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Session VIII: Cervix

Cervical cancer: Natural history, screening, and diagnosis

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Worldwide, cervical cancer is the second most common cause of cancer deaths in women. Virtually all cervical cancer is caused by human papillomavirus (HPV).

Over 30 HPV types infect the genital tract, approximately half of which are considered carcinogenic. Other risk factors include smoking, cervical inflammation/infection, and parity; however these co-factor impart increased risk only among HPV-positive women. While HPV is a necessary factor in cervical carcinogenesis, HPV infection is very common and most often regresses over 12–24 months. Persistence of carcinogenic HPV types increases risk for development of precancer and cancer. Among carcinogenic HPVs, HPV 16 is more likely to persist, and given persistence, more likely to cause precancer/cancer than any other HPV type. HPV 16, 18, 31, and 45 together account for approximately 80% of cervical cancers worldwide.

Cervical squamous abnormalities (less than invasive cancer) are described in cytologic terms as low-grade and high-grade squamous intraepithelial lesions and histologically as cervical intraepithelial neoplasia (CIN) grades 1, 2, and 3. While cell changes form a morphologic spectrum, biologically these HPV-associated lesions can be dichotomized into low-grade transient infections and precancers that rarely if ever regress. According to this concept, CIN 2 is not a biologic stage, but represents a heterogeneous mix of CIN 1 (the morphologic equivalent of transient HPV infection) and incipient precancer (CIN 3).

Evolution from infection to precancer usually takes several years to a decade. With accumulation of additional molecular alterations, some (but not all) precancerous lesions develop into invasive cancer. Historically, the vast majority of cervical cancers were squamous; about 5% were adenocarcinomas. Now approximately 25% of cervical cancers in the US are adenocarcinomas. This increase is due to both a relative increase (secondary to reduction in squamous cancers) and an absolute increase in adenocarcinoma. Adenocarcinomas arise in the endocervical canal and are less accessible by screening modalities than squamous cancers.

Cervical cancer screening for the past 50 years has relied on cytologic evaluation of cells scraped from the surface of the cervix – the Papanicolaou test. Cell abnormalities can be identified and treated before cancer develops. Over the past several years, we have translated our understanding of the role of HPV in cervical carcinogenesis into clinical utility. The first clinical application of HPV testing has been to clarify equivocal cytology results. Recently, HPV testing has been utilized as a primary screening test either alone or in conjunction with cytology in women older then 30. The higher prevalence of HPV in younger women precludes the use of HPV testing in that age group.

Colposcopy and biopsy (previously the gold standard of diagnosis) detects only about two-thirds of prevalent CIN 2 and above (CIN 2+). Taking more biopsies, regardless of the expertise of the colposcopist, improves sensitivity.

Optical imaging to monitor morphologic and molecular features of cervical precancer

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Progress toward a molecular characterization of cancer would have important clinical benefits, including detecting cancer earlier based on molecular characterization, predicting the risk of precancerous lesion

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progression, detecting margins in the operating room in real time, selecting molecular therapy rationally, and monitoring response to therapy in real time at a molecular level. While molecular markers can be visualized *in vitro* using complex immunohistochemical staining protocols, there is an important need to image the molecular features of cancer *in vivo*. Imaging the molecular features of cancer requires molecular-specific contrast agents which can safely be used *in vivo* as well as cost-effective imaging systems to rapidly and non-invasively image the uptake, distribution, and binding of these agents *in vivo*.

Our group has approached this problem using optically active contrast agents to image the expression of three well-known molecular signatures of cervical neoplasia, including overexpression of EGFR, matrix metalloproteases (MMPs), and oncoproteins associated with HPV infection. This same approach can be used to develop contrast agents to image the expression of promising new biomarkers. For example, serial analysis of gene expression (SAGE) libraries can be used to identify novel targets for contrast agent development from the pool of genes differentially expressed in early neoplasia. Alternatively, *in vivo* phage display can be used to identify peptides that specifically bind to the surface of neoplastic cells and tumor vascular endothelium in target organ sites. Discovering new biomarkers and developing techniques to image their expression *in vivo* could be particularly useful for monitoring response to therapy.

At the same time, we are developing inexpensive, portable optical systems to image the morphologic and molecular signatures of neoplasia noninvasively in real time. These systems image reflected light and fluorescent light at two spatial scales, confocal microscopy with micron resolution to image cell morphology from a small field of view, and multi-spectral digital imaging with millimeter resolution to image tissue morphology from large fields of view. These systems can assess both native optical contrast as well as that afforded by optically active contrast agents. These real-time, portable, inexpensive systems can provide tools to characterize the molecular features of cancer *in vivo*.