Editorial

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CIN Prognostication: Will Molecular Techniques Do the Trick?

Since the inception of cervical cancer screening, protocols for the management of cervical intraepithelial neoplasia (CIN) have been unanimous in requiring elimination of CIN 3 (severe dysplasia, carcinoma *in situ*) with surgery. However, there is general agreement that only a minority of these lesions will ultimately progress to invasive cervical carcinoma. Although follow-up studies of CIN 3 without intervention to determine the natural history of the lesion are no longer justified for ethical reasons, evidence in the literature suggests that only 20–35% of CIN 3 will ultimately develop into invasive carcinoma of the cervix.[1,12] Consequently, because of our inability to determine the risk of progression on an individual basis, the current strategy is one of massive overtreatment: we prophylactically treat all patients since we lack the means for individual risk assessment. This rather crude and unsophisticated approach is badly in need of remedy because it carries a considerable burden in cost, patient anguish and side effects.

In this issue of *Acta*, El Hamidi et al[3] apply clonality analysis to prognostication of CIN. Current knowledge assumes that human cancer is a monoclonal event, that all cancer cells in a given tumor can be traced to a single, transformed cell and its progeny. Invasive cervical carcinoma has been shown to be monoclonal in most cases, whereas CIN has proven to be a mixture of polyclonal and monoclonal lesions by genetic testing.[5-7] Hence, the assumption is that only monoclonal CIN lesions have the potential to progress. In the last couple of years, elegant, new techniques for clonality analysis became available. As targets for clonality assays, X chromosome inactivation, androgen receptor gene analysis, 3p deletions and others have been used on histologic material so far. In a novel approach, El Hamidi et al[3,4] used archival cervical smears and were able to prove its feasibility. Although the ultimate confirmatory evidence for invasive potential is hard to provide because of the restrictions outlined above, the data from that study point toward a potential application. By demonstrating the suitability of archival cervical smears for microdissection, nucleic acid amplification and gene analysis even after up to 10 years' storage time, the authors point to yet another exciting area for molecular studies in cytology. As highlighted in an editorial before,[13] introduction of these rapidly developing techniques of genomics and proteomics into cytology will be crucial to the future viability of our field.

Several other approaches to individual prognostication of CIN are currently being investigated. Recently a number of molecular markers were identified that are of great interest.[2,8-10,15] Most,[8,10] but not all, are cell cycle related. It is highly likely that other specific biomarkers will become available through gene expression studies of cervical carcinoma and comparison with their normal counterparts. Another approach concentrates on the molecular detection of HPV integration.[11] It has been shown that HPV genome fragments are integrated into host nuclear DNA only in 16% of CIN 3, whereas in the rest of cases, viral DNA is present in the episomal state. In contrast, integration was found to be as high as 88% in invasive cervical carcinoma. These developments confirm that we are rapidly moving beyond simple HPV typing, which

has been shown to be of little value for prognostication because the vast majority of lesions contain high-risk HPV.

Ultimately, it may become possible, in the not-so-distant future, to differentiate reliably between intraepithelial lesions with and without invasive potential. This would lead not only to a decrease in unnecessary surgery but also to simplification of precursor terminology. We could then move to a single-tier system, calling only those lesions intraepithelial neoplasia that truly deserve that term.[14]

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