Time series analysis of TP53 gene mutations in recurrent HPV-negative vulvar squamous cell carcinoma

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Disclosures

- Member of Clinical Oncology Advisory Board of Thermo Fisher
- Talks for Bristol-Myers Squibb
- Talks for AstraZeneca
Vulvar Cancer

- rare disease (1/100k women)
- ~4% of gynecological malignancies
- 90% squamous cell carcinoma

10 year survival (abs)

incidence/deaths/a in Germany

© Deutsches Krebsregister
Invasive Human Papilloma Virus (HPV) negative squamous cell carcinomas

- **Vulvar intraepithelial neoplasia (VIN)**
  - 80 % HPV, 20% HPV neg

- **Invasive vulvar cancer (IVC)**
  - 40% HPV, 60% HPV neg
  - warty/basaloid 70% HPV
  - keratinising 13% HPV

- HPV positive
  - slow progression
  - detected early

- HPV negative
  - fast progression

### Geographical region*

<table>
<thead>
<tr>
<th>Geographical region</th>
<th>All invasive vulvar cancer</th>
<th>Number</th>
<th>Crude</th>
<th>Adjusted *#</th>
</tr>
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<td>North America</td>
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<td>50</td>
<td>50.0</td>
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<td>35.2</td>
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<td>Oceania</td>
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### Period of diagnosis*

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<th>Crude</th>
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### Age at diagnosis*

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<th>All invasive vulvar cancer</th>
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<th>Crude</th>
<th>Adjusted *#</th>
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<td>&lt;56</td>
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<td>16.1</td>
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<td>365</td>
<td>16.4</td>
<td>15.1</td>
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<tr>
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<td>86</td>
<td>34.9</td>
<td>33.2</td>
</tr>
</tbody>
</table>

**Total** 1709 25.1 22.4

**HPV and P16 positivity**

S. de Sanjosé et al. / European Journal of Cancer 49 (2013) 3450–3461
Vulvar SCC
Vulvar SCC
Invasive Human Papilloma Virus (HPV) negative squamous cell carcinomas

- commonly arise in lichen sclerosus and lichen planus
  - World Health Organisation.: Classification of Tumours of the Female Genital Tract. 4 edn. IARC: Lyon; 2014. pp 232-6

- have a high recurrence rate despite complete excisions

- 76% harbor a wide range of somatic TP53 gene mutations
  - Kashofer, K; Regauer, S. Analysis of full coding sequence of the TP53 gene in invasive vulvar cancers: Implications for therapy. GYNECOL ONCOL. 2017; 146(2): 314-318

- inferior clinical outcome is attributed to chemo- and radio-resistance
  - the effects of radiation and many chemotherapeutic agents are mediated through the p53 pathway

- The impact of TP53 gene mutations in recurrent HPV-negative vulvar SCC is unclear
Two distinct pathways

HPV+
- E6
- p53
- p53 degradation

HPV-
- TP53 mutation
- LOF
- GOF
Invasive Human Papilloma Virus (HPV) - negative squamous cell carcinomas

- It is unknown
  - if and how TP53 gene mutational status of vulvar SCC influences disease-free survival
  - if the mutational status (wild-type or mutation) is maintained in recurrent invasive vulvar SCC and
  - if primary and recurrent SCC carry identical TP53 gene mutations

- “Recurrence”
  - new local vulvar cancer after complete resection of the invasive SCC with clear margins after ≥ 12 month disease-free intervals
Study Design

- Time series analysis of TP53 gene mutations in recurrent vulvar SCC
  - Cases from the last 7 years
  - Ion Torrent sequencing of entire coding region of TP53 gene

- Missense mutations including
  - “hot spot” TP53 mutations (missense mutations that occur at an unusual high frequency; defined as top 10% of the most commonly mutated amino acid positions in the TP53 gene according to the IARC TP53 database)

  - GOF
    - oncogenic gain-of-function: increased invasion/ migration, angiogenesis, dedifferentiation, anchorage-independent growth, rapid metastasis by interaction with other cellular proteins

  - LOF
    - Truncating TP53 mutations with loss-of-function (LOF) abolish function of p53 protein
Results

- 24 patients (median age 69 years, range 40 – 84 years)
  - 19/24 patients had one and
  - 5/24 patients had multiple recurrences
    - 1st recurrence after 46 months (median, range 12-180 months, in 24 pts.)
    - 2nd recurrence after 22 months (median, range 12-46 months, in 5 pts)
    - 3rd recurrence after 29 months (median, range 12-46 months, in 3 pt.)
    - 4th and 5th recurrences in 1 pt.

- Time intervals for 2nd and further recurrences reflect time from last recurrence, not overall elapsed time

- Local recurrences arose in skin / mucosa affected by residual chronic inflammatory diseases (lichen planus and lichen sclerosus)
TP53 status of primary invasive SCC

- 24 primary cancers:
- 7 (29%) WT TP53
- 17 (71%) with TP53 mutation in primary SCC
  - 14 cases with single TP53 mutation
  - 3 cases with multiple TP53 mutations
  - 12 missense and hotspot
  - 5 LOF (stop-gain and frameshift)
TP53 status of recurrent SCC in TP53 positive cases

- 17/24 (71%) primary TP53 mutated SCC
- 5 (29%) identical TP53 mutation
- 1 (6%) additional mutation
- 8 (47%) different mutation
- 3 (18%) reversion to WT
TP53 status of recurrent SCC in TP53 negative cases

- 7/24 (29%) primary TP53 WT SCC
- 3/7 (43%) patients maintained p53 wild type after 14, 20 and 69 months
- 4/7 (57%) patients presented with TP53 gene mutations in recurrence after disease free intervals between 60 and 144 months
  - notably all these recurred later than 5 years!

Length of disease-free survival until 1rst recurrence
- Overall: Median 46 months (range 12-180 months)
  - TP53 mutated patient group: 33 months
  - TP53 WT patient group: 65 months
Conclusions

- SCC recurred in residual vulvar dermatosis independent of TP53 gene mutational status of the 1° SCC
- The majority of TP53 gene mutated cancers recurred with different TP53 gene mutations, many of them more complex
- p53 wild type 1° SCC recurring with TP53 gene mutations possibly indicate increased genetic instability in longstanding chronic inflammatory dermatoses
- A change of TP53 gene mutational status after >5 years suggests de novo oncogenic events/carcinogenesis.
- Longer disease-free intervals in patients with p53 wild-type 1° SCC suggest that the TP53 gene mutational status may serve as a prognostic marker for disease-free intervals in patients with vulvar SCC.
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