

THERAPY

Operative treatment of cervical premalignant lesions and the presence of high-risk human papilloma virus as etiologic agent

Milanova E, Naumov J, Stojovski M, Todorovska I, Daneva K

1st Operative Oncologic Department of the Gynecology and Obstetrics, Clinic Medical Faculty, Skopje, Macedonia. beti.milanova@mol.net.mk

Abstract

The conization as an excisional method is used as an operative treatment of high-risk premalignant cervical lesions. Early detection and removal may stop the developing process that leads to invasive carcinoma. The study presents a group of 100 women, operated with „cold knife“ conization during the year 2002 at the 1st Operative Oncologic Department of the Gynecology and Obstetrician Clinic – Medical Faculty, Skopje. The operative material showed CIN 2 in 2 and CIN 3 in 31 women. In 7 of them, CIN 3 lesions were removed by punch biopsy or ECC, thus the cone showed only CIN 2. In two women out of the total of 67 with the preoperative diagnosis of CIS, CIN 3 lesions were postoperatively diagnosed. This is the result of the adequate punch biopsy during the diagnostic procedure. Three cones showed Ca microinvasivum and other 3 displayed Ca invasivum which then needed other surgical treatment. In 93 % of the women the conization had a therapeutic effect and in 7 % it was only of diagnostic value. HPV testing was made in 55 out of the operatively treated women. The most common type HPV 16 was identified in 27 % of the women. The second was HPV 31 in 25.5 %, then HPV 66 in 14.5 %, HPV 18 in 11 %, HPV CP 8304 and HPV 38 in 5.5 %, HPV 58 as well as MM9 in 2 (3.6 %). The dichotomic presence of HPV 31+18 and HPV 6+16 was identified in two women. (*Tab. 3, Ref. 10.*)

Key words: Sturmdorf conization, moderate and severe dysplasia, Ca in situ, HPV DNA testing, oncogenic HPV.

A number of procedures are used in the detection of cervical premalignant lesions. The tendency of early detection and removal began in 1976 when Zur Hausen in Germany reported the cause of cervical carcinoma. 120 types of HPV have been identified, with a special emphasis on 40 types associated with cervical premalignant lesion. The striving to different oncogenes or high-risk HPV types has enhanced a big progress in methods of HPV DNA testing. The use of in situ hybridization, polymerase chain reaction (PCR) being the only method available for us, and the methods used in high-developed countries: hybrid capture II and III, make the one-time detection of more than one viruse possible. The group of high-risk HPV includes HPV 16, 18, 31, 33, 38, 39, 51, 52, 56, 58, 59, 66, 68. The presence of high-risk virus is indicative for the development of cervical carcinoma, but approximately only 3–4 % of carcinomas develop cervical carcinoma. This “small” number results from preventive diagnostic procedures, therapeutic immunological modifiers, together with ablative and excisional modalities. “Cold knife” conisation from the group of excisional techniques is the most common method used in our country. It can be replaced by

laser conisation, but the significance of cold knife conization is in the histological verification because of “clear” margins. Conization is greatly significant in the treatment of high grade squamous intraepithelial lesion – HSIL (1), a long period before the cervical intraepithelial neoplasia (CIN) is discovered. Every untreated cervical lesion may lead to invasive carcinoma with high mortality rate beside the possibility of radiation or chemotherapy. The cervical screening in USA in the past 60 years has decreased the rate of invasive carcinomas down to 75 %.

Material and methods

The study presents a group of 100 women, operated with “cold knife” conisation during the year 2002 at the 1st Operative

1st Operative Oncologic Department of the Gynecology and Obstetrics, Clinic Medical Faculty, Skopje, Macedonia

Address for correspondence: E. Milanova, Ass, 1st Operative Oncologic Department of the Gynecology and Obstetrics, Clinic Medical Faculty, „Blagoja Davkov“ No 19/9, 1000 Skopje, R. Macedonia.

Tab. 1. Histological diagnose based on operative material (cone).

Histological diagnose	Number/percent	Other operative treatment
CIN ₂	2/2	
CIN ₃	31/31	
CIS	61/61	1 HTA
Ca microinvasion	3/3	3 HTA
Ca invasion	3/3	3 Werheim/Meigs

Tab. 2. HPV type distribution in different types of HSIL.

HPV type	CIN ₂	CIN ₃	CIS	Ca microinvasion
16		5	9	1
31	2	4	8	
18		3	3	
66		3	5	
58		2		
MM9			2	
CP8304		2	1	
38		2	1	
31+18			1	
6+16			1	
Total	2	21	31	1

Oncologic Department of the Gynecology and Obstetrician Clinic, Medical Faculty, Skopje. The preoperative diagnosis was based on cytological Papanicolaou smear (PAP), biopsy or endocervical curettage (ECC). The cytological results were worked out in the Cytological laboratory at our Clinic, while the histological results from the cervical biopsies, ECC and cones at the Institute for Radiotherapy and Oncology. HPV DNA testing with PCR was made in 55 women at the Macedonian Academy of Science and Art (MANU).

We used the Sturmdorf conization vaginal method and general anesthesia. The cutting procedure begins after visualizing the transformation zone with Lugol solution. The height and the width of the cone base depend on the woman's age and the lesion. After the excision, we put four Sturmdorf sutures. The treatment is over when excisional margins stay clear. In cases with unclear excisional margins in coincidence with HSIL or microinvasive carcinoma, we suggest total abdominal hysterectomy (HTA), while in women with invasive carcinoma, radical abdominal hysterectomy – Wertheim Meigs is to be performed.

Results

Among the total of 100 conizations, 2 women with preoperatively identified HPV 31 were with the histological diagnosis of CIN 2. In 7 out of the total of 31 women with CIN 3, the lesions were removed by diagnostic punch biopsy or ECC resulting in CIN 2.

The type of HPV was identified in 20 (65 %) women with CIN 3 before conization. HPV 16 was identified in 5 (25 %),

Tab. 3. Distribution of high-risk HPV types in HSIL.

HPV type	Number	Percent
16	15	27
31	14	25.5
66	8	14.5
18	6	11
CP8304	3	5.5
38	3	5.5
58	2	3.6
MM9	1	3.6
31+18	1	1.9
6+16	1	1.9
Total	55	100

HPV 31 in 4 (20 %), HPV 18 and HPV 66 in 3 (15 %), HPV 58, as well as CP 8304 and 38 in 2 (10 %) women.

In two women out of the total of 67 with the preoperative diagnosis of CIS, CIN 3 was postoperatively diagnosed. This is the result of adequate punch biopsy during the diagnostic procedure. Three cones showed Ca microinvasivum and other 3 cases displayed Ca invasivum which then needed further surgical treatment.

HPV testing with PCR was made in 31 women (46 %) with CIS. HPV 16 was identified in 9 (32 %), HPV 31 in 8 (26 %), HPV 66 in 5 (16 %), HPV 18 in 3 (9.7 %), HPV MM9 in 2 (6.5 %) and HPV CP 8304 as well as HPV 38 in 1 patient, dichotomic presence of HPV 6 and HPV16, as well as HPV 31 and HPV 18 in one patient which is 3.2 % (Tabs 1 and 2).

Dichotomic infection was identified in only two women with conisation. In the first patient two high-risk HPV types (31 and 18) were detected. In the other, one high and other low-risk viruses were identified. Repeated infections accelerate the process of developing premalignant lesion, because of the decreasing of the local cervical immunity. This kind of fast development has been corded in women with immunodeficient diseases-AIDS or in women after renal transplantation (2).

There are 9 identified oncogenic types of HPV virus, most commonly present in premalignant lesions (Tab. 3).

Among the total of 55 women with HPV testing, HPV 16 was identified in 15 (27 %) women, HPV 31 in 14 (25.5 %), HPV 66 in 8 (14.5 %), HPV 18 in 6 (11 %), HPV CP 8304 as well as HPV 38 in 3 (5.5 %), and HPV 58 as well as MM9 in 2 (3.6 %). Dichotomic infection is registered in 2 women – combination of HPV 31 and 18 in the first, and HPV 6 and 16 in the second patient. HPV 6 is in the group of low-risk types which may cause low-risk lesions (LSIL). More combinations of viruses in one patient are possible, especially in those with decreased general immunity where all present HPV types activate and stimulate the progress of the lesion. Vice versa in women with high-risk types of HPV, the infection may persist for a long period without high-risk progression.

Discussion

In our study the conisation had a therapeutic effect in 93 cases (93 %) with diagnosed high-risk lesions. In other 7 cases (7 %) the histological result was of diagnostic value as an indication for further surgical treatment. In these cases, after the further surgical treatment, the cervical lesions became less advanced. In the past 50 years, following the first description of the "cone biopsy" in the treatment of cervical neoplasia (3), conisation has not lost its meaning in therapeutic and diagnostic procedures. Although the intervention seems to be simple, it is one of the most difficult procedures and needs experience and skill (4).

The most common complications are hemorrhage and secondary structures, as well as dysmenorrhoea and colposcopy and cytological evaluation problems.

After the conisation in patient with HSIL, the follow-up should be made once a month, and after the first year, every 3–4 months. The following 3 years every 6th month, then, once a year. In case that sexual partners of women are HPV carriers, we recommend to use preservatives as well as to use vitamins, stop smoking or oral contraceptives (5). The follow up is based on smear (PAP), HPV DNA testing and colposcopy. Any abnormal results need further histological evaluation or immunological treatment (6). According to the distribution of HPV types in HSIL, because of the small number of women included into this study, the results we get are comparable to those from other our trials. We compare HPV 16 in 27 % with 39 % in a study with 77 women and with 34 % in another study with 112 women, as well as with a study made in MANU, which included 200 women where HPV was identified in 28.4 %. According to the study of Bronx University, HPV 16 was detected in 50 % of women with HSIL (7) and in the Greek study in 41 % (8). This type of oncogenic virus is the leading cause of cervical premalignant lesion and carcinoma almost everywhere in the world. The second is HPV 31 with 25.5 % and HPV 66 with 14.5 %, which is higher compared to some of our studies. In a study from 2001, HPV 31 was detected in 19 % and HPV 66 in 7.9 %. HPV 58 was detected in 3.6 %, which differs from the report from Mexico where in the year 2002 precancerous HPV was detected in 28.5 % of the total of 2000 women. Generally, there is a dynamical geographical distribution of oncogenic viruses in the World.

Except for "cold knife" conisation, there is an opportunity of laser conisation, which is of high theoretical value. To complete the therapeutical effect, prior to laser conisation, we must exclude advanced lesion from HSIL of endo and exocervix (9).

According to the latest guidelines, the following of HPV DNA testing after these both types of conisation enable detect reinfection with the same, type or other new infection.

Depending on the testing of high-risk HPV type results, we conclude about the different geographical distribution of HPV types. The detection of CP8304 which had been very rarely identified before namely in 5.5 % of women, as opposed to 50 % in Mexico, results from the viability of the virus antigens in our geographical area. There is a possibility of the development of new infective lines and their sexual transmission, which is the only way of transmission, in our population also in coincidence with other oncogenic types.

Thus, the monitoring of the distribution of various oncogenic types will show us the way of how to prevent cervical carcinoma by means of prophylactic and therapeutic vaccines. We must follow the dynamics of the geographical distribution of HPV for making steps forward in what is going to be and currently is used in the world. The immunological strengthening (10) and HPV immunization may represent our new chemopreventive approach.

Out of all all carcinomas, only the cervical carcinoma being one of the most frequent in women, may possibly be eliminated.

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