DIAGNOSTICO Y TRATAMIENTO DEL CÁNCER PROSTÁTICO

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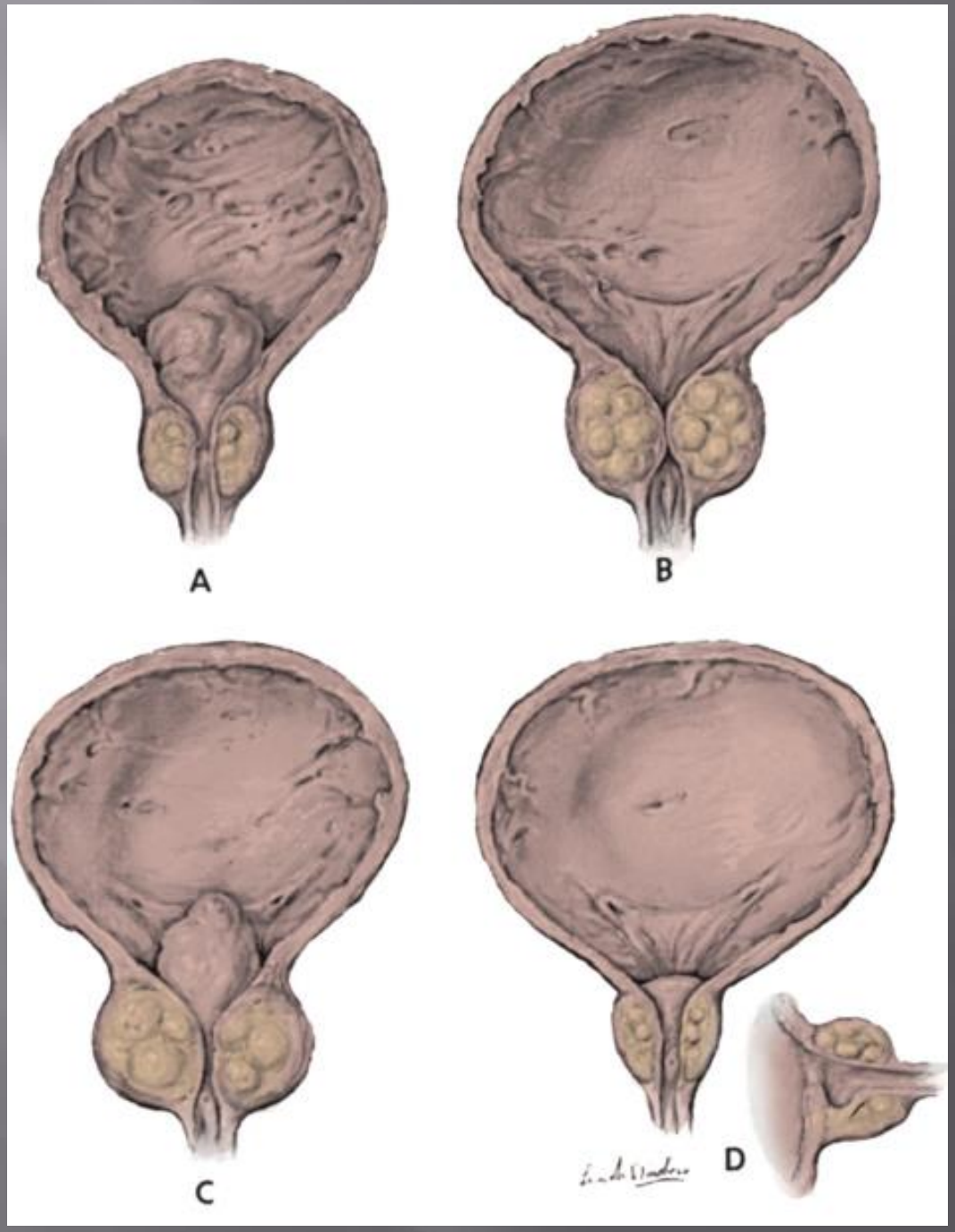
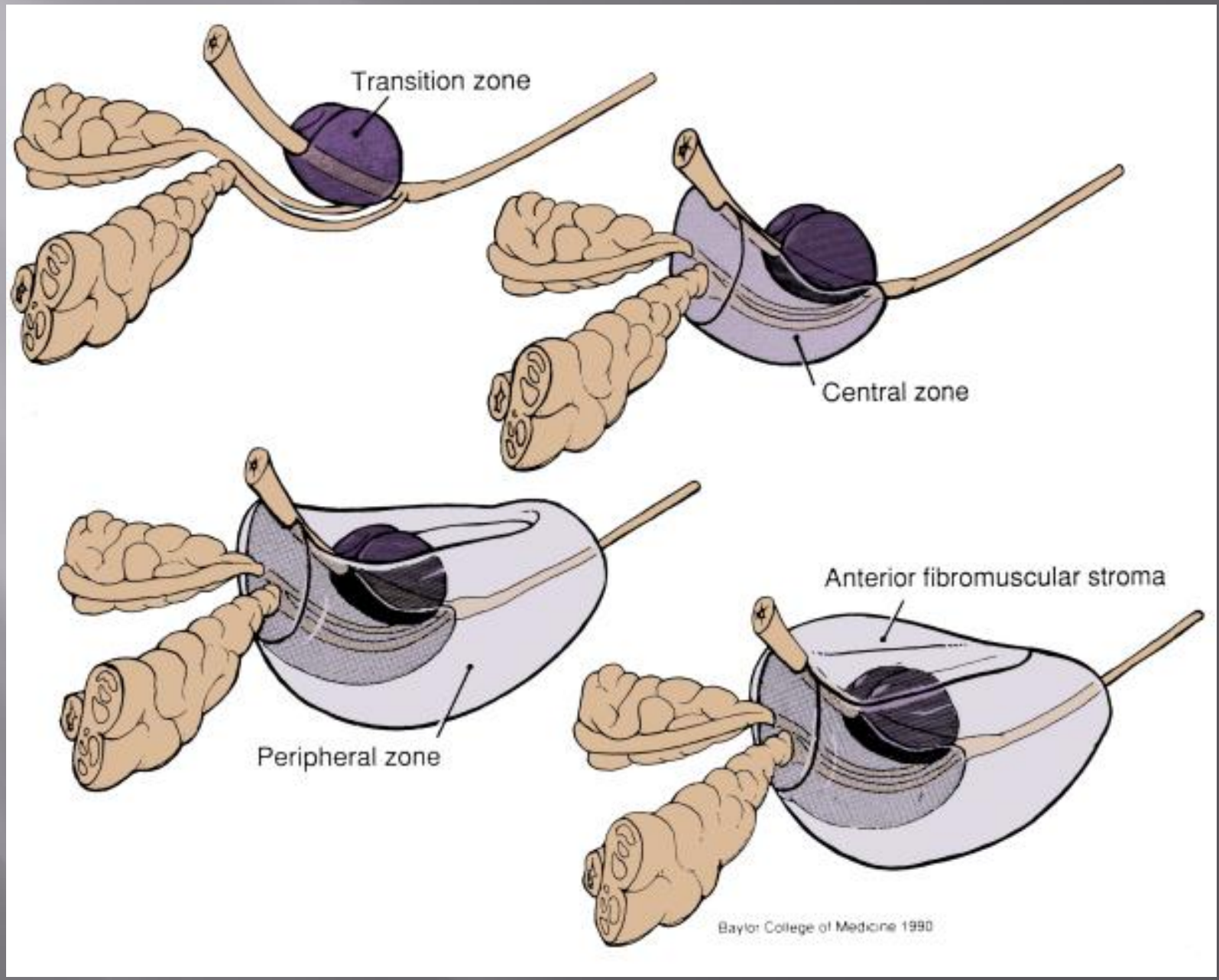
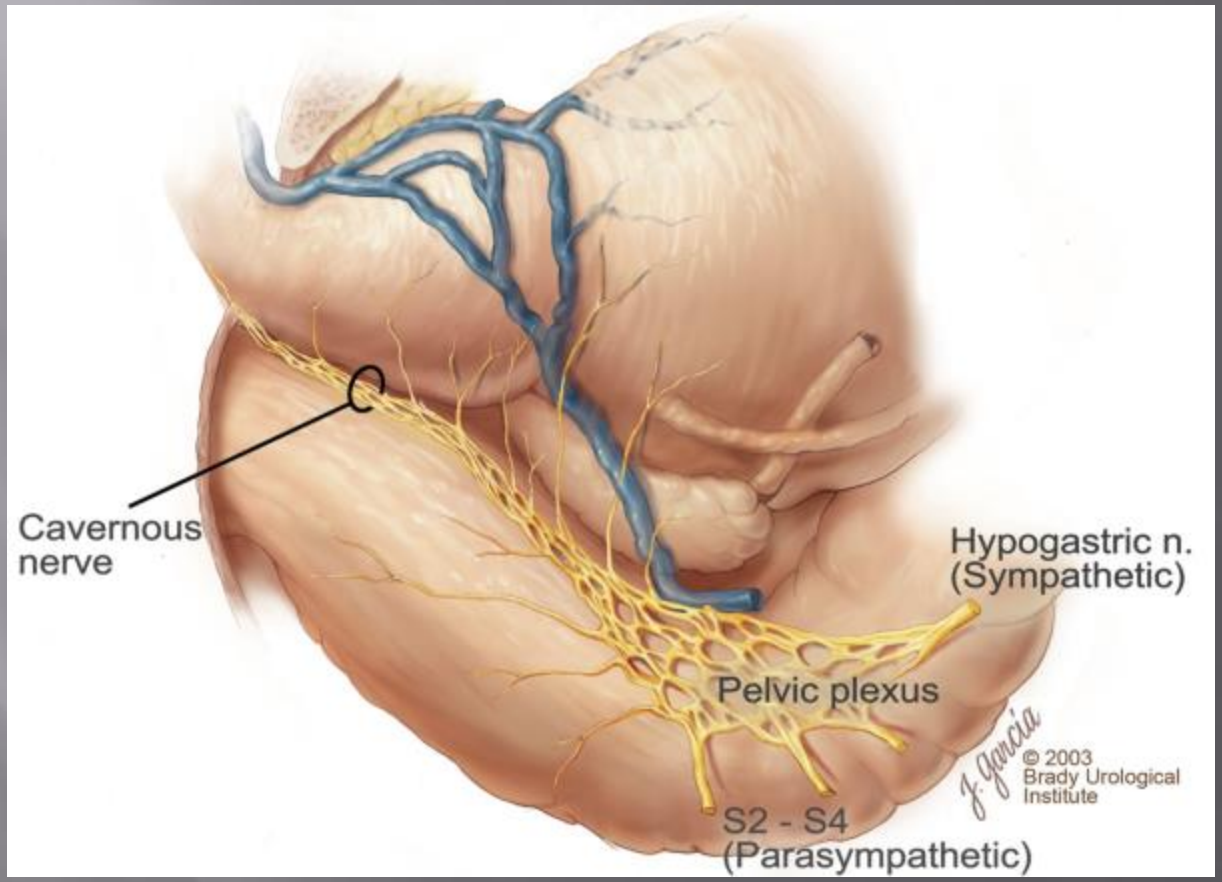

A
B
C
D


Transition zone
Central zone
Peripheral zone
Anterior fibromuscular stroma
Baylor College of Medicine 1990


Cavernous nerve
Hypogastric n. (Sympathetic)
Pelvic plexus
S2 - S4 (Parasympathetic)
J. García
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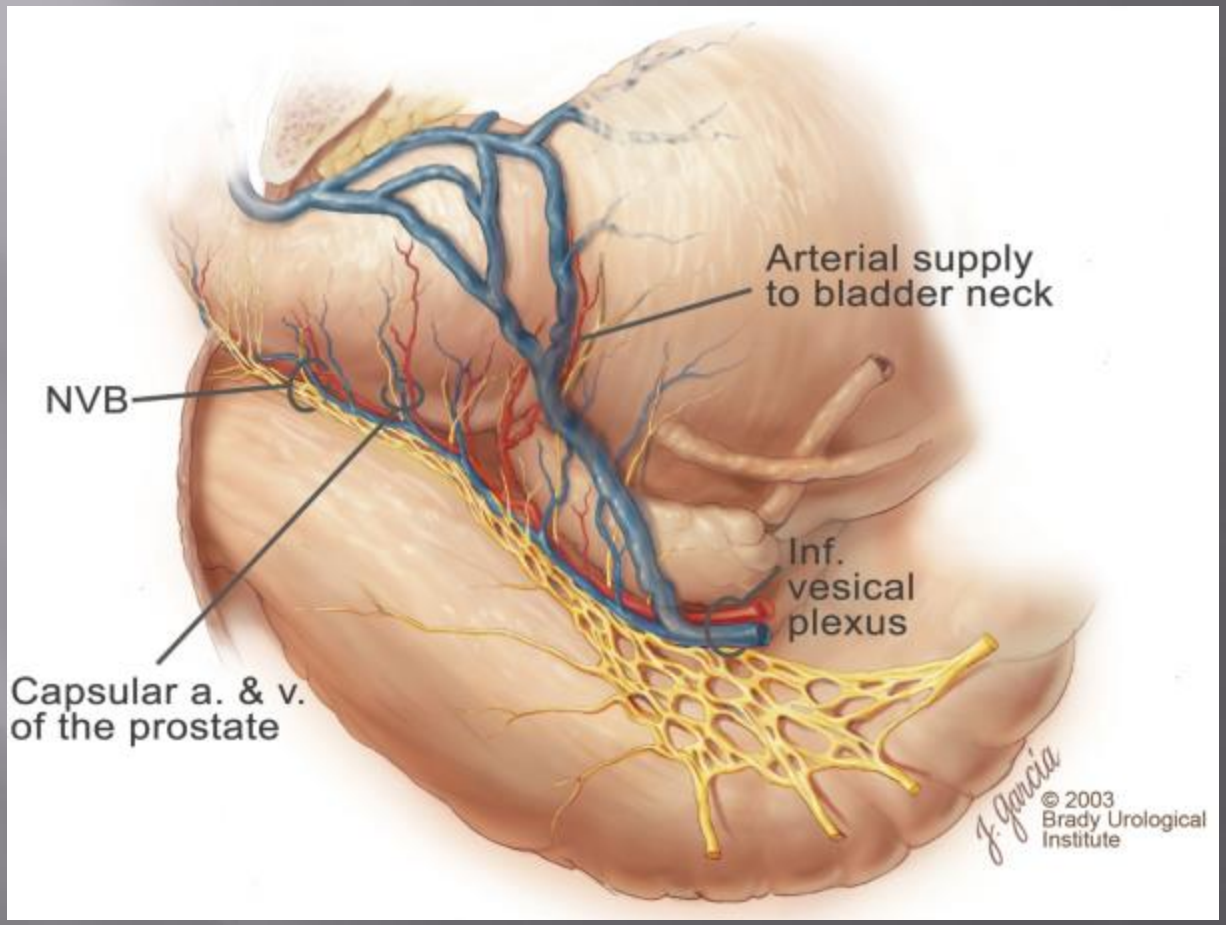
Arterial supply
to bladder neck
NVB
Inf.
vesical
plexus
Capsular a. & v.
of the prostate
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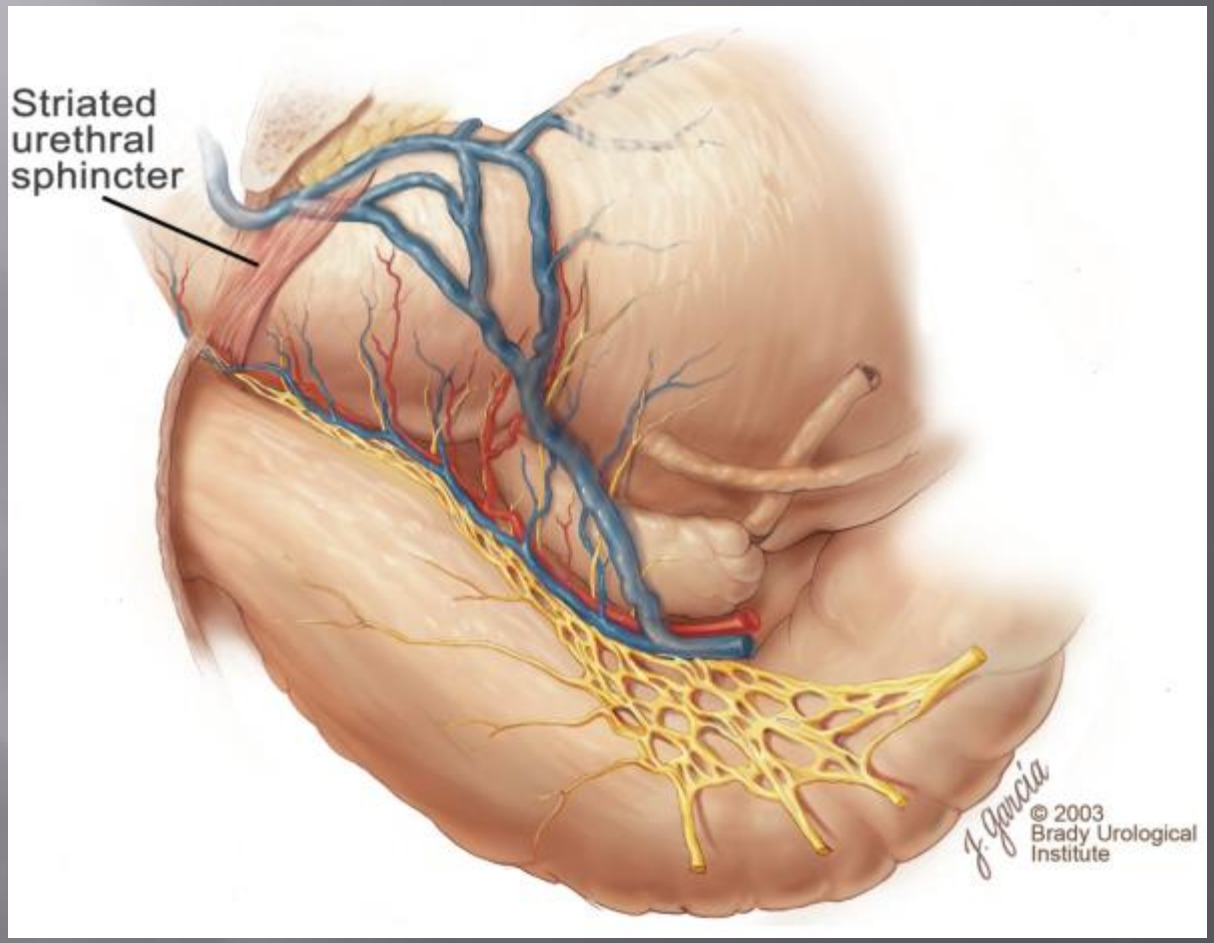
Striated
urethral
sphincter
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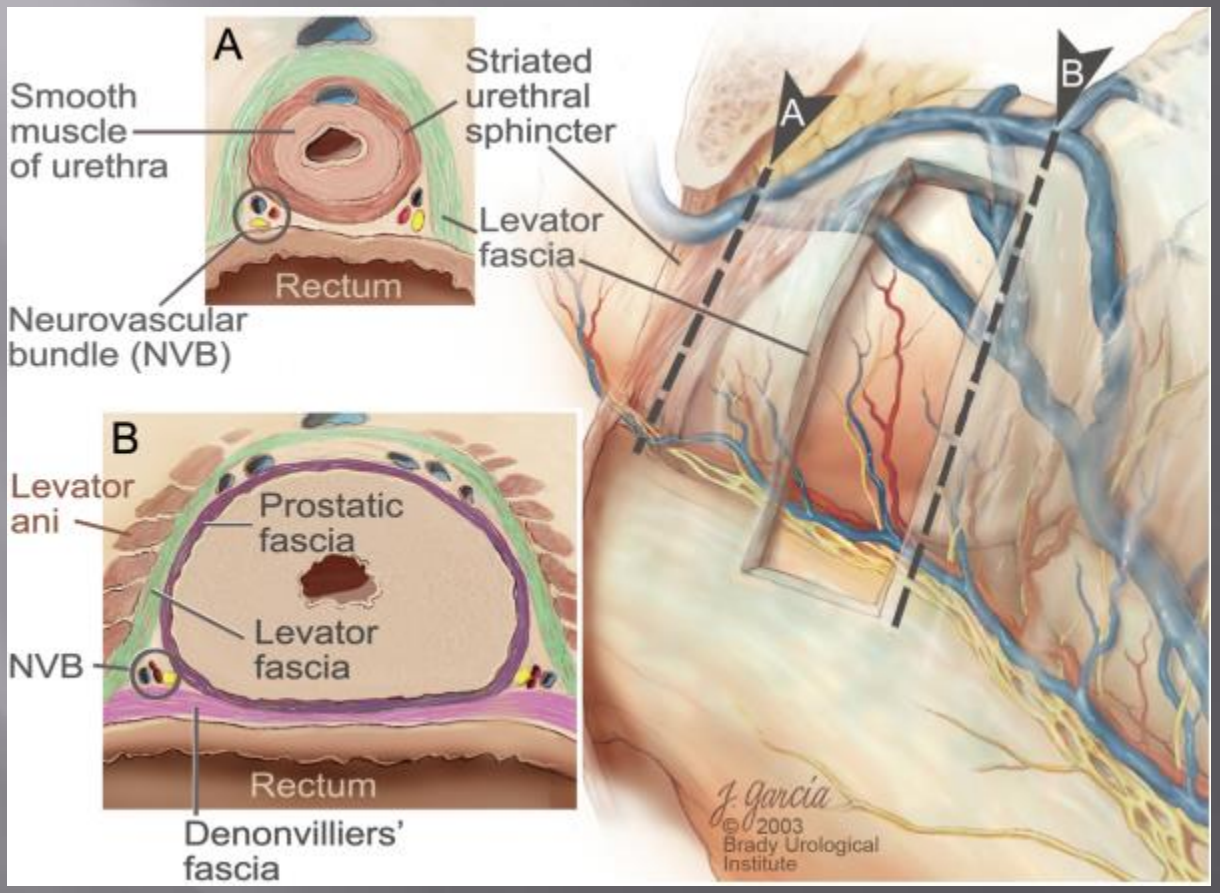
A
Smooth muscle of urethra
Striated urethral sphincter
Levator fascia
Rectum
Neurovascular bundle (NVB)
B
Levator ani
Prostatic fascia
Levator fascia
NVB
Rectum
Denonvilliers' fascia
A
B
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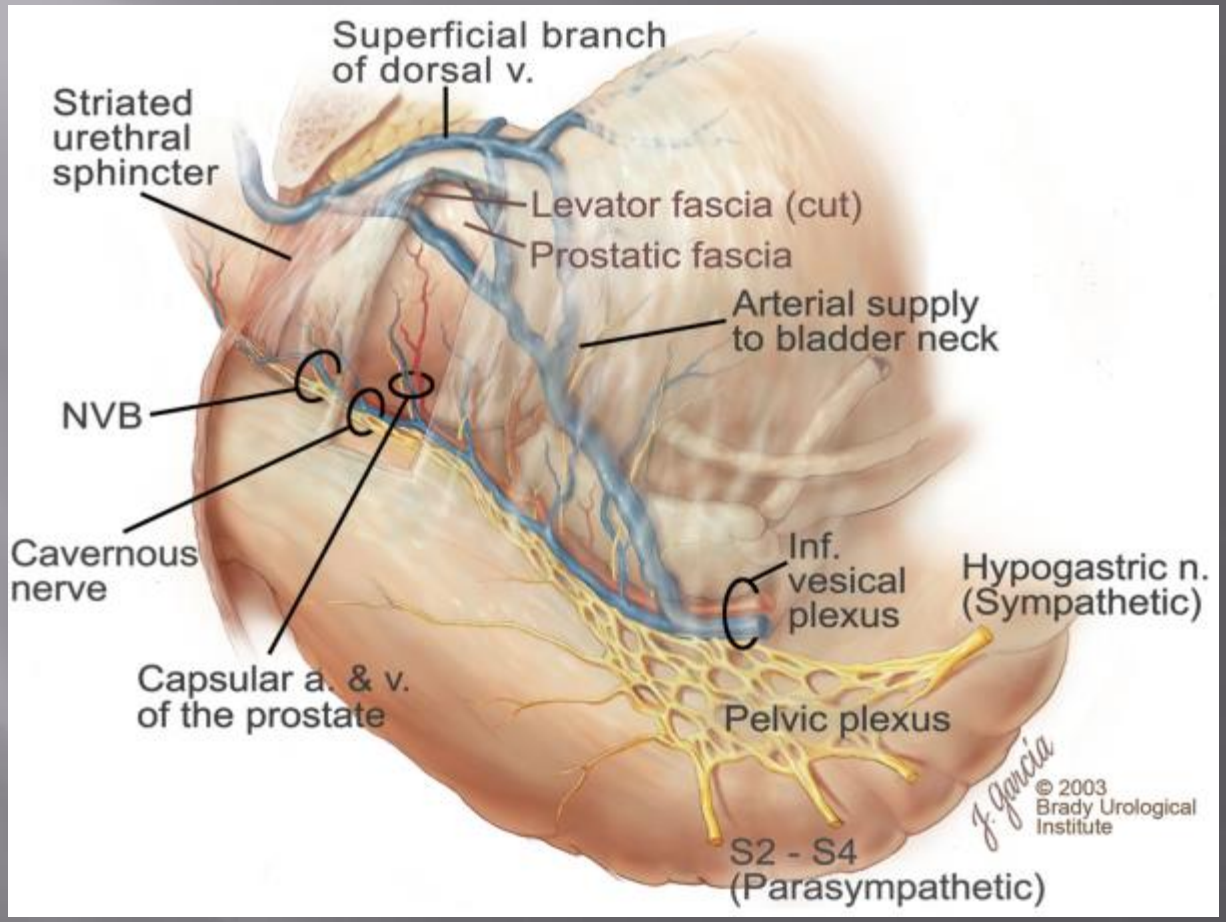
Superficial branch
of dorsal v.
Striated
urethral
sphincter
Levator fascia (cut)
Prostatic fascia
Arterial supply
to bladder neck
NVB
Cavernous
nerve
Inf.
vesical
plexus
Hypogastric n.
(Sympathetic)
Capsular a. & v.
of the prostate
Pelvic plexus
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S2 - S4
(Parasympathetic)

INCIDENCIA

- Mundo:

  4ta neoplasia en orden de frecuencia a nivel mundial

  La incidencia y mortalidad varían en forma acentuada entre los países

  Los países asiáticos presentan las tasas mas bajas de incidencia y mortalidad

  Las causas de variedad son múltiples y complejas

INCIDENCIA

- EUA:

  Neoplasia mas frecuente

  75´- 85´ 2.3%

  89´- 92´ 18,4%

  Segunda causa de muerte

  Los afro americanos tienen la incidencia mas elevada

  La incidencia anualizada mas baja del CaP se presenta en asiáticos norteamericanos

Leading Sites of New Cancer Cases and Deaths – 2010 Estimates

Estimated New Cases*		Estimated Deaths	
Male	**Female**	**Male**	**Female**
Prostate 217,730 (28%)	Breast 207,090 (28%)	Lung & bronchus 86,220 (29%)	Lung & bronchus 71,080 (26%)
Lung & bronchus 116,750 (15%)	Lung & bronchus 105,770 (14%)	Prostate 32,050 (11%)	Breast 39,840 (15%)
Colon & rectum 72,090 (9%)	Colon & rectum 70,480 (10%)	Colon & rectum 26,580 (9%)	Colon & rectum 24,790 (9%)
Urinary bladder 52,760 (7%)	Uterine corpus 43,470 (6%)	Pancreas 18,770 (6%)	Pancreas 18,030 (7%)
Melanoma of the skin 38,870 (5%)	Thyroid 33,930 (5%)	Liver & intrahepatic bile duct 12,720 (4%)	Ovary 13,850 (5%)
Non-Hodgkin lymphoma 35,380 (4%)	Non-Hodgkin lymphoma 30,160 (4%)	Leukemia 12,660 (4%)	Non-Hodgkin lymphoma 9,500 (4%)
Kidney & renal pelvis 35,370 (4%)	Melanoma of the skin 29,260 (4%)	Esophagus 11,650 (4%)	Leukemia 9,180 (3%)
Oral cavity & pharynx 25,420 (3%)	Kidney & renal pelvis 22,870 (3%)	Non-Hodgkin lymphoma 10,710 (4%)	Uterine corpus 7,950 (3%)
Leukemia 24,690 (3%)	Ovary 21,880 (3%)	Urinary bladder 10,410 (3%)	Liver & intrahepatic bile duct 6,190 (2%)
Pancreas 21,370 (3%)	Pancreas 21,770 (3%)	Kidney & renal pelvis 8,210 (3%)	Brain & other nervous system 5,720 (2%)
All sites 789,620 (100%)	All sites 739,940 (100%)	All sites 299,200 (100%)	All sites 270,290 (100%)

INCIDENCIA

- Perú:

  Según el Registro de Cáncer de Lima Metropolitana (1993) la incidencia es de 12.76/100 000hab

  Ocupa el segundo lugar luego del cáncer de Estomago

INCIDENCIA

- Edad al diagnostico:

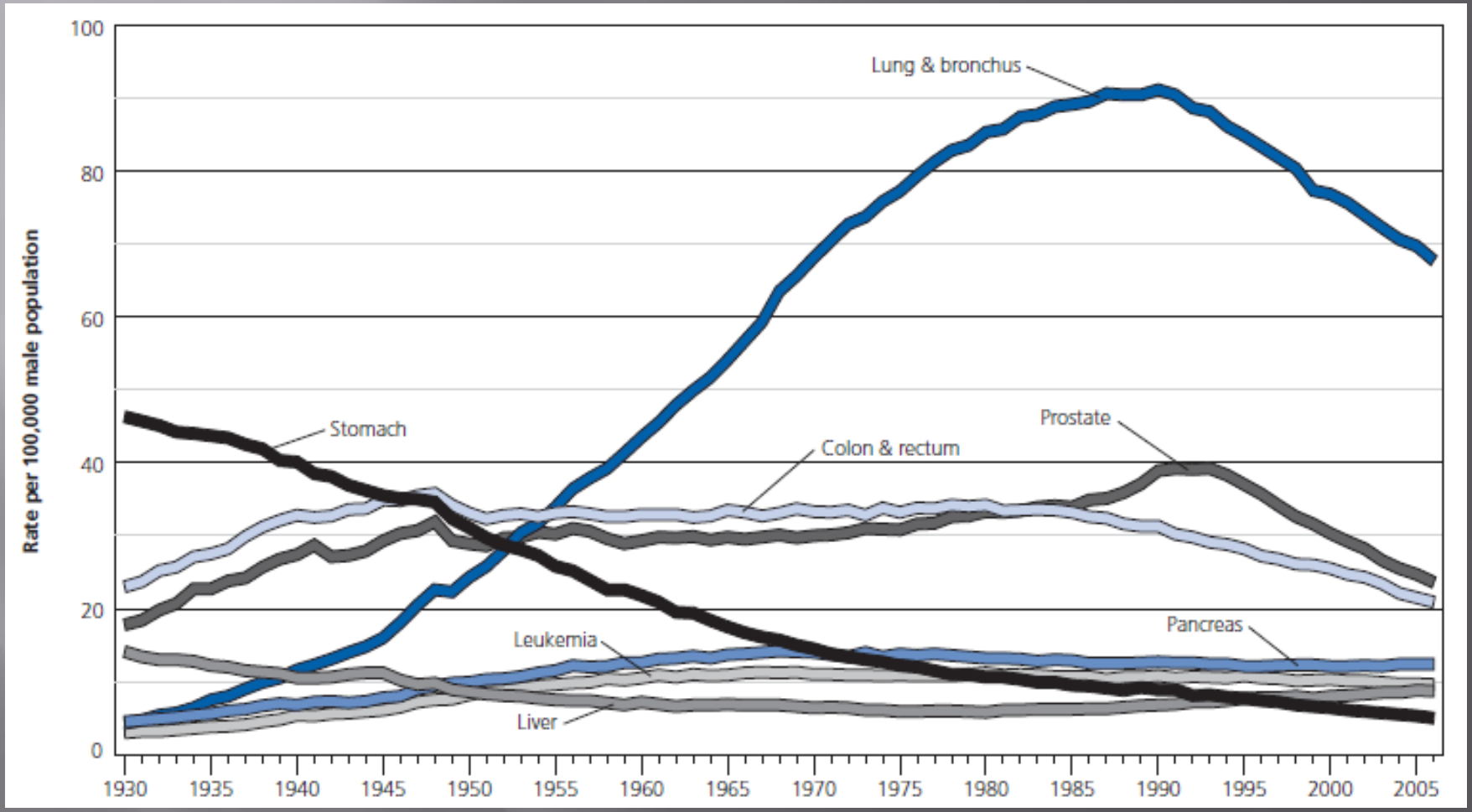
  75% de los casos nuevos son diagnosticados después de los 65 años

  Hay tendencia a decrecer debido al empleo del PSA

MORTALIDAD

- Aproximadamente 40 000 muertes por año en EUA
- Entre 87´- 91´ la mortalidad por CaP creció a un ritmo anual de 3,1% para luego descender a 1,9% por año hasta 95´
- No esta comprobado que la detección temprana modifique las cifras de mortalidad

Age-adjusted Cancer Death Rates,* Males by Site, US, 1930-2006



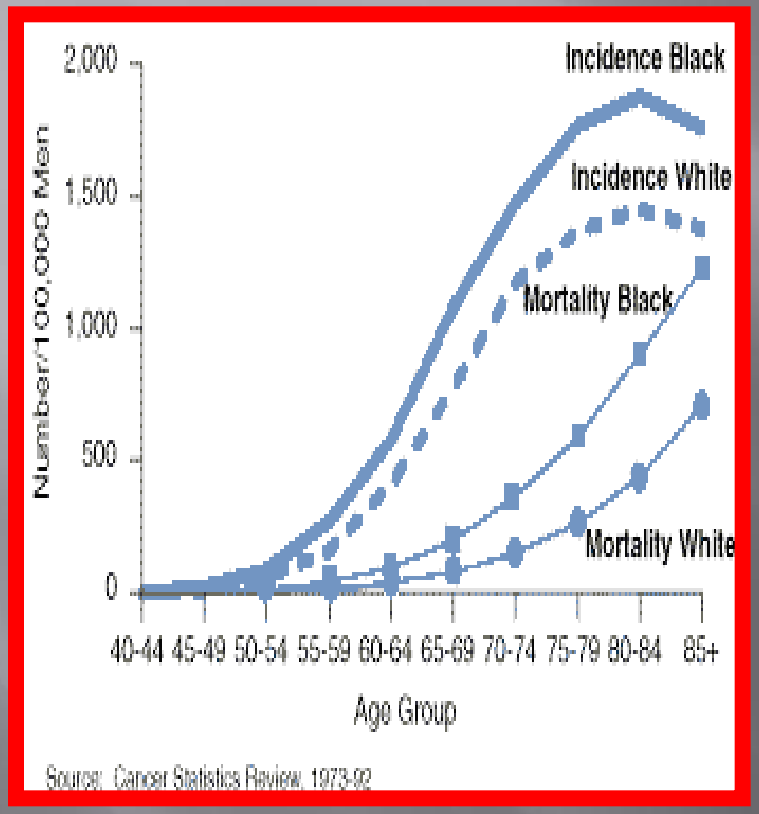
FACTORES DE RIESGO

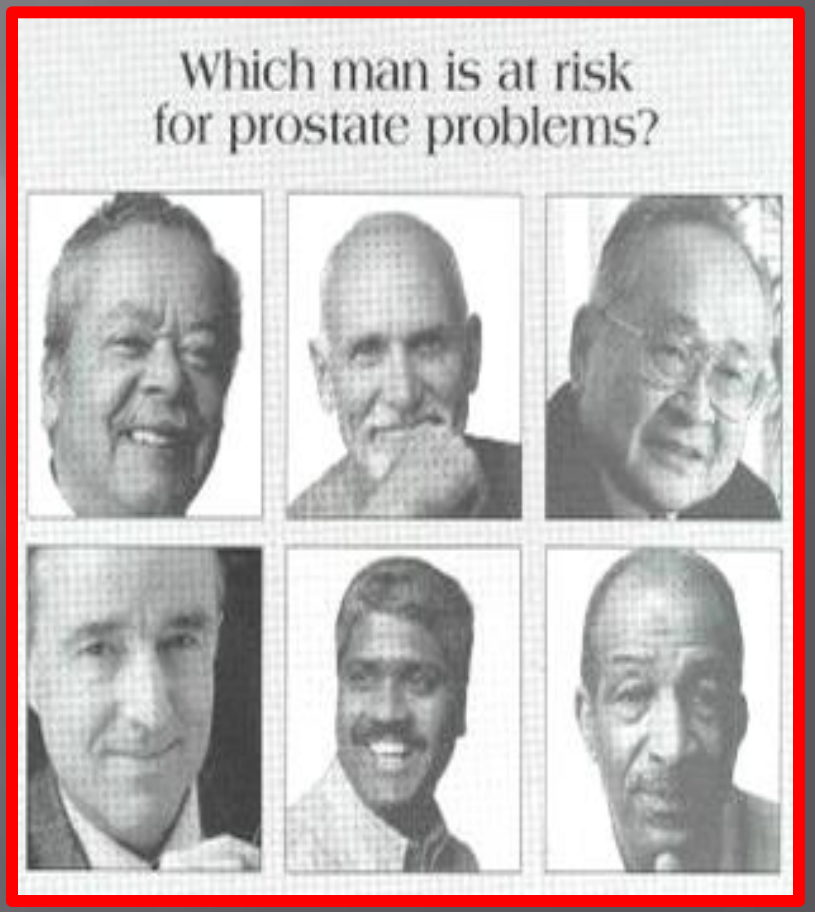
- CANCER DE PROSTATA HEREDITARIO

  9% de todas los CaP diagnosticados; puede alcanzar el 43% en los casos de instalación temprana

  Steinberg y col (90´)

  01 familiar : 2 veces
  02 familiares : 5 veces
  03 familiares : 11 veces


Incidence Black
Incidence White
Mortality Black
Mortality White
2,000
1,500
1,000
500
0
Number/100,000 Men
40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79 80-84 85+
Age Group
Source: Cancer Statistics Review, 1973-92


Which man is at risk
for prostate problems?

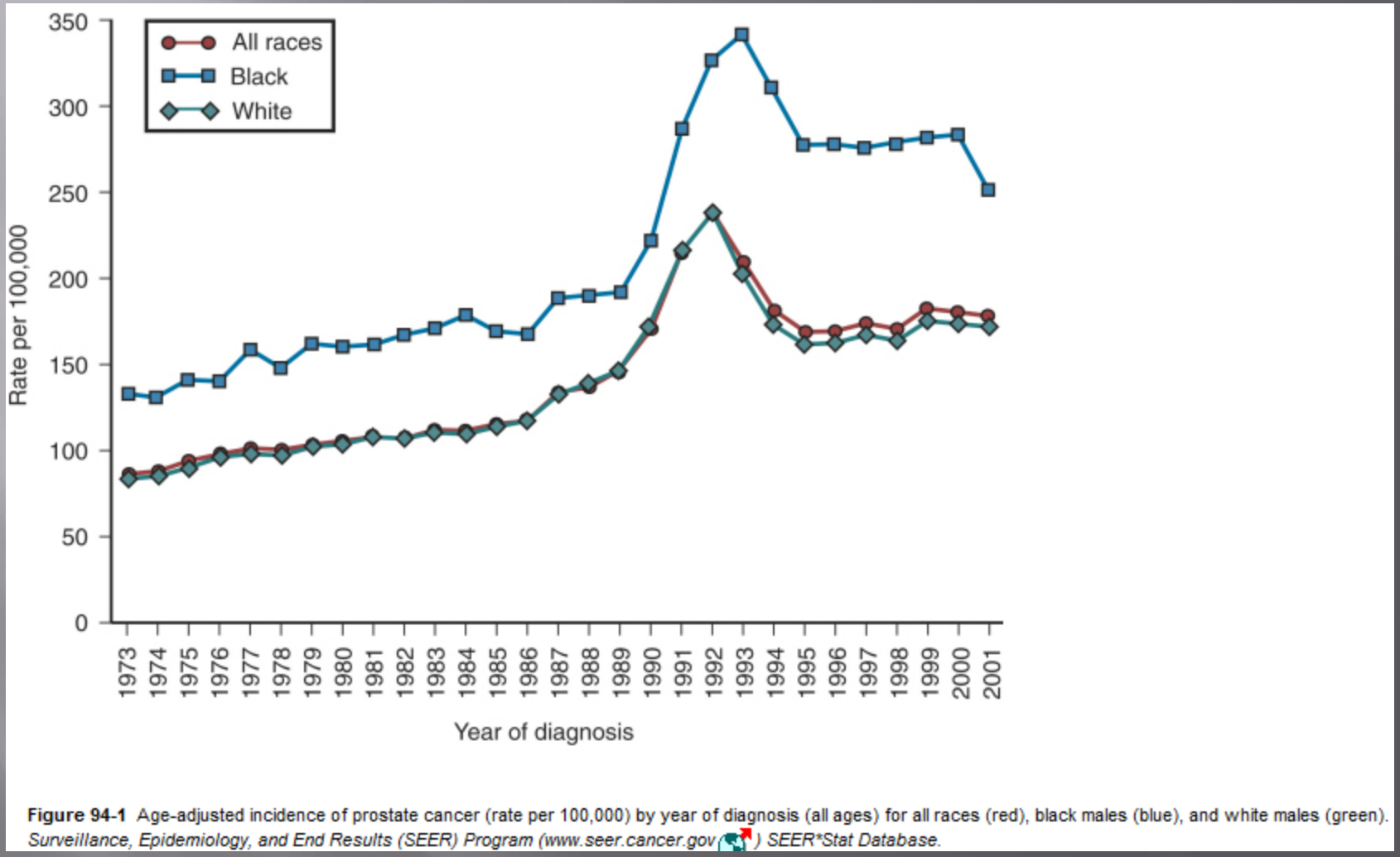


Figure 94-1 Age-adjusted incidence of prostate cancer (rate per 100,000) by year of diagnosis (all ages) for all races (red), black males (blue), and white males (green). *Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database.*

DETECCION DEL CANCER PROSTATICO

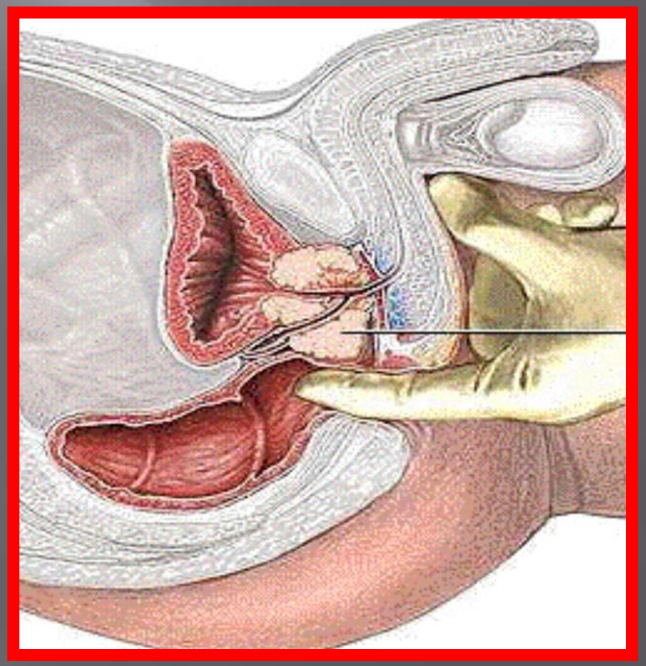
- Asintomático al inicio de la enfermedad
- Puede presentar síntomas irritativos u obstructivos, hematospermia o disminución del volumen eyaculado, impotencia, dolor óseo, anemia, edema de miembros inferiores, fibrosis retroperitoneal, CID
- La sospecha principal es por TR anormal o aumento del PSA

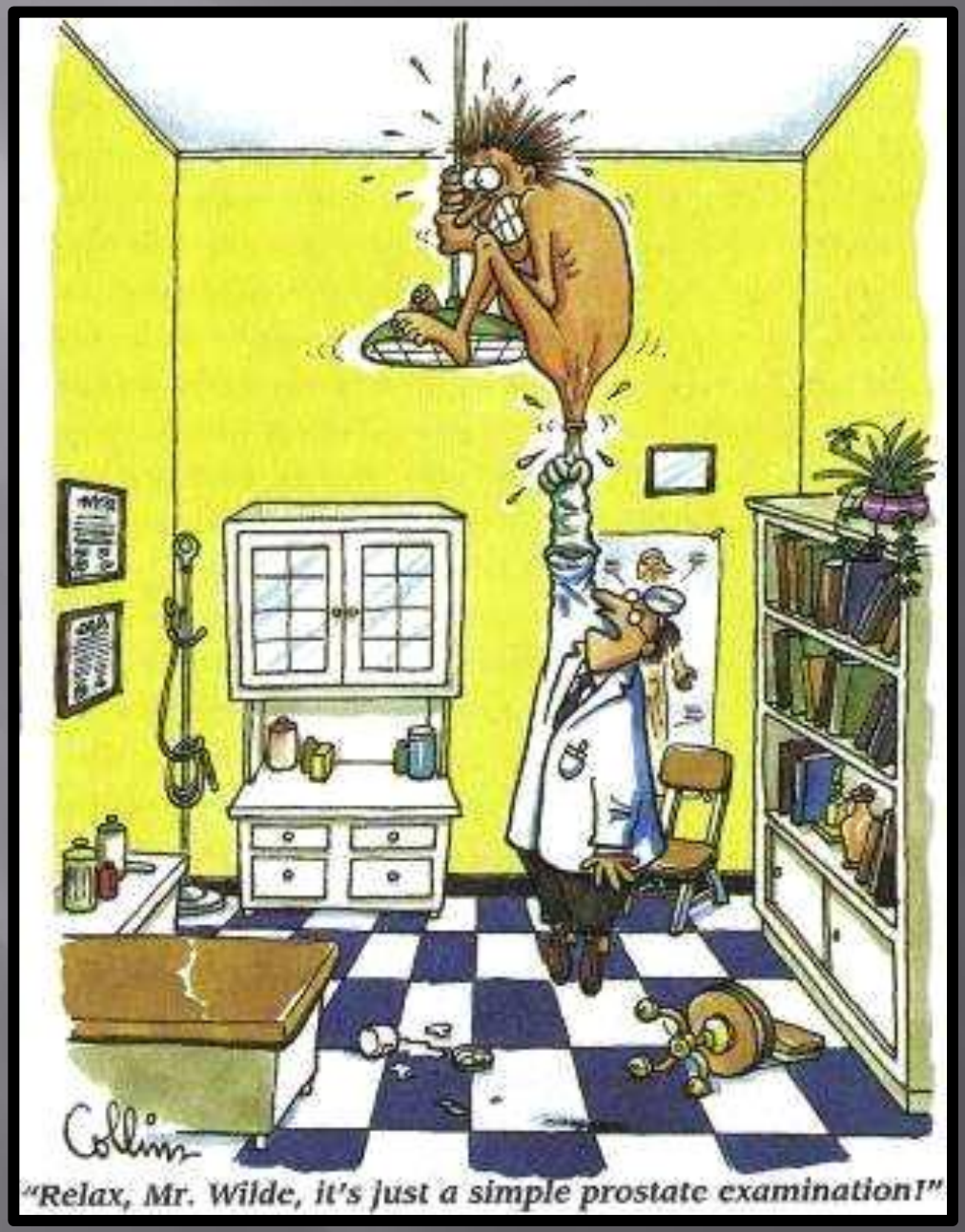
DIAGNOSTICO

- TRIADA: TR, PSA y Biopsia Prostática

  TACTO RECTAL:

  El examen anormal significa cáncer en el 15 a 40% de casos




Collins
"Relax, Mr. Wilde, it's just a simple prostate examination!"

DIAGNOSTICO

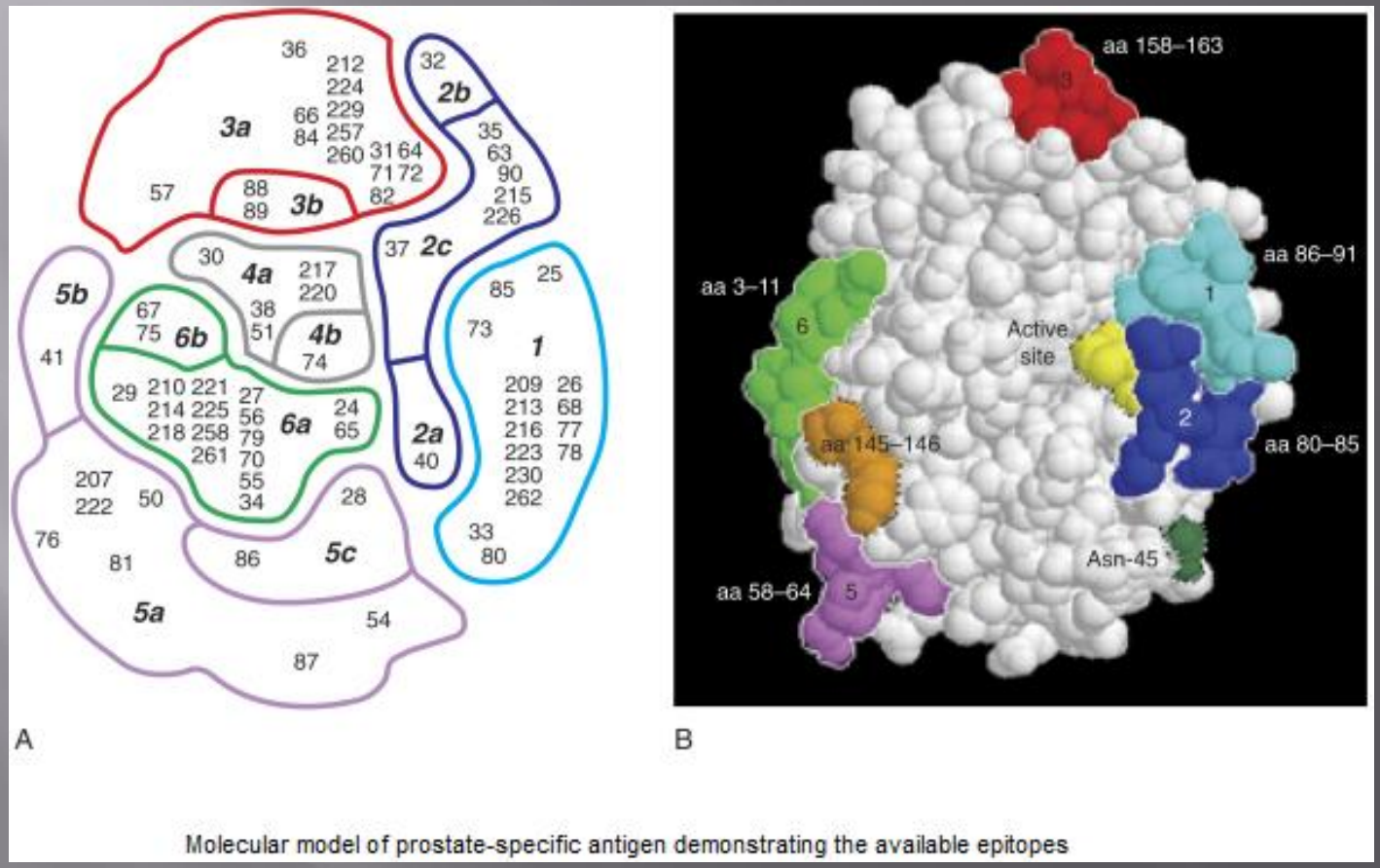
PSA:

Secretado en concentraciones elevadas en el liquido seminal, donde interviene en la licuefacción del coágulo seminal

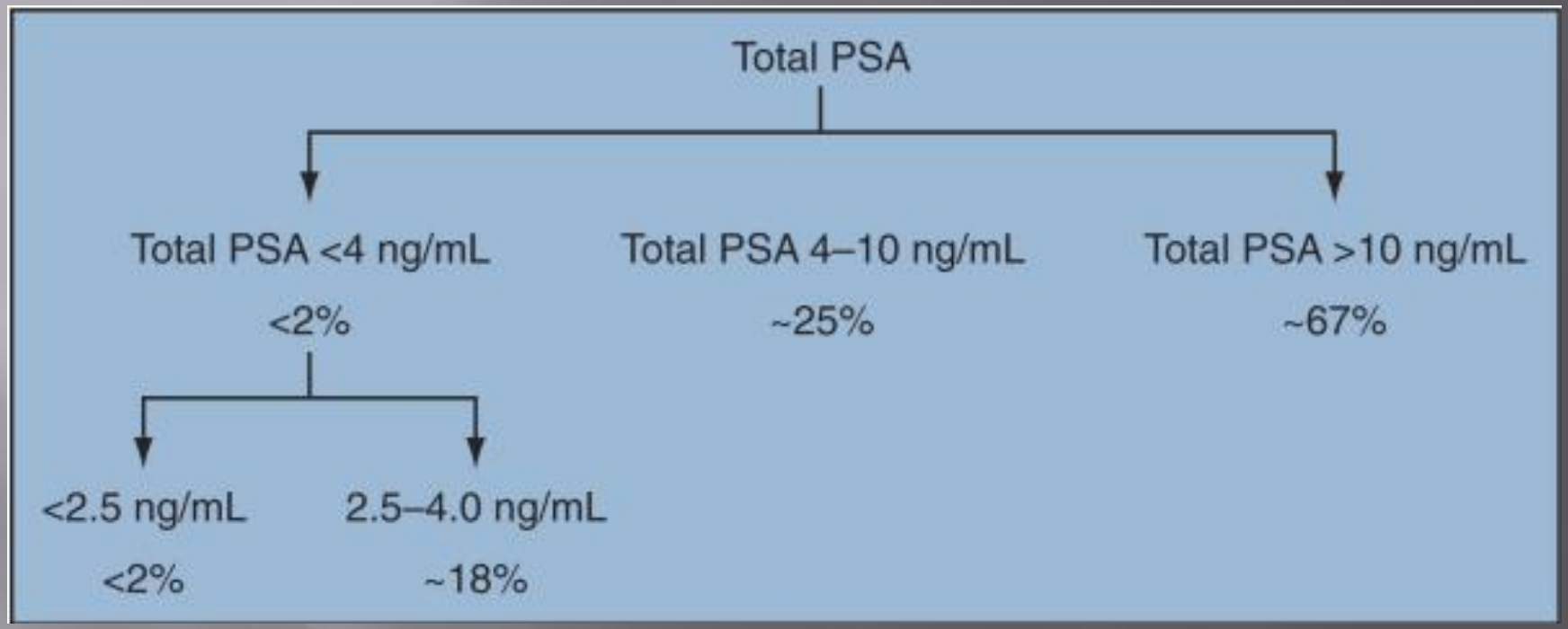
Circula en el suero en forma no ligada (10-35%) como ligada a proteínas (65-90%)

Vida media oscila entre 2 y 3 días (2,2d)

Se hace detectable en la pubertad junto con los incrementos de la hormona luteinizante y la testosterona



Molecular model of prostate-specific antigen demonstrating the available epitopes


Total PSA
Total PSA <4 ng/mL
<2%
Total PSA 4–10 ng/mL
~25%
Total PSA >10 ng/mL
~67%
<2.5 ng/mL
<2%
2.5–4.0 ng/mL
~18%

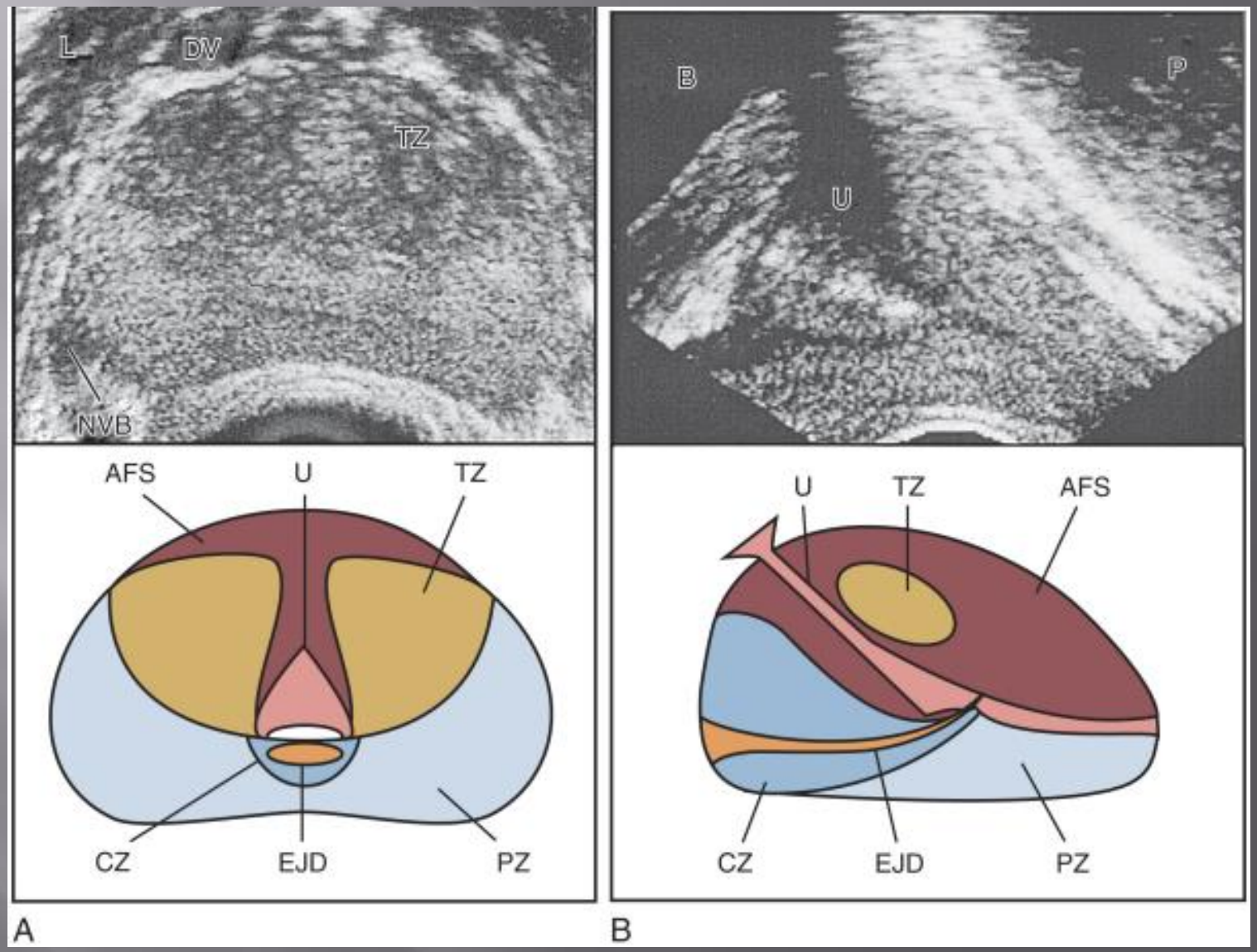
DIAGNOSTICO

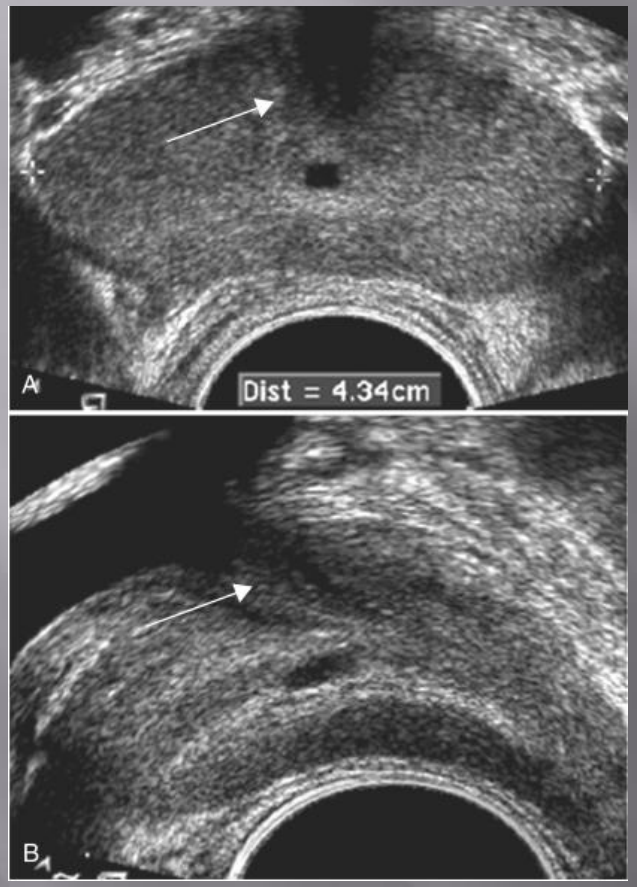
Edad por décadas (años)	Rango de PSA normal (ng/ml)			
	Especificidad 95%		Sensibilidad 95%	
	Blancos	Negros	Blancos	Negros
40	0 - 2,5	0 – 2,4	0 – 2,5	0 – 2
50	0 - 3,5	0 – 6,5	0 – 3,5	0 – 4
60	0 - 4,5	0 – 11,3	0 – 3,5	0 – 4,5
70	0 - 6,5	0 – 12,5	0 – 3,5	0 – 5,5

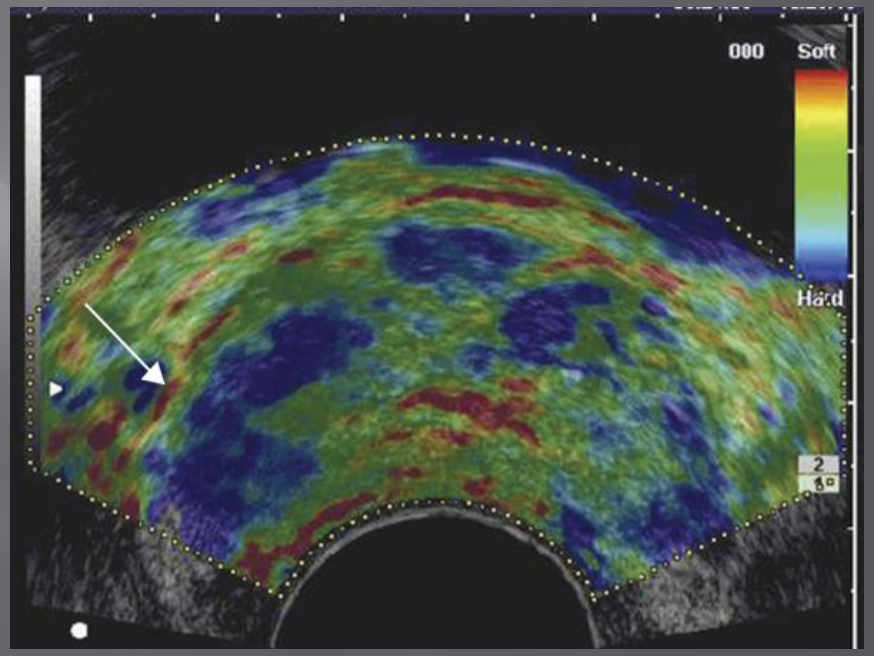
DIAGNOSTICO

Biopsia de Próstata por ETR

- La mayor parte de las lesiones hipoecoicas halladas no son canceres y el 50% de los cánceres no palpables con un diámetro mayor de 1cm no se observan en la ecografía
- Todos los pacientes con TR sospechoso y elevación del PSA deben realizarse una biopsia prostática
- El papel principal de la ETR es asegurar una biopsia precisa

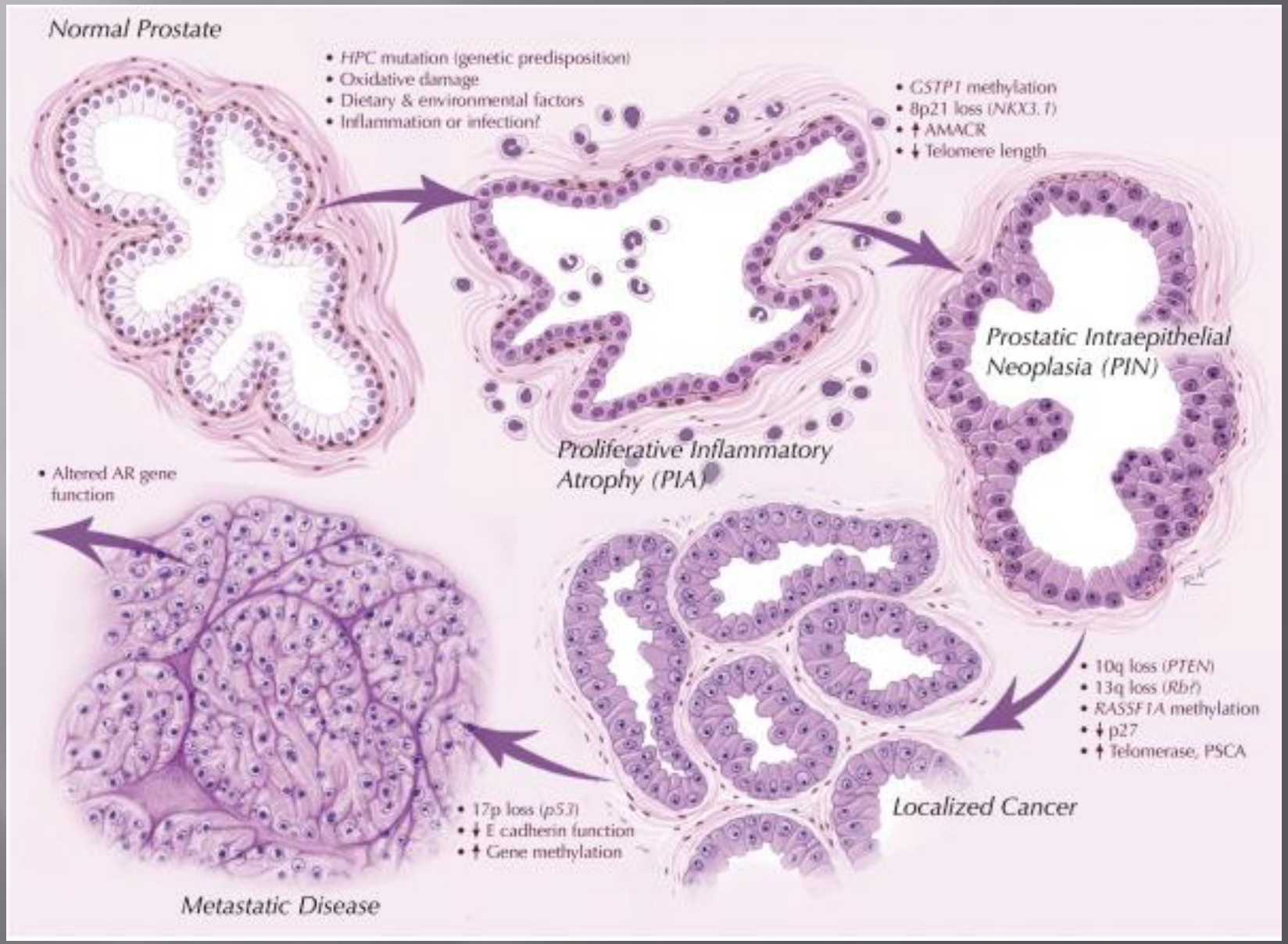

L
DV
TZ
NVB
B
P
U
AFS
U
TZ
CZ
EJD
PZ
U
TZ
AFS
CZ
EJD
PZ
A
B


A
Dist = 4.34cm
B


000
Soft
Hard

Complications	% of biopsies
• Haematospermia	37.4
• Bleeding from urethra, urinary bladder (> 1 day)	14.5
• Fever	0.8
• Urosepsis	0.3
• Rectal bleeding	2.2
• Urine retention	0.2
• Prostatitis	1.0
• Epididymitis	0.7

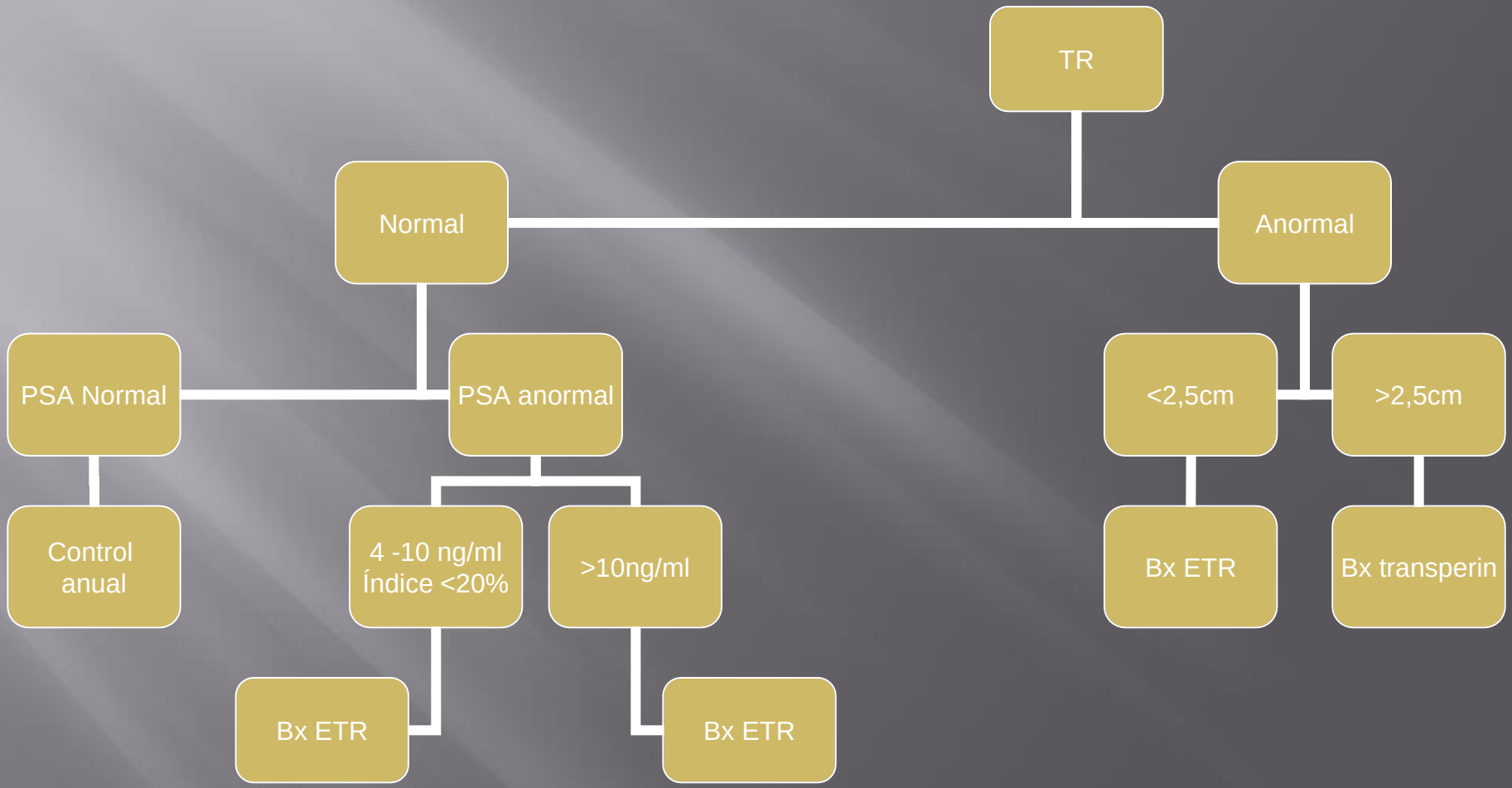
* *Adapted from Consensus Guidelines NCCN, Version 1.2007 (33).*


Normal Prostate
• HPC mutation (genetic predisposition)
• Oxidative damage
• Dietary & environmental factors
• Inflammation or infection?
• GSTP1 methylation
• 8p21 loss (NKX3.1)
• ↑ AMACR
• ↓ Telomere length
Prostatic Intraepithelial Neoplasia (PIN)
Proliferative Inflammatory Atrophy (PIA)
• Altered AR gene function
• 10q loss (PTEN)
• 13q loss (Rb?)
• RASSF1A methylation
• ↓ p27
• ↑ Telomerase, PSCA
Localized Cancer
• 17p loss (p53)
• ↓ E cadherin function
• ↑ Gene methylation
Metastatic Disease

Grupos de Riesgo en CaP

Risk Group	Clinical Stage	PSA (ng/mL)	Gleason Score	Biopsy Criteria
Low	T1a or T1c	<10	2-5	Unilateral or <50% of core involved
Intermediate	T1b or T2a	<10	6 or 3 + 4 = 7	Bilateral
High	T2b or T3	10-20	4 + 3 = 7	>50% of core involved or perineural invasion or ductal differentiation
Very high	T4	>20	8-10	Lymphovascular invasion or neuroendocrine differentiation

DIAGNOSTICO



TNM 2009 (Tumor Nódulo Metástasis)

T - Primary tumour			
TX	Primary tumour cannot be assessed		
T0	No evidence of primary tumour		
T1	Clinically inapparent tumour not palpable or visible by imaging		
	T1a	Tumour incidental histological finding in 5% or less of tissue resected	
	T1b	Tumour incidental histological finding in more than 5% of tissue resected	
	T1c	Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen [PSA] level)	
T2	Tumour confined within the prostate[1]		
	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[2]		
	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[3]			
	NX	Regional lymph nodes cannot be assessed	
	N0	No regional lymph node metastasis	
	N1	Regional lymph node metastasis	
M - Distant metastasis[4]			
	MX	Distant metastasis cannot be assessed	
	M0	No distant metastasis	
	M1	Distant metastasis	
		M1a	Non-regional lymph node(s)
		M1b	Bone(s)
		M1c	Other site(s)

Grupos Pronósticos

Group I	T1a-c	N0	M0 PSA < 10	Gleason ≤ 6
	T2a	N0	M0 PSA < 10	Gleason ≤ 6
Group IIA	T1a-c	N0	M0 PSA < 20	Gleason 7
	T1a-c	N0	M0 PSA ≥ 10 < 20	Gleason ≤ 6
	T2a, b	N0	M0 PSA < 20	Gleason ≤ 7
Group IIb	T2c	N0	M0 Any PSA	Any Gleason
	T1-2	N0	M0 PSA ≥ 20	Any Gleason
	T1-2	N0	M0 Any PSA	Gleason ≥ 8
Group III	T3a, b	N0	M0 Any PSA	Any Gleason
Group IV	T4	N0	M0 Any PSA	Any Gleason
	Any T	N1	M0 Any PSA	Any Gleason
	Any T	Any N	M0 Any PSA	Any Gleason

Note: When either PSA or Gleason is not available, grouping should be determined by cT category and whichever of either PSA of Gleason is available. When neither is available prognostic grouping is not possible, use stage grouping

Tratamiento diferido ("espera vigilante")

- Monitoreo activo en el que se pospone el tratamiento hasta que sea requerido.
- Seguimiento cuidadoso.
- Indicaciones:

CaP localizado (Nx - N0, M0):

- T1a bien y moderadamente diferenciados, pac jóvenes con expectativa de vida > 10a.

  Reevaluación con PSA y TR.

- T1b -T2b bien y moderadamente diferenciados, pac asintomático con expectativa de vida < 10a.

- Opciones:

CaP localizado (Nx - N0, M0):

- T1b - T2b, bien diferenciados, o Gleason 2-4 y expectativa de vida de 10 a 15a.
- No dispuestos a aceptar efectos colaterales del tratamiento activo.
- Paciente asintomático con nivel elevado de PSA y cuya cura es improbable.

Riesgo de desarrollar o morir por CaP en el transcurso de la vida en varones de 50 años (EUA)

Lifetime Risk for	Risk (%)	Risk Ratio	Proportional Risk
Development of incidental cancer	42	11.7	100
Development of clinical cancer	16.7	4.4	38
Dying of prostate cancer	3.6	1	8.6

Modified from Scardino, 1989 ; Scardino et al, 1992 ; Greenlee et al, 2000

Contraste entre vigilancia activa y espera vigilante

	Active Surveillance	Watchful Waiting
Aim	To individualize treatment	To avoid treatment
Patient characteristics	Fit for radical treatment	Age > 70 yr or life expectancy < 15yr
	Age 50-80 yr	
Tumor characteristics	T1-T2, GS ≤ 7, initial PSA < 15 ng/mL	Any T stage, GS ≤ 7, any PSA
Monitoring	Frequent PSA testing	PSA testing unimportant
	Repeated biopsies	No repeated biopsies
Indications for treatment	Short PSADT	
	Higher grade or more extensive cancer on biopsy	Symptomatic progression
Treatment timing	Early	Delayed
Treatment intent	Radical	Palliative

Prostatectomía radical

- Extirpación de la próstata y de las vesículas seminales.
- Aplicada por Young, Memmelaar y Millin.
- Walsh y Donker: complejo venoso dorsal y bandeletas neurovasculares.
- Abierta (retropúbica, transperineal), laparoscópica, asistida por robot.

- Indicaciones:

  Pacientes con T1b - T2, NX - N0, M0 y expectativa de vida mayor de 10a.

- Opcional:

  Pacientes con larga expectativa de vida y T1a.

- Siempre se realiza linfadenectomía pélvica bilateral por el estadío y el Gleason alto de los pacientes.

- La linfadenectomía puede omitirse en pacientes con Gleason menor o igual a 6 y PSA menor de 10 ng/ml.

- Si A.P.: enfermedad localizada en el órgano y PSA al mes de la cirugía es < 0.1 ng/ml:

  El paciente no requiere tratamiento adyuvante y es seguido cada 3 meses con TR y PSA

- Si PSA se incrementa posteriormente, se realiza biopsia de anastomosis vesico uretral para demostrar recurrencia:

  El paciente recibirá tratamiento adyuvante con RT radical (si no hay enfermedad a distancia)

- Si PSA nunca llegó a un valor menor o igual a 0.1ng/ml y se va incrementando:

  El paciente tiene enfermedad sistémica y es tratado con HT

- Si A.P.: compromiso extracapsular grosero:

  El paciente recibe RT radical adyuvante

Si hay compromiso de vesículas seminales y adenopatías regionales:

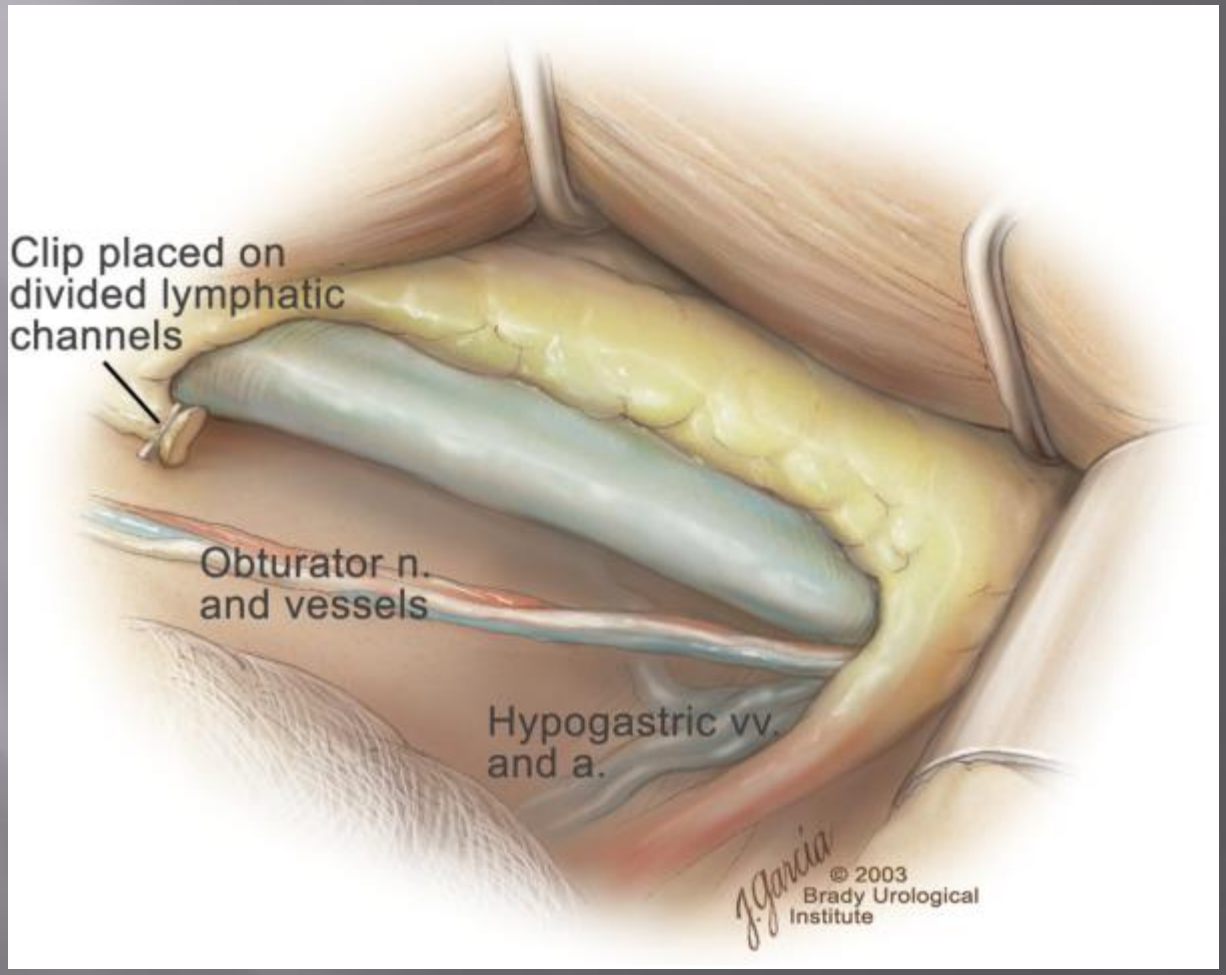
El paciente será tratado con HT

Terapia definitiva para el CaP: PR

- Técnica quirúrgica:
  - Linfadenectomía pélvica
  - Apertura de la fascia endopélvica y disección limitada de los ligamentos pubo – prostáticos
  - Ligadura y sección del complejo venoso dorsal de Santorini
  - Disección de la uretra y ápex prostático. Sección de la uretra
  - Disección prostática de las bandeletas neuro – vasculares

Terapia definitiva para el CaP: PR

- Ligadura y sección de los pedículos vasculares
- Sección y reconstrucción del cuello vesical
- Disección de las ampollas deferenciales y vesiculas seminales
- Anastomosis vesico – uretral


Clip placed on
divided lymphatic
channels
Obturator n.
and vessels
Hypogastric vv.
and a.
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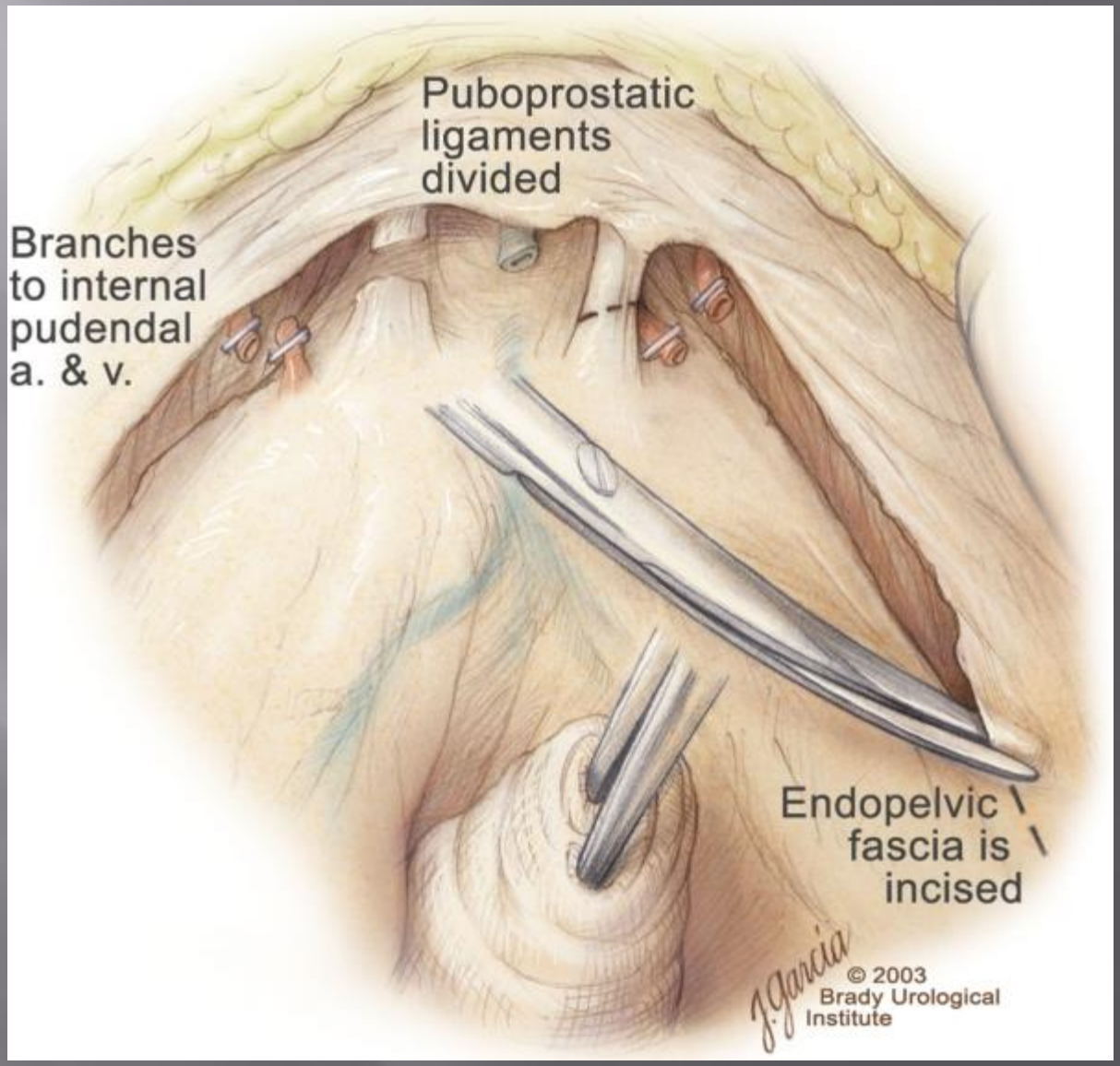
Puboprostatic ligaments divided
Branches to internal pudendal a. & v.
Endopelvic fascia is incised
J.Garcia
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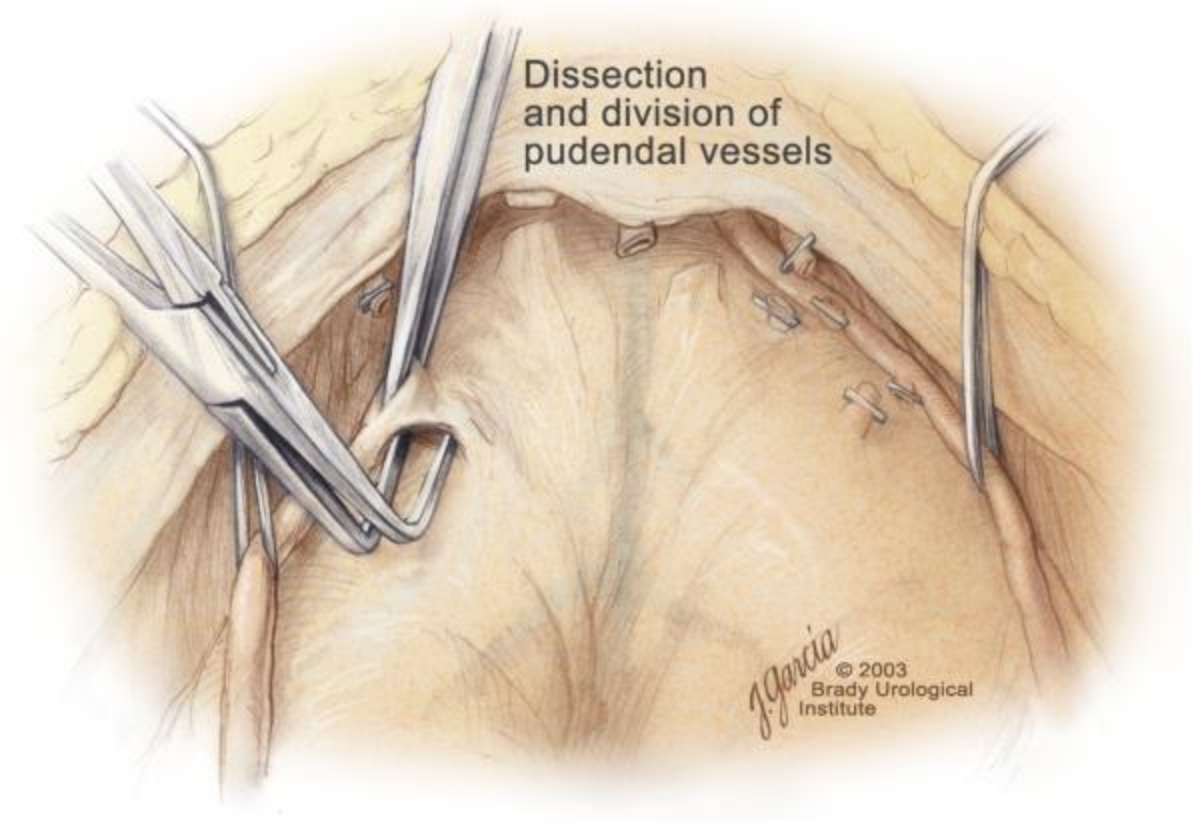
Dissection
and division of
pudendal vessels
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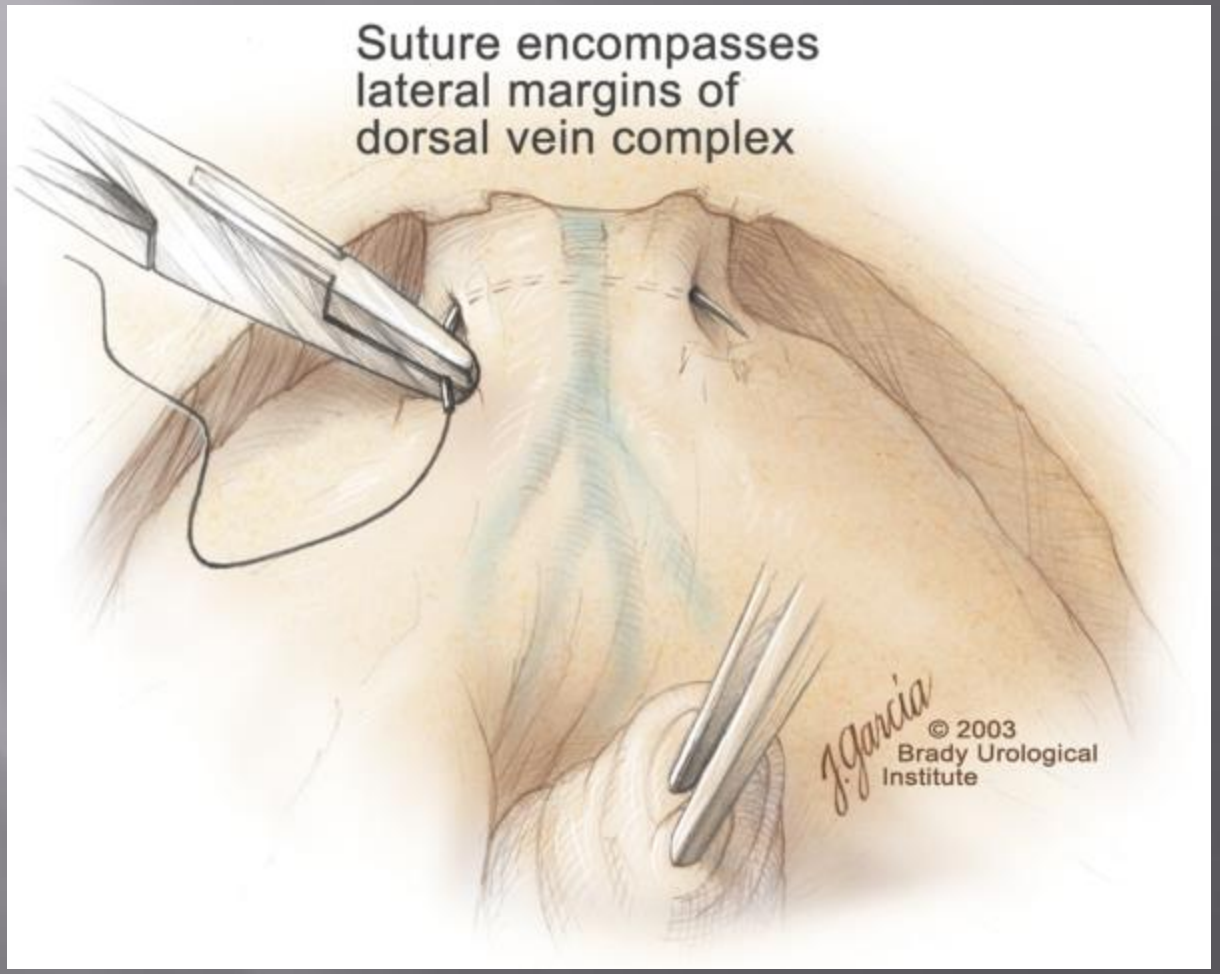
Suture encompasses
lateral margins of
dorsal vein complex
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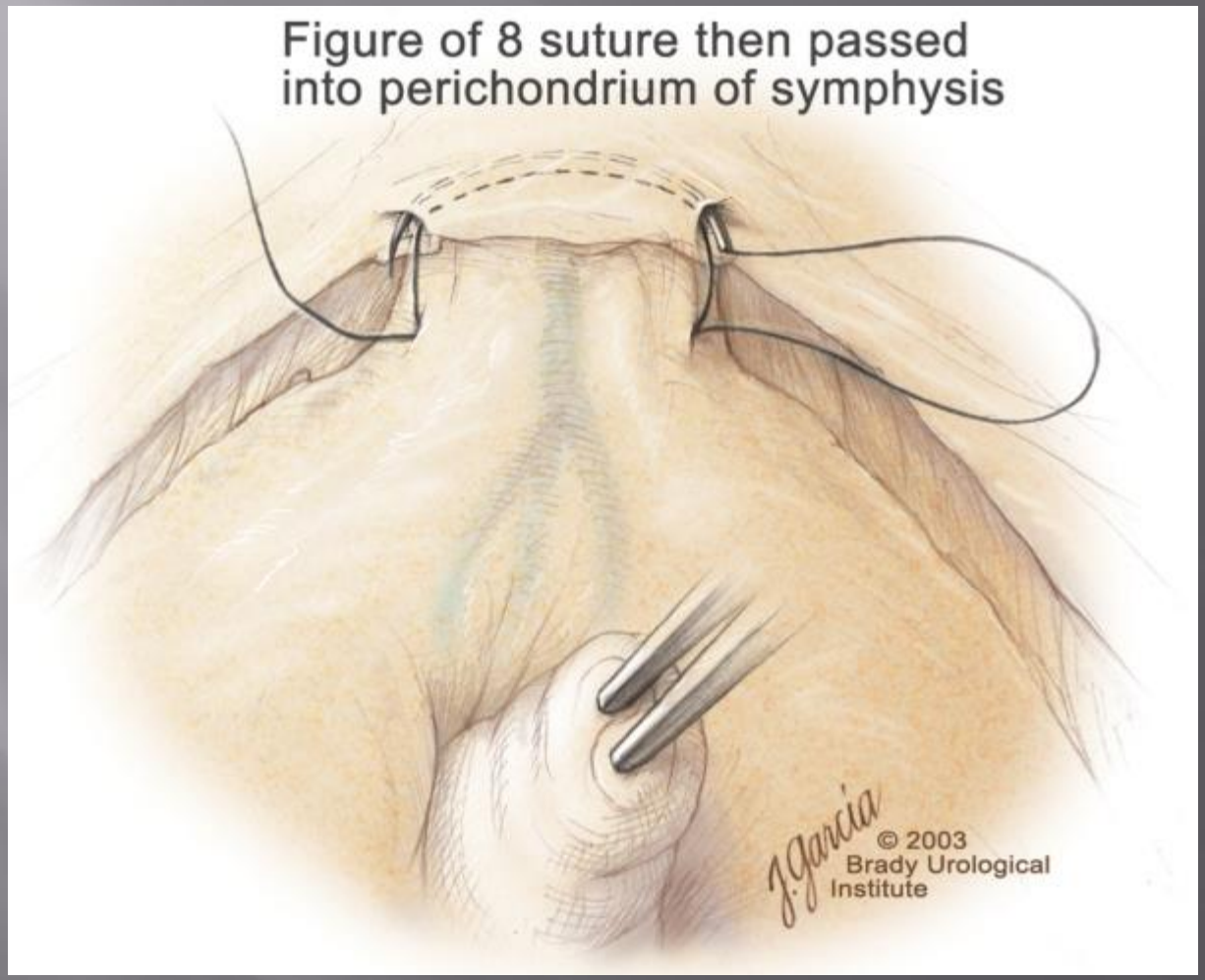
Figure of 8 suture then passed into perichondrium of symphysis
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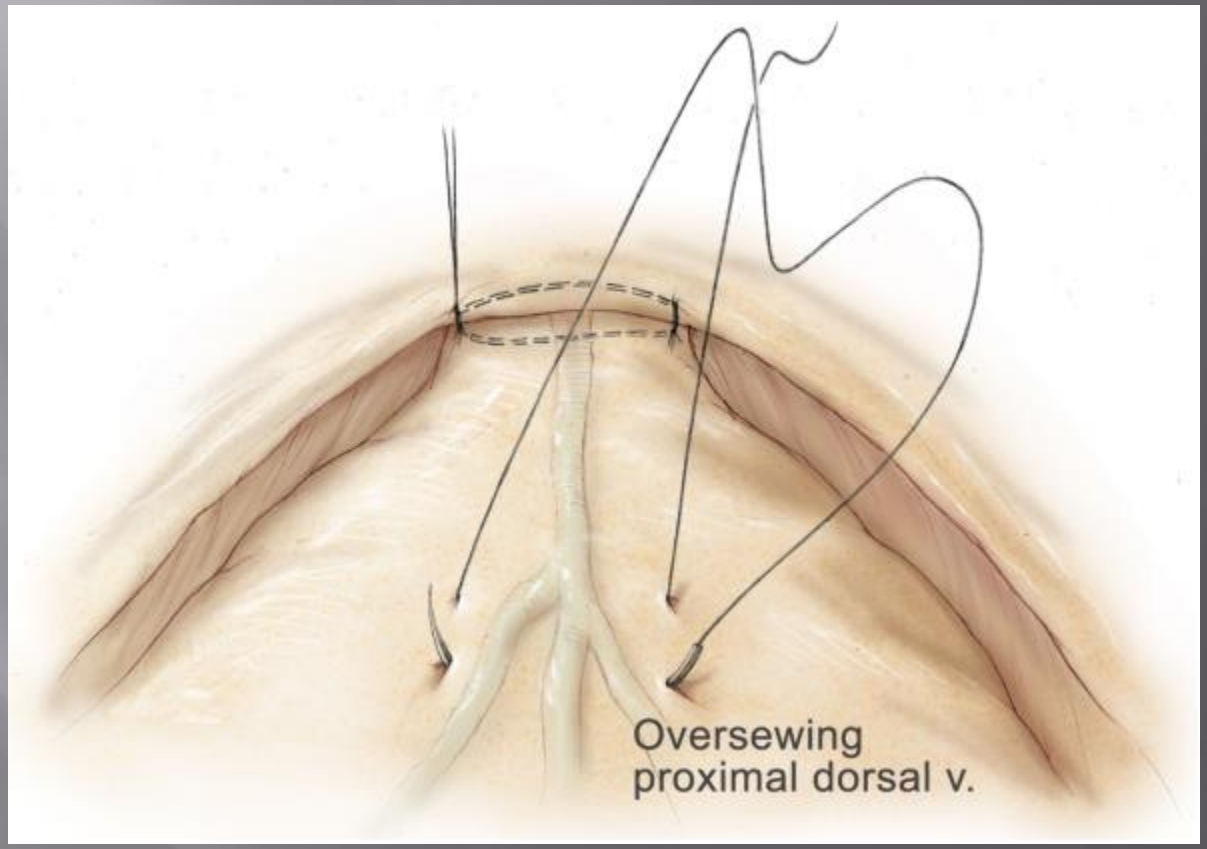
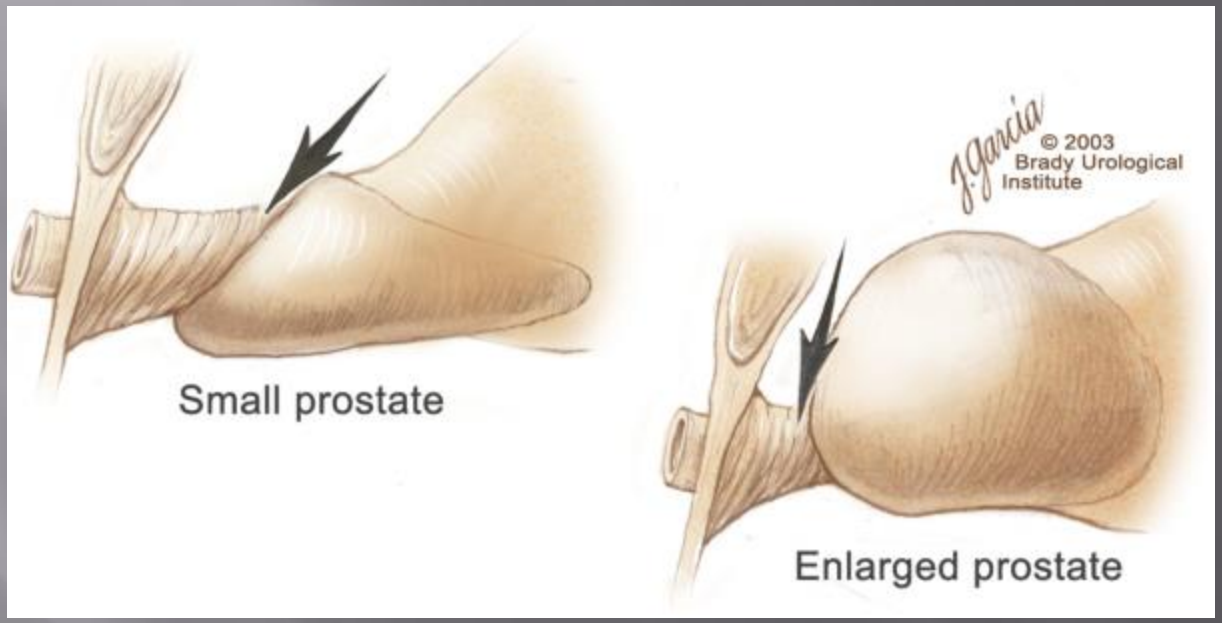

Oversewing
proximal dorsal v.


Small prostate
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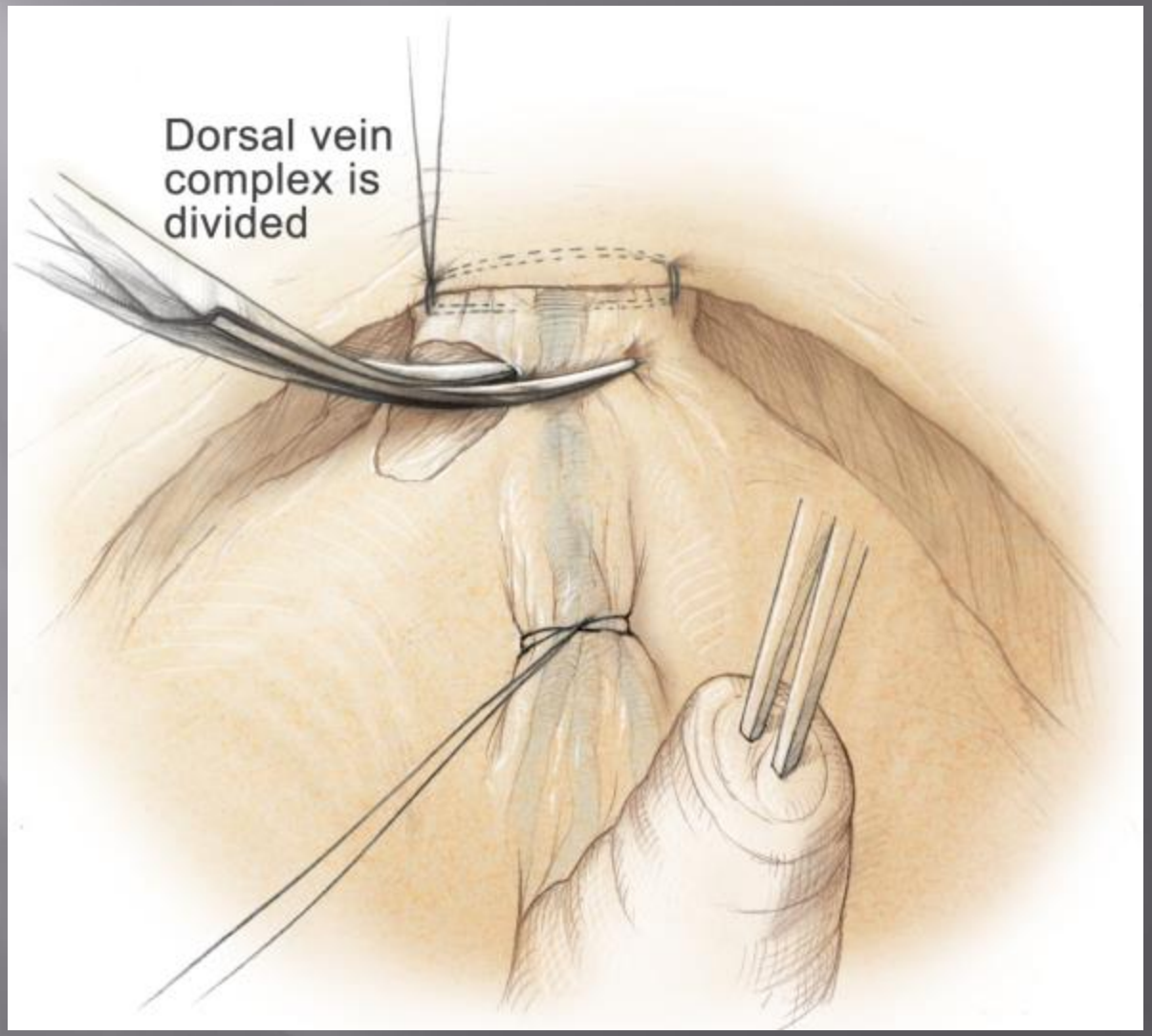
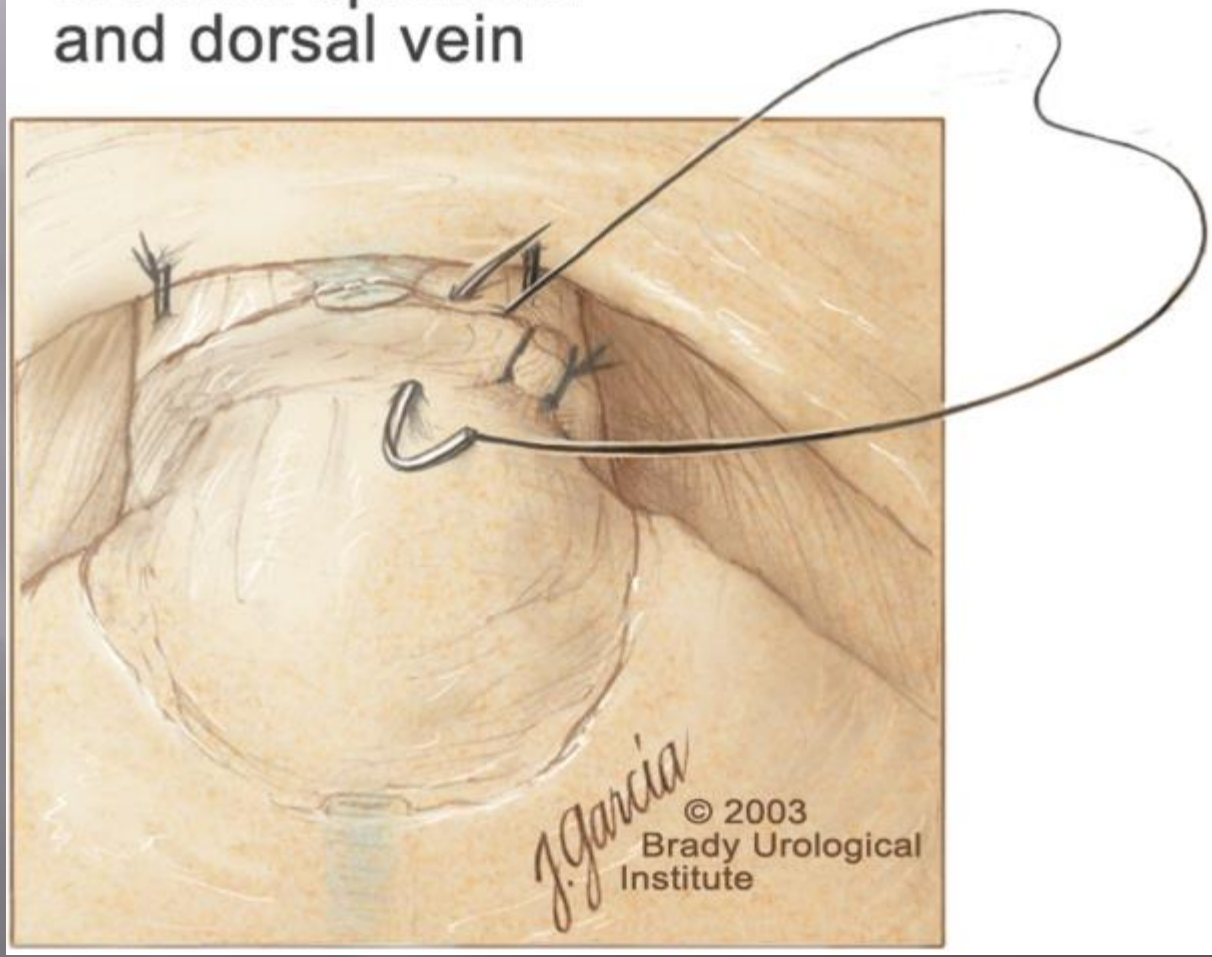
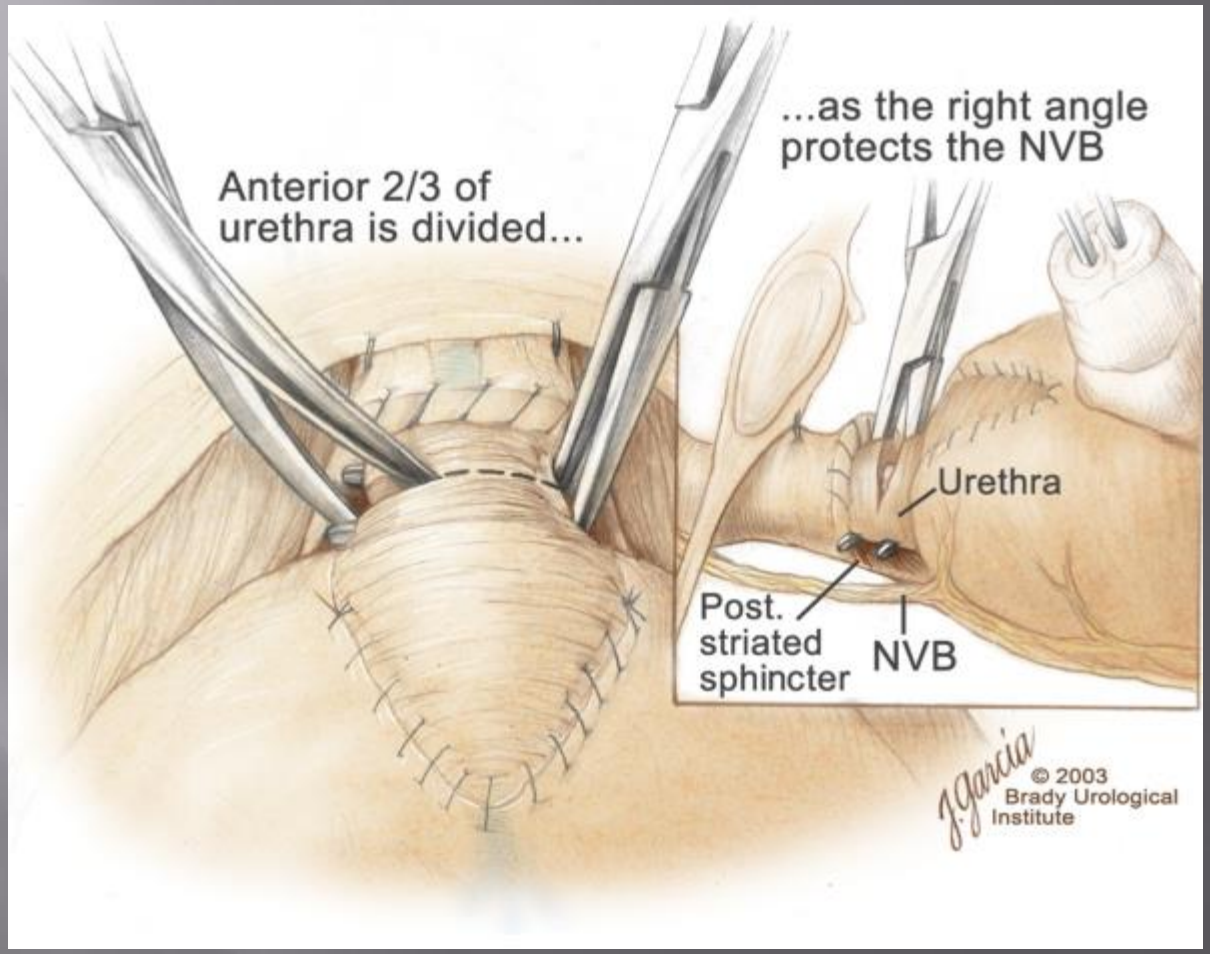
Enlarged prostate


Dorsal vein
complex is
divided

Oversewing of striated urethral sphincter and dorsal vein




Anterior 2/3 of
urethra is divided...
...as the right angle
protects the NVB
Urethra
Post.
striated
sphincter
NVB
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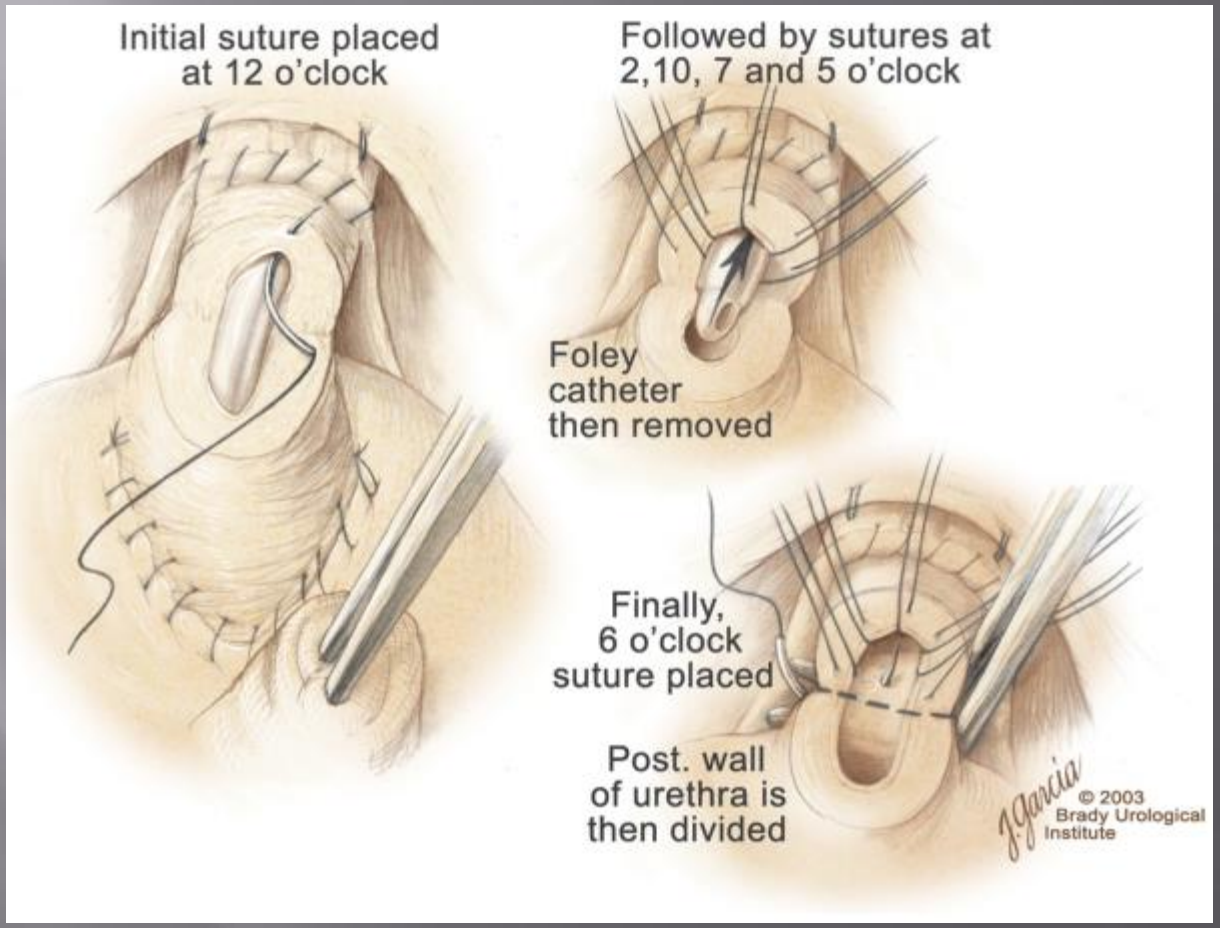
Initial suture placed at 12 o'clock
Followed by sutures at 2,10, 7 and 5 o'clock
Foley catheter then removed
Finally, 6 o'clock suture placed
Post. wall of urethra is then divided
J. Garcia
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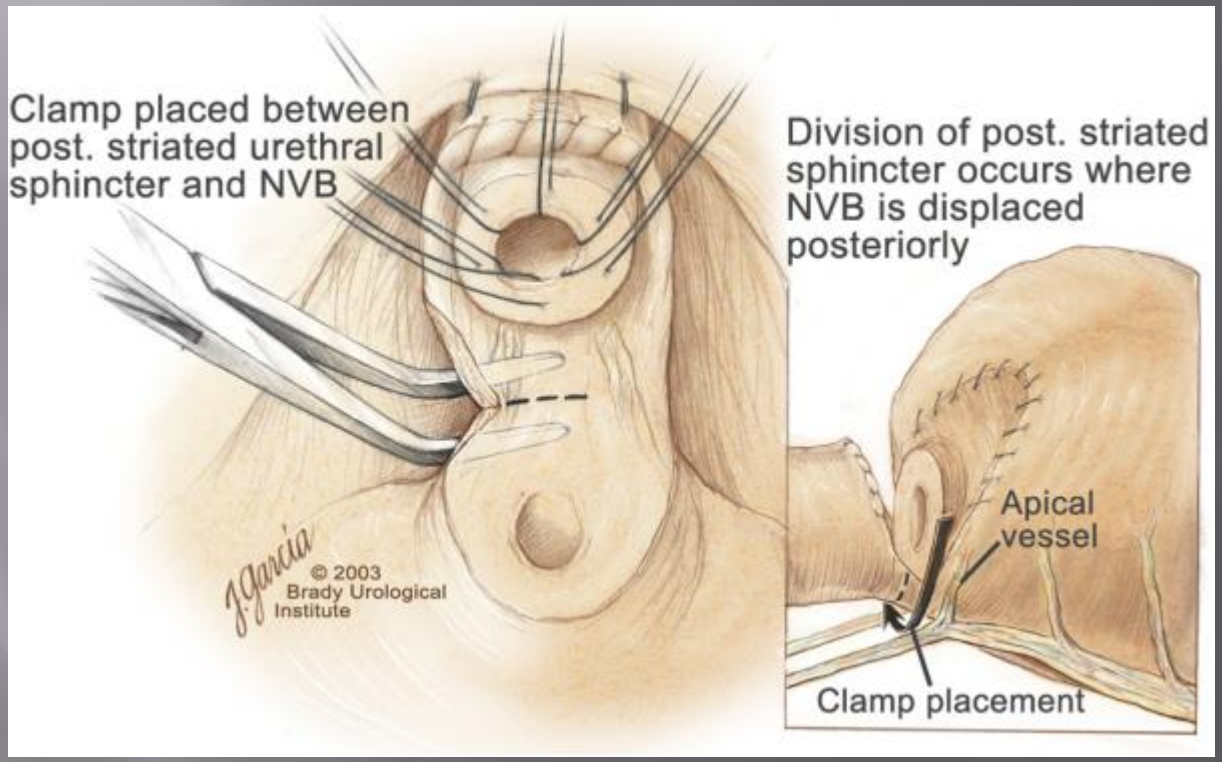
Clamp placed between post. striated urethral sphincter and NVB
Division of post. striated sphincter occurs where NVB is displaced posteriorly
Apical vessel
Clamp placement
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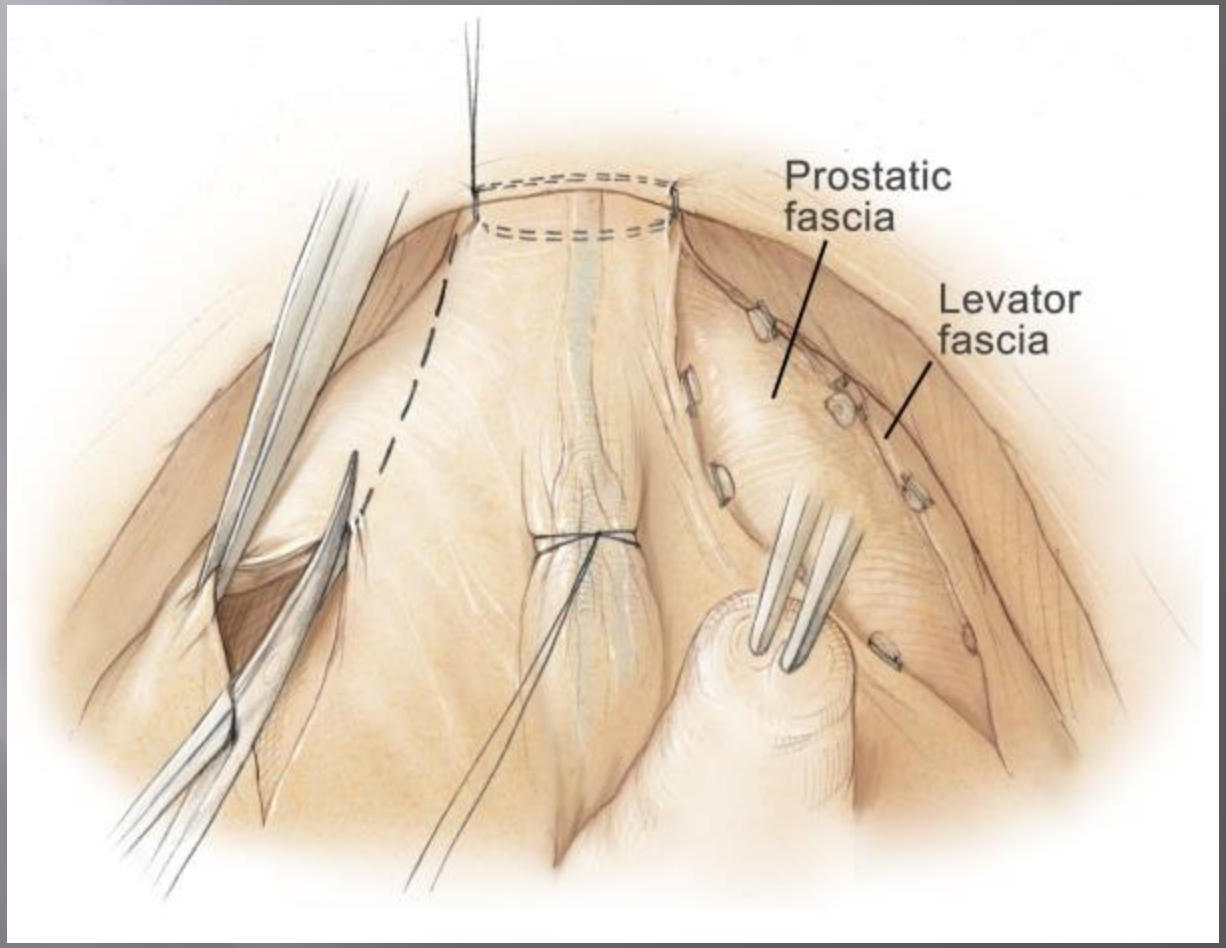
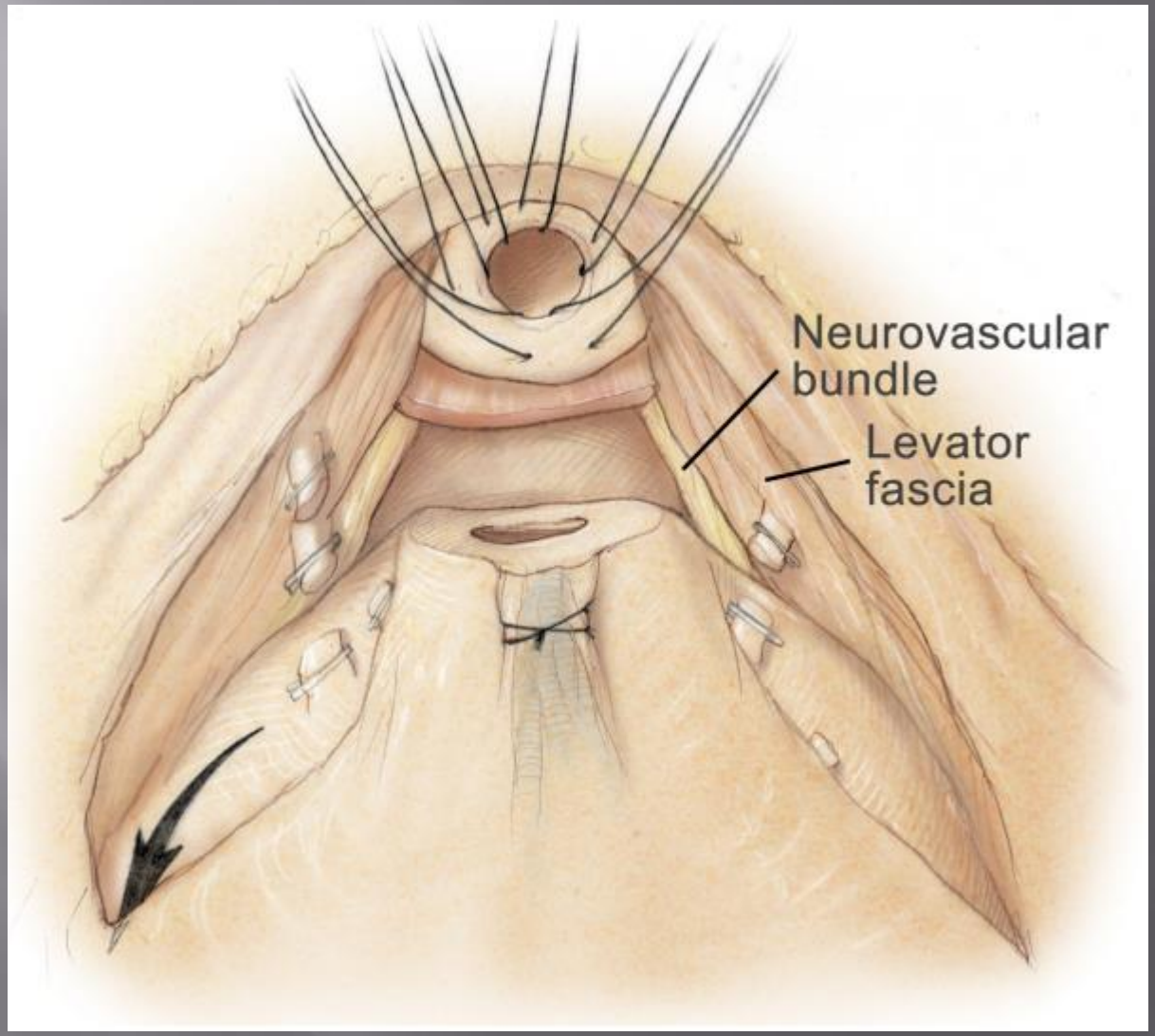
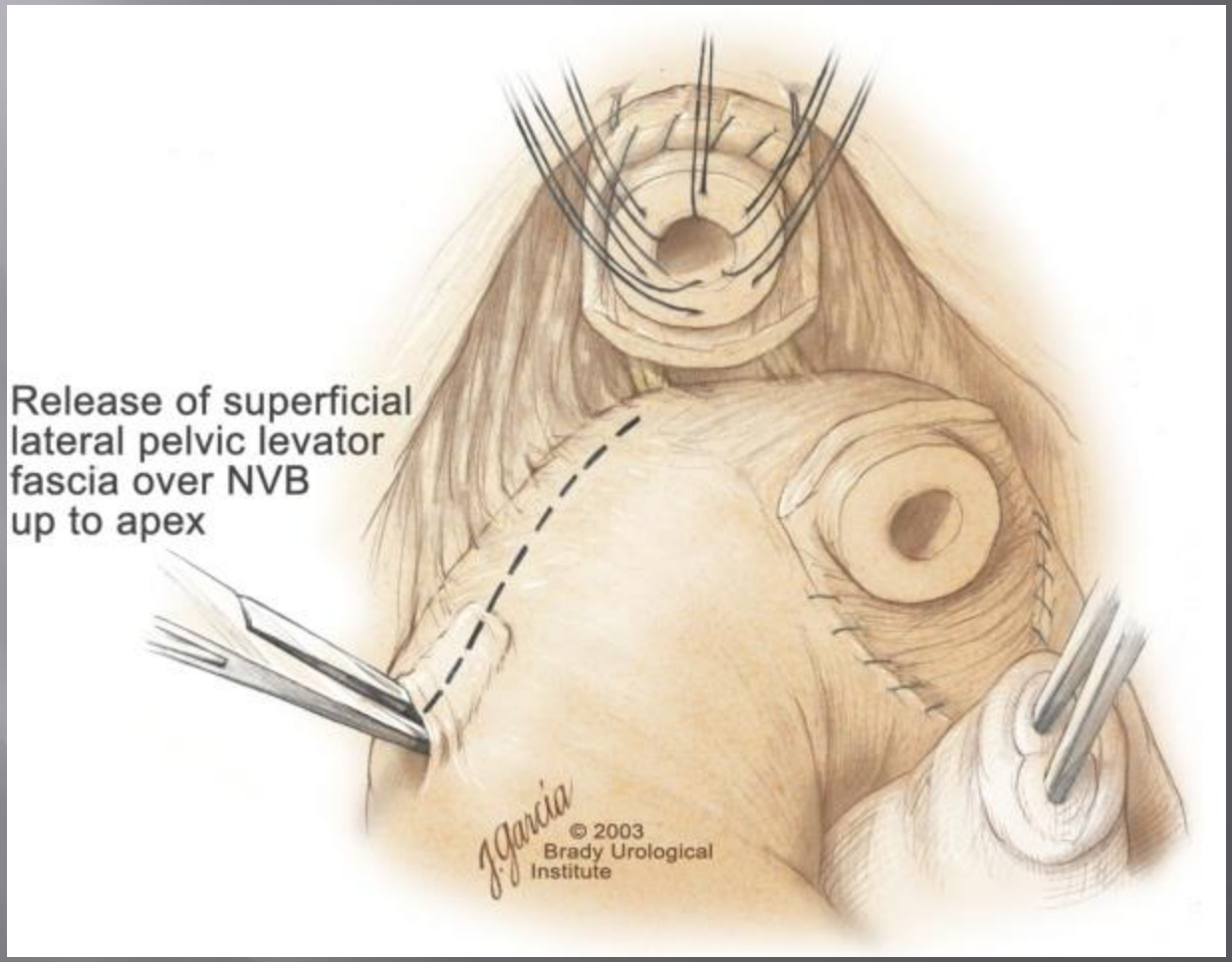

Prostatic
fascia
Levator
fascia


Neurovascular bundle
Levator fascia


Release of superficial lateral pelvic levator fascia over NVB up to apex
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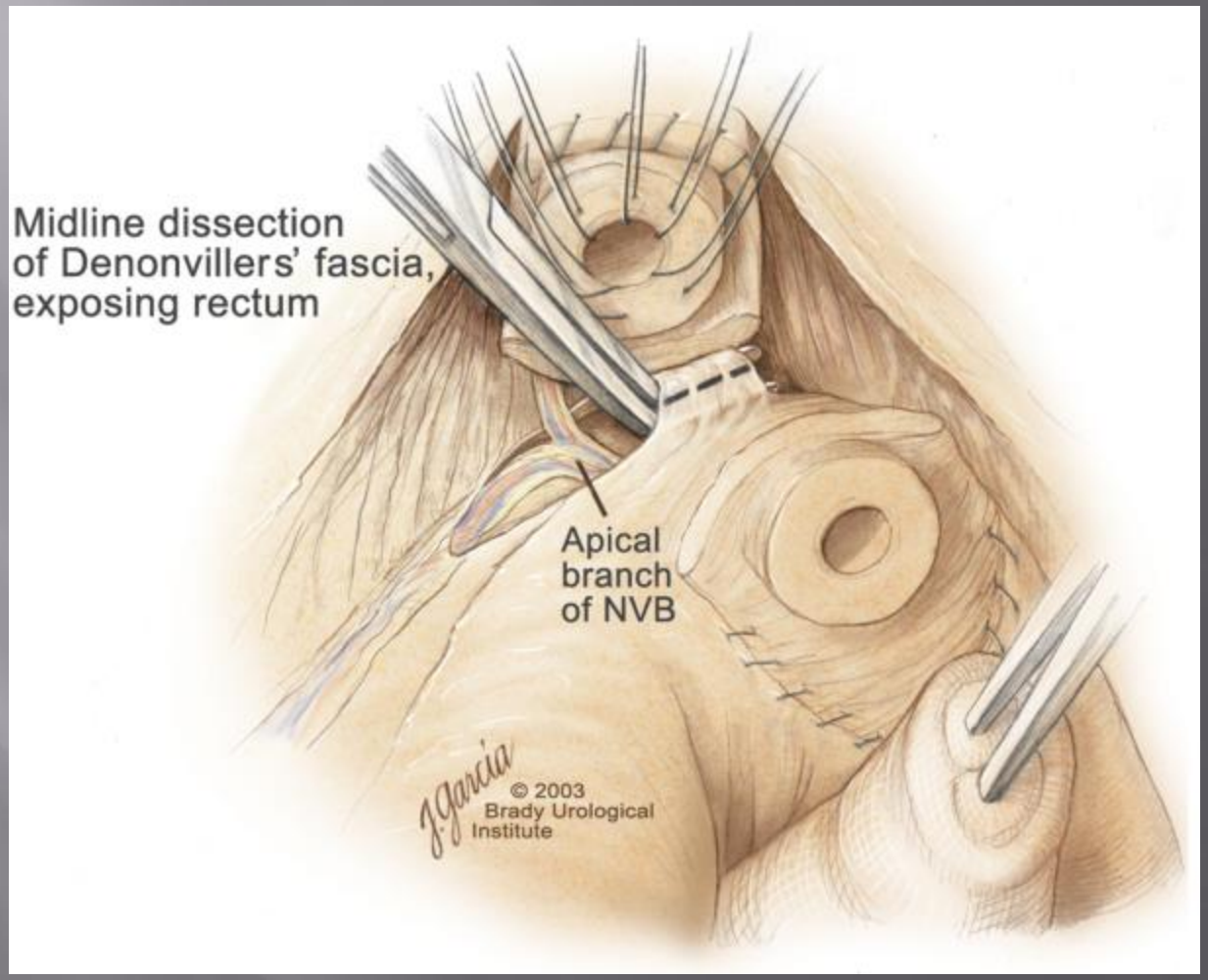
Midline dissection
of Denonvillers' fascia,
exposing rectum
Apical
branch
of NVB
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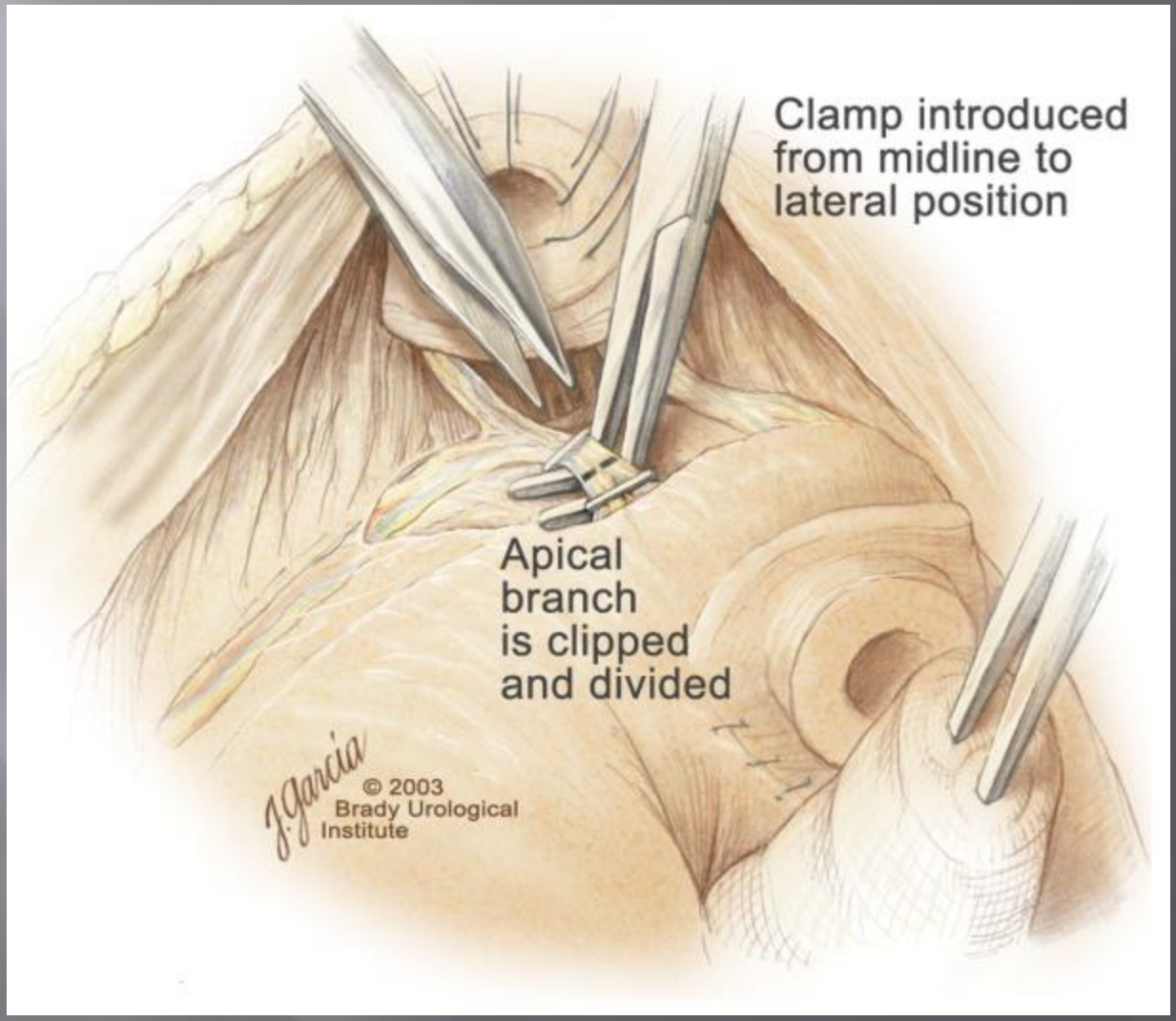
Clamp introduced from midline to lateral position
Apical branch is clipped and divided
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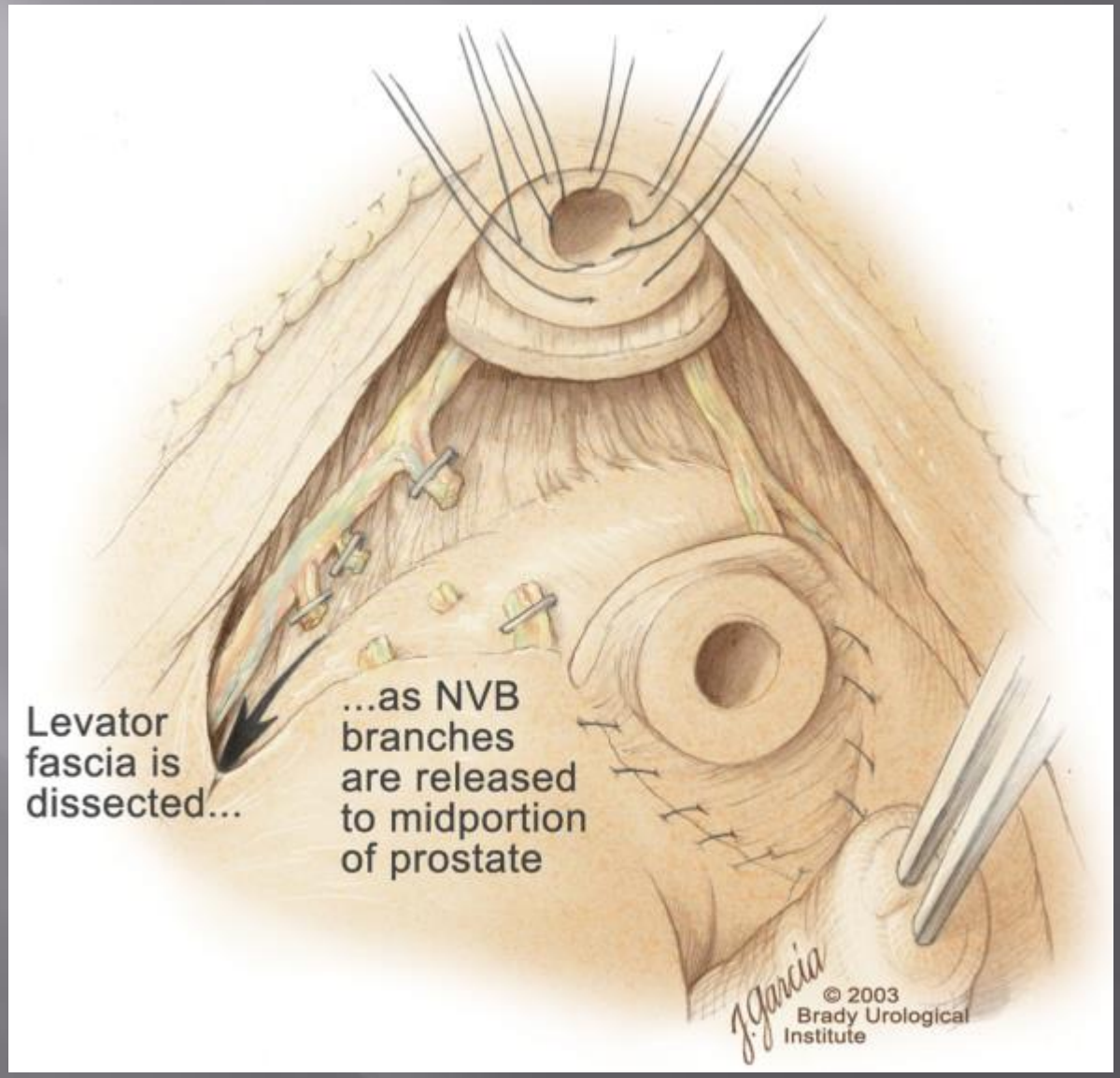
Levator fascia is dissected...
...as NVB branches are released to midportion of prostate
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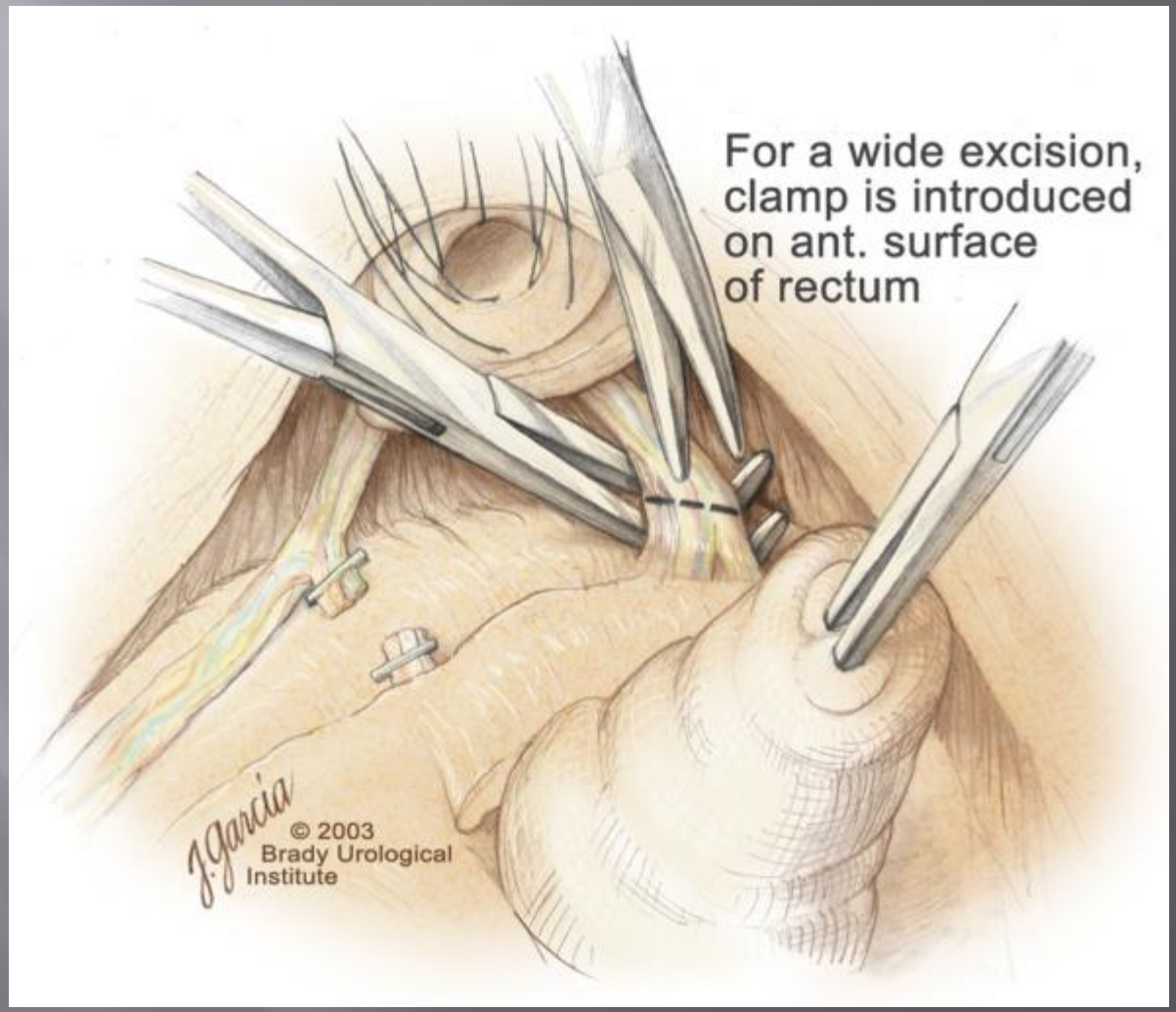
For a wide excision, clamp is introduced on ant. surface of rectum
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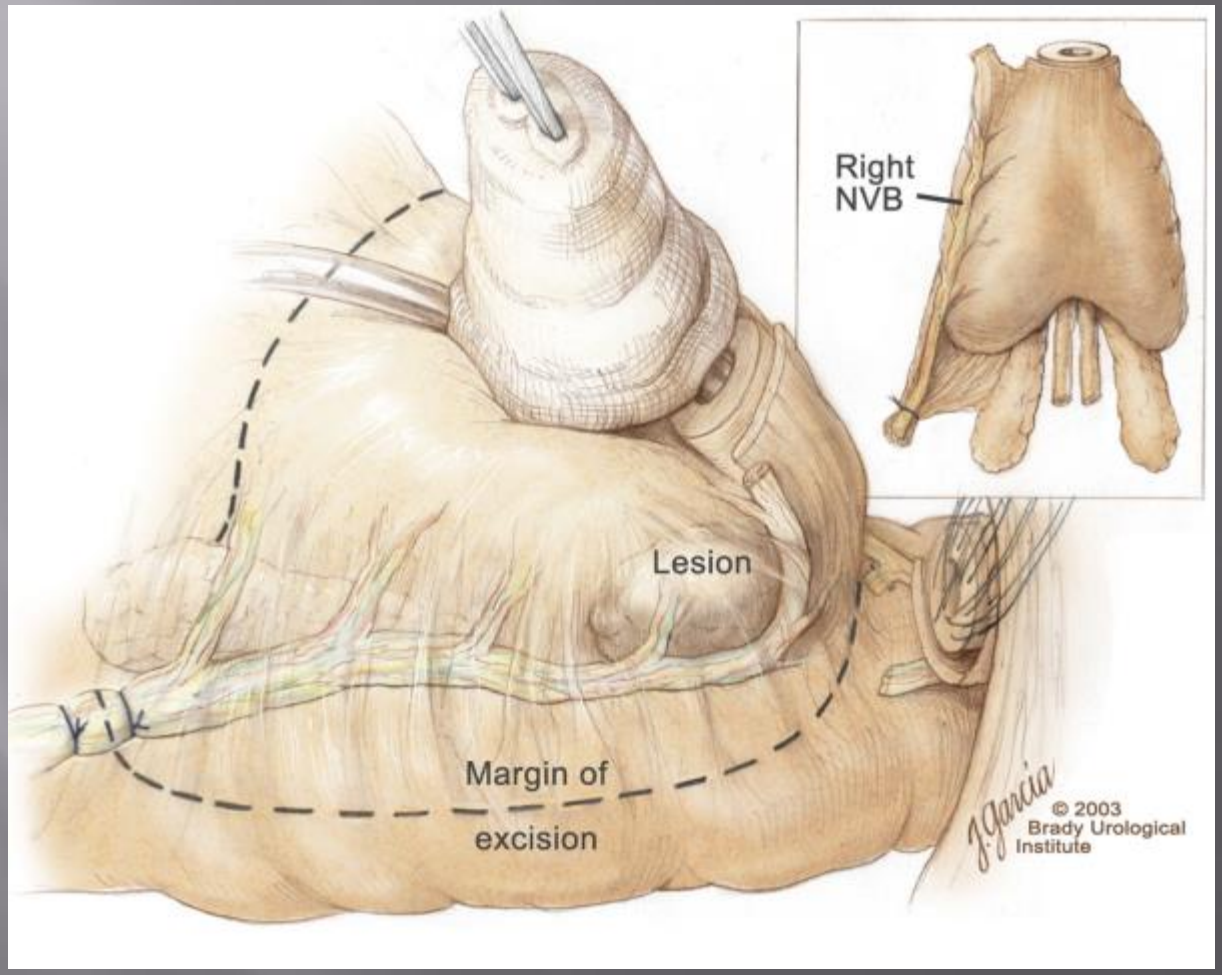
Right
NVB
Lesion
Margin of
excision
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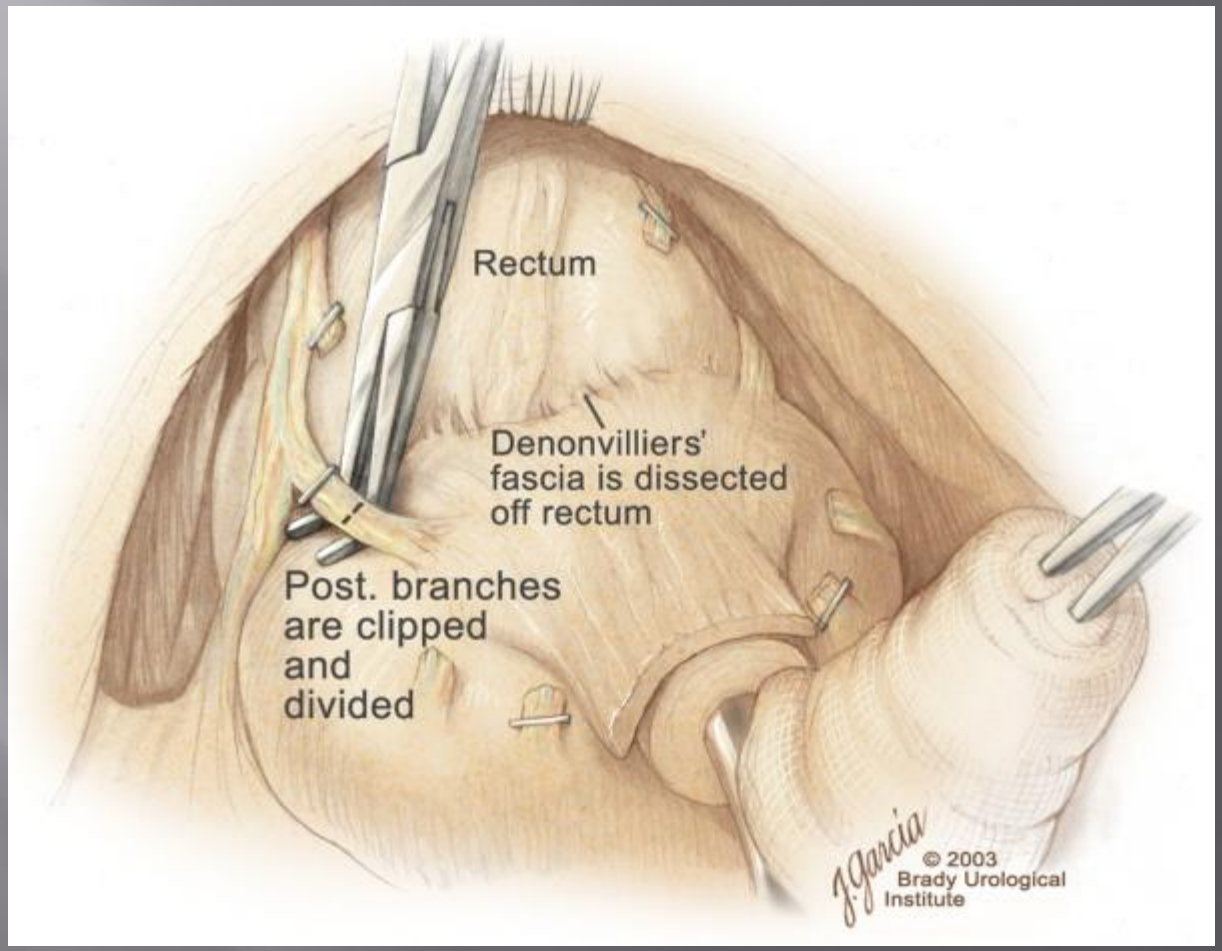
Rectum
Denonvilliers' fascia is dissected off rectum
Post. branches are clipped and divided
J.Garcia
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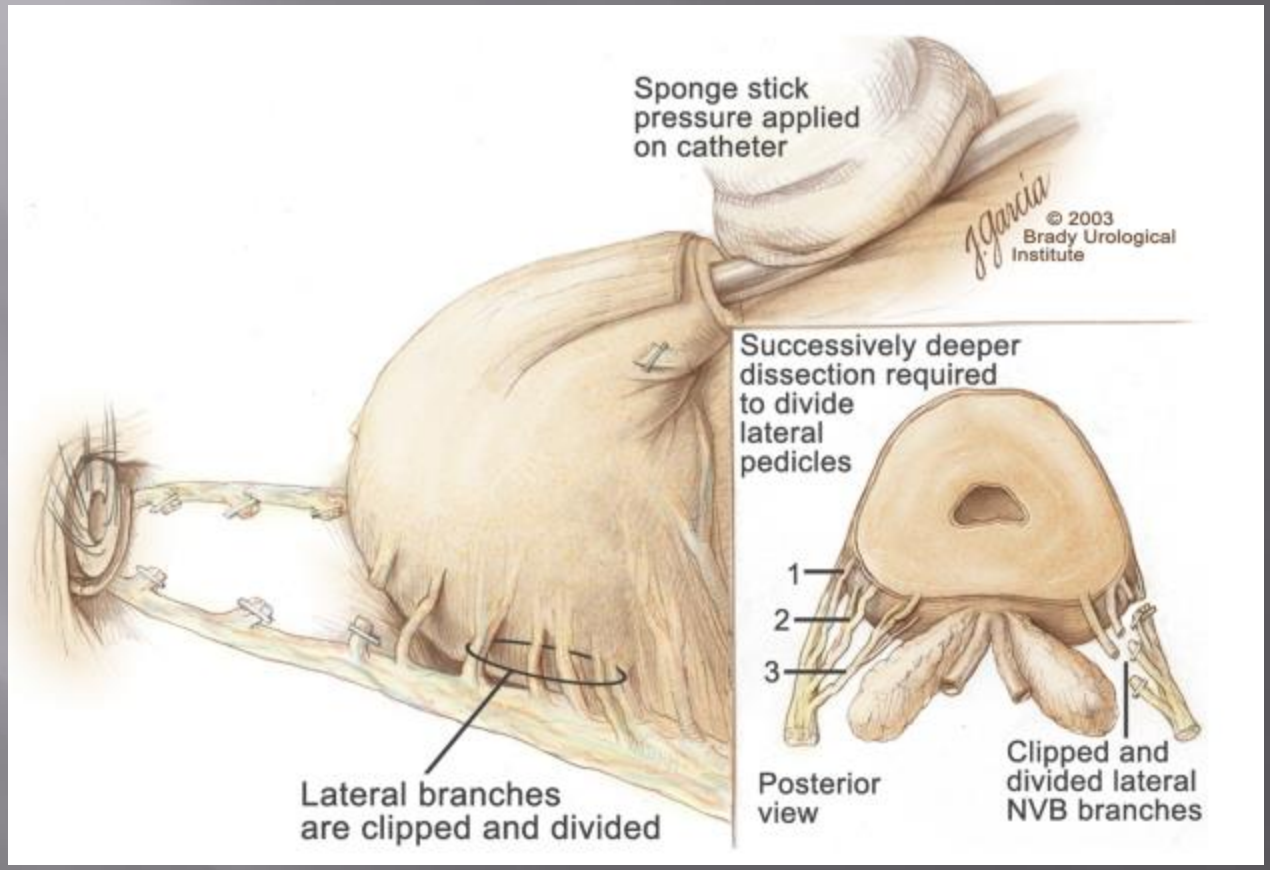
Sponge stick
pressure applied
on catheter
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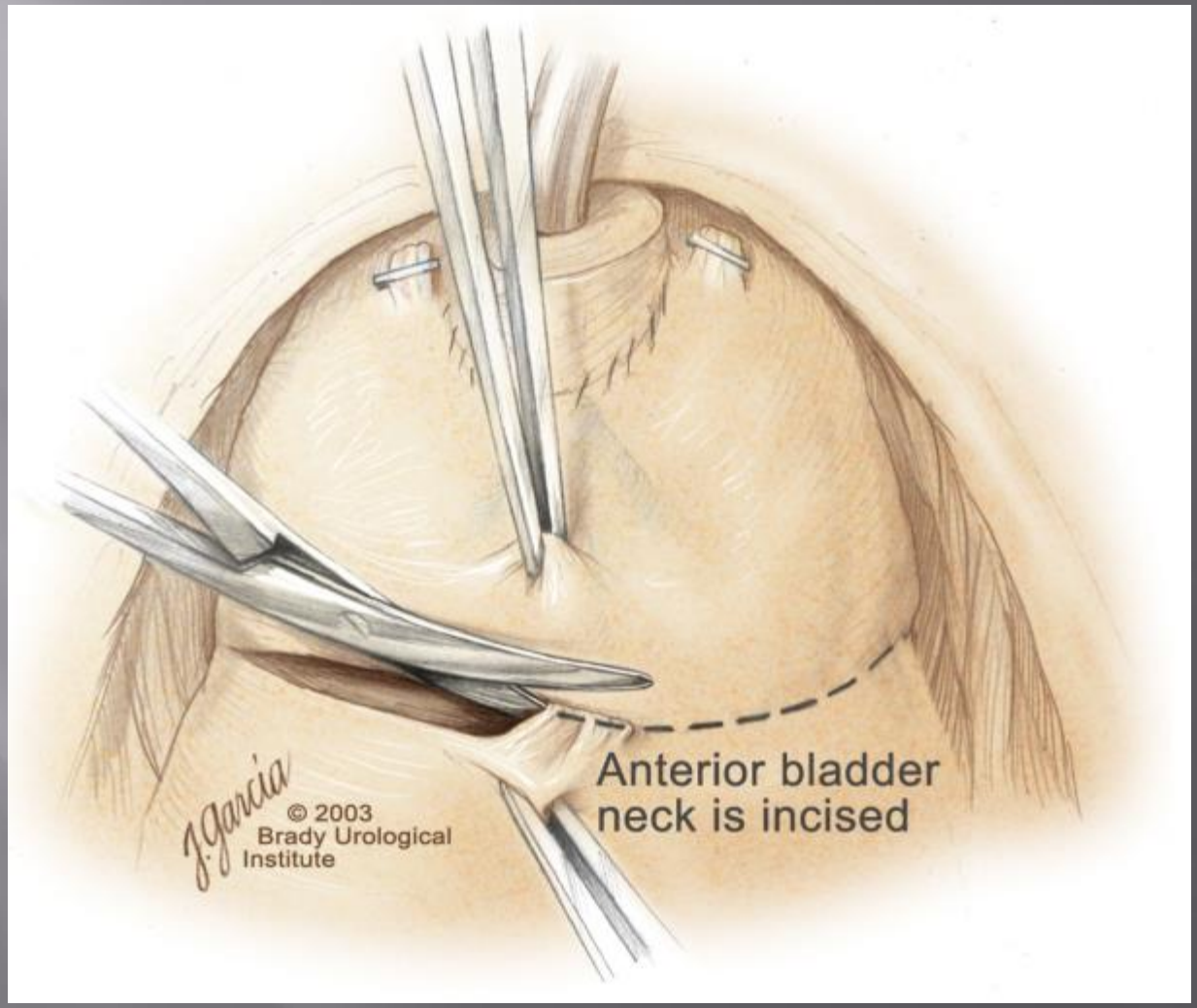
Successively deeper
dissection required
to divide
lateral
pedicles
1
2
3
Lateral branches
are clipped and divided
Posterior
view
Clipped and
divided lateral
NVB branches


Anterior bladder
neck is incised
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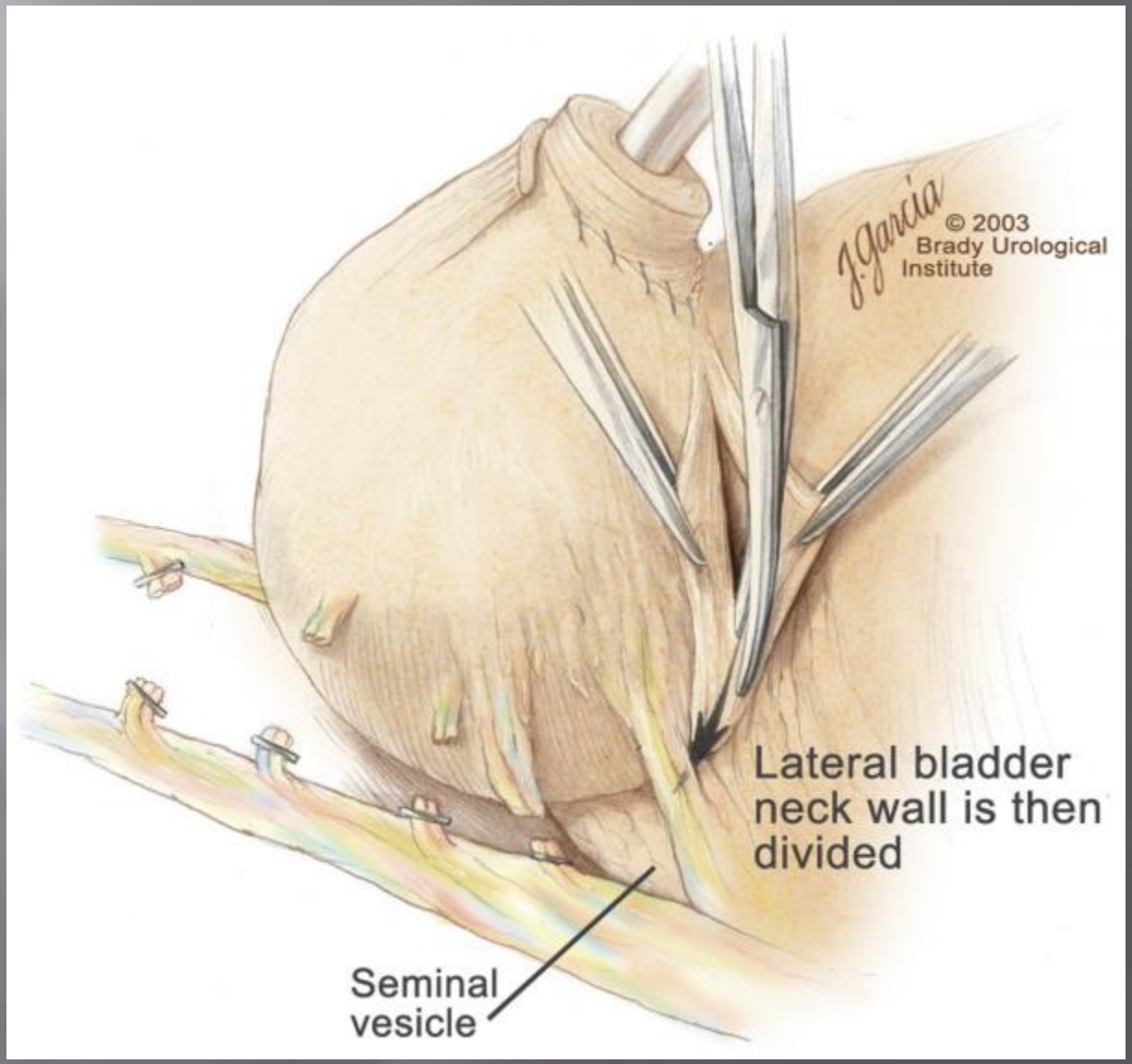
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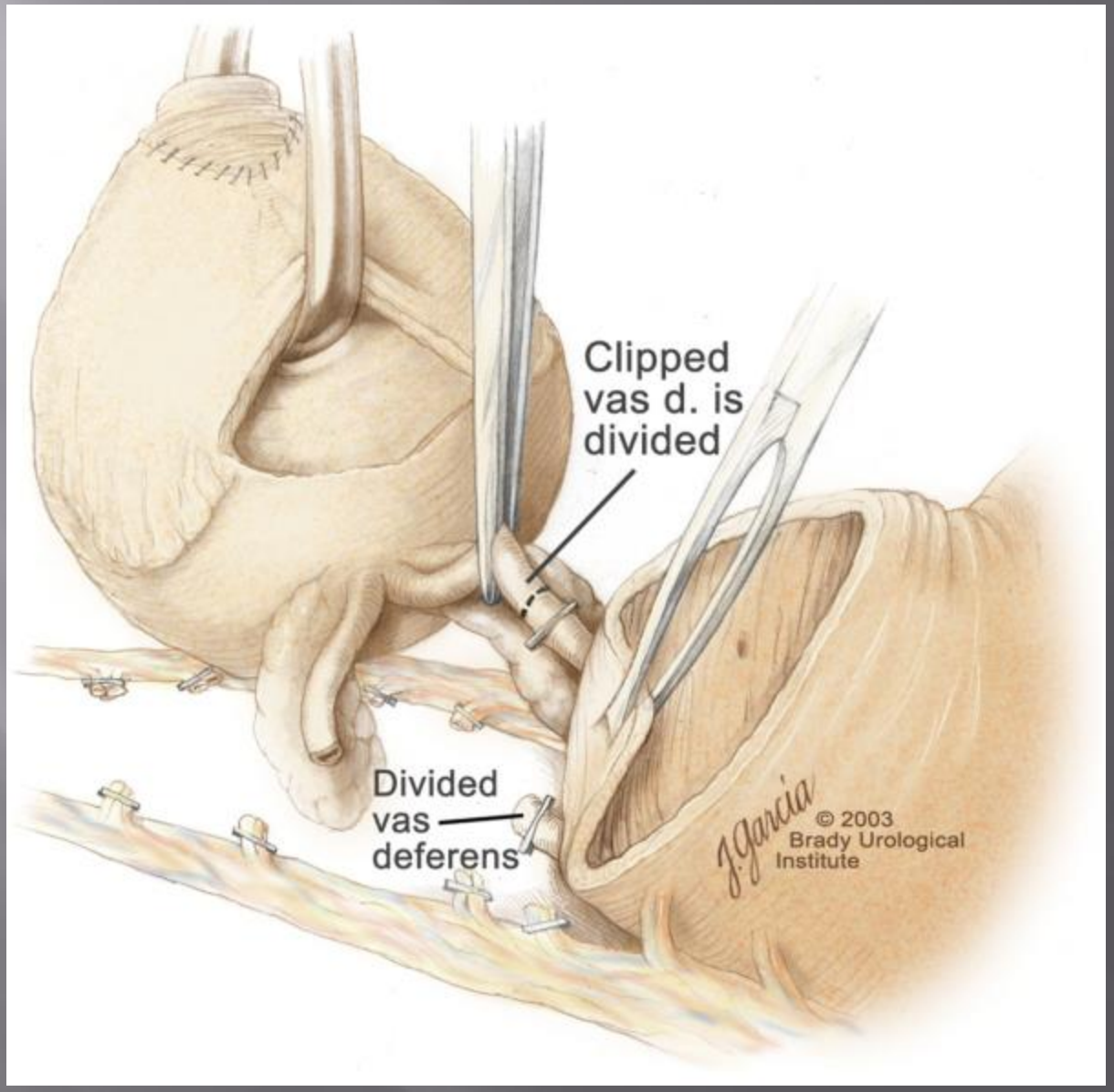
Lateral bladder
neck wall is then
divided
Seminal
vesicle


Clipped
vas d. is
divided
Divided
vas
deferens
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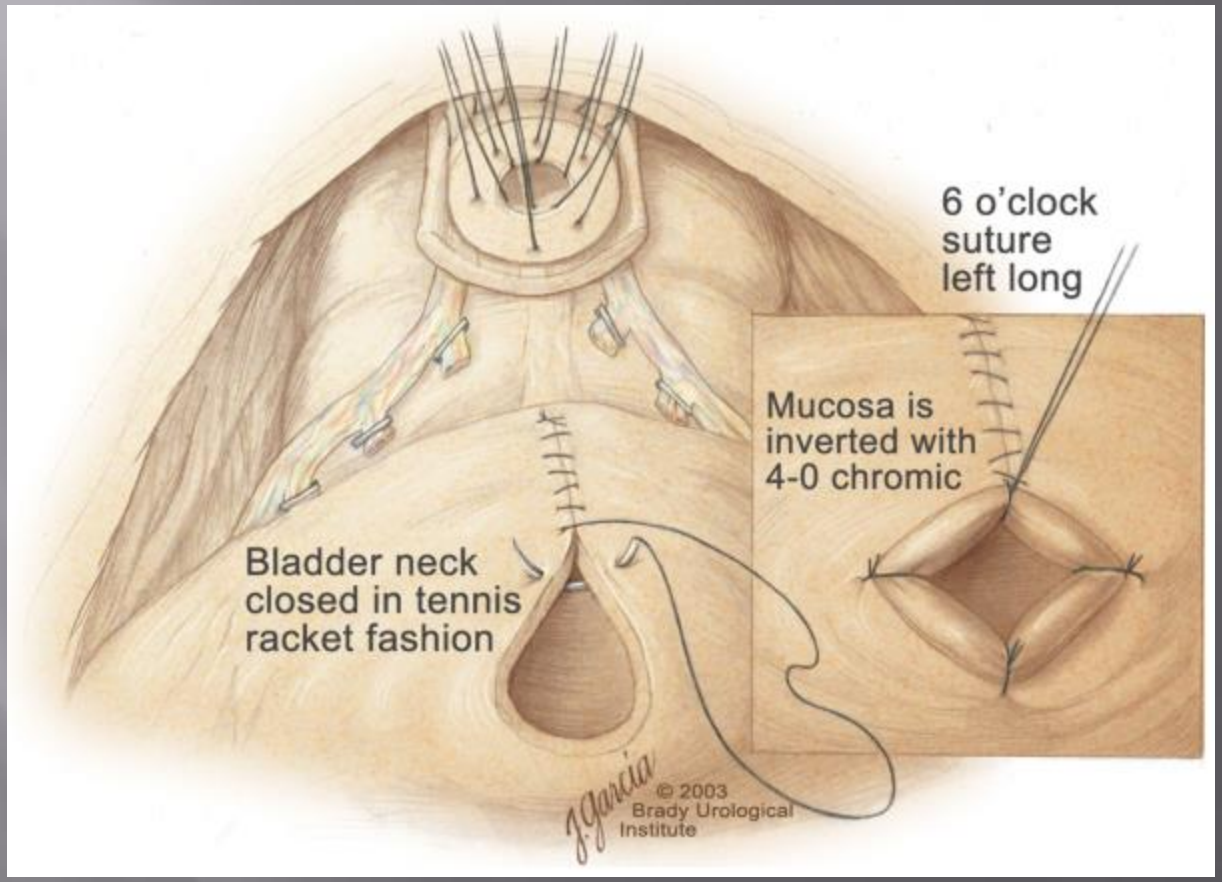
6 o'clock
suture
left long
Mucosa is
inverted with
4-0 chromic
Bladder neck
closed in tennis
racket fashion
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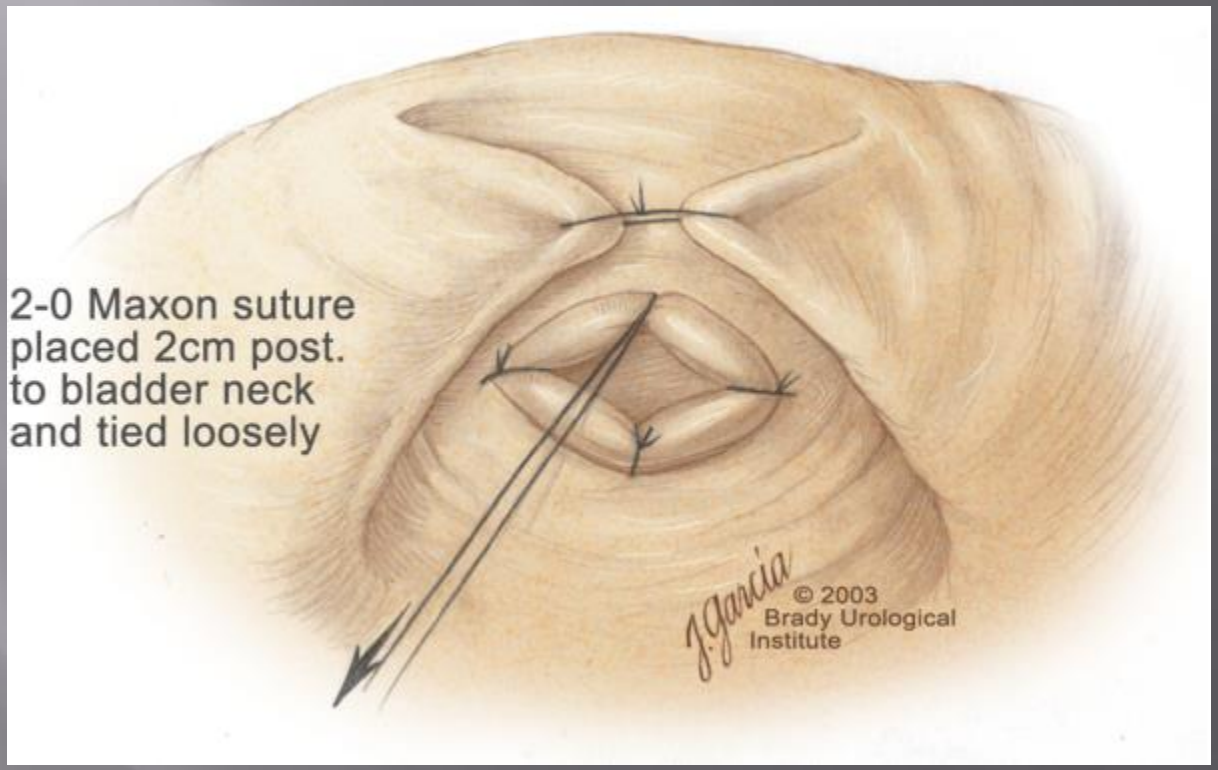
2-0 Maxon suture
placed 2cm post.
to bladder neck
and tied loosely
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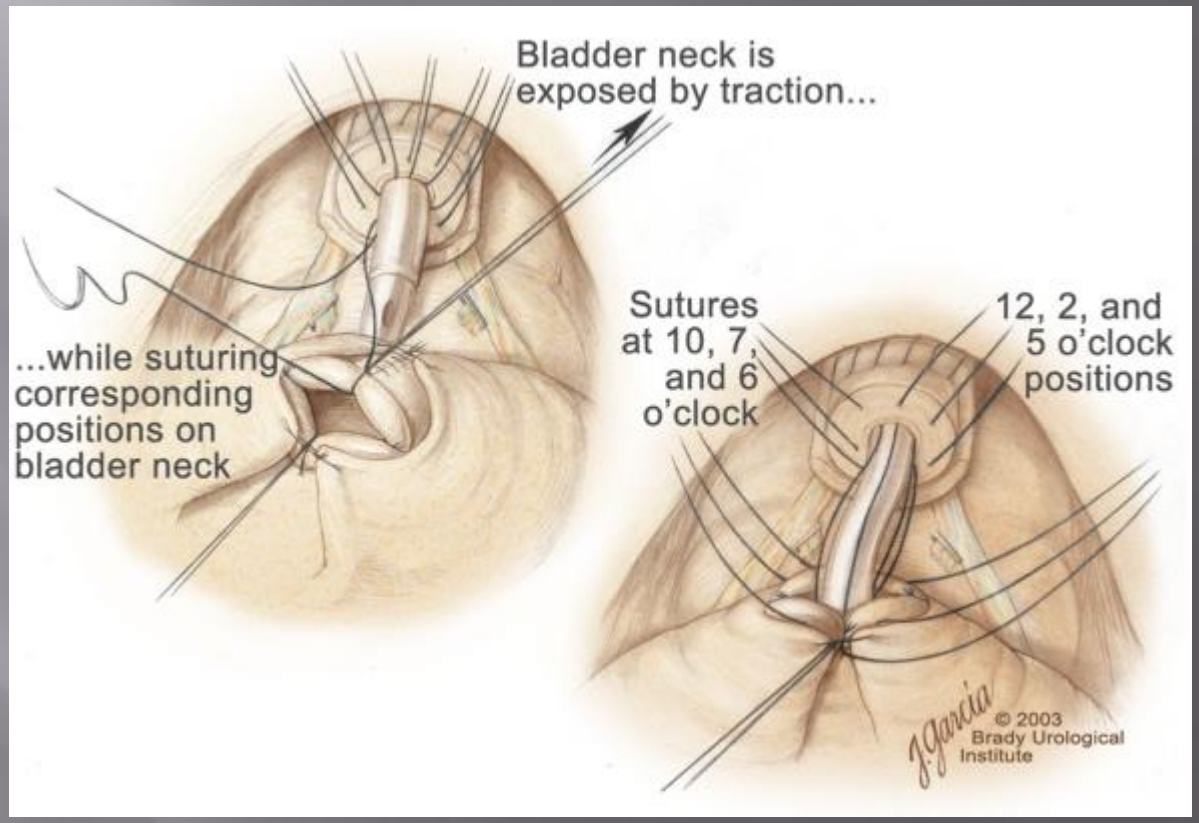
Bladder neck is exposed by traction...
...while suturing corresponding positions on bladder neck
Sutures at 10, 7, and 6 o'clock
12, 2, and 5 o'clock positions
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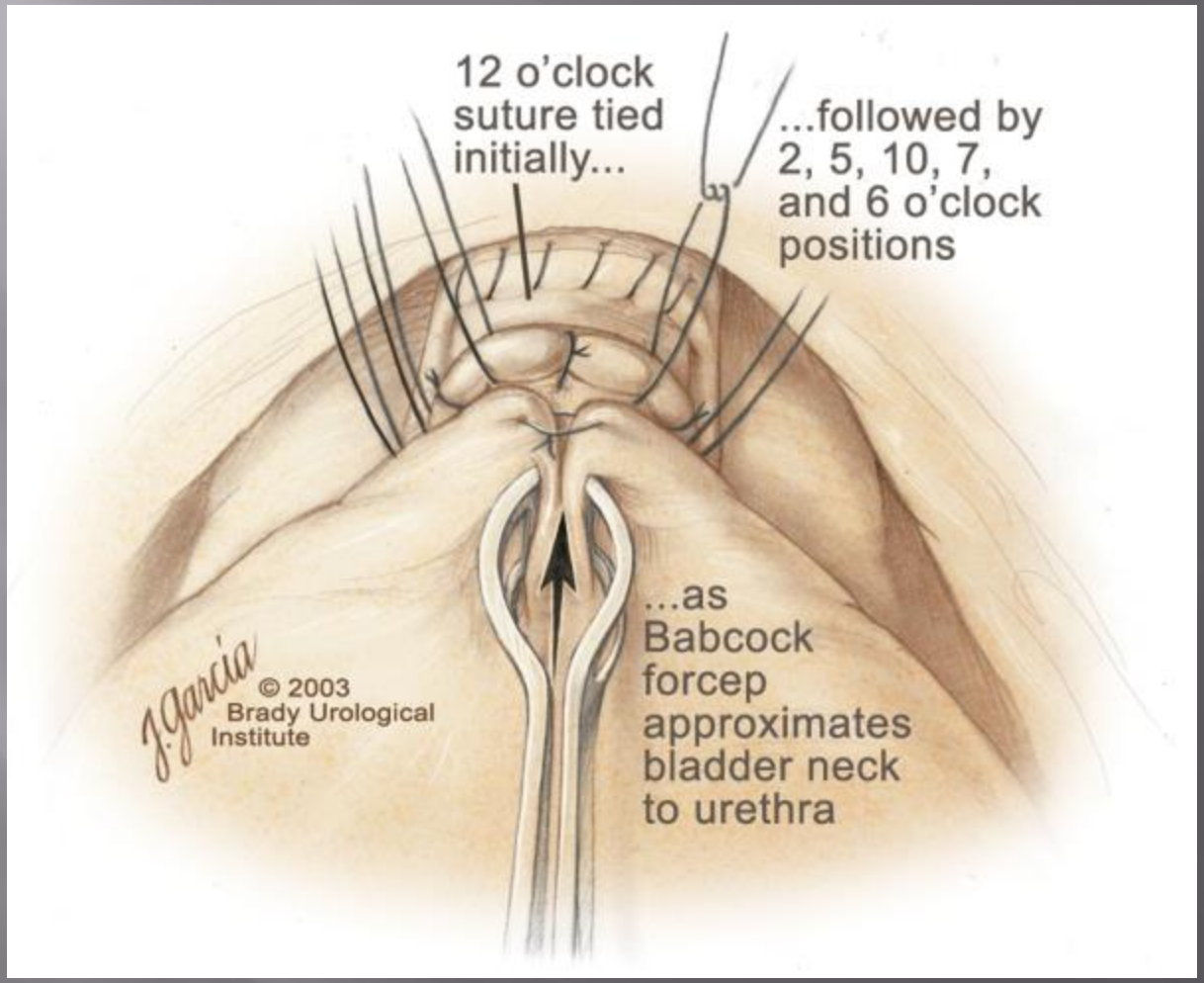
12 o'clock suture tied initially...
...followed by 2, 5, 10, 7, and 6 o'clock positions
...as Babcock forcep approximates bladder neck to urethra
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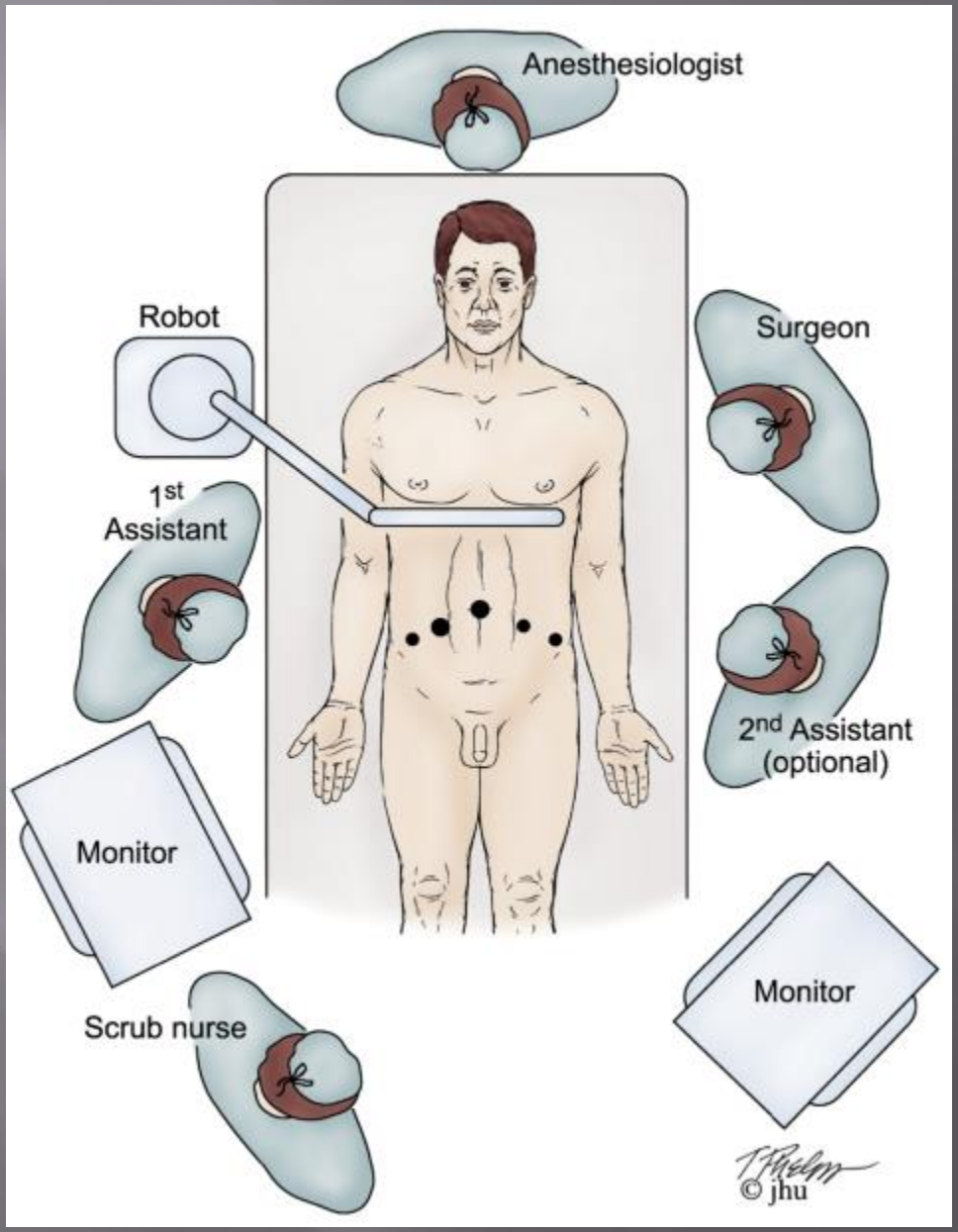
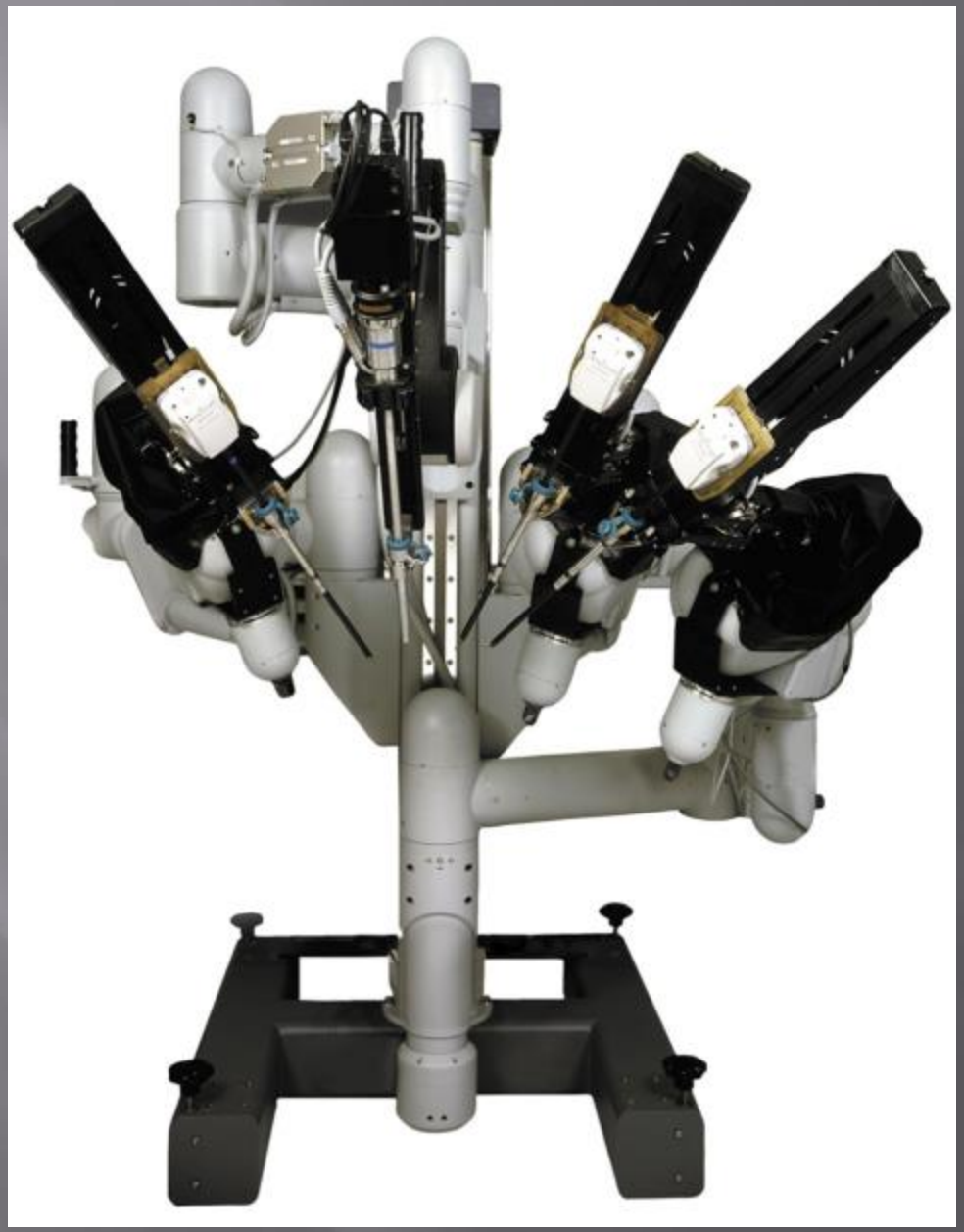
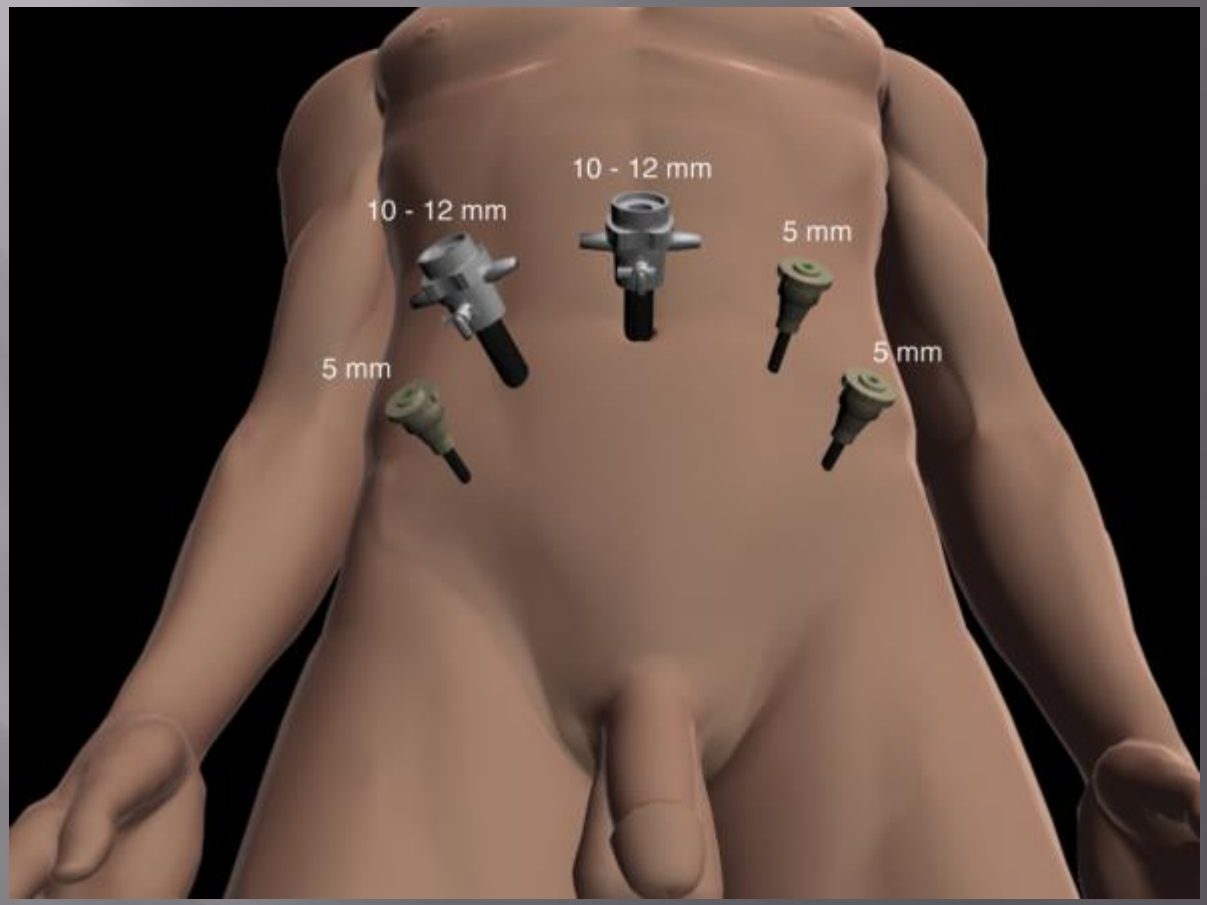

Anesthesiologist
Robot
Surgeon
1st Assistant
2nd Assistant (optional)
Monitor
Monitor
Scrub nurse
© jhu




10 - 12 mm
10 - 12 mm
5 mm
5 mm
5 mm

Resultados oncológicos de PR en enfermedad órgano confinada

Reference	No. of patients	Year of RP	Median follow-up (months)	10-year PSA-free survival	10-year cancer-specific survival
• Isbarn et al. (2009) (43)	436	1992-97	122	60	94
• Roehl et al. (2004) (44)	3478	1983-2003	65	68	97
• Han et al. (2001) (45)	2404	1982-99	75	74	96
• Hull et al. (2002) (46)	1000	1983-98	53	75	98
• Porter et al. (2006) (47)	752	1954-94	137	71	96

Complicaciones de la PR

Complication	Incidence (%)
• Peri-operative death	0.0-2.1
• Major bleeding	1.0-11.5
• Rectal injury	0.0-5.4
• Deep venous thrombosis	0.0-8.3
• Pulmonary embolism	0.8-7.7
• Lymphocoele	1.0-3.0
• Urine leak, fistula	0.3-15.4
• Slight stress incontinence	4.0-50.0
• Severe stress incontinence	0.0-15.4
• Impotence	29.0-100.0
• Bladder neck obstruction	0.5-14.6
• Ureteral obstruction	0.0-0.7
• Urethral stricture	2.0-9.0

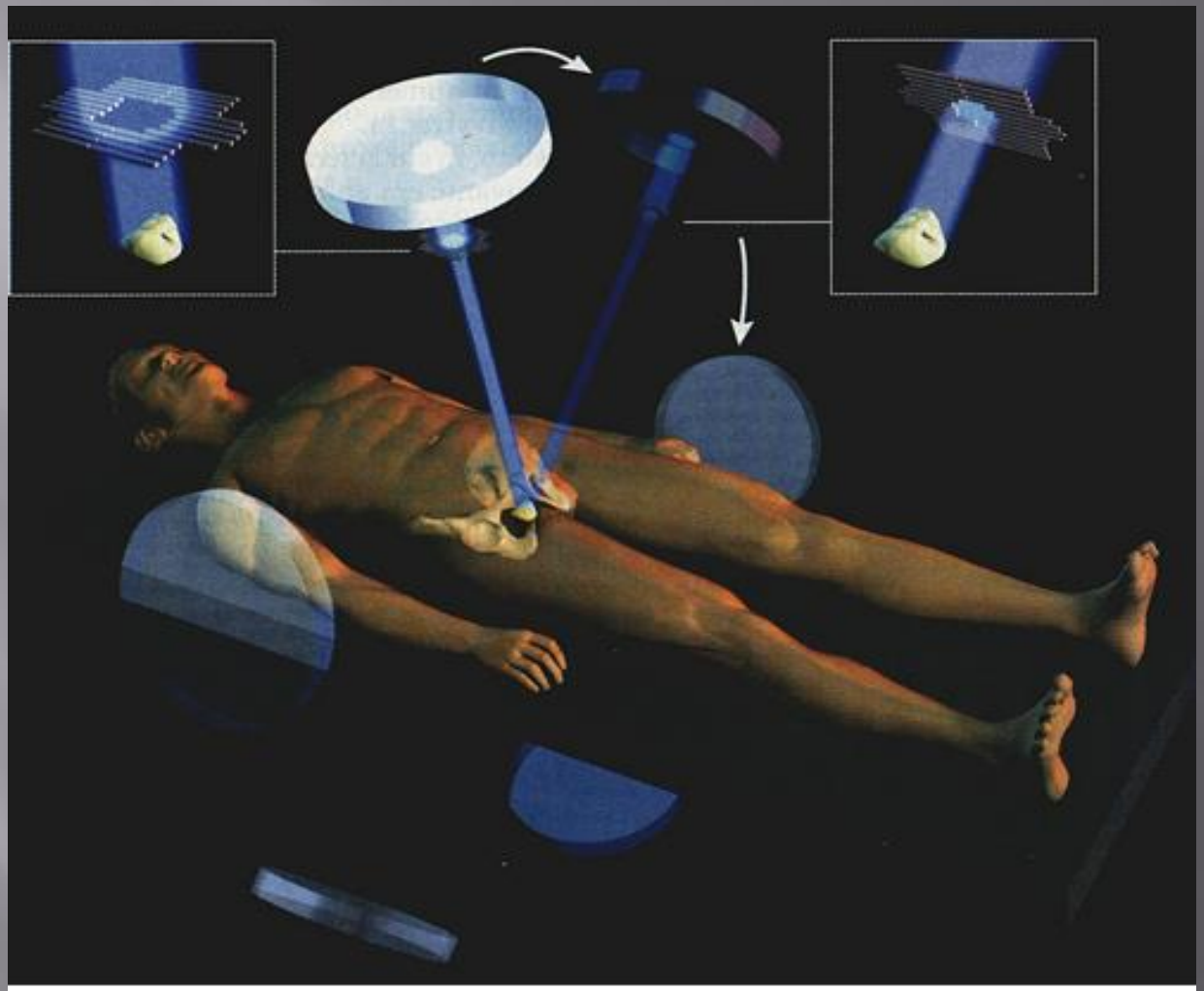
Radioterapia

- En pacientes con riesgo quirúrgico elevado, expectativa de vida menor de 10 años y negativa para la cirugía.

- CaP localizado T1 - 2c N0, M0
  - T1a-T2a, N0, M0; Gleason menor o igual a 6 y PSA menor de 10ng/ml (grupo de bajo riesgo): 72 Gy.

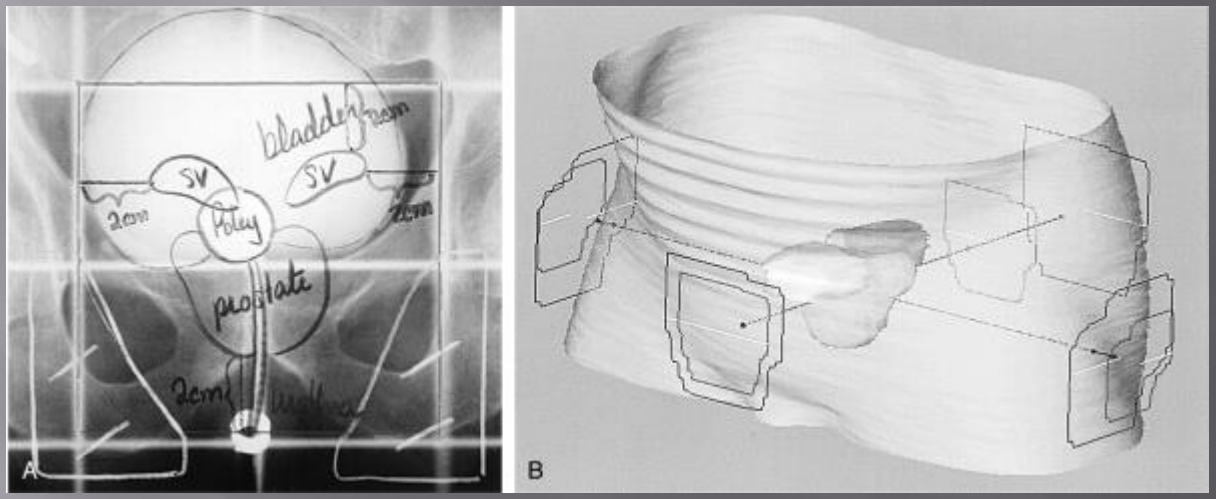
- T2b o PSA 10-20ng/ml o Gleason 7 (grupo de riesgo intermedio): 78 Gy.

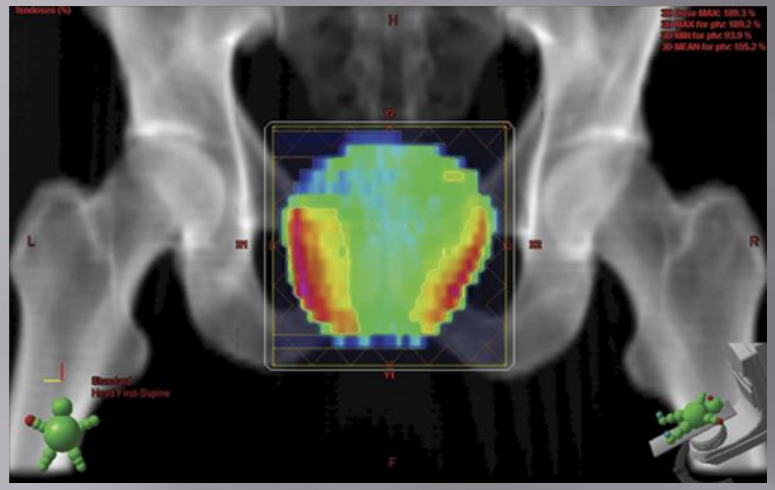
- T2c o PSA > 20ng/ml o Gleason > 7 (grupo de alto riesgo): adición de terapia de deprivación andrógena por corto tiempo previo y durante la radioterapia.

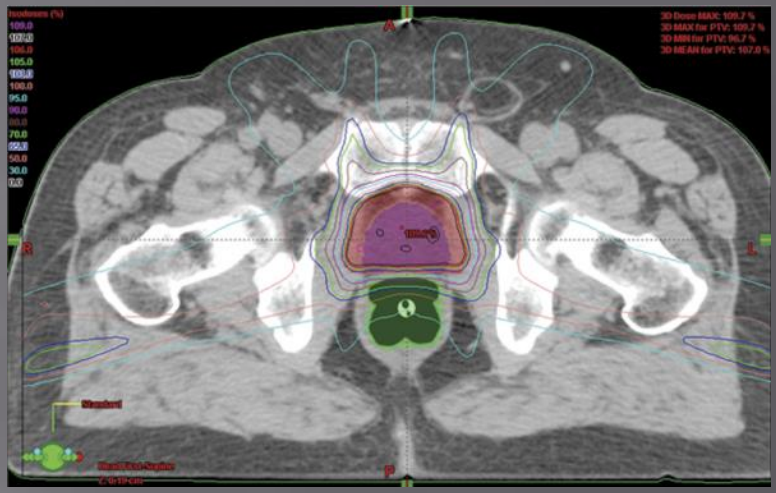


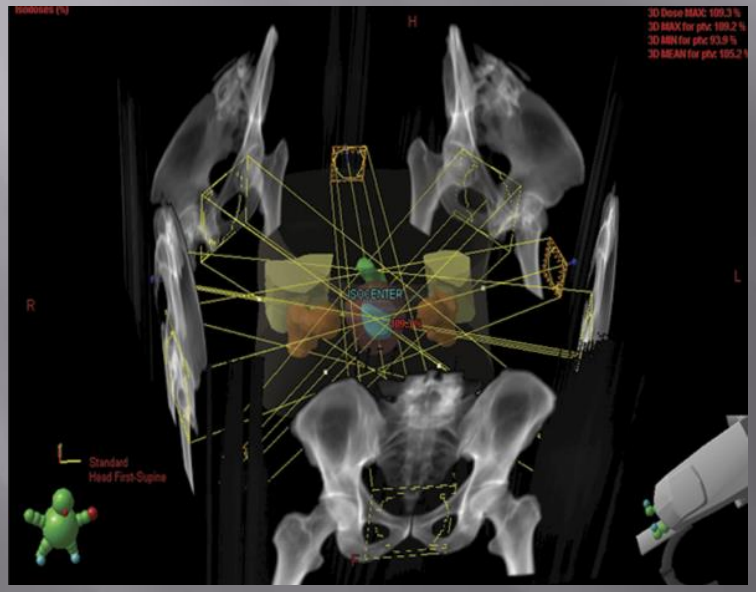
Radioterapia a fasci esterni

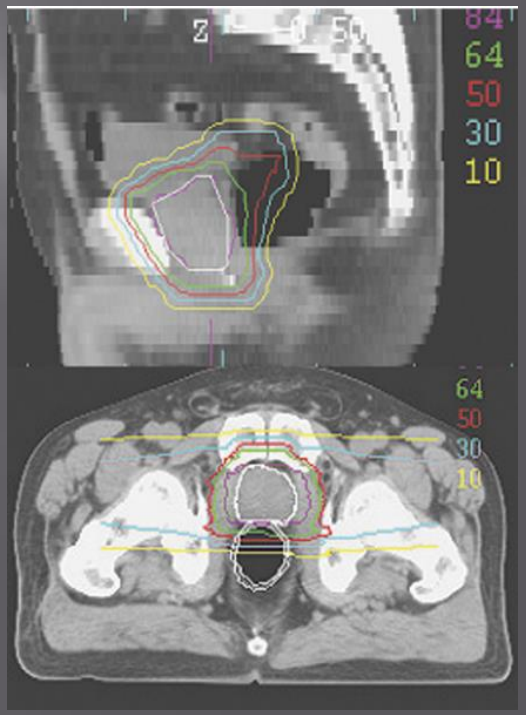
External beam radiotherapy


bladder
SV
SV
2cm
2cm
Foley
prostate
2cm
A
B






Standard
Head First-Supine

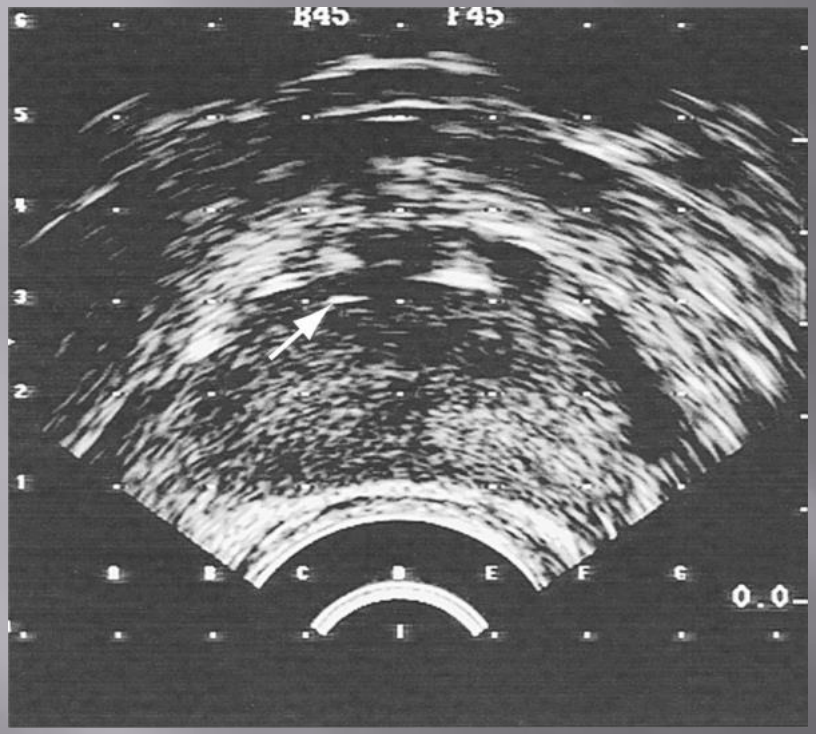

84
64
50
30
10
64
50
30
10

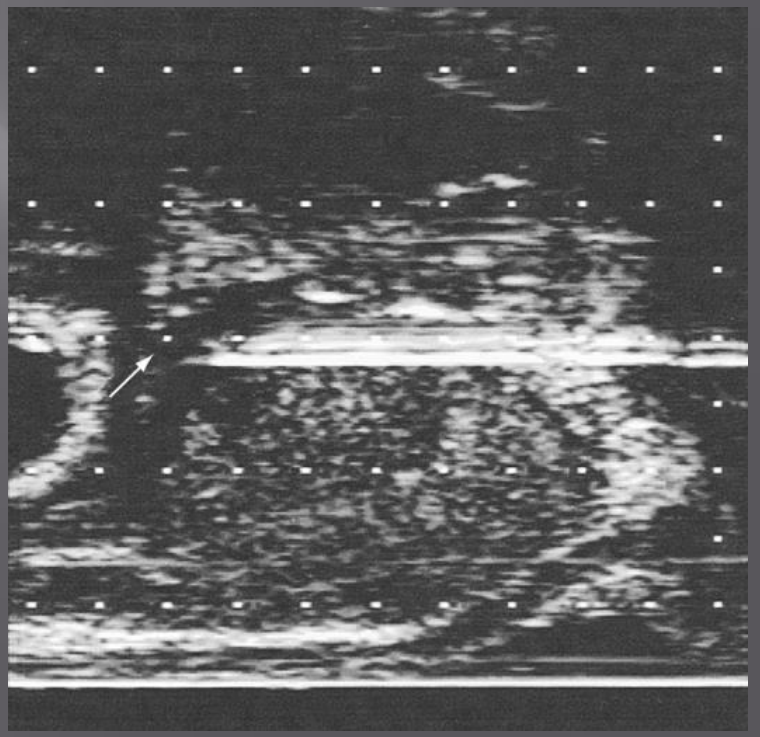
- Otras técnicas:

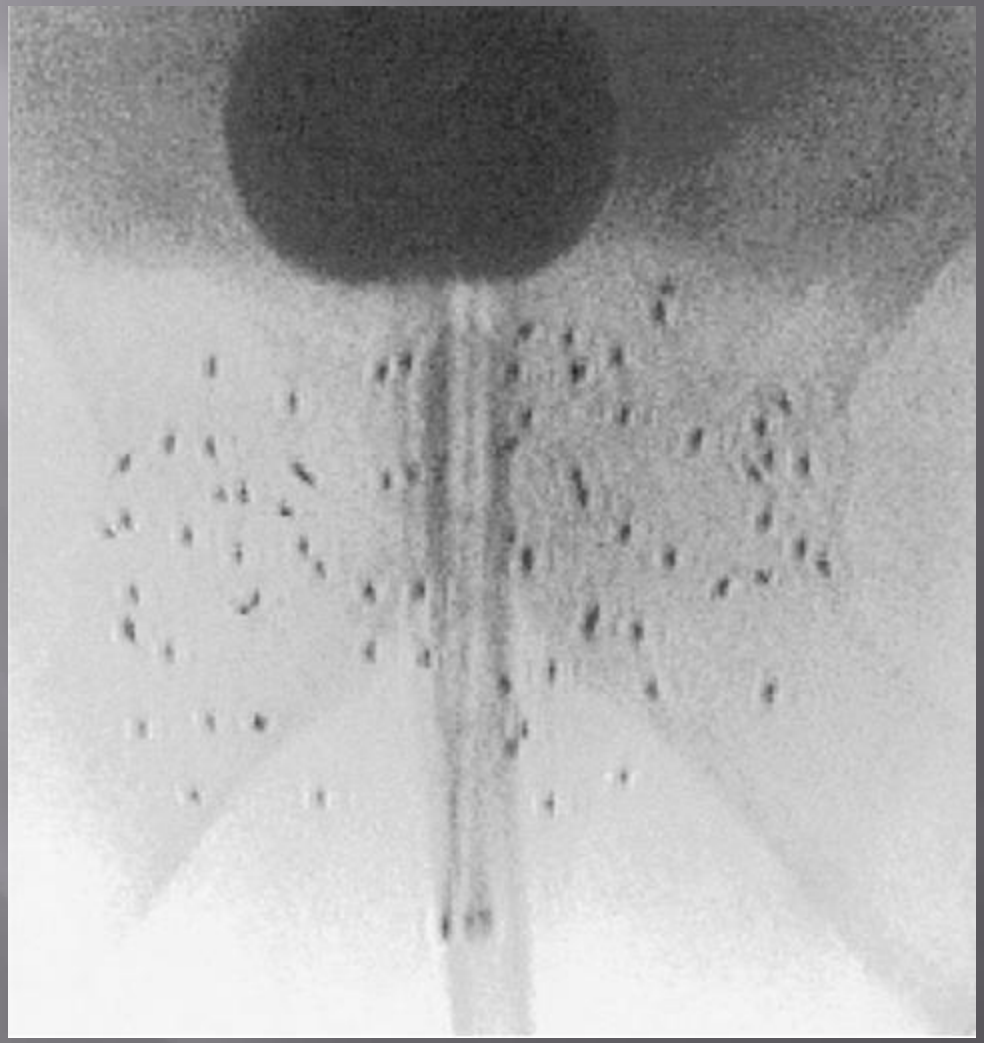
  -radioterapia de intensidad modulada.

  -braquiterapia transperineal (T1b - T2a N0, M0; Gleason menor o igual a 6, PSA inicial menor o igual a 10ng/ml, 50% o menos de cores con presencia de neoplasia, volumen prostático menor de 50cc. y un buen IPSS).

A B C D E F G
7
6
5
4
3
2
1


B45
F45
6
5
4
3
2
1
A B C D E F G
0.0





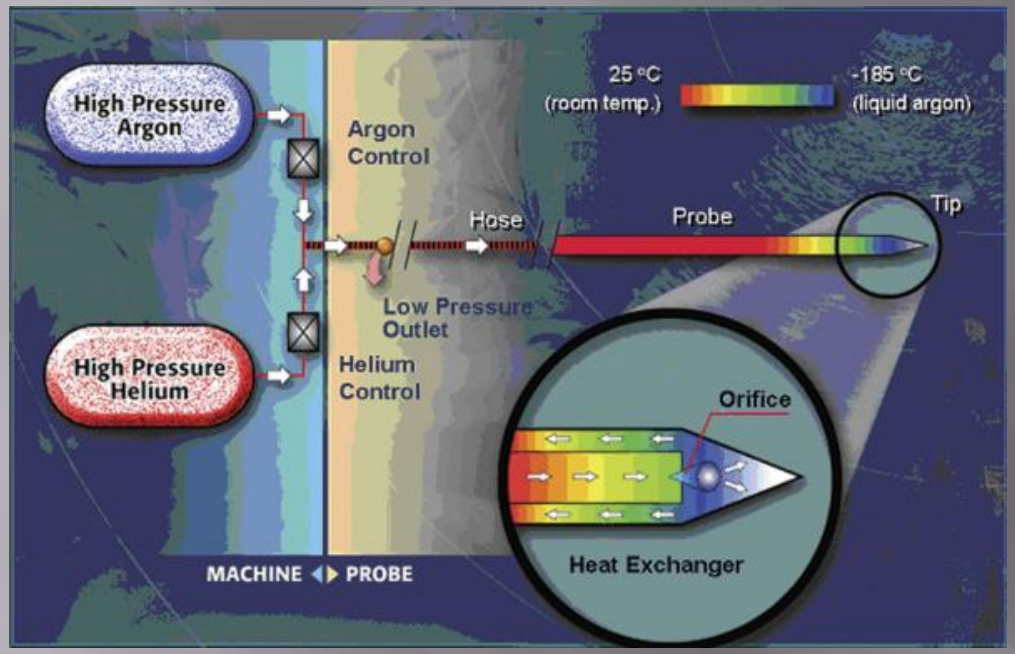
- En caso que a los 18 meses de finalizada la RT el PSA sea mayor de 0.5ng/ml, se procede a biopsia prostática. Si es positiva el paciente recibe HT.

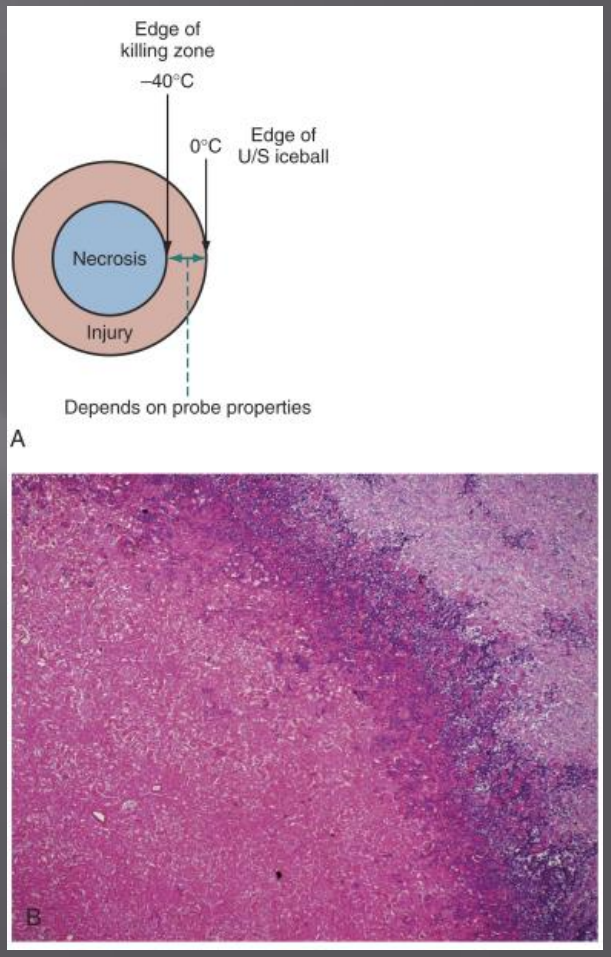
Otras alternativas

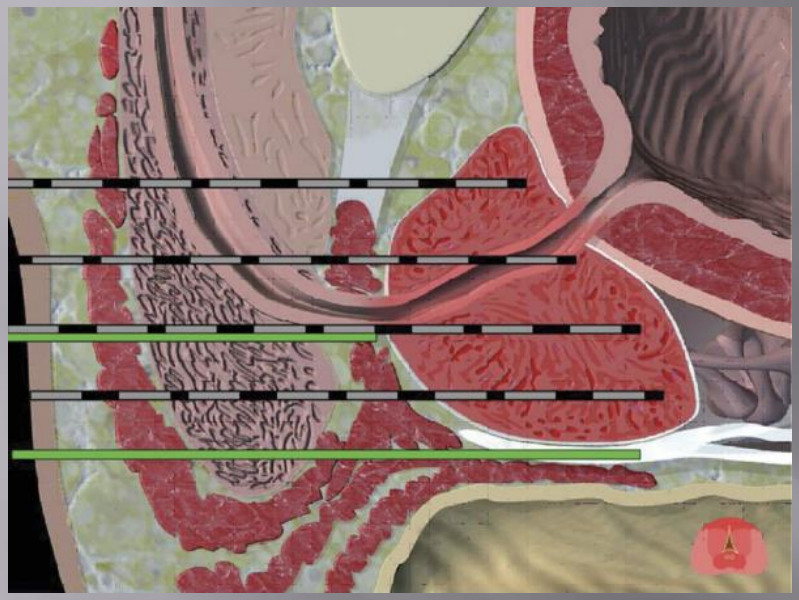
- Criocirugía de la próstata:

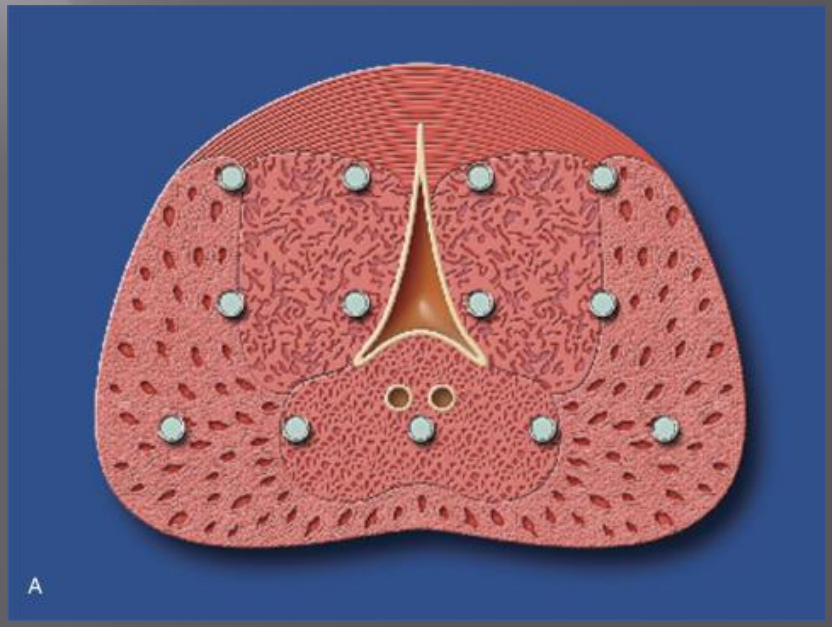
  Usa técnicas de congelación para inducir muerte celular (desnaturalización proteica, ruptura de membrana celular, isquemia y apoptosis).

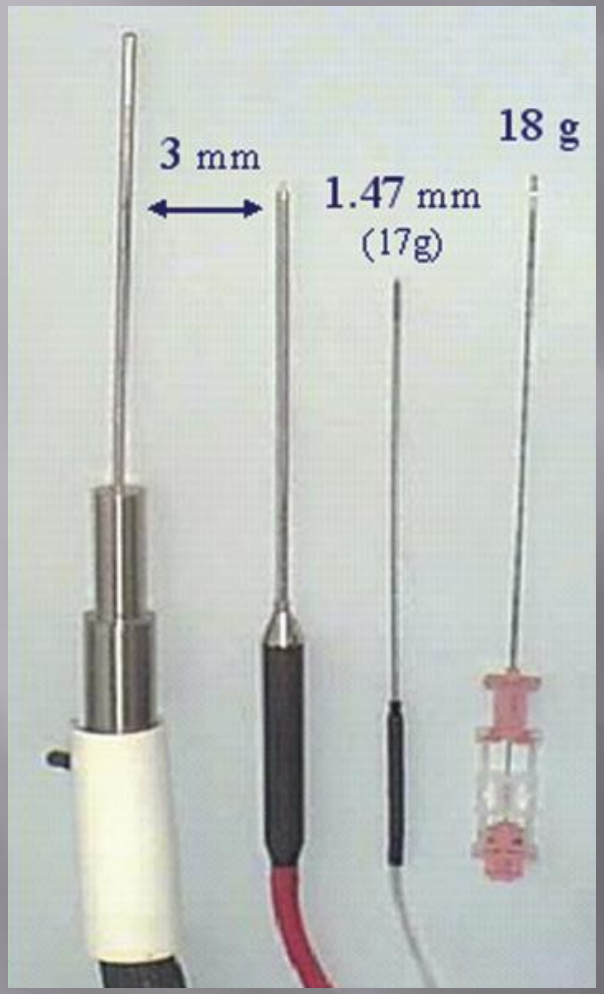
  Pacientes con CaP bajo riesgo, riesgo intermedio y con volumen prostático < 40cc.


High Pressure Argon
Argon Control
25 °C (room temp.)
-185 °C (liquid argon)
Hose
Probe
Tip
Low Pressure Outlet
High Pressure Helium
Helium Control
Orifice
MACHINE PROBE
Heat Exchanger


Edge of killing zone
–40°C
0°C
Edge of U/S iceball
Necrosis
Injury
Depends on probe properties
A
B




A


3 mm
1.47 mm
(17g)
18 g

A B C D E F G
7
6
5
4
3
2
1

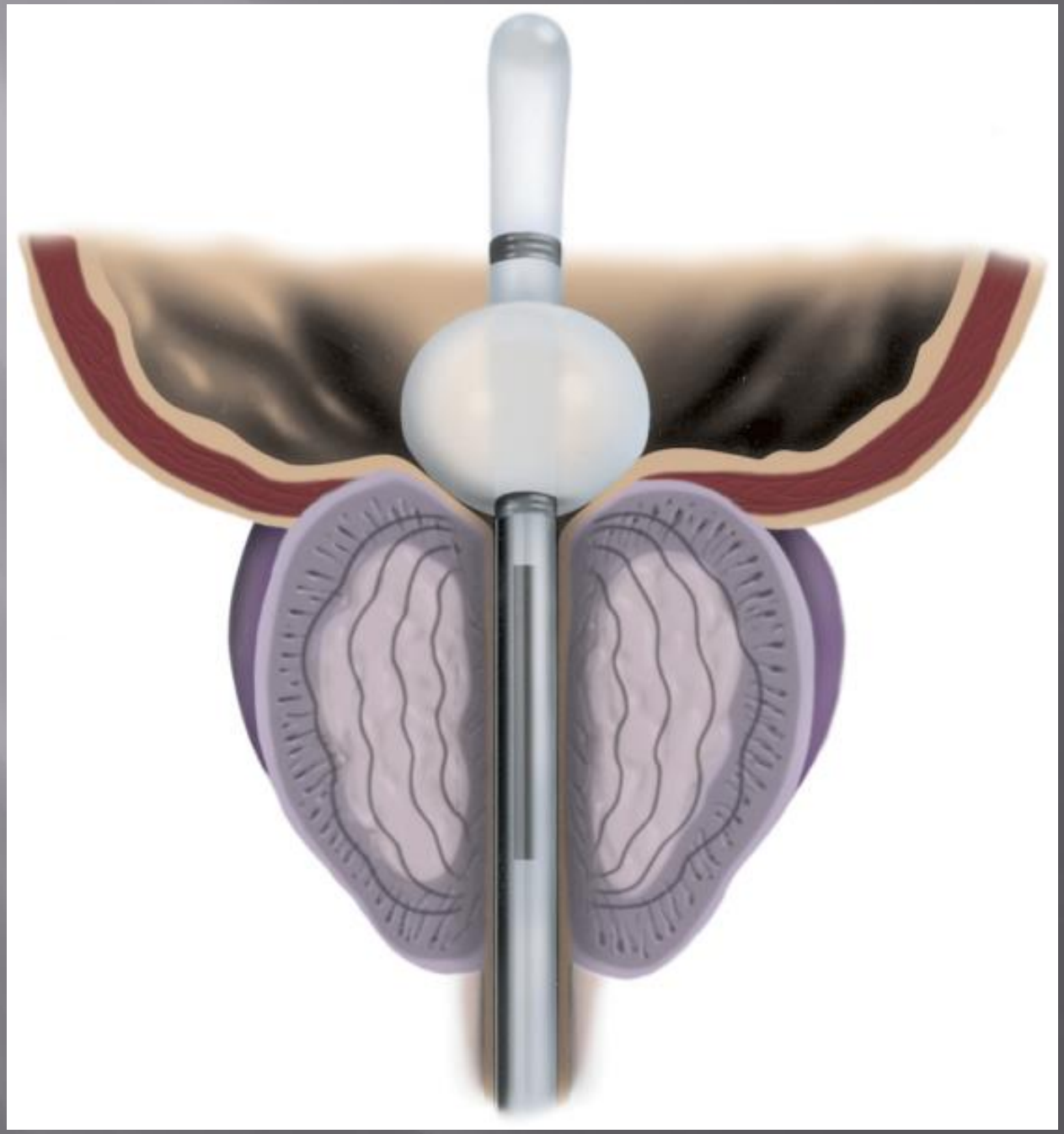
- Ultrasonido enfocado de alta intensidad

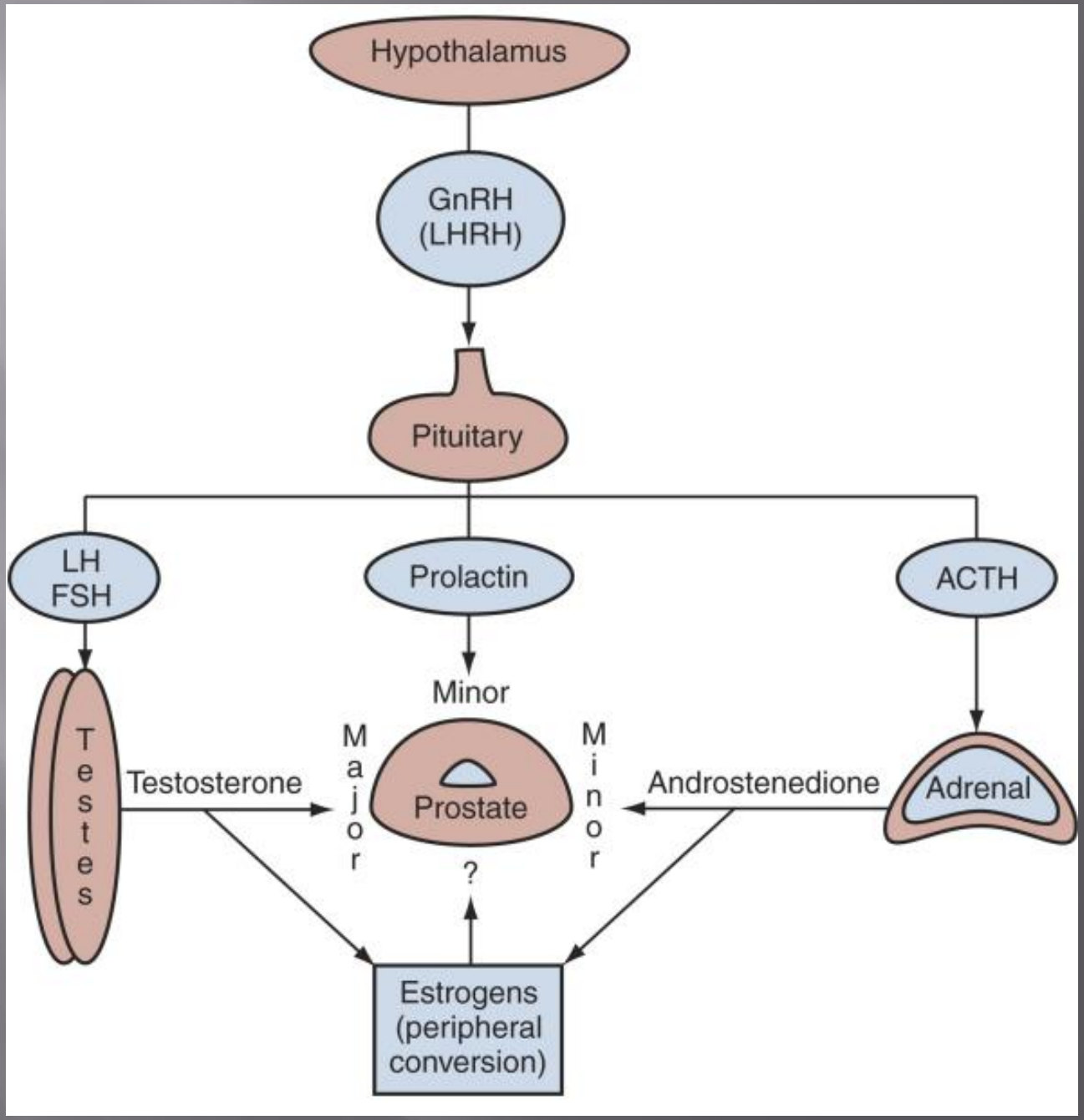
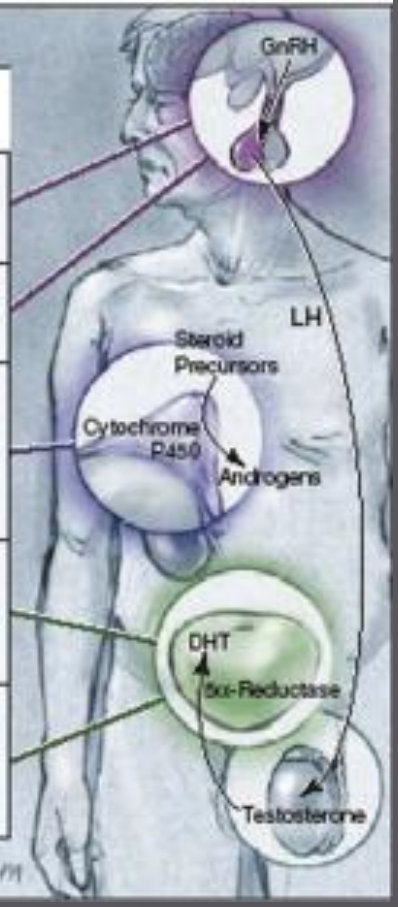
  Tratamiento experimental.

  Efecto térmico y mecánico: destrucción por necrosis coagulativa.
- Ablación de tumor intersticial por radiofrecuencia

  En investigación.

  Necrosis coagulativa.




Hypothalamus
GnRH
(LHRH)
Pituitary
LH
FSH
Prolactin
ACTH
Minor
Testes
Testosterone
Major
Prostate
Minor
Androstenedione
Adrenal
?
Estrogens
(peripheral
conversion)

Drug Class	Drugs	Site of Action	Mechanism of Action	Comments/Risks
Gondatropin-Releasing Hormone (GnRH) Agonists	Leuprolide Goserelin	Anterior Pituitary Gland	Decreases Release of LH Through Down-regulation of GnRH Receptors	Testosterone Surge
GnRH Antagonists	Abarelix®	Anterior Pituitary Gland	Directly Inhibits GnRH Receptors	Anaphylaxis
Adrenal Ablating Drugs	Ketoconazole	Adrenal Gland	Decreases Androgen Synthesis From Steroid Precursors Through Inhibition of Cytochrome P450 Enzymes	Administration Requires Steroid Supplementation to Prevent Adrenal Insufficiency
Androgen Receptor Antagonists	Flutamide Bicalutamide Nilutamide	Prostate Gland	Inhibits Androgen Receptor Ligand-Binding Domain Through Competitive Binding	Gynecomastia, Increased Liver Transaminases, and Mastodynia
5α-Reductase Inhibitors	Finasteride	Prostate Gland	Decreases Conversion of Testosterone to DHT Through Inhibition of 5α-Reductase	No Defined Role in Standard Care of Prostate Cancer