The Big 5 in Penile Cancer

Pedro Oliveira
Dept Pathology/Christie Hospital, Manchester, UK
No disclosures
The BIG 5
The “Problem”

How “HPV” is Penile Cancer?

L.A.S.T and WHO

Lessons from the “Others”

The way forward
What is the “problem” with Penile Cancer?
FIFTH EDITION

TEXTBOOK OF UNCOMMON CANCER

EDITED BY
DEREK RAGHAVAN
MANMEET S. AHLUWALIA
CHARLES D. BLANKE
JUBILEE BROWN
EDWARD S. KIM
GREGORY H. REAMAN
MIKKAIL A. SEKERE

WILEY Blackwell
Few cases in Europe and USA but very important in some countries like Brazil and Paraguay!
Dr Antonio Cubilla
Our “knowledge” is limited and can potentially be biased as we do not have warranty that the information from high incidence areas can be translated to Europe or USA!
Too few cases/year for any institution which means: “we treat the few guided by what others do who just treat a few more cases than us!”
Improving Outcomes in Urological Cancers

The Manual
Supraregional networks for Penile Cancer in UK

- 12 centres for penile cancer work (10 in England and Wales, 2 in Scotland)
- Incidence of penile cancer in UK is 1-2/100,000 per year (approx 600 new cases)
- Recommended that each team serves at least 4 million population with 25 cases minimum
- Organ sparing techniques with reconstruction more widely available (radical and partial penectomy performed less often)
- Inguinal sentinel lymph node surgery introduced
- Use of mega-blocks for interpretation of anatomical boundaries
- Annual meeting in London for penile cancer histopathologists/clinicians
- EQA/RCPath dataset (3rd ed 2015)
7.5 million habitants
150-200 major procedures per year
Over 800 cases in file
Benefits from Supraregional networks for Penile Cancer

The development of a supraregional network for the management of penile cancer

P Kumar¹, S Singh¹, JC Goddard¹, TR Terry¹, DJ Summerton¹

¹Barts and The London NHS Trust, UK
²Sherwood Forest Hospitals NHS Foundation Trust, UK
³University Hospitals of Leicester NHS Trust, UK

The development of a supraregional network for the management of penile cancer

Penile cancer treatment costs in England

Sam T. Keeping¹, Michael J. Tompest², Stephanie J. Stephens³*, Stuart M. Carroll¹ and Vijay K Sangar²

Penile Cancer Guidelines

North West & North Wales Cancer Networks’ Clinical and Referral Guidelines for Penile Cancer

Should centralized histopathological review in penile cancer be the global standard?


The Christie NHS Foundation Trust, Manchester and the *Royal Bolton NHS Foundation Trust, Bolton, UK
How “HPV” is Penile Cancer?
33% HPV
Does this value reflects “our” reality?
2018

#37 non-HPV

#46 HPV

= 55%
Over the last decade in the UK (between 2004-2006 and 2014-2016), penile cancer AS incidence rates for males increased by 13%.
It is plausible to think that HPV related penile cancers will be the most prevalent in the next decade!
Caveats...
Problems on HPV Penile Cancers

IDHPV

Terminology
3

L.A.S.T. and WHO
The L.A.S.T. project

COLLEGE of AMERICAN PATHOLOGISTS

American Society for Colposcopy and Cervical Pathology
Cervix, Vagina, Vulva, Penis, Anus, Perianus

All HPV are equal, but different...

All Pathology is CIN, VaIN, VIN, AIN, PeIN...
Cervix, Vagina, Vulva, Penis, Anus, Perianus
The L.A.S.T. project

The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: Background and Consensus Recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology

Teresa M. Darragh, MD, Jennifer J. Colgan, MD,2 John N. Cox, MD,1 Debra L. Holley, MD,1 Michael R. Henry, MD,1 Ronald D. Luft, MD,23 Timothy McCalmont, MD,1 Rita Nayar, MD,2 Joel M. Palefsky, MD,2 Mark P. Stoler, MD,12 Edward J. Wilkinson, MD,12 Richard J. Zane, MD,23 David C. Wilbur, MD,23 for members of the LAST Project Working Groups

The following LAST Steering Committee members, Work Group members, and/or Conference Moderators have no perceived conflicts of interest to report: Jill Allbritton, Sarah Bean Abraham, Joel Bette, Debra Holley, Coree Hietak, Robert Latov, and Teresa Darragh.

In 2007, the University of California—San Francisco, San Francisco, CA; Mount Sinai Hospital, Toronto, Ontario, Canada; UMN-New Jersey Medical School, Newark, NJ; Mayo Clinic, Rochester, MN; Quest Diagnostics, Teterboro, NJ; Thomas Jefferson University, Philadelphia PA; Northwestern University, Chicago, IL; University of Virginia Health System, Charlottesville, VA; University of Florida College of Medicine, Gainesville, FL; Mercy Medical Center, Scranton, PA; and Massachusetts General Hospital, Harvard Medical School, Boston, MA.

In 2012, this paper was published in collaboration with the American Society for Colposcopy and Cervical Pathology and the College of American Pathologists and has been jointly published by invitation and consent in both the Journal of Lower Genital Tract Disease and the Archives of Pathology & Laboratory Medicine. It has been reprinted in accordance with the standards established at the Journal of Lower Genital Tract Disease.

Copyright © 2013 College of American Pathologists and American Society for Colposcopy and Cervical Pathology. Published as an Early Online Release June 28, 2012. Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the Web sites of the Archives (www.archlabmed.org) and the Journal of Lower Genital Tract Disease (www.jlgt.org).

Dr. Cox has retired from Santa Barbara Student Health Service, University of California, Santa Barbara, CA.

The American Society for Colposcopy and Cervical Pathology (ASCCP) and College of American Pathologists (CAP) provided the funding for this project; no industry funds were used in the development of the consensus statements and recommendations.
Behind L.A.S.T. was not only a “Semantic” standardization but also a “Musical” note ...
There may be players for whom touch and assault are synonymous… The pianist can indeed assault the piano and, for good measure, the composer and the public… To avoid misunderstandings: it is perfectly possible to play vigorously and forcefully without ramming the sound through the keys like a knife.
With L.A.S.T. clinicians would be able not to “assault” the women with HPV...
They can follow-up them “vigorously and forcefully” without aggressive therapeutical procedures in many cases!
HPV and Cancer

≠ progression rates ...
The L.A.S.T. project

ONE SIZE FITS ALL: GREAT FOR SOCKS, BAD FOR BELIEFS.
L.A.S.T./Vulva

Consensus Terminology

The 2015 International Society for the Study of Vulvovaginal Disease (ISSVD) Terminology of Vulvar Squamous Intraepithelial Lesions

Jordi Brunsting, MD, MPH, PhD, Robert J. Eyre, MD, PhD, FRCPath, and Jonathan R. Smith, MD, PhD, for the ISSVD Terminology Committee

LSIL (condiloma planum/HPV)

HSIL (usual type VIN/HPV)

VIN differentiated (non-HPV)
“L.A.S.T.” was endorsed by the last WHO classification
But not “for men”...
Still based in “classic H&E histopathology” ...
We can evaluate “HPV” by a reliable and easy IHC marker: p16
ID-HPV = p16

positive + negative -
ID-HPV = p16
“our results indicated a concordance between HPV and \( p16^{\text{INK4a}} \) status and this observation may have diagnostic and prognostic implications”

Am. J. Surg. Path. 2011
p16 not done

= HPV ???
Audit on p16 on PeIN (2016/18)

Only 31% had p16
Why it should be routine?
#METOO

Lobby for HPV Vaccine in boys!
Because an “unknown” % of Penile Cancers of the Squamous Cell Carcinoma NOS are also HPV related!
Further clarification needed for HPV in Penile Cancer
Why is this relevant?
Lessons from the “others”
<table>
<thead>
<tr>
<th>HPV Vulvar Cancer</th>
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<td>HPV Anal Cancer</td>
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<td>HPV Oropharynx Cancer</td>
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What can we learn from them?
Less Radical Surgery
Use Chemo-radiation
Different TNM system
Better Outcome
Lack of $\text{P16}^{\text{ink4a}}$ Over Expression in Penile Squamous Cell Carcinoma is Associated with Recurrence after Lymph Node Dissection

Dominic H. Tang, Peter E. Clark, Giovanna Giannico, Omar Hameed,* Sam S. Chang and Lan L. Gellert

From the Department of Urologic Surgery (DHT, PEC, SSC) and Department of Pathology (GG, OH, LLS), Vanderbilt University Medical Center, Nashville, Tennessee

$p16^{\text{INK4a}}$ is a Marker of Good Prognosis for Primary Invasive Penile Squamous Cell Carcinoma: A Multi-Institutional Study

Sven Gunia,* Andreas Erbersdobler, Oliver W. Hakenberg, Stefan Koch and Matthias May

From the Institute of Pathology, HELIOS Clinic Bad Saarow (SG, SK), Bad Saarow, Institute of Pathology (AE) and Department of Urology (OHH), University of Rostock (AE), Rostock and Department of Urology, St. Elisabeth Clinic Straubing (MM), Straubing, Germany
The way forward ...
From a Pathology perspective ...
IN-SITU PENILE CANCER
Questions to be answered ...

1. p16
2. L.A.S.T./WHO
3. Follow-up
WHO Classification of Tumours
5th edition

1. HSIL
2. LSIL
3. Differentiated PeIN
LS-PeIN HPV+  

LSIL p16 (?)
INVASIVE PENILE CANCER
Questions to be answered ...

1. “HPV” adjustment
2. Improving “prediction”
“HPV” adjustment

Dissociate morphology from aetiology
Improving “prediction”

1. Tumour “Budding”

2. Immune landscape

3. Grade: HG vs LG (?)

4. TNM: Siscca (?)
The percentage of G1 tumors assigned ranged from 8.6 to 52.5 %, G2 tumors from 27.1 to 72.6 % and G3 tumors from 11.7 to 48.7 %. Only some observers assigned G4 with a range of 0.6–21.9 %.
Tumour budding in oral squamous cell carcinoma: a meta-analysis

Alhadi Almangush1,2,3, Matti Pirinen4,5,6, Ilkka Heikkinen1,2, Antti A Mäkitie7, Tuula Salo2,8,9,10 and Ilmo Leivo11

Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016

Alessandro Lugli1,2,22, Richard Kirsch2,22, Yoichi Ajioka3, Fred Bosman4, Gieri Cathomas5, Heather Dawson1, Hala El Zimaity6, Jean-François Fléjou7, Tine Plato Hansen8, Arndt Hartmann9, Sanjay Kakar10, Cord Langner11, Iris Nagtegaal12, Giacomo Pupa13, Robert Riddell14, Ari Ristimäki14, Kieran Sheehan15, Thomas Smyrk16, Kenichi Sugiura17, Benoit Terris18, Hideki Ueno19, Michael Vieth20, Inti Zlobec1 and Phil Quirke21

Defining the Tumor Microenvironment of Penile Cancer by Means of the Cancer Immunogram

Hielke-Martijn de Vries9, Sarah R. Ottenhof9, Simon Horenblas9, Michiel S. van der Heijden9, Ekaterina S. Jordanova9,9

1Department of Urology, Netherlands Cancer Institute, Amsterdam, The Netherlands; 2Department of Medical Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands; 3Department of Gynecology, Center for Gynecologic Oncology Amsterdam, Amsterdam University Medical Center Vume, Amsterdam, The Netherlands
Low-grade SISCCA p16+ ...
From a Clinical perspective ...
IN-SITU PENILE CANCER
Questions to be answered ...

1. HPV status. LSIL?

2. Follow-up. Invasive?

3. Therapy. Which?
Are HPV related lesions “really” different?
INVASIVE PENILE CANCER
Questions to be answered ...

1. Who needs SLNB
2. Who needs Lymphadenectomy
3. “Personalised” therapy
This study shows that histologic grade and LVI are independent predictors for occult metastasis. Although both predictors are incorporated into the current high-risk EAU guidelines, the stratification of patients in need of a lymph node dissection is inaccurate. Most of the penile cancers in this study (n = 245; 72%) are classified high risk according to current EAU guidelines. The 23% incidence of micro-metastatic disease in these high-risk patients is relatively low. Strict adherence to EAU guidelines would have led to negative bilateral inguinal lymphadenectomy in 77% (n = 188 of 245) of the high-risk patients.
Micro-metastases were found in 9 cases (18%), mean diameter 1.00mm (0.2-2.0mm). Completion ILND was performed in 7 of these cases (78%). No further positive nodes were noted in the completion ILND specimen. There were 0 local recurrences with a mean follow-up of 33 (12-76) months. In the two cases not undergoing completion ILND following positive identification of micro-metastases, one had isolated tumour cells and had no evidence of recurrence at 11 months. The second patient developed progressive disease from the contralateral side. Patients undergoing SLNB that shows micro-metastases are unlikely to have further disease in completion ILND samples, and unlikely to have local recurrence. However, it is not yet possible to recommend avoiding completion ILND in such patients. eUROGEN will work towards a large multicentre study to answer this important question.
Tis versus T1 versus T2 ...
From a Research perspective ...
PENILE CANCER
Questions to be answered ...

1. HPV role
2. “OMICS”
3. New Models (PBX)
4. Biobanking
Multidimensional integrative analysis uncovers driver candidates and biomarkers in penile carcinoma

Fabio Albuquerque Marchi², David Correa Martins², Mateus Camargo Barros-Filho¹, Hellen Kusne³, Ariane Fidelis Busso Lopes³, Helena Brentani⁴, Jose Carlos Souza Trindade Filho³, Gustavo Cardoso Guimarães³, Eliney F. Faria³, Cristovam Scapulatempo-Neto³, Ademar Lopes³ & Silvia Regina Rogatto³,⁴
But **H&E** is still a “special stain”
Clinical Case

72 yr-old male with induration of the penile shaft
Carcinoma Cuniculatum: A Distinctive Variant of Penile Squamous Cell Carcinoma

Report of 7 Cases

José E. Barreto, MD,* Elsa F. Velazquez, MD,† Enrique Ayala, MD,* José Torres, MD,* and Antonio L. Cabilla, MD*
Take Home Messages

@Ask4p16
Thanks