The driver mutational landscape of squamous cell carcinoma of the ovary arising in mature cystic teratoma

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Mature Cystic Teratoma aka Dermoid Cyst

T2 axial

Image c/o Dr Fiona Bryden, NHS GGC

Ref: https://www.flickr.com/photos/jianhua_qiao_md/sets/72157634596403309/with/9266547358/
Transformed Mature Cystic Teratoma

- 0.1 – 1% of MCT
- Commonly squamous cell carcinoma
- Incidental diagnosis
- Poor prognosis
Squamous-cell carcinoma in mature cystic teratoma of the ovary: systematic review and analysis of published data

Andreas Hackethal, Doerthe Bruegmann, Michael K Bohlmann, Folker E Franke, Hans-Rudolf Tinneberg, Karsten Münstedt

Average age at diagnosis 55yrs

49.8% stage I

50.2% stage II-IV
Scottish Genome Partnership

• Professor Iain MacNeish
• Archival FFPE samples
• Four large UK Gynae Cancer Centres
• Formal path review and mark up
• Macro/microdissected SCC, MCT and normal tissue
• 50 - 200ng DNA
• Agilent ClearSeq Comprehensive Cancer panel
• Mean read depth >100×
Cases of SCC arising in MCT

- Median age 51.0 years (25 – 86)
- 14 of 25 (56%) Stage I
- 11 of 25 (44%) Stage II – IV

Survival by stage

<table>
<thead>
<tr>
<th>% surviving</th>
<th>100</th>
<th>75</th>
<th>50</th>
<th>25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (months)</td>
<td>0</td>
<td>24</td>
<td>48</td>
<td>72</td>
</tr>
<tr>
<td>I</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>II - IV</td>
<td></td>
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</tbody>
</table>
MCT – somewhat dull....

Mature cystic teratoma

Count of mutations

Case number 1 2 5 6 7 8 9 10 11 12 13 14 15 19 20 21 22 23 24 25 27 28 29 30 31

TP53
PIK3CA
CDKN2A

Missense Mutation
SCC – overall mutation load

### SCC – mutations and CNA

| Case number | 1   | 2   | 5   | 6   | 7   | 8   | 9   | 10  | 11  | 12  | 13  | 14  | 15  | 19  | 20  | 21  | 22  | 23  | 24  | 25  | 26  | 27  | 28  | 29  | 30  | 31  |
|-------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| **TP53**    | 80% |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| **PIK3CA**  | 52% |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| **CDKN2A**  | 44% |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

- **Gain**: Blue bars
- **Homozygous Deletion**: Black bars
- **Missense Mutation**: Green bars
- **Truncating Mutation**: Red bars
- **Synonymous Mutation**: Pink bars
- **splice Mutation**: Orange bars

**Legend**

- **TP53** mutation frequency: 80%
- **PIK3CA** mutation frequency: 52%
- **CDKN2A** mutation frequency: 44%
Influence of mutations on outcome

Survival by TP53 mutation status

\[ p = 0.0013 \]
Influence of mutations on outcome

Survival by TP53 mutation status

- Mutant
- WT

% surviving

Time (months)

Survival by TP53 mutation status

- Biallelic
- Monoallelic
- Wildtype

% surviving

Time (months)

p=0.0013

p=0.028

p=0.007
Oogenesis and meiosis

Primordial Germ Cell → Oogonium → Primary oocyte → Meiosis I Completed → Secondary oocyte → Meiosis II Arrested Metaphase II → Second polar body

Arrested prophase Meiosis I

Chr1

Chr22

Maternal
Paternal

Adapted from a figure by Rdbickel, released under CCA4.0
Oogenesis and meiosis

Primordial Germ Cell → Oogonium → Primary oocyte → Primary oocyte → Meiosis I completed

Arrested prophase Meiosis I

2

4

Secondary oocyte → Meiosis II
Arrested Metaphase II

First polar body

2

4

Second polar body

Group A

Group D?

Group B

Group C?

Group C?
Specific Conclusions

• MCT few mutations but multiple potential different cells of origin
• SCC ovary HPV negative
• SCC mutations similar to SCC lung
• High overall mutational burden - ?immune checkpoint inhibitors
• Stage remains highly important for prognosis
• Bi-allelic TP53 mutations – ?good prognostic biomarker
General Conclusions

• For distinct, rare tumour types even small cohorts can be used to characterise the disease
• Large amounts of research can be done with small (and relatively cheap!) sequence capture experiments
• Archival FFPE material can give good quality sequencing data when processed carefully
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