

CAP-ASCCP LAST Project: History of Cervical/Vaginal Terminology

A. Cervical Precancer

Although descriptions of tumors arising in the female lower genital tract date back to the writings of Hippocrates, histologic descriptions of cervical malignancies do not appear in the western literature until the 19th Century. Rudolf Vichow, in Lecture XX of his Cellular Pathology delivered in 1858, gives an early description of the typical morphologic features of invasive squamous carcinoma of the cervix. In addition, he describes surface cell abnormalities that, "from the irregularity of their form, the size of the nuclei, and their own large dimensions, present rather the character of cancer than that of epithelium." However, he cannot conclude that these abnormal cells might be a source of origin for the underlying malignancy. Sir John Williams, in his "Cancer of the Uterus, Being the Haeveian Lectures of 1886," describes a case with cancerous cells present in the squamous epithelium, as well as occupying the adjacent cervical glands. He concludes that these changes represented the earliest form of cervical cancer.

By the end of the 19th century, considerable interest in these early carcinomas was fostered in the various Austro-German laboratories by investigators such as Schottländer, Schauenstein, Sitzenfrey, Pronai, von Hansermann and Pick. These pathologists, along with von Franque and Kermauer described the earliest histologic changes of cervical cancer as *surface carcinoma* or *intraepithelial carcinoma*.

Interest in early carcinoma of the cervix did not develop in the United States until the beginning of the last century, under the auspices of two individuals, T.S. Cullen and I.C. Ruben.

In 1900, Cullen published his text "Cancer of the Uterus." In it, he describes a number of early cases with adjacent surface epithelium showing "cellular alterations" which he described as "suspicious changes" and included an excellent picture of what was later described as CIS. As with Williams, he noted the presence of these abnormal cells within adjacent endocervical glands. He theorized that squamous carcinomas of the cervix arose from these surface cells and grew in two directions: "Inward" arising from the basaloid cells and "outward" from more mature squamous cells into more of a cerebroid growth.

Rubin, in 1910, described three cases with cervical squamous surface cells that demonstrated 1) indistinct cell outlines, 2) irregular large hyperchromatic nuclei and 3) loss of maturation with stratification which he termed "incipient cancer". Rubin concluded that these surface changes represented the starting point of

cervical cancer, a conclusion supported by Schottländer and Schauenstein, but not by Pick and others, who felt that cancer starts de novo and, therefore, cases demonstrating changes only in surface squamous cells represent carcinoma that was not sampled. The term "carcinoma in situ" appears to have been first used by Rubin in 1918.

The concept of carcinoma in situ (CIS) was firmly established in 1932 by Broders, who defined the term as a condition "in which malignant epithelial cells and their progeny are found in, or near, positions occupied by their ancestors before the ancestors underwent malignant transformation." He also stated that the basement membrane had to remain intact. The histologic criteria used for diagnosis were similar to those previously described by Rubin, although the presence of mitoses, particularly abnormal forms, was also noted.

In the ensuing 2 decades, interest increased in developing methodology to screen for early cervical carcinoma. One technique included the use of a magnifying colposcope, developed by Hinselmann, to find small (occult lesions) on the cervical surface. A classification system evolved to describe the histologic features of these surface abnormalities: 1) Atypical cornified epithelium, 2) Atypical cornified epithelium with proliferation, 3) Carcinoid epithelium with parakeratosis, mitoses, or polymorphism, 4) Carcinoid epithelium with proliferation into the periphery and 5) Carcinoid epithelium with proliferation into connective tissue. The second technique utilized the identification of abnormal cells acquired by cervical scrapes or by aspiration from the vagina, first described by Papanicolaou in 1928 but not introduced for clinical use until the 1943 publication by Papanicolaou and Traut titled Diagnosis of Uterine Cancer by the Vaginal Smear. In the description of the various cells associated with the subsequent finding of cervical carcinoma, they classified some cells as "intraepithelial carcinoma," while others were described as only "atypical." The classification of these cells was later refined to five classes: Class I - Absence of atypical or abnormal cells, Class II - Atypical cytology but no evidence of malignancy, Class III - Suggestive of, but not conclusive for, malignancy, Class IV - Strongly suggestive of malignancy and Class V - Conclusive for malignancy. Papanicolaou noted that the ability to distinguish between these "Classes" was poor, and the only category that could be diagnosed with certainty was Class V. In the end, confusion arose as to what CIS represented, as it no longer seemed to be a distinct entity made up of a particular type of malignant cell.

To better categorize various cell types into what constituted premalignant squamous cervical lesions, attempts in the 1950s were made to better define the cellular makeup of CIS and to categorize lesions that were considered abnormal, but less than what constituted an in situ lesion. CIS was thus separated into two types: 1) Small cell (undifferentiated-defined as sheets on

small basaloid cells extending from the base to within one to two cell layers of the surface) or 2) Large cell (differentiated-defined as atypical cells with more cytoplasm, but still lacking polarity, near the surface). It would then logically follow that the poorly differentiated basaloid type carcinomas arose from the former, while the large cell, better differentiated invasive squamous cell carcinomas evolved from the latter. However, it soon became apparent that a number of cases originally felt to be CIS by these morphologic criteria spontaneously regressed. This was inconsistent with a category of "carcinoma" so questions arose as to whether this category even existed.

During the 1950s, it became generally accepted that there existed surface lesions on the cervix demonstrating abnormal features that did not fulfill the histologic criteria consistent with CIS, and appeared to represent less risk for development of invasive disease. Unfortunately, nonstandard terminology such as "basal cell hyperplasia and anaplasia." and nonstandard criteria for diagnoses evolved for these lesions, leading to considerable confusion.

In 1952, Reagan concluded that there existed a category, which he called atypical hyperplasia, that corresponded to cervical abnormalities with "greater degrees of differentiation" and less risk for subsequent development of cancer. The following year he replaced the term "atypical hyperplasia" with "dysplasia", a term first mentioned by Papanicolaou in 1949. He graded dysplasia as mild, moderate or severe, depending on the degree of differentiation, the number of cells or the replacement of the basal layers with immature ("primitive") cells. "Dysplasia" was derived from the Greek word "dys" for "bad" and "plasia" for "molding" and has been used in many areas of medicine, usually to describe a benign process. It was acknowledged that it was often difficult to differentiate severe dysplasia from CIS.

Three years later, Koss and Durfee reported on unique cellular features, first noted by Ayre in 1949, of "ballooned out" cytoplasm and irregular nuclei found in these atypical lesions. Koss and Durfee called these cells "koilocytes" from the Greek word for "empty space", and histology containing large numbers of these cells, "koilocytotic atypia." Koilocytotic atypia appeared to represent a minimal degree of abnormality with a high rate of regression, similar to Reagan's "mild dysplasia or atypical hyperplasia".

Even in the 1950s, some pathologists and clinicians argued that CIS was not the precursor to cervical cancer. However, in 1956, the concept of carcinoma developing from an intraepithelial lesion was eventually supported by Hertig and Mansell, who noted that the incidence of both lesions was similar, and included similar ethnic groups. In addition, the patient ages of development CIS was earlier than that of invasive cancer by about 10 years, and some cases of cervical cancer had documented CIS proceeding invasion.

In 1961, The First International Congress of Exfoliative Cytology was held in Vienna, co-chaired by Reagan, to standardize the terminology for premalignant cervical abnormalities. Normal epithelium, carcinoma in situ and invasive carcinoma were classified as acceptable terminology, with the latter two differentiated by whether or not the basement membrane had been breached. CIS was defined as "Only those cases which, in the absence of invasion, show as surface lining an epithelium in which, throughout its whole thickness, no differentiation takes place. It may involve the lining of glands without creating a new group. It is recognized that the cells of the uppermost layers may show some flattening. The rare case of an otherwise characteristic carcinoma in situ that shows a greater degree of differentiation belongs to the exceptions for which no classification can provide." All other lesions that did not fulfill the criteria for CIS were to be termed "dysplasia", which could then be categorized as low or high grade, depending on the degree of differentiation of the cells within the dysplasia. These terms were thus accepted by the majority of pathologists and gynecologists throughout the 1960s, although the criteria to identify these lesions were still somewhat vague, and the reproducibility of these diagnoses was poor.

The relationship of age with the degree of abnormality and the topography was discussed by Wielenga et al in 1965, extending the understanding of the natural history of cervical precancer. Larger lesions, particularly those extending into the canal, were most likely to be CIS, rather than lesser atypias/dysplasias, and increasingly likely to be associated with invasive cancer. They noted that smaller, thinner lesions were rarely if ever seen with invasion and were more likely to be found in women in their late 20's and early 30's. In 1968 Demin asked if "we are we entitled to stress our patients and clinicians with the word "carcinoma" even if attached to "in situ?" when it was clear that Carcinoma Stage 0 was not cancer and should not be put into registries as cancer.

The most profound change in cervical histologic terminology came in 1968 with the proposal by Richart that cervical carcinogenesis is a continuum of disease from mild dysplasia to cervical cancer, breaking down the concept that dysplasia and carcinoma in situ must be treated differently. Because of this "continuum" he coined the term cervical intraepithelial neoplasia (CIN) to emphasize the association as a precursor to cancer. Mild dysplasia was now termed CIN 1, moderate dysplasia CIN 2 and severe dysplasia CIN 3. He found "an absence of objective evidence to support the arbitrary division of CIN into two diseases - dysplasia and CIS - and basing therapy on such a division. Because all levels of CIN were potentially on a continuum to cancer, treatment based on size and location of the lesion for all grades of CIN replaced the two-division dysplasia/CIS model which dictated hysterectomy for most CIS (and some severe dysplasia) but no treatment for many with dysplasia.

Although Koss suspected that koilocytotic atypia was “a warning that cancer may be present elsewhere in the cervical epithelium”, he did not consider it to be either precancerous or cancer and he did not suspect that it was due to a virus. In 1976 Meisels and Fortein established the HPV etiology of the koilocyte and demonstrated that many “so-called” dysplasias were manifestations of HPV. At the same time, zur Hausen proposed that cervical cancer might be caused by HPV.

In 1978, Koss gave support to the CIN terminology but raised the concern about using the term “neoplasia” for lesions, many of which are not destined to progress to cancer. However, he argues in the end that “neoplasia” does not mean cancer, but only “new growth”. He also argues for combining CIN3/CIS, as different management protocols continued for each, and interobserver studies had not shown that they could be reliably differentiated. Buckley et al argued in 1982 that the differentiation between CIN 2 and CIN 3 is as subjective and arbitrary as the differentiation between severe dysplasia and CIS, yet does not matter since the therapeutic approach was to treat more on location and extent of the lesion than on grade.

By 1983 considerable frustration was being expressed due to confusion over the continuance of two histologic classification systems; the WHO categories developed at the 1961 Vienna 1st International Conference on Exfoliative Cytology, and the Richart CIN nomenclature. The traditional WHO system described two classes - dysplasia and CIS, the later including squamous and adenocarcinoma in situ (AIS). In 1983, Giacomini and Simi argue that the WHO two-tiered system corresponded better with risk for progression and represented the “field theory” of carcinogenesis where different lesions arise de novo, whereas the CIN system was incorrect in arguing that all grades of CIN were on a continuum of progression to invasion. The authors also criticized the CIN system in that it excluded glandular lesions, i.e. AIS. In the same year, Richart was also affirming that, on the basis of behavior of lesions, there were likely only two categories of precancer.

Many expressed concern that the word “neoplasia” carried a connotation of cancer/irreversibility and therefore, word choices such as this should be thought through very carefully before they are proposed for nomenclature. The fact that CIN 1, which is not a true precancer, contains the word “neoplasia” highlighted this issue. In 1984 Drake, the Chair of the Terminology Committee of the International Academy of Cytology, argued that a “new terminology should 1) Increase understanding between pathologists and between pathologists and clinicians. 2) It should embrace the known biology of the morphology and should try to incorporate all the known morphologies. 3) It must use words in their correct sense. The construction of an ideal classification system should be seen

not as a challenge to tradition, or to science, but as an exercise in logic and semantics.

By 1989 a number of interobserver variability studies brought into question the validity of breaking down CIN into three grades, since intra- and interobserver agreement were excellent for CIN 3 and invasive carcinoma, in the fair to good range for CIN 2 and poor for CIN 1. Robertson proposed that the classification be changed to a low grade (CIN 1 and 2) and a high grade (CIN 3) category. Ismail proposed that the only lesions in this spectrum whose natural history justified the designation CIN are those lesions referred to as CIN 3, but that since there was considerable overlap between CIN 3 and CIN 2 lesions it was suggested that CIN 2 lesions be included with CIN 3 in the single CIN category.

Richard lent his support to a two-tier system in his 1990 reassessment of the theory of "continuum of progression of CIN 1 to CIN 2 to CIN 3 to invasion" that he first proposed in 1966. Instead he argued for two grades of histology, low-grade [CIN 1 and HPV] and high-grade [CIN 2,3]. However, in the same year, Fox and Buckley argued that going back to the "discredited two tier classification system" risked returning to the "undertreatment of some women" and to "overtreatment of others". They also argue that the 1990 movement to change the terminology back to two tiers did not come from gynecologists, but from pathologists who were concerned about the interobserver variability in diagnosis.

In 1993 Genest et al tied interobserver variability to HPV type, with HPV 16 lesions the most morphologically consistent lesions called. They also demonstrated that a "binary" two tier classification (Low Grade and High Grade as in TBS) was more reproducible than a three tier system. Proposals to make histologic terminology consistent with the 1988 Bethesda cytologic classification of LSIL and HSIL became more common. However, Ostor's classic 1993 study on progression rates for CIN1>CIN2>CIN3 provided some validity, on the basis of natural history, to the three-part CIN system. However, Ostor also predicted that "as morphology alone does not predict completely whether a lesion will progress or regress, new markers other than morphology will need to be found to accomplish this."

Heatley, in 2002, from her review of papers published between 1966-2000 on CIN2 reproducibility, epidemiology, response to treatment prognosis and biological factors, proposed the use of similar terminology for both cytology and histology, i.e. low and high-grade cervical intraepithelial abnormality. In 2003 Crum carried the argument for a two-tiered system forward, with low grade (CIN I) and high grade (CIN2-CIN3). He focused on the need to: 1)

differentiate low grade from non-dysplastic processes, 2) recognition of the transformation zone biology and morphology, and 3) separation of CIN1 from CIN 2-3 on criteria that identified the effects of viral oncogenes on replicating cells. However, the move to accepting a two-tier system is still questioned by some. Herbert, Arbyn, and Bergeron argued in 2008 that separating CIN 2 from 3 was justified on the basis of need to provide different management options for each and that epidemiological stats would be skewed with CIN2/3 combined.

B. Cervical Microinvasive cancer

In 1947 Mestwerdt first described "microcarcinoma" as invasion of not more than 5 mm. From 1947 to now, a number of terms have been used to describe microinvasive carcinoma: microcarcinoma, microinvasive carcinoma, early invasive carcinoma, very small carcinoma, early invasive preclinical carcinoma, pin-point invasion, and Stage 1A cervical carcinoma. FIGO changed the definition of Stage 1A, microinvasive carcinoma 6 times between 1961 and 1985, with treatment varying from conization only, to radical hysterectomy with pelvic lymphadenectomy. 1973 SGO defined microinvasive carcinoma as invasion ≤ 3 mm, without invasion of vascular-lymphatic spaces. In 1985 FIGO defined Stage 1A as "lesions with minimal microscopic stromal invasion." Early stromal invasion is a term first used by Stoddard in 1952 to define single or multifocal protrusions along the basement membrane below CIS that may be only a fraction of a mm in size. Concern continues to be expressed about marked interobserver variability in diagnosing microinvasion, with many cases of intraepithelial gland involvement being over-read and depth of invasion measured differently. The term "microinvasion" can only be applied to histology read from cone specimens and not from biopsies.

Vagina

The first description of a vaginal intraepithelial lesion was apparently made at the Mayo Clinic in 1933 over a century after vaginal cancer was first described by Cruveilhier in 1826, and as reported by Hummer in 1970. For several decades the lesion was termed vaginal carcinoma in situ and was felt to be very rare, an impression that continued with Woodruff's 1981 review of all literature on vaginal CIS in which he could find only 300 cases. However, increasing use of cytology and colposcopy soon demonstrated that vaginal HPV-induced lesions were very common, particularly those of lesser grade than CIS. By the 1980s the terminology of vaginal intraepithelial lesions was tracking that cervical; i.e. the

terminology of vaginal intraepithelial neoplasia (VaIN) came into common use, with VaIN 1 equating to low-grade, VaIN 2 to moderate grade, and VaIN 3 to severe dysplasia/CIS.

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