

Penile Cancer

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Case Presentation

- 55-year-old man with PMH of HIV, DM2, GERD, presents with several-year-history of irritative symptoms including dysuria and pruritis not responding to antibiotics.
- Complete ROS non-contributory.
- Exam significant for phimosis with a <1cm firm, hard, tender lesion under foreskin on the ventral aspect of the glans. Foreskin could not be fully retracted, but glans appear discolored and darkened.

Workup

- Punch or excisional biopsy
 - Excisional biopsy if punch is non-diagnostic
- CT A/P or pelvic MRI with contrast for primary and nodal evaluation, chest CT or XR to rule out intrathoracic dz
- PET/CT for patients with high BMI, prior inguinal procedures or palpable nodes
- cN+ → FNA
 - If (–) and low risk (Tis-T1a) → excisional biopsy
 - If (–) and high risk (T1b+) → inguinofemoral LN dissection

Case Presentation (cont.)

- Excisional biopsy with circumcision a month after was positive for invasive SCC with residual disease.
- By this time, he had difficulty voiding with crusted meatus.
- He was recommended either Mohs gland-sparing penile surgery or partial penectomy.

Case Presentation (cont.)

- Unfortunately, due to limited access to health insurance, patient was lost to follow up and represented ~10 years later with a ~1.5cm ulcerated penile mass with fixed unilateral painful inguinal LAD.
- EUA/Biopsy show invasive keratinizing SCC deep into glans involving distal 3cm of penis (had ~10cm of additional penile length).
- Inguinal LN Bx positive for metastatic SCC

Case Presentation (cont.)

- CT A/P and PET/CT with FDG-avid glans penis mass, nodular infiltrative soft tissue extending along the right spermatic cord, and bilateral inguinal and right inguinal/femoral LNs
- History complicated by recurrent admissions for wound healing issues in context of DM2
- At this point, he was referred to radiation oncology for definitive chemoradiation.

Staging

- T stage
 - is= carcinoma *in situ* (penile intraepithelial neoplasia)
 - a= noninvasive localized SCC
 - 1= glans/subepithelial connective tissue
 - a. G1-2, no LVSI, no PNI
 - b. G3-4 or sarcomatoid, +LVSI, and/or +PNI
 - 2= corpus spongiosum +/- urethral invasion
 - 3= corpus cavernosa +/- urethral invasion
 - 4= adjacent structures (ie, prostate, scrotum, bone)

T/N/M	Tis; Ta	Ta1	T1b	T2	T3	T4
N0	Ois; Oa	I	IIA	IIA	IIB	IV
N1		IIIA	IIIA	IIIA	IIIA	IV
N2		IIIB	IIIB	IIIB	IIIB	IV
N3	IV	IV	IV	IV	IV	IV
M1	IV	IV	IV	IV	IV	IV

- cN stage
 - 0= no palpable or visibly enlarged inguinal
 - 1= 1 unilateral inguinal
 - 2= ≥2 unilateral or bilateral inguinal
 - 3= fixed inguinal or pelvic, unilateral or bilateral
- M stage
 - 1= distant metastasis

- pN stage
 - 0= no LN met
 - 1= ≤2 unilateral inguinal, no ENE
 - 2= ≥3 unilateral or bilateral inguinal
 - 3= ENE, or pelvic LN no ENE

Case Presentation (cont.)

- We staged the patient as cT1aN3M0.
 - Wasn't clear if there was PNI +/- LVI, but either way he's stage IV disease given N3.
- What would you recommend?

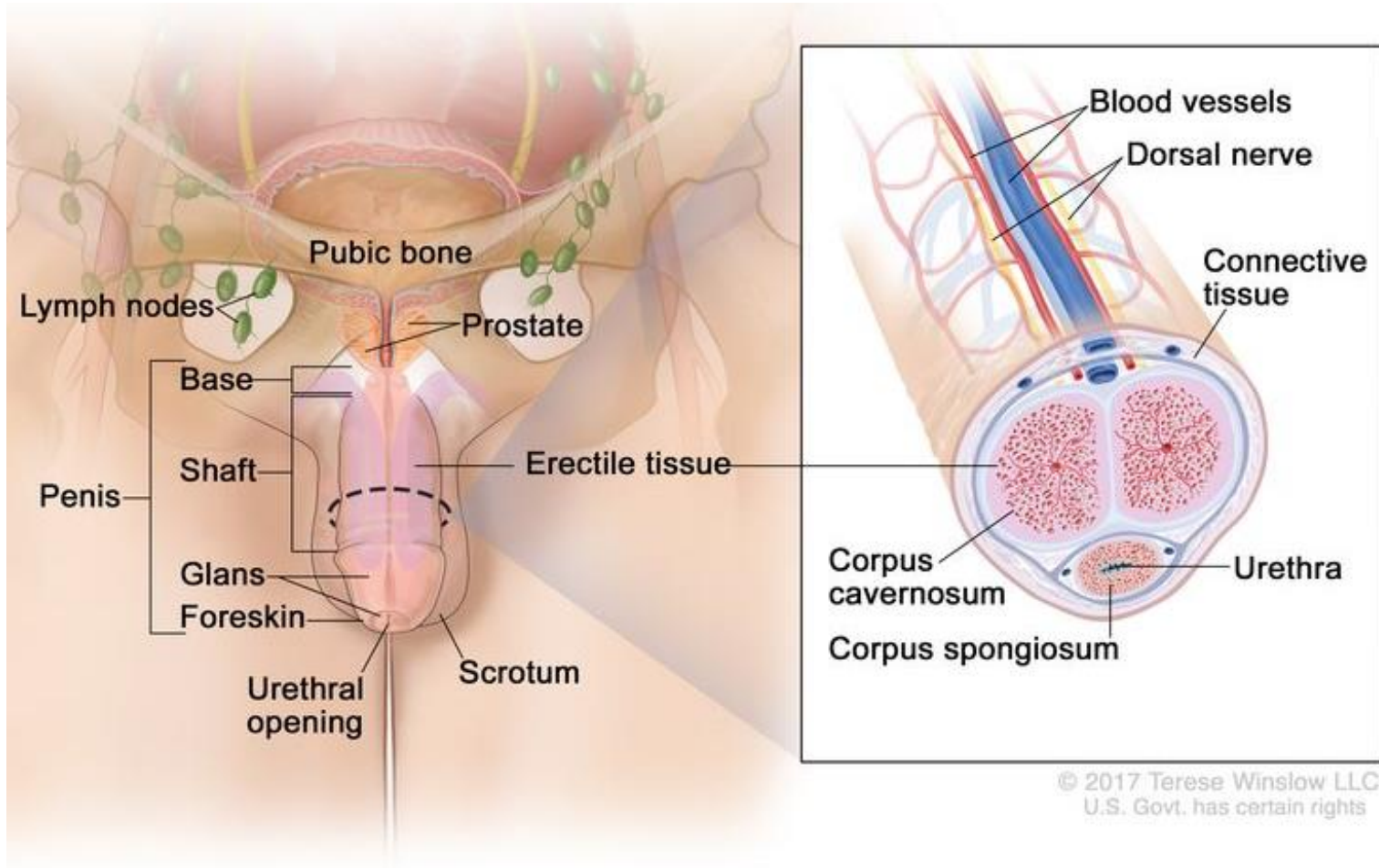
Statistics

- US ~2,100 cases/yr in 2023 (0.1% of all solid tumors)
- Worldwide incidence 0.80 per 100,000 in 2018
 - Predicted to increase by >50% by 2040 (due to aging population)
- Median age= 60yo
- ~95% SCC
 - Usual subtype most common, others include warty, papillary, basaloid, sarcomatoid

Background & Characteristics

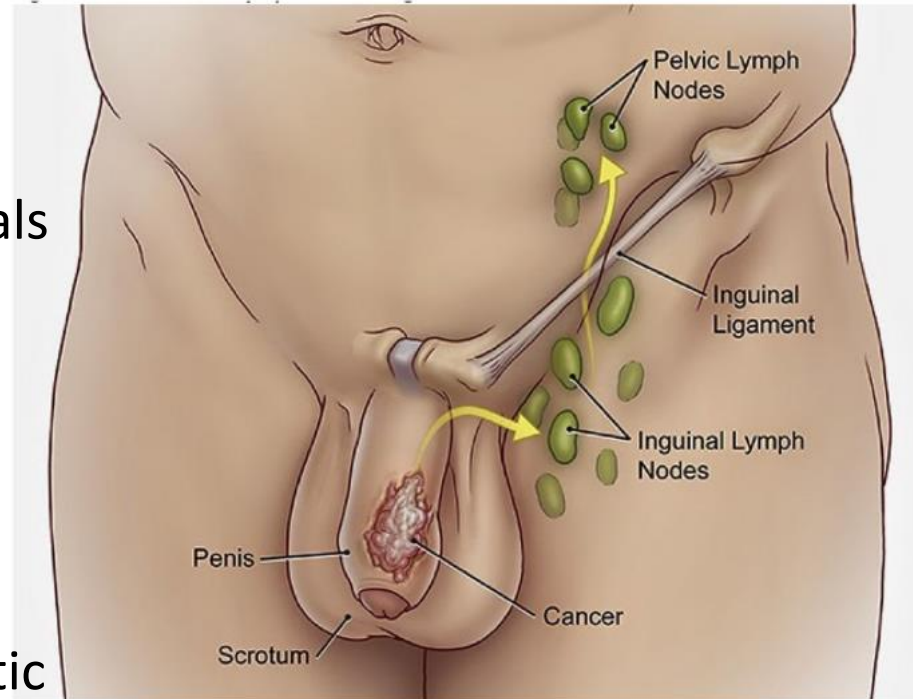
- Risk factors
 - HIV, HPV, phimosis, tobacco use, lichen sclerosis, uncircumcised
- Precancerous lesions/ddx
 - Bowen disease: solitary red plaque on follicle-bearing shaft epithelium
 - Erythroplasia of Queyrat: on glans/prepuce (~10% with invasive dz at dx)
 - Bowenoid papulosis: HPV-mediated papules on penile shaft

Anatomy of the Penis



Lymphatics

- Local >> distant spread
- Penile skin → inguinals
- Glans & corporal tissue → inguinals or iliacs
- Pelvic nodes rarely involved without inguinal involvement
- Presence and extent of nodal involvement = most imp prognostic factor



General Approach to Management

- Tis or Ta: topical 5-FU, imiquimod, or excision
- T1a: WLE, PP, or RT
 - G1, no LVSI= observe groins
 - G2, no LVSI= SLNBx
 - 1+ w/o ENE, observe
 - $\geq 2+$ or ENE, LND
- T1b: WLE, PP, TP, RT, or CRT
 - G3/4 or LVSI= B/L inguinal LND
- T2+: PP, TP, RT, or CRT
 - Organ preservation= IFLND -> brachytherapy (consider ENI if cN0 and no IFLND)

T/N/M	Tis; Ta	Ta1	T1b	T2	T3	T4
N0	0is; 0a	I	IIA	IIA	IIB	IV
N1		IIIA	IIIA	IIIA	IIIA	IV
N2		IIIB	IIIB	IIIB	IIIB	IV
N3	IV	IV	IV	IV	IV	IV
M1	IV	IV	IV	IV	IV	IV

ENI= elective nodal irradiation; IFLND= inguinofemoral lymph node dissection; PP= partial penectomy; TP= total penectomy; WLE= wide local excision

General Approach to Management (cont.)

- Histopathologic grouping for risk of nodal involvement
 - Low, 14.3%
 - Intermediate, 52.6%
 - High, 83.7%
- LAD is due to inflammation 30-50% of the time
- Up to 25% of non-palpable nodes harbor micromets.
 - Up to **25% of cN0 are pN+**
 - Only **~50% of cN+ are pN+**
- Follow up
 - Penectomy & nodal dissection= q6m x2y then q12m x3y
 - Penile sparing without LND= q3m x2y then q6m x3y

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Radiation Management

- Indications for Brachytherapy:
 - Tumor size <4 cm, depth of invasion <1 cm of corpora cavernosa, and typically all T1-T2 lesions with select T3 lesions.
- For more advanced lesions:
 - EBRT or EBRT + CHT or BT boost.

Non-Palpable Inguinal Nodal Management

Risk Category	Primary Tumor	Management
Low	pTis, T1, G1 and no LVSI	Surveillance
Intermediate	pT1a, G2, no LVSI	SLNBx <ul style="list-style-type: none"> - If (-) → surveillance - If 1 LN+, no ENE → complete inguinal LND - If ≥2 LN+ or ENE → completed inguinal & pelvic LND
High	pT1b or higher (G3 or LVSI)	SLNBx or modified inguinal LND <ul style="list-style-type: none"> - If LN- → surveillance - If 1 LN+, no ENE → complete inguinal LND - If ≥2 LN+ or ENE → complete inguinal or pelvic LND

Palpable Inguinal Nodal Management

Clinical scenario	Management
Single enlarged LN <4 cm Low-risk primary (Tis, T1, G1)	If FNA (-) → excisional biopsy If FNA (+) → complete inguinal LND <ul style="list-style-type: none"> - If 1 LN+, no ENE → surveillance - If 2+ LN+ or ENE → pelvic LND
Single enlarged LN <4 cm, High-risk primary (pT1 or higher with G3 or LVSI)	If FNA (-) → modified inguinal LND If FNA (+) → completed inguinal LND <ul style="list-style-type: none"> - If 1 LN+, no ENE → surveillance - If 2 LN+ or ENE → pelvic LND
Multiple or bilateral enlarged LNs	If FNA (-) → superficial inguinal LND If FNA (+) → complete LND OR neoadjuvant TIP (4C) followed by surgery

Pelvic Nodal Management

	Management
Biopsy positive	If surgical candidate → NA TIP* CTX +/- consolidation surgery If not surgical candidate → CRT

***TIP:**

Paclitaxel 175 mg/m² IV over 3 hours on Day 1

Ifosfamide 1200 mg/m² IV over 2 hours on Days 1–3

Cisplatin 25 mg/m² IV over 2 hours on Days 1–3

Repeat every 3 to 4 weeks

Indications for TIP

Type	Indications
Neoadjuvant	Unresectable primary tumors Bulky inguinal LN+ Bilateral inguinal LN+
Adjuvant	Pelvic LN+ ENE Bilateral inguinal LN+ >3 LN+
Metastatic	Good PS

XRT Notes

- Circumcise before treating!
 - To help visualize the tumor as well as minimize radiation side effects such as balanitis, phimosis, painful necrosis and ulceration.
- Finish within 45 days of starting, & treat with doses > 60 Gy
- High locoregional failure rates in general
 - Limited evidence suggest high recurrence even with adjuvant EBRT for LN+
- Setup
 - Supine, +foley, with immobilizing bolus
 - Frog leg if treating inguinal nodes
 - Prone with water bath

Dose and Technique

- Dose
 - Penile shaft 45 to 50 Gy with boost 65 to 70 Gy to GTV + 2cm
 - Elective nodal volume 45 to 50.4 Gy with GTV boost to 65 to 70 Gy
- Plan
 - 3D or IMRT using conventional beam arrangements

Toxicity

- Acute: urethral mucositis, edema, dermatitis
- Late: telangiectasia, necrosis, urethral stricture, meatal stenosis, sterility
- Brachytherapy:
 - Penile necrosis 3-15%. Higher with IS brachy and doses > 60 Gy
 - Penile V125 < 40%, V150 < 20% to limit penile necrosis
 - Urethral stricture 10-40%
 - Urethra V115 < 10%, V90 < 95% to limit urethral strictures
- Doses > 60 Gy associated with urethral stenosis and fibrosis
- LND side effects: edema, wound complications, DVT

Indications for XRT

Group	RT Treatment Options	Dose
T1-T2 N0 < 4 cm	Brachy alone or EBRT or CRT (primary +/- LNs)	65 – 70 Gy to primary lesion with 2-cm margin
T1-T2 N0 > 4 cm	Definitive CRT (primary site + LNs)	45 – 50.4 Gy to GTV + LNs with boost to 60-70 Gy with concurrent cisplatin.
T3-4 or N+	Definitive CRT (primary site + LNs)	
Resected with positive margins	Adjuvant EBRT to primary site and surgical scar +/- LNs if inadequate LND	
Resected LN+ 2+ or ENE	Adjuvant CRT to primary site and regional LNs, including pelvic LNs	
Any stage	Palliative	30 in 10 or alternative regimen

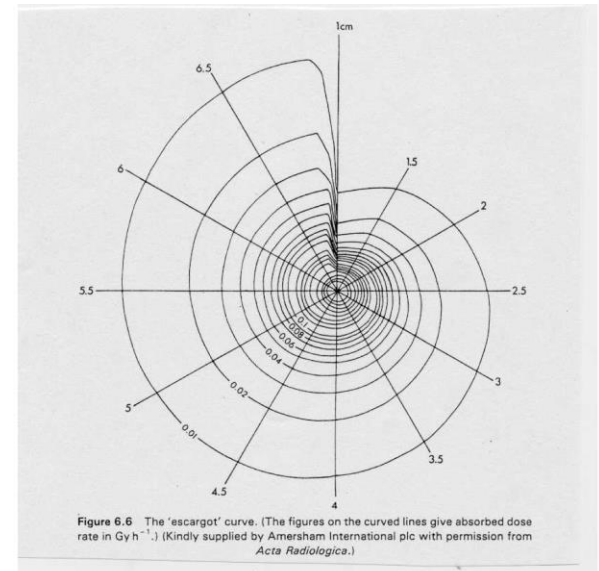
Essentials of Clinical Radiation Oncology, 2nd Ed. Sittenfeld, Ward, Tendulkar, Eidetic. 2021.
NCCN Guidelines Version 1.2023 Penile Cancer

Brachytherapy

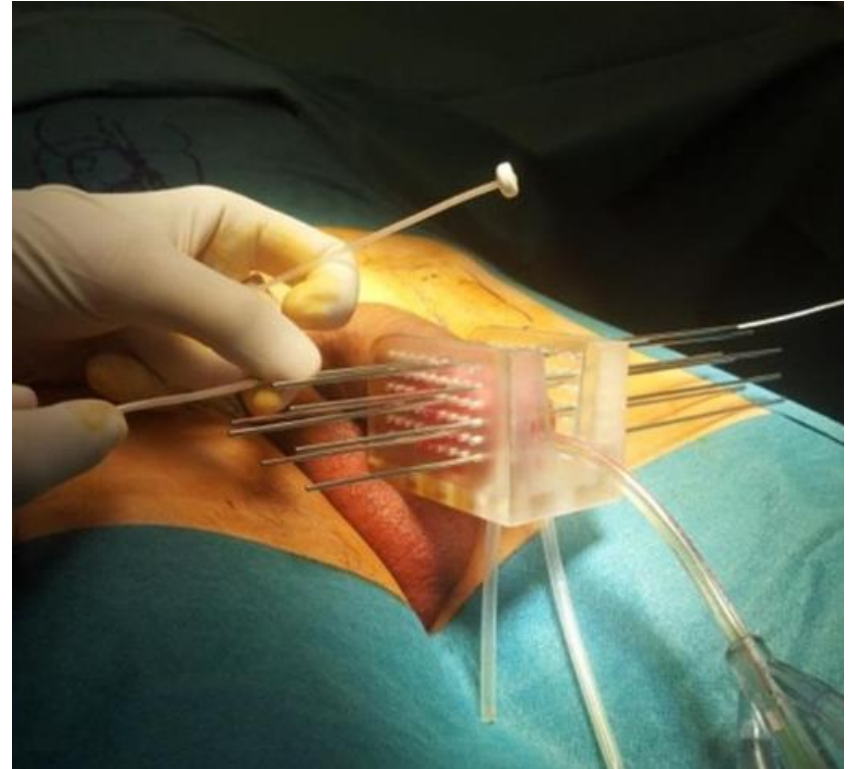
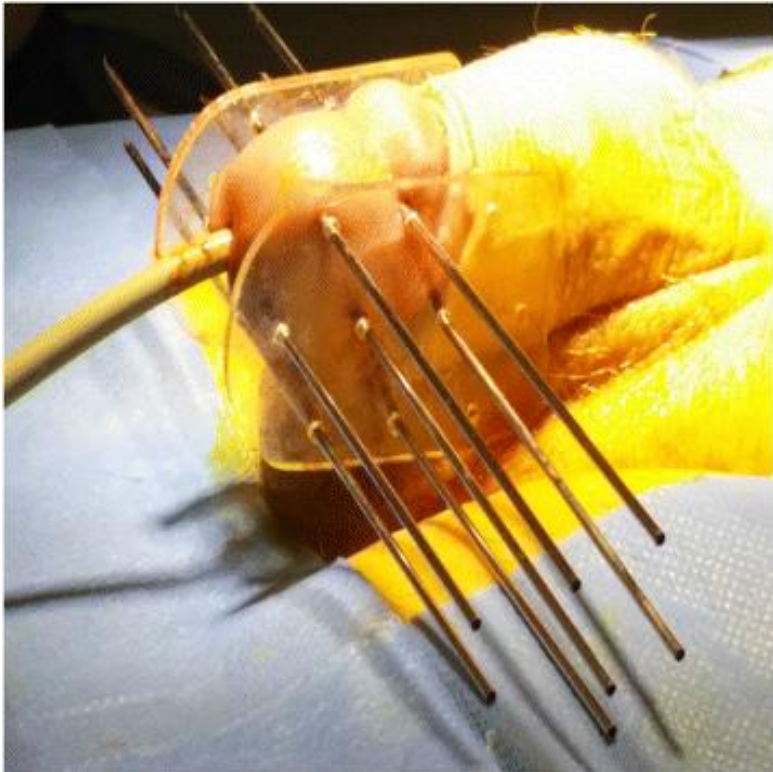
- Recall typically indicated for tumors <4 cm, DOI <1 cm T1-T2 lesions and select T3 lesions.
- Performed under general anesthesia or penile block with systemic sedation
- Foley catheter assists with urethral localization
- Paris system of dosimetry (**LDR and PLDR**)
 - System to define implant geometry
 - Prescription IDL encompasses the visible and palpable tumor
 - 1 cm margins around GTV = CTV
 - 2-3 planes of needles/catheters is sufficient
 - 14-16 mm spacing preferred

Brachytherapy

- Principles of the Paris System
 - Sources should be parallel and arranged so that their centers are in the same plane, the “central plane”.
 - The linear reference kerma rate (linear activity) should be uniform along each source and the same for all sources.
 - The radioactive sources should be equidistant. (Single plane or patterns in squares or triangles.)



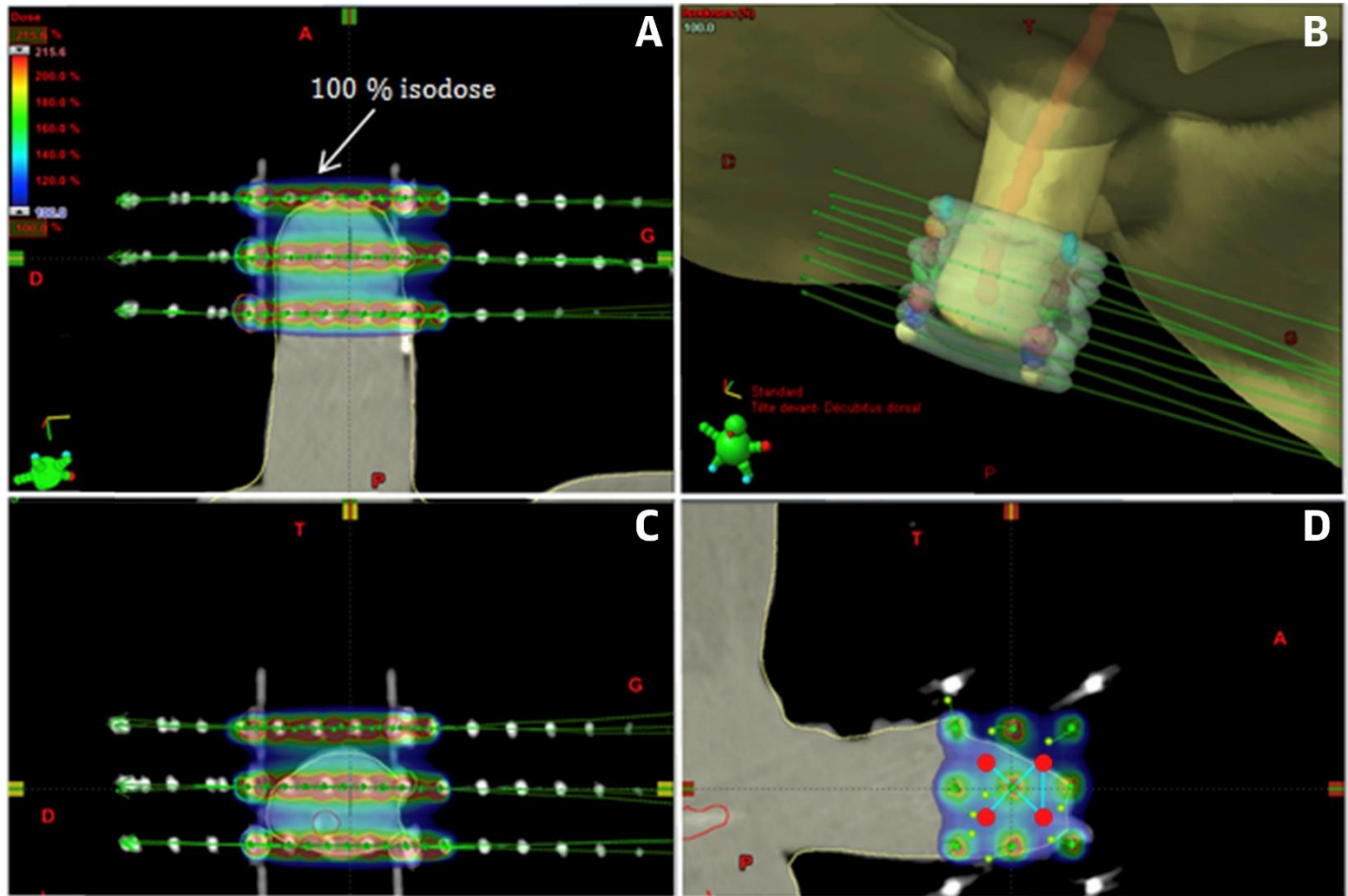
Brachytherapy



Cordoba et. al; Radiation Oncology 11, 96 (2016)
Rouscuff et. al; Radiation Oncology 9, 142 (2014)

Brachytherapy – LDR or PDR

60 Gy was prescribed at the reference isodose (85% of the basal isodose).



Escande et, al IJROBP 2017

February 6, 2023

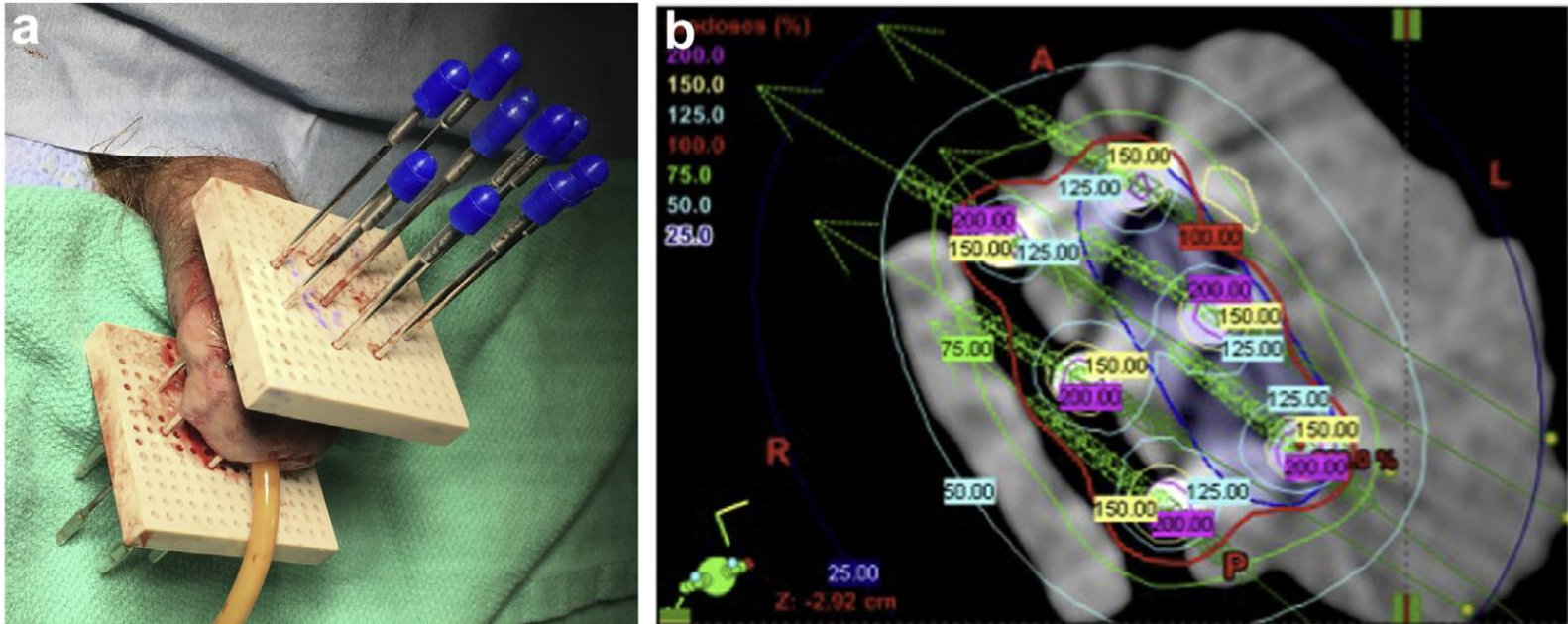
ASSOCIATION OF RESIDENTS IN RADIATION ONCOLOGY



Brachytherapy – HDR

- Dose ranged from 38.4 Gy BID in 6 days (3.2 Gy x 12) to 53 Gy BID in 9 days (3.12 x 17)

M. Marbán et al. / Brachytherapy 19 (2020) 201–209



Brachytherapy

Study	N	Dose	Outcomes	Toxicity	Other
French trial de Crevoisier 2009 IJROBP	144	65 Gy LDR Iridium needles	10y penile recurrence 20% 10y ILN recurrence 10%	10y painful ulceration 26% 10y stenosis 29%	Diameter of tumor correlates with local failure rate: <4cm= 20% >4cm= 55%
PMH RR Crook 2005 IJROBP	49	60 Gy IBT/PDR	5y OS 78% 5y CSS 90% 5y penile preservation 87%		
British Columbia Marban 2020 Brachytherapy	15	HDR (n=8) Surface mold (n=7)	HDR, ~7y OS and CSS 100% HDR, 1 local failure salvaged by PP and PLND Mold, 2y OS 87.5%; CSS 100%	HDR= G2 necrosis 43%; G2 meatal stenosis 29%; G3 stenosis 14%	HDR Penile preservation 86% Mold, penile preservation 87.5%
French RR Cordoba Radiation Oncology 2016	73	60 Gy IBT	5y OS 82% 5y CSS 91.4% 5y RFS 64.4% 5y LRFS 74%	Urethral stenosis 6.6% Painful sex 2.6% G2 dysuria 5.3% Penile amputation for necrosis 6.8%	Total or partial penile preservation 88% at 5y

Surgery Considerations

- **4 – 6 cm** of corpus cavernosum needed for ~50% of men to have **sex**
- **~2.5 – 3 cm** required to be able to **urinate in the standing position**
- Psychological trauma is common
 - Increased incidence of suicide after penectomy
 - Consider referring for counseling

Case Presentation (cont.)

- Simulation:
 - Supine in a mold with right leg frogged in mold, scrotal shields with folded towel underneath, penis to the side in a small mold with 1cm bolus over right groin.
- Treatment:
 - Definitive chemoradiation to penis, bilateral groins, and pelvis
 - 66 Gy in 33 daily fractions using IMRT plan followed by sequential boost to gross disease using 2D electrons to 70 Gy in 35 fractions, with concurrent cisplatin 75 mg/m² for 2 cycles.
 - TLDs were placed once weekly.

Case Presentation (cont.)

- During treatment he developed grade 2 dermatitis, penile pain, suprapubic pain, and mild diarrhea.
- In the next 12-16 months following therapy, he remains disease free, although unfortunately with fibrosis affecting quality of life with stenotic urethral meatus and difficulty urinating. He's also with ongoing penile edema and pain.
- He has been recommended suprapubic catheter placement or palliative penectomy to manage ongoing symptoms for which patient is reluctant to undergo either procedures.

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