Chapter 5
Pre-invasive Lesions of the Cervix

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Abstract Invasive Cervical carcinoma o Cervical Cancer (CCa) is the fourth leading cause of death among women. CCa is preceded by dysplastic alterations in the epithelial cells of the cervix that do not compromise the stroma. The most significant risk factor is one that is also required for the development of pre-invasive cervical lesions: persistent infection with a strain of human papilloma virus (HPV) that has a viral genotype. Timely detection programs consist of methods aimed at identifying women with asymptomatic pre-malignant lesions that can be healed with treatment. Current screening tests to detect CCa include cervical cytology, either conventional or liquid-based, and assays to detect high and low risk viruses or specific serotypes. Furthermore, because HPV is an etiological factor and because we know that primary prevention of HPV is a health-promoting strategy, prophylactic vaccines have been developed for this virus. Treatments for pre-malignant lesions depend on the degree of the lesion, the availability of medical resources, the experience of the surgeons in performing specific procedures and patient choice.

Keywords Human papilloma virus • Intra-epithelial lesion • Low-grade • High-grade

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5.1 Introduction

CCa is the fourth leading cause of death in women. A total of 528,000 new cases were reported on 2012, resulting in an estimated mortality of 266,000. This represents 7.5% of all cancer deaths in women around the world [1]. CCa is known to be preceded by dysplastic alterations in the cells of the cervical epithelium that do not compromise the stroma. The most important risk factors for CCa are linked to sexual behavior, and of these, HPV infection is fundamental to the development of these lesions. In recent decades, our understanding of the biology of HPV and its epidemiology has increased exponentially, leading to the creation of new screening methods and recommendations in addition to vaccines against HPV that serve to prevent CCa. Being aware of the natural history of these lesions provides us with a wide window of time in which to detect this condition early and to therefore treat affected patients in a timely and efficient manner.

5.2 Epidemiology

VPH infection is relatively common and it is thought that the risk of infection during a person's life is approximately 75%. The population under 30 years old has an HPV prevalence of roughly 58.9%. It is estimated that approximately 291 million women around the world have had contact with the virus at least once in their life, corresponding to a prevalence of 10.4%. In Latin America there is a second peak in prevalence at approximately 55 years of age, when the incidence is 52.8% for HPV 16 and 9.4% for HPV 18 [2].

5.3 Risk Factors for the Development of Pre-invasive Lesions

The most important and fundamental risk factors for the development of pre-invasive cervical lesions are persistent infection with HPV and its viral genotype. However, other co-factors have also been shown to increase the risk of infection and the risk of progression to malignant transformation.

The best known factors are an early onset of sexual activity, multiparity, potentially infective sexual partners, multiple sexual partners, and immunodeficiency [2]. These co-factors increase the risk of progressing to a high-grade intraepithelial lesion. Out of all of the previously mentioned co-factors, the most important factor is immunodeficiency. This is especially true in HIV-infected women because infection increases the risk of persistent infection with HPV at all ages [3]. Similarly, smoking and the prolonged use of oral contraceptives promote the development of squamous metaplasia by promoting persistent HPV infection [2].

Table 5.1 HPV classification

Low-risk: 6, 11, 40, 42, 54, 57
High-grade: 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68

5.4 Human Papilloma Virus

The causal link between HPV and the development of cervical cancer was first identified in 1970, when Dr. Harald zur Hausen suggested that the viral particles that were observed in genital warts were also responsible for malignant neoplasia of the cervix [4]. HPV 16 and 18 were later identified as being responsible for 70% of all CCa cases.

HPV belongs to the Papillomaviridae family, the members of which have a high affinity for mucous tissues and epithelia and are capable of inducing strong epithelial proliferation at the site of infection. There are at least 120 different HPV serotypes, and of these, at least 40 infect the genitals [5]. The latter group is classified as either low or high risk according to their contribution to the development of malignant neoplasia (Table 5.1). Low-risk HPV viruses are associated with genital warts, whereas high-risk HPV viruses are associated with intraepithelial high-grade lesions and CCa.

The HPV viral genome is DNA-based, consisting of a circular double-helix. It is divided into a series of early open reading frames (ORFs) (E1–E7) and late ORFs (L1–L2) that are encoded in approximately 8000 bp. VPH has a protein capsule that is formed by 72 capsomeres that are made of the proteins encoded in the L1 and L2 ORFs. These capsomeres serve as protection and a means of interaction with the proteins in the host cell. Early ORFs encode replication, regulation and cell proliferation proteins [6]. The precise functions of E6 and E7 are worth mentioning. Over-expressing the E6 ORF promotes the ubiquitination and subsequent degradation of the regulator protein p53, which results in the progression of the cell cycle and avoidance of apoptosis, which allows the transformed cells to replicate. Similarly, the oncoprotein E7 promotes the degradation of the Rb gene, which results in the disruption of the cell cycle [2]. Both of these events inhibit apoptosis, resulting in the promotion of carcinogenesis.

5.5 Vaccines

Because HPV as an etiological factor and it is known that preventing the spread of HPV is a significant health strategy, prophylactic vaccines have been developed. In 2006, the United States Food and Drug Administration (FDA) approved the first vaccine against HPV. Gardasil® is a quadrivalent vaccine that was developed by Merck laboratories to protect individuals against HPV serotypes 6, 11, 16 and 18. In 2009, the FDA approved a second bivalent vaccine (Cervarix® by GlaxoSmithKline) that was specific to HPV serotypes 16 and 18 [7]. Both vaccines were developed using the recombinant expression of proteins obtained from the viral capsid (L1), which self-assembles upon expression to form structures called virus-like particles

(VLPs) that are similar to those found in complete virions. These VLPs induce a substantial antigenic effect without also inducing infection, and they attain antibody levels 100-fold higher than those observed in natural infections [16]. Table 5.2 lists the most important characteristics of these two vaccines.

Routine administration has been recommended for both vaccines in girls and boys between 11 and 12 years old; however, administration can begin in children as young as 9 years old. The administration of these vaccines is also recommended in women between 13 and 26 years old who have not been previously vaccinated or who have not completed the three recommended doses. If a woman turns 26 years old before completing the three doses, the pending doses can be administered after she turns 26 years old. Ideally, the vaccine should be administered before the onset of sexual activity [10].

Several randomized studies have demonstrated the efficacy of HPV vaccinations. The efficacy of the quadrivalent vaccine was established in the FUTURE I and FUTURE II studies. In both of these studies, an efficacy of 100% was obtained for the prevention of HPV lesions 6/11/16/18. The vaccine also showed an efficacy of 75% for preventing intraepithelial vaginal neoplasias. A similarly high efficacy was found for its ability to prevent benign lesions of the vulva and the vagina that can be caused by HPV types not related to the vaccine [11].

The efficacy of the bivalent vaccine was evaluated in the randomized, double-blinded PATRICIA study. In the PATRICIA study, vaccinated patients showed a 100% efficacy for preventing lesions caused by HPV 16 and 18. Additionally, it demonstrated 100% efficacy in preventing in situ adenocarcinomas and reduced the risk of high-grade intra-epithelial lesions caused by HPV types that are not related to the vaccine [12].

The fact that a woman receives the full vaccination scheme does not exempt her from regular cytological analyses of the cervix and the vaginal, which favor the early detection of lesions of any kind [13].

Table 5.2 Characteristics of vaccines against human papilloma virus (HPV)

	Gardasil®	Cervarix®
Name	Quadrivalent vaccine against HPV	Bivalent vaccine against HPV
Pharmaceutical company	Merck & Co	GlaxoSmithKline Biologicals
HPV serotypes	6, 11, 16 and 18	16 and 18
Adjuvant	225 μmg Phosphate Hydroxysulphate amorphous of aluminum	500 μmg aluminum hydroxide,50 μmg de 3-O- deacetylated -4 –Lipid A mono-phosphorylated
Virus-like particles (VLPs)	20/40/40/20 μmg	20/20 μmg
Production	Leaven (saccharomyces cerevisiae)	Insect cells (SF9)/baculovirus
Doses and schemes	0, 2, 5 months; 0.5 mL; Intramuscular	0,1, 6 months; 0.5 mL; Intramuscular
Antibodies quantitation	1–19 times more than the natural infection	14–17 times more than the natural infection

5.6 Natural History of HPV Infection

In most infected women, the infection is asymptomatic, and immune responses result in the spontaneous disappearance of the infection after 12–18 months in 80% of cases. A strong relationship exists between persistent HPV infections and squamous intraepithelial lesions (SIL) incidence, particularly for HPV types 16 and 18, the risk of developing a neoplastic lesion is higher. In the beginning of this disease, the cells exhibit only signs of the viral infection, but they then turn into cervical intra-epithelial neoplasias (CINs) and ultimately progress to invasive cancer [14].

Most CINs develop in the transformation zone of the cervix, which is located in the squamous-columnar junction between the columnar epithelium of the endocervix and the squamous epithelium of the ectocervix. CINs make up a continuous spectrum of neoplastic cells that display changes in their cytoplasm and the loss of nuclear polarization, pleomorphism and mitotic index. They are divided into three types: CIN I, or mild dysplasia (Fig. 5.1), in which only one-third of the lower epithelium is affected; CIN II, or moderate dysplasia (Fig. 5.2), in which the lesion extends up to the middle third of the epithelium; and CIN III, or severe dysplasia, which is in situ carcinoma (Fig. 5.3), in which the lesion extends through the full thickness of the epithelium [15]. CIN I represents a transitory manifestation of a viral infection, during which the infected epithelium differs from a normal epithelium only in some slight cellular alterations. In CINs II and III, HPV prevents the maturation and differentiation of the infected basal cells, resulting in the generation of one or several clones of neoplastic cells. It is currently thought that CIN I is the only benign HPV infection-related process, and these cases are therefore called

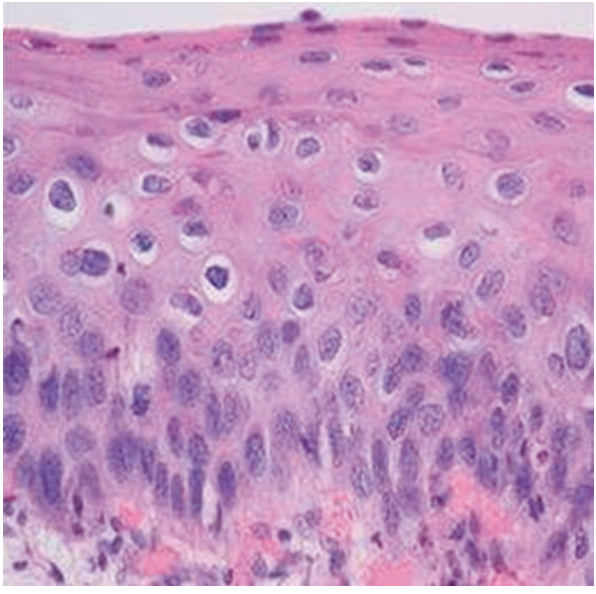

Fig. 5.1 Intra-epithelial cervical neoplasia (CIN) I. Immature epithelial cells are found only in the lower one-third of the epithelium

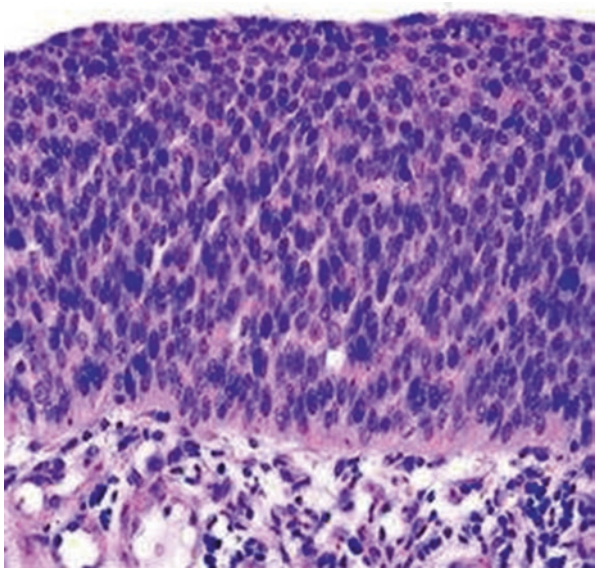

Fig. 5.2 Intra-epithelial cervical neoplasia (CIN) II. Immature epithelial cells are found in the two lower two-thirds of the epithelium

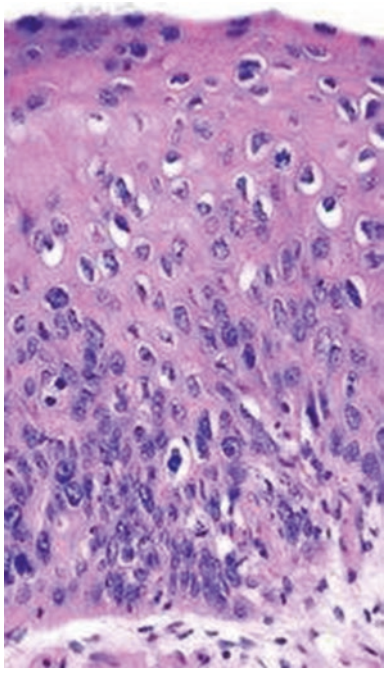

Fig. 5.3 Intra-epithelial cervical neoplasia (CIN) III. Immature epithelial cells are observed through the full thickness of the epithelium but do not extend beyond the basal lamina. This category includes cases of in situ carcinoma

low-grade intra-epithelial lesions. CINs II and III comprise the premalignant lesions, and they are referred to as high-grade intra-epithelial lesions. CIN I can be produced by both low-risk and high-risk viral serotypes, whereas CINs II and III are produced only by serotypes with high oncological risk.

Most low-grade intra-epithelial lesions disappear spontaneously after a period of 2 years, especially in patients found to be positive for low-risk HPVs. Only a small percentage (15%) of cases progress to high-grade intra-epithelial lesions over a 24 month period, and this is especially likely if the patient is positive for a high-risk HPV (17.3%) [16].

5.7 Screening

Timely detection programs consist of identifying asymptomatic women with premalignant lesions in whom treatment can lead to healing. When screening studies are routinely performed, there is an up to two to tenfold lower risk of developing invasive CCa than in patients who never submit themselves to this type of evaluation [16]. Current screening tests to detect CCa include cervical cytology, either conventional or liquid-based, and assays to detect high- versus low-risk viruses or specific serotypes.

In March 2012, the American Cancer Society (ACS), the American Society for Colposcopy and Cervical Pathology (ASCCP) and the American Society for Clinical Pathology (ASCP) reviewed their recommendations for Cervical Cancer screening. Simultaneously, the US Preventive Services Task Force (USPSTF) and the American Congress of Obstetricians and Gynecologists also reviewed their clinical practices [17].

The screening recommendations they proposed are summarized as follows:

- Screening must not be performed in patients younger than 21 years old.
- Cytological screening must be performed every 3 years in patients between 21 and 29 years old. The use of HPV-detecting tests is not advised for this group of young women.
- HPV-detecting tests and cytology must be performed every 5 years on patients between 30 and 65 years old. It is acceptable to perform the cytological screening only every 3 years.
- Screening can be suspended in patients who are older than 65 years old provided they have previously undergone appropriate and negative screenings. If they were previously diagnosed with CIN II, the screening must continue for at least 20 years because there was a diagnosis of a pre-invasive lesion.
- After a hysterectomy, patients must not be screened if the cervix was removed and there is no clinical history of CIN II or III.
- Women who were previously immunized with a bivalent or quadrivalent vaccine must follow the same recommendations as those made for non-immunized women [17].

5.8 Nomenclature

Cytology reports were first introduced in 1998 and subsequently revised in 2001 in the city of Bethesda, at which time both the terminology and the diagnosis reporting protocols were standardized. The Bethesda system was developed via a process that involved a literature revising omit, expert opinions and a discussion of the proposed changes [18]. Some of the terms that were revised in 2001 according to the Bethesda system are included in Table 5.3.

The classification of cervical epithelial alterations according to their histological characteristics differentiates groups of women based on the state of cellular maturation and the thickness of the affected area in the squamous epithelium, as has already been described in this chapter.

Table 5.3 Summary of the Bethesda system 2001 terminology [18]

Interpretation/Result
Negative for intraepithelial lesion or malignancy
Organisms: trichomonas vaginalis, fungal organisms, etc
Cellular changes:
consistent with herpes simplex virus other non-neoplastic findings (Optional to report; list not comprehensive)
Reactive cellular changes:
Inflammation (includes typical repair)
Radiation
Intrauterine contraceptive device
Glandular cells
Status posthysterectomy
Atrophy
Epithelial cell abnormalities:
Squamous cell atypical squamous cells (ASC)
ASC of undetermined significance (ASC-US)
ASC cannot exclude HSIL (ASC-H)
Low-grade squamous intraepithelial lesion (LSIL) encompassing: human papillomavirus/mild dysplasia/cervical intraepithelial neoplasia (CIN) 1
High-grade squamous intraepithelial lesion (HSIL) encompassing: moderate (CIN 2) and severe dysplasia (CIN 3) and carcinoma in situ
Glandular cell
Atypical glandular cell (AGC) (specify endocervical, endometrial, or not otherwise specified)
Atypical glandular cells, favor neoplastic (specify endocervical or not otherwise specified)
Endocervical adenocarcinoma in situ (AIS)
Adenocarcinoma
Endometrial cells in a woman with 40 years of age automated review and ancillary testing (Include as appropriate)

5.9 Approach and Treatment of Pre-invasive Lesions

5.9.1 Colposcopic Evaluation

Colposcopy is not a screening method because performing it adequately requires a large amount of resources and preparation. However, every cytological anomaly is considered an indication that prompts an Colposcopy. The objective is to reveal any anomalies that may direct the biopsy sampling to dismiss invasive cancer. Colposcopic evaluations are advised in patients with a macroscopically normal cervix but in whom abnormal cytology has been observed. Colposcopic characteristics are classified according to appearance and increase in value of a potentially subjacent malignity post-application of acetic acid, which is used to dissolve the cervical mucous and reveal the lesioned tissue, which is whiter than the surrounding epithelium. The more anomalies that are observed, the higher the possibility of a high-grade lesion or an invasive cancer. Using this method, a well-defined acetic-white lesion that does not display point markings, is not mosaic and has a normal vascular pattern is most likely to indicate a secondary lesion of HPV or a low-grade intra-epithelial lesion (Fig. 5.1). An anomaly that reveals itself as a thick acetic-white epithelium, a thick mosaic and an increased vascular pattern may correspond to a high-grade intra-epithelial lesion (Fig. 5.2) or an invasive carcinoma (Figs. 5.3, 5.4, 5.5 and 5.6) [19].

5.9.2 Treatment Generalities

The applied procedures depend mainly on the histological diagnosis. Nevertheless, this choice is influenced by the cytological diagnosis, the age and future fertility plans of the patient, and the presence of colposcopic findings or evidence of

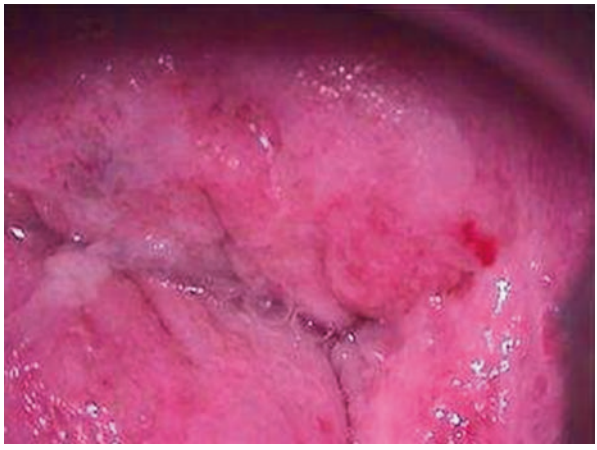

Fig. 5.4. Low-grade intra-epithelial lesion. Fine point markings can be seen that have poorly defined borders and a mild acetic-white epithelium

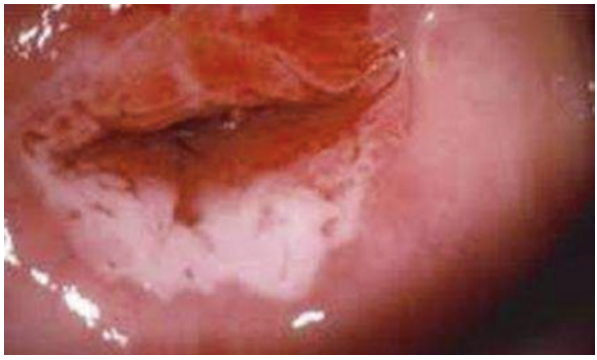

Fig. 5.5. High-grade intra-epithelial lesion. A thick acetic-white epithelium with regular and well-defined borders and a thick mosaic is shown

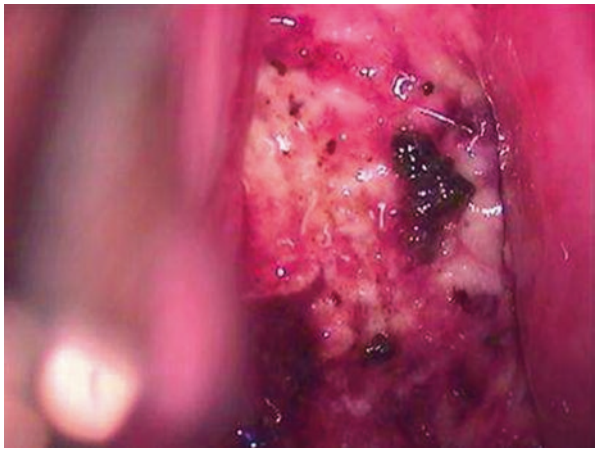

Fig. 5.6 Invasive Cervical carcinoma o Cervical Cancer (CCa)

endocervical dysplasia. The treatment also depends on the degree of the lesion, the availability of medical resources, the experience of the surgeons in performing specific procedures and the patient's choice.

5.9.3 Atypical Squamous Cells of Uncertain Significance (ASC-US) and Low-Grade Intra-epithelial Lesions

Most lesions undergo spontaneous resolution within a period no longer than 24 months. This is why surveillance is necessary as long as the results of colposcopy are satisfactory. In general terms, surveillance includes observing the patient for cervicovaginal cytologies every 6 months [16]. Hysterectomy is not a valid treatment option [16, 20]. Current recommendations for low-grade intra-epithelial lesions that are diagnosed by cytology are based on the results of a co-test. Low-grade intra-epithelial lesion diagnoses are indirect indicators of HPV seropositivity because

approximately 80% of such cases will have a positive HPV test. Still, there are women who have a negative HPV test with positive cytology for a low-grade intra-epithelial lesion. In these cases, it is advised that the practitioner perform a co-test after 1 year. If both tests are negative, then the co-test must be performed in 3 years. In women between 21 and 24 years old who have positive cytology for a low-grade intra-epithelial lesion, the tests must be performed annually for 2 years. The risk of cervical cancer in women younger than 25 years old is very low (1.4 in every 100 thousand women per year), and they frequently have a positive HPV test, even though their HPV-related lesions tend to be in regression [21]. If, upon repeating this tests on a patient, an ASC-H or high-grade intra-epithelial lesion is found, colposcopy is advised. If the patient has ASC-US or high-grade intra-epithelial lesions that become higher after two cytological assays, colposcopy is advised. In post-menopausal patients, low-grade intra-epithelial lesions can be monitored every 6 months using co-trials or by performing colposcopy. If an HPV test is negative or no dysplasia is identified in the colposcopy, the co-test can be performed after 1 year. If the result is ASC-US or a high-grade intra-epithelial lesion, a colposcopy must be performed [22].

In patients in whom a CIN I biopsy was detected that was preceded by a low-grade intra-epithelial lesion or ASC-US, a co-test must be performed after 1 year; if both are negative, the patient must return to a normal screening schedule. If a diagnosis of CIN I persists for 2 years, it is acceptable to continue with the follow-up or to treat the lesion as if it had a higher grade. In cases where the result of the second revision is CIN II or worse, the lesion must be treated. In patients in whom a diagnosis of CIN I is preceded by ASC-H or a high-grade intra-epithelial lesion, the follow-up must be more thorough, including an excisional biopsy, a follow-up and a review of the findings.

In patients between 21 and 24 years old, it is advised that the case is handled using a conservative approach. If such a biopsy is preceded by a high-grade intra-epithelial lesion or ASC-H, a cytological assay must be performed every 6 months, and colposcopies should be performed every two. If CIN II or worse is suspected, then a biopsy must be taken. If, after 2 years, the cytology-detected high-grade lesion persists without evidence of the same in the biopsy, then an excision process is advised. CIN I patients between 21 and 24 years old must never be treated [22].

5.9.4 High-Grade Intra-epithelial Lesion

High-grade intra-epithelial lesion are relatively rare, representing only 0.6% of such specimens [23]. However, if a high-grade intra-epithelial lesion is detected by cytology, there is a probability of approximately 70–75% that a CIN II or III will be found in a colposcopy, biopsy or excision [24]. Given the elevated rate of persistence and progression of these conditions, surveillance is mandatory, independent of the age of the patient or her menopause stage. In patients with a CIN II or III diagnosis that has been confirmed by biopsy with discarded invasion and a

satisfactory colposcopy, ablative methods (e.g., cryotherapy, electro-coagulation, or laser vaporization) and excision methods (e.g., loop diathermy, laser or cold knife cone biopsy, or total hysterectomy) are the approved therapies [16].

The present recommendations suggest that colposcopy must be performed whenever there is a cytological diagnosis of ASC-US with a positive HPV test, a high-grade intra-epithelial lesion, ASC-H or AGC [22]. After performing a cytological assay to detect high-grade intra-epithelial lesions with an inadequate colposcopy or a positive endocervical curettage, it is recommended that the practitioner perform an excision procedure both to obtain a sample for a more precise diagnosis and to treat the patient. Any histological CIN II or III diagnosis in the cervical biopsy must be directed to excision or the ablation of the transformation zone unless the patient is pregnant. The "see-and-treat" option is recommended in geographical zones with difficult access or very low economical resources or when a poor follow-up scheme is conducted in patients with a high-grade intra-epithelial lesion cytology in whom a biopsy was not performed. In patients between 21 and 25 years old with CIN II, the regression rate is high, i.e. 28% in 1 year, 63% in 2 years and 68% in 3 years [21]. If a CIN II is detected in a young women and was preceded by ASC-H or a high-grade intra-epithelial lesion, either an ablative or excision procedure could be considered to remove the transformation zone, or simply colposcopic observation every 6 months, especially in CIN II cases. If it persist after 2 years, excision is advised.

In patients with satisfied parity, if the excision reveals positive borders, a definitive surgical procedure is necessary (extrafascial hysterectomy) because the most important marker for recurrence/persistence is the state of the cervical cone margins 16. The incidence/recurrence rates in these cases can reach 16% in cases with positive margins, while a negative margin is associated with a risk of only 4% [16].

5.9.5 Glandular Lesions

For any kind of glandular lesion, the recommendation is to perform a colposcopy and endocervical curettage independent of the HPV test result. Moreover, endometrial curettage is recommended in women older than 35 years old with atypical glandular cell cytology (AGC) and adenocarcinoma in situ (AIS). In cases of AGC in which a CIN II or more is cytologically discarded, the patient can remain under surveillance every 12–24 months. If both results are negative, surveillance must continue for 3 years. In cases of AGC with CIN II or high-grade intra-epithelial lesions but without glandular neoplasia, if the AGC occurs with neoplastic risk or AIS in patients with satisfied parity and a histological diagnosis, a hysterectomy can be performed. Conservative treatments are performed in patients that are considering a future maternity, and an excision procedure is performed if the endocervical cancer sample has CIN or AIS. An incision is then performed and re-evaluated in 6 months using the co-test and colposcopy plus endocervical sampling [22].

5.10 Treatment Options

Treatment options consist of two types: excision (e.g., loop diathermy, laser or cold knife cone biopsy) and ablative (e.g., cryotherapy and laser). In a review, Cochrane 2010, analyzed 29 randomized, controlled studies that included 5441 women with CIN and found no evidence showing that any one procedure was better that any other [25]. In particular, the treatment must be selected in accordance with factors that benefit the patient, her diagnosis and the gynecologist's training. For ablative treatments, it must be certain that there was a satisfying colposcopy with a benign result from an endocervical curettage, the absence of invasion and a fully visible lesion. Some of the advantages of this procedure are its reduced cost and the fact that it does not increase the risk of pre-term delivery. However, it should be considered that there will be no sample available for histologic review. Regarding laser ablation, its requisites are similar to those for cryotherapy, and it is especially recommended for high-grade intra-epithelial lesions. Its main disadvantage is its elevated cost.

Excision procedures, or cone biopsies, are generally performed for diagnosis and therapeutic purposes and consist of removing a large cone-like portion of the cervix that includes the exocervical opening and various portions of the endocervical canal. It is important to mention that the surgeon's experience is fundamental to achieving the success of the procedure and a low rate of complications. This represents, in general, the second diagnosis option, right after colposcopy and biopsy.

Cold knife cone biopsies require local-regional or even general anesthesia and hospitalization, is associated with more complications and produces a more evident anatomic distortion. For these reasons, it is performed with much lower frequency. In contrast, CO^2 -laser cone biopsy can be performed in an ambulatory fashion. It usually preserves the reproductive integrity of the patient, is associated with minimum complications and an excellent healing rate, and facilitates follow-up. Its disadvantages are the fact that it involves thermal damage, the cost of the equipment is high, it requires extensive training, and the time of surgery is long. The loop diathermy cone biopsy (Fig. 5.7) method is based on the principle of monopolar procedures. Its

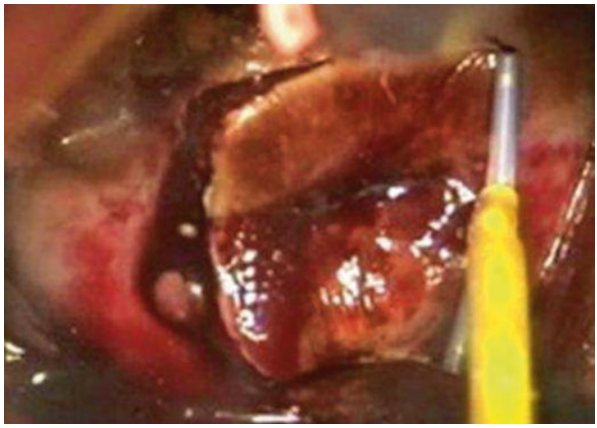

Fig. 5.7 Performance of a loop diathermy cone biopsy

advantages include the fact that it allows a sample to be obtained for histopathological analysis; it is an ambulatory, quick and economic procedure; it is relatively easy to learn; and it is associated with a high healing rate. Nonetheless, inadequate training and the apparent simplicity of the procedure can lead to incomplete excisions, which occurs 44% of the time. Another disadvantage is the high percentage of negative cones (ranging between 14 and 30%), which means that the surgery involves a high number of unnecessary treatment 16 however, there is a risk of removing too much cervical tissue, which would compromise the fertility of the patient.

5.11 Conclusion

Improving the diagnosis and treatment of cervical cancer is a priority for health systems, especially in developing countries. Both the etiology and the natural history of this neoplasia are known. The role of timely detection to identify premalignant lesions with healing potential, which facilitates efficacious and practical procedures, has also been extensively supported. The options for achieving the timely detection of these conditions are various and are focused on cytological analyses and the detection of HPV using molecular assays. Implementing measures that increase the rate of timely detection has lowered both the incidence and the mortality of cervical cancer.

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