

RESEARCH ARTICLE

Is the Loop Electrosurgical Excision Procedure Necessary for Minor Cervical Cytological Abnormalities?

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Abstract

Background: To investigate the indications of loop electrosurgical excision procedure (LEEP) and its overtreatment rates for the see and treat and three step strategies in cases of atypical squamous cells of undetermined cytology (ASC-US) and low grade intraepithelial neoplasia (LGSIL) cytology. **Materials and Methods:** We retrospectively analyzed colposcopy directed biopsy (CDB) and LEEP results of 176 patients with ASC-US or LGSIL cytologies who underwent colposcopic examination. **Results:** Initial cytologies were ASCUS in 120 women and LGSIL in 56. According to the see and treat approach immediate LEEP was performed for 38 women. Among the remaining 138 women, LEEP was performed for 32 whose CDB results revealed CIN2/3 lesions. In the see and treat group the recognition of CIN2/3 was found to be 39.4%. The overtreatment rate was 60% as compared to 25% in the three step group. In CDB group detection of CIN 2 or greater lesions increased with 3 or more biopsies. **Conclusions:** In patients with ASC-US/LGSIL cytologies CDB should be performed before LEEP to prevent overtreatment, with attention to all suspected areas and more than 2 biopsies taken.

Keywords: LEEP - ASCUS - LGSIL - overtreatment - colposcopy

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Introduction

Cervical cancer accounts for 15% of all female cancers in developing countries (Ferlay et al., 2000). According to Globocan (2008) data, it is the third most common gynecologic cancer (except breast cancer) in Turkey; its incidence is 4.2/100000, 1443 new cases and 556 deaths per year is reported (Globocan, 2008).

Due to the long preinvasive state, invasive cervical cancer has been considered a preventable disease. For this reason screening programmes are widely used in many developed and developing countries. Pap smear is the principal method for cervical cancer screening. Improper management of preinvasive lesions can increase the risk of cervical cancer, on the other hand overtreatment can cause some complications such as preterm delivery.

Generally accepted procedure for the management of cytologic abnormalities is colposcopy (Kyrgiou et al., 2007). The see and treat strategy is an alternative procedure for women with abnormal cytology, which provides immediate and concomitant diagnosis and treatment without previous biopsy. The most common treatment method used in this approach is loop electrosurgical excision procedure (LEEP). Another management strategy is colposcopy directed biopsy, and if histology is found to be cervical intraepithelial neoplasia (CIN) 2/3, LEEP is performed, this is called "three step strategy".

For cytologic high grade squamous intraepithelial

neoplasia (HGSIL) the benefit of the strategy of "see and treat" by LEEP outweighs the risk of overtreatment (Cho and Kim, 2009; Zhi Gang Li et al., 2009; Paula et al., 2012). On the other hand the role of LEEP in minor cytologic abnormalities as atypical squamous cells of undetermined cytology (ASC-US) and low grade intraepithelial neoplasia (LGSIL) remains unclear. There are few reports in this issue (Cho and Kim, 2009). In this study we searched indications, overtreatment rates and necessity of LEEP in ASCUS and LGSIL cytology.

Materials and Methods

We reviewed the medical reports of women who underwent colposcopic examination for minor cytological abnormalities (ASCUS and LGSIL) at the Baskent University Istanbul Hospital between January 2008 and January 2013. Colposcopies for HGSIL, Atypical Glandular Cells of Unknown Significance (AGUS), Atypical Squamous Cells can not exclude HSIL (ASC-H) cytologies; normal pap smear results and pregnant women were all excluded. Some patients with ASCUS results were followed up with repeat cytology. If the repeat cytologies were normal, colposcopic examination and biopsy were not performed. These patients were not included.

Pap smear before colposcopy, patient's age, gravidy and parity were documented. Pap smear results were classified according to the Bethesda System of 2001

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(Solomon et al., 2005). All cervical smears were conventional Pap smears.

Colposcopic examination was carried out after application of 4% acetic acid solution to cervix. After the examination with acetic acid, lugols iodine solution was performed. Visualization of the entire transformation zone was essential for adequate colposcopic examination. Patients' management were planned according to satisfactory colposcopy, visualization of transformation zone and squamocolumnar junction, acetowhite lesions, enlargement and margins of the lesions and pattern of the vessels. Patients with normal and satisfactory colposcopic examinations ; no biopsy performed and they were not included in this study. Patients with unsatisfactory colposcopy, suspicion of HGSIL, multiple and large lesions were treated with see and treat strategy. In some patients without HGSIL suspicion LEEP was performed for patients' wish for maximum safety. All of these patients had completed their families. Colposcopy-directed biopsy was performed for other patients. Endocervical curettage was also performed in all LGSIL patients. Biopsies were performed from all suspected areas and multiple biopsies were taken. If the biopsy results were CIN 2/3; LEEP was carried out as three step strategy.

LEEP was performed under general or local anesthesia at an outpatient department. The procedure was performed by using a diathermal electrocauterizer with a wire loop. The size of the loop was determined according to colposcopic examination of the lesion. The specimen was fixed in formalin and sent to the pathology department. Overtreatment was defined as final histological results CIN-1 or lesser lesions.

Complications of LEEP were; intraoperative cervical suturing requirement or postoperative bleeding from cervix that needs hemostatic interventions and infections.

Statistical analyses was done with SPSS software version 11.5. Chi-square test was used as a univariate analysis. Intergroup analysis is done with Wilcoxon test. P value <0.05 was considered as statistically significant.

Results

During the period, 176 women with minor cytological abnormalities underwent colposcopy and histopathological evaluations. According to see and treat approach immediate LEEP was performed to 38 women. Colposcopy directed biopsy (CDB) was performed to 138 women. Among these, in 32 women, pathology revealed CIN2/3 lesions. LEEP was performed following CDB to these patients so called "three step approach". To six women because of persistent CIN-1 lesions, LEEP is performed. The preceding pap smears of 176 women were ASCUS in 120 women and LGSIL in 56 women. Ages of the patients were between 20-67 years, and mean age was 34±9.1 years. Eighteen (10.2%) women were postmenopausal and 158 (89.8%) women were premenopausal. Seventy (39%) women were nulliparous. Of the 138 women whom CDB was performed, 98 had ASCUS and 40 had LGSIL cytology. 37 had a pathologic diagnosis on cervical biopsy as CIN 2 or greater: 22 with CIN 2, 13 with CIN 3 and 2 with invasive cancer. Of the remaining 101 patients, 50 had CIN 1 and

Table 1. Histologic Results of LEEP Specimens in Patients with ASC-US / LG-SIL Cytology

LEEP RESULTS	See and treat n (%)	Three step n (%)
No lesion	7 (18.4)	4 (12.5)
CIN-1	16 (42.1)	4 (12.5)
CIN-2	5 (13.1)	13 (40.6)
CIN-3	10 (26.3)	11 (34.3)
Total	38	32
*Overtreatment rate	23 (60.7)	8 (25)

*For the see-and-treat group overtreatment rate is 60.7 % and for the three-step group overtreatment rate is 25%, this finding is statistically significant (p=0.001)

Table 2. Colposcopy Directed Biopsy Results According to Initial Cervico-Vaginal Smear Results

	Colposcopy directed biopsy results					Total n (%)
	No lesion n (%)	CIN-1 n (%)	CIN-2+			
			CIN-2 n (%)	CIN-3 n (%)	SCC n (%)	
Cervico-vaginal smear results						
ASC-US	43(43.8)	35 (-35.70)	11 (-11.20)	8 (-8.10)	1 (-1.00)	98 (-100)
LG-SIL	8(-20)	15(-37.50)	11(-28.40)	5(-12.50)	1(-2.50)	40(-100)
Total	51(36.9)	50(36.2)	22(-15.90)	13(-9.40)	2(-1.40)	138(-100)

51 had no lesions. These results indicate that the CIN 2 or greater lesions on CDB was 26.8 % in minor cervical abnormalities. CDB results with respect to cytologies are presented in table 1. According to pathological results of CDB, 20.4 % of the ASCUS cytologies and % 42.5 of the LGSIL cytologies were found to be CIN 2 or greater. Mean number of biopsies was 3.9±1.8 (minimum 1 and maximum 12). According to number of biopsies patients grouped into two, one group had less than 3 biopsies and second group had 3 or more biopsies. Three or more biopsy taken group was more sensitive to detect CIN 2 and greater lesions.

In "see and treat" group the recognition of CIN2/3 is found as 39.4%. The clinical characteristics and histology results of the study objects regarding to LEEP indications are listed in table 2. In "three step" group, diagnosis of CIN2 and worse lesions are higher than CIN1 and lesser lesions (p<0.05). In "see and treat" group, CIN1 and lesser lesion rates are more than CIN 2 and greater lesions (p<0.05). Comparing these two groups according to detection of CIN 1 and lesser lesions or CIN2 and worse lesions; there is a statistically significant difference. Finally, the overtreatment rate in see and treat group is 60% and in three step group it is 25%. Three step group was more likely to have higher grade lesions (p<0.05). Another six women underwent LEEP in despite of CIN-1 results; because of persistent CIN-1 lesions or patients anxiety for maximum safety.

There were 8 women in whom the biopsy results was CIN 2 or greater but had negative (CIN1 or normal) LEEP results (Table 2). In this group the mean CDB number was 4.5±0.9. When the LEEP and CDB results were similar, CDB number was 4.5±1.8. There was no statistical significance. The mean time between the CDB and LEEP was 19.5±14.3 days (4-65 days). This period reflects a delay in the management of women with CIN2/3 due to additional CDB procedure rather than direct LEEP.

Discussion

See and treat approaches, especially LEEP, are investigated regarding to overtreatment rates since their introduction. The effectiveness of see and treat approaches depend on colposcopic findings. To decrease the overtreatment rates, patients must have a high probability of having CIN2/3 before undergoing this procedure. There is intra and inter observer variability in colposcopic examination and this may cause overtreatment. Patients may suffer unnecessary bleeding, infection and premature delivery due to overtreatment. According to Cho's opinion, "see and treat" protocol is only appropriate when an experienced colposcopist can differentiate low grade from high grade lesions (Cho and Kim, 2009).

Overtreatment rate is defined as the proportion of women whose excised specimens contained CIN 1 or less by the American Society for Colposcopy and Cervical Pathology (ASCCP) (Luesley and Leeson, 2010). In the current study, we compared the final histologic results and overtreatment rates of two approaches (see and treat and three step strategy).

Although there are some controversies in "see and treat" protocol and its overtreatment rates, similarly the CDB and its necessity is being evaluated in recent years. In a study of Byrom and colleagues, in HGSIL lesions on cervical smears or colposcopic examinations, CDB results were found to underevaluate the disease (Byrom et al., 2006). Similarly, Sadan and co-workers concluded that CDB did not improve the accuracy of diagnosis, it also delayed the treatment, and caused increased emotional anxiety in patients (Sadan et al., 2007). On the other hand Duesing et al. designed a study for the accuracy of preoperative assesment of CIN with cytology and CDB. They concluded that CDB is an accurate method. The concordance rate was higher for CIN2/3 (95.1%) when compared with CIN1 (63.2%) (Duesing et al., 2012). We did not perform the excisional procedure (LEEP) for all of the CIN 1 cases; so concordance rate between CDB and LEEP was not evaluated statistically in our study. The detection rate of CDB for CIN 2/3 lesions is 26.8%, whereas this rate is 39.4% in immediate LEEP group. This difference can be the result of application direct LEEP to high risk group.

See and treat approach is evaluated only for HGSIL cytologies in majority of studies. (Byrom et al., 2006; Sadan et al., 2007; Cho and Kim., 2009; Zhi Gang Li et al., 2009; Paula et al., 2012) Especially in low resource countries women with HSIL can be managed effectively using the see and treat approach with LEEP (Zhi Gang Li et al., 2009). A study from Brazil, concluded that for cytologic HGSIL the benefits of the strategy of see and treat by LEEP outweigh the risk of overtreatment (Paula et al., 2012). In Zang Li's study overtreatment rate was 7.8% and acceptable (Zhi Gang Li et al., 2009). According to the 2006 American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines see and treat approach is an alternative for management of women with HGSIL. But the role of LEEP is not investigated for the minor cytologic abnormalities as in HGSIL lesions. ASCUS/LGSIL Triage Study (ALTS) showed that only 15% of women referred

with ASCUS and 25% of women referred with LGSIL cytology had biopsy-proven CIN2/3. (Solomon et al., 2001; ALTS group 2003)) There are high overtreatment rates. So see and treat approach should be evaluated for these patients. In our study CIN 2 and greater lesions were seen 20.4% in the ASCUS cytology and 42.5% in LGSIL group. These rates are relatively higher when compared to previous studies. It may be due to high number of CDB's.

Only a few publications like Cho's study investigated ASCUS/LGSIL cytologies separately. In his study, respect the initial cervical smears, in the HGSIL cytology cases the addition of CDB did not reduce the ratio of overtreatment because the diagnosis did not differ at the initial and final results. In the see and treat group 19 women were diagnosed as invasive carcinoma and immediately treated the next day. But in the LGSIL and ASCUS cytology cases there were more cases of correct treatment in three step group than in see and treat group (63.3% versus 17.8%). And the author suggests that it was not appropriate to perform a LEEP without CDB in patients with low grade lesions found on cervical cytology (Cho and Kim, 2009). In Augkul's study overtreatment rate was 22.9% for HGSIL cytology/colposcopic findings. The overtreatment rate however was only 7% in women who had either pap smears or colposcopy suggesting a HGSIL. In women with ASCUS/LGSIL smears and only low grade lesions on colposcopic examination, rate of overtreatment was extremely high (68%) (Ae-Aungkul et al., 2011). In our study similar to Cho's findings the overtreatment rates are high in see and treat group than three step strategy (60.8% versus 25%).

Another issue is number of biopsies taken in three step strategy group. In 2012, Moss et al reported a study to determine the accuracy of the CDB to detect high grade CIN. In this study women with ASCUS and LGSIL cytologies with minor colposcopic changes had single CDB followed by LEEP. They concluded that single CDB appears to be insufficient to exclude underlying CIN 2 or 3 (Moss et al., 2012). In Nina's study he stated that accuracy of colposcopic biopsy (85.8% overall concordance rates) depends on the number of biopsies taken per patient (Sadan et al., 2007). In study of Gage, colposcopy with guided biopsy or biopsies detects approximately two thirds of CIN 3+. Although the sensitivity of the procedure does not differ significantly by type of medical training, it is greater when two or more biopsies are taken (Gage et al., 2006). In Pretorius study he concluded that sensitivity of colposcopy for CIN 3+ varies widely. Performing EndoCervical Curettage (ECC) with up to 4 random biopsies increases the diagnosis of CIN 3+. (Pretorius et al., 2011)

In our study CDB were performed in all suspicious areas and multiple biopsies were taken. In CDB group detection of CIN 2 or greater lesions increased with 3 or more biopsies. High number of CDB may cause negative LEEP results. In current study, there were 8 patients who had CIN2/3 results in CDB but their LEEP results had negative or CIN 1. Possible explanation is the high grade dysplasia may be completely removed with multiple CDB. In this situation, overtreatment rates should be less than 25% in three step group.

The most common complication following LEEP is perioperative bleeding and postoperative infections. In our study complications were seen in 6.3 % of the patients.

The limitations of current study are retrospective nature and small number of the sample size. Upto date only a few number of publications have been made for CDB and LEEP results in ASCUS/LGSIL cytology, but there are many publications for HGSIL cytology group. In this group see and treat strategy is thought to be appropriate. But according to our results in patients with ASCUS/LGSIL CDB should be performed before LEEP to prevent overtreatment rates. CDB should be performed to all suspected areas and more than 2 biopsies should be taken to be a more reliable method. If sufficient biopsies were taken, underdiagnosis decreases and more patients have correct therapies.

References

- ASCUS-LSIL Triage Study (ALTS) (2003). Group Results of a randomized trial on the management of cytology interpretations of atypical squamous cells of undetermined significance. *Am J Obstet Gynecol*, **188**, 1383-92.
- Aue-Aungkul A, Punyawatanasin S, Natprathan A, et al (2011). "See and treat" approach is appropriate in women with high-grade lesions on either cervical cytology or colposcopy. *Asian Pac J Cancer Prev*, **12**, 1723-6.
- Byrom J, Douce G, Jones PW, et al (2006). Should punch biopsies be used when high grade disease is suspected at initial colposcopic assessment :A prospective study. *Int J Gynecol Cancer*, **16**, 253-6.
- Cho HanByoul, Jae-Hoon Kim (2009). Treatment of the patients with abnormal cervical cytology: a "see-and-treat" versus three-step strategy. *J Gynecol Oncol*, **20**, 164-8.
- Duesing N, Schwarz J, Choschzick M, et al (2012). Assessment of cervical intraepithelial neoplasia (CIN) with colposcopic biopsy and efficacy of loop electrosurgical excision procedure (LEEP). *Arch Gynecol Obstet*, **286**, 1549-54.
- Ferlay J, Bray F, Pisani P (2000). Cancer incidence, mortality and prevalence worldwide, version 1.0. IARC Cancer Base No.5. Lyon:IARC Pres, 2001.
- Gage JC, Hanson VW, Abbey K, et al (2006). ASCUS LSIL Triage Study (ALTS) Group Number of cervical biopsies and sensitivity of colposcopy. *Obstet Gynecol*, **108**, 264-72.
- Globocan (2008). Estimated cancer incidence, mortality, prevalence and disability-adjusted life years (DALYs) worldwide in 2008, International Agency for Research on Cancer, WHO.
- HanByoul Cho, Jae-Hoon Kim (2009). Treatment of the patients with abnormal cervical cytology: a "see-and-treat" versus three-step strategy. *J Gynecol Oncol*, **20**, 164-8.
- Kyrgiou M, Koliopoulos G, Martin-Hirsch P, et al (2007). Management of minor cervical cytological abnormalities: A systematic review and a meta-analysis of the literature. *Cancer Treatment Reviews*, **33**, 514-20.
- Luesley D, Leeson S (2010). Colposcopy and programme management guidelines for the NHS Cervical screening programme, NHSCSP Publication, no. 20. Sheffield, UK:NHSCSP.
- Moss EL, Hadden P, Douce G, et al (2012). Is the colposcopically directed punch biopsy a reliable diagnostic test in women with minor cytological lesions? *J Low Genit Tract Dis*, **16**, 421-6.
- Nogara PR, Manfroni LA, da Silva MC, Consolaro ME (2012). The "see and treat" strategy for identifying cytologic high-grade precancerous cervical lesions among low-income Brazilian women. *Int J Gynaecol Obstet*, **118**, 103-6.
- Pretorius RG, Belinson JL, Burchette RJ, et al (2011). Regardless of skill, performing more biopsies increases the sensitivity of colposcopy. *J Low Genit Tract Dis*, **15**, 180-8.
- Sadan O, Yarden H, Schejter E, et al (2007). Treatment of high grade squamous intra-epithelial lesions: a "see-and-treat" versus three-step strategy. *Eur J Obstet Gynecol Reprod Biol*, **131**, 73-5.
- Solomon D, Nayar R (2005) Bethesda System for Cervicovaginal Cytology: Definitions, Criteria and Explanatory Notes. Second edition. Rio de Janeiro: Revinter.
- Solomon D, Schiffman M, Tarone R (2001). ALTS Study group. Comparison of three management strategies for patients with atypical squamous cells of undetermined significance: baseline results from a randomized trial. *J Natl Cancer Inst*, **93**, 293-9.
- Zhi Gang Li, De Ying, Jian Min Cen, et al (2009). Three-step versus "see-and-treat" approach in women with high-grade squamous intraepithelial lesions in a low-resource country. *Int J Gynaecol Obstet*, **106**, 202-5.