Cervical cancer

COLUMNAR EPITHELIUM IS THE ORIGINAL SITE OF MOST CERVICAL SQUAMOUS CELL CANCERS

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Introduction/Background Cervical HPV-research is based on mature squamous epithelium (Woodman, CB. Nat Rev Cancer 2007), however, only a minority of squamous cell cancer (SCC) arise in this type of epithelium. Surprisingly, it was only in the last years that immature squamous metaplastic epithelium in the transformation zone and reserve cells (RC) throughout the columnar epithelium moved into research focus.

Methodology This review will focus on recent aspects of HPV-induced cervical carcinogenesis.

Results UGS-derived p63/CK17-positive RC located within the columnar epithelium are precursor cells for metaplastic squamous epithelium and subsequent HSIL and SCC (Fritsch, Clin Ant 2021; Regauer S. Curr Opin Virol 2021). RC may be target for HPV-infection and act as reservoirs of HPV (Goyal A, Am J Surg Path 2020; Doorbar J, Curr Opin Virol 2021). A HPV-infection of proliferating RC and immature metaplasia that is not controlled by the immune system, allows development of small foci of thin HSIL as result of inhibition of p53- and Rb-protein-mediated cell-cycle processes by E6/7-protein (Reich, Int J Gynecol Pathol 2017; Regauer, Am J Surg Path 2021; Regauer, Curr Opin Virol 2021). Enlargement of thin HSIL and stepwise progression from thin to thick HSIL eventually produce larger lesions, and invasion begins from thick HSIL inside the TZ.

Conclusion Contrary to the prevailing opinion, cervical SCC arise most frequently from RC and immature metaplastic epithelium in the TZ. Cervical carcinogenesis is not limited to the SCJ, and cuboidal cells, that accomodate for the difference of epithelial thickness at the SCJ, are of no significance for carcinogenesis.

DISTRIBUTED CERVICAL INTRAEPITHELIAL NEOPLASIA (D-CIN) REPRESENTS A RARE HPV-INDEPENDENT PRECURSOR LESION OF SQUAMOUS CELL CANCER

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Introduction/Background Although our knowledge of HPV-independent squamous cell cancers (SCC) of the cervix is growing, the current 2020 WHO classification does not describe HPV independent cervical precancers. The main reason for this was that these exceedingly rare cervix HPV-independent precancerous lesions were not described at time of publication.

Methodology This review will focus on recent aspects of HPV-independent cervical carcinogenesis.

Results In 2020 we reported for the first time a preinvasive cervical lesion negative with 3 different HPV tests in a series of 474 cone specimens (Reich O. Gynecol Oncol 2020). In 2022 we demonstrated detailed characteristics of HPV-negative cervical intraepithelial precursors (Regauer S. Am J Surg Path 2022). HPV-negativity was defined as lack of both, DNA of 32 HPV subtypes and E6/E7 mRNA of 14 HPV subtypes, and additionally by the absence of HPV sequences in ~5 Mio’s WGS reads. The morphological hallmark of this cervical lesion was the presence of atypical keratinocytes confined to the basal and parabasal layers in squamous epithelium with hyper- and parakeratosis with elongated rete ridges. The subepithelial stroma had a dense inflammation with plasma cells and eosinophilic granulocytes. Finding an appropriate terminology for these differentiated intraepithelial precursor lesions, however, proves difficult. In analogy to terminology of vulvar carcinogenesis, differentiated cervical intraepithelial neoplasia (d-CIN) may be appropriate.

Conclusion The existence of primarily HPV-negative squamous cervical precancers (d-CIN type and basoid type) needs to be recognized (Regauer S. Int J Gynecol Cancer 2022). In a future classification squamous intraepithelial cervical precancers should be grouped into two categories: HPV-associated and HPV-independent.

GENOMIC CHARACTERISTIC ANALYSIS IN SQUAMOUS CELL CARCINOMA AND ADENOCARCINOMA OF CERVIX IDENTIFIES ALPELISIB AS A THERAPEUTIC OPTION FOR PIK3CA MUTATIONAL CARCINOMA

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Introduction/Background Cervical squamous cell carcinoma (CSCC) and cervical adenocarcinoma (CAdC) are the two most histological types in cervical carcinoma, with unequal outcomes and unclear mechanisms in tumor biology. We aim to explore the genomic characteristics between them and identify a promising target for cervical carcinoma.

Methodology We analyzed the genomic data of cervical carcinoma to identify genomic characteristics between SCC and CAdC. In vitro and in vivo assays were performed to testify the therapeutic effects of Alpelisib in PIK3CA mutational cervical carcinoma. Mutation analysis, Enrichment and pathway analysis, and co-immunoprecipitation were used to demonstrate the mechanisms of Alpelisib in cervical carcinoma.

Results CSCC showed higher point mutation density, high copy number cluster, low to intermediate CpG island methylator phenotype (CIMP) compared with CAdC, with the enrichment in the RTK/PI3K/MAPK pathway. In addition, point mutation of PIK3CA (P=0.0401) was significantly observed in CSCC, with different overall survival (P=0.0469) between the two histological types. In vitro, PIK3CA mutational cell lines (ME-180 and Ca-Ski) showed higher sensitivity to Alpelisib than cell lines without PIK3CA mutation. The correlation genes of PIK3CA in cervical carcinoma showed the enrichment of...
DNA replication and repair pathway. By performing co-immunoprecipitation, reduced interaction of p110α with ATR was found in cervical cancer cells with PIK3CA mutations, which made them sensitive to the combination of Alpelisib and cisplatin in vivo. Furthermore, we found that Alpelisib significantly suppressed tumor proliferation and migration in cervical carcinoma cells via inhibiting the AKT/mTOR pathway.

Conclusion Our study provides insights into the molecular characteristics between SCC and CaDc and identifies Alpelisib as a therapeutic option for PIK3CA mutational cervical carcinoma.

Introduction/Background To evaluate the impact of the Laparoscopic Approach to Cervical Cancer (LACC) Trial on patterns of care and surgery-related morbidity in early-stage cervical cancer.

Methodology This is a retrospective, multi-institutional study evaluating 90-day surgery-related outcomes of patients undergoing treatment for early-stage cervical cancer before (period I: 01/01/2016–06/01/2018) and after (period II: 01/01/2019–06/01/2021) the publication of the results of the LACC trial. Results Charts of 1,295 patients were evaluated: 581 (44.9%) and 714 (55.1%) before and after the publication of the LACC trial, respectively. After the publication of the LACC trial the number of patients treated with minimally-invasive radical hysterectomy decreased from 64.9% to 30.4% (p<0.001). Overall, 90-day complications occurred in 110 (18.9%) and 119 (16.6%) patients in period I and period II, respectively (p=0.795). Similarly, the number of severe (grade 3 or worse) complications did not differ between the two periods (38 [6.5%] vs. 37 [5.1%]; p=0.297). Overall and severe 90-day complications were consistent between periods (38 (6.5%) vs. 37 (5.1%); p=0.297). Overall and severe 90-day complications were consistent between periods (38 (6.5%) vs. 37 (5.1%); p=0.297). Similarly, there was no significant difference in OS between groups (HR=1.35, 95%CI [0.6–3.05], p=0.5). In the sub-group of patients with stage IB1 (FIGO 2009), there was no significant difference in DFS (HR=3.26, 95%CI [0.4–26.76], p=0.2) or in OS (HR=3.87, 95%CI [0.49–30.35], p=0.02).

Conclusion Cervical cancer counts among the only solid tumors for which increasing mortality has been observed in recent years. Radiation therapy is still a major source of morbidity for young patients. Therefore, key issues remain outstanding for the future management of young patients with cervical cancer and include reducing the morbidity of existing therapeutic options by identifying subgroups of patients at low or intermediate risk, and facilitating fertility-sparing surgery.