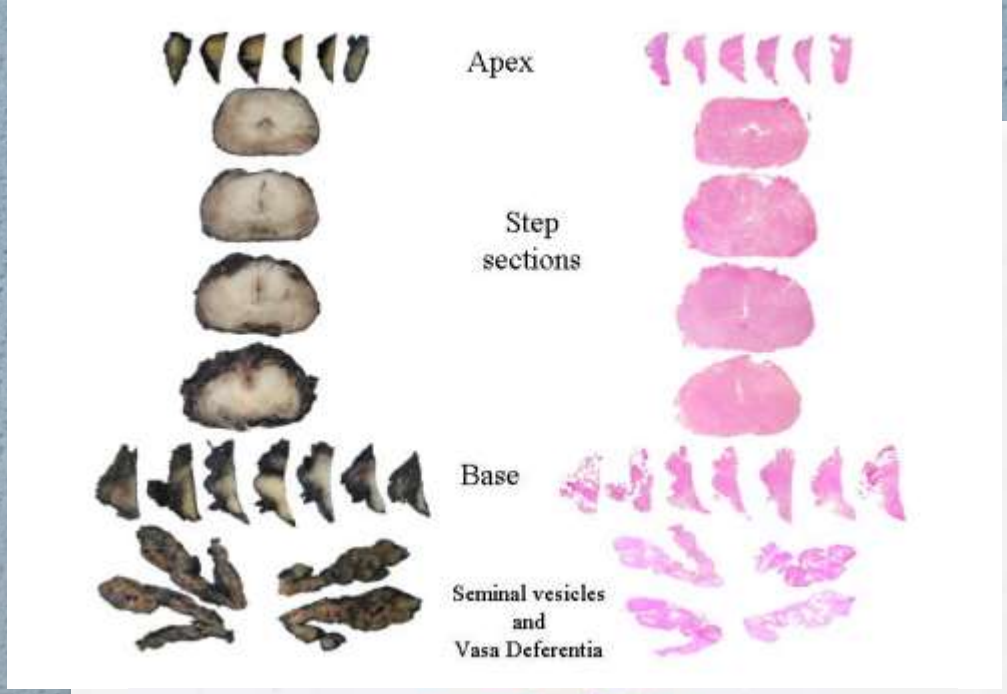
Antonio Lopez-Beltran

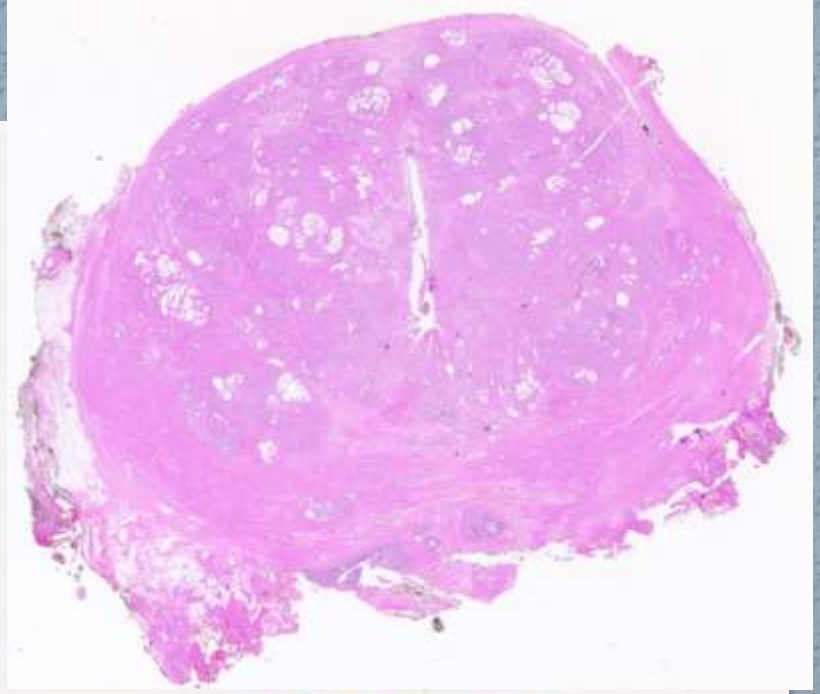
Radical prostatectomy specimens

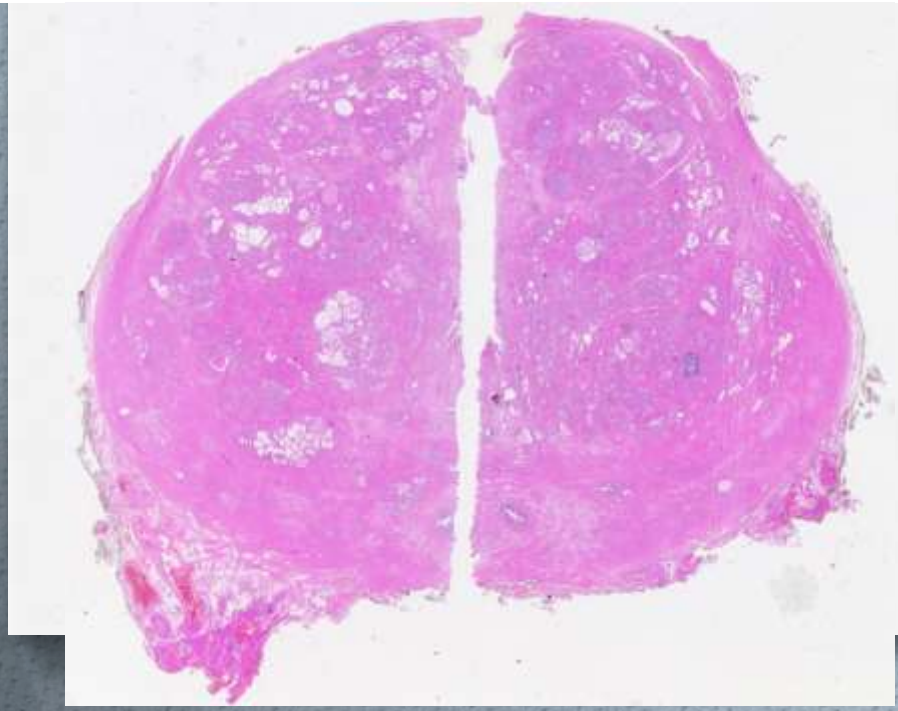


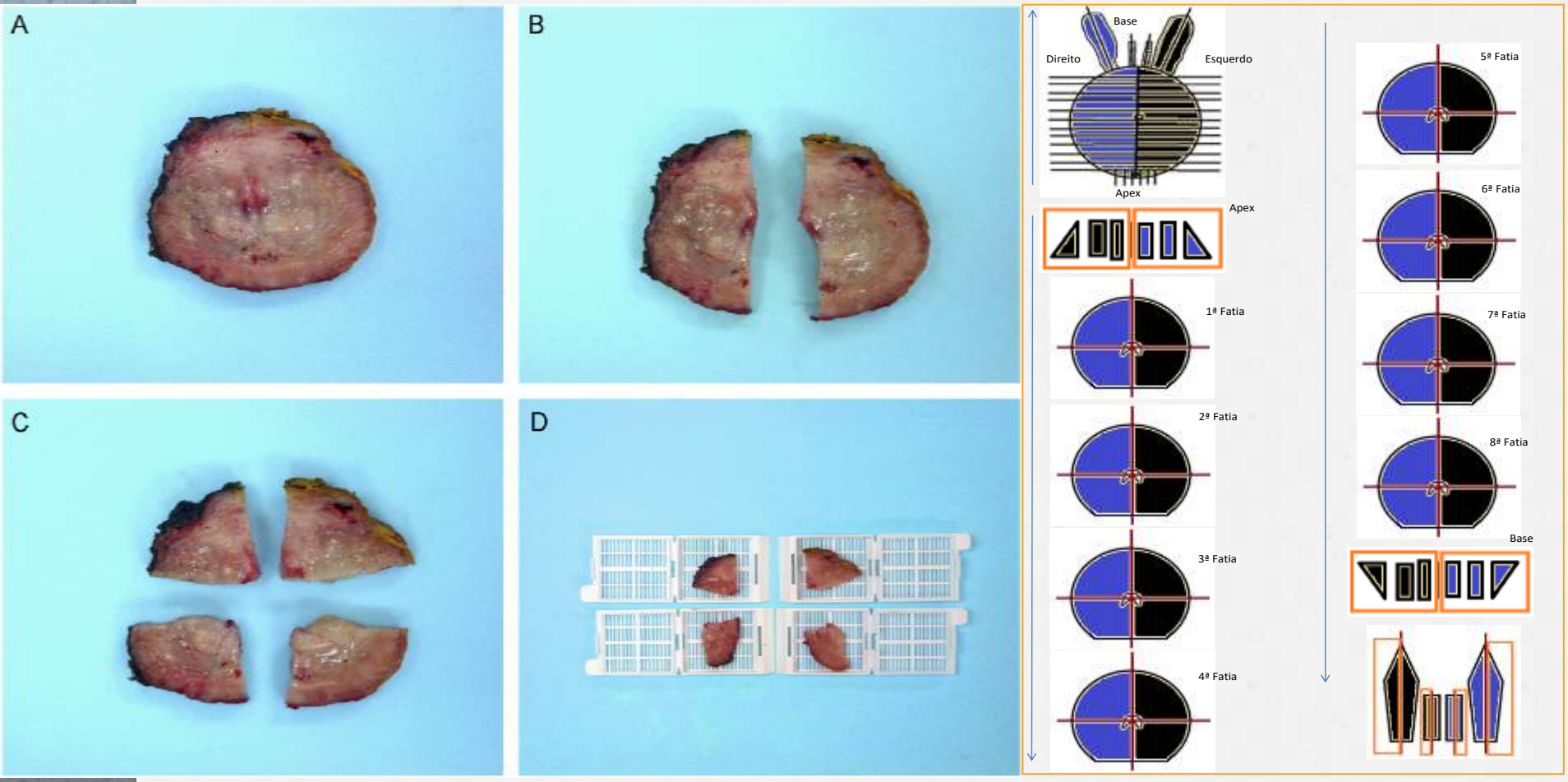





Apex
Step
sections
Base
Seminal vesicles
and
Vasa Deferentia





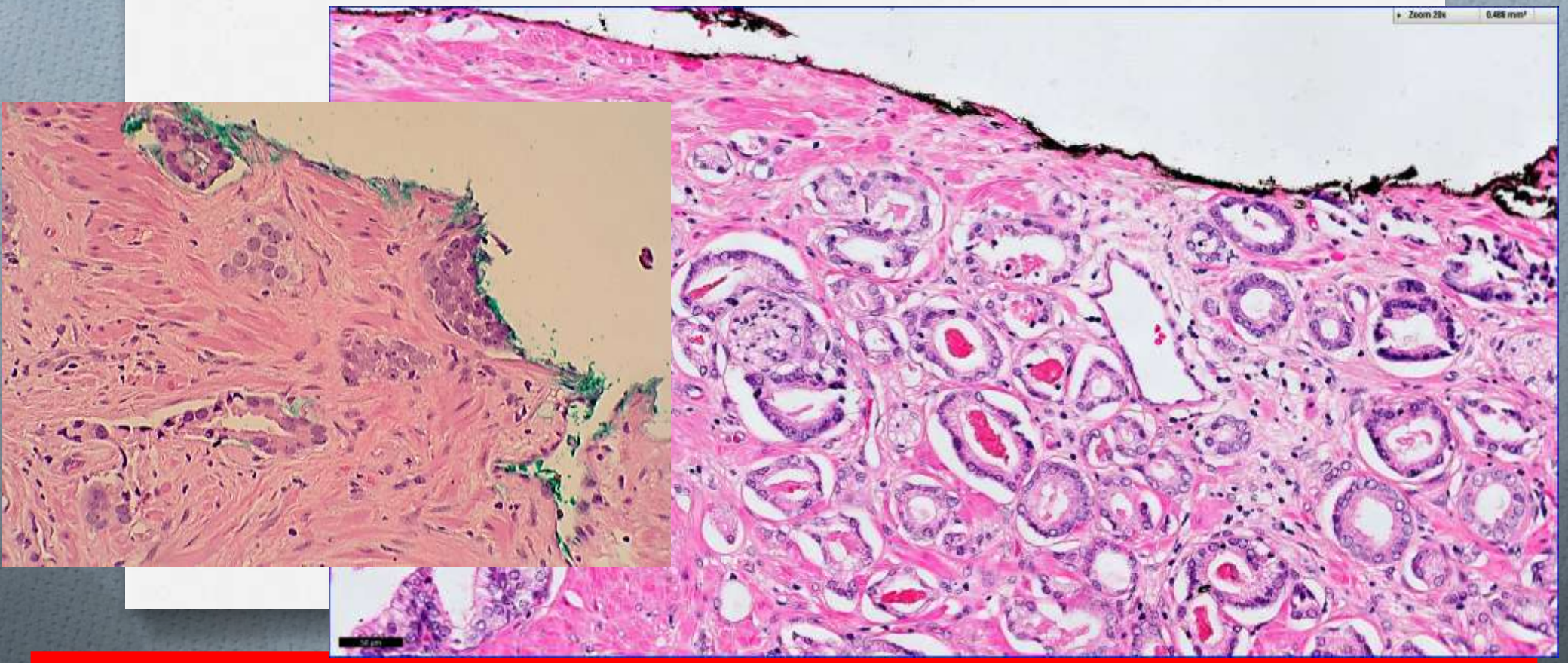


Sung, Montironi, Lopez-Beltran Current Diagn Pathol, 2014

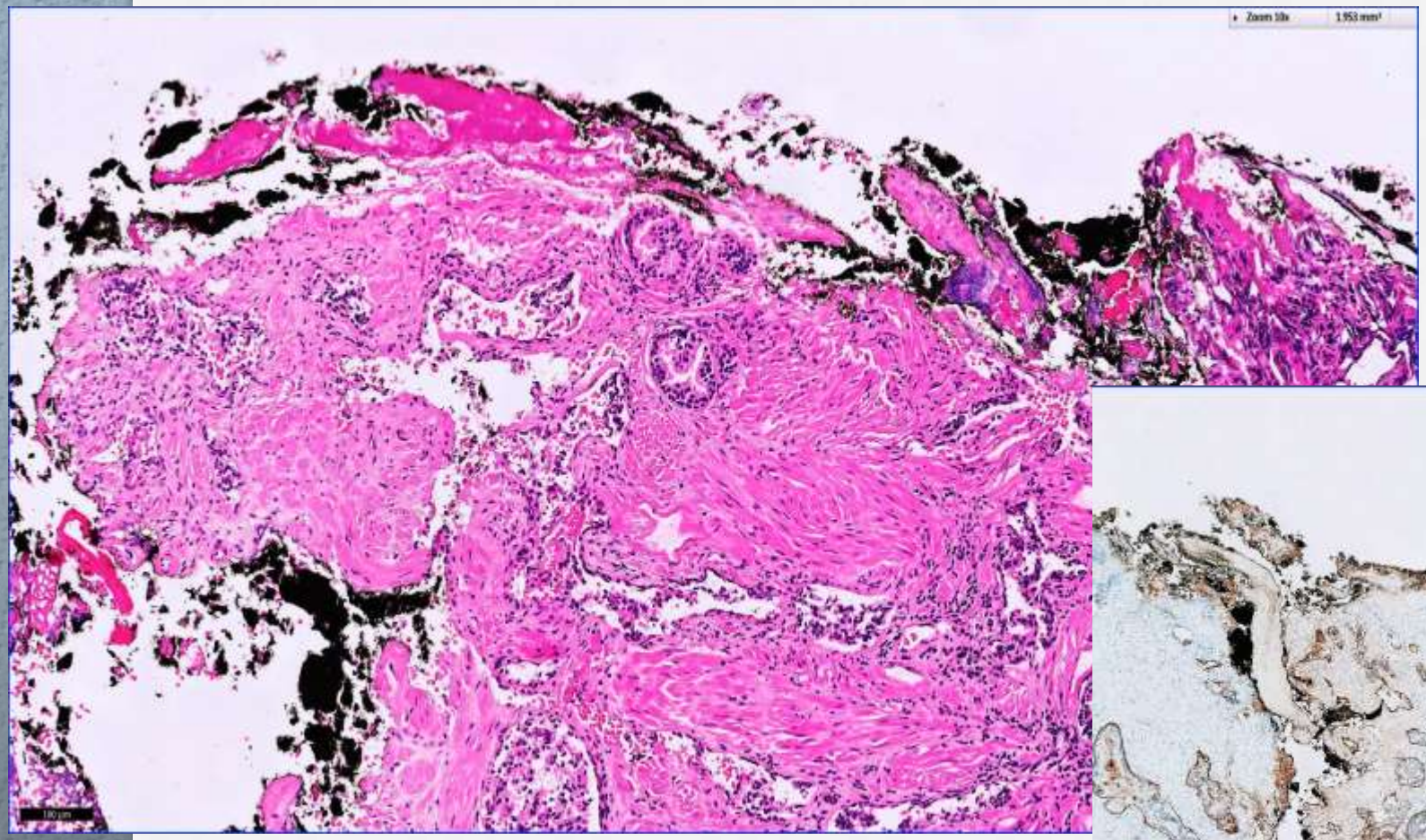
22-36

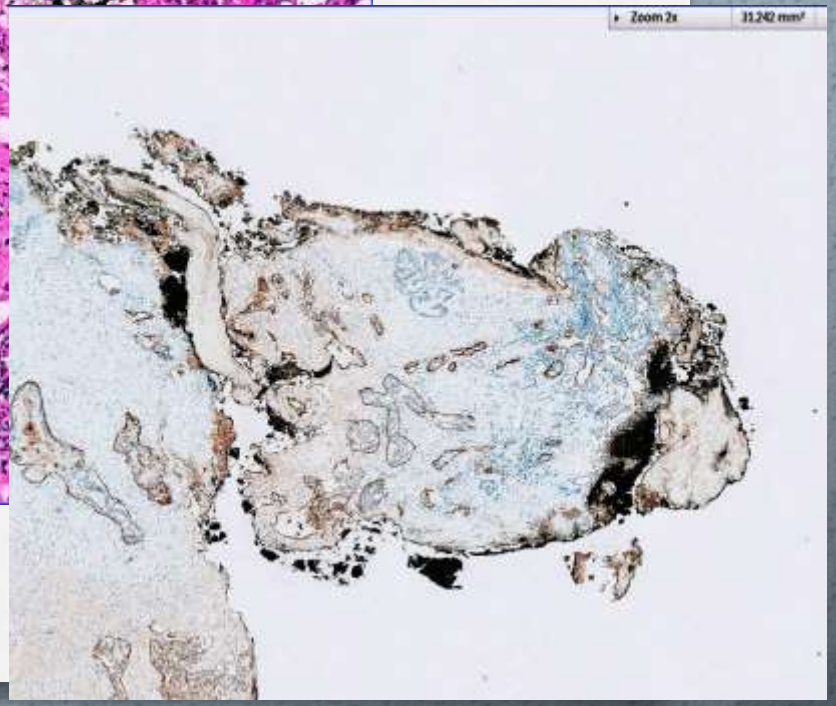
Positive surgical margins in RPs

- Definition: ink on tumor cells



M+?





Positive surgical margins

1. 15% incidence (6-30%)
2. Similar in Robotic than in open/laparoscopic RP
3. Increasing incidence with higher grade, volume, and stage of Pca
4. Strong dependent of surgeon “Experience”

Table 1 – Hazard ratios of biochemical recurrence, metastatic progression, and prostate cancer-specific mortality following radical prostatectomy in men with positive or negative surgical margins

Study	Year	*n*	PSMs, no. (%)	Median follow-up, yr	HR for BCR (95% CI), *p* value	HR for MP (95% CI), *p* value	HR for PCSM (95% CI), *p* value
Mauermann et al. [32]	2012	1712	281* (16.4)	6.2	1.7 (1.2–2.3), 0.001	1.07 (0.3–3.4), 0.9	1.4 (0.36–5.4), 0.63
			310* (18.1)	6.2	2 (1.5–2.7), <0.0001	0.9 (0.3–3.1), 0.98	1.15 (0.29–4.47), 0.84
Pfitzenmaier et al. [33]	2008	406	70 (17)	5.2	3.2 (2.1–4.8), <0.001	6.6 (1.9–23), 0.003	NR
Boorjian et al. [30]	2010	11 729	3651 (31.1)	8.2	1.6 (1.5–1.8), <0.0001	NS, 0.95	NS, 0.15
Wright et al. [34]	2010	65 633	21.2%	4.2	NR	NR	1.7 (1.3–2.2), NR**
Chalfin et al. [31]	2012	4461	462 (10.4)	10	5 (3.7–6.7), <0.001	NR	1.4 (1.0–1.9), 0.036

PSM = positive surgical margin; HR = hazard ratio; NR = not reported; NS = not significant; BCR = biochemical recurrence; MP = metastatic progression; PCSM = prostate cancer-specific mortality; CI = confidence interval.

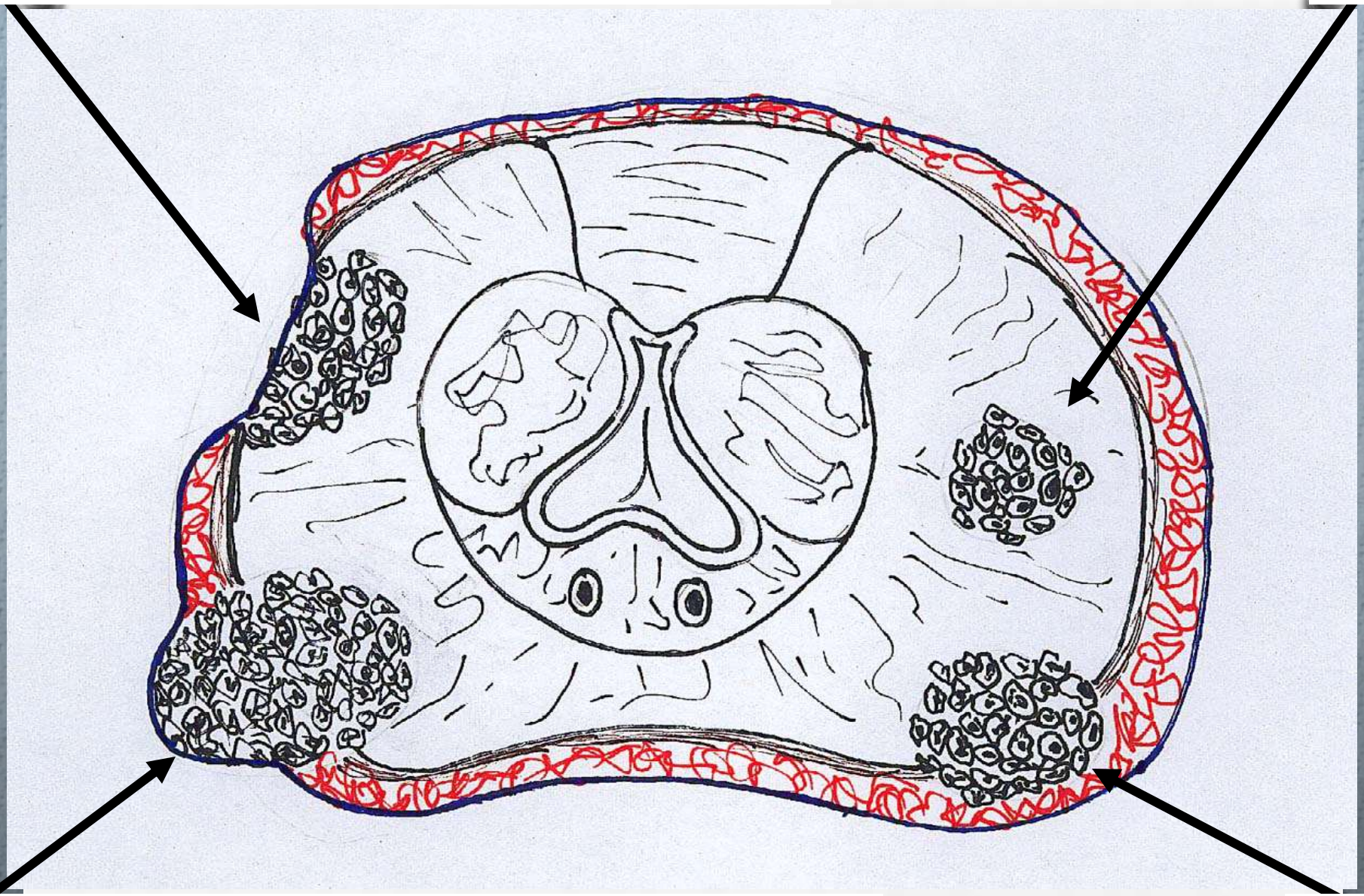
* There were 281 patients with a solitary positive margin and 310 patients with multiple positive margins.

** The *p* values were not reported; statistical significance was reached only in patients with high-grade tumors or extracap

Eur Urol 2014

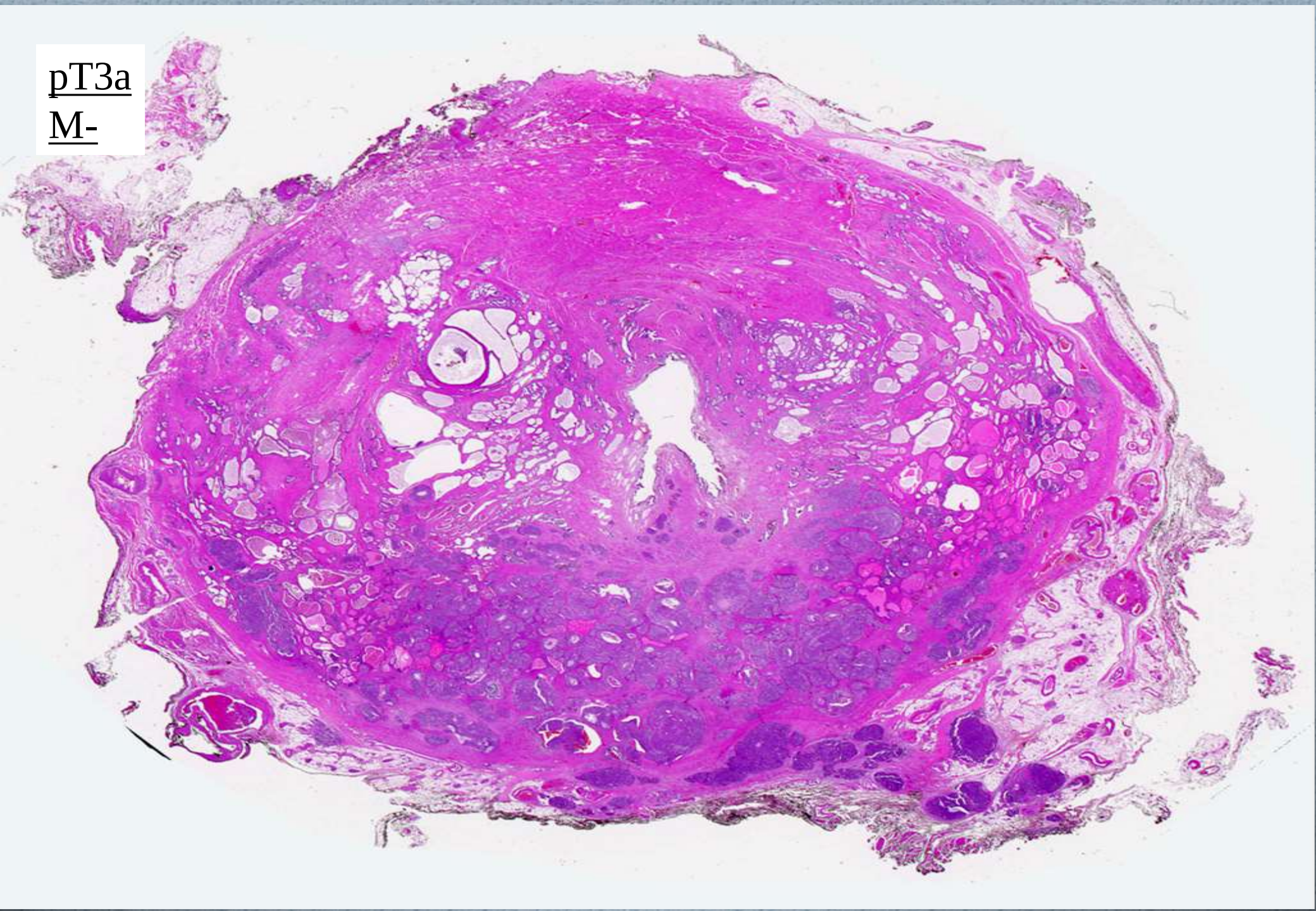
pT2 with + margin (intra-prostatic)

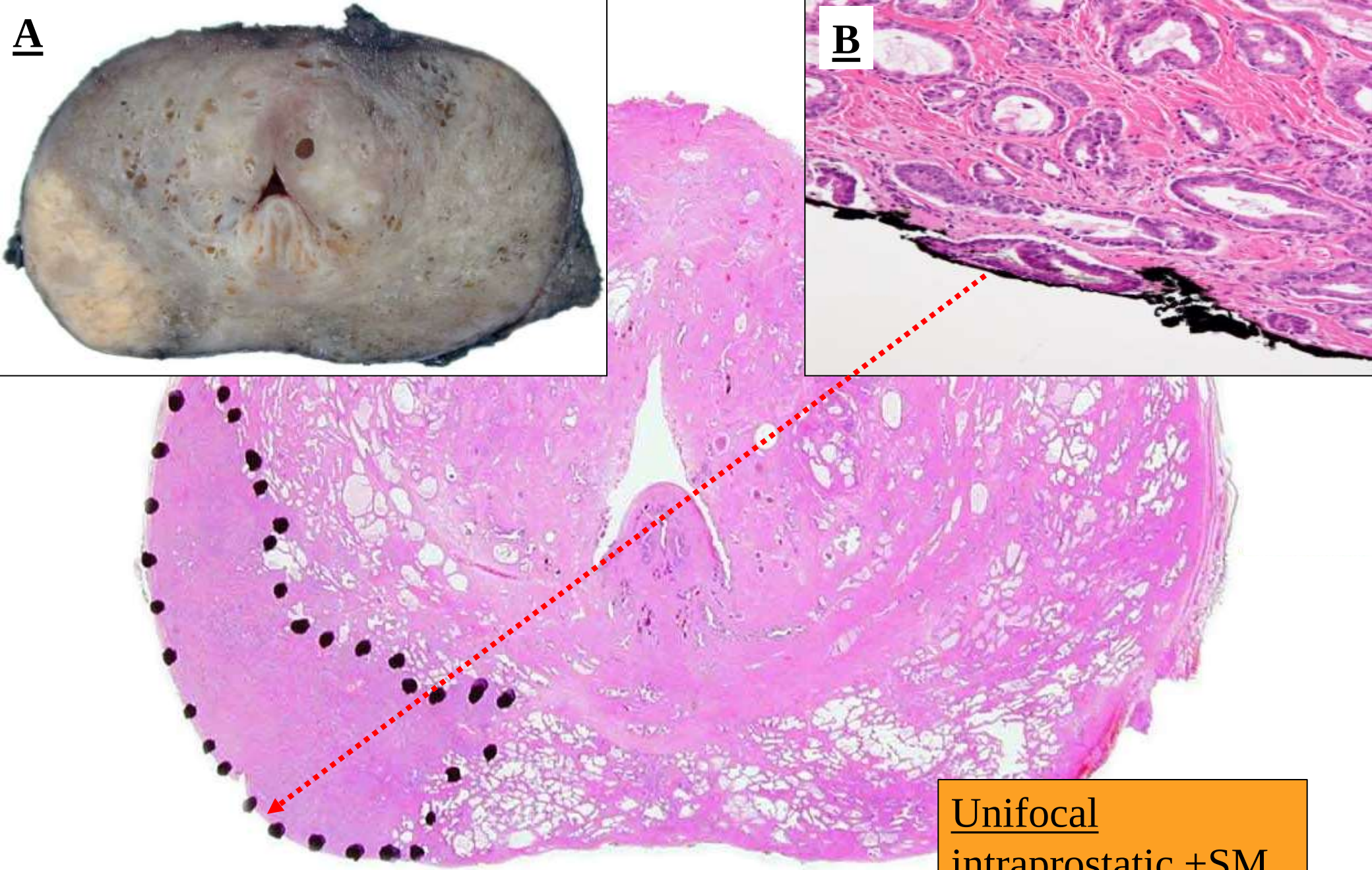
pT2

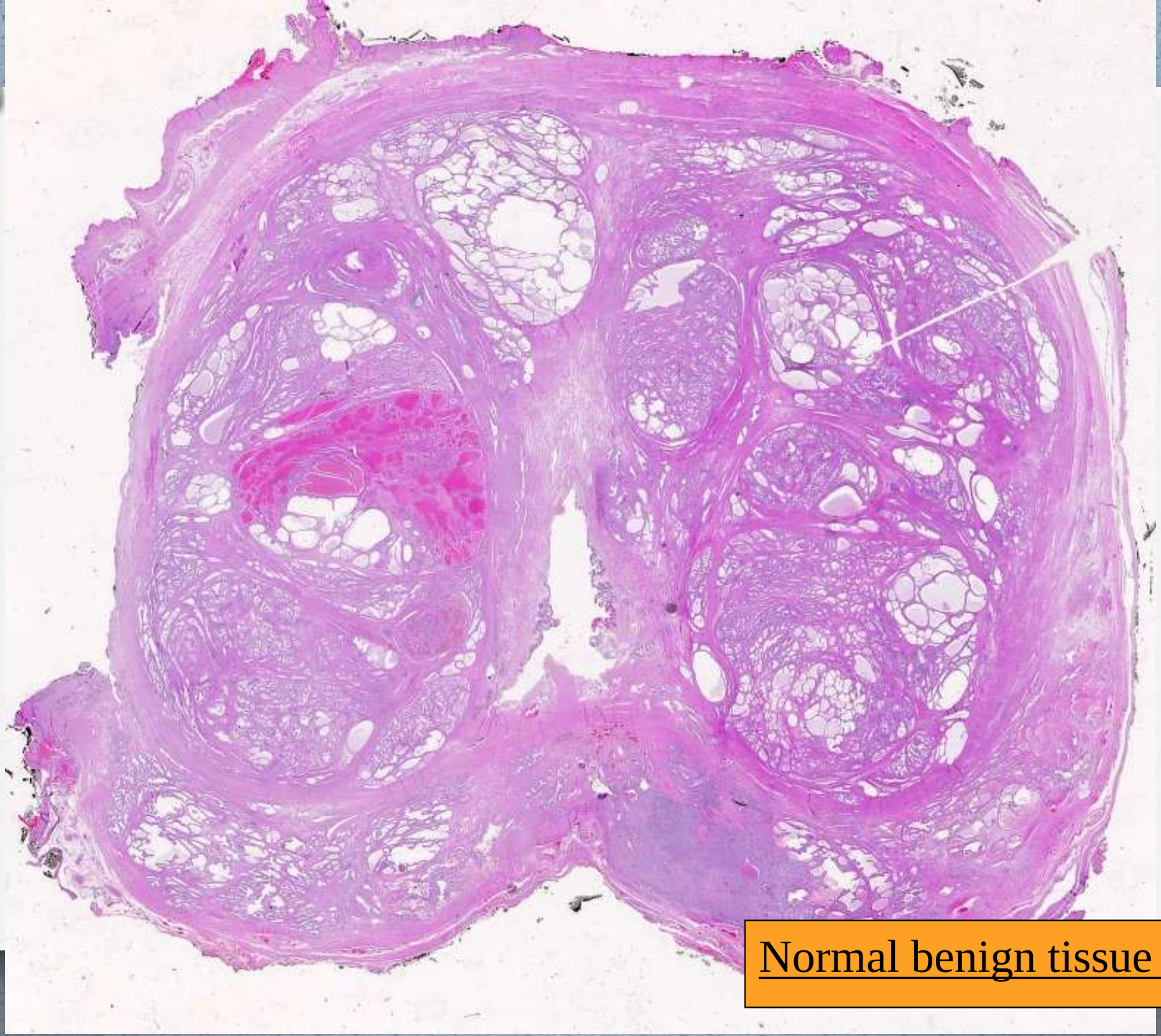


pT3a with + margin (extra-prostatic)

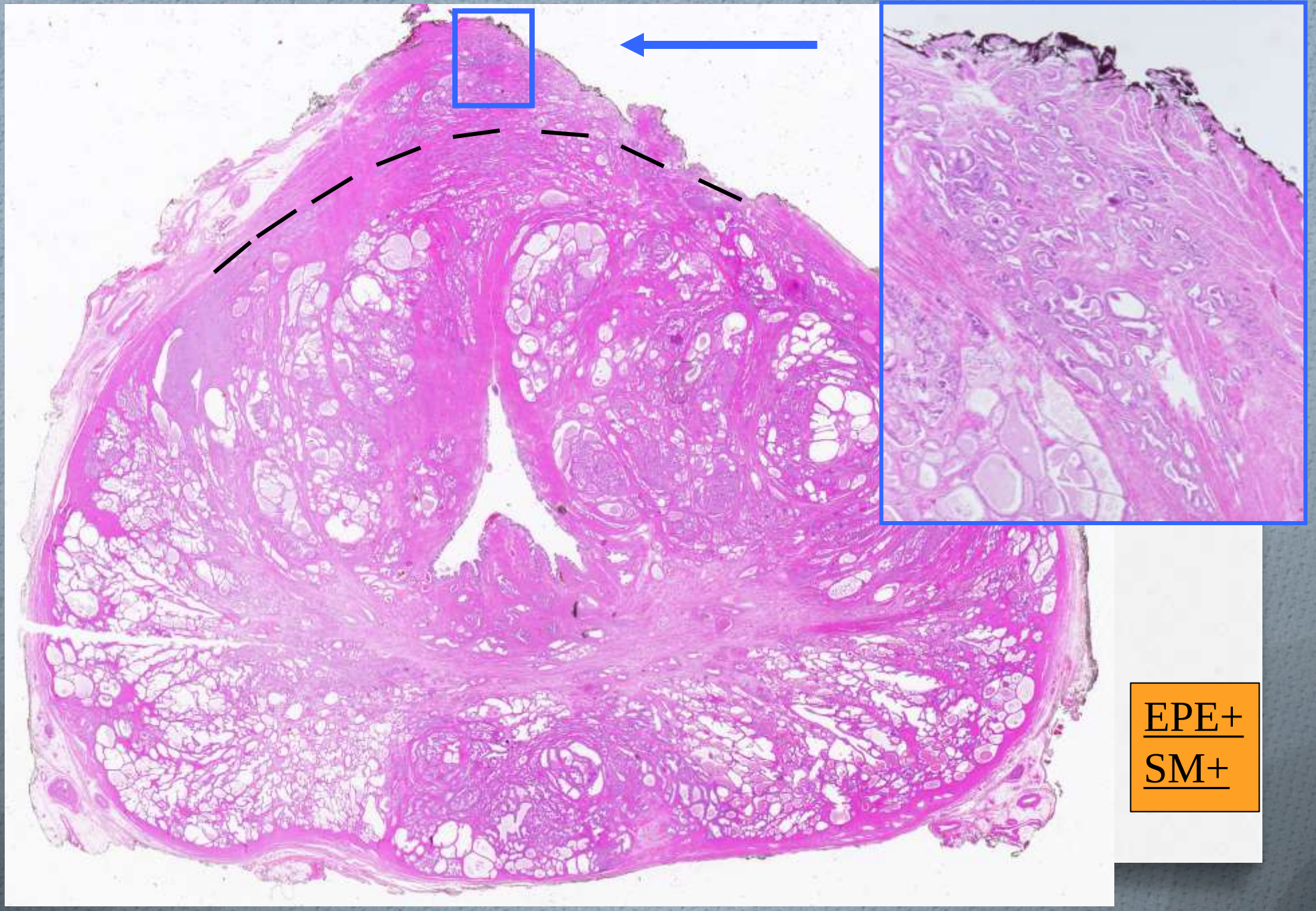
pT3a


pT3a
M-

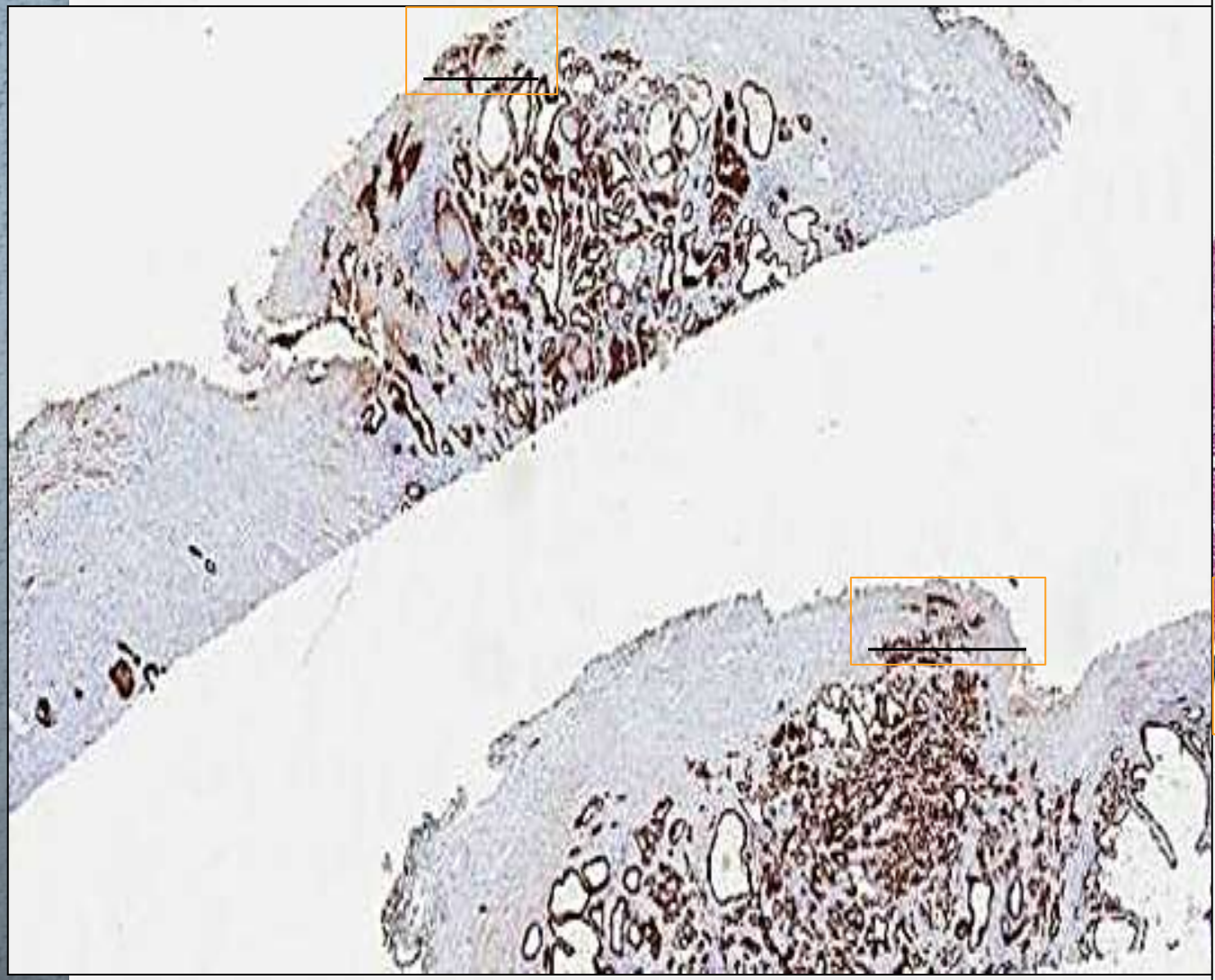

A
B
Unifocal
intraprostatic +SM

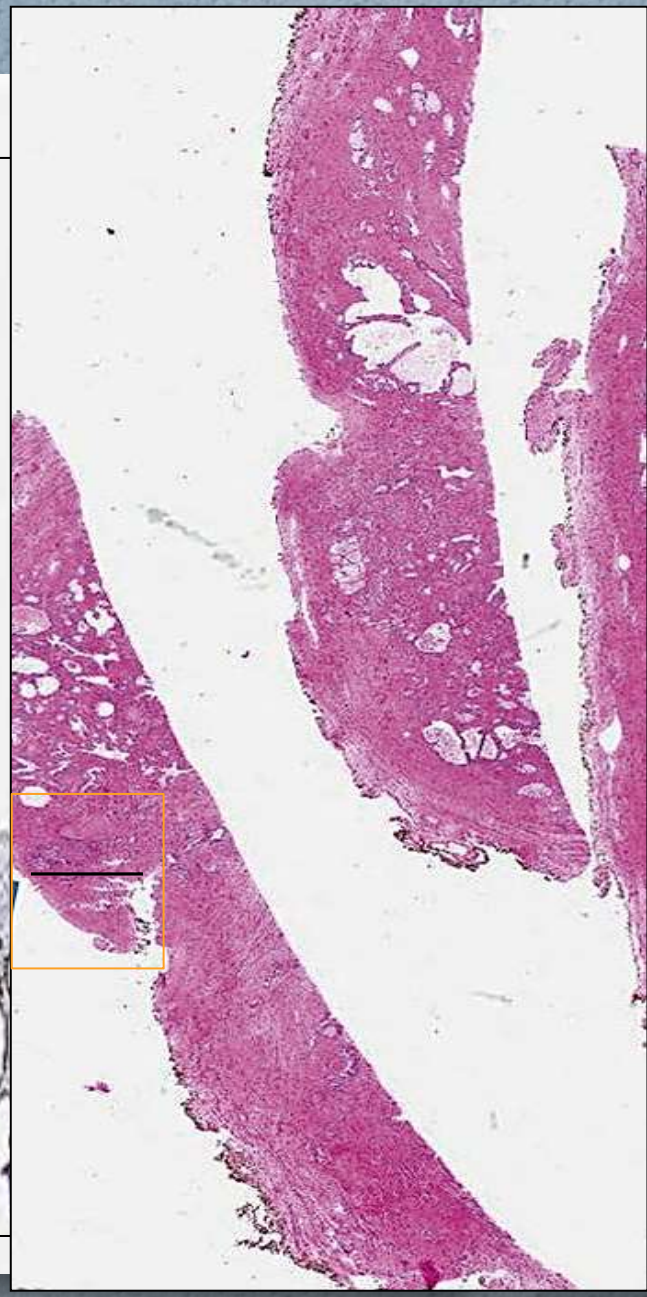


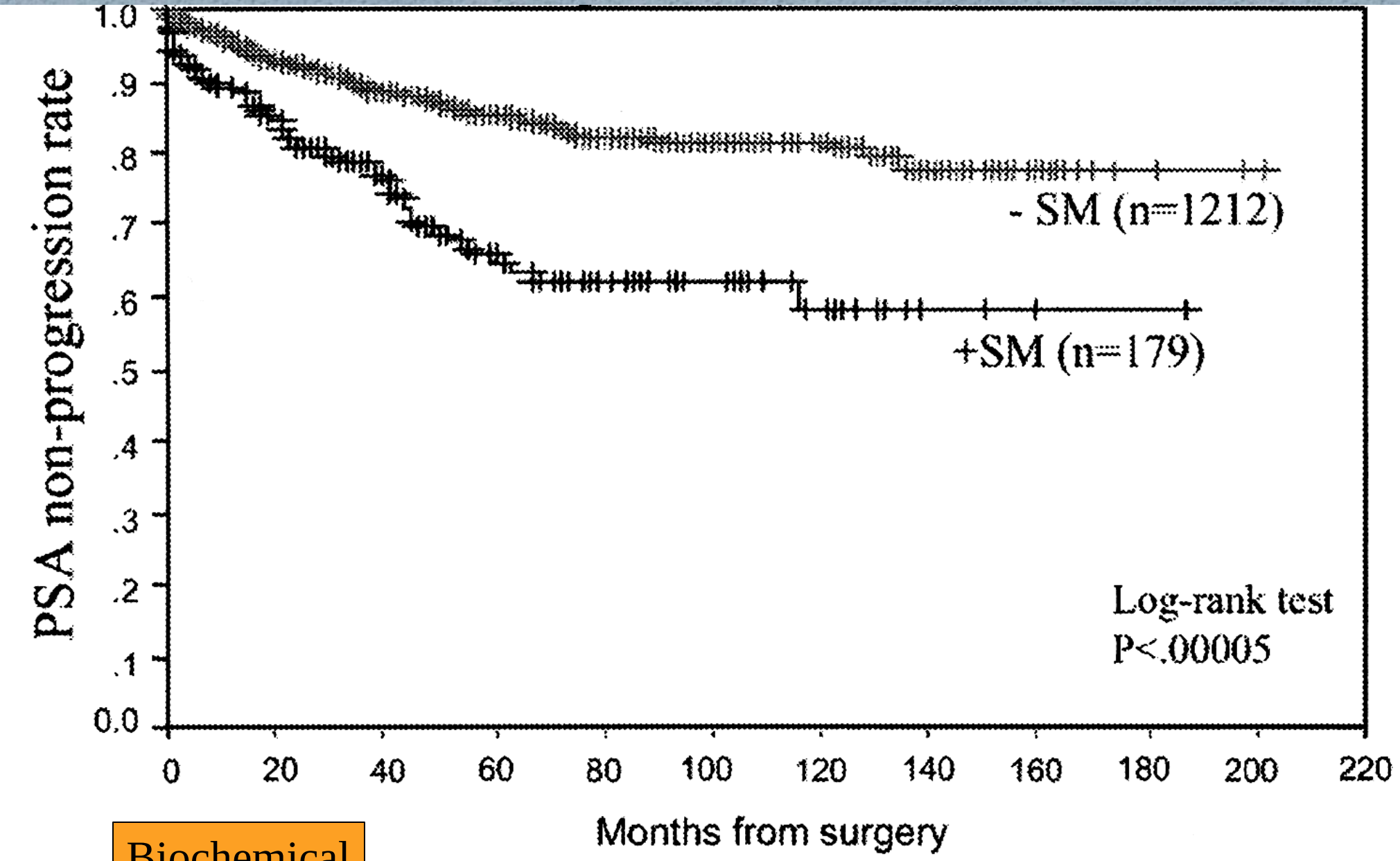
Normal benign tissue at SM



EPE+
SM+







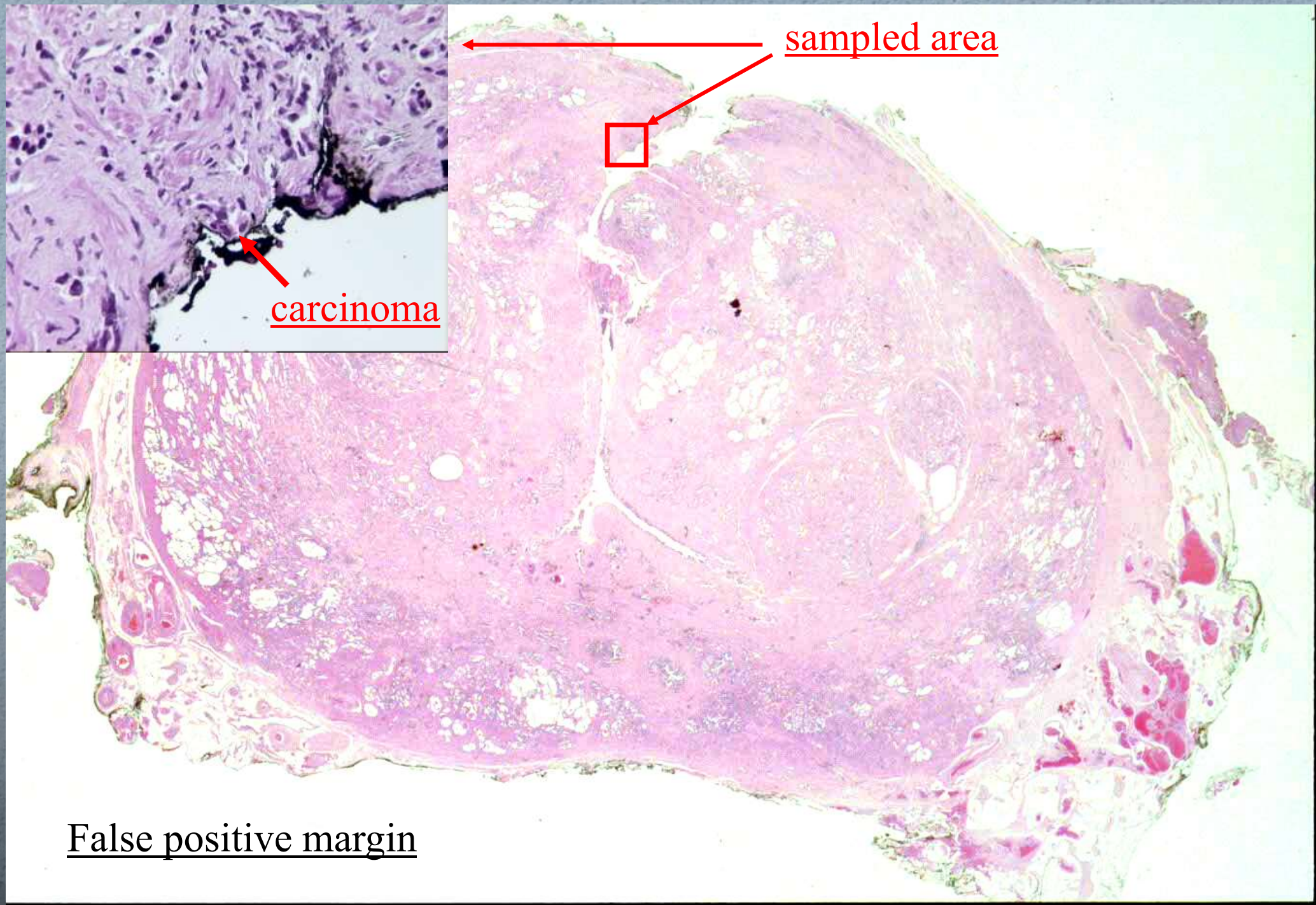
Biochemical recurrence

Swindle P et al, J Urol 174, 903, 2005

Surgical margins

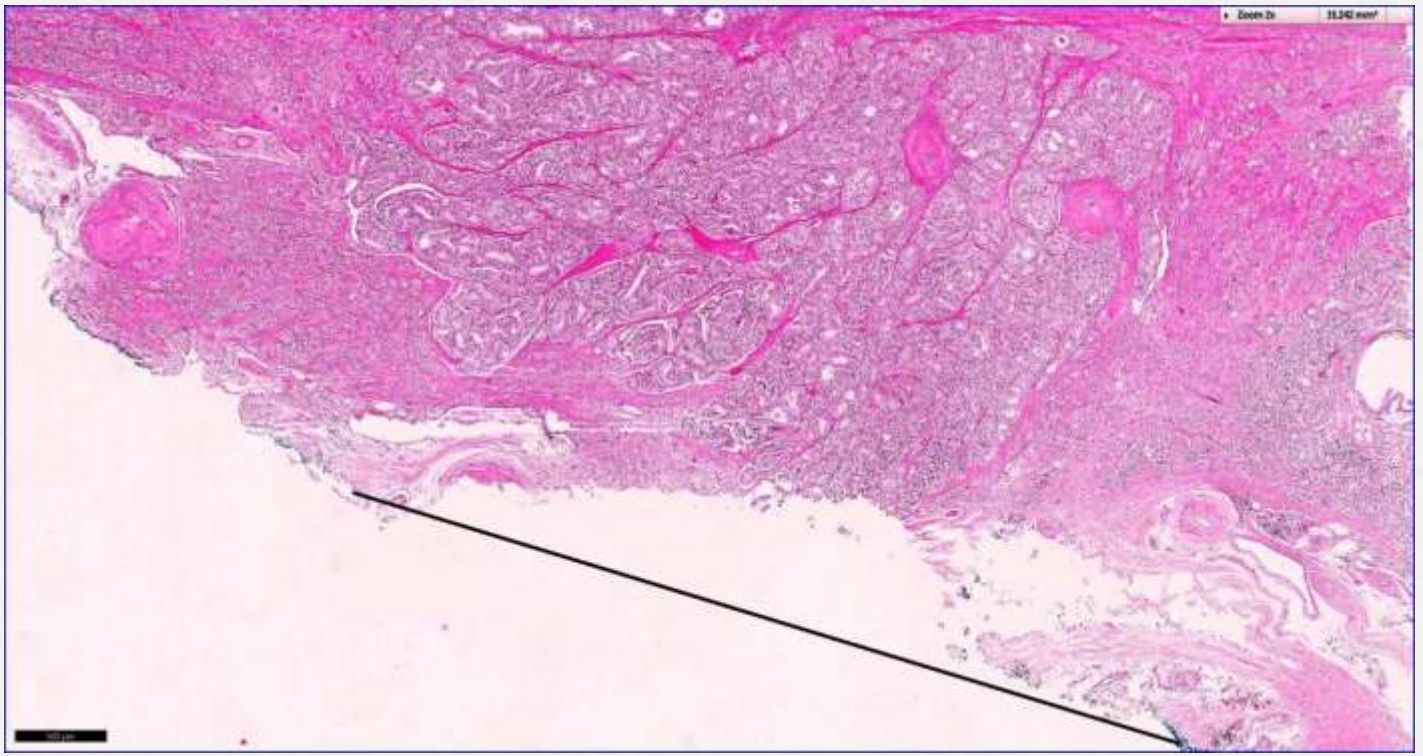
- Extent:
  - Focal vs. extensive
    1. number of blocks involved
    2. mm of involvement

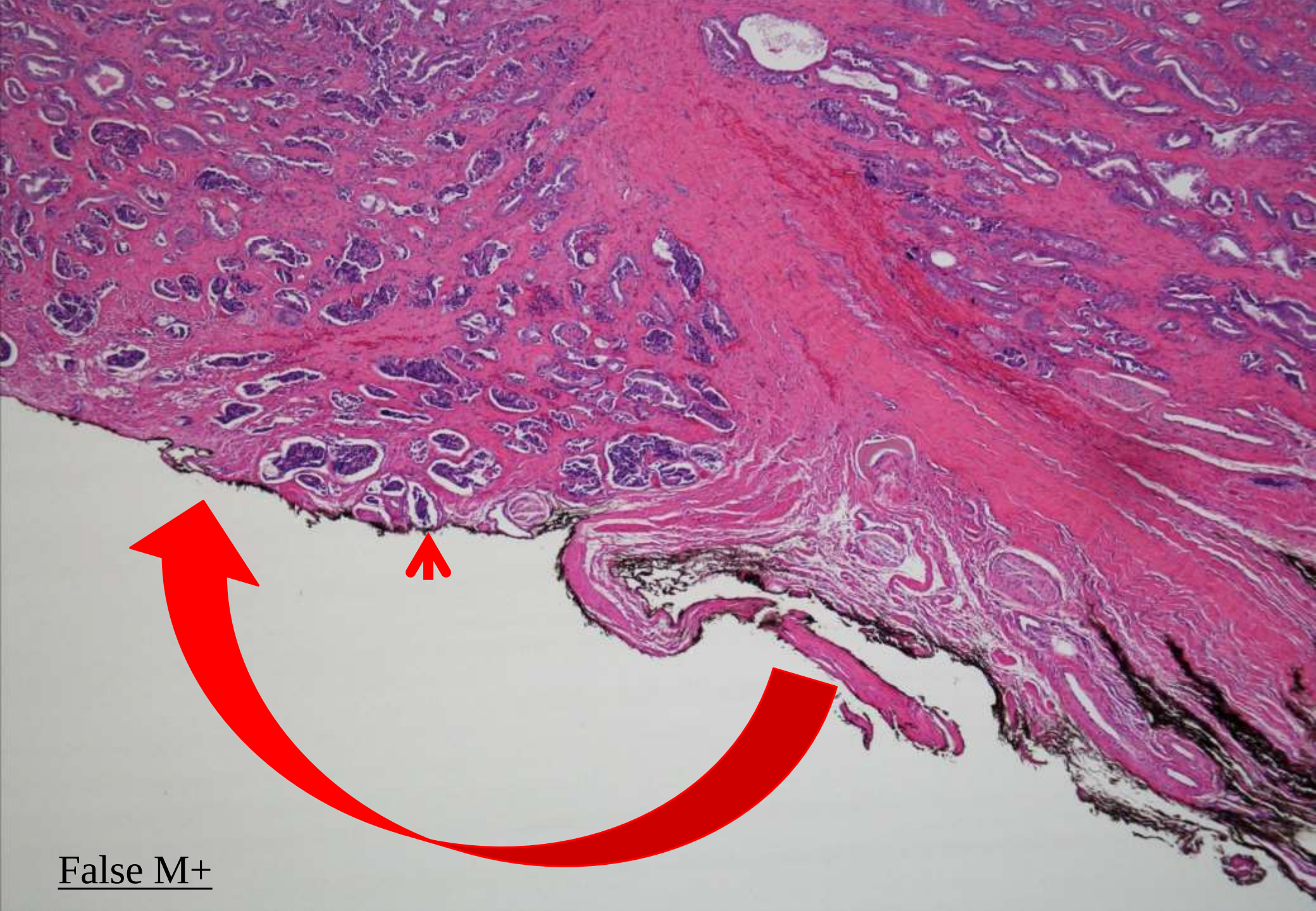
       ≤ 3mm *vs.* > 3 mm



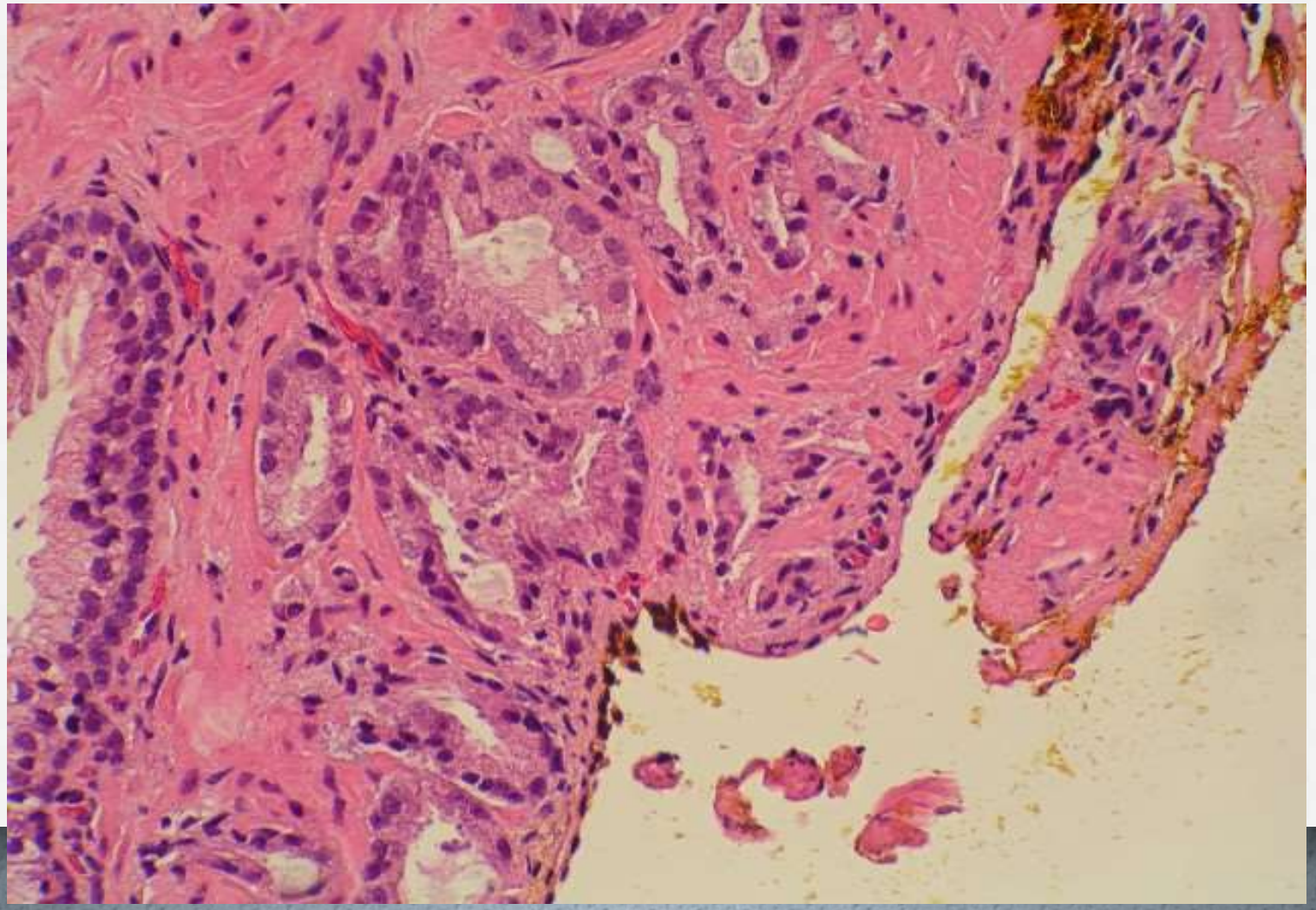
False positive margin

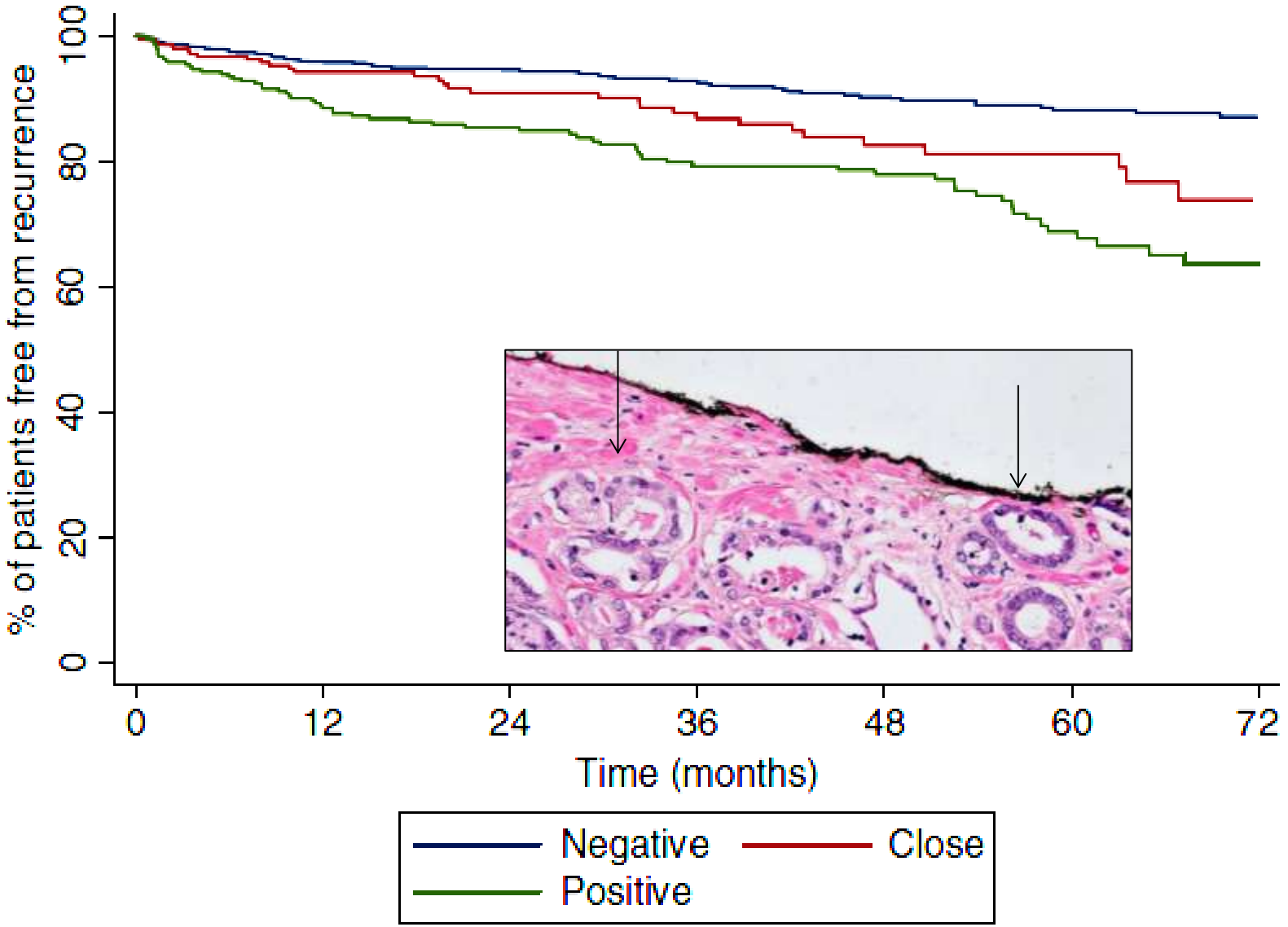
Missing Margin




False M+

Positive surgical margin in areas of capsular incision>>Biochem.

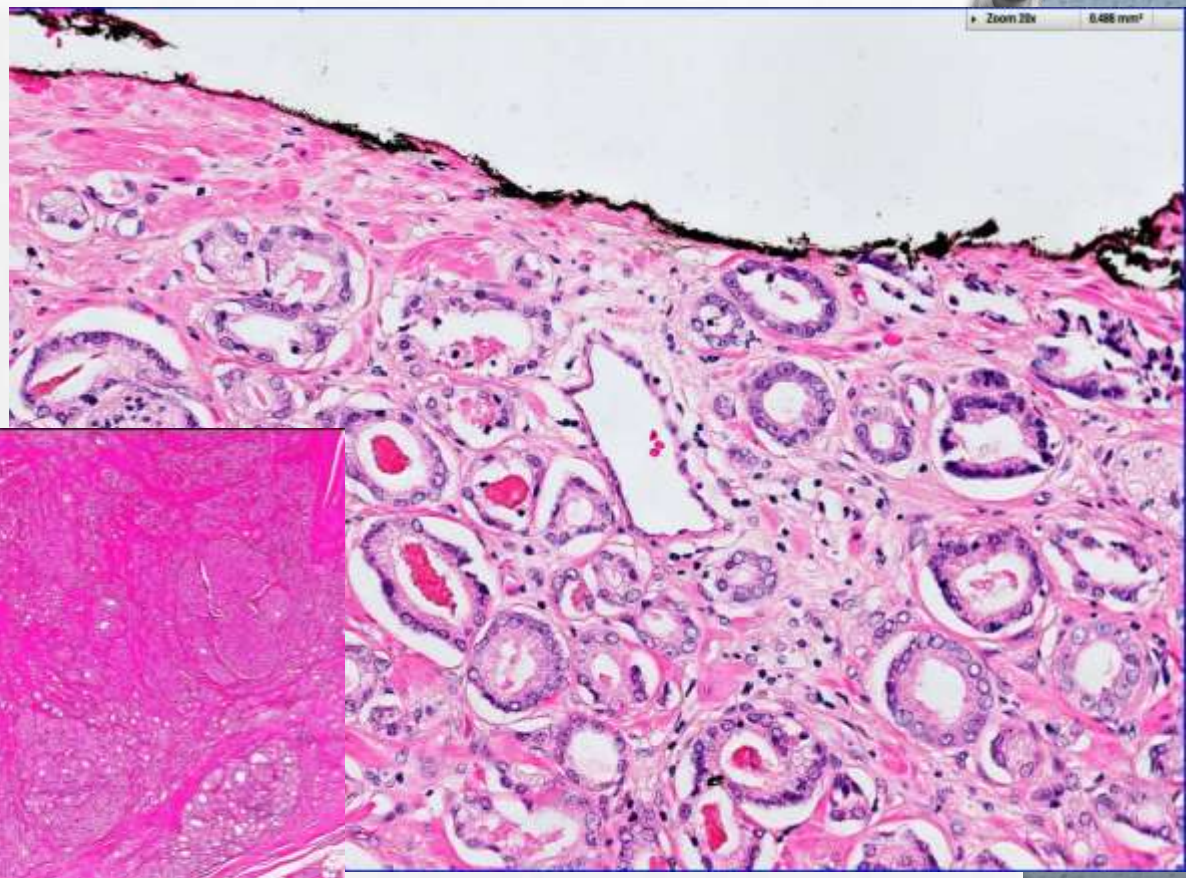


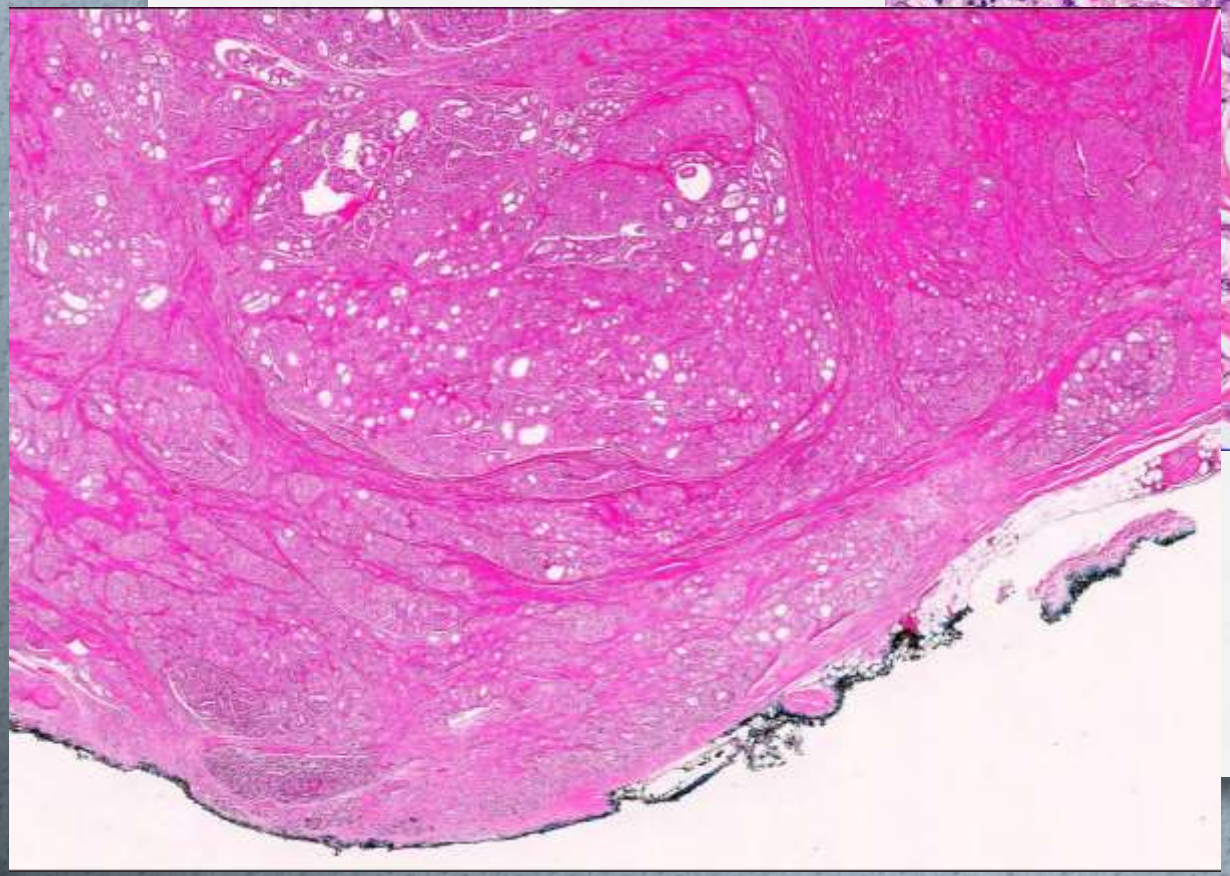


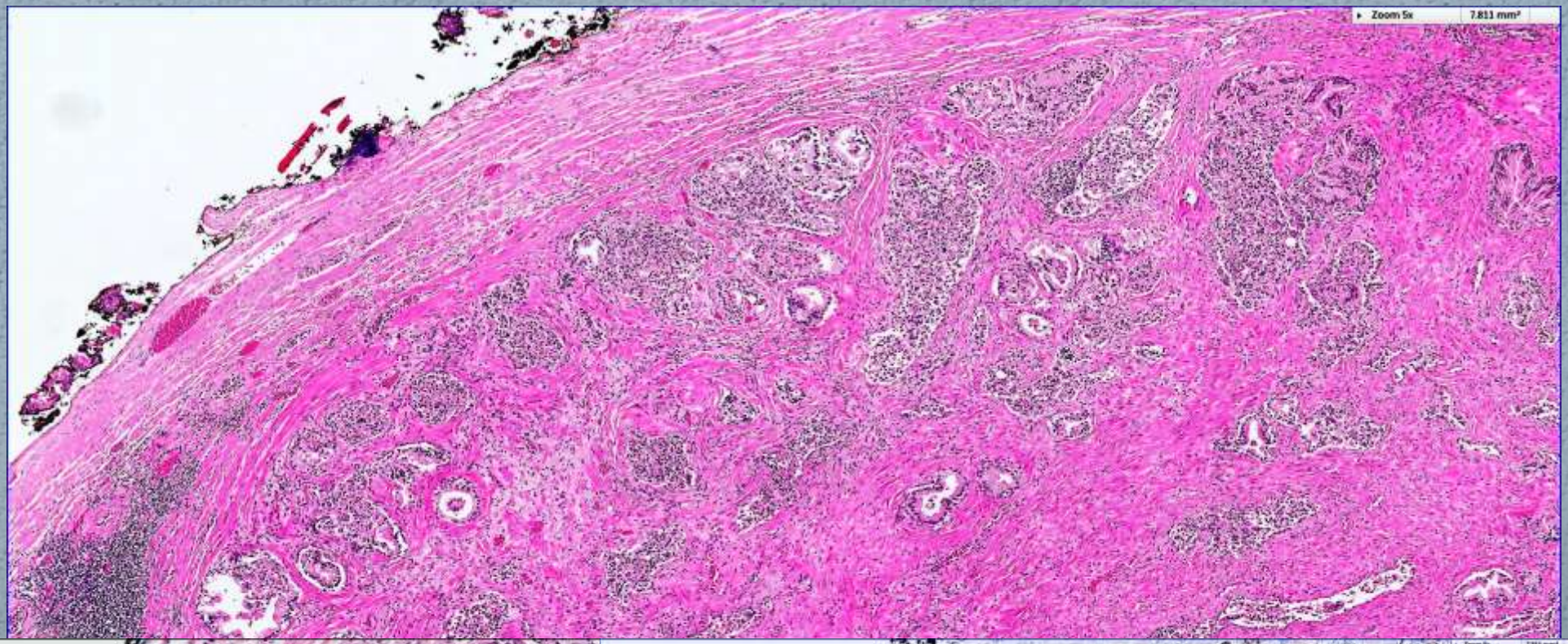
Close: < 0.1 mm from tumor cells

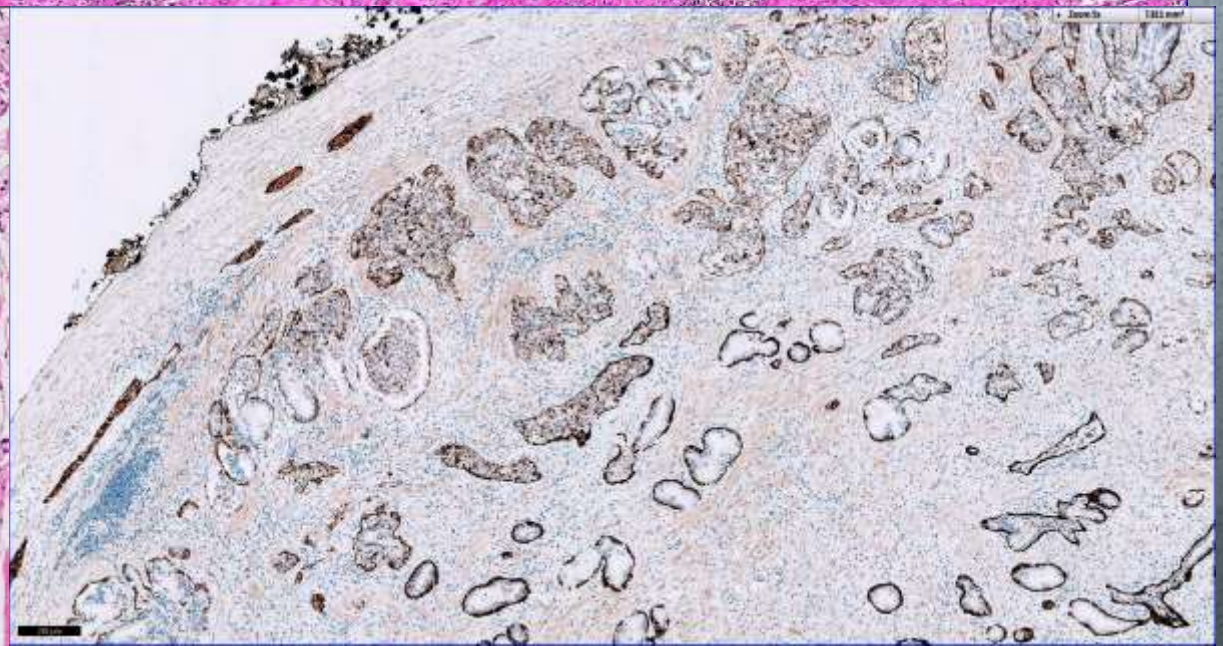
Izard JP et al, AJSP 38, 333, 2014

Gleason at M+






Zoom 5x
7.811 mm²



Virchows Archiv (2018) 472:451–460
https://doi.org/10.1007/s00428-018-2296-2

ORIGINAL ARTICLE

Digital versus light microscopy assessment of surgical margin status after radical prostatectomy

Metka Volavšek[1] · Ana Blanca[2] · Rodolfo Montironi[3] · Liang Cheng[4,5] · Maria R. Raspollini[6] · Nuno Vau[7] Jorge Fonseca[8] · Francesco Pierconti[9] · Antonio Lopez-Beltran[10,11]

Abstract

Positive surgical margin (PSM) extension reported as focal or non-focal/extensive is an important pathologic prognostic parameter after radical prostatectomy. Likewise, there is limited or no agreement on how to measure and what the best cut-off points to be used in practice are. We hypothesized that digital microscopy (DM) would potentially provide a more objective way to measure PSM and better define its clinical significance. To further our knowledge, we have evaluated PSM status in 107 laparoscopic radical prostatectomies using digital and conventional light microscopy (LM). DM evaluation detected three additional PSM cases, but no differences were seen (LM vs DM; $p = 0.220$). Mean linear measurement correlated to biochemical recurrence (BR) (LM, $p = 0.002$; DM, $p = 0.001$). ROC analysis identified a cut-off point to assess linear measurement by LM (3.5 mm) or DM (3.2 mm), but only digital measurement was significant for BR-free survival. Our study also evaluated a cut-off ≤3 mm that was associated to BR using LM ($p = 0.023$) or DM ($p = 0.001$). Finally, the number of paraffin blocks bearing PSM correlated with BR ($p < 0.001$) status with either LM or DM. In conclusion, DM produces similar data than LM but shows more accurate measurements. Reporting of PSM with score of ≤3 vs. >3 mm linear extent using LM (3.2 mm if digital microscopy is applied) might represent an important prognostic feature after radical prostatectomy. Alternatively, reporting the number of blocks with PSM 1 vs. 2 or more might also provide important prognostic data in practice.

Table 2 Patient and tumor characteristics for each patient having positive surgical margins in radical prostatectomy specimen

No.	Age (years)	pTN	LM (mm)	LM single (mm)	blocks-LM	DM (mm)	DM single (mm)	Blocks-DM	Follow up (months)	BR	BR time (months)	GS	GG
1	62	pT2cN0	2	2	1	0.36	0,36	1	19	0		7	2
2	67	pT2cNx	1	1	2	1.00	0.75	2	13	0		7	2
3	50	pT3aN0	5	3	2	3.92	2.28	2	20	1	6	7	3
4	58	pT3bN0	2	2	2	4.07	3.92	2	20	0		7	3
5	58	pT2cN0	2	2	1	1.92	1.92	1	16	0		7	3
6	58	pT3bN0	11	8	4	23.45	8	4	16	1	9	7	3
7	68	pT2cNx	1	1	1	0.604	0.604	1	16	0		7	2
8	56	pT2cN0	1	1	1	0.435	0.435	1	15	0		7	2
9	57	pT3aNx	4	2	1	0.056	0.056	1	15	0		7	2
10	65	pT3bNx	7	4	2	4.69	4.030	2	12	0		7	2
11	58	pT3aN0	19	7	3	8.05	3.34	2	10	0		8	4
12[a]	67	pT2cN0			1	2.54	2.541	1	12	0		7	2
13	54	pT3bN0	7	4	6	32.68	11.1	7	11	1	3	7	3
14	55	pT2cN0	2	2	1	9.18	7.820	2	9	0		7	2
15	53	pT3bN0	3	1	3	1.88	1.170	2	8	1	4	7	2
16	53	pT2cNx	4	2	2	10.83	0.023	5	9	1	6	7	2
17	56	pT2cNx	1	1	1	0.858	0.858	1	6	0		7	2
18[a]	59	pT2bNx			1	1.35	1.35	1	6	0		7	2
19	54	pT2bNx	6	3	2	7.12	4.310	2	6	1	2	7	2
20[a]	57	pT3aN0			1	0.196	0.196	1	3	0		7	3
21	63	pT2bN0	2	2	1	0.048	0.48	1	4	0		7	2
22	72	pT2bNx	2	2	1	0.97	0.873	2	3	0		7	2
23	75	pT3aNx	12	9	5	37.97	16.090	5	3	1	3	7	2
24	67	pT3aN0	2	2	1	0.448	0.448	1	4	0		7	2
25	60	pT3bN1	1	1	1	0.252	0.252	1	3	0		7	3
26	63	pT3bN0	3	2	3	6.25	2.080	3	3	1	3	7	2
27	62	pT2Nx	1	1	1	0.678	0.678	1	3	0		7	2
28	62	pT3bN0	3	3	1	2.19	1.3	3	3	0		7	2
29	57	pT2N0	3	2	2	1.41	1.41	1	3	0		7	2

pTN pathological T and N stage, according to UICC/TNM 2017, *LM* cumulative length of positive surgical margin in mm, determined by light microscopy, *LM single* greatest single margin in mm, determined by light microscopy, *blocks-LM* number of paraffin blocks with positive surgical margins, light microscopy, *DM* cumulative length of positive surgical margin in mm, determined digitally on whole slide images, *DM single* (greatest single margin in mm, determined digitally on whole slide images, *blocks-DM* number of paraffin blocks with positive surgical margins, determined digitally on whole slide images, *Follow-up* in months, *BR* biochemical recurrence, no = 0, yes = 1, *BR time* time to biochemical recurrence, in months, *GS* Gleason score, *GG* grade group

[a] Patient diagnosed as having negative surgical margins by light microscopy (LM)

Table 3 Surgical margin status as evaluated by light microscopy (LM) and digitally on whole slide images (DM)

	LM (*n*, %)	DM (*n*, %)	Chi-square test ($p = 0.220$)
Negative (*n*, %)	81 (75.5%)	78 (72.9%)	159
Positive (*n*, %)	26 (24.3%)	29 (27.1%)	55
Total	107 (107%)	107 (100%)	214

LM light microscopy, *DM* digital microscopy

Table 4 Quantification of positive surgical margins based on linear extent of positivity and disease characteristics

	LM (mm)	*p* value	LM single (mm)	*p* value	DM (mm)	*p* value	DM single (mm)	*p* value
pT2 vs pT3 (*n*) median ± SD		*0.006*[a]		0.022[a]		0.222[a]		0.252[a]
pT2	[13] 2.15 ± 1.49		[13] 1.69 ± 0.39		[14] 2.62 ± 3.45		[14] 1.64 ± 2.05	
pT3	[13] 6.08 ± 5.17		[13] 3.69 ± 2.65		[15] 9.00 ± 12.68		[15] 3.84 ± 4.72	
LN status (*n*) median ± SD		0.631[a]		0.428[a]		0.796[a]		0.458[a]
N0	[14] 4.47 ± 4.76		[14] 2.87 ± 2.03		[16] 5.82 ± 8.95		[16] 2.89 ± 3.18	
N1	–		–		–		–	
Nx	[10] 3.90 ± 3.60		[10] 2.60 ± 2.45		[11] 6.01 ± 11.13		[11] 2.65 ± 4.63	
Biochemical recurrence (*n*) median ± SD		*0.002*[a]		*0.047*[a]		*0.001*[a]		*0.041*[a]
No	[17] 3.1 ± 4.22		[17] 2.11 ± 1.45		[18] 1.96 ± 2.54		[18] 1.63 ± 1.90	
Yes	[8] 6.38 ± 3.46		[8] 4.00 ± 2.92		[8] 15.51 ± 13.94		[8] 5.55 ± 5.64	
Grade group, (*n*) median ± SD		0.436[a]		0.200[a]		0.474[a]		0.455[a]
GG2	[19] 3.16 ± 2.70		[19] 2.26 ± 1.82		[18] 4.32 ± 8.32		[18] 2.26 ± 3.65	
GG 3	[8] 6.38 ± 3.46		[6] 3.33 ± 2.50		[7] 9.49 ± 13.05		[7] 3.95 ± 4.12	
GG 4	–							

LN status lymph node status, *GG* grade group, *LM* light microscopy margins, cumulative length, *LM single* greatest single margin, light microscopy, *DM* digital margins, cumulative length, *DM single* greatest single margin, digital

[a] Mann–Whitney U test

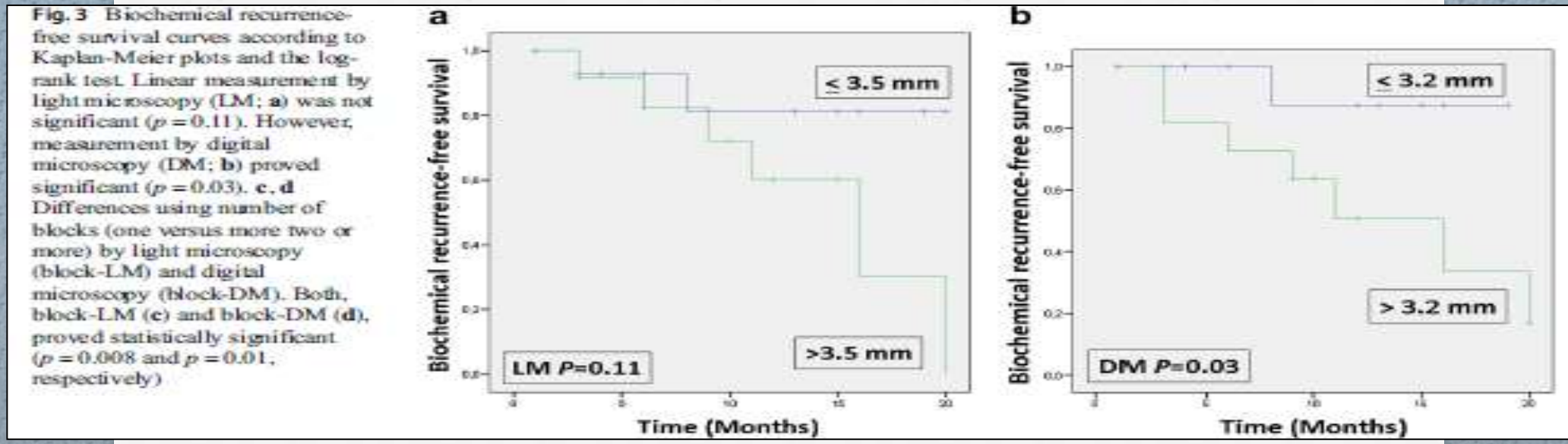


Fig. 3 Biochemical recurrence-free survival curves according to Kaplan-Meier plots and the log-rank test. Linear measurement by light microscopy (LM; **a**) was not significant ($p = 0.11$). However, measurement by digital microscopy (DM; **b**) proved significant ($p = 0.03$). **c**, **d** Differences using number of blocks (one versus more two or more) by light microscopy (block-LM) and digital microscopy (block-DM). Both, block-LM (**c**) and block-DM (**d**), proved statistically significant ($p = 0.008$ and $p = 0.01$, respectively)

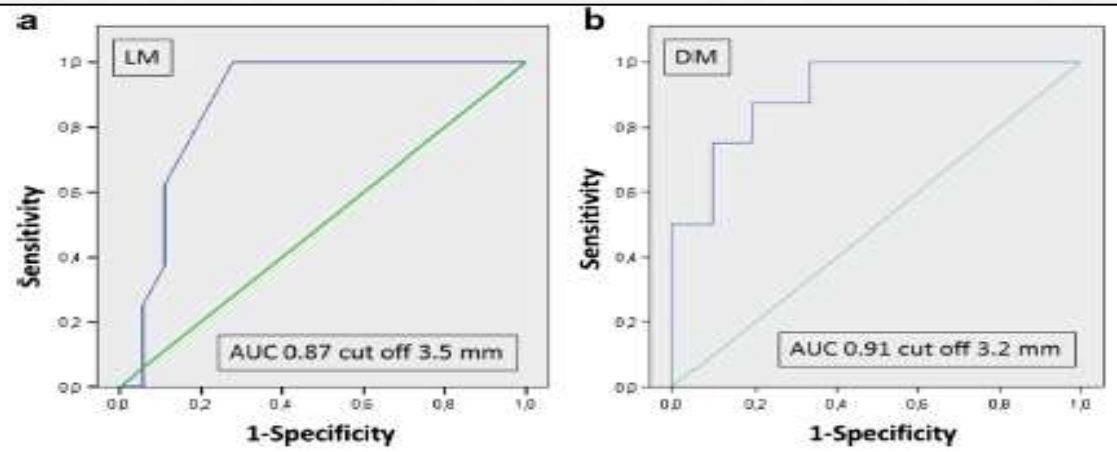


Fig. 2 Receiver operating characteristic (ROC) assessment of cut-offs for PSM seen by light microscopy (LM) and digital microscopy (DM)

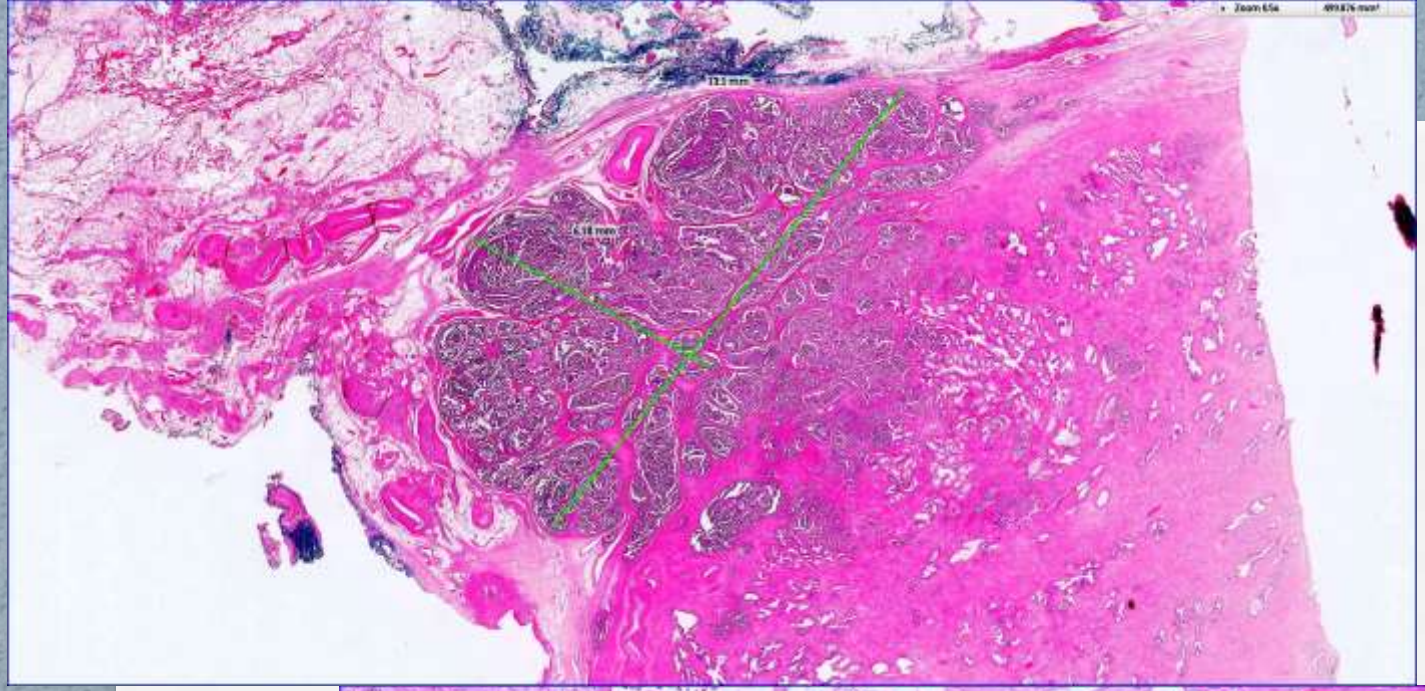
Table 5 Quantification of positive surgical margins based on linear extent of positivity and disease characteristics

	Overall	LM		*p* value[a]	LM single		*p* value[a]	DM		*p* value[a]	DM single		*p* value[a]
		≤ 3 mm	*> 3 mm*		*≤ 3 mm*	*> 3 mm*		*≤ 3 mm*	*> 3 mm*		*≤ 3 mm*	*> 3 mm*	
pT2 vs pT3				0.096			0.311			*0.039*			*0.075*
pT2	15 (100.0%)	11 (73.3%)	4 (26.7%)		13 (86.7%)	2 (13.3%)		12 (80.0%)	3 (20.0%)		13 (86.7%)	2 (13.3%)	
pT3	14 (100.0%)	6 (42.9%)	8 (57.1%)		10 (71.4%)	4 (28.6%)		6 (42.9%)	8 (57.1%)		8 (57.1%)	6 (42.9%)	
LN status				0.417			0.824			0.705			0.815
N0	17 (100.0%)	11 (64.7%)	6 (35.3%)		13 (76.5%)	4 (23.5%)		10 (58.8%)	7 (41.2%)		12 (70.6%)	5 (29.4%)	
N1	1 (100.0%)	1 (100.0%)	0 (0.0%)		1 (100.0%)	0 (0.0%)		1 (100.0%)	0 (0.0%)		1 (100.0%)	0 (0.0%)	
Nx	11 (100.0%)	5 (45.5%)	6 (54.5%)		9 (81.8%)	2 (18.2%)		7 (63.6%)	4 (36.4%)		8 (72.7%)	3 (27.3%)	
Biochemical recurrence				*0.023*			0.724			*0.001*			0.096
No	21 (100.0%)	15 (71.4%)	6 (28.6%)		17 (81.0%)	4 (19.0%)		17 (81.0%)	4 (19.0%)		17 (81.0%)	4 (19.0%)	
Yes	8 (100.0%)	2 (25.0%)	6 (75.0%)		6 (75.0%)	2 (25.0%)		1 (12.5%)	7 (87.5%)		4 (50.0%)	4 (50.0%)	
Grade group				0.260			0.099			0.172			0.122
GG2	21 (100.0%)	14 (66.7%)	7 (33.3%)		18 (85.7%)	3 (14.3%)		15 (71.4%)	6 (28.6%)		17 (81.0%)	4 (19.0%)	
GG3	7 (100.0%)	14 (66.7%)	7 (33.3%)		5 (71.4%)	2 (28.6%)		3 (42.9%)	4 (57.1%)		4 (57.1%)	3 (42.9%)	
GG4	1 (100.0%)	0 (0.0%)	1 (100.0%)		0 (0.0%)	1 (100.0%)		0 (0.0%)	1 (100.0%)		0 (0.0%)	1 (100.0%)	

LM cumulative length of positive surgical margin in mm, determined by light microscopy, *LM single* greatest single margin in mm, determined by light microscopy, *DM* cumulative length of positive surgical margin in mm, determined digitally on whole slide images, *DM single* greatest single margin in mm, determined digitally on whole slide images, *LN status* lymph node status, *GG* grade group

[a] Chi-square test

EPE
LM vs DIG



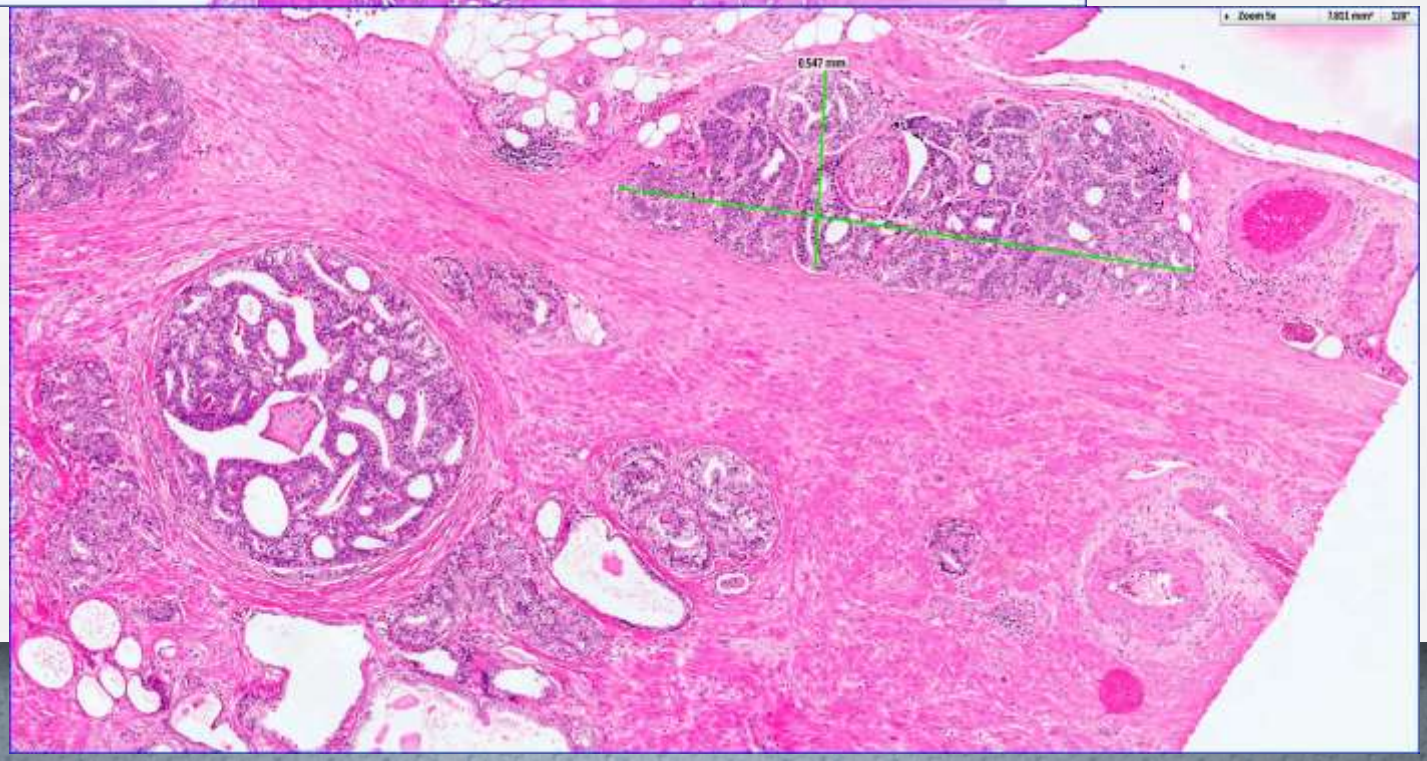


Table 3. Quantification of extraprostatic extension based on linear extent of positivity and disease characteristics.

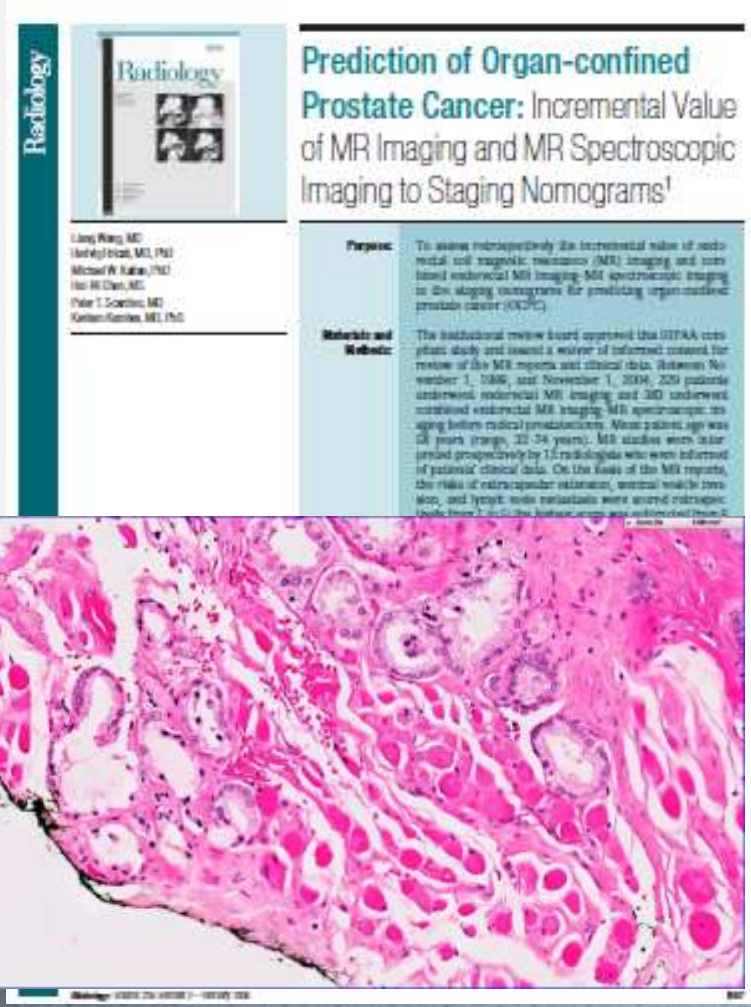
	EPE LM (mm)	p value	EPE LM single (mm)	p value	EPE DIG (mm)	p value	EPE DIG single	p value	EPE DIG R (mm)	p value
pT2 vs pT3; (n) median±SD		0.485*		0.663*		0.130*		0.156*		**0.034***
pT2	(2) 3.500±0.7071		(2) 3.500±0.707		(2) 2.240±1.456		(2) 1.890±0.961		(2) 0.240±0.135	
pT3	(39) 7.071±6.434		(39) 5.123±3.986		(39) 18.895±19.867		(39) 9.157±10.048		(39) 2.152 ± 2.137	
LN status; (n) median ± SD		0.418#		0.383#		0.330#		0.167#		0.138#
N0	(26) 6.730±6.115		(26) 4.538±3.373		(26) 18.274±21.541		(26) 7.353±6.310		(26) 1.815±2.031	
N1	(8) 9.487±8.278		(8) 7.362±5.333		(8) 18.865±13.339		(8) 11.577±10.464		(8) 3.178±2.554	
Nx	(7) 4.557±3.882		(7) 4.271±3.466		(7) 16.481±21.052		(7) 11.018±18.373		(7) 1.688±1.789	
Biochemical recurrence; (n) median±SD		0.221*		0.383*		0.239*		0.461*		**0.042***
No	(26) 5.992±5.592		(26) 4.415±3.031		(26) 14.123±14.510		(26) 8.016±9.977		(26) 1.429±1.155	
Yes	(15) 8.466±7.356		(15) 6.133±5.012		(15) 24.948±25.565		(15) 10.167±10.019		(15) 3.151±2.915	
Grade Group; (n) median±SD		**0.036#**		0.069#		0.211#		0.205#		**0.022#**
GG 2	(22) 4.900±4.409		(22) 4.036±3.325		(22) 15.502±20.955		(22) 7.712±11.037		(22) 1.799±2.261	
GG 3	(14) 6.857±4.671		(14) 4.785±2.636		(14) 17.243±17.243		(14) 8.289±6.202		(14) 1.577±0.951	
GG 4	(5) 15.800±10.183		(5) 10.200±5.718		(5) 32.390±17.722		(5) 15.042±12.797		(5) 4.554±2.525	

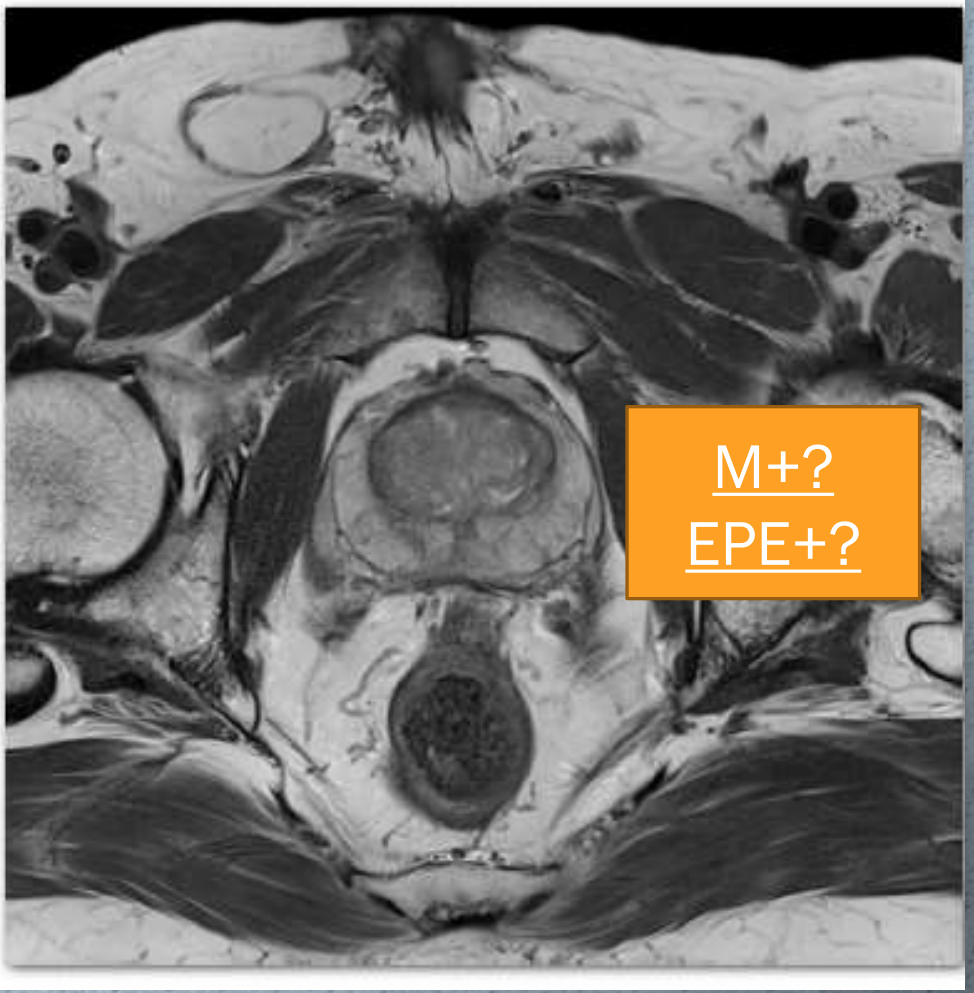
Kruskal Wallis test; * U de Mann Whitney test; † ANOVA test

Legend: EPE LM - cumulative length of extraprostatic extension in mm, determined by light microscopy; **EPE LM single** - greatest single extraprostatic extension in mm, determined by light microscopy, **EPE DIG** - cumulative length of extraprostatic extension in mm, determined digitally on whole slide images; **EPE DIG single** - single greatest extraprostatic extension in mm, determined digitally on whole slide images; **EPE DIG R** - greatest single radial length of extraprostatic extension in mm, determined digitally on whole slide images; **LN status** -lymph node status; **GG** - grade group

Any Role for Artificial Intelligence?

Impact of New Imaging methods

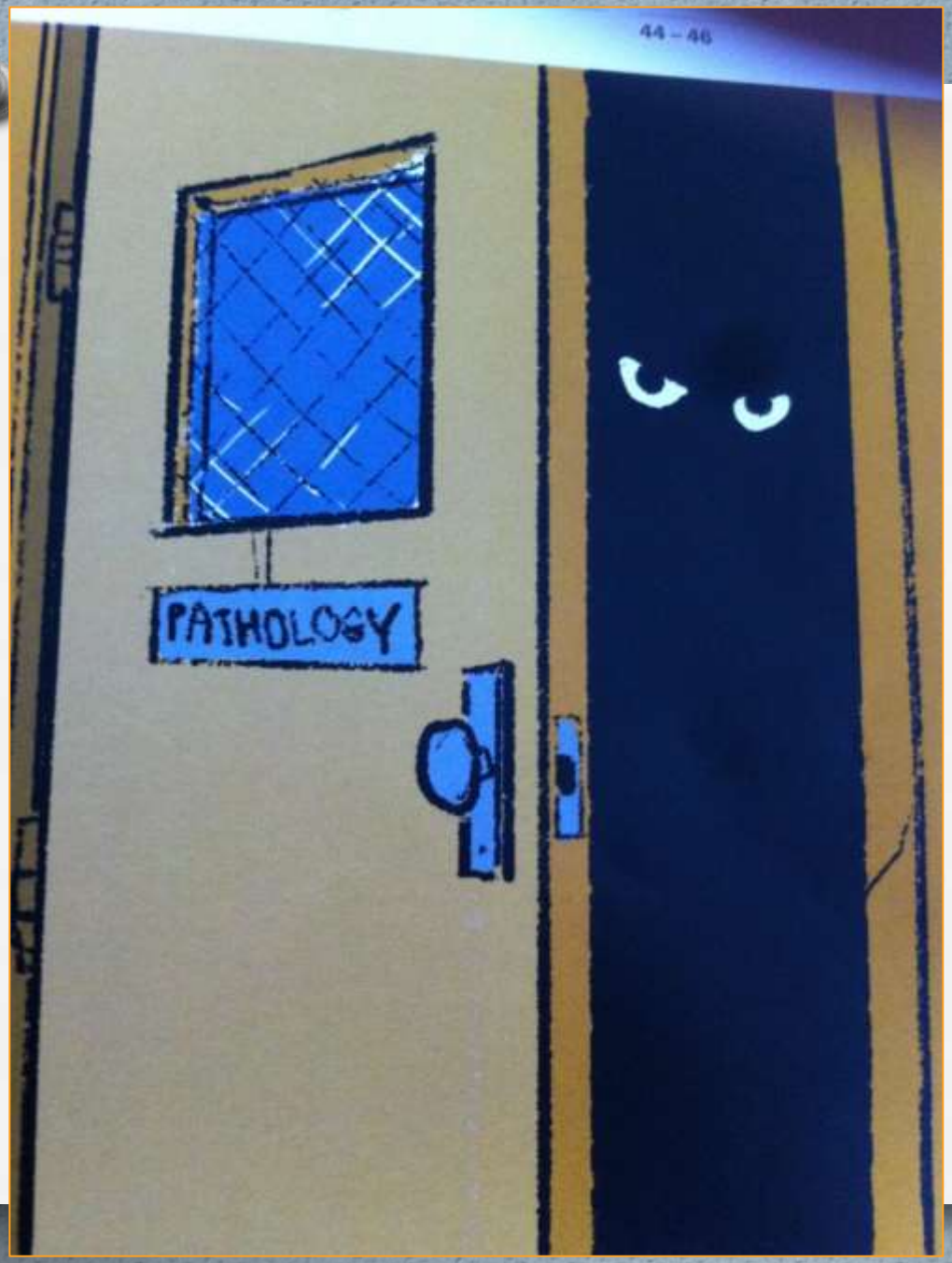




M+?
EPE+?

Conclusion

- En general, las mediciones totales (agregado longitudinal) tienen mejor poder discriminante que las mediciones del foco mayor individual.
- Patologia digital mejora el reconocimiento y medición del M+ lo que tiene implicaciones clinicas.
- Patologia digital mejora el reconocimento y medición de la EPE, en particular del EPE radial, lo que tiene implicaciones clínicas.



GRACIAS