Prostate Cancer

Prof. Luigi F. Da Pozzo

Clinical case – 1

Doctor… I'm 45 years old

- My grandfather died of a prostate cancer.
- My father had surgery for prostate cancer 5 years ago (familiarity).
- I am in good health. I have no urinary symptom.

When should I start checking my prostate ?
Which checks?

Clinical case – 2

Doctor… I am 57 years old

- My PSA is 6.5 ng/mL
- I also did a transrectal ultrasound of the prostate and the radiologist reassured me: there's nothing wrong.
- I have no lower urinary tract symptoms (dysuria)

I can rest easy, can't I?

Clinical case – 3

Doctor… I am 57 years old

- My PSA is 6.5 ng/mL.
- Your colleague prescribed me a multiparametric Magnetic Resonance Imaging of the prostate and it's negative…

I can rest easy, can't I?

Clinical case – 4

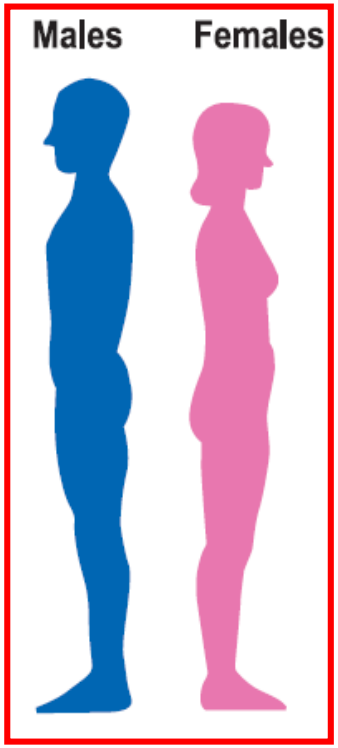
Doctor…

- I did prostate biopsies and they found me cancer.
- it's defined as a prostate adenocarcinoma Gleason 3+3, Grading Group 1.

There is no time to waste. I want to be operated as soon as possible…before it's too late.

Cancer Statistics Incidence
Prostate Cancer

1. **Prostate 19%**
2. Lung 14%
3. Colon 9%
4. Bladder 7%
5. Melanoma 6%
6. Kidney 5%



1. Breast 28%
2. Lung 14%
3. Colon 9%
4. Uterus 7%
5. Thyroid 5%
6. NH-Lymphoma 4%
7. Kidney 3%

Jemal et al. CA Cancer J Clin 2018 60(5):277-300

EPIDEMIOLOGY
INCIDENCE

	Common Types of Cancer	Estimated New Cases 2018	Estimated Deaths 2018
1.	Breast Cancer (Female)	266,120	40,920
2.	Lung and Bronchus Cancer	234,030	154,050
3.	**Prostate Cancer**	**164,690**	**29,430**
4.	Colorectal Cancer	140,250	50,630
5.	Melanoma of the Skin	91,270	9,320
6.	Bladder Cancer	81,190	17,240
7.	Non-Hodgkin Lymphoma	74,680	19,910
8.	Kidney and Renal Pelvis Cancer	65,340	14,970
9.	Uterine Cancer	63,230	11,350
10.	Leukemia	60,300	24,370

Prostate cancer represents 9.5% of all new cancer cases in the U.S.

20% of all new cases in **men** in the U.S.

https://seer.cancer.gov/statfacts/html/prost.html

EPIDEMIOLOGY
INCIDENCE

- Most frequent solid cancer in men.
- Incidence increases with age from 45-50 years.
- Nearly 11.2% of men will be diagnosed with prostate cancer during their lifetime.
- Microscopic foci of adenocarcinoma are found in more than 60% of autopsies in men older than 80 years

EPIDEMIOLOGY
MORTALITY

Estimated New Cases

Males

Prostate	164,690	19%
Lung & bronchus	121,680	14%
Colon & rectum	75,610	9%
Urinary bladder	62,380	7%
Melanoma of the skin	55,150	6%
Kidney & renal pelvis	42,680	5%
Non-Hodgkin lymphoma	41,730	5%
Oral cavity & pharynx	37,160	4%
Leukemia	35,030	4%
Liver & intrahepatic bile duct	30,610	4%
All Sites	**856,370**	**100%**

Estimated Deaths

Males

Lung & bronchus	83,550	26%
Prostate	29,430	9%
Colon & rectum	27,390	8%
Pancreas	23,020	7%
Liver & intrahepatic bile duct	20,540	6%
Leukemia	14,270	4%
Esophagus	12,850	4%
Urinary bladder	12,520	4%
Non-Hodgkin lymphoma	11,510	4%
Kidney & renal pelvis	10,010	3%
All Sites	**323,630**	**100%**

Siegel et al. CA Cancer J Clin 2018

EPIDEMIOLOGY
LIFE EXPECTANCY

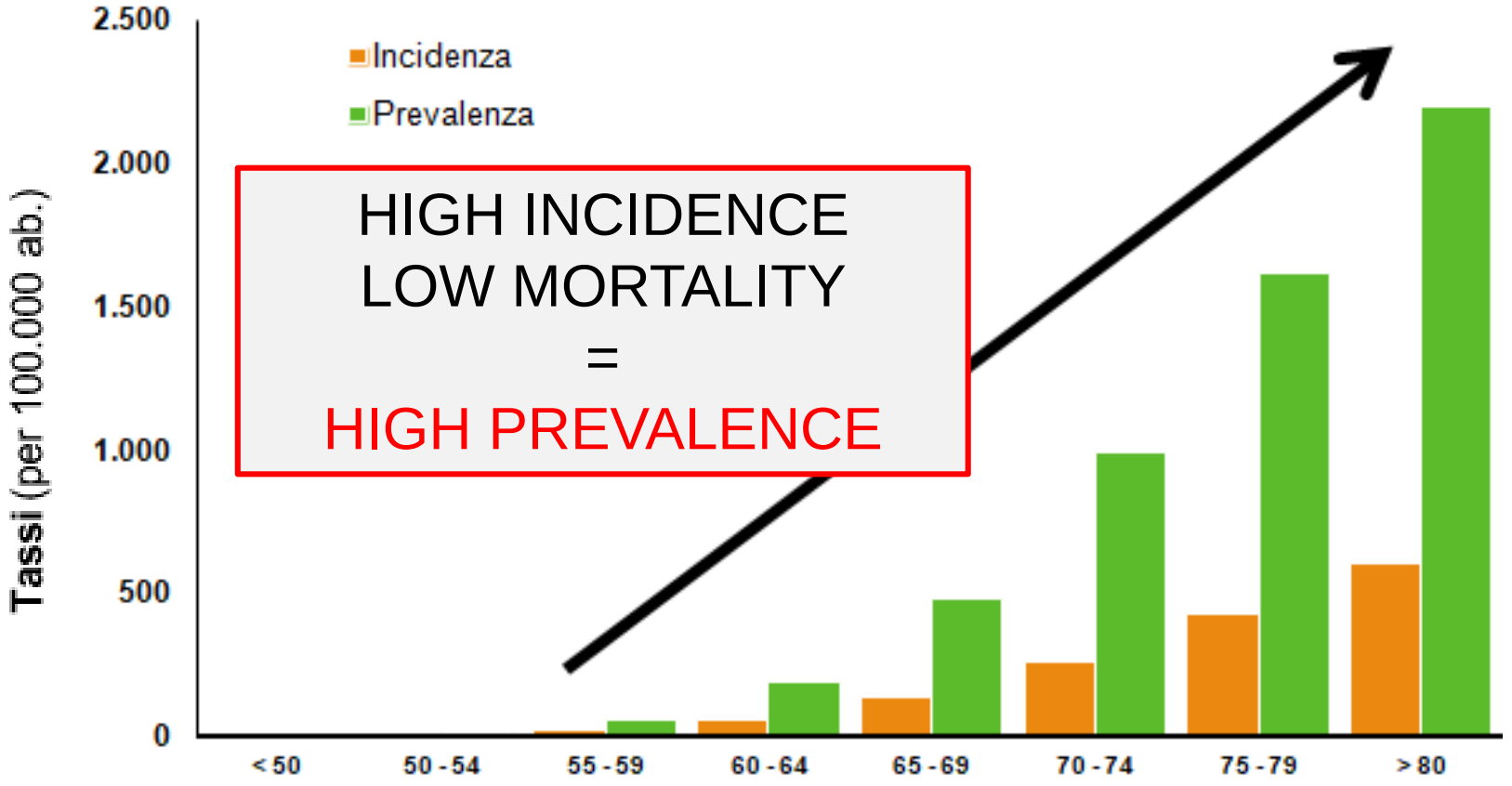
Estimated New Cases in 2018	164,690
% of All New Cancer Cases	9.5%

Estimated Deaths in 2018	29,430
% of All Cancer Deaths	4.8%

Percent Surviving 5 Years
98.2%
2008-2014

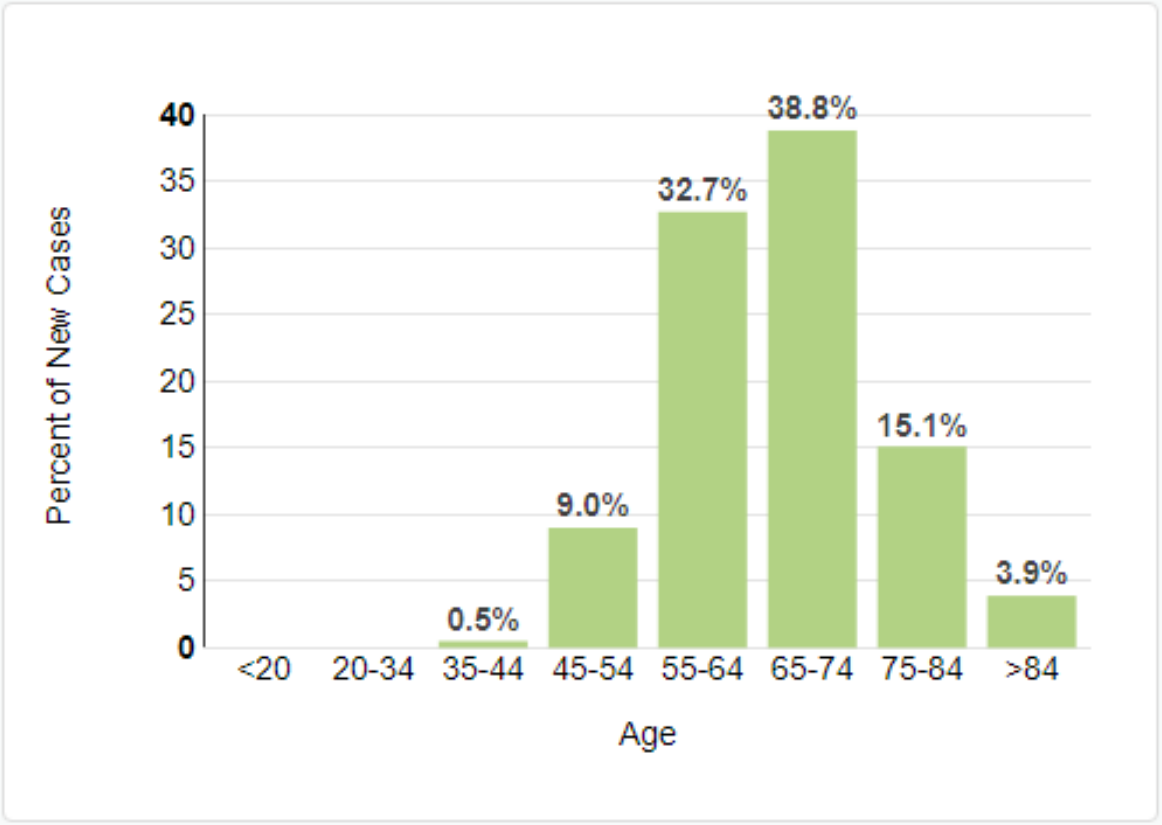
https://seer.cancer.gov/statfacts/html/prost.html

EPIDEMIOLOGY
PREVALENCE



INCIDENCE AND PREVALENCE OF PROSTATE CANCER BY AGE, IN ITALY

EPIDEMIOLOGY

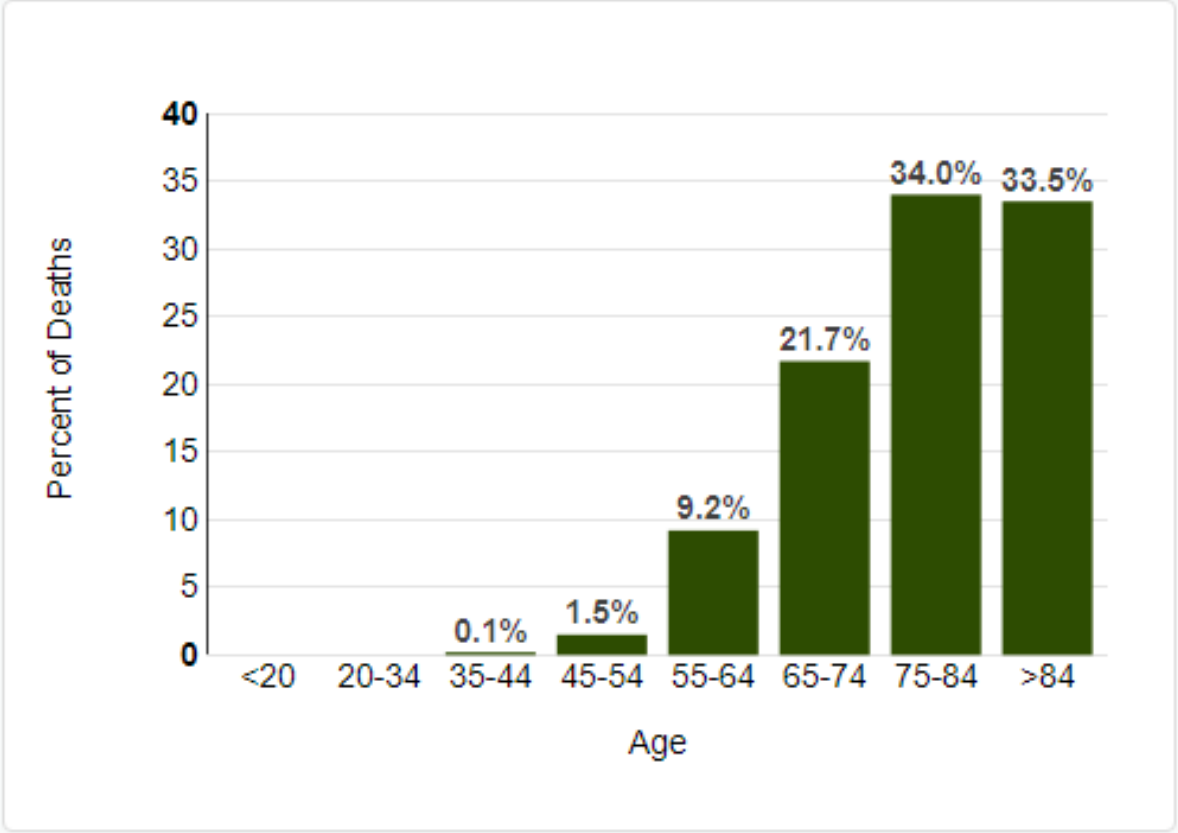


Prostate cancer is most frequently diagnosed among men aged 65-74.

Median Age At Diagnosis
66

https://seer.cancer.gov/statfacts/html/prost.html

EPIDEMIOLOGY



The percent of prostate cancer deaths is highest among men aged 75-84.

Median Age At Death

80

.... and a large number of patients affected by prostate cancer do not die for it.

https://seer.cancer.gov/statfacts/html/prost.html

RISK FACTORS

Age	
Hormonal factors	**(testosterone)**
Genetic factors	**(familiarity)**
Phenotipe	**(African descent)**
Dietary factors	**(animal fat, smoke)**
Occupational factors	**(exposure to cadmium)**

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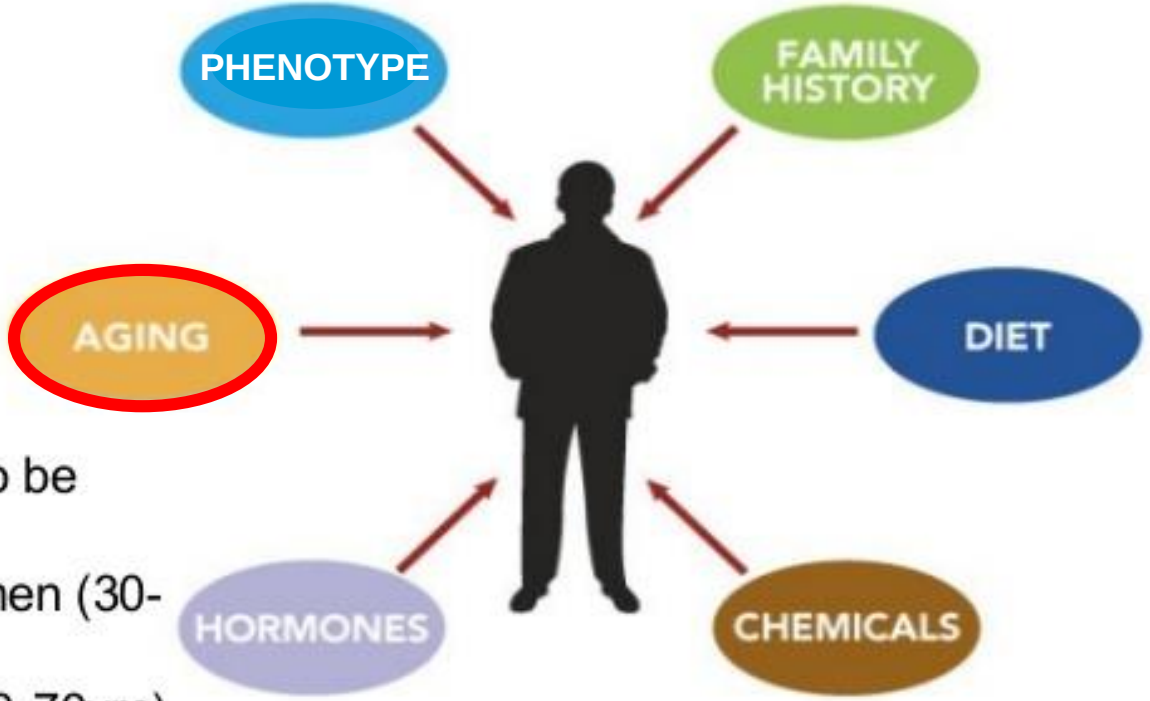
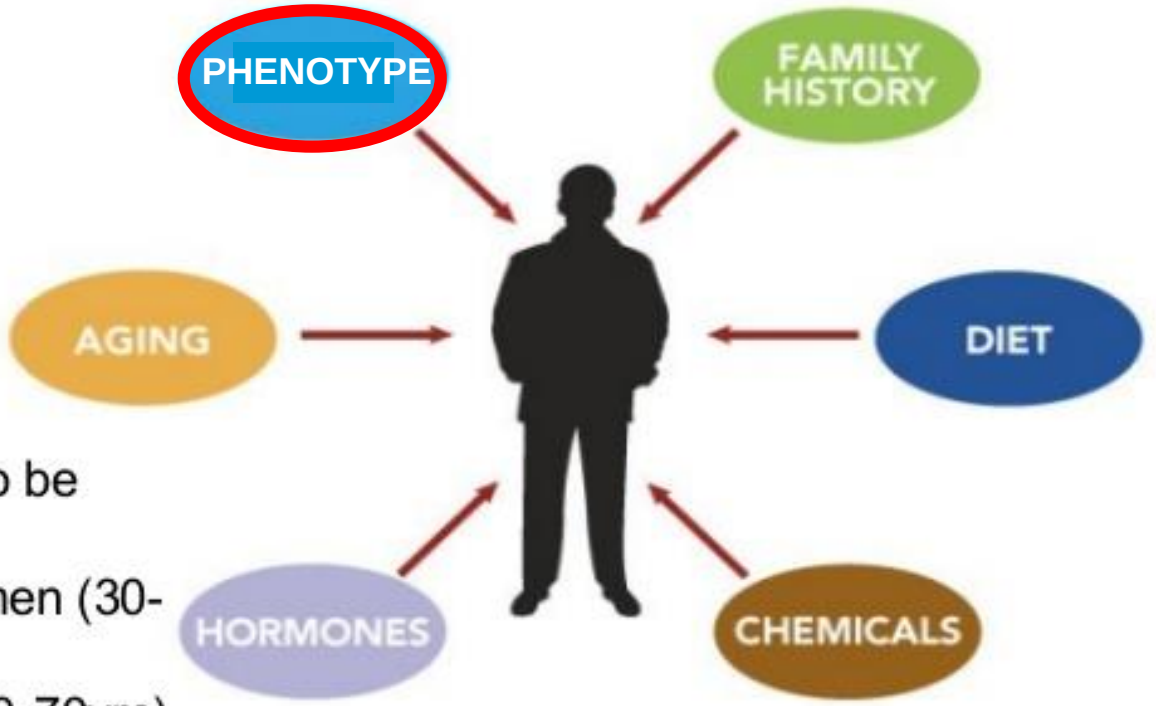
Risk Factors to Prostate Cancer



It is estimated to be found in

- Up to 29% of men (30-40yrs)
- 64% of men (60-70yrs)
- in almost all men over the age of 90

Risk Factors to Prostate Cancer



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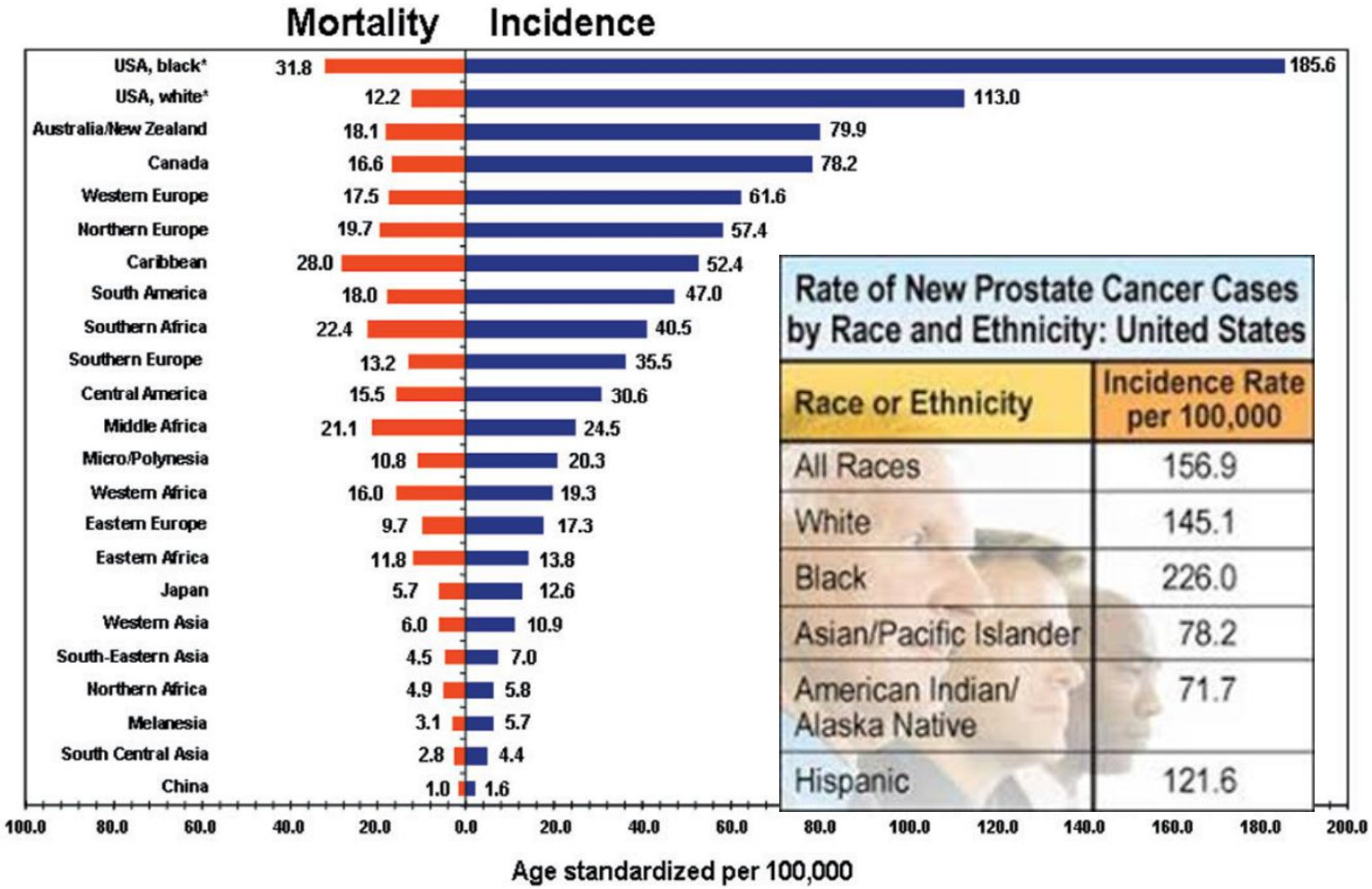
Premise: There are no different races within the *homo sapiens species* but only different phenotypes

RISK FACTORS

Phenotype and Ethnicity



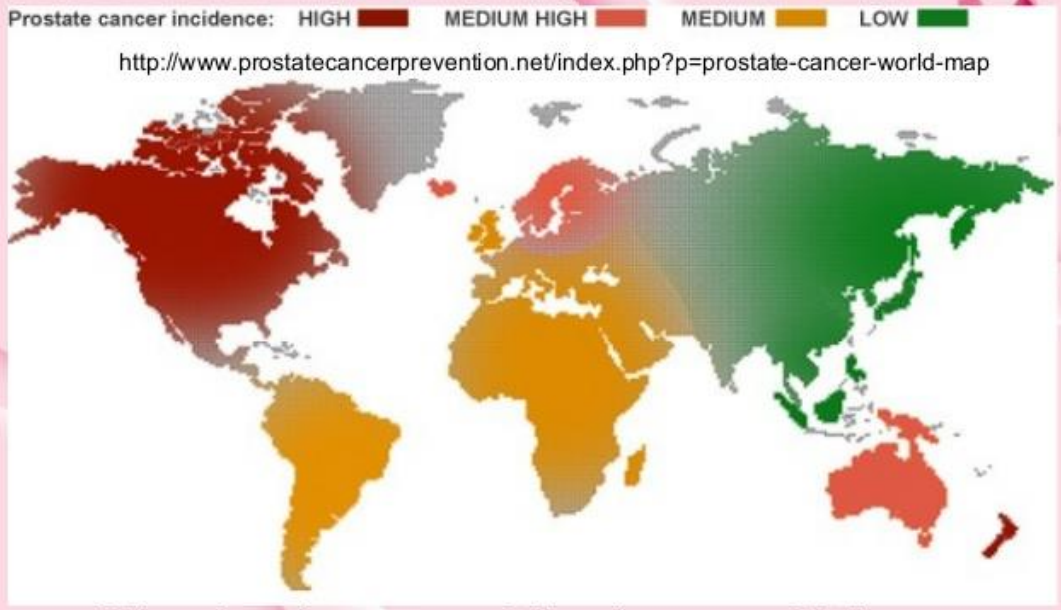
Rate of New Prostate Cancer Cases by Race and Ethnicity: United States

Race or Ethnicity	Incidence Rate per 100,000
All Races	156.9
White	145.1
Black	226.0
Asian/Pacific Islander	78.2
American Indian/ Alaska Native	71.7
Hispanic	121.6

RISK FACTORS

Geophraphic Distributon

Racial difference and risk for Prostate Cancer



- African-American men and Jamaican men of African ancestry have the highest risk and are likely to be diagnosed at an advanced stage.

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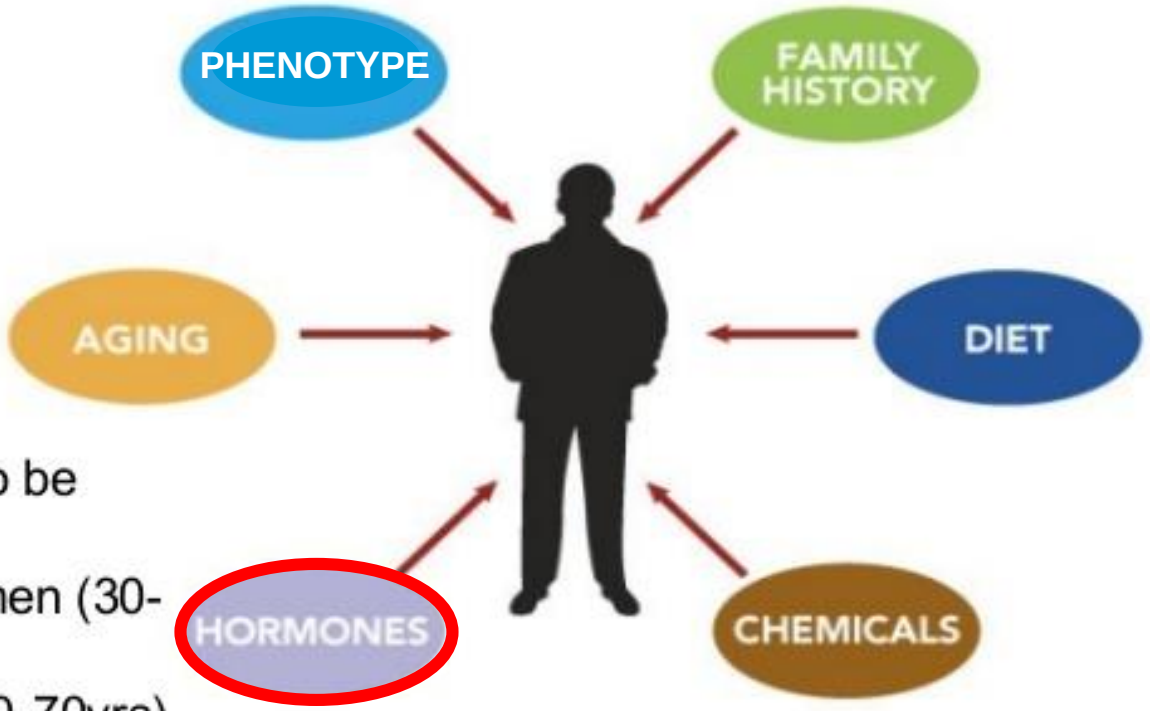

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HORMONAL FACTORS

There is evidence in the literature that sex steroid hormones, especially androgens, play a role in the etiology and pathogenesis of prostate cancer

Gann PH, et al. J Natl Cancer Inst, 88:1118-26, 1996
Carter HB, et al. Prostate, 27:25-31, 1995
Eaton NE, et al. Br J Cancer, 80:930-4, 1999
Garcia JM, et al. Cancer, 106:2583-91, 2006

In fact, sex hormones are involved in prostate carcinogenesis and it seems that they modulate cell growth by altering the balance between cell proliferation and apoptosis

Yuen MT, et al. Int J Oncol, 27:1685-95, 2005
Webber MM, et al. Prostate, 30:58-64, 1997

Urol Oncol. 2016 Nov;34(11):482.e1-482.e4. doi: 10.1016/j.urolonc.2016.05.023. Epub 2016 Jul 14.

The testosterone conundrum: The putative relationship between testosterone levels and prostate cancer.

Loughlin KR[1].

Abstract

Background: The controversy surrounding the relationship between testosterone and prostate cancer has existed for decades. The literature surrounding this topic is confusing and at times contradictory. There is no level-one quality evidence that confirms or refutes the relationship between either high or low serum testosterone levels and the subsequent development of prostate cancer. This commentary aims to review the issues involved and to provide an interpretation as to the causes of the confusion and to provide a framework for ongoing discussion and investigation.

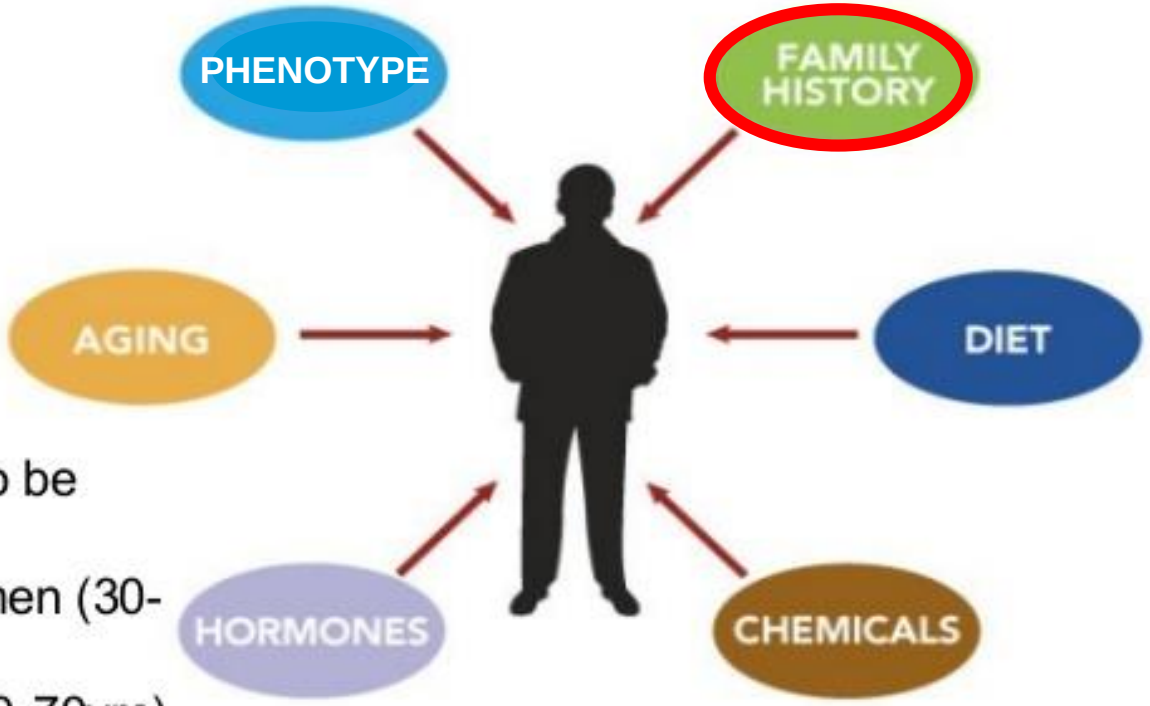
Materials and methods: A Medline and PubMed search was conducted using search terms: testosterone levels and prostate cancer to identify pertinent literature.

Results: There is no consistent evidence that a single testosterone level is predictive of prostate cancer risk.

Conclusion: The development of prostate cancer is a complex biologic process potentially involving genetics,dietary, life style and hormonal factors. Serum testosterone levels do not accurately reflect the internal prostatic milieu. Finally, if testosterone levels are to be considered in the etiology of prostate cancer they should be measured and interpreted on a chronic basis with multiple measurements over a period of years.

Serum testosterone levels are not directly associated with an increased risk of prostate cancer

Risk Factors to Prostate Cancer



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Hereditary and genetic factors

- ✓ Only a small subpopulation of men with prostate cancer (~9%) has true hereditary disease.
- ✓ The risk of prostate cancer is higher in relatives of affected men.

Positive family history is an important prognostic information useful for genetic clinical counseling and can lead to the adoption of preventive measures for high-risk men

Family history and Prostate Cancer

FAMILY HISTORY	RELATIVE RISK	95% CONFIDENCE INTERVAL
None	1	
Father affected	2.17	1.90-2.49
Brother affected	3.37	2.97-3.83
First-degree family member affected, age less than 65 years at diagnosis	3.34	2.64-4.23
Greater than two first-degree relatives affected	5.08	3.31-7.79
Second-degree relative affected	1.68	1.07-2.64

Men with first-degree relatives with prostate cancer have an increased risk of two to five times that of the general population.

Family history and Prostate Cancer

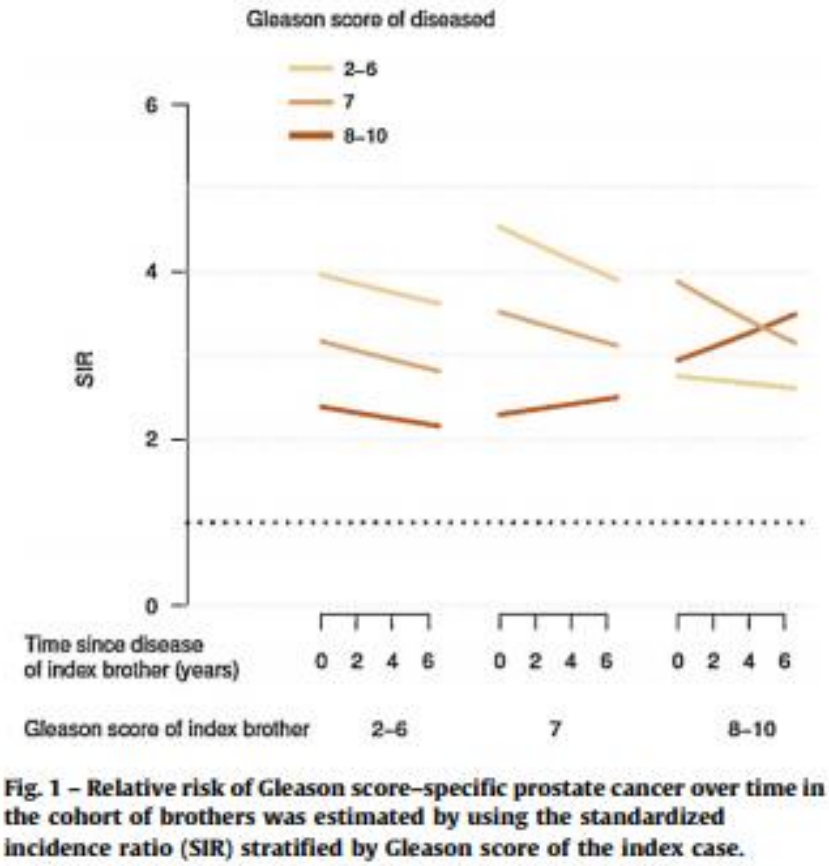


Fig. 1 – Relative risk of Gleason score–specific prostate cancer over time in the cohort of brothers was estimated by using the standardized incidence ratio (SIR) stratified by Gleason score of the index case.

Brothers or sons of men with high-grade sancer have a higher risk of developing a high-grade prostate cancer.

Counseling and Earlier screening

Jansson KF et al, Eur Urol 2012

Hereditary and genetic factors

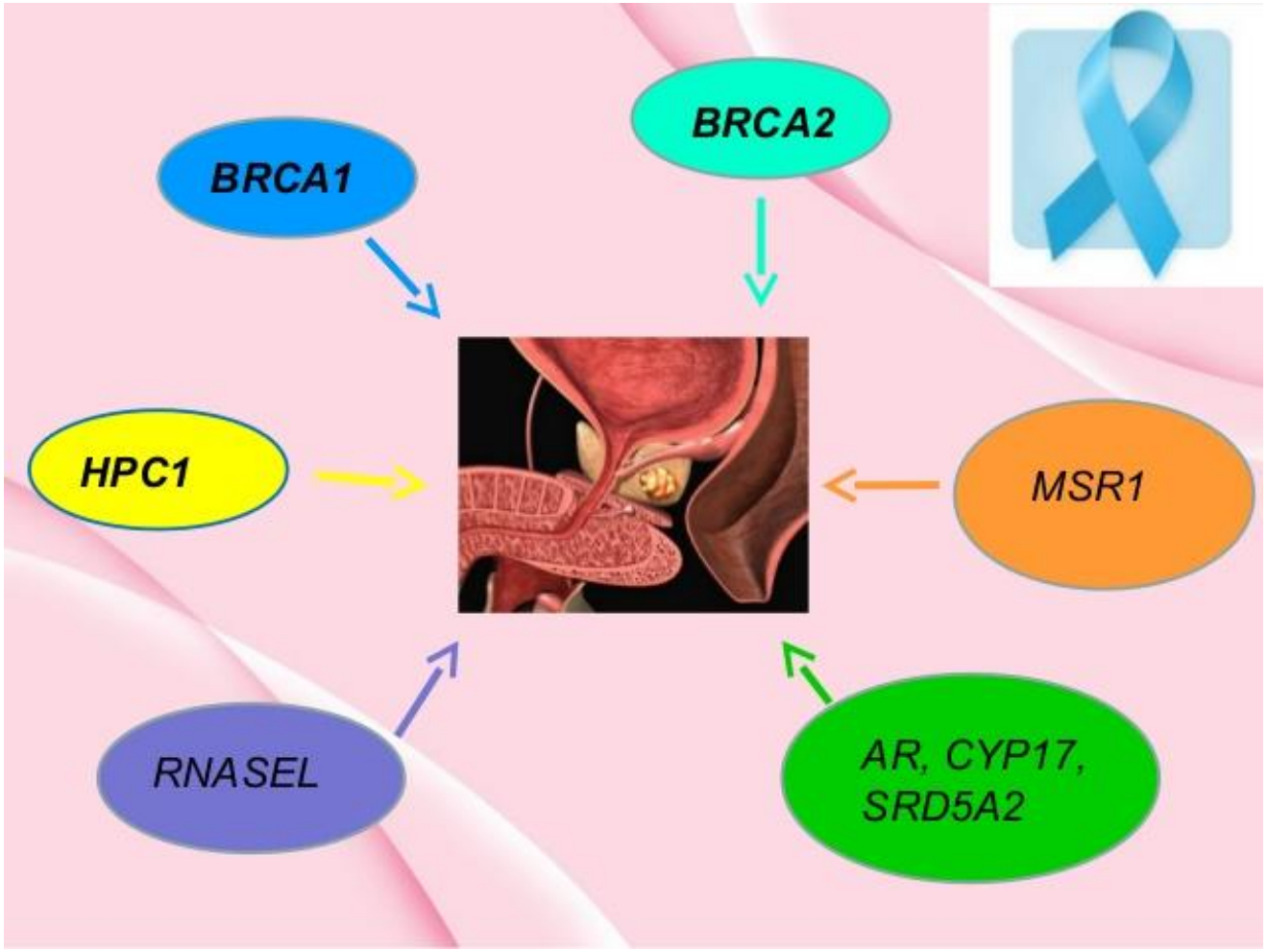
It is estimated that **9% of prostate cancers are hereditary forms:**

- ✓ The onco-soppressor genes BRCA1 and BRCA2, involved in the pathogenesis of breast cancer, seem to play an important role in the development of prostate cancer, and mutations in these genes increase the risk of prostate cancer.

- ✓ Mutations in onco-suppressor genes are often associated with more aggressive forms of prostate cancer.

Powell IJ et al Arch Esp Urol 2011
Hemminki K. Word J Urol 2012
Sinclair CS et al. Cancer Research 2000.

Hereditary and genetic factors



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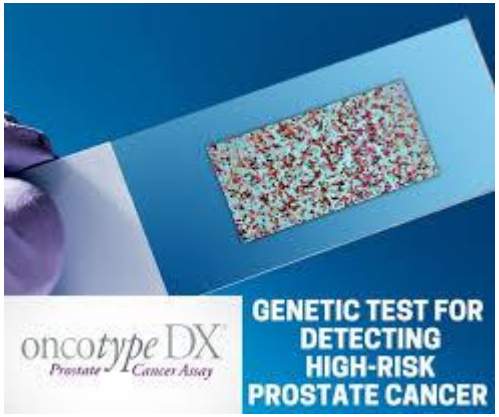

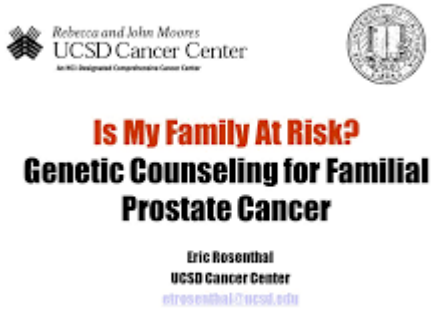

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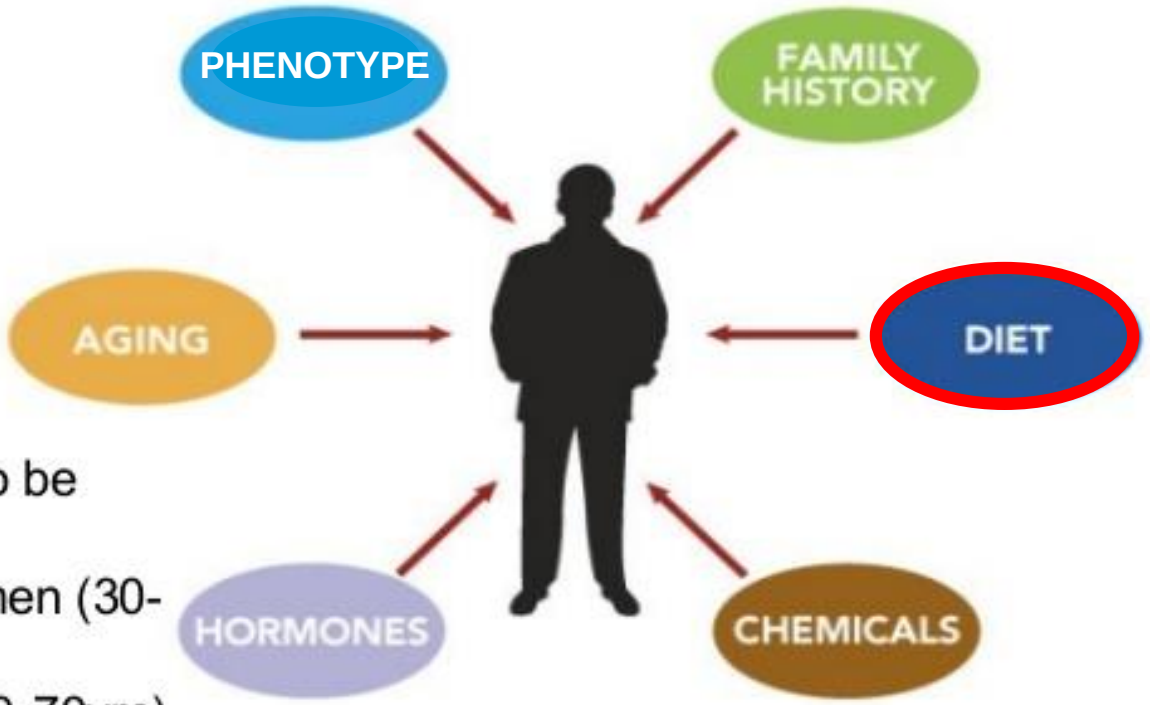

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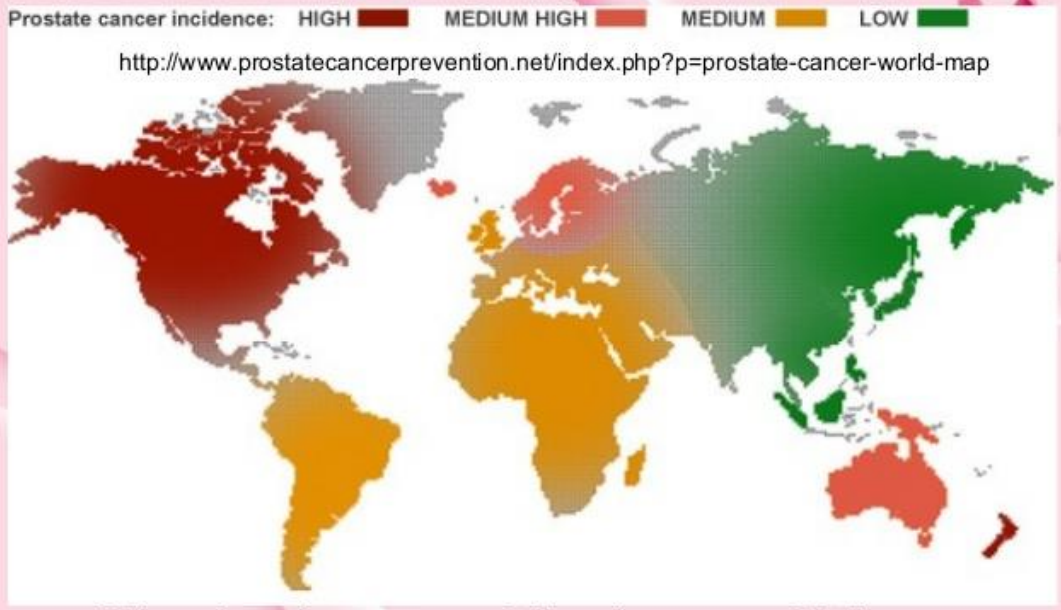

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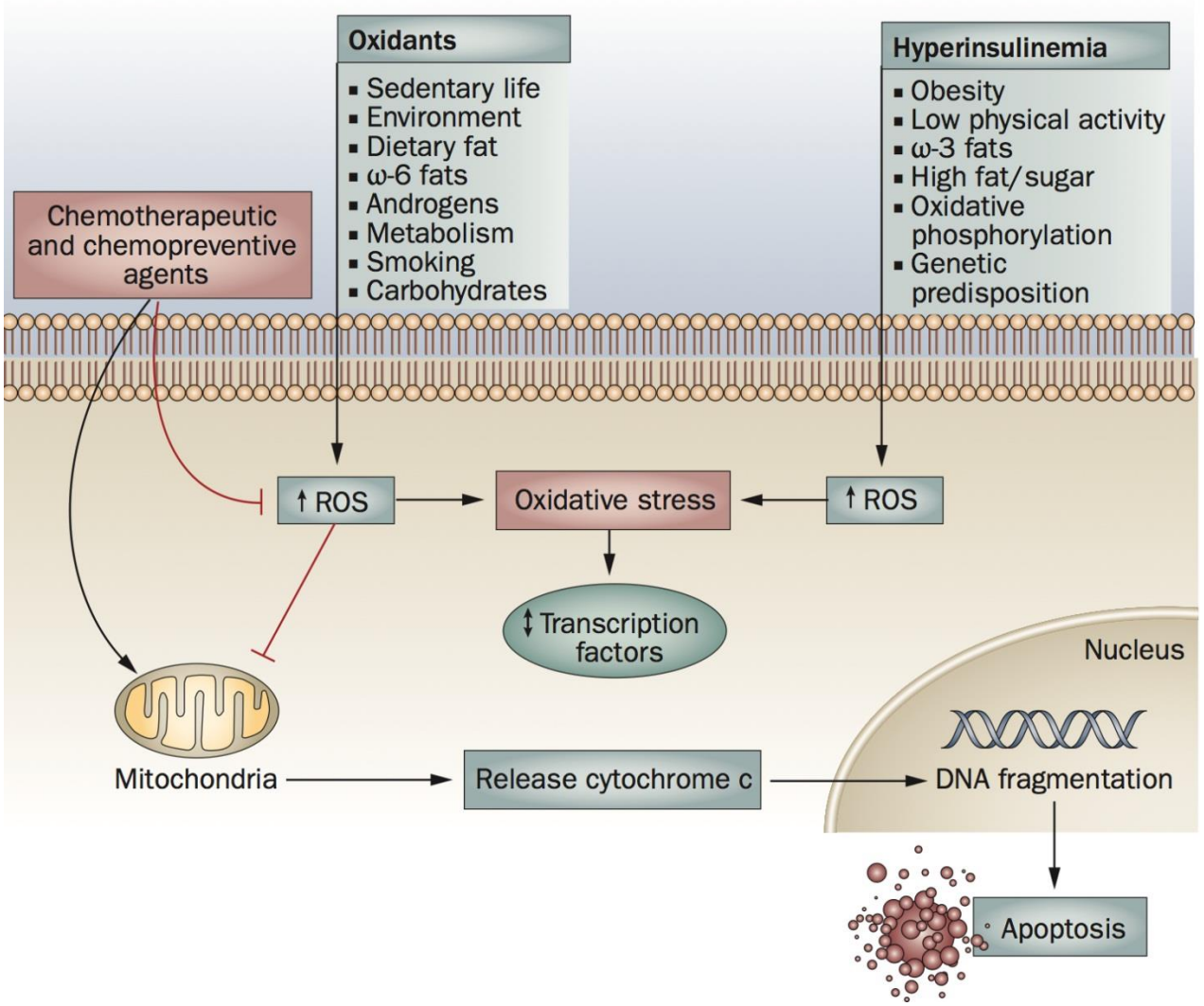
Dietary factors



Dietary factors

no definitive conclusions can be drawn for those seeking answers in this important topic.

Table 3.1: Dietary factors that have been associated with PCa

Alcohol	High alcohol intake, but also total abstention from alcohol has been associated with a higher risk of PCa and PCa-specific mortality [34]. A meta-analysis shows a dose-response relationship with PCa [35].
Dairy ↑	Dairy products such as milk, butter, cheese
Fat ↑	High total fat intake
Lycopenes (carotenes) ↓	A trend towards a favourable effect of lycopene on PCa incidence has been identified in meta-analyses [39]. Randomised controlled trials comparing lycopene with placebo did not identify a significant decrease in the incidence of PCa [40].
Meat ↑	Increased meat intake
Phytoestrogens	Phytoestrogen intake was significantly associated with a reduced risk of PCa in a meta-analysis [42].
Vitamin D	A U-shaped association has been observed, with both low- and high vitamin-D concentrations being associated with an increased risk of PCa, and more strongly for high-grade disease [43, 44].
Vitamin E/Selenium ↓	An inverse association of blood, but mainly nail selenium levels (reflecting long-term exposure) with aggressive PCa have been found [45, 46]. Selenium and Vitamin E supplementation were, however, found not to affect PCa incidence [47].

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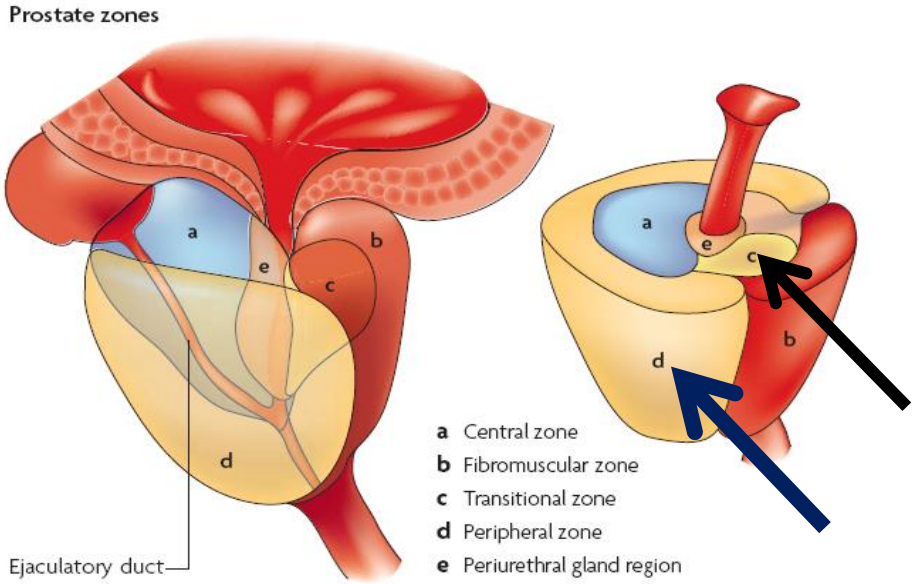
Protective factors

- ✓Reduction of protein and fat intake
- ✓Increased consumption of lycopene, soybeans, tomatoes
- ✓Vitamin E
- ✓Green tea (antioxidant flavonoids)

Anatomical location of Prostate Cancer



	Prostate zone		
	Peripheral	Transition	Central
Focal atrophy			
Acute inflammation			
Chronic inflammation			
Benign prostatic hyperplasia			
High-grade PIN			
Carcinoma			

High prevalence
Medium-high prevalence
Low prevalence
None

- Most **cancers** are located in the **peripheral zone of the gland**, a small part in the transition area while those of the central area are very rare.

- **Benign Prostate Hyperplasia** , on the other hand, develops in the **transition zone** which can be considerably increased

De Marzo et al. Nat Rev Cancer. 2007;7:256-69

Histology

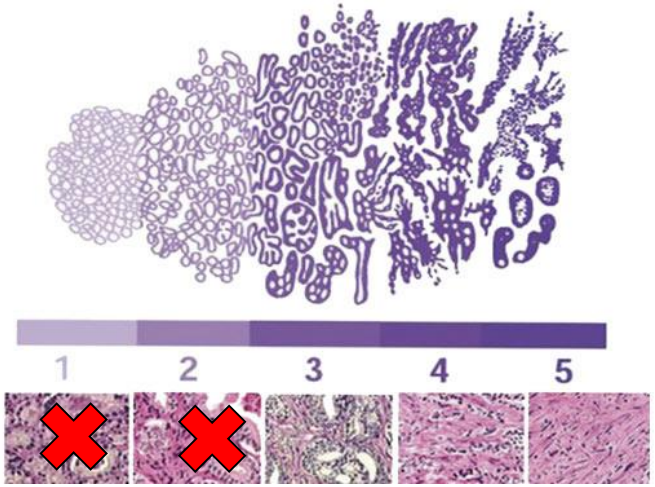
Epithelial origin

- 95% Adenocarcinoma secretory columnar cells of the ducts and acini
- 5% Transitional cell carcinoma (90%) Neuroendocrine carcinoma (serotonin cells)

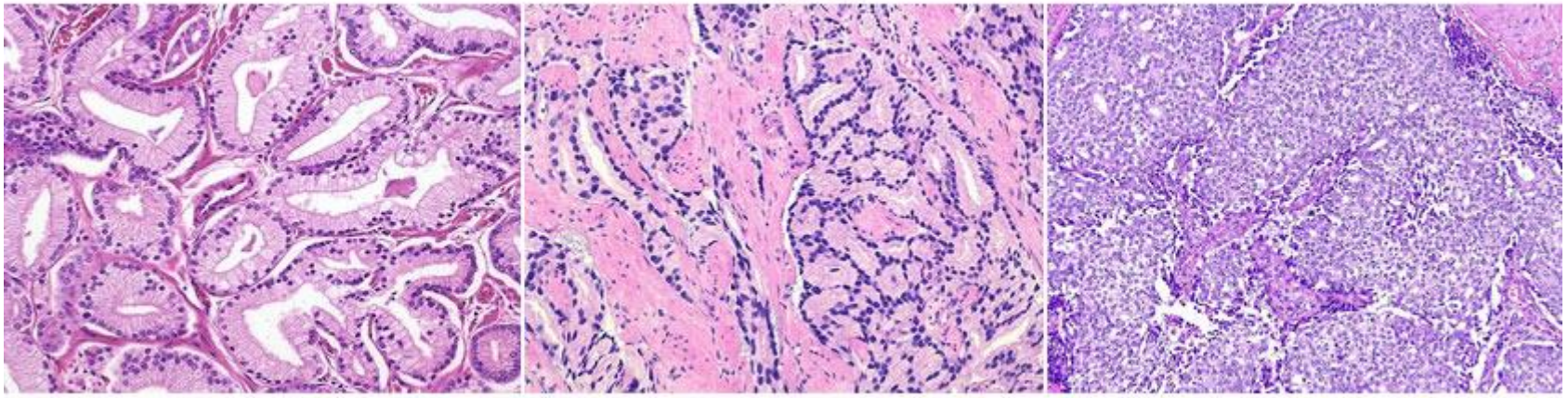
Stromal origin (rare)

- Rhabdomyosarcoma: higher incidence in <10 years old
- Leiomiosarcoma: higher incidence in >40 years old

Prostate adenocarcinoma
Grading: Gleason classification



GLEASON

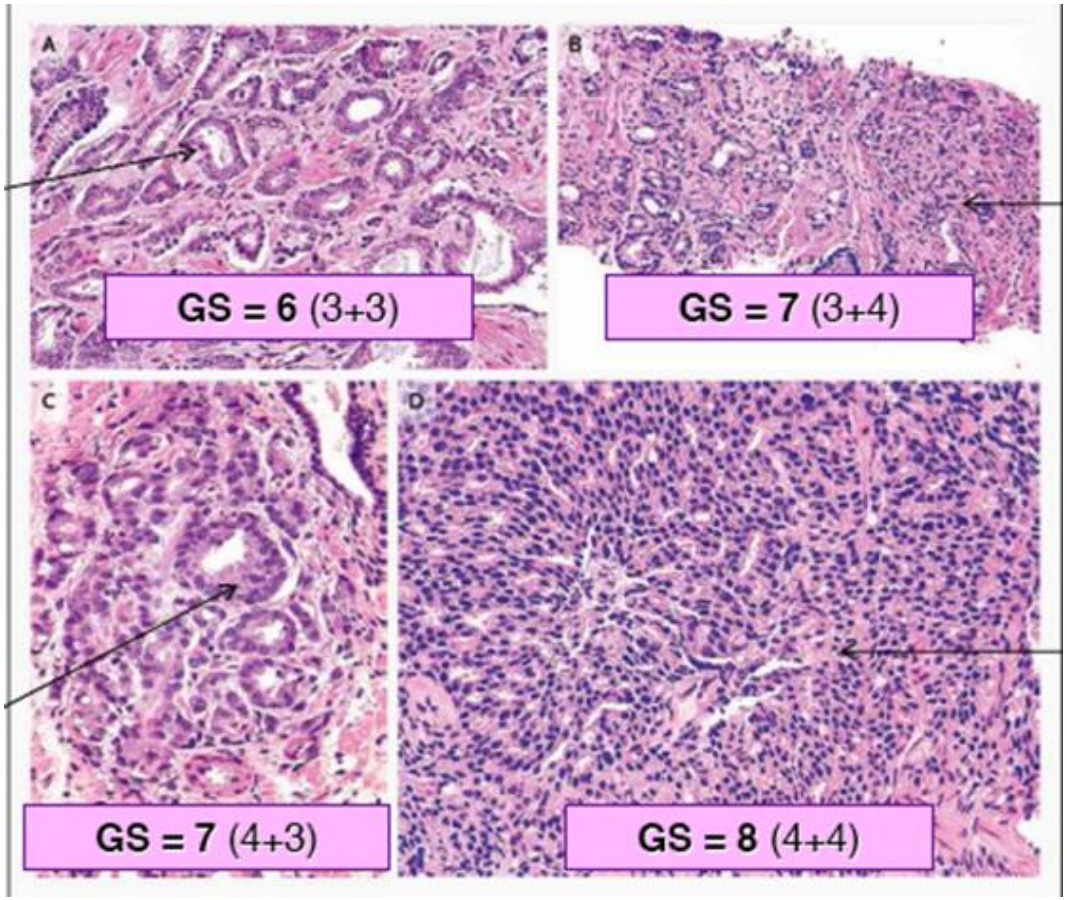


Pattern 3 | Pattern 4 | Pattern 5

PROSTATE CANCERS are always a mosaic combination of the three patterns

Prostate adenocarcinoma
Grading: Gleason classification

GLEASON SCORE
Primary pattern + Secondary pattern



2016 WHO GU Classification

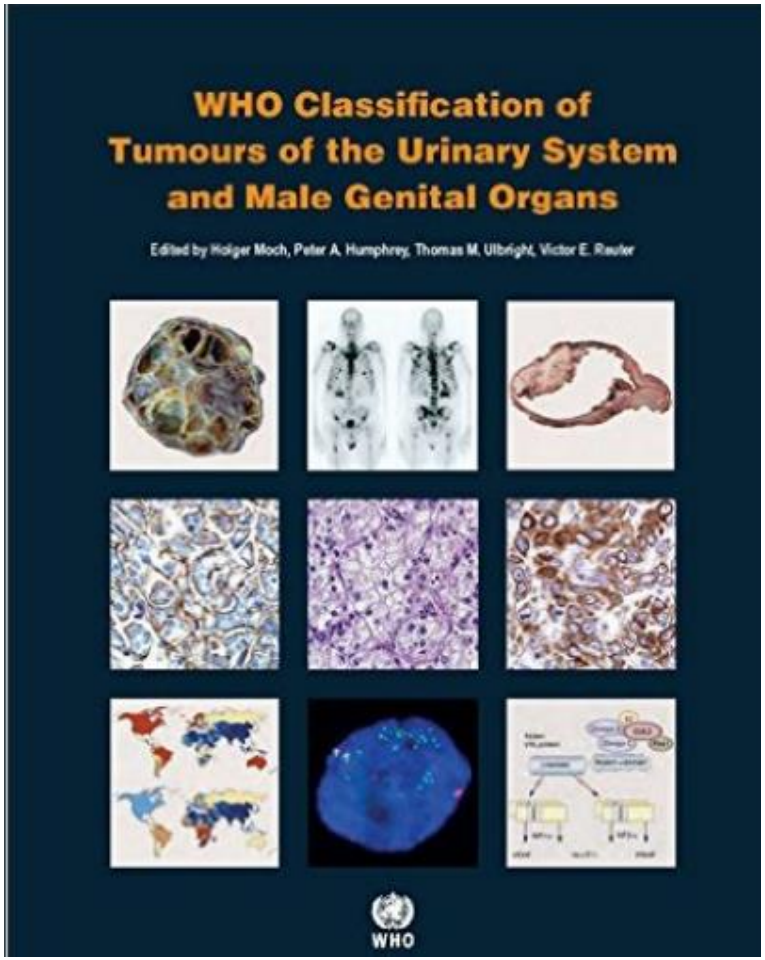
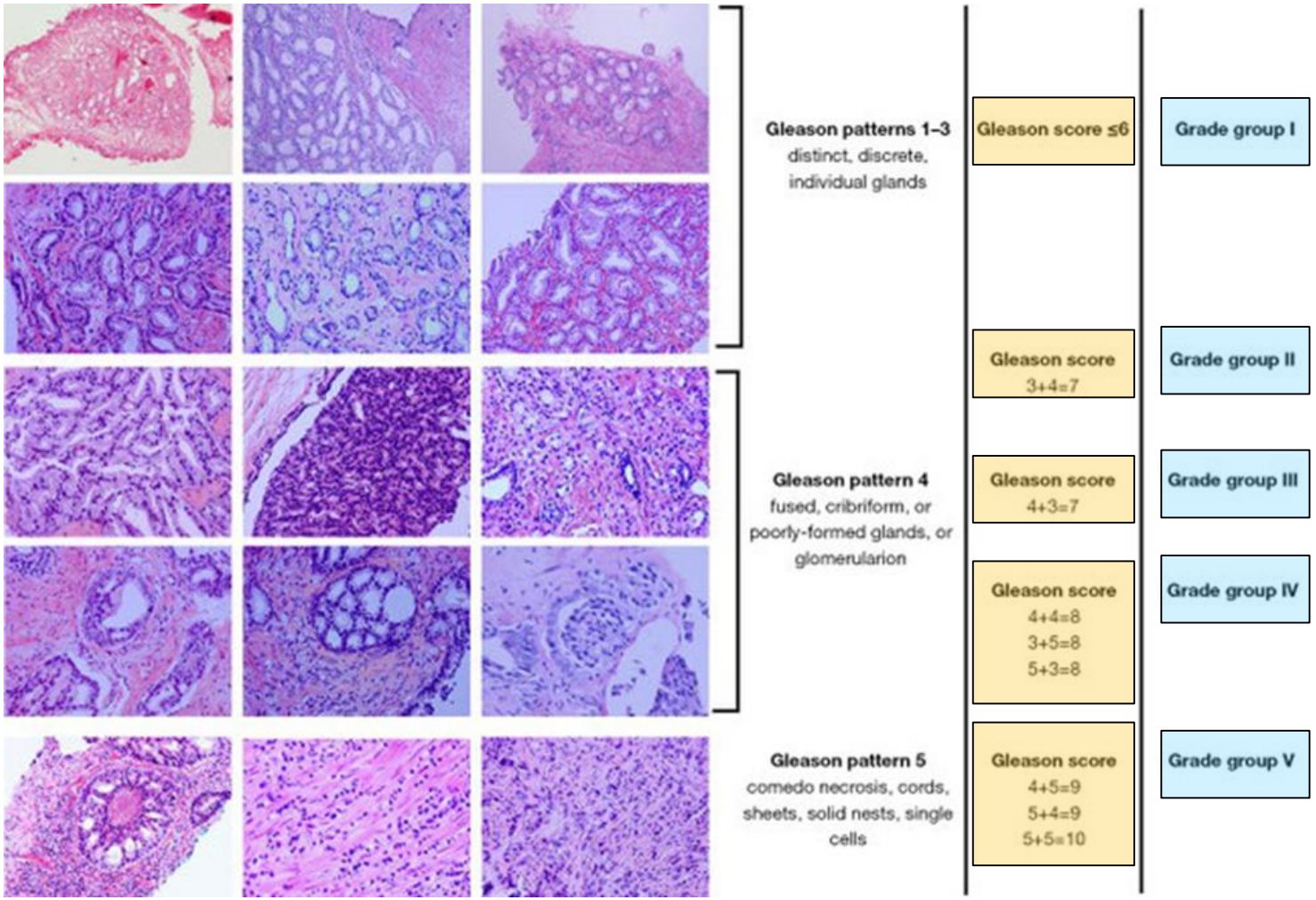


Table 3.03
Grade group 1: Gleason score ≤ 6 Only individual discrete well-formed glands
Grade group 2: Gleason score 3+4=7 Predominantly well-formed glands with lesser component of poorly formed / fused / cribriform glands
Grade group 3: Gleason score 4+3=7 Predominantly poorly formed / fused / cribriform glands with lesser component of well-formed glands
Grade group 4: Gleason score 4+4=8; 3+5=8; 5+3=8 Only poorly formed / fused / cribriform glands Predominantly well-formed glands and lesser component lacking glands Predominantly lacking glands and lesser component of well-formed glands
Grade group 5: Gleason scores 9-10 Lack gland formation (or with necrosis) with or without poorly formed / fused / cribriform glands

Prostate adenocarcinoma
Grading: WHO classification



NATURAL HISTORY OF PROSTATE CANCER

TNM

T - Primary Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	
	T1c Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen [PSA])
T2	Tumour that is palpable and confined within the prostate
	T2a Tumour involves one half of one lobe or less
	T2b Tumour involves more than half of one lobe, but not both lobes
	T2c Tumour involves both lobes
T3	Tumour extends through the prostatic capsule*
	T3a Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
	T3b Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall
N - Regional Lymph Nodes[1]	
NX	
N0	
N1	
M - Distant Metastasis[2]	
M0	No distant metastasis
M1	
	M1b Bone(s)
	M1c Other site(s)

T = local extension

N = nodal extension of a tumor

M = metastatic visceral extension of a tumor

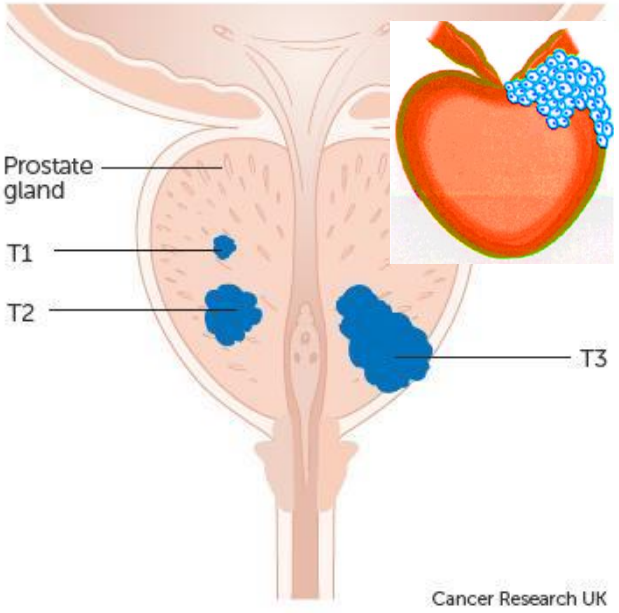
TNM classification (Clinical or Pathological)
Local extension

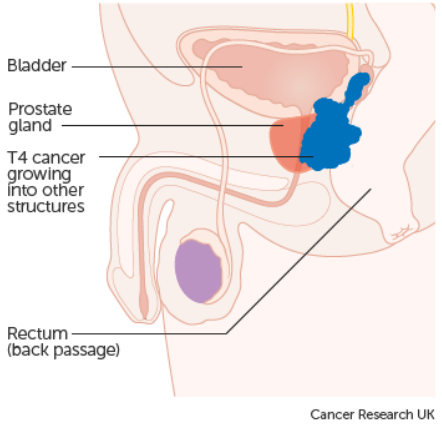
T1 stage (only clinical)
T1a-T1b incidental histological finding after TURP
T1c tumor not visible at MRI and not palpable at digital rectal examination

T2 stage (clinical) tumor visible at MRI and/or palpable at digital rectal examination
T2a small unilateral tumor
T2b bigger unilateral tumor
T2c bilateral tumor

T3 stage extracapsular extension
T3a extra-capsular infiltration
T3b infiltration of seminal vesicles

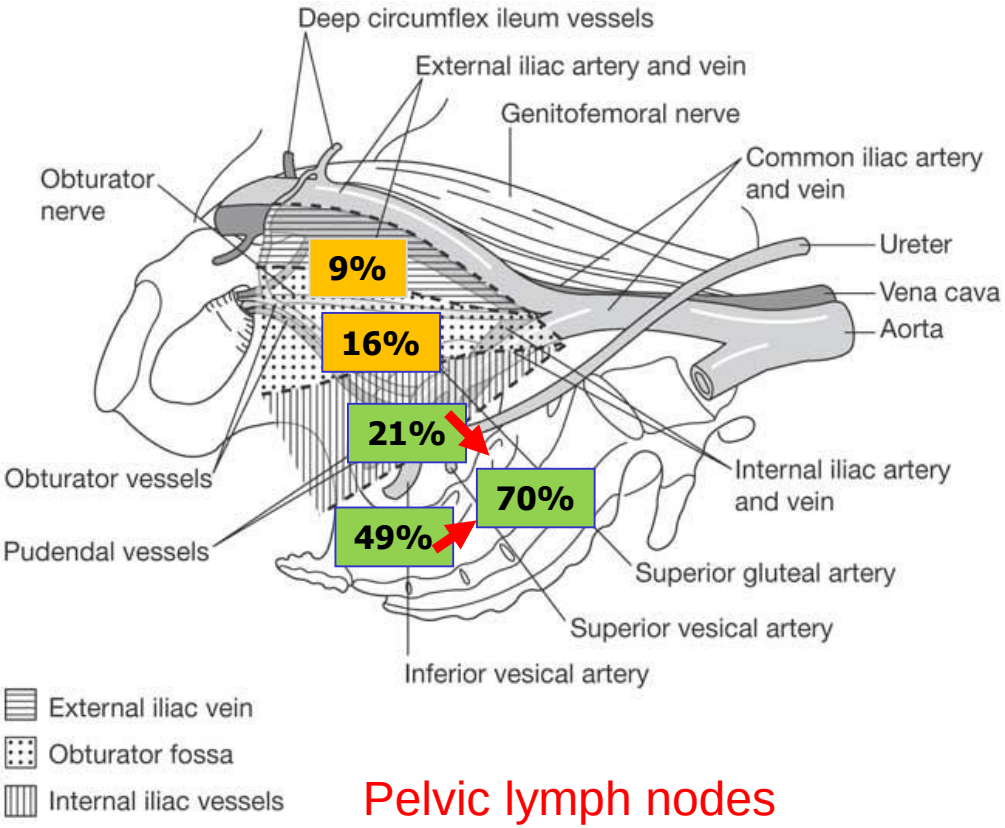
T4 stage invades adjacent structures (bladder, rectum)





TNM classification (Clinical or Pathological)

Lymphatic diffusion



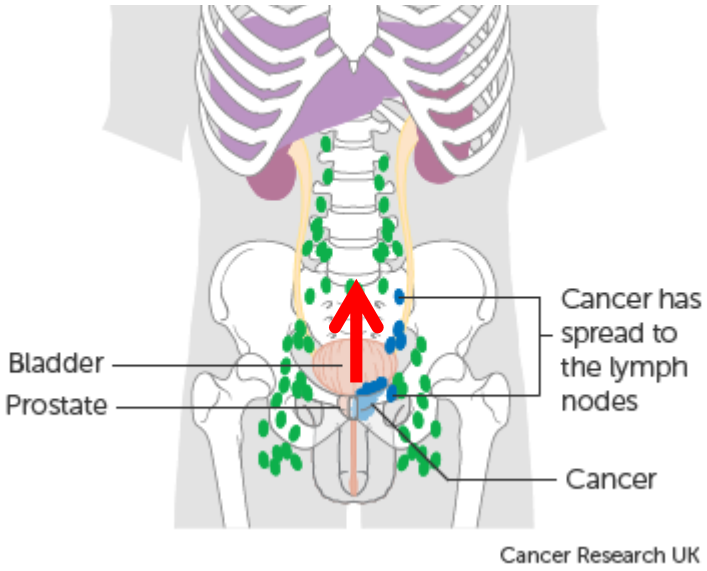
Pelvic lymph nodes

External iliac

Obturator

Internal iliac (hypogastric)

Retropertitoneal lymph nodes



N0: No regional lymph node metastasis

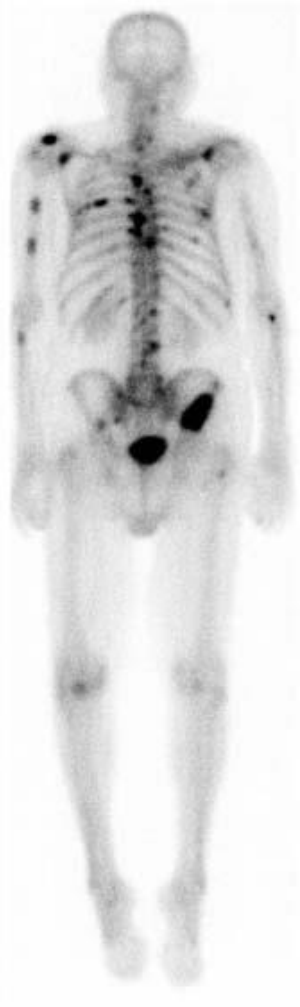
N1: Regional lymph node metastasis

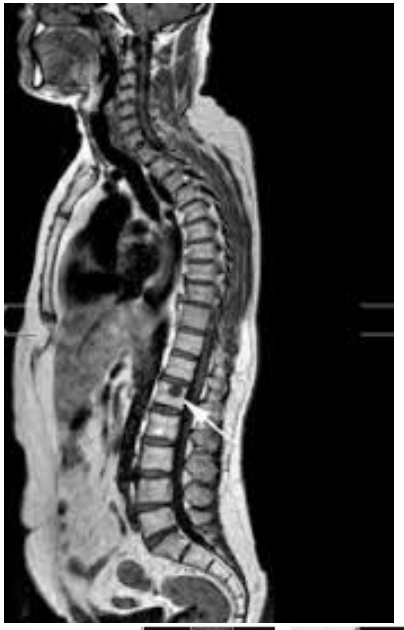
TNM classification (Clinical or Pathological)

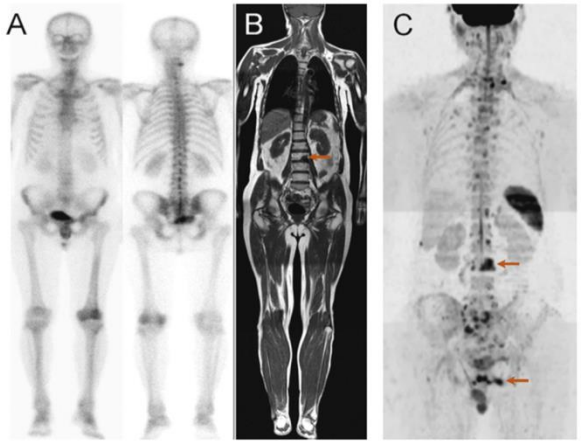
Hematogenous diffusion

Bone metastasis: most frequent

Parenchymal metastasis: Late, liver, lungs, etc







Prostate Cancer Symptoms

Prostate cancer rarely causes symptoms in the early stages, and most cases are diagnosed in a preclinical stage

Very frequently LUTS (dysuria) secondary to prostate hypertrophy coexist (Average age at diagnosis: 63 yrs)

Rare clinical manifestations

Locally advanced prostate cancer:

- Urethral obstruction, with LUTS or kidney failure
- Hematospermia
- Erectile dysfunction

Metastatic disease:

- Bone pain and pathological fractures
- Anemia

Diagnosis

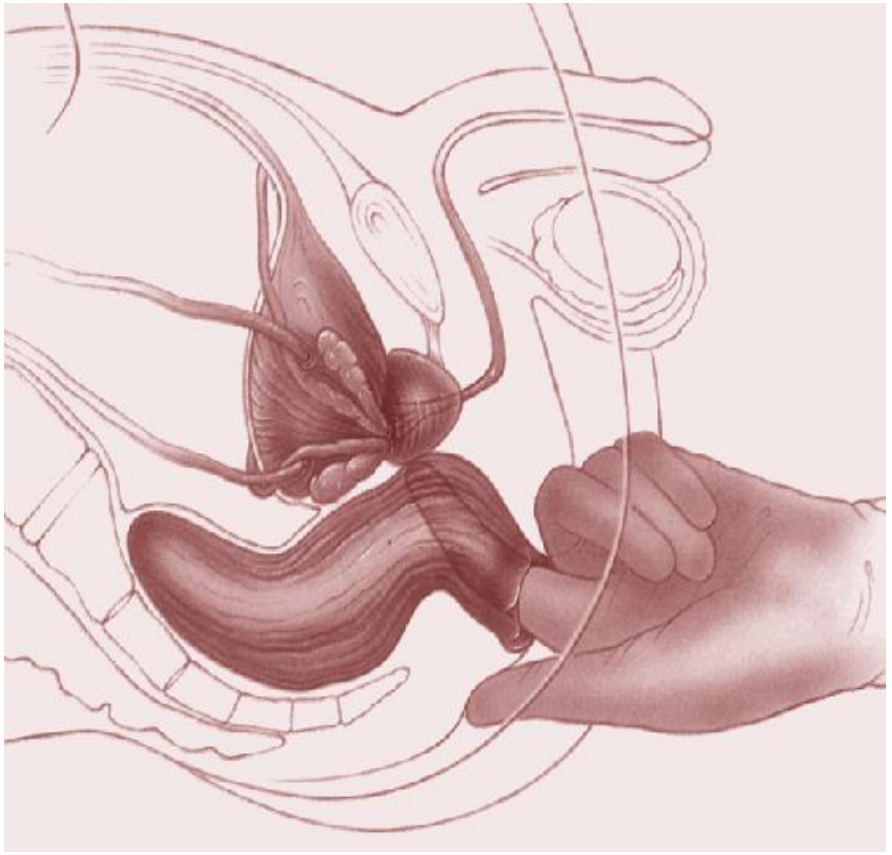
First line	- PSA - Digital rectal examination - Transrectal ultrasound
Second line	- mpMRI
Definitive diagnosis	- Biopsy

DIGITAL RECTAL EXAMINATION

Aims:
- Nodules
- Consistency
- Size
- Mobility

Sensitivity: very low!

Specificity high (70-96%)



DIGITAL RECTAL EXAMINATION

Nowadays most prostate cancers are NOT appreciable at examination

Nodular area of increased consistency

Slight increase in consistency
Asymmetry of the gland
Negative examination

Classical presentation

Other presentations

Need for instrumental confirmation

PSA: Prostate Specific Antigen

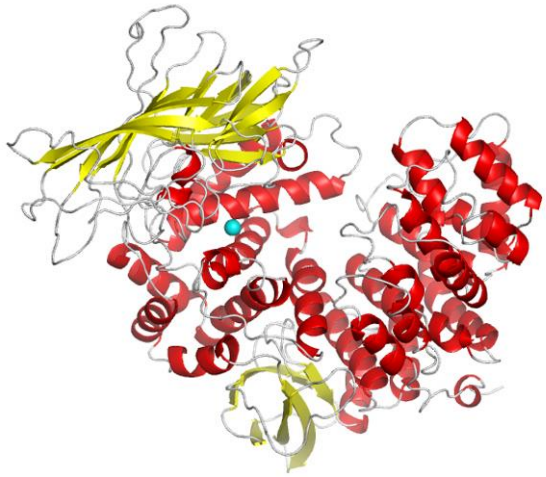
- ✓ It is a glicoprotein, encoded by the KLK3 gene, and produced by the prostate gland
- ✓ Its physiological function is to keep the semen fluid after ejaculation, allowing sperm to move more easily through the uterine cervix
- ✓ A small fraction of PSA enters the blood flow and its dosage is used for the diagnosis of prostate cancer

It is an organ-specific but
not a cancer-specific marker

PSA: Prostate Specific Antigen

SPECIFICITY DEFICIT:

- PSA is a specific marker of the prostate but not necessarily of cancer
- Serum PSA also increases in several benign pathologies and after manipulations or maneuvers of different types



- **Not all elevated PSA levels are related to cancer.**

SENSITIVITY DEFICIT:

- **Not all prostate cancers have a high PSA**

Specificity

Traditional cut-off = 4 ng/m

PSA 4-10 ng/ml

70% of men do not have prostate cancer

Only 25% of biopsies are positive if PSA exceeds 4 ng/ml, while more than 50% of biopsies are positive if the value exceeds 10 ng/ml.

High PSA: causes

- Benign prostate hypertrophy (25% of men with IPB have PSA >4.0 ng/ml)
- Acute and chronic prostatitis (PSA <4 ng/ml in 71% of acute prostatitis and 15% of chronic prostatitis)
- Prostate cancer (3.5 ng/ml for each gram of tumor tissue)

- Intense physical activity
- Digital rectal examination
- Ejaculation
- Prostate massage
- Transrectal ultrasound
- Prostate biopsy
- Bladder catheter
- Cystoscopy

Sensitivity

ABOUT 25% OF MEN WITH PSA <4 ng/ml CAN HARBOUR PROSTATE CANCER

Table 5.2.1: Risk of PCa in relation to low PSA values

PSA level (ng/mL)	Risk of PCa (%)	Risk of Gleason ≥ 7 PCa (%)
0.0-0.5	6.6	0.8
0.6-1.0	10.1	1.0
1.1-2.0	17.0	2.0
2.1-3.0	23.9	4.6
3.1-4.0	26.9	6.7

PSA is a continuous parameter: higher levels indicate a higher probability of prostate cancer

New markers for prostate cancer

PCA3 (urine test after digital rectal examination)

PCA3 prostate protein and corresponding MRI

2 Pro PSA (blood test)

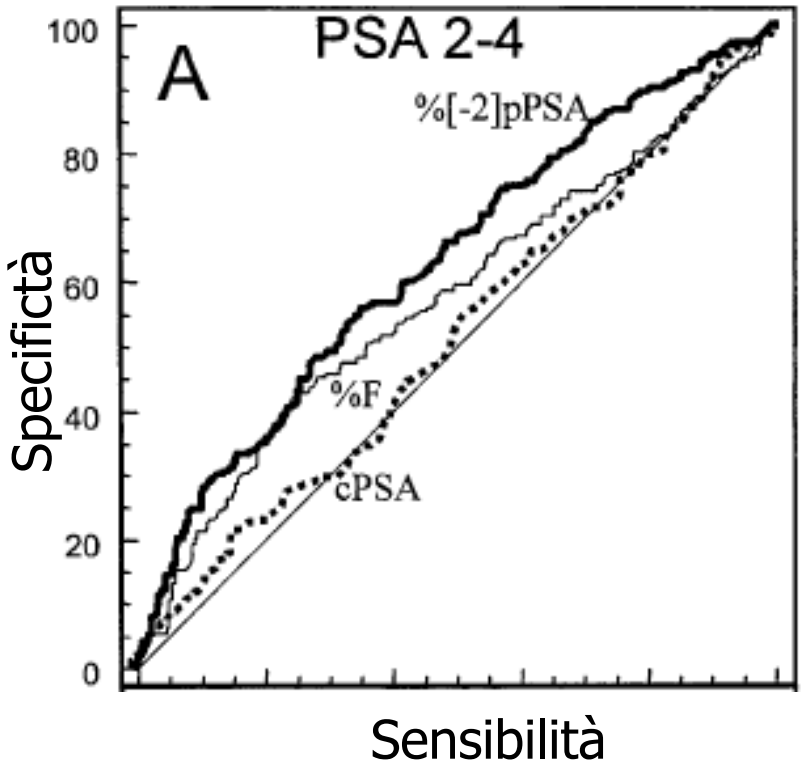
Isoform of PSA

Prostate Health Index (PHI)

***Phi* = (*p2PSA/fPSA*) x √ PSA**

-2 Pro PSA

SERUM PRO PROSTATE SPECIFIC ANTIGEN IMPROVES CANCER DETECTION COMPARED TO FREE AND COMPLEXED PROSTATE SPECIFIC ANTIGEN IN MEN WITH PROSTATE SPECIFIC ANTIGEN 2 TO 4 NG/ML



Catalona has shown that ProPSA improves predictive accuracy in prostate cancer diagnosis when total PSA is between 2.0-4.0 ng/mL

This improvement was superior to all the other markers together

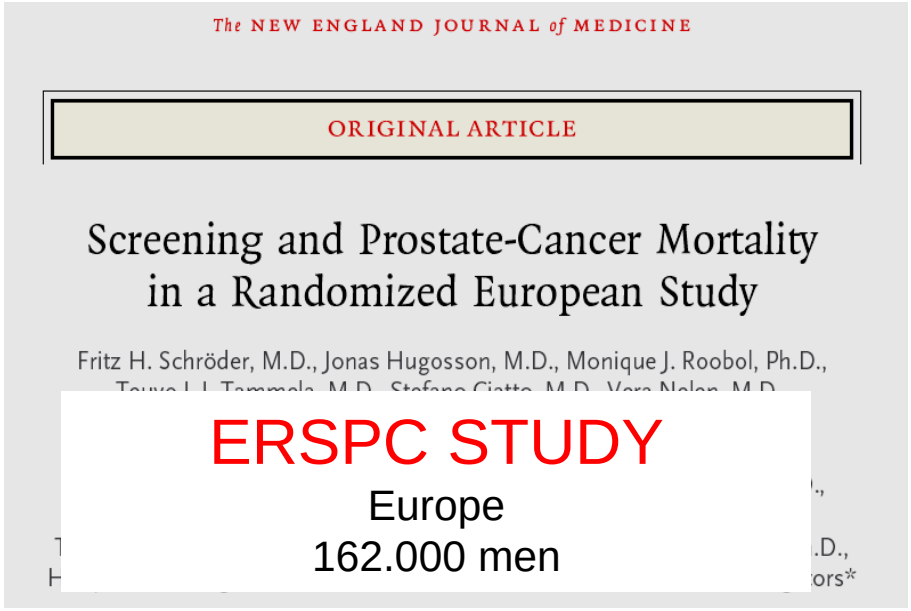
Catalona et al, J Urology 2003

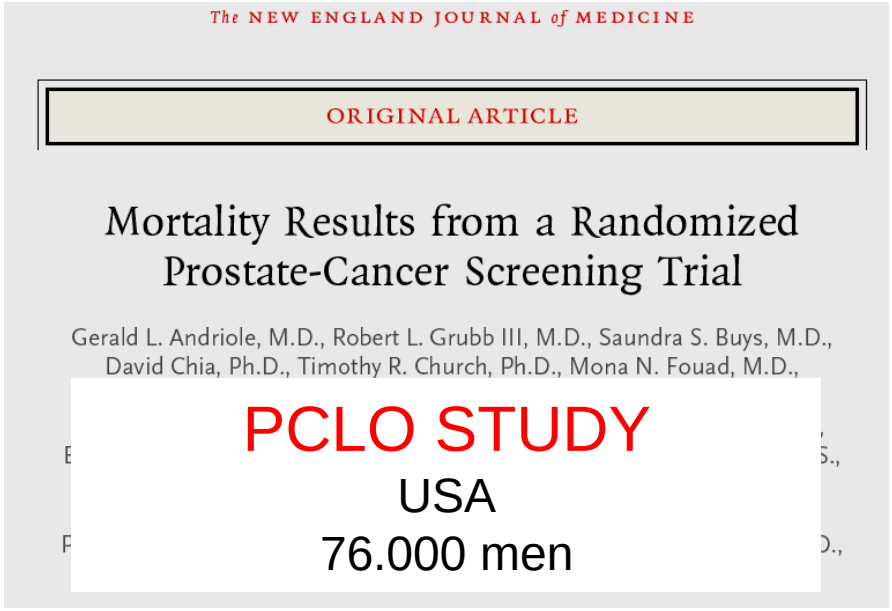
Screening

Prostate cancer

Criteria	Application for PCa
• Common disease with severe prognosis	• Yes. First tumor for incidence, second tumor for mortality
• Simple and easy tests able to detect early-stage and asymptomatic disease	• Yes. PSA. (DRE?)
• Treatment of early-stage disease leads to a reduction of morbidity and mortality	?
• Favorable cost/effectiveness ratio: cost of test, of treatments, of complications	• Not yet demonstrated

Prostate Cancer Screening in Europe and the USA





👍 Sceening with PSA reduces prostate cancer mortality

👎 Sceening with PSA does not reduce prostate cancer mortality

N Engl J Med 2009

Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up

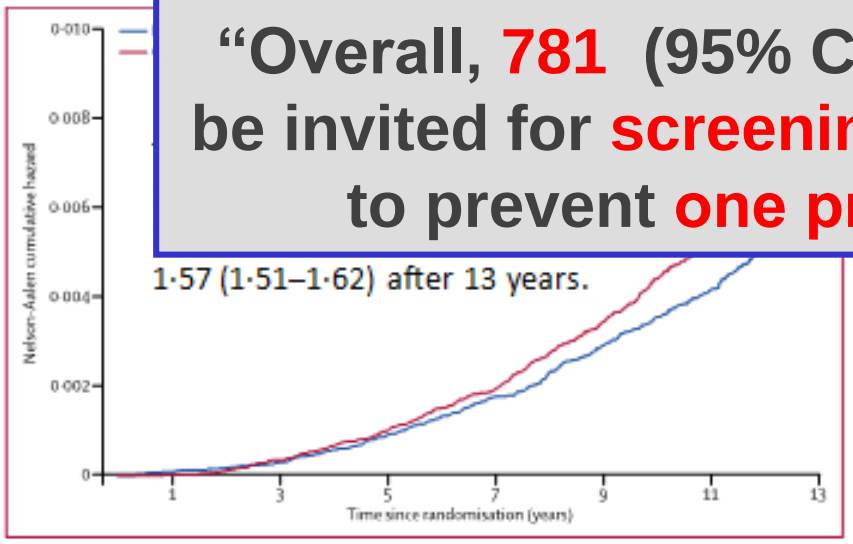
*Fritz H Schröder, Jonas Hugosson, Monique J Roobol, Teuvo L J Tammela, Marco Zappa, Vera Nelen, Maciej Kwiatkowski, Marcos Lujan, Liisa Määttänen, Hans Lilja, Louis J Denis, Franz Recker, Alvaro Paez, Chris H Bangma, Sigrid Carlsson, Donella Puliti, Arnauld Villers, Xavier Rebillard, Matti Hakama, Ulf-Hakan Stenman, Paula Kujala, Kimmo Taari, Gunnar Aus, Andreas Huber, Theo H van der Kwast, Ron H N van Schaik, Harry J de Koning, Sue M Moss, Anssi Auvinen, for the ERSPC Investigators**

7408 men in screening harm (SA)

6107

MORTALITY REDUCTION = 44%

"Overall, 781 (95% CI 177–799) men needed to be invited for screening and 27 to be diagnosed to prevent one prostate cancer death"



1·57 (1·51–1·62) after 13 years.

		ed to treat
11	979	35
13	781	27

THE LANCET

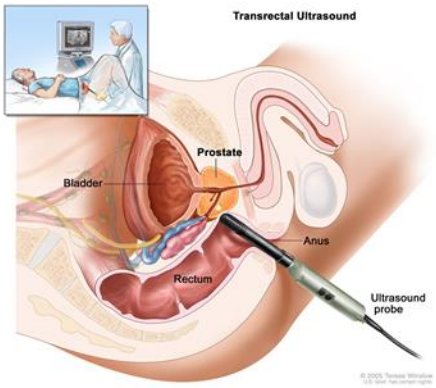
2014

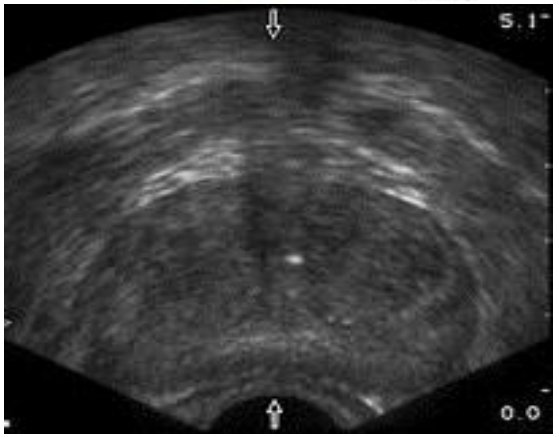
To decide for further diagnostic evaluations it is essential to always associate

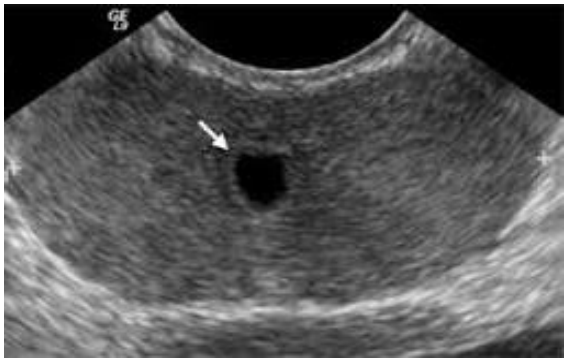
PSA + UROLOGICAL VISIT

Transrectal ultrasound of the prostate

- ✓ Transrectal ultrasound is not an accurate examination for local staging of prostate cancer
- ✓ Low sensitivity (false negative results)
- ✓ Low specificity (false positive results)
- ✓ The ability of transrectal ultrasound to predict extracapsular invasion ranges from 37 to 83%
- ✓ **Transrectal ultrasound is similar to digital rectal examination in T staging**







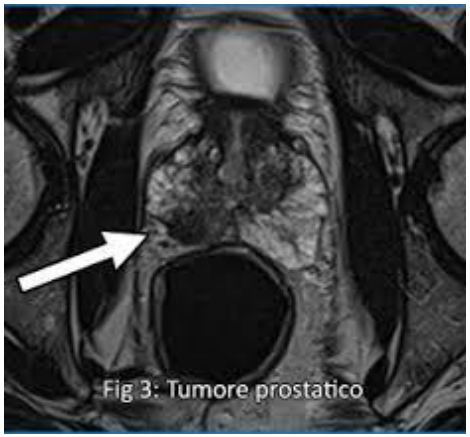
Multiparametric MRI

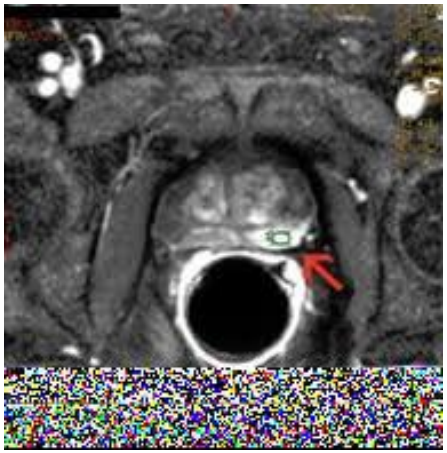
Multiparametric:

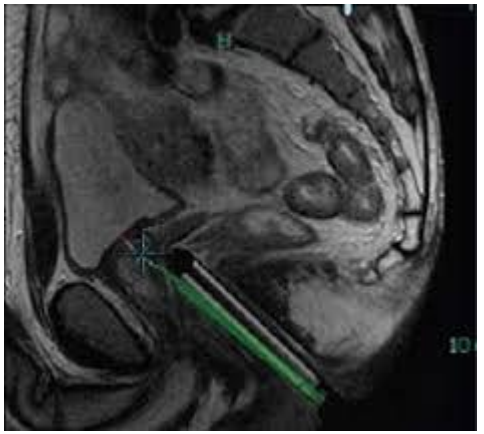
- ✓ **T2**
- ✓ **Diffusion**
- ✓ **Contrast-enhanced**

Classificazione PI-RADS	Definizione	Punteggio totale T2+DWI+DCE	Punteggio totale T2+DWI+DCE+MRS
I	Molto probabilmente benigna	3 - 4	4 - 5
II	Probabilmente benigna	5 - 6	6 - 8
III	Indeterminata	7 - 9	9 - 12
IV	Probabilmente maligna	10 - 12	13 – 15
V	Molto probabilmente maligna	13 - 15	17 - 20

Tratta da Barentsz JO, Richenberg J, Clements R et al. ESUR prostate MR guidelines 2012. Eur Radiol 2012; 22:746-757







Multiparametric MRI

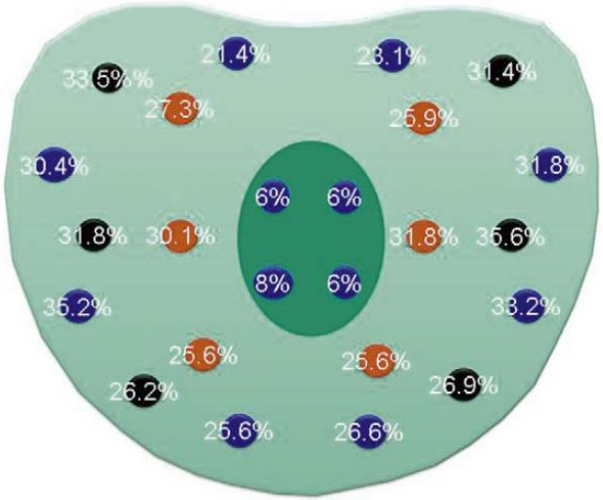
Sensitivity: 90%	**Specificity: 40%**

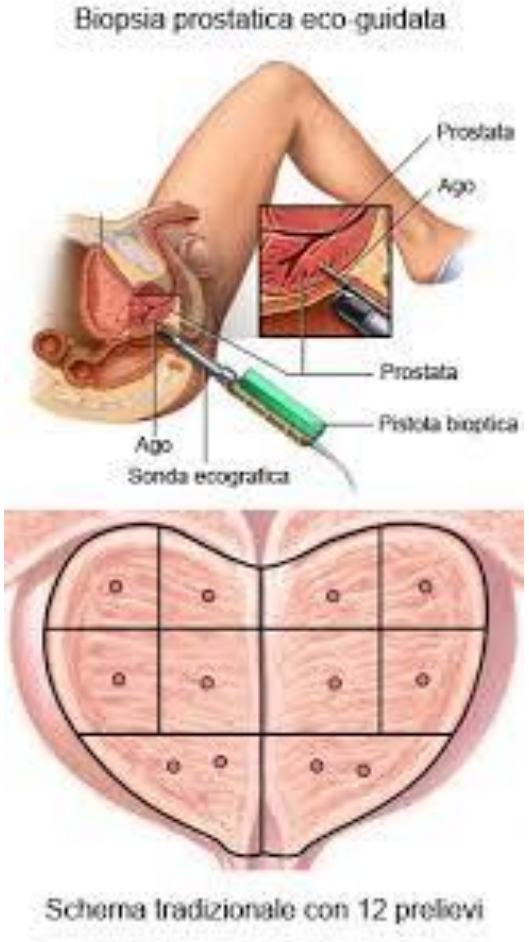
Negative predictive value:	**80-85%**
Positive predictive value:	**60%**

- ✓ It's not an alternative to biopsy
- ✓ It allows you to do more accurate biopsies (Fusion biopsies)

Systematic Prostate Biopsy

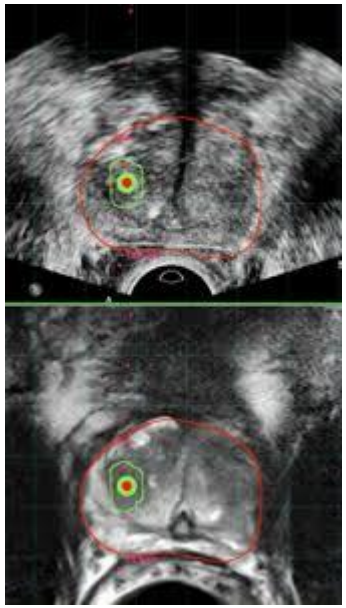
- ✓ Ultrasound assisted
- ✓ Transrectal or transperineal access





Fusion Prostate Biopsy

- ✓ Fusion biopsy: systematic (random) + target on suspicious lesion at MRI
- ✓ Merging MRI images with US images
- ✓ Biopsies can be precisely directed to target lesions



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PROSTATE CANCER

STAGING AND THERAPY

Prostate cancer
Staging

Local staging: to carry out investigations aimed at assessing the local extent of the disease

Systemic staging: to carry out investigations aimed at evaluating any secondary metastatic lesions (lymph nodes or systemic)

RISK GROUPS

Grading: ISUP grade 1 - 2-3 - >3
PSA: <10 ng/ml - 10-20 ng/ml - >20 ng/ml
Clinical T stage: cT1/T2a - cT2b - cT2c - cT3-4

Definition			
Low-risk	**Intermediate-risk**	**High-risk**	
PSA < 10 ng/mL and GS < 7 (ISUP grade 1) and cT1-2a	PSA 10-20 ng/mL or GS 7 (ISUP grade 2/3) or cT2b	PSA > 20 ng/mL or GS > 7 (ISUP grade 4/5) or cT2c	any PSA any GS (any ISUP grade) cT3-4 or cN+
Localised			**Locally advanced**

GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen.

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Prostate cancer
Staging

Low risk: no staging needed

Intermediate risk: local staging

High risk: local and systemic staging

Locally advanced: local and systemic staging

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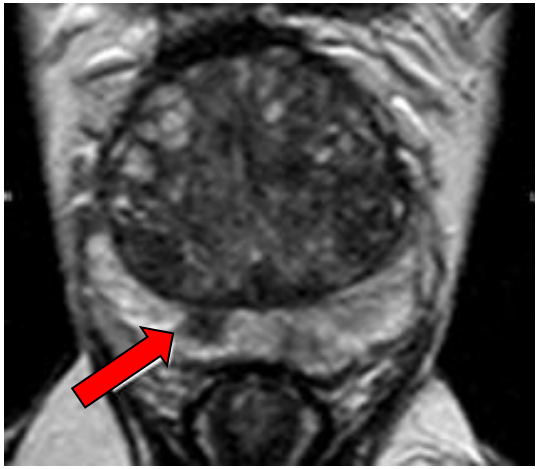
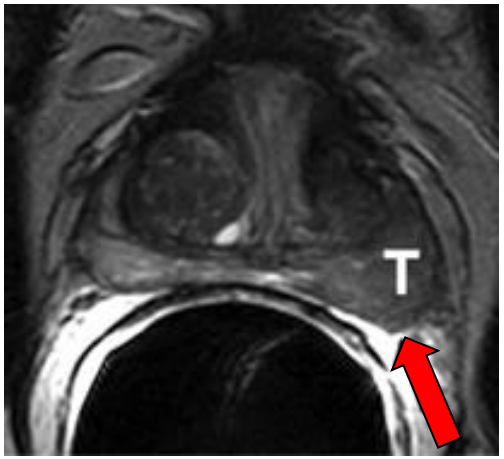
Multiparametric MRI
Local staging

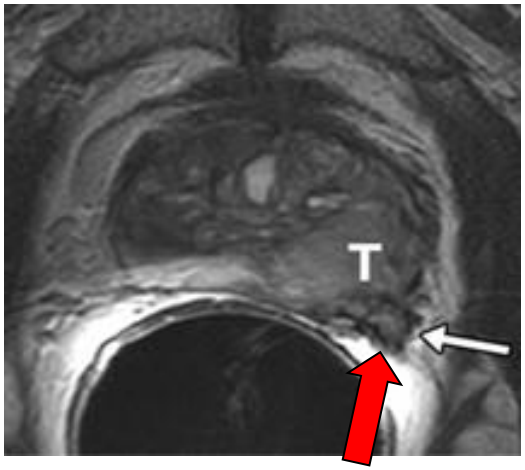
Diagnosis of extra-capsular disease



INTRA CAPSULAR



Probably
EXTRA CAPSULAR



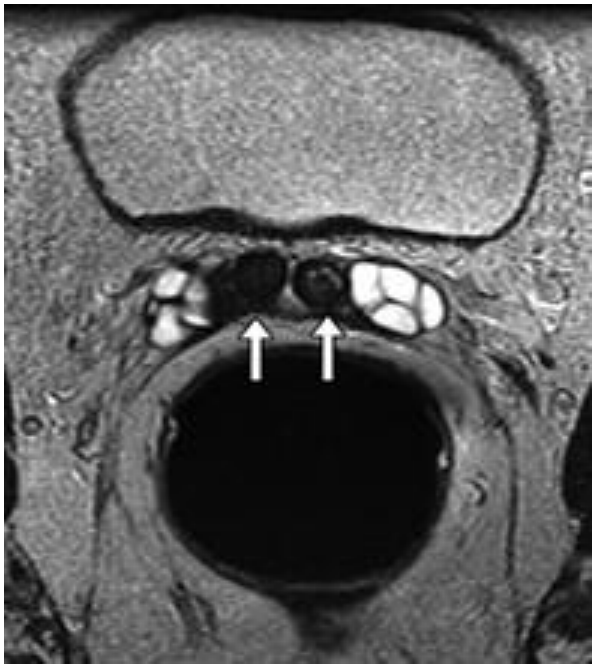
EXTRA CAPSULAR

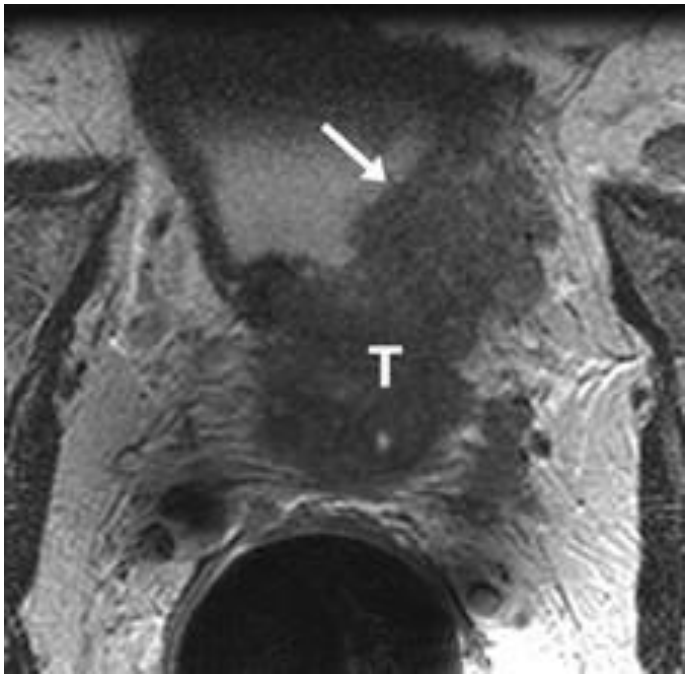
Multiparametric MRI

Local staging

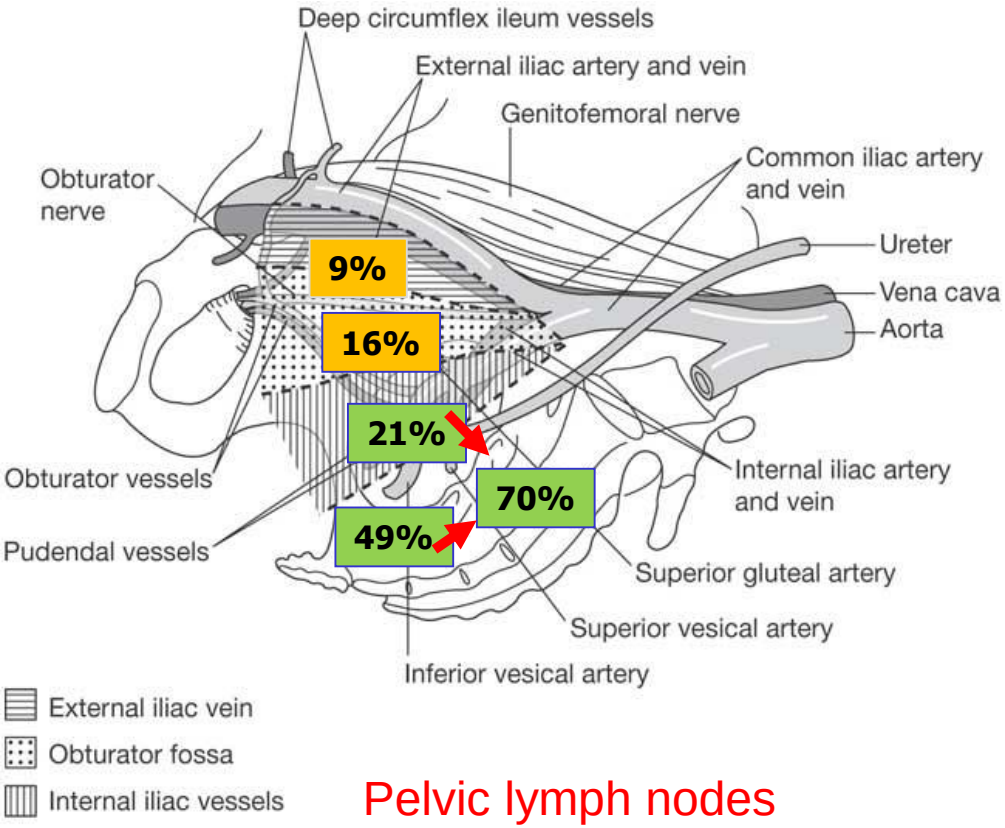
Extra-capsular disease

Seminal Vesicles – Bladder





Lymph node staging



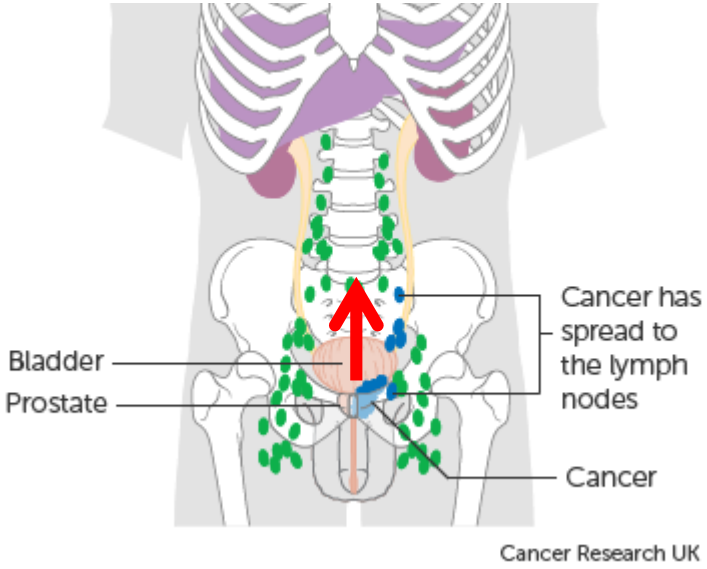
Pelvic lymph nodes

External iliac

Obturator

Internal iliac (hypogastric)

Retropertitoneal lymph nodes



N0: No regional lymph node metastasis

N1: Regional lymph node metastasis

Lymph node staging

- It should be carried out only if it affects the treatment
- This is usually the case of patients for whom curative treatment has been planned
- Lymph node staging is required for clinical intermediate and high risk disease
- Nomograms should be used to define the risk of lymph node invasion

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Lymph node staging
CT of the abdomen and MRI

- CT and MRI have **low sensitivity** in detecting lymph node invasion (about 40%).

- This low sensitivity can be explained by the fact that the lymph node invasion is determined solely by dimensional criteria.

- MRI with DWI sequences can diagnose lymph node metastases in normal-sized lymph nodes, but its negativity does not exclude the presence of lymph node metastases.

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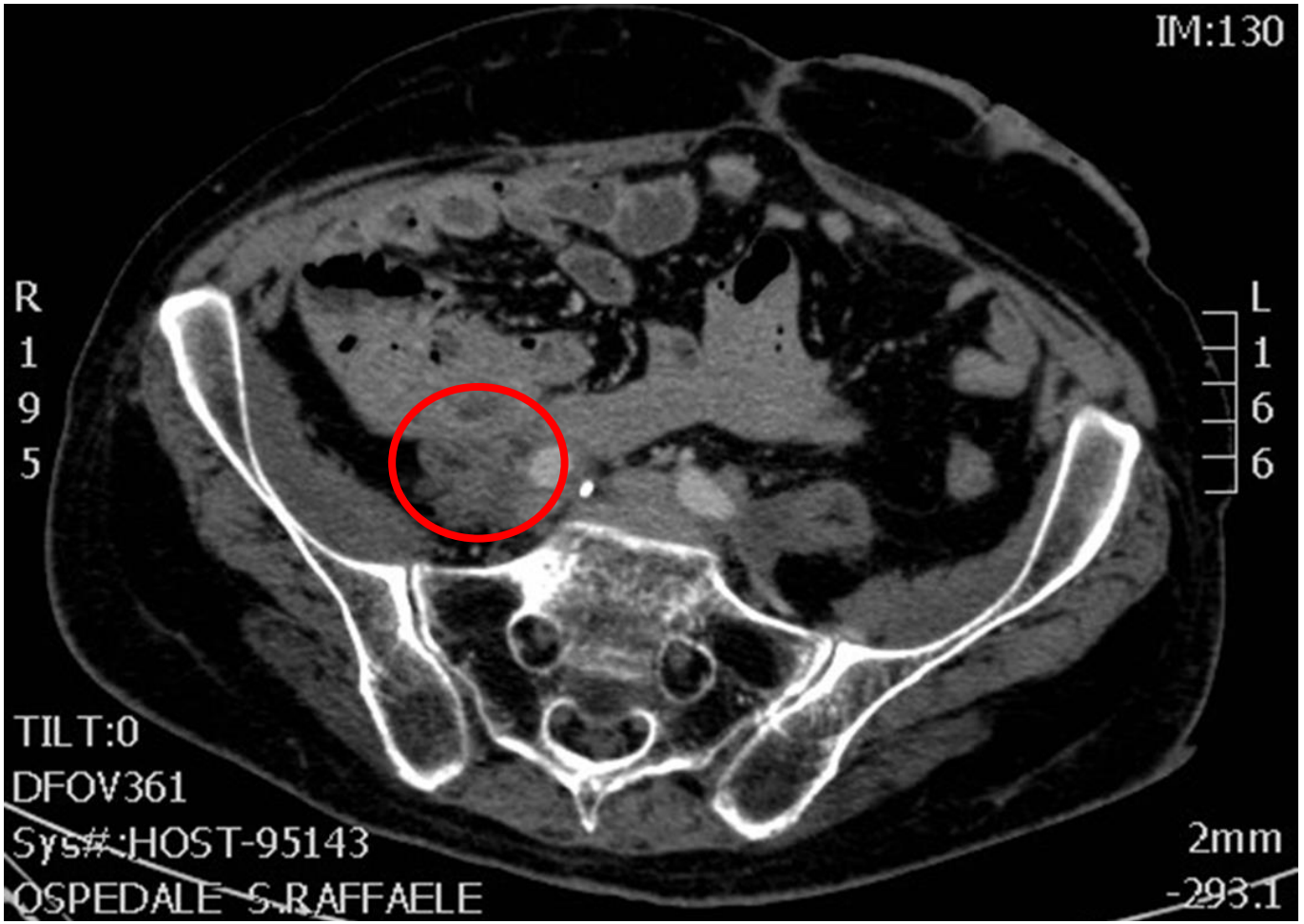
Performance Characteristics of Computed Tomography in Detecting Lymph Node Metastases in Contemporary Patients with Prostate Cancer Treated with Extended Pelvic Lymph Node Dissection

	Sensitivity, %	Specificity, %	NPV, %	PPV, %	Accuracy, %
Overall population, $n = 1541$	13.0	96.0	89.1	32.9	54.6
Low-risk patients, $n = 471$	8.3	96.3	97.6	5.6	52.3
Intermediate-risk patients, $n = 689$	3.6	97.3	92.1	10.5	50.5
High-risk patients, $n = 381$	17.9	94.3	72.7	58.3	56.1
LNI calculated risk ≥30,* $n = 193$	22.0	95.5	78.3	62.4	58.7
LNI calculated risk ≥50,* $n = 161$	23.9	94.7	76.2	63.6	59.3

Predictors	Univariable analyses		Multivariable analyses	
	OR (95% CI)	AUC, %	Base model OR (95% CI)	Full model OR (95% CI)
Prostate-specific antigen	1.04 (1.03–1.05)†	70.5	1.02 (1.01–1.03)†	1.02 (1.01–1.03)†
Clinical tumor stage				
T1c	1.00 (Ref.)	66.7	1.00 (Ref.)	1.00 (Ref.)
T2	1.88 (1.28–2.75)†		1.27 (0.84–1.92)	1.29 (0.85–1.96)
T3	5.96 (4.04–8.8)†		2.37 (1.5–3.72)†	2.33 (1.48–3.68)†
Biopsy Gleason score				
≤6	1.00 (Ref.)	75.3	1.00 (Ref.)	1.00 (Ref.)
7	4.21 (2.8–6.33)†		3.41 (2.23–5.19)†	3.46 (2.27–5.28)†
≥8	16.98 (10.83–26.6)†		9.92 (6.06–16.22)†	9.37 (5.7–15.38)†
CT scan findings				
Negative	(Ref.)†	54.6		1.00 (Ref.)
Positive	3.1 (1.9–5.1)†		–	2.14 (1.1–4.13)‡
AUC, %	–	–	81.3	81.4
Gain in predictive accuracy	–	–	–	0.1*

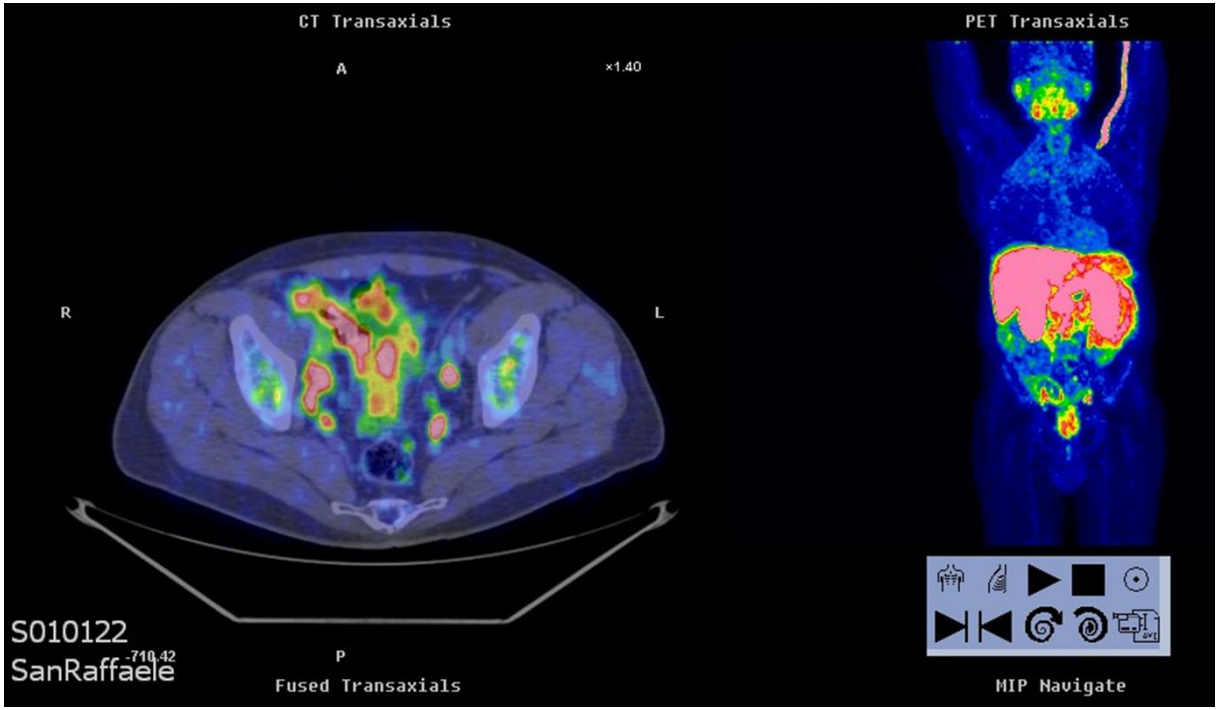
Briganti et al. Eur Urol 2012;61:1132-8

N-Staging - CT of the abdomen

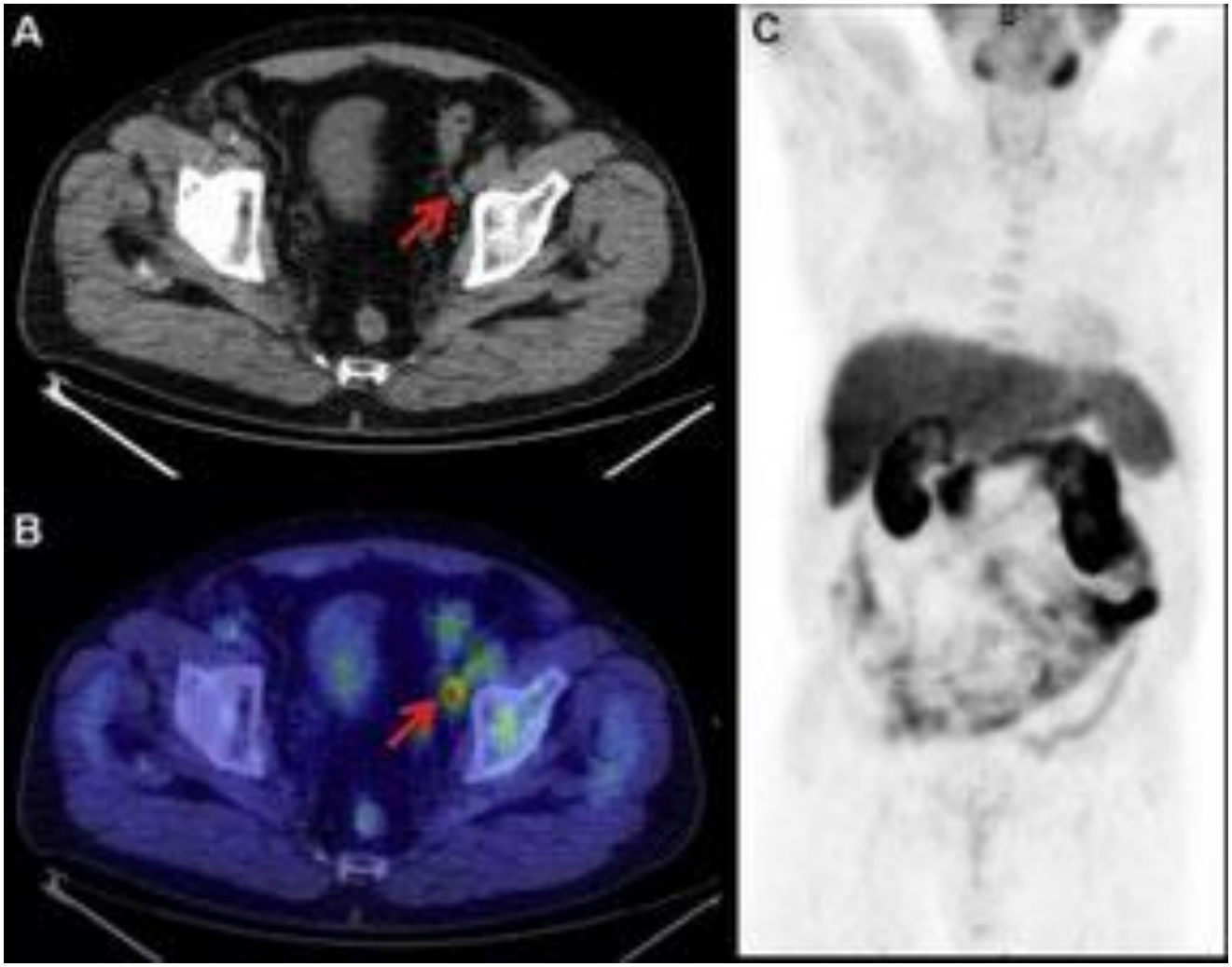


N-staging - Choline PET/CT

- ✓ Sensitivity: **10%-73%**
- ✓ Limited by the spatial resolution of the method (about 5 mm)
- ✓ Not suitable for lymph node staging

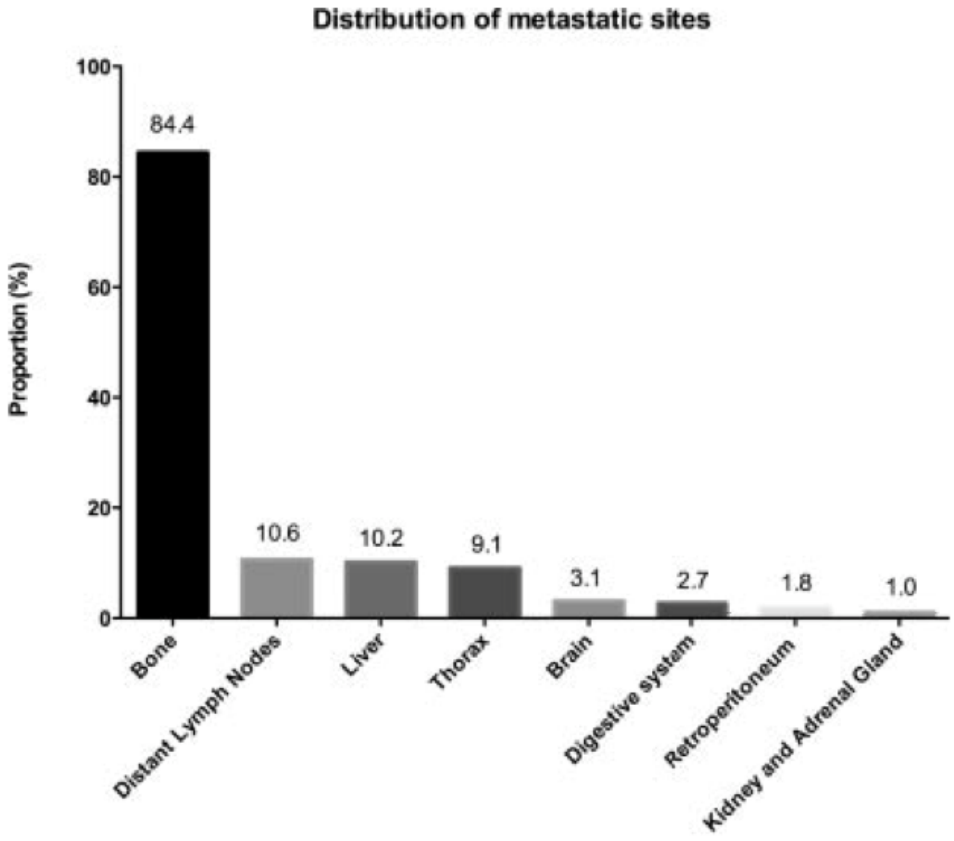


PSMA PET/CT



M-Staging
Bone scintigraphy

- Axial skeleton is involved in 85% of patients with metastatic prostate cancer
- Early diagnosis of bone metastases allows to avoid pathological fractures
- **Bone scintigraphy is still the gold standard for the diagnosis of bone metastases** (sensitivity 79%; specificity 82%



Gandaglia et al. The Prostate 2014(2):210-6

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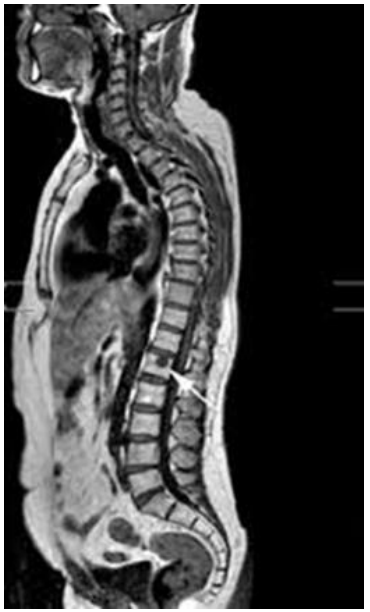
M-Staging
MRI and choline PET/CT

- **MRI is superior to bone scintigraphy** in the diagnosis of bone metastases.
- It is not yet clear whether Choline or PSMA **PET/CT** are more sensitive than bone scintigraphy, but they are **more specific**.
- MRI and choline PET/CT may also highlight the presence of visceral metastases.



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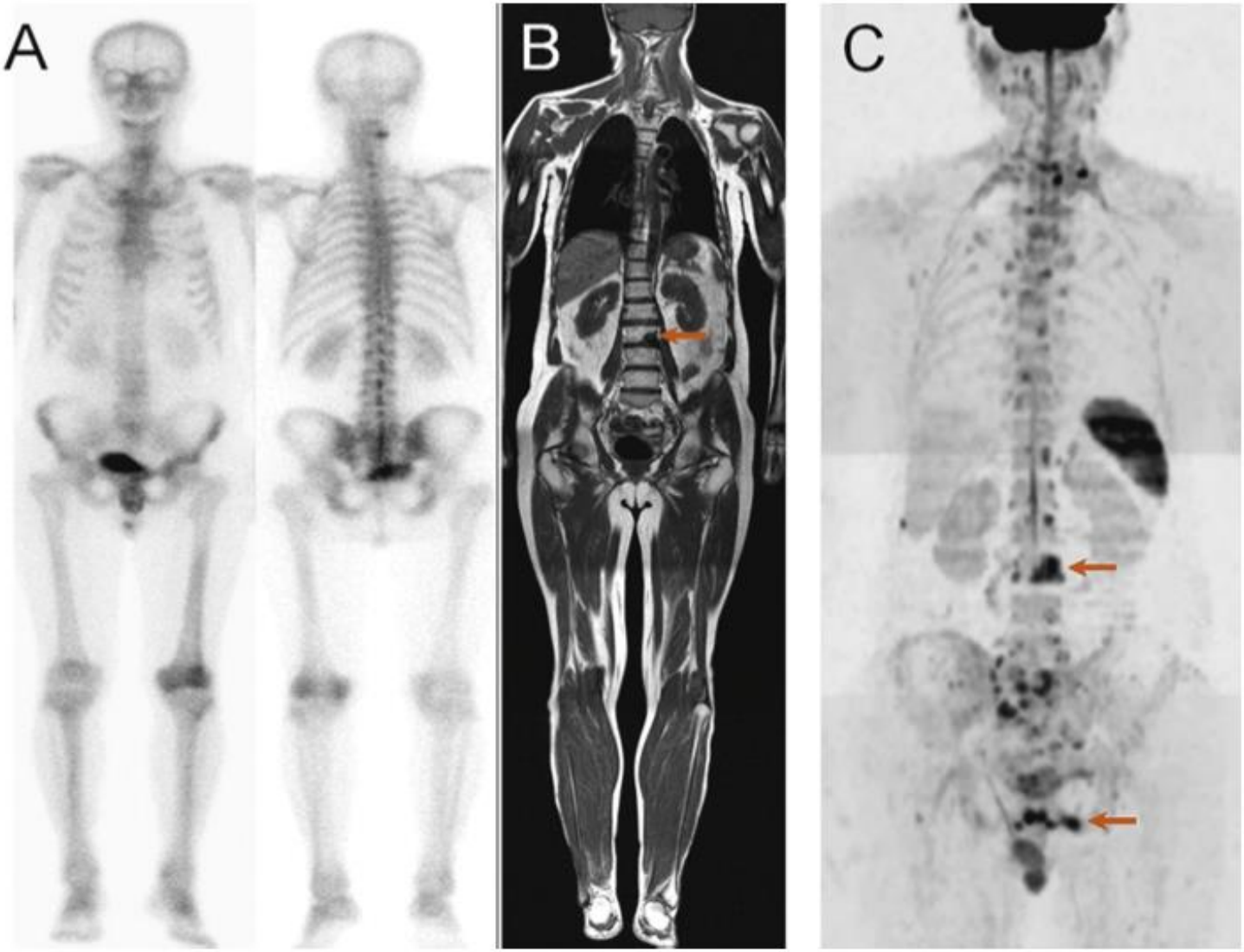
M-Staging



Prostate Cancer

TREATMENT

Risk Groups

Definition			
Low-risk	**Intermediate-risk**	**High-risk**	
PSA < 10 ng/mL and GS < 7 (ISUP grade 1) and cT1-2a	PSA 10-20 ng/mL or GS 7 (ISUP grade 2/3) or cT2b	PSA > 20 ng/mL or GS > 7 (ISUP grade 4/5) or cT2c	any PSA any GS (any ISUP grade) cT3-4 or cN+
Localised			**Locally advanced**

GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen.

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Treatment options

- ✓ Active surveillance
- ✓ Surgery: Radical prostatectomy
- ✓ Radiotherapy / Brachytherapy
- ✓ Focal therapy
- ✓ Hormonal therapy

Treatment options

- ✓ **Active surveillance**
- ✓ Surgery: Radical prostatectomy
- ✓ Radiotherapy / Brachytherapy
- ✓ Focal therapy
- ✓ Hormonal therapy

Active Surveillance

- ✓ Therapeutic option offered to patients with clinical low risk prostate cancer to avoid over treatment.
- ✓ Follow-up of patients over time with periodical re-staging assessments: PSA, multiparametric MRI, biopsies (every three years).
- ✓ Offer a therapeutic option with radical intent if the disease switches to a higher risk category: 30% of cases.

Active Surveillance – Definition

Table 6.1.1: Definitions of active surveillance and watchful waiting [384]

	Active surveillance	Watchful waiting
Treatment intent	Curative	Palliative
Follow-up	Predefined schedule	Patient-specific
Assessment/markers used	DRE, PSA, re-biopsy, mpMRI	Not predefined
Life expectancy	> 10 years	< 10 years
Aim	Minimise treatment-related toxicity without compromising survival	Minimise treatment-related toxicity
Comments	Mainly low-risk patients	Can apply to patients with all stages

DRE = digital rectal examination; PSA = prostate-specific antigen; mpMRI = multiparametric magnetic resonance imaging.

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Watchful Waiting – Definition

Table 6.1.1: Definitions of active surveillance and watchful waiting [384]

	Active surveillance	Watchful waiting
Treatment intent	Curative	Palliative
Follow-up	Predefined schedule	Patient-specific
Assessment/markers used	DRE, PSA, re-biopsy, mpMRI	Not predefined
Life expectancy	> 10 years	< 10 years
Aim	Minimise treatment-related toxicity without compromising survival	Minimise treatment-related toxicity
Comments	Mainly low-risk patients	Can apply to patients with all stages

DRE = digital rectal examination; PSA = prostate-specific antigen; mpMRI = multiparametric magnetic resonance imaging.

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Active surveillance: Outcomes

Table 6.1.2: Active surveillance in screening-detected prostate cancer

Studies	N	Median FU (mo)	pT3 in RP patients*	10-year OS (%)	10-year CSS (%)
Van As, *et al.* 2008 [389]	326	22	8/18 (44%)	98	100
Carter, *et al.* 2007 [390]	407	41	10/49 (20%)	98	100
Adamy, *et al.* 2011 [391]	533-1,000	48	4/24 (17%)	90	99
Soloway, *et al.* 2010 [392]	99	45	0/2	100	100
Roemeling, *et al.* 2007 [393]	278	41	-	89	100
Khatami, *et al.* 2007 [394]	270	63	-	n.r.	100
Klotz, *et al.* 2015 [395]	993	77	-	85	98.1
Tosoian, *et al.* 2015 [388]	1,298	60	-	93	99.9
Total	**4,204-4,671**	**46.5**	-	**93**	**100**

** Patients receiving active therapy following initial active surveillance.*

CSS = cancer-specific survival; FU = follow-up; mo = months; n = number of patients; n.r. = not reported; OS = overall survival; RP = radical prostatectomy.

Active Surveillance Recommendations

Recommendations	Strength rating
Watchful waiting (WW)	
Offer a WW policy to asymptomatic patients with a life expectancy < ten years (based on comorbidities).	Strong
Active surveillance (AS)	
Offer AS to patients suitable for curative treatment but with low-risk PCa.	Strong
Perform multiparametric magnetic resonance imaging before a confirmatory biopsy.	Strong
During confirmatory biopsy include systematic and targeted biopsies.	Strong
Base follow up on digital rectal examination, prostate-specific antigen and repeated biopsies.	Strong
Counsel patients about the possibility of needing further treatment in the future.	Strong

FIRST OPTION FOR LOW RISK PROSTATE CANCER

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Treatment options

- ✓ Active surveillance
- ✓ **Surgery: Radical Prostatectomy**
- ✓ Radiotherapy / Brachytherapy
- ✓ Focal therapy
- ✓ Hormonal therapy

Radical prostatectomy

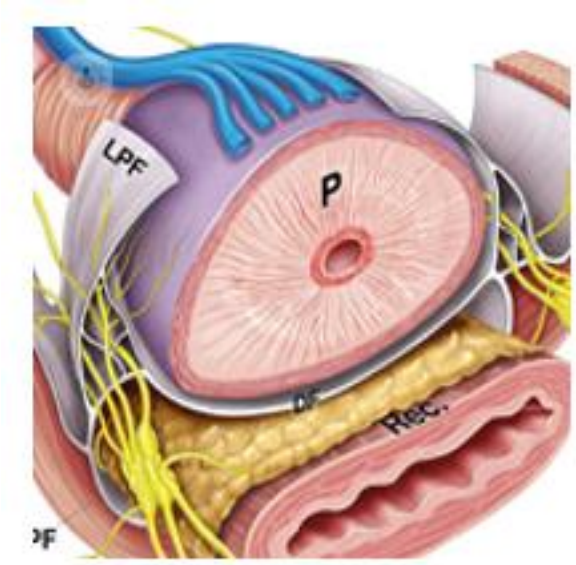
RADICAL PROSTATECTOMY

Surgical removal of the entire prostate gland + seminal vesicles + pelvic lymph nodes

Risks related to surgery:

- ✓ Incontinence
- ✓ Erectile disfunction

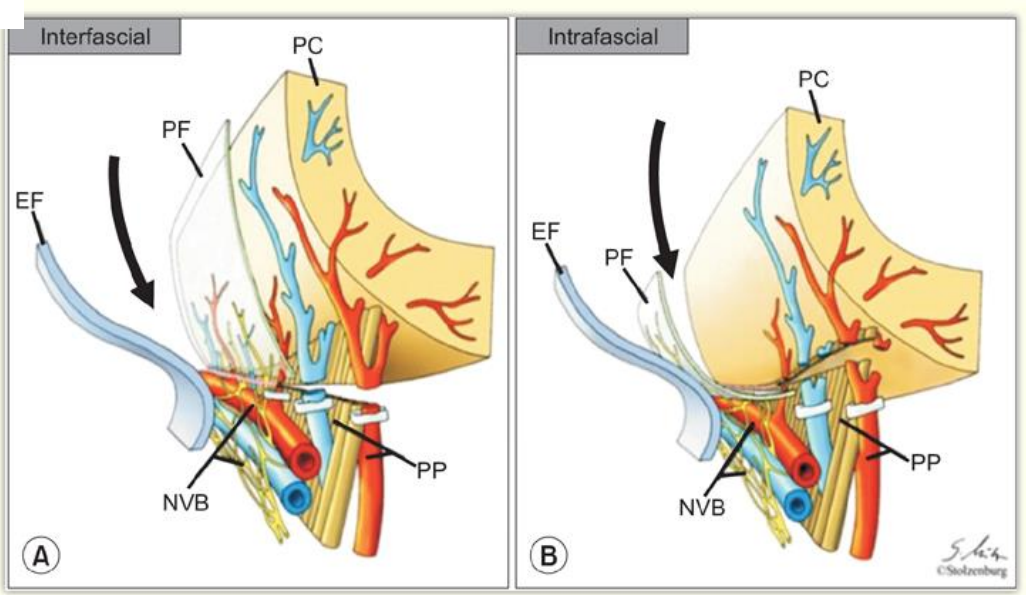
RADICAL PROSTATECTOMY



INTRINSIC SPHINCTER:
risk of incontinence

NEUROVASCULAR BUNDLES:
risk of erectile disfunction

NERVE SPARING SURGERY



Radical prostatectomy

Historically indicated for clinical low/intermediate risk disease

Table 6.1.4: Oncological results of radical prostatectomy in organ-confined disease in RCTs

Study	Acronym	Population	Year of treatment	Median FU (mo)	Risk category	CSS (%)
Bill-Axelson, *et al.* 2018 [400]	SPCG-4	Pre-PSA era	1989-1999	283	Low risk and Intermediate risk	80.4 (at 23 yr.)
Wilt, *et al.* 2017 [396]	PIVOT	Early years of PSA testing	1994-2002	152	Low risk Intermediate risk	95.9 91.5 (at 19.5 yr.)
Hamdy, *et al.* 2016 [386]	ProtecT	Screened population	1999-2009	120	Mainly low- and intermediate risk	99 (at 10 yr.)

CSS = cancer-specific survival; FU = follow-up; mo = months; PSA = prostate-specific antigen; yr. = year.

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IS LOW RISK PROSTATE CANCER A LETHAL DISEASE?

The NEW ENGLAND JOURNAL of MEDICINE

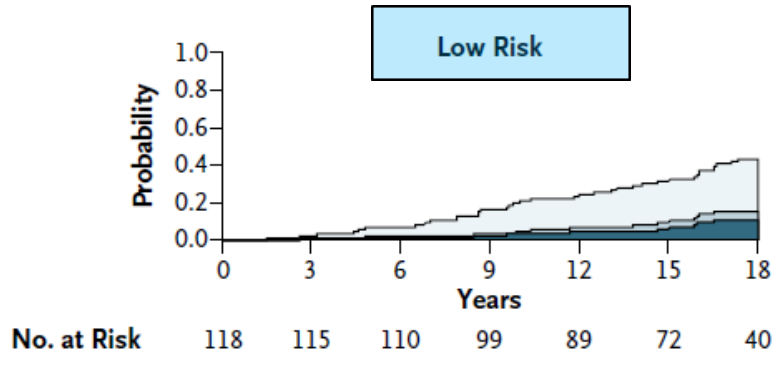
ORIGINAL ARTICLE

Radical Prostatectomy or Watchful Waiting in Early Prostate Cancer

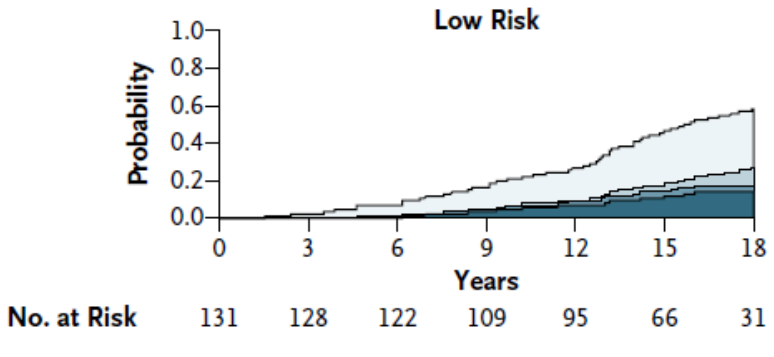
695 MEN:

- ✓ 348 Radical prostatectomy
- ✓ 348 Watchful Waiting

Radical prostatectomy



Watchful Waiting



Death from prostate cancer

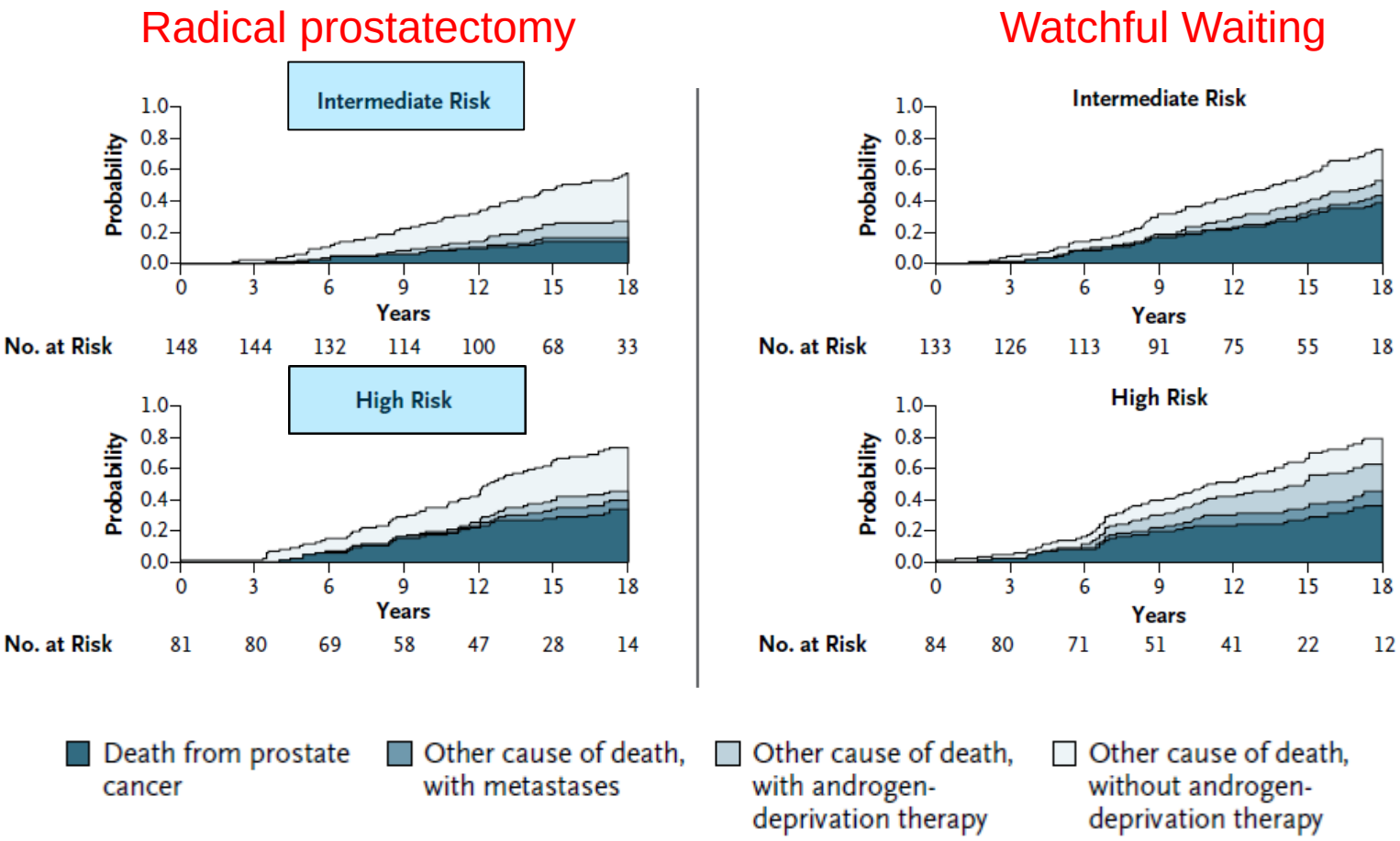
Other cause of death, with metastases

Other cause of death, with androgen-deprivation therapy

Other cause of death, without androgen-deprivation therapy

N Engl J Med 2014; 370:932-942

ARE INTERMEDIATE AND HIGH RISK PROSTATE CANCER LETHAL DISEASES?



N Engl J Med 2014; 370:932-942

Long-term outcomes after RP in high-risk patients

	Year	N. HR pts	Time	BCR-free %	PFS %	CSS %	OS %	Adj Tx %	High risk def
Loeb et al	2007	288	**10**	X	35	**88**	74	27	cT2b/cT3, PSA >15 , Gleason 8-10
Yossepowitch et al	2007	274-1752	10	x	41-74	x	x	0	8 definitions
D'Amico et al	2007	660	5 (1 RF – 4RFs)	x	x	97.7- 80	x	x	≥cT2b, PSA ≥10, Gleason ≥7, PSA velocitiy >2 ng/mL/year
Walz et al	2010	887	10	35.7	x	x	x	x	≥cT2c, PSA ≥20, Gleason 8-10
Ku et al	2011	199	5	49.2	x	x	x	0	≥cT2b, PSA >20 , Gleason 8-10
Boorjian et al	2011	1238	**10**	X	85	**92**	77	40	≥cT3, PSA ≥20, Gleason 8-10
Ploussard et al	2011	813	5	x	74.1	96.1	98.2	36	>cT2c, PSA >20 , Gleason 8-10
Hong et al	2011	206	5	60	x	x	x	0	≥cT2b, PSA >20 , Gleason 8-10
Briganti et al	2015	2,065	5	55.2	X	**85.2**	X	0	≥cT2b, PSA >20 , Gleason 8-10

Radical prostatectomy

Historically reserved for clinical low/intermediate risk disease

Table 6.1.4: Oncological results of radical prostatectomy in organ-confined disease in RCTs

PRESENT INDICATIONS FOR RADICAL PROSTATECTOMY

- ✓ INTERMEDIATE RISK PROSTATE CANCER
- ✓ HIGH RISK PROSTATE CANCER

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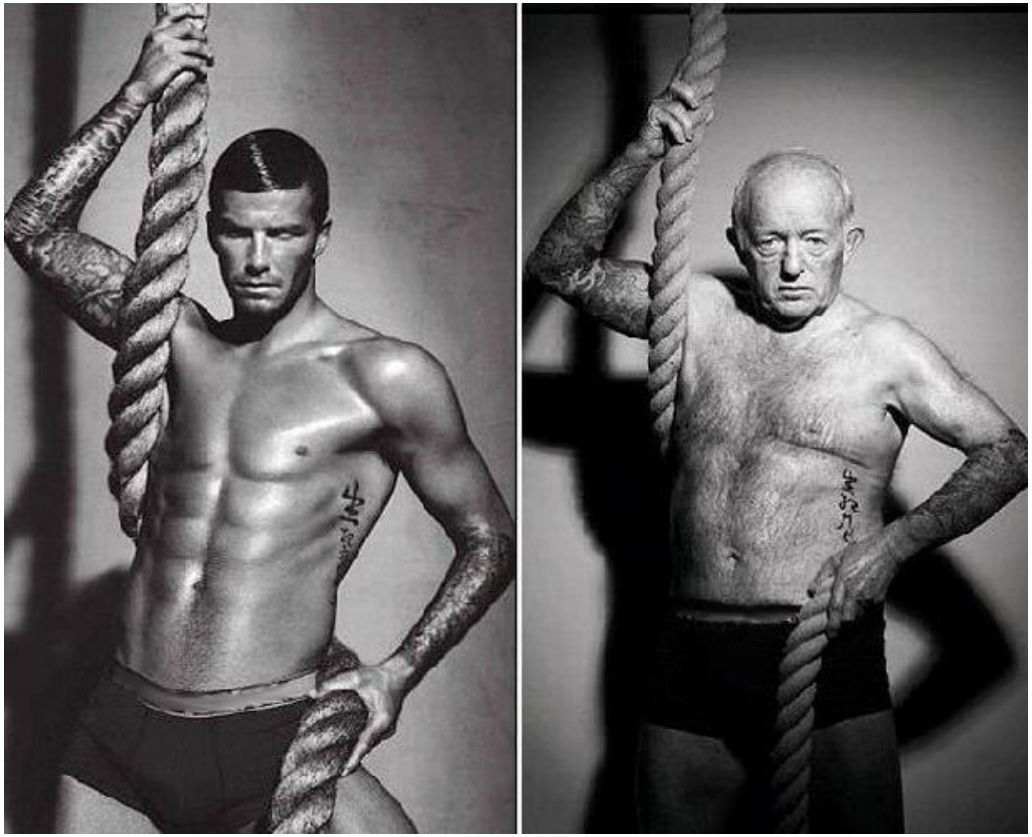
Radical prostatectomy

In addition to the characteristics of the pathology, it is important to evaluate the characteristics of the patient:

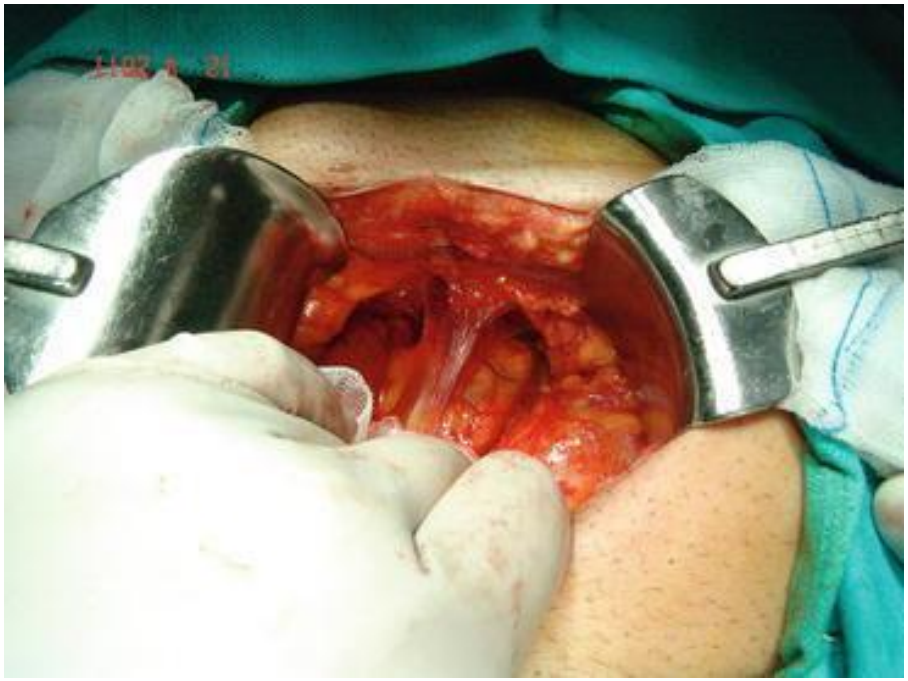
- ✓ Age
- ✓ Performance status
- ✓ Life expectancy

Rarely indicated in patients

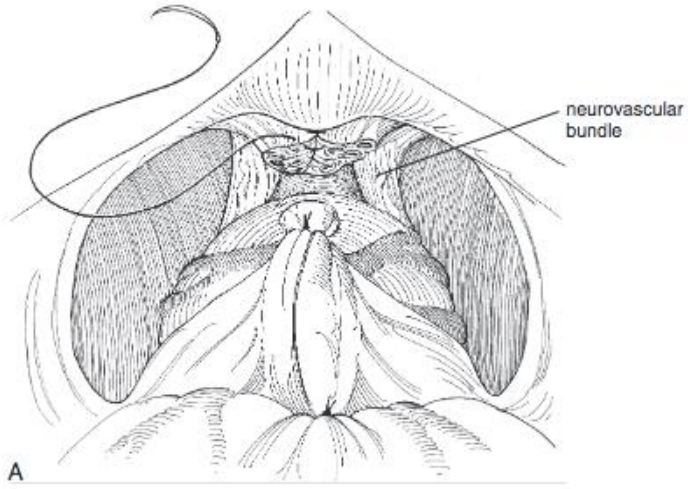
- ✓ Aged > 75 yrs
- ✓ Low performance status

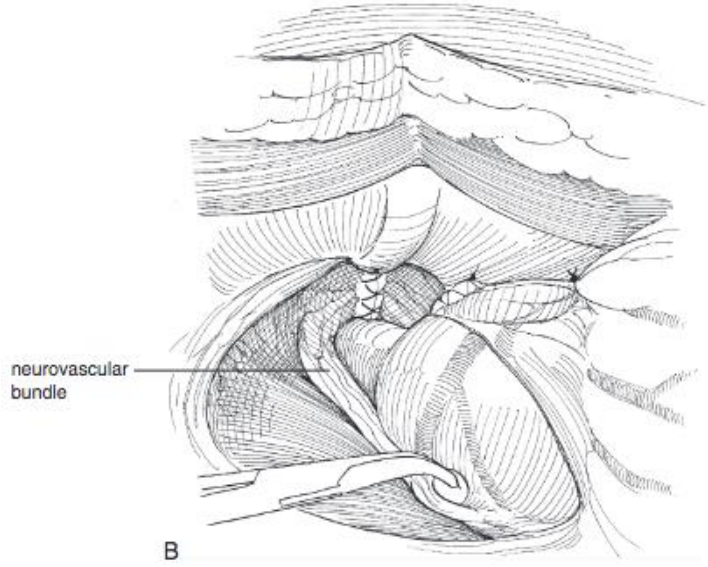


Open Surgery



OPEN SURGICAL TECHNIQUE





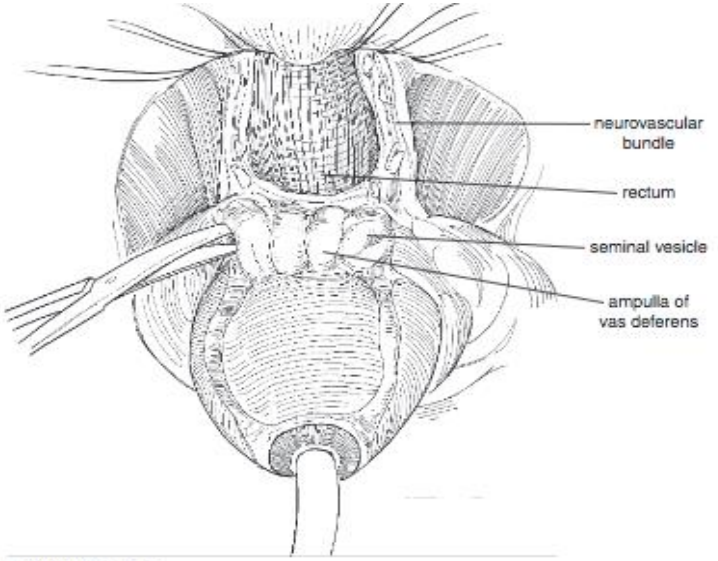


FIGURE 66-7.

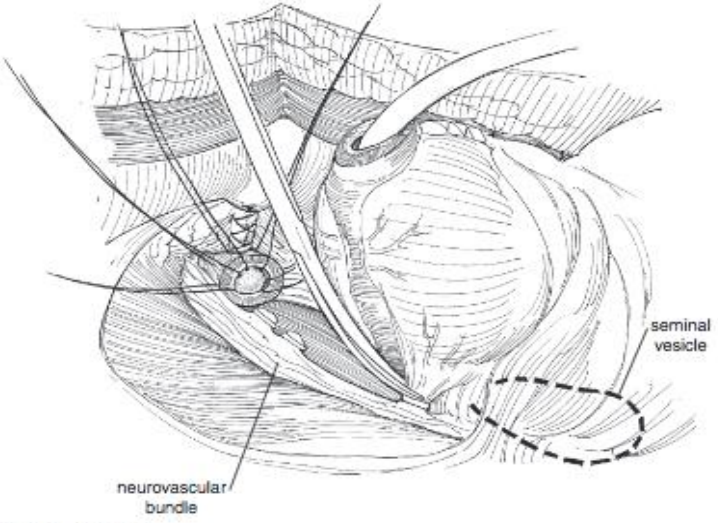


FIGURE 66-8.

OPEN SURGICAL TECHNIQUE

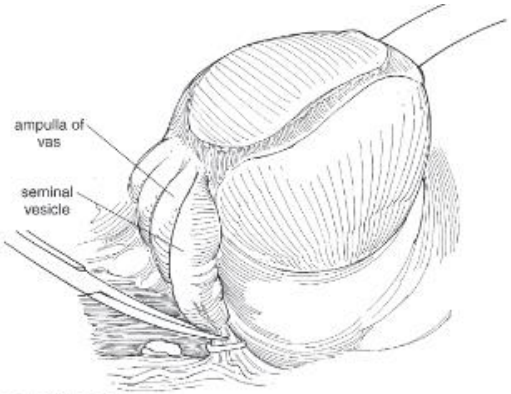


FIGURE 66-9.

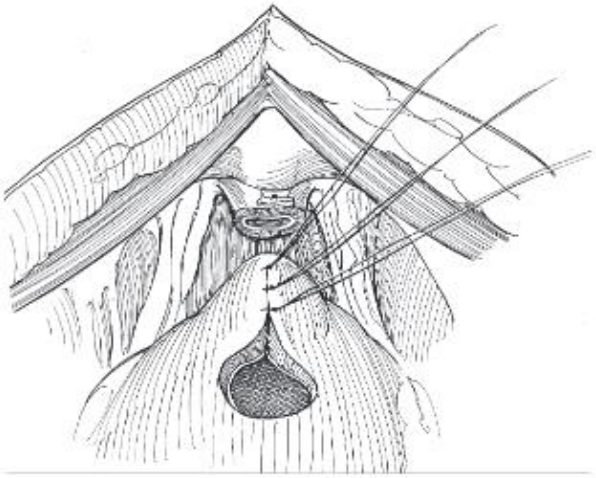
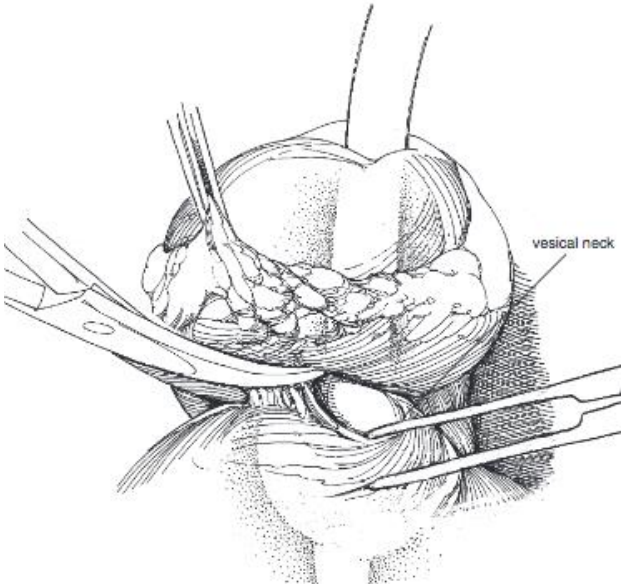


FIGURE 66-13.



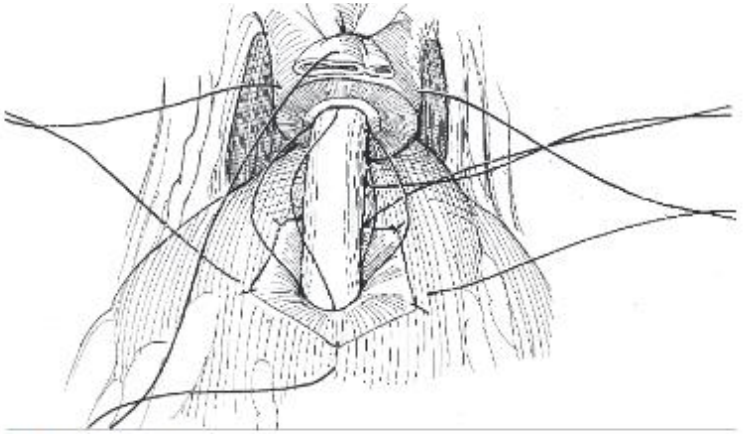
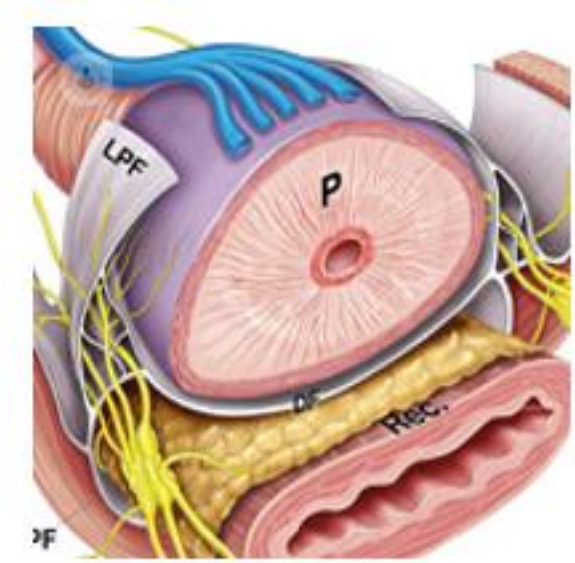


FIGURE 66-15.

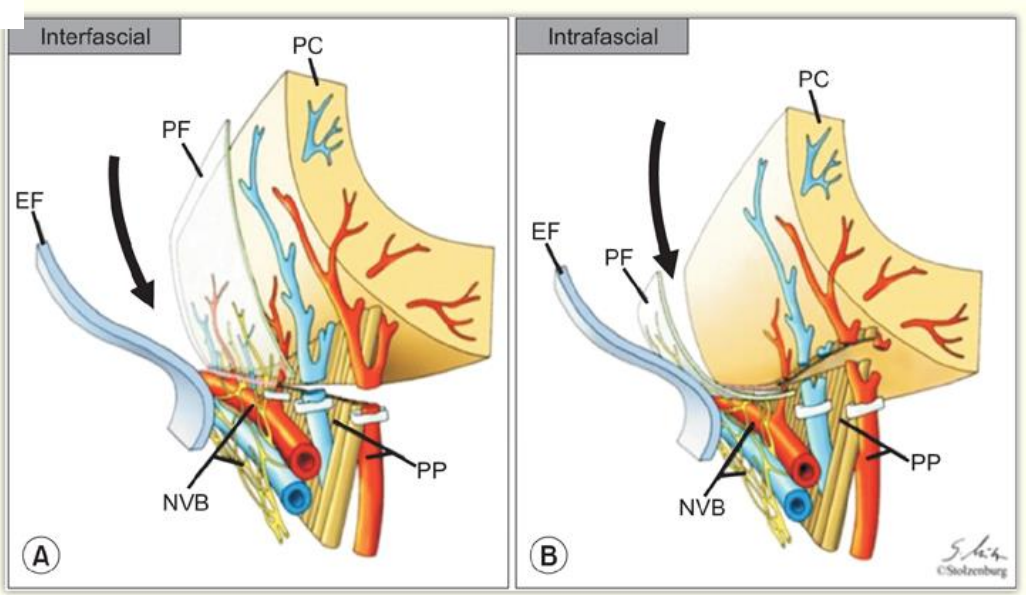
OPEN SURGICAL TECHNIQUE



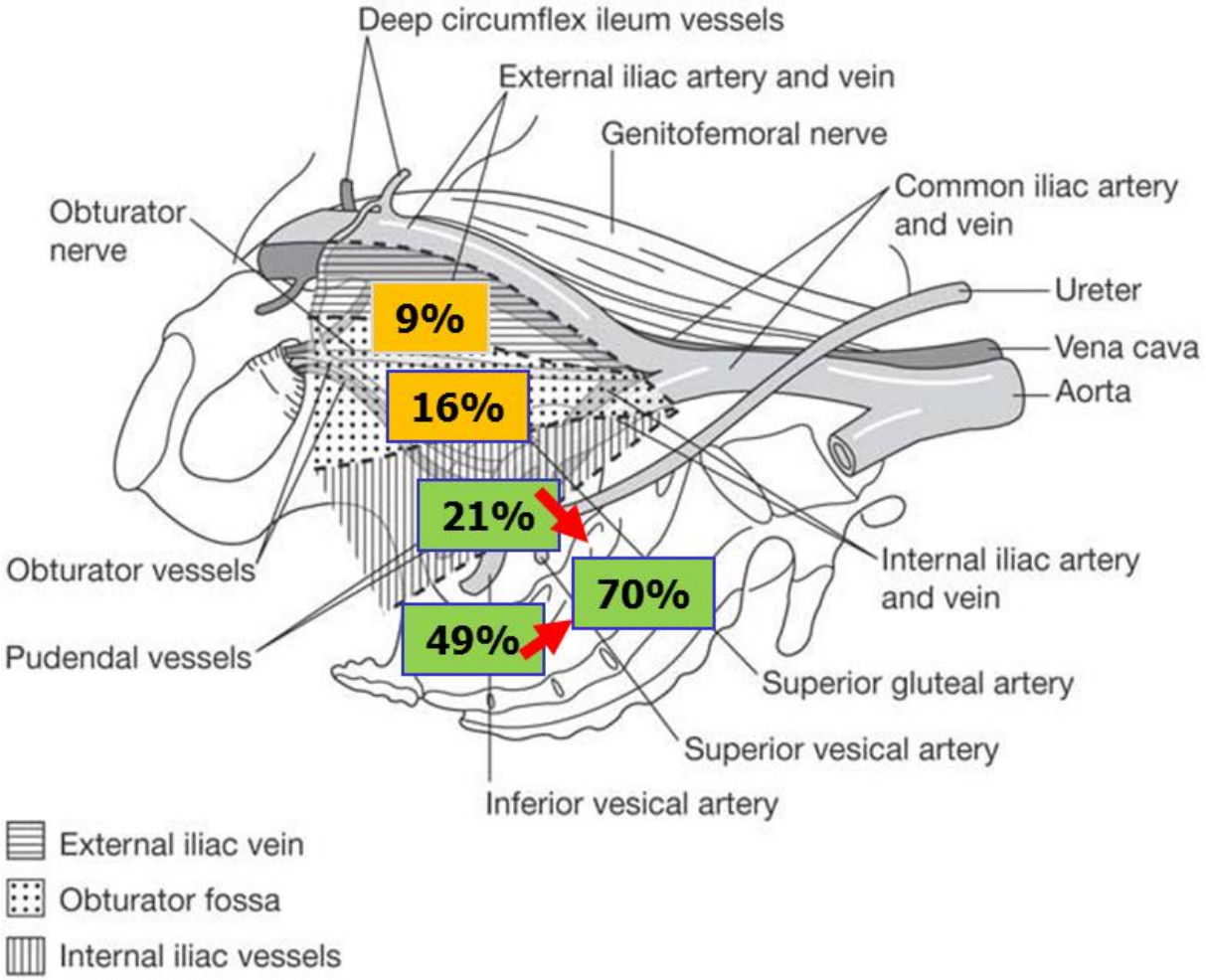
INTRINSIC SPHINCTER:
risk of incontinence

NEUROVASCULAR BUNDLES:
risk of erectile disfunction

NERVE SPARING SURGERY

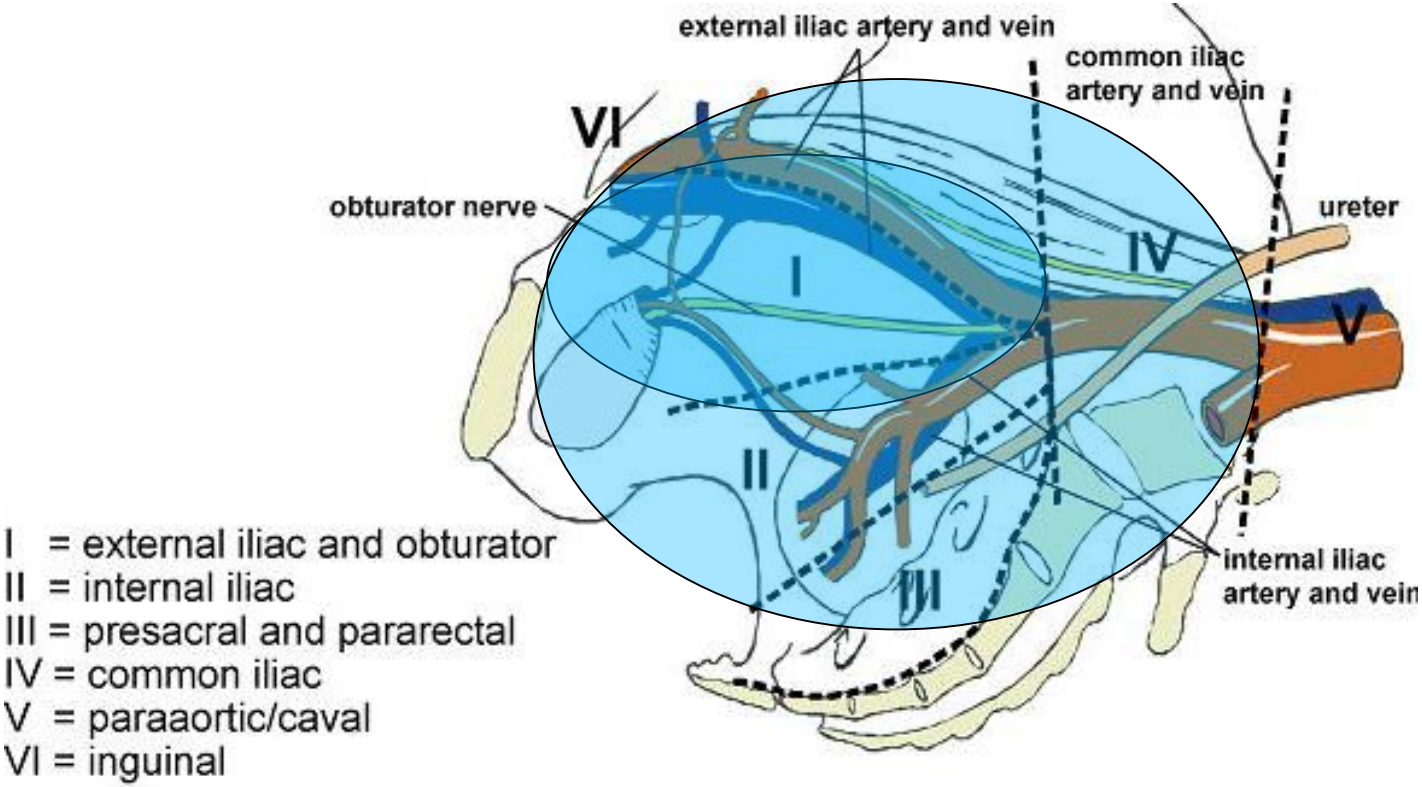


Radical prostatectomy and lymphadenectomy



Mattei et al European Urology 2008, 53:118-125

Radical prostatectomy and lymphadenectomy

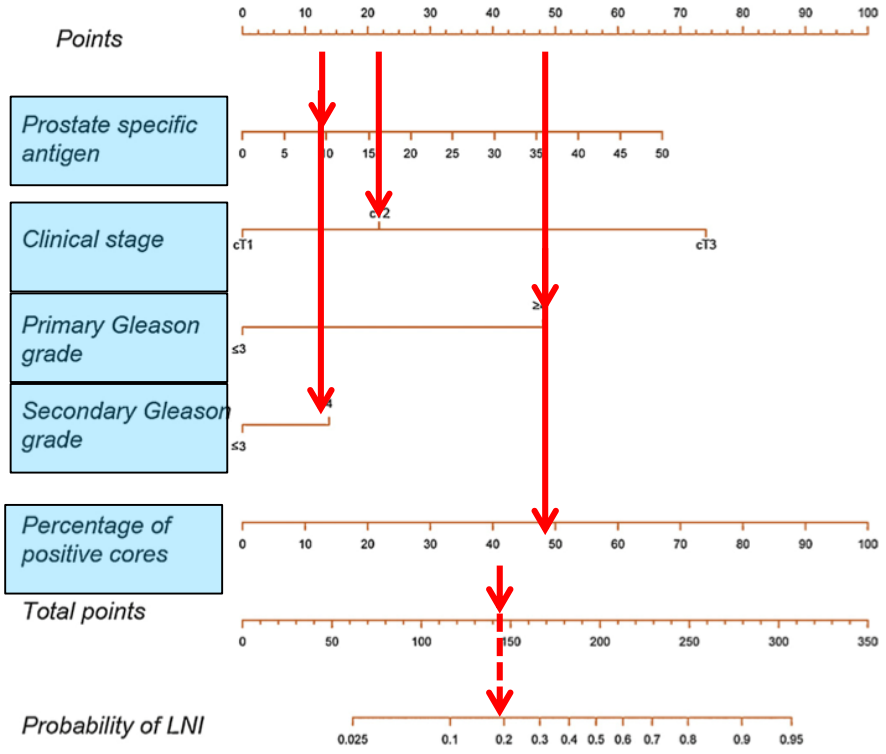


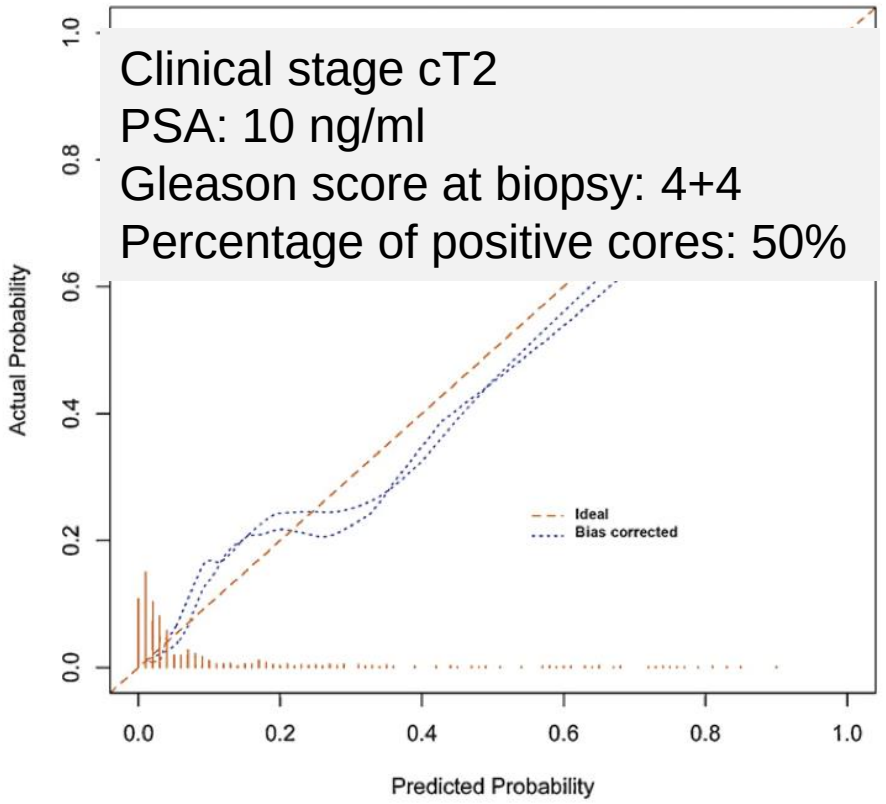
When a lymph node dissection (LND) is deemed necessary, perform an extended LND template for optimal staging.

Mattei et al European Urology 2008, 53:118-125

Nomogram: mathematical tool to calculate the probability of an event

Nomogram for the risk of lymph node invasion





Clinical stage cT2
PSA: 10 ng/ml
Gleason score at biopsy: 4+4
Percentage of positive cores: 50%

Risk of lymph node invasion: 20%

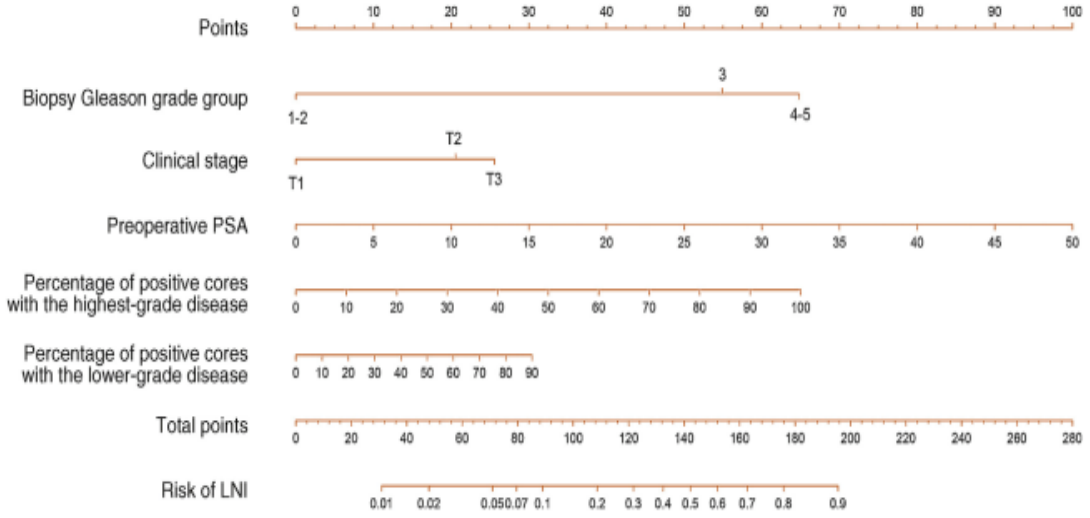
Briganti et al. Eur Urol 2012(61):480-7

EUROPEAN UROLOGY 72 (2017) 632–640

Development and Internal Validation of a Novel Model to Identify the Candidates for Extended Pelvic Lymph Node Dissection in Prostate Cancer

Giorgio Gandaglia [a,b], *Nicola Fossati* [a,b], *Emanuele Zaffuto* [a,b,c], *Marco Bandini* [a,b], *Paolo Dell'Oglio* [a,b], *Carlo Andrea Bravi* [a,b], *Giuseppe Fallara* [a,b], *Francesco Pellegrino* [a,b], *Luigi Nocera* [a,b], *Pierre I. Karakiewicz* [c], *Zhe Tian* [c], *Massimo Freschi* [d], *Rodolfo Montironi* [e], *Francesco Montorsi* [a,b], *Alberto Briganti* [a,b,*]

[a] *Unit of Urology/Division of Oncology, URI, IRCCS Ospedale San Raffaele, Milan, Italy;* [b] *Vita-Salute San Raffaele University, Milan, Italy;* [c] *Cancer Prognostics and Health Outcomes Unit, University of Montreal Health Center, Montreal, Canada;* [d] *Unità Operativa Anatomia Patologica, IRCCS Ospedale San Raffaele, Milan, Italy;* [e] *Section of Pathological Anatomy, Polytechnic University of the Marche Region, School of Medicine, United Hospitals, Ancona, Italy*



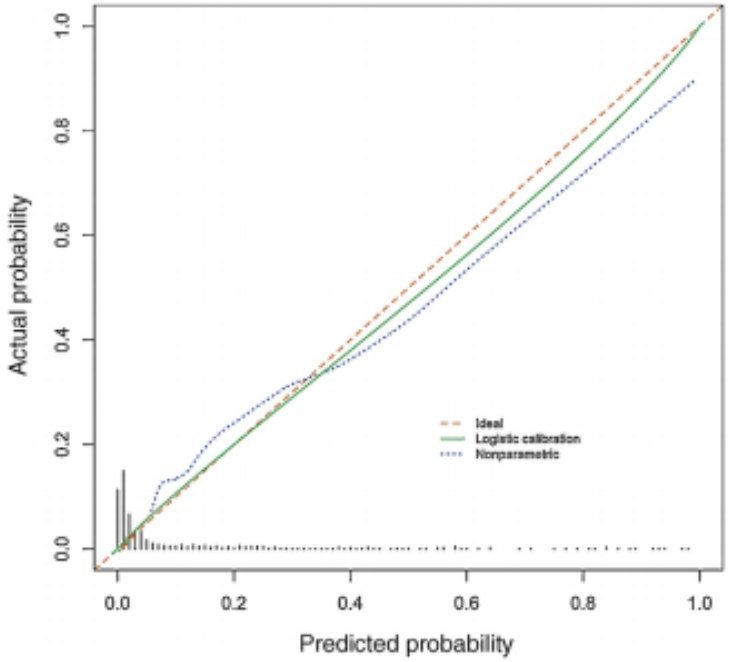
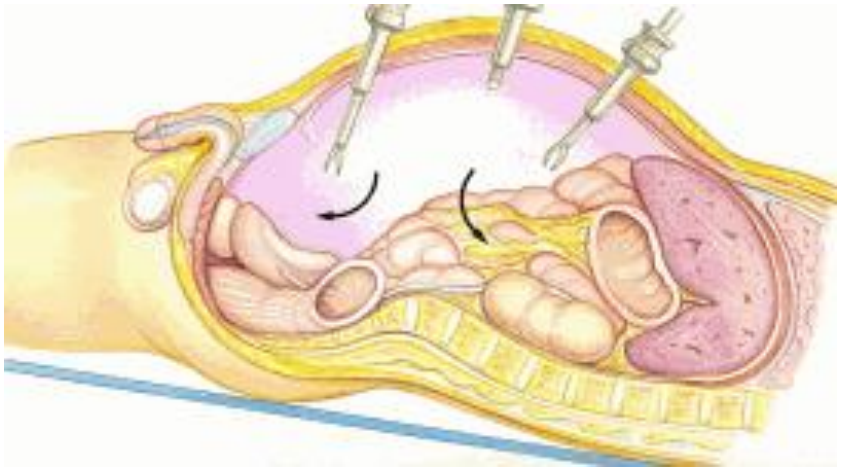
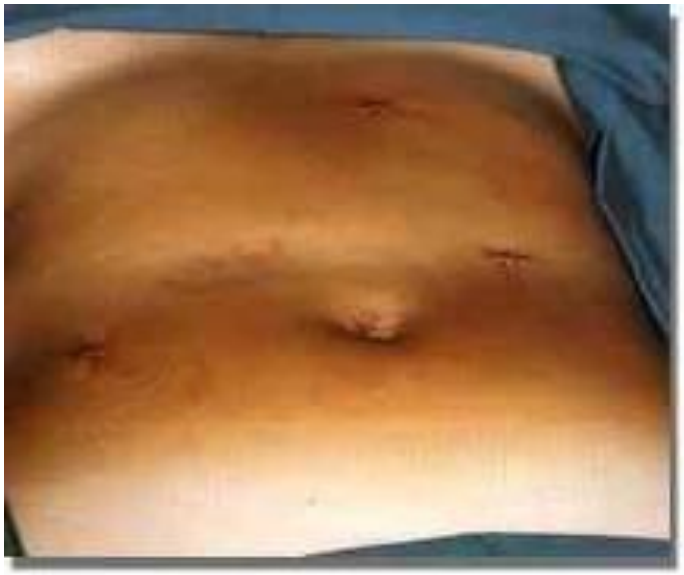
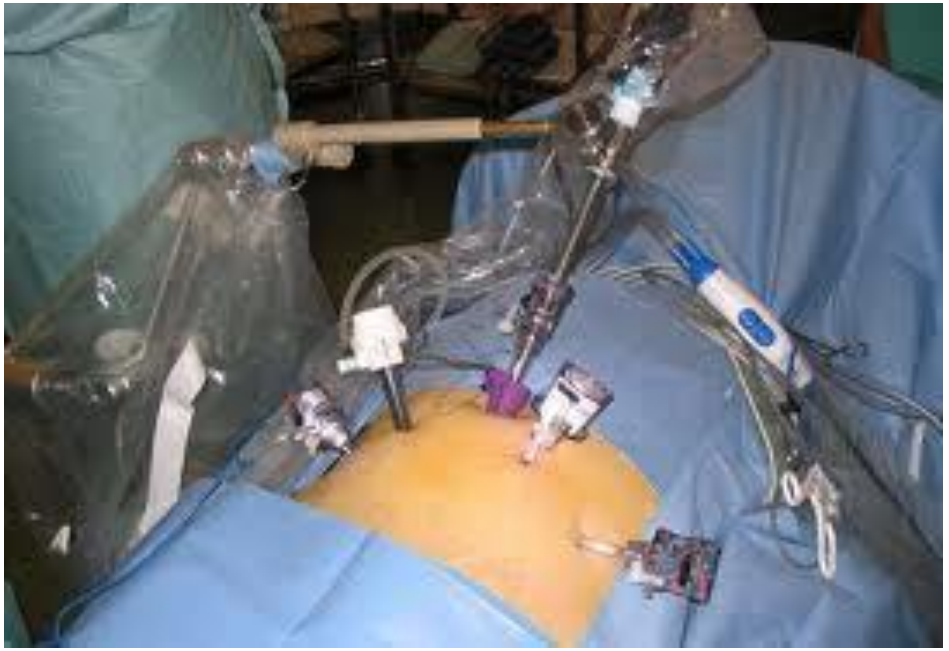


Fig. 2 – Calibration plot of observed proportion versus predicted probability of lymph node invasions of the novel nomogram.

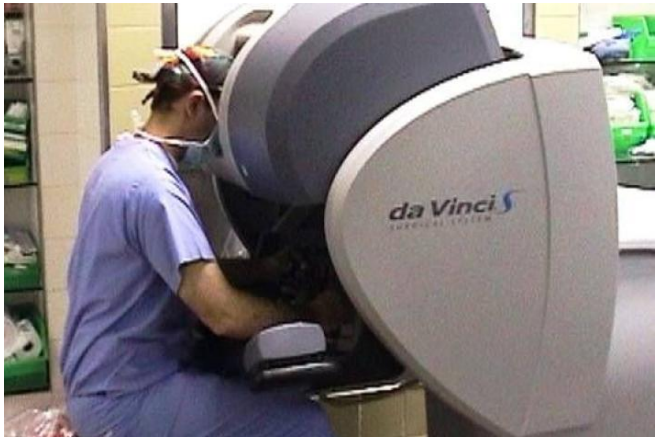
Laparoscopic prostatectomy





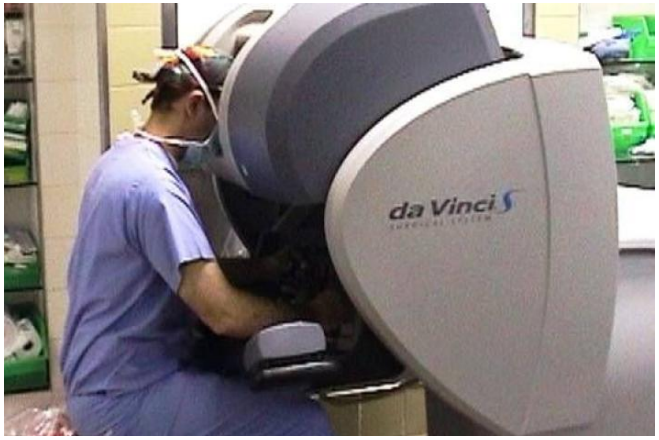


Robotic Surgery: RARP



- Robotic surgery is developed laparoscopy.
- Robotic instruments are flexible and simulate surgeon's fingers and wrist movements.
- The operator can move them in a 3D up to 10 x magnificated vision.

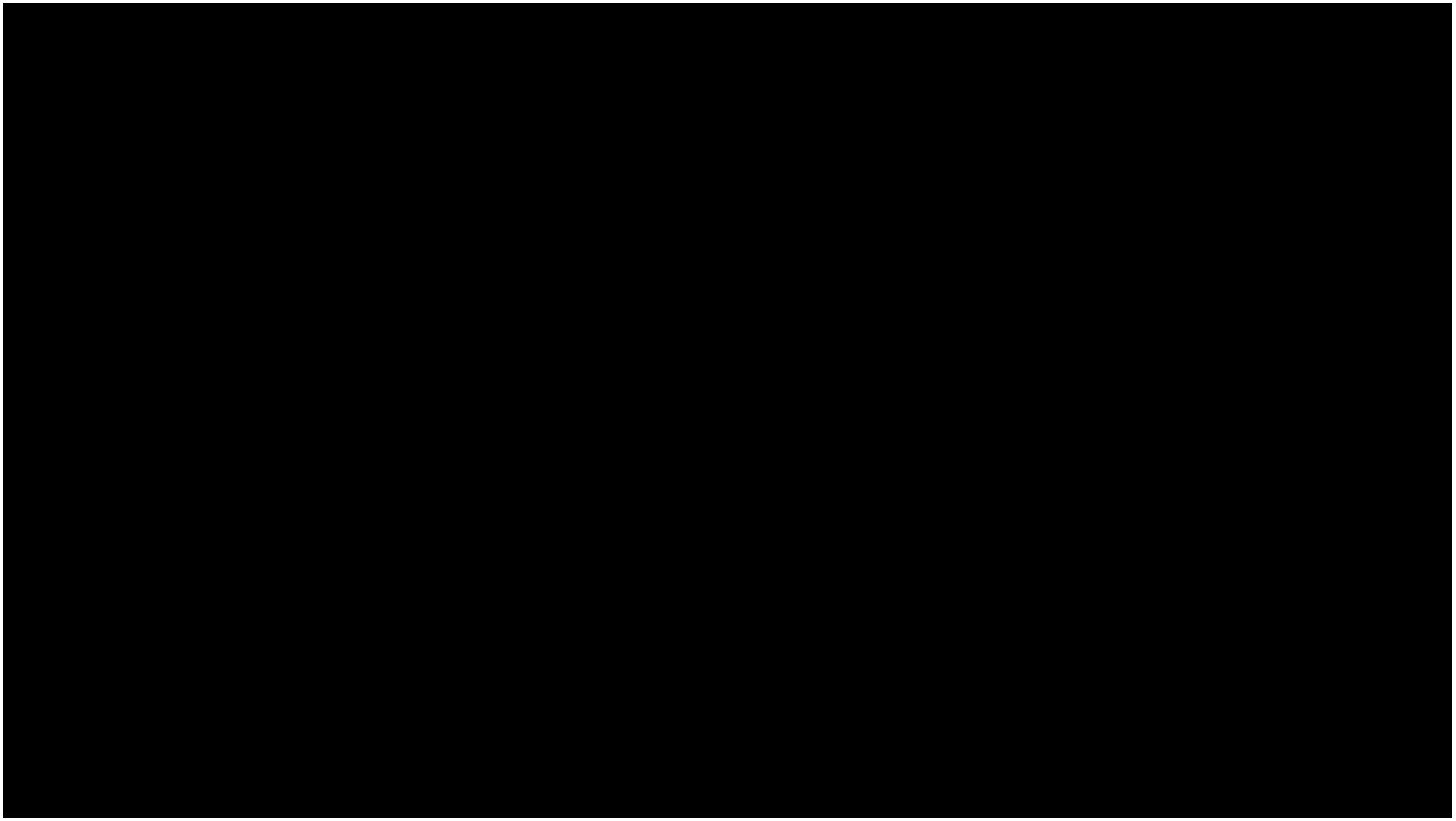
Robotic Surgery: RARP



- Robotic radical prostatectomy (RARP) has shown shorter hospitalization times and reduced intra-operative blood loss, but the benefits relative to functional or oncological outcomes are still doubtful.

- Some studies show higher rates of erectile function recovery and faster continence recovery in patients treated with RARP. Others do not.

Robotic Surgery: Surgical Technique



Robot-Assisted Radical Prostatectomy (RARP)

- Robotic prostatectomy (**RARP**) is replacing open prostatectomy as the **gold standard treatment for clinically localized prostate cancer.**

- However, **this trend is not supported by high level evidence** demonstrating the superiority of a surgical technique over the other.

Treatment options

- ✓ Active surveillance
- ✓ Surgery: Radical prostatectomy
- ✓ **Radiotherapy / Brachytherapy**
- ✓ Focal therapy
- ✓ Hormonal therapy

External –beam Radiotherapy

External beam Radiotherapy

- Intensity-modulated radiotherapy (IMRT), with or without image-guided radiotherapy (IGRT), is the gold standard for external beam radiation therapy (EBRT)

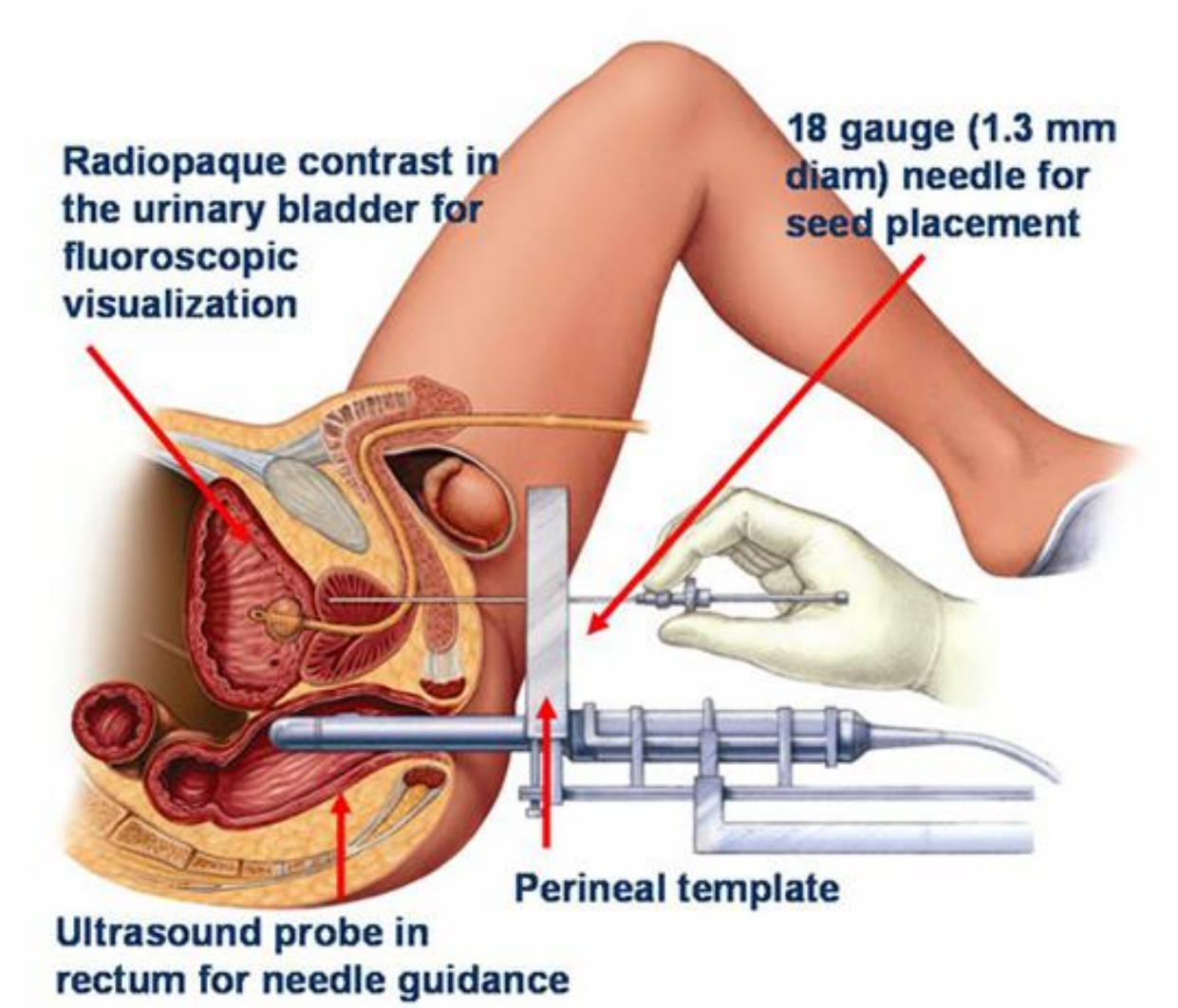
- IMRT employs dynamic multileaf collimators, which automatically and continuously adapt to the contours of the target volume seen by each beam. The modulation of the radiation allows to diversify the radiation dose directed towards the tumor from that directed towards the surrounding tissues.

- Gastrointestinal and urinary side effects are common during and after EBRT.

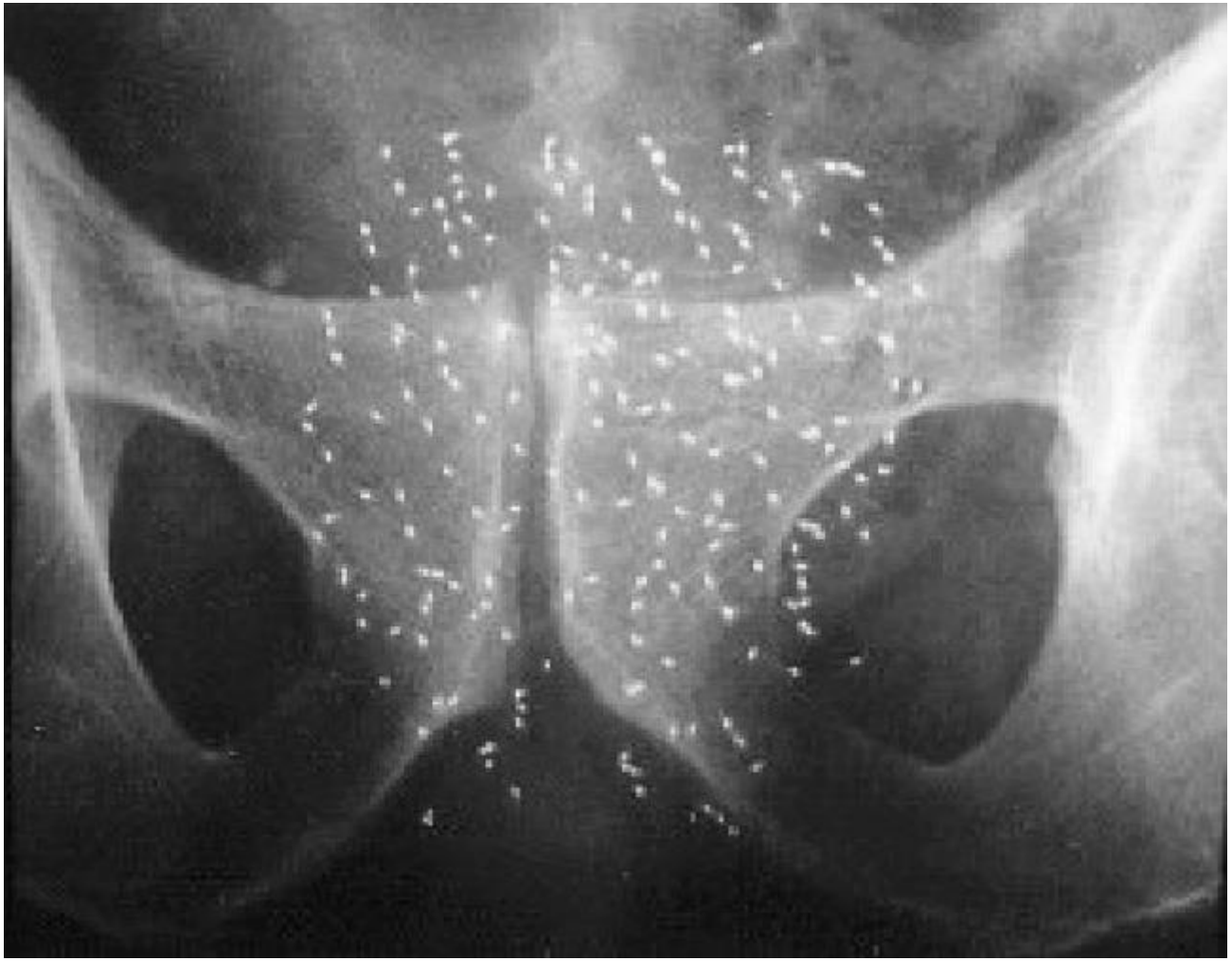
Intensity-modulated radiotherapy

Intermediate/high risk category

Brachytherapy



Brachytherapy



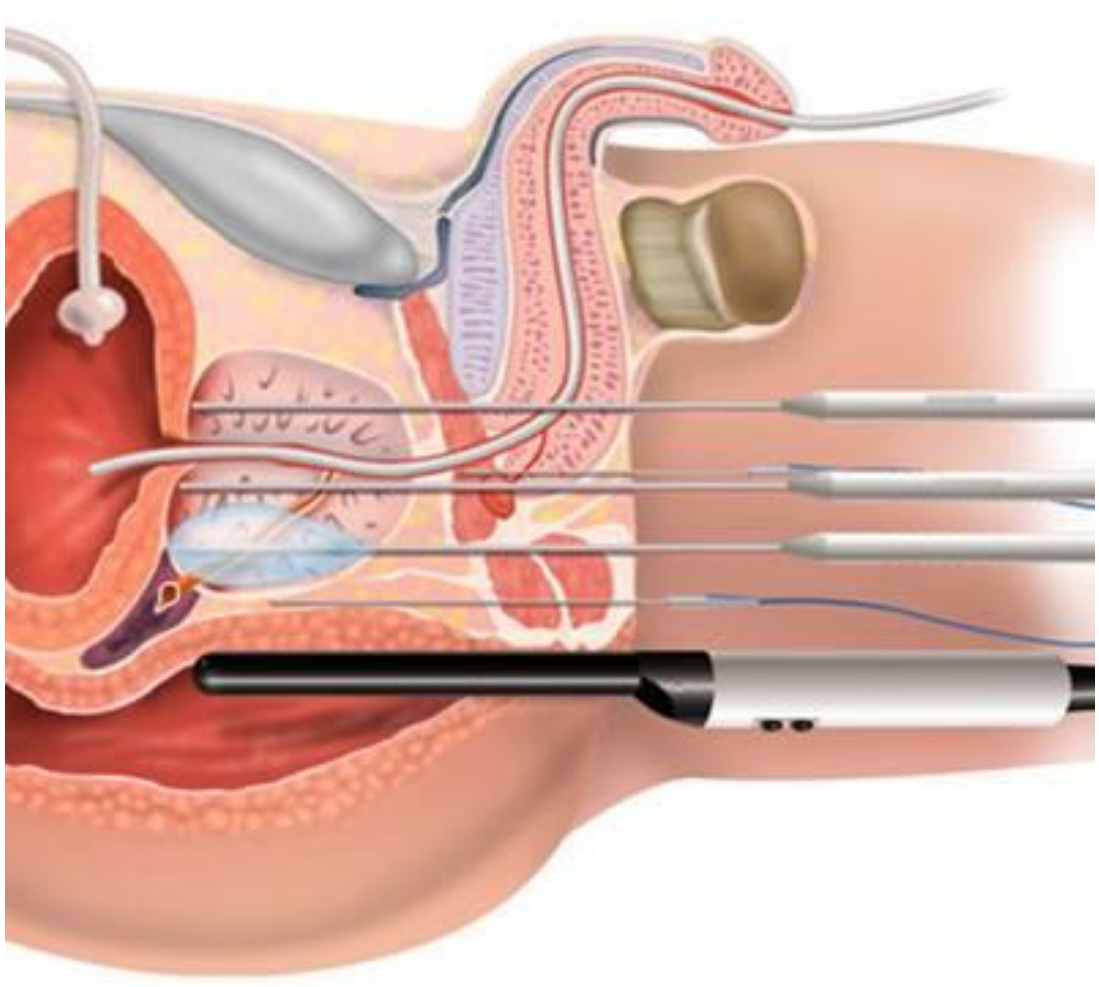
Treatment options

- ✓ Active surveillance
- ✓ Surgery: Radical prostatectomy
- ✓ Radiotherapy / Brachytherapy
- ✓ **Focal therapy**
- ✓ Hormonal therapy

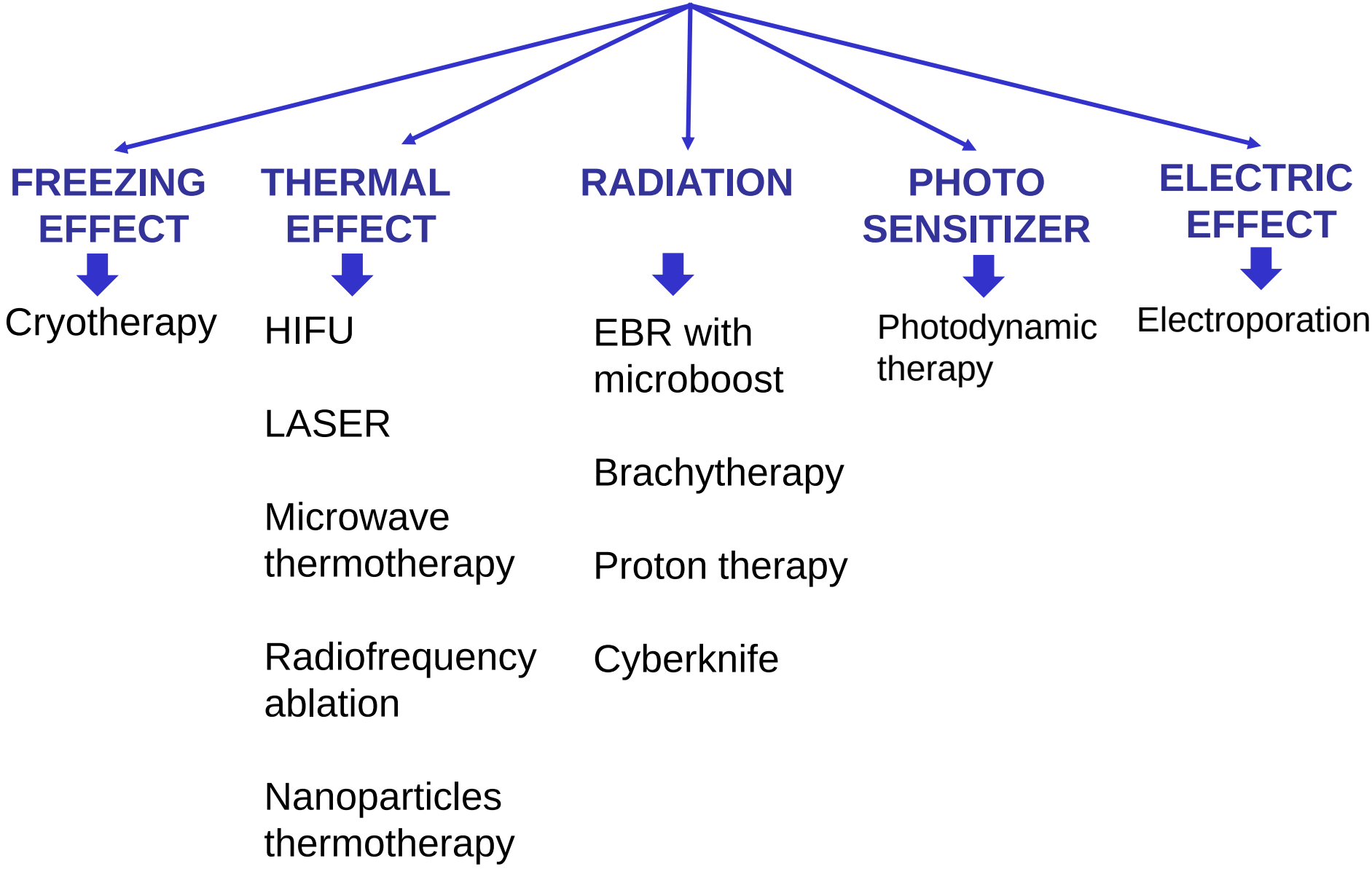
Focal Therapy

- ✓ Early identification of prostate cancer has reduced the use of radical treatments in favor of conservative approaches.
- ✓ However, many men are still reluctant to active surveillance or watchful waiting.
- ✓ For these patients, an alternative approach is **focal therapy.**

Focal Therapy



ENERGIES USED IN FOCAL THERAPY



Focal Therapy

- ✓ Focal therapy is today reserved only for patients with clinical low risk prostate cancer.
- ✓ Focal therapy is an alternative to active surveillance (cancer-specific mortality: 1%).

What is a better treatment than no treatment?

Treatment options

- ✓ Active surveillance
- ✓ Surgery: Radical prostatectomy
- ✓ Radiotherapy / Brachytherapy
- ✓ Focal therapy
- ✓ **Hormonal therapy**

Charles Brenton Huggins, MD

The prostate gland is under the control of male sex hormones

Hormone manipulation caused the tumors to shrink

Similar regulation of some forms of breast cancer later discovered

These discoveries formed the basis of hormone therapy prescribed for >50% of breast and prostate cancer

Medicine, 1966

Hormonal therapy

The reduction of serum testosterone levels, necessary to counteract the growth of cancer cells, can be achieved in various ways:

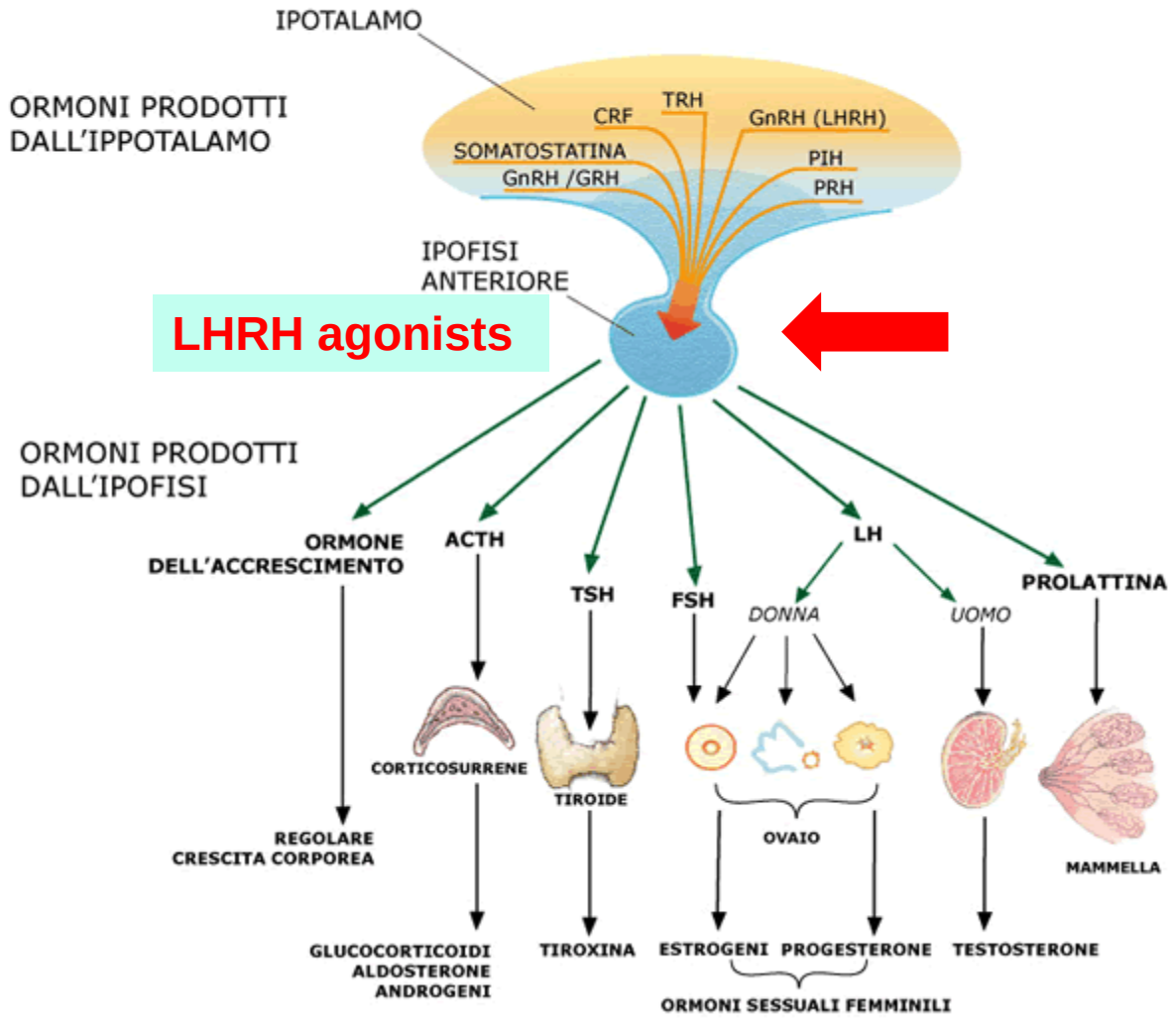
- **Bilateral orchiectomy**

- **LHRH agonists** act on the hypothalamus-pituitary axis blocking the testicular production of LH an thus testosterone (*Leuprolide* – *Triprorelina*)

- **Peripheral antiandrogens** block the interaction between the male sex hormone and its receptors, thus inhibiting tumor growth (*Ciproterone acetato, Bicalutamide, Flutamide, Nilutamide)*

- **LHRH antagonists** block, at the level of the hypothalamus, the initial stimulus from which the cascade of messages that pushes testicles to produce sex hormones starts (*Degarelix)*

SINTESI DEGLI ORMONI DELL'ASSE IPOTALAMO - IPOFISI - OVAIO COINVOLTI NELLA RIPRODUZIONE

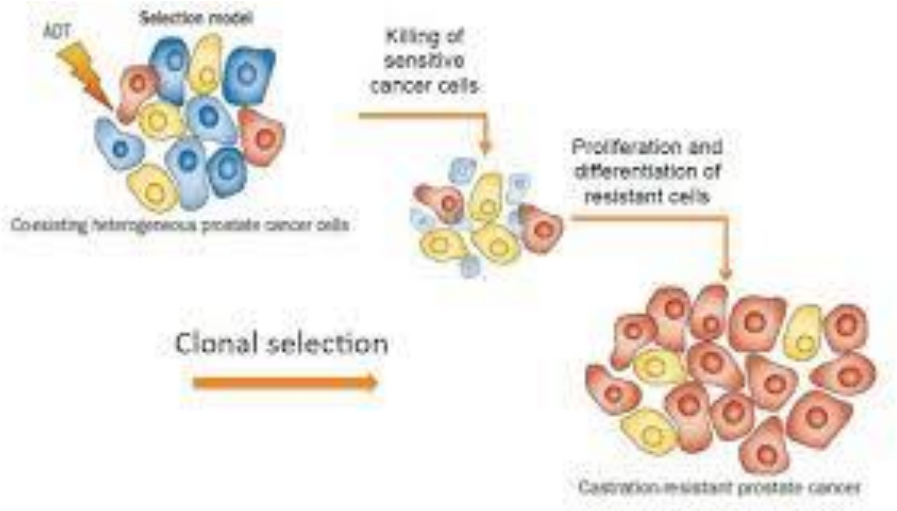


Treatment of Metastatic Prostate Cancer
LHRH agonists

- Offer immediate systemic treatment with androgen deprivation therapy (ADT) to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction) to M1 symptomatic patients.

- Offer immediate systemic treatment also to M1 asymptomatic patients to improve survival, postpone progression to a symptomatic stage and prevent serious complications related to the progression of the disease.

CASTRATION-RESISTANT PROSTATE CANCER DEFINITION



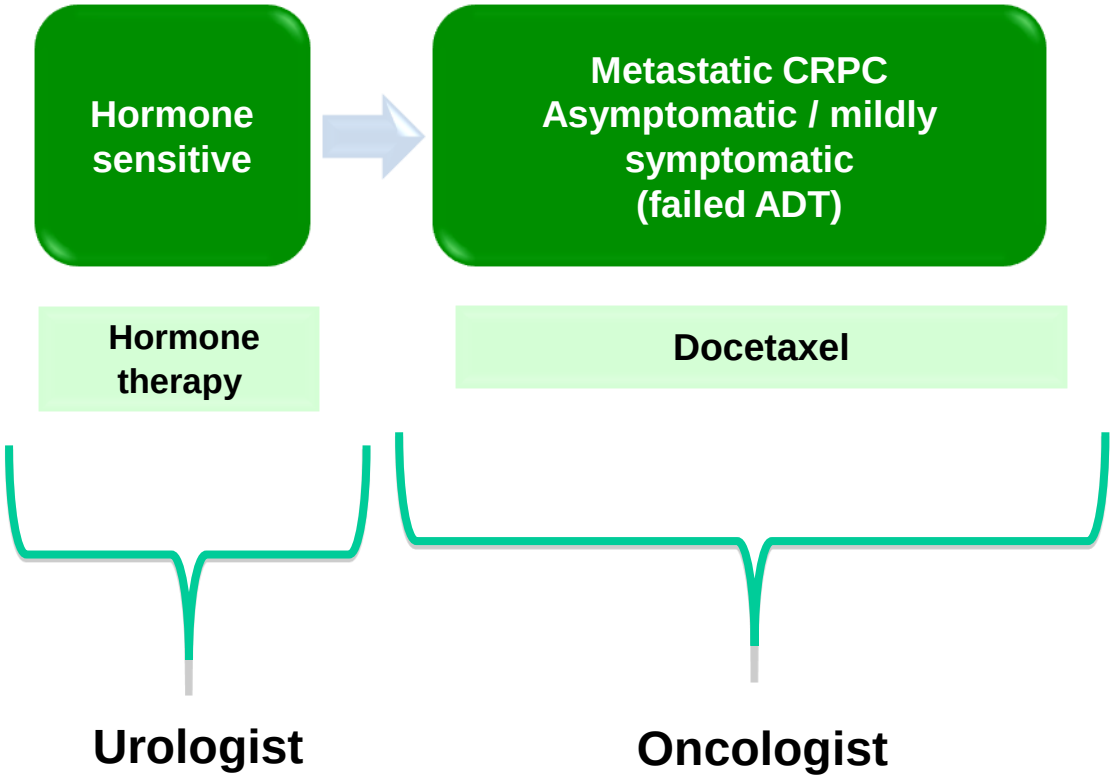
Castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either:

- **Biochemical progression**: Three consecutive rises in PSA at least one week apart resulting in two 50% increases over the nadir, and a PSA > 2 ng/mL

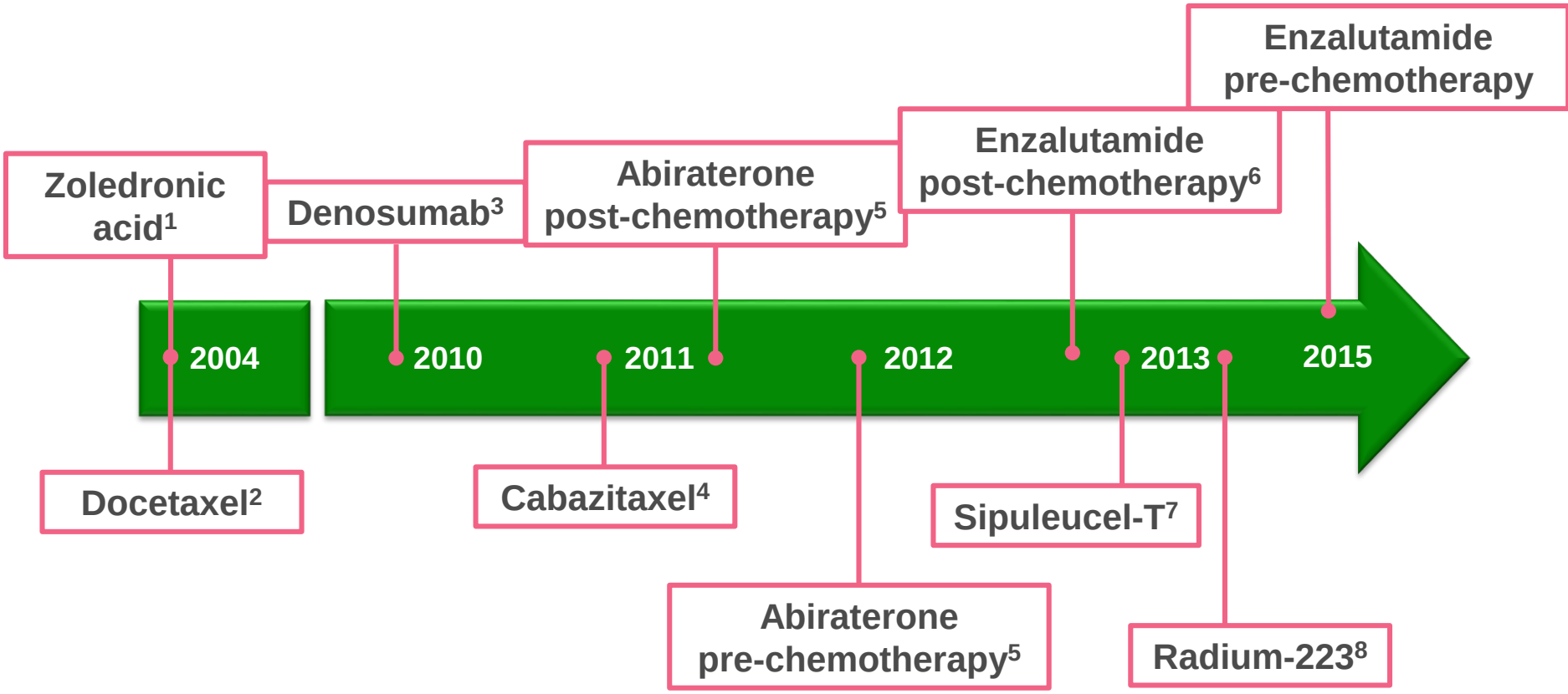
or

- **Radiological progression**: The appearance of new lesions: either two or more new bone lesions on bone scan or a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumours).

Treatment of Metastatic Prostate Cancer



Changing in treatment paradigm



Dates correspond to EMA approval.
EMA=European Medicines Agency; mCRPC=metastatic castration-resistant prostate cancer.

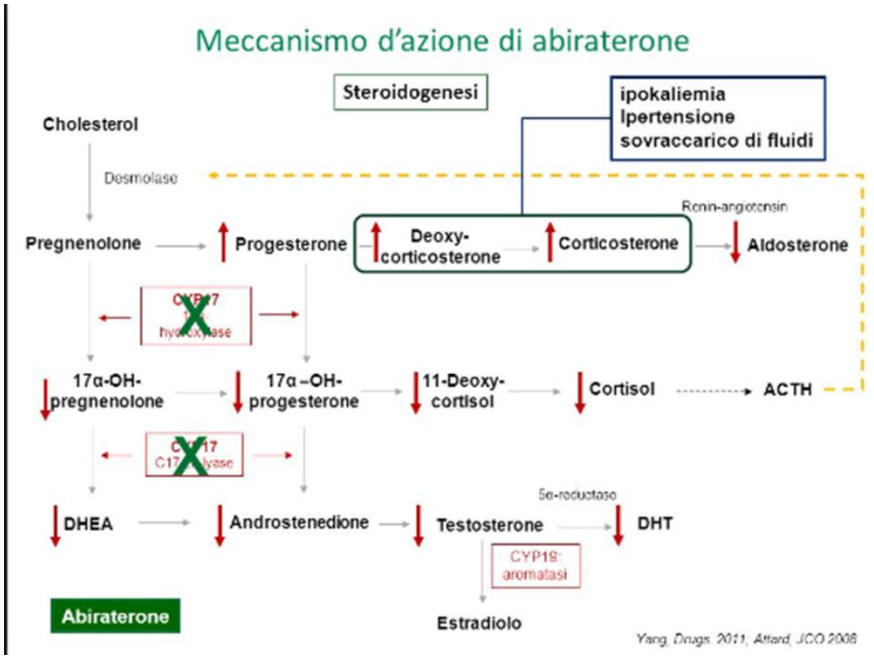
1.Zometa (zoledronic acid). Summary of product characteristics. February 2014.
2.Taxotere (docetaxel). Summary of product characteristics. August 2013.
3.Prolia (denosumab). Summary of product characteristics. May 2010.
4.Jevtana (cabazitaxel). Summary of product characteristics. September 2013.
5. Zytiga (abiraterone). Summary of product characteristics. August 2013.
6. Xtandi (enzalutamide). Summary of product characteristics. July 2013.
7. Provenge (sipuleucel-T). Summary of product characteristics. October 2013.
8. Xofigo (radium 223). Summary of product characteristics. November 2013.

NEW ANTIANDROGENS

ABIRATERONE ACETATE

Selective and irreversible CYP17 inhibitor that can significantly reduce intracellular testosterone levels.

It suppresses testosterone synthesis in the adrenals and within cancer cells.

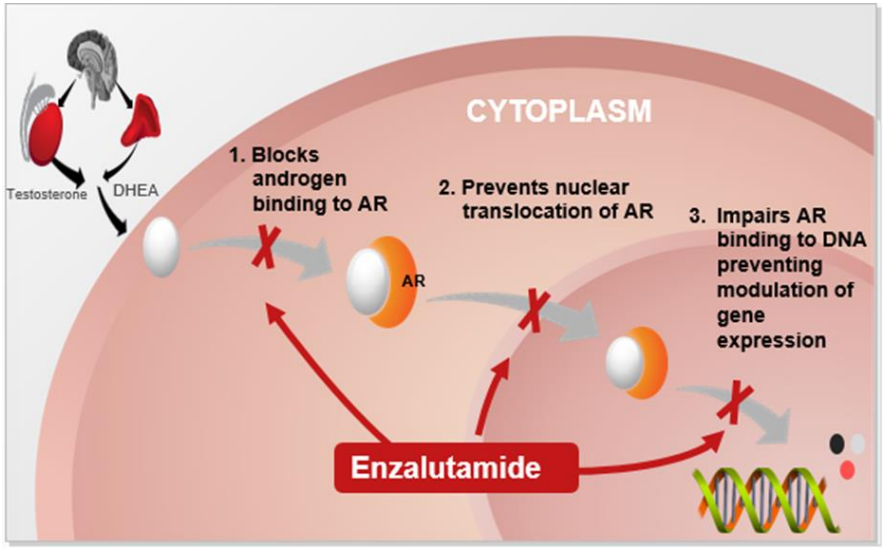


NEW ANTIANDROGENS

ENZALUTAMIDE

New peripheral anti-androgen with greater affinity for AR receptor than bicalutamide.

It also blocks the nuclear transfer of AR thus suppressing its transcriptional activity.



PROSTATE CANCER UNIT

Core Team

Urologists
Radioterapists
Oncologists
Psychologists
Anatomopathologists
Professional Nurses

Non Core Team

Radiotherapists (for brachytherapy)
Medical Physicists
Nuclear Doctors
Radiologists
Rehabilitators
Specialists in Support and Palliative Therapies

Project Team*

Project Manager
Secretary
Research Nurses
Data entry e management

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Critical Reviews in Oncology/Hematology xxx (2015) xxx–xxx

Oncology Hematology

www.elsevier.com/locate/critrevonc

Prostate Cancer Unit Initiative in Europe: A position paper by the European School of Oncology

Riccardo Valdagni[a,b,c,*], Hendrik Van Poppel[d], Michael Aitchison[e], Peter Albers[f], Dominik Berthold[g], Alberto Bossi[h], Maurizio Brausi[i], Louis Denis[j,k], Lawrence Drudge-Coates[l], Maria De Santis[m,n], Günther Feick[j,o], Chris Harrison[p], Karin Haustermans[q], Donal Hollywood[r,1], Morton Hoyer[s], Henk Hummel[t], Malcolm Mason[u], Vincenzo Mirone[v], Stefan C. Müller[w], Chris Parker[x], Mahasti Saghatchian[y], Cora N. Sternberg[z], Bertrand Tombal[aa], Erik van Muilekom[bb], Maggie Watson[cc], Simone Wesselmann[dd], Thomas Wiegel[ee], Tiziana Magnani[b], Alberto Costa[a]

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1 In memoriam Prof. Donal Hollywood, President-Elect of the European Society for Radiotherapy & Oncology 2011–2013.

http://dx.doi.org/10.1016/j.critrevonc.2015.05.014
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Clinical case – 1

Doctor… I'm 40 years old

- ✓ Tripled risk of developing prostate cancer (familiarity)
- ✓ The lack of symptoms has no relevance
- ✓ You must perform a PSA and a urological visit and then start screening.

When should I start screening?
Which checks?

Clinical case – 2

PSA (ng/ml)	rischio di tumore
< 1	8%
1-2	17%
2-4	25%
4-10	47%
> 10	59%

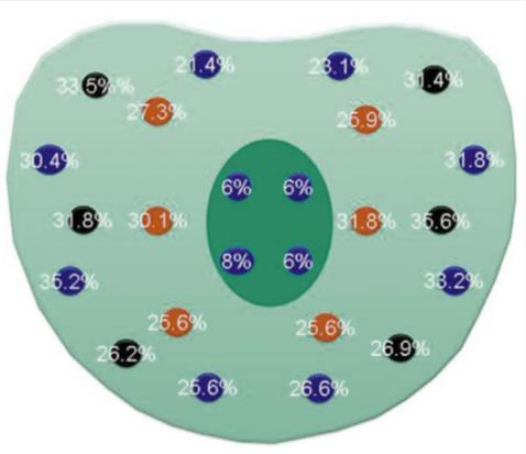
No you cant!

Transrectal ultrasound of the prostate: very low sensitivity

You should have e multiparametric MRI of the prostate

… and biopsies

Clinical case – 3



It is nice to have a negative MRI but ….

Multiparametric MRI → negative predictive value: 80-85%

We should take in consideration systematic biopsies

Clinical case – 4

Table 6.1.2: Active surveillance in screening-detected prostate cancer

Studies	n	Median FU (mo)	pT3 in RP patients	OS (%)	CSS (%)
Van As, *et al.* 2008 [325]	326	22	8/18 (44%)	98	100
Carter, *et al.* 2007 [326]	407	41	10/49 (20%)	98	100
Adamy, *et al.* 2011 [327]	533-1,000	48	4/24 (17%)	90	99
Soloway, *et al.* 2010 [328]	99	45	0/2	100	100
Roemeling, *et al.* 2007 [329]	278	41	-	89	100
Khatami, *et al.* 2007 [330]	270	63	-	n.r.	100
Klotz, *et al.* 2015 [322]	993	77	-	85	98.1
Total	**2,130-3,000**	**43**		**90**	**99.7**

** Patients receiving active therapy following initial active surveillance.*

CSS = cancer-specific survival; FU = follow-up; mo = months; n = number of patients; n.r. = not reported; OS = overall survival; RP = radical prostatectomy.

FOLLOW-UP

Follow-up after treatment with curative intent

7.1.5 Summary of evidence and guidelines for follow-up after treatment with curative intent

Summary of evidence	**LE**
After radical prostatectomy rising serum PSA level is considered a BCR.	3
After radiotherapy, an increase in PSA > 2 ng/mL above the nadir, rather than a specific threshold value, is considered as clinically meaningful BCR.	3
Palpable nodules and increasing serum PSA are signs of local recurrence.	2a

Recommendations	**Strength rating**
Routinely follow up asymptomatic patients by obtaining at least a disease-specific history and serum prostate-specific antigen (PSA) measurement. These should be performed at 3, 6 and 12 months after treatment, then every 6 months until 3 years, and then annually.	Strong
At recurrence, only perform imaging to detect local recurrence if the outcome will affect treatment planning.	Strong
Only offer bone scans and other imaging modalities to men with biochemical recurrence or symptoms suggestive of progression without signs of biochemical relapse.	Strong

Follow-up during hormonal treatment

7.2.7 Guidelines for follow-up during hormonal treatment

Recommendations	Strength rating
Evaluate patients at 3 to 6 months after the initiation of treatment.	Strong
The follow-up strategy must be individualised based on stage of disease, prior symptoms, prognostic factors and the treatment given.	Strong
In patients with stage M0 disease, schedule follow-up at least every 6 months. As a minimum requirement, include a disease-specific history, serum prostate-specific antigen (PSA) determination, as well as liver and renal function in the diagnostic work-up.	Strong
In patients with stage M1 disease, schedule follow-up every 3 to 6 months. As a minimum requirement, include an initial FRAX-score assessment, disease-specific history, digital-rectal examination (DRE), serum PSA, haemoglobin, serum creatinine and alkaline phosphatase measurements in the diagnostic work-up. The testosterone level should be checked, especially during the first year. Pay attention to symptoms associated with metabolic syndrome as a side effect of androgen deprivation therapy. Phospholipid profiles and glucose levels should be checked and treated if abnormal.	Strong
Counsel patients (especially with M1b status) about the clinical signs suggestive of spinal cord compression.	Strong
When disease progression is suspected, adapt/individualise follow-up.	Strong
In patients with suspected progression, assess the testosterone level. By definition, castration resistant PCa requires a testosterone level < 50 ng/dL (< 1 mL/L).	Strong
Do not offer routine imaging to otherwise stable asymptomatic patients.	Weak

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Prostate Cancer

TREATMENT

First line treatment of prostate cancer

The therapeutic approach of prostate cancer, even when clinically localized, has become very complex due to the multiple approaches available depending on the stage

Heidenreich et al. Eur Urol 2014

RISK GROUPS

Definition			
Low-risk	**Intermediate-risk**	**High-risk**	
PSA < 10 ng/mL and GS < 7 (ISUP grade 1) and cT1-2a	PSA 10-20 ng/mL or GS 7 (ISUP grade 2/3) or cT2b	PSA > 20 ng/mL or GS > 7 (ISUP grade 4/5) or cT2c	any PSA any GS (any ISUP grade) cT3-4 or cN+
Localised			**Locally advanced**

GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen.

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Treatment options

- ✓ **Active surveillance**
- ✓ Surgery: Radical prostatectomy
- ✓ Radiotherapy / Brachytherapy
- ✓ Focal therapy

Recommendations Therapeutic Options

Recommendations	Strength rating
Inform patients that no active treatment modality has shown superiority over any other active management options in terms of survival.	Strong
Inform patients that all active treatments have side-effects.	Strong
Surgical treatment	
Inform patients that no surgical approach (open, laparoscopic- or robotic radical prostatectomy) has clearly shown superiority in terms of functional or oncological results.	Strong
Perform an extended lymph node dissection (LND), when a LND is deemed necessary.	Strong
Do not perform nerve sparing surgery when there is a risk of extracapsular extension (based on cT stage, Gleason score, nomogram, multiparametric magnetic resonance imaging).	Strong
Do not offer neoadjuvant androgen deprivation therapy before surgery.	Strong
Radiotherapeutic treatment	
Offer intensity-modulated radiation therapy (IMRT) or volumetric arc external-beam radiotherapy (VMAT) for definitive treatment of PCa by external-beam radiation therapy.	Strong
Only offer moderate hypofractionation (HFX) with IMRT/VMAT, including image-guided radiation therapy to the prostate, to carefully selected patients with localised disease.	Strong
Ensure that moderate HFX adheres to radiotherapy protocols from trials with equivalent outcome and toxicity, i.e. 60 Gy/20 fractions in four weeks or 70 Gy/28 fractions in six weeks.	Strong
Active therapeutic options outside surgery and radiotherapy	
Only offer cryotherapy and high-intensity focused ultrasound within a clinical trial setting.	Strong
Only offer focal therapy within a clinical trial setting.	Strong

Active surveillance

- Active surveillance is a therapeutic option for patients with low-risk, organ confined prostate cancer.

- The aim is to reduce overtreatment in patients in whom treatment can be avoided without giving up curative treatment in case of disease progression.

- Active surveillance may mean not treating patients older than 70 years, while treatment of younger patients can be postponed by several years, also postponing its side effects.

Soloway et al. BJU Int, 2007
Klotz L, J Clin Oncol , 2005

Active Surveillance – Definition

Table 6.1.1: Definitions of active surveillance and watchful waiting [384]

	Active surveillance	Watchful waiting
Treatment intent	Curative	Palliative
Follow-up	Predefined schedule	Patient-specific
Assessment/markers used	DRE, PSA, re-biopsy, mpMRI	Not predefined
Life expectancy	> 10 years	< 10 years
Aim	Minimise treatment-related toxicity without compromising survival	Minimise treatment-related toxicity
Comments	Mainly low-risk patients	Can apply to patients with all stages

DRE = digital rectal examination; PSA = prostate-specific antigen; mpMRI = multiparametric magnetic resonance imaging.

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Active surveillance: selection criteria

Authors	Criteria
Epstein et al	Clinical stage T1c PSA density <0.15 ng/ml No Gleason pattern 4 or 5 <3 positive cores <50% cancer per core
D'Amico et al	PSA level 10 ng/ml No Gleason pattern 4 or 5 Clinical stage T2a or lower
Soloway et al	Clinical stage T2 or lower PSA level <15 ng/ml No Gleason pattern 4 or 5 <50% cancer per two positive Cores
Dall'Era et al	Gleason sum 6 PSA level <10 ng/ml and stable PSA kinetics 50% single core involvement 33% positive cores
Van den Bergh et al. (PRIAS)	Clinical stage T1c–T2b No Gleason pattern 4 or 5 PSA density <0.20 ng/ml PSA level <10 ng/ml Fewer than three positive cores
Klotz et al.	Clinical stage T1c/T2a Age > 70: PSA <15 ng/ml; Gleason ≤3+4 Age < 70: PSA < 10 ng/ml; Gleason 6

Active surveillance: follow-up

	Toronto	Johns Hopkins	PRIAS	UCSF	Miami	Japan
PSA and DRE monitoring	3 monthly PSA and 6 monthly DRE for 2 years; 6 monthly PSA and annual DRE thereafter	6 monthly PSA and DRE	3 monthly PSA and 6 monthly DRE	3 monthly PSA with TRUS at 6-12 month interval	3-4 monthly PSA and DRE for 2 years; 6 monthly thereafter	2 monthly PSA for 6 months; 3 monthly tehreafter. DRE with TRUS every 6 months
Re-biopsy	6-12 months in the first year then every 2-3-years	annually	1, 2 and 7 years or cT3 or PSADT<3 yrs	Every 1-2 years	Annually or triffered by PSA or DRE	At 1 year
Trigger for intervention	PSADT<3 years	Surveillance biopsy breaching selection criteria	Gleason score > 6 or more than 2 positive cores	Gleason upgrade; increase in PSA velocity of 0.75 per year	Gleason upgrade; increase in tumor volume; >2 positive cores	PSADT < 2 yrs; pathological change breaching selection criteria

Active surveillance: PRIAS project

- **PRIAS is an international multicenter active surveillance protocol: enrolled patients are followed with the same follow-up strategy**

- In Italy SIUrO – PRIAS – ITA offers the opportunity to participate in the international protocol (Coordinating Centre: Programma Prostata, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano)

- Once the inclusion criteria and the absence of exclusion criteria have been verified, the patient is entered into the database by the coordinator center

Active surveillance: PRIAS project

- **Follow-up is entrusted to the center to which the patient adheres** through the website www.prias-project.org

- Follow-up
  - PSA every 3 months
  - PSA and DRE every 6 months
  - Biopsy at 12, 48 and 84 months after the first diagnosis
  - mpRM before re-biopsy

- If PSA Doubling Time less than 10 years: extra biopsy if not performed during the last 12 months; as an alternative to biopsy, prostate MRI, possibly followed by targeted biopsy of suspected lesions

- If PSA > 20 ng/ml: bone scintigraphy

Active surveillance: PRIAS project

- ***The interruption of the observational path is the responsibility of the coordinating centre***

Criteria for interrupting the observational program

- Number of positive cores >2 at re-biopsy (upsizing) (if mpMRI not carried out at the time of inclusion)
- Gleason Score >3+3=6 at re-biopsy (upgrading)
- Clinical stage at digital rectal examination ≥T2b
- Patient choice

Active surveillance: Outcomes

Table 6.1.2: Active surveillance in screening-detected prostate cancer

Studies	N	Median FU (mo)	pT3 in RP patients*	10-year OS (%)	10-year CSS (%)
Van As, *et al.* 2008 [389]	326	22	8/18 (44%)	98	100
Carter, *et al.* 2007 [390]	407	41	10/49 (20%)	98	100
Adamy, *et al.* 2011 [391]	533-1,000	48	4/24 (17%)	90	99
Soloway, *et al.* 2010 [392]	99	45	0/2	100	100
Roemeling, *et al.* 2007 [393]	278	41	-	89	100
Khatami, *et al.* 2007 [394]	270	63	-	n.r.	100
Klotz, *et al.* 2015 [395]	993	77	-	85	98.1
Tosoian, *et al.* 2015 [388]	1,298	60	-	93	99.9
Total	**4,204-4,671**	**46.5**	**-**	**93**	**100**

** Patients receiving active therapy following initial active surveillance.*

CSS = cancer-specific survival; FU = follow-up; mo = months; n = number of patients; n.r. = not reported; OS = overall survival; RP = radical prostatectomy.

Watchful Waiting – Definition

Table 6.1.1: Definitions of active surveillance and watchful waiting [384]

	Active surveillance	Watchful waiting
Treatment intent	Curative	Palliative
Follow-up	Predefined schedule	Patient-specific
Assessment/markers used	DRE, PSA, re-biopsy, mpMRI	Not predefined
Life expectancy	> 10 years	< 10 years
Aim	Minimise treatment-related toxicity without compromising survival	Minimise treatment-related toxicity
Comments	Mainly low-risk patients	Can apply to patients with all stages

DRE = digital rectal examination; PSA = prostate-specific antigen; mpMRI = multiparametric magnetic resonance imaging.

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Recommendations

Recommendations	Strength rating
Watchful waiting (WW)	
Offer a WW policy to asymptomatic patients with a life expectancy < ten years (based on comorbidities).	Strong
Active surveillance (AS)	
Offer AS to patients suitable for curative treatment but with low-risk PCa.	Strong
Perform multiparametric magnetic resonance imaging before a confirmatory biopsy.	Strong
During confirmatory biopsy include systematic and targeted biopsies.	Strong
Base follow up on digital rectal examination, prostate-specific antigen and repeated biopsies.	Strong
Counsel patients about the possibility of needing further treatment in the future.	Strong

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Treatment options

- ✓ Active surveillance
- ✓ **Surgery: Radical prostatectomy**
- ✓ Radiotherapy / Brachytherapy
- ✓ Focal therapy

Radical prostatectomy

Indications	LE
Patients with low- and intermediate-risk localized PCa (cT1a–T2b and Gleason score 6–7 and PSA ≤20) and a life expectancy >10 yr	1b
Optional	
Patients with stage T1a disease and a life expectancy >15 yr or Gleason score 7	3
Selected patients with low-volume, high-risk, localized PCa (cT3a or Gleason score 8–10 or PSA >20 ng/ml)	3
Highly selected patients with very high-risk localized PCa (cT3b–T4N0 or any TN1) in the context of multimodality treatment	3
Short-term (3-mo) or long-term (9-mo) neoadjuvant therapy with gonadotrophin releasing–hormone analogs is not recommended in the treatment of clinically localized low-risk or high-risk PCa.	1a
Nerve-sparing surgery may be attempted in preoperatively potent patients with low risk for extracapsular disease (T1c and Gleason score <7 and PSA <10 ng/ml).	3
Unilateral nerve-sparing procedures are an option in stage T2a–T3a disease.	4

LE = level of evidence; PCa = prostate cancer; PSA = prostate-specific antigen.

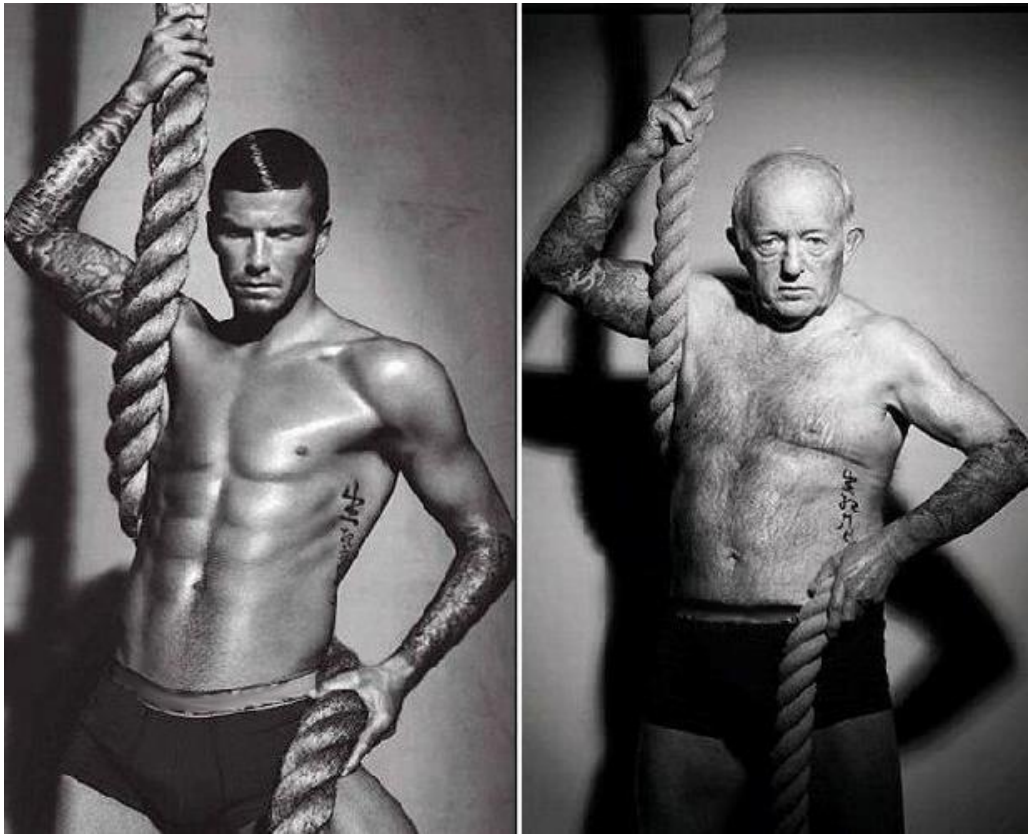
The aim of Radical Prostatectomy is to eradicate the disease and, when possible, preserve urinary continence and erectile function.

Heidenreich et al. Eur Urol 2014,

Radical prostatectomy

In addition to the characteristics of the pathology, it is important to evaluate the characteristics of the patient:

- ✓ Age
- ✓ Performance status
- ✓ Life expectancy



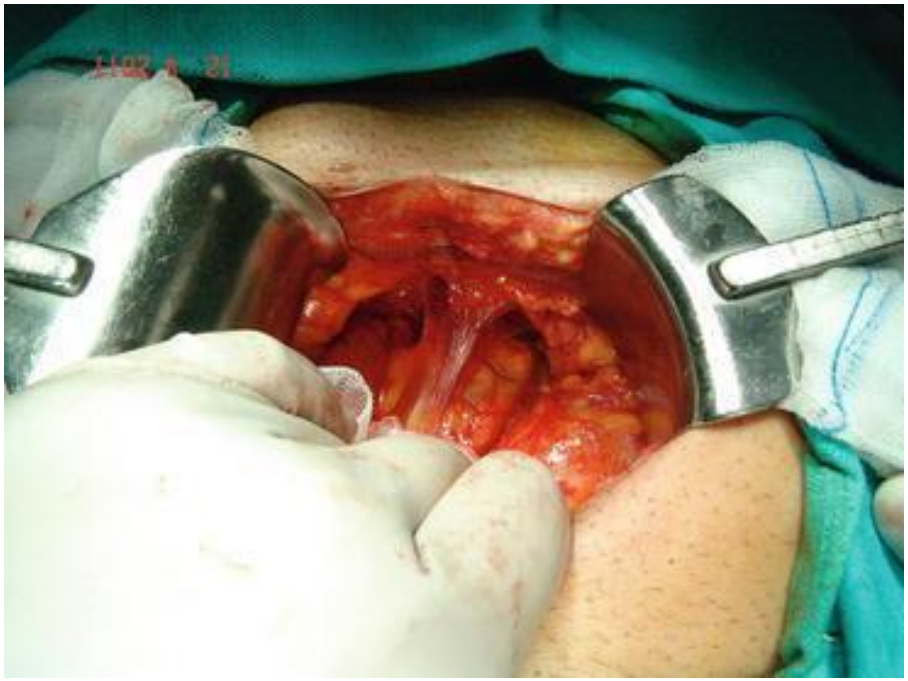
Radical Prostatectomy

Table 6.1.4: Oncological results of radical prostatectomy in organ-confined disease in RCTs

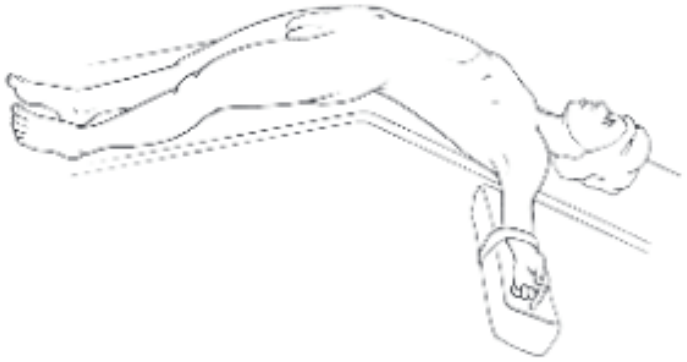
Study	Acronym	Population	Year of treatment	Median FU (mo)	Risk category	CSS (%)
Bill-Axelson, *et al.* 2018 [400]	SPCG-4	Pre-PSA era	1989-1999	283	Low risk and Intermediate risk	80.4 (at 23 yr.)
Wilt, *et al.* 2017 [396]	PIVOT	Early years of PSA testing	1994-2002	152	Low risk Intermediate risk	95.9 91.5 (at 19.5 yr.)
Hamdy, *et al.* 2016 [386]	ProtecT	Screened population	1999-2009	120	Mainly low- and intermediate risk	99 (at 10 yr.)

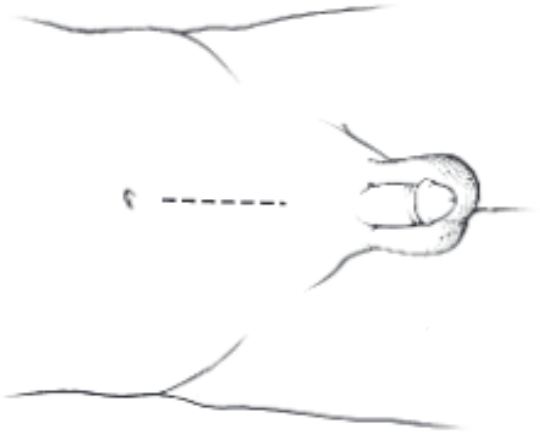
CSS = cancer-specific survival; FU = follow-up; mo = months; PSA = prostate-specific antigen; yr. = year.

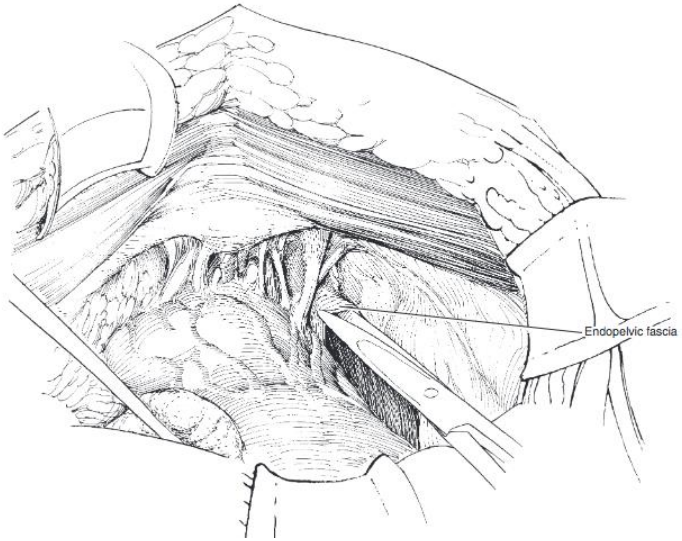
Open Surgery

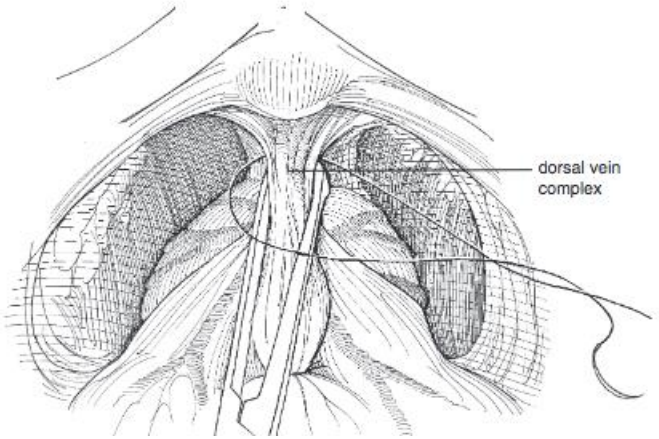


OPEN SURGICAL TECHNIQUE

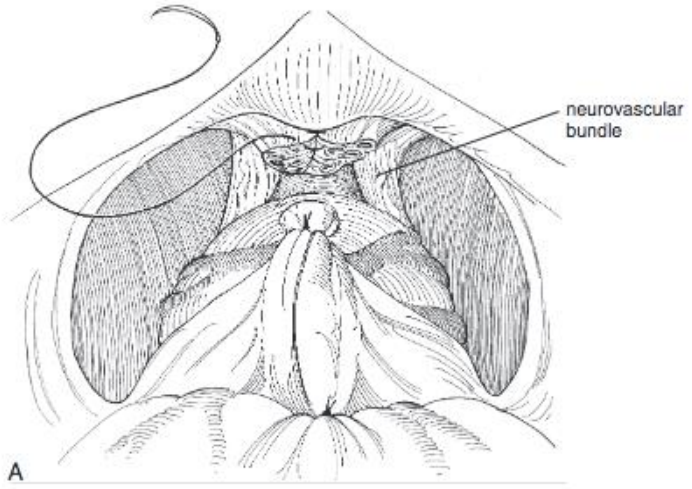


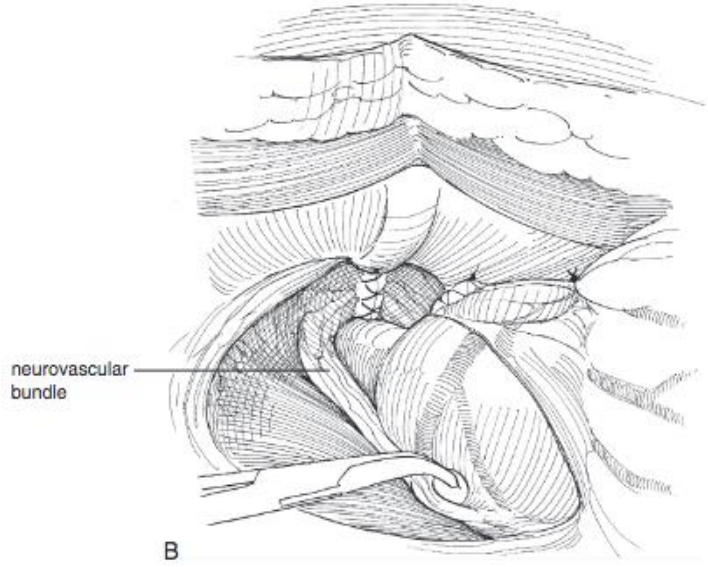






OPEN SURGICAL TECHNIQUE





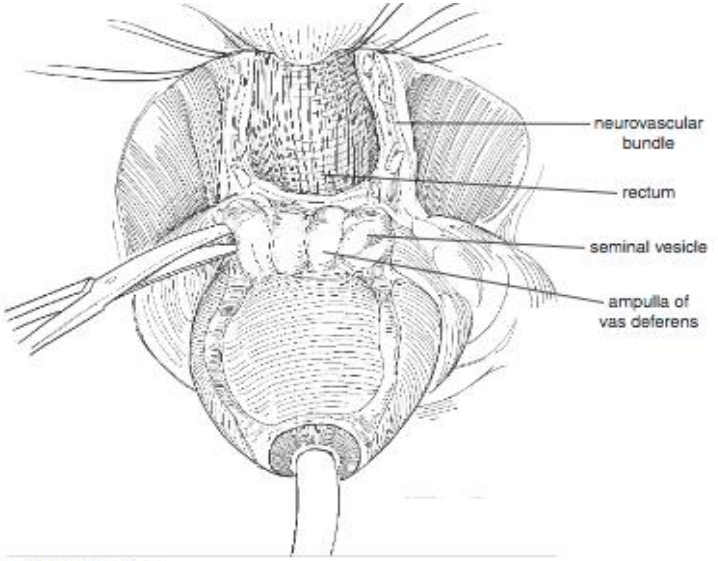


FIGURE 66-7.

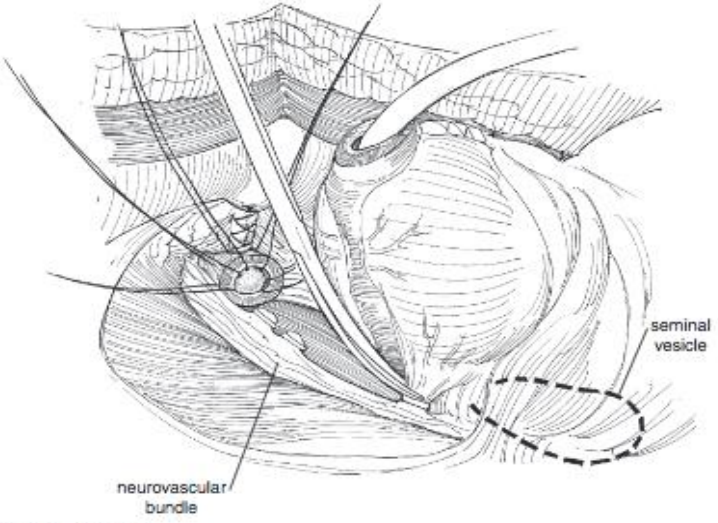


FIGURE 66-8.

OPEN SURGICAL TECHNIQUE

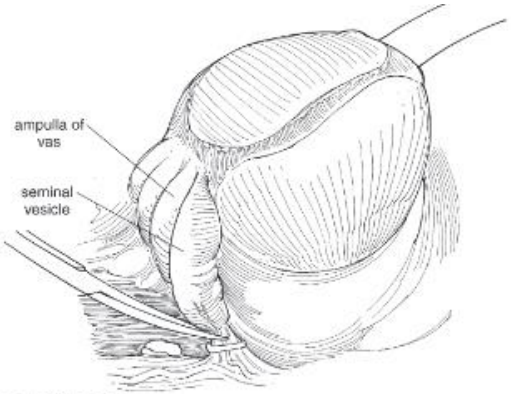


FIGURE 66-9.

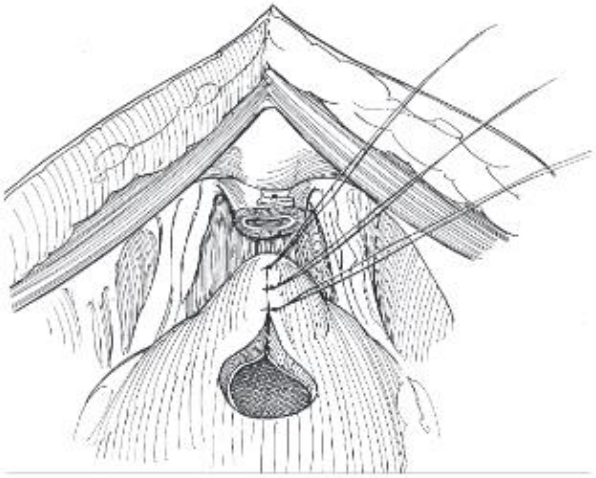
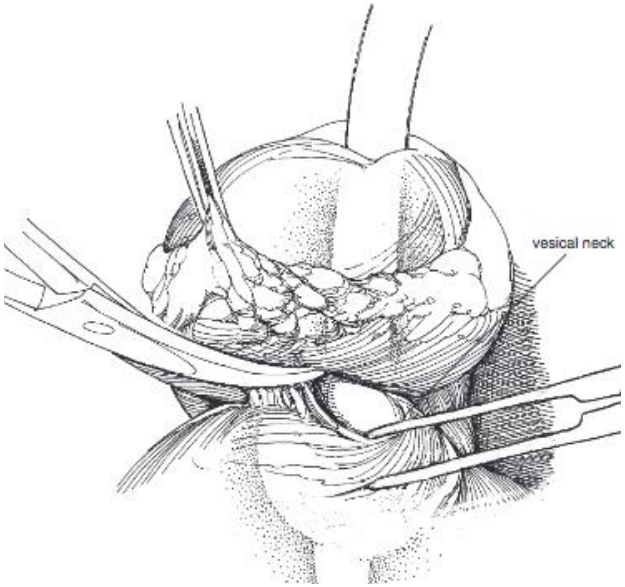


FIGURE 66-13.



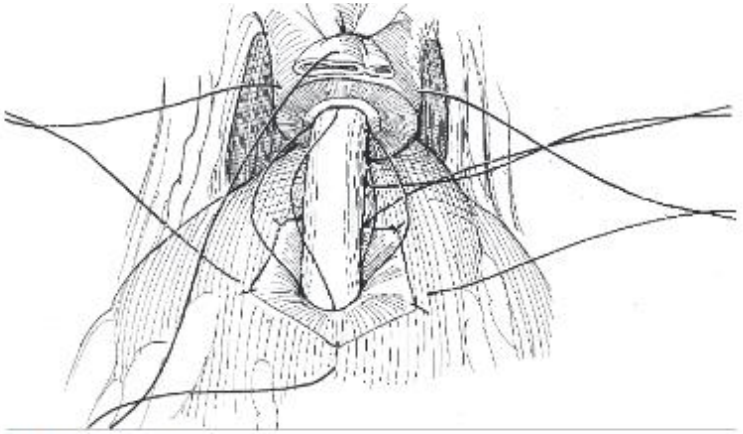
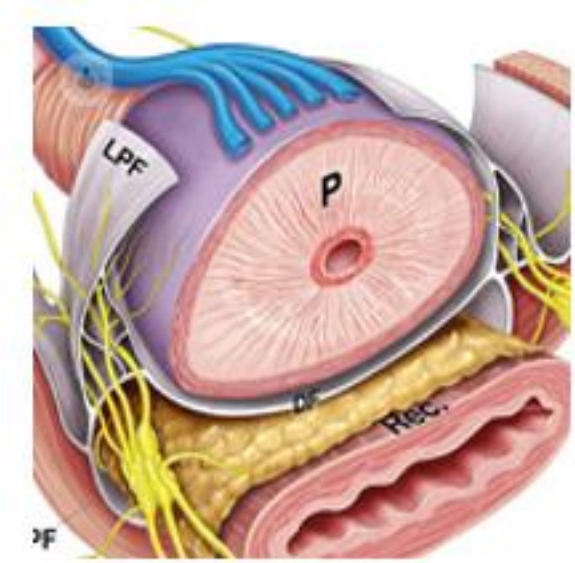


FIGURE 66-15.

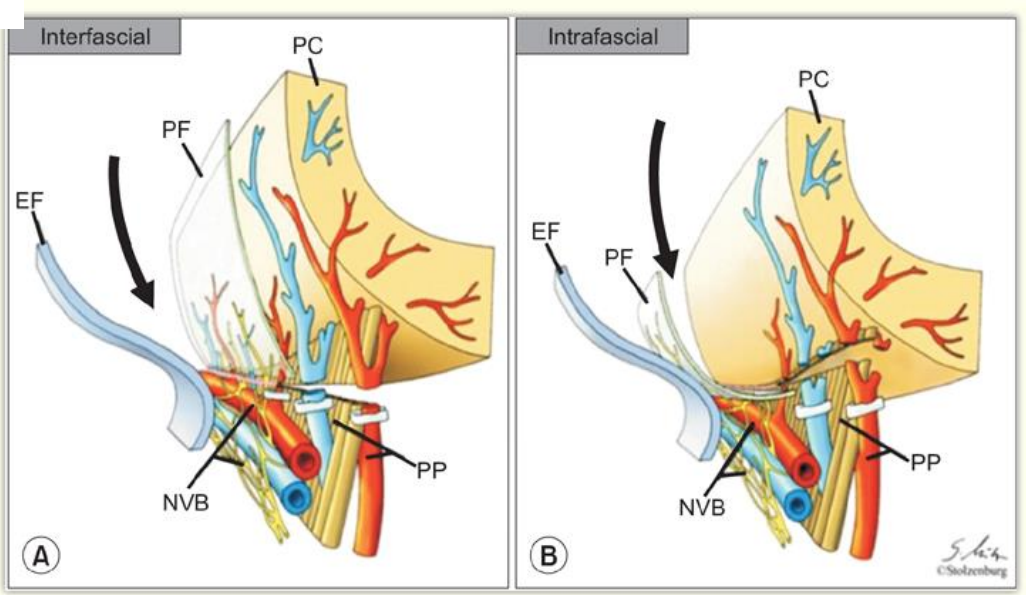
OPEN SURGICAL TECHNIQUE



INTRINSIC SPHINCTER:
risk of incontinence

NEUROVASCULAR BUNDLES:
risk of erectil disfunction

NERVE SPARING SURGER



Radical prostatectomy and lymphadenectomy

EUROPEAN UROLOGY 72 (2017) 84–109

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Review – Prostate Cancer

The Benefits and Harms of Different Extents of Lymph Node Dissection During Radical Prostatectomy for Prostate Cancer: A Systematic Review

Nicola Fossati[a,1], *Peter-Paul M. Willemse*[b,1], *Thomas Van den Broeck*[c], *Roderick C.N. van den Bergh*[d], *Cathy Yuhong Yuan*[e], *Erik Briers*[f], *Joaquim Bellmunt*[g,h], *Michel Bolla*[i], *Philip Cornford*[j], *Maria De Santis*[k], *Ekelechi MacPepple*[l], *Ann M. Henry*[m], *Malcolm D. Mason*[n], *Vsevolod B. Matveev*[o], *Henk G. van der Poel*[p], *Theo H. van der Kwast*[q], *Olivier Rouvière*[r], *Ivo G. Schoots*[s,t], *Thomas Wiegel*[u], *Thomas B. Lam*[v,w], *Nicolas Mottet*[x], *Steven Joniau*[c,*]

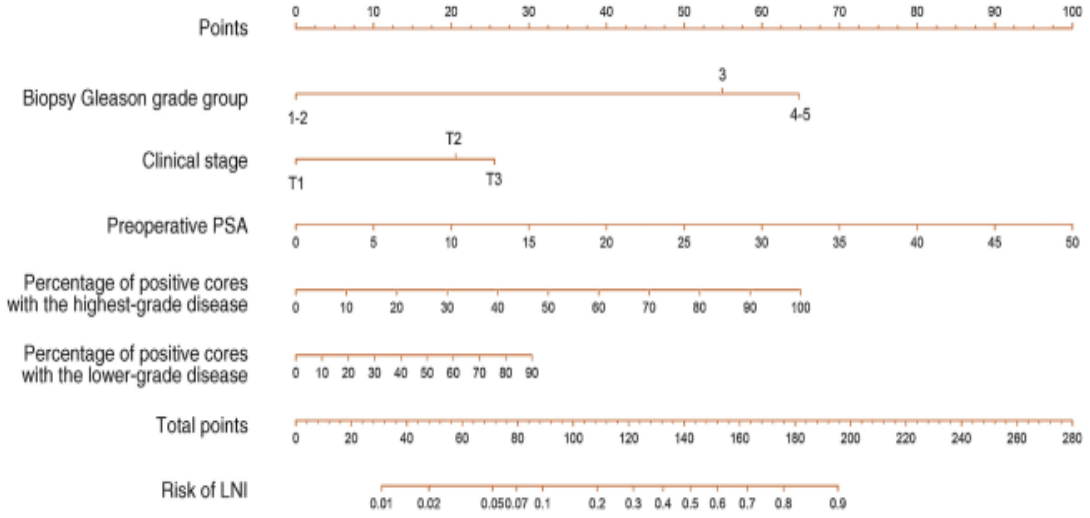
Conclusion: Performing pelvic lymph node dissection (PLND) during RP failed to improve oncological outcomes, including survival. However, it is generally accepted that extended pelvic LN dissection (eLND) provides important information for staging and prognosis which cannot be matched by any other currently available procedure

EUROPEAN UROLOGY 72 (2017) 632–640

Development and Internal Validation of a Novel Model to Identify the Candidates for Extended Pelvic Lymph Node Dissection in Prostate Cancer

Giorgio Gandaglia [a,b], *Nicola Fossati* [a,b], *Emanuele Zaffuto* [a,b,c], *Marco Bandini* [a,b], *Paolo Dell'Oglio* [a,b], *Carlo Andrea Bravi* [a,b], *Giuseppe Fallara* [a,b], *Francesco Pellegrino* [a,b], *Luigi Nocera* [a,b], *Pierre I. Karakiewicz* [c], *Zhe Tian* [c], *Massimo Freschi* [d], *Rodolfo Montironi* [e], *Francesco Montorsi* [a,b], *Alberto Briganti* [a,b,*]

[a] *Unit of Urology/Division of Oncology, URI, IRCCS Ospedale San Raffaele, Milan, Italy;* [b] *Vita-Salute San Raffaele University, Milan, Italy;* [c] *Cancer Prognostics and Health Outcomes Unit, University of Montreal Health Center, Montreal, Canada;* [d] *Unità Operativa Anatomia Patologica, IRCCS Ospedale San Raffaele, Milan, Italy;* [e] *Section of Pathological Anatomy, Polytechnic University of the Marche Region, School of Medicine, United Hospitals, Ancona, Italy*



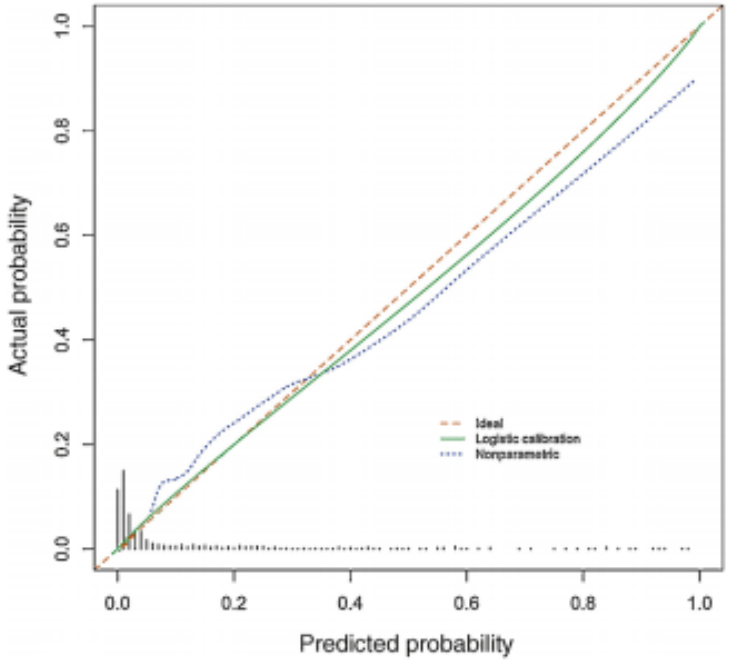
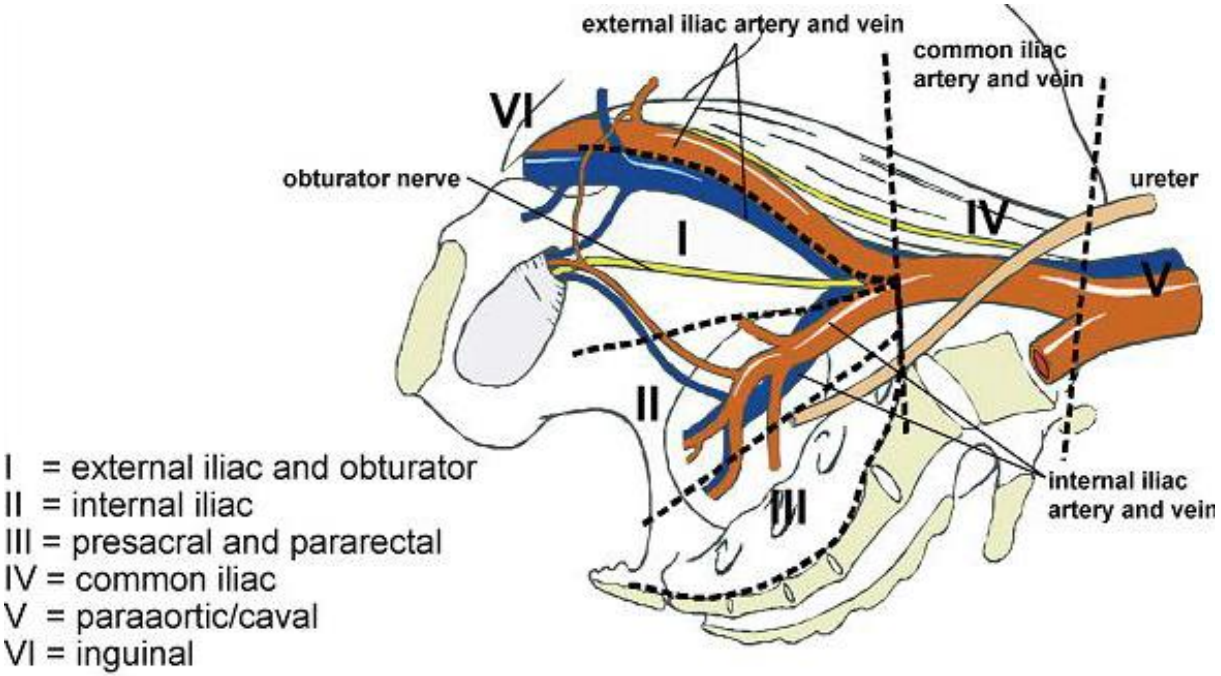


Fig. 2 – Calibration plot of observed proportion versus predicted probability of lymph node invasions of the novel nomogram.

Radical prostatectomy and lymphadenectomy

When a lymph node dissection (LND) is deemed necessary, perform an extended LND template for optimal staging.

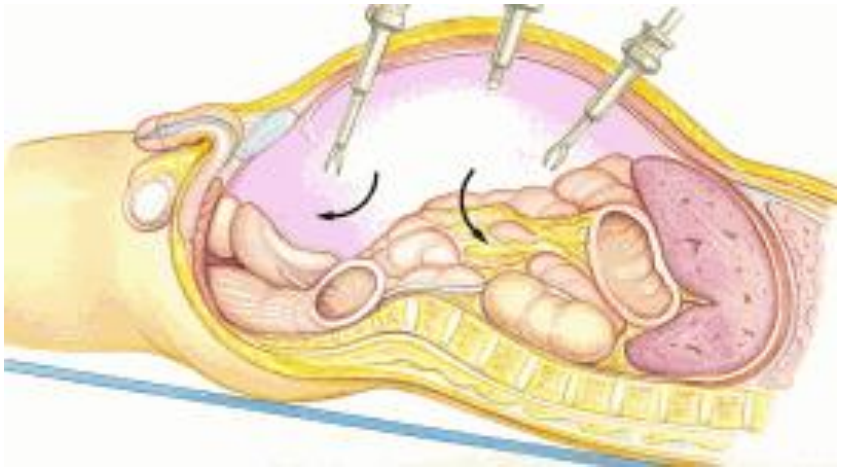
I + II = 94% of the men correctly staged

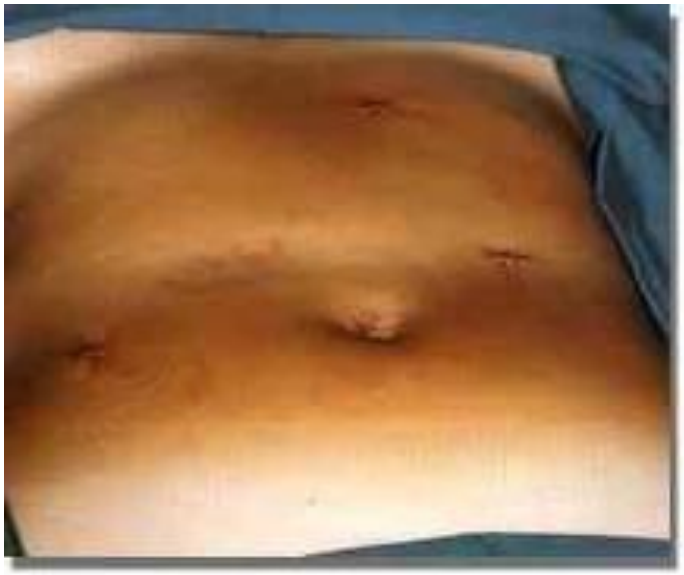


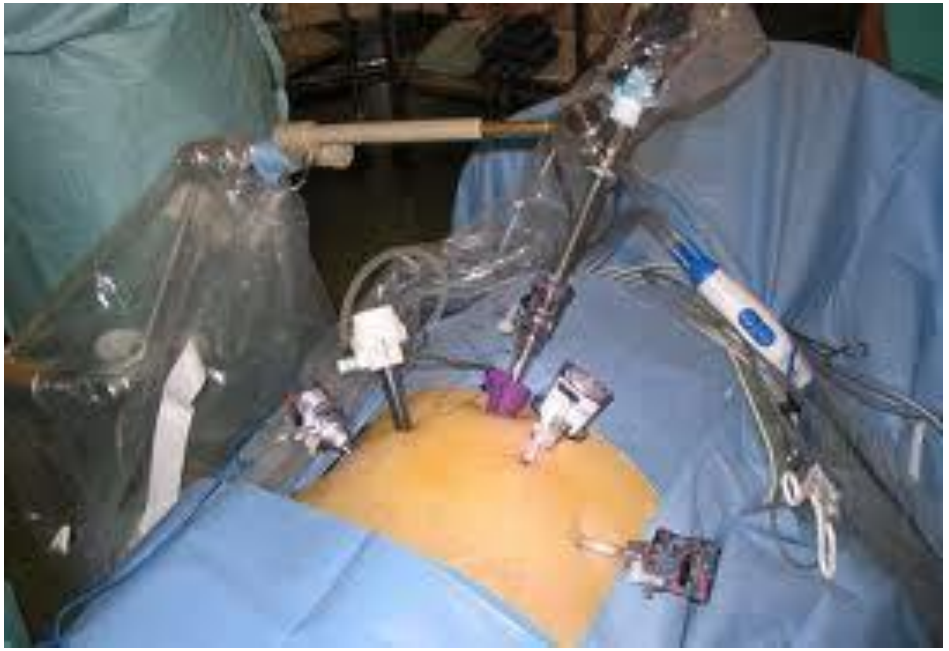
Boundaries of pelvic lymph node dissection (PLND) subdivided into different regions. "Limited" PLND removes tissue along the external iliac vein and from the obturator fossa corresponding to region I. "Extended" template PLND removes tissue along the major pelvic vessels (external iliac vein, obturator fossa and internal iliac artery and vein) corresponding to regions I and II.

Mattei et al European Urology 2008, 53:118-125

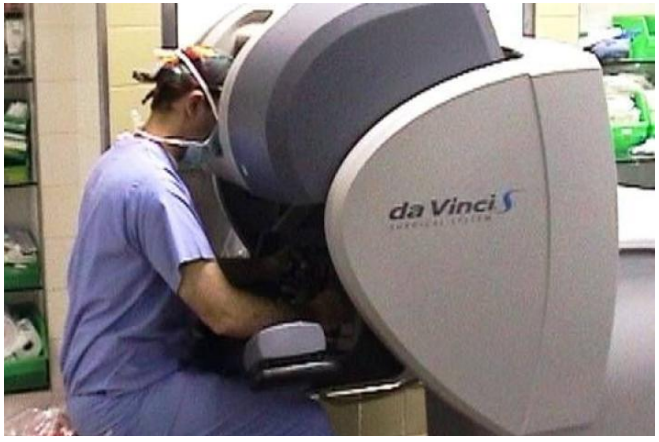
Laparoscopic prostatectomy







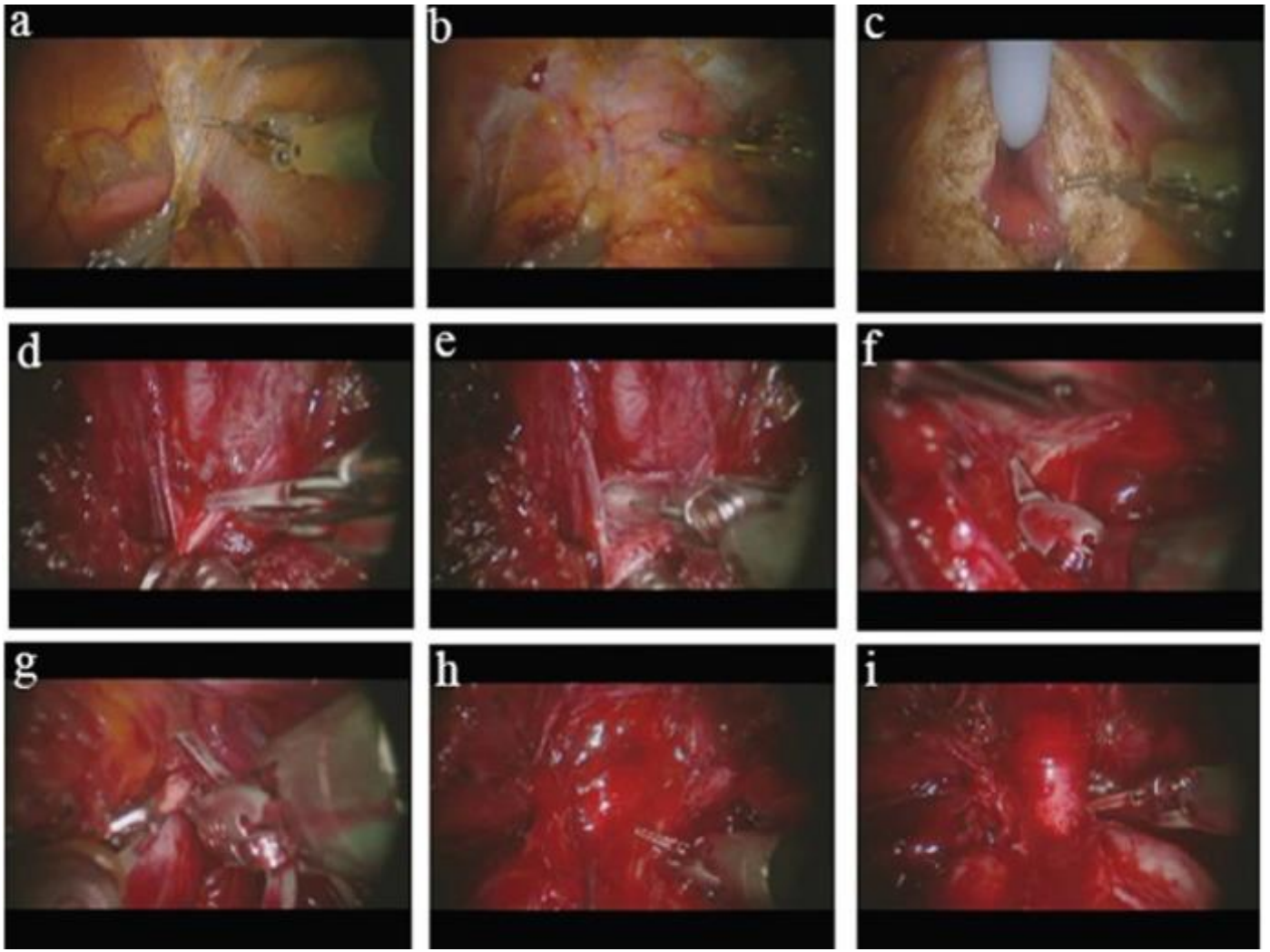
Robotic Surgery: RARP



- The robotic approach (RARP) has shown shorter hospitalization times and reduced intra-operative blood loss, but the benefits relative to functional or oncological outcomes are still doubtful.

- Some studies show higher rates of erectile function recovery and faster continence recovery in patients treated with RARP.

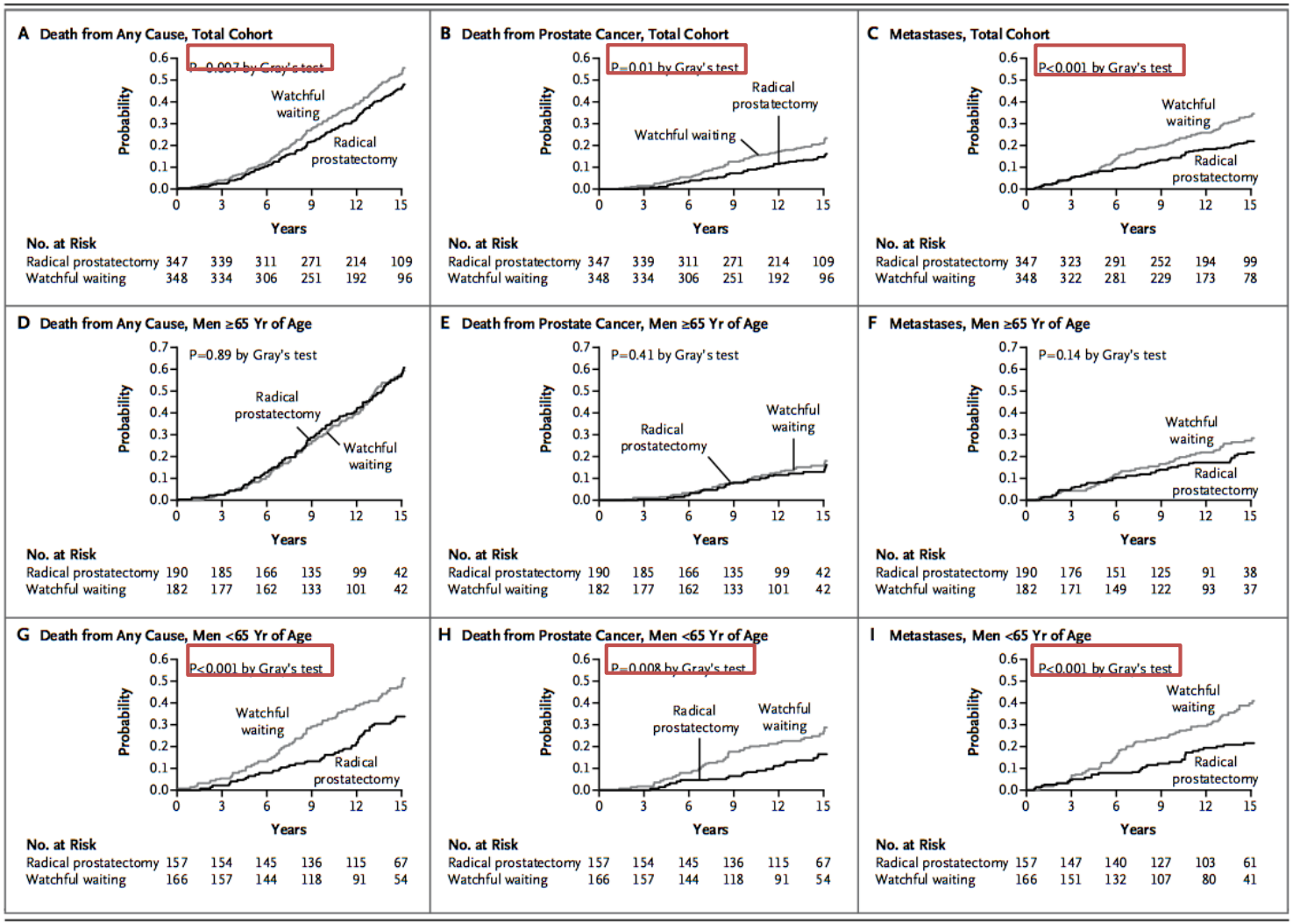
Robotic Surgery: Surgical Technique



Carlucci JR et al,Int J Biomed.Sci 2009 Sep;5(3):201-8

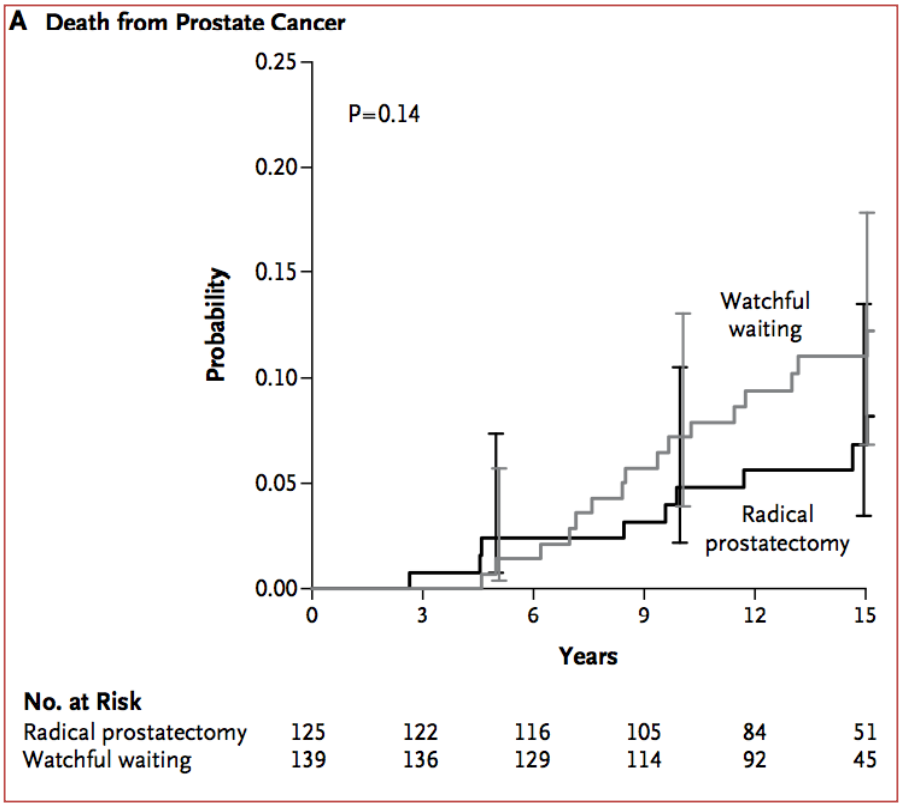
Robotic Surgery: Surgical Technique

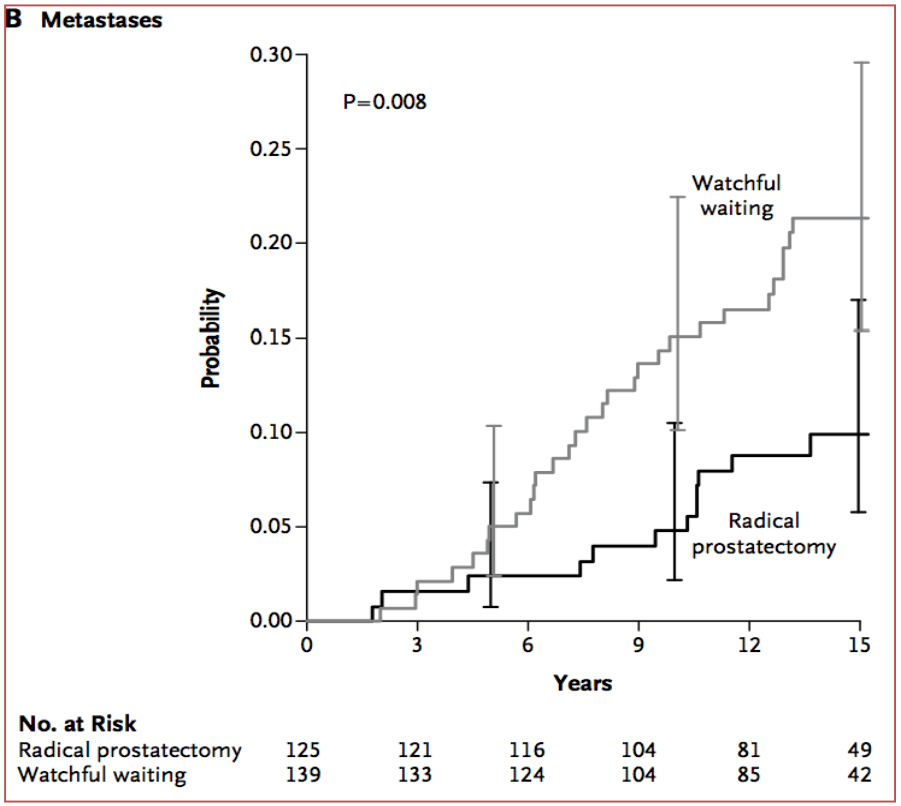
Cumulative incidence of death and metastases in low-risk prostate cancer



Bill-Axelson et al. NEJM 2011

Cumulative incidence of death and metastases in low-risk prostate cancer





Bill-Axelson et al. NEJM 2011

ORIGINAL ARTICLE

Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer

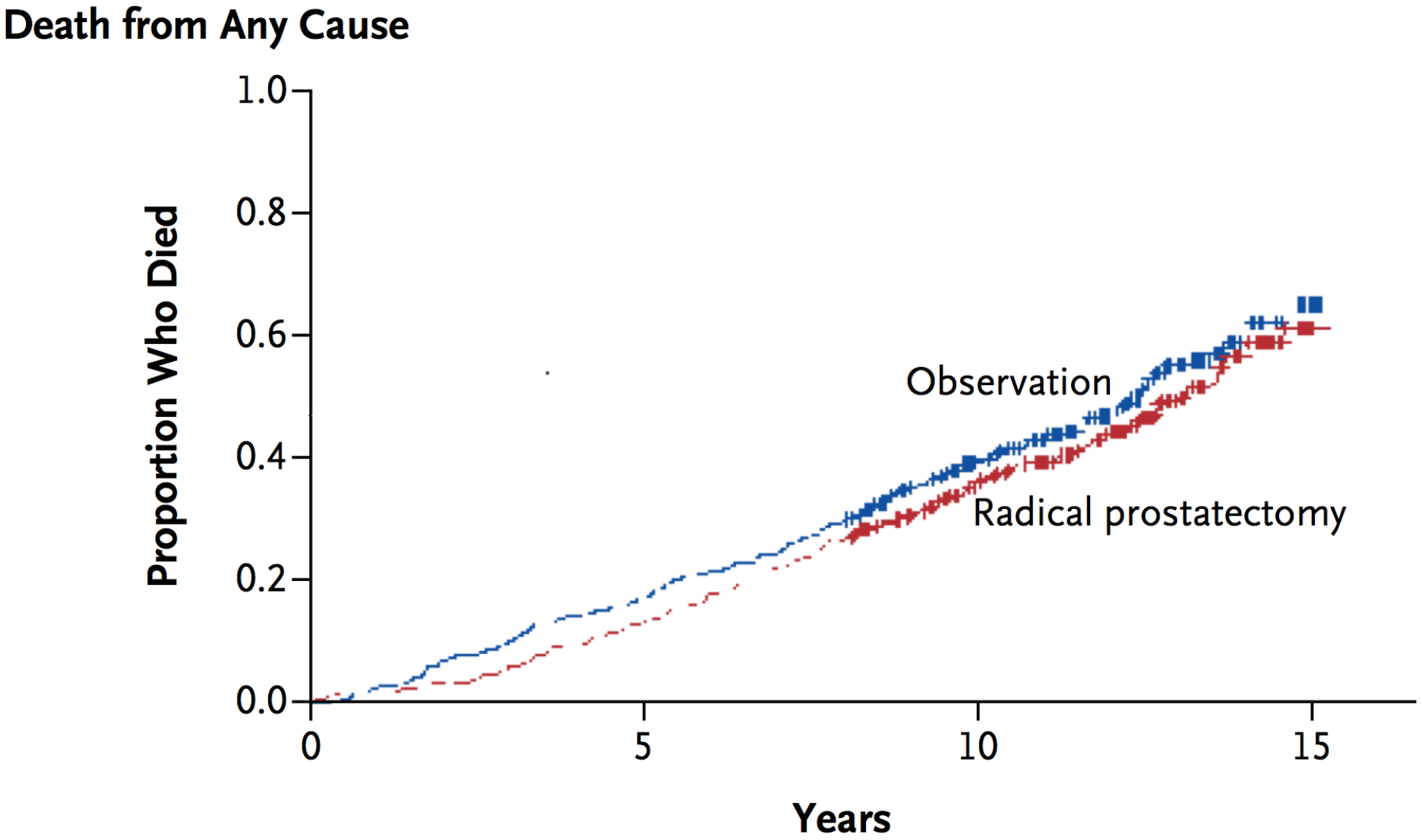
Relative risk of dying of prostate cancer after surgery = 0.62 (P=0.01)

Number of patients to treat: 15 considering all patients, 7 for men younger than 65 years old

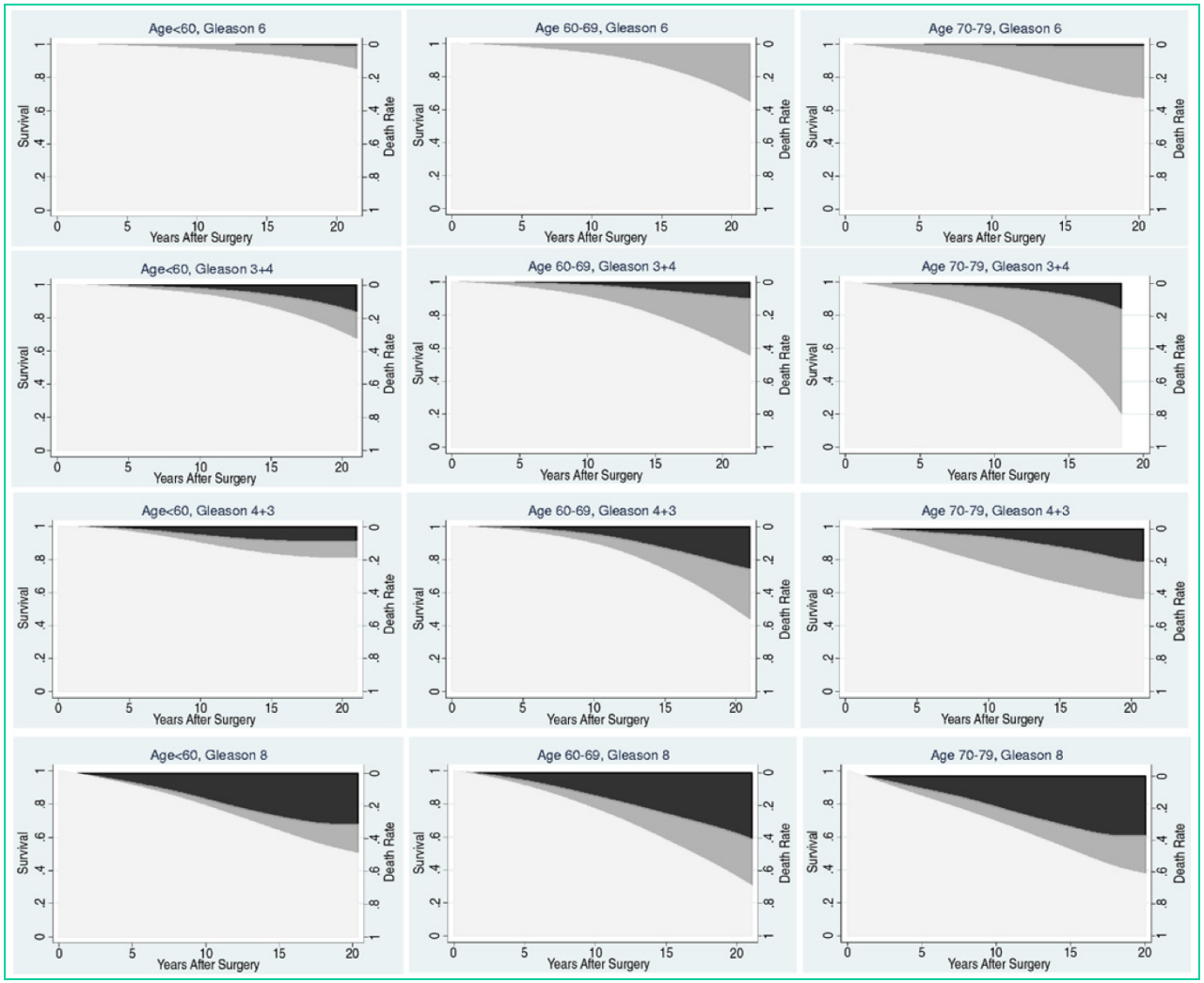
Among men undergoing radical prostatectomy, those with an **extracapsular disease** have a 7-fold higher risk of death than those who do not have an extracapsular extension

Bill-Axelson et al. NEJM 2011

Radical prostatectomy

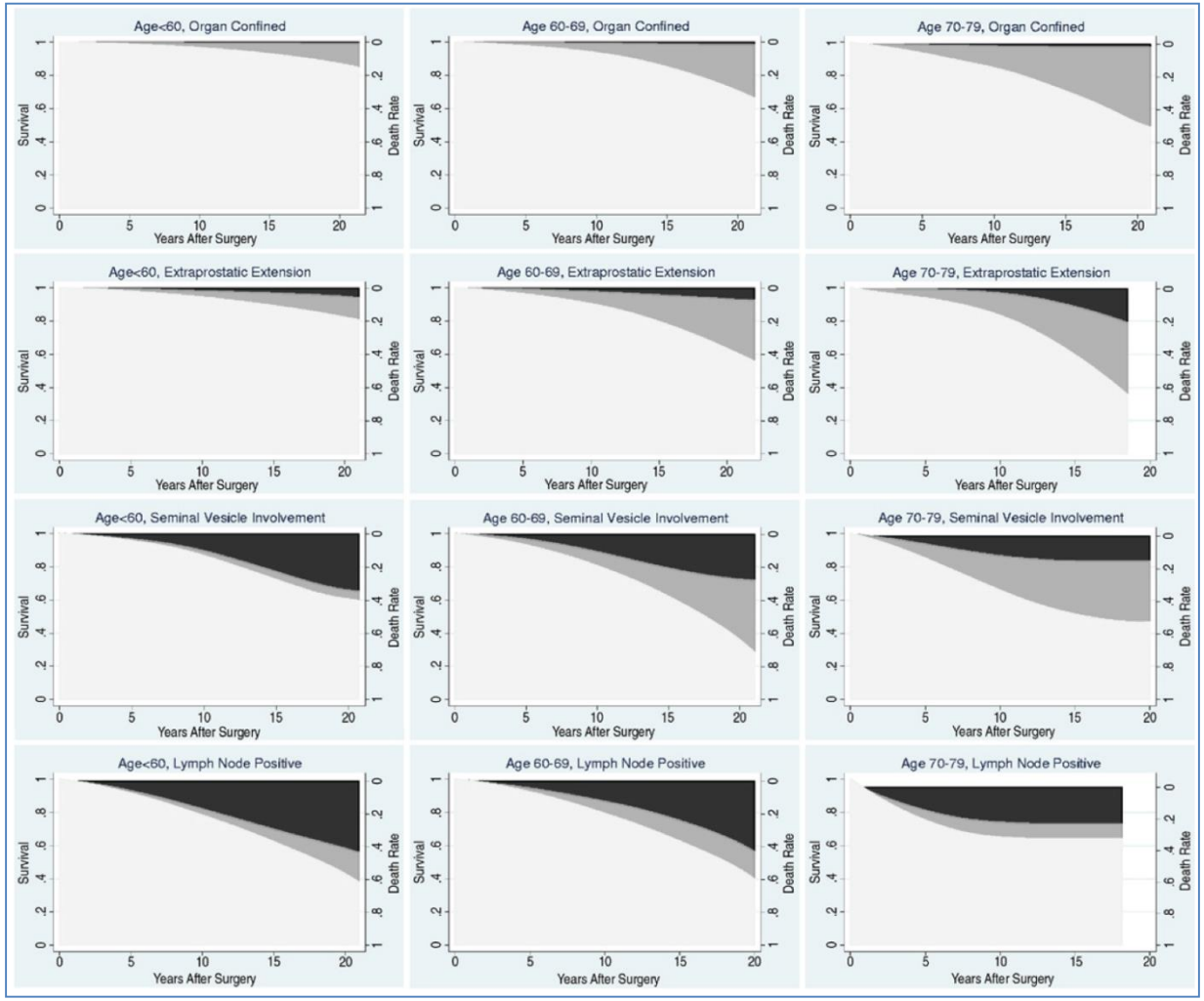


Cancer-specific survival according to age and Gleason Score



Eggener et al. J Urol 2009

Cancer-specific survival according to age and grade of disease



Eggener et al. J Urol 2009

Radical prostatectomy

- In conclusion, **only patients younger than 65 years of age with an intermediate or high risk of progression benefit from radical prostectomy.**
- In patients at low risk of progression radical prostatectomy does not demonstrate an advantage in terms of overall survival and metastasis-specific survival.
- Robotic prostatectomy (**RARP**) is replacing open prostatectomy as the **gold standard treatment for clinically localized prostate cancer.**
- However, this trend is not supported by high-level evidence demonstrating the superiority of a surgical technique over the other.

Heidenreich et al. Eur Urol 2014, in press

Radical prostatectomy: complications

Table 3 Meta-analysis results: robot-assisted surgery versus open surgery

Outcome	Measure	Studies	Sample	I^2	Effect	(95% CI)	*P*-value	Prediction interval
Operative time (min)	WMD	17	4325	97.8	37	(17, 58)	0.000	(–54, 129)
Hospital stay (days)								
All studies	WMD	18	5864	99.4	–2	(–2, –1)	0.000	(–4, 1)
European studies	WMD	5	846	96.2	–2.1	(–3.1, –1.1)	0.000	(–5.9, 1.6)
USA studies	WMD	9	3782	98.5	–0.7	(–1.2, –0.2)	0.006	(–2.5, 1.1)
Blood loss (mL)	WMD	17	5366	98.0	–564	(–664, –463)	0.000	(–999, –129)
Complications	RR	17	6384	71.8	0.74	(0.56, 1)	0.047	(0.27, 2.06)
Transfusion	RR	20	9246	16.8	0.23	(0.18, 0.29)	0.000	(0.14, 0.38)
Positive surgical margin								
pT2	RR	15	2946	27.7	0.63	(0.49, 0.81)	0.000	(0.35, 1.15)
pT3	RR	15	1179	57.7	1.06	(0.85, 1.34)	0.591	(0.51, 2.22)
Sexual function	RR	9	1949	69.8	1.60	(1.33, 1.93)	0.000	(0.95, 2.71)
Urinary function	RR	7	1820	50.7	1.06	(1.02, 1.11)	0.009	(0.94, 1.21)

Moran et al. Int J Urol 2013;20:321-21

Radical prostatectomy: complications

Table 6.1.5: Intra-and peri-operative complications of retropubic RP and RALP (Adapted from [364])

Predicted probability of event	RALP (%)	Laparoscopic RP (%)	RRP (%)
Bladder neck contracture	1.0	2.1	4.9
Anastomotic leak	1.0	4.4	3.3
Infection	0.8	1.1	4.8
Organ injury	0.4	2.9	0.8
Ileus	1.1	2.4	0.3
Deep-vein thrombosis	0.6	0.2	1.4
Predicted rates of event	**RALP (%)**	**Laparoscopic RP (%)**	**RRP (%)**
Clavien I	2.1	4.1	4.2
Clavien II	3.9	7.2	17.5
Clavien IIIa	0.5	2.3	1.8
Clavien IIIb	0.9	3.6	2.5
Clavien IVa	0.6	0.8	2.1
Clavien V	< 0.1	0.2	0.2

RALP = robot-assisted laparoscopic prostatectomy; RP = radical prostatectomy; RRP = radical retropubic prostatectomy.

EAU - ESTRO - ESUR - SIOG Guidelines on Prostate Cancer 2018

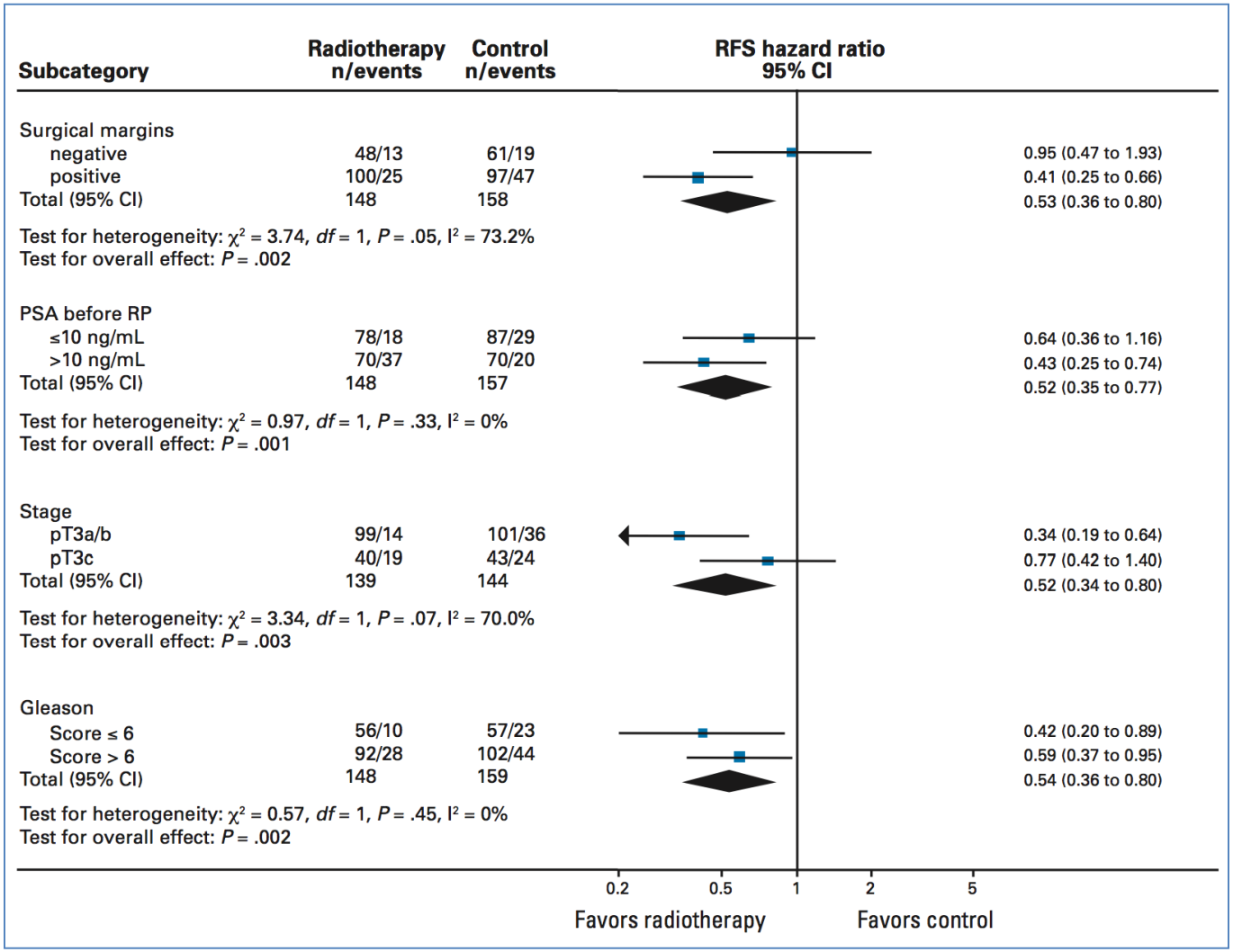
Radical prostatectomy in locally advanced prostate cancer

Phase III Postoperative Adjuvant Radiotherapy After Radical Prostatectomy Compared With Radical Prostatectomy Alone in pT3 Prostate Cancer With Postoperative Undetectable Prostate-Specific Antigen: ARO 96-02/AUO AP 09/95

Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911)

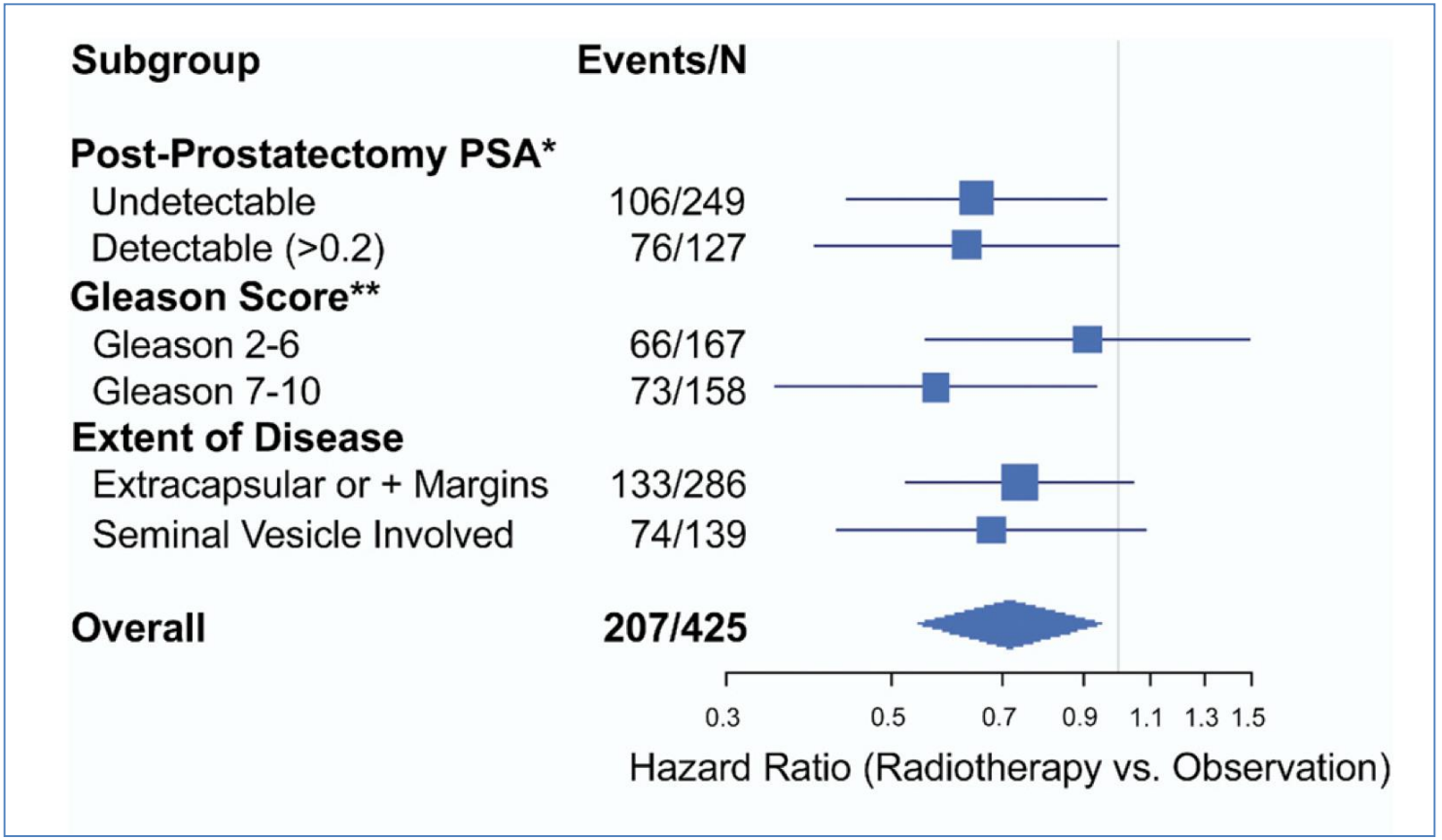
Adjuvant Radiotherapy for Pathological T3N0M0 Prostate Cancer Significantly Reduces Risk of Metastases and Improves Survival: Long-Term Followup of a Randomized Clinical Trial

ADJUVANT RADIOTHERAPY: RECURRENCE-FREE SURVIVAL



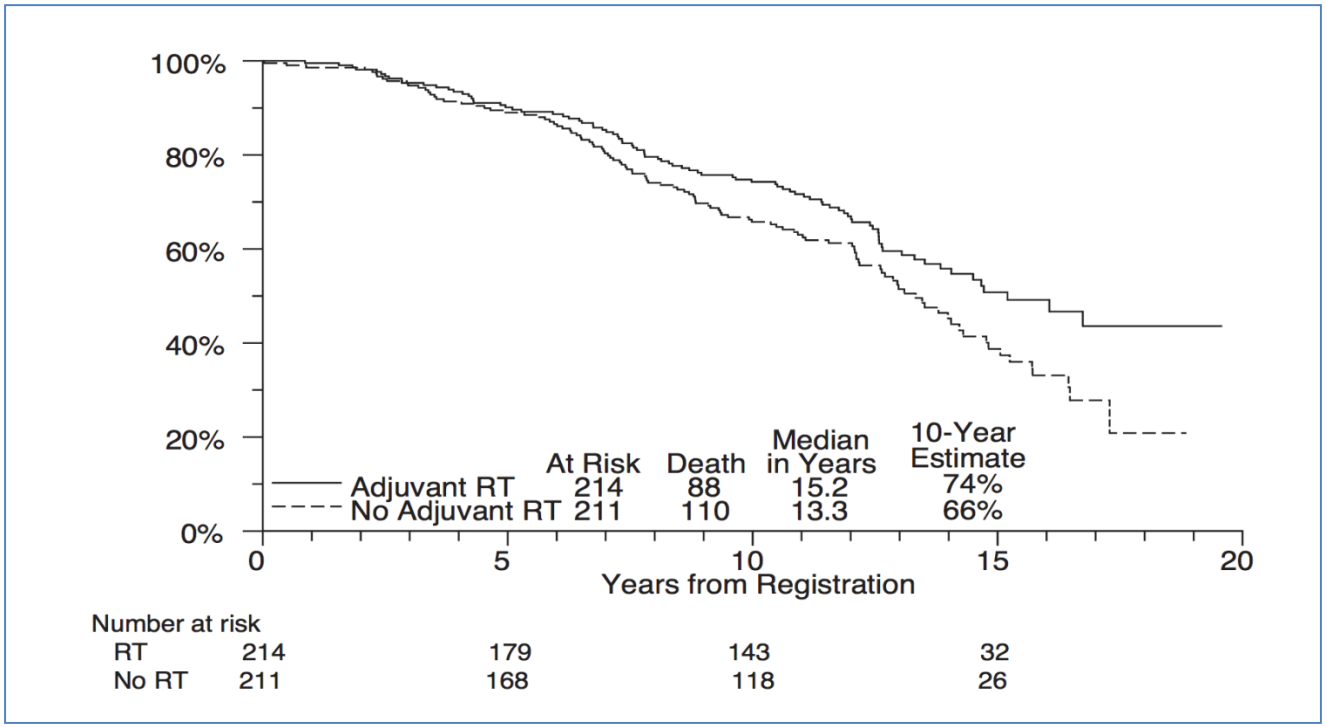
Wiegel T et al. JCO 2009

ADJUVANT RADIOTHERAPY: METASTASES-FREE SURVIVAL



Thompson et al. J Urol 2009

ADJUVANT RADIOTHERAPY: SURVIVAL RATES



The HR for overall survival with adjuvant radiotherapy is 0.72 (95% CI 0.55, 0.96; p=0.023)

The number needed to treat with adjuvant radiotherapy to prevent 1 death at a median follow-up of 12.6 years is 9.1

Thompson et al. J Urol 2009

Early Salvage Radiation Therapy Does Not Compromise Cancer Control in Patients with pT3N0 Prostate Cancer After Radical Prostatectomy: Results of a Match-controlled Multi-institutional Analysis

- 390 (43.8%) and 500 (56.2%) patients received aRT and initial observation, respectively
- Among patients undergoing initial observation, 225 (45.0%) of patients experienced BCR and underwent eSRT

PATIENT STRATIFICATION ACCORDING TO pT3 SUBSTAGE, SURGICAL MARGIN STATUS AND TREATMENT TYPE IN THE OVERALL MATCHED POPULATION

Disease characteristics	No. of patients (%)	aRT, *n* (%)	Observation, *n* (%)	Patients not recurring within the observation group, *n* (%)	Patients receiving eSRT within the observation group due to biochemical recurrence after RP, *n* (%)
pT3a any SM	535 (100)	261 (48.8)	274 (51.2)	158 (57.7)	116 (42.3)
pT3b any SM	245 (100)	129 (52.7)	116 (48.3)	41 (35.3)	75 (64.7)
NSM	297 (100)	145 (48.8)	152 (51.2)	97 (63.8)	55 (36.2)
PSM	483 (100)	245 (50.7)	238 (49.3)	102 (42.9)	136 (57.1)
pT3a with NSM	197 (100)	97 (49.2)	100 (50.8)	73 (73)	27 (27.0)
pT3a with PSM	338 (100)	164 (48.5)	174 (51.5)	85 (48.9)	89 (51.1)
pT3b with NSM	100 (100)	48 (48.0)	52 (52.0)	24 (46.2)	28 (53.8)

Briganti et al. Eur Urol; 62: 472 – 487 (2012)

Hormonal therapy

The reduction of serum testosterone levels, necessary to counteract the growth of cancer cells, can be achieved in various ways:

- **Bilateral orchiectomy** allows to get the best results in the shortest time but is more difficult to accept psychologically.

- **Estrogens** increase the risk of thromboembolic events.

- **LHRH agonists** are also prescribed with antiandrogens to prevent so-called tumour flare. Treatment can be carried on continuously or be discontinued (intermittent therapy) for short periods, to reduce the impact of its side effects. (*Leuprolide – Triprorelina*).

- **Peripheral antiandrogens:** Testosterone stimulates replication of prostate cancer cells by binding to specific receptors that are located on the surface of the cells. Antiandrogens are drugs that block the interaction between the male sex hormone and these receptors, thus inhibiting tumor growth. (*Ciproterone acetato, Bicalutamide, Flutamide, Nilutamide).*

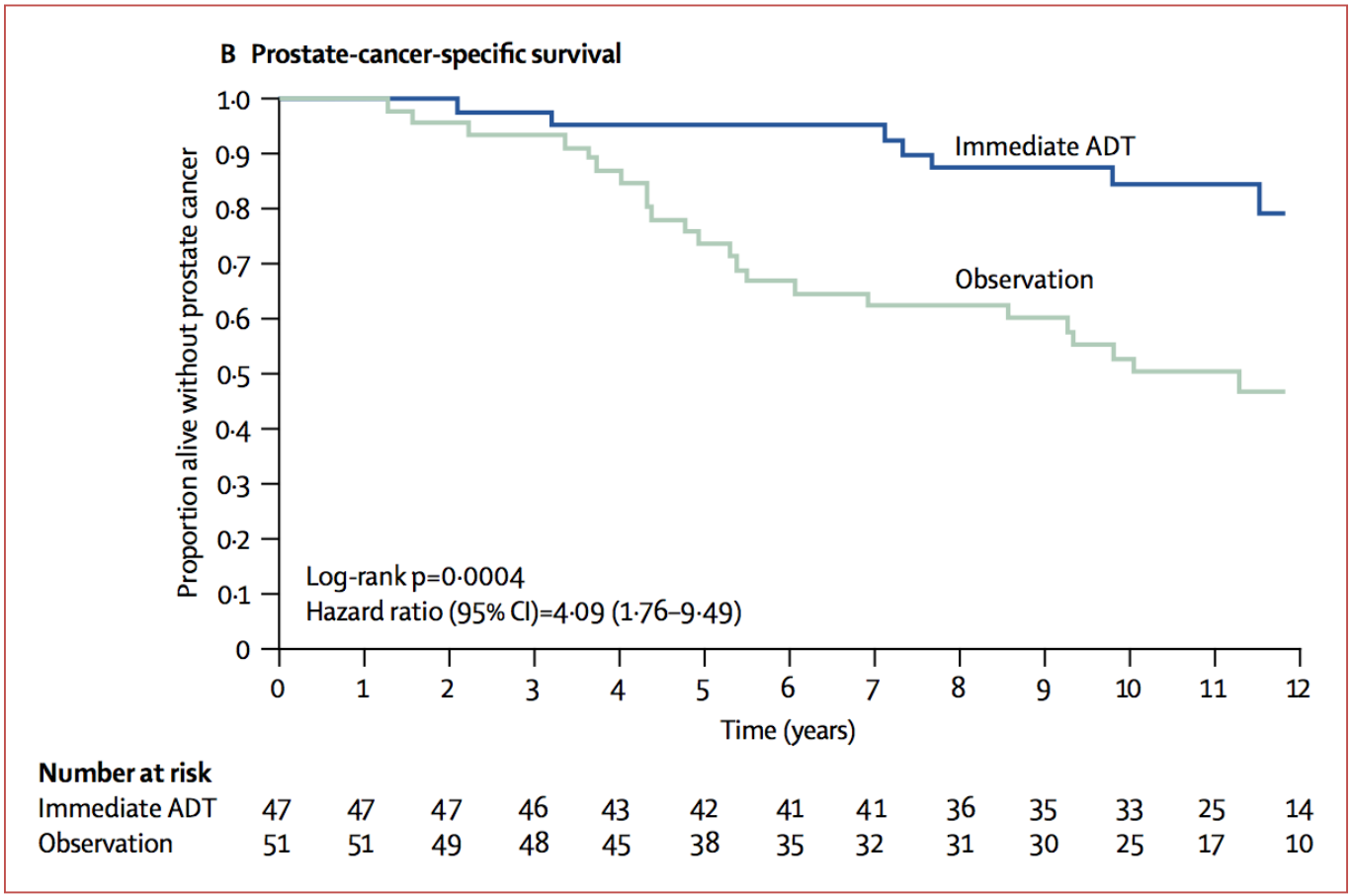
- **LHRH antagonists** block, at the level of the hypothalamus, the initial stimulus from which the cascade of messages that pushes testicles to produce sex hormones starts. (*Degarelix).*

Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy

An early androgenic blockage is superior to deferred androgenic blockage in patients with lymph node metastases who have undergone radical prostatectomy and lymphadenectomy.

Messing et al. Lancet 2006

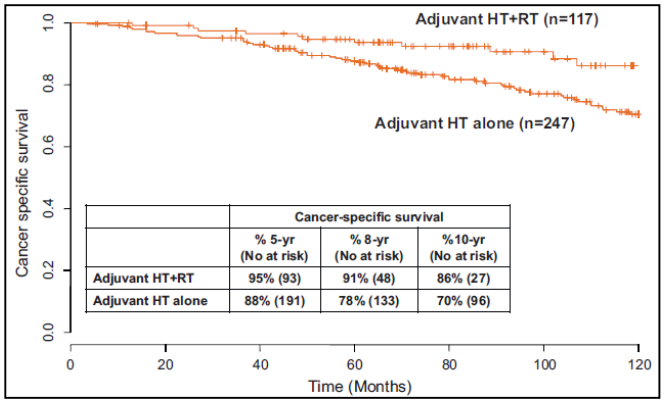
ADJUVANT ADT: PROSTATE-CANCER SPECIFIC SURVIVAL



Messing et al. Lancet 2006

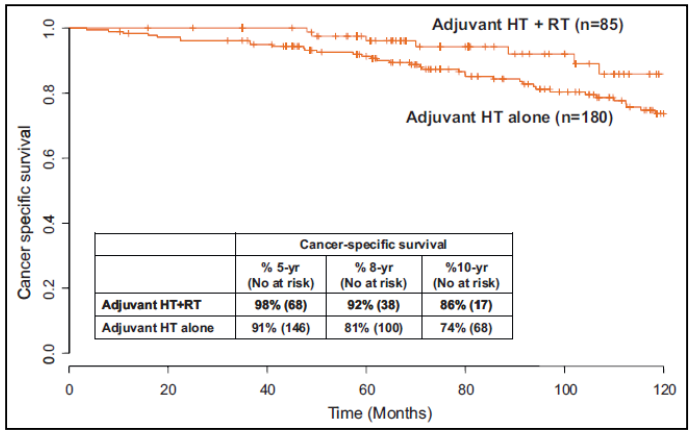
Combination of Adjuvant Hormonal and Radiation Therapy Significantly Prolongs Survival of Patients With pT2–4 pN+ Prostate Cancer: Results of a Matched Analysis

CSS ACCORDING TO THE TYPE OF ADJUVANT TREATMENT



	Cancer-specific survival		
	% 5-yr (No at risk)	% 8-yr (No at risk)	%10-yr (No at risk)
Adjuvant HT+RT	95% (93)	91% (48)	86% (27)
Adjuvant HT alone	88% (191)	78% (133)	70% (96)

CSS ACCORDING TO THE TYPE OF TREATMENT IN PATIENTS WITH TWO OR FEWER POSITIVE NODES



	Cancer-specific survival		
	% 5-yr (No at risk)	% 8-yr (No at risk)	%10-yr (No at risk)
Adjuvant HT+RT	98% (68)	92% (38)	86% (17)
Adjuvant HT alone	91% (146)	81% (100)	74% (68)

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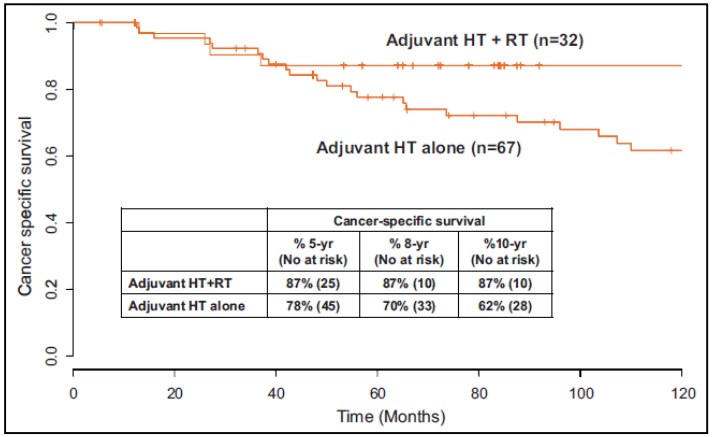
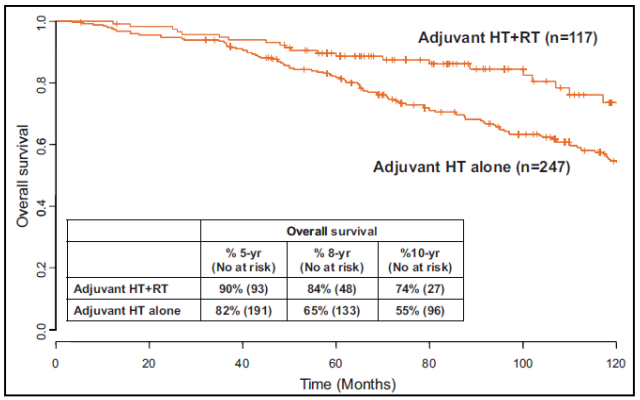


	Cancer-specific survival		
	% 5-yr (No at risk)	% 8-yr (No at risk)	%10-yr (No at risk)
Adjuvant HT+RT	87% (25)	87% (10)	87% (10)
Adjuvant HT alone	78% (45)	70% (33)	62% (28)

Briganti A. et al. Eur Urol 59 (2011); 832-840

Combination of Adjuvant Hormonal and Radiation Therapy Significantly Prolongs Survival of Patients With pT2–4 pN+ Prostate Cancer: Results of a Matched Analysis

OS ACCORDING TO THE TYPE OF ADJUVANT TREATMENT



	Overall survival		
	% 5-yr (No at risk)	% 8-yr (No at risk)	%10-yr (No at risk)
Adjuvant HT+RT	90% (93)	84% (48)	74% (27)
Adjuvant HT alone	82% (191)	65% (133)	55% (96)

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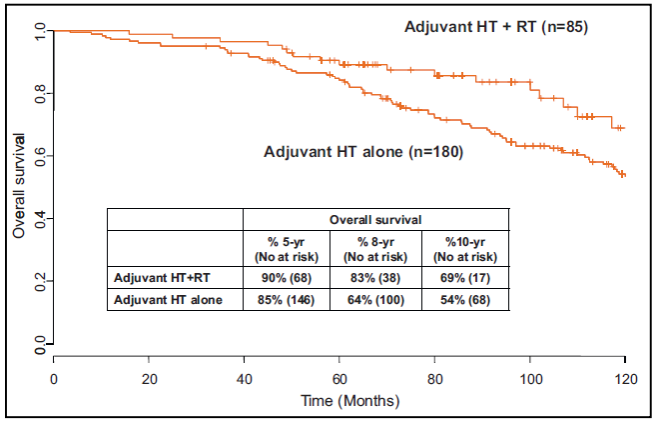
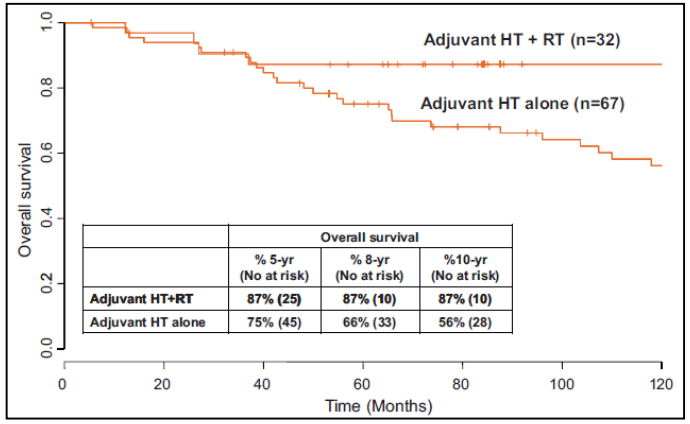


	Overall survival		
	% 5-yr (No at risk)	% 8-yr (No at risk)	%10-yr (No at risk)
Adjuvant HT+RT	90% (68)	83% (38)	69% (17)
Adjuvant HT alone	85% (146)	64% (100)	54% (68)

OS ACCORDING TO THE TYPE OF TREATMENT IN PATIENTS WITH MORE THAN TWO POSITIVE NODES



	Overall survival		
	% 5-yr (No at risk)	% 8-yr (No at risk)	%10-yr (No at risk)
Adjuvant HT+RT	87% (25)	87% (10)	87% (10)
Adjuvant HT alone	75% (45)	66% (33)	56% (28)

Briganti A. et al. Eur Urol 59 (2011); 832-840

Treatment options

- ✓ Active surveillance
- ✓ Surgery: Radical prostatectomy
- ✓ **Radiotherapy / Brachytherapy**
- ✓ Focal therapy

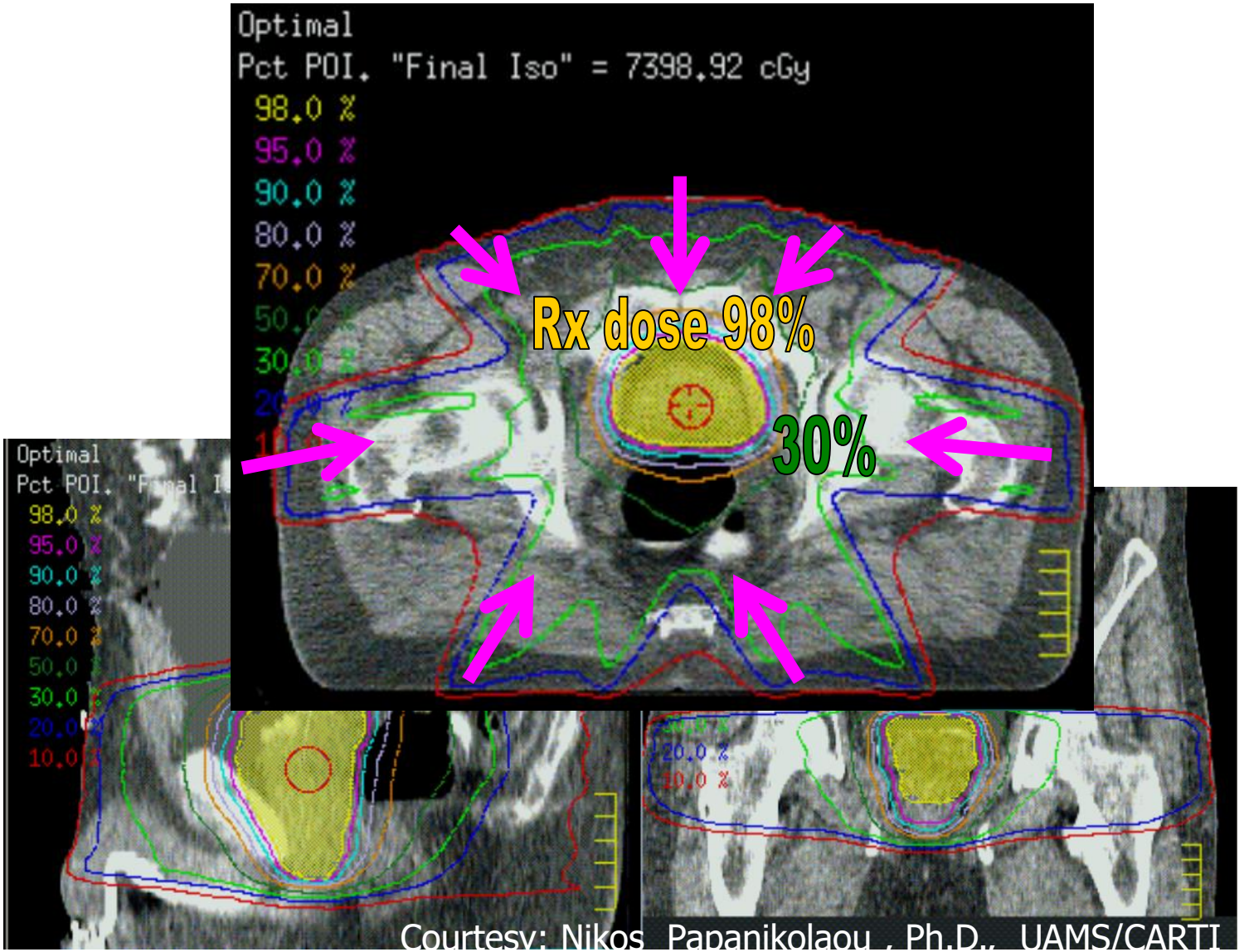
Radiotherapy

Radiotherapy

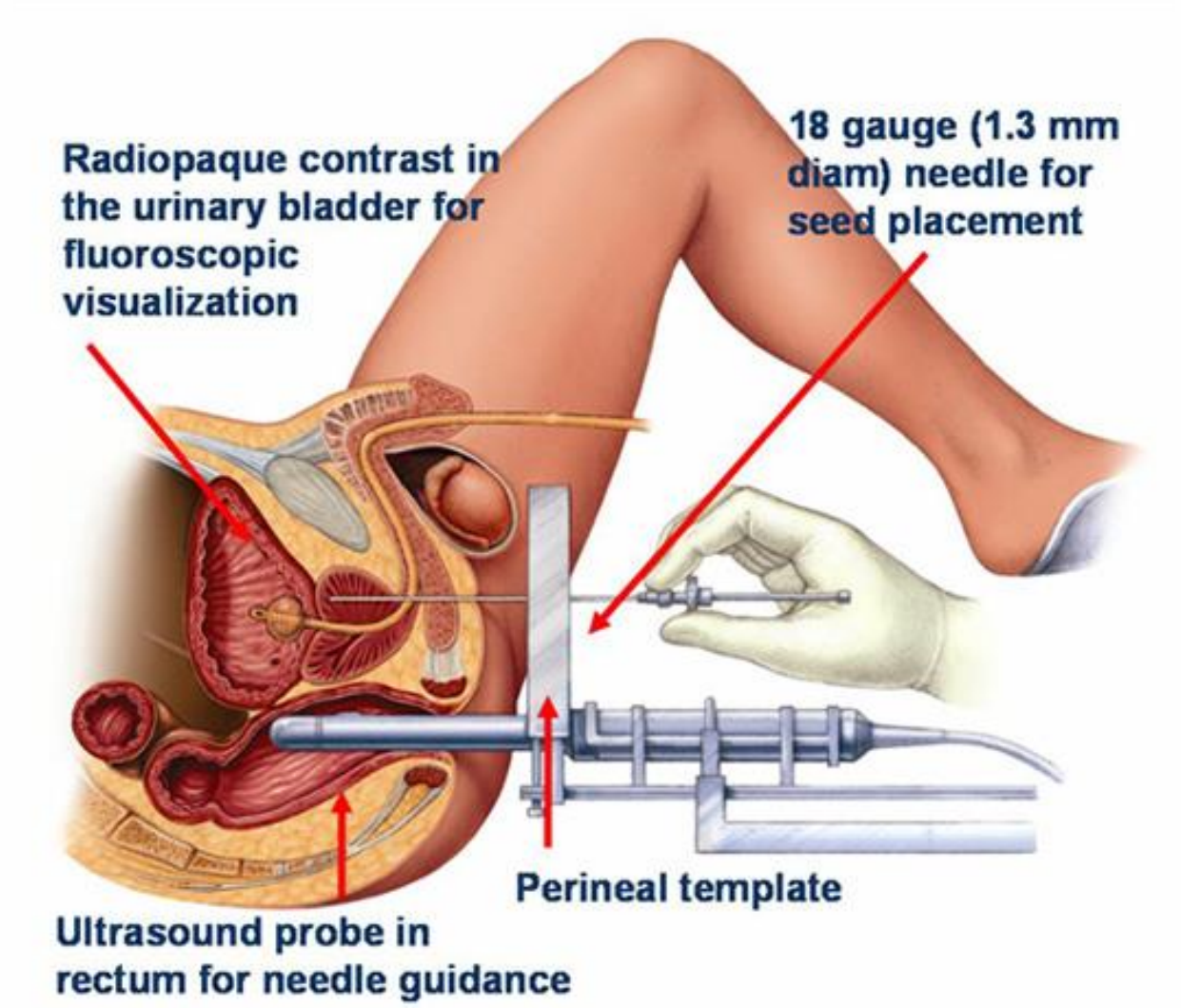
Guideline/recommendation	LE	GR
In localized PCa (T1c–T2cN0M0), 3D-CRT with or without IMRT is recommended even for young patients who refuse surgical intervention.	2	B
For high-risk patients, long-term ADT before and during RT is recommended, as it results in increased overall survival.	2a	B
In patients with locally advanced PCa (T3–T4N0M0) who are fit enough to receive EBRT, the recommended treatment is EBRT plus long-term ADT. The use of ADT alone is inappropriate.	1b	A
Transperineal interstitial brachytherapy with permanent implants is an option for patients with cT1–T2a, Gleason score ≤7a, PSA ≤10 ng/ml, prostate volume ≤50 ml, without a previous TURP and with a good IPSS.	2b	B
Immediate postoperative external irradiation after RP for patients with pathologic tumor stage T3N0M0 improves biochemical and clinical disease-free survival.	1	A
In patients with pathologic tumor stage T3N0M0, immediate postoperative external irradiation after RP may improve biochemical and disease-free survival, with the highest impact in cases with positive surgical margins.	1b	A
In patients with pathologic tumor stage T2–T3N0M0, salvage irradiation is indicated in cases of persisting PSA or biochemical failure with rising PSA levels ≤0.5 ng/ml. Salvage RT might be initiated, even at low PSA levels of 0.1–0.2 ng/ml, if a continuous PSA increase has been documented.	3	B
In patients with locally advanced PCa, T3–T4N0M0,concomitant and adjuvant hormonal therapy for a total duration of 3 yr, with external-beam radiation for patients with WHO 0–2 performance status, is recommended, as it improves overall survival.	1b	A
In a subset of patients with T2–T3N0M0 and Gleason score 2–6, short-term ADT before and during RT can be recommended, as it may favorably influence overall survival.	1b	A
In patients with very-high-risk PCa, c–pN1M0, and no severe comorbidities, the therapeutic role of pelvic external irradiation and immediate long-term ADT is unclear; the adjuvant treatment options have to be discussed on an individual basis, taking into consideration the age of the patient, comorbidities, and biology of the cancer.	3	B

Heidenreich et al. Eur Urol 2014, in press

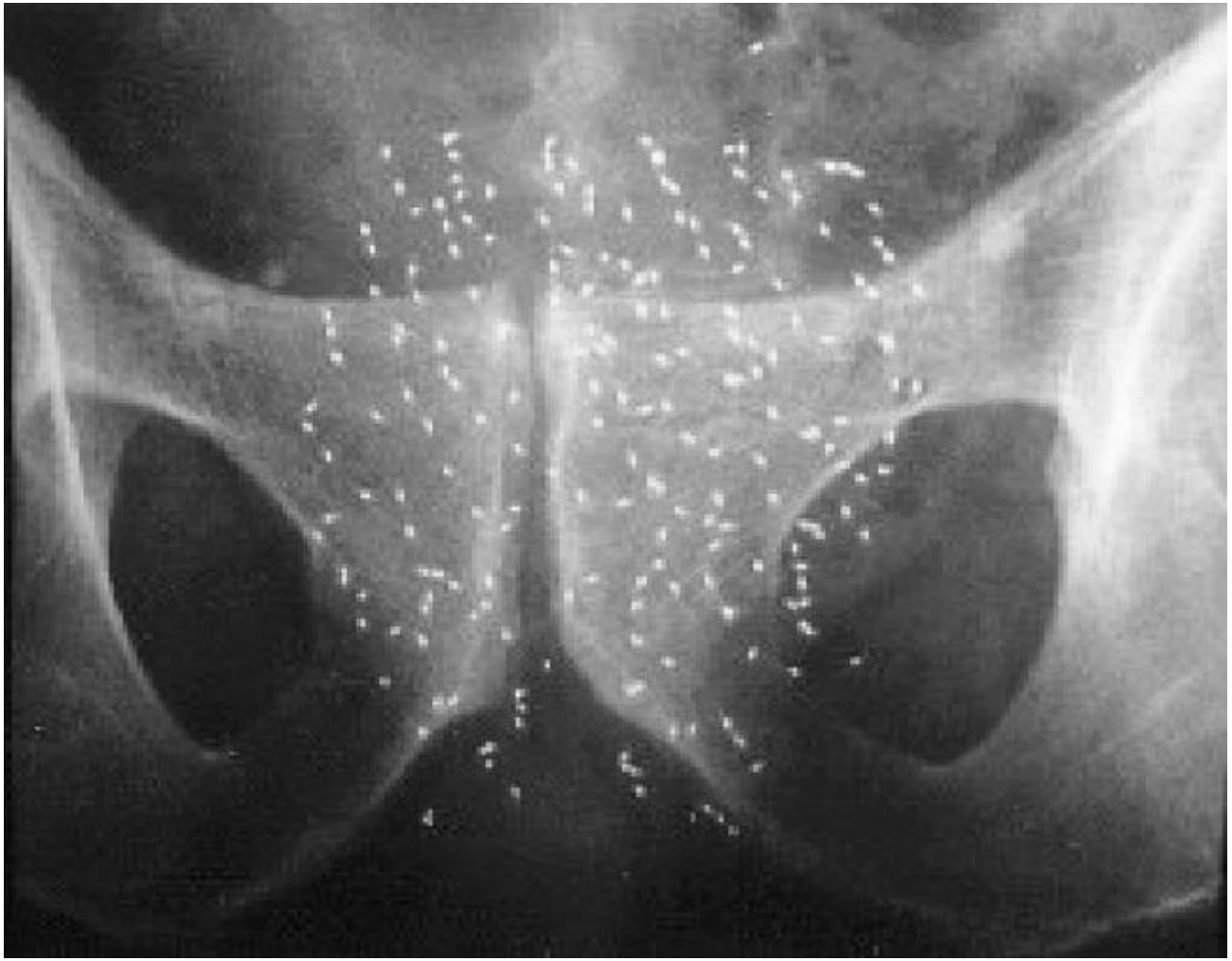
Radiotherapy



Brachytherapy



Brachytherapy



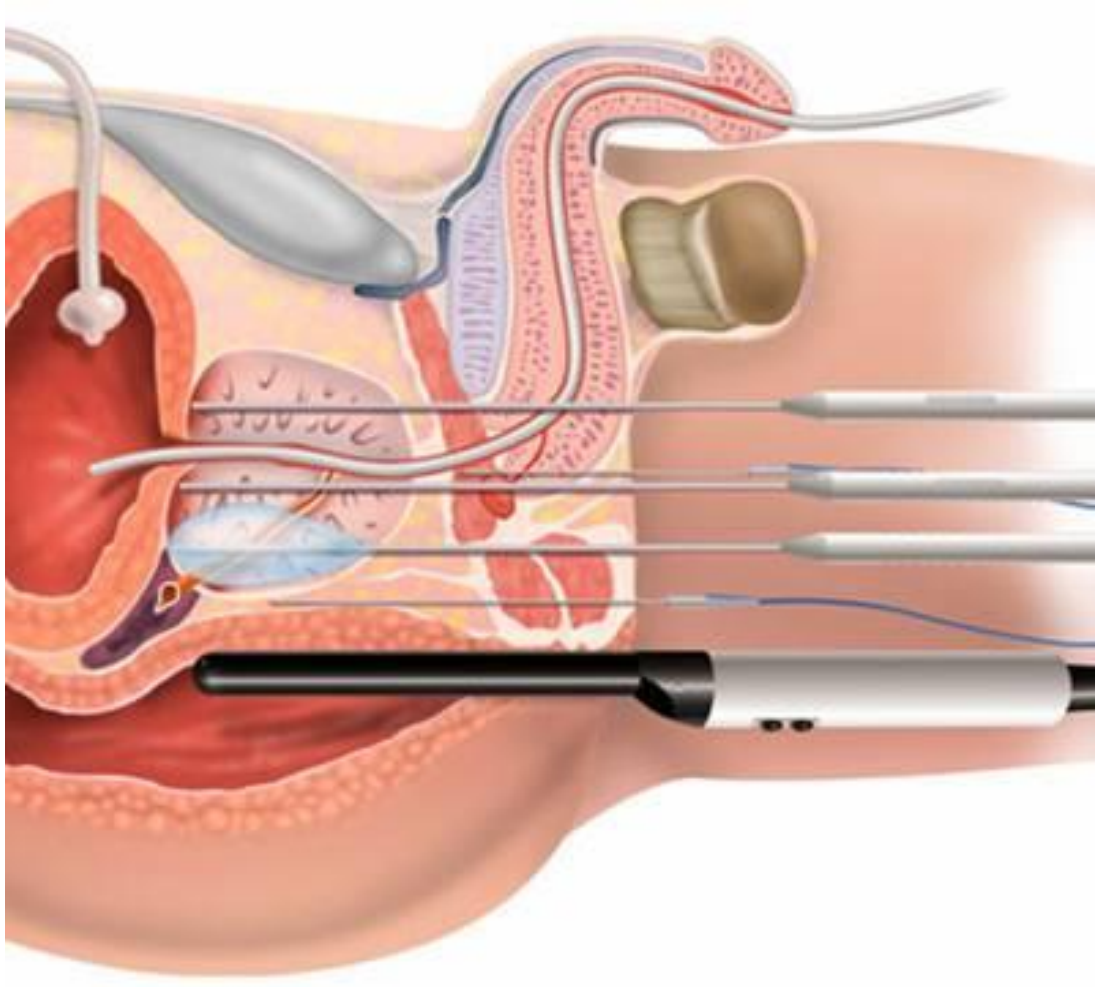
Treatment options

- ✓ Active surveillance
- ✓ Surgery: Radical prostatectomy
- ✓ Radiotherapy / Brachytherapy
- ✓ **Focal therapy**

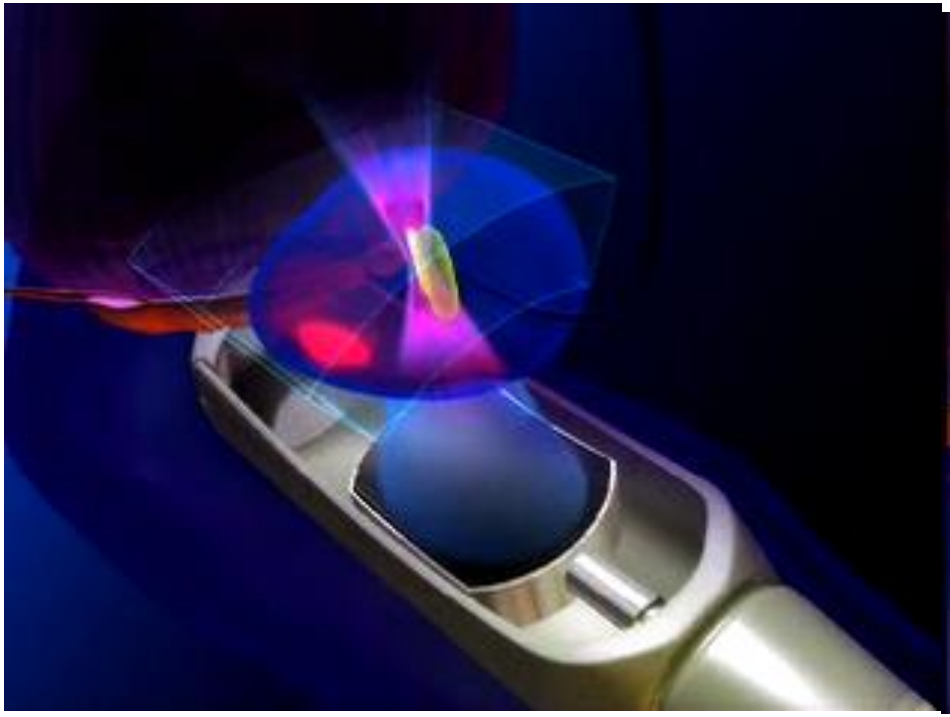
Focal Therapy

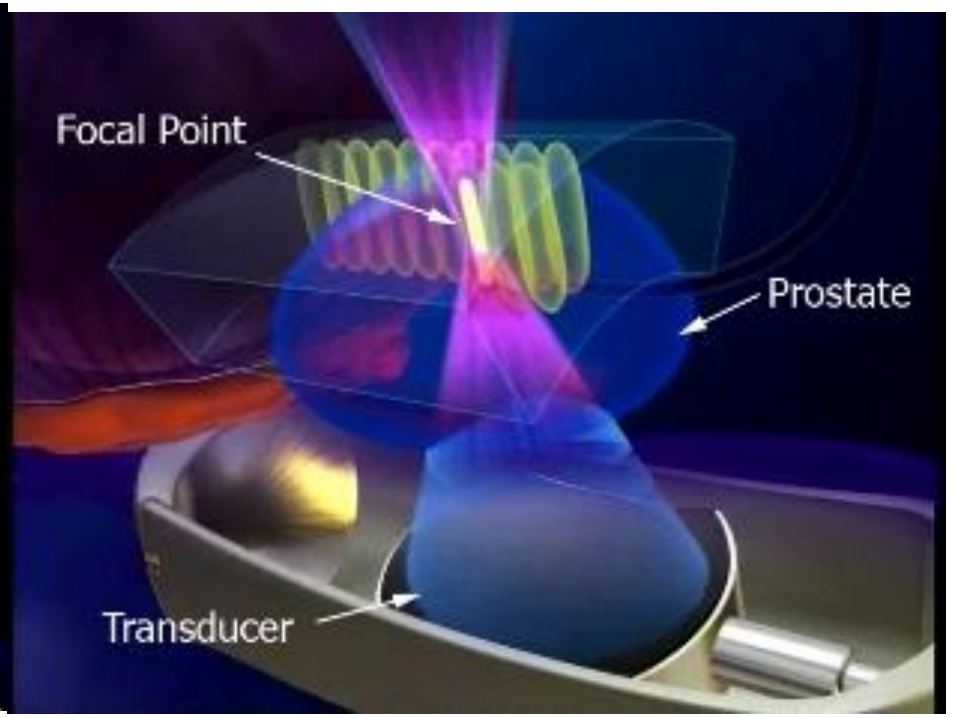
- ✓ Early identification of prostate cancer has reduced the use of radical treatments in favor of conservative approaches.
- ✓ However, many men are still reluctant to active surveillance or watchful waiting.
- ✓ For these patients, an alternative approach is **focal therapy**.

Focal Therapy

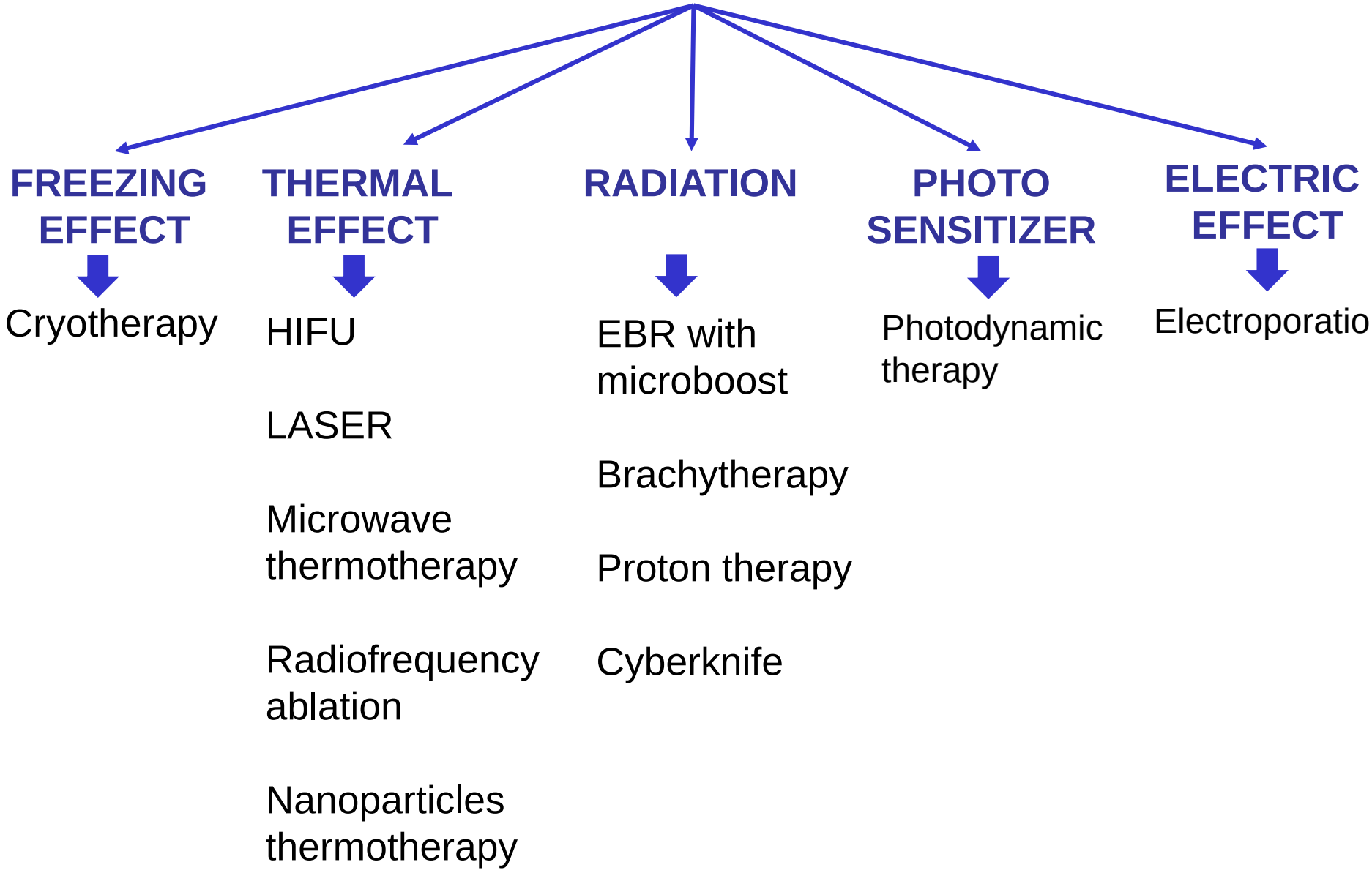


Focal Therapy





ENERGIES USED IN FOCAL THERAPY



CONCLUSIONS

RISK GROUPS

Definition			
Low-risk	**Intermediate-risk**	**High-risk**	
PSA < 10 ng/mL and GS < 7 (ISUP grade 1) and cT1-2a	PSA 10-20 ng/mL or GS 7 (ISUP grade 2/3) or cT2b	PSA > 20 ng/mL or GS > 7 (ISUP grade 4/5) or cT2c	any PSA any GS (any ISUP grade) cT3-4 or cN+
Localised			**Locally advanced**

GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen.

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Low-risk disease

Recommendations		Strength rating
Low-risk disease		
Active surveillance (AS)	Offer AS to patients with life expectancy > 10 years and low-risk disease.	Strong
	If a patient has had upfront multiparametric magnetic resonance imaging (mpMRI) followed by systematic and targeted biopsies there is no need for confirmatory biopsies.	Weak
	Patients with intraductal and cribiform histology on biopsy should be excluded from AS.	Strong
	If required, perform mpMRI before a confirmatory biopsy.	Strong
	Take both targeted biopsy (of any PI-RADS ≥ 3 lesion) and systematic biopsy if confirmatory biopsy performed.	Strong
	Perform serum prostate-specific antigen (PSA) assessment every 6 months.	Strong
	Perform digital rectal examination (DRE) every 12 months.	Strong
	Repeat biopsy should be performed if there is evidence of PSA progression, clinical progression on DRE or radiological progression on mpMRI.	Strong
	During follow-up, if mpMRI is negative (i.e., PI-RADS ≤ 2), and clinical suspicion of PCa progression is low (e.g. low PSA velocity, long PSA doubling time), omit biopsy based on shared decision making with the patient.	Weak
	Counsel patients about the possibility of needing further treatment in the future.	Strong
Active treatment	Offer surgery and radiotherapy (RT) as alternatives to AS to patients suitable for such treatments and who accept a trade-off between toxicity and prevention of disease progression.	Weak
Pelvic lymph node dissection (PLND)	Do not perform a PLND (estimated risk for pN+ ≤ 5%).	Strong
Radiotherapeutic treatment	Offer low-dose rate (LDR) brachytherapy to patients with low-risk PCa, without a previous transurethral resection of the prostate (TURP), with a good International Prostatic Symptom Score (IPSS) and a prostate volume < 50 mL.	Strong
	Use intensity-modulated radiation therapy (IMRT) with a total dose of 74-80 Gy or moderate hypofractionation (60 Gy/20 fx in 4 weeks, or 70 Gy/28 fx in 6 weeks), without androgen deprivation therapy (ADT).	Strong
Other options	Only offer whole gland treatment (such as cryotherapy, high-intensity focused ultrasound [HIFU], etc.) or focal treatment within a clinical trial setting or well-designed prospective cohort study.	Strong

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Intermediate-risk disease

Intermediate-risk disease		
Active surveillance	Offer AS to highly selected patients (< 10% Gleason pattern 4) accepting the potential increased risk of further metastases.	Weak
Radical Prostatectomy (RP)	Offer RP to patients with intermediate-risk disease and a life expectancy > 10 years.	Strong
	Offer nerve-sparing surgery to patients with a low risk of extracapsular disease.	Strong
Extended pelvic lymph node dissection (ePLND)	Perform an ePLND in intermediate-risk disease if the estimated risk for positive lymph nodes exceeds 5%.	Strong
Radiotherapeutic treatment	Offer LDR brachytherapy to selected patients; patients without a previous TURP, with a good IPSS and a prostate volume < 50 mL.	Strong
	For external-beam radiation therapy (EBRT), use a total dose of 76-78 Gy or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks), in combination with short-term neoadjuvant plus concomitant ADT (4 to 6 months).	Strong
	In patients not willing to undergo ADT, use an escalated dose of EBRT (76-80 Gy) or a combination with brachytherapy.	Weak
Other therapeutic options	Only offer whole-gland ablative therapy (such as cryotherapy, HIFU, etc.) or focal ablative therapy for intermediate-risk disease within a clinical trial setting or well-designed prospective cohort study.	Strong
	Do not offer ADT monotherapy to intermediate-risk asymptomatic men not able to receive any local treatment.	Weak

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High-risk localised disease

High-risk localised disease		
Radical prostatectomy	Offer RP to selected patients with high-risk localised PCa, as part of potential multi-modal therapy.	Strong
Extended pelvic lymph node dissection	Perform an ePLND in high-risk PCa.	Strong
	Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure.	Strong
Radiotherapeutic treatments	In patients with high-risk localised disease, use ERBT with 76-78 Gy in combination with long-term ADT (2 to 3 years).	Strong
	In patients with high-risk localised disease, use EBRT with brachytherapy boost (either HDR or LDR), in combination with long-term ADT (2 to 3 years).	Weak
Therapeutic options outside surgery and radiotherapy	Do not offer either whole gland or focal therapy to high-risk patients.	Strong
	Do not use ADT monotherapy in asymptomatic patients.	Strong

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Locally-advanced disease

Locally-advanced disease		
Radical prostatectomy	Offer RP to highly selected patients with cT3b-T4 N0 or any cN1 only as part of multi-modal therapy.	Strong
Extended pelvic lymph node dissection	Perform an ePLND in high-risk PCa.	Strong
Radiotherapeutic treatments	In patients with locally advanced cN0 disease, offer RT in combination with long-term ADT.	Strong
	Offer long-term ADT for at least two years.	Weak
Therapeutic options outside surgery and radiotherapy	Do not offer whole gland treatment or focal treatment to high-risk patients.	Strong
	Only offer ADT monotherapy to those patients unwilling or unable to receive any form of local treatment if they have a PSA-doubling time < 12 months, and either a PSA > 50 ng/mL, a poorly-differentiated tumour or troublesome local disease-related symptoms.	Strong
	Offer patients with cN1 disease a local treatment (either RP or EBRT) plus long-term ADT.	Weak

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Adjuvant treatment after radical prostatectomy

Adjuvant treatment after radical prostatectomy		
	Do not prescribe adjuvant ADT in pN0 patients.	Strong
	Offer adjuvant EBRT to the surgical field to highly-selected patients.	Strong
	Discuss three management options with patients with pN+ disease after an ePLND, based on nodal involvement characteristics: 1. Offer adjuvant ADT; 2. Offer adjuvant ADT with additional RT; 3. Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes with microscopic involvement, and a PSA < 0.1 ng/mL and absence of extranodal extension.	Weak

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FOLLOW-UP

Follow-up after treatment with curative intent

7.1.5 Summary of evidence and guidelines for follow-up after treatment with curative intent

Summary of evidence	**LE**
After radical prostatectomy rising serum PSA level is considered a BCR.	3
After radiotherapy, an increase in PSA > 2 ng/mL above the nadir, rather than a specific threshold value, is considered as clinically meaningful BCR.	3
Palpable nodules and increasing serum PSA are signs of local recurrence.	2a

Recommendations	**Strength rating**
Routinely follow up asymptomatic patients by obtaining at least a disease-specific history and serum prostate-specific antigen (PSA) measurement. These should be performed at 3, 6 and 12 months after treatment, then every 6 months until 3 years, and then annually.	Strong
At recurrence, only perform imaging to detect local recurrence if the outcome will affect treatment planning.	Strong
Only offer bone scans and other imaging modalities to men with biochemical recurrence or symptoms suggestive of progression without signs of biochemical relapse.	Strong

Follow-up during hormonal treatment

7.2.7 Guidelines for follow-up during hormonal treatment

Recommendations	Strength rating
Evaluate patients at 3 to 6 months after the initiation of treatment.	Strong
The follow-up strategy must be individualised based on stage of disease, prior symptoms, prognostic factors and the treatment given.	Strong
In patients with stage M0 disease, schedule follow-up at least every 6 months. As a minimum requirement, include a disease-specific history, serum prostate-specific antigen (PSA) determination, as well as liver and renal function in the diagnostic work-up.	Strong
In patients with stage M1 disease, schedule follow-up every 3 to 6 months. As a minimum requirement, include an initial FRAX-score assessment, disease-specific history, digital-rectal examination (DRE), serum PSA, haemoglobin, serum creatinine and alkaline phosphatase measurements in the diagnostic work-up. The testosterone level should be checked, especially during the first year. Pay attention to symptoms associated with metabolic syndrome as a side effect of androgen deprivation therapy. Phospholipid profiles and glucose levels should be checked and treated if abnormal.	Strong
Counsel patients (especially with M1b status) about the clinical signs suggestive of spinal cord compression.	Strong
When disease progression is suspected, adapt/individualise follow-up.	Strong
In patients with suspected progression, assess the testosterone level. By definition, castration resistant PCa requires a testosterone level < 50 ng/dL (< 1 mL/L).	Strong
Do not offer routine imaging to otherwise stable asymptomatic patients.	Weak

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TREATMENT OF METASTATIC PROSTATE CANCER

TREATMENT OF METASTATIC PROSTATE CANCER

Hormonal therapy Indications for castration	Benefits	LE
• M1 symptomatic	To palliate symptoms and to reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathologic fractures, ureteral obstruction, extraskeletal metastasis).	1b
	Even without a controlled randomised trial, this is the standard of care and must be applied and considered as level 1 evidence.	1
• M1 asymptomatic	Immediate castration to defer progression to a symptomatic stage and prevent serious disease progression–related complications.	1b
	An active clinical surveillance protocol might be an acceptable option in clearly informed patients if survival is the main objective.	3
Antiandrogens		
• Short-term admini	flare-up phenomenon in patients with advanced metastatic disease who are to receive an LHRH agonist.	1b
	It may be sufficient to give an antiandrogen for 3 wk of concomitant use, starting treatment on the same day as LHRH analogue treatment is started, or for up to 7 d before the first LHRH analogue injection.	4
• Long-term administration	This is an option in highly selected and motivated patients with a low PSA.	3
Intermittent androgen deprivation		
Threshold to start and stop ADT	The threshold is empirically chosen. However, it should reproduce what has been used in clinical trials. In trials, treatment is usually stopped when the PSA level is <4 ng/ml (M1) and <0.5–4 ng/ml (relapsing).	4
	Treatment is usually restarted when the PSA is >4–10 (relapsing) and >10–15 ng/ml (M1).	
Drug	LHRH analogue plus flare-up prevention *or* combined treatment.	1
Population	Metastatic patients: asymptomatic, motivated, with a clear PSA response after the induction period.	2
	Relapsing after radiotherapy: patients with a clear response after the induction period.	1b

ADT = androgen-deprivation therapy; LE = level of evidence; LHRH = luteinising hormone-releasing hormone; PSA = prostate-specific antigen.

Heidenreich et al. Eur Urol 2014, in press

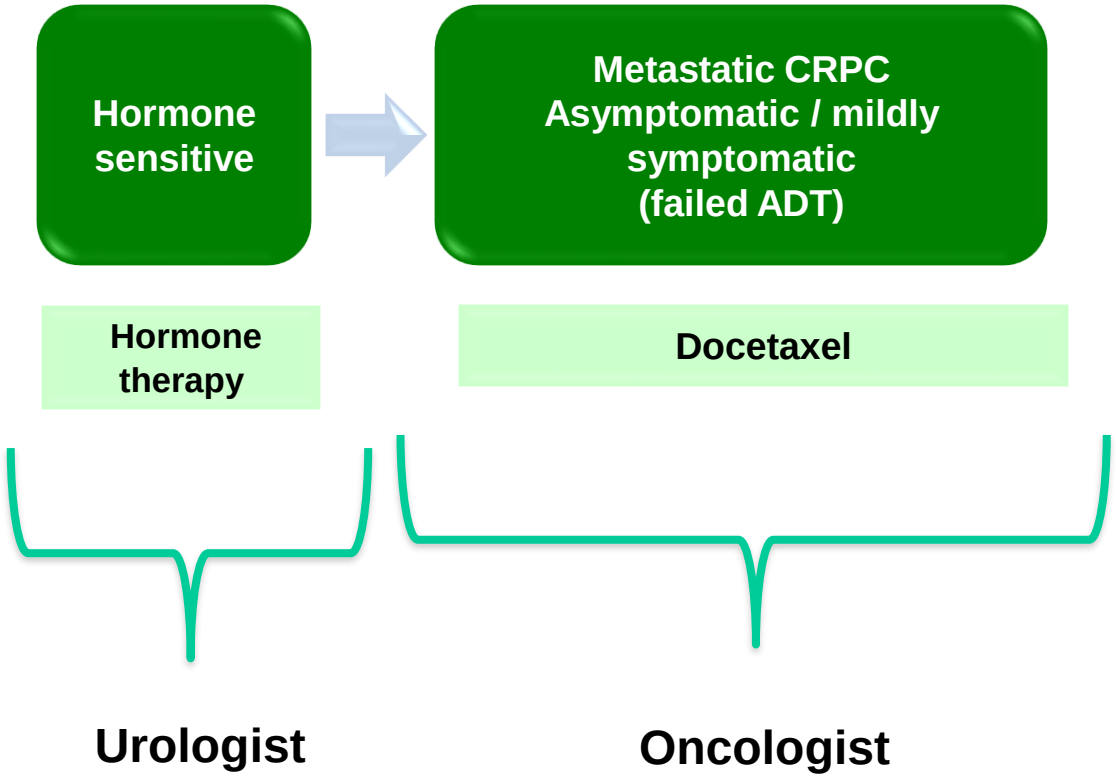
TREATMENT OF METASTATIC PROSTATE CANCER

Recommendations	GR
• Ideally, patients with CRPC should be counselled, managed, and treated in a multidisciplinary team.	B
• In nonmetastatic CRPC, cytotoxic therapy should only be considered in clinical trials.	B
• In patients with a rise in PSA only, two consecutive increases of PSA serum levels above a previous reference level should be documented.	B
• Prior to treatment, PSA serum levels should be >2 ng/ml to assure correct interpretation of therapeutic efficacy.	B
• Abiraterone/prednisone should be considered in CRPC patients with asymptomatic or mildly symptomatic metastases and a low metastatic burden due to its survival benefit.	A
• In patients with metastatic CRPC and who are candidates for cytotoxic therapy, docetaxel 75 mg/m^2 every 3 wk has shown a significant survival benefit.	A
• Abiraterone/prednisone should be considered in CRPC patients who received prior docetaxel treatment as an effective second-line treatment option due to its benefit in overall survival and radiographic progression-free survival and QoL.	A
• Enzalutamide should be considered in CRPC patients as an effective second-line treatment due to its benefit in overall survival and radiographic progression-free survival and QoL.	B
• Cabazitaxel should be considered as effective second-line treatment following docetaxel.	A
• Second-line docetaxel may be considered in previously responding patients to docetaxel. Otherwise, treatment is tailored to the individual patient.	C
• Radium-223 should be considered in CRPC patients with osseous metastases due to its benefit in overall survival, QoL, and pain.	A

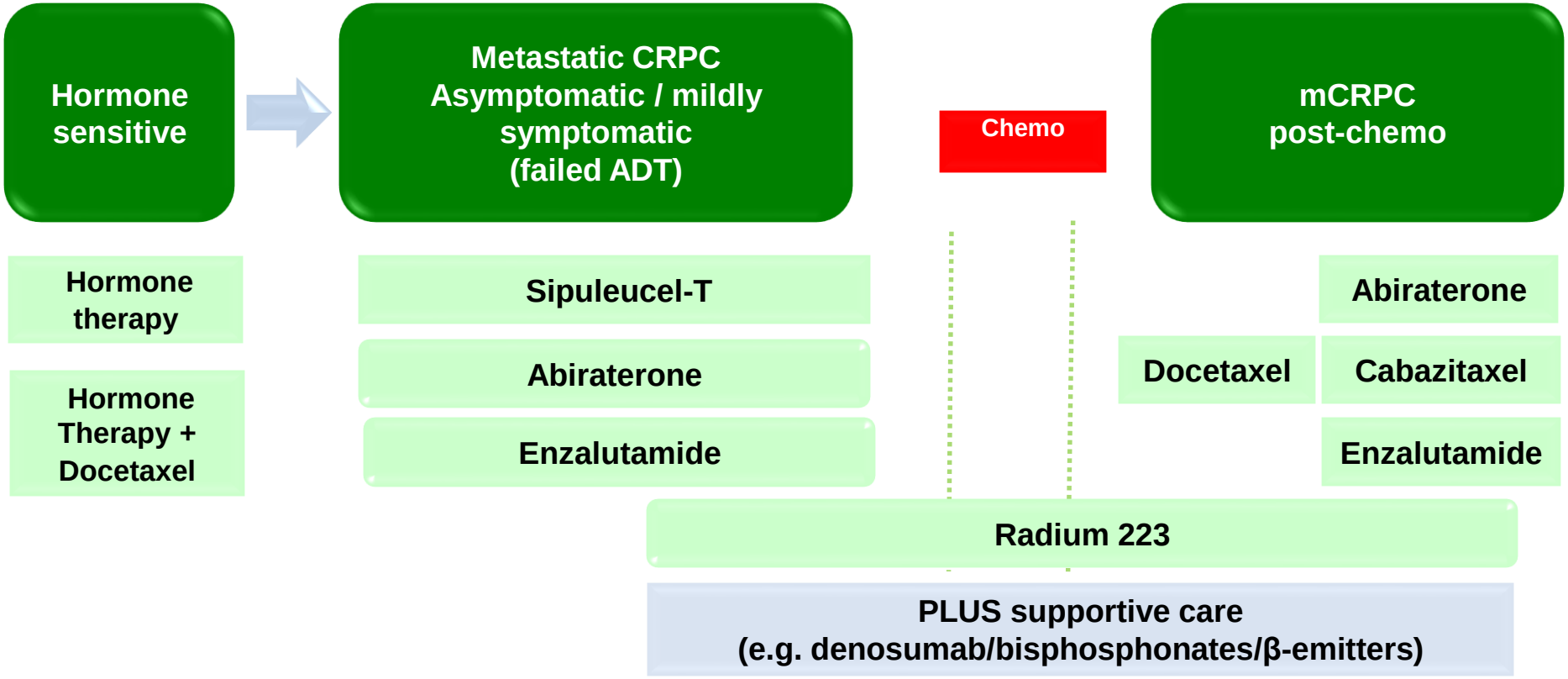
CRPC = castration-resistant prostate cancer; GR = grade of recommendation; PSA = prostate-specific antigen; QoL = quality of life.

Heidenreich et al. Eur Urol 2014, in press

TREATMENT OF METASTATIC PROSTATE CANCER



TREATMENT OF METASTATIC PROSTATE CANCER



Multidisciplinary team

PROSTATE CANCER UNIT

Core Team

Urologists
Radioterapists
Oncologists
Psychologists
Anatomopathologists
Professional Nurses

Non Core Team

Radiotherapists (for brachytherapy)
Medical Physicists
Nuclear Doctors
Radiologists
Rehabilitators
Specialists in Support and Palliative Therapies

Project Team*

Project Manager
Secretary
Research Nurses
Data entry e management

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Oncology Hematology

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Prostate Cancer Unit Initiative in Europe: A position paper by the European School of Oncology

Riccardo Valdagni[a,b,c,*], Hendrik Van Poppel[d], Michael Aitchison[e], Peter Albers[f], Dominik Berthold[g], Alberto Bossi[h], Maurizio Brausi[i], Louis Denis[j,k], Lawrence Drudge-Coates[l], Maria De Santis[m,n], Günther Feick[j,o], Chris Harrison[p], Karin Haustermans[q], Donal Hollywood[r,1], Morton Hoyer[s], Henk Hummel[t], Malcolm Mason[u], Vincenzo Mirone[v], Stefan C. Müller[w], Chris Parker[x], Mahasti Saghatchian[y], Cora N. Sternberg[z], Bertrand Tombal[aa], Erik van Muilekom[bb], Maggie Watson[cc], Simone Wesselmann[dd], Thomas Wiegel[ee], Tiziana Magnani[b], Alberto Costa[a]

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1 In memoriam Prof. Donal Hollywood, President-Elect of the European Society for Radiotherapy & Oncology 2011–2013.

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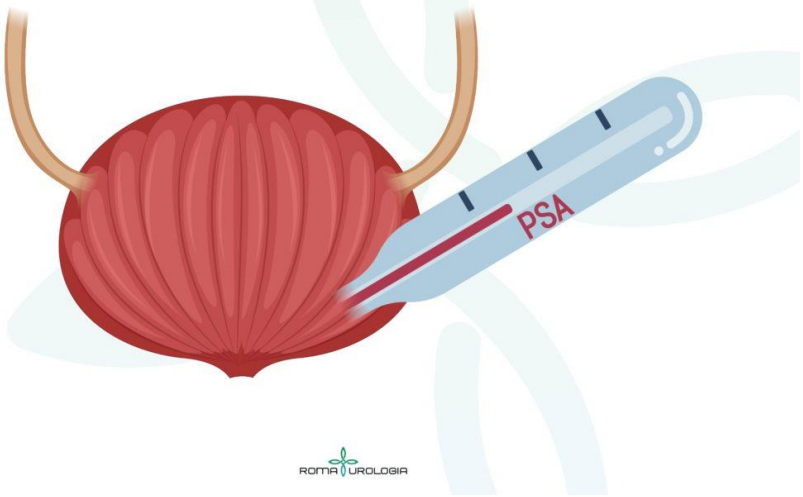
Clinical case – 1

Doctor… I'm 40 years old

- My grandfather died of prostate cancer.
- My father had surgery for prostate cancer 5 years ago (familiarity).
- I'm in good health. I don't have any symptoms.

Am I at risk?
When should I start screening?
Which checks?



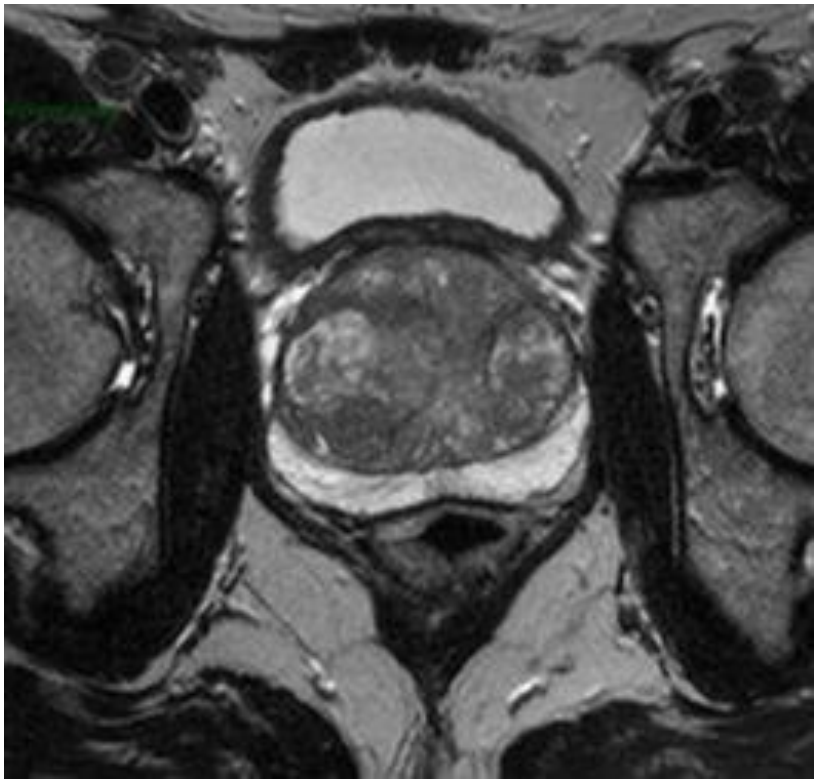
Clinical case – 2

Doctor…

- I’m 55 years old and my PSA is 6.5 ng/mL
- Your colleague prescribed me a multiparametric magnetic resonance imaging of the prostate and it's negative…

I can rest easy, can't I?

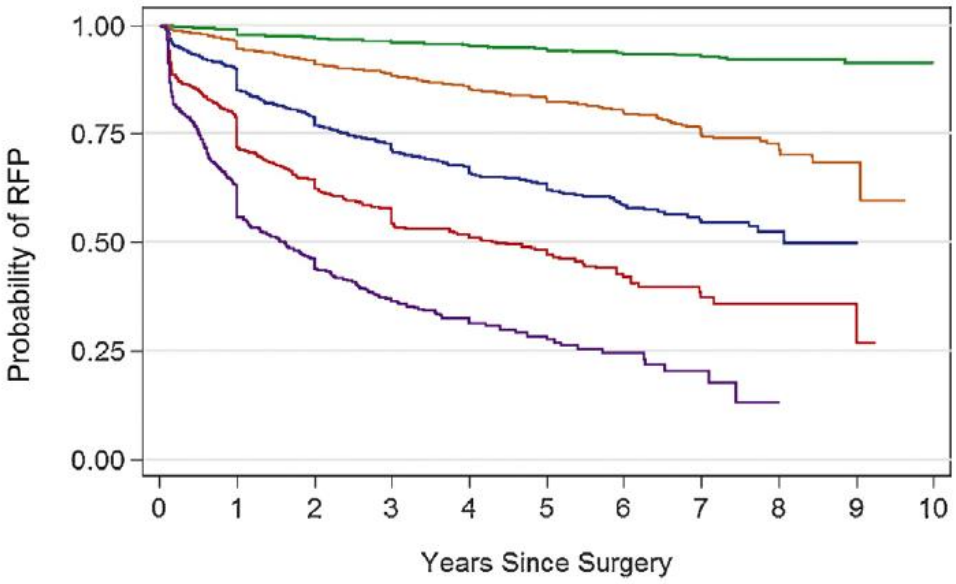
PSA (ng/ml)	rischio di tumore
< 1	8%
1-2	17%
2-4	25%
4-10	47%
> 10	59%



Clinical case – 3

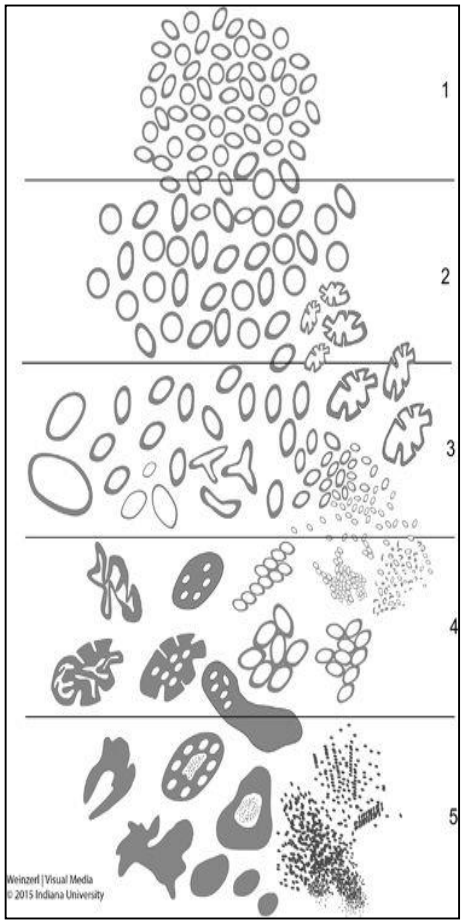
Doctor…I did prostate biopsies and they found me prostate cancer, it's called Gleason 3+3, grading group 1.

Do I have to operate right now?



Number at risk

≤6	8039	7264	5154	3943	3018	2177	1383	818	371	80	1
3+4	4595	3875	2624	1845	1291	845	470	244	102	21	0
4+3	1872	1511	934	634	432	282	157	90	35	5	0
8	1005	710	413	279	185	120	68	33	13	4	0
≥9	661	365	199	118	75	41	25	11	2	0	0



Clinical case – 4

Doctor…

- **3 years ago I had radical prostatectomy**
- **Now PSA is going up**
- **What can I do?**