Rare GU Tumors (Penile Cancer)

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Management of Inguinal Lymph Nodes in Patients with Penile Cancer *and* No Palpable Adenopathy *or* Non-Bulky Lymph Nodes (<3-4 cm)

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3 Take Home Messages

- Very difficult to salvage bad decision making, or bad surgery for penile cancer (groin)
- Our risk assessment tools are imperfect
- **Err on the side of DOING a groin dissection**

AJCC Update on Staging -8th edition

- **Histology matters**
- Best: verrucous carcinoma, pseudohyperplastic carcinoma, and carcinoma cuniculatum have the best prognosis
- *Worst: basaloid and sarcomatoid carcinomas have the worst prognosis*
- Intermediate: warty and papillary carcinoma, not otherwise specified
- HPV genotypes high risk 16/18
- P16 protein positive patients do better

AJCC 8th Ed 2018
NODES – Important changes

- **7th Edition**
- **pN0 =No lymph node metastasis**

- **pN1 Metastasis in a single inguinal lymph node**

- **8th Edition**
  pN0 =No lymph node metastasis

- **pN1= ≤2 unilateral inguinal metastases, no extra-nodal extension**

https://handouts.uscap.org/AN2017/2017_CM05_Tambo_0701_post.pdf

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Advanced Nodal Disease in Penile Cancer

- 7th Edition
- pN2
- Metastasis in multiple or bilateral inguinal lymph nodes
- pN3
- Extra-nodal extension of lymph node metastasis or pelvic lymph node(s) unilateral or bilateral

- 8th Edition
- pN2
  ≥3 unilateral metastases
  or
- bilateral metastases

- pN3
  Extra-nodal extension OR pelvic lymph node metastases

https://handouts.uscap.org/AN2017/2017_CM05_Tambo_0701_post.pdf

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Staging 8th ed update 2018

- **T- Primary Tumor**
  - **Tis Carcinoma in situ**
  - **Ta Non-invasive verrucous carcinoma**
  - **T1 Tumor invades subepithelial connective tissue,**
    - **T1a not poorly differentiated, no lymphovascular invasion, no perineural invasion**
    - **T1b poorly differentiated OR lymphovascular invasion, OR perineural invasion**
  - **T2 Tumor invades corpus spongiosum +/-urethra**
  - **T3 Tumor invades copora cavernosa +/-urethra**
  - **T4 Tumor invades other adjacent structures**
- **N - Regional lymph nodes CLINICAL**
  - **N0 No evidence of palpable or visibly enlarged lymph node metastasis**
  - **N1 Palpable mobile inguinal node**
  - **N2 Palpable mobile multiple or bilateral inguinal node**
  - **N3 Palpable FIXED inguinal nodes or pelvic adenopathy unilateral or bilateral**
- **M - Distant metastasis**
  - **M0 No evidence of distant metastases**
  - **M1 Distant metastases**

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Clinical Staging 8th ed update 2018

- **T- Primary Tumor**
  - **Tis Carcinoma in situ**
  - **Ta Non-invasive verrucous carcinoma**
  - **T1 Tumor invades subepithelial connective tissue,**
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- **N - Regional lymph nodes CLINICAL**
  - **N0 No palpable or visibly enlarged lymph node**
  - **N1 Palpable mobile UNILATERAL inguinal node**
  - **N2 Palpable mobile ≥2 unilateral or BILATERAL inguinal nodes**
  - **N3 Palpable FIXED inguinal nodal mass or pelvic adenopathy unilateral or bilateral**
- **M - Distant metastasis**
  - **M0 No evidence of distant metastases**
  - **M1 Distant metastases**

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Pathologic Staging 8th ed update 2018

- **T- Primary Tumor**
  - **Tis Carcinoma in situ**
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  - **T1 Tumor invades subepithelial connective tissue,**
    - **T1a not poorly differentiated, no lymphovascular invasion, no perineural invasion**
    - **T1b poorly differentiated OR lymphovascular invasion**
  - **T2 Tumor invades corpus spongiosum +/-urethra**
  - **T3 Tumor invades copora cavernosa +/-urethra**
  - **T4 Tumor invades other adjacent structures**
- **N - Regional lymph nodes ~~PATHOLOGICAL~~**
  - **N0 No lymph node metastasis**
  - **N1 metastases in ≤2 inguinal inguinal node, No ENE**
  - **N2 ≥3 unilateral OR bilateral inguinal inguinal nodes, No ENE**
  - **N3 Extranodal extension OR pelvic adenopathy, unilateral or bilateral**
- **M - Distant metastasis**
  - **M0 No evidence of distant metastases**
  - **M1 Distant metastases**

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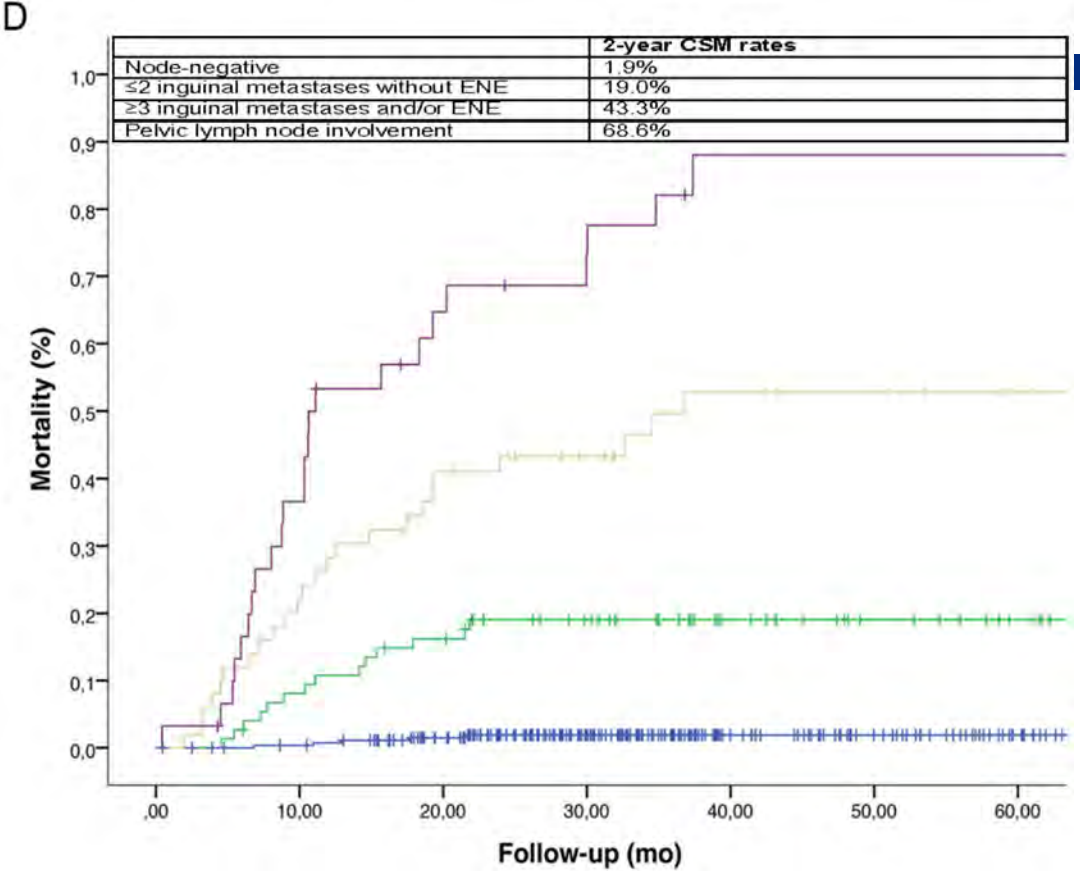
Penile Cancer Guidelines recently updated –emphasis on nodes

- EAU 2010, updated 2014, *Eur Urol 2015 67:142*
- **'Management of the Regional Lymph Nodes is decisive for long term survival. Cure can be achieved in metastatic disease confined to the regional LN's' –look for upcoming ASCO/EAU guidelines**

- NCCN 2022 (Flaig, Spiess, et al)
- 'The presence and extent of regional inguinal lymph node metastases has been identified **as the single most important prognostic indicator** in determining long-term survival in men with invasive penile SCC

D

	2-year CSM rates
Node-negative	1.9%
≤2 inguinal metastases without ENE	19.0%
≥3 inguinal metastases and/or ENE	43.3%
Pelvic lymph node involvement	68.6%



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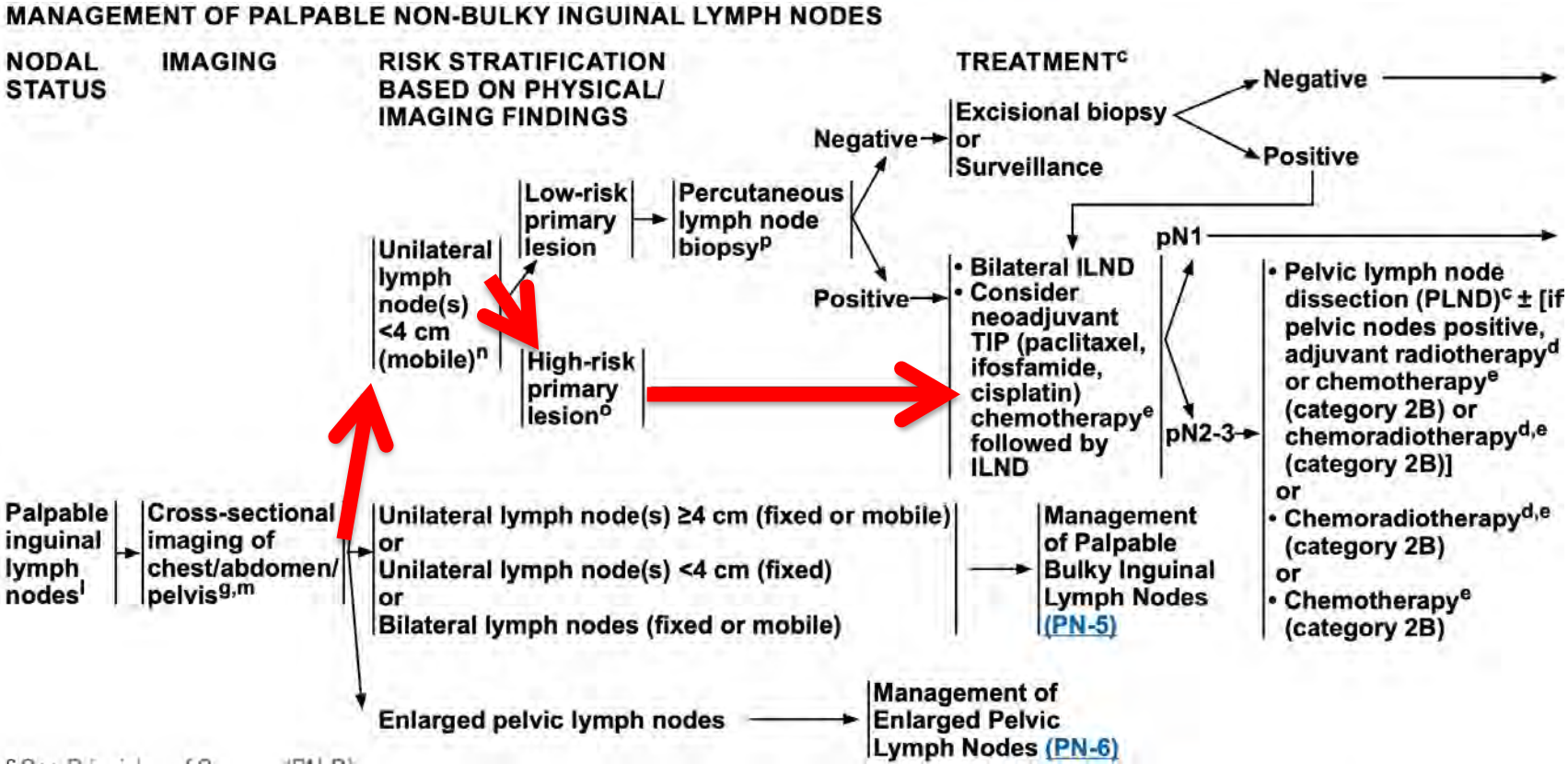
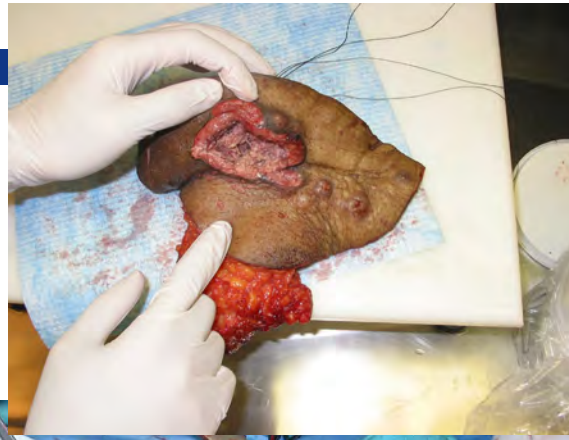
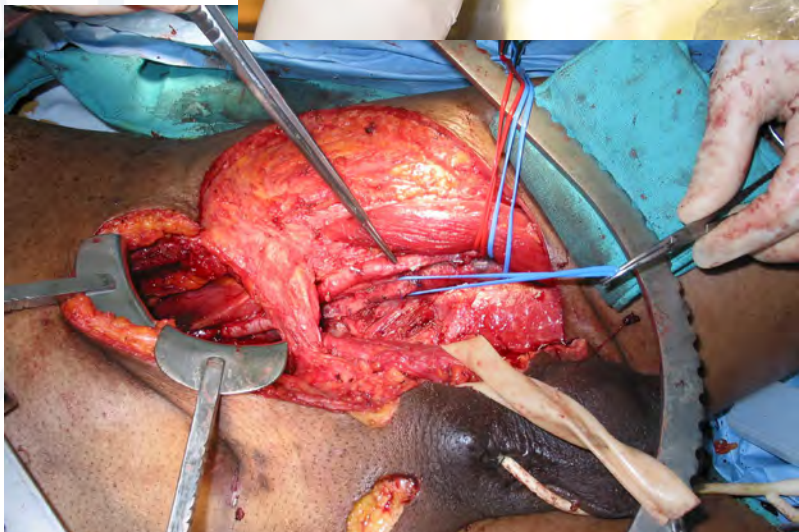
2022 NCCN guidelines
Palpable (NON-bulky [<?3-4cm] nodes)



What about Antibiotics?

- NOT part of either guideline!





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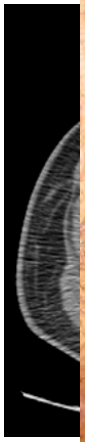
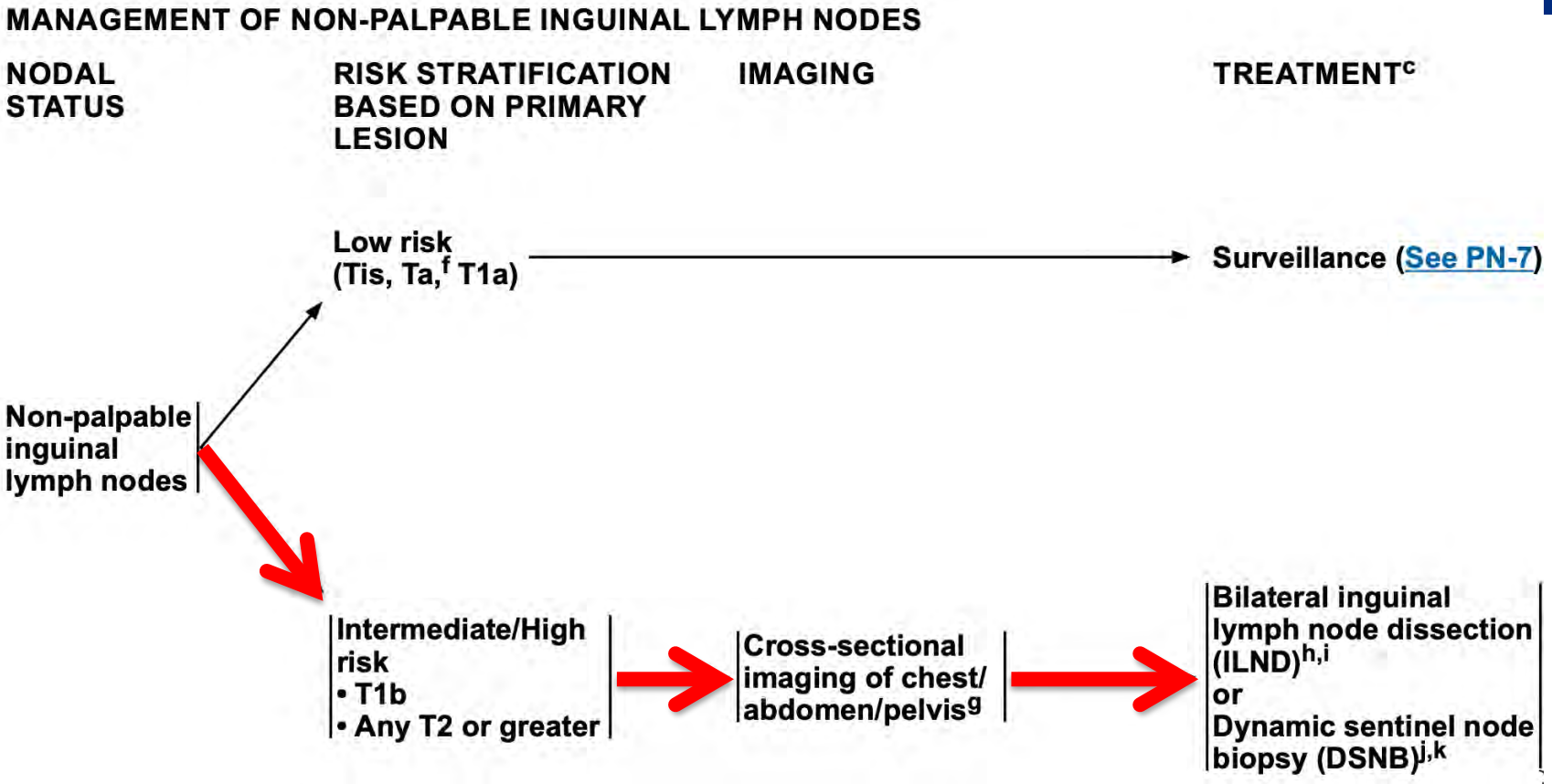


2022 NCCN guidelines
Non-palpable disease/cN0



What are ‘High Risk’ Penile Tumors?

- **≥pT1b or ≥pT2**
- **Vascular Invasion/Perineural Invasion**
- **Poorly differentiated**

AJCC 8th edition 2018 staging system

Magnon C et al Science 2013 – prostate cancer

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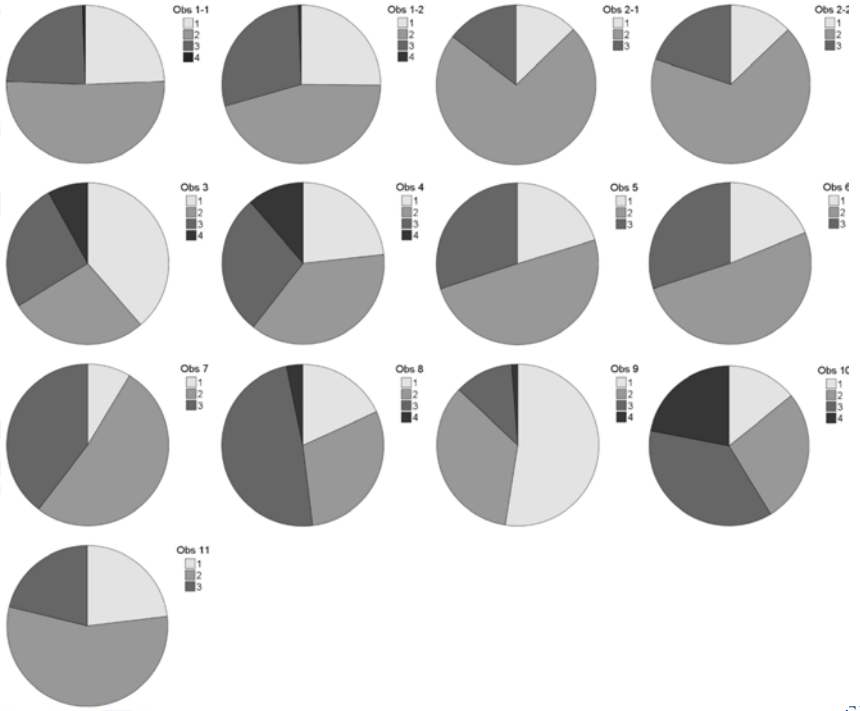
But how accurate is our ability to really diagnose ‘high risk’ penile cancer?

Interobserver accuracy of grading penile cancer specimens is **not** good

- 90 penile SCC
- Multiple different uropathologists
- 5 different European countries

- G1 8.6 - 52.5 %
- G2 27.1 - 72.6 %
- G3 11.7 - 48.7 %
- G4 0.6 - 21.9 %

- Kappa = 0.34 (low agreement)



Kakies, C. Virchows Arch 2014

Non-palpable Groins may still harbor cancer

- 25% of impalpable groins have micro-metastatic disease

Kirrander P BJUI 2013
Djajadningrat RS Eur Urol Supp 2013 a394
Slaton JW J Urol 2001

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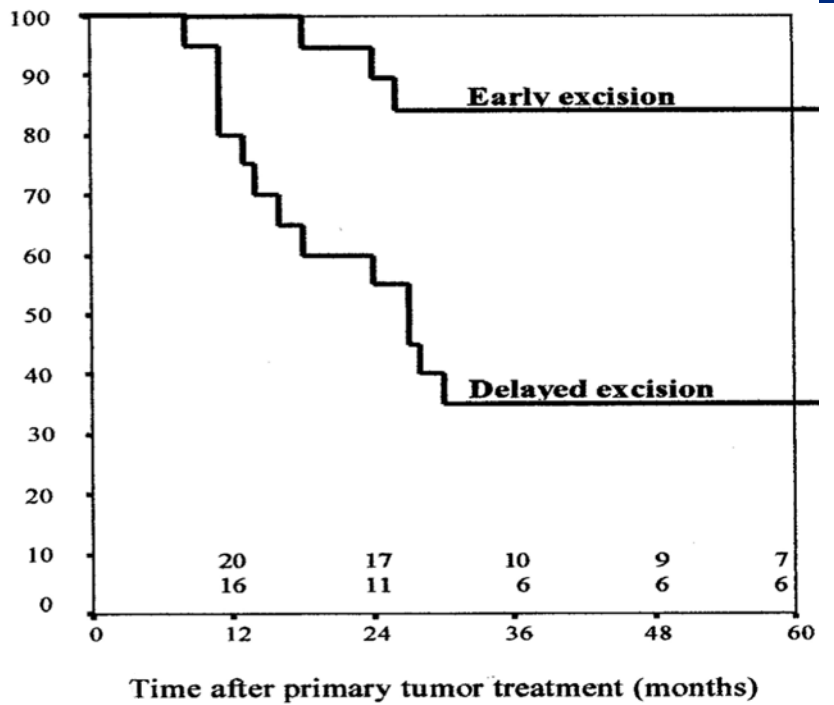
T1G2 with nonpalpable nodes - High proportion have cancer

- Retrospective review 20 pts
- 44% of cohort had lymph node mets

Naumann CM BJU 2008

Delayed Lymphadenectomy for cN0 inguinal nodes is not good

Variable	p Value	Hazard Ratio (95% confidence interval)
Clinical T-stage (T2 or T3)	0.57	1.50 (0.37–6.20)
Vascular invasion (absent or present)	0.97	0.98 (0.45–2.17)
Tumor grade (I or II/III)	0.82	1.14 (0.35–3.75)
Invasion depth (5 or less or greater than 5 mm)	0.89	1.09 (0.32–3.67)
Timing of lymphadenectomy (early or late)	0.006	0.17 (0.05–0.60)



Kroon BK. J Urol 2005

35% vs 84% 3 yr DSS p=.0016

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What about DSNB (Dynamic Sentinel Lymph Node Biopsy?

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DSNB (In the USA)

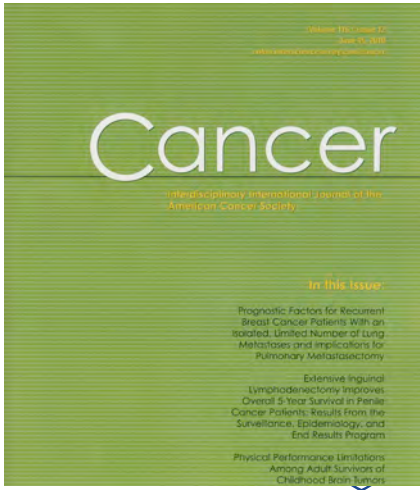
- DSNB should be limited to centers with experience
- Because of technical challenges, DSNB should be done at centers where at least 20 procedures/year are performed
- DSNB should not be done on patients with palpable LN's (do a groin dissection)

NCCN Guidelines

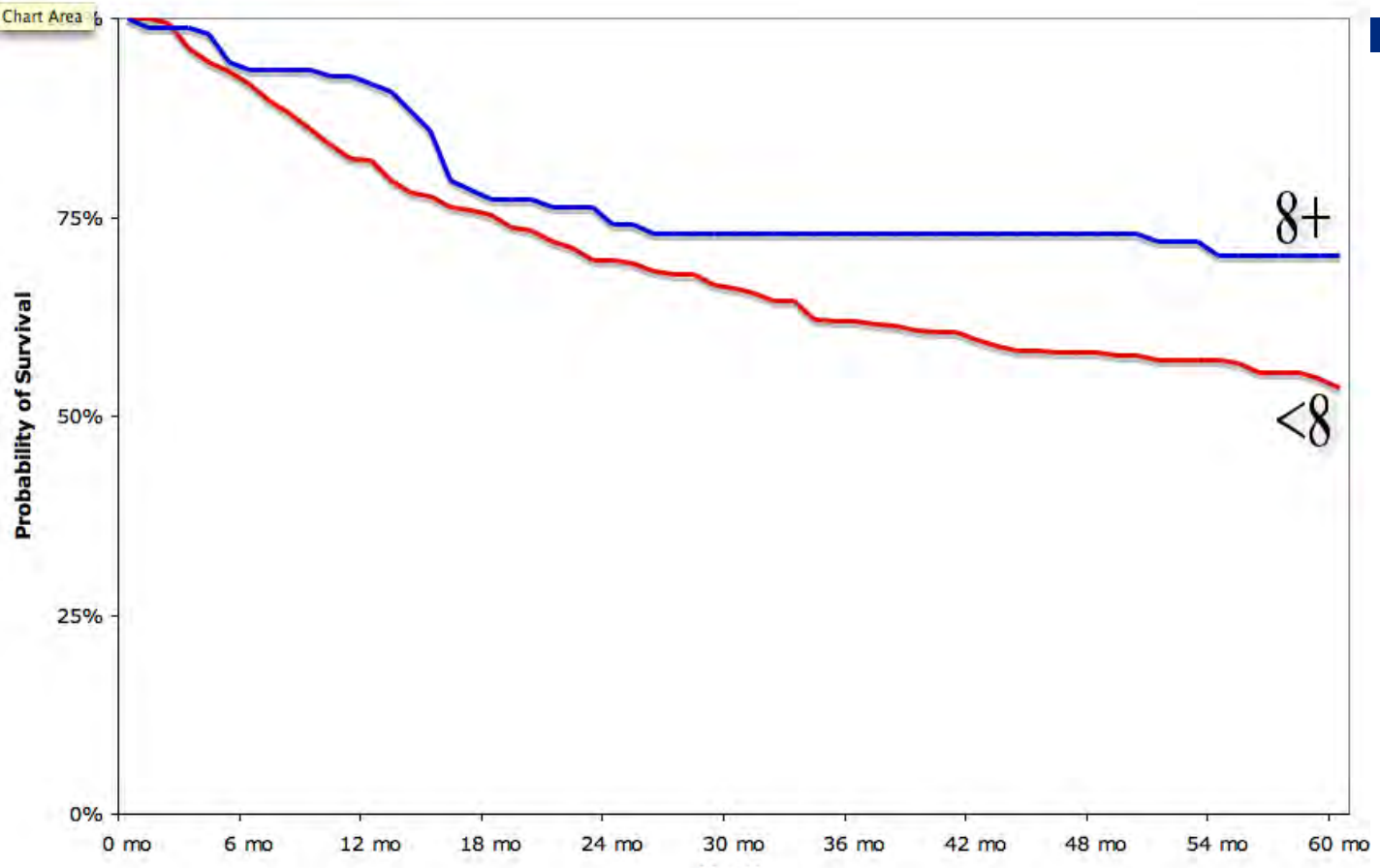
How many patients received appropriate indication LN dissection in the US?

- SEER
- 158 (26.5%) patients had inguinal sampling of at least one node:
  - 24 (4.1%) 1 lymph node,
  - 27 (4.5%) 2-7 lymph nodes
  - 107 (18.0%) ≥8 lymph nodes

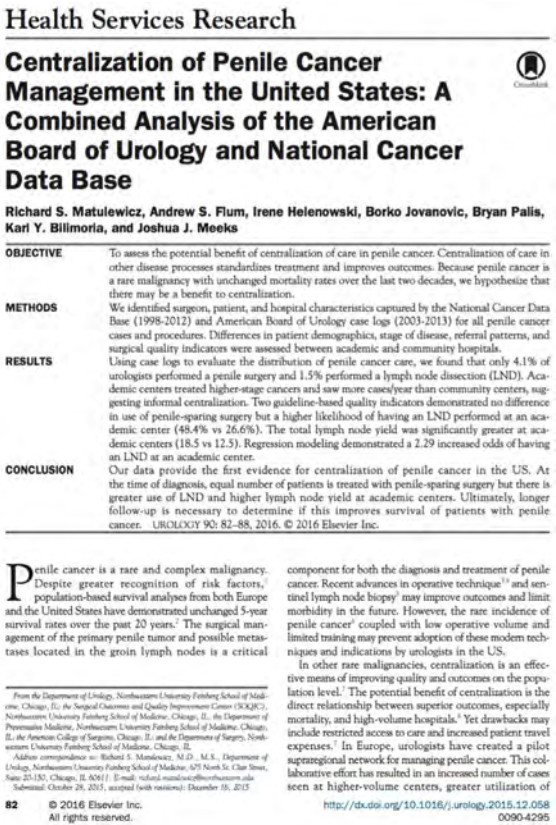
Johnson TV. Cancer 2010



Survival is improved for pT2-4Gx primary tumors with increased number of lymph nodes dissected



What about **current day**?



Health Services Research

Centralization of Penile Cancer Management in the United States: A Combined Analysis of the American Board of Urology and National Cancer Data Base

Richard S. Matulewicz, Andrew S. Flum, Irene Helenowski, Borko Jovanovic, Bryan Palis, Kari Y. Billimoria, and Joshua J. Meeks

OBJECTIVE To assess the potential benefit of centralization of care in penile cancer. Centralization of care in other disease processes standardizes treatment and improves outcomes. Because penile cancer is a rare malignancy with unchanged mortality rates over the last two decades, we hypothesize that there may be a benefit to centralization.

METHODS We identified surgeon, patient, and hospital characteristics captured by the National Cancer Data Base (1998-2012) and American Board of Urology case logs (2003-2013) for all penile cancer cases and procedures. Differences in patient demographics, stage of disease, referral patterns, and surgical quality indicators were assessed between academic and community hospitals.

RESULTS Using case logs to evaluate the distribution of penile cancer care, we found that only 4.1% of urologists performed a penile surgery and 1.5% performed a lymph node dissection (LND). Academic centers treated higher-stage cancers and saw more cases/year than community centers, suggesting informal centralization. Two guideline-based quality indicators demonstrated no difference in use of penile-sparing surgery but a higher likelihood of having an LND performed at an academic center (48.4% vs 26.6%). The total lymph node yield was significantly greater at academic centers (18.5 vs 12.5). Regression modeling demonstrated a 2.29 increased odds of having an LND at an academic center.

CONCLUSION Our data provide the first evidence for centralization of penile cancer in the US. At the time of diagnosis, equal number of patients is treated with penile-sparing surgery but there is greater use of LND and higher lymph node yield at academic centers. Ultimately, longer follow-up is necessary to determine if this improves survival of patients with penile cancer. UROLOGY 90: 82–88, 2016. © 2016 Elsevier Inc.

Penile cancer is a rare and complex malignancy. Despite greater recognition of risk factors,[1] population-based survival analyses from both Europe and the United States have demonstrated unchanged 5-year survival rates over the past 20 years.[2] The surgical management of the primary penile tumor and possible metastases located in the groin lymph nodes is a critical component for both the diagnosis and treatment of penile cancer. Recent advances in operative technique[3,4] and sentinel lymph node biopsy[5] may improve outcomes and limit morbidity in the future. However, the rare incidence of penile cancer[2] coupled with low operative volume and limited training may prevent adoption of these modern techniques and indications by urologists in the US.

In other rare malignancies, centralization is an effective means of improving quality and outcomes on the population level.[7] The potential benefit of centralization is the direct relationship between superior outcomes, especially mortality, and high-volume hospitals.[8] Yet drawbacks may include restricted access to care and increased patient travel expenses.[7] In Europe, urologists have created a pilot supraregional network for managing penile cancer. This collaborative effort has resulted in an increased number of cases seen at higher-volume centers, greater utilization of

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Address correspondence to: Richard S. Matulewicz, M.D., M.S., Department of Urology, Northwestern University Feinberg School of Medicine, 675 North St. Clair Street, Suite 20-150, Chicago, IL 60611. E-mail: richard.matulewicz@northwestern.edu

Submitted: October 28, 2015, accepted (with revisions): December 18, 2015

http://dx.doi.org/10.1016/j.urology.2015.12.058
0090-4295

- 26.6% of indicated patients had a groin dissection
- (more so in the academic centers, but still only 2x)
- Mean number of nodes dissected still under the quality threshold (>7)

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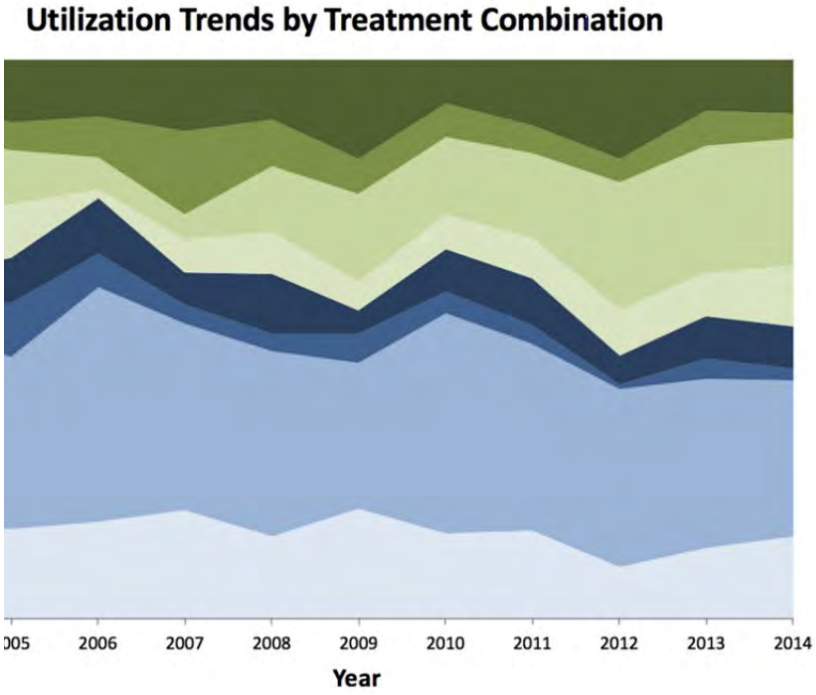
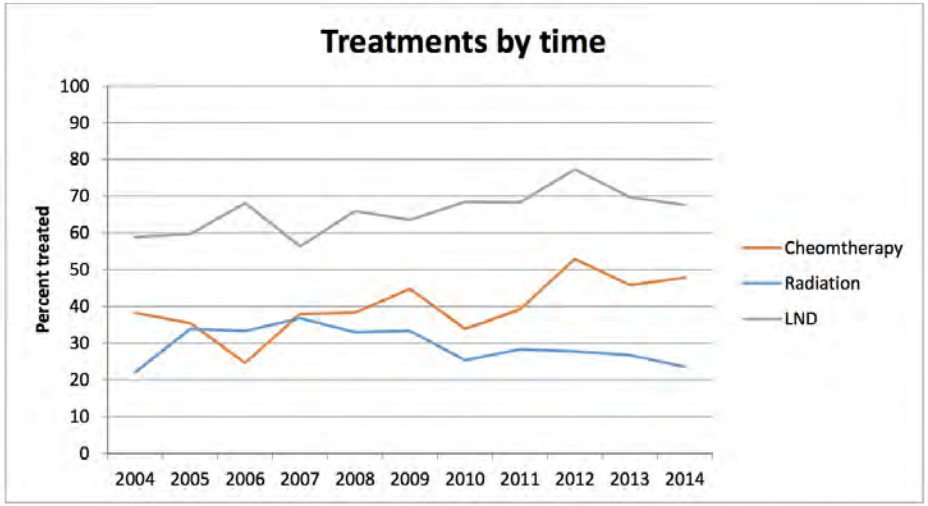
Multimodal Treatment Trends in the USA 2004-2014: Influence of LND





Joshi S et al, JAMA Oncol May 2018

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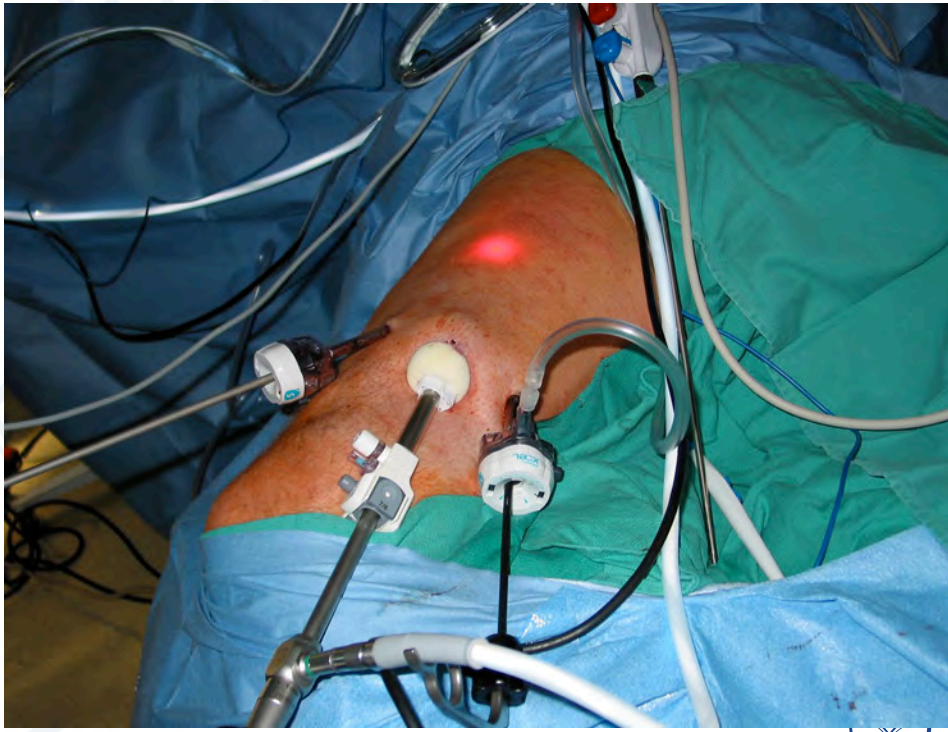
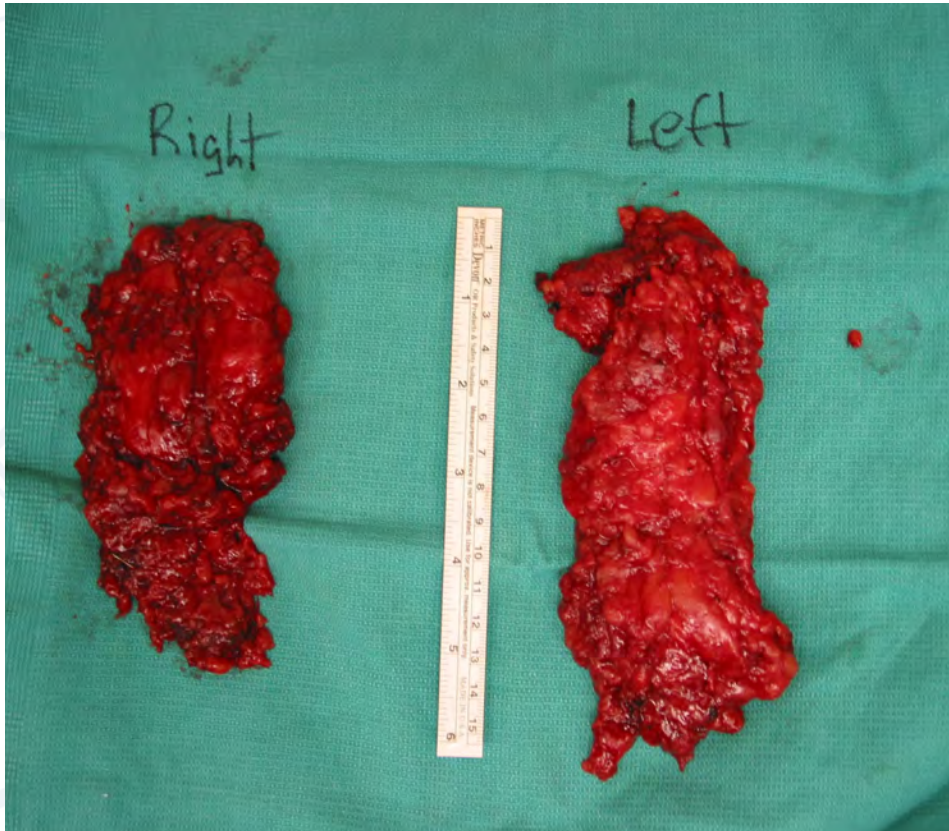
Open vs Videoscopic??

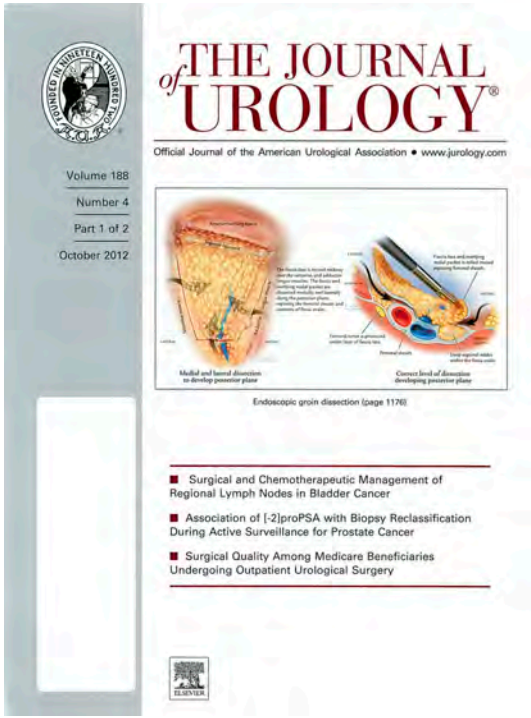


Simultaneous Bilateral Dissection



Herrel LA CJU 2014

Videoscopic Groin Dissection



Master VA, J Urol 2012

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Methods

- Patients with regional nodal metastases from any malignancy were offered the option of a videoscopic approach
- Patients were informed of the novel nature of the technique
- The first 5 patients also underwent direct inspection of the groin through the sentinel biopsy scar, which was excised as part of the procedure

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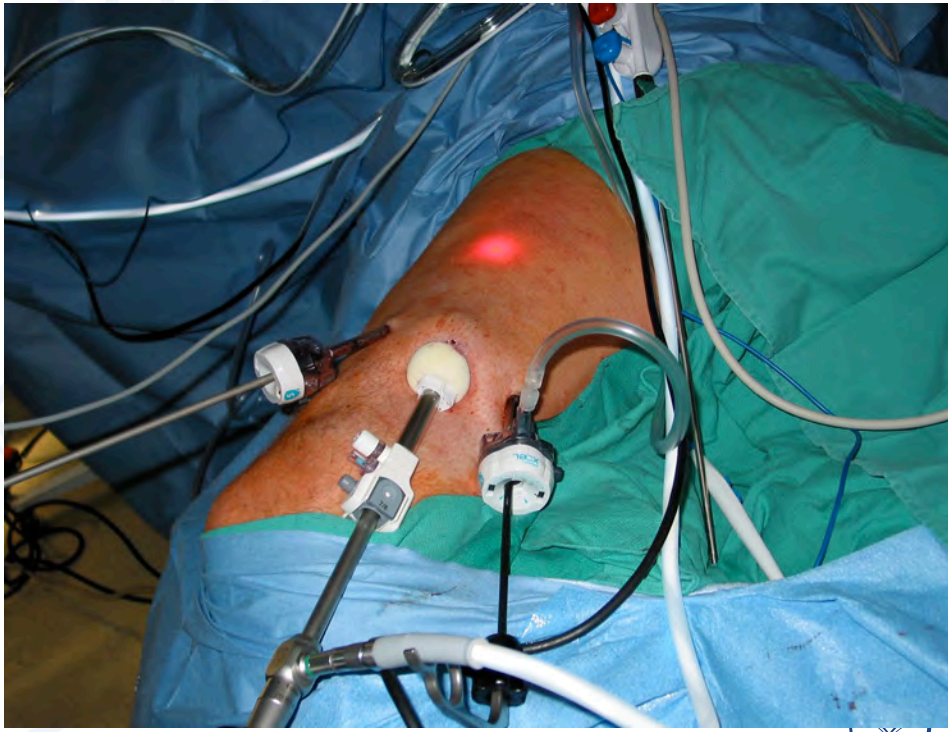
Getting Level 1 data

- A planned, randomized, prospective trial (NCT01526486, clinicaltrials.gov) was designed to compare technical, post-operative, and oncologic outcomes

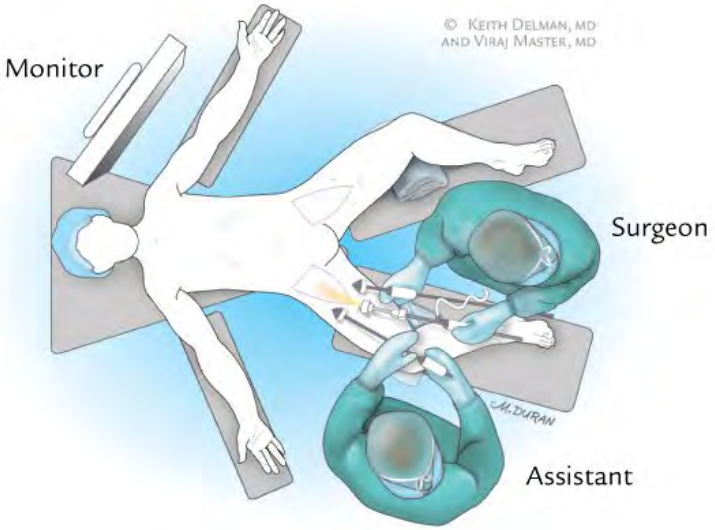
- **Failed** (important for modern surgical trials)
  - Accrual

Postlewait LM, Ann Surg Oncol 2017

Open vs Videoscopic??



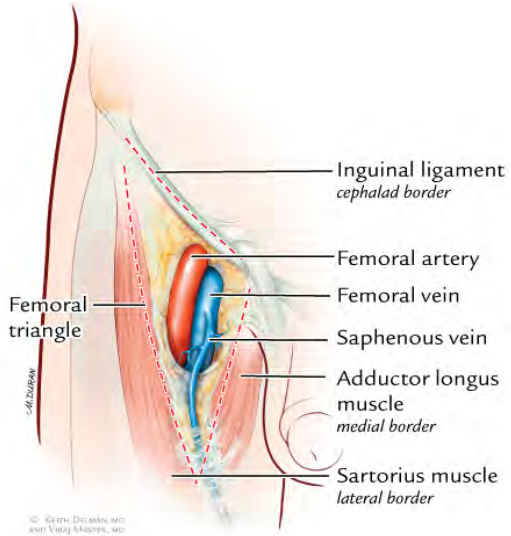
Positioning



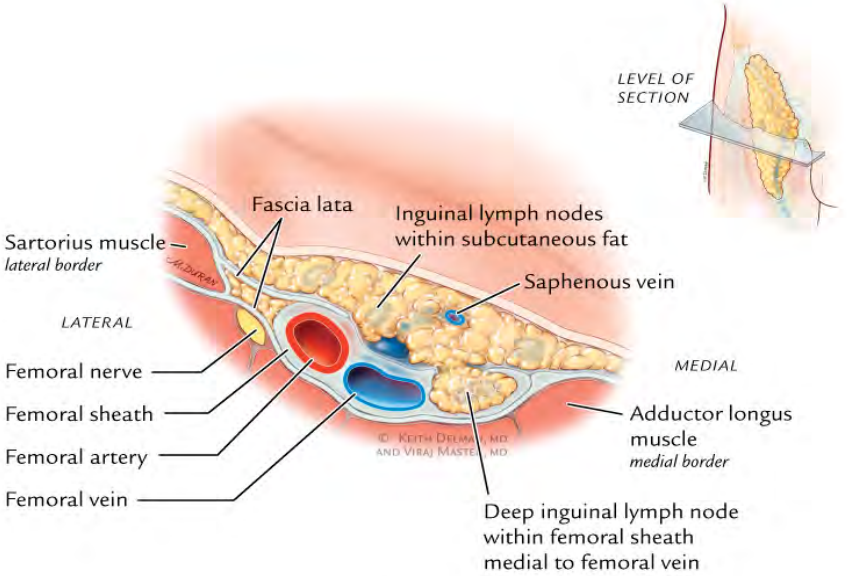
A Surgeon positioning in OR

B Patient positioning with split-leg table

Anatomic Landmarks

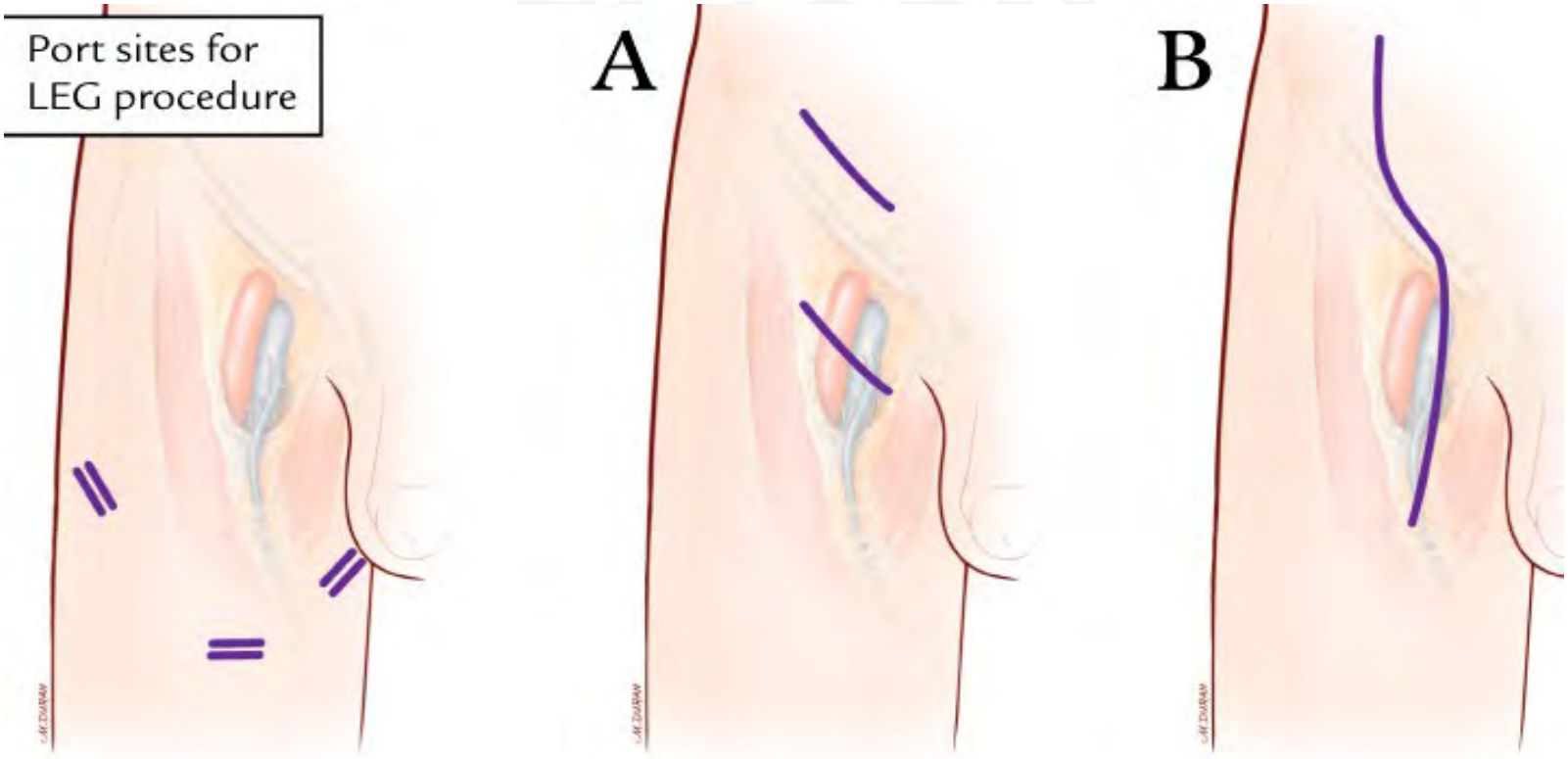


A Anatomy of femoral triangle

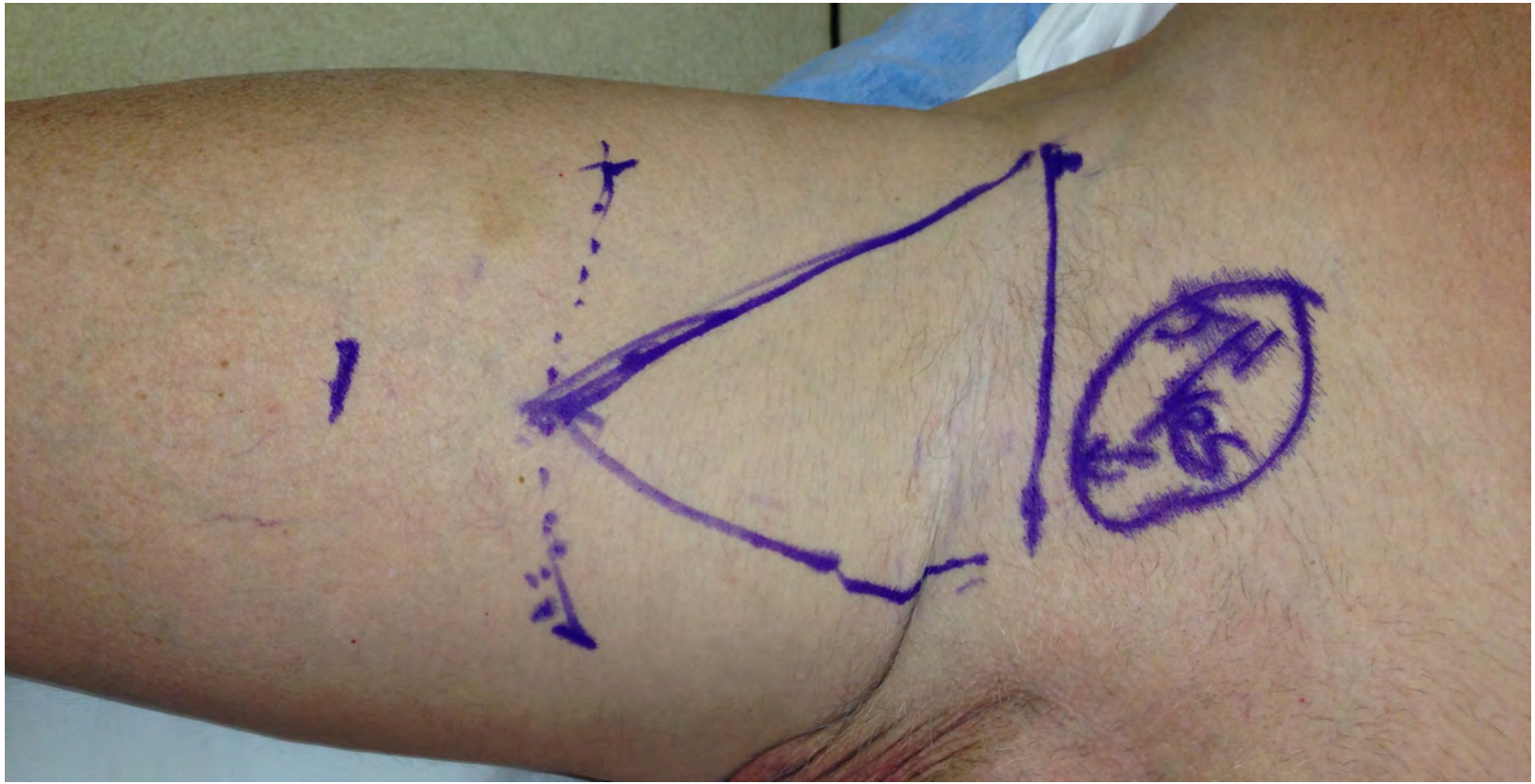


B Cross-sectional anatomy of right femoral triangle

Location of Ports



Port sites



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Port Sites

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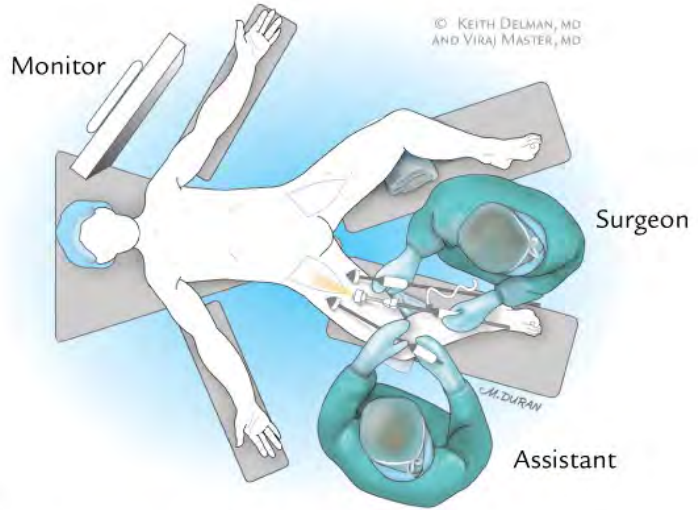
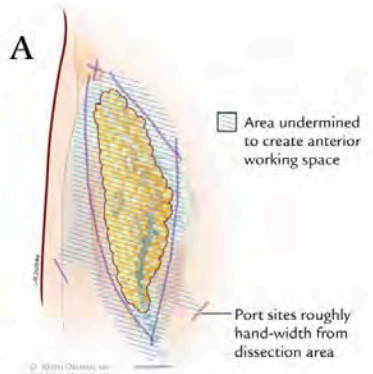
Surgeon Position – Two monitors helpful

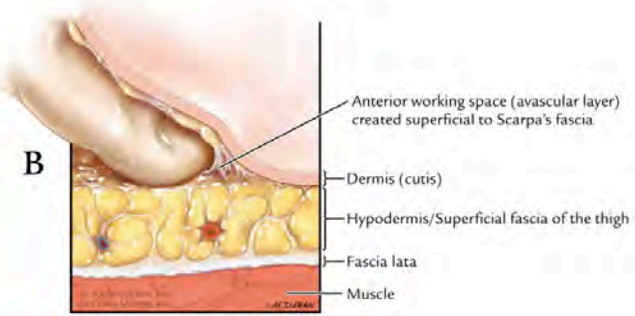


A Surgeon positioning in OR

Flaps



Port placement and undermining to create anterior working space



Correct level for development of anterior plane of dissection

- A 12-mm incision made 3 cm inferior to apex of the triangle
- Bluntly develop plane 5cm on either side of skin incision
- Insert 12-mm trocar—insufflate with CO_2
- Two 10-mm trocars placed hands' breadth from camera port

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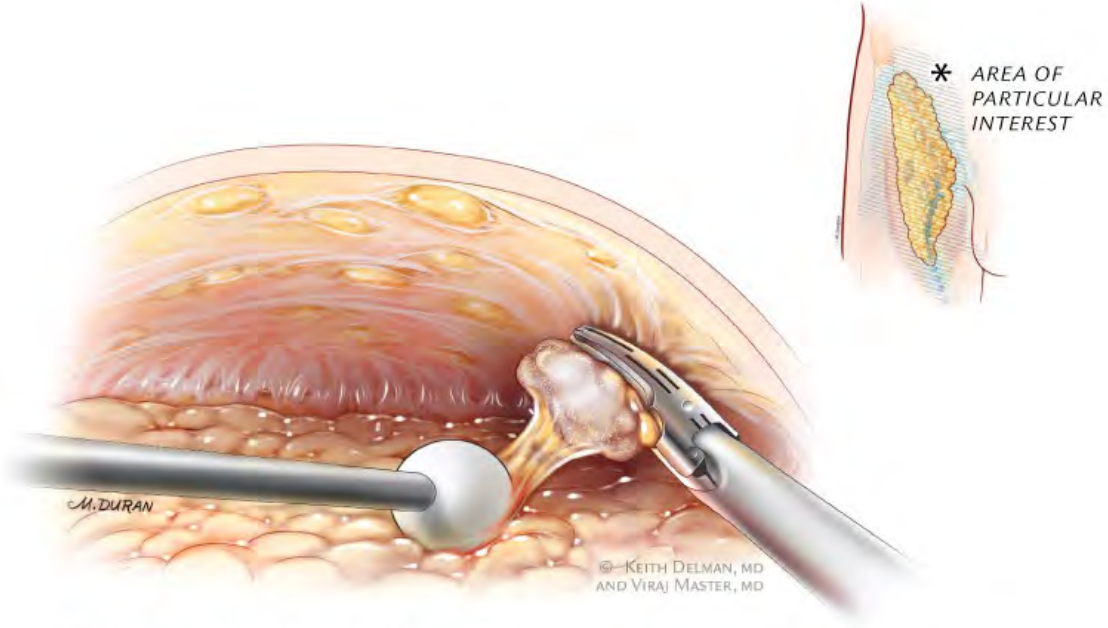
Don’t be afraid to go very superficial



Anterior abdominal wall in superior anterior space should be inspected for remaining attached lymph nodes

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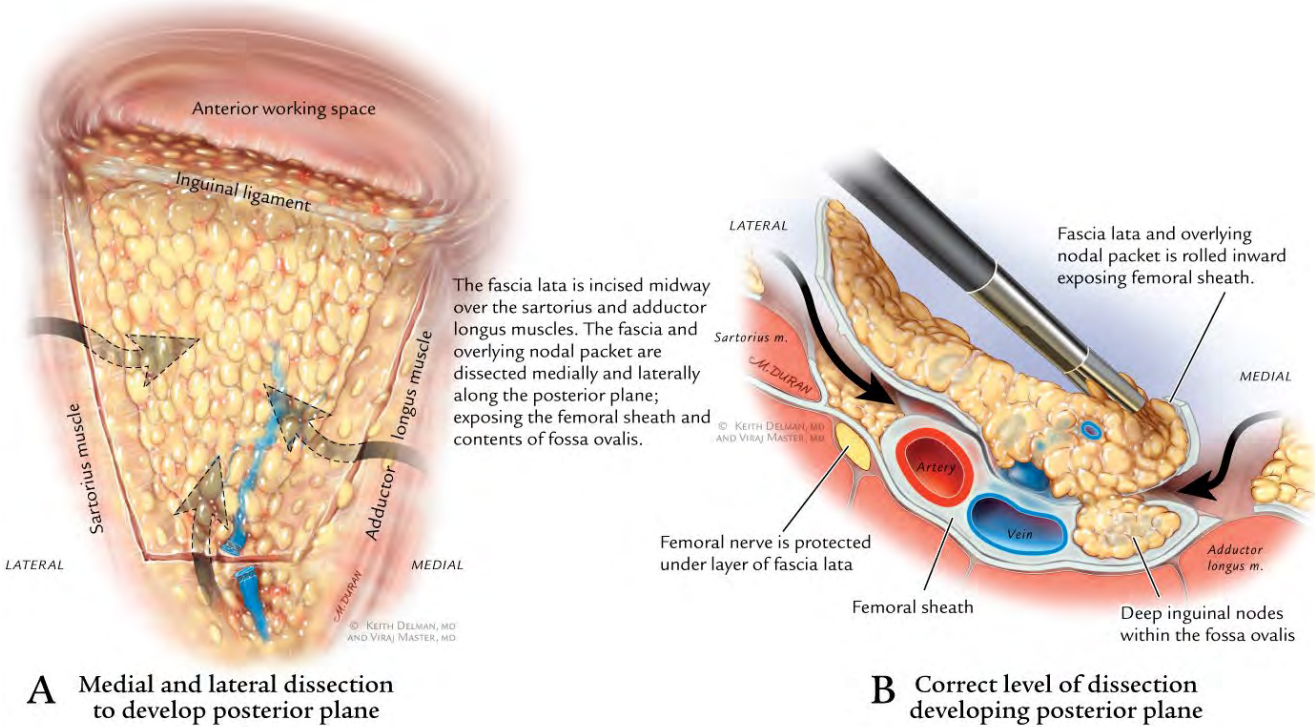
Trans-illumination is key for flap viability

Extent of Dissection



A Medial and lateral dissection to develop posterior plane

B Correct level of dissection developing posterior plane

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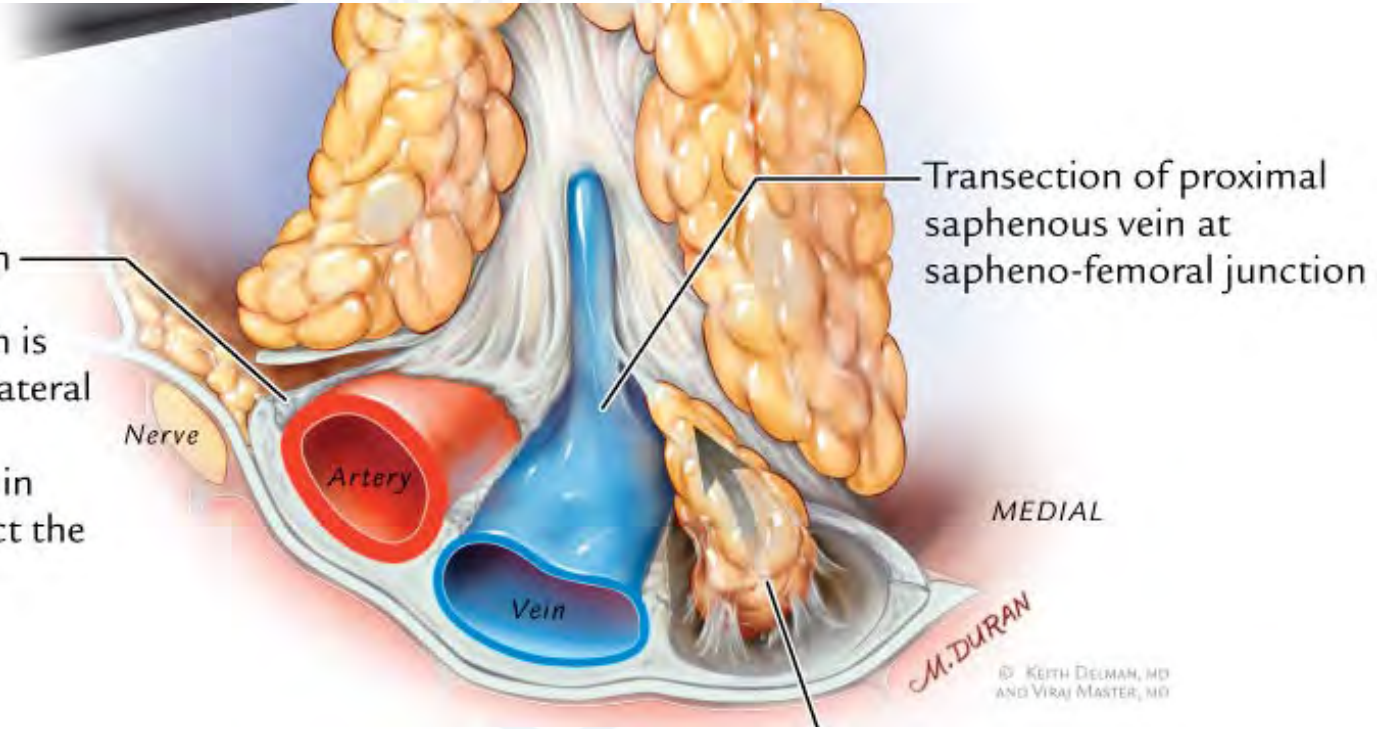
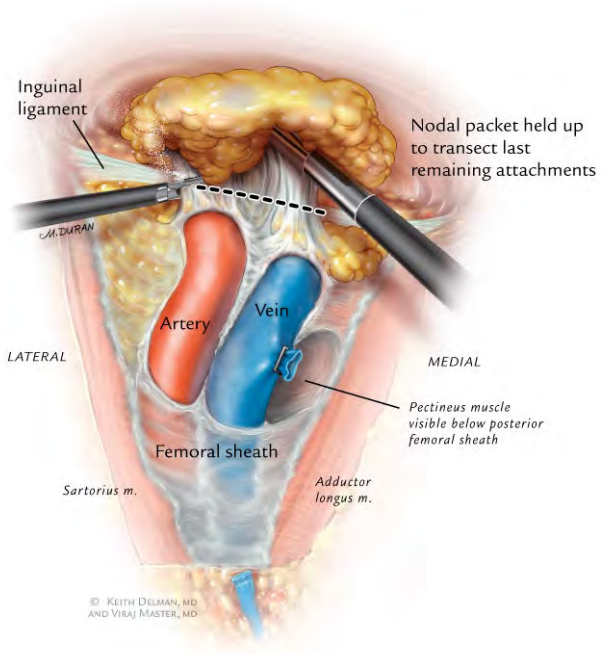
“Deep” Dissection



Dissection at Inguinal Ligament



Release of tissue at superior border along inguinal ligament

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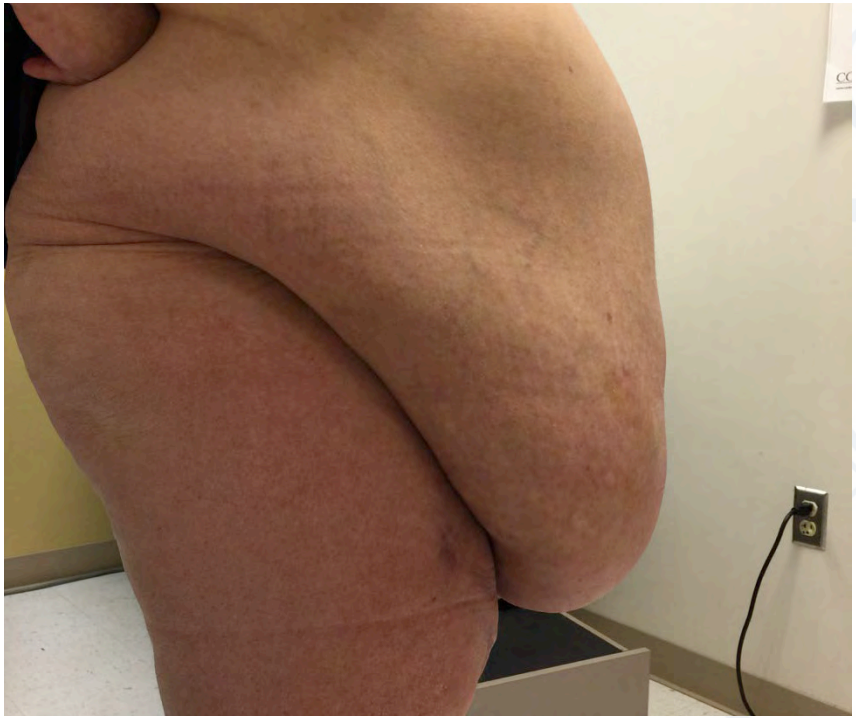
Super Obese
BMI >50

Follow-up - 4 months later



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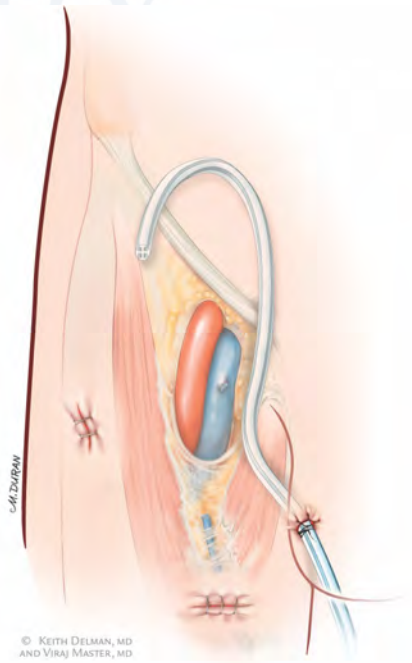
Nodal packet is placed in endoscopic



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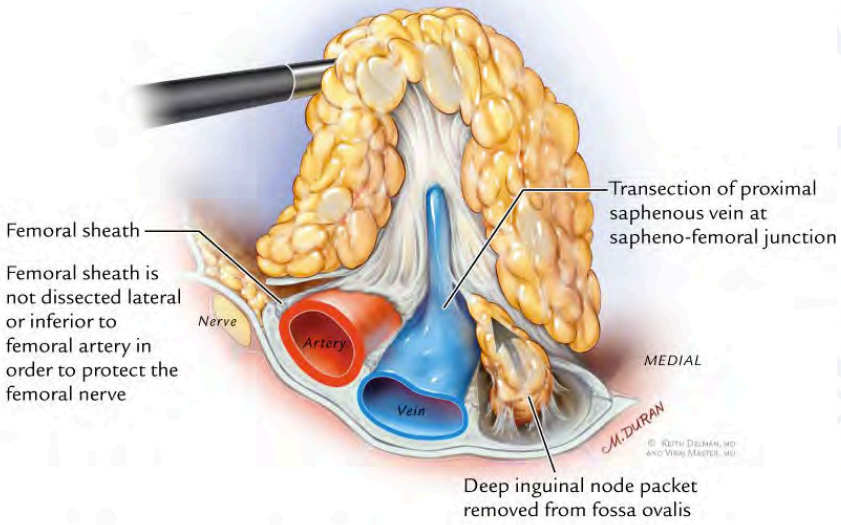
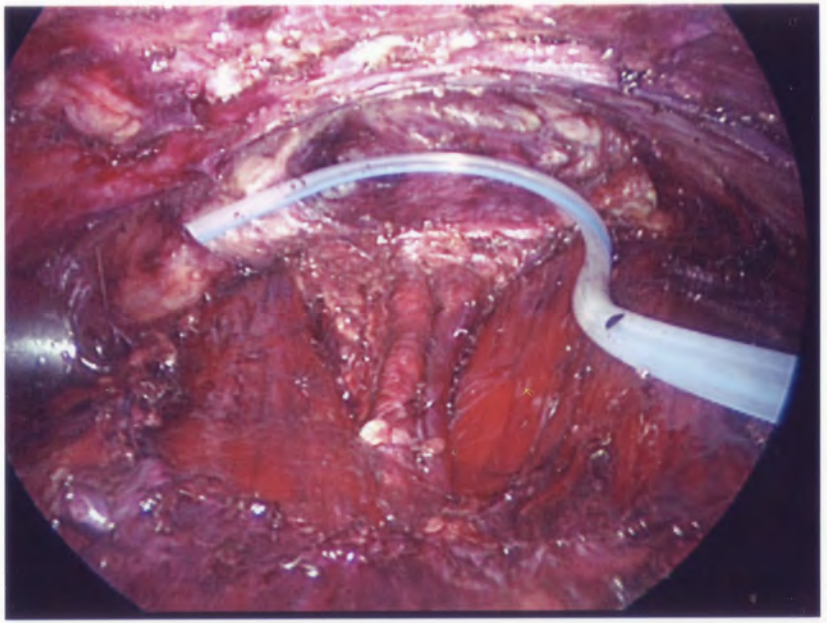
Courtesy Keith Delman MD

EMORY



Femoral sheath opened to remove deep inguinal nodes and transect proximal saphenous vein



2 years post op

Videoscopic Groin Dissection: Emory Experience (n=108)

Variable	All Cases (n=108)	Melanoma (n=47)	GU Malignancy (n=61)	p-value
Male Gender	73 (68%)	**18 (38%)**	**55 (90%)**	**<0.001**
Age, yrs	58.0 +/- 13.1	**50.1 +/- 14.9 yrs**	**61.4 +/- 8.9 yrs**	**<0.001**
BMI > 30 kg/m2	48 (44%)	**14 (30%)**	**34 (56%)**	**0.01**
ASA Class				**<0.001**
1	8 (7%)	**8 (17%)**	**0**	
2	33 (30%)	**21 (45%)**	**12 (20%)**	
3	61 (57%)	**18 (38%)**	**43 (71%)**	
4	6 (6%)	**0**	**6 (10%)**	
Smoking	43 (40%)	**9 (19%)**	**34 (56%)**	**<0.001**
Diabetes	25 (23%)	**5 (11%)**	**20 (33%)**	**0.01**
# LN's Harvested	12 +/- 5	13 +/- 5	12 +/- 5	0.64
Operative Time, min	180 +/- 52	188 +/- 49	196 +/- 55	0.44
Conversion Rate	6 (6%)	4 (9%)	2 (3.2%)	0.40
Infectious Complications	36 (33%)	16 (34%)	20 (33%)	1.00
Infection Requiring IV Antibiotics	15 (14%)	4 (9%)	11 (18%)	0.18
Flap Necrosis / Dehiscence	6 (6%)	2 (4%)	4 (7%)	0.70

EMORY

What about Radiation Therapy?

- Prophylactic radiotherapy in patients with cN0 groins is **not recommended** because of:
  - failure to prevent the development of metastatic lymph nodes
  - complications of radiotherapy
  - more difficult follow-up due to fibrotic changes
- Adjuvant radiotherapy may improve locoregional control in patients with extensive metastases and/or extranodal spread
  - control is achieved at the cost of severe side effects including severe edema and pain

Hard to Salvage a Bad Decision

Case

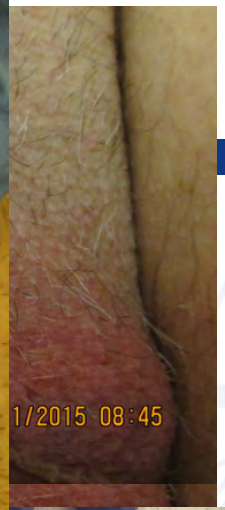
- 46 yo man
- Multiple medical problems, including kidney transplant from Prune Belly

- Referred to Dermatology (Moh's surgeon)

- **Final Pathologic Diagnosis**

- SKIN, PENIS, STAGE I, PIECE 2 (MOHS ORIENTED EXCISION): SQUAMOUS CELL CARCINOMA, **MODERATELY DIFFERENTIATED**, DIFFUSELY INVADING THE DERMIS AND SUBCUTIS. FOCAL PERINEURAL INVASION IS PRESENT. (SEE COMMENT).

EMORY



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- Post op course…6 months later, palpable groin adenopathy

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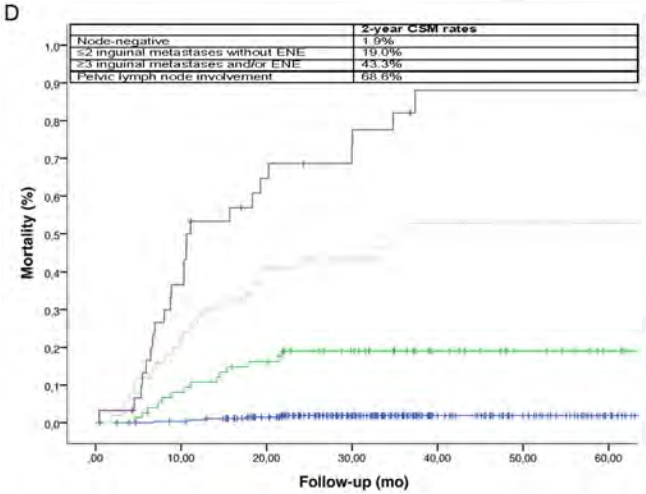
- Open groin dissection
- 4.2 cm metastatic node
- +Extranodal extension



These are weak walled nodes For large necrotic nodes, I'll do it open (with a very gentle touch)

Often densely attached to the pubic tubercle, consider getting some periosteum with the node

My ‘Real’ Take Home Message

- *If it is difficult to obtain high-fidelity pathologic information (grade), and imaging has poor sensitivity, AND if outcome is poor when we wait for positive nodes to appear, then…*
- **ERR ON THE SIDE OF PERFORMING A GROIN DISSECTION!**

Thank you!