Cervical cancer screening: The role of bio/tumor markers

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Different pathology

SCC

AdenoCA

Sarcoma

Malignant meloma

Neuroendocrine ca

Cervical SCC; epidemiology

*Fourth most common ca globally

*85% in developing countries

*CC leading cause of cancer death in developing countries

*SCC Screening (smear, HPV)

*SCC Vaccination

SCC risk factors; NCCN 2021

The most important factor:

- Persistent HR-HPV

Other risk factors

- Hx of smoking
- Parity/ OCP
- 1st coitus at early age/ larger N0. of sexual partners
- Hx of STD
- Autoimmune disease/ Chronic immunosupression

Cervical SCC progression and prognosis

The progression from HPV infection to CC is a long process

- that takes over several years

Early CC

- can be treated surgically
- its prognosis is significantly better than advanced CC.

Cx Scc; Serum markers

The occurrence of CC is related to

- HPV & immune system

Immune functions and tumor marker levels

- are altered with the genesis and development of CC
- may contribute to the early detection and prevention of CC

TMs

- SCC Ag, CEA, CA19-9, CA125

Immune function

Closely related to T cells, B cells, NK cells

- If CD8+ & CD4+ T cells reduced, immune function impaired
  - infected cells cannot be removed effectively
- NK cells, B cells (play a vital role in immune protection):
  - Effectively eliminate invading HPV, kill infected cells
- Regulatory T cells
  - inhibit the antitumor ability of cytotoxic T cells, NK cells
  - promoting the development and progression of tumors.

L. Zhang; July 2020 IJGC Volume 30-7…

The correlation between the levels of immunocytes (T cell subsets, NK cells, B cells) & TMs

- **82 cases**:
  - (early stage: IA–IB1 & IIA1; locally advanced: IB2 & IIA2)
- **54 cases**:
  - (CIN)
- **54 control** GP

…L. Zhang; July 2020 IJGC

SCC Ag , CEA:

- significantly lower in con& CIN gps vs Ca gp ($p<0.01$)

Increased SCC Ag, CEA, $CD4^+$ $CD25^+/CD4^+$ ratio

- were RFs for Cx Ca Gp by logistic regression analysis ($p<0.05$)

peripheral blood immune cells + serum TMs

- may be helpful for early detection, Dx, prognosis CC.

O. Kurmyshkina; 2020 Sep Int J Mol Sci...

Markers in CIN and Early Invasive CC

- Angiogenesis,
- Lymphangiogenesis,
- Epithelial-Mesenchymal Transition EMT (Plasticity) :
  - Exploring Putative Molecular Mechanisms Involved in Early Tumor Invasion

…O. Kurmyshkina; 2020 Sep Int J Mol Sci.

The establishment of a proangiogenic phenotype and EMT :

- promote the induction of invasive growth in epithelial tumors,
- stimulate the lymphangiogenesis
- confer the capacity for early dissemination to ca cells.

…O. Kurmyshkina; 2020 Sep Int J Mol Sci.

Recent research:

- substantial interdependence between these processes
  - at the molecular level as they rely on common signaling networks.

The molecular mechanisms of (lymph-)angiogenesis and EMT

- associated with the earliest stages of transition from CIN to cc,
- source of potentially valuable tools for targeting tumor metastasis

In early-stage cc, the players of (lymph-)angiogenesis and EMT

- still remain substantially uncharacterized

…O. Kurmyshkina; 2020 Sep Int J Mol Sci.

1- RNA sequencing

- to compare transcriptomes of HPV(+) CIN and early-stage CC
- to identify (lymph-)angiogenesis- and EMT-related genes
- To identify pathways that may underlie early acquisition of invasive phenotype and mets properties by cc cells.

2- Flow cytometric analysis

- to evaluate the expression of three key lymphangiogenesis/EMT markers (VEGFR3, MET, and SLUG) in epithelial cells derived from enzymatically treated tissue specimens.

…O. Kurmyshkina; 2020 Sep Int J Mol Sci

Among 201# expressed genes

- N0. of (lymph-)angiogenesis & EMT regulatory factors identified
  - encoding cytokines, GF receptors, transcription factors, adhesion molecules
- Confirmed enrichment for angiogenesis, epithelial #, cell guidance CIN to CC
- Immune-regulatory/inflammatory pathways, implicated in initiation of invasive growth

Results:

- driving forces of angiogenesis and mets in HPV-associated cc

Han Nie 2020 Scientific report…

29 immune-related genes pairs (IRGPs) predict the prognosis of cc

machine learning, analyzed/ evaluated.

The AUC value> 0.9

The model GP survival rate # ($P < 0.001$).

IRGPs play an important role in the occurrence and development of cc

- can be used as a prognostic marker and potential new target of cc.

Bin Zhu 2020 Risk Manag Healthc Policy…

Combined ACTN4 + SCC-Ag

- α-Actinin 4(ACTN4) is overexpressed in CC,
- Dx value for CC is unclear.

105 patients CIN3+ cases and 106 NILM/CIN1/CIN2 as controls.

ACTN4 mRNA (PCR) & protein levels (IHC) detected

Median ACTN4; in case=10.6, in control= 4.15

...Bin Zhu 2020 Risk Manag Healthc Policy

ACTN4:

- Sen=68.6, spe=76.3, PPV=76.2, NPV=72.5, PLR=2.89, NLR = 041, YI=44.9

SCC-Ag

- Sen=75.6, spe=87.5, PPV=88.6, NPV=73.7, PLR=6.05, NLR=0.28, YI=63.1
- similar Dx value (P>0.05),

ACTN4 + SCC-Ag

- [ACTN4] & [SCC-Ag] in cases> controls (P_{ACTN4}=0.0007; P_{SCC-Ag}=0.0067).
  - superior Dx value
- promising serological biomarker for patients with ≥CIN3

M Zajkowska Dec 2018…

Plasma Levels of TMs in Dx of CC Dx

- VEGF,
- Matrix Metalloproteinase 9 (MM9),
- Tissue Inhibitor of Matrix Metalloproteinase 1 (TIMM1)

Power of those parameters *vs* CA125 & SCC-Ag

100 cases/ 50 healthy control gp

…M Zajkowska Dec 2018

Plasma levels of all parameters in the cases

- showed statistical significance ($P < .05$)
  - In stage I ca,
    - only VEGF and TIMM1
  - In stage II,
    - all the tested parameters and CA 125
  - In stage III & IV,
    - VEGF, MMP-9, CA 125

…M Zajkowska Dec 2018

highest value of sensitivity: VEGF

- (I: 75%, II: 76%, III & IV: 94%, 82% in total CC GP).

highest specificity

- MMP-9 (94%).

Total:

- stage I, stage II, all tested parameters statistically significant area
- max range: VEGF + SCC-Ag (I: 0.9146, II: 0.8941, III&IV: 0.9139)
- total CC (0.9347).

M Farzaneh 2014 APJCP

Application of TMs SCC-Ag, CEA, TPA in patients with CIN

A case-control study

120 women (46 histologically confirmed CIN /74 controls).

CINI 69.6%, CINII 23.9%, CINIII 6.5%,

Results:

cut-off 0.55 ng/ml SCC-Ag, 2.6 ng/ ml CEA, 25.5 U/ml TPA; (highest sensitivity 93%, 61%, 50%)

Largest AUC for SCC-Ag (0.95) then CEA 0.61 and TPA 0.60

Highly significant direct correlation between [SCC-Ag] & degree of CIN ($r=0.847$, $p<0.00$)

Conclusions:

The new cutoff of 0.5 for SCC-Ag test might be useful as a TM for CIN

D. Shengye June 2020 *Scientific Reports*

- **Serum Proteins & MicroRNA as Novel Biomarkers: Early-Stage CC**
  - Non-invasive approaches using serum biomarkers: miRNA & proteins
  - Biomarker panel SCC Ag, miRNA-29a, miRNA-25, miRNA-486-5p in blood
  - 140 early-stage CC & 140 healthy controls
  - Sensitivity 88.6% & specificity 92.9%
  - This study:
    - Multiple serum biomarkers could improve the accuracy of non-invasive detection of early-stage CC
    - A new liquid biopsy approach for detecting early-stage cc.

The American Cancer Society

Individuals with a cx

- Cx Ca testing (screening) should begin at age 25.
- 25-65 should have a primary HPV test Q 5 yrs.
- If HPV testing not available
  - co-test Q 5 yrs
  - or Pap test Q 3 yrs.
- F/U with colpos
- ***The most important thing to remember is to get screened regularly, no matter which test you get.***