Suspicious for Malignancy (SfM)
Milan system for reporting salivary gland cytopathology

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Malignant

Confident diagnosis of malignancy of an identified tumor type, supported by ancillary tests if necessary

Requires adequate diagnostic material and presence of diagnostic criteria

Allows definitive clinical management and the diagnosis can stand up to scrutiny and be confirmed on subsequent histology
A salivary gland FNA is classified as SM when some, but not all the criteria for a specific diagnosis of malignancy are present, and yet the overall cytologic features are suggestive of malignancy.

Markedly atypical cells with poor smear preparation, poor cell preservation, fixation artifact, or obscuring inflammation and blood.

Presence of limited cytologic features of a specific malignant lesion (e.g. adenoid cystic carcinoma, mucoepidermoid carcinoma, and acinic cell carcinoma) in an otherwise sparsely cellular aspirate.

Presence of markedly atypical and/or suspicious cytologic features in a subset of cells but admixed with features of a benign salivary gland lesion.
Markedly atypical cells suspicious for high-grade carcinoma, but with obscuring blood limiting the assessment (smear, Romanowsky stain)
The smear shows rare markedly atypical cells suggestive of carcinoma, but the classification is limited by scant cellularity (smear, Papanicolaou stain)
The smear shows a group of epithelial cells suggestive of acinic cell carcinoma, but hypocellularity and background blood in the absence of ancillary studies limits the evaluation (smear, Papanicolaou stain)
This smear is composed of basaloid cells and abundant matrix spheres with a pattern suspicious for adenoid cystic carcinoma (smear, Papanicolaou stain)
• The smear consists of epithelial cells with epidermoid features, suggestive of mucoepidermoid carcinoma (smear, Romanowsky stain)
SfM

• This aspirate shows a monotonous population of intermediate- size lymphocytes that, based upon cytomorphology alone, are highly suspicious for lymphoma

• Additional ancillary studies including immunophenotyping are needed for classification (smear, Papanicolaou stain)
Case 1

Male, 82 years
Presented with sudden appearance of a painless nodule in the parotid
USG FNA performed
Scanned slide discussion
SfM onsite evaluation: low cellularity

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<th>Cell type</th>
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<td>• Fibrillary</td>
<td>• Mucin</td>
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<td>• Squamous</td>
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# SfM onsite evaluation

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SfM diagnostic algorithm

Glandular cell type

Low grade cytology: acinic cell carcinoma, secretory carcinoma, polymorphous adenocarcinoma, metastatic carcinoma

High grade cytology: salivary duct carcinoma, metastatic carcinoma
SfM diagnostic algorithm for this case

- **Glandular cell type**
  - High grade + Necrosis
    - Salivary duct carcinoma
    - Metastatic carcinoma
TTF1, PSA, PRAP, AR, GCDFP1
PSMA+
Findings on cell block

- TTF1, PSA, PRAP, AR, GCDFP1 –
- PSMA+

- Metastatic prostatic adenocarcinoma

- Fukasawa Y. · Honda T. · Natsume M. et al. A Case of Advanced Submandibular Gland Cancer in Which Increased Prostate-Specific Antigen and Multiple Bone Metastases Wrongly Suggested Concurrent Prostate Cancer.
Salivary duct carcinoma
Histological findings of salivary duct carcinoma

- **a** H&E staining of submaxillary gland duct carcinoma (×100). Cancer cells grow to solidity and invade striated muscles (arrow).

- **b** Circular or irregular nucleus with clear nucleoli, and cells with abundant basic cell grow to solidity. These are rich in color, such as large nuclei and polyhedral cells, and oncocyte-like cells also mix (×400).

- **c** Immunostaining for PSA shows the focal presence of PSA-positive cells (×400).
Salivary duct carcinoma vs metastatic prostate carcinoma

Specific similarities are that (1) HE staining of the ductal lumens shows the characteristic findings of both comedo necrosis and cribriform pattern

(2) tumor cells do not show a keratinizing tendency or intercellular bridges;

(3) mucus staining (with mucicarmine alcian blue) shows no evidence of mucus production in the cytoplasm.

Metastatic prostate carcinoma to salivary glands

More commonly prostate cancer metastasis can occur in-
- Bone, Lymph node, Lung, Liver, Brain

Rare locations of prostate cancer metastasis include-
- Adrenal gland, Breast, Eye, Kidney, Muscle, Pancreas, Salivary gland, Spleen
Metastatic prostatic adenocarcinoma


• Hélissey, C; Rouanne, M; Arnaud, F; Le Moulec, S. Parotid gland metastasis from prostate cancer. Anti-Cancer Drugs: March 2015 - Volume 26 - Issue 3 - p 367–370.

• Is docetaxel still the best treatment option?

• Important clinical question to answer- any neuroendocrine differentiation
Case 2

Female, 84 years

Painful lump left parotid

Scanned slide
Carcinoma ex-pleomorphic adenoma
Incidence

4% of salivary neoplasms, 12% of salivary malignancies but only 1% of intraoral salivary gland or minor salivary gland neoplasms

5% of parotid tumors but 18% of malignant parotid tumors

Associated with pleomorphic adenomas: 2% risk of malignant transformation if present < 5 years, 10% risk if 15 years

Clinically, have sudden increase in growth, pain or facial paralysis, facial tingling, trismus
A 48-year-old woman with a carcinoma ex pleomorphic adenoma (case 1).
A 76-year-old man with a carcinoma ex pleomorphic adenoma (case 2).
a Ca ex PA demonstrating the coexistence of PA (left) and carcinoma (right) components (H&E, original magnification ×10). b Higher magnification of the PA area in a composed of glands with myoepithelial cells radiating out in a myxoid stroma (H&E, original magnification ×40). c Higher magnification of the carcinoma area in a composed of a poorly differentiated adenocarcinoma with scanty glandular formation, marked nuclear pleomorphism and atypical mitosis (H&E, original magnification ×40)
Incidence of detection by FNA

Zbären et al reported that 44% (7 of 16) Ca ex PA cases showed malignant cells at FNAC.


Nouraei et al noted that 29% (4 of 14) of the cancers were positive for malignancy by FNAC.

Carcinoma ex-pleomorphic adenoma

Because the incidence of malignancy is correlated with the duration of pleomorphic adenoma, the risk of developing malignancy is only about 1.5% for a duration of <5 years but increases to 9.5% for a duration of >15 years.

Carcinoma ex pleomorphic adenoma is an infrequent aggressive malignancy that is believed to evolve from a pre-existing benign adenoma. It accounts for 3.6% (range, 0.9%–14%) of all salivary neoplasms and for 11.7% (range, 2.8%–42.4%) of salivary malignancies.
Prognosis of Ca ex-PA

Loco-regional recurrence is considered to be a major prognostic factor for patients with Ca ex PA. Olsen et al reported local recurrence in 23% of patients and regional recurrence in 18% of patients with Ca ex PA.

The prognosis after detection of progression or recurrence is poor, with a median survival of less than 1 year. Olsen et al noted that all disease specific deaths occurred within 6 years after the initial operation.

Olsen et al noted a 5 year disease-specific survival rate of 37% in 73 patients with the cancer.

Nouraei et al reported 44% survival rates in 28 patients with the cancer.

Zbären et al noted a higher survival rate of 75% in their series of 24 patients.

Luers et al reported a survival rate of 60% in 22 patients with the cancer.

The higher survival rate noted by Zbären et al may due to the higher proportion of intra-capsular Ca exPA.
Molecular studies have revealed that the development of Ca ex PA follows a multi-step model of carcinogenesis.

- Progressive loss of heterozygosity at chromosomal arms 8q, then 12q and finally 17p.
- There are specific candidate genes in these regions that are associated with particular stages in the progression of Ca ex PA.
- In addition, many genes which regulate tumour suppression, cell cycle control, growth factors and cell–cell adhesion play a role in the development and progression of Ca ex PA.

Prognostic factors

Stage, extent of invasion beyond the capsule (< 8 mm is associated with benign behavior)

Histologic type and grade of carcinoma, proliferation index, proportion of carcinoma

Extent of invasion, vascular invasion, atypical mitoses

Pathological stage, tumor size, proliferation index
Clinicians may regard even a malignant diagnosis as insufficient till specific type (primary vs metastatic) is confirmed.

Sometimes a suspicious diagnosis is sufficient for clinical management.
RCPATH ENDORSES THE PARIS AND MILAN TERMINOLOGIES

CLINICAL SAFETY NET TO AVOID OVERTREATMENT

PRESSURE BY CLINICIANS AT MDM TO UPGRADE SFM TO MALIGNANT

SFM AT ROSE- HOLDING CATEGORY, ALLOWING PROVISIONAL DIAGNOSIS AND FEEDBACK TO RADIOLOGISTS AND TO CLINICIANS

NO ROSE NO FNA SERVICE

SAFE HAVEN- SOME STUDIES SHOW HIGHER PPV FOR SFM THAN MALIGNANT

TRAINEES- LEARN SALIVARY GLAND HISTOPATHOLOGY ALONGSIDE

ANCILLARY TESTS—GREAT IMPACT ON UPGRADING TO MALIGNANT NAMED PRIMARIES AND IN ASCERTAINING THE SITES OF METASTATIC CARCINOMA
Summary:

Suspicious for malignancy (SfM)

You believe that the aspirate is malignant but wish you had more cells with diagnostic features to be sure.

Quantitative factor mainly

Not so much about a particular number of cells, rather about the presence of adequate diagnostic criteria in appropriate clinical context.

Decision for SfM vs Malignant based on clinical context and experience of pathologist.

ROSE and collection of adequate material may help in upgrading to Malignant category.
References


Case history & ROSE findings

• 12 year old boy with a lump in the parotid gland
• USG FNA yielded a haemorrhagic mucoid aspirate on a single pass only
Case history & ROSE findings

• 12 year old boy with a lump in the parotid gland ?duration
• USG FNA yielded a haemorrhagic mucoid aspirate on single pass

• ROSE: SfM favour mucoepidermoid carcinoma
• Intradepartmental consensus meeting (Dr G Dixon): Malignant, favour secretory carcinoma
• Insufficient material on cell block for ancillary tests
• Excision of nodule in the accessory lobe of the parotid
Histology

- S100 and GCDFP positive
- DOG1 negative
- Genetics (FISH) demonstrated t(12;15)(q13;q25) translocation, a fusion of the $ETV6$ and $NTRK3$ gene
- Features confirm secretory carcinoma