

Original Research - Özgün Araştırma

First Year Evaluation of Negative Cervical Conizations Performed for Various Reasons in A Tertiary Center

Tersiyer Bir Merkezde Farklı Nedenlerle Uygulanmış Negatif Konizasyon Olgularının Birinci Yıl Değerlendirilmesi

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ABSTRACT

Aim: We aimed in current study to identify the frequency of abnormal cytology, human papilloma virus (HPV) status and their clinical significance in patients with negative conization results performed for various reasons.

Materials and Method: We evaluated the pathologic results of cold knife conization and loop electrosurgical excision procedures (LEEP) performed for 317 patients in our institution in between January 2010 and January 2017. We studied 56 patients with negative conization after excluding 261 patients with preinvasive or invasive results. We compared their cytologic and HPV status before excisional procedure with 12th month results and discussed its clinical significance.

Results: The histopathologic evaluation results of negative conization performed for various indications were as follows: Chronic cervicitis: 34/56 (60.7%), immature squamous metaplasia: 6/56 (10.7%), normal transformation zone: 5/56 (8.9%), wide cautery artifact: 4/56 (7.1%), foreign body reaction: 3/56 (5.3%), normal ectocervical epithelium: 2/56 (3.5%), atrophic findings: 2/56 (3.5%). For 39 patients with a known human papilloma virus deoxyribonucleic acid (HPV DNA) status, pre-conizational HPV positivity and negativity was 27/39 (69.2%) and 12/39 (30.7%) respectively. HPV status of 17 (30.4%) patients had not been known before conization. In the 12th month following conization, HPV positivity for 46 patients with a known HPV status was 9/46 (19.5%) and negativity was 37/46 (75.5%). HPV status for 10 (17.9%) patients was not known. Seven of nine patients who had positive HPV in post-conizational follow-up had positive HPV results before conization, too. Pre-conizational HPV status of three patients had not been determined. Seven of 27 pre-conizational HPV positive patient was HPV positive in the first year of follow-up. With excisional procedure a clearance with a rate of 20/27 (74.1%) was rendered. For two patients with pre-excisional positivity, the HPV DNA results were not found. For eight of 50 patients in follow-up group the cytologic results were as follows: high grade squamous intraepithelial lesion (HSIL): 4, low grade intraepithelial lesion (LSIL): 1, atypical squamous cells of undetermined significance (ASCUS): 2, atypical glandular cells (AGC): 1.

Conclusion: Although the diagnosis of cervical preinvasive disease can be done with biopsy samplings, some histopathologic evaluations for excisional procedures like conization or LEEP will reveal will a negative result for preinvasive or invasive disease. But, HPV positivity and abnormal cytologic results has not been reported uncommon in such groups. In the light of this data, we can reduce the undesirable clinical results after a negative conization result with a thorough follow-up.

Keywords: negative conization, HPV DNA, cervical cytology

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ÖZET

Amaç: Bu çalışmada farklı nedenlerle servikal konizasyon yapılmış ve konizasyon spesimeninin patolojik incelemesi sonucunda preinvaziv veya invaziv lezyon bulunmayan hastalarda birinci yıl sonunda anormal sitoloji sıklığını, HPV durumunu ve bunların klinik önemini araştırmayı amaçladık.

Yöntem ve Gereçler: Kurumumuzda Ocak 2010 – Ocak 2017 arasında soğuk konizasyon ve LEEP uygulanmış 317 hastanın patolojik inceleme sonuçlarını değerlendirdik. Preinvaziv ve invaziv sonucu olan 261 hastayı çalışma dışı bırakarak negatif konizasyon sonucu olan 56 hastayı çalışmaya dahil ettik. Eksizyonel işlem öncesindeki HPV sonuçlarını 12.ayda yapılan HPV sonuçlarıyla karşılaştırıp bu durumun klinik önemini tartıştık.

Bulgular: Çeşitli nedenlerle konizasyon yapılan ve premalign/malign hastalık açısından negatif konizasyon sonucu olan olguların patolojik inceleme sonuçları; Kronik servisit 34/56 (%60.7), immatür skuamöz metaplazi: 6/56 (%10.7), normal transformasyon zonu: 5/56 (%8.9), geniş koter artefaktı: 4/56(%7.1), yabancı cisim reaksiyonu: 3/56 (%5.3), atrofi bulguları: 2/56(%3.5) şeklinde idi. Konizasyon öncesi HPV DNA durumu bilinen 39 hastanın HPV açısından pozitiflik ve negatiflik oranı sırası ile 27/39 (%69.2) ve 12/39(%30.7) olarak saptandı. 17 hastanın konizasyon işlemi öncesi HPV durumu ile ilgili bilgi elde edilemedi. Konizasyonu takiben 12. aydaki HPV durumu bilinen 46 hastanın 9(%19.5)'unda HPV DNA pozitif, 37(%75.5)'sinde HPV DNA negatif olarak saptandı. 10(%17.9) hastanın ise HPV durumu tespit edilemedi. Konizasyon sonrası izlemde birinci yılda HPV pozitif olan 9 hastanın 7'sinde konizasyon işlemi öncesinde de HPV pozitif idi. Konizasyon öncesi HPV pozitif olan 27 hastanın 7'sinde birinci yıl sonundaki izlemde HPV pozitifliği görüldü. Eksizyonel prosedür ile 20/27(%74.1) oranında klirens sağlanmış olduğu saptandı. Konizasyon öncesi HPV pozitif olan 2 hastanın izlemindeki HPV durumu tespit edilemedi. Konizasyon sonrası takibine gelerek sitolojik inceleme yapılan 50 kişilik izlem grubunda 8 hastada birinci yıl sonunda anormal sitoloji sonucu elde edilmiş olup, dağılımı şu şekilde bulundu; yüksek dereceli intraepitelyal lezyon (HSIL):4, düşük dereceli intraepitelyal lezyon (LSIL):1, önemi belirlenemeyen atipik skuamöz hücreler (ASCUS):2, atipik glandüler hücreler (AGC):1.

Sonuç: Servikal preinvaziv ve invaziv lezyonlar biyopsi ile tanı alınmasına karşın, takiben yapılan konizasyon ve LEEP gibi eksizyonel prosedürlerle elde edilen dokuların patolojik incelemesi zaman zaman bu hastalıklar açısından negatif sonuç vermektedir. Bu hasta grubunda HPV pozitifliği ve anormal sitoloji sonuçları nadir görülmeyen durumlardır. Negatif konizasyon durumlarında uygun bir izlem yöntemi ile istenmeyen sonuçları azaltmak mümkündür.

Anahtar Kelimeler: negatif konizasyon; HPV DNA; servikal sitoloji

INTRODUCTION

Cold knife conization and LEEP are commonly employed methods in the definitive diagnosis and treatment of cervical intraepithelial neoplasias and glandular diseases within the endocervical canal. Though, cold knife sometimes is the preferred one thanks to its lack of cautery artifact, in many studies LEEP procedure have been revealed nearly similar clinical results with former one with some advantages such being done in an outpatient setting with local anesthesia, few perioperative complications and low cost (1). Thereof, we combined the methods of cold knife conization and LEEP under the title of "conization". Most histopathologic evaluation of conization specimens will confirm the HSIL biopsy results but, a number of them will not due to particular reasons such as incorrect biopsy diagnosis, insufficient excisional technique, total removal of lesion by biopsy or secondary destruction of the lesion by postbiopsy inflammation (2). Despite the well-known significant rate of recurrence of an HSIL or emergence of an invasive disease in patients diagnosed after excisional procedure, the clinical significance of a negative conization result is poorly understood. In some studies recurrent rates were reported as similar for positive and negative conization findings following a biopsy diagnosis of high grade lesions (3). There is no sufficient published data on negative HSIL frequency on conizations following a diagnosis of a positive biopsy diagnosis and its clinical implications. Studied in few studies, negative conization had been indicated as % 10-20 (2-4). There is no any optimal follow-up protocol for these cases, but single or combined use of conventional cytology, colposcopy and HPV testing may be options. Currently, HPV testing is not a part of routine follow-up in patients with preinvasive lesions confirmed in conization specimens, but has a potential. Some authors advocate routine use of HPV test in addition to cytology for the follow-up after conizations owing to its high detection rates (5). Due to the similar recurrence rates of HSIL after positive and negative conization results for it, HPV testing can be a reasonable option or a component for follow-up of negative conization results.

MATERIALS AND METHOD

The current retrospective study was performed at a tertiary referral hospital, Goztepe Research and Training Hospital affiliated with Medeniyet University in Istanbul, Turkey after obtaining approval from the institutional review board. Gynecology and Pathology Department database were retrospectively reviewed between January 2010 and December 2016 for cases underwent cold knife conization or LEEP for various indications. We excluded 261 of 317 patients whose final histopathologic results following cold knife conization or LEEP had been preinvasive or invasive. We picked the cytologic, colposcopy, biopsy and HPV DNA results of remaining 56 patients. Cytologic evaluations were done along with the Bethesda System. For determination of HPV DNA polymerase chain reaction method was used to identify high-risk HPV DNA (Type-16, 18, 31, 33, 35, 39, 45,

51, 52, 56, 58, 59, 66, 68 and 82). 38 of 56 excisional procedure were cold conization and 18 were LEEP. We combined the results of cold conizations and LEEPs under the same title of "conization" due to their similar clinical efficiency. All patients in our study had follow-up visits at least in third, sixth or twelfth months following conization. We evaluated the data of patients on their cytologic result and HPV status only on the twelfth month. We did not take into account former results in follow-up and called patients without results for the twelfth month cytologic examination and HPV DNA tests. Eight patients had already required tests for our study.

For the statistical analysis, the SPSS statistical software package, version 22.0 (Chicago, IL, USA), was used. Descriptive data were statistically described in terms of range, means \pm SDs, frequencies (number of cases), and percentages when appropriate.

RESULTS

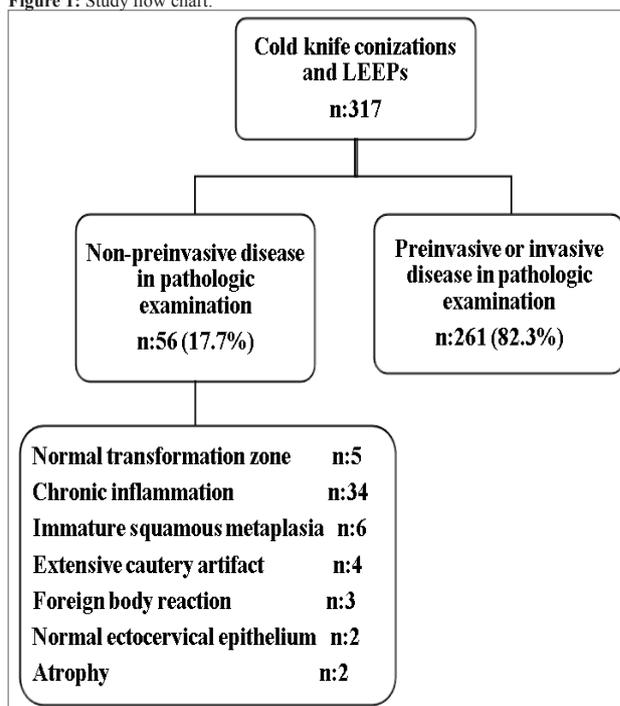
Demographic and clinical characteristics of the patients is presented in Table 1. The final histopathologic results of 56 patients in their negative conization report were as follows: 34 chronic cervicitis, 6 squamous metaplasia, 5 normal transformation zone (TZ), 4 widespread cautery artifact, 3 foreign body reaction, 3 normal ectocervical epithelium and 2 atrophy findings. We identified 19 cases of HSIL, 7 of LSIL, 19 of ASCUS, 2 of AGC in cytologic evaluations performed before conization. We could not obtain the cytologic results of three patients. The indications for conization were; cervical intraepithelial neoplasia I (CINI) in 15 patients, CIN II in 21, CIN III in 14, adenocarcinoma in situ (AIS) in 1 and inadequate colposcopy in 5 (Figure 1). In the first year postconizational follow-up we could reach cytologic results of 50 patients. Eight of them were reported as abnormal. 4 HSIL, 1 LSIL, 2 ASCUS and 1 AGC. In 6 of those 8 patients with a follow-up abnormal cytology HPV DNA was positive. In one patient with HSIL and one with ASCUS, HPV DNA were negative. All 4 HSIL cases had undergone repeat conization. Two of them had positive margins in cone specimen, two were margin free. We offered hysterectomy to patients with margin positive results. One of the patients with negative margin asked hysterectomy. Only one chose further follow-up. In the final pathologies of those underwent hysterectomy not any invasive lesion is reported. In two ASCUS result the further tests showed chronic infection and LSIL. In LSIL, not any abnormal result was found in biopsy examination. In AGC one, we found an endometrial hyperplasia. In the 12th month follow-up visit 9 patients had a positive HPV DNA result (9/46, 19.5%). 27 of 39 patients whose HPV DNA tests positive before conization were found again HPV DNA positive after conization (69.2%). First year follow-up HPV DNA test results were positive for 7 patients and negative for 20 in the group of 27 patients who had positive HPV DNA results before conization. HPV clearance rate was identified as 74.1%. The preconizational HPV status for two patients who had positive results after conization were not known (Table 2 and 3).

Table 1: Patient characteristics.

Age, mean ± sd (range)	40.8 ± 9.9 (22-62)
Parity	
0	7 (%12.5)
1	12 (%21.4)
≥2	37 (%66.1)
Cytology before conization	
ASCUS	15 (%26.8)
LSIL	7 (%12.5)
HSIL	19 (%33.9)
ASC-H	2 (%3.6)
AGC	2 (%3.6)
Not performed	8 (%14.3)
Unknown	3 (%5.3)
Conization indications	
CIN 1	15 (%26.8)
CIN 2	21 (%37.5)
CIN 3	14 (%25.0)
Adenocarcinoma insitu	1 (%1.8)
Unsatisfactory colposcopy	5 (%8.9)
HPV statement (preconization)	
HPV DNA negative	12(%21.4)
HPV DNA unknown	17(%30.4)
HPV DNA positive	27(%48.2)
Type 16	10(%17.8)
Type 18	4(%7.1)
Type 31	2(%3.6)
Type 33	2(%3.6)
Type 35	1(%1.8)
Type 45	1(%1.8)
Type 51	1(%1.8)
Type 56	1(%1.8)
Type 58	1(%1.8)
Type 68	1(%1.8)
Double (16+33)	1(%1.8)
Double (18+45)	1(%1.8)
Multiple (16+18+51)	1(%1.8)
Surgical method	
Cold knife	38(%67.9)
LEEP	18(%32.1)

Table 2: First year results following negative conization.

Cytologic Evaluation			HPV DNA Status		
Normal	Abnormal	Unknown	Negative	Positive	Unknown
42/50 (84%)	8/50 (16%)	6/56 (10.7%)	37/46 (80.4%)	9/46 (19.6%)	10/56 (17.9%)

Figure 1: Study flow chart.**Table 3:** Details of patients with abnormal cytology and positive HPV DNA.

Cytology (1.year)	HPV type (1.year)	Conization result	Preoperative biopsy	Preoperative cytology	Preoperative HPV statement	
1	HSIL	Type 18	Chronic cervicitis	CIN 2	LSIL	Type 18
2	HSIL	Negative	Chronic cervicitis	Unknown	HSIL	Type 16
3	HSIL	Type 16	Immatur squamous metaplasia	CIN 3	HSIL	Type 16+33
4	HSIL	Type 45	Cautery artifact	CIN 2	ASCUS	Type 31
5	ASCUS	Type 31	Chronic cervicitis	CIN 1	HSIL	Type 16
6	ASCUS	Negative	Normal transformation zone	CIN 1	HSIL	Unknown
7	LSIL	Type 16+33	Chronic cervicitis	CIN 2	Unknown	Type 16
8	AGC	Type 18	Foreign body reaction	CIN 2	ASCUS	Unknown
9	Normal	Type 51	Immatur squamous metaplasia	CIN 2	LSIL	Unknown
10	Normal	Type 16	Chronic cervicitis	CIN 3	LSIL	Type 18+45
11	Normal	Type 16	Chronic cervicitis	CIN 3	ASCUS	Type 51

DISCUSSION

LEEP has proved to be an effective, safe and widely used method for treatment of HSIL. Although most LEEP result confirm the diagnosis of a biopsy proven HSIL, a minority of them will yield inconsistent results. Published data indicate that it occurs in 10-20 % of cases (2). Diakomanolis et al reported that approximately 16% of cone biopsies following a biopsy diagnosis of CIN II to III would show no evidence of cervical dysplasia. Similarly, Livasy et al reported a series of 674 patients with biopsy-confirmed HSIL treated by LEEP. In this series, 14% of LEEP specimens were negative for dysplasia (3, 4). These negative results from LEEP may be a result of a number of causes including diagnostic errors in pathologic specimens, complete removal of preinvasive focus by the biopsy or inflammation in specimen following biopsy. The clinical significance of a negative LEEP following a biopsy proven HSIL is poorly understood. We aimed to evaluate the clinical outcome of such cases in this study. The analysis of final histopathologic results showed that 56 of 317 cases of (17,6 %) that underwent conization for CIN II/III had been free of any cervical intraepithelial dysplasia. This finding is consistent with previous reports. We tested the recurrence rate of HSIL and HPV DNA status after a negative LEEP result exactly in the first year. Our findings showed that 8 % of 50 patients with a negative LEEP result for HSIL had positive result on their clinical follow-up. Totally, sixteen percent of 50 patients had abnormal smear results on the following 12th month. In recent years, many papers assessed the predictive value of HPV status alongwith the margin status for the risk of persistent or recurrent cervical intraepithelial neoplasia. Nevertheless the timing of follow-up after conization is still unclear. The great majority of these studies showed a relations between positive HPV status following treatment and high disease failure (6). Even in lesions with negative margins rate of the residual/recurrent disease rates were found to be high (7). In our study, HPV DNA test positivity rate was found quite high at the 12 month after a negative conization in patients with abnormal cytology at 12th month (75,0%, 6/8) compared with the patients with normal cytology results (4%, 2/50). HPV DNA positivity appears to be an important risk factor for an abnormal cytology during follow-up of a negative conization. In the lights of current study, we suggest that initial HPV DNA test can be used a surveillance tool to predict future disease recurrence. Our study confirms the importance of close follow-up of patients who had a positive cytology or biopsy results but a negative conization for an high grade intraepithelial cervical lesion. On the basis of our data, patients with both positive and negative LEEP findings following a biopsy diagnosis of HSIL should be followed up similarly.

The major limitations of this study were its retrospective nature, short time of follow-up (12 months) and relatively low number of patients. Nevertheless, results are largely compatible with available data.

CONCLUSION

A negative conization result does not provide a guarantee for absence of persistence or recurrence of disease. Particularly in patients with an initial positive HPV testing, evaluating HPV status after a negative conization result following a positive cytology or biopsy results may assist to foresee a persistent or a recurrent cervical intraepithelial lesion. Establishment of a clear follow-up protocol for such cases needs further studies.

KAYNAKLAR

1. Greenspan DL, Faubion M, Coonrod DV, Hart KW, Mathieson K. Compliance After Loop Electrosurgical Excision Procedure or Cold Knife Cone Biopsy. *ObstetGynecol* 2007;110(3):675-680.
2. Witt BL, Factor RE, Jarboe EA, Layfield LJ. Negative Loop Electrosurgical Cone Biopsy Finding Following a Biopsy Diagnosis of High-Grade Squamous Intraepithelial Lesion Frequency and Clinical Significance. *Arch Pathol Med.* 2012; 136(10):1259-1261.
3. Livasy CA, Moore DT, Van Le L. The clinical significance of a negative loop electrosurgical cone biopsy for high-grade dysplasia. *Obstet Gynecol.* 2004;104(2):250-254.
4. Diakomanolis E, Haidopoulos D, Chatzipapas I, Rodolakis A, Stefanidis K, Markaki S. Negative cone biopsies: a reappraisal [erratum in *J Reprod Med.* 2003;48(10):833]. *J Reprod Med.* 2003;48(8):617-621.
5. Dogan NU, Salman MC, Yuce K. The role of HPV DNA testing in the follow-up of cervical intraepithelial neoplasia after loop electrosurgical excision procedure. *Arch Gynecol Obstet.* 2011;283(4):871-877.
6. Rositch AF, Soeters HM, Offutt-Powell TN, Taylor SM, Smith JS. The incidence of human papillomavirus infection following treatment for cervical neoplasia: a systematic review. *Gynecol Oncol*;132(3): 767-779.
7. Wu D, Zheng Y, Chen W, Guo C, Yu J, Chen G, Huang Y. Prediction of residual/recurrent disease by HPV genotype after loop excision procedure for high-grade cervical intraepithelial neoplasia with negative margins. *Aust N Z J Obstet Gynaecol* 2011;51(2):114-118.