



Analysis of cold-knife conization results in HPV positive patients

HPV pozitif hastalarda soğuk konizasyon sonuçlarının analizi

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Abstract

Introduction: To perform the retrospective analysis of cases with cold-knife conization operation. We aimed to determine the risk of positive surgical margins in HPV 16/18 positive and postmenopausal women.

Methods: After approval of the Ethical Committee, the medical record of patients who had undergone a cold-knife conization surgical procedure in our clinic between January 2015 and July 2017 were reviewed. The study included 51 cold-knife conization case that were referred to our colposcopy department for HPV positivity and cervical high-grade intraepithelial neoplasia. We have investigated parameters such as age, menopausal status, cervical smear, human papilloma virus (HPV), colposcopic biopsy/conization histopathological evaluation and positive surgical margin. HPV analysis results were grouped as follows to investigate the effect of HPV 16 and 18. Group I: positivity of HPV 16 and / or 18, group II: other high risk (HR) HPV positive (HPV 16/18 negative). Cold-knife conization results were divided in two groups; normal/low dysplasia group (Normal and CIN I), severe dysplasia group (CIN II / III and CIS).

Results: Cervical smear results were as follows; Normal 27 (52.9%), ASCUS 2 (3.9%), LGSIL 14 (27.5%) and HSIL 8 (15.7%). The results of colposcopy were as follows; CIN I 18 (35.3%), CIN II / III 33 (64.7%). Cold-knife conization histopathological results were as follows; 12 (23.5%) Normal, 8 (15.7%) CIN I, 23 (45.1%) CIN II / III, 8 (15.7%) CIS. 28 patients were in group I (HPV 16/18 positive), whereas 23 patients were in group II (other HR-HPV positive). Normal/low dysplasia rate was 35.7% (10/28), severe dysplasia rate was 64.3% (18/28), positive surgical margin rate was 21.4% (6/28) in the group I. And normal/low dysplasia rate was 43.5% (10/23), severe dysplasia rate was 56.5% (13/23), positive surgical margin rate was 8.6% (2/23) in the group II. In generally positive surgical margin rate after cold-knife conization operation was 15.7% (8/51). In postmenopausal patients, more positive surgical margin was detected (21.1%–12.5%).

Özet

Amaç: Çalışmamızda soğuk konizasyon operasyonu olan hastaların retrospektif analizini yapmak. Amacımız konizasyon sonrası cerrahi alan pozitifliği olan hastalarda HPV 16/18 pozitifliği ve menapozal durumun etkisini ortaya koymayı amaçladık.

Gereç ve Yöntem: Etik kurul onayı sonrası Ocak 2015 ile Temmuz 2017 arasında kliniğimizde soğuk konizasyon ameliyatı olan hastaların medikal kayıtları incelendi. HPV pozitifliği nedeniyle yönlendirilen 51 soğuk konizasyon vakası çalışmaya dahil edildi. Yaş, menapozal durum, servikal smear, Human papillomavirüs (HPV), kolposkopik biyopsi / konizasyon histopatolojik değerlendirmesi ve cerrahi sınır pozitifliği değerlendirildi. HPV 16 ve 18'in etkisini değerlendirmek için hastalar iki gruba ayrıldı; Grup I: HPV 16 ve/veya 18 pozitifliği, grup II: diğer yüksek riskli (HR) HPV pozitifliği (HPV 16/18 negatif). Soğuk konizasyon sonuçları da iki gruba ayrıldı; normal/düşük displazi grup (Normal and CIN I), ağır displazi grup (CIN II / III and CIS).

Bulgular: Servikal smear sonuçları şu şekilde idi; Normal 27 (52.9%), ASCUS 2 (3.9%), LGSIL 14 (27.5%) and HSIL 8 (15.7%). Kolposkopi sonuçları ise şöyle idi; CIN I 18 (35.3%), CIN II / III 33 (64.7%). Soğuk konizasyon sonuçları ise şu şekilde idi; 12 (23.5%) normal, 8 (15.7%) CIN I, 23 (45.1%) CIN II / III, 8 (15.7%) CIS. 28 hasta grup I (HPV 16/18 pozitif) iken 23 hasta grup II (diğer yüksek riskli HPV pozitif) olarak bulundu. Grup I'de normal/düşük displazi oranı 35.7% (10/28), ağır displazi oranı 64.3% (18/28), cerrahi sınır pozitifliği oranı 21.4% (6/28) idi. in the group I. Grup II'de ise normal/düşük displazi oranı 43.5% (10/23), ağır displazi oranı 56.5% (13/23), cerrahi sınır pozitifliği oranı 8.6% (2/23) idi. Sonuç olarak konizasyon sonrası cerrahi sınır pozitifliği 15.7% (8/51) olarak bulundu. Postmenapozal hastalarda ise daha fazla cerrahi sınır pozitifliği saptandı (21.1%–12.5%).

Sonuç: Serviks kanseri etyopatogenezinde HPV 16 ve 18'in diğer yüksek riskli HPV'lere oranla daha etkili olduğunu biliyoruz. Ancak



Discussion and Conclusion: We know that HPV 16 and 18 are more effective than other HR HPVs in the etiopathogenesis of cervical cancer. But there was no significant difference between the groups in terms of severe dysplasia and positive surgical margin. More extensive studies will give more promising results. We also think more emphasis should be given to HR HPVs in routine screening, colposcopy follow-up and vaccination program.

Keywords: Cold-knife conization; human papilloma virus; menopause; positive surgical margin.

The cervix is anatomically located between the uterus and vagina and is divided into two parts as ectocervical and endocervical canal. Between the squamous epithelium in the ectocervix and the glandular epithelium in the endocervical canal, is called the squamocolumnar junction. This junction is far outside the cervix in the first years of life (original squamocolumnar junction). This junction shifts towards the endocervical canal (squamocolumnar junction) with conversion of the glandular epithelium to squamous epithelium (squamous metaplasia). This change zone is called the transformation zone.^[1] Human papillomavirus (HPV) responsible for 95-100% of cervical cancer causes infection in this transformation zone.^[2-4] Infection may spontaneously eradicate 70% to 90% at 1-2 years, but in some cases it may lead to dysplasia and neoplastic changes in the cervical epithelium.^[5]

Cold-knife conization is a surgical procedure that is used in the diagnosis and treatment of cervical preinvasive lesions and generally aims to remove the entire transformation zone together with the lesion in the cervix. Cold-knife conization is a method applied with many indications for diagnosis and treatment. Generally it is used in some indications as follow; suspicion of invasive cervical carcinoma and cervical adenocarcinoma in situ, discordance of cytology / histology specimen, dysplasia in the endocervical canal, severe suspect of neoplasm in spite of inadequate colposcopy (unsatisfactory colposcopy), surgical treatment of cervical severe dysplasia (CIN II +) and stage 1A1 squamous cervical carcinoma. It is preferred to hysterectomy because it has low complication ratio and allows the continuation of fertility.^[1,6]

In addition to that, there are also some contraindications. These are too thighy vagina that not allow vaginal intervention (anatomical, menopausal atrophy), small and insignificant cervix (anatomical, menopausal atrophy, post cervical excisional procedures), orthopedic problems that can not be achieved by the lithotomy position. Pregnancy and adolescence age are relative contraindications for the procedure and timing of surgery should be deferred as far as possible. In case of severe cervicitis and anticoagulant use; the procedure should be postponed to avoid complications. Finally, general anesthesia is required for the procedure, a surgical tecniq LEEP (Loop electrosurgical excision procedure) can be applied under local anesthesia instead of cold-knife conization in the case of contraindication for general anesthesia.^[1]

çalışmamızda gruplar arasında ağır displazi ve cerrahi sınır pozitifliği açısından anlamlı bir fark saptamadık. Daha ileri çalışmalar ile daha net sonuçlar alınabileceğini düşünmekteyiz. Bu bilgiler ışığında rutin tarama, kolposkopi takibi ve aşılama programlarında diğer yüksek riskli HPV'lere gereken önemin verilmesi gerektiğini düşünüyoruz.

Anahtar Sözcükler: Soğuk konizasyon; human papillomavirüs; menapoz; cerrahi alan pozitifliği.

The most important complication is intraoperative and postoperative bleeding. To stop the blood flow from the cervical branches of the uterine artery prior to the start of the surgical procedure, hemostasis syringes placed at the cervix hour 3 and 9 in order to prevent intraoperative hemorrhage may need additional suturation or even hysterectomy as a last resort in cases where the hemorrhage can not be stopped. Postoperative bleeding, which can cause great fear for the patient, can be seen in 5-15% in the first two weeks. Monsel solution, silver nitrate, vaginal gas paking can be put under control. Another complication, infection, is rare and can usually be controlled by local and / or oral antibiotic therapy. The cervical stenosis at the level, which may prevent menstrual bleeding, is rare and can be treated with cervical dilation. Cervical insufficiency is another late complication associated with preterm birth and premature rupture of membranes. Patients who wish to have children afterwards should be informed about this.^[1]

We performed a retrospective analysis of cases with cold conization operation. We aimed to investigate parameters such as cervical smear, human papilloma virus (HPV), colposcopic biopsy / conization histopathologic evaluation and positive surgical margine.

Materials and Method

Ethics Committee approvals were obtained. Included in the study were 51 cases of cold conization operation that were referred to colposcopy unit for HPV positivity between January 2015 and July 2017. All histopathological evaluations of patients except for cervical smears and HPV DNA analysis performed by the Cancer Early Diagnosis Screening and Training Center (KETEM) were reviewed by our hospital pathology laboratory and all patient records were obtained from hospital system.

Cervical smear results; Normal, ASCUS, LGSIL and HGSIL.

13 (HR) HPV types with high risk of inducing cervical cancer in the KETEM program are studied. The HPV types examined were 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68. HPV positive patients were divided into two groups to investigate the effect of HPV 16 and 18 positivity: 16/18 positive (GROUP I), Other HR HPV positive (GROUP II)

Results of colposcopic biopsy; CIN I and CIN II / III.

Cold-knife conization results; Normal, CIN I, CIN II / III, and CIS (carsinoma in situ). Two groups were created for evaluation;

normal / mild dysplasia group (Normal and CIN I), severe dysplasia group (CIN II / III and CIS).

In addition, positive surgical margin was evaluated from the pathology records.

Results

The mean age of the patients was 43.3 + 9.2 (30 - 68). There was no significant difference between groups in terms of age. ($p=0,79$)

Cervical smear results were as follows; Normal 27 (52.9%), ASCUS 2 (3.9%), LGSIL 14 (27.5%) and HSIL 8 (15.7%). Hpv types and smear results is shown in Figure 1.

The results of colposcopy were as follows; CIN I 18 (35.3%), CIN II / III 33 (64.7%). Histopathological evaluation of the cold conization cases revealed that 12 (23.5%) normal, 8 (15.7%) CIN I, 23 (45.1%) CIN II / III, 7 cases were detected as CIS.

After the cold conization operation, positive surgical margin was detected in 8 (15.7%) patient. Hpv type and margin positivity is shown at Figure 2. The mean age of patients with negative surgical margin was 42.2, while the mean age of patients with positive surgical margin was 49.5. That was statistically significant ($p=0,04$). However, in postmenopausal group the positivity of surgical margin rate was 21.1% whereas it was 12.5% in premenopausal group. To understand whether margin positivity is effected from menopause condition; statistics showed that menopause group is not different from pre-menopause group in terms of margin positivity ($p=0,333$).

According to the HPV positivity ingroups; there was 28 patients in Group I and 23 patients in group II. Cold conization results in Group I; normal / slight dysplasia rate was 35.7% (10/28), and severe dysplasia rate was 64.3% (18/28). Cold conization results in group II; normal / slight dysplasia rate was 43.5% (10/23), and severe dysplasia rate was 56.5% (13/23). There was no statistically significant difference in terms of conization results between groups. ($p=0,390$) The rate of positive surgical margin was 8.6% (2/23) in group 2 while the rate of positive surgical margin was 21.4% (6/28) in group 1. Although difference seems to be significant; it is insignificant. ($p=0,26$)

Discussion

Cervical cancer is the fourth most common cancer seen in women worldwide. The second most common cancer in women aged 15 to 44 years. More than 500,000 women are diagnosed each year and approximately 265,000 women die from this cancer.^[7]

HPV viruses are divided into two groups as low risk (LR HPV) and high (HR HPV) risk compared to cancer development potentials. International cancer research agency (IARC) recently identified 25 HR HPV in 2012. These are in turn; 16, 18, 26, 30, 31, 33, 34, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70 and 73.^[8] There is a national cervical cancer screening programme in Turkey. Cervical cancer screening and HPV DNA analysis is

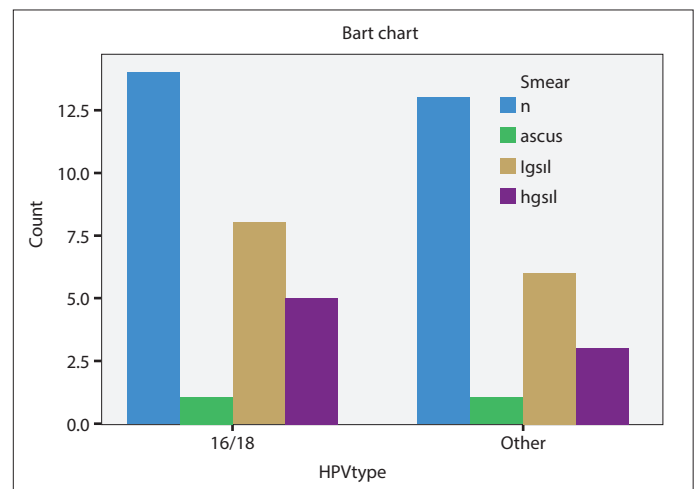


Figure 1. HPV type and smear results.

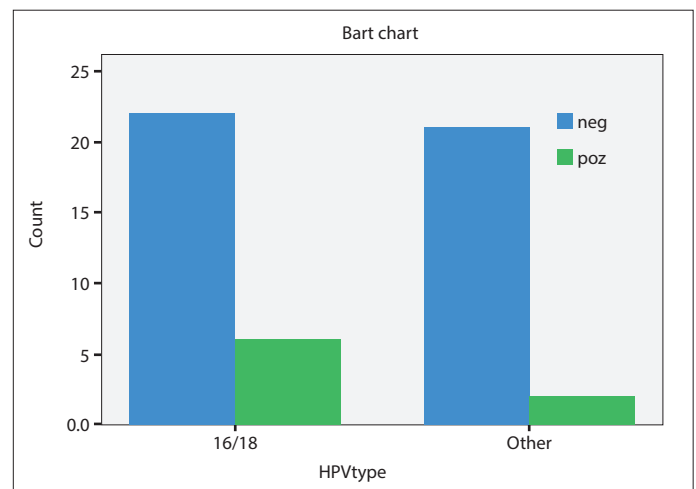


Figure 2. Hpv type and margin positivity.

done by central laboratories. In the case of HPV positivity, related patients are informed by family doctors and directed to gynecologists and obstetricians. 13 high-risk HPV DNA is being screened under the screening program. The types of HPV examined were 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68.^[9] Patients with HPV positive in our study were divided into two groups to investigate the effect of HPV 16 and 18 positivity: 16/18 positive (Group I), and other HR HPV positive (Group II).

Cervical smear results were as follows; Normal 27 (52.9%), ASCUS 2 (3.9%), LGSIL 14 (27.5%) and HSIL 8 (15.7%). The results of colposcopy were as follows; CIN I 18 (35.3%), CIN II / III 33 (64.7%). The high dysplasia rates in the colposcopy results are the result of the study group consisting of convalescent patients. Histopathological evaluation of the cold conization cases revealed 12 (23.5%) normal, 8 (15.7%) CIN I, 23 (45.1%) CIN II / III, 7) was detected as CIS.

There are few articles on the postoperative positivity of the surgery. In the meta-analysis involving 1596 patients, lesions were detected at surgical margins in 200 patients (13%). In an interesting study questioning the surgeon's influence at the

positive surgical margin, the surgical field positivity was found between 5% and 22% among different senior professionals. In this study, it was emphasized that the question of the positivity of surgical field over 25%.^[10,11] In our study, we found the positivity of the surgical field after cold salvage operation to be 15.7% in accordance with the literature. The relationship between HPV type and margin positivity was statistically insignificant. Whether HPV type is 16–18, margin positivity is same with other risky HPV groups. ($p=0,269$)

There are some studies investigating the optimal cone size to reduce surgical site positivity. As a result of these studies, the optimal cone size and depth value that can be routinely applied to each patient has not been reached. It is essential to remove the transformation zone precisely and it seems more reasonable to avoid unnecessary deep excision. Positive surgical field conditions have been shown to be most affected by menopausal status - a new transformation zone with endocervical canal.^[12] In our study, we also found more positivity of the surgical field due to menopausal status. The mean age of the patients who were positive in the surgical field was 42.2 versus 49.5 years. And 50% of the patients who were positive for surgery were menopausal, whereas 34.8% of the negative group were postmenopausal. Although, in our study, margin positivity was related with age increasing but not with menopause; that means how many years after menopause may have importance; but this study cannot explain that condition related with menopause time.

In a worldwide retrospective study of HPV types in cervical cancer, HPV was detected in 8,977 (85%) of 10,575 patients with cervical cancer. HPV 16 and 18 were the most common types of HPV in the pathogenesis of cervical cancer, accounting for 71% of invasive cervical cancers.^[13] Vaccine studies were based on this foundation. Cervarix® and Gardasil® HR, two HPV vaccines that were initially marketed, provided protection against only 16 and 18 HPVs. However, these developments are not enough and it is necessary to develop protective vaccines against also other HPV types. And finally to the Gardasil 9® market, which is also a protective against 31, 33, 45, 52, 58 in addition to the double and quadruple vaccination. Although this vaccine appears to be particularly protective for European countries in particular, it has raised questions about adequate protection, especially in countries where different HPV types, such as Asia and Latin America, are more common.

In that study, between the groups according to the HPV results, we found 16 HRV positives (Group I) in 28 patients and another HR HPV positivity (Group II) in 23 patients except 16/18. In Group I, 64.3% of the results of cold conization were severe dysplasia and 21.4% were positive for surgery. In Group II, however, these rates were 56.5% and 8.6%, respectively. The rate of severe dysplasia was similar among the groups, but surgical site positivity was higher in the HPV 16-18 positivity group.

We know that HPV 16 and 18 are more effective than other HR HPVs in the etiopathogenesis of cervical cancer. HPV 16 and /

or 18 positivity is associated with more severe dysplasia and surgical site positivity, but the rates are close to the other but are not statistically significant. The larger groups and smarter design studies may improve the understanding the importance of HPV type in improving of dysplasia and choosing the most perfect way of treatment for women having what kind of HPV type.

Conclusion

The results of our cold conization and colposcopy results were consistent with each other. We found that the surgical margin of the conization was compatible with littermate. Menopausal status and HPV 16–18 positivity were found to be effective in this case. For this reason, we believe that it may be beneficial to remove wider and deeper tissue in postmenopausal patients, avoiding long-term complications such as preterm labor and cervical stenosis. In addition, HPV 16-18 positive cases during reproductive age should be informed that there is an increased risk of long-term complications or surgical site positions in the current surgical setting.

In the literature we know that HPV 16–18 positivity is associated with more cervical cancer. However, in terms of severe dysplasia and surgical field positivity, we found that other HR HPV types were also risky as HPV 16-18. We think that in this regard, more intensive studies will lead to more clear results.

We also think that the cervical cancer screening program should also show the necessary standard for other HR HPV types. And we think that vaccination programs should be developed rapidly and new generation vaccines should be produced, especially those with low and middle income levels, where deaths from cervical cancer are more common.

Conflict of interest: There are no relevant conflicts of interest to disclose.

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