

NordBioMedNet Summer School 2019 in Computational Biomedicine - Imaging, machine learning and precision medicine

Prostate Cancer Diagnostics – Opportunities and Pitfalls of Machine Learning

Pekka Taimen, Ass. Prof.

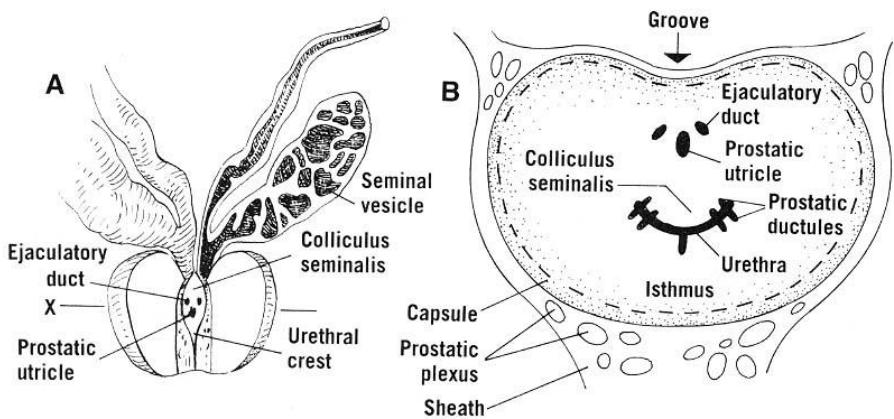
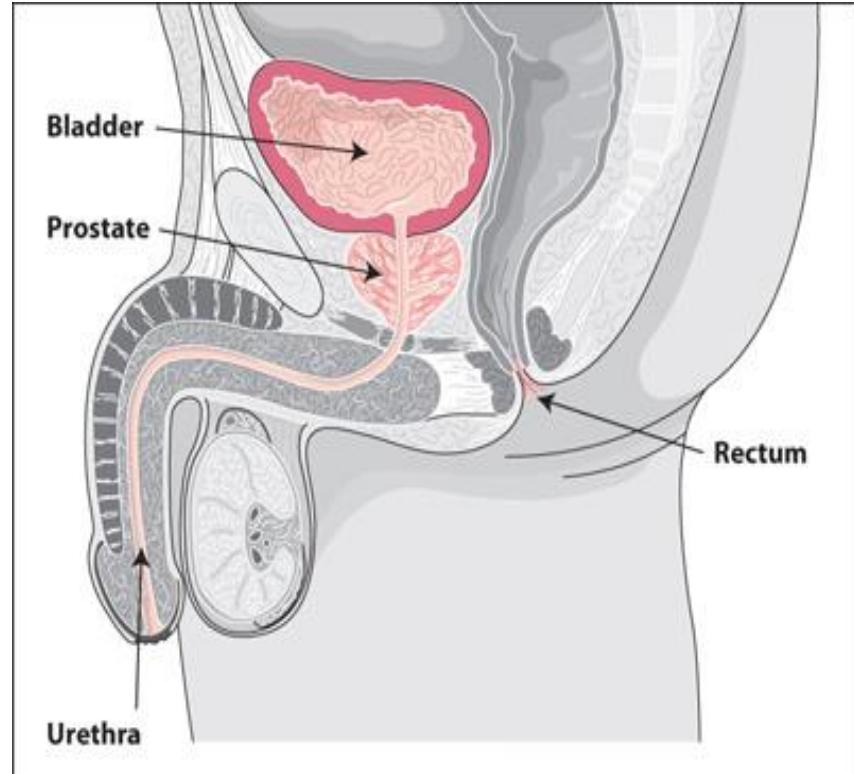
Institute of Biomedicine, University of Turku
Department of Pathology, Turku University Hospital

My background

- M.D. in 2001, Ph.D. in 2004 cell and cancer biology
- Postdoctoral researcher at Northwestern University in 2008-2009
- Specialist in pathology 2010 (responsible for genitourinary pathology)
- Group leader since 2011
- Adj. Prof. in clinical pathology 2014 (UTU) and in molecular pathology 2015 (ÅA)
- Clinical Lecturer in pathology 2012-2018
- Assistant Professor in Molecular Pathology from 2019
- Research:
 - Intermediate filament related research (nuclear lamins and inherited diseases such as familial cardiomyopathies)
 - Urological cancers (prostate, bladder); prognostic/predictive biomarkers, imaging and histopathology correlation studies, machine learning projects, patient-derived cell lines, etc.

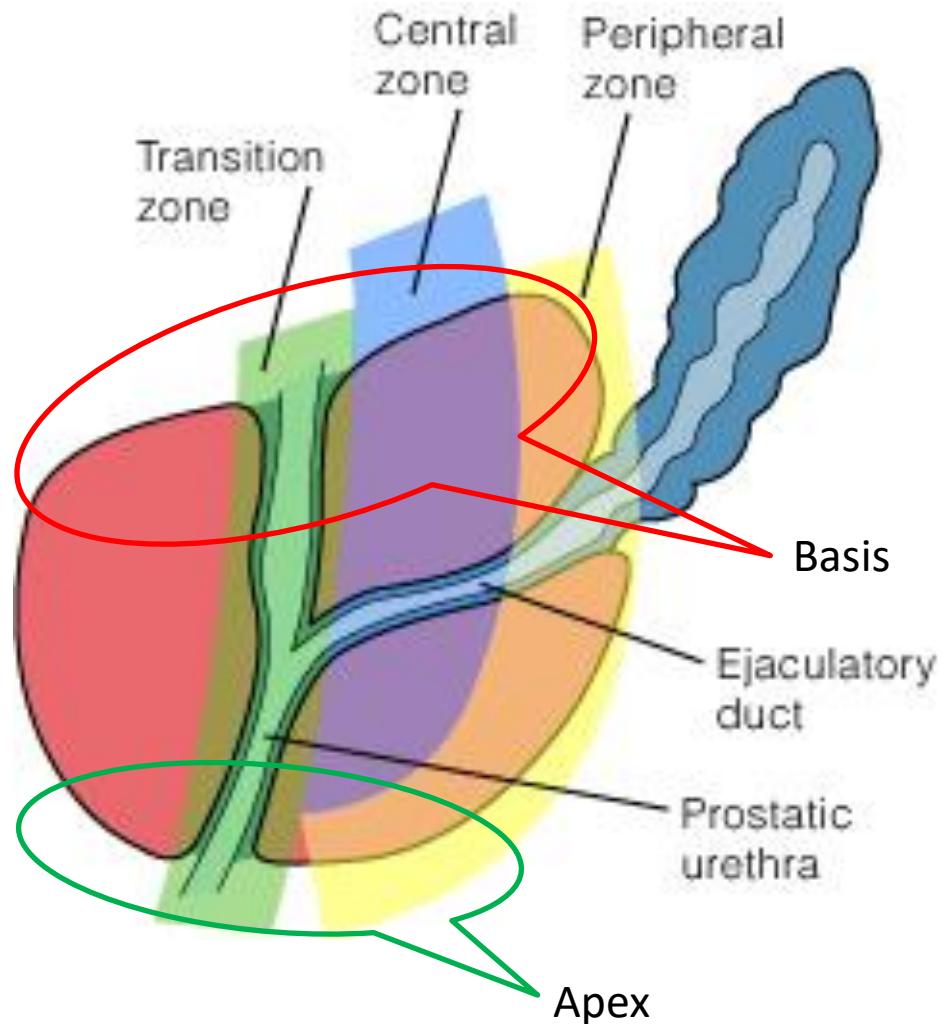
Prostate anatomy

- Surrounds the proximal urethra below urinary bladder
- Composed of fibromuscular stroma and acinar/glandular structures
- During ejaculation, prostatic secretion is mixed with semen and seminal vesicle secretions at colliculus seminalis
- Normal weight <50 g but upon aging and enlargement, even more than 100 g

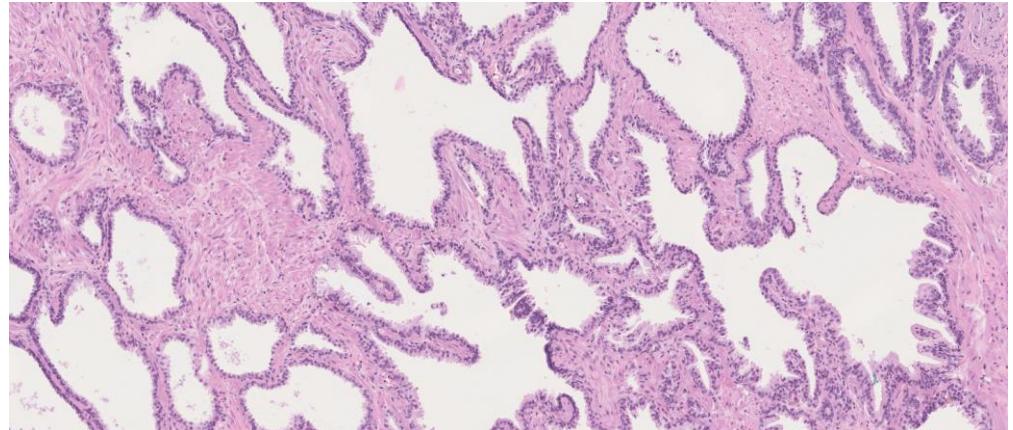
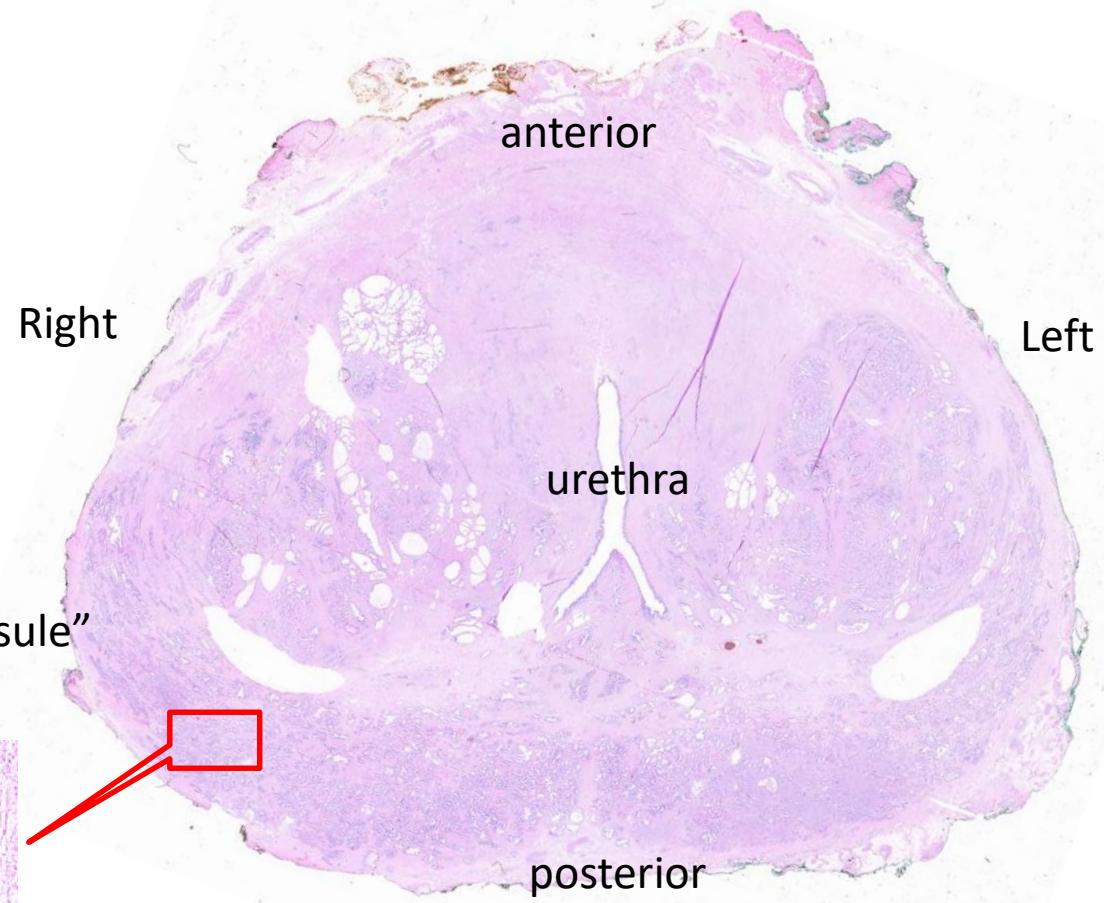
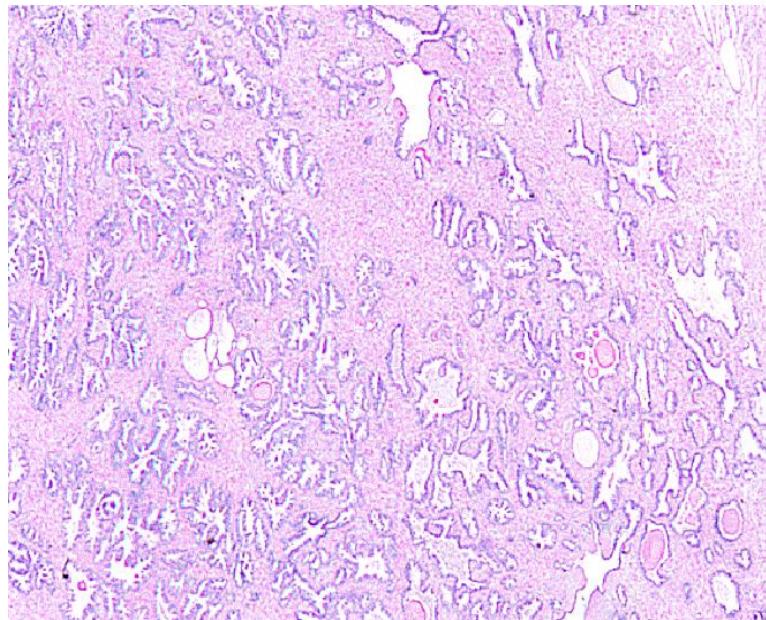


Anatomical zones of prostate

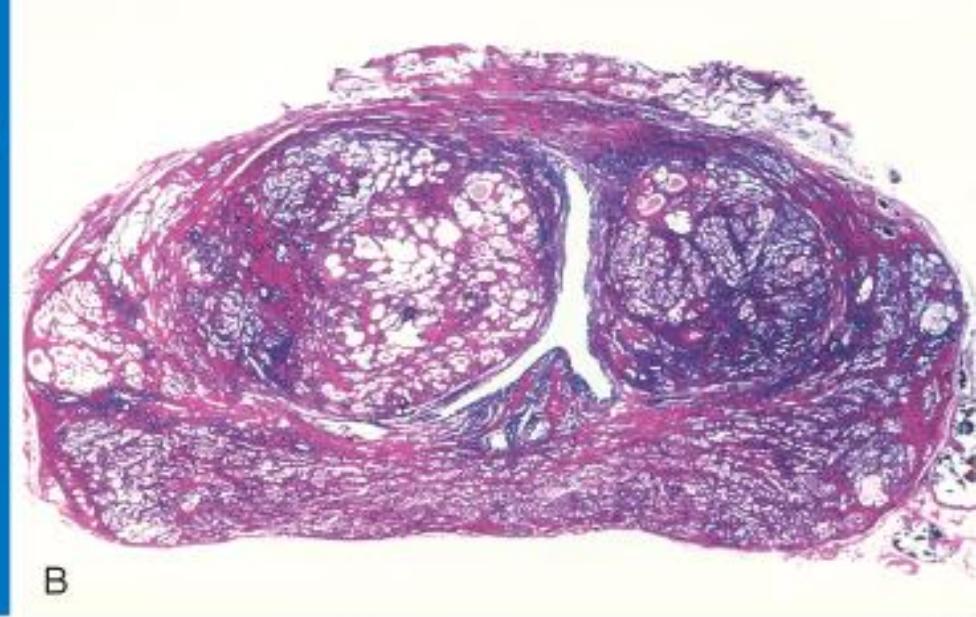
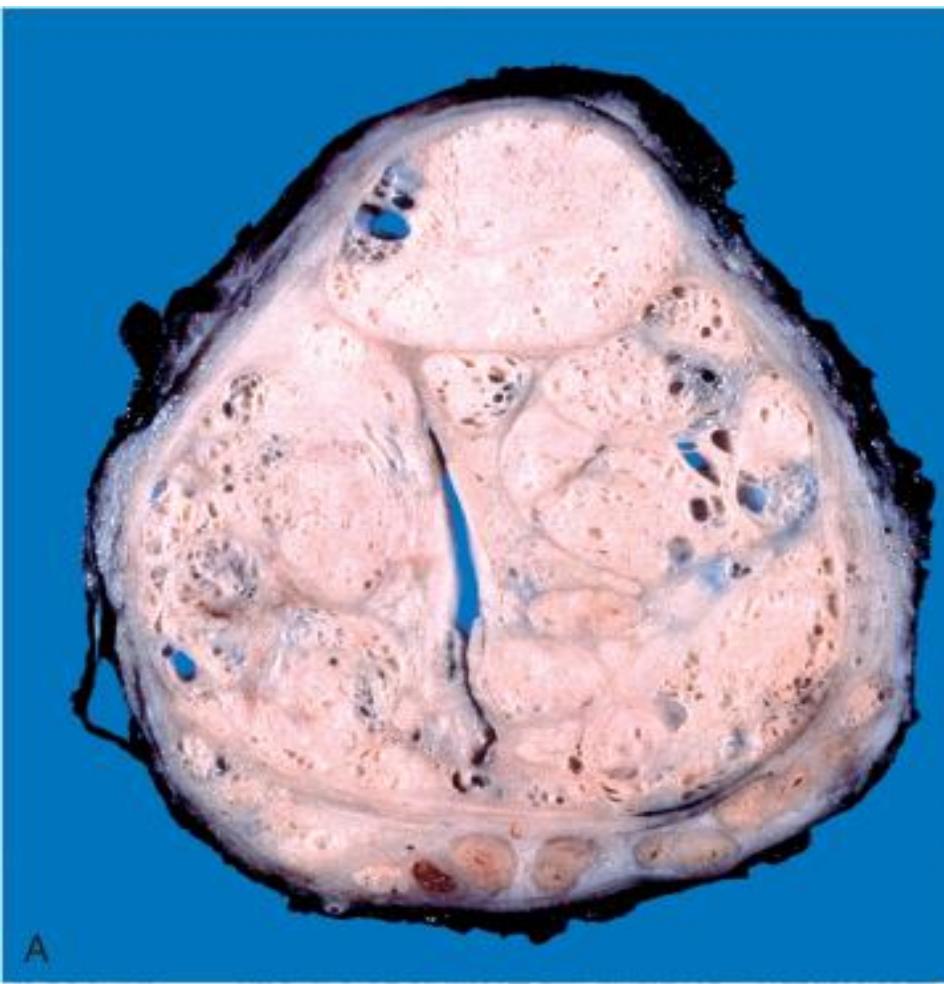
- Peripheral zone (PZ) - Up to 70% of normal volume
 - The sub-capsular portion of the posterior aspect of the prostate gland.
 - Has ~70–80% of prostate cancers
- Central zone (CZ) - 25% of normal volume
 - Surrounds the ejaculatory ducts.
 - Has roughly 2.5% of prostate cancers
- Transition zone (TZ) - 5% of volume at puberty
 - Surrounds the proximal urethra
 - Grows throughout life and may cause benign prostatic enlargement (hyperplasia)
 - ~10–20% of prostate cancers.
- In clinic, often referred to right and left lobe, anterior and posterior, inferior (apex) and proximal region (basis)



Whole mount prostate cross section



Hyperplasia-related nodules compress urethra → urinary obstruction



Prostate cancer – general features

- 2nd most common cancer among men worldwide and #1 in Europe/USA
- ~4500 new cases in Finland annually
- 99% of cases among men over 50-y
- 80% located posterolaterally
- 99% are adenocarcinomas (others neuroendocrine and mesenchymal origin)
- Androgen-dependent but androgen deprivation therapy (ADT) may lead to castration resistant prostate cancer (CRPC)

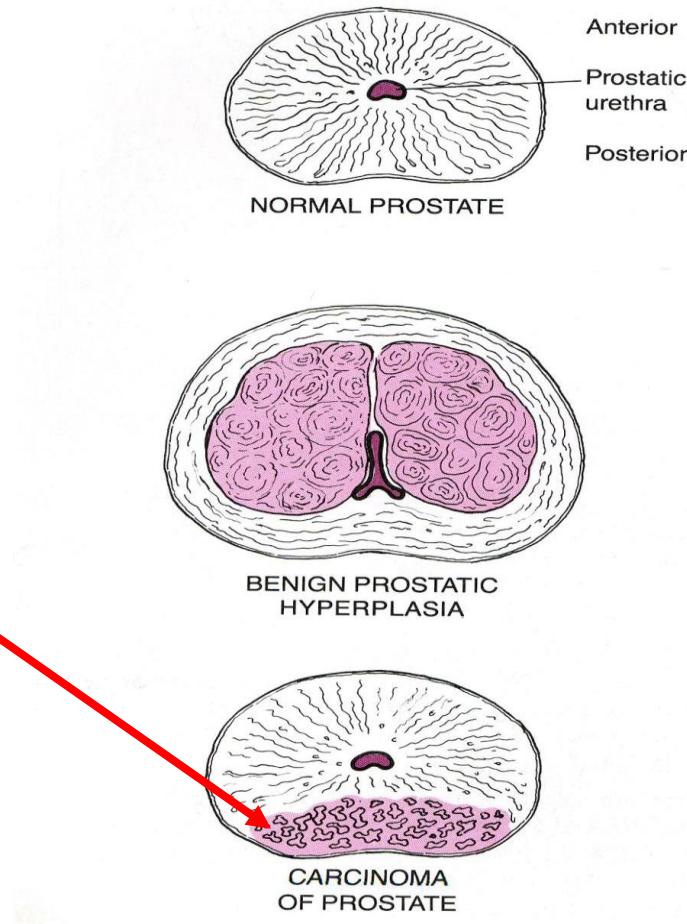
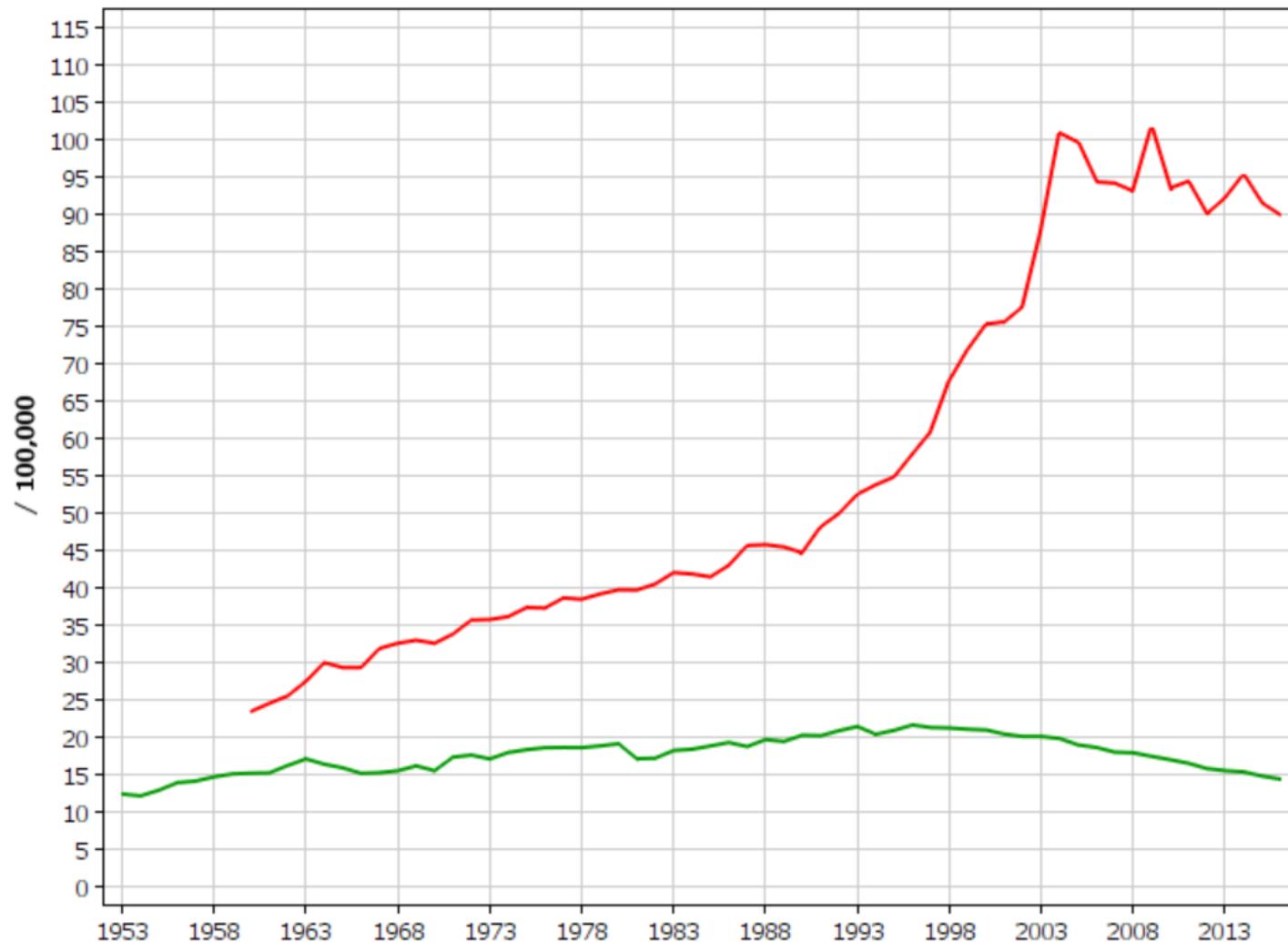


Figure 17-30. Normal prostate, nodular hyperplasia, and adenocarcinoma. In benign prostatic hyperplasia the nodules distort and compress the urethra and exert pressure on the surrounding normal prostatic tissue. Prostatic carcinoma usually arises from peripheral glands, in which case it does not compress the urethra.

Incidence and mortality in Nordic countries



Nordcan statistics, 10.8.2019

How common is Pca?

Prevalence of Prostate Cancer on Autopsy: Cross-Sectional Study on Unscreened Caucasian and Asian Men

Alexandre R. Zlotta, Shin Egawa, Dmitry Pushkar, Alexander Govorov, Takahiro Kimura, Masahito Kido, Hiroyuki Takahashi, Cynthia Kuk, Marta Kovylina, Najla Aldaoud, Neil Fleshner, Antonio Finelli, Laurence Klotz, Jenna Sykes, Gina Lockwood, Theodorus H. van der Kwast

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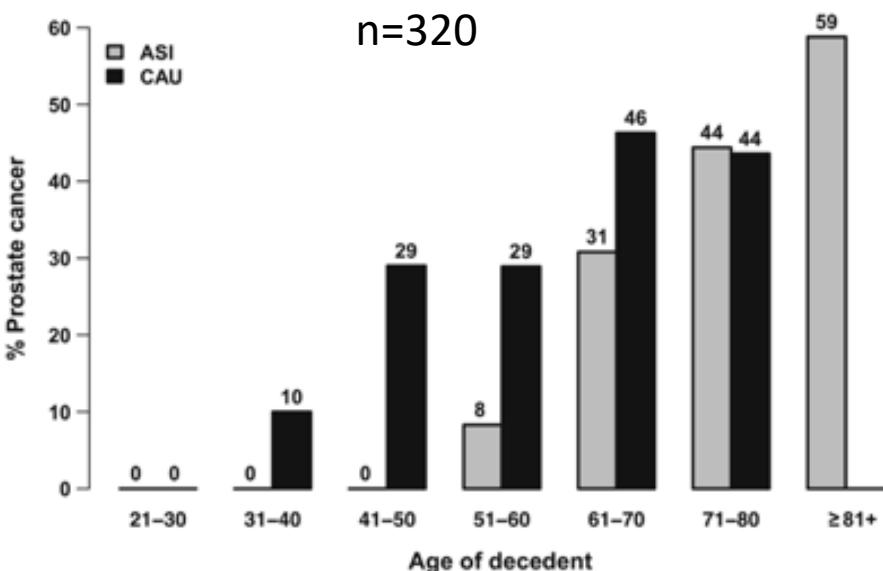


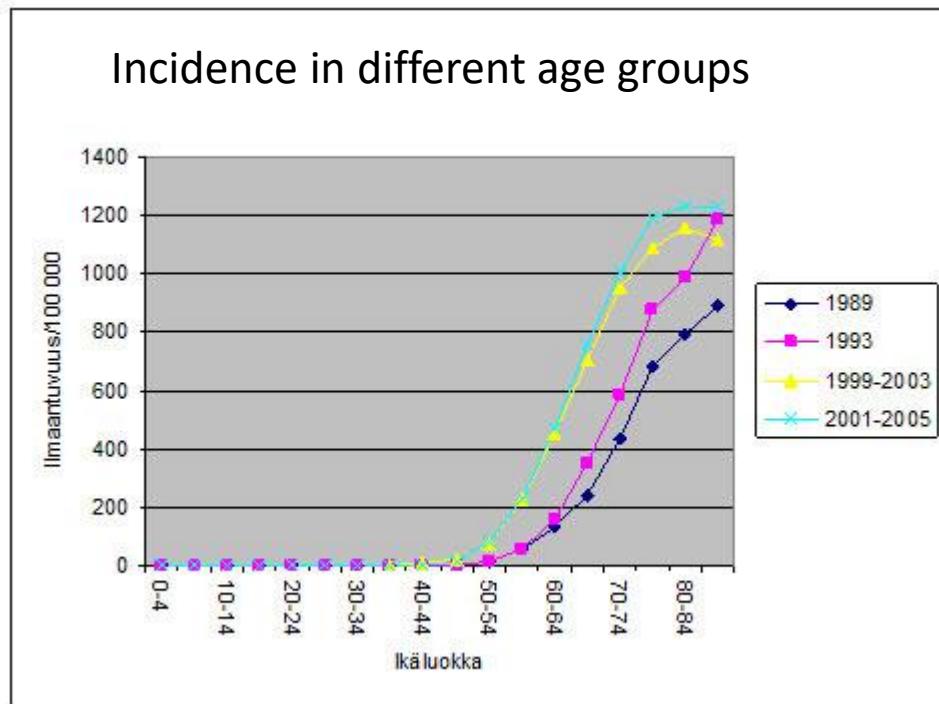
Table 3. Prevalence of Gleason score 7 or greater cancers in Asian and Caucasian men (core group aged 50–80 years)

Age, years	Asian men		Caucasian men		P
	HG*, No.	% HG	HG*, No.	% HG	
51–60	0/1	0	4/13	30.8	.99
61–70	2/8	25	4/25	16.0	.62
51–70	2/9	22.2	8/38	21.1	.99
71–80	9/16	56.3	10/34	29.4	.12

* HG = high grade/ Gleason score of 7 or greater.

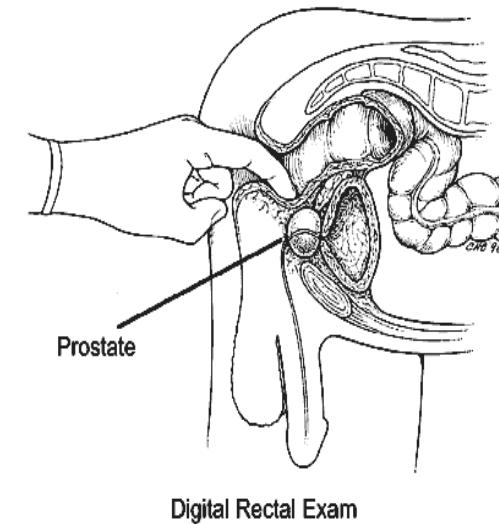
Incidence is increasing – why?

- Improved diagnostics
 - PSA testing
 - Increased life expectancy
 - Improved imaging
- Risk factors:
 - Age
 - Race /family history (genetics)
 - Western-type diet
 - Obesity
 - Smoking (increased mortality)
 - Low antioxidant levels/uptake (sele, vitamin E)
 - Low vitamin D
 - Inflammatory conditions (prostatis)?



Characteristics of prostate cancer

- Typically asymptomatic at time of diagnosis; some patients experience hyperplasia-like symptoms or symptoms from distal metastasis (e.g. back pain)
- Majority (but not all!) has elevated serum PSA
- Posterolateral carcinoma may form palpable tumor
- Increasingly visualized by MRI, large tumors be be visible in trans-rectal ultra sound (TRUS)
- Carcinomas tend to invade through stroma, grow perineurally, invade prostatic "capsule", seminal vesicles and extraprostatic tissues
- Metastasizes to pelvic and distant lymph nodes, bone, lungs, etc.

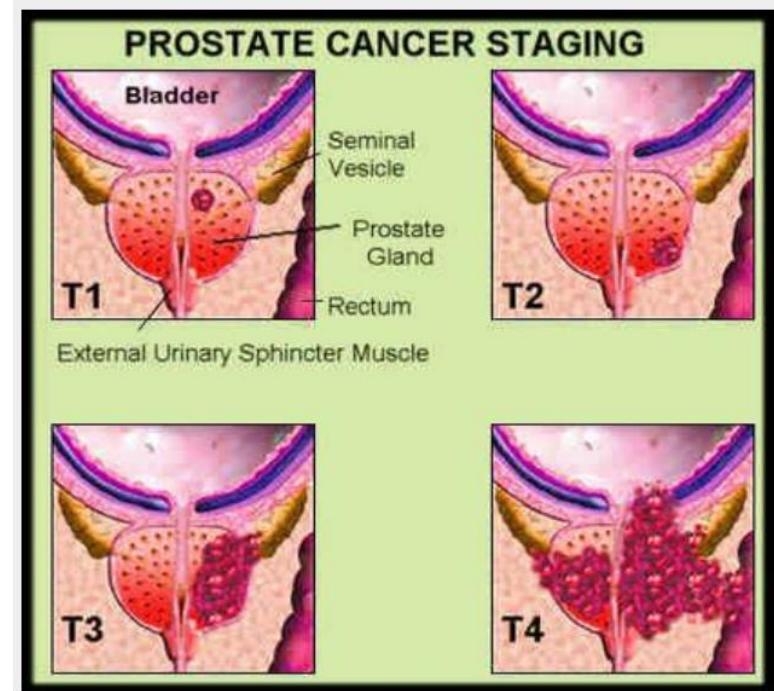


Prostate cancer – clinical examination

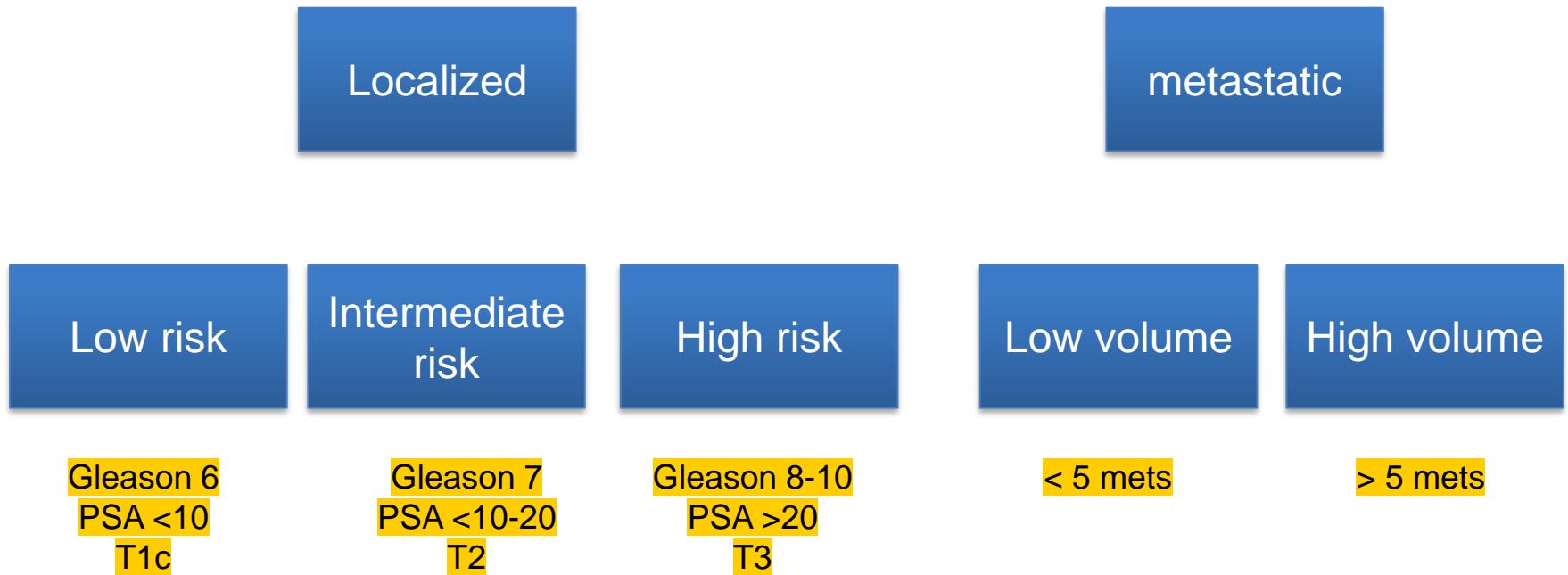
- Clinical symptoms and findings (rectal examination)
- Family history
- PSA (prostate specific antigen)
 - Glycoprotein secreted by prostate
 - Total-PSA range is age-dependent: under 50 y < 2,5 µg/L, 50-60 y < 3,5 µg/L, 60-70 y < 4,5 µg/L, >70 y <6,5 µg/L
 - Free/total PSA:n ratio: if below 10%, risk of Pca is >50%; ratio >25%, risk of 8% (when PSA is 4-10)
 - PSA is not entirely specific (e.g. in breast milk and in periurethral glands) and poorly differentiated carcinomas may secrete little PSA
- Imaging: TRUS (transrectal ultra sound), increasingly magnetic resonance imaging (MRI), bone scan, PSMA-PET
- Needle biopsies: 12 routine biopsies or MRI-based targeted biopsies

Pathologic TNM staging of prostate, AJCC 8th edition

- Primary tumor (pT)
 - **(T0: no tumor)**
 - **(T1: in clinical staging only)**
 - **pT2:** Organ confined
 - **pT3a:** Extraprostatic extension
 - **pT3b:** Seminal vesicle muscle wall invasion
 - **pT4:** Invasion of external sphincter, rectum, bladder, levator muscles or pelvic wall
- Regional lymph nodes (pN)
 - **pNX:** Cannot be assessed
 - **pN0:** No regional lymph node metastasis
 - **pN1:** Regional lymph node metastasis
(regional lymph nodes = periprostatic, pelvic, hypogastric, obturator, internal iliac, external iliac, sacral)
- Distant metastasis (pM)
 - **pM1a:** Metastasis in nonregional lymph node (ex: aortic, common iliac, deep / superficial inguinal, retroperitoneal)
 - **pM1b:** Metastasis in bone
 - **pM1c:** Metastasis in other distant site



Clinical risk stratification



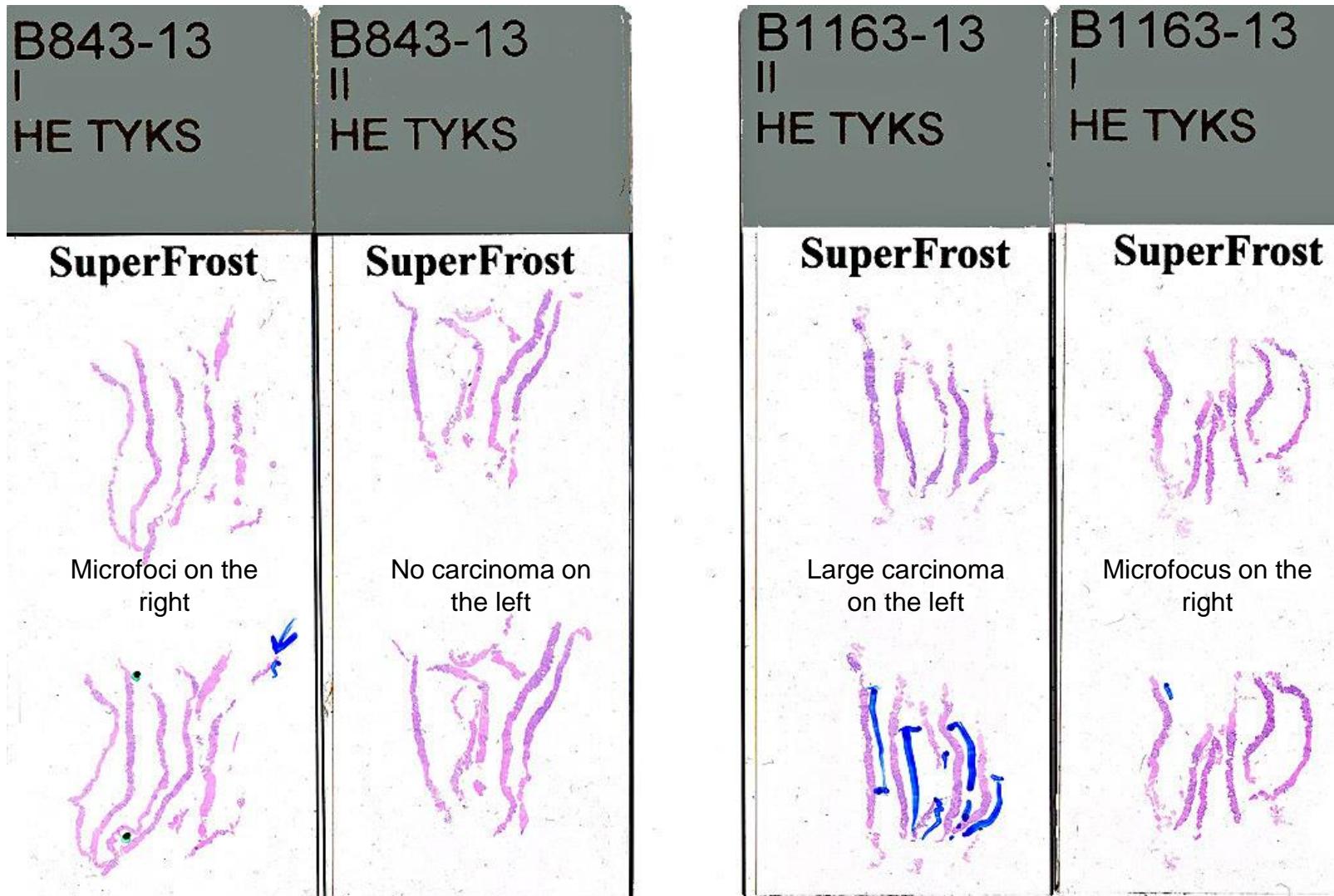
Treatment of prostate cancer

- Surgery: Robot-assisted laparoscopic prostatectomy (RALP) for local disease. Patients up to 70-75 years and in good physical state
- Radiotherapy (external and brachytherapy): surgery is not found feasible or as an adjuvant/salvage therapy after surgery
- Active surveillance: patients with low risk disease (Gleason 3+3), annual check-ups, control biopsies.
- Passive surveillance: patients at very high age
- Castration: orchectomy or nowadays chemical castration with LHRH-analog/antagonist, antiandrogens
- Chemotherapy: Castration resistant prostate cancer (CRPC)
- 2nd generation antiandrogens (abiraterone, enzalutamide, darolutamide)
- PSA-follow-up and imaging to monitor disease progression upon/after therapy

Role of pathology in Pca diagnosis

- Needle biopsies
 - Traditionally (3-6) biopsies per lobe, increasingly targeted biopsies
 - Length and representativeness of biopsy material
 - Abundance of carcinoma (% of material, # of cores), Gleason grade/score, perineural invasion, extraprostatic extension, inflammation.
- Radical prostatectomy specimens
 - Abundance of carcinoma (% of material)
 - Gleason grade/score
 - Perineural invasion?
 - Extraprostatic extension?
 - Seminal vesicle invasion?
 - Marginal positivity?
 - Lymph node metastasis?
- Transurethral resection of prostate (TURP): diagnostic TURP to determine carcinoma at periurethral region or palliative TURP to relieve urinary obstruction (especially castration resistant Pca); Ca-%, Gleason.

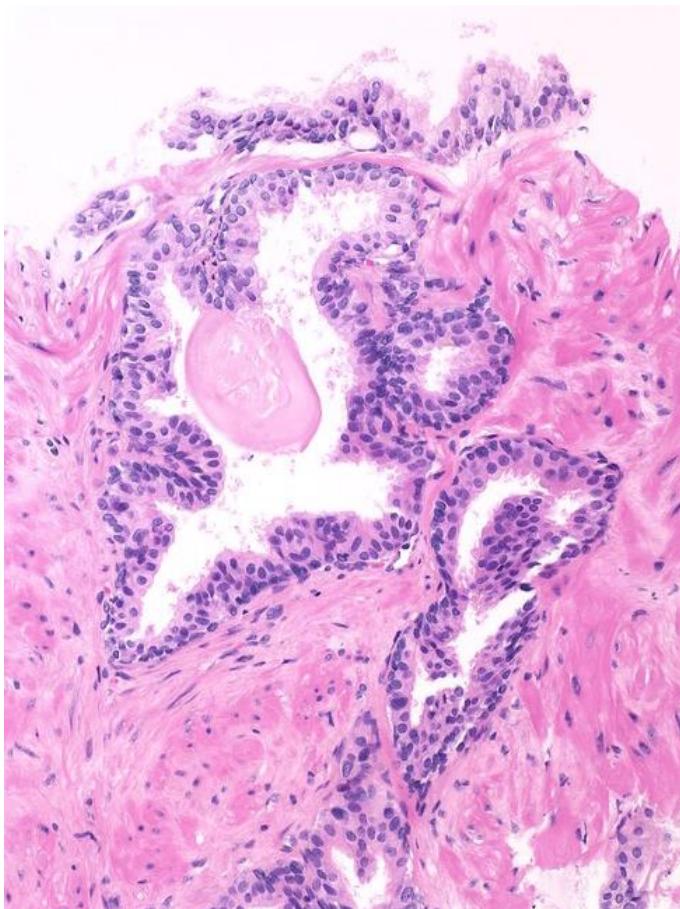
Typical prostate biopsy specimen (I=right, II=left; 6 biopsies per lobe)



Normal prostate

Basal and luminal epithelial cell layer present

Hematoxylin-eosin routine stain

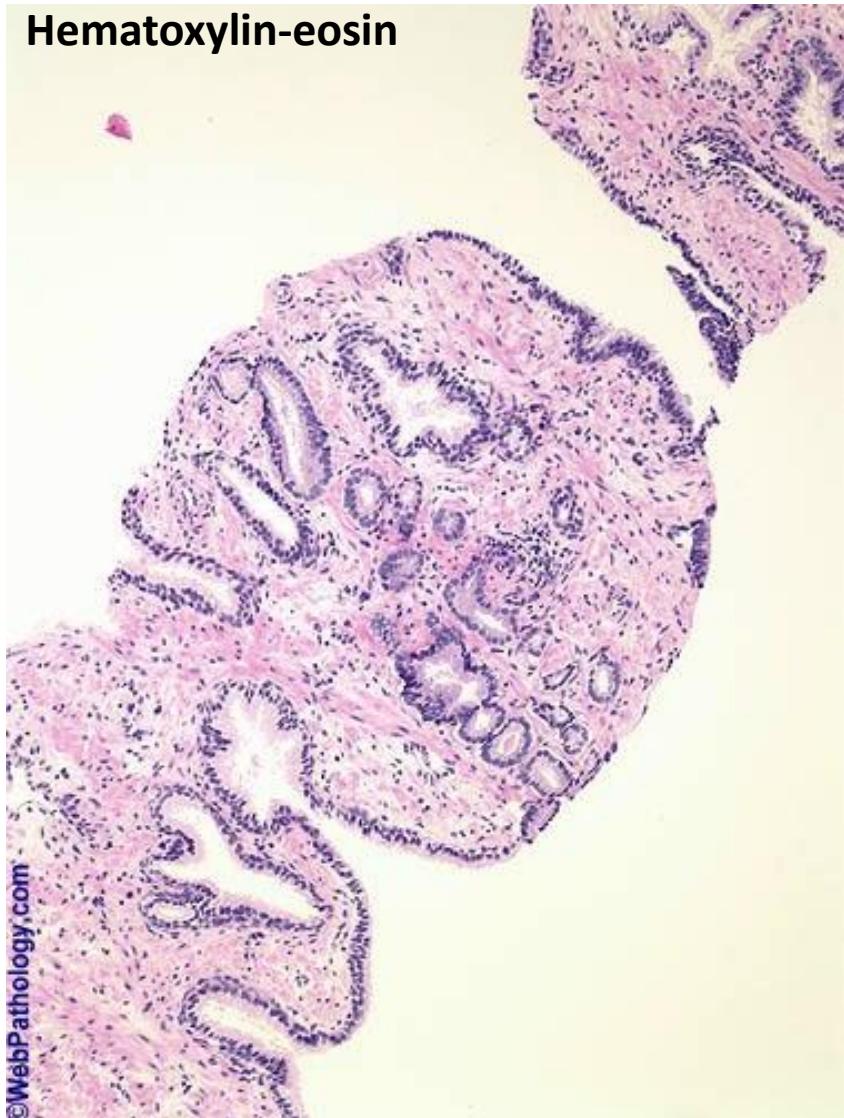


Keratin 5/6 immuno-staining shows
normal basal cell layer (not present in
carcinoma)



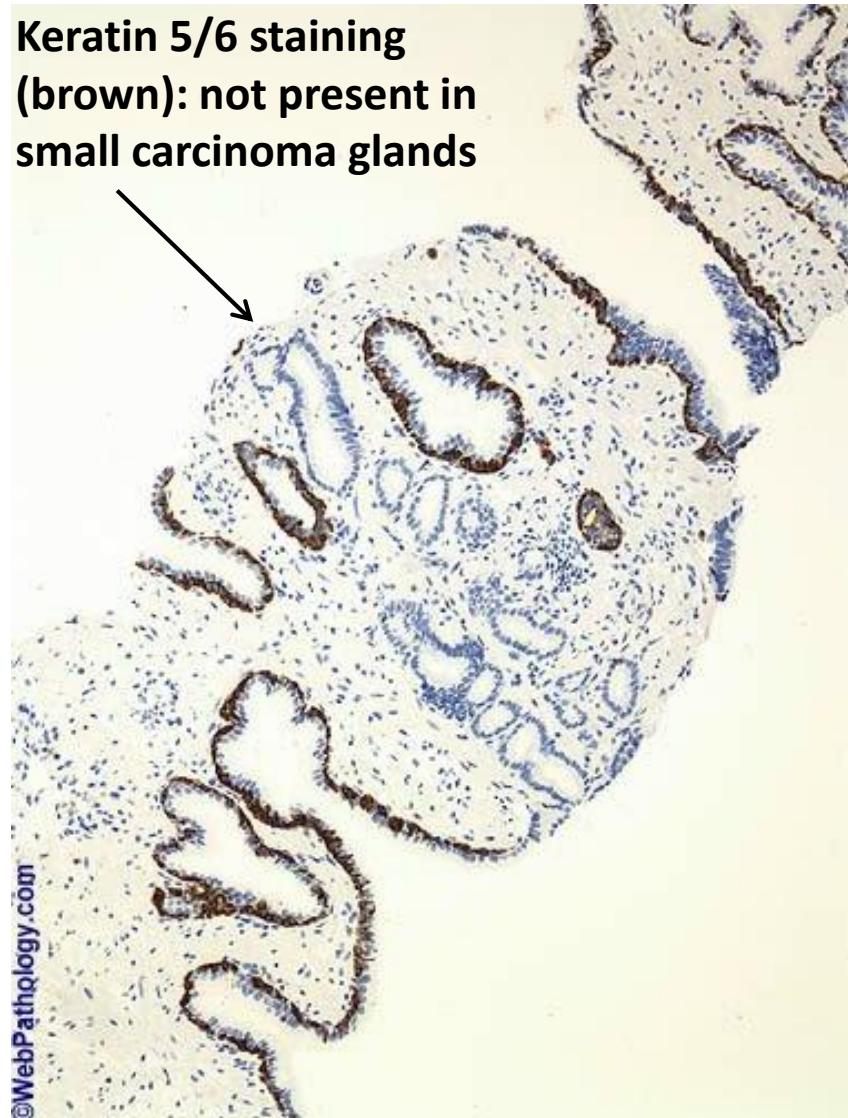
Prostatic adenocarcinoma (biopsy)

Hematoxylin-eosin



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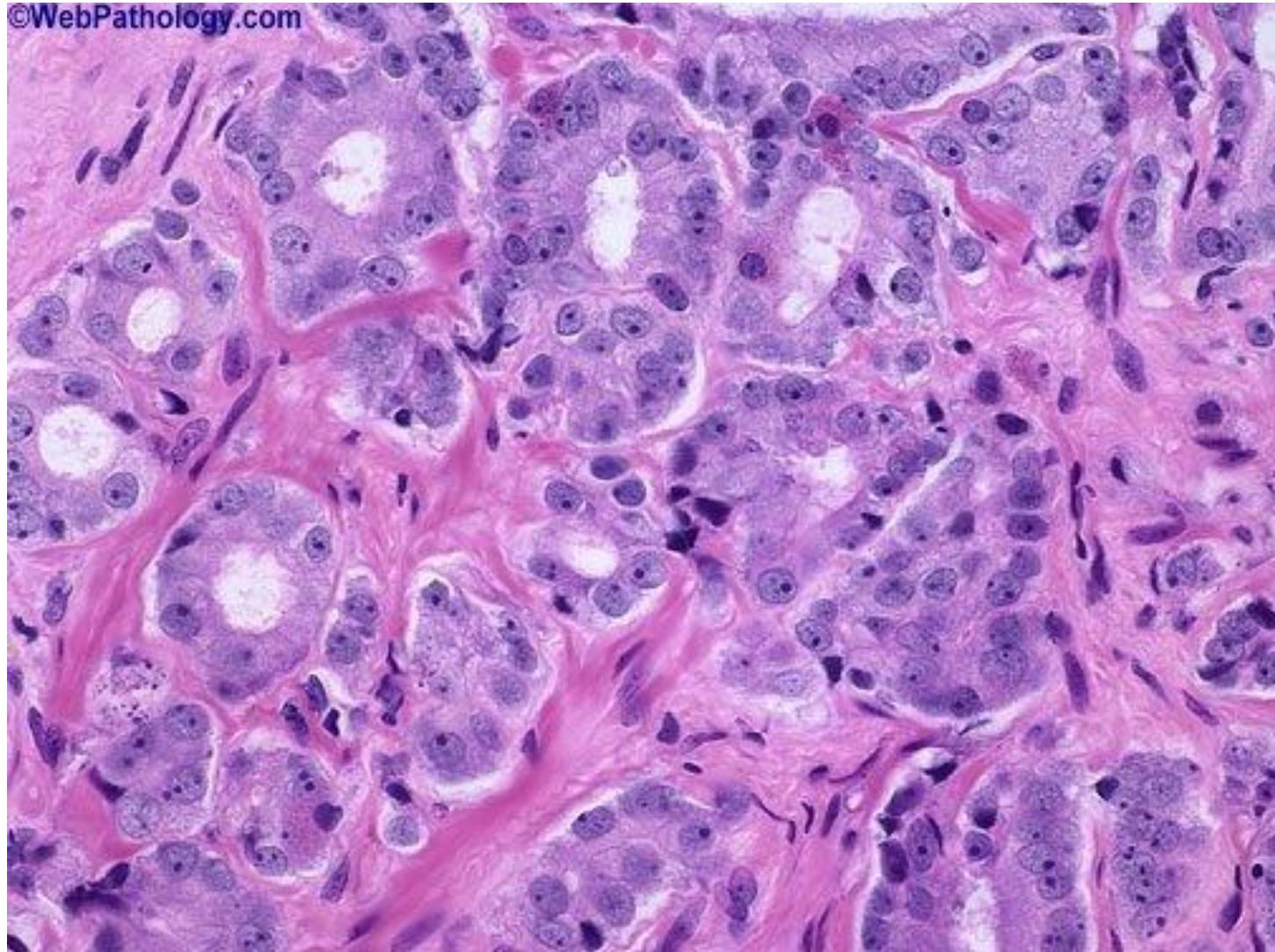
Keratin 5/6 staining
(brown): not present in
small carcinoma glands



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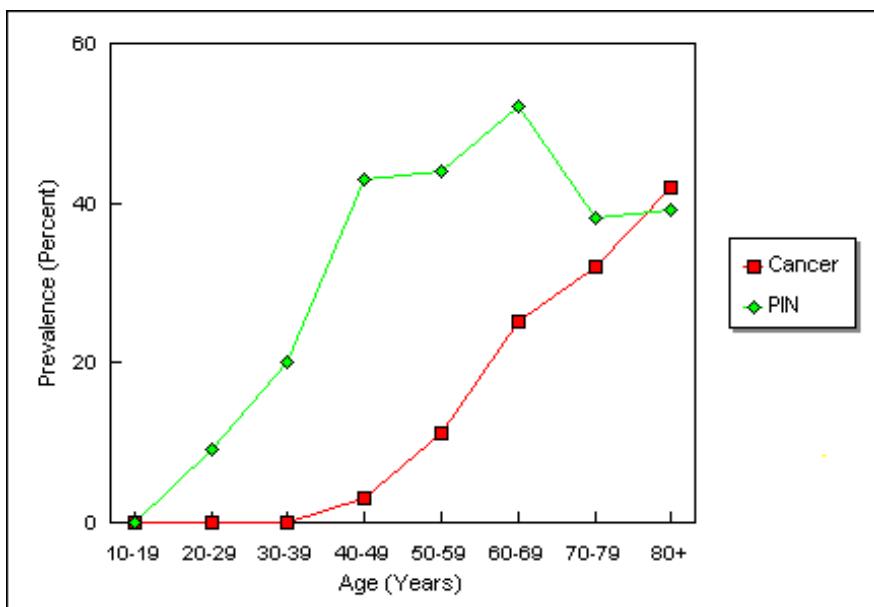
Cytological features of prostatic adenocarcinoma

- enlarged nuclei and nucleoli!

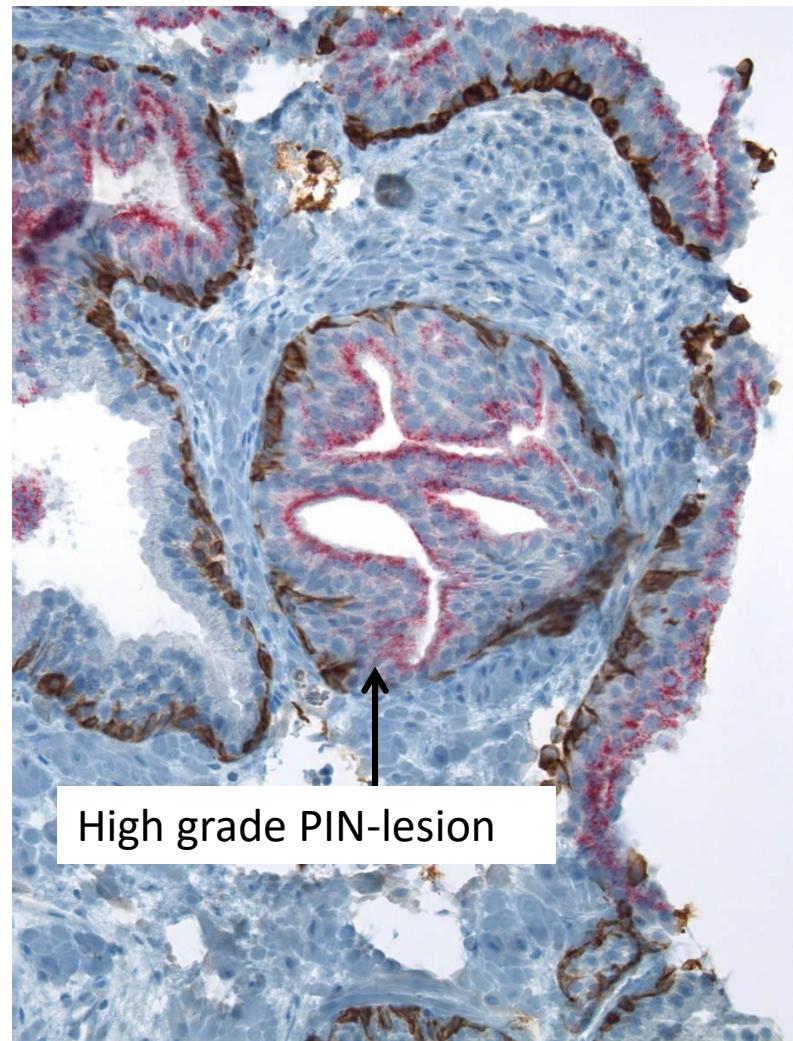
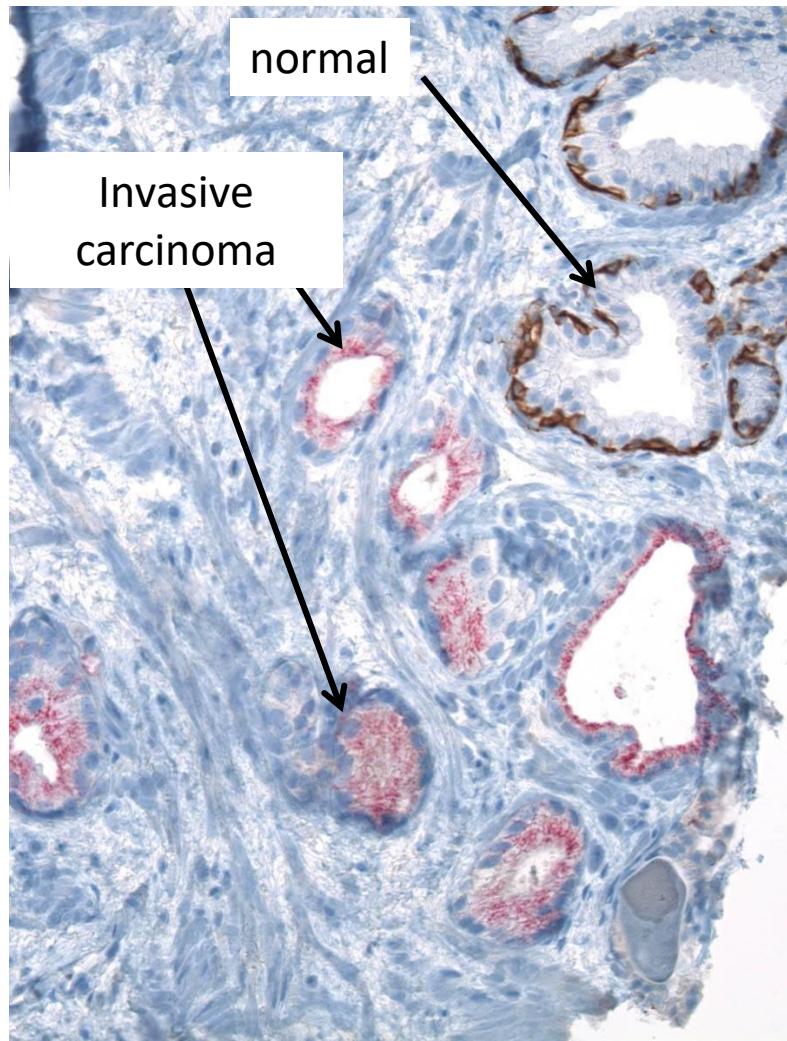


High grade PIN (prostatic intraepithelial neoplasia)

- Considered a precursor of adenocarcinoma
- Altered architecture (stratification of epithelium, cribriform and micropapillary features PLUS cytologic atypia (enlarged nuclei and nucleoli)
- Basal cell layer at least partly present (no invasion outside the gland)



Immunohistochemistry in Pca diagnostics:
α-Methylacyl-CoA racemase (AMACR; shown in red) is expressed in 90% of adenocarcinomas and in high grade PIN-lesions. Keratin 5/6 in brown.



Pathogenesis of Pca

Shen and Abate-Shen

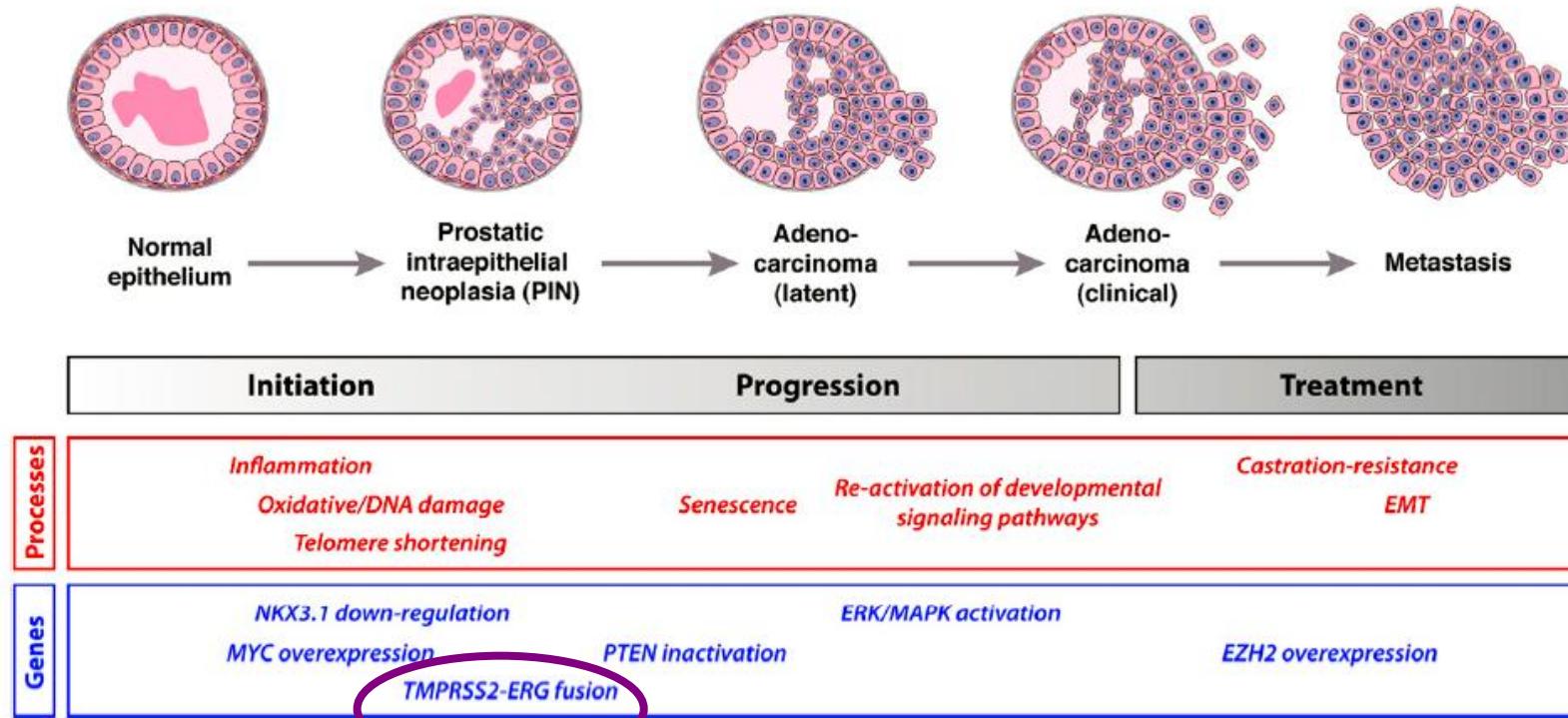
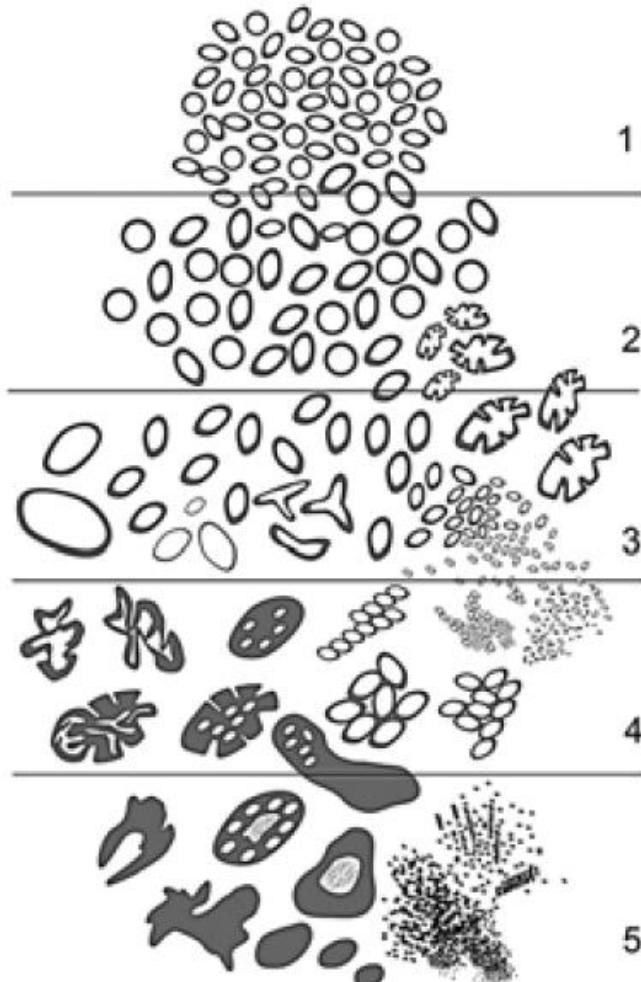


Figure 1. Progression pathway for human prostate cancer. Stages of progression are shown, together with molecular processes and genes/pathways that are likely to be significant at each stage. Adapted from Abate-Shen and Shen (2000).

- TMPRSS2-ERG translocation is present in ~50% of adenocarcinomas but has no clear prognostic/predictive role alone

Gleason grading – the gold standard

The best histological parameter to determine cancer aggressiveness and heterogeneity!

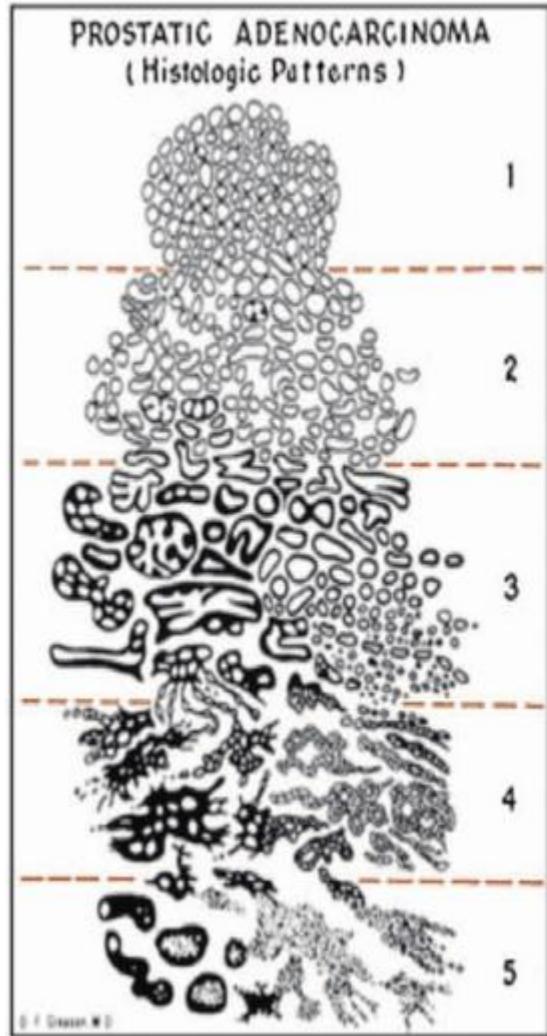


1. Clearly defined area of small and regularly shaped glands with atypia
2. Some variation in size and architecture of glands
3. The most common pattern, variation in glandular size and arrangement, infiltrative growth pattern
4. Cribriform, fused or disintegrated glands with atypia, infiltration into stroma and outside prostate
5. Undifferentiated carcinoma cells with no glandular arrangement (solid growth, single cells)

Evolution of Gleason grading

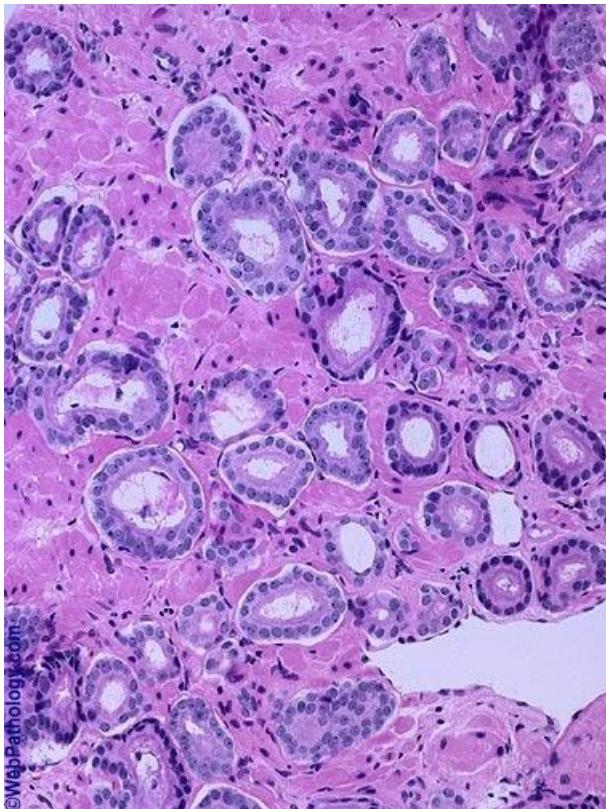
A

Original Gleason

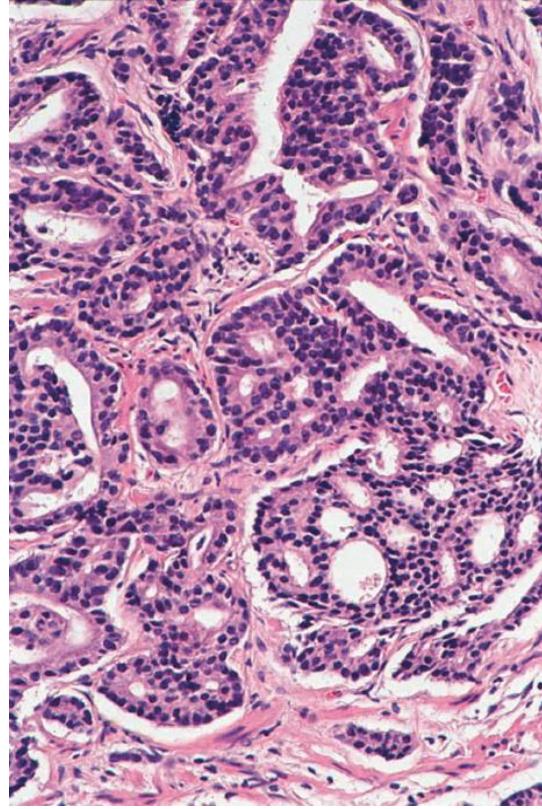


Many faces of prostatic adenocarcinoma

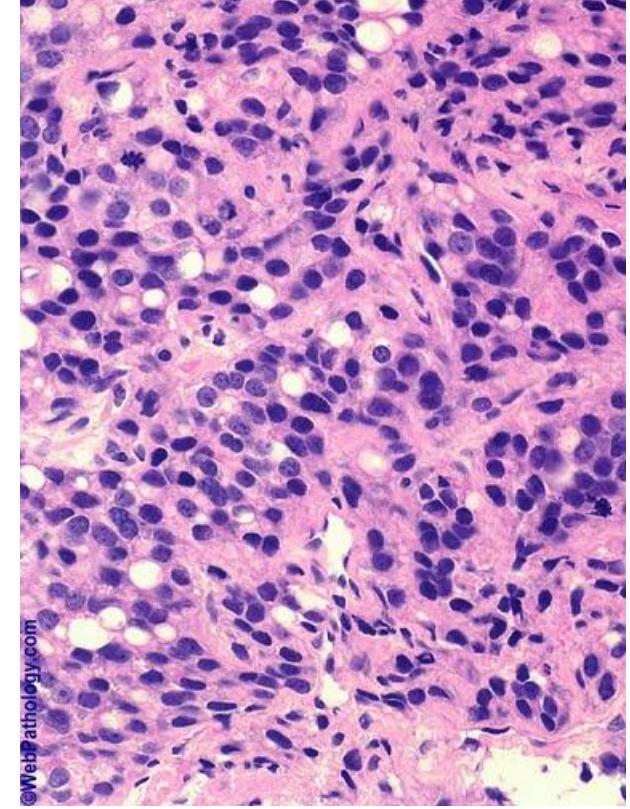
Gleason 3



Gleason 4

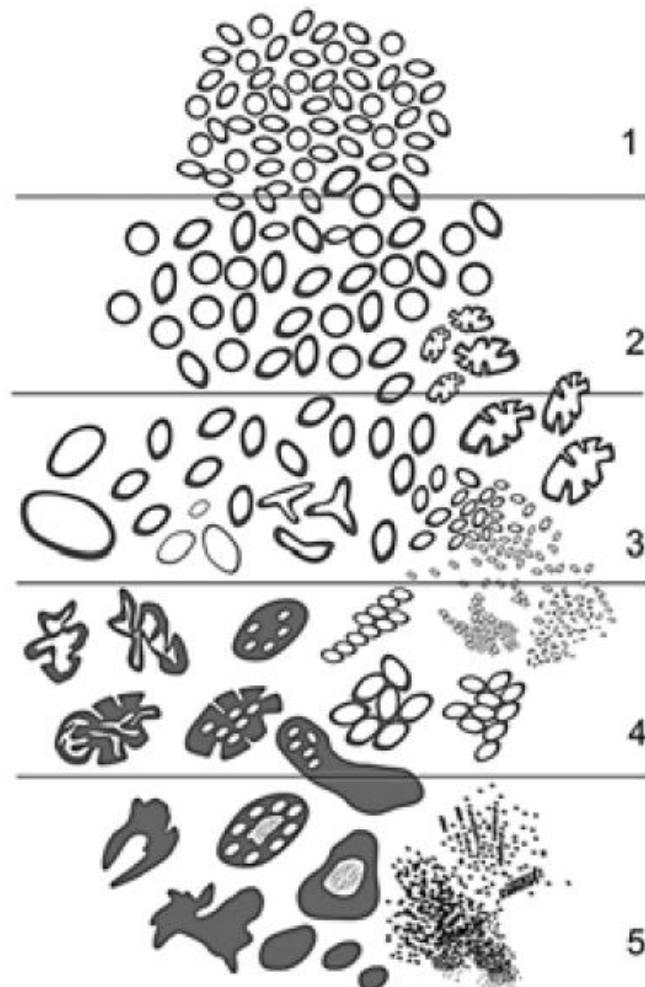


Gleason 5

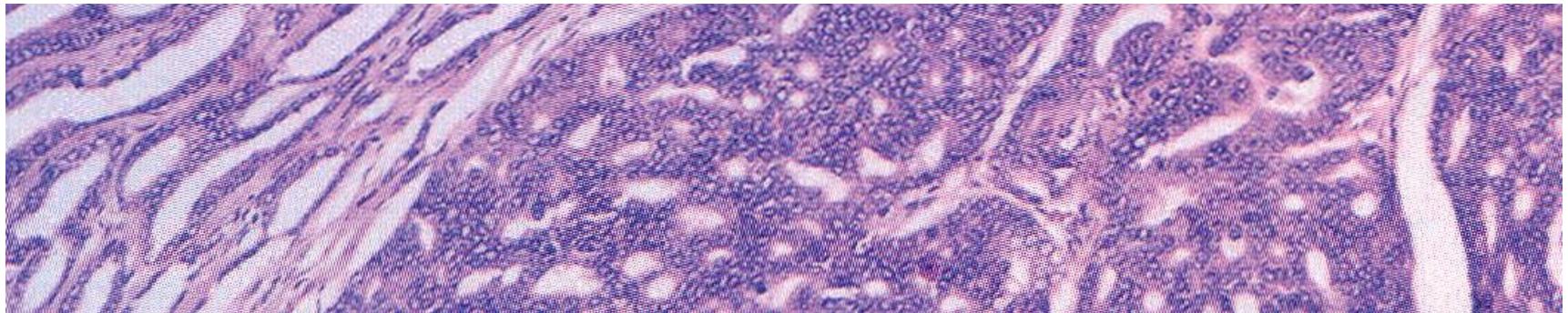


Gleason grading

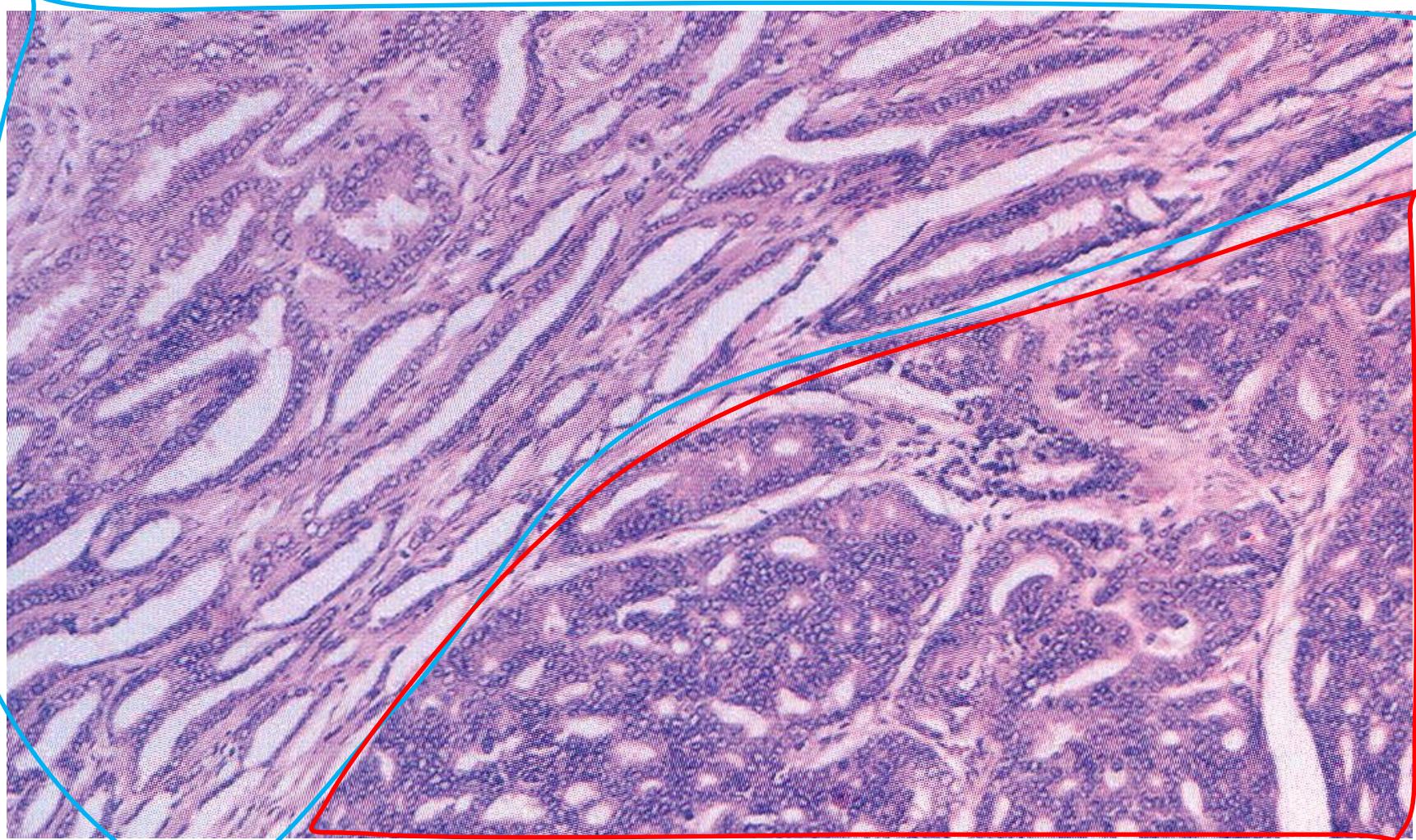
- Gleason score (2-10)
 - Determine the most common growth pattern (**dominant Gleason grade**) and the second most common pattern (**non-dominant Gleason grade**); both 1-5.
 - Sum dominant and non-dominant Gleason grade to get **Gleason score** (e.g. 3+3=6).
 - Gleason-grades 1-2 are not used in biopsies which is why Gleason score is in practice between 6-10.
- From 2016: Gleason Grade Group (GGG):
 - $3+3 = \text{GGG } 1$
 - $3+4 = \text{GGG } 2$
 - $4+3 = \text{GGG } 3$
 - $4+4 = \text{GGG } 4$
 - $\geq 4+5 = \text{GGG } 5$



What is Gleason grade/score for
this biopsy?



Prostate adenocarcinoma, Gleason score
 $3+4 = 7$ (Gleason grade group 2)



Gleason grade group predicts biochemical recurrence after radical prostatectomy (PSA-relapse)

Am J Surg Pathol • Volume 40, Number 2, February 2016

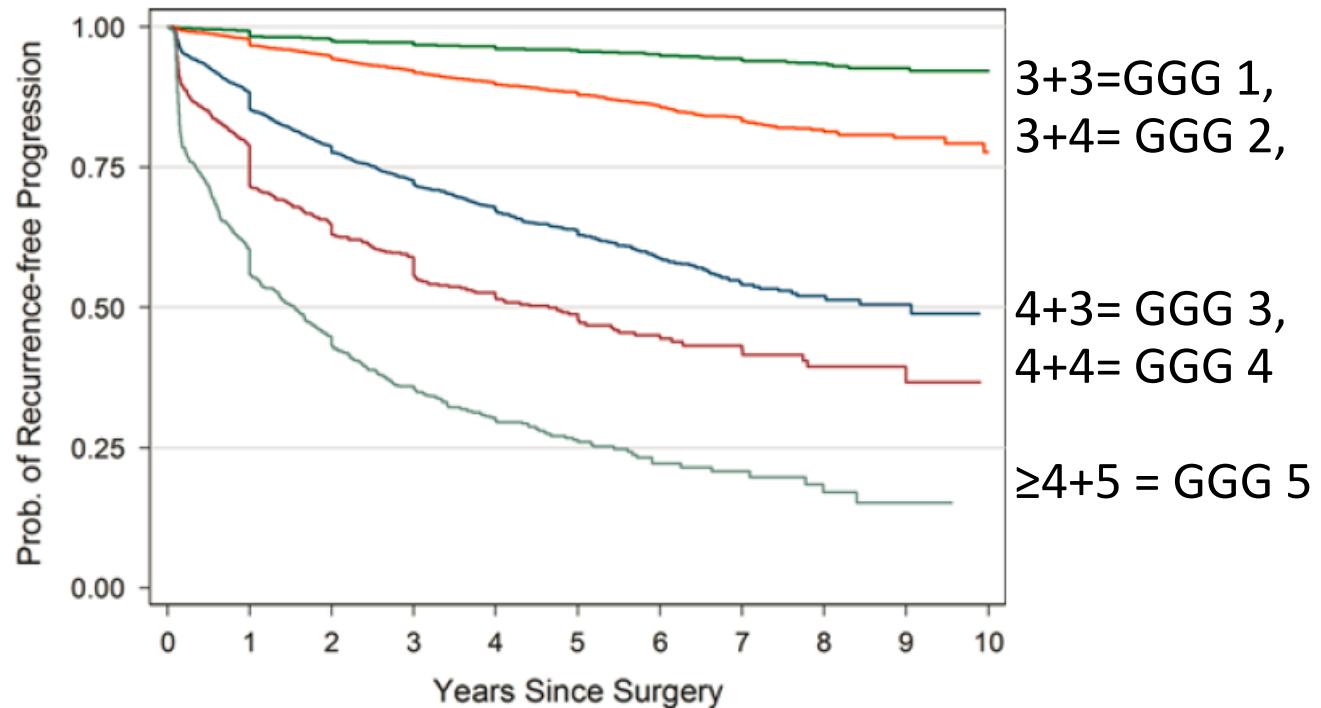


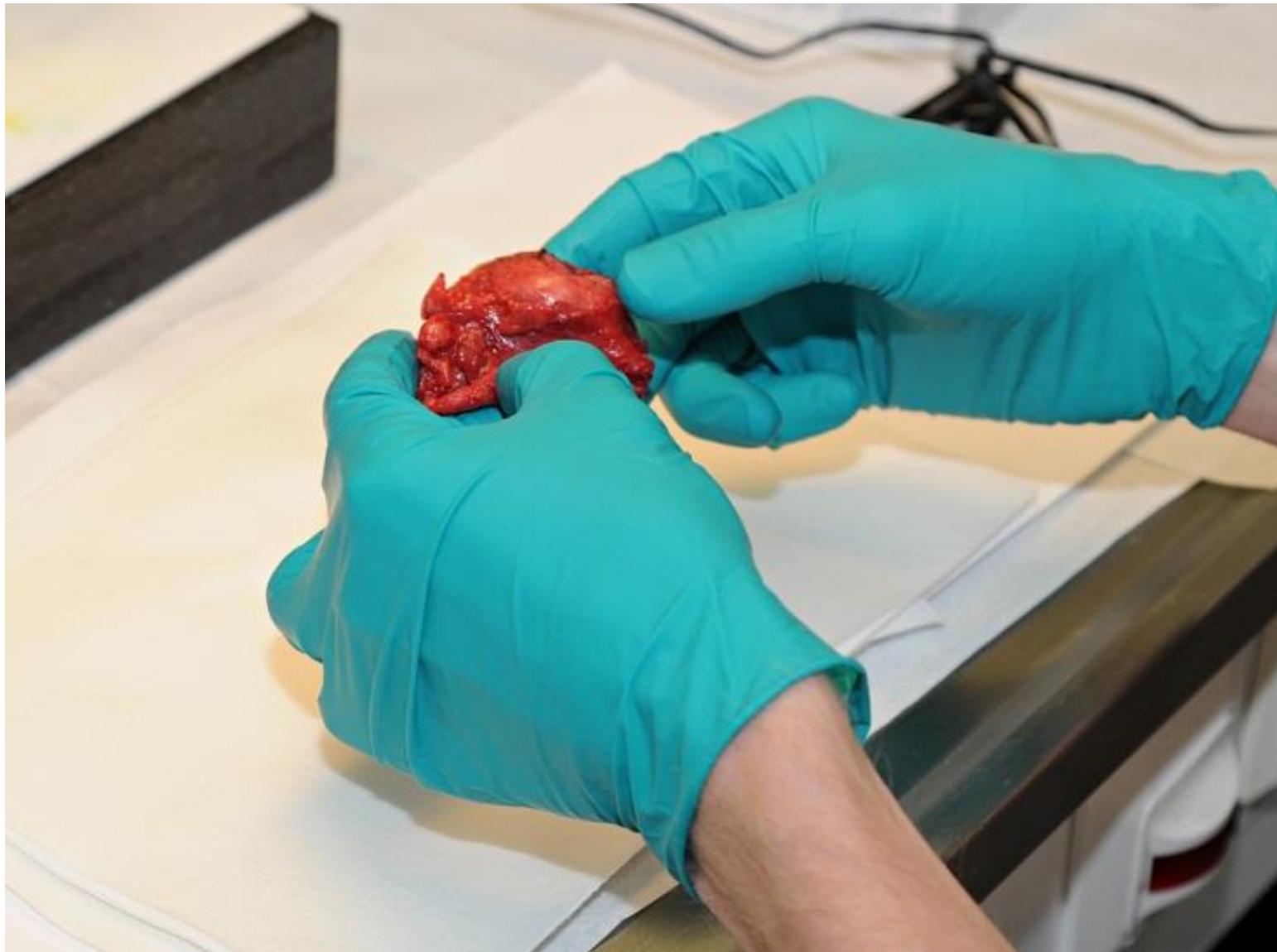
FIGURE 3. Biochemical recurrence-free progression after RP stratified by grade (green line—Gleason score 6 [grade group 1], orange—Gleason score 3+4 [grade group 2], dark blue—Gleason score 4+3 [grade group 3], brown—Gleason score 8 [grade group 4], gray—Gleason score ≥ 9 [grade group 5]).

Biopsy vs. radical prostatectomy specimen

- In biopsy, pathologists report the most common (dominant) Gleason pattern + highest Gleason pattern
 - E.g. 60% of Gleason 3, 35% of Gleason 4 and 5% of Gleason 5 gives Gleason grading $3+5=8$
- In RALP specimens “ground truth” (dominant and non-dominant) is used. A minor higher tertiary Gleason ($\leq 5\%$) pattern, if present, is reported
 - E.g. 60% of Gleason 3, 35% of Gleason 4 and 5% of Gleason 5 gives Gleason grading $3+4=7$ with tertiary Gleason 5

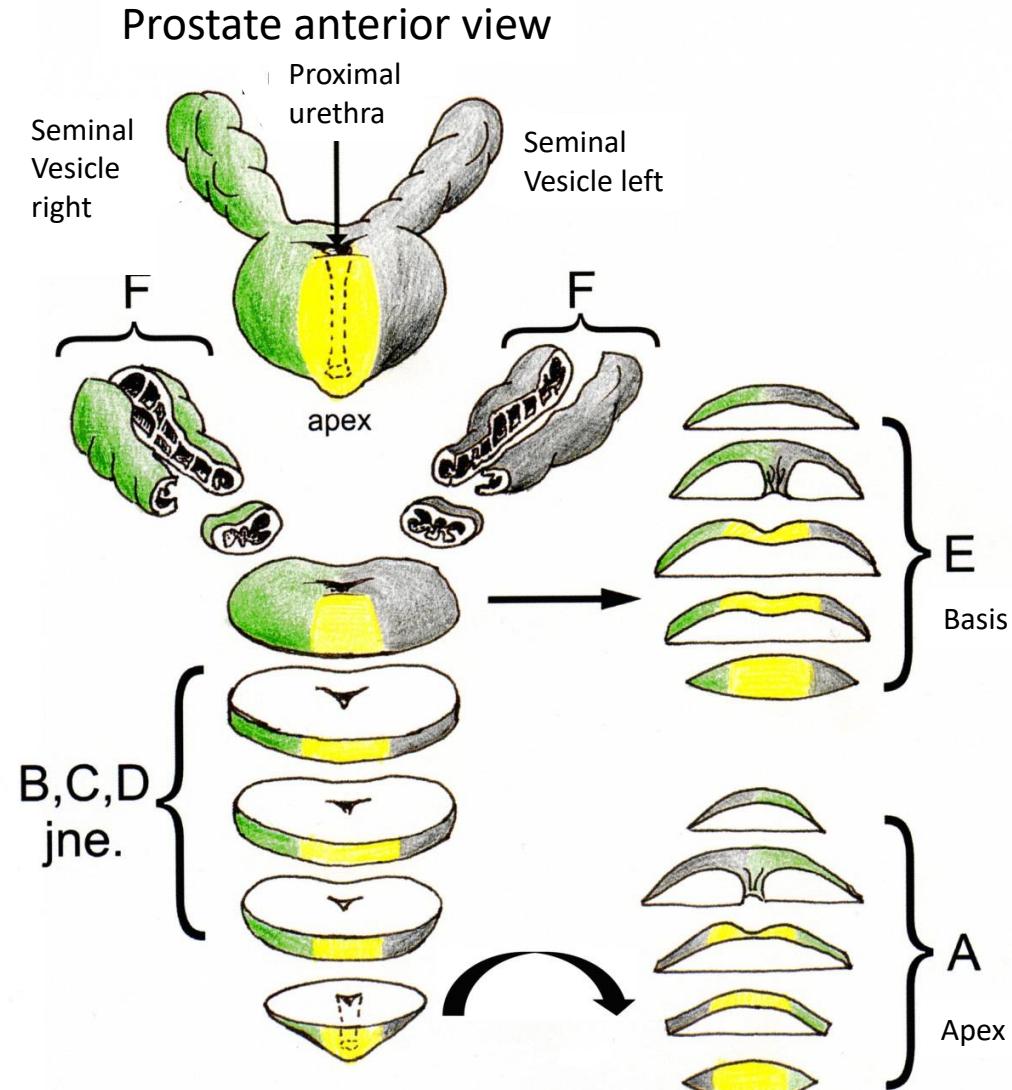
Adenocarcinoma was found in the biopsies and treated with radical prostatectomy. What next?

Radical prostatectomy specimen handling: macroscopic features, measures, suspicious lesions...

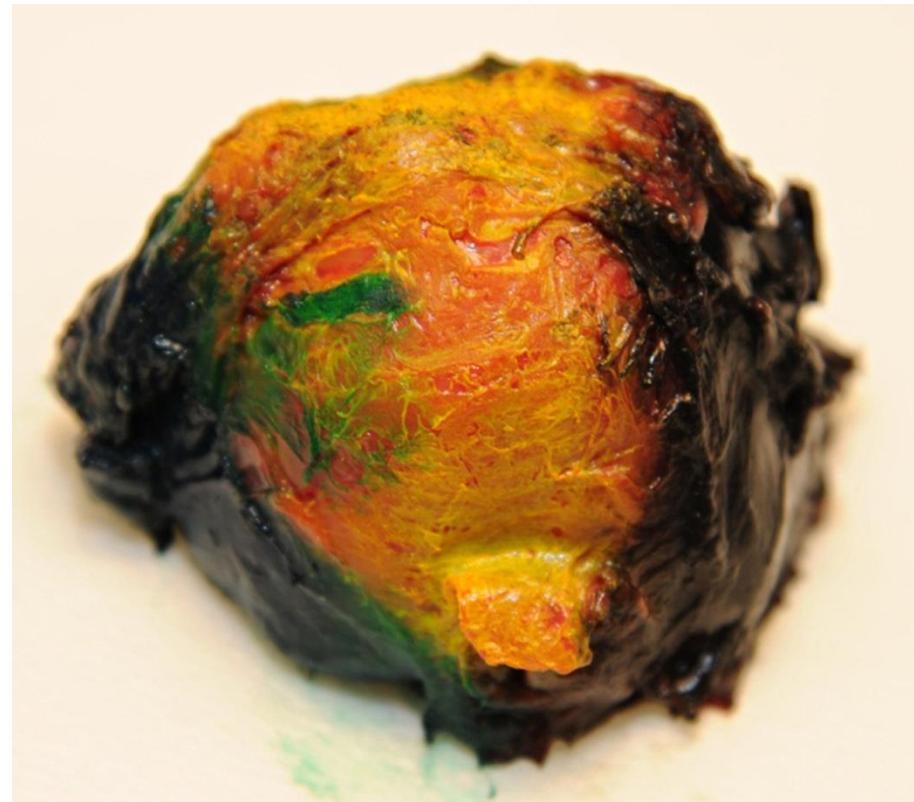


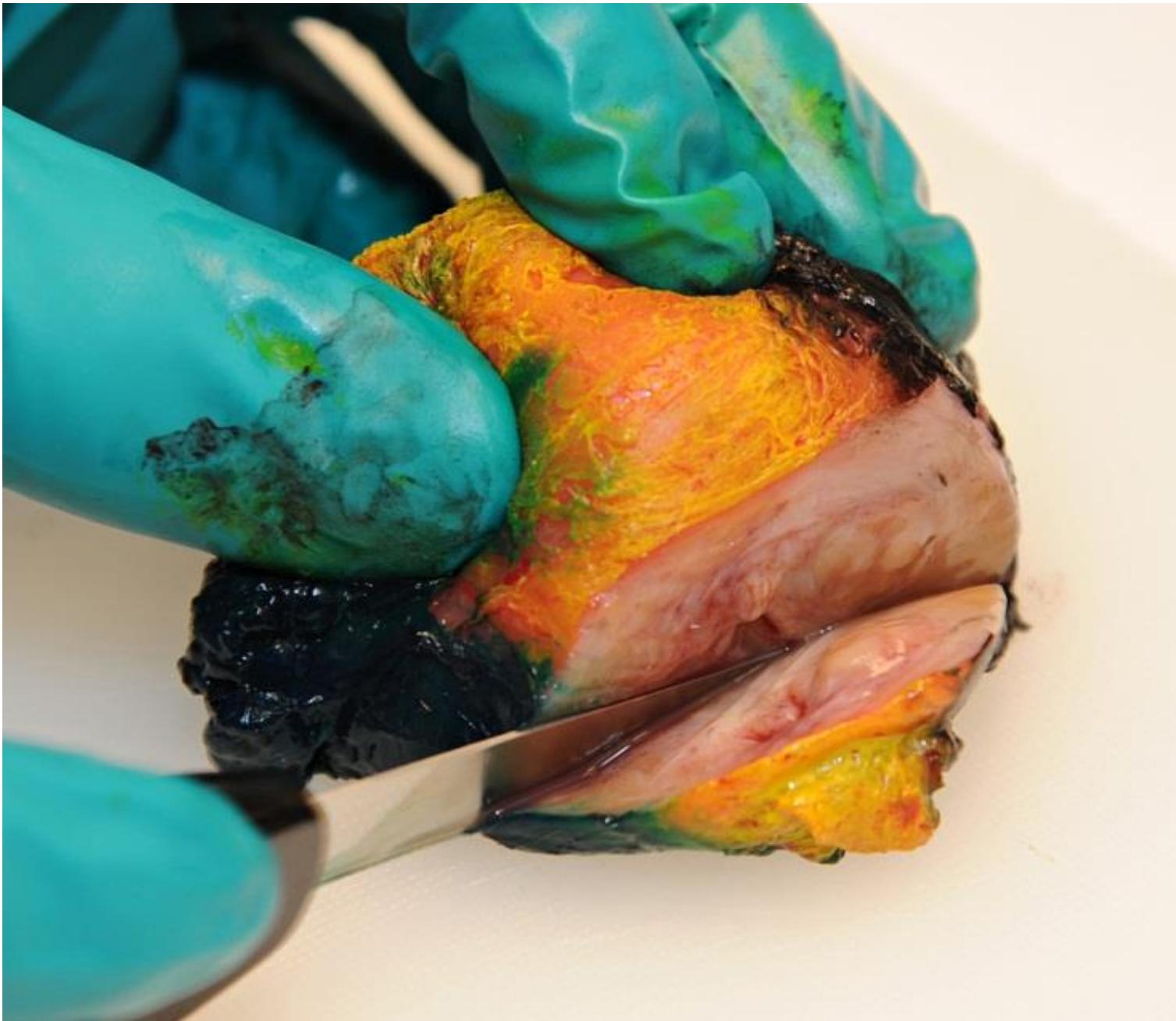
Macro-dissection of prostatectomy specimen

- Transferred to pathology laboratory as a fresh tissue specimen or fixed in formalin.
- Surgical margins marked with tissue ink (needed to determine orientation under microscope; cancer location, margin positivity).
- Whole prostate embedded into paraffin using tissue macro blocks.
- Pathology report provided with a table including clinically relevant features



Staining of surgical margins (tissue ink;
green=right, black=left, yellow=anterior





Macroscopic dissection

Apex

Mid prostate

Basis

Seminal vesicles



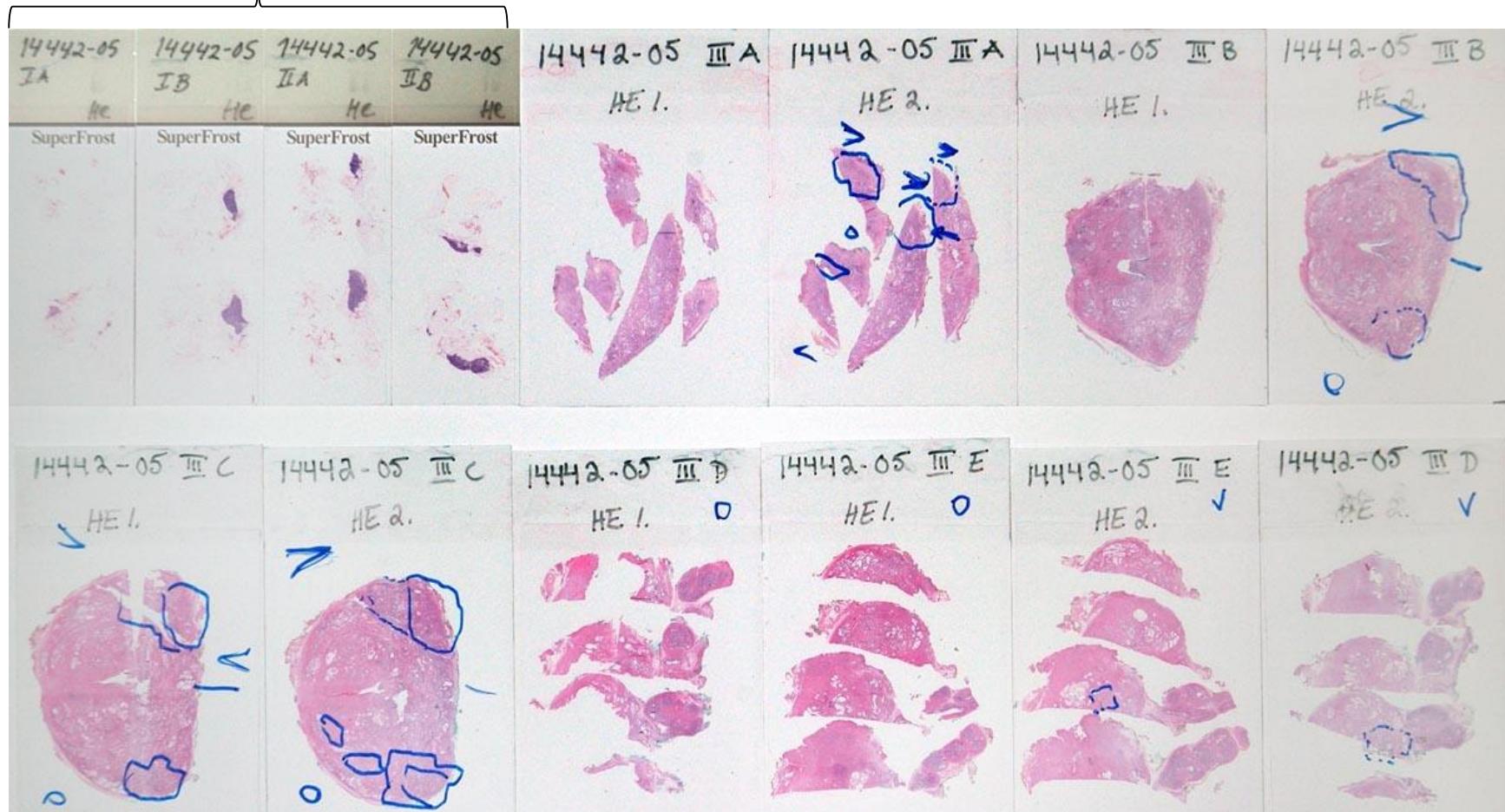
Whole mount embedding using macro cassettes

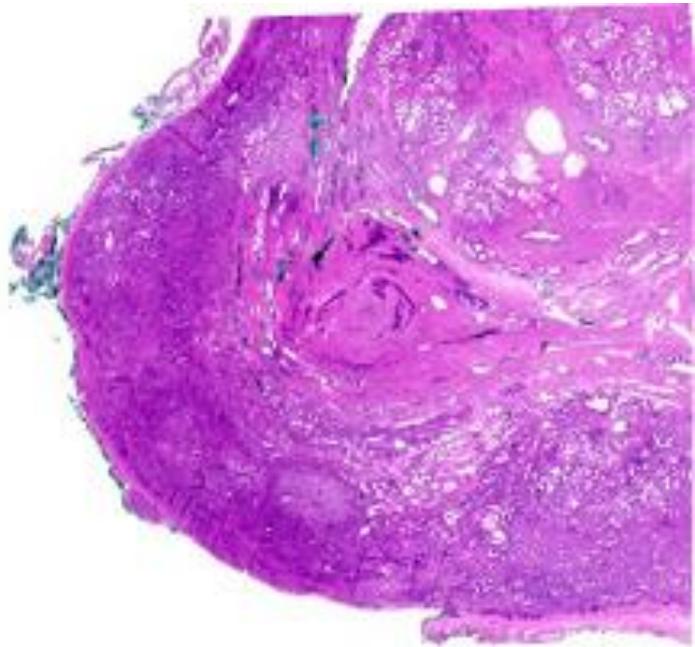


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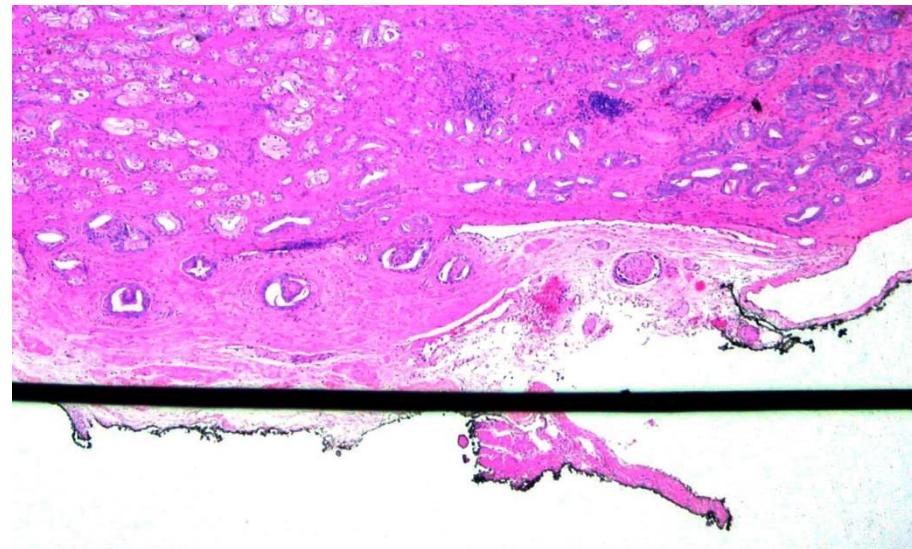
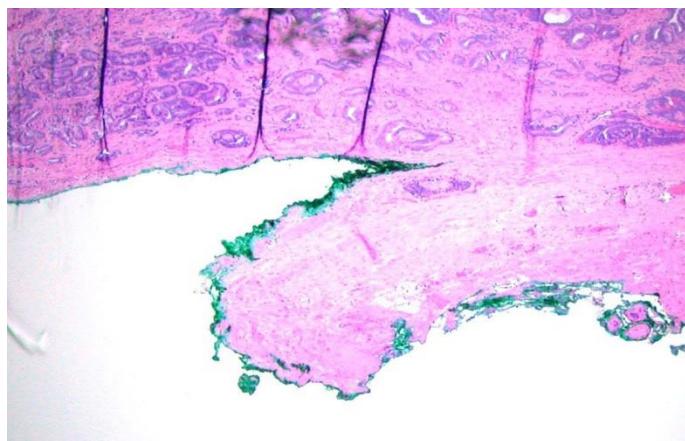
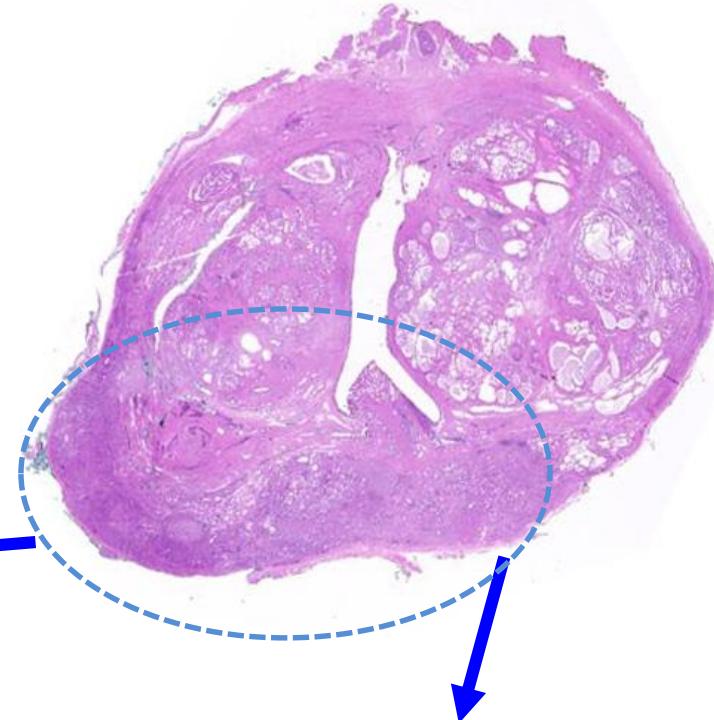
Hematoxylin-eosin stained slides (carcinoma lesions marked with blue ink)

Lymph nodes





Adenocarcinoma
on the right
posterolateral
region is
stretching capsule
and close to
surgical margin

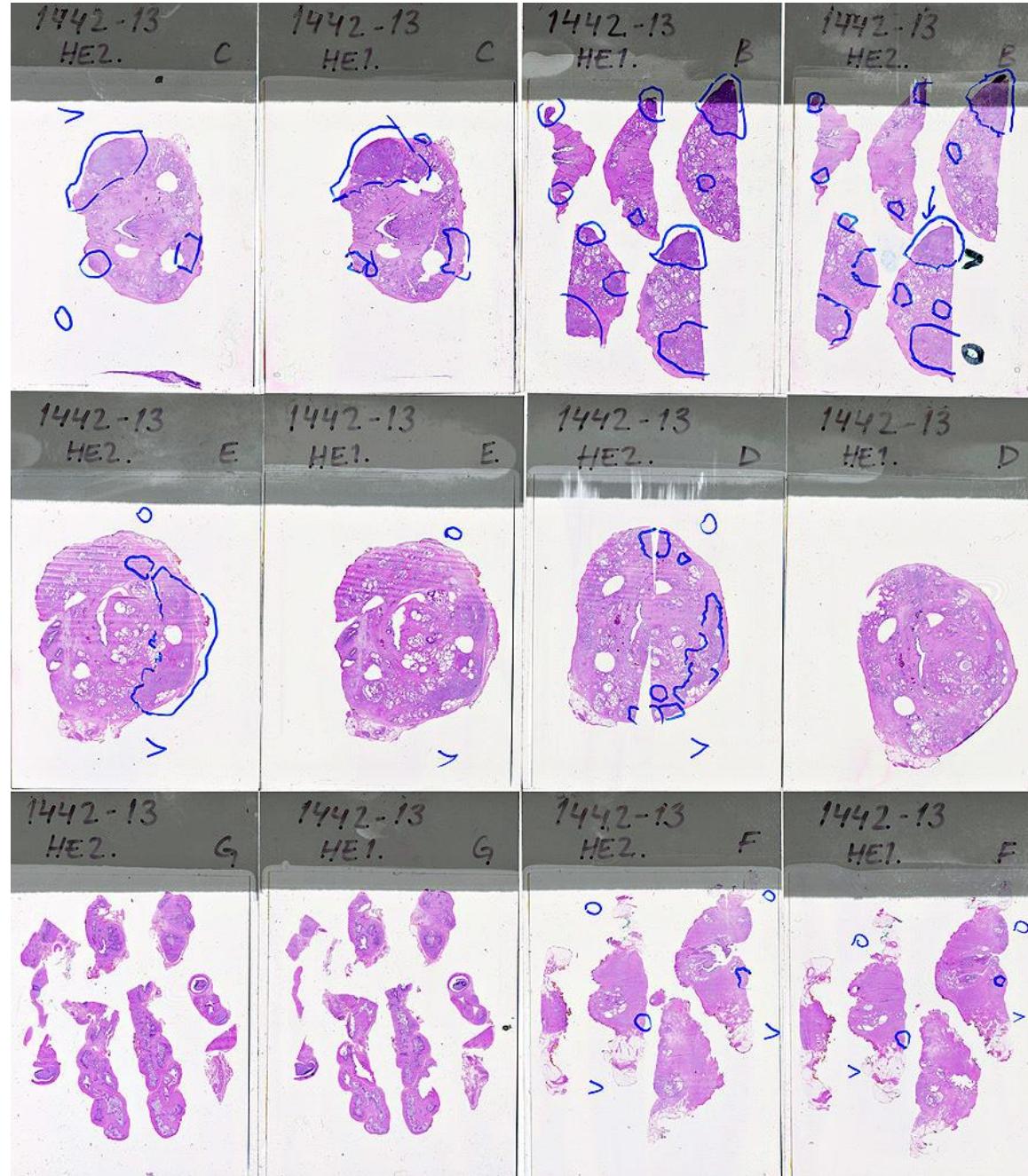


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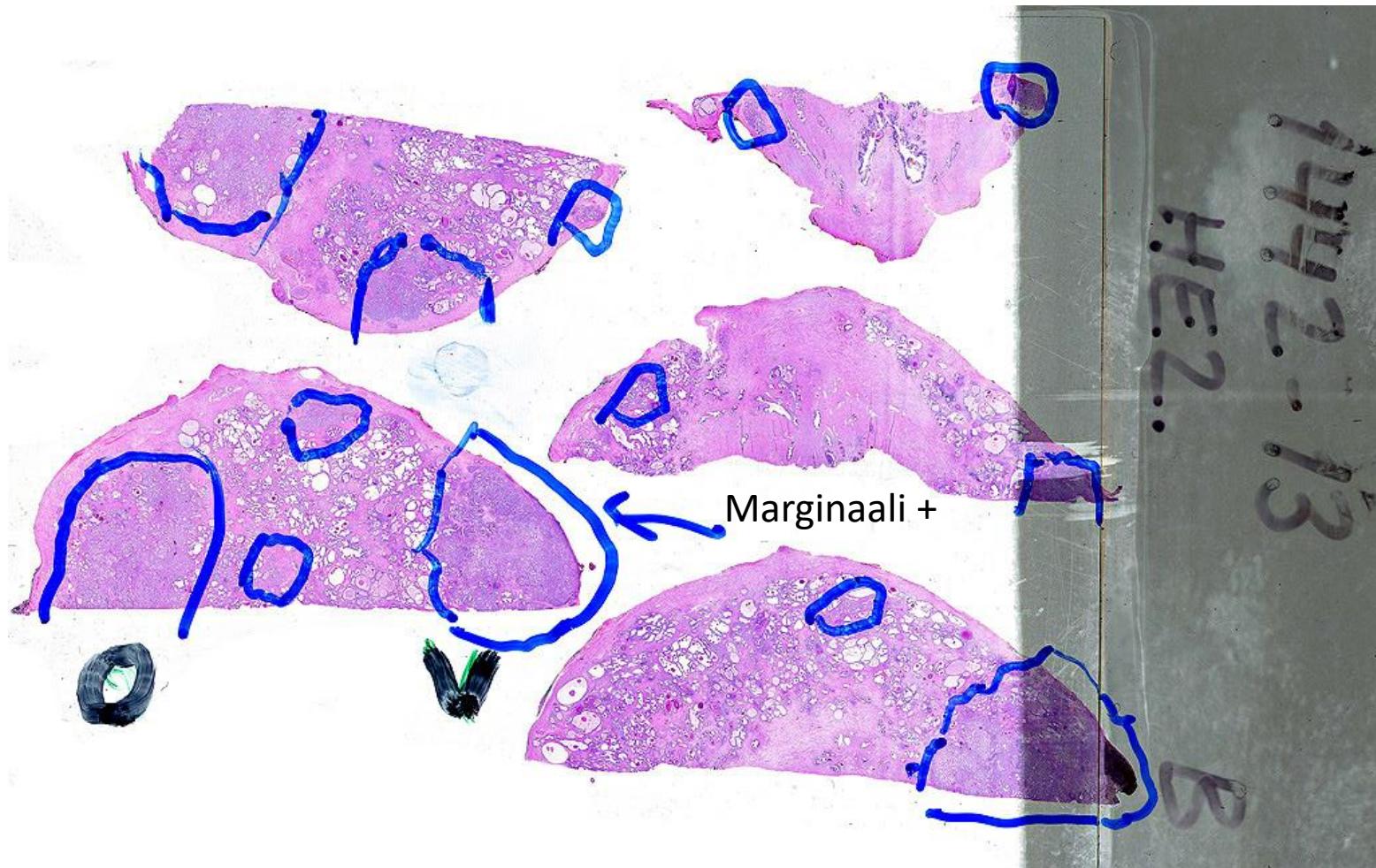
Patient #1.

62-y male, PSA 9,8,
f/t-ratio 9,2. Minor
Gleason 3+3=6
adenocarcinoma in
biopsies.

> Radical
prostatectomy
shows Gleason
3+4=7 carcinoma
20% of area plus
minor tertiary
Gleason 5 pattern



Surgical margin is 5 mm positive in apex

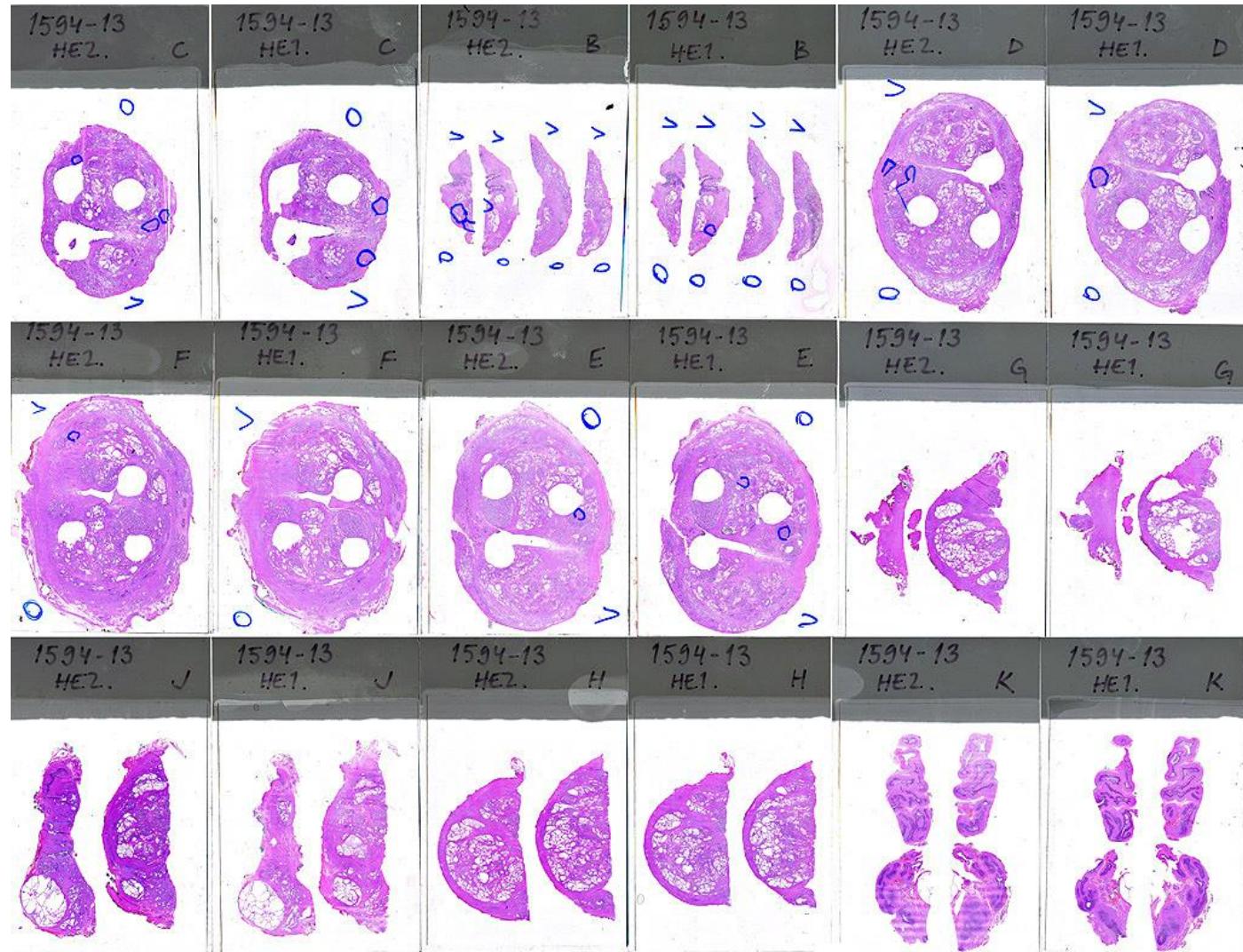


Despite the minimal finding in biopsies, the patient had clinically significant (aggressive) and relatively large carcinoma with positive surgical margin. Recurrence is possible and additional treatment (e.g. adjuvant radiation therapy) may be needed.

Tapaus 2.

51-year old male,
PSA >10. Minor
Gleason 3+3
adenocarcinoma
in biopsies on the
right.

> Radical
prostatectomy
shows Gleason
3+3=6 carcinoma
covering 1% of
prostate. No
extraprostatic
extension. Major
hyperplasia.



Despite the high PSA level, histological finding is minor (clinically insignificant) and presumably related to hyperplasia. This case shows the low specificity and sensitivity of PSA in Pca diagnostics. However, better serum marks are not in routine use.

Pca diagnosis and AI

- Imaging
- Histopathology
- Genetics
- Surgery (e.g. robot-assisted surgery, teaching)
- Nomograms:
 - prediction tools designed to help patients and their physicians understand the nature of their prostate cancer
 - assess risk based on specific characteristics of a patient and his disease
 - predict the likely outcomes of treatment

Prostate cancer imaging

- Used for detection and staging
- Transrectal ultra sound has poor sensitivity and specificity
- **Multiparametric magnetic resonance imaging (mpMRI) is widely used and becoming very accurate**
 - With or without intravenous contrast agent
 - Option for multiple imaging sequences and image processing
 - T2-weighted imaging (T2w)
 - Diffusion weighted imaging (DWI)
 - T2-mapping
 - *PI-RADS classification* (prostate imaging-reporting and data system) scores 1-5 (1=highly unlikely carcinoma, 3=suspicious, 5=highly likely cancer)
- PET imaging (different tracers; e.g. PSMA-PET)
- Bone scan
- CT

How does it show up?

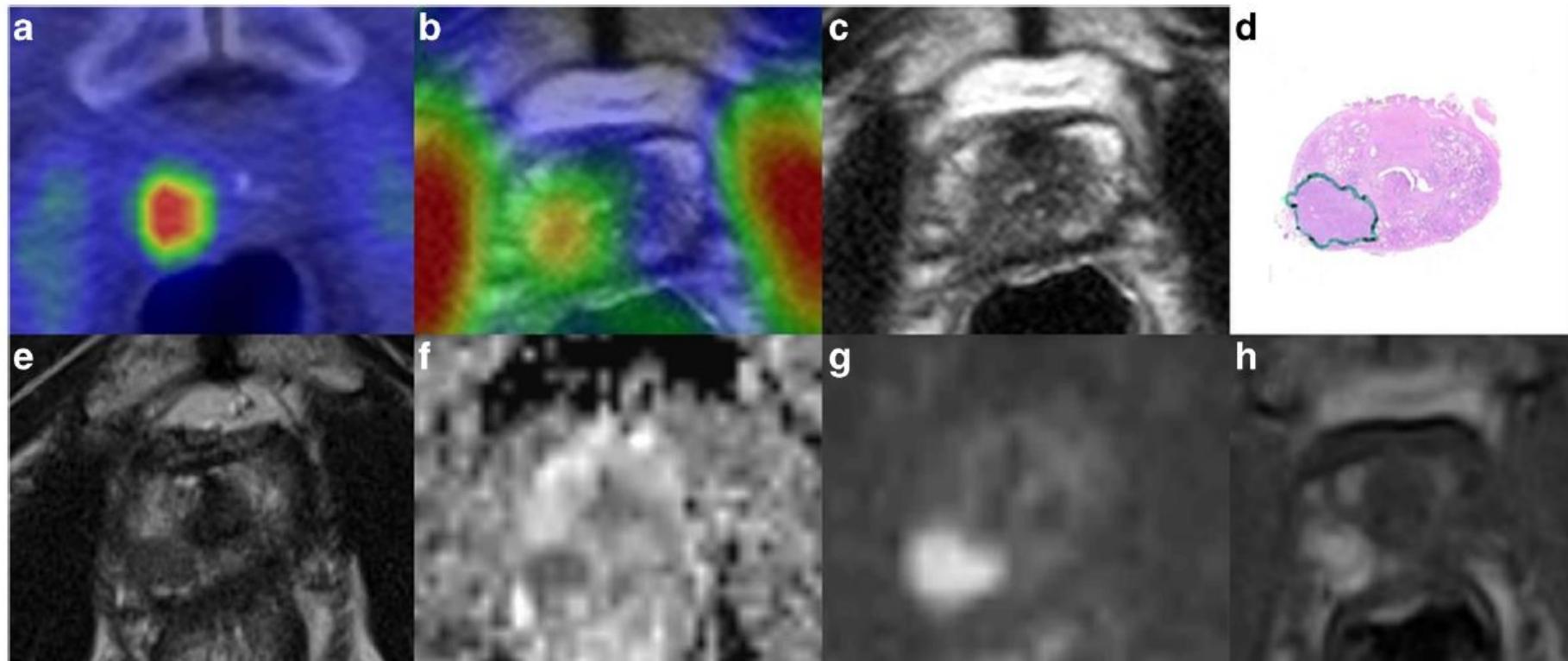


Fig. 2 Right peripheral lesion on ^{18}F -FACBC PET/CT (A) and PET/MRI (B); less conspicuous on T2w PET/MRI (C) of patient no. 3. Whole-mount prostatectomy section (D): tumor classified as pT3a GS 4 + 4. On T2w (E), ADC (F), DWI ($\text{b} \text{ value} = 2000 \text{ s/mm}^2$; G), and

DCE (H) of mpMRI, the lesion is well demonstrated. Note decreased ^{18}F -FACBC uptake over time for PET/CT vs. PET/MRI. A is scaled to SUV, with a minimum at 0.00 and maximum at 4.7. B is scaled to SUV, with a minimum at 0.00 and maximum at 2.5

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MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis

V. Kasivisvanathan, A.S. Rannikko, M. Borghi, V. Panebianco, L.A. Mynderse, M.H. Vaarala, A. Briganti, L. Budäus, G. Hellawell, R.G. Hindley, M.J. Roobol, S. Eggener, M. Ghei, A. Villers, F. Bladou, G.M. Villeirs, J. Virdi, S. Boxler, G. Robert, P.B. Singh, W. Venderink, B.A. Hadaschik, A. Ruffion, J.C. Hu, D. Margolis, S. Crouzet, L. Klotz, S.S. Taneja, P. Pinto, I. Gill, C. Allen, F. Giganti, A. Freeman, S. Morris, S. Punwani, N.R. Williams, C. Brew-Graves, J. Deeks, Y. Takwoingi, M. Emberton, and C.M. Moore, for the PRECISION Study Group Collaborators*

Validation of IMPROD biparametric MRI in men with clinically suspected prostate cancer: A prospective multi-institutional trial

Ivan Jambor , Janne Verho, Otto Ettala, Juha Knaapila, Pekka Taimen, Kari T. Syvänen, Aida Kiviniemi, Esa Kähkönen, Illeana Montoya Perez, Marjo Seppänen, Antti Rannikko, Outi Oksanen, Jarno Riikonen, Sanna Mari Vimpeli, Tommi Kauko, Harri Merisaari, Markku Kallajoki, Tuomas Mirtti, Tarja Lamminen, Jani Saunavaara, Hannu J. Aronen, Peter J. Boström
[view less]

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Radiomics and machine learning of multisequence multiparametric prostate MRI: Towards improved non-invasive prostate cancer characterization

Jussi Toivonen , Ileana Montoya Perez, Parisa Movahedi, Harri Merisaari, Marko Pesola, Pekka Taimen, Peter J. Boström, Jonne Pohjankukka, Aida Kiviniemi, Tapio Pahikkala, Hannu J. Aronen, Ivan Jambor

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- In this study, a classifier system was built and evaluated based on multiple texture features of MRI data for prediction of PCa Gleason score 3+3 (low risk) vs >3+3 (high risk).
- **Methods:**
 - MRI data sets of 62 patients with histologically confirmed PCa.
 - T2w, DWI (the monoexponential and kurtosis functions), and T2 maps were used.
 - Local statistics and 8 different radiomics/texture descriptors were utilized at different configurations to extract a total of 7105 unique per-tumor features. Logistic regression with implicit feature selection and leave pair out cross validation was used to discriminate tumors with 3+3 vs >3+3 GS.

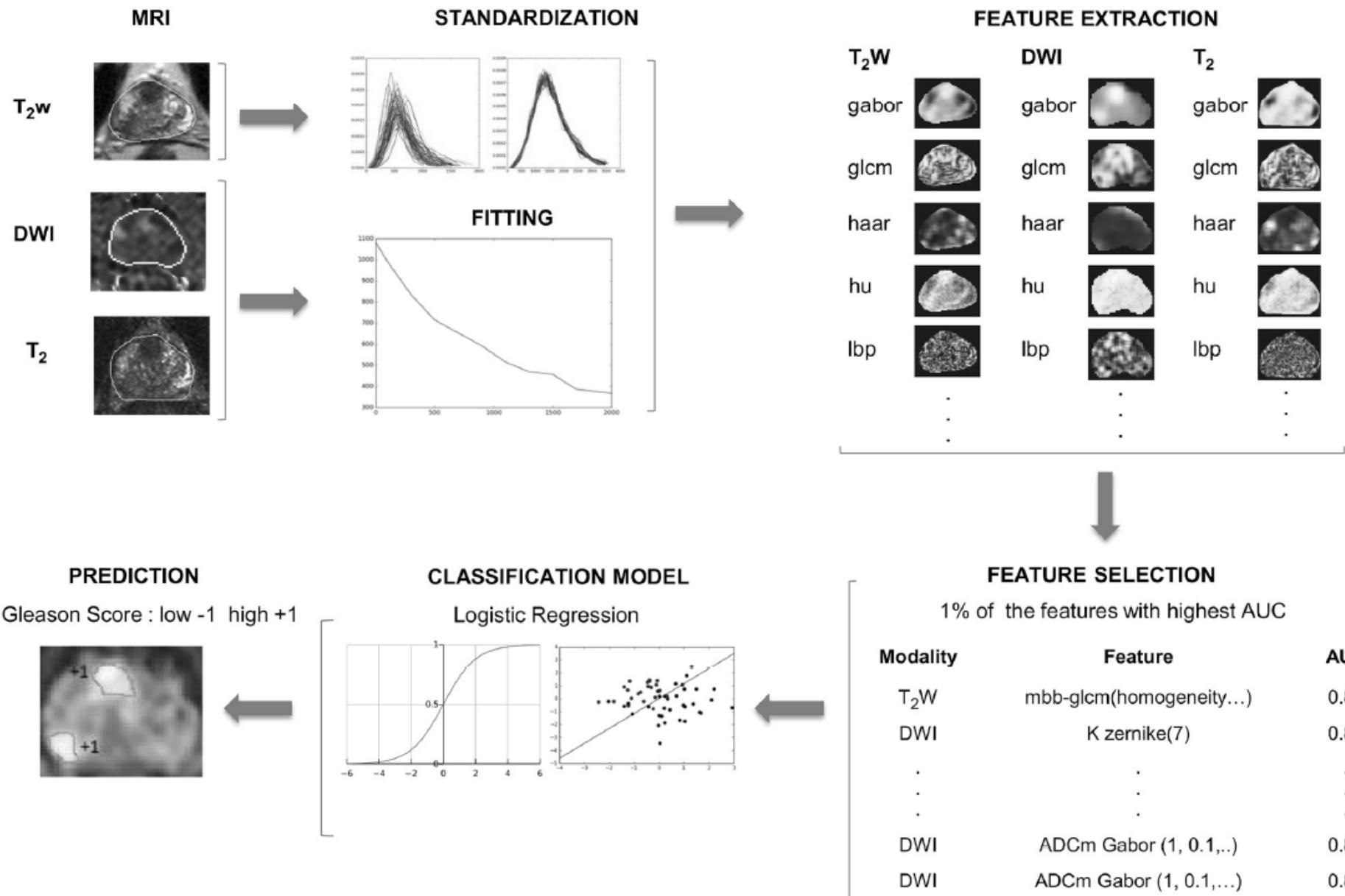


Fig 1. The pipeline. The T₂-weighted images (T₂w) are standardized, the monoexponential and kurtosis models are fitted to the diffusion weighted images (DWI), and the T₂ relaxation values are obtained using a two parameter monoexponential function. Texture features are extracted subsequently. Top 1% of the features are selected by AUC. A logistic regression model is fitted to the selected features, and is used to predict the lesion's Gleason score class.

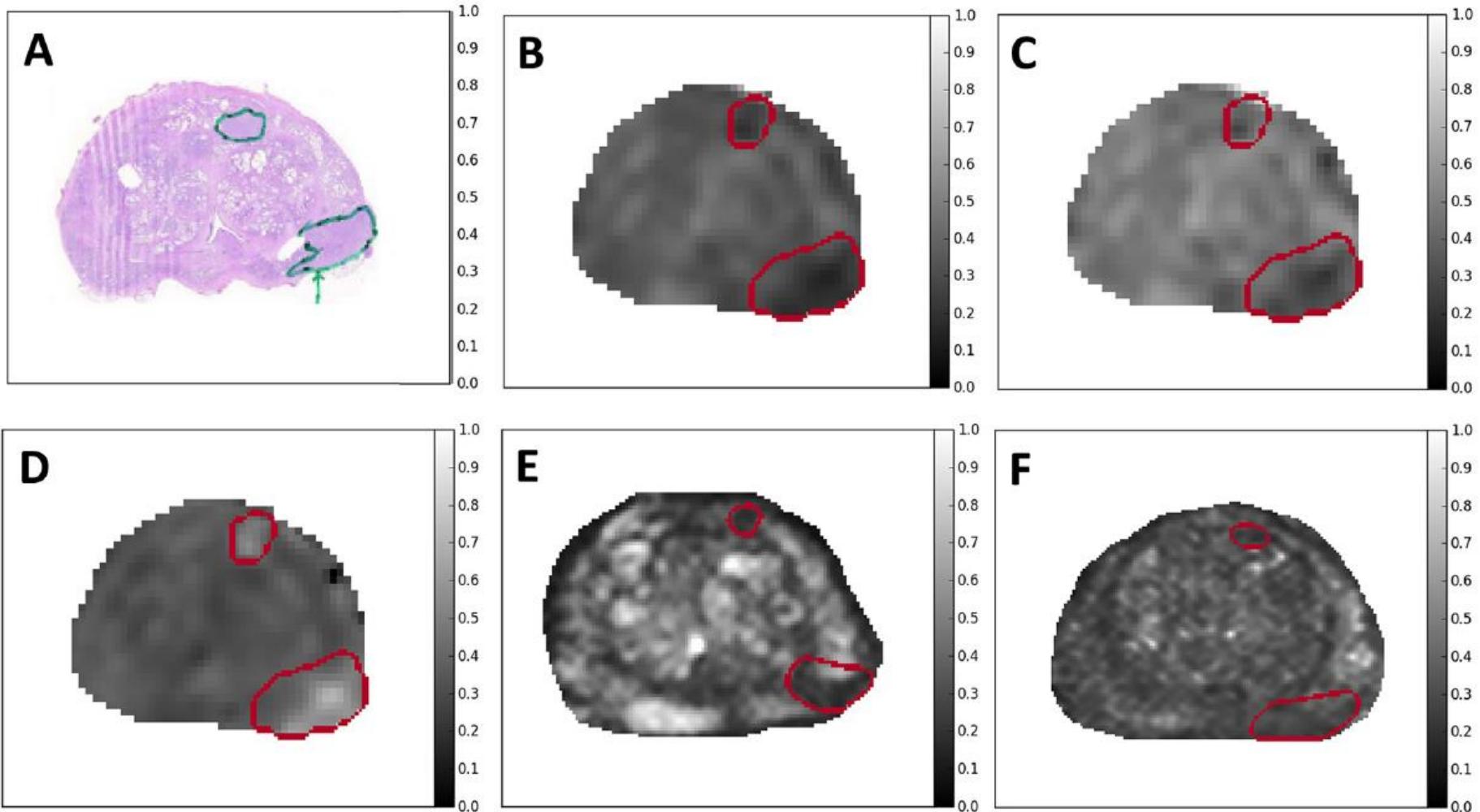


Fig 2. An example case with parametric maps. A: Whole mount prostate histological section. B: ADC_m (apparent diffusion coefficient, monoexponential model). C: ADC_m (apparent diffusion coefficient, kurtosis model). D: K (kurtosis parameter, kurtosis model). E: T₂w (T₂-weighted imaging). F: T₂ (T₂-mapping). This is from patient #43 (see Table A in [S1 File](#)). The two lesions are outlined; their Gleason scores are 4+3 (lower, posterolateral region) and 3+4 (upper, anterior region).

Results

- In total, 100 PCa lesions were analysed, of those 20 and 80 had GS of 3+3 and >3+3, respectively. The best model performance was obtained by selecting the top 1% features of T2w, ADCm and K with **ROC AUC of 0.88 (95% CI of 0.82–0.95)**. Features from T2 mapping provided little added value. The most useful texture features were based on the gray-level co-occurrence matrix, Gabor transform, and Zernike moments.

Conclusion

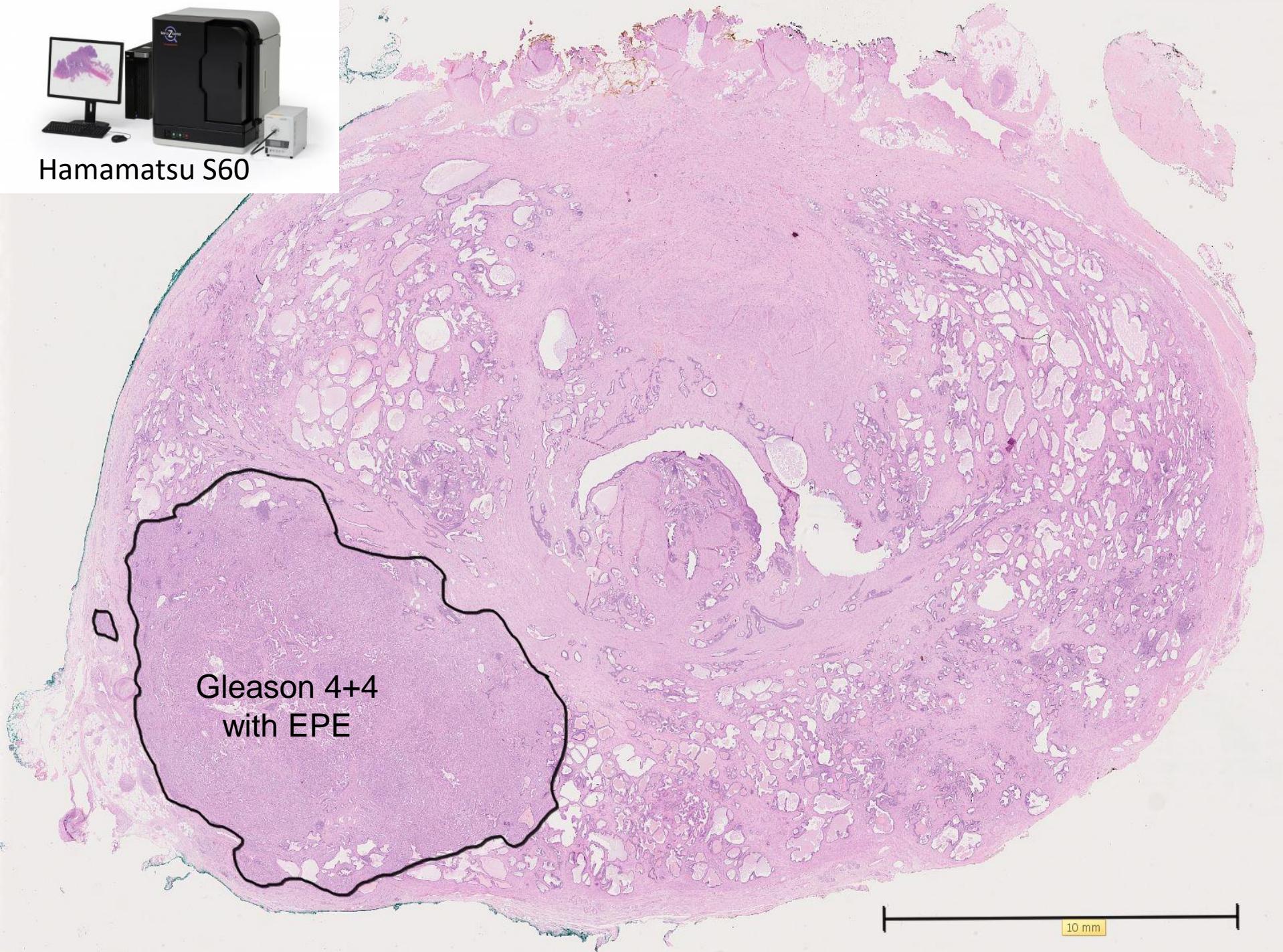
- Texture feature analysis of DWI, post-processed using monoexponential and kurtosis models, and T2w demonstrated good classification performance for GS of PCa.

How about histopathology and AI?

- Digital pathology (digitized histological slides) has enabled processing of image data from tissues, similar to radiology
- **Computer-aided detection/diagnosis (CAD)**
 - Data sets are typically labelled by an expert.
 - Image processing techniques are used to extract histological features that are deterministic in defining cancer of various grades.
 - A supervised ML technique is applied to develop a classifier that mimics the experts
 - Classifier is validated on a subset of the expert-labelled images.
- Supervized vs. unsupervised, traditional machine learning vs. deep learning
- Algorithms can/could:
 - Help pathologists in simple and labourous work (e.g measure biopsy length, determine cancer volume from annotated areas, etc.), same time and money
 - Provide new tools for diagnostics (identify cancerous lesions, predict Gleason grade)
 - Give additional data hidden from human eye (extract features predicting cancer aggressiveness, mutation signature, you name it!)



Hamamatsu S60



Gleason 4+4
with EPE

10 mm

Computerized histomorphometric features of glandular architecture predict risk of biochemical recurrence following radical prostatectomy: A multisite study.

ASCO 2019 Abstract No: 5060

Patrick Leo¹, Andrew Janowczyk¹, Robin Elliott², Nafiseh Janaki², Rakesh Shiradkar¹, Xavier Farré³, Kosj Yamoah⁵, Timothy R. Rebbeck⁶, Natalie NC Shih⁴, Francesca Khani⁷, Brian D. Robinson⁷, Lauri Eklund⁸, Otto Ettala⁹, Pekka Taimen⁸, Peter J. Boström¹⁰, Michael Feldman⁴, Sanjay Gupta^{11,12}, Priti Lal⁴, Anant Madabhushi^{1,12}

Background: Following a radical prostatectomy (RP) for prostate cancer, a patient may experience biochemical recurrence (BCR), defined as two consecutive prostate specific antigen (PSA) readings > 0.2 ng/mL. BCR is correlated with metastasis and disease specific survival. Extant molecular based companion diagnostic tests for predicting risk of BCR and disease progression tend to be expensive and tissue destructive. We sought to evaluate whether computer extracted features of glandular architecture from routine digitized H&E slides could predict post-RP BCR risk. **Methods:** RP specimens from 683 patients (184 with BCR, 499 without) with post-surgical PSA follow-up information were gathered from six sites. Median non-BCR follow-up was 3.2 years. A representative tumor area was annotated on the diagnostic H&E slide of each patient. 324 (131 BCR) patients from two sites formed the training set. The other 359 (53 BCR) patients formed the validation set. Glands were segmented by a deep learning model. 216 features describing gland arrangement, shape, and disorder were then extracted. An elastic net Cox proportional hazards model was constructed from the training set using the top 10 stable features identified via feature selection. Risk score thresholds were chosen on the training set to stratify patients into low-, medium-, or high-risk. Validation set results were evaluated by the log-rank test and hazard ratio. For the 172 (37 BCR) patients for whom Gleason grade and preoperative PSA values were available, risk classifications were compared using Cox proportional hazards regression. **Results:** Nine of the top features were gland shape features and one was a gland arrangement feature. The hazard ratio between the low- and high-risk groups on the validation set was 3.04 ($p < 0.05$). The histomorphometric classifier was predictive of BCR ($p < 0.05$, hazard ratio = 1.63) independent of Gleason grade group and preoperative PSA in multivariate testing. **Conclusions:** Computer extracted features of gland morphology can stratify post-RP patients by BCR risk. Our computerized histomorphometric model could serve as a prognostic tool in the post-RP setting.

Genetics and AI

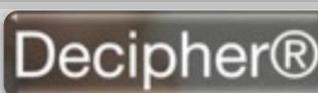
Table 1 Genes included in molecular profiling tests for prostate cancer

Cell Cycle Progression (9)	Genomic Prostate Score (10)	Genomic Classifier (11)	ProMark (12)
<i>ASFIB</i>	<i>AZGP1</i>	<i>ANO7</i>	<i>ACTN1</i>
<i>ASPM</i>	<i>BGN</i>	<i>CAMK2NI</i>	<i>CUL2</i>
<i>BIRC5</i>	<i>COL 1AI</i>	<i>EPPK1</i>	<i>DERLII</i>
<i>BUB1B</i>	<i>DUSPI</i>	<i>GLYATLIP4/PCAT-80</i>	<i>FUS</i>
<i>C18orf24</i>	<i>FAM13C</i>	<i>IQGAP3</i>	<i>HSPA9</i>
<i>CDC2</i>	<i>FLNC</i>	<i>LASP1</i>	<i>PDSS2</i>
<i>CDC20</i>	<i>FOS</i>	<i>MYBPC1</i>	<i>PLAG1</i>
<i>CDCA3</i>	<i>GSN</i>	<i>NFIB</i>	<i>pS6</i>
<i>CDCA8</i>	<i>GSTM2</i>	<i>NUSAPI</i>	<i>SMAD2</i>
<i>CDKN3</i>	<i>KLK2</i>	<i>PBX1</i>	<i>SMAD4</i>
<i>CENPF</i>	<i>LAMB3</i>	<i>PCAT-32</i>	<i>VDAC1</i>
<i>CENPM</i>	<i>SFRP4</i>	<i>PCDH7</i>	<i>YBX1</i>
<i>CEP55</i>	<i>SRD5A2</i>	<i>RABGAPI</i>	
<i>DLGAP5</i>	<i>TPM2</i>	<i>SIPR4</i>	
<i>DTL</i>	<i>TPX2</i>	<i>THBS2</i>	
<i>FOXMI</i>		<i>TNFRSF19</i>	
<i>KIAA0101</i>		<i>TSPB</i>	
<i>KIF11</i>		<i>UBE2C</i>	
<i>KIF20A</i>		<i>ZWILCH</i>	
<i>MCM10</i>			
<i>NUSAPI</i>			
<i>ORC6</i>			
<i>PBK</i>			
<i>PLKI</i>			
<i>PRCI</i>			
<i>PTTG1</i>			
<i>RAD51C RAD54L</i>			
<i>RRM2</i>			
<i>TOP2A</i>			
<i>TKI</i>			

\$4520

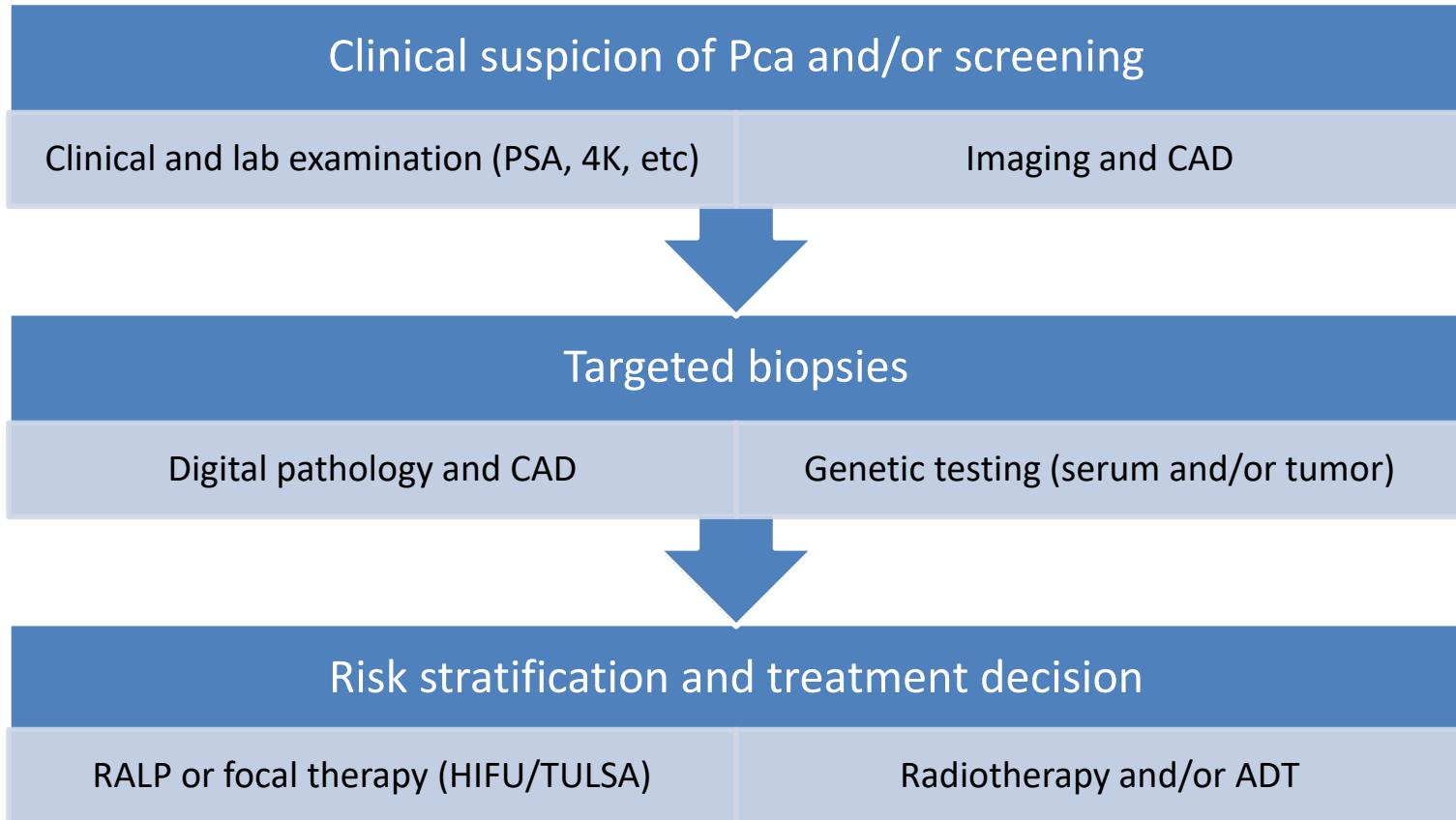
Test may produce a net cost savings by reducing the number of patients receiving treatment

Methylation Status
GSTP1
APC
RASSF1



Sternberg et al. Ann Rev Med 2016

Pca diagnostics and treatment in 2030?



Take home messages

- Tremendous potential of both feature-based and DL-based classification techniques exist. However, before implementing widely, large validation studies of algorithms developed on heterogeneous training data sets must be initiated to avoid ‘overfitting’.
- The data used must be accurate, not just adequate, so that the system does not learn from misinformation arising from technical issues such as tissue sampling, specimen preparation, slide staining, imaging variability.
- The data used and generated is huge, especially in digital pathology. Health care system in general is not ready to use such data in routine clinical practice and more resources are needed.
- Pca is VERY heterogenous disease and many patients have more than one tumor with different malignant potential. How to choose the material for various analysis?
- AI will augment — but not replace — human expertise. Diagnoses will still need to be monitored and signed off by a qualified pathologist/radiologist.

Goldenberg et al., “A new era: artificial intelligence and machine learning in prostate cancer” Nature Reviews in Urology 16:391-403, 2019