Post-ASCO GenitoUrinary 2016: *Penile Cancer: what is changing?*

Nicola Nicolai
Penile cancer: basic line

• Penile cancer is the epitome of an orphan cancer
• Few ecological data; survival did not improve in the last 15 years across Europe
• Worse prognosis where clinical resources are

  • Clinical studies have been exploring which is the best therapy sequence
  • Some molecular signatures, with fair clinical implications

Trama A et al, Eur J Cancer 2015:51,2206
Is something changing?

• Treatment of T
• Management of N0 cases
• Management of cN+
• Which expectations for unresectable metastatic patient? New drugs
• Biological insight and clinical implications
Treatment of T: conservative surgery Vs amputation

- Fewer penile amputations
- Greater risk of recurrence with conservative surgery
- No increased risk of death (which depends on N/M)

**Figure 1.** Estimated probability of amputation by diagnosis year. Gray areas indicate point wise 95% CI.

**Figure 2.** Cumulative incidence of local recurrence as first event by penile preservation vs (partial) amputation (p <0.001).

Penile Sparing Surgery for Penile Cancer—Does it Affect Survival?

Rosa S. Djajadiningrat, Erik van Werkhoven, Wim Meinhardt, Bas W. G. van Rhijn, Axel Bex, Henk G. van der Poel and Simon Horenblas*

*From the Departments of Urology and Biometrics (EvW), The Netherlands Cancer Institute Amsterdam, Amsterdam, The Netherlands

**Figure 4.** CSS after first recurrence by recurrence type.
An update on penile cancer: Evaluating management trends and clinical outcomes using the National Cancer Data Base

- Mossanen M al et al Washington Univ. Seattle
- *trends in the use of partial penectomy (PP) in early stages and chemo in M+*
- 2677 early stage SCC; 819 M+
- National Cancer Database 1998-2012-14
- Proportion of PP increased from 73.9% in 1998-2000 to 80.4% in 2010-12 (p<.001)
- PP more common in older than 80 (OR 1.52) and younger than 50 (OR 1.47) Rate of PP
- Use of chemo increased from 39% in 1998-2000 to 49% in 2010-12 (p<.003)
- Elderly, higher Charlson index, Afro-American ethnicity, distance (> 50 miles) from hospital associated with a lower chance of receiving chemo

Partial penectomy and use of chemo are becoming more commonly used
**Management of cN0: there is not a referral standard!**

<table>
<thead>
<tr>
<th>Policy</th>
<th>advantage</th>
<th>limitation</th>
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<tbody>
<tr>
<td>Formal prophylactic ILND</td>
<td>Early staging and early Rx</td>
<td>Useless and toxic for 80%</td>
</tr>
<tr>
<td>Wait and see</td>
<td>Sparing useless Rx to 80%</td>
<td>Undertreatment for 20%</td>
</tr>
<tr>
<td>Modified ILND (Catalona)</td>
<td>Lower morbidity</td>
<td>Uneffective staging procedure</td>
</tr>
<tr>
<td>Risk category (Chaux)</td>
<td>Selection based on category</td>
<td>Insufficient as personalised strategy</td>
</tr>
<tr>
<td>DSNB (Horenblas, Lam)</td>
<td>Individualised Rx according to biopsy finding</td>
<td>Some series do not reach the excellent performances of top series</td>
</tr>
</tbody>
</table>

More recent cN0 cases have a better prognosis

Did it depend on DSNB?

Djajadiningrat RS et al, J Urol 2014;191:68-73
Management of cN+: there is not a referral standard!

- Prognosis depends on burden of disease

Contemporary Management of Regional Nodes in Penile Cancer—Improvement of Survival?

Rosa S. Djajadiningrat, Niels M. Graafland, Erik van Werkhoven, Wim Meinhardt, Axel Bex, Henk G. van der Poel, Hester H. van Boven, Renato A. Valdés Olmos and Simon Horenblas*
Surgery is the most effective Rx for nodal metastases

El-Demiry et al, Br J Urol. 1984 Dec;56(6):724-8
Management of cN+

- Prognosis depends on burden of disease and extent of surgery

**Fig. 2** Kaplan–Meier survival curves showing CSS rates after stratification according to LNR (< 22% vs ≥ 22%).

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Multivariable analysis (7th TNM edition)</th>
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<tbody>
<tr>
<td></td>
<td>HR (95% CI); P</td>
</tr>
<tr>
<td>Patient age</td>
<td>1.022 (0.990–1.066); 0.181</td>
</tr>
<tr>
<td>Pathological T stage</td>
<td>1.111 (0.287–4.300); 0.682</td>
</tr>
<tr>
<td>pT2 vs pT1</td>
<td></td>
</tr>
<tr>
<td>pT3 vs pT1</td>
<td>1.517 (0.378–6.081); 0.352</td>
</tr>
<tr>
<td>Tumour grade</td>
<td>2.236 (0.600–9.025); 0.222</td>
</tr>
<tr>
<td>G2 vs G1</td>
<td></td>
</tr>
<tr>
<td>G3 vs G1</td>
<td>4.396 (1.044–18.515); 0.044</td>
</tr>
<tr>
<td>Type of lymph node dissection</td>
<td>0.788 (0.306–2.029); 0.622</td>
</tr>
<tr>
<td>Inguinal vs Inguinopelvic</td>
<td></td>
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<tr>
<td>Pathological N stage (6th TNM edition)</td>
<td></td>
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<tr>
<td>pN2 vs pN1</td>
<td></td>
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<tr>
<td>pN3 vs pN1</td>
<td></td>
</tr>
<tr>
<td>Pathological N stage (7th TNM edition)</td>
<td></td>
</tr>
<tr>
<td>pN2 vs pN1</td>
<td>2.134 (0.513–8.883); 0.298</td>
</tr>
<tr>
<td>pN3 vs pN1</td>
<td>2.574 (0.686–9.664); 0.161</td>
</tr>
<tr>
<td>Extracapsular extension</td>
<td></td>
</tr>
<tr>
<td>Yes vs No</td>
<td></td>
</tr>
<tr>
<td>LNM laterality</td>
<td>0.950 (0.416–2.168); 0.902</td>
</tr>
<tr>
<td>Bilateral vs Unilateral</td>
<td></td>
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<tr>
<td>Number of positive lymph nodes</td>
<td></td>
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<tr>
<td>Number of lymph nodes removed</td>
<td></td>
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<tr>
<td>LNR (continuously coded)</td>
<td></td>
</tr>
<tr>
<td>LNR (categorically coded: ≥22% vs &lt;22%)</td>
<td>4.581 (2.144–9.790); P &lt; 0.001</td>
</tr>
<tr>
<td>Predictive accuracy of multivariable models (% gain relative to the model without LNR)</td>
<td>68.7% (+10.5%)</td>
</tr>
</tbody>
</table>

Relationship between lymph node ratio and cancer-specific survival in a contemporary series of patients with penile cancer and lymph node metastases

Giovanni Lughezzani*1, Mario Catanzaro*, Tullio Torelli*, Luigi Piva*, Davide Biasoni*, Silvia Stagni*, Andrea Necchi1, Patrizia Giancatempa1, Daniele Raggi3, Elena Fari1, Maurizio Colecchia1, Giorgio Pizzacaro8, Roberto Salvioni* and Nicola Nicolai*
Management of cN+: when pelvic dissection is indicated

**Always**, in case of suspicious imaging

**Always**, when imaging is suggestive avoidable only in very small burden (pN<3; < 3 LNM, no ENE+) → 1/4-1/3 of patients

Lughezzani G et Al, J Urol 2014

When a pelvis is positive, perform **contralateral** pelvic dissection

Zargar-Shostani K et al W J Urol 2015
Management of cN+: when bilateral pelvic dissection is indicated

In case of at least 4 inguinal NM, independently of bilateral nodal involvement

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multivariate</th>
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<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p Value</td>
</tr>
<tr>
<td>No. inguinal LNMs:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous</td>
<td>1.38 (1.07—1.78)</td>
<td>0.01</td>
</tr>
<tr>
<td>2 or Less vs 3 or greater</td>
<td>—</td>
<td>0.99</td>
</tr>
<tr>
<td>3 or Less vs 4 or greater</td>
<td>13.8 (1.7—113)</td>
<td>0.01</td>
</tr>
<tr>
<td>4 or Less vs 5 or greater</td>
<td>7.90 (1.97—31.7)</td>
<td>0.004</td>
</tr>
<tr>
<td>Inguinal ENE (yes vs no)</td>
<td>0.74 (0.17—3.28)</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Zargar-Shostani K et al J Urol 2015
Management of cN+: plus chemo?

• **Neoadjuvant chemo** (recently: cisplatin-Taxane) is active, inducing 40-60% response and 15-18% of pCR)
• Impact on survival is not well defined

Management of cN+: plus chemo?

8 (28.6%) recurrence-free at a median FU of 17 mos
7.1% 2-yrs recurrence-free rate


20 (32.8%) recurrence-free at a median FU of 67.4)

Dieckstein, RJ et al. 2016;117:118
Management of cN+: plus chemo?

• **Adjuvant chemo** – some experiences – associates with long-term CSS

Pizzocaro G & Piva L, Acta Oncol, 1988
Nicolai, N et al Clin Genitourin Cancer. 2015
Management of cN+: plus chemo?

- Adjuvant chemo – multi-institutional series of 84 pts with pelvic NM, 36 receiving AC

  - median OS AC 21.7 (IQR: 11.8–104) mos
  - not AC 10.1 (IQR: 5.6–48.1) mos ($P = 0.048$)

  AC was independently associated with improved OS on MVA
  - (HR: 0.40; 95% CI: 0.19–0.87; $P = 0.021$).

  Sharma P et al Urol Oncol. 2015 Nov;33(11):496.e17-23
Node management
Urological and radiation oncological perspectives
International Penile Advanced Cancer Trial (International Rare Cancers Initiative Study) (InPACT)

This study is not yet open for participant recruitment. (see Contacts and Locations)

Verified November 2014 by Institute of Cancer Research, United Kingdom

Sponsor:
Institute of Cancer Research, United Kingdom

Collaborators:
ECOG-ACRIN Cancer Research Group
European Organisation for Research and Treatment of Cancer - EORTC

Information provided by (Responsible Party):
Institute of Cancer Research, United Kingdom

ClinicalTrials.gov Identifier:
NCT02305654

First received: September 23, 2014
Last updated: November 27, 2014
Last verified: November 2014

History of Changes

International Penile Advanced Cancer Trial (InPACT)

Steve Nicholson, MD (Study Chair)
Curtis Pettaway, MD (USA Study Chair)
Dan Canter, MD (ECOG Surgical Chair)

- ECOG-EA8134
- Questions:
  - Role of neoadjuvant therapy (chemotherapy or chemoradiation)?
  - Does prophylactic PLND provide a survival benefit compared to chemoradiation alone?

- 20 sites anticipated
- Target: 200 patients
  - 2 patients/year per site
  - 40 patients/year for 5 years
- Bayesian Approach
  - No formal hypothesis testing
  - Estimates probability of choosing the better of two therapies
  - ITT analysis
- Primary endpoint: Survival
- Secondary endpoints: DSS, DFS, pN0, Toxicity, QoL, Surgical complications
InPACT – International Penile Advanced Cancer Trial

Penis cancer patient with clinical evidence of inguinal node metastases following treatment for primary cancer

R1 Randomisation

Arm A
Therapeutic inguinal node dissection
Pathological LOW risk
Pathological HIGH risk

Arm B
Neo-adjuvant Chemo
RESTAGE
Therapeutic inguinal node dissection
Pathological HIGH risk
Pathological LOW risk

Arm C
Neo-adjuvant ChemoRT
RESTAGE
Therapeutic inguinal node dissection
Pathological LOW risk
Pathological HIGH risk

R2 Randomisation

Arm A
Adjuvant ChemoRT
Prophylactic Pelvic lymph node dissection
Restage
Adjuvant ChemoRT

Arm B
Prophylactic Pelvic lymph node dissection

Arm C
Surveillance
Prophylactic Pelvic lymph node dissection

Stage 1 (InPACT-adj vant)
Role of neo-adjuvant therapy

Stage 2 (InPACT-palliative)
Risk of PLND

v2.9 (Sept 2015)

* RT to groin & pelvis
*RT to groin alone or groin and pelvis

The International Rare Cancers Initiative (IRCI) is a strategic collaboration between Cancer Research UK, the UK National Institute for Health Research Cancer Research Network (NCRN), the US National Cancer Institute (NCI), and the European Organisation for Research and Treatment of Cancer (EORTC). The initiative will support the development of international clinical trials for rare cancers.

Presented By Thomas Powles at Genitourinary Cancers Symposium 2016
Far advanced PSCC: dismal prognosis!

- Chemo in 19 pretreated M+ pts
- Median OS < 6 mos
Pan-HER tyrosine-kinase inhibitors (TKI) dacomitinib and afatinib in penile squamous cell carcinoma (PSCC): Results from an ongoing open-label, single-group, phase 2 trial of dacomitinib in chemonaive patients (pts)

- Raggi et Al, INT Milano
- **Phase 2 trial with Dacomitinib in N2-M1 SCC pts**
- 16 pts btw 6/2103 &10/2015
- Median PFS 4.4 mos
- Median OS 13.7 mos
- Toxicity:
  - Skin 8 (G1:7; G3:1)
  - Diarrhea 2(G2)
  - Cutaneous bleeding 1
- **Response rate (15 valuable):**
  - 5 (33%) PR
  - 8 (53%) SD
  - 2 (13%) PD
Far advanced PSCC: anti-EGFR Rx

- Panitumumab in 11 pretreated M+ pts
- Median OS: 9.5 mos

Panitumumab Treatment for Advanced Penile Squamous Cell Carcinoma When Surgery and Chemotherapy Have Failed

Andrea Necchi,1 Patrizia Giannatempo,1 Salvatore Lo Vullo,2 Daniele Raggi,1 Nicola Nicolai,3 Maurizio Colecchia,4 Federica Perrone,4 Luigi Mariani,2 Roberto Salvioni3
Biological insight and clinical implications: HPV and p16

Human Papillomavirus Prevalence in Invasive Penile Cancer
and Association with Clinical Outcome

Rosa S. Djajadiningrat, Ekaterina S. Jordanova, Bin K. Kroon, Erik van Werkhoven, Jeroen de Jong, Divera T. M. Pronk, Peter J. F. Snijders, Simon Horenblas* and Daniëlle A. M. Heideman

5 yr DSS hrHPV positive tumors (53) : 96%
hrHPV negative tumors (159): 82%
log rank test p1⁄40.016).

Lack of P16INK4a 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

Overall Recurrence P16INK4A negative tumors were more likely to recur overall (p: 0.04), especially if patients had positive lymph nodes at diagnosis (p: 0.002).
Biological insight and clinical implications: p53

A Combination of Cisplatin and 5-Fluorouracil With a Taxane in Patients Who Underwent Lymph Node Dissection for Nodal Metastases From Squamous Cell Carcinoma of the Penis: Treatment Outcome and Survival Analyses in Neoadjuvant and Adjuvant Settings

Nicola Nicolai, Laura Maria Sangalli, Andrea Necchi, Patrizia Giannatempo, Anna Maria Paganoni, Maurizio Colecchia, Luigi Piva, Mario Achille Catanzaro, Davide Biasoni, Silvia Stagni, Tullio Torelli, Daniele Raggi, Elena Faré, Giorgio Pizzocaro, Roberto Salvioni

median DFS
p53+ve 8.9 mos
p53-ve not reached (p .051)

median OS
p53+ve 17.2 mos
p53-ve not reached (p .037)
Is something changing?

- Treatment of T → **yes**
- Management of N0 cases → **no**
- **Management of cN+** → work in progress
- Which expectations for unresectable metastatic patient? **New drugs** → work in progress
- **Biological insight** and clinical implications → work in progress
Post-ASCO
GenitoUrinary 2016:
*Penile Cancer: what is changing?*

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