Salivary gland neoplasms: an update

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WHO Blue Book 2017: salivary gland

• Some non neoplastic entities included
• Expanded molecular pathogenesis
• Newly defined entities: e.g. secretory carcinoma, polymorphous adenocarcinoma
New entities: Secretory Carcinoma
Mammary analogue secretory carcinoma

- First recognised as tumour similar to secretory carcinoma of breast
- Defined by specific molecular finding of balanced chromosomal translocation t(12;15)(p13;q25) – identical to secretory carcinoma of breast
Secretory carcinoma

- balanced chromosomal translocation \( t(12,15)(p13:q25) \)
- results in formation of \( ETV6-NTRK3 \) fusion gene
  - (Also seen in infantile fibrosarcoma and others)
  - Detected either by break-apart \( ETV6 \) FISH probe or RT-PCR for the fusion transcript
Variable fusion partners described

• Rather than *ETV6-NTRK3* fusion – there may be others e.g. *ETV6-Xgene* fusion

• *Morphology may tend to be different* - more *infiltrative growth and sclerotic stroma*
Secretory carcinoma

- Adults, wide age range mean 47y
- Male predominance
- Parotid > minor glands > submandibular gland
- Defined in molecular terms
- Characteristic morphology
- About 250 cases reported
Secretory carcinoma

- Often lobules with thin septae
- Tubular, solid, microcystic, follicular or papillary growth patterns
- Fibrotic stroma less common
- Cystic – less common
Secretory carcinoma

- Low grade vesicular nuclei
- Foamy/ granular/ vacuolated cytoplasm
- “Bubbly” secretions
- Atypia and mitoses rare
Secretory carcinoma *versus* acinic cell carcinoma

**Secretory carcinoma**
- Multiple growth patterns
- Papillary cystic
- More solid and bubbly
- Multivacuolated cytoplasm
- Luminal and cytoplasmic mucin
  - DPAS+ globules
- No basophilic granules
- Diffuse S100, mammaglobin positive
- DOG1 negative

**Acinic cell carcinoma**
- Multiple growth patterns, rarely papillary
- Papillary cystic less likely
- DPAS: granular cytoplasmic positivity
- May have basophilic granules
- S100, mammaglobin negative
- DOG1 positive (intense apical membranous and variable cytoplasmic)
Acinic cell carcinoma (zymogen rich)
DOG 1 in acinic cell carcinoma
Secretory carcinoma

Mammaglobin

HE
Mammaglobin

- Polymorphous low grade adenocarcinoma: 60% may have S100 and mammaglobin positivity
- Adenoid cystic: 13% mammaglobin positive
- Low grade salivary duct adenocarcinoma
- Salivary duct carcinoma
Secretory carcinoma: differential

• Low grade ductal adenocarcinoma/cystadenocarcinoma:
  - *S100* and *mammaglobin* diffusely positive
  - Intraductal micropapillary or cribriform
  - usually *p63* positive myoepithelial layer help to distinguish

• Mucoepidermoid carcinoma: *S100* and *mammaglobin* usually negative
Secretory carcinoma: Prognosis

- Usually indolent behaviour but may result in locoregional recurrence and metastasis
- Up to 25% nodal metastases described
- Prognosis: depends on stage
- High grade transformation has been described
- Due to nature of fusion: TRK inhibitors may have a role
Acinic cell carcinoma (after SC)

- >50% of zymogen granule poor acinic cell carcinomas are secretory carcinomas
- Secretory M:F ratio 8:2
- Acinic M:F ratio 1:1.5
Secretory carcinoma in thyroid

- Recently 6 cases from 2 centres
- Morphologically like salivary counterpart
- Nodal metastases/ high stage
- S100 and mammaglobin positive
- ETV6 rearrangement confirmed by FISH
- Negative for thyroglobulin and TTF-1
- ETV6-NTRK3 rearrangement also described in radiation associated thyroid PTC
- PAX8 was positive focally

- Probably true thyroid origin
New entity: polymorphous adenocarcinoma
Polymorphous adenocarcinoma

• New nomenclature 2017 – *probably most contentious area*
• Includes cases previously called
  • **polymorphous low grade adenocarcinoma** and
  • **cribriform adenocarcinoma of tongue (CAT)/ cribriform adenocarcinoma of minor salivary glands (CAMSG)**
• “Low grade” was dropped due to aggressive behaviour of some tumours, tumours with not so low grade appearance
• **CAMSG** - emerging entity, may be recognised as an entity in the future
PLGA and CAMSG - ? distinct entities or variants on a spectrum

<table>
<thead>
<tr>
<th>Cribiform adenocarcinoma</th>
<th>PLGA</th>
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<tbody>
<tr>
<td>• Base of tongue predominates</td>
<td>• Palate, buccal mucosa predominate</td>
</tr>
<tr>
<td>• Papillary/ glomeruloid structures</td>
<td>• Streaming columns of cells, concentric whorls, tubular, solid papillary and cribriform</td>
</tr>
<tr>
<td>• Also cribriform, tubular, solid</td>
<td>• Pale vesicular nuclei</td>
</tr>
<tr>
<td>• Optically clear/ ground glass nuclei</td>
<td>• PNI</td>
</tr>
<tr>
<td>• Propensity for LVI</td>
<td>• Rearrangements of PRKD1-3 in 10%</td>
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<tr>
<td>• Rearrangements of PRKD1-3 in 80%</td>
<td>• PRKD1 E710D mutations 80%</td>
</tr>
<tr>
<td>• PRKD1 E710D mutations 10%</td>
<td>• Nodal metastasis rare</td>
</tr>
<tr>
<td>• Early nodal metastasis common</td>
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Historically - polymorphous low grade adenocarcinoma

- Described in 1984
- Infiltrative growth
- Overlap with features of adenoid cystic carcinoma – but much better prognosis
- Local recurrence 10-33%
- Distant metastases and death from disease rare
• PLGA

• Adenoid cystic carcinoma
PLGA

• But......
• historical difficulty over inclusion or exclusion of cases with prominent papillary growth pattern
• Some felt the papillary ones would be better categorised as adenocarcinoma, NOS
• associated with worse prognosis than PLGA without papillary growth
• Also cases with necrosis, higher grade areas
• Suggested since 2002 that low grade should be dropped
Cribriform adenocarcinoma of minor salivary gland

- Originally described as cribriform adenocarcinoma of the tongue (CAT) usually base of tongue
- Later expanded as seen in other sites – CAMSG (minor salivary gland)
- Some base of tongue tumours were more papillary and more aggressive

- Growth pattern is mostly papillary/ glomeruloid despite the name
microcystic /cribriform
Infiltrative growth
CAMSG – papillary with PTC like nuclei
WHO 2017
Polymorphous adenocarcinoma

- Submucosal, unencapsulated, infiltrative
- Small bland cells
- Minimal hyperchromatism, many with pale washed out nuclei
- PNI common
- Mitoses uncommon, no necrosis
- Variability within and between tumours characteristic: lobular, trabecular, microcystic, cribriform, solid, papillary /cystic
- S100 often diffusely positive
- Do not have a prominent basal or myoepithelial phenotype although p63 seen (but not in biphasic pattern as in adenoid cystic)
<table>
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<th>Adenoid cystic</th>
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<tr>
<td>• Pale vesicular nuclei</td>
<td>• Hyperchromatic angulated nuclei</td>
</tr>
<tr>
<td>• Multiple growth patterns, focally cribriform</td>
<td>• Glandular / tubular, cribriform, solid</td>
</tr>
<tr>
<td>• Monotypic cells</td>
<td>• Biphasic pattern usually seen, inner cells CD117 +</td>
</tr>
<tr>
<td>• PNI with perineural whorling at periphery</td>
<td>• PNI, often larger nerves</td>
</tr>
<tr>
<td>• MIB 1 &lt;10%</td>
<td>• MIB1 &gt; 10%</td>
</tr>
<tr>
<td>• P63+p40-</td>
<td>• P63+p40+</td>
</tr>
<tr>
<td></td>
<td>• MYB-NFIB fusion in 80%</td>
</tr>
</tbody>
</table>
Tumour upper lip 35 year old female
Tumour of upper lip
Mitoses, microcystic pattern
Polymorphous adenocarcinoma
(CAMSG type)
Small left lateral tongue tumour
Diagnosis: Metastatic adenocarcinoma from the oesophagus mimicking primary
Adenoid cystic carcinoma – 2017
Adenoid cystic carcinoma

- 5 yr survival 90%
- 15 yr survival <70%
- Growth pattern and stage important
- Solid growth pattern > 30% - worse outcome
Adenoid cystic carcinoma: molecular

- t (6;9) translocation that joins the MYB (chros 6) and NFIB (chros 9) transcription factors into fusion gene product
- 80% of adenoid cystic carcinomas, not in HGT
  - 6q22-23 translocations MYB fusion/activation 89%
  - 8q13 translocations MYBLI fusion/activation 10%
  - NOTCH1 mutation 5-10%
- MYB antibody also available but not specific for diagnosis of ACC
Clear cell carcinoma

• Previously: clear cell carcinoma, NOS
• hyalinising clear cell carcinoma

• *EWSR1*-*ATF1* fusion recently identified
• 85-90% of tumours
Clear cell carcinoma

• Rare low grade minor salivary gland carcinoma
• Lack of myoepithelial differentiation
• Until recently a diagnosis of exclusion

• Distinction from clear cell mucoepidermoid carcinoma, clear cell odontogenic carcinoma was not always possible
Clear cell carcinoma

- Palate, tongue base, tongue
- Appear clinically and grossly circumscribed but infiltrative on histology
- Growth pattern: small nests, cords, thin trabeculae, single cells
- Pale, uniform eosinophilic or clear cytoplasm
- Desmoplastic response most often in centre of tumour
- Infiltrative edge and can have pagetoid surface involvement
- PNI and intraneural involvement common
“Clear cell carcinoma”

- Foci of squamous differentiation may be seen
- Origin from surface epithelium can be seen
- No duct formation
- Diffuse p63
- EM: features suggesting squamous differentiation
- At least not an adenocarcinoma
- Weinreb 2013
Clear cell carcinoma: molecular

- *EWSR1-ATF1* fusion recently identified (85-90%)
- Also present in clear cell odontogenic carcinoma but not other clear cell mimics
- *EWSR1* gene rearrangements are present in soft tissue myoepithelial tumours but fusions are distinct from salivary counterparts
Salivary duct carcinoma

- Papillary cribriform tumour with comedo necrosis, apocrine appearance
- High grade
- **ER PR** negative
- Androgen positivity discovered inadvertently (90%) 
- Some PSA positive
- High grade carcinoma that is AR negative, non apocrine – probably another type of carcinoma e.g. HGT of another type, SCC
Salivary duct carcinoma: androgen receptor positive
androgen deprivation therapy under investigation
Salivary duct carcinoma:
Her2 antibody (approximately 15%)
Intraductal carcinoma

- Intraductal carcinoma
  (low grade salivary duct adenocarcinoma/ low grade cribriform cystadenocarcinoma)
- Outer myoepithelial layer should be identifiable
Salivary duct carcinoma vs intraductal carcinoma

**Salivary duct carcinoma**
- High grade, invasive
- AR positive
- S100 negative
- SOX10 negative
- P63, p40 negative

**Intraductal carcinoma**
- Low grade, intraductal
- AR negative
- S100 positive
- SOX10 positive
- P63, p40 highlights intraductal component
Mucoepidermoid carcinoma
Grading in mucoepidermoid carcinoma

- AFIP: Goode/Auclair/Ellis 1998
- Brandwein: modification of AFIP score 2001
- Modified Healey (MD Anderson) 2009
- Katabi/MSKCC 2014

- Low grade: local excision
- High grade: excision, neck dissection +/- radiotherapy
Quantitative grading systems

**AFIP**
- Intracystic <20% +2
- Neural invasion +2
- Mitoses >4/10 hpf +3
- Necrosis +3
- Anaplasia +4
- Low 0-4
- Intermediate 5-6
- High >7

**Brandwein**
- Intracystic <25% +2
- Neural invasion +2
- Mitoses >4/10 hpf +3
- Necrosis +3
- Nuclear atypia +3
- *Invades in small nests* +2
- Vascular invasion +3
- Bone invasion +3
- Low 0
- Intermediate 2-3
- High >4
Qualitative systems

**Modified Healey**
- **LG**: macrocysts, minimal pleomorphism, circumscribed invasive edge
- **IG**: fewer microcysts, non macrocysts, more solid, mild – moderate pleomorphism
- **HG**: solid, no macrocysts, easily found mitoses, cytologically high grade

**MSKCC**
- **LG**: cystic, circumscribed, 0-mitoses1/10 hpf, no necrosis
- **IG**: mostly solid, circumscribed or infiltrative mitoses<4/10hpf, non necrosis
- **HG**: mitoses >4/10 hpf, necrosis present
Katabi (MSKCC)

• Compared grading systems with outcome
• Lack of consensus among grading systems
• AFIP more likely to downgrade, Brandwein more likely to upgrade (e.g. bone invasion)
• Modified Healey: descriptors too ambiguous
• Suggest MSKCC criteria are relatively more objective
• High grade mucoepidermoid carcinoma is rare
• All scoring systems correlate with DSS and RFS
• No difference in outcome for low grade and intermediate grade (no matter which scoring system is used)
Mucoepidermoid carcinoma: unique translocation

- t(11;19)(q21;p13) results in MECT1-MAML2 fusion
- only seen in mucoepidermoid, but also at other sites e.g. lung
- useful in diagnosis
- >50% tumours show fusion
- Initially - fusion positive associated with better prognosis
- Associated with low/intermediate grade tumours only
- Later fusion positive high grade carcinomas identified
Mucoepidermoid carcinoma

- Jee et al: genome wide copy number alterations study subdivide MEC into 3 groups
  - Low grade, fusion positive, few genomic imbalances: favourable prognosis
  - High grade, fusion positive, multiple genomic imbalances: unfavourable prognosis

*Genomic profiles and CRTC1-MAML2 fusion distinguish different subtypes of mucoepidermoid carcinoma.*

Carcinoma ex pleomorphic adenoma

- About 12% (7-27%) of all salivary carcinomas
- Often change in pre existing mass
- Grossly sclerotic nodule (pre existing PA) within infiltrative tumour
Carcinoma ex pleomorphic adenoma

• 1 -Must identify the subtype of carcinoma
• Many are salivary duct carcinoma but also less aggressive subtypes
Carcinoma ex pleomorphic adenoma

- **2- identify extent**

- **Intracapsular**: abnormal proliferation within/ between ducts in PA, capsule not breached

- **Minimally invasive**: breach of capsule by carcinoma, measurable in mm

- Unclear what cut off is associated with good prognosis - *previously 1.5mm but possibly 4-6mm*

- **Widely invasive**: extensive invasion outside capsule, may be hard to find PA
Carcinoma ex pleomorphic adenoma
58 year old male FNA “neck mass”

• Poorly differentiated carcinoma
• p16 antibody positive
• “No primary”

• Treated as p16 positive metastatic squamous carcinoma with unknown primary
Metastasising pleomorphic adenoma

- Histologically identical to PA but metastases: regional or distant
- Arises after multiple recurrences
- Spreads to lung and bone
- 40% die of disease
- Previously under malignant category – now under benign
- *Still considered biologically aggressive*


Seethala RR¹, Stenman G².
Summary

• Secretory carcinoma
• Polymorphous adenocarcinoma (combined PLGA and CAMSG)
• More definition required in carcinoma ex PA
• Increasing molecular signatures: secretory, adenoid cystic, mucoepidermoid, clear cell carcinoma
• Grading in mucoepidermoid remains a problem
Mammary analog secretory carcinoma, low-grade salivary duct carcinoma, and mimickers: a comparative study.

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Patel KY1, Solomon IH, El-Naggar AK, Lewis JS Jr, Chernock RD

Hyalinizing clear cell carcinoma of salivary gland: a review and update.

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Prognostic features in mucoepidermoid carcinoma of major salivary glands with emphasis on tumour histologic grading.

Katahi N1, Ghosein R, Ali S, Dogan S, Klimstra D, Ganly I

Diagnostic difficulties in lesions of the minor salivary glands

Khurram, Syed A. et al.
Diagnostic Histopathology, Volume 23, Issue 6, 250 - 259

DOG1: a novel marker of salivary acinar and intercalated duct differentiation.


Seethala RR¹, Stenman O²


Predictors of Outcome in the Phenotypic Spectrum of Polymorphous Low-grade Adenocarcinoma (PLGA) and Cribriform Adenocarcinoma of Salivary Gland (CAGS): A Retrospective Study of 69 Patients.

Xu B¹, Anjia A, Ghossein R, Katabi N


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