효과적인 의학논문 작성전략
(IMRD 구성전략과 피해야할 점, reject 되는 이유)

울산의대 서울아산병원 산부인과 **박정열**

서울아산병원
Asan Medical Center

목차

- IMRD 구성 전략
- 피해야 할 점
- Reject 되는 이유
- Take home massage

실제 논문 작성 순서


지도교수배정 & 논문주제결정
연구자 자격 갖추기 (필수)
GCP 교육 / ABLE 교육
연구계획서작성
IRB 승인
후향적연구:
자료수집, 통계분석
전향적연구
Meta-analysis
논문작성 (Writing)
논문 제출
Reject
논문의 revision
논문의 출간

논문의 작성 전 고려 사항 : Authorship 결정

- Authorship (ICMJE-모든 요소 만족)
  - 연구의 개념과 설계에 참여
  - 데이터 수집과 해석 담당
  - 논문 초안 작성에 참여
  - 논문 최종본 승인
- Authorship의 원칙을 미리 정하여 그 원칙에 따라 authorship을 결정
  저자들의 역할 배분 (Author contribution)
- 주저자 (제1저자, 교신저자), 공저자
  공저자 순서 : 기여도에 따른 순서
  공동주저자 (Journal guideline 준수)
- 저자 수의 제한 (Journal guideline 준수) – 되도록 적게
- Contributor → Acknowledgement
  - 단순 재정 취득, 자료 수집, 일반적인 감독, 연구재료제공, 조사자, 자문 등
- Gift author (선물저자), 유령저자 (ghost author), 교환저자 (swap author), 도용저자

논문 작성 시 고려할 사항

- Journal style 준수
  - 각 journal 마다 제공하는 author guideline
  - Journal-specific policy & instruction for authors
- Publication and research ethics guidelines 준수
  - ICMJE : International Committee of Medical Journal Editors
  - CONSORT : Consolidated Standards of Reporting Trials

    COPE : Committee on publication Ethics
  - WMA Declaration of Helsinki
  - STROBE: STrengthening the Reporting of OBservational studies in Epidemiology

논문의 구성 (Original Article) : Word File

- Title page : Title, Running title, 저자, 페이지수, word count, 그림표수, Synopsis
- **Abstract**
- **Introduction**
- **Materials and Methods**
- **Results**
- **Discussion / Conclusion**
- Acknowledge / Conflict of Interest / Funding Source
- Reference
- Figure legend, Table legends
- Tables – 별도의 word file
- Figures – 별도의 file

논문 쓰기 (Writing) 순서

- Title
- Materials and Methods
- Table, Figure
- Results
- Conclusion / Discussion
- Introduction
- Abstract

Title 정하기

- Reflecting the content of paper
- Specific & Descriptive
- Avoid unnecessary detail
- 단어수, 글자수 제한 (투고규정준수)
- 연구형태를 반영하는 것이 좋다
  - Prospective study, retrospective study, review
- Avoid abbreviations
- Use the common name
- Chemicals by fomulas

Human Papillomavirus Test After Conization in Predicting Residual Disease in Subsequent Hysterectomy Specimens

Jeong-Yeol Park, MD, Dae-Yeon Kim, MD, PhD, Jong-Hyeok Kim, MD, PhD, Yong-Man Kim, MD, PhD, Young-Tak Kim, MD, PhD, and Joo-Hyun Nam, MD, PhD

OBJECTIVE: To estimate the effectiveness of the human papillomavirus (HPV) test performed after conization in predicting residual disease in patients who subsequently underwent hysterectomy.

METHODS: A total of 115 patients who underwent hysterectomy after conization caused by cervical intraepithelial neoplasia grade 3 (CIN 3) and microinvasive cervical cancer (IA1 cancer) were included in this prospective study. All patients underwent HPV testing with a liquid hybridization assay immediately before hysterectomy. Differences in sensitivity, specificity, and accuracy between resection margin and the HPV test in predicting residual disease in subsequent hysterectomy samples were estimated using the McNemar exact test.

RESULTS: Univariable analysis showed that age, parity, menopausal status, glandular extension, and severity of disease were not predictive for residual disease, but positive resection margin and positive HPV tests were significant factors for predicting residual disease. These factors were also significant in a multivariable analysis (positive resection margin 45.5%, odds ratio [OR] 3.09, 95% confidence interval [CI] 1.19–8.03, $P=.021$; positive HPV test 57.6%, OR 11.05, 95% CI 4.01–30.49, $P<.001$). With resection margin, the sensitivity, specificity, and accuracy in predicting residual disease were 75%, 53%, and 61%, respectively, whereas, with the HPV test, these values were 85%, 67%, and 73%, respectively ($P=.454$, .080, and .044, respectively). Of patients with positive resection margins, 79% of HPV-negative patients had no residual disease. Of patients with negative resection margins, no HPV-negative patient had residual disease.

CONCLUSION: The HPV test after conization was significantly more accurate than resection margin for predicting residual disease. The predictive value of resection margin for predicting residual disease was much improved when used in combination with the HPV test. Use of the HPV test is recommended for identifying patients for subsequent hysterectomy after conization for CIN 3 and IA1 cancer.

(Obstet Gynecol 2009;114:87–92)

LEVEL OF EVIDENCE: III

Conization of the uterine cervix by procedures such as cold knife conization and loop electrosurgical excision procedure (LEEP) is considered an appropriate treatment for cervical intraepithelial neoplasia grade 3 (CIN 3) and microinvasive cervical cancer (IA1 cancer). However, residual disease after conization due to CIN 3 and IA1 cancer is found in 23–34% of patients who subsequently undergo hysterectomy.[1] Therefore, accurate prediction of residual disease after conization is important for the conservative treatment and counseling of patients with CIN 3 and IA1 cancer, both for the physician and patient.

Although several demographic and clinicopathologic factors, including age, parity, menopausal status, severity of lesion, glandular extension, and resection margin, have been reported to be predictive for residual disease after conization,[2] resection margin remains the gold-standard technique for prediction of residual disease after conization. However, residual disease can be found subsequently in up to 2–31% of patients with negative resection margins.[3–10] This may be due to multiple lesions that were not resected during conization; by contrast, residual disease is not found in up to 10–60% of patients with positive resection margins.[3–10] This may be because residual

From the Department of Obstetrics and Gynecology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea.

Corresponding author: Jong-Hyeok Kim, MD, PhD, Obstetrics and Gynecology, College of Medicine, University of Ulsan, Asan Medical Center, #388-1 Poongnap-2 dong, Songpa-gu, Seoul, 138-736, Korea; e-mail: hyeokkim@amc.seoul.kr.

Financial Disclosure

The authors did not report any potential conflicts of interest.

ISSN: 0029-7844/09

Materials and Methods 쓰기

- 연구를 어떻게 수행하였는지 기술
- 이미 잘 알려진 연구방법을 사용한 경우 이전의 논문을 인용하고 간략히 기술
- 새로운 연구 방법을 사용한 경우에는 상세히 기술
- Ethic approval과 patient consent에 대하여 기술
- Primary outcome measure가 무엇이며, 이를 위해 통계 분석은 어떻게 하였는지 기술
- 부제목 (subheading)을 사용
  - Study population
  - Statistical analysis
  - Etc.
- 과거시제

disease at the resection margin of the cervix after conization is eliminated by vaginal acidity and rapid cell turnover during cervical healing and because of frequent use of fulguration to produce hemostasis at the base of conization crater margins, which can destroy residual tumor cells.[4] Therefore, resection margin is not sufficient for the prediction of residual disease after conization in a large proportion of patients, and a more accurate predictive factor is required.

Recently, the preconization human papillomavirus (HPV) test has been evaluated as a predictor of residual disease or recurrence of disease after conization in several studies,[10,11] and a prehysterectomy HPV test has been proposed as a possible predictor of residual disease in some studies.[12,13] High-risk HPV is known to cause up to 99.7% of cervical cancers and high-grade precursor lesions and is found in most of these lesions[14,15]; therefore, the presence of high-risk HPV after conization may be an accurate indicator of residual disease. The aim of this study was to estimate the role of the HPV test performed after conization (immediately before a hysterectomy) in predicting residual disease in subsequent hysterectomy samples.

MATERIALS AND METHODS

A total of 120 consecutive patients who underwent hysterectomy after conization for CIN 3 or IA1 cancer were enrolled in this prospective study from March 2007 to November 2008 at the Asan Medical Center (Seoul, Korea). Only those patients with positive HPV test results before conization were eligible for this study. All patients underwent the HPV test using the Hybrid Capture II system (Digene Diagnostics Inc., Valencia, CA) after conization (1 day before hysterectomy). Demographic data (including age, menopausal status, body mass index, and parity) and clinicopathologic data (including CIN degree, glandular extension, size and resection margin-status of conization specimen, HPV test results, and residual disease in subsequent hysterectomy samples) were obtained. The study protocol was approved by the institutional review board of the Asan Medical Center.

In all patients, LEEP was used for conization. Briefly, the procedure was as follows. The cervix was swabbed with an acetic acid solution to assist in locating the ectocervical margins of the lesion, and a 1 mL solution of local anesthetic was injected into the cervix at the 5 and 7 o'clock positions. A loop was selected according to the size of the area to be excised. The goal was to excise the complete cervical lesion via a single excision for better orientation and margin-status interpretation. The base of the resulting crater and resection margin was coagulated and cauterized using a ball diathermy. A suture was placed at the 12 o'clock position of the LEEP specimen for orientation, the inner surface was inked, and the specimens were fixed in 10% formalin for pathologic examination. Cone specimens were sectioned. Paraffin blocks were cut at 5-micrometer intervals and stained with hematoxylin and eosin. The specimens were assessed for severity of lesion, margin status (exocervical or endocervical, clear or involved), and glandular involvement (present or absent).

Cervical samples for the Hybrid Capture II test were obtained using a cytobrush (Digene Cervical Sampler, Digene Diagnostics, Inc., Valencia, CA), transferred to a vial containing Digene Specimen Transport Medium (Digene Diagnostics, Inc.) and analyzed according to the manufacturer's instructions. Light intensity was measured using a luminometer and expressed by comparing the relative light units of clinical samples with the positive control, a 1.0 pg/mL HPV 16 cutoff standard. A relative light unit:positive control ratio of 1 or more was considered a positive result. Of several HPV tests, the commercially available Hybrid Capture II is the only one approved by the U.S. Food and Drug Administration for HPV DNA detection and involves a liquid hybridization assay designed to detect 13 high-risk HPV types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). This test is widely used owing to its high sensitivity and predictive value (greater than 90–95%), objectivity, ease of use, and accessibility for use in routine clinical practice.[16,17]

After hysterectomy, the cervix was cut at 2-mm intervals perpendicular to the long axis of the cervical canal for pathologic evaluation. Residual disease was defined as any degree of CIN or invasive cancer.

Several factors, including age, parity, menopausal status, body mass index, the severity of disease (CIN 3 compared with IA1 cancer), glandular extension, resection margin of conization specimen, and HPV test results immediately before hysterectomy, were associated with residual disease in subsequent hysterectomy samples. Frequency distributions were compared using the χ^2 and Fisher exact tests, and mean or median values were compared using the Student's t- and Mann–Whitney U-tests. A logistic regression model was used to analyze the relationship between covariates and the probability of residual disease in subsequent hysterectomy samples. Differences in sensitivity, specificity, and accuracy between resection margin and the HPV test in predicting residual disease in subsequent hysterectomy samples were estimated using the McNemar exact test. P-values (from

통계 분석 결과를 표와 그림으로 작성하기

Table 2. Characteristics of recurrent cases (n=9)

Case	Age	FIGO Stage	Tumor Size (cm)	Histology	Grade	Cervical Stromal Invasion	Lymph Node	Adjuvant Chemo-	Recur Site	Recur Tx
1	29	IIA1	3	AdenoSCCa	3	< 50%	Neg	Not done	Pelvis, Abdomen	Chemo-
2	33	IB1	2.5	SCCa	3	> 50%	Neg	Not done	Uterus, ovary, LNs	Chemo-
3	29	IB1	3	SCCa	3	> 50%	Neg	Not done	Pelvis	OP, RT
4	27	IB1	1.5	SCCa	1	< 50%	Neg	Not done	Pelvis, LNs	CCRT
5	37	IB1	1.5	SCCa	2	> 50%	Neg	Not done	Pelvis, LNs	OP CCRT
6	30	IB1	2.2	SCCa	3	> 50%	Pos	Not done	Pelvis, LNs	Chemo-
7	26	IB1	4	SCCa	2	> 50%	Neg	Not done	LNs	Chemo-
8	34	IB1	1.2	AdenoSCCa	3	< 50%	Neg	Not done	Lung	Chemo-
9	28	IB1	3	SCCa	2	< 50%	Neg	Not done	Pelvis	OP, CCRT

FIGO, International Federation of Obstetrics and Gynecology; Chemo-, chemotherapy; Tx, treatment; AdenoSCCa, adenosquamous carcinoma; Neg, negative; SCCa, squamous cell carcinoma; LNs, lymph nodes; CCRT, concurrent chemoradiation therapy; OP, operation; Pos, positive

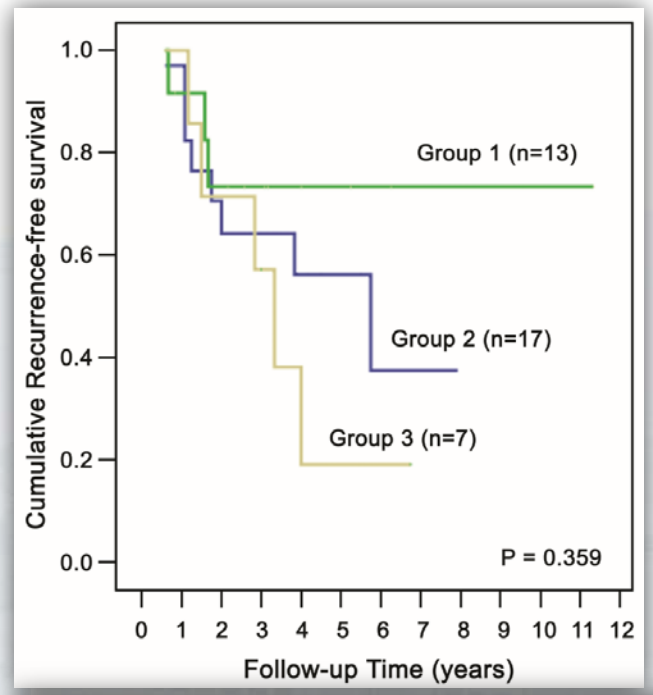


FIGURE LEGEND

Figure 1. Recurrence-free survival according to the grade of differentiation and myometrial invasion.

Group 1: grade 2-3 & myometrial invasion (-), Group 2: grade 1 & superficial myometrial invasion (+), Group 3: grade 2-3 & superficial myometrial invasion (+)

- Abstract와 함께 논문의 얼굴
- 핵심적인 주요 결과
- 갯수 제한 : 저널의 논문 투고 규정 확인
- 그림 해상도 향상은 여러가지 서비스 이용

Results 쓰기

- 주요 결과를 표와 그림으로 만든다 : 논문의 얼굴
- 표와 그림을 바탕으로 결과를 기술한다.
  - 과거시제
  - 표와 그림은 현재 시제
- 결과를 잘 보여 주어야 한다.
  - 핵심적인 결과를 보여주고
  - Supplementary materials를 이용한다.
  - Subheadings 사용
  - 순서를 논리적으로 잘 배열
- 하지 말아야 할 것
  - 본문과 표 / 그림은 중복되지 않도록 한다.
  - Materials and methods section이나 Discussion section에 들어가야 할 내용을 넣지 않도록 한다.

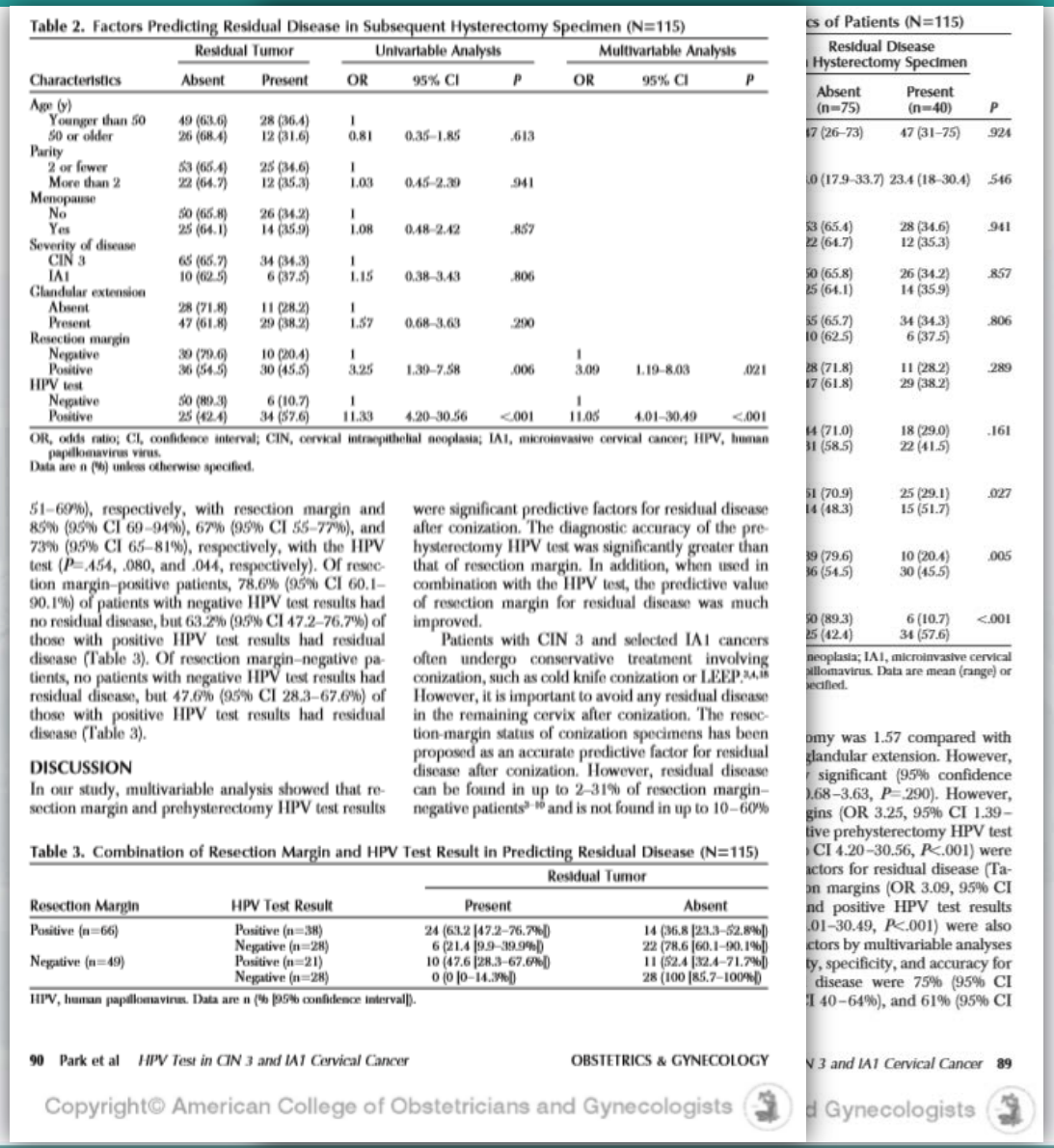


Table 2. Factors Predicting Residual Disease in Subsequent Hysterectomy Specimen (N=115)

Characteristics	Residual Tumor: Absent	Residual Tumor: Present	Univariable Analysis: OR	Univariable Analysis: 95% CI	Univariable Analysis: P	Multivariable Analysis: OR	Multivariable Analysis: 95% CI	Multivariable Analysis: P
Age (y)								
Younger than 50	49 (63.6)	28 (36.4)	1					
50 or older	26 (68.4)	12 (31.6)	0.81	0.35–1.85	.613			
Parity								
2 or fewer	53 (65.4)	25 (34.6)	1					
More than 2	22 (64.7)	12 (35.3)	1.03	0.45–2.39	.941			
Menopause								
No	50 (65.8)	26 (34.2)	1					
Yes	25 (64.1)	14 (35.9)	1.08	0.48–2.42	.857			
Severity of disease								
CIN 3	65 (65.7)	34 (34.3)	1					
IA1	10 (62.5)	6 (37.5)	1.15	0.38–3.43	.806			
Glandular extension								
Absent	28 (71.8)	11 (28.2)	1					
Present	47 (61.8)	29 (38.2)	1.57	0.68–3.63	.290			
Resection margin								
Negative	39 (79.6)	10 (20.4)	1			1		
Positive	36 (54.5)	30 (45.5)	3.25	1.39–7.58	.006	3.09	1.19–8.03	.021
HPV test								
Negative	50 (89.3)	6 (10.7)	1			1		
Positive	25 (42.4)	34 (57.6)	11.33	4.20–30.56	<.001	11.05	4.01–30.49	<.001

OR, odds ratio; CI, confidence interval; CIN, cervical intraepithelial neoplasia; IA1, microinvasive cervical cancer; HPV, human papillomavirus virus.
Data are n (%) unless otherwise specified.

51–69%), respectively, with resection margin and 85% (95% CI 69–94%), 67% (95% CI 55–77%), and 73% (95% CI 65–81%), respectively, with the HPV test (P=.454, .080, and .044, respectively). Of resection margin–positive patients, 78.6% (95% CI 60.1–90.1%) of patients with negative HPV test results had no residual disease, but 63.2% (95% CI 47.2–76.7%) of those with positive HPV test results had residual disease (Table 3). Of resection margin–negative patients, no patients with negative HPV test results had residual disease, but 47.6% (95% CI 28.3–67.6%) of those with positive HPV test results had residual disease (Table 3).

DISCUSSION

In our study, multivariable analysis showed that resection margin and prehysterectomy HPV test results were significant predictive factors for residual disease after conization. The diagnostic accuracy of the prehysterectomy HPV test was significantly greater than that of resection margin. In addition, when used in combination with the HPV test, the predictive value of resection margin for residual disease was much improved.

Patients with CIN 3 and selected IA1 cancers often undergo conservative treatment involving conization, such as cold knife conization or LEEP.[3,4,8] However, it is important to avoid any residual disease in the remaining cervix after conization. The resection-margin status of conization specimens has been proposed as an accurate predictive factor for residual disease after conization. However, residual disease can be found in up to 2–31% of resection margin–negative patients[9–10] and is not found in up to 10–60%

Table 3. Combination of Resection Margin and HPV Test Result in Predicting Residual Disease (N=115)

Resection Margin	HPV Test Result	Residual Tumor: Present	Residual Tumor: Absent
Positive (n=66)	Positive (n=38)	24 (63.2 [47.2–76.7%])	14 (36.8 [23.3–52.8%])
	Negative (n=28)	6 (21.4 [9.9–39.9%])	22 (78.6 [60.1–90.1%])
Negative (n=49)	Positive (n=21)	10 (47.6 [28.3–67.6%])	11 (52.4 [32.4–71.7%])
	Negative (n=28)	0 (0 [0–14.3%])	28 (100 [85.7–100%])

HPV, human papillomavirus. Data are n (% [95% confidence interval]).

90 Park et al *HPV Test in CIN 3 and IA1 Cervical Cancer* OBSTETRICS & GYNECOLOGY

Conclusion 쓰기

51–69%), respectively, with resection margin and 85% (95% CI 69–94%), 67% (95% CI 55–77%), and 73% (95% CI 65–81%), respectively, with the HPV test (P=.454, .080, and .044, respectively). Of resection margin–positive patients, 78.6% (95% CI 60.1–90.1%) of patients with negative HPV test results had no residual disease, but 63.2% (95% CI 47.2–76.7%) of those with positive HPV test results had residual disease (Table 3). Of resection margin–negative patients, no patients with negative HPV test results had residual disease, but 47.6% (95% CI 28.3–67.6%) of those with positive HPV test results had residual disease (Table 3).

DISCUSSION

In our study, multivariable analysis showed that resection margin and prehysterectomy HPV test results were significant predictive factors for residual disease after conization. The diagnostic accuracy of the prehysterectomy HPV test was significantly greater than that of resection margin. In addition, when used in combination with the HPV test, the predictive value of resection margin for residual disease was much improved.

Patients with CIN 3 and selected IA1 cancers often undergo conservative treatment involving conization, such as cold knife conization or LEEP.[3,4,18] However, it is important to avoid any residual disease in the remaining cervix after conization. The resection-margin status of conization specimens has been proposed as an accurate predictive factor for residual disease after conization. However, residual disease can be found in up to 2–31% of resection margin–negative patients[3–10] and is not found in up to 10–60% of resection margin–positive patients.[3–10] Therefore, the identification of patients for hysterectomy based on the resection-margin status alone likely would result in overtreatment of many women and undertreatment of a small but significant proportion of women. In our series, 54.5% of patients were overtreated and 20.4% were undertreated based on the resection-margin status. The sensitivity, specificity, and accuracy of resection margins in predicting residual disease were 75%, 53%, and 61%, respectively. These figures are similar to those in previous reports.[3–10] Therefore, more accurate predictive factors are required.

High-risk HPV is known to cause up to 99.7% of cervical cancers and high-grade precursor lesions and is found in most of these lesions.[14,15] The HPV test has been approved as an additional cervical cytologic test in primary screening and as a follow-up test after conservative management of CIN and cervical cancer. Therefore, it is reasonable to assume that use of the high-risk HPV test after conization might be an accurate predictor of residual disease. This hypothesis is supported further by reports that effective conization can eliminate HPV DNA[19] and that HPV DNA is rarely present in normal squamous epithelium adjacent to CIN.[20] However, to our knowledge, only two studies have investigated the role of the prehysterectomy HPV test in predicting residual disease.[12,13] Jain et al investigated the use of the Hybrid Capture II high-risk HPV test immediately before hysterectomy in 79 patients who underwent conization owing to CIN 3, and they correlated the resection-margin status and HPV test results with the presence of residual disease in subsequent hysterectomy specimens.[12] In their series, no residual lesions were found in HPV-negative cases; hence, they report that the HPV test was associated with a negative predictive value of 100% for predicting residual disease.[12] Lin et al investigated the use of the Hybrid Capture II high-risk HPV test immediately before hysterectomy in 75 patients who underwent conization owing to CIN 3 and had cone margins or endocervical curettage specimens showing disease, and they correlated the HPV test results with the presence of residual disease in subsequent hysterectomy specimens.[13] In their series, both the sensitivity and negative predictive value of the HPV test were shown to be 100%.[13] The potential role of prehysterectomy HPV testing in predicting residual disease was confirmed further in our series. The sensitivity, specificity, and accuracy of the HPV test (85%, 67%, and 73 %, respectively) were higher than those of resection margin (75%, 53%, and 61%, respectively). In resection margin–positive patients, the HPV test indicated that 78.6% did not have residual disease, and in resection margin–negative patients, the HPV test indicated that 47.6% had residual disease. No patient with a negative resection margin and a negative HPV test result was shown to have residual disease. When used in combination with resection margin, the diagnostic accuracy of the HPV test was increased.

Unlike previous reports,[12,13] the sensitivity and negative predictive value of the HPV test were not 100% in our study. There are several reasons that the HPV test may not accurately detect the presence of residual disease in some patients. First, in rare situations, latent HPV infection can persist in a histologically normal cervix after conization. This phenomenon has been reported by Kanamori et al[21] and is supported by reports that the HPV genotype detected in residual or recurrent disease after successful conization is the same as that detected before conization in most cases.[22] Second, it is possible for a new HPV infection to occur after eradication of HPV DNA by conization but before hysterectomy; this is likely if patients have different HPV genotypes. Third, the timing of the HPV test may affect the results. The 2001 American Society for Colposcopy and Cervical Pathology guidelines recommend that the HPV test be performed at least 6 months after conization to provide sufficient time for clearance of the HPV infection.[23] However, some studies have reported that the predictive value of the HPV test is not affected by the time after conization.[13,24] For a more accurate evaluation of the role of the prehysterectomy HPV test in predicting residual disease, future studies should investigate the high-risk HPV genotypes and the HPV test should be performed at least 6 months after conization. However, care should be taken not to delay diagnosis and appropriate treatment of occult or

In conclusion, the prehysterectomy HPV test is associated with significantly greater diagnostic accuracy in predicting residual disease after conization compared with resection margin. When used in combination with the HPV test, the predictive value of resection margin in predicting residual disease was increased. Therefore, use of the HPV test is recommended when selecting patients for hysterectomy after conization for CIN 3 and IA1 cancer.

REFERENCES

1. Buxton EJ, Luesley DM, Wade-Evans T, Jordan JA. Residual disease after cone biopsy: completeness of excision and follow up cytology as predictive factors. Obstet Gynecol 1987; 70:529–32.

- 논문의 결과를 바탕으로 한 결론을 간략하고 명확히 기술한다.
- 결과가 뒷받침 되는 결론만 적고, 과장해서는 안 된다.
- Preliminary outcome인 경우 future study에 대해 언급한다.

Discussion 쓰기

- 대개 4개의 paragraph 정도의 분량
  - 주요 결과를 요약하고 해석
  - 이전 연구들의 고찰
  - 본 연구의 차이점
  - 본 연구의 장단점

51–69%), respectively, with resection margin and 85% (95% CI 69–94%), 67% (95% CI 55–77%), and 73% (95% CI 65–81%), respectively, with the HPV test (P=.454, .080, and .044, respectively). Of resection margin–positive patients, 78.6% (95% CI 60.1–90.1%) of patients with negative HPV test results had no residual disease, but 63.2% (95% CI 47.2–76.7%) of those with positive HPV test results had residual disease (Table 3). Of resection margin–negative patients, no patients with negative HPV test results had residual disease, but 47.6% (95% CI 28.3–67.6%) of those with positive HPV test results had residual disease (Table 3).

DISCUSSION

In our study, multivariable analysis showed that resection margin and prehysterectomy HPV test results were significant predictive factors for residual disease after conization. The diagnostic accuracy of the prehysterectomy HPV test was significantly greater than that of resection margin. In addition, when used in combination with the HPV test, the predictive value of resection margin for residual disease was much improved.

Patients with CIN 3 and selected IA1 cancers often undergo conservative treatment involving conization, such as cold knife conization or LEEP.[3,4,18] However, it is important to avoid any residual disease in the remaining cervix after conization. The resection-margin status of conization specimens has been proposed as an accurate predictive factor for residual disease after conization. However, residual disease can be found in up to 2–31% of resection margin–negative patients[3–10] and is not found in up to 10–60%

- 연구 결과를 어떻게 해석하는지 기술
  - 주요 결과는 반드시 discussion
  - 중요한 결과에서 중요성이 낮은 결과 순으로 discussion
  - 본 연구결과와 다른 연구 결과를 비교
  - 논문의 장점을 부각하고 단점에 대한 방어
- 피해야 할 것
  - 장황한 book review
  - Results section에 없는 본 연구 결과의 제시

of resection margin–positive patients.[3–10] Therefore, the identification of patients for hysterectomy based on the resection-margin status alone likely would result in overtreatment of many women and undertreatment of a small but significant proportion of women. In our series, 54.5% of patients were overtreated and 20.4% were undertreated based on the resection-margin status. The sensitivity, specificity, and accuracy of resection margins in predicting residual disease were 75%, 53%, and 61%, respectively. These figures are similar to those in previous reports.[3–10] Therefore, more accurate predictive factors are required.

High-risk HPV is known to cause up to 99.7% of cervical cancers and high-grade precursor lesions and is found in most of these lesions.[14,15] The HPV test has been approved as an additional cervical cytologic test in primary screening and as a follow-up test after conservative management of CIN and cervical cancer. Therefore, it is reasonable to assume that use of the high-risk HPV test after conization might be an accurate predictor of residual disease. This hypothesis is supported further by reports that effective conization can eliminate HPV DNA[19] and that HPV DNA is rarely present in normal squamous epithelium adjacent to CIN.[20] However, to our knowledge, only two studies have investigated the role of the prehysterectomy HPV test in predicting residual disease.[12,13] Jain et al investigated the use of the Hybrid Capture II high-risk HPV test immediately before hysterectomy in 79 patients who underwent conization owing to CIN 3, and they correlated the resection-margin status and HPV test results with the presence of residual disease in subsequent hysterectomy specimens.[12] In their series, no residual lesions were found in HPV-negative cases; hence, they report that the HPV test was associated with a negative predictive value of 100% for predicting residual disease.[12] Lin et al investigated the use of the Hybrid Capture II high-risk HPV test immediately before hysterectomy in 75 patients who underwent conization owing to CIN 3 and had cone margins or endocervical curettage specimens showing disease, and they correlated the HPV test results with the presence of residual disease in subsequent hysterectomy specimens.[13] In their series, both the sensitivity and negative predictive value of the HPV test were shown to be 100%.[13] The potential role of prehysterectomy HPV testing in predicting residual disease was confirmed further in our series. The sensitivity, specificity, and accuracy of the HPV test (85%, 67%, and 73 %, respectively) were higher than those of resection margin (75%, 53%, and 61%, respectively). In resection margin–positive patients, the HPV test indicated that 78.6% did not have residual disease, and in resection margin–negative patients, the HPV test indicated that 47.6% had residual disease. No patient with a negative resection margin and a negative HPV test result was shown to have residual disease. When used in combination with resection margin, the diagnostic accuracy of the HPV test was increased.

Unlike previous reports,[12,13] the sensitivity and negative predictive value of the HPV test were not 100% in our study. There are several reasons that the HPV test may not accurately detect the presence of residual disease in some patients. First, in rare situations, latent HPV infection can persist in a histologically normal cervix after conization. This phenomenon has been reported by Kanamori et al[21] and is supported by reports that the HPV genotype detected in residual or recurrent disease after successful conization is the same as that detected before conization in most cases.[22] Second, it is possible for a new HPV infection to occur after eradication of HPV DNA by conization but before hysterectomy; this is likely if patients have different HPV genotypes. Third, the timing of the HPV test may affect the results. The 2001 American Society for Colposcopy and Cervical Pathology guidelines recommend that the HPV test be performed at least 6 months after conization to provide sufficient time for clearance of the HPV infection.[23] However, some studies have reported that the predictive value of the HPV test is not affected by the time after conization.[13,24] For a more accurate evaluation of the role of the prehysterectomy HPV test in predicting residual disease, future studies should investigate the high-risk HPV genotypes and the HPV test should be performed at least 6 months after conization. However, care should be taken not to delay diagnosis and appropriate treatment of occult or residual invasive carcinoma.

In conclusion, the prehysterectomy HPV test is associated with significantly greater diagnostic accuracy in predicting residual disease after conization compared with resection margin. When used in combination with the HPV test, the predictive value of resection margin in predicting residual disease was increased. Therefore, use of the HPV test is recommended when selecting patients for hysterectomy after conization for CIN 3 and IA1 cancer.

REFERENCES

1. Buxton EJ, Luesley DM, Wade-Evans T, Jordan JA. Residual disease after cone biopsy: completeness of excision and follow up cytology as predictive factors. Obstet Gynecol 1987; 70:529–32.

Introduction 쓰기

- 왜 이 연구를 시행하게 되었는지 배경과 연구 목적을 기술
- 3 paragraph / 1 page
  - 질환에 대한 간단한 기술과 이제까지 이루어진 연구 내용 기술
  - 아직 연구가 이루어지지 않은 것, 왜 이 연구를 시행하게 되었는지 기술
  - 본 연구의 목적을 명확하게 기술
- 짧고 명확하게 기술
- 관련된 내용만 기술
- 문헌 review나 Book review가 되지 않도록 기술
- 이전 연구 결과들에 대해 한 쪽으로 치우치지 않도록 기술

samples were estimated using the McNemar exact test.

RESULTS: Univariable analysis showed that age, parity, menopausal status, glandular extension, and severity of disease were not predictive for residual disease, but positive resection margin and positive HPV tests were significant factors for predicting residual disease. These factors were also significant in a multivariable analysis (positive resection margin 45.5%, odds ratio [OR] 3.09, 95% confidence interval [CI] 1.19–8.03, P=.021; positive HPV test 57.6%, OR 11.05, 95% CI 4.01–30.49, P<.001). With resection margin, the sensitivity, specificity, and accuracy in predicting residual disease were 75%, 53%, and 61%, respectively, whereas, with the HPV test, these values were 85%, 67%, and 73%, respectively (P=.454, .080, and .044, respectively). Of patients with positive resection margins, 79% of HPV-negative patients had no

From the Department of Obstetrics and Gynecology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea.

Corresponding author: Jong-Hyeok Kim, MD, PhD, Obstetrics and Gynecology, College of Medicine, University of Ulsan, Asan Medical Center, #388-1 Poongnap-2 dong, Songpa-gu, Seoul, 138-736, Korea; e-mail: kyeokkim@amc.seoul.kr.

Financial Disclosure
The authors did not report any potential conflicts of interest.

ISSN: 0029-7844/09

Conization of the uterine cervix by procedures such as cold knife conization and loop electrosurgical excision procedure (LEEP) is considered an appropriate treatment for cervical intraepithelial neoplasia grade 3 (CIN 3) and microinvasive cervical cancer (IA1 cancer). However, residual disease after conization due to CIN 3 and IA1 cancer is found in 23–34% of patients who subsequently undergo hysterectomy.[1] Therefore, accurate prediction of residual disease after conization is important for the conservative treatment and counseling of patients with CIN 3 and IA1 cancer, both for the physician and patient.

Although several demographic and clinicopathologic factors, including age, parity, menopausal status, severity of lesion, glandular extension, and resection margin, have been reported to be predictive for residual disease after conization,[2] resection margin remains the gold-standard technique for prediction of residual disease after conization. However, residual disease can be found subsequently in up to 2–31% of patients with negative resection margins.[3–10] This may be due to multiple lesions that were not resected during conization; by contrast, residual disease is not found in up to 10–60% of patients with positive resection margins.[3–10] This may be because residual

disease at the resection margin of the cervix after conization is eliminated by vaginal acidity and rapid cell turnover during cervical healing and because of frequent use of fulguration to produce hemostasis at the base of conization crater margins, which can destroy residual tumor cells.[4] Therefore, resection margin is not sufficient for the prediction of residual disease after conization in a large proportion of patients, and a more accurate predictive factor is required.

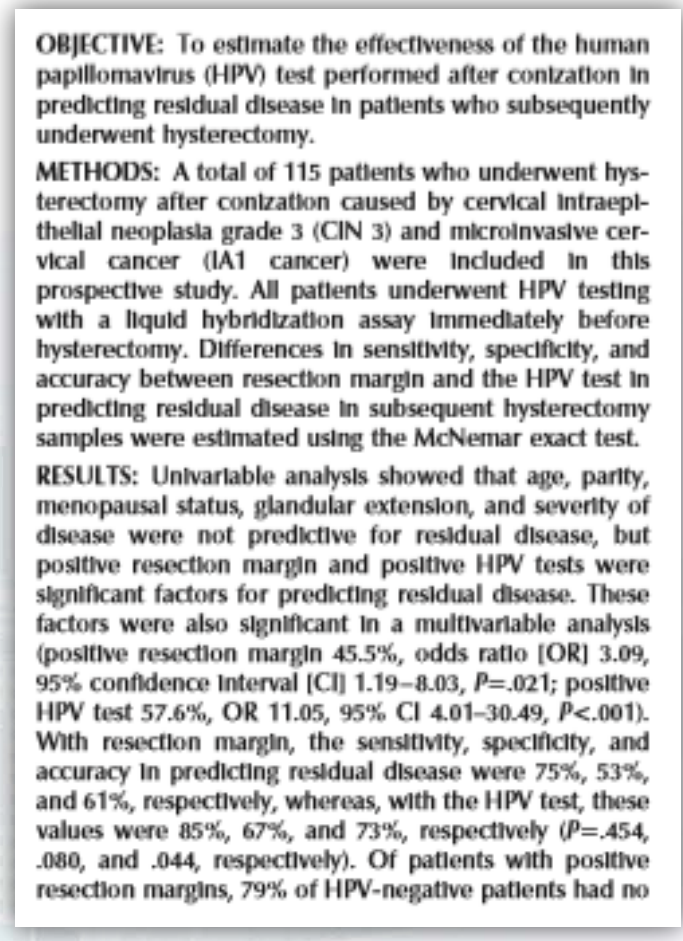
Recently, the preconization human papillomavirus (HPV) test has been evaluated as a predictor of residual disease or recurrence of disease after conization in several studies,[10,11] and a prehysterectomy HPV test has been proposed as a possible predictor of residual disease in some studies.[12,13] High-risk HPV is known to cause up to 99.7% of cervical cancers and high-grade precursor lesions and is found in most of these lesions[14,15]; therefore, the presence of high-risk HPV after conization may be an accurate indicator of residual disease. The aim of this study was to estimate the role of the HPV test performed after conization (immediately before a hysterectomy) in predicting residual disease in subsequent hysterectomy samples.

and resection margin was coagulated and cauterized using a ball diathermy. A suture was placed at the 12 o'clock position of the LEEP specimen for orientation, the inner surface was inked, and the specimens were fixed in 10% formalin for pathologic examination. Cone specimens were sectioned. Paraffin blocks were cut at 5-micrometer intervals and stained with hematoxylin and eosin. The specimens were assessed for severity of lesion, margin status (exocervical or endocervical, clear or involved), and glandular involvement (present or absent).

Cervical samples for the Hybrid Capture II test were obtained using a cytobrush (Digene Cervical Sampler, Digene Diagnostics, Inc., Valencia, CA), transferred to a vial containing Digene Specimen Transport Medium (Digene Diagnostics, Inc.) and analyzed according to the manufacturer's instructions. Light intensity was measured using a luminometer and expressed by comparing the relative light units of clinical samples with the positive control, a 1.0 pg/mL HPV 16 cutoff standard. A relative light unit:positive control ratio of 1 or more was considered a positive result. Of several HPV tests, the commercially available Hybrid Capture II is the only one approved by the U.S. Food and Drug Administration for HPV

Abstract 쓰기

- Editor와 reviewer가 논문을 파악하기 위해 제일 먼저 보는 것
- 논문의 핵심 내용이 반드시 들어가야 한다.
- 제목과 본문에 사용된 동일한 용어를 사용하고, 동일한 내용이 들어가야 한다.
- 본문에 없는 내용이 초록에 기술되어서는 안 된다.
- Structure 준수
  - Background (Objective) : 30%
  - Materials and Methods : 10%
  - Results : 40% → 구체적인 수치와 *p*-value
  - Conclusions : 20%
- 단어 수 준수
- Reference, Abbreviation은 피할 것
- Keywords
  - Index Medicus의 Medical Subject Heading (MeSH) 법으로



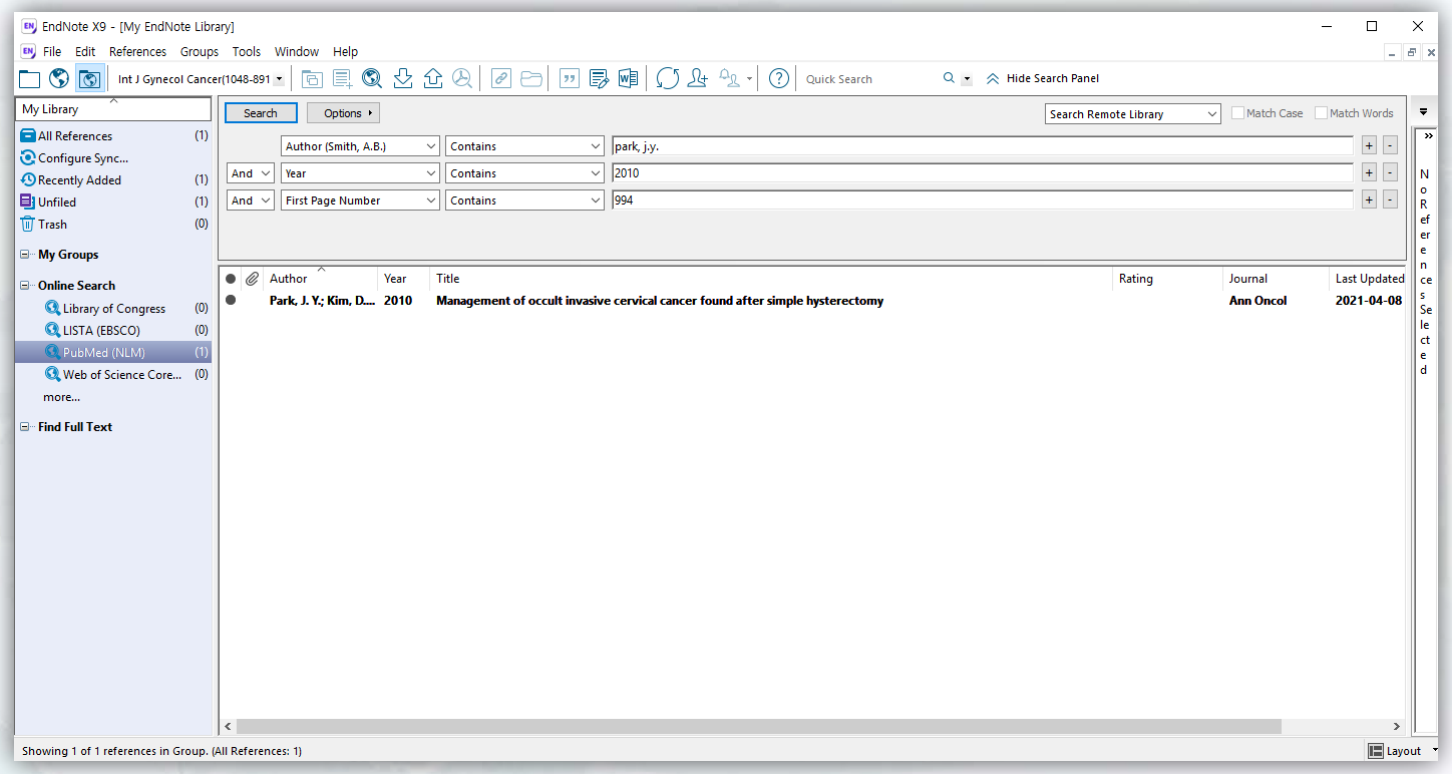
OBJECTIVE: To estimate the effectiveness of the human papillomavirus (HPV) test performed after conization in predicting residual disease in patients who subsequently underwent hysterectomy.

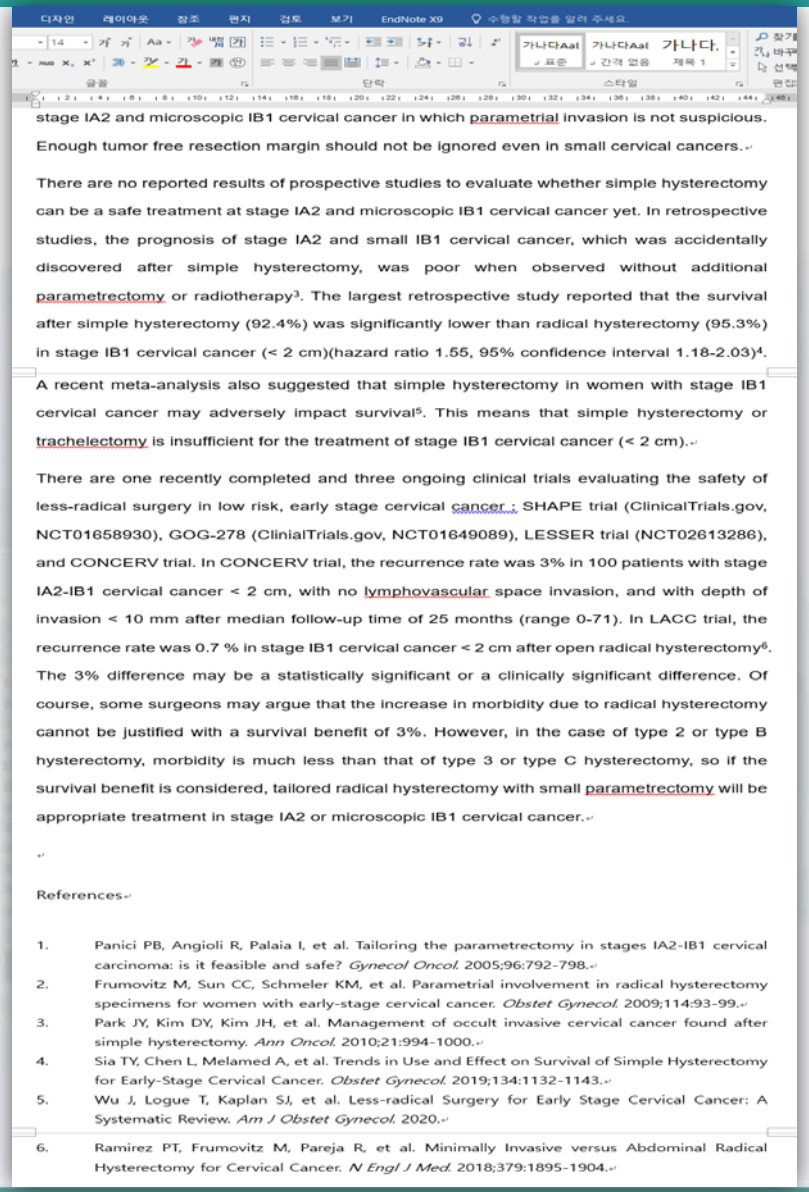
METHODS: A total of 115 patients who underwent hysterectomy after conization caused by cervical intraepithelial neoplasia grade 3 (CIN 3) and microinvasive cervical cancer (IA1 cancer) were included in this prospective study. All patients underwent HPV testing with a liquid hybridization assay immediately before hysterectomy. Differences in sensitivity, specificity, and accuracy between resection margin and the HPV test in predicting residual disease in subsequent hysterectomy samples were estimated using the McNemar exact test.

RESULTS: Univariable analysis showed that age, parity, menopausal status, glandular extension, and severity of disease were not predictive for residual disease, but positive resection margin and positive HPV tests were significant factors for predicting residual disease. These factors were also significant in a multivariable analysis (positive resection margin 45.5%, odds ratio [OR] 3.09, 95% confidence interval [CI] 1.19–8.03, *P*=.021; positive HPV test 57.6%, OR 11.05, 95% CI 4.01–30.49, *P*<.001). With resection margin, the sensitivity, specificity, and accuracy in predicting residual disease were 75%, 53%, and 61%, respectively, whereas, with the HPV test, these values were 85%, 67%, and 73%, respectively (*P*=.454, .080, and .044, respectively). Of patients with positive resection margins, 79% of HPV-negative patients had no

참고문헌 (Reference) 관리

- Citation management program 사용 - Endnote
- 형식과 개수는 Journal 투고 규정에 따라서 (30개 이내)
- Up-to-date reference 를 인용 : 대개 최근 10여 년 이내
- 주요 연구는 반드시 인용 (landmark study)
- Original study를 인용





stage IA2 and microscopic IB1 cervical cancer in which parametrial invasion is not suspicious. Enough tumor free resection margin should not be ignored even in small cervical cancers.

There are no reported results of prospective studies to evaluate whether simple hysterectomy can be a safe treatment at stage IA2 and microscopic IB1 cervical cancer yet. In retrospective studies, the prognosis of stage IA2 and small IB1 cervical cancer, which was accidentally discovered after simple hysterectomy, was poor when observed without additional parametrectomy or radiotherapy[3]. The largest retrospective study reported that the survival after simple hysterectomy (92.4%) was significantly lower than radical hysterectomy (95.3%) in stage IB1 cervical cancer (< 2 cm)(hazard ratio 1.55, 95% confidence interval 1.18-2.03)[4].

A recent meta-analysis also suggested that simple hysterectomy in women with stage IB1 cervical cancer may adversely impact survival[5]. This means that simple hysterectomy or trachelectomy is insufficient for the treatment of stage IB1 cervical cancer (< 2 cm).

There are one recently completed and three ongoing clinical trials evaluating the safety of less-radical surgery in low risk, early stage cervical cancer ; SHAPE trial (ClinicalTrials.gov, NCT01658930), GOG-278 (ClinialTrials.gov, NCT01649089), LESSER trial (NCT02613286), and CONCERV trial. In CONCERV trial, the recurrence rate was 3% in 100 patients with stage IA2-IB1 cervical cancer < 2 cm, with no lymphovascular space invasion, and with depth of invasion < 10 mm after median follow-up time of 25 months (range 0-71). In LACC trial, the recurrence rate was 0.7 % in stage IB1 cervical cancer < 2 cm after open radical hysterectomy[6]. The 3% difference may be a statistically significant or a clinically significant difference. Of course, some surgeons may argue that the increase in morbidity due to radical hysterectomy cannot be justified with a survival benefit of 3%. However, in the case of type 2 or type B hysterectomy, morbidity is much less than that of type 3 or type C hysterectomy, so if the survival benefit is considered, tailored radical hysterectomy with small parametrectomy will be appropriate treatment in stage IA2 or microscopic IB1 cervical cancer.

References

1. Panici PB, Angioli R, Palaia I, et al. Tailoring the parametrectomy in stages IA2-IB1 cervical carcinoma: is it feasible and safe? *Gynecol Oncol.* 2005;96:792-798.
2. Frumovitz M, Sun CC, Schmeler KM, et al. Parametrial involvement in radical hysterectomy specimens for women with early-stage cervical cancer. *Obstet Gynecol.* 2009;114:93-99.
3. Park JY, Kim DY, Kim JH, et al. Management of occult invasive cervical cancer found after simple hysterectomy. *Ann Oncol.* 2010;21:994-1000.
4. Sia TY, Chen L, Melamed A, et al. Trends in Use and Effect on Survival of Simple Hysterectomy for Early-Stage Cervical Cancer. *Obstet Gynecol.* 2019;134:1132-1143.
5. Wu J, Logue T, Kaplan SJ, et al. Less-radical Surgery for Early Stage Cervical Cancer: A Systematic Review. *Am J Obstet Gynecol.* 2020.
6. Ramirez PT, Frumovitz M, Pareja R, et al. Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer. *N Engl J Med.* 2018;379:1895-1904.

논문 초고 작성 후 할 일

- Acknowledgement
  - All kinds of support or contributors for writing and editing the manuscript
  - Funding
  - 사전 동의를 얻어야 한다
- Declare conflicts of interest of all authors
  - 이해관계 : 논문의 출판관 관련된 사람 (저자, 편집인, 전문가심사자, 출판인 등) 또는 기관이 특정 논문에 재정적인 이익이 걸려 있거나 사적인 특별한 관련이 있는 경우
  - 재적적인 관계, 사적인 관계, 연구의 경쟁, 지적인 관심사
- Copyright transfer form
- Make sure all authors see the final version of the manuscript before submission
- 추천 사항 : 동료들 (2인 이상) 로부터 논문 review를 받아 본다
- 고치고 또 고치고
- '저자를 위한 투고지침(페이지 크기, 줄 간격, 페이지 매김, 형식, 스타일 등)'의 검토 : 도서관에 도움 요청
- Language editing (영문교정) : 병원 지원

논문 작성 시 반드시 피해야 할 것

- Fabrication (날조)
- Falsification (변조)
- Plagiarism (표절) : 자기만의 언어로 표현하고 자료를 사용 (iThenticate 로 표절검사)
  - Verbatim – 따옴표, 참고문헌 인용
  - Paraphrasing (바꿔쓰기) – 참고문헌 인용
  - Summarizing (요약) – 참고문헌 인용
  - 아이디어의 표절
  - Reprint – 사전 허가를 받아야 한다
  - 자기표절
  - 다른 언어로 변역 하여도 마찬가지

Reject

- Reject 는 당연지사
  - Probability 40-90%...
  - Most journals accept 30% or less (NEJM, Lancet, JAMA accept less than 10%)
  - Do not discouraged

Reject 되는 흔한 이유

- Results are not sound
  - Control group needed
  - Further statistical analysis needed
  - Methods are inappropriate
- Interpretations are wrong or overstated
  - Important references or previous studies are missed
  - Conclusions are not supported by data

Reject 되는 흔한 이유

- Findings are not a big enough advance
  - Previous studies reported similar results
  - Conclusions are not clear and strong
- Findings are not significant enough
  - Not broad
  - Below the journal's threshold

Reject 되는 흔한 이유

- Ethical problem
  - Lack of ethical approval
  - Reporting guidelines are not followed
  - Plagiarism
  - Duplication
- Badly presented manuscript
  - Poor quality of figures and tables
  - Poor English

Next step after reject

- Do it
  - Try to find out the reasons why
  - Accept the advantage of the reviewer's comments
  - They may review your manuscript for the other journal too
  - Submit the manuscript to another journal (after appropriate change and revision)
- Don't do it
  - Do not ask editor to reconsider your manuscript
  - Don't let it deter you from submitting to the journal in the future!

Take Home Massage

경청해 주셔서 감사합니다!

효과적인 의학논문 작성전략
(IMRD 구성전략과 피해야할 점, reject 되는 이유)

울산의대 서울아산병원 산부인과 **박정열**

서울아산병원
Asan Medical Center