PRIMARY, SECONDARY AND TERTIARY PREVENTION OF CERVICAL CANCER

2nd Completely Revised Edition

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Attached to the inside back cover is a DVD with accompanying Video Clips and E-Learning Modules for more detailed information and step-by-step instruction on the topics covered by the textbook.
Please note:

Attached to the inside back cover is a DVD (KS 775) titled ‘Primary, Secondary and Tertiary Prevention of Cervical Cancer’ by Achim Schneider, M.D., M.P.H., Berlin, Germany.

The Video Clips (No. 1–24) provided on the interactive DVD (see inside back cover) are referenced in the book as shown on the icon.

The DVD (see inside back cover) also includes E-Learning Modules (No. 1–5) referenced in the book as shown on the icon.

In a handy format, the reader is offered the checklist ‘The Rules of Colposcopy’ as a concise guide and learning aid.

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Primary Prevention of Cervical Cancer
Cervical Cancer

This booklet addresses all important aspects of prevention of cervical cancer encompassing primary, secondary and tertiary prevention. We start with primary prevention, which is synonymous to prophylactic vaccination against certain human papillomaviruses and intended to completely replace secondary prevention provided vaccination coverage is adequate.

1.0 Primary Prevention

Introduction

The ultimate goal of the cervical cancer initiative is primary prevention which should eventually lead to elimination of the disease.

In 2008, the Nobel committee awarded the Prize for Physiology or Medicine to Harald zur Hausen for his discovery of human papillomaviruses (HPV) causing anogenital cancer. His seminal research unveiled the causal relationship between HPV and the malignant transformation of epithelial cells. This knowledge led eventually to the development of prophylactic vaccines.

1.1 Epidemiology of HPV-Associated Diseases

Spectrum of HPV Genotypes and Neoplasia

More than 150 human papillomavirus genotypes have been defined, of which approximately 40 HPV types are mainly prevalent in the anogenital tract. At present, 19 so-called low-risk HPV types have been defined, which are mainly associated with genital warts, condyloma or low-grade intraepithelial neoplasia. The types HPV 6 and HPV 11 are found in 90% of genital warts. A total of 17 high-risk HPV types have been defined, of which four HPV types are highly prevalent in high-grade precancer and invasive cancer. However, they are also the most commonly detected HPV types in healthy individuals. HPV 16 and HPV 18 are detected in 70% of invasive cervical cancers. Precancer and cancer of cervix, vagina, vulva and anus, and of larynx, oral cavity and tonsils are also to a varying degree caused by HPV.

Infection with HPV 16 and 18 and CIN III

Development of CIN grade III and of invasive cervical cancer is mainly associated with infection by HPV 16 or HPV 18. A prospective cohort study from Portland (Oregon, USA) by a group of the National Cancer Institute (Bethesda, USA) on more than 20,000 women over a ten-year period showed that the women, who were positive for HPV 16 or 18 and free of cervical disease at initiation of the study, had a risk of 21% or 18% respectively, for developing CIN grade III. The risk was not age-dependent. The risk to develop CIN grade III in the presence of infection with low-risk HPV types or high-risk HPV types other than HPV 16 or 18, was very low with 0.5% or 1.5%, respectively. This shows that vaccination against HPV 16 and HPV 18 has the potential to be highly efficacious in the prevention of high-grade precancer and invasive cancer of the cervix.
Prevalence of HPV Infection in Women
In women, the prevalence of HPV infection increases dramatically after sexual debut. Especially in the age group between 15 and 30 years, the prevalence of high-risk HPV infection is twice the rate of low-risk HPV infection. Following their first attendance to college 33% of female students were found to be HPV-positive after two years, and 60% were HPV-positive after five years. These data show clearly that sexual activity is causally associated with genital HPV infection. In women, thus, genital HPV infection is a natural consequence of sexual activity. HPV prevalence decreases continuously up to the age of 40 and levels out at old age. Several reports in the literature indicate a slight increase with old age, which may be attributed to impairments of the immunity system in the elderly.

Prevalence of HPV Infection in Men
In men, the prevalence pattern of HPV DNA in genital swabs is clearly different from that of women: the prevalence remains high with increasing age. As compared to women, this finding is attributed to a different range of HPV types and the fact, that sexual activity in general has been found to show no age-dependency in men.

Age-Specific Incidence of HPV Infection in Women
The cumulative risk of acquiring a new HPV infection over a period of five years varies significantly between the different age groups and is highest in young women, who initiate sexual activity. However, even in women aged 45 years or older, there is a 13% risk of acquiring a new HPV infection within five years. In comparison, this risk is 43% in the age group between 15 and 19 years.

Natural History of HPV Infection and Cervical Neoplasia
Eighty out of 100 women who become infected with HPV during their sexual debut are supposed to experience spontaneous regression of HPV infection within a period of 8 to 18 months due to their intact natural immunity. In the remaining group of 20 women, HPV infection will persist leading to high-grade CIN in ten women and invasive cancer in one woman. If this cohort of women does not participate in the cytologic screening program, up to five women will develop cancer. Through secondary prevention of cervical cancer by screening programs it is possible to detect the majority of CIN in the cohort screened. However, women with a diagnosis of suspected CIN need to undergo colposcopy, biopsy, and excisional or ablative therapy. Primary prevention and prophylaxis of HPV infection by vaccination is capable of preventing infection, CIN and cancer, and accordingly, the whole spectrum of associated disease burden that accrues to both women and men.
Burden of HPV-Associated Findings

In a study by Koutsky and coworkers, presented in absolute numbers and based on data collected from the sexually active U.S. population, the lifetime risk of infection with mucosal HPV types ranges from 70–80%. Only 25% of females have never become infected with HPV in the anogenital tract. The majority of females have a history of anogenital HPV infection. In the female population, HPV DNA can be detected in 10% of anogenital swabs using highly sensitive PCR techniques. In 4% of all women, colposcopy is capable of detecting HPV-related lesions on the uterine cervix and in 1% of the cohort investigated either CIN and/or genital warts are found. The numbers on the anterior surface of the pyramid show the absolute prevalence in the sexually active female population of the U.S.A. with a total of 114 million women.

The chart shows the incidence rates of HPV-induced diseases of the female genital tract in the European population. With regard to precancer and cancer, more than 75% of diseases involve the uterine cervix. Cervical intraepithelial neoplasia grade I occurs at a rate that is fifteen times higher, and cervical intraepithelial neoplasia grade II or III at a rate that is five times higher compared to invasive disease. In the European population, scientific evidence suggests that each day 40 women die from cervical cancer, 450 women are faced with a diagnosis of high-grade cervical intraepithelial neoplasia and 1,500 women are confronted with a diagnosis of cervical intraepithelial neoplasia, grade I. The most prevalent HPV-induced disease of vulva, vagina, perineum, or anus are genital warts with an incidence rate of 1 million per year in Europe.

1.2 Vaccines: Efficacy and Safety

HPV Vaccine Production

Twenty five years after the description of the most important oncogenic HPV types, HPV 16 and HPV 18, the first prophylactic vaccines became available. This was a landmark achievement in the global fight against one of the major threats to women’s health.

Since HPVs grow only in humans and cannot be propagated in tissue culture, genetic engineering technology had to be used in order to produce a vaccine. The L1 gene being the main capsid protein, can be produced either in bacteria, yeast, or insect cells. L1 protein subunits produce and self-assemble into so-called ‘virus-like particles’ (VLPs) consisting of empty virus capsids that contain no oncogenic viral DNA and are therefore considered highly immunogenic, but safe.

The Vaccines

Shown on the chart are two prophylactic vaccines that already have been approved. The vaccines differ in their antigen composition and adjuvantation. The quadrivalent vaccine is produced in yeast and protects against HPV types 6 and 11, which induce 90% of genital warts and against HPV types 16 and 18, which account for 70% of cervical cancer. The bivalent vaccine is produced in a baculovirus / insect cell system and protects against HPV types 16 and 18. The adjuvant AS04 of the bivalent vaccine is based on toll-like receptor 4 (TLR4), agonistic lipopolysaccharides and enhances the immune response significantly. In December, 2014, the U.S. Food and Drug Administration (FDA) granted approval for the nonavalent vaccine Gardasil 9, which is directed against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.
HPV Antibodies – Mechanism and Chronology
For immunological defense of the cervical epithelium, antibodies need to be present in the serum and transudate through the epithelium. Neutralizing antibodies are critical for inhibition of early infection before viral entry into cells occurs. Thus, systemic serum antibodies have the capacity to neutralize oncogenic virus types in the cervix. Immunization against HPV will increase serum levels of HPV-specific antibodies, however, in order to attain protective immunity, anti-HPV antibodies need to be present within the genital tract at the site of infection. Higher levels of serum IgG, induced by prophylactic vaccination, have the potential to diffuse across the cervical epithelium at a concentration that is sufficient for neutralization of the virus. It has been shown that a higher magnitude of antibodies in the serum correlates with higher antibody levels in the cervico-vaginal secretions (CVS).

As shown in the charts, vaccination with a quadrivalent vaccine induces antibodies to all four vaccine HPV types that peak at month 7, four weeks after the third dose, indicated by the solid black line. Peak titers fall until month 24 and then level out. For HPV types 6, 11, and 18, the antibody titers are not significantly higher than after natural infection indicated by the red dotted line. For HPV type 16, antibody titers stay at a level 7 to 10 times higher than that acquired following natural infection.

As shown in the charts, the bivalent vaccine induces antibody titers that are 100 to 1000 times higher at month 7 than those observed after natural infection, indicated by the red line. These titers level out at a value more than 10 times higher than natural titers. Importantly, the same goes for HPV 18. These titers are maintained for up to 8.4 years measured by ELISA and Pseudovirion-based neutralisation assay (PBNA).

Vaccine Protection Against CIN
The protective effect of the bivalent vaccine against HPV 16-/HPV 18-associated CIN II+ disease is 99%. The single HPV-positive patient in the vaccinated verum group occurred 42 months after vaccination and HPV 52 + HPV 18 were found by type assignment in the biopsy. The quadrivalent vaccine shows similar efficacy.
Due to the prevalence of vaccine HPV types in CIN, the estimated efficacy of the bivalent vaccine is 52% for CIN grade II, and 71% for CIN III. The anticipated maximal efficacy was exceeded by the bivalent vaccine at the end of the study in that the results of the PATRICIA trial in the HPV-naive (for 14 high-risk HPV types) group of vaccinated women were found to be 15% and 20% higher, respectively. HPV-naive women had a 93% protection against CIN III, the true precursor of cancer. This enhanced efficacy can only be explained by assuming a certain degree of cross-protection against related non-vaccine HPV types.

One third of high-grade premalignant disease can be prevented within a 4-year observation period, provided all women irrespective of their sexual activity or HPV status in the age group between 15 and 25 years (TVC cohort) are vaccinated with the bivalent (shown here) or quadrivalent vaccine. To see the final result, however, a prolonged observation period is needed (here 48 months) taking into account the long latency period of the infection cycle ranging from 8 to 18 months, inherent to HPV. Only when these primary infections have been eliminated by the natural immune response, the capability of the host organism to prevent newly acquired infections becomes evident, as of month 18. Therefore, only at month 18, the graphs separate and the incidence of new lesions slows down in the vaccinated cohort.

Genetic Relatedness of HPV Genotypes

This genealogic drawing illustrates the genetic relatedness of HPV types. HPV 16 is closely related to HPV 31 and 33. HPV 18 is closely related to HPV 45. The greater the degree of similarity of gene sequences between different HPV species, the more similar are the resulting protein sequences and structures that allow for antibody cross-reactivity and neutralisation.
Primary, Secondary and Tertiary Prevention of Cervical Cancer

Reduction in Women’s Morbidity

The clinical effect of vaccination with the bivalent vaccine is directly reflected in the reduced burden for the patients and the health care system. Colposcopy referrals drop by 26% and cervical excisional procedures by 69% in the total vaccinated cohort (TVC) of initially HPV-naïve women.

Decrease in Genital Warts Following Vaccination

The graph shows the incidence of newly diagnosed external genital warts (GW) in different patient cohorts visiting a clinic that specializes in sexually transmitted infections (STI) before and after introduction of HPV vaccination in Australia. In older, non-vaccinated women, no change in the incidence rate was observed. Likewise, in the MSM cohort (men who have sex with men), no change was found. In young women eligible for vaccination, a sharp drop in incidence was found after implementation of HPV vaccination which correlated well with the start of the organized vaccination program. In Australia, a very high vaccination rate of 80% of the target population was achieved within one year. During this period, the incidence of external GWs declined by nearly 93%. Interestingly, this decline in young women is accompanied by a decline of 82% also in young men, explained by herd immunity effects and lower infection rate of young men being in contact with vaccinated young women.

Decrease in CIN Following Vaccination

An epidemiological study on the early effect of the HPV vaccination program on cervical abnormalities in Victoria, Australia, revealed the following results:

Incidence of CIN II+ prior to introduction of the vaccination program between January 2003 till March 2007 was 0.80% in women younger than 18 years. Following introduction of HPV vaccination between April 2007 till December 2009, the incidence of CIN II+ was 0.42% which is a 50% reduction. The vaccination attendance rate in this cohort of women was 70%.

HPV Vaccines Are Safe

All of the side effects observed after vaccination with HPV vaccines are typical for vaccinations in general. The local and systemic effects are of short term and resolve after 3 days. All of the reported late side effects have a chronological, but no causal association and their incidence rate is not higher than the spontaneous incidence rates in the unvaccinated population.

In 2013, Arnheim-Dahlström et al. published the results of a 2006–2010 Danish-Swedish cohort study with a data base of 997,585 girls 10 to 17 years of age, 296,826 of whom had been vaccinated with the quadrivalent HPV vaccine. The participants were evaluated for 53 different autoimmune, neurological and thromboembolic adverse events up to 180 days after each vaccine dose. None of the outcomes were found to be significantly associated with exposure to the HPV vaccine.

Prevention of Disease: Reduction of Excisional Procedures by HPV Vaccination (Cervarix®)

Vaccine efficacy versus colposcopy referrals and cervical excisional rate.

Incidence Rate of Newly Diagnosed Genital Warts

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<tbody>
<tr>
<td>Relative Incidence Rate of Genital Warts (GW)</td>
<td>14.7</td>
<td>36.4</td>
<td>14.7</td>
<td>36.4</td>
<td>14.7</td>
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Incidence of CIN Following HPV Vaccination

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<tr>
<td>Number of women examined &lt; 18 years</td>
<td>13,620</td>
</tr>
<tr>
<td>Number of CIN II+ in women &lt; 18 years</td>
<td>109 (0.80%)</td>
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Safety Issues: Incidence of Side Effects

<table>
<thead>
<tr>
<th>Local effect</th>
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<tbody>
<tr>
<td>pain</td>
</tr>
<tr>
<td>redness</td>
</tr>
<tr>
<td>swelling</td>
</tr>
<tr>
<td>itching</td>
</tr>
<tr>
<td>bleeding</td>
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<table>
<thead>
<tr>
<th>Systemic effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>fever</td>
</tr>
<tr>
<td>head ache</td>
</tr>
<tr>
<td>vomiting</td>
</tr>
<tr>
<td>bronchospasm</td>
</tr>
<tr>
<td>gastritis</td>
</tr>
<tr>
<td>urinary bleeding</td>
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<table>
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<tr>
<th>Late effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmunity</td>
</tr>
<tr>
<td>arthritis</td>
</tr>
<tr>
<td>diabetes</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 reported (Gardasil®)</td>
</tr>
</tbody>
</table>

Typically occurring side effects included from placebo-controlled studies as significant difference. Spontaneous incidence concluded from placebo-controlled studies and fatal application.
HPV Vaccines Recommended in the Whole of Europe

The vaccine is highly immunogenic with 100% seroconversion, has a very good safety profile, and an extraordinary efficacy of 100% for more than 6 years.

In view of the key role HPV vaccination plays in the protection of women’s health against malignant disease as well as premalignant lesions, and its added benefit of being a cost-efficient prophylaxis, most countries of the European Union recommend HPV vaccination of certain birth cohorts of girls and young women. The majority of countries endorsed vaccination in 2007, starting at an age of 10 to 12 years. Finland is conducting an experimental study that investigates the impact of including boys in vaccination prophylaxis and, thus, the introduction of general vaccination has been put on hold till the study is completed.

Cost-Benefit Analysis of HPV Vaccination

Compared to cost-benefit ratios of other infectious diseases or traffic accidents, prophylactic vaccination against HPV is a highly cost-effective measure: 480 girls need to be vaccinated in order to prevent one case of cervical cancer, and 10 girls have to be vaccinated in order to prevent one case of high-grade CIN. Concerning the risk of dying from Varicella, 34,000 individuals need to be vaccinated in order to prevent one death, while in the case of influenza, 5,000 individuals need to be vaccinated in order to prevent one death. In comparison, 40,000 airbags need to be installed in order to prevent one death from car accident.
2.0 Secondary Prevention

Introduction
Secondary prevention is targeted at detecting precancer before it becomes symptomatic and involves the use of screening techniques, such as cytology and/or HPV testing, including therapeutic measures that are suited to inhibit progress and, if possible, remove the disease. Patients with abnormal findings in cytology or HPV testing are evaluated by colposcopy and histologic evaluation of disease. If high-grade precancer is diagnosed, excisional or ablative surgical techniques are used to remove the precancerous lesion.

2.1 Histology

WHO Classification of Tumors of Female Reproductive Organs, 4th Edition 2014


**Terminology of Precancer of the Cervix uteri**

Colposcopists must have a good knowledge of cervical histopathology. They should reevaluate all the biopsies or specimen with the pathologist in order to correlate directly colposcopic findings with histologic findings. Several histologic nomenclatures are in use. The colposcopists should always try to predict the histologic findings differentiating between normal, minor change, major change or invasive cancer. Minor change is consistent with low grade squamous intraepithelial lesion (SIL), or cervical intraepithelial neoplasia (CIN), and major change is consistent with high grade SIL or CIN.

**Histological Evaluation for CIN**

Precancerous lesions of the cervix are changes of the epithelium and not of the stroma. Therefore, the severity of the precancerous lesions can be evaluated on the epithelium without stroma. The interaction between epithelium and stroma is only important in invasive disease. The histophotographs show CIN I (a) and CIN III (b). The histopathological appearance of individual cells of CIN III mimicks invasive cancer, however in CIN III, the basal layer, marked by yellow arrows (b) is intact, which excludes invasive disease.

**CIN III and Atypical Mitotic Figures**

Besides the uniformity of atypical cells in all layers with increased nuclear-to-cytoplasmic ratio, the presence of atypical mitotic figures is the most important criterion for diagnosis of CIN III (c).

**Biomarkers**

Biomarkers are playing an increasingly important role in both histologic and cytologic testing. p16\(^{INK4a}\) is a specific biomarker for HPV-transformed proliferating cells. The E7 protein of high-risk HPV types interferes with the retinoblastoma protein and activates DNA synthesis and a transition from the G1 to S phase in the cell cycle. This leads to an overexpression of p16.

Ki67 is associated with cellular proliferation. It is detected only in cell nuclei and correlates with the biological activity of cancer and its precursors.

Stathmin 1 (STMN1) corresponds to oncoprotein 18, which destabilizes the microtubules, increases cellular proliferation, and is linked to invasiveness. It is overexpressed in malignant tumors of the Müllerian duct.

An example is CIN III as demonstrated by conventional hematoxylin-and-eosin (H&E) stain (d), Ki67 and p16 stain (e), and STMN1 stain (f).
2.2 Cytology

History and Rationale of Cytology
The so-called PAP test was introduced by G. N. Papanicolaou and H. F. Traut in the 40s of the last century and is still the most widely used cervical screening technique. Due to subjectivity in reading and problems in harvesting the relevant target cells sensitivity and specificity for detection of precancer has to be improved. In addition, reproducibility of results and quality control are inherent problems of this technique. The sensitivity of the conventional single PAP test for detection of high-grade CIN or cancer is around 50%.

Taking a Smear
Different instruments such as swab, brush, or spatule are used to harvest representative cellular material from the uterine cervix. Ecto- and endocervical cells are collected and are spread on the glass slide. The material must be fixed immediately using for instance 95% alcohol and should not be air dried.

Evaluating a Smear
Using light microscopy basal cells, parabasal cells, intermediate cells and/or superficial cells can be identified. In addition columnar cells and in the presence of metaplasia metaplastic cells can be seen. In the presence of precancer dyskaryotic cells are present. The upper cytophotogram shows two normal eosinophilic, red-stained cells and two basophilic, blue-stained superficial cells. In addition two dyskaryotic cells with an halo in the cytoplasm, so-called koilocytes, which are marked by arrows can be seen. The nuclei of these koilocytes contain papillomavirus particles. The ratio between the nucleus and cytoplasm is increased in the koilocyte compared to the normal cell. Therefore these cells are mature dyskaryotic cells. This Pap smear is suggestive of CIN I or low-grade SIL. According to the Munich III classification, this smear is classified as class IIID1.

The cytological image (b) shows four normal eosinophilic red-stained superficial cells on the lower border. Above these cells, there is a syncytium of severe dyskaryotic cells with a highly distorted ratio between nucleus and cytoplasam marked by arrows. The nuclei are hyperchromatic and anisokaryotic. This Pap smear is suggestive of CIN III or high-grade SIL. According to the Munich III classification, this smear is classified as IVa-p.
Principle of Liquid-based Cytology

The quality of conventional cytology is technically improved by the monolayer technique. Exfoliated cells are collected in liquid and applied to the glass slide in a monolayer. Evaluation of the monolayer specimen can be done conventionally by a cyto-technician or automated. However, the problem of adequate sampling is not solved by this technique. To date, no prove has been provided that sensitivity or specificity of monolayer technique is higher as compared to the conventional technique.

Shown is the cervical sample collection system using liquid-based cytology (LBC). A brush-like instrument is used to collect cell samples from the cervix, which are then transferred to a liquid medium and sent to a central laboratory for analysis. Liquid with cells not used for the monolayer slide is stored. If abnormal cells are present, the stored sample can be analysed for human papillomaviruses (HPV) or other molecular markers.

Cytological Classification in Germany

The most widely used cytological classification system in Germany is version III of the Munich Nomenclature, which draws upon the Bethesda system used in the U.S.

<table>
<thead>
<tr>
<th>Class</th>
<th>Definition in Munich Nomenclature III</th>
<th>Correlate in the Bethesda system</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Inadequate sample</td>
<td>Unsatisfactory for evaluation</td>
</tr>
<tr>
<td>I</td>
<td>Normal or unsuspicious findings</td>
<td>Negative for intraepithelial lesion or malignancy (NILM)</td>
</tr>
<tr>
<td>II-a</td>
<td>Normal findings in patients with an eventful history</td>
<td>Negative for intraepithelial lesion or malignancy (NILM)</td>
</tr>
<tr>
<td>II</td>
<td>Findings suggesting a limited protective value</td>
<td></td>
</tr>
<tr>
<td>II-p</td>
<td>Squamous epithelial cells with milder nuclear changes than in CIN I, also with koiocyte plasm or parakeratosis</td>
<td>Atypical squamous cells of undetermined significance (ASC-US)</td>
</tr>
<tr>
<td>II-g</td>
<td>Cervical glandular cells with anomalies that go beyond the spectrum of reactive changes</td>
<td>Atypical glandular endocervical cells not otherwise specified (AGC endocervical NOS)</td>
</tr>
<tr>
<td>II-e</td>
<td>Endometrial cells in women &gt; age 40 in the second half of their menstrual cycle</td>
<td>Endometrial cells</td>
</tr>
<tr>
<td>III</td>
<td>Doubtful or inconclusive findings</td>
<td></td>
</tr>
<tr>
<td>III-p</td>
<td>CIN II/III or squamous cell carcinoma cannot be excluded</td>
<td>Atypical squamous cells of undetermined significance, cannot exclude HSIL (ASC-H)</td>
</tr>
<tr>
<td>III-g</td>
<td>Atypical glandular epithelial cells, adenocarcinoma in situ or invasive adenocarcinoma cannot be excluded</td>
<td>Atypical glandular endocervical cells favor neoplastic (AGC endocervical, favor neoplastic)</td>
</tr>
<tr>
<td>III-e</td>
<td>Abnormal endometrial cells (especially in postmenopausal women)</td>
<td>Atypical glandular endometrial cells (AGC endometrial)</td>
</tr>
<tr>
<td>III-x</td>
<td>Doubtful glandular cells of uncertain origin</td>
<td>Atypical glandular cells, favor neoplastic (AGC favor neoplastic)</td>
</tr>
<tr>
<td>IIID</td>
<td>Dysplasia with potential for regression</td>
<td></td>
</tr>
<tr>
<td>IIID1</td>
<td>Features of mild dysplasia, analogous to CIN I</td>
<td>Low-grade squamous intraepithelial lesion (LSIL)</td>
</tr>
<tr>
<td>IIID2</td>
<td>Features of moderate dysplasia, analogous to CIN II</td>
<td>High-grade squamous intraepithelial lesion (HSIL)</td>
</tr>
<tr>
<td>IV</td>
<td>Immediate precursors of cervical cancer</td>
<td></td>
</tr>
<tr>
<td>IVa-p</td>
<td>Features of severe dysplasia or carcinoma in situ, analogous to CIN III</td>
<td>High-grade squamous intraepithelial lesion (HSIL)</td>
</tr>
<tr>
<td>IVa-g</td>
<td>Features of adenocarcinoma in situ</td>
<td>Adenocarcinoma in situ (AIS)</td>
</tr>
<tr>
<td>IVb-p</td>
<td>Features of CIN III, invasion cannot be excluded</td>
<td>High-grade squamous intraepithelial lesion (HSIL) with features suspicious for invasion</td>
</tr>
<tr>
<td>IVb-g</td>
<td>Features of adenocarcinoma in situ, invasion cannot be excluded</td>
<td>Adenocarcinoma in situ (AIS) with features suspicious for invasion</td>
</tr>
<tr>
<td>V</td>
<td>Cancer</td>
<td></td>
</tr>
<tr>
<td>V-p</td>
<td>Squamous cell carcinoma</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>V-g</td>
<td>Endocervical adenocarcinoma</td>
<td>Endocervical adenocarcinoma</td>
</tr>
<tr>
<td>V-e</td>
<td>Endometrial adenocarcinoma</td>
<td>Endometrial adenocarcinoma</td>
</tr>
<tr>
<td>V-x</td>
<td>Other malignancies, including those of uncertain origin</td>
<td>Other malignant neoplasms</td>
</tr>
</tbody>
</table>

Class 0 – Inadequate Sample

Example of class 0: obscuring leucocytosis in a 25-year-old patient with vaginal discharge.

Classes I and II-a – Normal Findings

Example (a) of class I: eosinophilic and basophilic squamous epithelial cells with a normal nuclear-cytoplasmic ratio and Döderlein’s cytolysis in a 33-year-old patient.

Example (b) of class II-a: eosinophilic and basophilic squamous epithelial cells with a normal nuclear-cytoplasmic ratio in a 50-year-old patient with perimenopausal bleeding.
Class II – Findings Suggesting a Limited Protective Value

**Class II**

Findings suggesting a limited protective value

- **II-p:** Squamous epithelial cells with milder nuclear changes than in CIN I, also with koilocytic cytoplasm or parakeratosis.
- **II-g:** Cervical glandular cells with anomalies that go beyond the spectrum of reactive changes.
- **II-e:** Endometrial cells in women > age 40 in the second half of their menstrual cycle.

Example of **class II-p:** eosinophilic and basophilic squamous epithelial cells with an increased nuclear-cytoplasmic ratio in a 34-year-old patient.

Cytology at 6 months’ follow-up was normal.

Example of **class II-g:** basophilic glandular epithelial cells of the endocervix with an increased nuclear-cytoplasmic ratio in a 31-year-old patient.

Cytology at 6 months’ follow-up was normal.

Example of **class II-e:** syncytium of eosinophilic glandular epithelial cells of the endometrium with an increased nuclear-cytoplasmic ratio in a 48-year-old patient, 3 weeks after her last menstrual period. Office hysteroscopy showed a normally appearing uterine cavity with normal mucosa. Endometrial biopsy was normal.
Class III

Doubtful or inconclusive findings

- **III-p**: CIN II/III or squamous cell carcinoma cannot be excluded.
- **III-g**: Atypical glandular epithelial cells, adenocarcinoma in situ or invasive adenocarcinoma cannot be excluded.
- **III-e**: Abnormal endometrial cells (especially in postmenopausal women).
- **III-x**: Doubtful glandular cells of uncertain origin.

Example (a) of class III-p: eosinophilic and basophilic squamous epithelial cells with a markedly increased nuclear-cytoplasmic ratio in a 45-year-old patient. Colposcopic examination showed an atypical T-zone type 2 with major change and CIN III on biopsy.

Example (b) of class III-g: basophilic glandular epithelial cells of the endocervix with a markedly increased nuclear-cytoplasmic ratio in a 48-year-old patient. Colposcopy showed an atypical T-zone type 2 with major change and adenocarcinoma in situ (ACIS) on biopsy.

Example (c) of class III-e: syncytium of basophilic glandular epithelial cells of the endometrium with a markedly increased nuclear-cytoplasmic ratio in a 52-year-old patient. Office hysteroscopy showed a hyperplastic endometrium with atypical endometrial hyperplasia in curettage material.

Example (d) of class III-x: syncytium of basophilic glandular epithelial cells in a papillary arrangement with a markedly increased nuclear-cytoplasmic ratio in a 72-year-old patient. Histology showed serous papillary carcinoma of the endometrium, pT1b pN0 M0.
**Class IIID – Dysplasia with Potential for Regression**

Example (a) of class IIID1: eosinophilic, mature dyskaryotic cells and koilocytes of squamous epithelium in a 31-year-old patient.

Colposcopic examination showed an atypical T-zone type 1 with minor change and CIN I on biopsy.

Example (b) of class IIID2: eosinophilic, moderately mature dyskaryotic squamous epithelial cells in a 29-year-old patient.

Colposcopic examination showed an atypical T-zone type 2 with major change and CIN II on biopsy.

---

**Class IV – Immediate Precursors of Cervical Cancer**

Example (a) of class IVa-p: eosinophilic and basophilic immature dyskaryotic squamous epithelial cells in a 41-year-old patient.

Colposcopic examination showed an atypical T-zone type 1 with major change and CIN III on biopsy.

Example (b) of class IVa-g: syncytium of basophilic immature dyskaryotic glandular epithelial cells from the endocervix of a 45-year-old patient.

Colposcopic examination showed a T-zone type 3. Endocervical curettage and histology revealed adenocarcinoma in situ (ACIS).

---

**Class IIID**

Dysplasia with potential for regression

- **IIID1**: Features of mild dysplasia, analogous to CIN I.
- **IIID2**: Features of moderate dysplasia, analogous to CIN II.

---

**Class IV**

Immediate precursors of cervical cancer

- **IVa-p**: Features of severe dysplasia or carcinoma in situ, analogous to CIN III.
- **IVa-g**: Features of adenocarcinoma in situ.
- **IVb-p**: Features of CIN III, invasion cannot be excluded.
- **IVb-g**: Features of adenocarcinoma in situ, invasion cannot be excluded.
Class V – Cancer

- **V-p:** Squamous cell carcinoma.
- **V-g:** Endocervical adenocarcinoma.
- **V-e:** Endometrial adenocarcinoma.
- **V-x:** Other malignancies, including those of uncertain origin.

Example of **class V-p:** eosinophilic squamous epithelial tumor cells with marked pleomorphism, anisokaryosis, hyperchromasia, and a dirty background in a 65-year-old patient.

Colposcopic examination showed an atypical transformation zone suspicious for invasive cancer. Biopsy histology revealed invasive squamous cell carcinoma.

Example of **class V-g:** syncytium of eosinophilic and basophilic immature dyskaryotic cells with pronounced anisokaryosis, hyperchromasia and nucleoli of endocervical glandular epithelium, and tumor diathesis in the background of a smear from a 46-year-old patient.

Loop excision and histology showed extensive adenocarcinoma in situ and invasive adenocarcinoma G2 of the endocervix.

Example (c) of **class IVb-p:** eosinophilic immature dyskaryotic cells with pronounced anisokaryosis and hyperchromasia of the squamous epithelium plus enlarged bare nuclei in a 48-year-old patient.

Colposcopic examination showed an atypical T-zone type 3 suspicious for cancer. Loop excision and histopathology revealed invasive squamous cell carcinoma pT1A2, graded as G2 R0 L0 V0 Pn0.

Example (d) of **class IVb-g:** syncytium of eosinophilic and basophilic immature dyskaryotic cells with pronounced anisokaryosis, hyperchromasia and nucleoli of endocervical glandular epithelium, and tumor diathesis in the background of a smear from a 46-year-old patient.

Loop excision and histology showed extensive adenocarcinoma in situ and invasive adenocarcinoma G2 of the endocervix.
Example of **class V-g**: eosinophilic tumor cells of endocervical glandular epithelium with marked pleomorphism and hyperchromasia in a 52-year-old patient.

Colposcopic examination showed a T-zone type 3. Endocervical curettage and histology revealed invasive adenocarcinoma.

Example of **class V-e**: eosinophilic tumor cells of endometrial glandular epithelium with marked hyperchromasia in a 49-year-old patient.

Colposcopic examination showed a T-zone type 3. Hysteroscopic biopsy and histology revealed endometrial carcinoma G2.

Example of **class V-x**: eosinophilic tumor cells with marked hyperchromasia and macronucleoli in a 73-year-old patient with rectal carcinoma that had spread to the vagina.
2.3 HPV Test

Since cervical neoplasia is always associated with HPV, detection of HPV in cellular material from the uterine cervix is an alternative method to detect cervical precancer.

Indications for HPV Testing

HPV testing is useful for triaging women with atypical smears in order to exclude the presence of precancer or cancer, and is more valid than a repeat Pap smear. This holds also true for the follow-up of patients with a history of conization. In Germany, HPV testing is covered by health insurance in patients with a history of atypical (class III) or abnormal (class IIID, IVA, IVB, or V) Pap smear result, abnormal colposcopic finding, or follow-up after conization. In Germany, the costs of HPV testing for screening purposes must be borne by the woman herself as an individual health service. However, every woman undergoing screening for CIN must be informed that HPV testing is by far more sensitive than a Pap smear at the expense of a higher rate of false-positive results.

HPV Test versus Cytologic Screening

Several screening studies have compared sensitivity and specificity of cytology with that of HPV tests, reporting a sensitivity of > 90% for HPV tests compared to between 20 and 76% for cytology.

The high sensitivity of the HPV test to detect CINII+ lesions comes on the expense of a lower specificity with a false-positive rate of 9% for HPV test compared to 4% for cytology. HPV test followed by cytologic evaluation of the positive samples is an approach that combines the advantage of both screening methods.

Another advantage of the HPV test is a high negative predictive value. If there is no HPV detected, there will be no CIN or cervical cancer.

Collection of Cells for HPV Test

HPV testing can be done by using a separate cytologic sample in addition to the Pap smear or in combination with cervical samples yielded from liquid-based cytology.

The cellular material not used for liquid-based cytology is stored and if abnormal cells are diagnosed in the mono-layer slide, the stored sample is analysed for high-risk HPV types or the individual HPV type involved.
HPV Types and HPV Test Systems

HPV tests aim at detection of HPV infection, which is a key factor in lesion development and progression to cervical cancer. HPV types infecting mucosal surfaces are grouped according to their epidemiologic prevalence in premalignant and invasive cervical cancer and are distinguished by their specific DNA sequence.

HPV tests are designed to detect groups of HPV, e.g., those bearing a 'high-risk' potential for the development of cervical cancer, or to identify the individual HPV(s) types present in the sample. In order to discriminate active viral infection from viral deposit, the detection of viral mRNA has been developed as a screening tool.

Detection of 25 mucosal HPV types

- High-risk HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82
- Putative high-risk HPV types: 26, 53, 66
- Low-risk HPV types: 6, 11, 40, 42, 43, 44, 70

HPV Test

- Non-amplifying
- Amplifying (PCR)
- High-risk/low-risk HPV type discrimination
- HPV genotyping
- RNA detection of active infection

Amplifying Versus Non-amplifying HPV Tests

Detection of the various genital HPV types is done by direct detection of HPV DNA or following amplification by polymerase chain reaction, i.e. PCR. PCR-based test systems have a higher sensitivity, which may be useful for epidemiologic studies. Occasionally, however, they may detect infections or lesions that are irrelevant to clinical decision making.

HPV nucleic acid detection methods should meet the following requirements: First, 14 high-risk HPVs should be detected, namely types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. And second, the method should achieve 90% of the sensitivity and 98% of the specificity of Hybrid Capture 2 (HC2) and/or the GP5+/GP6+ PCR assay.

Hybrid Capture II

One of the well-established generic HPV tests is the Hybrid Capture II. Using two different probes, the test discriminates high-risk from low-risk HPV types and detects at a moderate level of sensitivity.

The principle of the Hybrid Capture Test is the preferential strong binding of DNA and RNA hybrids. The RNA probe sets contain in probe A 5 low-risk and in probe B 14 high-risk HPV specific RNA molecules which hybridize to HPV DNA in the specimen if present. Hybrid Capture is a robust screening test for detection of clinically relevant HPV-related disease.

The principle of the Hybrid Capture Test is explained in this flow chart. Different RNA probe cocktails, covering a good part of the viral genomes of the low- or high-risk types, are denatured together with the HPV DNA present in the patient sample. RNA and DNA form DNA:RNA hybrids. Such heteroduplexes can be bound by a specific antibody that is used to capture the HPV-DNA-derived heteroduplexes. Non-bound material is washed away. The captured HPV DNA containing heteroduplexes are detected by an antibody which is labelled with an enzyme that converts a substrate emitting light. The extent of light emission is indicative of the amount of HPV DNA present in the specimen and can be semiquantitatively measured.
Primary, Secondary and Tertiary Prevention of Cervical Cancer

Principle of PCR-based HPV Tests
The rationale of the polymerase chain reaction (PCR)-based HPV tests is explained in this and the following graph. The HPV genome has a canonical structure shared by all papillomaviruses. It is small with only 8 kb and codes for only 8 genes.

For genotyping, the most heterogeneous sequences are chosen. Due to evolutionary pressure, the outer shell protein L1 is the most heterogeneous sequence in the genome. It can be amplified by different general primer systems that allow for PCR amplification of all HPV types. The most commonly used L1 general primer PCR (GP-PCR) systems are the MY09/11, the GP5+/6+, and the SPF10 system.

Another approach targets the oncogenes E6 and E7 of the viral genome. These genes have the advantage that they are indispensable for transformation of the cells and cannot be deleted during integration of the viral genome.

PCR-based amplified HPV DNA assays are much more sensitive than non-amplified assays. This is due to an efficient target sequence amplification by PCR procedures. Very low copy numbers of HPV DNA (theoretically single viruses) can be detected by PCR. In addition by choosing the right primers, different HPV types or different regions of the HPV genome can be targeted. Due to the high sensitivity of PCR-based HPV detection assays, generally the specificity to detect true disease is reduced. Denaturation leads to single strands which are duplicated using specific primers and heat-resistant Taq polymerase. Thus, by thermal melting, primer binding, and DNA synthesis, each cycle doubles the amount of DNA by which the reaction is started.

HPV RNA-based or Oncoprotein-based Tests
Two commercial HPV tests target mRNA derived from the oncogenes E6 and/or E7. Expression of these genes verifies active infection and potentially progression to high-grade disease. Both assays use a molecular amplification method to enhance the signal and thereby the sensitivity of the test.

PreTect™ HPV Proofer (Biomerieux): addresses the 7 most prevalent high-risk HPV types. Therefore, it misses several high-risk HPV types and has a lower clinical sensitivity.

Aptima HPV Assay (Hologic): contains 14 high-risk HPV types and provides higher clinical sensitivity for the detection of CIN.

The Arbor vitae or Pipavir test systems can detect the E6 or E7 oncoproteins of various high-risk HPV types.
Comparison of HPV Tests

On this graph, the results of various molecular HPV tests are compared. The vertical axis is sensitivity and the horizontal axis is specificity achieved with each test to detect histologically confirmed CIN II+ lesions. A perfect test would be located at the upper left corner with sensitivity and specificity each 1.0. None of the tests achieve this, which is not surprising, given that, among other factors, histology is not a perfect reference and each of the molecular assays should be regarded only as a surrogate marker for risk of disease.

The dotted line indicates the minimal sensitivity of 95 which would be clinically acceptable. Overall, there is no statistically significant difference in sensitivity between the Aptima test, the Roche Amplicor or Linear Array Assays, and the Digene HC2 test. These other tests were positive in a few more cases of CIN II+ than was the Aptima test; however, the 95% confidence intervals for the sensitivities of each test overlap.

Considering these results, it is important to remember that about one third of high-grade CIN regress. Prospective studies will be required to determine whether or not the Aptima test distinguishes those that progress from those that do not.

The Aptima HPV test shows higher specificity with a 95% confidence interval that did not overlap the other tests with adequate sensitivity. Among the remaining tests, p16INK4a, the Norchip HPV Proofer, and the Genomicar Clinical Arrays assay did not achieve adequate sensitivities, although the p16INK4a test's 95% confidence interval extends above the sensitivity threshold. While two of the assays showed superior specificities, they would not be clinically useful with their demonstrated sensitivities.

HPV-related and Non-HPV-related Prognostic Markers

Only 30% of low-grade CIN progress to high-grade CIN. Therefore, it would be important to determine the progressive potential of low-grade CIN in order to avoid over- or undertreatment and prolonged follow-up. HPV-related and non-HPV-related markers are available:

HPV-related prognostic markers are specific HPV types (such as types 16, 18, or 45), expression of the viral oncogenes E6 and E7 in the form of RNA or protein, integration of HPV DNA in the cellular genome, viral load, methylation of the control region or the L1-gene of HPV 16, which are linked to progression, whereas detection of the HPV-L1 protein is associated with regression.

Non-HPV-related progression biomarkers are overexpression of the cyclin-dependent kinase inhibitors p16, possibly associated with overexpression of the proliferation marker Ki 67, detection of aneuploidy by DNA-cytometry, and image analysis.

However, none of these markers has yet been integrated in clinical practice because no evidence in terms of predictive validity has been provided so far.
2.4 Colposcopy

Definition of Colposcopy

Colposcopy is the morphological method used for topographic classification and severity assessment of lesions detected on the vaginal part of the uterine cervix. A target biopsy under colposcopic guidance leads from a tentative cytological finding to reliable histological diagnosis.

Hans Hinselmann – Light and Darkness

Hans Hinselmann introduced colposcopy for early diagnosis of cervical cancer in the nineteen twenties. The Hamburg Senate had assigned him the task of reducing the mortality of cervical cancer. In the following years of his career, he endeavored to cope with this challenge and finally made important contributions to the field of gynecology.

However, unfortunately Hans Hinselmann was also a criminal. He supported experiments on Jewish women in the concentration camp at Auschwitz performed by his coworker Helmut Wirths, a fact which was detected only recently. Helmut Wirths’ brother, Eduard Wirths, the chief Schutz-Staffel (SS) doctor of Auschwitz, had also delegated a colposcopic research project conducted on female inmates of Block 10 in Auschwitz to an inmate doctor in Auschwitz named Maximilian Samuels who in 1943 completed his research and submitted it to Wirths, titled ‘Carcinom: die Geißel der Frauen der Welt ist heilbar’ (Carcinoma: the scourge of women of this world is curable). As soon as Samuels finished his report, he was shot.

For his complicity in the undescrivable suffering inflicted on women in Block 10 in Auschwitz, Hinselmann’s contribution to women’s health must be seen in a different light.

The First Coloscope

Hans Hinselmann developed a magnification device that can be used to examine the uterine cervix. The cervix is visualized with a hand-held speculum during the colposcopic examination.

“Assembling the colroscope was a task I have undertaken together with Mr. Hans Hilgers, Bonn, Heerstraße 43, the representative of Leitz Enterprises.”
Colposcope in Use
Shown is a state-of-the-art HD video camera mounted to a modern colposcope. During colposcopic examination, the cervix is best viewed with a frosted duckbill speculum. The transformation zone (also called the transition zone) and the border between squamous and columnar epithelium is evaluated utilizing six- to tenfold magnification.

Conventional Colposcopy

VITOM Exoscopy – The Future of Colposcopy
- VITOM exoscopy is completely performed under control of a high-definition video screen.
- The patient can be involved in the process.
- Instrument handling is facilitated.
- Documentation and archiving of findings in patient records is done in the form of digital video clips and still images.
- Teaching of students and residents via video screen is considerably facilitated.

The Results of Diagnostic VITOM Exoscopy
In a pilot study we evaluated 76 patients with cervical, vaginal or vulvar lesions. Following VITOM exoscopy, biopsies were taken from the most severe areas. The majority of women were not pregnant and premenopausal, mean age was 34 years.

The overall concordance rate between grading of the lesion using VITOM exoscopy and histology is 74%.
The kappa value for high-grade lesions is excellent, for low-grade lesions satisfactory.

**The Seven Rules of Colposcopy**

The nomenclature and implementation of colposcopy is described in the panel ‘Rules of Colposcopy’. The colposcopy rules 1-2-3-4-5-6(4-4-6)-7 contain the definition of colposcopy, guidelines for patient care, definition of the transformation zone including all features of its normal and abnormal morphology, the criteria for grading, and the steps of a complete colposcopic examination.

Rule 6 for grading is subdivided in a 4-4-6 nomenclature and is the essential part of the system.

Observing these rules, every clinician will become a good colposcopist. Following is a description of the various rules, which are the key issue of this panel. The nomenclature and principle of colposcopy is based on these rules. The colposcopist who strictly observes these rules stands a good chance of reaching an high level of proficiency after a short learning curve. In order to become an expert colposcopist, every examination session should include taking a punch biopsy and still images, or even better, video recordings. Both the colposcopist and pathologist should jointly evaluate the histologic sections. The ultimate goal of this collaboration is to allow the established link between colposcopic and histologic images become engrained in the mind of the colposcopist, who, as a result, should be able to determine the biology of a lesion with a high level of accuracy.

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### The Rules of Colposcopy

<table>
<thead>
<tr>
<th>Rule</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>Method</strong></td>
<td>Triaging of abnormal cytologic, virologic, or clinical findings</td>
</tr>
<tr>
<td>2. <strong>Patient</strong></td>
<td>Reduce fear, Build trust</td>
</tr>
<tr>
<td>3. <strong>Transformation Zone</strong></td>
<td>Type 1: Squamocolumnar junction completely visible, Type 2: Squamocolumnar junction partly visible, Type 3: Squamocolumnar junction not visible</td>
</tr>
<tr>
<td>4. <strong>Normal Transformation Zone</strong></td>
<td>Non-keratinizing squamous epithelium, Columnar epithelium, Ovulum Nabothi, Open glands</td>
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<td>5. <strong>Atypical Transformation Zone</strong></td>
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<td>6. <strong>Grading</strong></td>
<td>Classification: Normal: No neoplasia, Minor change: Condyloma, CIN I, Major change: CIN II, CIN III, Cancer: Invasive cancer, Pathognomonic Signs: Cuffed crypt (gland) openings absent vs present, Ridge sign absent vs present, Inner border sign absent vs present, Rag sign absent vs present, Graduating Signs: Color of acetowhite area thin vs dense, Dynamic of acetowhite area slow vs rapid, Surface of mosaic or punctuation fine vs coarse, Intercapillary distance of mosaic or punctuation small vs large, Border blurred vs well-defined, Iodine uptake partial vs absent</td>
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<td>7. <strong>Course of Examination</strong></td>
<td>Inspection by using a self-holding speculum, Application of 5% acetic acid, Is the squamocolumnar junction fully visible (T-zone type 1, 2 or 3)? Is there a typical or atypical transformation zone? Application of grading criteria including application of 3% iodine, Where should a biopsy be taken from? Which treatment should be done under magnification?</td>
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### Rule 1: Establish the Indication for Colposcopy

Initially, colposcopy was inaugurated to screen women for the presence of cancer or precancer. However, after invention of the Pap smear, colposcopy fell behind, mainly due to its low specificity. Today, colposcopy is mainly used for triaging women with a history of abnormal Pap smears or for those who have been found positive for high-risk HPV or for women diagnosed with abnormal clinical findings of the lower genital tract.
Rule 2: Live Empathy with the Patient

The second rule is the most important one. To reduce fear and to build trust, the emotional intelligence of the colposcopist needs to be adequately developed. Each physician has its own approach in order to reach these two goals. Accompanying the patient on her way from the waiting area to the examination room, taking care of her coat, sitting next and not in front of her, and causing no discomfort during the examination are means which can help to reduce fear and to build trust.

Good Information Reduces Fear

While waiting for the examination, the patient is encouraged to read this information explaining to her the procedure and purpose of colposcopy, the nature and meaning of dysplasia and its differentiation from cancer. The most important message meant for the patient prior to the examination is ‘You Have No Cancer!’ Even though this may not be true in one out of several hundred women who undergo colposcopy, a soothing attitude will be for the benefit of the patient.

The course of examination is explained to the patient including the part involving biopsy sampling. A telephone number and email address are offered, in case complications occur or if questions arise post colposcopy.

Patient Information

Dear Patient,

You have an appointment for a colposcopic examination.

What is colposcopy?

Κολποϛ is Greek and means vagina. The colposcope is an instrument which is used to examine the vagina and especially the cervix of the uterus at a magnification of 7 to 10 times. For this examination you sit on a gynecologic examination chair. Using magnification, the gynecologist looks for dysplasia.

What is dysplasia?

The cells of the cervix regenerate constantly. If the cells regenerate abnormally, for instance by an infection with human papilloma viruses (HPV), the cells are called dysplastic and the tissue harboring the cells is called dysplasia. Dysplasia occurs in various degrees varying from mild, to moderate or severe dysplasia. Dysplasia can also be called precancer, intraepithelial neoplasia or squamous intraepithelial lesion. Using colposcopy we want to determine the presence/absence of dysplasia. Provided cervical dysplasia is found, its grade needs to be established.

Even the most severe degree of dysplasia is not to be put on a level with cancer. Dysplasia may develop into cancer, but such event is rare and takes usually several years. You are here in order to be protected from cancer, not because you are suspected of having cancer.

What will be done during the examination?

You will sit on the gynecologic examination chair. A self-holding speculum will be introduced to visualize cervix and vagina. The gynecologists will evaluate cervix and vagina under magnification and apply 5% acetic acid and later 3% iodine solution. If indicated, a biopsy – small piece of tissue of 3 to 5 mm in size – may have to be taken with a special biopsy forceps. This may also cause mild discomfort and bleeding. Bleeding will be controlled by application of a tampon or coagulation substance. The tampon should be removed after 2 to 3 hours.

You may follow the entire examination on a monitor if you wish.

If you should experience pain, bleeding or any other abnormalities after the examination, please contact us.

If you have any questions or need more information, please do not hesitate to ask the gynecologist performing your examination. In case, you do not get the result of the examination within two weeks, please contact us.
Rule 3: Define the Type of T-Zone

The squamocolumnar junction (SCJ) is the area where cervical neoplasia originates and is located. The squamocolumnar junction must be visible in order to make a safe colposcopic assessment. Therefore, the classification of the transformation zone (T-zone) according to the visibility of the SCJ is important. Colposcopic examination is only valid in the presence of a transformation zone type 1 or type 2.

Types of Junctions

Cervical cancer and precancer originate at the squamocolumnar junction which is indicated by green arrows. Columnar epithelium borders directly on squamous epithelium.

The squamocolumnar junction can be the congenital or post-puberty junction. In this colposcopic image of an adolescent, the squamocolumnar junction is the congenital junction.

Metaplasia – A Physiological Process

Histology shows the squamous epithelium on the left side bordering the columnar epithelium on the right side. The green arrow indicates the congenital junction which is identical to the squamocolumnar (SC) junction before puberty. In (a), red arrows point to SC junction cells which have the biologic potential of stem cells. In (b), the SC junction cells have undergone metaplasia and metaplastic epithelium is present. Thus, the congenital junction is still visible next to the metaplastic epithelium, indicated by the green arrow. Now, the squamocolumnar junction has shifted and is called adult or functional junction, indicated by the blue arrow. The purple arrows indicate the extent of the T-zone which lies in between the congenital and the adult or functional junction. In (c), metaplastic epithelium has been transformed to squamous epithelium. Thus, the left portion of the squamous epithelium is original squamous epithelium, the right portion of the squamous epithelium is secondary squamous epithelium since it originated from metaplasia. This whole area is the T-zone, indicated by the purple arrows. The congenital junction indicated by the green arrow is no longer distinguishable in terms of histopathology. The squamocolumnar junction is identical to the adult or functional junction indicated by the blue arrow and may shift more to the right with age.
Replacement by Overgrowth
Apart from metaplastic transformation, the columnar epithelium can be replaced directly by squamous epithelium. As shown in (a), the congenital junction (green arrow) is consistent with the original squamocolumnar junction. In (b), squamous epithelium has overgrown glandular epithelium forming a new squamocolumnar junction termed as adult or functional junction, which is indicated by the blue arrow. The resulting expanse of the transformation zone is indicated by the double-tipped purple arrow. In (c), the squamocolumnar junction, which is consistent with the adult or functional junction, has shifted even more to the right, resulting in an even larger expanse of the transformation zone.

Zones and Junctions – Definitions
Junction is a term used to define the border between different epithelia, whereas T-zone describes the area between junctions.
The original squamocolumnar junction between squamous and columnar epithelium remains unchanged till puberty and is called the congenital junction.
During and post puberty, in addition to the congenital junction, the adult or functional junction is formed, subsequently termed the new squamocolumnar junction.
The T-zone becomes larger with age and expands centrally towards the cervical opening.
Initially, the T-zone is made of metaplastic epithelium, which changes to secondary squamous epithelium. Secondary squamous epithelium cannot be distinguished by histopathology from primary squamous epithelium.
The adult or functional junction can always be identified by histopathology whereas the congenital junction cannot be seen using this diagnostic modality post puberty. Colposcopically, the location of the congenital junction can be guessed by the extension of Ovula Nabothi, open glands or metaplastic epithelium.

Natural History of a Cervical HPV Infection
The schematic diagram shows the squamocolumnar (SC) junction, which is composed of non-keratinizing squamous epithelium (S) on the left and columnar epithelium (C) on the right. The cells in between are SC junction cells (red) which are the main target of HPV on the cervix (red arrow). This is due to the SC cells lying exposed to the attacking HPVs on the outer surface. Unlike SC junction cells, the intact cell structure of squamous epithelium is capable of withstanding an HPV attack (blue arrow). In order to successfully accomplish an attack, a breach or lesion is needed that allows the virus to reach its target (black arrow) which are the rounded cells in the base layer with stem cell (St) character. The gene expression profile of the discrete population of SC junction cells is different from that of neighbouring cells and shares common features with CIN and invasive cancers.
Virus Binding and Cell Entry

Molecular mechanisms of virus binding and cell entry are now understood. The basal membrane partially comprises of collagen which has a triple helix structure. The basal membrane and the cell surface are also connected to heparan sulfate proteoglycan (HSPG) molecules, that are negatively charged and account for elasticity. HPV attaches to HSPG molecules of the basal membrane or the cell surface. Furin, a protease, is an important enzyme released during wound repair by the dividing cells. In all instances, when stem cells are involved in tissue repair by closing a gap in the basal epithelium layer, furin is released. Furin activity leads to cleavage of the HPV L1 capsid protein and promotes its conformational changes, which in turn, allows the L1 capsid protein to bind to the cellular receptor tetraspanin and opens up a gateway for the virus particle to enter the cell. During this binding process, the HPV L2 capsid protein becomes accessible, which therefore may be a suitable target for future vaccines. Considering, that the entire process of binding and cell entry takes up several days, there should be enough time for vaccine interaction.

Once infection of the squamocolumnar junction cells has occurred (see diagram, ‘Natural History of a Cervical HPV Infection’, p. 39), the metaplasia progresses to intraepithelial neoplasia if the immune system cannot eradicate the HPV infection.

As shown in this image, the congenital junction is indicated by the green arrow. The adult or functional junction is indicated by the blue arrow. The resulting expanse of the transformation zone which is covered by CIN is indicated by the double-tipped purple arrow.

Identification of Congenital and Adult Junction

This colposcopic image shows the result of persistent infection with high-risk HPV, which leads to CIN. The congenital junction is indicated by green arrows, the adult or functional junction is shown by blue arrows. The area between the green and blue arrows is the transformation zone, which in this patient is occupied by CIN.
HPV and Natural History of CIN
As a rule, HPV infection initially develops at the adult or functional junction since it generally occurs post puberty. Accordingly, CIN starts at the adult or functional squamo-columnar junction centrally and usually spreads peripherally towards the congenital junction.

Hence, the most severe changes of cervical intraepithelial neoplasia are found centrally, where the HPV infection emanated, usually decreasing in severity towards the periphery.

The Pap smear must always be taken at the adult or functional squamocolumnar junction in order to sample the cells with the most pronounced changes.

Three Types of Transformation Zones
In the T-zone type 1, the squamocolumnar junction indicated by the arrow is fully visible on the ectocervix.

In the T-zone type 2, the squamocolumnar junction indicated by the arrow becomes only fully visible if the cervical os is open and the endocervix can be inspected.

In the T-zone type 3, the squamocolumnar junction indicated by the arrow is not visible and colposcopic examination cannot be used to diagnose or exclude CIN or cancer.

T-Zone Type 3 Following Conization
Normal colposcopic findings are insignificant and indeterminate if the border between squamous and columnar epithelium cannot be visualized. To underline this statement, we show the colposcopic image of a 45-year-old patient with a history of conization for CIN III at a time when Sturmdorf sutures were still in use. Cytology revealed normal findings, HPV test was positive for high-risk HPV. A normal transformation zone is recognizable; columnar epithelium is not visible due to cervical stenosis.

The ectocervix is iodine-positive.
Endocervical curettage was performed and histology showed non-keratinizing squamous cell carcinoma.

**Three Types of Transformation Zones**

All three types of T-zones are shown in the following colposcopic images: type 1 (a, b), type 2 (c), and type 3 (d).

- **T-zone type 1 (a).** The squamocolumnar adult or functional junction is fully visible, presenting the columnar epithelium in red color prior to application of acetic acid.

- **T-zone type 1 (b).** Following application of acetic acid, aceto-white columnar epithelium borders directly on squamous epithelium, the major features of a normal transformation zone. In this adolescent, the squamocolumnar junction indicated by green arrows is identical with the congenital junction.

- **T-zone type 2 (c):** The adult or functional squamocolumnar junction is fully visible and a small tongue of squamous epithelium expands into the cervical canal at 12 o'clock.

- **T-zone type 3 (d):** The adult or functional squamocolumnar junction is located inside the endocervix and is therefore invisible to the colposcopist.
Rule 4: The Core Features of a Typical T-Zone
Colposcopy allows to differentiate between a normal and an atypical transformation zone. The well-distinguishable characteristics of a normal transformation zone are as follows:
Columnar epithelium, non-keratinizing squamous epithelium, Nabothian cysts, and gland openings.

Squamous and Columnar Epithelium, Gland Openings
Gland openings, indicated by green arrows, are a distinct feature of a normal transformation zone, here of type 1. Note the presence of non-keratinizing squamous epithelium and columnar epithelium.

Nabothian Cysts, Squamous Epithelium
This colposcopic image shows Ovula Nabothi, another typical feature of a normal transformation zone, here of type 2. Also note the non-keratinizing squamous epithelium.

This is another example of a normal transformation zone, type 2 with multiple Nabothian cysts between 9 and 3 o’clock. Note the presence of non-keratinizing squamous epithelium and columnar epithelium.
Rule 5: The Core Features of an Atypical T-Zone

The following colposcopic findings are detected in the atypical transformation zone: Leukoplakia, acetowhite epithelium, mosaicism, punctation, and/or atypical vessels.

Leukoplakia

Leukoplakia (*white patch*) is caused by hyperkeratosis of the squamous epithelium. It is the only colposcopic finding which must be identified prior to application of acetic acid.

This colposcopic image is from a 64-year-old gravida 0, para 0 with a fibroid uterus. The smear was reported as class II-p, and HPV was not detected.

Leukoplakia in this case covers the external os and is classified as a nonspecific abnormal colposcopic finding.

The leukoplakic area was removed by curettage. Histopathology shows superficial hyperkeratosis with heavy fungal colonization, which stains purple in the periodic acid-Schiff (PAS) reaction.

Acetowhite Epithelium

Cervical epithelium with neoplastic changes undergoes a whitish discoloration following the application of 3–5% acetic acid.

Colposcopic findings in a 31-year-old gravida 0, para 0 with no prior history of disease. The smear was reported as class IVa-p, and HPV was detected. An acetowhite lesion is visible at 3 o’clock in an atypical T-zone type 1 that borders directly on the squamocolumnar junction and is classified as grade 2 (*major change*) abnormal colposcopic finding.
Histopathology of tissue biopsied from the opaque acetowhite lesion at 3 o’clock shows atypical cells that express high concentrations of the markers p16 and Ki 67 into the upper third of the epithelium. The diagnosis is grade 3 cervical intraepithelial neoplasia (CIN III).

**Punctation**

Punctation refers to individual red dots that may appear on the surface of acetowhite epithelium.

Colposcopic findings in a 32-year-old gravida 0, para 0 with no prior history of disease. The smear was reported as class IIID2. A non-PCR-based method did not detect HPV DNA. Colposcopy shows an acetowhite lesion with coarse punctation between 12 and 4 o’clock in an atypical T-zone type 2, which is classified as grade 2 (major change) abnormal colposcopic finding.

The diagram shows the morphologic basis for the colposcopic finding of *punctation*. The stromal papillae (*yellow arrows*) are interposed between the rete pegs (*blue arrows*) of the epithelium. Inside the stromal papillae, capillary vessels form loops that closely approach the epithelial surface, where they appear as separate red dots. When viewed from above, the capillary loops form a stippled pattern that colposcopists call ‘punctation’. High-grade CIN (right) differs from low-grade CIN (left) in that the rete pegs in biologically active tissue are widened, causing the dots to be spaced farther apart.

Histopathology of tissue sampled by punch biopsy from the opaque acetowhite lesion at 3 o’clock shows atypical cells that express high concentrations of the Ki 67 marker into the middle third of the epithelium and of p16 into the upper third of the epithelium. The stromal papillae and rete pegs are clearly visible.

The diagnosis is grade 2 cervical intraepithelial neoplasia (CIN II).
Coarse Punctuation – Major Change

- Coarse punctation is one of the colposcopic signs of varying degree, that suggest major change.
- The distinction between coarse and fine punctation is subjective, which is why the classification of this colposcopic sign is poorly reproducible.

Mosaicism

Mosaicism denotes a pattern of intersecting red ridges in acetowhite epithelium.

Colposcopic findings in a 30-year-old gravida 0, para 0 with no prior history of disease. The smear was reported as class IIID1, and high-risk HPV DNA and RNA were detected. Colposcopy shows an acetowhite lesion with a coarse mosaic pattern between 3 and 8 o’clock in an atypical T-zone type 2, which is classified as grade 2 (major change) abnormal colposcopic finding.

The diagram shows the morphologic basis for the colposcopic finding of mosaicism. The stromal papillae (yellow arrows) are interposed between the rete pegs (blue arrows) of the epithelium. Inside the stromal papillae, capillary vessels form loops that rise close to the epithelial surface, where they appear as individual lines. When viewed from above, the capillary vessels form a crisscross pattern that colposcopists call ‘mosaicism’. High-grade CIN (right) differs from low-grade CIN (left) in that the rete pegs in biologically active tissue are widened, causing the vessels to be spaced farther apart.

Histopathology of tissue sampled by punch biopsy from the opaque acetowhite lesion at 6 o’clock shows atypical cells that express high concentrations of Ki 67 marker into the middle third of the epithelium and of p16 marker into the upper third of the epithelium. The stromal papillae and rete pegs are clearly visible.

Diagnosis is grade 2 cervical intraepithelial neoplasia (CIN II).
A fine mosaic differs from a coarse mosaic in that the tissue surface is smoother and the vascular lines are spaced closer together.

Colposcopic findings in a 29-year-old gravida 1, para 1, with no prior history of disease. The smear was reported as class IIID1, and high-risk HPV DNA and RNA were detected.

Colposcopy shows a peripheral acetowhite lesion between 10 and 12 o’clock in an atypical T-zone type 2, which is classified as normal colposcopic finding.

Histopathology of tissue sampled by punch biopsy from the peripheral acetowhite lesion at 11 o’clock shows normally maturing cells that express the marker Ki 67 only in the lower third of the epithelium; they are negative for p16. The wide spacing of the stromal papillae is clearly noticeable.

The diagnosis is normal metaplastic epithelium.

**Atypical Vessels**
Atypical vessels are the hallmark of invasive cervical cancer and are best demonstrated with a green filter in unstained specimens.

By definition, atypical vascular patterns are pathognomonic for malignancy. A variety of atypical vascular patterns may be seen such as an irregular shapes, abnormal branching, or abrupt caliber changes. Hairpin loops (c) and corkscrew capillaries (e) are specific examples. Any vessel that does not show a regular branching pattern is classified as atypical. It should be noted, however, that inflammatory processes unrelated to cancer are also associated with neovascularization. This type of angiogenesis is difficult to distinguish from the neovascularization of tumors. Thus, in order to determine the diagnostic significance of atypical vessels, the colposcopist must look for other malignant features such as necrosis, erosion, ulceration, exophytic or endophytic growth, bleeding, and/or opaque acetowhiteness. If the diagnosis is at all uncertain, a biopsy should be obtained.
Squamous Cell Cancer
Colposcopic findings in a 29-year-old gravida 0, para 0 with no prior history of disease. The smear was reported as class V-p, and HPV 16 was detected. The SPECTRA A* mode (KARL STORZ IMAGE1 S) uses the color-shift principle to detect atypical vessels in an atypical T-zone type 2, classified as abnormal colposcopic finding suspicious for cancer.

H&E stain of tissue sampled by loop biopsy shows atypical cells that have penetrated the basement membrane and infiltrated the stroma. Blood vessels are clearly visible among the strands of tumor cells and extend almost to the tissue surface. The diagnosis is undifferentiated invasive squamous cell carcinoma. Following laparoscopic sentinel lymphadenectomy and radical vaginal trachelectomy, the disease was finally staged as pT1b1 pN0 (0/2 sn) G3 L0 V0 Pn0.

Atypical Vessels – Squamous Cancer
- Atypical vessels have bizarre shapes and may resemble a comma, corkscrew, or hairpin. These and other atypical shapes are suspicious for invasive disease.
- A clinical diagnosis of cancer requires the presence of secondary features that are suggestive of invasive disease. These include:
  - yellow or white discoloration,
  - irregular surface,
  - bleeding, and
  - fragility.

Adenocarcinoma
Atypical vessels associated with adenocarcinoma are indistinguishable from squamous cell carcinoma based on their external appearance. Colposcopic findings in a 33-year-old gravida 0, para 0 with no prior history of disease. The smear was reported as class III-g, and HPV 18 was detected. Atypical vessels are found in an atypical T-zone type 1, classified as abnormal colposcopic finding suspicious for cancer.

*SPECTRA A: Not for sale in the U.S.*
Tissue sampled by punch biopsy shows atypical glandular complexes, which are classified as ACIS between 11 and 6 o’clock and as invasive adenocarcinoma between 7 and 11 o’clock. All the glandular cells express high concentrations of the markers p16 and Ki 67.

Magnified view of the invasive tumor component shows atypical cell complexes that have penetrated the basement membrane (green arrows). After a nerve-sparing laparoscopic hysterectomy, the disease was finally staged as pT1b2 pN0 (0/23) G2 L1 V0 Pn0.

Atypical Vessels – Adenocarcinoma
- Atypical vessels display irregular arborizing patterns and considerable variation in caliber.
- Atypical vessels can be truncated.
- In adenocarcinoma, the tumor shows glandular appearance and mucin production.

‘Atypical Vessels’ – Differential Diagnosis
- Neovascularization is induced by hormonal changes inherent to pregnancy.
- Primary features of ‘atypical vessels’, such as hairpins, irregular loops and varying caliber can be present.
- There should be no secondary features.
Primary, Secondary and Tertiary Prevention of Cervical Cancer

Rule 6: The Grading Criteria

The art of colposcopy is the grading of lesion, which has to be classified as normal, minor or major change or consistent with invasive cancer in accordance with IFCPC terminology. We modify the IFCPC concept when we grade a lesion using primarily highly specific pathognomonic signs, and secondarily, signs that are assessed subjectively, called graduating signs.

There are four pathognomonic signs, such as ‘cuffed crypt openings’, ‘ridge sign’, ‘inner border sign’, and ‘rag sign’, the latter three described by the author and colleagues. The severity of a lesion may also be graded according to the six graduating signs, such as ‘color of acetowhite area’, ‘dynamic of acetowhiteness’, ‘surface structure’ and ‘intervascular distance of mosaic or punctuation’, ‘demarcation of the border’ of the lesion, and ‘intensity of iodine staining’.

### Rule 6

#### Grading

**Classification**

- Normal  
  - no neoplasia, but including inflammation, metaplasia and atrophy
- Minor change  
  - Condyloma, CIN I
- Major change  
  - CIN II, CIN III
- Cancer  
  - invasive cancer

#### Pathognomonic Signs

- Cuffed crypt (gland) openings  
  - absent vs present
- Ridge sign  
  - absent vs present
- Inner border sign  
  - absent vs present
- Rag sign  
  - absent vs present

#### Graduating Signs

- Color of acetowhite area  
  - thin vs dense
- Dynamic of acetowhiteness  
  - slow vs rapid
- Surface of mosaic or punctation  
  - fine vs coarse
- Intercapillary distance of mosaic or punctation  
  - small vs large
- Border  
  - blurred vs well-defined
- Iodine uptake  
  - partial vs absent

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**The IFCPC Colposcopic Terminology**

In 2011, the *International Federation of Cervical Pathology and Colposcopy (IFCPC)* issued a new colposcopic terminology to classify normal and abnormal colposcopic findings. Abnormal colposcopic findings are graded as minor or major change. Dense acetowhite epithelium and and rapid acetowhiteness, cuffed crypt openings, coarse mosaic or punctation, well-defined border, inner border sign, and ridge sign are the main features indicative of a major change. Erosion, leukoplakia and Lugol’s staining in Schiller’s test are classified as non-specific signs, which however, according to our experience, have shown to be helpful in establishing a correct diagnosis. Application of the IFCPC terminology can be difficult in clinical practice. Therefore, we present a more pragmatic grading strategy in the following part of this manual.

**Grading Categories**

Colposcopic grading of a lesion allows the gynecologist to predict the histopathologic basis of what is seen by colposcopy:

The assessment class ‘normal’ includes all changes that are not associated with precancer or cancer. ‘Minor change’ (abnormal colposcopic findings grade 1) involves disease associated with productive human papillomavirus infection such as condyloma or CIN I. ‘Major change’ (abnormal colposcopic findings grade 2) comprises CIN II and CIN III. If the lesion is classified as ‘cancer’, the colposcopist must be convinced that the patient suffers from invasive disease.
Pathognomonic Colposcopic Signs

Among the four pathognomonic colposcopic signs, ‘cuffed crypt (gland) openings’ was first described by Dexeus et al. in 2002 and later included in the IFCPC terminology. The author and colleagues managed to identify the pathognomonic significance of ridge sign, inner border sign and rag sign. These colposcopic signs are either absent or present, allowing the examiner to make a yes/no decision, which considerably contributes to an increase in specificity of the colposcopic diagnosis.

Rule 6

- Pathognomonic Colposcopic Signs
  - Cuffed crypt (gland) openings absent vs present
  - Ridge sign absent vs present
  - Inner border sign absent vs present
  - Rag sign absent vs present

Cuffed Crypt (Gland) Openings

- Pathognomonic grading criterion for major change.
- Associated with the presence of cervical intraepithelial neoplasia grade II or III.

Prominent gland openings (arrows) with an opaque acetowhite border are considered pathognomonic for high-grade CIN. Colposcopic findings in a 28-year-old gravida 0, para 0 with no prior history of disease. The smear was assigned to class IIID1, and high-risk HPV DNA and RNA were detected. Colposcopy shows a circular acetowhite lesion with opaque, prominent gland openings between 6 and 10 o’clock (arrows) in an atypical T-zone type 2, which is classified as grade 2 (minor change) abnormal colposcopic finding.

Tissue sampled by loop excision shows endocervical gland orifices (arrows) rimmed by atypical squamous epithelium. The cells express high concentrations of Ki 67 marker into the middle third of the epithelium and of p16 marker into the upper third of the epithelium.

The diagnosis is grade 2 cervical intraepithelial neoplasia (CIN II).
A less pronounced colposcopic finding of *prominent gland openings*, noticeable in a 45-year-old patient with a T-zone type 2 after application of 5% acetic acid. The cuffed crypt (gland) openings, visible in a sector of the acetowhite area between 12 and 1 o'clock, exhibit intensely opaque acetowhite margins. The findings were classified as *major change*. The histopathologic workup of the samples obtained from the above sector by punch biopsy reported a diagnosis of CIN III.

**Ridge Sign**

The ridge sign is also considered pathognomonic for high-grade CIN.

Colposcopic findings in a 25-year-old gravida 1, para 0 with no prior history of disease. The smear was reported as class IVa-p, and high-risk HPV DNA and RNA were detected. Colposcopy shows a circular acetowhite lesion with opaque ridges directly at the squamocolumnar junction between 1 and 5 o'clock and 9 and 11 o'clock in an atypical T-zone type 2, classified as grade 2 (*minor change*) abnormal colposcopic finding.

H&E stain of tissue sampled from the ridge lesion at 5 o'clock by punch biopsy shows atypical cells that uniformly occupy the full width of the epithelium and are indistinguishable from the surface cells. We clearly see the termination of atypical epithelium at its junction with columnar epithelium.

Diagnosis is grade 3 cervical intraepithelial neoplasia (CIN III).

In a study (published in 2009) based on colposcopic images, the colposcopic feature *ridge sign* was shown to be highly specific for major change. In 83 out of 592 (14.0%) patients, the presence of a *ridge sign* is diagnosed. CIN II/III is confirmed histologically in 53 of these 83 women (63.8%).

The sensitivity for CIN II/III is 33.1%, specificity is 93.1%, and negative predictive value is 79.0%.

Women with a *ridge sign* are significantly younger.

The colposcopic feature *ridge sign* is significantly associated with HPV 16.

Validity of the Colposcopic Criterion ‘Ridge Sign’

In a study, published in 2013, evaluation was based on a review of video recordings taken from 335 patients who were referred for diagnostic colposcopy, involving either cervical biopsies or loop excisions. The objective was to assess the correlation between the pathognomonic criterion ‘ridge sign’ and high-grade cervical intraepithelial neoplasia (hgCIN) employing video exoscopy (VITOM exoscopy system). Sensitivity, specificity, PPV and NPV of ‘ridge sign’ to detect hgCIN was 52.5%, 96.4%, 96.8% and 46.6%, respectively. The LR+ and LR– ratio was 13.2 and 0.49, respectively.

Ridge Sign – Major Change

- Pathognomonic grading criterion for major change.
- Sensitive and specific for the presence of cervical intraepithelial neoplasia grade II or III.

Another representative colposcopic example of the ‘ridge sign’, noticeable in a T-zone type 2 of a 28-year-old patient after application of 5% acetic acid. There is an acetowhite lesion between 9 and 2 o’clock and a distinct, conspicuous ridge with high opacity at 12 o’clock close to the squamocolumnar junction reaching into the cervical canal. There are several cuffed crypt openings. Due to the presence of two pathognomonic signs, this lesion is classified as major change.

Histopathologic examination confirmed CIN III.
Primary, Secondary and Tertiary Prevention of Cervical Cancer

Inner Border

The inner border sign is considered pathognomonic for high-grade CIN.

Colposcopic findings in a 35-year-old gravida 0, para 0 with no prior history of disease. The smear was reported as class III-p, and HPV 16 was detected. Colposcopy shows a circular lesion with partial iodine uptake at 11 to 1 o’clock and at 5 to 7 o’clock with a second, central lesion located between 6 and 2 o’clock in an atypical T-zone type 2.

The lesions are classified as grade 2 (major change) abnormal colposcopic finding.

Tissue was sampled by loop excision in the transitional area between the two lesions. Histopathology of the central lesion (left of the green arrow) shows atypical cells that uniformly occupy the full width of the epithelium and express high concentrations of the p16 and Ki 67 immune markers into the highest cell layer. The diagnosis is grade 3 cervical intraepithelial neoplasia (CIN III). This epithelium is abruptly replaced (right of the green arrow) by epithelium whose cells express Ki 67 only into the middle and do not express p16.

The diagnosis is grade 1 cervical intraepithelial neoplasia (CIN I).

In a study (published in 2009) based on colposcopic images, the authors demonstrated that the prevalence of the colposcopic sign ‘inner border’ in women with an atypical transformation zone is 7.6% and observed in 53 out of 695 women.

In 70% of women with ‘inner border’, CIN II/III is confirmed histologically. The sensitivity for ‘inner border’ for detection of CIN II/III is 20%, specificity is 97%. In patients with ‘inner border’, the odds ratio for CIN II/III is 7.7 (95% CI [4.2; 14.3]). CIN II/III associated with ‘inner border’ is significantly more frequent in patients younger than 35 years.

Thus, ‘inner border’ is a rare colposcopic sign, but highly specific for CIN II/III in young women.

Validity of ‘Inner Border’ for Detection of High-Grade Cervical Intraepithelial Neoplasia

<table>
<thead>
<tr>
<th>High-Grade CIN</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>+LR</th>
<th>-LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inner Border</td>
<td>20%</td>
<td>99%</td>
<td>97%</td>
<td>97%</td>
<td>3.4%</td>
<td>0.8</td>
</tr>
</tbody>
</table>

CIN (Cervical Intraepithelial Neoplasia), PPV (Positive Predictive Value), NPV (Negative Predictive Value) LR+ (Positive Likelihood Ratio), LR- (Negative Likelihood Ratio).

**Inner Border**

- Pathognomonic grading criterion for major change.
- Associated with the presence of cervical intraepithelial neoplasia grade II or III.

Shown on this colposcopic image is an ‘inner border sign’ at 1 o’clock in a T-Zone of type 2 of a 28-year-old patient following application of 5% acetic acid. Several ‘cuffed crypt openings’ can be identified. The finding is classified as a **major change**.

**Rag Sign – CIN III**

The rag sign is a fourth pathognomonic sign for high-grade CIN.

Colposcopic findings in a 35-year-old gravida 0, para 0, with no prior history of disease. The smear was reported as class III-p, and HPV 16 was detected. Colposcopy shows a circular acetowhite lesion with ‘ragged’ epithelium at 6 o’clock in an atypical T-zone type 2, classified as grade 2 (**major change**) abnormal colposcopic findings.

The ragged epithelial strip was retrieved with a forceps. Histologic workup of the specimen shows atypical cells that occupy the full width of the epithelium and express high concentrations of the immune markers p16 and Ki 67 into the highest cell layer. The epithelium is covered superficially by a non-nucleated keratin layer. Diagnosis is grade 3 cervical intraepithelial neoplasia (CIN III).
Validity of ‘Rag Sign’ for Detection of High-Grade Cervical Intraepithelial Neoplasia

<table>
<thead>
<tr>
<th>High-Grade CIN</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>+LR</th>
<th>–LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rag Sign</td>
<td>38.4%</td>
<td>96%</td>
<td>85.7%</td>
<td>34%-47%</td>
<td>9.7</td>
<td>0.6</td>
</tr>
</tbody>
</table>

CIN (Cervical Intraepithelial Neoplasia), PPV (Positive Predictive Value), NPV (Negative Predictive Value)

+LR (Positive Likelihood Ratio), –LR (Negative Likelihood Ratio).


Validity of the Colposcopic Criterion ‘Rag Sign’

In the aforementioned study, published in 2013, another objective was to assess the correlation between the pathognomonic criterion ‘rag sign’ and high-grade cervical intraepithelial neoplasia (hgCIN) employing video exoscopy (VITOM exoscopy system, KARL STORZ Germany). Sensitivity, specificity, PPV and NPV of ‘rag sign’ to detect hgCIN was 38.4%, 96%, 95.7% and 40.2%, respectively. The +LR and –LR ratio was 9.7 and 0.6, respectively.

Rag Sign – Major Change

- Pathognomonic grading criterion for major change.
- Associated with the presence of cervical intraepithelial neoplasia grade II or III.

Rag Sign – CIN III

The ‘rag sign’ shown in this atypical T zone type 2 of a 36-year-old patient is less pronounced and less obvious, demonstrating erosions right underneath the cotton-tipped swab at the entrance to the cervical canal between 11 and 1 o’clock. The lesion, diagnosed as major change, was histopathologically confirmed to be CIN III.

In a survey comparing the three pathognomonic criteria, the highest prevalence is found for ‘ridge sign’, followed by ‘rag sign’ and ‘inner border’ in this cohort of patients. The correlation of each of the three pathognomonic signs with hgCIN is highly significant (p < 0.001).
This comparative tabular data representation of three pathognomonic signs shows the highest sensitivity for ‘ridge sign’, highest specificity for ‘inner border’, best positive predictive value for ‘inner border’, best negative predictive value for ‘ridge sign’ and highest positive likelihood ratio for ‘inner border’ and lowest negative likelihood ratio for ‘ridge sign’.

Detection of at least one of three pathognomonic signs is a clinically significant contributing factor in the diagnosis of hgCIN, whereas the simultaneous presence of two signs increases the probability of detecting hgCIN even more. However, due to the lower prevalence of two signs as compared to one sign, sensitivity is decreased from 78% to 29%.

Unlike pathognomonic colposcopic signs, noted as present versus absent, there are six grading criteria, that apply to findings which manifest to varying degrees and are therefore termed ‘graduating signs’. The criteria color and dynamic of acetowhiteness, surface structure and intervascular distance in mosaic or punctuation, demarcation of the border of a lesion, and degree of iodine uptake need to be rated accordingly.

When faced with the task of defining the ‘color of acetowhite epithelium’, the terms ‘thin’ or ‘clear white’ are used in contrast to ‘dense’ or ‘opaque’. The assessment varies considerably between different observers. The same holds true when the ‘dynamic of acetowhiteness’ needs to be interpreted distinguishing between a slow versus rapid reaction.

---

**Color – Normal**

The color of the acetowhite epithelium provides a graduating sign.

Colposcopic findings in a 21-year-old gravida 0, para 0 who had been vaccinated against HPV with quadrivalent vaccine at 14 years of age. The smear was reported as class III D1, and HPV DNA was not detected.

Colposcopy shows a bright, circular acetowhite atypical T-zone type 1, which is classified as normal colposcopic finding.

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**Rule 6**

- **Grading Graduating Signs**
  - Color of acetowhite area: thin vs dense
  - Dynamic of acetowhiteness: slow vs rapid
  - Surface of mosaic or punctuation: fine vs coarse
  - Intercapillary distance of mosaic or punctuation: small vs large
  - Border: blurred vs well-defined
  - Iodine uptake: partial vs absent

---

**Comparison of Validity of 3 Pathognomonic Colposcopic Criteria in 335 Women with Atypical Transformation Zone Correlated with Histological Diagnosis**

<table>
<thead>
<tr>
<th>hgCIN</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>+ LR</th>
<th>– LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inner Border</td>
<td>20%</td>
<td>15%–28%</td>
<td>19%</td>
<td>97%</td>
<td>20%</td>
<td>21%</td>
</tr>
<tr>
<td>Ridge Sign</td>
<td>52.5%</td>
<td>50%–59%</td>
<td>52%</td>
<td>96%</td>
<td>6%</td>
<td>16%</td>
</tr>
<tr>
<td>Rag Sign</td>
<td>38.6%</td>
<td>30%–45%</td>
<td>38%</td>
<td>94%</td>
<td>1%</td>
<td>15%</td>
</tr>
</tbody>
</table>

hg (high-grade), CIN (Cervical Intraepithelial Neoplasia), PPV (Positive Predictive Value), NPV (Negative Predictive Value), + LR (Positive Likelihood Ratio), – LR (Negative Likelihood Ratio).


---

**Presence of At Least One of Three Pathognomonic Signs Compared to the Presence of Two Signs**

<table>
<thead>
<tr>
<th>hgCIN</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>+ LR</th>
<th>– LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one sign</td>
<td>77.8%</td>
<td>71%–82%</td>
<td>93%</td>
<td>90%–97%</td>
<td>96%</td>
<td>6%</td>
</tr>
<tr>
<td>At least two signs</td>
<td>29%</td>
<td>24%–36%</td>
<td>98%</td>
<td>95%–99%</td>
<td>97%</td>
<td>3%</td>
</tr>
</tbody>
</table>

hg (high-grade), CIN (Cervical Intraepithelial Neoplasia), PPV (Positive Predictive Value), NPV (Negative Predictive Value), + LR (Positive Likelihood Ratio), – LR (Negative Likelihood Ratio).

Histopathology of tissue sampled at 11 o’clock by strip biopsy shows normal metaplastic squamous epithelium. The immune marker Ki 67 is expressed only in the basal cell layer, and p16 is not detected.

Histopathology findings are interpreted as normal.

Color – Minor Change
An acetowhite color that appears ‘more opaque’ suggests the presence of low-grade CIN.

Colposcopic findings in a 20-year-old gravida 0, para 0 not previously vaccinated against HPV. The patient suffers from condylomata acuminata of the vulva. Her cervical smear was reported as class IIID1. HPV 6 and 42 were detected. Colposcopy shows a circular, acetowhite atypical T-zone type 2, which is classified as grade 1 (minor change) abnormal colposcopic finding.

Histopathology of tissue sampled at 6 o’clock by strip biopsy shows atypical squamous epithelium in which the immune marker Ki 67 is expressed into the middle third of the epithelium. The marker p16 is detected only focally and at low concentration.

The histopathologic diagnosis is grade 1 cervical intraepithelial neoplasia (CIN I).

Color – Major Change
An opaque acetowhite reaction is associated with the presence of high-grade CIN.

Colposcopic findings in a 25-year-old gravida 0, para 0 not previously vaccinated against HPV. The patient wears a copper IUD for contraception. Her cervical smear was reported as class IIID1, and high-risk HPV DNA and RNA were detected. Colposcopy shows a circular atypical T-zone type 1 with an opaque acetowhite reaction at 1 o’clock and at 5 to 7 o’clock, classified as grade 2 (major change) abnormal colposcopic finding.
Histopathology of tissue sampled at 1 o’clock by strip biopsy shows atypical squamous epithelium in which expression of the immune marker Ki 67 extends into the middle third of the epithelium and p16 is expressed into the highest cell layer. The histopathologic diagnosis is grade 2 cervical intraepithelial neoplasia (CIN II).

An intense, opaque color reaction after the application of acetic acid is a graduating sign that may indicate the presence of invasive cancer. Colposcopic findings in a 37-year-old gravida 1, para 2. Her cervical smear was reported as class V-p, and high-risk HPV DNA and RNA were detected. The squamous cell carcinoma antigen (SCCA) tumor marker in the serum showed a 7-fold increase to 10.9 ng/ mL. Colposcopy demonstrates a circular, opaque acetowhite atypical T-zone type 3 with ulceration, bleeding, and atypical vessels, classified as abnormal colposcopic finding suspicious for invasive cancer.

H&E stain of tissue sampled at 12 o’clock by punch biopsy shows aggregates of highly atypical squamous cells with malignancy criteria of anisonucleosis, hyperchromasia, altered nuclear-cytoplasmic ratio, and atypical mitoses. The histopathologic diagnosis is invasive squamous cell carcinoma G2. Laparoscopic lymph node staging classified the disease as FIGO stage IIb pN0, and the patient was treated with primary chemoradiation.

Dynamic of Acetowhitening
- Slow versus rapid acetowhite reaction is a graduating criterion.
- Used to differentiate between normal, minor and major change.
Primary, Secondary and Tertiary Prevention of Cervical Cancer

Surface – Normal
The surface characteristics of a colposcopic lesion provide another graduating sign.
Colposcopic findings in a 27-year-old gravida 0, para 0. The smear was reported as class IIID1, and HPV DNA was not detected. Colposcopy shows a fine mosaic pattern with a smooth surface at 4 to 6 o’clock in an atypical T-zone type 1, which is classified as a normal colposcopic finding.

H&E stain of tissue sampled at 5 o’clock by strip biopsy shows metaplastic squamous epithelium of normal maturation. Histopathology findings are interpreted as normal.

Surface – Minor Change
Minor surface alterations may indicate the presence of low-grade CIN.
Colposcopic findings in a 34-year-old gravida 1, para 0 with an uneventful history. The smear was reported as class II-p, and HPV detection was not performed. Colposcopy shows an atypical T-zone type 1, which is classified as grade 1 (minor change) abnormal colposcopic finding.

H&E stain of tissue sampled at 3 o’clock by strip biopsy shows atypical squamous epithelium with basal cell hyperplasia and delayed maturation. The histopathologic diagnosis is grade 1 cervical intraepithelial neoplasia (CIN I).
**Surface – Major Change**

A cobblestone surface pattern seen at colposcopy indicates the presence of high-grade CIN.

Colposcopic findings in a 32-year-old gravida 1, para 1 with an uneventful history. The cervical smear was reported as class IVa-p. High-risk HPV DNA and RNA were detected. Colposcopy shows a circular, opaque acetowhite atypical T-zone type 2 with a coarse mosaic at 12–1 o’clock and 5–7 o’clock, which is classified as grade 2 (*major change*) abnormal colposcopic finding.

Histopathology of tissue sampled at 6 o’clock by punch biopsy shows atypical squamous epithelium in which expression of the immune markers Ki 67 and p16 extends into the highest cell layer. Note the widened rete pegs, which cause the stromal papillae to be spaced farther apart.

The histopathologic diagnosis is grade 3 cervical intraepithelial neoplasia (CIN III).

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**Surface – Cancer**

If the surface structure is irregular and disrupted, this signifies the presence of invasive cancer.

Colposcopic findings in a 37-year-old gravida 1, para 2. The cervical smear was reported as class V-p, and high-risk HPV DNA and RNA were detected. The tumor marker SCCA in the serum was increased 7-fold to 10.9 ng/mL. Colposcopy shows ulceration and disruption of an atypical T-zone type 3 with bleeding and atypical vessels – classified as abnormal colposcopic finding suspicious for invasive cancer.

H&E stain of tissue sampled from the center of the affected area by punch biopsy shows papillary aggregates of highly atypical squamous epithelium with malignancy criteria of anisonucleosis, hyperchromasia, altered nuclear-cytoplasmic ratio, and atypical mitoses. The histopathologic diagnosis is invasive squamous cell carcinoma G2.

Laparoscopic lymph node staging assigned the disease to FIGO stage IIb pN0, and the patient was treated with primary chemoradiation.
**Intervascular Distance – Normal**

The distance between the ‘dots’ or ‘lines’ in a punctation or mosaic pattern, respectively, is interpreted as a graduating sign.

Colposcopic findings in a 29-year-old gravida 1, para 1 with an uneventful history. The smear was reported as class III D1. High-risk HPV DNA and RNA were detected. Colposcopy shows a fine mosaic pattern between 4 and 7 o’clock in an atypical T-zone type 1, which is classified as a normal colposcopic finding.

H&E stain of tissue sampled at 5 o’clock by punch biopsy shows normal metaplastic squamous epithelium with normal maturation and stromal papillae that rise into the upper third of the epithelium. The findings are interpreted as normal.

**Intervascular Distance – Minor Change**

An increase in the intervascular distance suggests the presence of low-grade CIN.

Colposcopic findings in a 22-year-old gravida 0, para 0 who had been vaccinated against HPV with quadrivalent vaccine at 15 years of age. Her cervical smear was reported as class III D1, and high-risk HPV DNA (of undetermined type) was detected. Colposcopy shows a mosaic with a slightly increased intervascular distance at 11–1 o’clock in an atypical T-zone type 1, which is classified as grade 1 (minor change) abnormal colposcopic finding.

Histopathology of tissue sampled at 12 o’clock by punch biopsy shows atypical squamous epithelium with marked basal cell hyperplasia. Numerous stromal papillae rise close to the epithelial surface among widened rete pegs. The histopathologic diagnosis is grade 1 cervical intraepithelial neoplasia (CIN I).
Intervascular Distance – Major Change
A greatly increased intervascular distance in a punctate or mosaic pattern signifies the presence of high-grade CIN. Colposcopic findings in a 21-year-old gravida 0, para 0, who had not been vaccinated against HPV. Her cervical smear was reported as class IIID1. High-risk HPV DNA and RNA were detected. Colposcopy shows an atypical T-zone type 1 with a semicircular mosaic between 11 and 2 o’clock, which is classified as grade 2 (major change) abnormal colposcopic finding.

Histopathology of tissue sampled at 12 o’clock by punch biopsy shows atypical squamous epithelium in which expression of the immune markers Ki 67 and p16 extends into the highest cell layer. The rete pegs are greatly widened and the interposed stromal papillae extend into the upper third of the epithelium. The histopathologic diagnosis is grade 3 cervical intraepithelial neoplasia (CIN III).

Intervascular Distance – Cancer
A high degree of cell proliferation and neovascularity may cause atypical vessels to be spaced farther apart, suggesting the presence of invasive cancer. Colposcopic findings in a 24-year-old gravida 0, para 0. Her cervical smear was reported as class V-g, and HPV 18 was detected. Colposcopy shows an opaque, acetowhite atypical T-zone type 3, which is classified as abnormal colposcopic finding suspicious for invasive cancer. Atypical vessels with a large intervascular distance are visible at 12 o’clock through the intact squamous epithelium.

Histopathology of tissue sampled by loop biopsy shows highly atypical glands whose epithelium expresses high levels of the marker STMN1. Normal endocervical glands between 3 and 6 o’clock do not express STMN1. Within the stroma are numerous vessel lumina (arrowheads) whose endothelium is clearly marked by a positive stathmin1 reaction. The histopathologic diagnosis is invasive endocervical adenocarcinoma G2. The patient was treated by laparoscopic sentinel lymphadenectomy and radical vaginal trachelectomy and was staged as pT1b1 pN0 (0/2 sn) G2 L0 V0 Pn 0.
Border – Normal
The delineation of lesion margins from normal squamous epithelium is another useful graduating sign at colposcopy. Colposcopic findings in a 26-year-old gravida 0, para 0 who had not been vaccinated against HPV. The smear was reported as class IIID1. High-risk HPV DNA and RNA were detected. Colposcopy shows a bright acetowhite lesion between 12 and 2 o’clock in an atypical T-zone type 1. It is not sharply demarcated from adjacent squamous epithelium and is classified as normal colposcopic finding.

H&E stain of tissue sampled at 12 o’clock by punch biopsy shows normal and metaplastic squamous epithelium at the biopsy site. These findings are interpreted as normal.

Border – Minor Change
The sharper delineation of a lesion suggests the presence of low-grade CIN. Colposcopic findings in a 27-year-old gravida 0, para 0, who is taking hydroxychloroquine for rheumatoid arthritis. Her cervical smear was reported as class IIID1. DNA and RNA of high-risk HPV were detected. Colposcopy shows an opaque acetowhite atypical T-zone type 2 that has sharp margins between 10 and 3 o’clock and indistinct margins between 3 and 9 o’clock. This is classified as grade 1 (minor change) abnormal colposcopic finding.

Histopathology of tissue sampled at 11 o’clock by punch biopsy shows atypical squamous epithelium in which the immune markers Ki 67 and p16 are expressed in the lower third of the epithelium. Normal squamous epithelium is visible at left. At the center of the image is an oblique boundary line separating the normal epithelium from immunohistochemically positive, atypical epithelium. The histopathologic diagnosis is grade 1 cervical intraepithelial neoplasia (CIN I).
**Border – Major Change**

The sharp colposcopic delineation of a lesion is associated with the presence of high-grade CIN.

Colposcopic findings in a 26-year-old gravida 0, para 0, who had not been vaccinated against HPV. Her cervical smear was reported as class IIID1. High-risk HPV DNA (not type 16 or 18) was detected. Colposcopy shows a sharply marginated acetowhite lesion at 12–1 o’clock in an atypical T-zone type 2, which is classified as grade 2 (*major change*) abnormal colposcopic finding.

Histopathology of tissue sampled by loop biopsy shows atypical squamous epithelium in which expression of the immune markers Ki 67 and p16 extends into the highest cell layer. This is also apparent in the affected endocervical gland at the bottom of the image. Note the sharp delineation from normal squamous epithelium at the left edge of the image.

The histopathologic diagnosis is grade 3 cervical intraepithelial neoplasia (CIN III).

**Border – Cancer**

Sharp and elevated borders relative to normal squamous epithelium may indicate the presence of invasive cancer.

Colposcopic findings in a 29-year-old gravida 0, para 0, with no prior history of disease. Her smear was reported as class V-p, and HPV 16 was detected. Colposcopy shows a sharply defined atypical T-zone type 2 that is elevated relative to the squamous epithelium. It is classified as abnormal colposcopic finding suspicious for cancer.

Histopathology of tissue sampled by loop biopsy shows atypical cells that have penetrated the basement membrane and infiltrated the stroma. The margins of the cancer are sharply defined. The diagnosis is undifferentiated invasive squamous cell carcinoma. Following laparoscopic sentinel lymphadenectomy and radical vaginal trachelectomy, the disease was finally staged as pT1b1 pN0 (0/2 sn) G3 L0 V0 Ph0.
Iodine Uptake – Normal

Though described in the IFCPC classification as a nonspecific colposcopic criterion, the degree of iodine uptake can provide a useful graduating sign at colposcopy. Colposcopic findings in a 37-year-old gravida 2, para 2 who has experienced contact bleeding for several months. Her smear was reported as class II-a. HPV DNA was not detected. Colposcopy shows partial iodine uptake in a typical T-zone type 2, which is classified as a normal colposcopic finding.

Histopathology of tissue sampled at 6 o’clock by strip biopsy shows normal endocervical glands surrounded by normal stromal tissue. The findings are interpreted as normal.

Iodine Uptake – Minor Change

Partial iodine uptake by a lesion may indicate the presence of low-grade CIN. Colposcopic findings in a 47-year-old gravida 2, para 2 with no prior history of disease. Her cervical smear was reported as class IIID1. High-risk HPV DNA and RNA were detected. Colposcopy shows a circular atypical T-zone type 1 with partial iodine uptake, classified as grade 1 (minor change) abnormal colposcopic finding.

Histopathology of a central tissue sample taken at 12 o’clock by punch biopsy shows thinned, atypical squamous epithelium in which expression of the immune marker Ki 67 extends into the middle third of the epithelium, while p16 is detected only at low concentration in the upper cell layers. The histopathologic diagnosis is grade 1 cervical intraepithelial neoplasia (CIN I).
**Iodine Uptake – Major Change**

Absence of iodine uptake is associated with the presence of high-grade CIN.

Colposcopic findings in a 37-year-old gravida 2, para 2. Two years before this examination, the patient underwent treatment for locally advanced breast cancer that included adjuvant chemotherapy. Her cervical smear was reported as class IIID2. High-risk HPV types 16, 59 and 66 were detected.

Colposcopy shows a semicircular, iodine-negative atypical T-zone type 1, which is classified as grade 2 (*major change*) abnormal colposcopic finding due in part to the complete absence of iodine uptake at 1 o’clock.

Histopathology of tissue sampled at 1 o’clock by strip biopsy shows atypical squamous epithelium in which expression of the immune markers Ki 67 and p16 extends into the upper third of the epithelium. The histopathologic diagnosis is grade 2 cervical intraepithelial neoplasia (CIN II).

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**Iodine Uptake – Cancer**

Complete absence of iodine uptake may signify invasive cancer.

Colposcopic findings in a 29-year-old gravida 0, para 0 with no prior history of disease. The cervical smear was reported as class V-p, and HPV 16 was detected. Colposcopy after iodine application and color shift with the SPECTRA A* mode (KARL STORZ IMAGE1 S) shows central iodine-negative areas at 1 to 3 o’clock and 5 o’clock in an atypical T-zone type 2. This is an abnormal colposcopic finding suspicious for cancer.

Histopathology of tissue sampled by loop biopsy shows atypical cells with strong expression of the markers Ki 67 and p16 extending into the upper third of the epithelium. While the basement membrane on the left side of the image is still intact, it is penetrated by atypical cell complexes in the right third of the image.

The diagnosis is undifferentiated invasive squamous cell carcinoma. Following laparoscopic sentinel lymphadenectomy and radical vaginal trachelectomy, the disease was finally staged as pT1b1 pN0 (0/2 sn) G3 L0 V0 Pn0.

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*SPECTRA A*: Not for sale in the U.S.
Schiller’s Iodine Test – Cancer

- Cancer is completely negative for iodine staining.
- Low-grade CIN shows some iodine uptake.

Validity of Pathognomonic Signs

<table>
<thead>
<tr>
<th>hgCIN</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>+ LR (95% CI)</th>
<th>− LR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inner Border</td>
<td>19.3 %</td>
<td>99.2 %</td>
<td>98.3 %</td>
<td>35.8 %</td>
<td>26.70 (0.7–190.7)</td>
<td>0.81 (0.7–0.8)</td>
</tr>
<tr>
<td>Ridge Sign</td>
<td>53.1 %</td>
<td>93.5 %</td>
<td>94.7 %</td>
<td>47.6 %</td>
<td>11.30 (4.7–27.0)</td>
<td>0.62 (0.6–0.68)</td>
</tr>
<tr>
<td>Rag Sign</td>
<td>40.7 %</td>
<td>96.4 %</td>
<td>96.1 %</td>
<td>42.5 %</td>
<td>8.20 (4.32–15.5)</td>
<td>0.44 (0.44–0.57)</td>
</tr>
<tr>
<td>Cuffed Crypt</td>
<td>51.5 %</td>
<td>84.9 %</td>
<td>88.2 %</td>
<td>44.3 %</td>
<td>4.31 (2.5–1.13)</td>
<td>0.57 (0.6–0.65)</td>
</tr>
</tbody>
</table>

Validity of Graduating Signs

<table>
<thead>
<tr>
<th>hgCIN</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>+ LR (95% CI)</th>
<th>− LR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coarse mosaic</td>
<td>12.4%</td>
<td>94.9%</td>
<td>82.2%</td>
<td>33.0%</td>
<td>2.47 (1.3–5.46)</td>
<td>0.92 (0.8–1)</td>
</tr>
<tr>
<td>Coarse punctuation</td>
<td>3.6%</td>
<td>97.8%</td>
<td>78.2%</td>
<td>31.6%</td>
<td>1.67 (0.9–1.2)</td>
<td>0.50 (0.6–1.0)</td>
</tr>
<tr>
<td>Fast dynamic</td>
<td>59.3%</td>
<td>41.7%</td>
<td>60.9%</td>
<td>31.8%</td>
<td>1.92 (0.9–1.2)</td>
<td>0.97 (0.9–1.2)</td>
</tr>
<tr>
<td>Opacification</td>
<td>83.9%</td>
<td>71.9%</td>
<td>86.7%</td>
<td>67.0%</td>
<td>2.99 (2.3–3.8)</td>
<td>0.22 (0.2–0.3)</td>
</tr>
<tr>
<td>Sharp border</td>
<td>65.2%</td>
<td>68.3%</td>
<td>81.8%</td>
<td>47.2%</td>
<td>2.06 (2.6–2.7)</td>
<td>0.51 (0.4–0.6)</td>
</tr>
<tr>
<td>Iodine negativity</td>
<td>84.5%</td>
<td>69.7%</td>
<td>81.8%</td>
<td>47.2%</td>
<td>2.81 (2.2–3.6)</td>
<td>0.22 (0.9–1.1)</td>
</tr>
</tbody>
</table>

In another study the authors compared the validity of pathognomonic versus graduating colposcopic criteria for detection of high-grade cervical intraepithelial neoplasia (hgCIN). Evaluation was based on a review of video recordings taken from 444 patients referred for diagnostic colposcopy employing video exoscopy (VITOM system*) and involving either cervical biopsies or loop excisions. The authors showed that the pathognomonic signs ‘inner border’, ‘ridge sign’, ‘cuffed crypt openings’ and the newly defined ‘rag sign’ are significantly associated with high-grade CIN. ‘Ridge sign’ has the highest sensitivity, negative predictive value, and the lowest negative likelihood ratio. ‘Inner border sign’ has the highest specificity, the highest positive predictive value and the highest positive likelihood ratio.

Validity of Pathognomonic Versus Graduating Signs

Based on receiver operating characteristic (ROC) analysis, we know that pathognomonic signs have less sensitivity than graduating signs, but they have higher specificity in the diagnosis of CIN II and III. This is reflected in the steeper curves for 1 or 3 pathognomonic signs compared with 1 or 4 graduating signs. The result is a significantly higher positive predictive value, which is of key importance in colposcopic examinations for reducing false-positive rates and preventing unnecessary biopsies.
Adenocarcinoma in situ (ACIS)

The colposcopic diagnosis of ACIS is difficult, and often the examiner must rely entirely on the opaque acetowhitteness of the glandular epithelium and/or an accentuated pattern of vascular markings.

Colposcopic findings in a 25-year-old gravida 0, para 0. The patient was vaccinated against HPV with quadrivalent vaccine at 18 years of age. Her cervical smear was reported as class III-g. High-risk HPV types 16 and 18 were detected. Colposcopic findings appear normal before the application of acetic acid.

Following the application of 5% acetic acid, colposcopy shows an isolated, opaque acetowhite lesion at 12 o’clock in an atypical T-zone type 1, which is classified as grade 2 (major change) abnormal colposcopic finding.

H&E stain of tissue sampled from the exophytic lesion at 12 o’clock by punch biopsy shows an arborizing pattern (‘tree’) of atypical glandular complexes. Polypoid exophytic growth is interpreted as endocervical ACIS.

The histopathologic diagnosis is adenocarcinoma in situ (ACIS).

Detection of the immune markers Ki 67 and p16 is strongly positive throughout the epithelium of the biopsy specimen.
Rule 7: The Seven Steps of Examination

The colposcopic examination usually comprises seven steps. Occasionally, difficulties may be encountered during central exposure of the cervix by use of a duckbill (Cusco) speculum. The patient should not feel uncomfortable and should be relaxed. Acetic acid is applied and the squamo-columnar junction is evaluated. The typical (normal) and atypical features of the transformation zone are appreciated. Provided an atypical transformation zone is diagnosed, the lesion is graded and the area exhibiting the most severe change is identified and biopsied. At the same time, the lesion is assessed with respect to the most appropriate treatment modality.

Diagnostic VITOM Exoscopy

During colposcopic examination the patient should always be given the option to obtain the same visual information as the colposcopist and should be encouraged to be actively involved in the decision-making. As shown on the opposite image, the VITOM exoscopy system is employed by the colposcopist allowing a high-definition video image to be displayed on the screen, which can be discussed with the patient in real time.

Visualization and Staining

Once the cervix is visualized with a frosted duckbill speculum, the squamo-columnar junction is evaluated by 7- to 10-fold magnification and the presence of leukoplakia (‘white patch’) is excluded. 5% acetic acid is applied, followed by 3% iodine solution. The colposcopic image (a) shows the native cervix, and (b) its appearance following application of acetic acid. The image below (c) presents the result of iodine staining.
Acetic Acid and Schiller’s Iodine Test

- Application of acetic acid and Schiller’s iodine test complement each other.
- Acetic acid is useful to grade an atypical transformation zone and to localize the area of most severe change for targeted punch biopsy.
- Schiller’s iodine test is helpful in delineating the extent of the lesion for tissue-sparing surgical treatment.

Punch Biopsy – Instrument

Atypical-looking areas may be biopsied with a special forceps, such as the Tischler-Morgan type. The specimen collected in this way should be examined histologically. An important feature of the forceps shown in the superimposed image, is the small hook at the tip of both jaws. The hooks allow the forceps to be anchored in the tissue and permit the specimen to be harvested with virtually no pain, while still obtaining sufficient tissue material. Bleeding, occasionally occurring post biopsy, is controlled by local compression or application of hemostyptics.

Colposcopically Directed Punch Biopsy

- Colposcopically directed punch biopsy must be focused on the most atypical site.
- The ideal biopsy specimen should be composed mainly of epithelium with little underlying stroma.

Biopsy – Histopathologic Evaluation

Tissue biopsies for diagnosis of CIN or cancer must be evaluated using 6 to 9 histologic sections. The report must state the grade of CIN and exclude or confirm the presence of invasive disease.

Histopathologic Evaluation of Biopsy Samples

- Up to 9 histologic sections.
- Histologic grading of CIN.
- Presence or absence of invasive disease.
Endocervical Curettage – Instrument
If the squamocolumnar junction in a transformation zone of type 3 is not amenable to colposcopic examination, endocervical curettage is usually performed with a small-diameter sharp curette. Usually, the patient should experience only mild discomfort without pain. While histopathologic diagnosis of CIN or cancer in the curettage specimen can be positive, negative findings do not exclude the presence of neoplasia.

Endocervical Curettage – Transformation Zone Type 3
- If the squamocolumnar junction is not visible, validity of colposcopy is low.
- Endocervical curettage (ECC) may be used for endocervical assessment.
- However, normal findings of ECC do not exclude the presence of precancer or cancer.
- Endocervicoscopy, loop excision or conization may be indicated to explore the endocervix more thoroughly.
2.5 Therapy

**Surgical Techniques and CIN**

For treatment of precancer or CIN, a variety of destructive and excisional modalities are available. Excision is done with a loop electrode or a laser unit. Laser vaporization or cryotherapy are referred to as destructive techniques. In patients with high-grade CIN and a T-zone of type 2 or 3, loop excision is the first-line treatment option.

If a cone with a small base and a length of more than 2 cm is required, laser conization must be used. Destructive treatment modalities should only be used in the presence of a T-zone of type 1 and low-grade CIN. Laser vaporization and loop excision are combined if the lesion covers the ectocervix and/or extends to the vaginal vault.

**Management of Patients with Abnormal Pap Smears**

In patients with abnormal PAP smears, colposcopy and biopsy sampling is recommended. If histopathologic evaluation of the biopsy specimen confirms CIN II or III, treatment by loop excision or laser application, in combination with endocervical curettage is the first-line therapeutic modality. In pregnant patients, usually therapy can be postponed till after delivery, provided invasive cancer has been excluded. In patients with confirmed diagnosis of invasive cancer, laparoscopic staging is mandatory in order to define the extent of disease.

**CIN and Pregnancy**

In pregnant women diagnosed with an abnormal Pap smear, specific conditions apply (see Algorithm for CIN in Pregnancy). The primary goal of colposcopic examination is the exclusion of invasive disease. If invasion has been ruled out, treatment is postponed till 5 weeks post partum. Spontaneous vaginal delivery can be attempted. If cancer cannot be excluded by colposcopy and Pap smear, biopsy or even loop excision must be performed. Loop excision in pregnancy can be associated with extensive hemorrhage. The gynecologist has to be prepared to manage extensive bleeding. The optimal period for loop excision is between gestational week 16 and 20.

**Preservation of Fertility and Resection**

Complete surgical removal of the tissue involved by CIN is one aim of therapy. Since most of the women who undergo surgery are still seeking preservation of fertility, as much healthy tissue as possible should be maintained in order to address another priority issue of therapy. Both objectives are partly exclusive since in sano resection can be achieved easily when a big cone is removed. If only a superficial and small-sized excision is made, the majority of cervical tissue is preserved, however, in terms of oncological safety, possibly at the cost of incomplete resection margins.

Thus, the challenge of surgery is to combine oncologic and reproductive safety preserving as much healthy tissue as possible while still removing the lesion completely.
Rules of Loop Excision
The goal of tissue preservation and complete resection of the lesion can be achieved if removal of tissue is always done with the help of magnification and the resection line is kept as close to the lesion as possible and adapted to the size of lesion. Therefore, the surgeon must be completely confident as to which path to be taken when guiding the loop through the cervix. Inverting sutures are obsolete and should not be performed since residual disease may become obscured by the stitches and may therefore become uncontrollable during follow-up. Loop excision is not a procedure for a novice in gynecologic surgery: even though the procedure takes only a few seconds and may therefore considered to be a minor and easy procedure, this conclusion is wrong. In these few seconds, the loop is under the surgeon's exclusive control and nobody can interfere or readjust the path which the loop is taking.

Treatment of CIN in T-Zone Type 1
A transformation zone of type 1 is characterized by visibility of the entire squamocolumnar junction on the ectocervix and, usually, the full extent of the lesion (highlighted in green) can be seen.

As a rule, superficial loop excision is performed in one step or, in case of purely ectocervical location of the lesion, CO2 laser vaporization may be used.

Treatment of CIN in T-Zone Type 2
In the case of a transformation zone of type 2, the squamocolumnar junction is only fully visible if access to the lower segment of the endocervix is obtained. By spreading the cervical os, usually the full extent of the lesion (highlighted in green) can be inspected.

Given the morphological characteristics above, with a lesion extending into the endocervical canal, loop excision either in one or two steps is feasible. The surgeon uses a loop with larger diameter for the outer part and finishes with a loop of smaller diameter for the endocervical part ('top hat' procedure). If the ectocervical part of the lesion covers a large area involving the vaginal vault, the combined use of central loop excision and CO2 laser vaporization or superficial strip excision of the periphery is the best choice.

Treatment of CIN in T-Zone Type 3
In the case of a transformation zone of type 3, the squamocolumnar junction is not visible. Accordingly, the extent of the lesion (highlighted in green) cannot be seen.

Given the morphological characteristics above, with a lesion located in the endocervical canal, CO2 laser conization or multiple-step loop excision are feasible. If a specimen with small base and long axis is required to be assessed by pathology, laser conization is mandatory. If the surgeon opts for loop excision, multiple specimens have to be sent for histopathologic evaluation. The pathologist must be given a record allowing for exact topographic allocation of each specimen. Endocervicography with a 3-mm hysteroscope can be helpful to locate the lesion and determine its endocervical extent. Based on these findings, the anticipated depth of conization can be defined.
Blind Excision

Loop excision under ‘naked-eye conditions’ is referred to as ‘blind excision’ and should be avoided under any circumstances. Not only there is inadequate control of the ectocervical margin but also guidance of the loop through the tissue has shown to pose difficulties. Complete excision and preservation of uninvolved tissue is not feasible.

Colposcopic-Guided Excision

In the hands of a well-trained specialist, loop excision under colposcopic guidance is a valid procedure that allows to obtain excellent results regarding completeness of removal and preservation of healthy cervical tissue. However, a good level of hand-eye coordination under colposcopic vision is needed and requires the user to go through a long learning curve with good practice. The surgical facility should be equipped with a high-quality colposcope.

VITOM-Guided Excision

The new generation of gynecologists is offered a valid alternative option to treat patients by loop excision using an exoscope (VITOM system) instead of a standard colposcope.

Steps of Loop Excision

Loop excision involves that the cervix and vagina are visualized with a self-holding duckbill speculum to which a smoke evacuation system is attached. Once the VITOM exoscope or colposcope has been adjusted to its working position, the lesion is identified and its size is evaluated. In a previous colposcopy session, the surgeon should have examined the patient and obtained adequate knowledge about the location and extent of the lesion. A written record should be kept providing evidence of the strategy that will be used for surgery. A loop of adequate size is selected and the settings of the high-frequency electro-surgical generator are preadjusted. Excision is performed either proceeding from left to right or from bottom to top. Hemostasis is achieved by careful use of spray coagulation. The cone is labeled at 12 o’clock with a stitch through the stroma, followed by volumetric measuring of the tissue resected, applying the fluid displacement technique based on Archimedes’ principle.

Loop Excision

- Visualize and elevate cervix
- Identify lesion
- Select loop size
- Preadjust settings of high-frequency surgical generator
- Take one or multiple specimens
- Proceed from 9 to 3 o’clock or from 6 to 12 o’clock
- Apply spray coagulation only if needed to achieve hemostasis
- Label and measure specimen
Setup of the VITOM Exoscope
Surgery should always be performed under magnification. Since nowadays, laparoscopic instrumentation and video equipment are included in the standard armamentarium of a gynecologic operating room, surgical procedures can be performed using a VITOM exoscope (KARL STORZ Tuttlingen, Germany). Gynecologic surgeons usually feel very comfortable with video-guided surgery which involves that an operation is performed relying on the magnified video image on the screen. Thus, the use of the VITOM exoscope is a valid alternative to the colposcope. The rationale for using magnification is first to identify the lesion to be removed in its entirety, and second, to remove only the diseased tissue, thus keeping damage to healthy tissue to a minimum.

The VITOM exoscope is coupled to a high-definition video camera and mounted to a holding system, that allows to maintain an adequate working distance from the patient. In this way, the surgeon is given full freedom of motion by using both hands, holding the speculum with the non-dominant hand while guiding the handpiece, to which a loop electrode is attached, with the dominant hand.

Schiller’s Iodine Test
Schiller’s iodine test is applied to the cervix prior to loop excision. Also the upper vagina is stained with 3% iodine solution in order to detect or exclude involvement of the vaginal vault. Care must be taken to make sure that the area of resection always includes the iodine-positive margins, which however, should be kept as small as possible.

Various Types of Loops
Depending on the size of the lesion, a choice is made from a set of loops available in diameters of 15 mm, 10 mm, and 5 mm. Apart from the ones shown here, there is a variety of different types of loops on the market. The surgeon should be familiar with their specific diameter and feel free to use the type of loop that matches the individual preferences.
Handpiece and Foot Pedal
While holding the speculum in one hand and the handpiece with the mounted loop in the other hand, excision is performed (a). The high-frequency electrosurgical generator is activated via the two-pedal footswitch (b). This is advantageous over push-button activation of the generator via handpiece because the surgeon can fully concentrate on maneuvering exclusively the handpiece with the mounted loop. In this way, less cognitive resources are taken up, allowing the surgeon to accomplish an enhanced level of quality in the excision procedure.

Guiding the Wire
Once activated, the wire of the loop is put into contact with the cervix at 9 o’clock (a). The loop has been passed halfway through the tissue (b). The loop is pulled away from the cervix at 3 o’clock (c). Spray coagulation is applied carefully to bleeding vessels or oozing tissue using a ball electrode (d).

Archimedes Principle
The volume of all tissue removed is measured based on the method of Archimedes and the results are documented in the patient record. As a rule of thumb, less than 15% of the volume of the cervix should be removed in order to prevent the risk of complications in future pregnancies (a, b).

VITOM-Guided Loop Excision
Excisional or destructive techniques for treatment of cervical disease mandate the use of a magnifying aid to ensure oncologically sound removal of the lesion and preservation of healthy tissue. In the absence of a colposcope, the VITOM exoscope may be used alternatively, considering that laparoscopic sets are part of the standard armamentarium available in a modern gynecologic operating room.
In a prospective comparative study, 200 patients with histologically confirmed high-grade CIN were evaluated. 100 patients underwent VITOM-guided loop excision, 100 patients were treated by colposcopic-guided loop excision. Mean age was 33 years, 93% of women were premenopausal, and one patient was pregnant.

In the VITOM group, more patients were postmenopausal, had a higher rate of previous surgeries, and a T-Zone type 3 was observed more frequently. However, the in sano resection rate and the volume of tissue removed did not differ significantly between both groups, demonstrating that VITOM-guided loop excision is of identical quality as compared to colposcopic-guided loop excision. Accordingly, VITOM exoscopy represents a valid alternative to standard colposcopy and allows to achieve high quality surgery. VITOM can be fully integrated in any laparoscopic unit enabling gynecologic surgeons, who have a good command of laparoscopic surgery to perform excisional procedures under magnification to the benefit of patients (see also Ref. No. 116, p. 114).

**Histopathologic Evaluation**

An intact cone, labelled with a stitch at 12 o’clock is a key precondition for adequate histopathologic evaluation. The cone specimen is sectioned into segments of 2–3 mm and completely embedded in paraffin. From each paraffin bloc, 4 to 6 sections are taken. The histopathology report must mention the size (especially the length) and give a description of the excised tissues. The type of lesion (CIN, ACIS), localization (endo- or ectocervical) and extent (description clockwise, e.g., from 2 till 6 o’clock) of CIN and HPV-related morphologic changes are evaluated. In case of invasive cancer, the extent of invasion (depth of invasion and horizontal extension) and presence or absence of vascular invasion (L- and V-status) need to be defined. It is mandatory that the status of resection margins (vaginal and endocervical) be described.

**Multifocality of CIN**

Even if the pathologist confirms the presence of histologically clear margins, this should not be received as a guarantee that there is no residual lesion left behind in the endocervical canal. Very rarely, CIN is interrupted by normal columnar epithelium which is called ‘discontinuous growth’. In such a case, the pathologist will refer to the resection of CIN as ‘in sano’, since normal columnar epithelium is seen at the site where the resection line is crossing the columnar epithelium (arrow). However, due to discontinuous growth, CIN may have been missed higher up in the endocervical canal and recurrence or even invasive cancer may develop. Therefore, patients should be advised to adhere to a close follow-up program, even in the presence of histopathologically sound margins.
Lymphovascular Space Involvement
The invasion of lymphatic vessels and/or blood vessels by tumor cells is an important prognostic factor in patients diagnosed with cervical cancer. The invasion of blood vessels is a particularly unfavorable prognostic sign. Consequently, the pathology report in patients with invasive cervical cancer should indicate whether the lymphatics and/or blood vessels are involved. The histologic section shows involvement of lymphatic vessels by a tumor embolus (green arrows).

Cone Specimen of the ‘Previous Century’
This image shows a formalin-fixed cervical cone with a diameter of 3 cm and a height of 2.5 cm. Given a transformation zone of type 1 or 2 in a woman who is still seeking parenthood, such a big loss of tissue is highly unreasonable and justified only in a patient with extensive ecto- and endocervical disease, who no longer opts for preserving fertility. Even though specimens of such size were a common standard, especially at the time of knife conization, cervical surgery for pre-invasive disease has become increasingly conservative over the last decade.

Incomplete Excision of CIN and Risk of Treatment Failure
Complete excision of CIN is of paramount importance. As shown in the literature, the rate of incomplete (non-in-sano) resections varies between 6.2 and 34.9% while the rate of persistent disease following excision ranges between 2.2 and 31%. There is a strong correlation between R1 resection and post-treatment high-grade disease. In a meta-analysis based on 66 studies, 23% of 35,109 women had at least one margin of the excised tissue involved with disease. Compared with the reference group, who had complete excision, diagnosis of post-treatment disease was 18 versus 3% with a relative risk (RR) of 6.1 for high-grade CIN. The authors conclude that every effort should be made to avoid incomplete excision. They also dissuade from adding extensive ablation to compensate for inadequate excision.

Based on the morphometry of CIN, pathologists have been attempting to establish guidelines related to the depth and width of excision. However, the table shows that over the years the recommended depth has increased from 3.8 mm to more than 10 mm. This underscores that an individualized approach relying on colposcopic and endohysteroscopic evaluation is indicated.

### Morphometric Recommendations

<table>
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<th>Author</th>
<th>n</th>
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<td>≤ 10 &gt; 35 yrs</td>
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<tr>
<td>ADAMSON MC, HARTLEY RB.</td>
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<td>ANDERSON MC, HARTLEY RB.</td>
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**Video-Guided Office Hysteroscopy**

Hysteroscopie Video-Endocervicoscopy

Video-endocervicoscopy performed by office hysteroscopy requires no general or local anesthesia and allows the squamocolumnar junction to be identified in patients positively diagnosed with an endocervical lesion. Using a small-diameter hysteroscope, the horizontal extent of the lesion can be determined accurately. Application of this modality significantly contributes to a reduction in the rate of endocervical R1-resections in patients with cervical intraepithelial neoplasia and a T-Zone type 3.

**Office Hysteroscopy – Identification of the Squamocolumnar Junction (SCJ)**

- In patients where the SCJ is not visible.
- Mainly in patients with T-zone type 3.
- Allows individualized treatment.
- Treatment is not determined based on morphometric rules.

**Excisional and ablative surgical techniques for the treatment of women with CIN are found to be associated with negative sequelae for subsequent pregnancies. The relative risk for premature delivery following loop excision varies between 1.7 and 2.2. This risk is directly correlated with the volume and depth of the tissue excised.**

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<table>
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<th>Author</th>
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<tr>
<td>Bruinsma 2011</td>
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**Condition after Loop Excision – T-Zone Type 1**

Loop excision under magnification-guided exoscopy offers the benefits of little tissue loss and a fully visible squamo-columnar junction.

- There is no evidence of adverse post-loop excision effects that might affect future childbearing potential.
- The anatomical result achieved with the above method allows for optimal exposure of the whole squamocolumnar junction.
CIN – A Scourge for Women

Even though gynecologic oncologists and gynecologists may hold the opinion that CIN is a minor disease because it is amenable to treatment via minor surgical procedures, the negative impact on the patient and her sexuality can be very serious or even disastrous. For patients who have been diagnosed with HPV-related CIN, the condition is frequently tainted with the stigmata of sexually transmitted disease, infection, infertility, cancer, and even death. The transmissibility of the disease can jeopardize relationship and marriage.

Adverse Side Effects of CIN

- Negative association of sexuality with
- Disease
- Infection
- Transmission
- Distrust
- Infertility
- Cancer
- Death

Training Loop Excision with the VITOM Exoscope

Teaching and training are essential for developing the proficiency required in the treatment of intraepithelial and early invasive cervical disease. The VITOM exoscope is the perfect tool for this purpose. Panel (a) shows a special training model being demonstrated for workshop participants.

Panel (b) shows a participant seated comfortably at a training model with the VITOM exoscope, which is connected to a video camera and mounted on a holder. The handpiece with the loop electrode is held in the dominant hand (b).

The VITOM exoscope ② is coupled to a video camera ③ and held securely in place with a holding system ① (c).

The training specimen is shown in panel (d). A turkey heart, which is similar in size and shape to a human cervix, has been positioned on a monopolar electrode.
Neoadjuvant Therapy – Monitoring Response

- Response to neoadjuvant therapy can be monitored by digital recording of findings obtained by VITOM-guided colposcopy.
- Videocolposcopic control and documentation is essential for monitoring tumor size.
Tertiary Prevention of Cervical Cancer
3.0 Tertiary Prevention

Introduction

Tertiary prevention is defined as prevention of metastasizing disease in the presence of primary disease. In women with cervical cancer we may not know at the time of diagnosis if we are dealing with locally limited, regionally extended, or metastasizing disease. The focus of this section is to address mainly localized cervical carcinoma. Metastasizing and recurrent disease will also be dealt with in order to give an overview of the whole range of diagnostic and therapeutic modalities currently available.

3.1 Diagnosis

Clinical Symptoms

- Vaginal bleeding
  - on contact
  - spontaneous
- Odorous discharge
- Loss of weight
- Urinary tract infection
- Enlarged supraclavicular or inguinal lymph nodes

Clinical Examination

Gynecological speculum examination with colposcopy and bimanual palpation forms the basis for diagnosis and assessment of extent of disease. Colposcopically directed biopsy leads to histopathologically-based diagnosis.

Shown on this colposcopic image is an exophytic invasive squamous cancer FIGO* stage IB2. Whenever possible, a diagnosis of invasive cancer should be established by biopsy and not by conization. In this way, inadvertent spread of tumor cells from the tissue that is cut through during conization is reliably prevented.

Bimanual rectovaginal examination allows assessment of tumor size and cervix, while affording the opportunity to evaluate the risk of possible parametrial infiltration. Endometriosis or inflammation may mimick tumor infiltration.

* Fédération Internationale de Gynécologie et d’Obstétrique
Colposcopy
The most conclusive pathognomonic colposcopic finding indicative of invasive cancer is the presence of atypical vessels (Figs. a–c). Due to neovascularization meandering vessels may assume a curved, corkscrew- or j-shaped appearance. Abnormal branching and differences in caliber are encountered. Mesh-like, comma-shaped capillaries should be distinguished from non-cancerous capillaries caused by atrophy.

Another colposcopic finding, indicative of invasive cancer, is the yellow-orange color due to necrosis and neovascularisation.

Applying Chrobak’s test, which breaks into cancerous tissue, confirmation of diagnosis is facilitated.

Cytology
The domain of cytologic screening is secondary prevention and, accordingly, is aimed at confirming a diagnosis of precancer. Presence of blood, superinfection and necrosis may impede sampling of representative cellular material. In only 50% of women with invasive cervical cancer, tumor cells are yielded from the cytologic smear. A diagnosis of invasive cancer is suggested if the cytologic smear reveals tumor cells that exhibit enlarged, hyperchromatic nuclei of variable size, as illustrated in the lower cytophotogram of invasive squamous cell cancer. The nucleus indicated by a blue arrow, is three times larger than the adjacent nuclei. A pathognomonic sign suggestive of invasive cancer, is a ‘dirty’ background caused by protein deposits (red arrow) shown in the upper cytophotogram.

Histology
Histologic evaluation of malignant cervical tumors is based on the most recent WHO Classification (see page 20). Among this entity, squamous cell carcinoma, adenocarcinoma and neuroendocrine tumors are the principal cancers seen in routine clinical practice.
Histology – Keratinizing Squamous Cell Carcinoma
Squamous cell cancers, either keratinizing or non-keratinizing, account for 70 to 80% of cancers. The histophotogram shows a keratinizing, highly differentiated squamous carcinoma. ‘Pearls of keratin’ are indicated by blue arrows.

Histology – Undifferentiated, Nonkeratinizing Squamous Cell Carcinoma
Shown on this histophotogram is an undifferentiated, non-keratinizing squamous cell carcinoma. Note the strand of tumor cells (red arrow) and stroma (blue arrow).

Histology – Invasive Adenocarcinoma
Invasive adenocarcinoma account for 20 to 30% of invasive cervical cancers, the rate of which is constantly on the rise. The histophotogram shows a moderately differentiated adenocarcinoma with abnormal growth pattern and cellular abnormalities.

Histology – Neuroendocrine Carcinoma
The rare, but aggressive neuroendocrine form accounts for less than 1% of cervical cancers. Immunohistochemical detection of specific markers such as neuron-specific enolase and chromogranin is essential to confirm diagnosis and to initiate the correct therapy which is a combination of surgery, radiation and chemotherapy.
3.2 Staging

The extent of disease is described by the FIGO and TNM classification systems.

Extent of Disease
Assessment of the extent of disease should be based on laparoscopic staging, which includes sampling of lymph nodes and histopathological evaluation, as well as inspection of abdominal cavity, bladder, ureter, cul-de-sac and rectosigmoid for tumor involvement.

Patterns of Proliferation
Cervical cancer has been shown to spread by four patterns of proliferation:
- Via direct continuous growth into cervical stroma, corpus, vagina, parametrium, bladder and/or rectum.
- Via lymphatic vessels into the pelvic and/or para-aortic lymph nodes.
- Via blood vessels into lungs, liver and/or bones.
- Via transperitoneal growth into the abdominal cavity.

Four different stages are defined, with tumor limited to the cervix in Stage I, vaginal and/or parametrial extension in Stage II, extension to the lateral pelvic wall and/or lower third of vagina in Stage III, and finally beyond the pelvis or to adjacent organs, such as bladder and/or rectum in Stage IV.

Stage I
For clinical staging, the FIGO system is used while the TNM system is applied for surgical-histopathologic staging. In stage I, the tumor is limited to the uterine cervix and, if invading at least 5 mm and/or extending over at least 7 mm, classified as stage IB.

Histological Stage IA1
By definition, a stage IA1 stromal invasion is less than 3 mm in size. Diagnosis can only be based on tissue excised from the cervix. The histophotogram shows cervical glands occupied by atypical cells, consistent with CIN III. The red arrows indicate an area of microinvasion surrounded by lymphocytic infiltration.
Surgical Specimen Stage IB2

Shown on the lower macroscopic image is a surgical specimen obtained as a result of radical hysterectomy with bilateral salpingo-oophorectomy (BSO). The uterine fundus is indicated by the red arrow. The tumor in the close-up view (above) has a diameter of 9 cm. This large tumor is clearly an indication for primary chemoradiation. However, taking into account that a neuroendocrine carcinoma was diagnosed, surgery was performed prior to initiating chemotherapy using cisplatin and etoposide in conjunction with external beam radiotherapy.

Stage II

In Stage II, the tumor transgresses the boundaries of the uterine cervix and invades the inner part of parametrium and / or upper part of vagina.

<table>
<thead>
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<th>TNM</th>
<th>FIGO</th>
<th>Description</th>
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<tr>
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<td>II</td>
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<td>IIA</td>
<td>Tumor without parametral invasion</td>
</tr>
<tr>
<td>T2a1</td>
<td>IIA1</td>
<td>Clinically visible lesion ≤ 4.0 cm in greatest dimension</td>
</tr>
<tr>
<td>T2a2</td>
<td>IIA2</td>
<td>Clinically visible lesion &gt; 4.0 cm in greatest dimension</td>
</tr>
<tr>
<td>T2b</td>
<td>IIB</td>
<td>Tumor with obvious parametral invasion</td>
</tr>
</tbody>
</table>


Stage III

In Stage III, the tumor has infiltrated the parametrium all the way to the lateral pelvic wall and / or involves the lower third of vagina.

<table>
<thead>
<tr>
<th>TNM</th>
<th>FIGO</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3</td>
<td>III</td>
<td>Tumor extends to the pelvic wall and / or involves lower third of the vagina and / or causes hydronephrosis or non-functioning kidney</td>
</tr>
<tr>
<td>T3a</td>
<td>IIIA</td>
<td>Tumor involves lower third of the vagina, but without extension to the pelvic wall</td>
</tr>
<tr>
<td>T3b</td>
<td>IIIB</td>
<td>Extension to the pelvic wall and / or causes hydronephrosis or non-functioning kidney</td>
</tr>
</tbody>
</table>


Pyelogram of Ureteral Obstruction

The intravenous pyelogram of a patient with Stage III disease shows ureteral obstruction on the right side prior to and after transvesical placement of a double-J stent.

Paradoxically, findings based on sonography, MRI, CT, PET-CT or laparoscopy cannot be used to redefine a clinically based FIGO stage.
Stage IV

In Stage IVA, adjacent organs, such as bladder and / or rectum, are invaded by tumor. Distant metastases to liver, lungs or bones are classified as stage IVB.

Rules for Staging of Cervical Cancer according to FIGO

Cervical cancer is the only gynecological cancer that is staged with the FIGO system according to clinical findings. Clinical examination, X-ray examinations such as i.v. urogram, contrast enema, bone scan, histologic results of biopsy, conization, hysteroscopy, endocervical curettage and cystoscopy or rectoscopy are accepted.

Findings derived from sonography, MRI, CT, PET-CT or laparoscopy cannot be used to redefine a clinically established FIGO stage.

A stage that has been assigned to a patient on the basis of clinical findings, cannot be changed later as new clinical or histologic findings crop up. If there is discrepancy on stage assignment arising from differing assessments of various examiners, automatically the lower stage is recorded as reference.

Laparoscopic Staging

Surgical staging has replaced FIGO staging because tumor involvement of lymph nodes, bladder, rectum or abdominal cavity are independent predictive factors that need to be considered when defining the optimal individualized disease-based therapy for each patient. Laparoscopy is the ideal surgical technique to reach this goal.

Involvement of the Bladder

Not amenable to detection by cystoscopy or rectoscopy, incipient tumor invasion of the bladder wall, noticeable as retraction during laparoscopy (red arrow), is subsequently confirmed by histopathological evaluation of the biopsy sampled from the supracervical septum. In this patient, cystoscopy was normal, which proves that laparoscopic evaluation is more accurate. The biology of the tumor is consistent with Stage IVa disease.

Staging of Cervical Cancer according to FIGO Classification System

Above Stage Ib, cervical cancer is staged clinically:

- only results of bimanual examination, cystoscopy, rectoscopy, biopsy or conization and X-ray (i.v. urogram, chest X-ray) are accepted.
- results of CT, PET-CT, scintigraphy, lymphography, MRI and/or laparoscopy are not allowed to redefine a clinically established FIGO stage.

Laparoscopic Staging

- Lymph nodes
- Invasion of bladder and / or rectum
- Intraabdominal tumor spread

Involvement of Rectal Pillar
This intraoperative panoramic view demonstrates tumor infiltration of the right rectal pillar (red arrows). Note the presence of atypical vessels. Cytologic analysis of washings obtained from the cul-de-sac confirmed the presence of tumor cells and provided evidence of spread into the abdominal cavity.

Involvement of Cervical Wall
In this patient, there is serosal infiltration from a tumor involving the posterior cervical wall. Atypical vessels can be seen (red arrow). Even though the clinical stage is IB1, the biology of underlying disease is quite different from that usually found in patients diagnosed with this stage, because the fluid from the cul-de-sac (blue arrow) contains tumor cells, suggestive of intraabdominal spread.

Positive Pelvic Lymph Nodes
Tumor involvement of pelvic lymph nodes (red arrows) missed by imaging modalities is detected laparoscopically at the left iliac bifurcation. Removal of positive lymph nodes prior to initiating primary chemoradiation therapy has been found to improve the patient’s prognosis.

Removal of Positive Lymph Nodes
This panoramic laparoscopic image was taken during removal of a positive para-aortic lymph node (red arrow). Note the inferior vena cava (blue arrow) and right common iliac artery (green arrow).
3.3 Treatment Modalities

Treatment of patients with cervical cancer constitutes a conflict between oncolgic safety and quality of life (QoL). Oncologic safety and QoL do not exclude each other but should be merged in an individualized disease-based therapeutic concept, the cornerstone of which is laparoscopic histopathology-based staging. Interdisciplinary counseling between gynecologists, radio-oncologists, pathologists, medical oncologists, and psychooncologists is designed to fashion a highly appropriate treatment plan that matches the needs of each individual patient. Age, comorbidity, and health status, lymph node status, grading, tumor size, lymphovascular space involvement, proliferation index, pattern of tumor spread, and reproductive status must be considered in order to define an individualized scheme of therapy. Recommendations of the interdisciplinary council are based on these findings, which may comprise surgery or chemoradiation alone or a combination of surgery, radiation and/or chemotherapy.

CxCa Stage IA1

Patients with tumors of less than 3 mm in depth and no wider than 7 mm (without invasion of lymphovascular space) seeking parenthood should be treated by loop excision and sentinel lymphadenectomy.

Simple hysterectomy and sentinel lymphadenectomy (LN) is feasible in patients who do not seek parenthood. In the presence of lymphovascular space involvement, radical hysterectomy and sentinel LN should be performed whereas in patients who wish to preserve childbearing potential, radical vaginal trachelectomy (RVT) and sentinel LN are indicated. If the sentinel lymph node harbors tumor cells, pelvic and para-aortic LN is completed and primary chemoradiation should be performed.

There is controversy whether adjuvant therapy, such as chemotherapy, is of benefit when tumor embolization is seen in blood vessels.

CxCa Stage IA2

Patients with tumors between 3 and 4.9 mm in depth and no wider than 7 mm, who do not seek parenthood, radical hysterectomy and pelvic LN based on the sentinel lymph node concept is indicated. In patients, who wish to preserve childbearing potential, pelvic LN based on the sentinel lymph node concept should be performed followed by RVT. If the sentinel lymph node harbors tumor cells, pelvic and para-aortic LN is completed and primary chemoradiation therapy should be performed.

There is controversy whether adjuvant therapy, such as chemotherapy, is of benefit when tumor embolization is seen in blood vessels.

CxCa Stage IB1

In patients not seeking parenthood, radical hysterectomy in conjunction with pelvic LN is indicated, in tumors smaller or equal to 2 cm in diameter using the sentinel concept. In patients, who wish to preserve fertility, RVT with pelvic LN should be performed. Given a tumor size of ≥ 2 cm in diameter, para-aortic LN in addition to pelvic LN is recommended. In patients with a tumor size of ≥ 2 cm and a desperate desire to have a child of their own, laparoscopic pelvic and para-aortic LN need to confirm histologically negative lymph nodes, and may be followed by adjuvant chemotherapy for 2 to 3 cycles. If tumor response leads to a diameter of less than 1 cm, RVT can be offered to the patient. If a lymph node harbors tumor cells, pelvic and para-aortic lymphadenectomy are completed and primary chemoradiation is performed.

There is controversy whether adjuvant therapy, such as chemotherapy, is of benefit when tumor embolization is seen in blood vessels.
Primary, Secondary and Tertiary Prevention of Cervical Cancer

**CxCa Stage IB2**
Surgical staging using laparoscopic pelvic and para-aortic lymphadenectomy followed by primary chemoradiation is indicated.

Surgical treatment alone – even in the presence of negative lymph nodes – is not recommended. The elevated recurrence rate associated with surgery alone would make an adjuvant chemoradiation necessary. Such a bimodal therapy will lead to increased morbidity with no gain in cure and should therefore be avoided.

There is controversy whether adjuvant therapy, such as additional chemotherapy, is of benefit when tumor embolization is seen in blood vessels.

**Algorithm for CxCa Stage IB2**

Stage IB2

Laparoscopic Pelvic and Para-aortic LN
Primary Chemoradiation

LN: Lymphadenectomy

---

**CxCa Stage II**

Laparoscopic pelvic and para-aortic lymphadenectomy followed by primary chemoradiation is the first-line treatment modality. For teletherapy and brachytherapy, MRI-based imaging techniques should be used in order to allow for an improved, individualized treatment planning.

In FIGO Stage IIA, with a small primary tumor and negative lymph nodes, radical hysterectomy with partial colpectomy in conjunction with pelvic and para-aortic lymphadenectomy may be of benefit to the patient, who should be given to understand, that vaginal length will be decreased.

There is controversy whether adjuvant therapy, such as chemotherapy, is of benefit when tumor embolization is seen in blood vessels.

**Algorithm for CxCa Stage II**

Stage II

Laparoscopic Pelvic and Para-aortic LN
Primary Chemoradiation

Tumor involves para-uterine

Tumor involves only vaginal vault

Vaginal function to be preserved

LN: Lymphadenectomy

---

**CxCa Stage III**

Following laparoscopic staging and tumor debulking of potentially involved lymph nodes, primary chemoradiation should be performed.

**Algorithm for CxCa Stage III**

Stage III

Laparoscopic Pelvic and Para-aortic LN
Primary Chemoradiation

LN: Lymphadenectomy

---

**CxCa Stage IV**

Provided the tumor is strictly confined to the small pelvis, with the bladder and/or rectum being infiltrated by cancer, primary chemoradiation or primary pelvic exenteration followed by adjuvant chemoradiation can be performed.

Pelvic exenteration is mandatory in the presence of fistula formation between tumor and bladder, rectosigmoid or small bowel.

In patients with distant metastases, primary systemic therapy – including the option of using concomitant palliative radiation – is the first-line treatment modality.

**Algorithm for CxCa Stage IV**

Stage IV

Tumor limited to pelvis

Fistula formation

Exenteration
Adjuvant chemoradiation

Tumor not limited to pelvis

Laparoscopic Pelvic and Para-aortic LN
Primary Chemoradiation or Primary Chemotherapy

LN: Lymphadenectomy
Oncologic Safety and Quality of Life

Formerly, oncologic safety and quality of life were considered competitive objectives in the treatment of women with cervical cancer: if a high degree of oncologic safety was the primary goal, surgery had to be as radical as possible and should even be combined with adjuvant treatment to improve tumor response to therapy. This paradigm of the last century has been replaced by a disease-based risk-adapted individualized treatment plan, which includes a variety of new options, such as surgical techniques that offer the benefit of sparing lymph nodes, autonomic nerve supply and fertility. The keystone of this new paradigm, that will be described in detail, is accurate histopathologic assessment of the biology of disease, underpinned by laparoscopic staging.

Treatment Modalities for Cervical Cancer

Among the various treatment modalities currently available for primary therapy, surgery or chemoradiation – depending on the nature of the tumor – are most widely used. Bimodal primary treatment should be avoided due to increased toxicity and no additional benefit in terms of oncological safety. If disease recurs, decision-making as to which secondary treatment should be used, is determined by the modality chosen for primary treatment. If chemoradiation has not been used in the first place, it may be implemented as secondary therapy, whereas surgery always remains a last resort.

Treatment Modality Depends on Extent of Disease

Laparotomy or open surgery for the treatment of patients with cervical cancer should be considered as obsolete. Therefore, as a matter of principle, laparoscopic staging is performed in every patient, independent of clinical tumor stage, except for patients presenting with distant metastases. Accordingly, the patient can be scheduled for surgery or primary chemoradiation. Laparoscopic lymphadenectomy is based on the sentinel lymph node concept in patients with a tumor diameter of ≤ 2 cm. If lymph nodes are negative and the tumor is confined to the cervix and ≤ 4 cm in diameter, radical hysterectomy is indicated. In this way, bimodal therapy (radical hysterectomy in conjunction with adjuvant chemoradiation) can be avoided in more than 90% of women treated by surgery used as single-modality primary therapy.

Today, radical hysterectomy is only used in the context of a nerve-sparing technique, where hypogastric and pelvic plexus serve as anatomical landmarks.

Women with cervical cancer, who wish to preserve childbearing potential, may undergo radical trachelectomy with preservation of the uterus, provided the tumor is ≤ 2 cm in size. Given a tumor width of > 2 cm in diameter and a biopsy-proven negative histopathological status of lymph nodes, neoadjuvant chemotherapy in conjunction with trachelectomy can be attempted to preserve fertility. In patients with a tumor size of ≤ 2 cm, radical lymphadenectomy can be replaced by the sentinel lymph node concept under study conditions. In patients with positive lymph nodes and / or a tumor diameter of ≥ 4 cm, primary chemoradiation is the first-line treatment modality. Debulking of positive lymph nodes during laparoscopic staging – which should be performed prior to chemoradation – can have a beneficial impact on survival.
Surgery Versus Chemoradiation as Primary Therapy for Stage I Disease

Comparing both modalities reveals equal efficacy, however with different side-effects. In surgery, ovarian and vaginal functions are well preserved and intraoperative injuries to bladder, ureter, vessels or rectum can be repaired without negative sequelae if recognized and treated in a timely fashion. Brachytherapy is associated with considerable morbidity of the vagina. Therefore, in stage I disease and negative lymph nodes, surgery is the first-line treatment modality for sexually active, not morbidly obese patients. Older patients with medical disorders or obesity can profit from primary chemoradiation.

### Surgery Versus Chemoradiation for Primary Therapy of Patients with Stage I Disease

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>Chemoradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>85%</td>
<td>85%</td>
</tr>
<tr>
<td>Fistulae</td>
<td>1 – 2%</td>
<td>1.4 – 5.3%</td>
</tr>
<tr>
<td>Vaginal function</td>
<td>preserved</td>
<td>Fibrosis, stenosis</td>
</tr>
<tr>
<td>Ovarian function</td>
<td>preserved</td>
<td>50% preservation by ovaripexy</td>
</tr>
<tr>
<td>Long-term morbidity</td>
<td>3%</td>
<td>6 – 8%</td>
</tr>
<tr>
<td>Indication</td>
<td>QI &lt; 40, fit for anaesthesia</td>
<td>All patients</td>
</tr>
<tr>
<td>Mortality</td>
<td>1%</td>
<td>&lt; 1%</td>
</tr>
</tbody>
</table>

QI: Quetelet index

### Areas of Laparoscopic Lymphadenectomy

- **red** = infrarenal left
- **black** = left inframesenteric
- **green** = right para-aortic
- **violet** = pelvic
- **yellow** = parametric
- **blue** = cysterna chyli

### Laparoscopic Lymphadenectomy

Laparoscopic lymphadenectomy can be performed in all retroperitoneal pelvic, para-aortic and peri-renal areas amenable to open surgery. Compared to open surgery, the number of lymph nodes harvested is the same, the rate of peri- and postoperative complications is lower, mean duration of surgery is longer, postoperative admission is reduced, and quality of life is improved. Therefore, the current recommendation opts for a laparoscopic approach.

Via laparoscopic staging, up to 87% of patients are up-staged mainly on the basis of their lymph node status, and in up to 45% of patients, the therapy plan initially proposed needs to be modified.

### Para-aortic Lymphadenectomy

This E-Learning Module provides a step-by-step guide to laparoscopic para-aortic lymphadenectomy in the style of a surgical atlas with many accompanying schematic drawings and video clips.
- In patients with tumor size of more than 2 cm.
- In patients with positive pelvic lymph nodes.
- Challenging procedure in patients with a body mass index above 30.
- Due caution required to prevent iatrogenic vascular injury.
Tumor-involved Para-aortic Region Prior and After Laparoscopic Debulking

In a patient with a squamous cell carcinoma of the cervix (FIGO stage IB2), the upper para-aortic region is completely encased by tumor-involved lymph nodes. The duodenum is elevated using an alligator forceps (a).

Following laparoscopic debulking of lymph nodes (b), aorta with inferior mesenteric artery, vena cava with left renal vein and right ovarian vein come into view. Debulking has been found to enhance success of therapy and cure rates are comparable to patients who are diagnosed with micrometastatic lymph node involvement.

Pelvic Lymphadenectomy

This E-Learning Module provides a step-by-step guide to laparoscopic pelvic lymphadenectomy in the style of a surgical atlas with many accompanying schematic drawings and video clips.

- Indication independent of tumor size.
- Sentinel lymph node concept applicable given a tumor size of less than 2 cm.
- Independent of body mass index.
- Due caution to be taken to prevent iatrogenic injury to vessels and nerves.

Sentinel Lymph Node Concept

In more than 90% of lymph nodes harvested from patients diagnosed with cervical cancer, a tumor-free status is confirmed by histopathological assessment. Accordingly, the majority of these lymph nodes are removed without any oncological benefit. In fact, lymph node removal may even adversely affect the patient’s condition considering that postoperative morbidity rate following radical lymphadenectomy – mainly related to lymphedema – has been found to reach 40%. Therefore, a lymph node concept that is based on a few selected lymph nodes with highest risk of tumor involvement, i.e., the sentinel lymph nodes, can be used in patients with early-stage cervical cancer by adequately trained gynecologic surgeons. The intraoperative situs shows a blue-stained sentinel lymph node with efferent lymphatic vessels at the right iliac bifurcation.

SLN Concept and Tumor Size in Cervical Cancer

Quality-of-life can be improved for 82 out of 100 patients with a tumor diameter ≤ 2 cm at the cost of one case diagnosed with a false-negative result. In this woman, recurrence must be detected as early as possible by meticulous evaluation of follow-up examinations. In patients with larger tumors the rate of false-negative outcomes is too high and sentinel lymphadenectomy alone is too risky.

### Multicenter Validation Study of the Sentinel Lymph Node (SLN) Concept in Cervical Cancer

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Tumor size ≤ 2 cm</th>
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</thead>
<tbody>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>SLN detected</td>
<td>89</td>
<td>94</td>
</tr>
<tr>
<td>Positive lymph nodes</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>SLN correct positive</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>SLN false negative</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Profit from SLN concept</td>
<td>65</td>
<td>82</td>
</tr>
</tbody>
</table>

Radical Hysterectomy – History

Metastases of cervical cancer spread primarily into the adjacent connective tissue, that is to say, the parametrium, either directly or by encroaching on lymph vessels or parametrial lymph nodes along the pelvic or abdominal blood vessels. These facts became evident at the end of the 19th century and it was concluded that simple hysterectomy alone was insufficient for curative treatment. Therefore, J.G. Clark (1867–1927) in the USA, and F. Schauta (1849–1919) and his disciple E. Wertheim (1864–1920) from Austria established radical hysterectomy, which included resection of parametrial tissue. The historical reprint shows the original surgical specimen of Schauta’s first radical vaginal hysterectomy. The parametria are marked by red arrows.

Schauta’s procedure is done transvaginally while Wertheim’s operation uses the transabdominal route. Owing to an inherently lower infection rate in the preantibiotic era, Schauta’s procedure enjoyed more widespread acceptance at the beginning of the 20th century. Walter Stoeckel (1871–1961), former chairman of gynecology at the Charité University Hospital (Berlin, Germany), modified and improved Schauta’s approach in the 30s of the 20th century. However, as it became increasingly clear that removal of lymph nodes was of prognostic value and therapeutic benefit for the patient – while considering that a transvaginal approach does not allow systematic lymphadenectomy – use of the transabdominal approach prevailed for many years. It was only after the introduction of laparoscopic lymphadenectomy in the 1980s, that laparoscopic-vaginal techniques for radical hysterectomy lead to a renaissance of Schauta’s procedure.

History of Classification Systems

Several classification systems describing the extent or radicality of hysterectomy have been defined over the years, such as type I–V according to Rutledge and Piver or type A–D according to Querleu and Morrow.

This coronary schematic sectional diagram shows the outer boundaries of resection for radical trachelectomy (inner black line), type II radical hysterectomy (middle black line) and type III radical hysterectomy (outer black line).

However, the practical value of the above classification systems is limited because nowadays radical hysterectomy is geared to the use of anatomical landmarks such as the autonomic nerves which allows to resect all parametrial tissue at risk while at the same time preserving functional integrity of pelvic organs.

Specimens After Radical Hysterectomy

The extent of surgical resection of the parametrial tissue varies with the type of radical hysterectomy: the adjacent surgical specimens are the result of a type II radical hysterectomy (a), and a type III radical hysterectomy (b). The yellow arrows indicate the parametrial line of resection. Both specimen were harvested in the pre-nerve-sparing period and are a result of laparoscopic-assisted radical vaginal hysterectomy (LARVH). Autonomic nerve fibers that travel through the lateral parametrium are of significant importance for the nerve supply of pelvic viscera. During a standard type III radical hysterectomy, these fibers are partially transected, which results in an increased morbidity rate due to functional impairment of bladder, rectum or vagina. Note the striking resemblance of the type II specimen (a) to the first specimen of Schauta, shown above.
Techniques of Radical Hysterectomy Currently in Use

For patients with FIGO stage I and histologically confirmed negative status of lymph nodes (LN), surgery is the first-line treatment option. Radical hysterectomy is defined as removal of uterus including the surrounding parametrial tissue. This type of surgery can have a detrimental effect on bladder, vagina, and/or rectum, since autonomic nerves in the parametrium can be damaged. Accordingly, nerve-sparing techniques are clearly preferable.

Eight different techniques for radical hysterectomy are currently in use, which can be done by a laparoscopic, laparoscopic-vaginal, or by an open surgery approach.

This is the classic Wertheim Meigs operation and the open total mesometrial resection (TMMR), total laparoscopic or robotic assisted radical hysterectomy and a combined nerve-sparing laparoscopic vaginal approach with emphasis either on the laparoscopic or vaginal part of the procedure. The author holds the opinion, that an open surgery approach is a largely obsolete treatment option that belongs to the last century.

The author and colleagues clearly prefer a combination of laparoscopy with transvaginal surgery. Accordingly, we achieve a synergetic use of the benefits inherent to each approach. Over the years, the overall design of the technique involved has been updated by extending the laparoscopic part while reducing the transvaginal part.

Laparoscopic-Assisted Radical Vaginal Hysterectomy (LARVH)

This E-Learning Module provides a step-by-step guide to laparoscopic-assisted radical vaginal hysterectomy (LARVH) in the style of a surgical atlas with many accompanying schematic drawings and video clips.

- Similar to Schauta operation.
- Key stage of the procedure: identification of ureter.
- Risk of iatrogenic injury to ureter and bladder.
- Autonomic nerves not identified.

Nerve-Sparing Vaginal-Assisted Laparoscopic Radical Hysterectomy (VALRH)

In nerve-sparing radical hysterectomy, the integrity of the autonomic nerve supply to rectum, bladder, ureter and vagina must be preserved. This is accomplished by identifying first the course of the hypogastric nerve and making sure that exclusively tissue located medial to it is resected. In this way, only nerves supplying the uterus are transected and removed together with the parametrial tissue.

Legend: Hypogastric nerve (blue arrow), sympathetic chain (red arrow), pelvic splanchnic nerves (black arrow). The blue line is the resection margin.
Nerve-Sparing Vaginal-Assisted Laparoscopic Radical Hysterectomy (VALRH)

This E-Learning Module provides a step-by-step guide to nerve-sparing vaginal-assisted laparoscopic radical hysterectomy (VALRH) in the style of a surgical atlas with many accompanying schematic drawings and video clips.

- Short vaginal phase.
- Reduced risk of iatrogenic injury to ureter and bladder.
- Autonomic nerves identified and spared.
- Complete mesometrial resection.

Radical Hysterectomy and Survival in Stage I Disease

Women with a primary tumor of less than 4 cm in diameter, histopathology-proven negative lymph nodes and no concomitant tumor cell invasion in blood and lymphatic vessels have an overall survival of 98% following combined laparoscopic vaginal radical hysterectomy. In this study, only a few patients underwent adjuvant therapy, and therefore, they are considered ideal candidates for pure surgical treatment.

Similar data were recorded in 123 patients who underwent nerve-sparing radical hysterectomy, of which 111 were diagnosed with cervical cancer: the recurrence rate was 4.9%.

Laparoscopic Staging Helps to Avoid Bimodal Therapy

Radical hysterectomy followed by adjuvant chemoradiation, also termed 'bimodal therapy', should be avoided due to increased morbidity. Based on data obtained from 401 patients with primary cervical cancer, laparoscopic staging was capable of identifying surgery as the best-suited treatment option, a result which was later confirmed in 90% of patients, who did not receive adjuvant treatment. However, microscopic parametrial involvement, tumor-infiltrated resection margins, and/or micrometastatic encroachment on lymph nodes cannot be ruled out pre- and intraoperatively. For these reasons, even patients who have been staged laparoscopically may need adjuvant therapy in up to 10% of cases.

Bimodal Therapy in Patients With Cervical Cancer

- 39 of 401 patients needed bimodal therapy
- Vaginal R1 resection was confirmed in 6 patients, Rx resection in 6 patients
- Positive lymph nodes reported in 10 patients (parametrium n = 3, pelvic n = 5, para-aortic n = 1, pelvic and para-aortic n = 1) with pN1 in 5 patients and pN0i+ in 5 patients
- Microscopic parametrial involvement in 12 patients
- V1 in 8 patients, L1 in 21 patients

Randomized Study – VARRH versus VALRH

In a randomized study conducted on 48 patients with primary cervical cancer, the outcomes of vaginal-assisted robotic radical hysterectomy (VARRH) were compared with those of vaginal-assisted laparoscopic radical hysterectomy (VALRH). Both groups were comparable in terms of age, BMI and Karnofsky index. There was significant difference with respect to duration of surgery and set-up time, favoring laparoscopy. Blood loss, number of lymph nodes harvested and duration of hospital stay were similar in both groups as well as complication rate. However, thermal injuries to the ureter were only observed in two patients treated by VARRH. Recurrence rate was identical, with two patients in each group. It is therefore concluded that robotic assistance does not provide an advantage in this setting and only increases costs.
The ‘Dargent Operation’
Another option to improve quality of life especially for women with early-stage cervical cancer and a desire for childbearing, is preservation of fertility by radical vaginal trachelectomy, also known as ‘Dargent operation’ named after Daniel Dargent (1937–2005), its inaugurator. To date, this treatment option has constantly gained in importance because the mean age of pregnant women in the Western world is still on the rise, which is reflected by an increasing number of nulliparous women diagnosed with cervical cancer.

Radical Vaginal Trachelectomy
Radical vaginal trachelectomy comprises en bloc removal of about two thirds of the uterine cervix, which is resected with approximately half of the parametrial tissue. As shown in the coronary sectional diagram, the extent of resection is highlighted by a red oval. On each side a blue sentinel lymph node is shown in its typical location. Following resection, the vaginal cuff is readapted to the remaining cervical portion.

The final decision as to whether radical trachelectomy is indeed indicated or simple trachelectomy or even conization is deemed sufficient, remains unclear in most patients with small-volume disease, since only in 7% of parametrial tissue obtained from radical vaginal trachelectomy (RVT) specimens, lymph nodes can be detected.

Indication for Radical Vaginal Trachelectomy
In patients diagnosed with cervical cancer who have a desire for childbearing, radical vaginal trachelectomy with the potential of preserving fertility is indicated if the following major eligibility criteria are met:
- Tumor size of \( \leq 2 \) cm.
- Histopathologically negative lymph nodes
- Tumor removal achieved with sound margins
- No signs of tumor encroachment on blood vessels.

Radical Vaginal Trachelectomy (RVT)
This E-Learning Module provides a step-by-step guide to vaginal radical trachelectomy (RVT) in the style of a surgical atlas with many accompanying schematic drawings and video clips.
- Temporary clipping of uterine arteries decreases blood loss.
- Key stage of the procedure: identification of the ureter.
- Prophylactic cerclage performed.
- Endocervical mucosa everted.
Literature Review on Oncological Outcome After RVT

<table>
<thead>
<tr>
<th>RVT</th>
<th>n</th>
<th>Median follow-up (months)</th>
<th>Recurrence Rate %</th>
<th>Death Rate %</th>
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<tbody>
<tr>
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<td>118</td>
<td>95 (31–234)</td>
<td>7 (5.9%)</td>
<td>5 (4.2%)</td>
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<td>Plante</td>
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<td>60 (5–145)</td>
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<td>Shepherd</td>
<td>112</td>
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<td>Covenos</td>
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<td>Dargent</td>
<td>95</td>
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<td>109</td>
<td>76 (4–178)</td>
<td>4 (3.6%)</td>
<td>3 (2.7%)</td>
</tr>
<tr>
<td>Burnett</td>
<td>21</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lanowska</td>
<td>212</td>
<td>37 (0–171)</td>
<td>8 (3.8%)</td>
<td>4 (1.9%)</td>
</tr>
<tr>
<td>Einstein</td>
<td>28</td>
<td>25</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Fertility Outcome After RVT

<table>
<thead>
<tr>
<th>n</th>
<th>First Trimester Losses</th>
<th>Second Trimester Losses</th>
<th>Delivery (weeks)</th>
<th>Ongoing Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>24–28</td>
<td>29–32</td>
</tr>
<tr>
<td>Schlaerth</td>
<td>10</td>
<td>4/4</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Burnett</td>
<td>21</td>
<td>3/3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dargent</td>
<td>47</td>
<td>25/18*</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Shepherd</td>
<td>158</td>
<td>88/31</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td>Plante</td>
<td>72</td>
<td>50/31</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Hertel</td>
<td>100</td>
<td>18/unknown</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Speiser</td>
<td>212</td>
<td>60/75</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

First trimester losses include abortions, terminations and ectopic pregnancy.

Laparoscopic Cerclage

- After multiple conizations.
- After trachelectomy with size of cervix less than 1 cm.
- After miscarriage.
- Uterine artery needs to be identified and spared.

Saling Procedure – Early Total Cervical Occlusion (ETCO)

- Performed in conjunction with abdominal cerclage.
- Performed on a pregnant uterus.
- No evidence of pathologic vaginal microorganisms.
- Deepithelialization by use of CO2 laser.

Oncological Outcome after RVT

In a literature review based on a total number of more than 1,000 patients treated by radical vaginal trachelectomy (RVT), oncological outcomes are expressed as recurrence rates and death rates, ranging between 0 and 7.5%, and 0 and 4.3%, respectively. In the largest mono-institutional series of 212 patients, recurrence rate is 3.8% and death rate is 1.9%.

Fertility Outcome After RVT

In more than 700 patients subjected to radical vaginal trachelectomy, fertility outcome was studied. Pregnancy and delivery rates showed a considerably degree of variation between the different cohorts. In the largest study based on 212 patients, only half of the women were seeking parenthood, resulting in 60 pregnancies and only 3 very early premature deliveries before gestational week 29. The high rate of premature labor remains a major concern after RVT with 30% of deliveries prior to 32nd gestational week and 10% prior to 28th week.
Neoadjuvant Chemotherapy Followed by RVT

- Still an experimental procedure, only in studies.
- 2–3 cycles of chemotherapy.
- Tumor response to < 1 cm in diameter is ideal.
- Laparoscopic stage of the procedure is challenging.

Fertility Preservation in Patients with Tumor $\geq 2$ cm

Women with cervical cancer of $\geq 2$ cm in diameter, seeking parenthood, are offered the chance for preserving fertility following neoadjuvant chemotherapy and subsequent radical or simple trachelectomy or conization. The results of less than 50 patients have been reported in the literature with a recurrence rate of 2.1% and a pregnancy rate of almost 40%. For safety reasons, the eligibility criteria ‘laparoscopic staging’ and ‘histology-proven negative lymph nodes’ should also be met prior to initiating a fertility-sparing approach and all patients need to be treated and followed up in a prospective study. Tumor response is monitored best by use of videocolposcopy. A tumor size not exceeding 10 mm in diameter after neoadjuvant chemotherapy seems to confer a more favorable prognosis of cure.

Cervical Cancer in Pregnancy

Colposcopic image of a cervical cancer in a woman at 3 weeks post partum, unrecognized during pregnancy and vaginal delivery.

Cervical cancer is the most frequent malignancy in pregnancy with an incidence of 1 in 2000. Especially in the second trimester, the balance between oncologic safety for the mother and preservation of child is challenging. Therapy depends on the stage of disease, lymph node status, age of pregnancy, and most importantly, the decision-making of the future mother and father. Up to 24th week of gestation, laparoscopic lymphadenectomy can be performed to yield significant findings on the biology of disease. Favero et al. submitted 19 patients with a median gestational age of 18 weeks to laparoscopic lymphadenectomy in whom an average number of 17 lymph nodes was removed.

Laparoscopic Lymph Node Dissection Prior to Neoadjuvant Chemotherapy Followed by RVT

<table>
<thead>
<tr>
<th>Author</th>
<th>Tumor size prior to treatment (cm)</th>
<th>NACT</th>
<th>Tumor size after treatment</th>
<th>Amount of PLN</th>
<th>Surgery</th>
<th>Recurrences</th>
<th>Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kobayashi</td>
<td>3</td>
<td>cis + bleo + vin + mito</td>
<td>0</td>
<td>none</td>
<td>conus</td>
<td>0/1</td>
<td>1/1</td>
</tr>
<tr>
<td>Plante</td>
<td>2, 2, 3, 4</td>
<td>tax + ifos + cis</td>
<td>0, 0, 0</td>
<td>21, 18, mm</td>
<td>RVT + PLND</td>
<td>0/3</td>
<td>3/3</td>
</tr>
<tr>
<td>Liu</td>
<td>2</td>
<td>cis + bleo</td>
<td>0.5</td>
<td>nm</td>
<td>ART + PLND</td>
<td>0/1</td>
<td>1/1</td>
</tr>
<tr>
<td>Rob</td>
<td>range 1.5–4.4</td>
<td>cis + ifos or cis + doxo for adeno</td>
<td>range 0–1.3</td>
<td>range 15–31</td>
<td>trach + PLND</td>
<td>1/7</td>
<td>3/7</td>
</tr>
<tr>
<td>Mannino</td>
<td>range 1–3</td>
<td>tax + ifos + cis or tax + epi + cis for adeno</td>
<td>range 0–&gt; 0.3</td>
<td>nm</td>
<td>conus + PLND</td>
<td>0/16</td>
<td>6/16</td>
</tr>
<tr>
<td>Robova</td>
<td>1.5, 2, 2.1, 3, 4</td>
<td>cis + ifos or cis + doxo for adeno</td>
<td>0.05, 0, 1.3, 0.2, 0</td>
<td>22, 16, 22, nm, 20</td>
<td>trach + PLND</td>
<td>0/5</td>
<td>2/5</td>
</tr>
<tr>
<td>Palaia</td>
<td>&gt; 2</td>
<td>tax + ifos + cis</td>
<td>0</td>
<td>none</td>
<td>trach + PLND</td>
<td>0/1</td>
<td>0/1</td>
</tr>
<tr>
<td>Marchiekie</td>
<td>range 3–4.5</td>
<td>tax + ifos + cis or tax + epi + cis for adeno</td>
<td>range 0–2.4</td>
<td>range 8–53</td>
<td>RVT + PLND</td>
<td>0/7</td>
<td>1/7</td>
</tr>
<tr>
<td>Vercellino</td>
<td>range 2.3–4</td>
<td>tax + ifos + cis, 1 patient cis + tax</td>
<td>range 0–2</td>
<td>range 12–43</td>
<td>RVT + LPPLND</td>
<td>0/6</td>
<td>1/6</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1/47 (2.1%)</td>
<td>18/47 (38.3%)</td>
</tr>
</tbody>
</table>

NACT = neoadjuvant chemotherapy, RVT = radical vaginal trachelectomy, ART = abdominal radical trachelectomy, trach = simple trachelectomy, conus = conization, bleo = bleomycin, tax = paclitaxel, cis = cisplatin, doxo = doxorubicin, ifos = ifosfamide, epi = epirubicin, mito = mitomycin, vin = vincristine, adeno = adenocarcinoma, nm = not mentioned, PLN(D) = pelvic lymph node (dissection), LPPLND = laparoscopic pelvic and paraaortic lymphnode dissection.

nodes were removed. In 3 patients, positive lymph nodes were found and 16 children could be saved until vital. Accordingly, in most patients, pregnancy can be prolonged until fetal maturity is achieved. Neoadjuvant chemotherapy can be used safely to prolongate the duration of pregnancy. Definitive treatment of pregnant patients with cervical cancer in terms of surgery or chemoradiation is identical to non-pregnant patients, however with the modification that radical surgery is usually combined with caesarean section.

**Lymphadenectomy at 16th Week of Gestation**
- Cervical cancer in pregnancy.
- Lymph node staging mandatory.
- Technique identical to the one used in non-pregnant patients.
- Size of uterus needs to be determined preoperatively.

**Lymphadenectomy at 22nd Week of Gestation**
- Lymph node staging is mandatory.
- Challenging technique.
- Size of uterus needs to be determined preoperatively.
- Increased weight of uterus facilitates exposure.

**Unrecognized Cervical Cancer Treated by Simple Hysterectomy**
Approximately 1% of cervical cancers are preoperatively missed and patients are treated by simple hysterectomy for abnormal bleeding, which in fact is due to cervical cancer. Several scenarios are noted:
- Microinvasive cancer of FIGO stage IA1 without lymphovascular invasion.
- Tumor limited to the cervix, negative resection margins (R0).
- R1 situation.
- R2 situation.

Secondary treatment should be started by laparoscopic staging of lymph nodes and peritoneal cavity. If there is a risk of parametrial invasion or vaginal cuff involvement, which can be cured surgically, laparoscopic-vaginal radical parametrectomy should be performed. If surgery proves to be insufficient, secondary chemoradiation is the first-line treatment option. However, radical parametrectomy obviates the need for chemoradiation in 80% of patients. The schematic diagram shows the resected parametrial tissue (green) which includes the cardinal ligament, bladder and rectum pillar and a vaginal cuff.

Treatment of Adnexae

In premenopausal women with squamous cervical cancer and negative lymph nodes, preservation of adnexae is possible. If primary chemoradiation is indicated, adnexae can be mobilized and transposed to the paracolic gutter to keep them out of the radiation field. However, only 50% of ovaries, transposed in this way, maintain endocrine function. In patients with adenocarcinoma, up to 5% of adnexae are involved by tumor. Therefore, the adnexae should be either removed or subjected to chemoradiation. In patients seeking parenthood and undergoing chemoradiation, oocytes or ovarian tissue can be harvested and cryopreserved prior to initiating treatment.

Oncological Safety and Quality of Life

Oncological safety and quality of life are mutually compatible objectives provided laparoscopic surgery is used for staging, sentinel lymphadenectomy, nerve-sparing radical hysterectomy or radical vaginal trachelectomy. In accordance with these premises, a disease-based, individualized treatment plan can be offered to the patient.

3.5 Radiotherapy

For patients with positive lymph nodes, a tumor diameter of more than 4 cm, or extension of disease beyond the cervix, primary chemoradiation is the first-line treatment modality. Radiation therapy alone has been replaced by weekly administration of platin-based chemotherapy. Teletherapy always needs to be combined with brachytherapy. If brachytherapy cannot be performed due to tumor-related anatomic abnormality, secondary hysterectomy is indicated. Even though para-aortic lymph node metastases are classified as distant metastases, a survival rate of up to 50% is achieved by primary chemoradiation. Debulking of such tumor-involved lymph nodes in the pelvic and para-aortic area appears to be of added benefit to the patient.

Chemoradiation and Cervical Cancer

Radiotherapy for women diagnosed with cervical cancer is performed as primary therapy or used in an adjuvant setting or for treatment of recurrent disease. Primary treatment always comprises a combination of external beam radiotherapy (EBRT) to the pelvis and local brachytherapy. In case of positive para-aortic lymph nodes, extended field radiation is applied to the para-aortic region. In addition, radiotherapy should be combined with platinum-based chemotherapy in order to increase efficacy.

In chemoradiation, cisplatin is administered intravenously on a weekly basis 40 mg/m² (per body-surface area) 5 to 6 times. If cisplatin is contraindicated, carboplatin may be used. Combination with other chemotherapeutic agents increases toxicity. Entire duration of therapy should not exceed 56 days.
Primary Radiation Versus Chemoradiation

With the combination of percutaneous and intracavitary radiotherapy an effective treatment modality is available. The decision-making depends on patient-related criteria as well as on expertise and experience of the staff involved. In prospective randomized trials evidence was provided to show that - for primary treatment as well as for adjuvant treatment in the presence of risk factors - a combination of radiotherapy and chemotheraphy termed chemoradiation is superior to radiotherapy alone. By simultaneous application of platin-based chemotherapy, recurrence-free survival, disease-free survival and overall survival are improved significantly. The absolute survival benefit of platin-based chemoradiation compared with radiation therapy alone is 12 %.

Standard Tomotherapy Versus Rapid Arc

Primary radiotherapy is done following 3-D visualization and treatment planning by use of a linear accelerator, commonly in a 3- or 4-field-technique. By modern irradiation techniques such as intensity-modulated radiotherapy (IMRT), tomotherapy or volumetric-modulated arc therapy (VMAT, rapid arc) risk organs such as small bowel can be spared much better. In conventional fractionation five doses of 1.8 Gy are administered weekly for about 6 weeks up to a maximum cumulative dose of 45 to 50.4 Gy depending on the state of pelvic lymph nodes. Above this dose, the target volume has to be focused on uterus, cervix, positive lymph nodes and/or parametrium or vagina, provided there is tumor involvement. The adjacent figures demonstrate extension of the radiation field planned with standard tomotherapy and compared to VMAT.

Intracavitary Isotope Therapy (Brachytherapy)

Intracavitary brachytherapy is an integral part of a comprehensive treatment plan in that it allows to deliver an adequately sized biological dose suited for tumor eradication. By use of imaging techniques, extent and spacial configuration of the tumor is documented. The target volume comprises the cervix and adjacent parts of corpus uteri, parametrium and vagina. Organs at risk of iatrogenic injury are rectum, sigmoid colon, small bowel, urinary bladder, ureter, urethra and vagina. It is of utmost importance that dose and volume delivered to parts of adjacent organs be kept as low as possible.

To allow optimal results and to minimize toxicity, a safe and reproducible positioning of the applicator is mandatory and should be taken to the records. The relative dose of percutaneous radiation and brachytherapy as well as the onset of brachytherapy should be constantly readjusted, subject to initial tumor volume, preservation of risk organs and regression of tumor. The complete duration of radiotherapy should not exceed 56 days. Prolongation of therapy is associated with impairment of local control and survival.

Routine secondary hysterectomy following primary chemoradiation results in a better local control, but does not improve overall survival. Residual tumor following limited response or remnant of a large primary tumor should be treated surgically provided the clinical condition of the patient allows it and toxicity is tolerable. Brachytherapy should be performed under MRI-assistance due to improved tumor coverage and sparing of organs at risk.
Brachytherapy Applicator
Among the radionuclides used for gynecologic brachytherapy high-dose-rate (HDR)-Iridium 192 is the most commonly used radionuclide. For application, various systems with an intra-uterine and intra-vaginal component are in use. Pin applicators in combination with paired colpostats or ovoids are advantageous, especially with respect to dose distribution and treatment volume. The applicator shown in the adjacent image has the advantage that it can be used in conjunction with MRI. HDR-brachytherapy applicators with fixed geometry are most commonly used. The applicator should be chosen in such a manner that it allows to enclose the target volume with the calculated dose. Considering that the volume of large tumors to be treated may amount to 100 cc or more, applicators containing multiple probes should be used.

Acute Radiation Toxicity
Acute radiation toxicity comprises therapy-related side effects commonly observed within a 90-day period from the onset of treatment. Acute toxicity, relatively common and mostly reversible, is manageable by symptomatic and supportive care. Acute and chronic side effects potentially involve all adjacent organs or systems of viscera such as urinary bladder, ureter, urethra, recto-sigmoid colon, small bowel, vagina, kidneys and the lymphatic system. All side effects are correlated with the applied single and cumulative dose. Pollakisuria, urge and painful burning of micturition are common. Urinary tract infections occur especially with concomitant application of chemotherapy. Brachytherapy is associated with vaginal mucositis and increased risk of infections. The fields of percutaneous radiotherapy encompass the lymphatic system and parts of small and large bowel. Diarrhea and imperative urge to defecation are observed. In the case of extended-field radiotherapy delivered to the upper abdominal quadrant, parts of the small bowel are affected resulting in nausea, vomiting and diarrhea. If adjacent organs are tumor-infiltrated, vesicovaginal and recto-vaginal fistula may occur. Concomitant chemotherapy can have hematotoxic, nephrotoxic and/or ototoxic side effects. Constant surveillance of these organ systems is mandatory during therapy and the dosage may have to be adapted. Prior to establishing a chemoradiation schedule, liver, kidney and hearing function and blood count need to be evaluated. Rash of the vaginal skin is rather frequent whereas skin erythema within the radiation field and hyperpigmentation are rarely seen in women treated for cervical cancer. Chemoradiation leads to a higher rate of acute toxicity compared to radiation therapy alone. The rate of gastrointestinal toxicity of grade 3 to 4 is 4% following radiation and 8% following chemoradiation. The rate of late toxicity is similar for both modalities.

Acute Radiation Toxicity
- Pollakisuria
- Mucositis
- Diarrhea
- Fistula formation
- Bone marrow sequelae
- Nephrotoxic effects
- Ototoxic side effects
- Erythema
- Hyperpigmentation
Late Radiation Toxicity

- Chronic proctitis.
- Chronic cystitis.
- Contracted bladder.
- Stenosis of rectosigmoid, urethra, ureter and/or vagina.
- Hearing loss.
- Impaired kidney function.
- Lymphedema.

Chemotherapy in Cervical Cancer

- Active agents
  - Cisplatin and Carboplatin.
  - 5-Fluorouracil.
  - Irinotecan.
  - Topotecan.
  - Gemcitabine.
  - Vinorelbine.
  - Paclitaxel and Docetaxel.

Patient-Related Predictive Factors

- Young age.
- Positive HIV status.
- Comorbidity*.
- Diabetes.
- Afro-American provenience.
- Smoking.
- Thrombocytosis.
- Low hemoglobin level.
- Elevated blood pressure.
- Elevated body temperature.

* Vaginal bleeding, pain, dysuria, weight loss

Tumor-Related Predictive Factors

- Advanced-stage disease.
- Lymph node involvement.
- Large tumor size.
- Grade 3.
- Deep stromal invasion.
- Invasion of isthmus and/or corpus uteri.
- Involvement of lymphovascular and/or hemovascular space.
- Involvement of parametrium.
- Neuroendocrine type.
- Positive peritoneal washing.
- Elevated squamous carcinoma cell antigen (SCC) in squamous cancer.
- Elevated carcino-embryonal antigen (CEA) and/or CA 125 in adenocarcinoma.

Late Radiation Toxicity

Late radiation toxicity comprises therapy-associated side effects commonly observed after a 90-day period from the onset of treatment. These side effects are usually of chronic course and hardly amenable to any kind of treatment.

Typical late toxicities are chronic proctitis with recurrent rectal bleeding, chronic cystitis and decreased volume of urinary bladder, stenosis of the rectosigmoid colon, urethra, ureter, or vagina, especially following brachytherapy with chronic vaginal dryness, occlusion and dyspareunia. Late toxicity of the bowel is associated with bloating, meteorism and/or painful defecation usually starting within the first two years after treatment, whereas late toxicity related to the urogenital system may manifest much later. Chemotherapy given concomitantly to radiotherapy may lead to hearing loss and may compromise kidney function which cannot be treated causally. The rate of lymphedema is mostly mild and commonly not associated with functional impairment. Lymphedema is usually located in the lower extremities and the mons pubis and can be relieved by regular manual lymphdrainage.

3.6 Chemotherapy

In patients with primary or recurrent distal metastasis, median survival rate varies between six and nine months. For these patients, systemic therapy is an option of last resort, which in most instances may be used for palliative rather than curative intent.

Tumor response to chemotherapy is more effective in chemonai
e patients. Cisplatin monotherapy shows a response rate ranging between 20 and 30%. Between 50–100 mg/m² (of body surface area) are given in a 3-week schedule. The highest response rate of 30% is achieved with cisplatin 100 mg/m², but progression-free survival and overall survival are not improved by an elevated dose, which is associated with higher toxicity. Several other substances, such as taxane, topotecan, gemcitabine and vinorelbine have been studied in patients with metastasized or recurrent cervical cancer. A combination of cisplatin and topotecan has been shown to increase survival from 6.5 to 9.5 months at the expense of higher toxicity. Therefore, combination therapy is considered the first-line treatment option in patients with a good performance status.

3.7 Prognosis

The prognosis of each patient is subject to patient- and tumor-related predictive factors that should be used in a well-balanced manner in order to tailor a therapy which is geared to individual circumstances of the disease and considering the recurrence risk for the benefit of the patient.

Patient-Related Predictive Factors

Specific patient-related factors may be used as significant predictors of a poor prognosis.

Tumor-Related Predictive Factors

There are various tumor-related predictive factors that are indicative of a poor prognosis.
Predictive Significance of Lymph Node Status

Irrespective of the stage of disease, patients with negative lymph nodes (yellow) have a five-year overall survival rate (OSR) of 90% compared to those with positive lymph nodes (green), who have a five-year OSR ranging only between 20 and 60%. In the schematic diagram, the primary tumor is also indicated in green.

Predictive Score in Stage I Disease according to GOG

In patients with cervical cancer of FIGO stage I, depth of invasion, clinical tumor size and invasion of blood and/or lymph vessels are identified as independent predictive factors.

The relative risk expressed by predictive factors is multiplied to yield the risk score finally used for prognosis. A score of 40 is correlated with a recurrence risk of less than 5%, whereas a score exceeding a threshold of 40 suggests that the risk of recurrence increases up to 20%. A risk score of more than 120 is associated with an anticipated recurrence rate of more than 40%.

* Gynecologic Oncology Group

3.8 Follow-up Care

Patients who were treated for cervical cancer should be closely monitored on the basis of regular follow-up examinations. However, the physician must be aware of the limited validity of this regimen: 80% of recurrences are diagnosed on the basis of symptoms and only 25% are detected by a standardized follow-up scheme.

Follow-up Scheme for Cervical Cancer

Following primary chemoradiation, the outcomes of treatment need to be evaluated. Tumor regression may take up as much as three months. Invasive diagnostic procedures employed at an earlier date can lead to false-positive results. In most patients, 80% of recurrences occur within the first two years after surgical treatment. Following primary chemoradiation, recurrences are usually observed later. The major goal of follow-up is physical, psychological and social rehabilitation of the patient. This should include early detection of recurrence or metastasis, treatment of side effects or sequelae of therapy, continuation of adjuvant therapy, detection of secondary cancer, and documentation of treatment results and quality control. Ideally, follow-up care is provided at the same institution where primary treatment took place. Considering that this often cannot be accomplished, information exchange between healthcare professionals is paramount. While examinations are scheduled more frequently in the first two years of follow-up, the intermediate intervals are longer in the period between year 3 and 5. After five years, the patient is usually subjected to a regular screening.
Standard Protocol of Follow-up Care
in Cervical Cancer Patients
- Detailed medical history
- Weight
- Inspection and colposcopy of entire lower genital tract.
- Pap smear and HPV test.
- Rectovaginal bimanual palpation.
- Tumormarker
  - SCC antigen: squamous cell carcinoma.
  - CA125, CEA: adenocarcinoma.
- Sonography of kidneys (uterus and adnexae, if preserved).
- Palpation of inguinal and supraclavicular lymph nodes.
- Additional examinations only if suggested by symptoms or abnormal findings.

3.9 Loco-regional Recurrence
If loco-regional recurrence is confirmed by diagnosis, treatment depends on primary therapy: if the patient was irradiated, exenteration is the first-line treatment option, that offers a five-year survival rate of 40%. Prior to exenteration, staging laparoscopy is useful and helps to prevent unwarranted laparotomy in 50% of patients. In patients with recurrence following primary surgery, secondary chemoradiation is usually the treatment of choice. However, if the patient suffers from vesico- and/or rectovaginal fistula, exenteration must be performed prior to secondary chemoradiation.

Anatomic Location and Extent of Disease
In order to establish the best-suited therapeutic strategy for a patient with recurrent disease, anatomic location and extent of tumor growth need to be evaluated. Shown on this MRI scan is a tumor infiltrating the vagina and right paracolpium (red arrows) without reaching to the lateral pelvic wall. However, as a matter of fact, imaging techniques have shown to be of limited predictive value in terms of in sano resection. In most instances, the surgeon relies on intra-operative findings to predict surgical respectability accurately.

MRI Scan of Lateral Tumor Recurrence
Shown on this MRI scan is a case of lateral tumor recurrence (red arrows) originating from the parametrial tissue and infiltrating the lateral pelvic wall. Unlike the patient with central recurrence, this case is more demanding because resection with oncologically sound margins is more difficult. The tumor is close to vessels, nerves and bone and, therefore, surrounded by less healthy tissue. Clinical manual palpation is of limited value for detection of recurrent disease especially in patients with a history of radiotherapy: differentiation between radio-genic scar formation and recurrence is difficult or may not be feasible at all. MRI or PET CT are currently the most reliable imaging techniques used for detection of recurrence in patients with a history of cervical cancer.
Topography of Recurrent Disease
Local peripheral recurrence is encountered at the lateral pelvic wall. In an attempt to establish a systematic topography of recurrent disease, a distinction is made between infra- and peri-iliac recurrence, ischiopubic, acetabular and iliosacral or sacrococcygeal recurrence.

A1 stands for infra-iliac and A2 for peri-iliac ischiopubic recurrence, B1 for infra-iliac and B2 for peri-iliac acetabular recurrence, C1 for sacrococcygeal and C2 for iliosacral recurrence.

Complete resection with negative margins may be accomplished in areas A and B, whereas in area C this objective often cannot be met due to involvement of critical neural structures.

Key:
1 = Truncus lumbo-sacralis
2 = Plexus sacralis
3 = M. piriformis
4 = Fossa suprapiriformis
5 = Fossa infrapiriformis
6 = Nervus ischiadicus
7 = M. iliococcygeus
8 = M. ischiococcygeus
9 = M. obturatorius internus
10 = Nervus obturatorius

Topography of Pelvic Vessels and Nerves
- Exenterative surgery requires the surgeon to have a sound knowledge of anatomical-topographical relationships between vessels and nerves.
- Ramification of internal iliac vessels is complex and shows several anatomical variations.

Secondary Treatment Depends on Primary Treatment
In patients with central or limited peripheral recurrence, chemoradiation or surgery may be used with a curative intent. In patients with a history of radiation, exenterative surgery is the first-line treatment modality, that may be combined with intraoperative interstitial brachytherapy or small-volume re-radiation within the confines of a strictly circumscribed area.

Performed with the intent of improving quality of life, exenteration may even be indicated in patients who are free of tumor recurrence but faced with fistula or cloacal formation.

<table>
<thead>
<tr>
<th>Treatment Modalities For Recurrent Cervical Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary treatment</strong></td>
</tr>
<tr>
<td>Surgery</td>
</tr>
<tr>
<td>Surgery – Chemoradiation</td>
</tr>
<tr>
<td>Surgery – Chemotherapy</td>
</tr>
<tr>
<td>Chemoradiation</td>
</tr>
<tr>
<td>Chemoradiation – Surgery</td>
</tr>
<tr>
<td>Chemotherapy – Surgery</td>
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</table>
Types of Exenteration
Total exenteration (red circle) comprises removal of urinary bladder and rectosigmoid colon and complete or incomplete vaginal resection. If still in place, uterus and adnexae are removed en bloc with the specimen. Urinary diversion is performed by an ileum conduit or ileo-coecal pouch. Continuity of bowel is usually reestablished by a colorectal or coloanal reanastomosis. In irradiated patients, protective temporary colostomy or ileostomy is mandatory in order to secure the anastomosis. Loss of vagina can be managed by reconstruction using musculocutaneous flaps from the thigh or abdomen. If only the anterior compartment is involved by tumor, an anterior exenteration (purple oval) comprising urinary bladder and complete or partial resection of vagina, and – if deemed necessary – including uterus and adnexae, is performed. Provided the tumor has invaded the posterior compartment only, a posterior exenteration (green oval) comprising rectosigmoid colon and complete or partial resection of vagina and – if deemed necessary – including uterus and adnexae, is performed.

Supralevator versus Translevator Exenteration
According to J.F. Magrina et al. (1997), a classification has been established that is subject to the extent of pelvic floor resection. The subclassification of exenteration is as follows:
- Supralevator type (blue arrow), where pelvic organs are resected above the levator plate,
- Translevator type (green arrow), where part of the levator plate and urogenital diaphragm are resected and
- Translevator type in conjunction with radical vulvectomy (red arrow), where levator plate, urogenital diaphragm and vulvoperineal tissue are resected.

Total Exenteration of Supralevator Type
The panoramic view shows the topographical anatomy of the operative site following total exenteration of supralevator type with urethra transsected (white arrow), vaginal stump closed (red arrow) and rectal stump (blue arrow) closed by staples.

Restoration of Bowel Continuity
The panoramic view from the same patient presented above shows restoration of bowel continuity using a circular stapling device (blue arrow). Given the fact that this patient has a history of chemoradiation, a temporary protective transverse colostomy was created and taken down 3 months later.
**Urinary Diversion**

Panoramic view of urinary diversion by creation of an orthotopic ileal neobladder. An Overholt clamp is advanced through the newly formed *‘urethra’* (white arrow) that will later be sutured to the urethral stump. The ureters that have been implanted into the ileal neobladder are highlighted by *blue arrows*. Later, the detubularized ileum will be closed to form a reservoir that serves as neobladder. An ileal neobladder is used occasionally only in those patients who encountered recurrence after treatment for cervical cancer, because preservation of the bladder trigonum is a sine qua non of the technique, which frequently is not feasible in these patients due to oncologic safety.

---

**Laterally Extended Endopelvic Resection (LEER)**

If tumor recurrence extends to the lateral pelvic wall, laterally extended endopelvic resection (LEER) is performed. The extended surgical resection of pelvic floor muscles allows oncologically sound margins and in sano resection in cases of pelvic lateral wall recurrence.

The panoramic view shows resection of the pelvic floor muscles in the B1 region. The internal iliac vessels have been removed and the pelvic floor muscles located in the area between the red arrows have been resected. In this patient, resection was followed by intraoperative radiotherapy (IORT).

---

**Exenteration – Morbidity and Efficacy**

The survival of patients who underwent pelvic exenteration with curative intent for primary, persistent or recurrent cervical cancer was evaluated in a multicentric retrospective study based on 167 patients. A histopathologically confirmed resection with negative margins and no residual tumor (R0) was achieved in 121 patients (72.5%). 49 patients had metastases of lymph nodes (29.3%) and 44 (26.3%) had pelvic lateral wall involvement. 82.6% of patients required blood transfusion. The mean operative time was 446 (95–970) minutes and the median hospital stay was 24 days (7–210).

The rate of major complications was 33.5% comprising mainly abdominal infections or abscesses. Perioperative death rate amounted to 3% calculated within 30 days.

Overall survival (OS) at the end of the study was 40.7%. Pelvic exenteration is a valid therapeutic option for patients with locally advanced primary, persistent or recurrent cervical cancer and is associated with an acceptable complication rate and post-operative mortality.

---

**Exenteration: Morbidity and Efficacy**

- Rate of major complications is 34%.
- Perioperative death rate is 3%.
- Overall survival following exenteration is 40%.
- Independent prognostic factors
  - Resection margin
  - Status of pelvic lymph nodes
  - Tumor involvement of the lateral pelvic wall

4.0 References


13. BRUINSMA FJ, QUINN MA. The risk of preterm birth following treatment for precancerous changes in the cervix: a systematic review and meta-analysis. BJOG. 2011;118(9):1031–41.


108. STANLEY M. HPV: a master at avoiding the hosts defenses. HPV Today. 2007;11:1–16.


Recommended Literature:

S3-Leitlinie Impfprävention HPV assoziierter Neoplasien. 082/002
S3-Leitlinie Prävention des Zervixkarzinoms. 015-027O
S3-Leitlinie Zervixkarzinom; Diagnostik, Therapie und Nachsorge der Patientin mit Zervixkarzinom. 032-033O
http://www.awmf.org/leitlinien/
Videoexoscope System and Instruments for Loop Excision
VITOM® Instrumentation for Loop Excision

System Overview

The VITOM® System is compatible with your KARL STORZ Endoscopy equipment:
Only components marked with * are additionally required for a VITOM® exoscope system

Exoscope* and Illumination

VITOM® 90° Exoscope* with Integrated Illuminator
VITOM® 25 Exoscope*
Fiber Optic Light Cable
XENON 300 SCB Cold Light Fountain

Instrumentation for Loop Excision

Electrode Handle
Loop Electrode
High Frequency Electrosurgical Unit
Ring Curette

Kamera und Display

IMAGE1 S Platform with IMAGE1 CONNECT and IMAGE1 H3-LINK
IMAGE1 S H3-Z Three-Chip FULL HD Camera Head
FULL HD Monitor 16:9

Holding System*

VERSACRANE Holding Arm*
Mechanical Holding Arm*

Documentation System

AIDA Documentation System
VITOM® 90° and 0° Exoscopes and Illumination

VITOM® Telescope 90° with Integrated Illuminator,
VITOM® HOPKINS® telescope 90°, working distance 25–75 cm,
length 11 cm, autoclavable, with green filter for colposcopy and
incorporated fiber optic light transmission and condensor lenses,
color code: blue

VITOM® 25 HOPKINS® Straight Forward Telescope 0°,
working distance 25–75 cm, diameter 10 mm, length 11 cm,
autoclavable, fiber optic light transmission incorporated,
color code: green

Recommended Fiber Optic Light Cable 495 TIP

Fiber Optic Light Cable,
with straight connector,
extremely heat-resistant,
enhanced light transmission,
diameter 4.8 mm, length 300 cm

Wire Tray for Cleaning, Sterilization and Storage
of two rigid endoscopes and one light guide cable,
including holder for light post adaptors,
silicone telescope holders and lid,
external dimensions (w x d x h): 352 x 125 x 54 mm,
for rigid endoscopes up to diameter 10 mm
and working length 20 cm
Loop Electrodes for Conization

- **26 5200 43**  
  **Electrode Handle**, with 2 buttons for activating the unipolar generator, yellow button: unipolar cutting, blue button: unipolar coagulation, High Frequency Cord **26 5200 45** required

- **26 5200 45**  
  **High Frequency Cord**, for Electrode Handle **26 5200 43**, length 400 cm, for use with AUTOCON® II 400 SCB **20 5352 20-111** and **20 5352 20-115**

- **26 165 UG**  
  **Loop Electrode**, with insulated sheath, **autoclavable**, size 22 x 17 mm, working length 11 cm

- **26 165 UM**  
  **Loop Electrode**, with insulated sheath, **autoclavable**, size 15 x 13 mm, working length 10 cm

- **26 165 UK**  
  **Loop Electrode**, with insulated sheath, **autoclavable**, size 10 x 8 mm, working length 9 cm

Ring Curette for Endocervical Curettage

- **26 165 RK**  
  **Ring Curette**, bayonet-shaped, 45° curved upwards, very sharp, diameter 5 mm, with round handle, working length 16 cm
VERSACRANE™ Holding System

28272 GS  VERSACRANE™ Holding Arm, low, for use in the lithotomy position, spring-supported, with quick release coupling KSLOCK, for use with Mobile Stand 28272 GM and KARL STORZ clamping jaws. The VERSACRANE™ holding arm is intended for use with VITOM® scopes/exoscopes.

WARNING: The VERSACRANE™ holding arm cannot be used with rigid endoscopes!

28272 GM  Mobile Stand, for use with VERSACRANE™ Holding Arm 28272 GS

28272 UGN  Clamping Jaw, metal, clamping range 16.5 up to 23 mm, with quick release coupling KSLOCK (male), for use with all square-headed KARL STORZ HOPKINS® telescopes

28272 CN  Clamping Cylinder, folding, for flexible mounting of 10 mm telescopes to telescope sheath, autoclavable. The clamping cylinder allows vertical movement and rotation of the telescope. For use with Clamping Jaw 28272 UGN, 28272 UGK and POINT SETTER® universal adaptor 10–15 mm.

*041150-20  Cover, elasticated, package of 20

VERSACRANE™ adaptor set for examination chairs from Schmitz u. Söhne (alternative to Mobile Stand 28272 GM)

28272 GA  Adaptor Set, for mounting the VERSACRANE™ holding arm to examination chairs from Schmitz u. Söhne, with 2 adaptors for colposcope bracket, 1 mounting rod and mounting material, for use with VERSACRANE™ Holding Arm 28272 GS and colposcope bracket for examination chairs from Schmitz u. Söhne

Note: A colposcope bracket compatible with the examination chair model must be ordered directly from Schmitz u. Söhne. It is possible to mount the VERSACRANE™ holding arm to gynecological examination chairs from other manufacturers. Please contact us for further information.*
Mechanical Holding System

28272 HD  **Articulated Stand**, reinforced version, U-shaped, with one mechanical central clamp for all five joint functions, with quick release coupling KSLOCK (female)

28172 HR  **Rotation Socket**, to clamp to the operating table, with one mounted Butterfly Nut 28172 HRS, for European and US standard rails, with lateral clamp for height and angle adjustment of the articulated stand

28272 UGK  **Clamping Jaw**, with ball joint, large, clamping range 16.5 to 23 mm, with quick release coupling KSLOCK (male), for use with all square-headed KARL STORZ HOPKINS® telescopes.

28272 CN  **Clamping Cylinder**, folding, 10 mm, for flexible mounting of 10 mm telescopes to telescope sheath, autoclavable. The clamping cylinder allows vertical movement and rotation of the telescope. For use with Clamping Jaw 28272 UG, 28272 UGN and POINT SETTER universal adaptor 10–15 mm.
Primary, Secondary and Tertiary Prevention of Cervical Cancer

Unique benefits of the KARL STORZ TELE PACK X LED at a glance

**Crystal clear image**
- 15" LCD monitor with LED backlight
- Rotatable image display
- 24 Bit color intensity for natural color rendition
- DVI video input for pristine picture quality
- DVI video output for connecting HD monitors

**Easy control combined with highest safety**
- Membrane keyboard approved for wipe disinfection
- Hot-Keys assuring fast and direct adjustment
- Arrow keys for intuitive control
- Pedal control available

**Flexible storage possibilities**
- SD card-slot allows high storage capacity
- USB-slot for external HDDs and flash drives
- Picture gallery for records
- Playback of saved videos
- Print-ready patient report documentation

**Additional information**
- Sturdy, portable casing
- Ergonomic design allows comfortable transport
- Universal power supply unit: 100–240 VAC, 50/60 Hz
- Measurement (H x W x D): 450 mm x 350 mm x 150 mm
- Weight: 7 kg

**Natural illumination**
- LED high-performance light source
- Natural colour rendition close to sunlight with a colour temperature of 6400 K
- Up to 30,000 hours lamp operating time

**Ordering Information**
TP100 EN TELE PACK X LED, endoscopic video unit for use with all KARL STORZ TELECAM one-chip camera heads and video endoscopes, incl. LED-light source on a similar niveau as the Power LED 175, with integrated digital Image Processing Module, 15" LCD monitor with LED backlight, USB/SD memory module, color systems PAL/NTSC, power supply 100 - 240 VAC, 50/60 Hz, including:
- USB Silicone Keyboard with Touchpad, with US character set
Unique benefits of the KARL STORZ TELE PACK X LED at a glance

Compatible camera heads

<table>
<thead>
<tr>
<th>Code</th>
<th>Format</th>
<th>Camera Head Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>202120 40</td>
<td>PAL</td>
<td>TELECAM One-Chip Camera Head, autoclavable, with integrated Parfocal Zoom Lens, ( f = 14 - 28 \text{ mm} ) (2x), 2 freely programmable camera head buttons, including plastic container for sterilization</td>
</tr>
<tr>
<td>202121 40</td>
<td>NTSC</td>
<td>TELECAM One-Chip Camera Head, with integrated Parfocal Zoom Lens, ( f = 25 - 50 \text{ mm} ) (2x), 2 freely programmable camera head buttons</td>
</tr>
<tr>
<td>202120 30</td>
<td>PAL</td>
<td>TELECAM C-Mount One-Chip Camera Head, 2 freely programmable camera head buttons</td>
</tr>
<tr>
<td>202121 30</td>
<td>NTSC</td>
<td>TELECAM B Beamsplitter One-Chip Camera Head with 2 freely programmable camera head buttons and rotating CCD sensor, ( f = 25 \text{ mm} )</td>
</tr>
<tr>
<td>202120 31</td>
<td>PAL</td>
<td>TELECAM-B Beamsplitter One-Chip Camera Head with 2 freely programmable camera head buttons and rotating CCD sensor, ( f = 30 \text{ mm} )</td>
</tr>
<tr>
<td>202620 30</td>
<td>PAL</td>
<td>DCI\textsuperscript{II} One-Chip Camera Head, ( f = 16 \text{ mm} ), for use with DCI\textsuperscript{II} HOPKINS\textsuperscript{©} telescopes</td>
</tr>
</tbody>
</table>

Compatible Video-Endoscopes

**ENT**

<table>
<thead>
<tr>
<th>Code</th>
<th>Format</th>
<th>Video Endoscope Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>11101 VP</td>
<td>PAL</td>
<td>Video Rhino-Laryngoscope</td>
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<tr>
<td>11101 VN</td>
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**Pneumology**

<table>
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<tr>
<td>11900 BP</td>
<td>PAL</td>
<td>Video Bronchoscope</td>
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<td>11900 BN</td>
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**Urology**

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<th>Code</th>
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<th>Video Endoscope Description</th>
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<tr>
<td>11272 VP</td>
<td>PAL</td>
<td>Video-Cysto-Urethroscope</td>
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<tr>
<td>11272 VN</td>
<td>NTSC</td>
<td></td>
</tr>
<tr>
<td>11272 VPU</td>
<td>PAL</td>
<td></td>
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<tr>
<td>11272 VNU</td>
<td>NTSC</td>
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</table>
## Unique benefits of the KARL STORZ TELE PACK X LED at a glance

### Accessories

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>202000 43</td>
<td>C-Mount Lens, f = 38 mm</td>
<td></td>
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<tr>
<td>202000 42</td>
<td>C-Mount Lens, f = 30 mm</td>
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<tr>
<td>202301 41</td>
<td>C-Mount Lens, f = 25 mm</td>
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<tr>
<td>202301 45</td>
<td>C-Mount Lens, f = 12 mm</td>
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</table>

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>200142 30</td>
<td>One-pedal-Footswitch, digital, two stage</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Specifications</th>
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</thead>
<tbody>
<tr>
<td>200143 30</td>
<td>Two-pedal Footswitch, one step</td>
<td></td>
</tr>
</tbody>
</table>

### Fiberscope adaptors for other manufacturers

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>29020 GM</td>
<td>Adaptor for Machida fiberscopes</td>
<td></td>
</tr>
<tr>
<td>29020 GN</td>
<td>Adaptor for Olympus fiberscopes, new type</td>
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<tr>
<td>29020 GO</td>
<td>Adaptor for Olympus fiberscopes, old type</td>
<td></td>
</tr>
<tr>
<td>29020 GP</td>
<td>Adaptor for Pentax and Fujinon fiberscopes</td>
<td></td>
</tr>
</tbody>
</table>
Primary, Secondary and Tertiary Prevention of Cervical Cancer

**IMAGE1 S Camera System**

**NEW**

**Economical and future-proof**
- Modular concept for flexible, rigid and 3D endoscopy as well as new technologies
- Forward and backward compatibility with video endoscopes and FULL HD camera heads
- Sustainable investment
- Compatible with all light sources

**Innovative Design**
- Dashboard: Complete overview with intuitive menu guidance
- Live menu: User-friendly and customizable
- Intelligent icons: Graphic representation changes when settings of connected devices or the entire system are adjusted
- Automatic light source control
- Side-by-side view: Parallel display of standard image and the Visualization mode
- Multiple source control: IMAGE1 S allows the simultaneous display, processing and documentation of image information from two connected image sources, e.g., for hybrid operations

**Dashboard**

**Live menu**

**Intelligent icons**

**Side-by-side view: Parallel display of standard image and Visualization mode**
Brilliant Imaging
- Clear and razor-sharp endoscopic images in FULL HD
- Natural color rendition

- Reflection is minimized
- Multiple IMAGE1 S technologies for homogeneous illumination, contrast enhancement and color shifting

FULL HD image

CLARA

FULL HD image

CHROMA

FULL HD image

SPECTRA A*

FULL HD image

SPECTRA B**

* SPECTRA A: Not for sale in the U.S.
** SPECTRA B: Not for sale in the U.S.
TC 200EN

**IMAGE1 S CONNECT**, connect module, for use with up to 3 link modules, resolution 1920 x 1080 pixels, with integrated KARL STORZ-SCB and digital Image Processing Module, power supply 100–120 VAC/200–240 VAC, 50/60 Hz including:

- **Mains Cord**, length 300 cm
- **DVI-D Connecting Cable**, length 300 cm
- **SCB Connecting Cable**, length 100 cm
- **USB Flash Drive**, 32 GB, USB silicone keyboard, with touchpad, US

*Available in the following languages*: DE, ES, FR, IT, PT, RU

**Specifications:**

<table>
<thead>
<tr>
<th>HD video outputs</th>
<th>2x DVI-D, 1x 3G-SDI</th>
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<tbody>
<tr>
<td>Format signal outputs</td>
<td>1920 x 1080p, 50/60 Hz</td>
</tr>
<tr>
<td>LINK video inputs</td>
<td>3x</td>
</tr>
<tr>
<td>USB interface</td>
<td>4x USB, (2x front, 2x rear)</td>
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<tr>
<td>SCB interface</td>
<td>2x 6-pin mini-DIN</td>
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<tr>
<td>Power supply</td>
<td>100–120 VAC/200–240 VAC</td>
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<tr>
<td>Power frequency</td>
<td>50/60 Hz</td>
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<tr>
<td>Protection class</td>
<td>I, CF-Defib</td>
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<tr>
<td>Dimensions w x h x d</td>
<td>305 x 54 x 320 mm</td>
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<tr>
<td>Weight</td>
<td>2.1 kg</td>
</tr>
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</table>

**For use with IMAGE1 S**

**IMAGE1 S CONNECT Module TC 200EN**

TC 300

**IMAGE1 S H3-LINK**, link module, for use with IMAGE1 FULL HD three-chip camera heads, power supply 100–120 VAC/200–240 VAC, 50/60 Hz, for use with **IMAGE1 S CONNECT TC 200EN** including:

- **Mains Cord**, length 300 cm
- **Link Cable**, length 20 cm

**Specifications:**

<table>
<thead>
<tr>
<th>Camera System</th>
<th>TC 300 (H3-Link)</th>
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</thead>
<tbody>
<tr>
<td>Supported camera heads</td>
<td>TH 100, TH 101, TH 102, TH 103, TH 104, TH 106 (fully compatible with IMAGE1 S)</td>
</tr>
<tr>
<td></td>
<td><strong>222200055-3, 222200056-3, 222200053-3, 222200060-3, 222200061-3, 222200054-3, 222200055-3</strong> (compatible without IMAGE1 S technologies CLARA, CHROMA, SPECTRA*)</td>
</tr>
<tr>
<td>LINK video outputs</td>
<td>1x</td>
</tr>
<tr>
<td>Power supply</td>
<td>100–120 VAC/200–240 VAC</td>
</tr>
<tr>
<td>Power frequency</td>
<td>50/60 Hz</td>
</tr>
<tr>
<td>Protection class</td>
<td>I, CF-Defib</td>
</tr>
<tr>
<td>Dimensions w x h x d</td>
<td>305 x 54 x 320 mm</td>
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<tr>
<td>Weight</td>
<td>1.86 kg</td>
</tr>
</tbody>
</table>

* SPECTRA A: Not for sale in the U.S.
** SPECTRA B: Not for sale in the U.S.
IMAGE1 S Camera Heads

For use with IMAGE1 S Camera System
IMAGE1 S CONNECT Module TC 200EN, IMAGE1 S H3-LINK Module TC 300
and with all IMAGE1 HUB™ HD Camera Control Units

TH 100

**IMAGE1 S H3-Z Three-Chip FULL HD Camera Head**, 50/60 Hz, IMAGE1 S compatible, progressive scan, soakable, gas- and plasma-sterilizable, with integrated Parfocal Zoom Lens, focal length \( f = 15–31 \text{ mm} \) (2x), 2 freely programmable camera head buttons, for use with IMAGE1 S and IMAGE1 HUB™ HD/HD

TH 103

**IMAGE1 S H3-P Three-Chip FULL HD Pendulum Camera Head**, 50/60 Hz, IMAGE1 S compatible, with pendulum system and fixed focus, progressive scan, soakable, gas- and plasma-sterilizable, focal length \( f = 16 \text{ mm} \), 2 freely programmable camera head buttons, for use with IMAGE1 S and IMAGE1 HUB™ HD/HD

---

**Specifications:**

<table>
<thead>
<tr>
<th>IMAGE1 FULL HD Camera Heads</th>
<th>IMAGE1 S H3-Z</th>
<th>IMAGE1 S H3-P</th>
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</thead>
<tbody>
<tr>
<td>Product no.</td>
<td>TH 100</td>
<td>TH 103</td>
</tr>
<tr>
<td>Image sensor</td>
<td>3x ( \frac{1}{3} ) CCD chip</td>
<td>3x ( \frac{1}{3} ) CCD chip</td>
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<tr>
<td>Dimensions w x h x d</td>
<td>39 x 49 x 114 mm</td>
<td>35 x 47 x 88 mm</td>
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<tr>
<td>Weight</td>
<td>270 g</td>
<td>226 g</td>
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<tr>
<td>Optical interface</td>
<td>integrated Parfocal Zoom Lens, ( f = 15–31 \text{ mm} ) (2x)</td>
<td>pendulum system, fixed focus ( f = 16 \text{ mm} )</td>
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<tr>
<td>Min. sensitivity</td>
<td>F 1.4/1.17 Lux</td>
<td>F 1.4/1.17 Lux</td>
</tr>
<tr>
<td>Grip mechanism</td>
<td>standard eyepiece adaptor</td>
<td>standard eyepiece adaptor</td>
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<td>Cable</td>
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<td>non-detachable</td>
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<tr>
<td>Cable length</td>
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<td>300 cm</td>
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</table>
IMAGE1 S Camera Heads

For use with IMAGE1 S Camera System
IMAGE1 S CONNECT Module TC 200EN, IMAGE1 S H3-LINK Module TC 300
and with all IMAGE1 HUB™ HD Camera Control Units

TH 104

IMAGE1 S H3-ZA Three-Chip FULL HD Camera Head, 50/60 Hz, IMAGE1 S compatible, autoclavable, progressive scan, soakable, gas- and plasma-sterilizable, with integrated Parfocal Zoom Lens, focal length f = 15–31 mm (2x), 2 freely programmable camera head buttons, for use with IMAGE1 S and IMAGE1 HUB™ HD/HD

Specifications:

<table>
<thead>
<tr>
<th>IMAGE1 FULL HD Camera Heads</th>
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<td>Image sensor</td>
<td>3x 1/3&quot; CCD chip</td>
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<tr>
<td>Dimensions w x h x d</td>
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<td>Weight</td>
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<td>Grip mechanism</td>
<td>standard eyepiece adaptor</td>
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<tr>
<td>Cable</td>
<td>non-detachable</td>
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<tr>
<td>Cable length</td>
<td>300 cm</td>
</tr>
</tbody>
</table>

39301 Z3TS

Plastic Container for Sterilization and Storage of camera heads IMAGE1 H3-Z, H3-ZA, H3-FA, IMAGE1 S H3-Z, H3-ZA and H3-FA, autoclavable, suitable for use with steam, gas and hydrogen peroxide sterilization, Sterrad® compatible, external dimensions (w x d x h): 385 x 255 x 75 mm

Please note: The instrument displayed is not included in the plastic container. Only camera heads marked “autoclave” can be placed in the tray for steam sterilization.

39301 PHTS

Plastic Container for Sterilization and Storage of camera heads IMAGE1 H3-P, H3-ZI, IMAGE1 S H3-P and H3-ZI, autoclavable, suitable for use with steam, gas and hydrogen peroxide sterilization, Sterrad® compatible, external dimensions (w x d x h): 385 x 255 x 75 mm

Please note: The instrument displayed is not included in the plastic container. Only camera heads marked “autoclave” can be placed in the tray for steam sterilization.
Monitors

9619 NB

19" HD Monitor,
color systems \textbf{PAL/NTSC}, max. screen
resolution 1280 x 1024, image format 4:3,
power supply 100–240 VAC, 50/60 Hz,
wall-mounted with VESA 100 adaption,
including:
\textbf{External 24 VDC Power Supply}
\textbf{Mains Cord}

9826 NB

26" \textbf{FULL HD Monitor},
wall-mounted with VESA 100 adaption,
color systems \textbf{PAL/NTSC},
max. screen resolution 1920 x 1080,
image format 16:9,
power supply 100–240 VAC, 50/60 Hz
including:
\textbf{External 24 VDC Power Supply}
\textbf{Mains Cord}
Monitors

<table>
<thead>
<tr>
<th>KARL STORZ HD and FULL HD Monitors</th>
<th>19&quot;</th>
<th>26&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wall-mounted with VESA 100 adaption</td>
<td>9619 NB</td>
<td>9826 NB</td>
</tr>
<tr>
<td>Inputs:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVI-D</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Fibre Optic</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3G-SDI</td>
<td>–</td>
<td>✗</td>
</tr>
<tr>
<td>RGBS (VGA)</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>S-Video</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Composite/FBAS</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Outputs:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVI-D</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>S-Video</td>
<td>✗</td>
<td>–</td>
</tr>
<tr>
<td>Composite/FBAS</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>RGBS (VGA)</td>
<td>–</td>
<td>✗</td>
</tr>
<tr>
<td>3G-SDI</td>
<td>–</td>
<td>✗</td>
</tr>
<tr>
<td>Signal Format Display:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4:3</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>5:4</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>16:9</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Picture-in-Picture</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>PAL/NTSC compatible</td>
<td>✗</td>
<td>✗</td>
</tr>
</tbody>
</table>

Optional accessories:
9826 SF Pedestal, for monitor 9826 NB
9626 SF Pedestal, for monitor 9619 NB

Specifications:

<table>
<thead>
<tr>
<th>KARL STORZ HD and FULL HD Monitors</th>
<th>19&quot;</th>
<th>26&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desktop with pedestal</td>
<td>optional</td>
<td>optional</td>
</tr>
<tr>
<td>Product no.</td>
<td>9619 NB</td>
<td>9826 NB</td>
</tr>
<tr>
<td>Brightness</td>
<td>200 cd/m² (typ)</td>
<td>500 cd/m² (typ)</td>
</tr>
<tr>
<td>Max. viewing angle</td>
<td>178° vertical</td>
<td>178° vertical</td>
</tr>
<tr>
<td>Pixel distance</td>
<td>0.29 mm</td>
<td>0.3 mm</td>
</tr>
<tr>
<td>Reaction time</td>
<td>5 ms</td>
<td>8 ms</td>
</tr>
<tr>
<td>Contrast ratio</td>
<td>700:1</td>
<td>1400:1</td>
</tr>
<tr>
<td>Weight</td>
<td>7.6 kg</td>
<td>7.7 kg</td>
</tr>
<tr>
<td>Rated power</td>
<td>28 W</td>
<td>72 W</td>
</tr>
<tr>
<td>Operating conditions</td>
<td>0–40°C</td>
<td>5–35°C</td>
</tr>
<tr>
<td>Storage</td>
<td>-20–60°C</td>
<td>-20–60°C</td>
</tr>
<tr>
<td>Rel. humidity</td>
<td>max. 85%</td>
<td>max. 85%</td>
</tr>
<tr>
<td>Dimensions w x h x d</td>
<td>469.5 x 416 x 75.5 mm</td>
<td>643 x 396 x 87 mm</td>
</tr>
<tr>
<td>Power supply</td>
<td>100–240 VAC</td>
<td>100–240 VAC</td>
</tr>
<tr>
<td>Certified to</td>
<td>EN 60601-1, protection class IPX0</td>
<td>EN 60601-1, UL 60601-1, MDD93/42/EEC, protection class IPX2</td>
</tr>
</tbody>
</table>
Cold Light Fountain XENON 300 SCB

20133101-1 Cold Light Fountain XENON 300 SCB with built-in antifog air-pump, and integrated KARL STORZ Communication Bus System SCB power supply: 100 – 125 V AC/220 – 240 V AC, 50/60 Hz including:
- Mains Cord
- SCB Connecting Cable, length 100 cm

20133027 Spare Lamp Module XENON with heat sink, 300 watt, 15 volt

20133028 XENON Spare Lamp, only, 300 watt, 15 volt

Fiber Optic Light Cable

495 NCS Fiber Optic Light Cable, with straight connector, extremely heat-resistant, enhanced light transmission, diameter 4.8 mm, length 250 cm

495 TIP Fiber Optic Light Cable, with straight connector, extremely heat-resistant, enhanced light transmission, diameter 4.8 mm, length 300 cm

AUTOCON® II 400 SCB

20535201-125 AUTOCON® II 400 High End, Set SCB power supply 220 - 240 V AC, 50/60 Hz, HF connecting sockets: Bipolar combination, Multifunction, Unipolar 3-pin + Erbe Neutral electrode combination 6.3 mm, jack and 2-pin, System requirements: SCB R-UI Software Release 20090001-43 or higher including:
- AUTOCON® II 400, with KARL STORZ SCB Mains Cord
- SCB Connecting Cable, length 100 cm
Data Management and Documentation
KARL STORZ AIDA® – Exceptional documentation

The name AIDA stands for the comprehensive implementation of all documentation requirements arising in surgical procedures: A tailored solution that flexibly adapts to the needs of every specialty and thereby allows for the greatest degree of customization.

This customization is achieved in accordance with existing clinical standards to guarantee a reliable and safe solution. Proven functionalities merge with the latest trends and developments in medicine to create a fully new documentation experience – AIDA.

AIDA seamlessly integrates into existing infrastructures and exchanges data with other systems using common standard interfaces.

WD 200-XX* AIDA Documentation System, for recording still images and videos, dual channel up to FULL HD, 2D/3D, power supply 100-240 VAC, 50/60 Hz including:

- **USB Silicone Keyboard**, with touchpad
- **ACC Connecting Cable**
- **DVI Connecting Cable**, length 200 cm
- **HDMI-DVI Cable**, length 200 cm
- **Mains Cord**, length 300 cm

WD 250-XX* AIDA Documentation System, for recording still images and videos, dual channel up to FULL HD, 2D/3D, including SMARTSCREEN® (touch screen), power supply 100-240 VAC, 50/60 Hz including:

- **USB Silicone Keyboard**, with touchpad
- **ACC Connecting Cable**
- **DVI Connecting Cable**, length 200 cm
- **HDMI-DVI Cable**, length 200 cm
- **Mains Cord**, length 300 cm

*XX Please indicate the relevant country code (DE, EN, ES, FR, IT, PT, RU) when placing your order.
Workflow-oriented use

**Patient**
Entering patient data has never been this easy. AIDA seamlessly integrates into the existing infrastructure such as HIS and PACS. Data can be entered manually or via a DICOM worklist. All important patient information is just a click away.

**Checklist**
Central administration and documentation of time-out. The checklist simplifies the documentation of all critical steps in accordance with clinical standards. All checklists can be adapted to individual needs for sustainably increasing patient safety.

**Record**
High-quality documentation, with still images and videos being recorded in FULL HD and 3D. The Dual Capture function allows for the parallel (synchronous or independent) recording of two sources. All recorded media can be marked for further processing with just one click.

**Edit**
With the Edit module, simple adjustments to recorded still images and videos can be very rapidly completed. Recordings can be quickly optimized and then directly placed in the report. In addition, freeze frames can be cut out of videos and edited and saved. Existing markings from the Record module can be used for quick selection.

**Complete**
Completing a procedure has never been easier. AIDA offers a large selection of storage locations. The data exported to each storage location can be defined. The Intelligent Export Manager (IEM) then carries out the export in the background. To prevent data loss, the system keeps the data until they have been successfully exported.

**Reference**
All important patient information is always available and easy to access. Completed procedures including all information, still images, videos, and the checklist report can be easily retrieved from the Reference module.
Equipment Cart

Equipment Cart
wide, high, rides on 4 antistatic dual wheels equipped with locking brakes 3 shelves, mains switch on top cover, central beam with integrated electrical subdistributors with 12 sockets, holder for power supplies, potential earth connectors and cable winding on the outside,

Dimensions:
Equipment cart: 830 x 1474 x 730 mm (w x h x d),
shelf: 630 x 510 mm (w x d),
caster diameter: 150 mm

including:
Base module equipment cart, wide
Cover equipment, equipment cart wide
Beam package equipment, equipment cart high
3x Shelf, wide
Drawer unit with lock, wide
2x Equipment rail, long
Camera holder

Monitor Swivel Arm,
height and side adjustable, can be turned to the left or the right side, swivel range 180°, overhang 780 mm, overhang from centre 1170 mm, load capacity max. 15 kg, with monitor fixation VESA 5/100, for usage with equipment carts UG xxx
Recommended Accessories for Equipment Cart

**Isolation Transformer**,
200 V–240 V; 2000 VA with 3 special mains socket, expulsion fuses, 3 grounding plugs,
dimensions: 330 x 90 x 495 mm (w x h x d),
for usage with equipment carts UG xxx

**Earth Leakage Monitor**, 
200 V–240 V, for mounting at equipment cart, 
control panel dimensions: 44 x 80 x 29 mm (w x h x d), 
for usage with isolation transformer UG 310

**Monitor Holding Arm**, 
height adjustable, inclinable, 
mountable on left or right, 
turning radius approx. 320°, overhang 530 mm, 
load capacity max. 15 kg, 
monitor fixation VESA 75/100, 
for usage with equipment carts UG xxx
For additional faculty-specific information, please refer to Product Catalog:

**Recommended Instrument Sets for Gynecology**
- Laparoscopic Gynecologic Procedures
- Minilaparoscopy
- Colposcopy and Conization by Loop Excision

To place an order for this *product catalog*, (item number 9612009E), which will be shipped free of charge, please contact:

**KARL STORZ GmbH & Co. KG**
P.O. Box 230, 78503 Tuttlingen, Germany
- Telefax: +49 (0) 7461 708-105
- E-mail: info@karlstorz.de
- www.karlstorz.com

Charité – Universitätsmedizin Berlin
Department of Gynecology and Gynecologic Oncology

Instrument Sets in Gynecology
Recommended by Prof. A. Schneider, M.D., M.P.H.
Children want to make something of themselves, even if they have sensory disabilities, are blind, hearing impaired, or deaf-blind. Unfortunately, these children’s disabilities are often severe enough to keep them from attending “normal” schools.

The “stiftung st. franziskus heiligenbronn” is building two new schools for children with sensory disabilities to give these boys and girls a future and the opportunity to lead a successful life. You can help – with your donation for children with sensory disabilities.

KARL STORZ will help, too.

As an ambassador for the fundraising campaign “Wir machen Schule. Machen Sie mit!” [We set an example. Get involved!], KARL STORZ is again taking social responsibility. We have made it our mission to help children with sensory disabilities throughout the German state of Baden-Wuerttemberg, and to familiarize our customers and business partners with this fundraising campaign’s worthy cause.

Please help support the fundraising campaign “Wir machen Schule. Machen Sie mit.”
For additional information, go to www.wir-machen-schule-machen-sie-mit.de

For bank transfers from abroad:
IBAN: DE56642500400000540340
SWIFT/BIC-Code: SOLA DE S1 RWL