ABSTRACT

The aim of the presented thesis is to introduce modern procedures of histopathological analysis including immunohistochemical and molecular methods for the diagnosis, prevention and innovative surgical approaches for the therapy of precancerous lesions and malignant tumors of the lower female genital tract (vulva, uterine cervix).

In the *first part* of the thesis, we focused on the prevalence of human papillomavirus (HPV) types in non-precancerous, precancerous and neoplastic squamous cell lesions of the vulva. We aimed at estimating the efficacy of prophylactic HPV vaccination as well as at evaluating the usefulness of the modified classification scheme of vulvar intraepithelial neoplasia (VIN). We analyzed the spectrum of HPV types in particular histological categories of vulvar lesions and confirmed the justification of the concept of two independent pathways of vulvar carcinogenesis - HPV associated and HPV negative. We identified several heterogeneous groups of precancerous vulvar lesions with variable HPV profiles, for which the application of the new revised VIN classifications may be misleading for the estimation of their biological behavior. We also pointed out the fact that the efficacy of the prophylactic HPV vaccination will depend on the extent of cross-protection against the non-vaccine types of HPV, which are more prevalent in the Czech Republic in comparison with other geographic regions.

The *second part* of the thesis was dedicated to the evaluation of the impact of the $p16^{INK4a}$ and CK 17 immunohistochemistry on the differential diagnosis of squamous cell proliferations of the uterine cervix. We identified the characteristic $p16^{INK4a}$ immunoprofiles of different lesions with well defined precancerous potential and confirmed that the diffuse $p16^{INK4a}$ positivity is significantly associated with the presence of dysplastic changes. The strong intensity of the reaction together with the extension of positivity into the superficial layers of the epithelium is indicative for the high grade squamous intraepithelial lesion (HSIL). Based on that, we reclassified lesions with the uncertain precancerous potential previously diagnosed as an atypical immature squamous metaplasia (AIM) into the three proportional groups, which corresponded to HSIL, low grade squamous intraepithelial lesions and immature squamous metaplasia. Thus, the diagnostic category of AIM should be considered as obsolete. Furthermore, we addressed the low diagnostic contribution of CK 17 immunohistochemistry in comparison with $p16^{INK4a}$.

In the *third part* of the thesis we considered the indication criteria and therapeutic-diagnostic algorithms for the fertility sparing and less radical surgery in patients with the early stage of carcinoma of the uterine cervix. We used different techniques of

intraoperative surgical detection and frozen section analysis of sentinel lymph nodes (SLN) followed by subsequent serial sectioning and immunohistochemical analysis. We demonstrated that the risk of the tumor dissemination into the sentinel lymph node increases with the growing volume of the tumor and with the depth of infiltration into the stromal tissue of the uterine cervix. The risk of tumor progression into the parametria grows analogously and it dramatically increases with the presence of metastatic deposits in SLN. Negativity of SLN can therefore be considered as a significant and clinically relevant prognostic factor, which may be exploited for the reduction of the radicality of surgical therapy in early stages of carcinoma of the uterine cervix. Similar therapeutic approach might be used after neoadjuvant chemotherapy also in patients with the borderline sized tumors, in which the primary fertility sparing surgery or less radical therapy were not indicated previously.