Salivary Duct Carcinoma: Update

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21nd National Congress of Pathology, İzmir, 16 -20 November 2011

Salivary duct carcinoma (SDC)

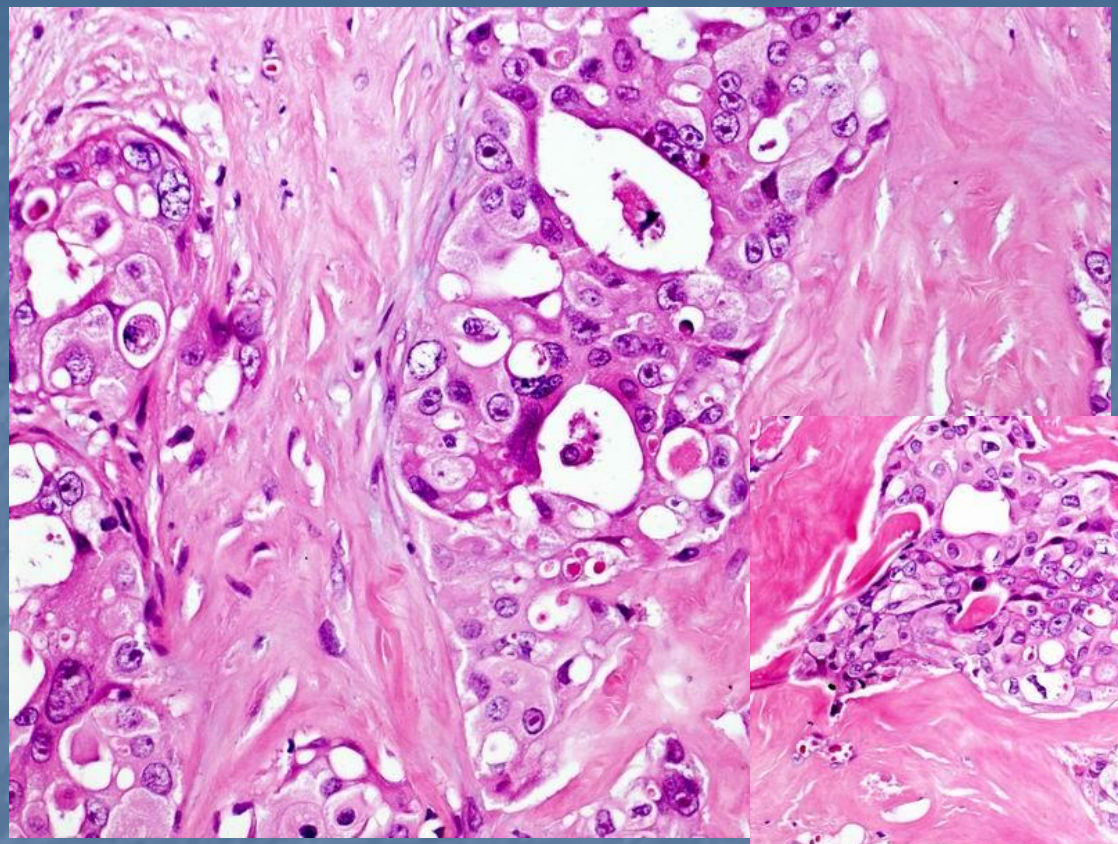
- aggressive neoplasm of salivary glands that shows a considerable histological similarity to ductal invasive breast cancer with DCIS component
- First described Kleinsasser in 1968
  - *Arch Klin Exp Ohren Nasen Kehlkopfheilkd* 1968;**192**:100-5.
- recognised as a distinct entity in the World Health Organization (WHO) classification of 1991, and confirmed in the latest 2005 edition

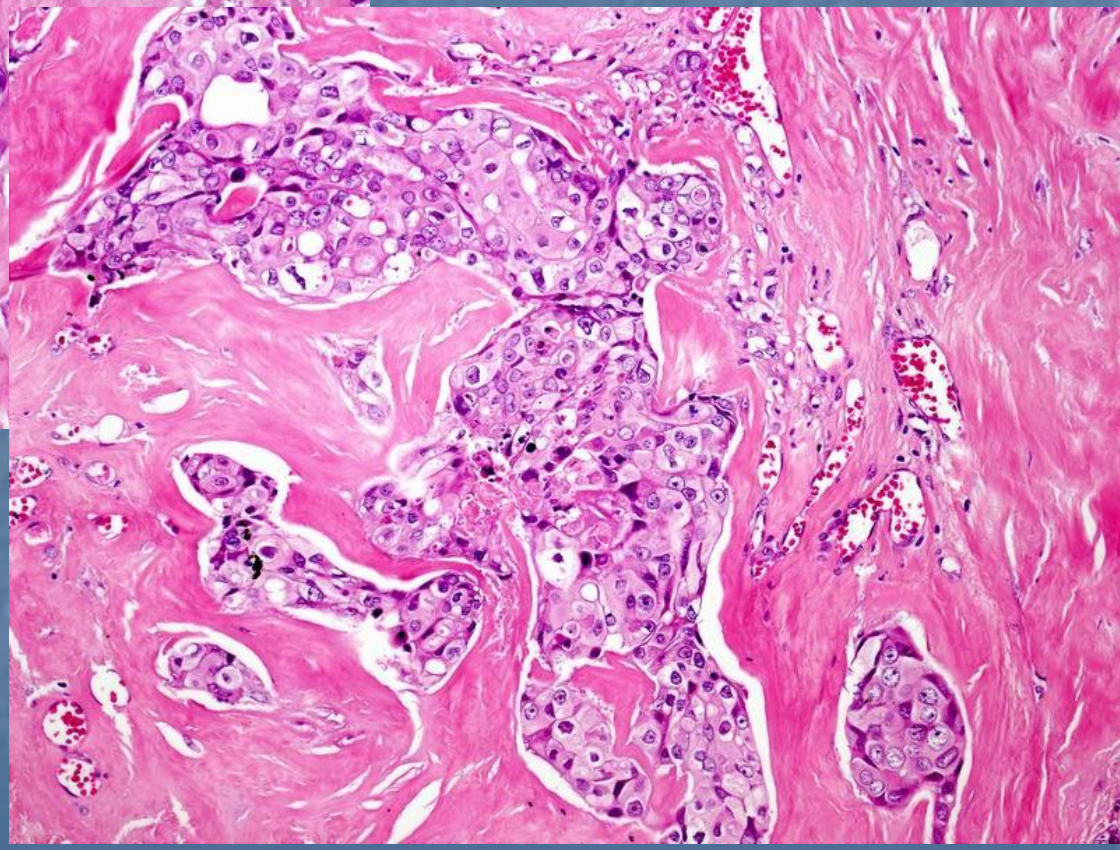
Salivary duct carcinoma (SDC)

- often invade the facial nerve
- recur locally and give rise to distant metastases
- over 60% of patients die of disease within 5 years of the initial diagnosis, despite radical surgery and adjuvant chemo/radiotherapy

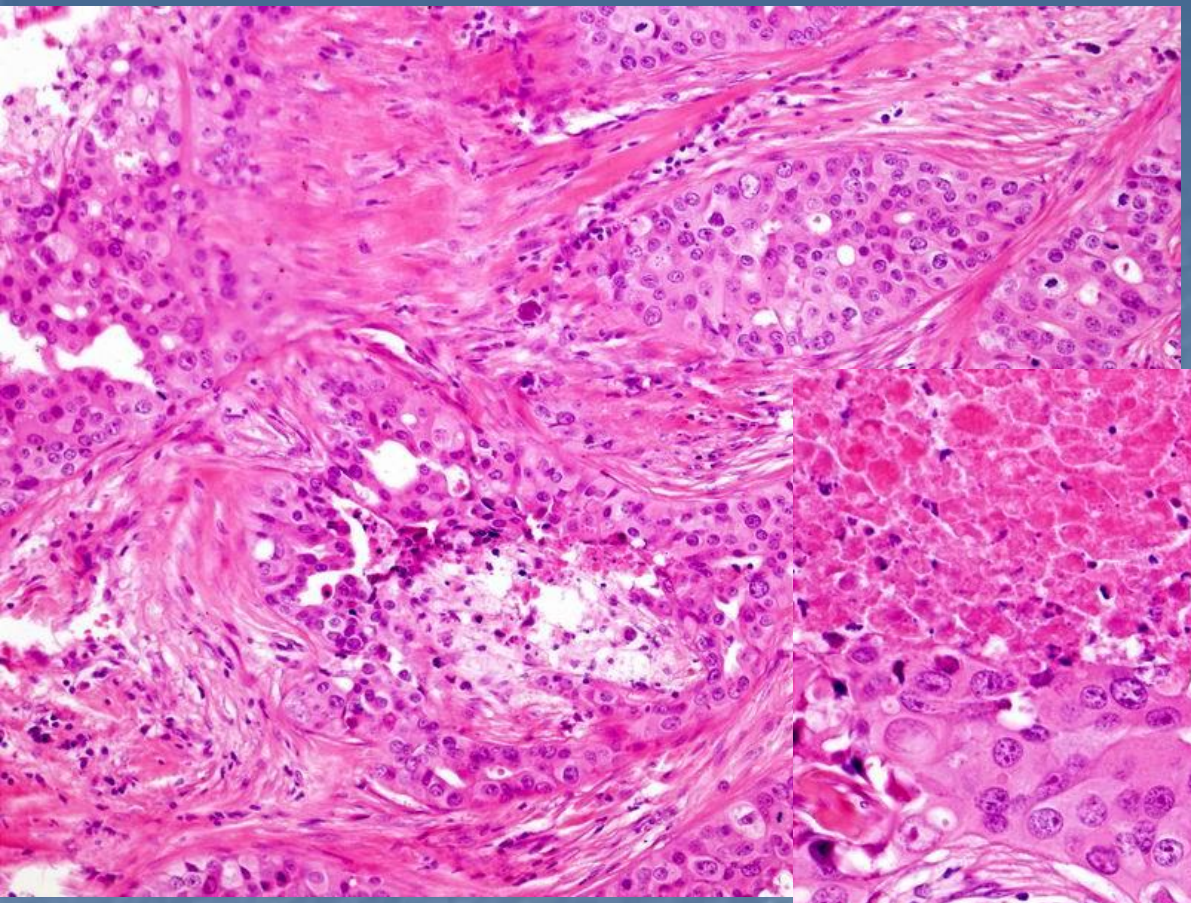
Histomorphology

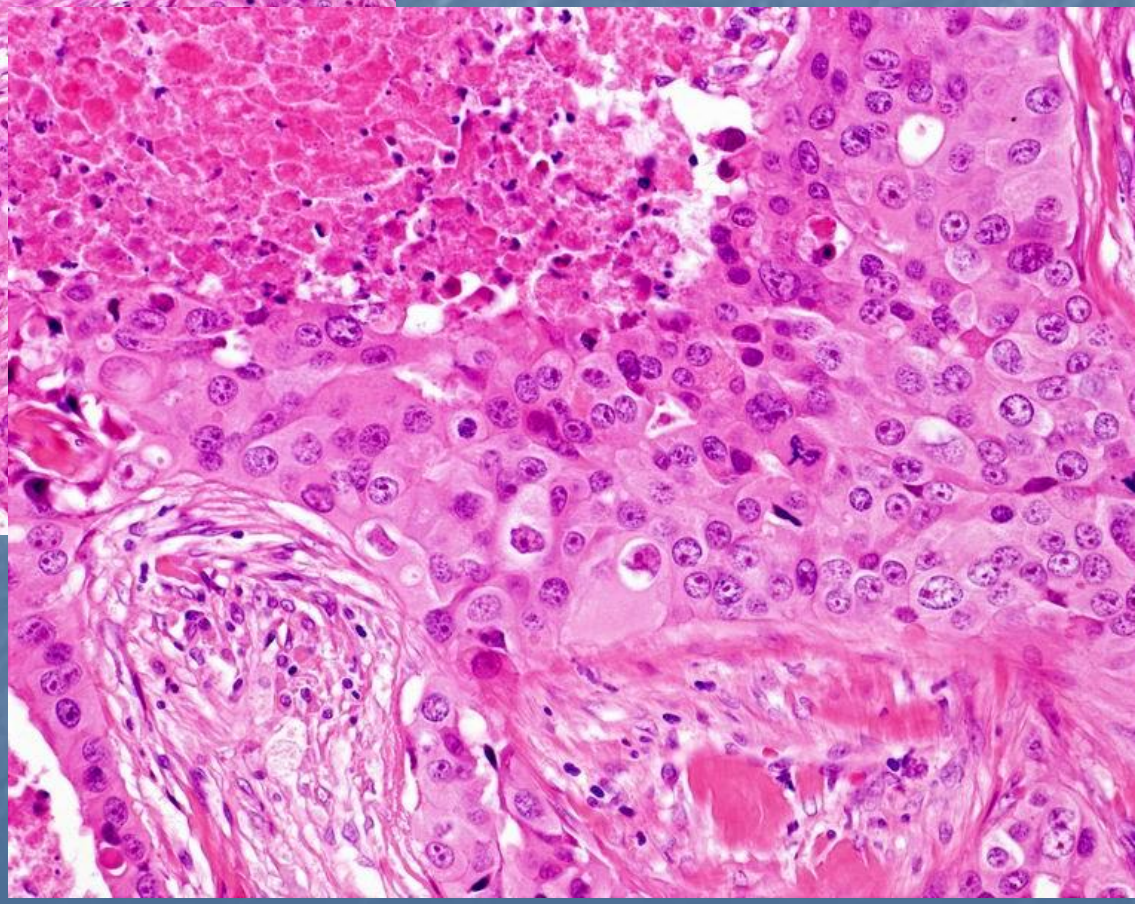
- composed of a mixture of ducts, cribriform structures, nests and cords of cells often embedded in a desmoplastic stroma
- papillary and solid patterns often with central comedo necrosis
- Eosinophilic/granular cytoplasm
- vesicular nuclei containing prominent central nucleoli
- poorly defined margins with perineural and vascular invasion



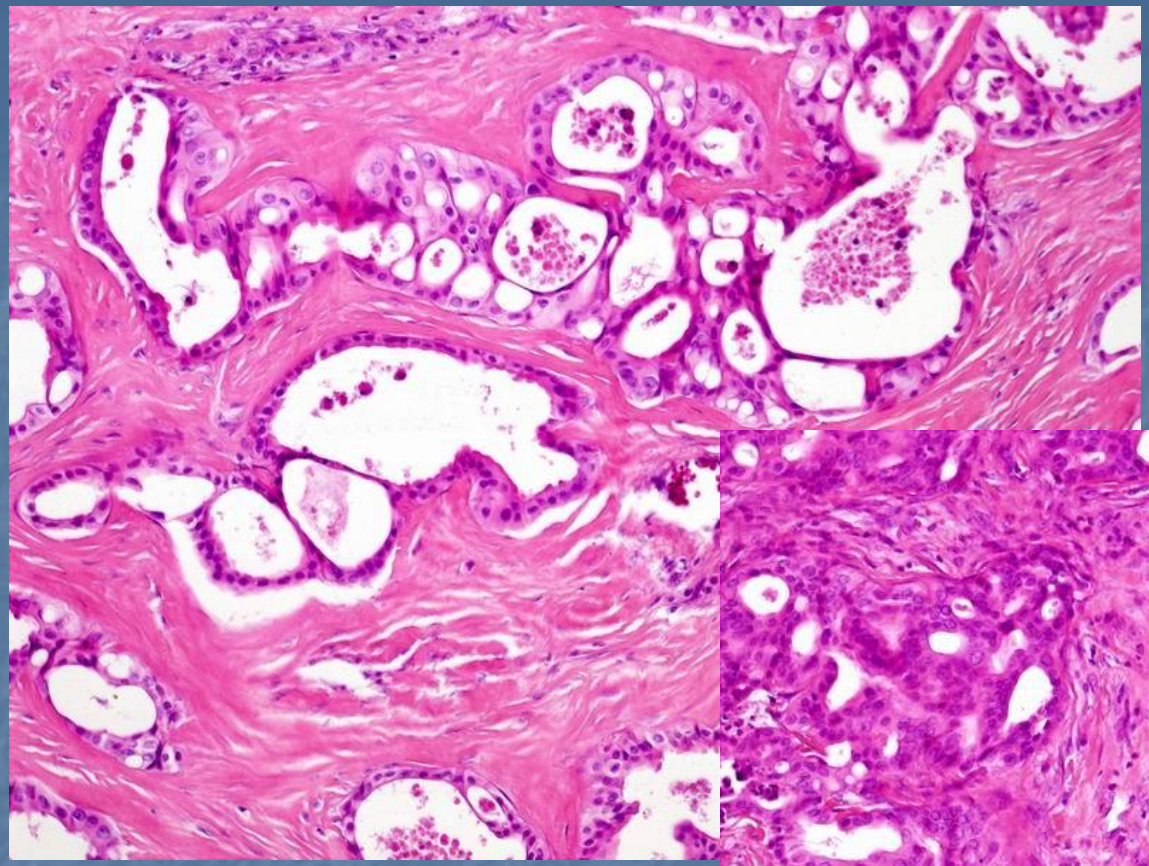


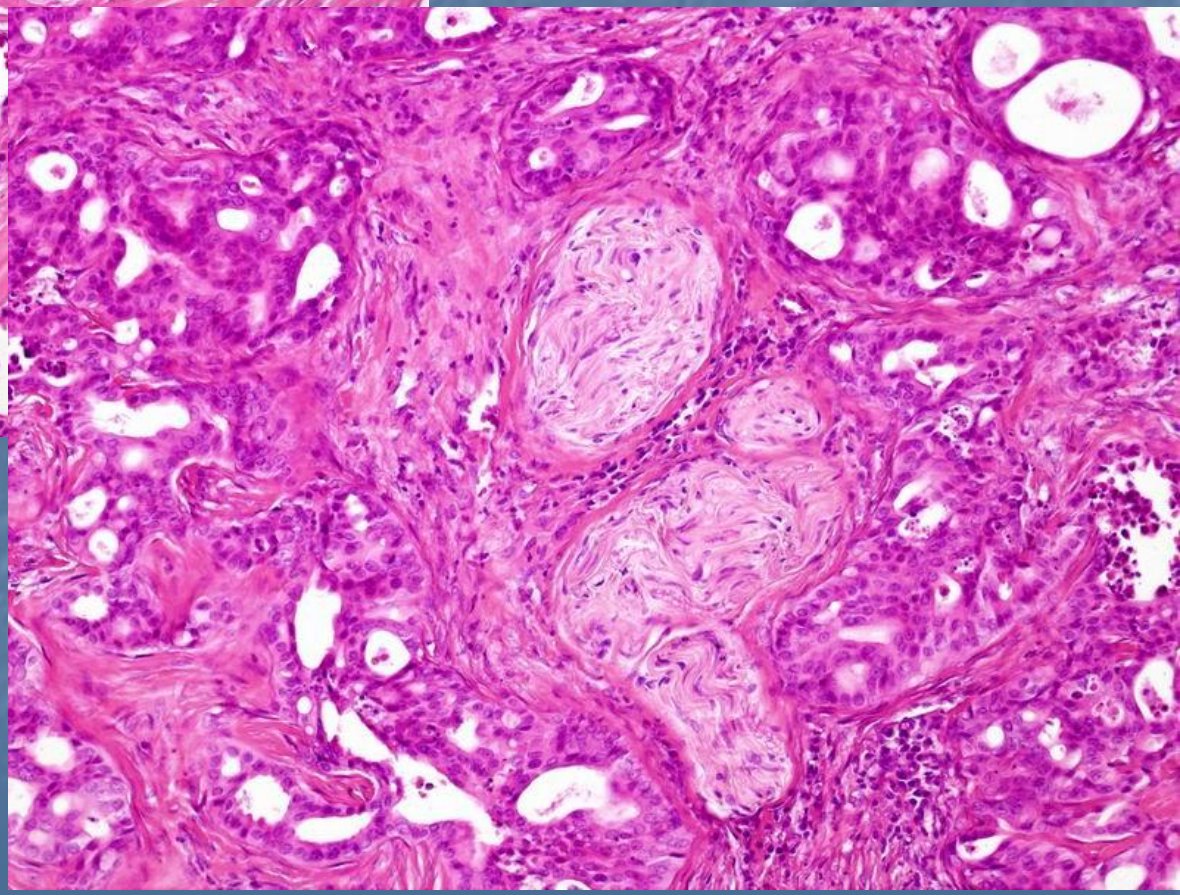
SDC solid cribriform, desmoplastic stroma





SDC solid patterns with central comedo necrosis, atypical mitoses





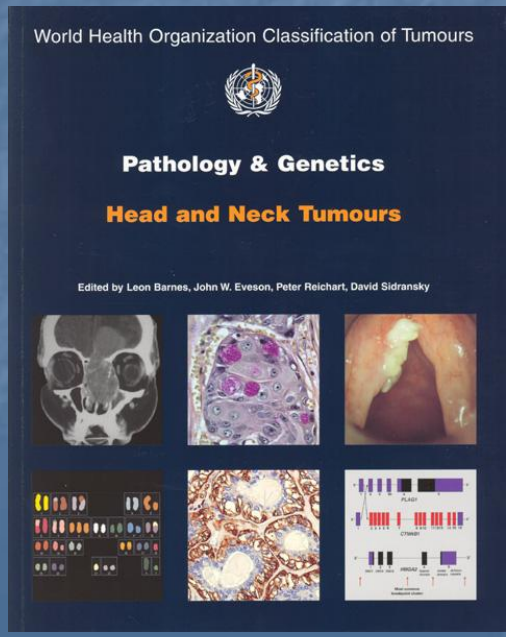
SDC tubular, cribriform, perineural invasion

Variants of SDC

- sarcomatoid
  - Henley et al. Hum Pathol 2000:31:208-213
- Papillary-cystic with psammoma bodies
  - Brandwein et al. Cancer 1990:65:2307-14
- oncocytic
- mucinous
  - Simpson et al. Am J Surg Pathol 2003:27:1070-1079
- micropapillary
  - Nagao et al: Am J Surg Pathol 2004:28:319-326

Histomorphological variability „Low-grade SDC"

- **Delgado R,** et al. Low grade SDC. A distinctive variant with low grade morphology and a predominant intraductal growth patern
  - ***Cancer 1993;72:1503-12.***
- Low-grade cribriform adenoca
  - ***WHO 2005***

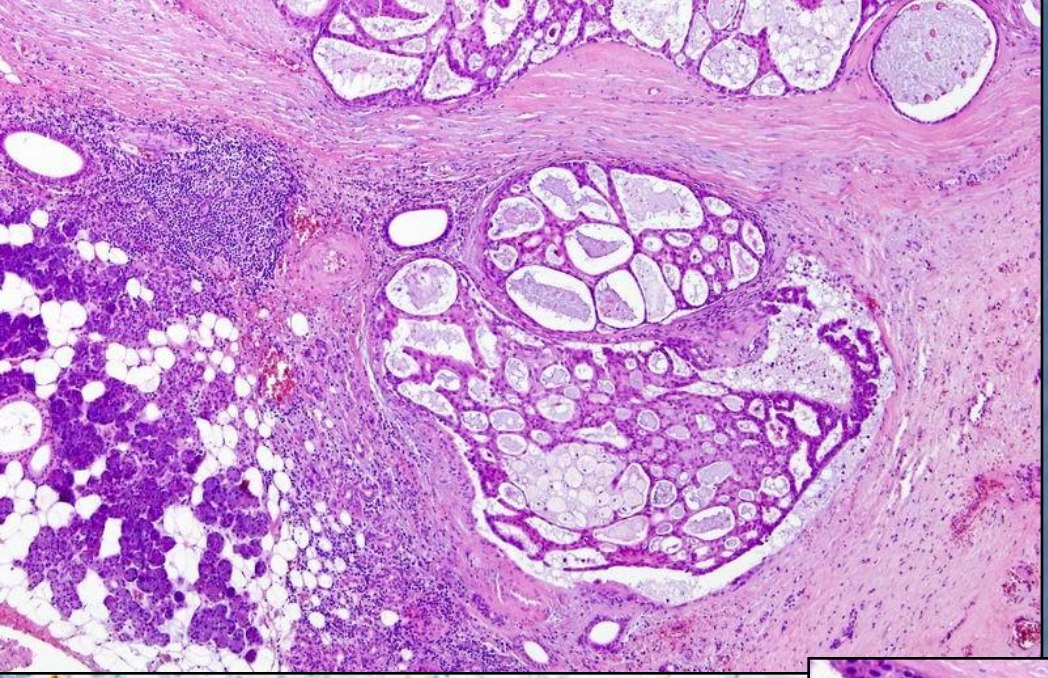


Intraductal carcinoma

- First described by Chen in 1983
- Not recognized in WHO 2005
- Characterized by pure intraductal proliferation as in breast DCIS
- concept of intraductal carcinoma has not gained wide acceptance
- Defined by intact myoepithelial cell layer

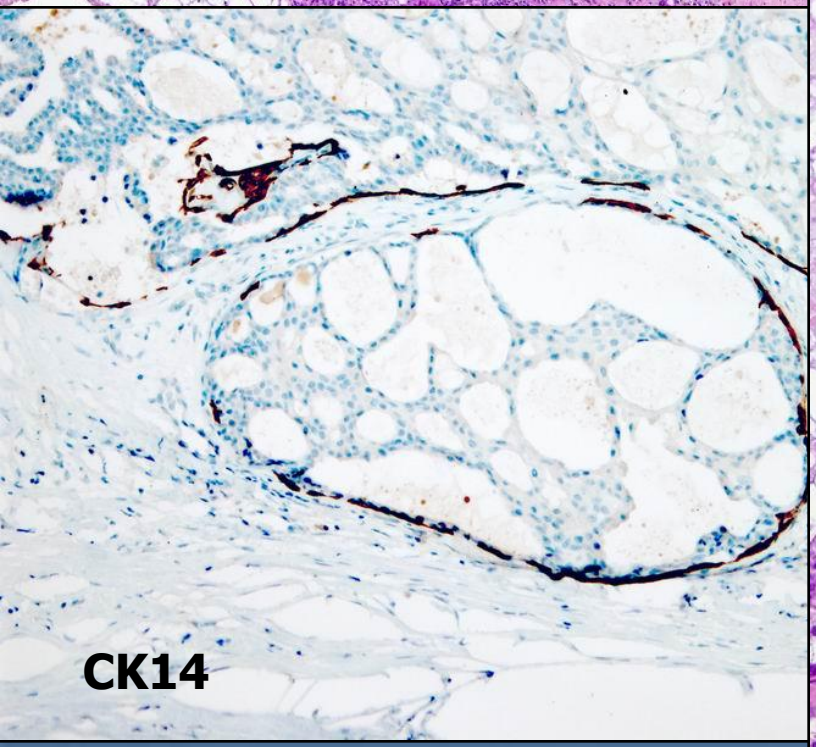
Intraductal carcinoma

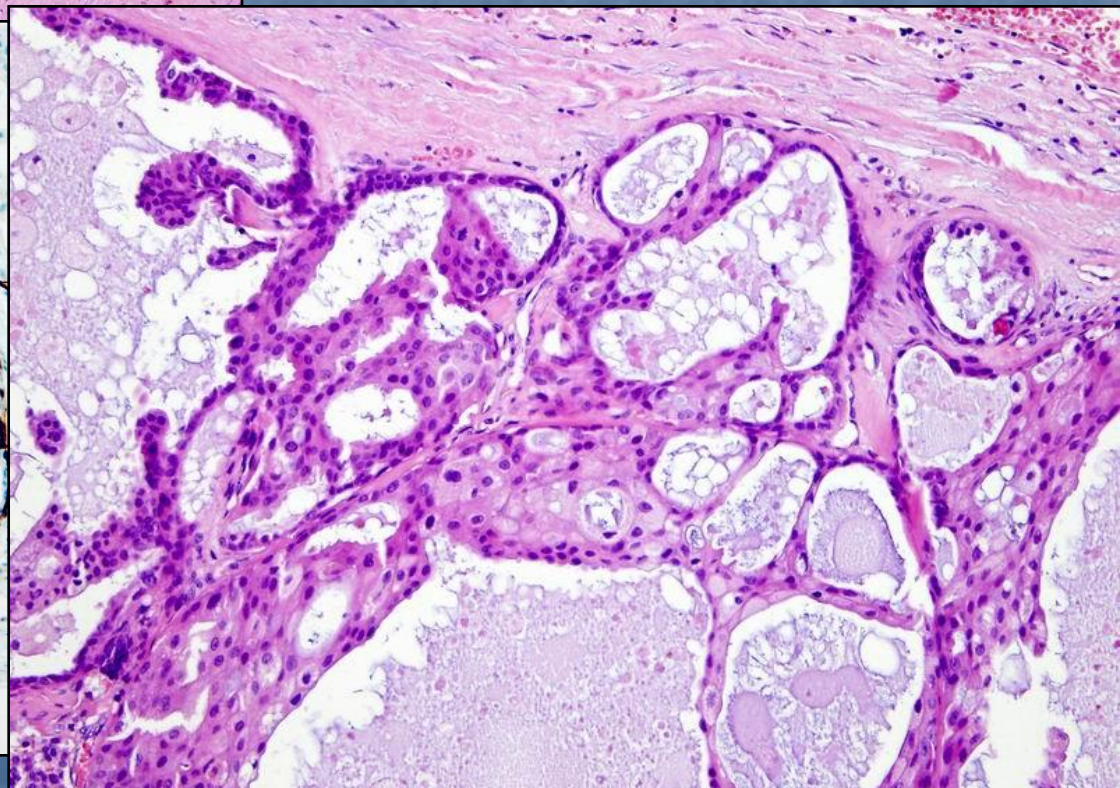
- Frequently affects parotid gland, minor glands can be involved
- Outcome is excellent, recurrences result from incomplete excision
- Composed of multiple ductal cystic spaces expanded by cribriform, solid, micropapillary structures, etc.
- Rule out invasive component- MEC layer



Intraductal carcinoma

Low-grade cribriform cystadenocarcinoma WHO 2005





Whether intraductal ca represents precursor lesion of SDC or is biologically separate entity remains to be clarified

Histopathology 2008, **53**, 416–425. DOI: 10.1111/j.1365-2559.2008.03135.x

Salivary duct carcinoma *in situ* of the parotid gland

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Date of submission 8 January 2008
Accepted for publication 11 April 2008

Simpson R H W, Desai S & Di Palma S
(2008) *Histopathology* **53**, 416–425

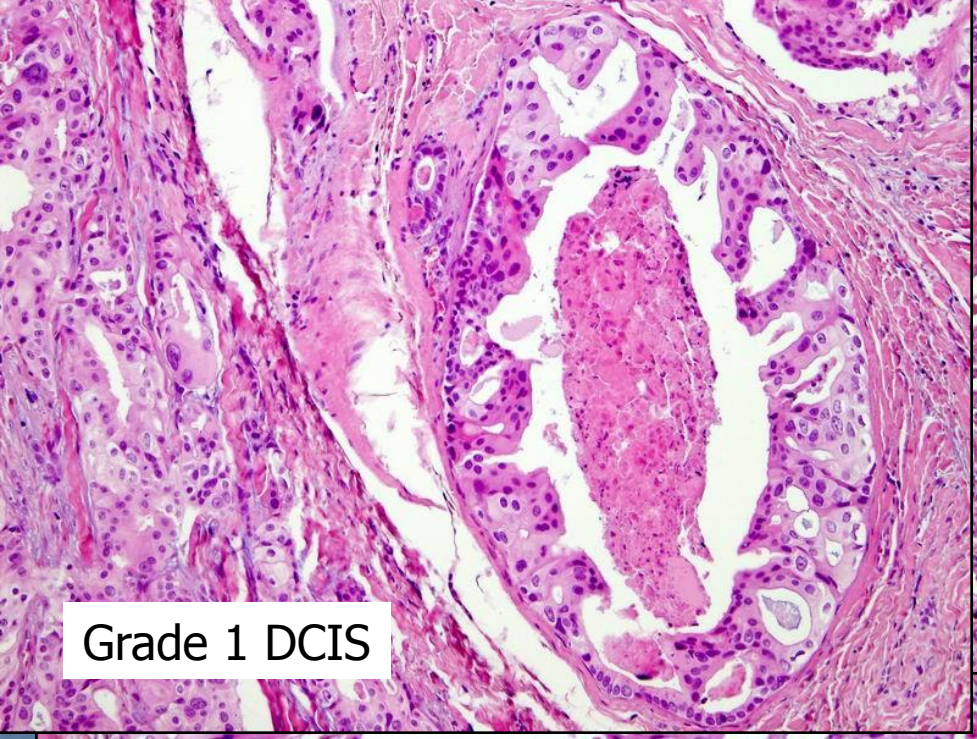
Salivary duct carcinoma *in situ* of the parotid gland

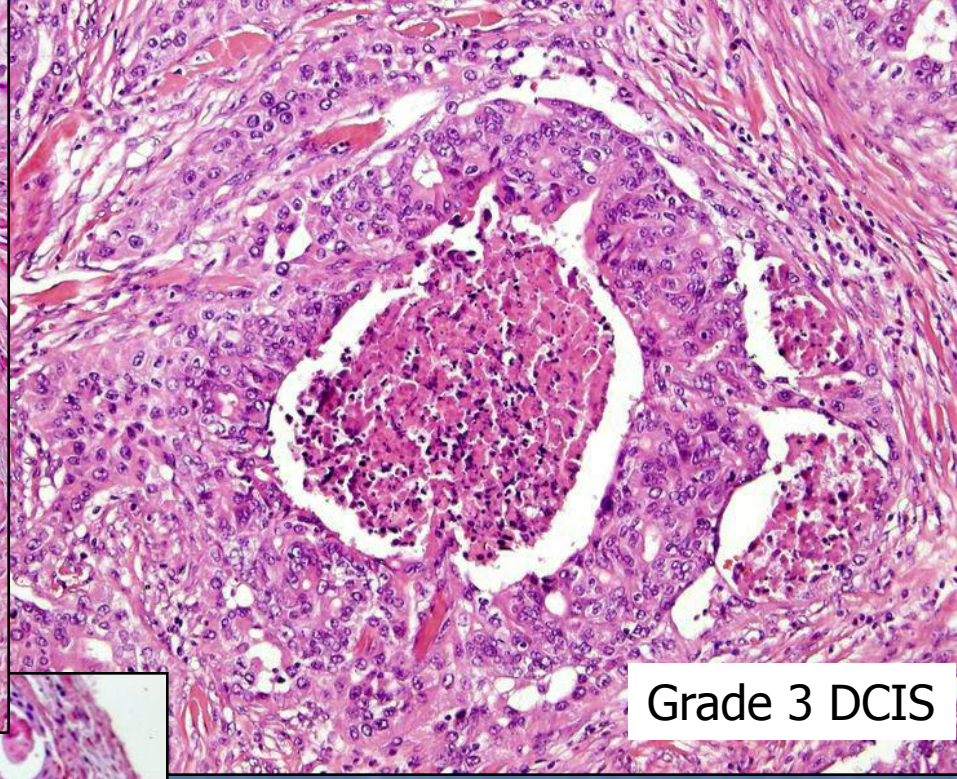
Aims: To describe three cases of purely *in situ* salivary duct carcinoma, so as better to define the entity.

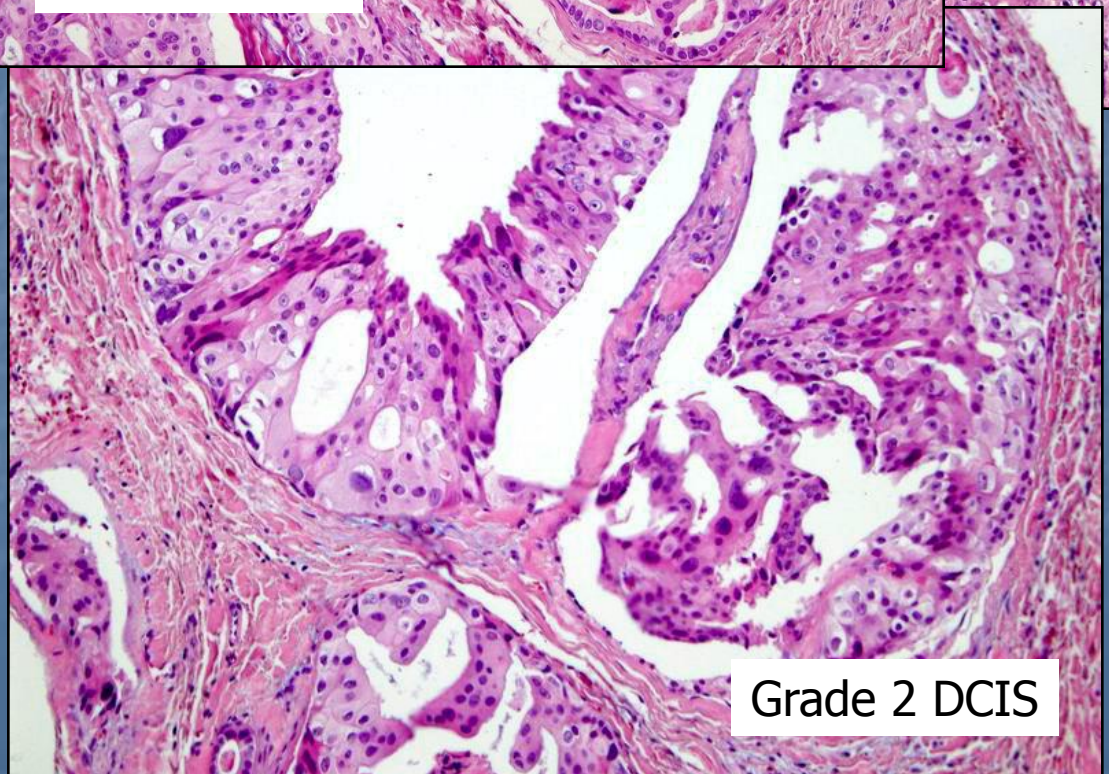
Methods and results: Three primary tumours of the parotid gland are presented, in each case composed of cysts and ducts and lined by high nuclear grade epithelial cells. All parts of each tumour were surrounded by a myoepithelial cell rim and there was no evidence of invasion. The tumour cells expressed immunohistochemical markers seen in invasive salivary duct carcinoma of usual (high-grade) type. In two cases the androgen receptor (AR) reaction was strong, but there was no immunohistochemical expression of HER2 protein or gene amplification by *in situ* hybridization. In the remaining case, fewer nuclei stained for AR, but both HER2 protein and gene amplification were demonstrated.

Conclusions: Salivary duct carcinoma *in situ* is morphologically similar to breast ductal carcinoma *in situ* and, although our cases are few, salivary duct carcinoma *in situ* can possibly be subdivided into luminal and non-luminal cell types, as can analogous mammary neoplasms. The present study cannot determine whether low-grade cribriform cystadenocarcinoma, architecturally similar but immunohistochemically different, is part of the spectrum of salivary duct carcinoma *in situ*, or whether it represents a separate entity.

Keywords: immunohistochemistry, parotid gland, salivary gland neoplasms, silver *in situ* hybridization



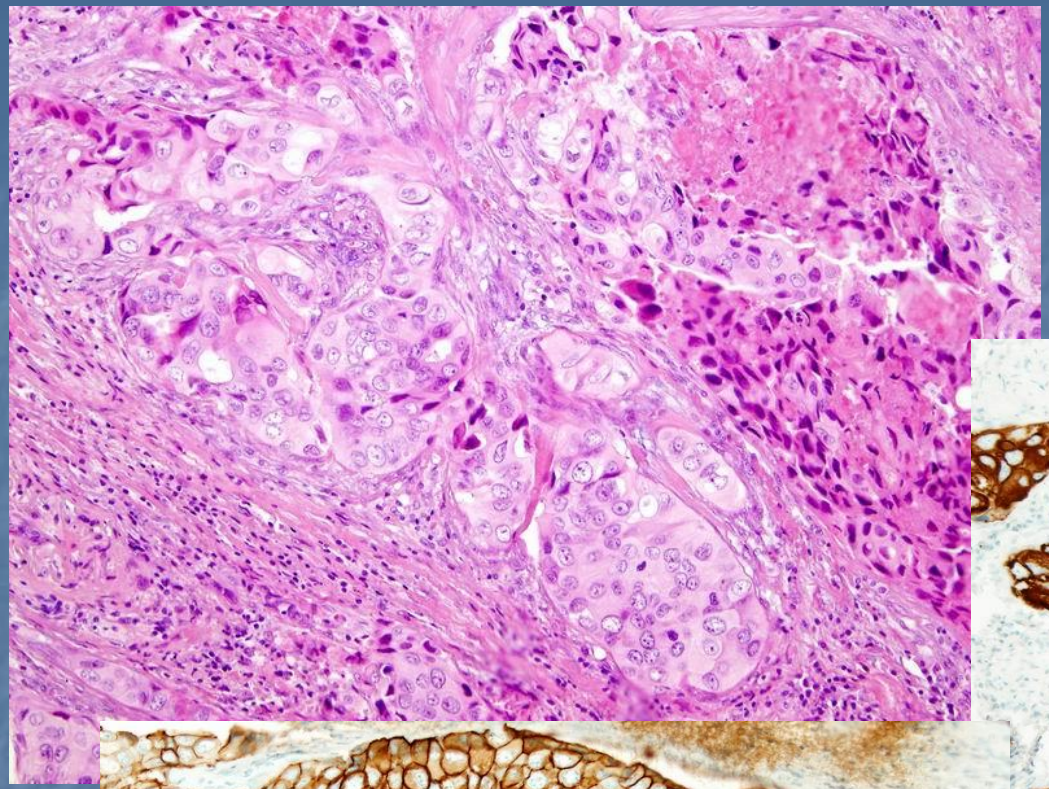


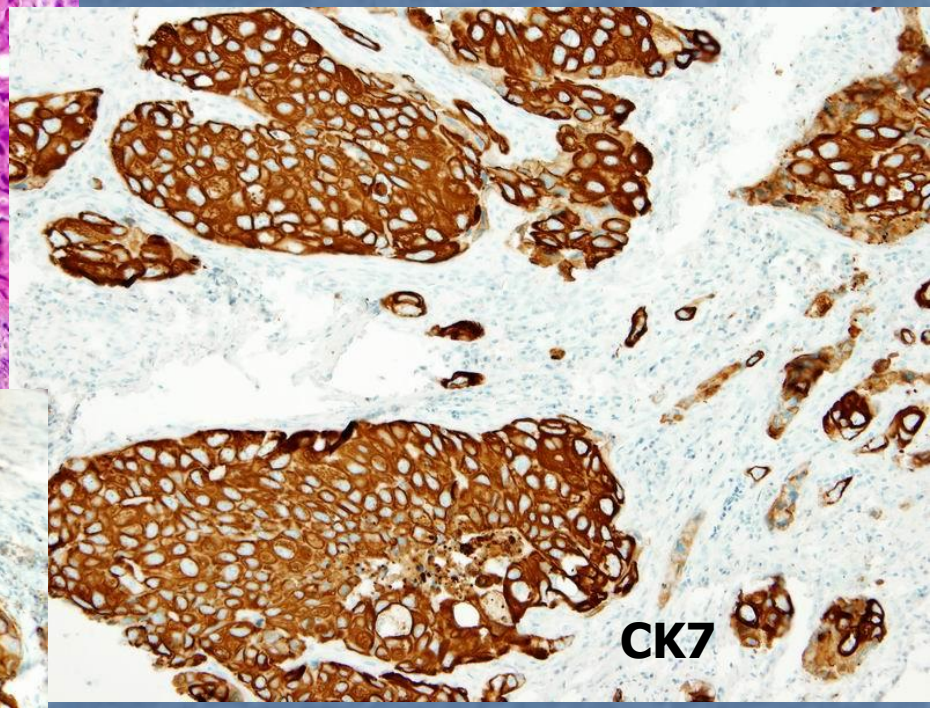


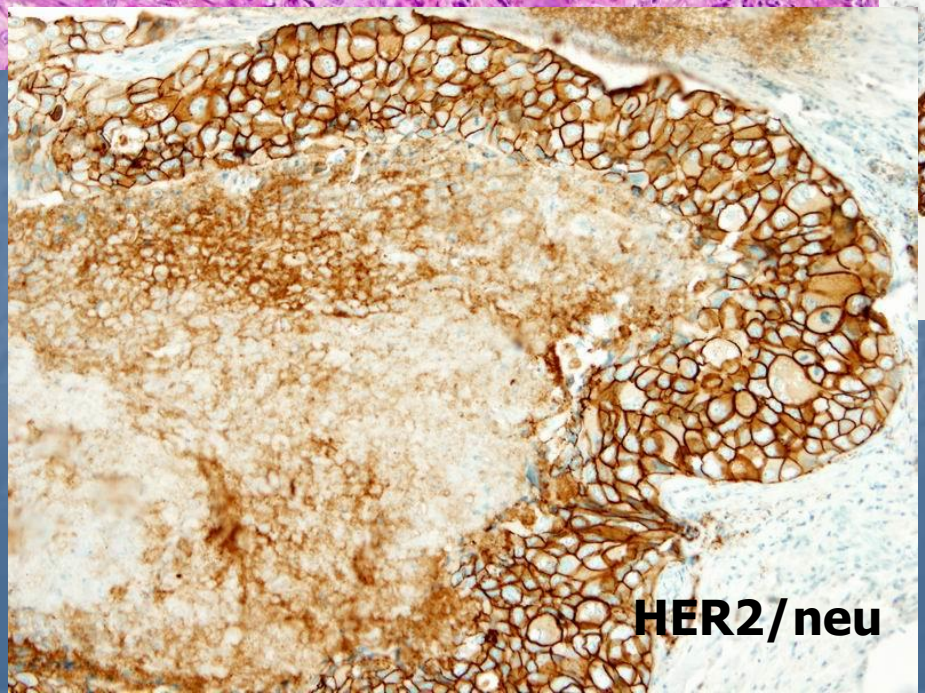
Salivary duct carcinoma with in situ component DCIS

Immunohistochemical variability

SDC oncocytic, G3, HER2/neu+

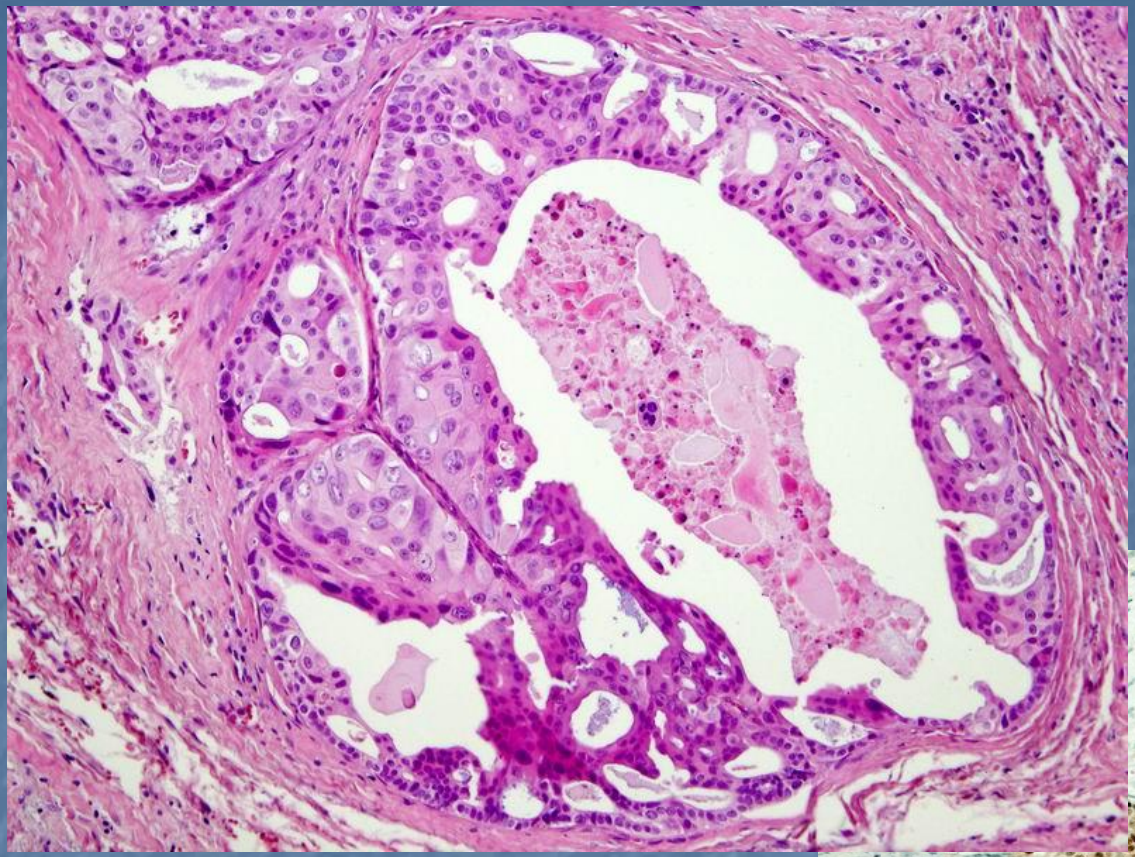


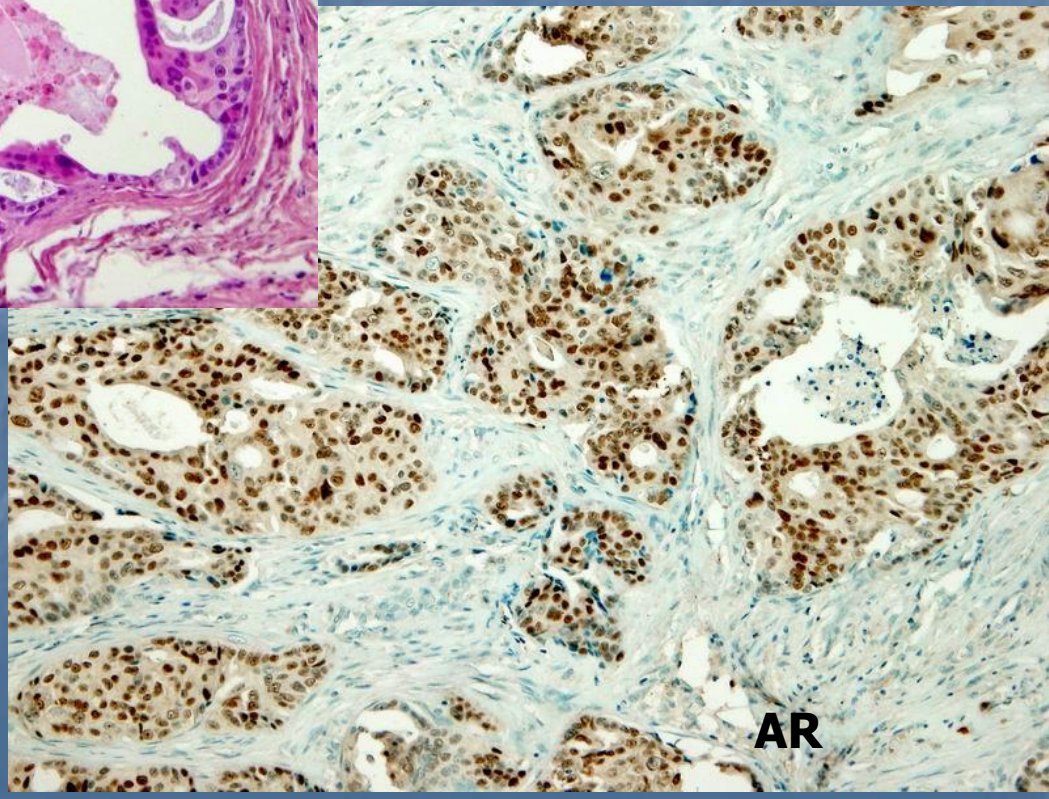




Skalova, et al. Histopathology 2003;42:348-56.

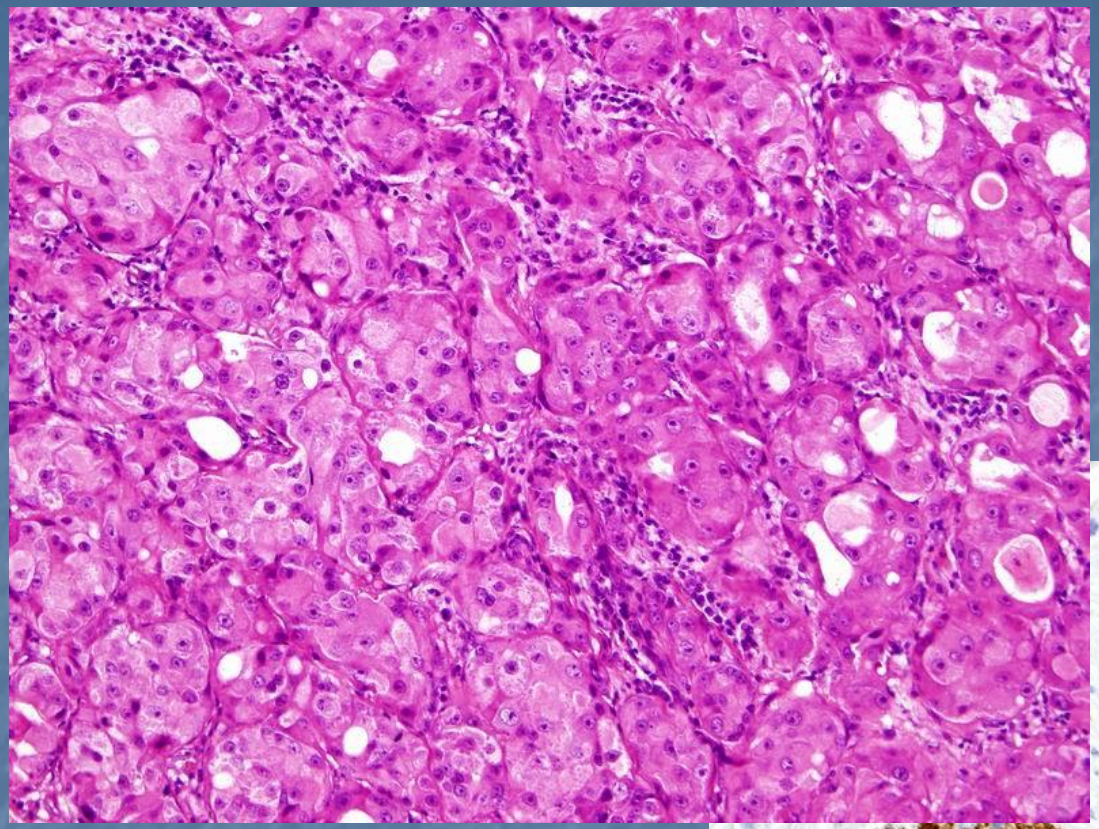
SDC, G2, androgen receptor+

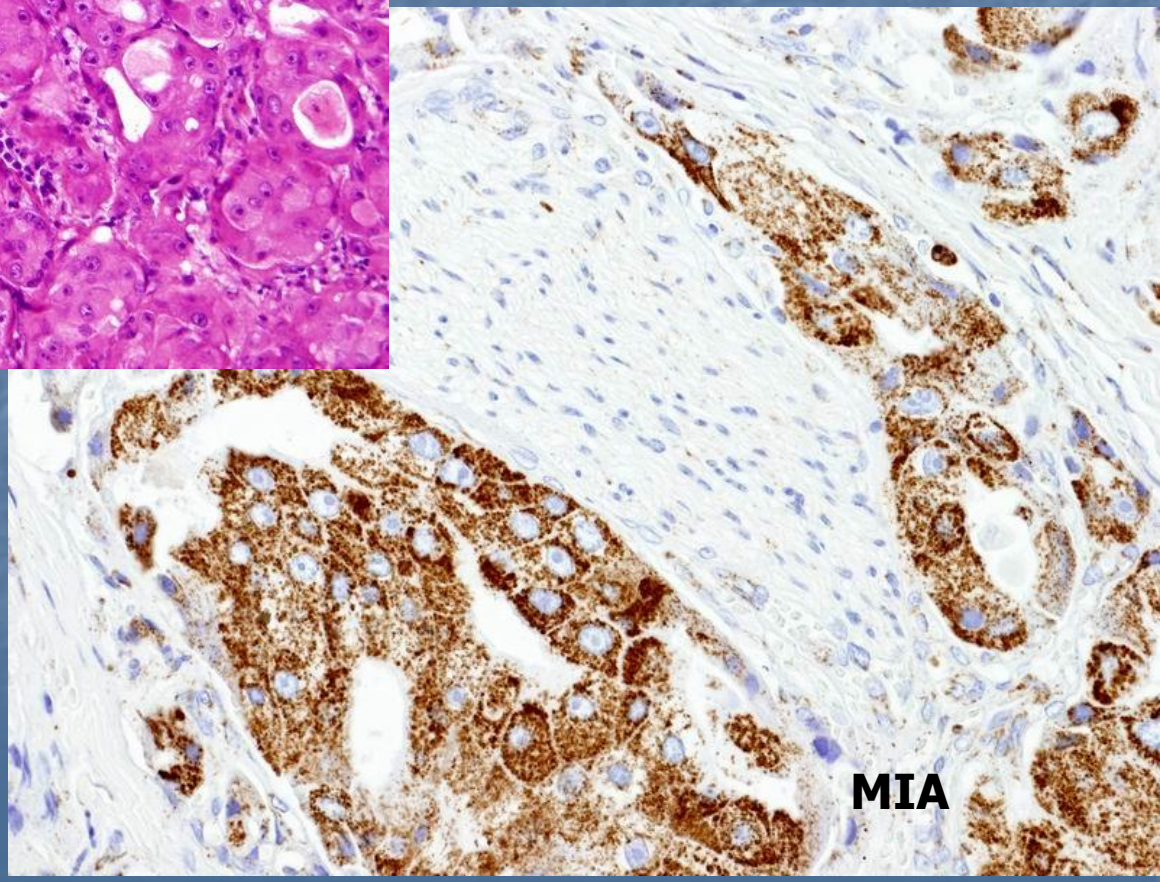




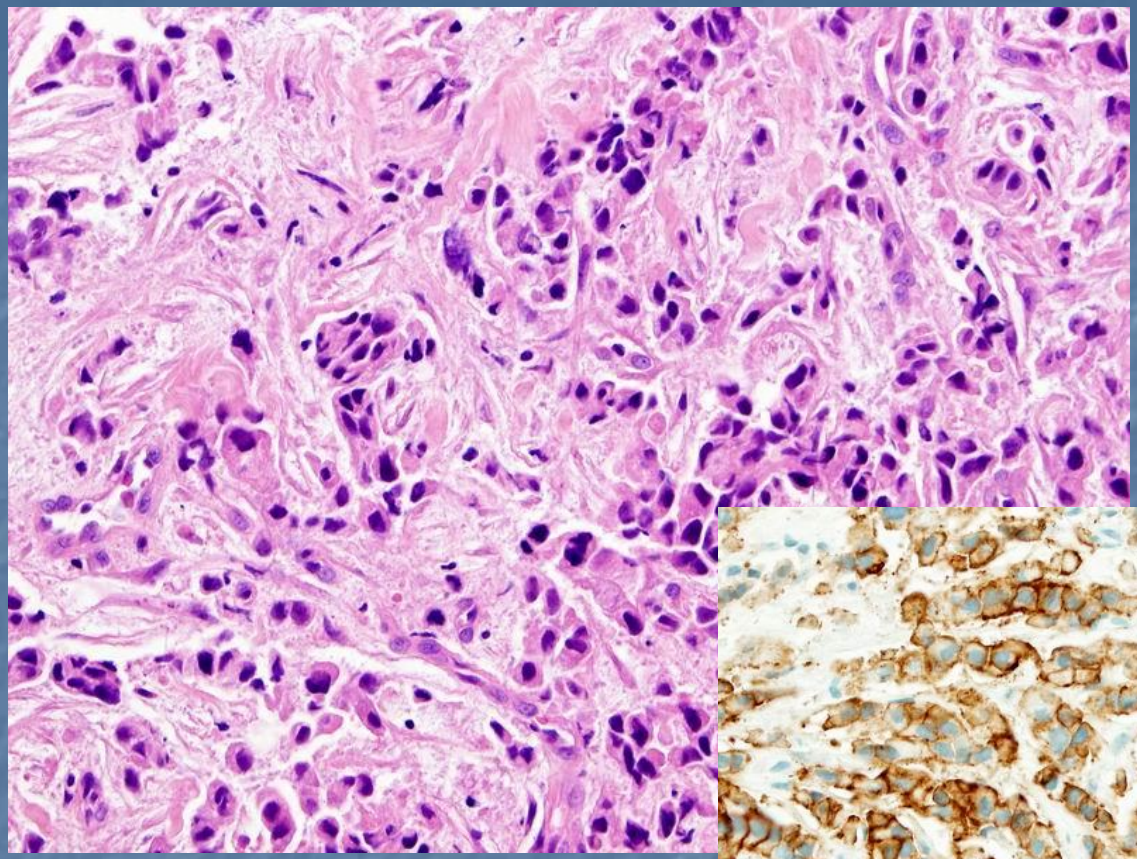
Kapadia, et al. Mod Pathol 1998;11:1033-8.

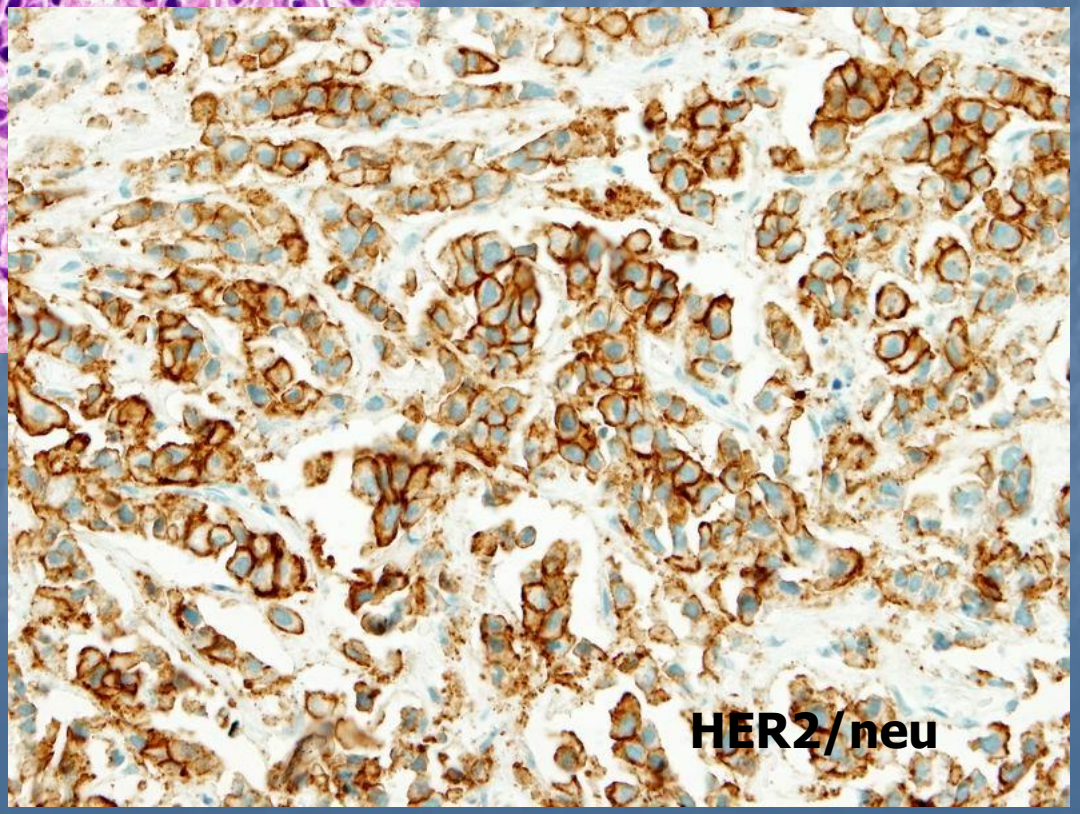
Simpson- study to be published



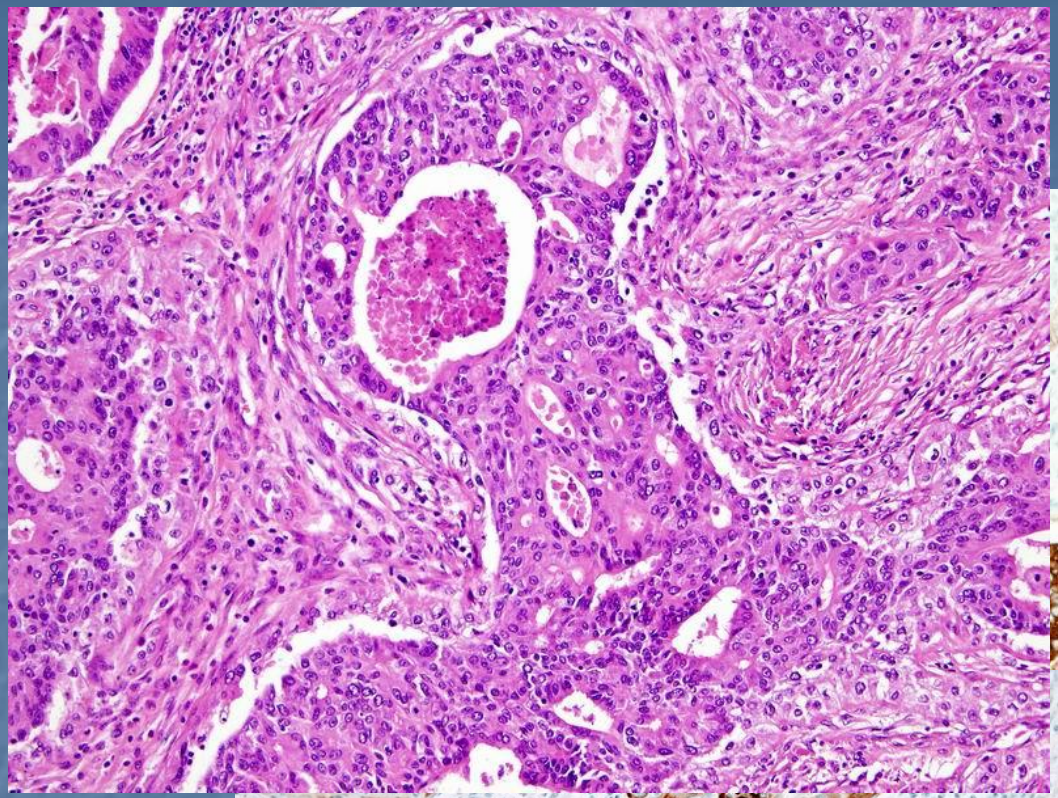


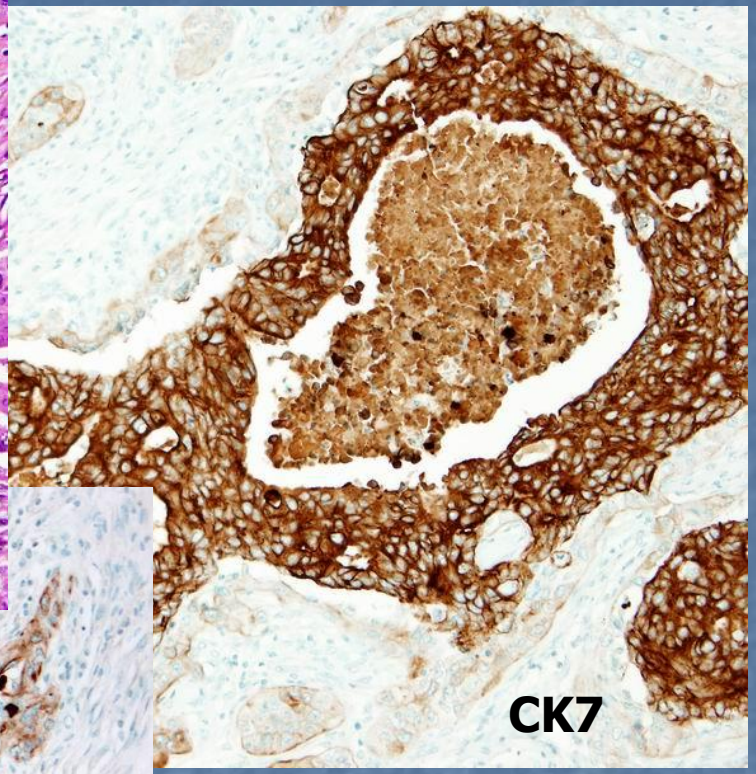
SDC oncocytic, G2

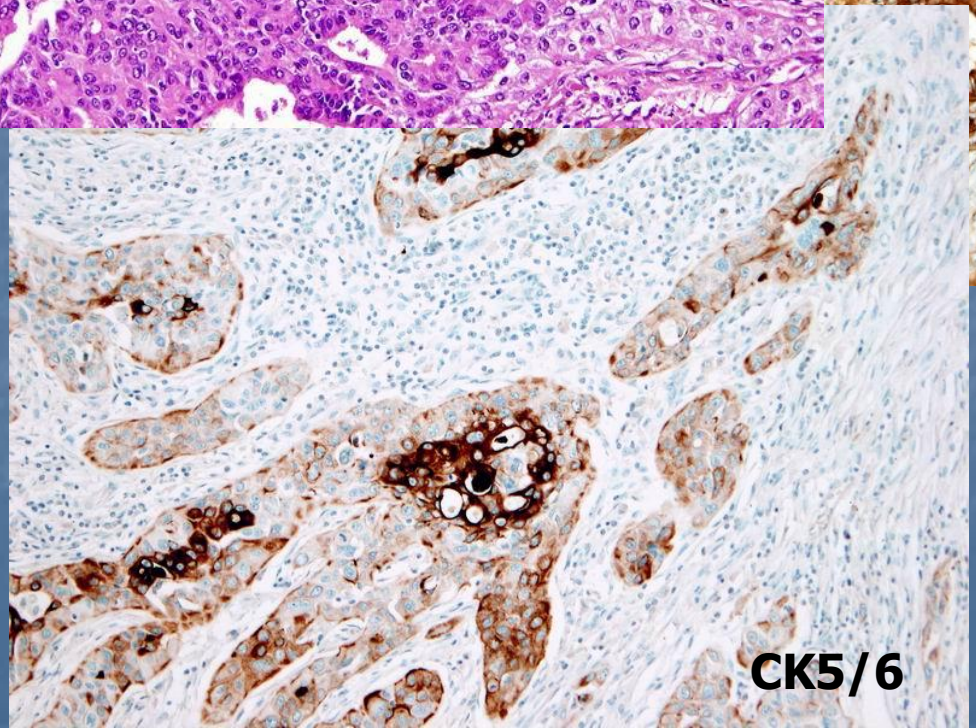




SDC lobular growth, HER2+

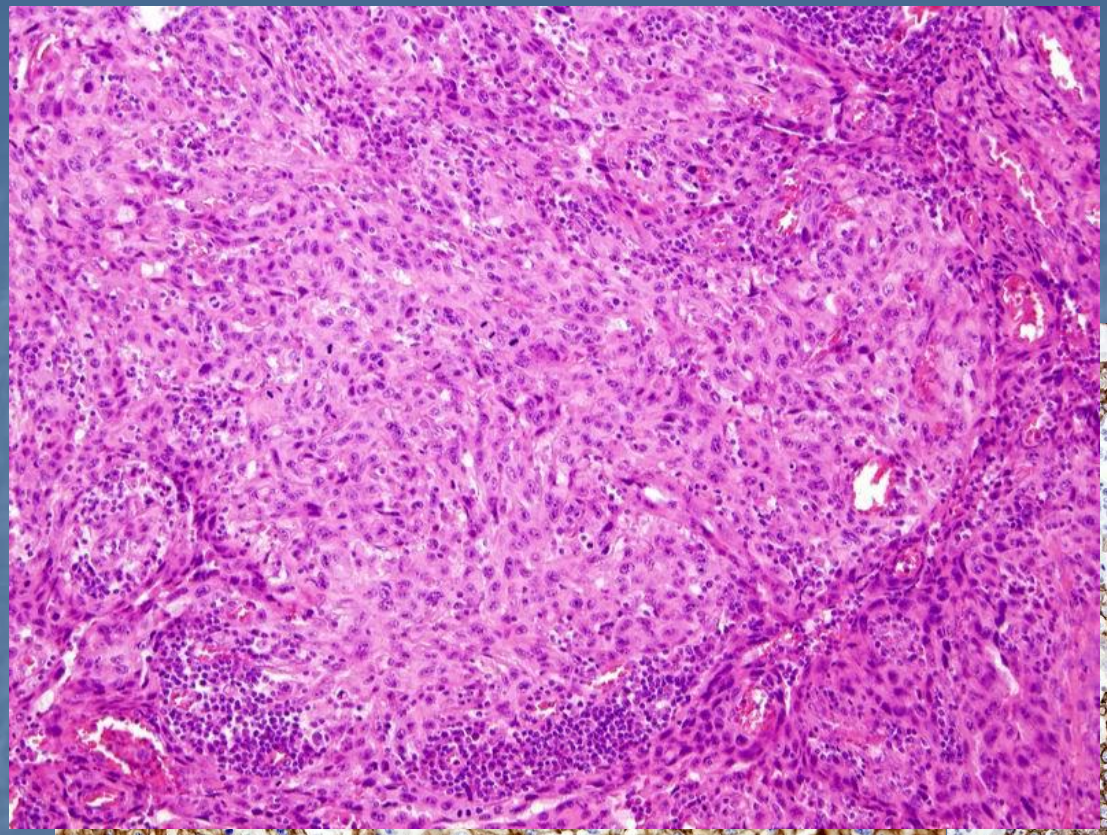


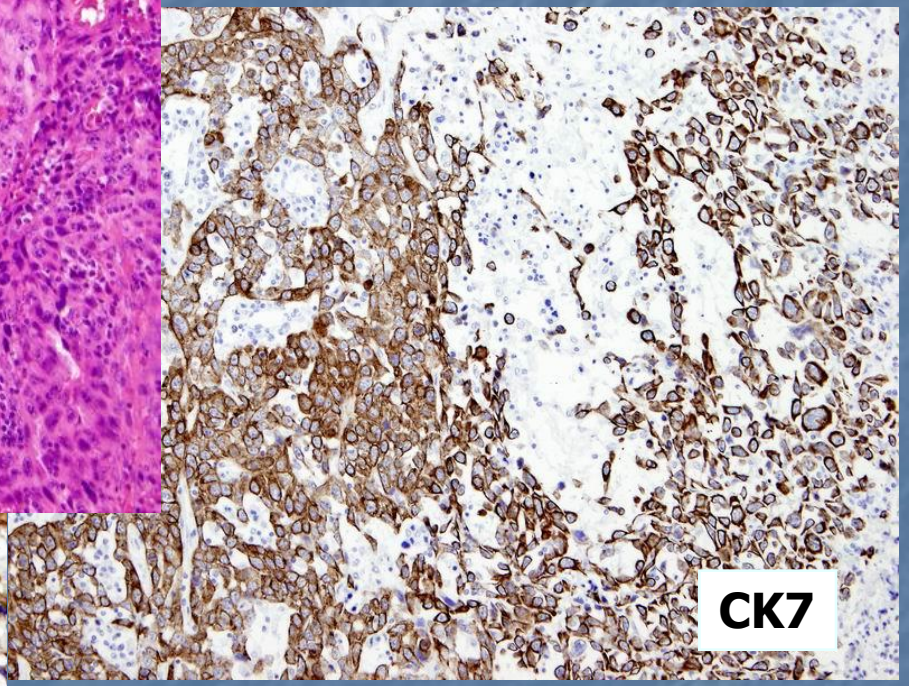


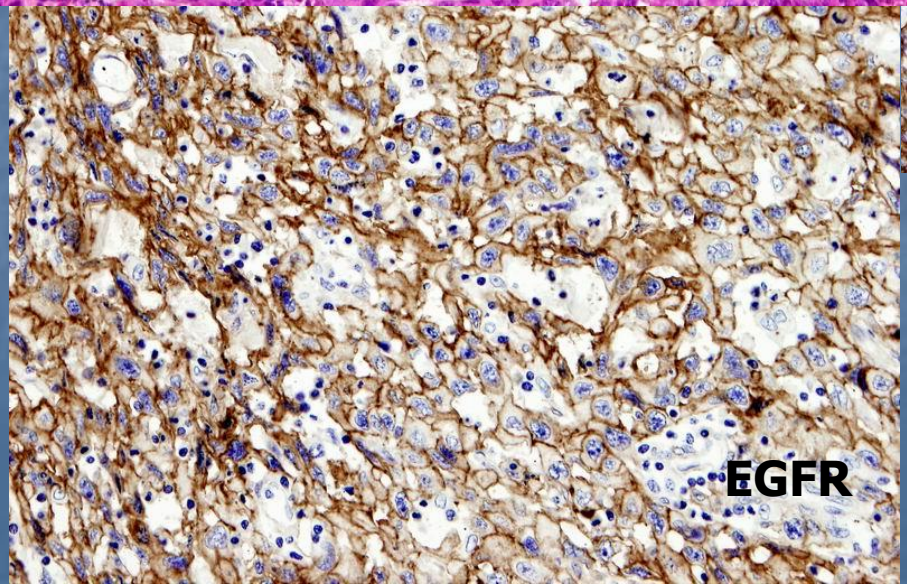


SDC G3

SDC, G3, basal-like phenotype





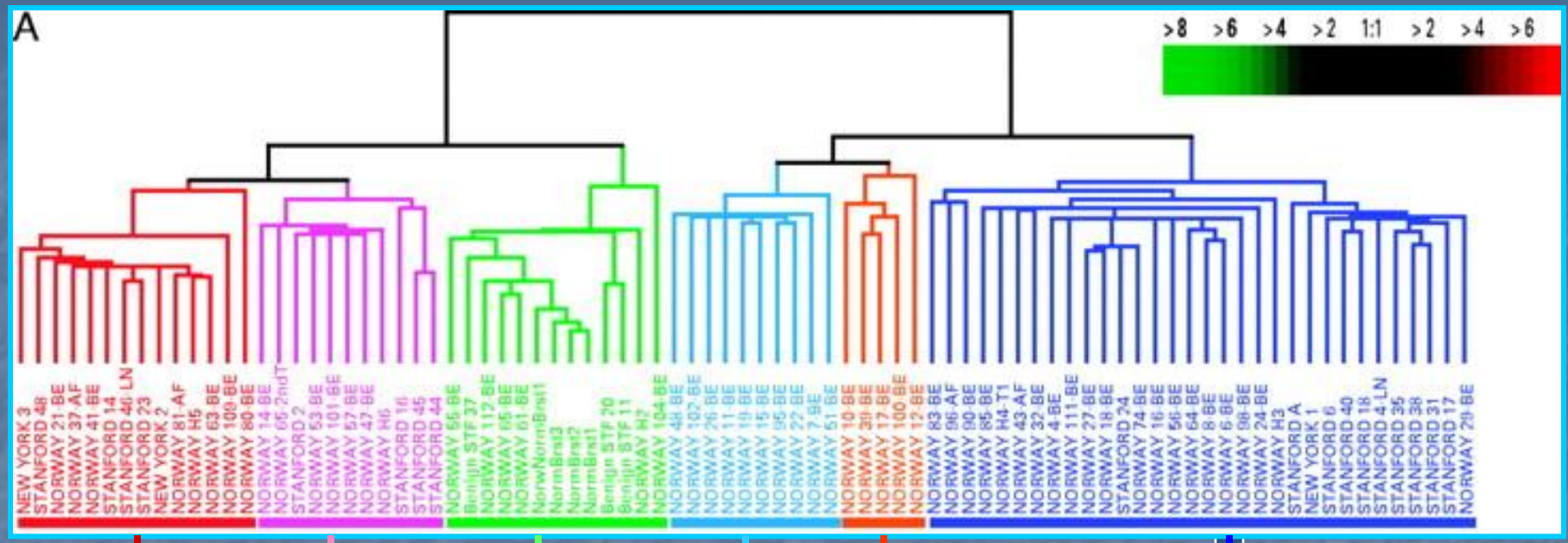


Di Palma , et al. USCAP 2008-proffered paper Mod Pathol 2008: 21 (Suppl 1); 234A.

Salivary duct carcinoma (SDC)

- histomorphological similarities with breast IDC and DCIS
- Microarray studies have demonstrated that mammary IDCs can be subclassified into biologically and clinically distinctive molecular subgroups
  - luminal, HER-2 neu, basal-like, and normal breast-like cancers

Molecular Classification of Breast Cancer



Basal-Like

ERBB2+

Normal Breast-Like

Luminal Subtype C

Luminal Subtype B

Luminal Subtype A

Sorlie T et al. Proc Nat Acad Sci 2001

Di Palma S, Skalova A, Ungari M, et al. Salivary duct carcinomas can be classified into luminal, HER2 and basal-like phenotypes. Mod Pathol 2008: 21 (Suppl 1); 234A.

Salivary duct carcinomas can be classified into luminal/molecular apocrine, HER2 and basal-like phenotypes.

Silvana Di Palma, Roderick HW Simpson, Caterina Marchiò, Alena Skálová, Marco Ungari, Ann Sandison, Stephen Whitaker, Suzanne Parry, Jorge S Reis-Filho.

Histopathology – in press 2011

The aim of this study

- to apply an immunohistochemical panel previously validated for breast cancer to determine whether SDCs could likewise be classified into analogous molecular groups
- surrogate of gene expression analysis to classify breast carcinomas into molecular subgroups was described
  - proposed by Nielsen et al.

Materials and Methods

- **64 cases of SDC**, including SDC ex PA were retrieved from the files
  - All fulfilled the criteria for SDC according to the WHO classification 2005
- **cases were considered SDC**
  - if they resembled a IDC of the breast
  - lacked any features suggestive of other specific types of salivary malignancy
  - displayed expression of cytokeratin CK 7

Materials and Methods

- Tumors were graded according to the modified Nottingham grading system
  - combination of tubule formation, degree of nuclear pleomorphism and mitotic count produces a 3 tier grading system
  - MIB1 index included
- In situ component was recorded and graded 1-3

Materials and Methods

- For HER2 the ASCO/CAP scoring system was applied:
  - negative-no membrane staining or <10% of cells
  - Cases were **considered HER2 positive** if HER2 was 3+, or 2+ with *HER2* gene amplification as defined by *ISH method*
- Only membrane staining was accepted for scoring

Materials and Methods

- Cases were **considered positive for CK 5/6** when >10% of morphologically unequivocal neoplastic cells expressed moderate-to-strong membrane and cytoplasmic staining
- Positive staining for abluminal cells of non-neoplastic intra/extralobular salivary ducts was used as an internal control for CK 5/6

Clinical Features

- 64 patients with SDC comprised 42 males; 22 females and were aged between 35 and 86 years (mean 66.7 years)
- Primary sites
  - parotis (56), submandibular gland (6), minor gland (2)
- LN metastases were present in 23 (36%) patients at presentation

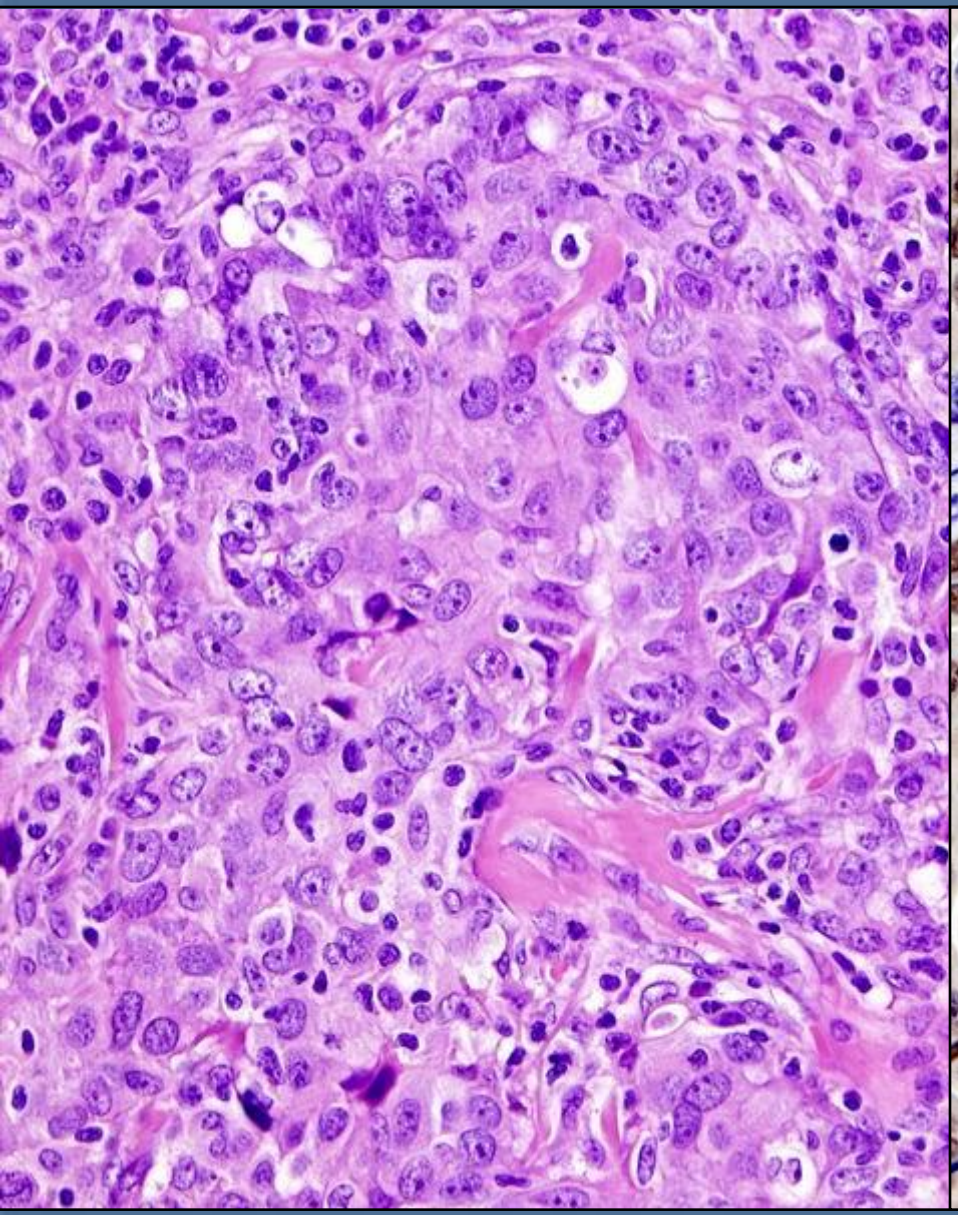
Histological Features

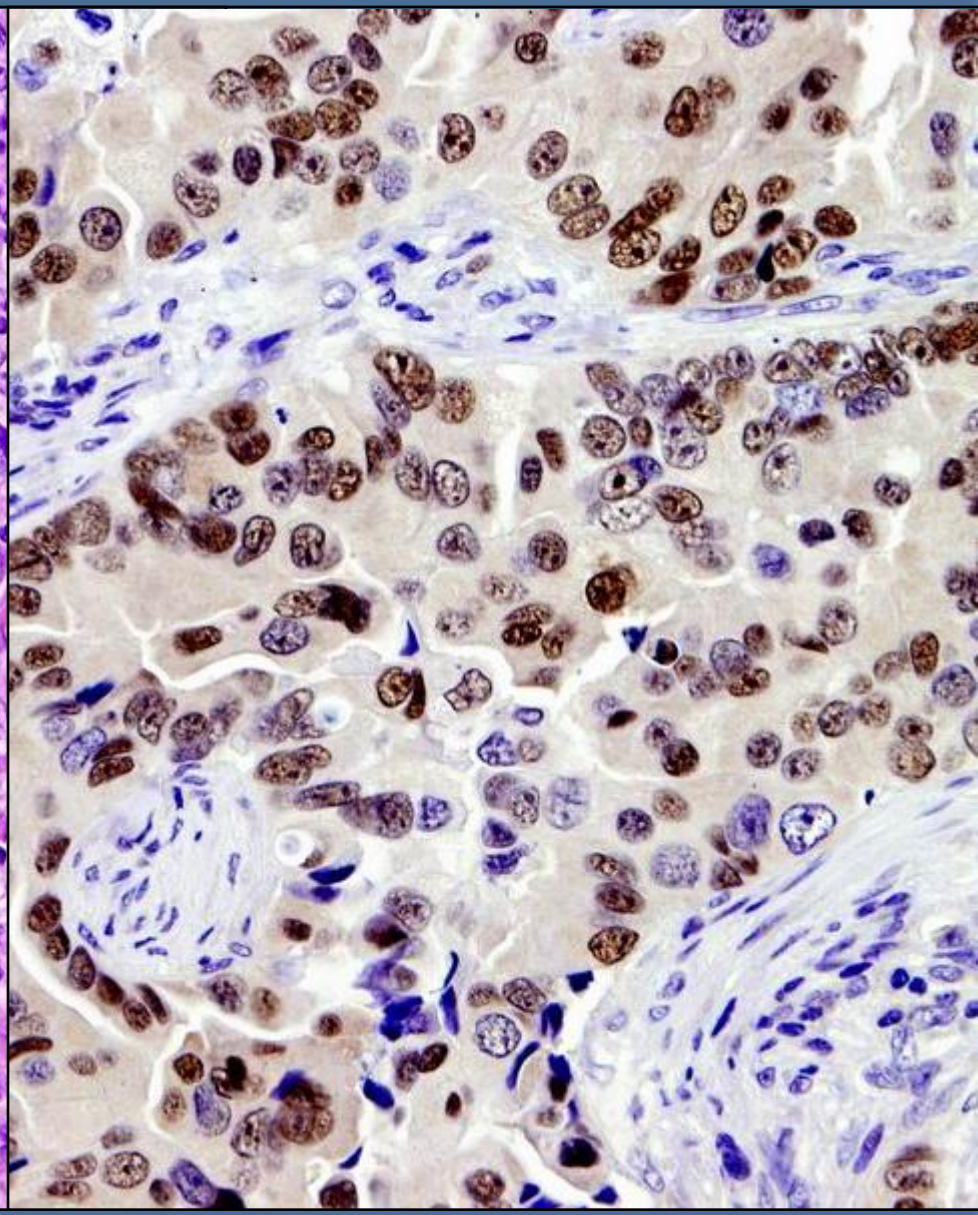
- SDCs were assessed as grade 1 (7x), grade 2 (22x), as grade 3 (35x)
- lobular-like pattern (2)
- CXPA (24), HG solid component (3), AdCCa component (1), pure SDC (36)
- prevailing *in situ* (DCIS) component (5)
- Prominent oncocytic features (11)

Classification of salivary duct carcinomas into the molecular subgroups

Luminal phenotype

- Tumors expressed ER, PR or AR
- lack HER-2/neu expression regardless of the expression of other markers
- **23 cases/64 (38%)**

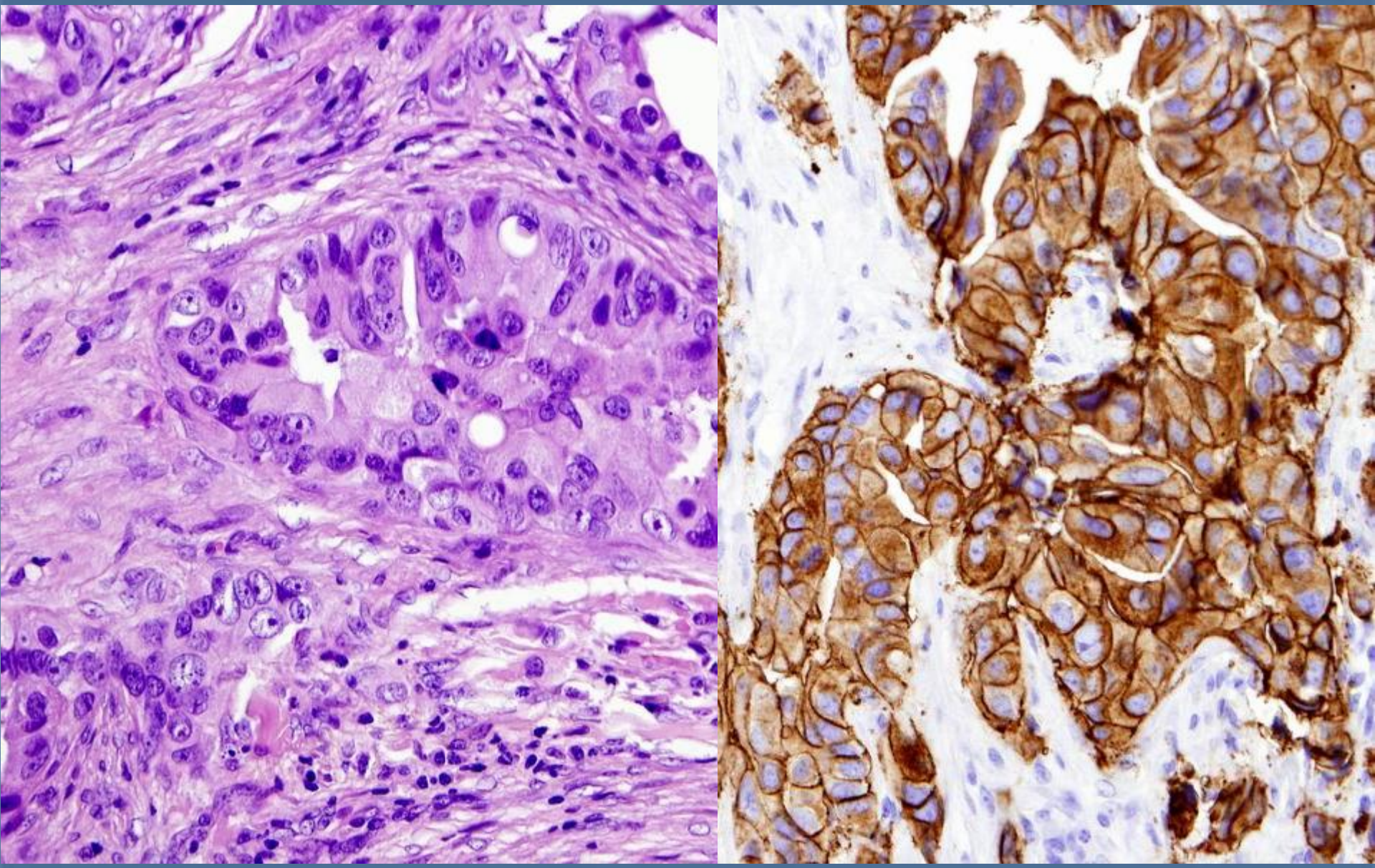




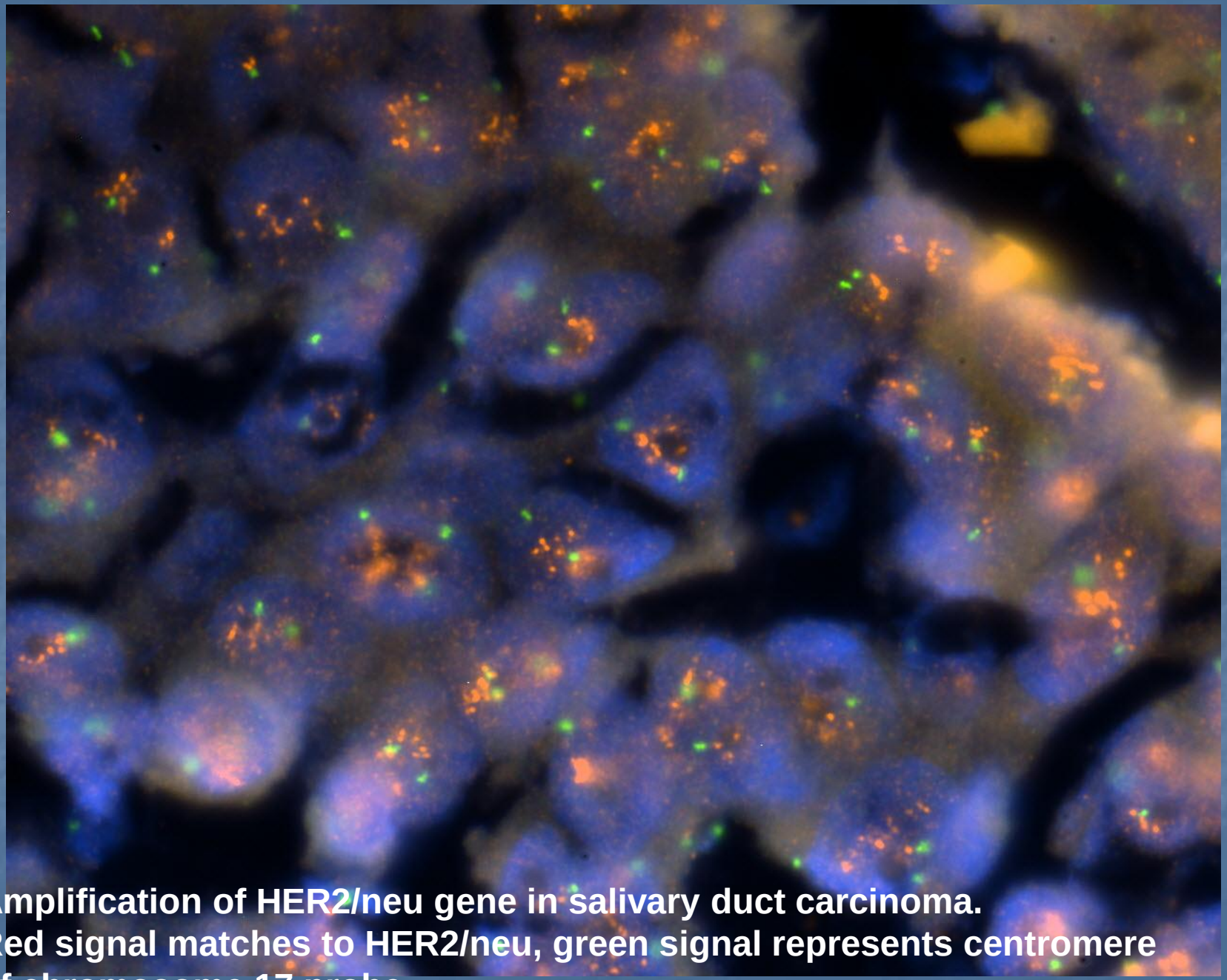
Salivary duct carcinoma G3 luminal phenotype AR+

HER-2/neu phenotype

- tumor cells expressed HER-2/neu protein (score 3+ or 2+)
- confirmed HER-2/neu gene amplification, regardless of the expression of other markers
- **20 cases/64 (33%)**



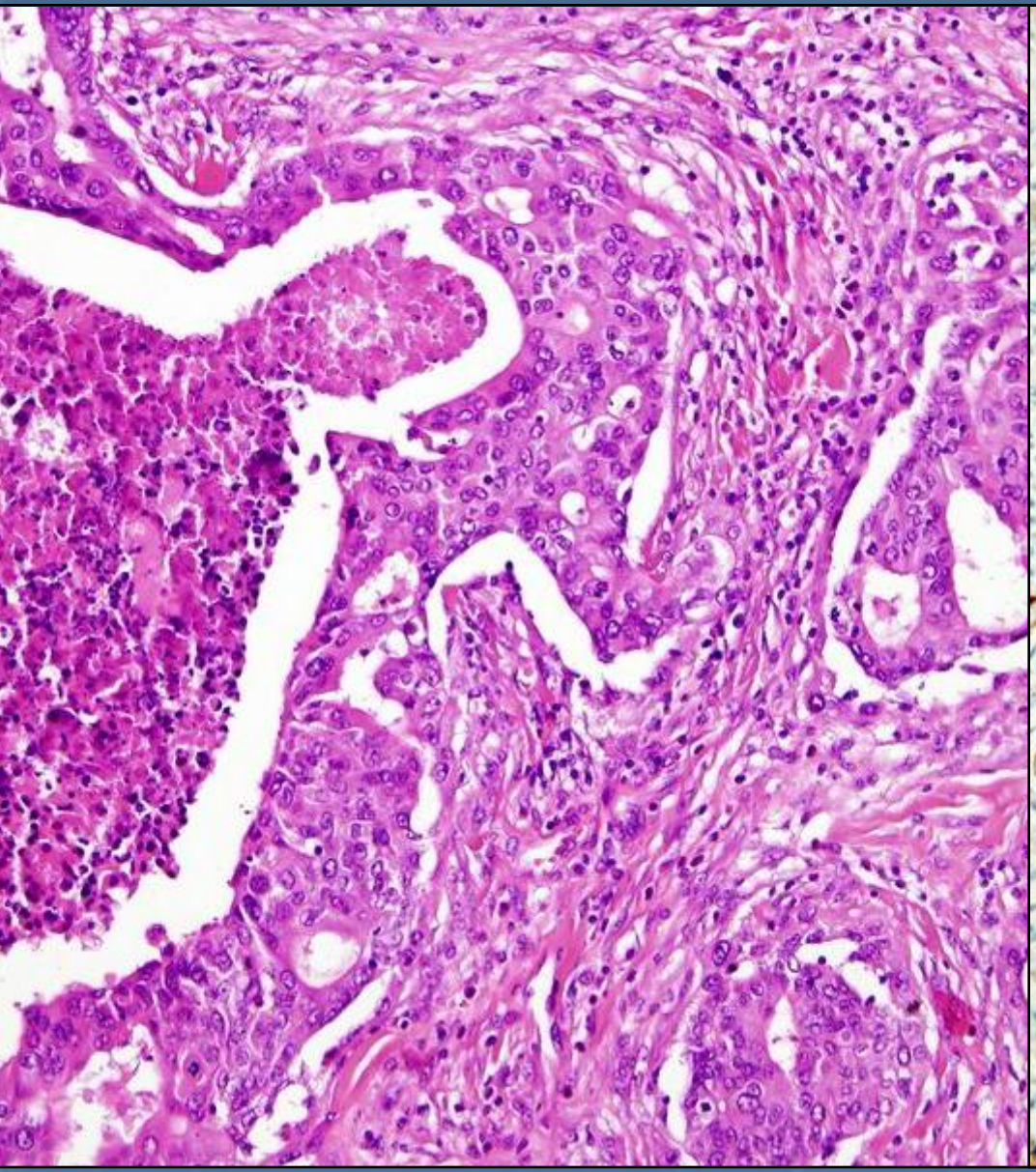
Salivary duct carcinoma G3: HER-2/neu score 3+

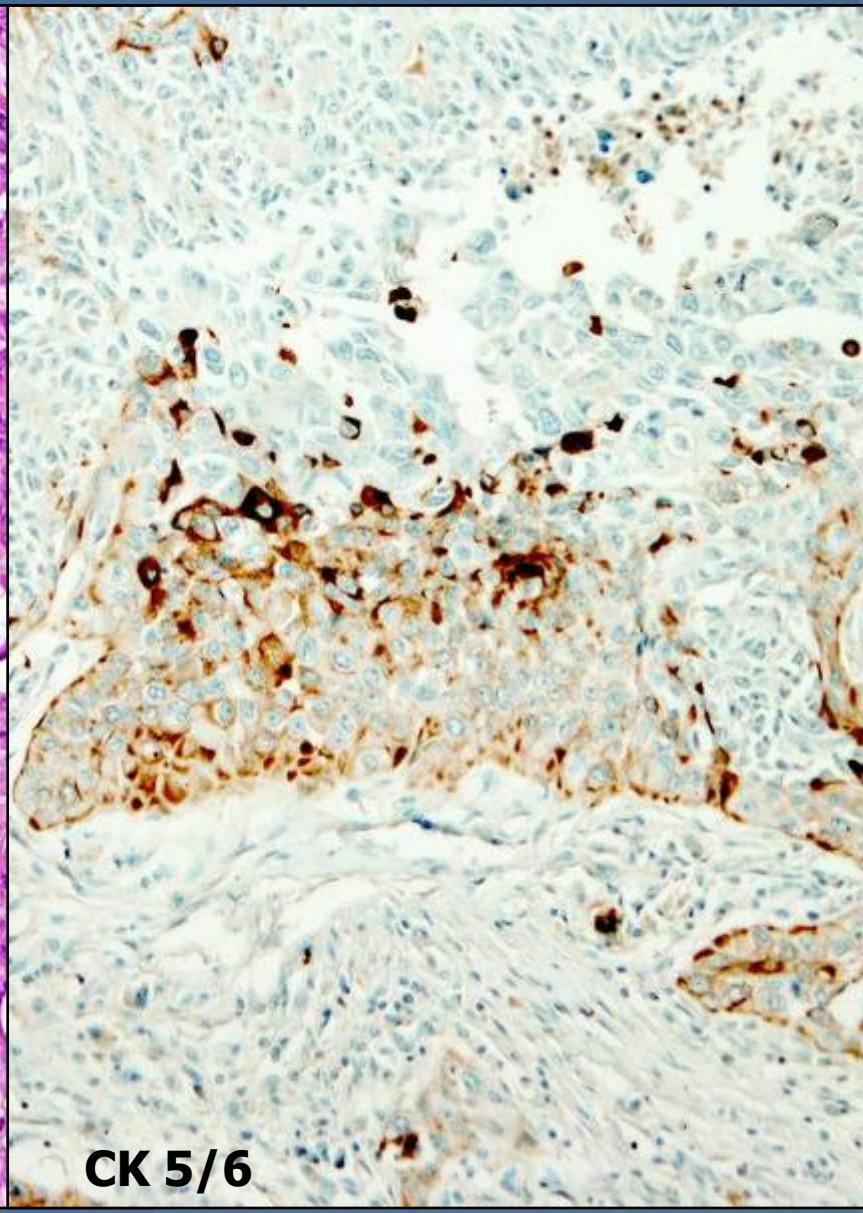


Amplification of HER2/neu gene in salivary duct carcinoma.
Red signal matches to HER2/neu, green signal represents centromere of chromosome 17 probe.

Basal-like phenotype

- Cases negative for HER-2/neu, ER, PR or AR which expressed either EGFR and/or CK 5/6
- **12 cases/64 (19%)**
- Carcinomas which were negative for all markers were considered of indeterminate phenotype





Salivary duct carcinoma G2 basal-like phenotype

Results

- majority of SDCs in our series represent luminal subtype AR-positive (23 cases, 38 percent)
- second most prevalent group was HER-2/neu subtype (20 cases, 33 percent)
- 12 cases fulfilled the criteria of the basal-like phenotype (19 percent)
- 9 cases of SDC (10 percent) were considered indeterminate phenotype

Conclusions 1

- our results demonstrate that SDC can be classified into molecular subgroups equivalent to those in the breast
- Most of SDCs conformed to luminal subtype (38%) - expression of AR
- Importance of hormonal regulation in progression of subset of SDCs
- SDC possible target of anti-AR therapy

Conclusions 2

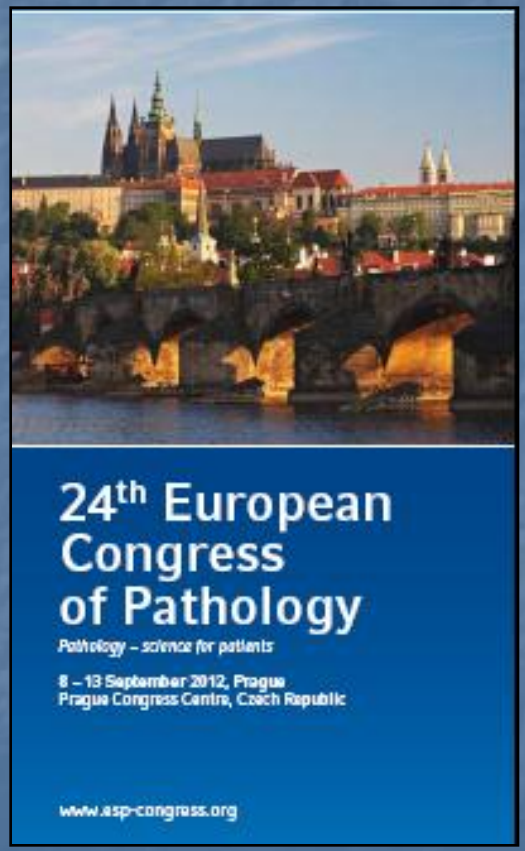
- study also shows that a considerable subset of SDC represents the HER-2/neu phenotype (33%)
- therefore selected patients with SDC may benefit from therapeutic use of trastuzumab (Herceptin) treatment in a way akin to breast cancer patients

Conclusions 3

- SDC despite relatively homogenous morphology represents a heterogenous spectrum of immunophenotypes
  - luminal, HER2/neu+, and basal-like profiles
- Prognostic impact of the proposed classification of SDCs is still to be determined in future studies

Welcome in Prague at ESP Congress, Sept 8th-13th 2012

www.esp-congress.org



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Thank you for your attention
21nd National Congress of Pathology, İzmir, 16 -20 November 2011