RESEARCH ARTICLE

Long Term Outcomes of Laser Conization for High Grade Cervical Intraepithelial Neoplasia in Thai Women

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Abstract

Aim: To report long term outcomes of laser conization for high grade cervical intraepithelial neoplasia (CIN) in Thai women. Materials and Methods: A retrospective cohort study was conducted in patients undergoing laser conization due to abnormal cervical cytology suggesting neoplasia during 1989 to 1994 and having follow-up data until December 2010. Conization was performed under colposcopy using a 0.5-mm CO_2 laser beam with power density of 18,000-20,000 watts/cm^2, and the surgical base was vaporized using a low power defocused beam. The follow-up protocol included cervical cytology and colposcopy. Long term outcome measures were failure rate (persistence and recurrence), post-conization status of transformation zone, and obstetric outcomes. Results: Of 104 patients undergoing conization, 71 had therapeutic conization for high grade CIN and were followed up for a median time of 115 (range 12-260) months. There was one case of persistent and one of recurrent disease comprising a failure rate of 2.8%. The post treatment transformation zone was well visualized in 68.3% of 63 patients with an intact uterus. Sixteen patients achieved 25 pregnancies; none had second trimester miscarriage. The obstetric outcomes were unremarkable. Conclusions: Laser conization under colposcopic visualization for the treatment of high grade CIN in Thai women has a low failure rate of 2.8%. The post-conization transformation zone could not be evaluated completely in approximately 30% of cases; therefore the follow-up protocol should include both cytology and colposcopy. Obstetric outcomes are not adversely affected by this therapeutic procedure.

Keywords: Cervical intraepithelial neoplasia - laser conization - long term outcomes - Thailand

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Introduction

Cervical cancer is the second most common cancer in Thai women. The annual incidence of invasive cervical cancer in Thailand is 21.1 per 100,000 women in 2004 to 2006 (Khuhaprema et al., 2012). The presence of screening measures and treatment for precancerous lesions of cervix, i.e. cervical intraepithelial neoplasia (CIN), is secondary prevention of cervical cancer. Nowadays the incidence of cervical neoplastic diseases would be certainly declining by means of primary prevention using human papilloma vaccine. Nevertheless, the cervical cancer remains a significant health problem for Thai women, especially those residing in the distant rural area.

Cervical cytology is the standard screening test for cervical cancer in Thailand. The conventional cytology, i.e. Papanicolaou's smear, is still the standard screening test. In our institute, a liquid-based cytology (LBC), i.e. the Siriraj LBC, was invented and has been routinely used for cervical cancer screening since 2005. The Siriraj LBC was proven to be an effective screening tool for cervical neoplasia as the detection rate of abnormal cytology suggesting neoplasia increased from 1.7% in the conventional cytology to 11.1% in the Siriraj LBC (Laiwejpithaya et al., 2008). These women would then undergo further diagnostic process.

Colposcopy with or without cervical punch biopsy is used as the primary diagnostic procedure for the women who have abnormal cytology test. If the diagnosis cannot be concluded with colposcopy, diagnostic conization would be performed as the next step of diagnostic process. The cervical conization is not only the diagnostic procedure but also the therapeutic measure for CIN.

Technique of cervical conization has been evolved and introduced to clinical practice since 1938 (Miller and Todd, 1938). Cold knife conization (CKC), the procedure being done using a scalpel under general or regional anesthesia, is the original and still a standard procedure for conization (Baser et al., 2013). Laser conization, the procedure being done using laser surgery technique, was established in 1975 (Dorsey and Diggs, 1979). Currently, loop electrical excision procedure (LEEP) is the most

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popular technique for conization, as the procedure is safe, convenient, and provides good quality cervical specimen both for diagnostic and therapeutic purposes, at lower cost than CKC or laser conization (Oyesanya et al., 1993; Mathevet et al., 1994; Duggan et al., 1999).

Our institute carried out laser conization for diagnosis and treatment of cervical neoplasia during 1989-1994. Although laser conization has been unavailable at our institute since 1995, the majority of the patients undergoing such procedure are still currently being followed up. The present study aimed to evaluate long term outcomes of laser conization for the management of high grade CIN in Thai women

Materials and Methods

A retrospective cohort study was conducted at the Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand, a tertiary care university hospital. After approval from Siriraj Institutional Review Board (SIRB), the medical records of patients who underwent laser conization from September 1989 to July 1994 were reviewed. Follow-up data until December 2010 were analyzed for long term outcomes. Patients of CIN 2 and 3 who were lost to follow up were excluded from the analysis of long term outcomes.

Colposcopy and laser conization procedure

Colposcopy and laser conization procedure were performed by experienced gynecologic oncologist. Patients with abnormal cervical cytology were examined under colposcopy. If the colposcopic findings suggestive for neoplastic diseases, the lesions were biopsied and laser conization was carried out as indicated by histopathology of the biopsied specimens; or laser conization would be proceeded in the same setting of colposcopy for the purpose of diagnosis and treatment. The laser conization was performed under colposcopic visualization using a carbon dioxide laser machine, SURGILASE 400 p Model SL 40 op SSW CO_2 Max. A 35-40 watts continuous laser beam focused to a 0.5 mm spot size, giving a power density of 18,000-20,000 watts/cm^2, was used for excision of cervical tissue. Lugol's solution was applied on the cervical mucosa to identify dysplastic areas. Local anesthesia was applied by injecting 1.5 mL of 2% lidocaine with epinephrine 1:200,000 into the ectocervix around the transformation zone and encompassing the lesions. A circumferential incision was made around the transformation zone and encompassing the lesions using single shot laser beam to outline the surgical site. Gentle traction using a laser conization hook was applied to the cervical tissue to tailor the shape, size and height of cone specimen. A defocused continuous 2-mm laser beam with a power density of 650 watts/cm^2 was used to vaporize the surgical base. During the procedure, smoke was evacuated using filter suction. The specimen was subjected to routine hematoxylin and eosin staining within the same day of the operation. Histopathology of the specimen was examined and reported by a team of gynecologic pathologists at the Department of Pathology.

Management after conization

The patients with histopathology of cervical specimens showing high grade CIN were appointed to postoperative follow-up visits at one month, every three months during the first year, every six months during the second year, then once a year thereafter. At each visit, the patients underwent routine pelvic examination, cervical cytology and colposcopy. Further management depended on the severity of disease, comorbidity, health status, reproductive status, and the findings at each follow up visit.

The patients with invasive lesions were treated according to their clinical staging, following the International Federation of Gynecology and Obstetrics (FIGO) guidelines. Those without a neoplastic disease were scheduled for annual pelvic examination and cervical cytology screening.

Definitions

The outcomes of therapeutic conization were defined as: *i*) remission, if no evidence of high grade CIN or more severe disease was demonstrated during the follow-up period; *ii*) persistent disease, if the disease was demonstrated within 6 months after the treatment; and *iii*) recurrent disease, if a new lesion occurred after 6 months of remission.

Statistical analysis

Data were analyzed using descriptive statistics. Data were presented in mean and standard deviation (SD), median and range, or number (n) and percentage (%) as appropriate.

Results

Figure 1 illustrates flow of the 104 patients undergoing laser conization. Characteristics of the patients were demonstrated in Table 1. The patients were 31.2±7.5 years old. The majority of the patients (81.7%) had cytological result of high grade squamous intraepithelial lesion

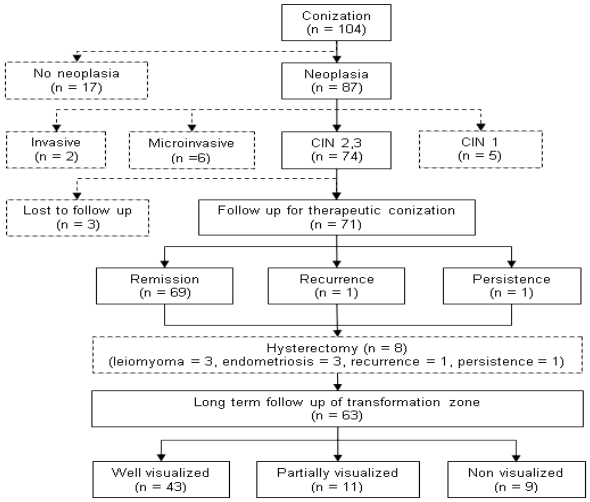

Figure 1. Flow of 104 Patients Undergoing Laser Conization at the Faculty of Medicine Siriraj Hospital, Mahidol University During 1989-1994. Data in dashed boxes were excluded from the analysis of long term outcomes below such boxes

(moderate dysplasia, severe dysplasia or carcinoma *in situ*). Final diagnoses were CIN (76.0%), microinvasive squamous cell carcinoma (5.8%), and invasive squamous cell carcinoma (1.9%). Of 104 cone specimens, 16.3% had no neoplastic lesion.

Table 2 demonstrates characteristics of the cone specimens of 74 patients with high grade CIN. (CIN 2 and 3). The margins of 70 (94.6%) cone specimens were free of disease. Four (5.4%) specimens had lesion involving margins, i.e., positive ectocervical margin (n=3, 4.1%) and positive both ecto and endocervical margins (n=1, 1.3%). Thirteen (17.6%) patients had lesions with glandular involvement.

Three cases of 74 patents with high grade CIN were lost to follow up and were excluded from the analyses of long term outcomes. Long term outcomes were obtained from the data of 71 patients who had a median follow up time of 115 (range 12 to 260) months. These comprised oncologic and obstetric outcomes. Oncologic outcomes of 71 patients demonstrated a failure of treatment in two patients (2.8%) which comprised one recurrent and one persistent disease. Both of them were 47 and 45 years old respectively and their cone specimens had free margin and no glandular involvement. The recurrent case was diagnosed at 12 months after treatment. Hysterectomy was later performed in 8 patients due to recurrent disease (n=1), persistent disease (n=1), leiomyoma (n=3), and endometriosis (n=3). Therefore 63 cases with an intact uterus had long term follow-up data for transformation zone (T Z) evaluation which were categorized into three groups, i.e. well visualized T Z (n=43, 68.2%), partially visualized T Z (n=11, 17.5%), and non-visualized T Z (n=9, 14.3%).

Table 3 demonstrates obstetric outcomes of 16 patients who conceived 25 pregnancies, resulting in two first trimester spontaneous abortion, three induced abortions, and 20 viable pregnancies. There was no second trimester miscarriage. Modes of delivery were 17 vaginal and 3 caesarean deliveries. The average neonatal birth weight was 3,207.5±511.9 grams (range 2,120-4,000); two newborns (10.0%) had low birth weight.

Table 1. Characteristics of 104 Patients Undergoing Laser Conization Due to Abnormal Cervical Cytology at the Faculty of Medicine Siriraj Hospital during 1989-1994

Characteristics	N	mean±SD or n (%)
Age, yr	104	31.2±7.5
<20		4 (3.9)
20-29		41 (39.4)
30-39		43 (41.3)
40-49		14 (13.5)
≥50		2 (1.9)
Cytological results (WHO classification)	104	
Mild dysplasia		8 (7.7)
Moderate dysplasia		38 (36.5)
Severe dysplasia		21 (20.2)
Carcinoma in situ		26 (25.0)
Invasive squamous cell carcinoma		8 (7.7)
Atypical squamous cell		3 (2.9)
Histopathological results	104	
Non neoplasia		17 (16.3)
CIN		79 (76.0)
CIN 1		5 (4.8)
CIN 2		14 (13.5)
CIN 3		60 (57.7)
Microinvasive SCC		6 (5.8)
Invasive SCC		2 (1.9)

*CIN, cervical intraepithelial neoplasia; SCC, squamous cell carcinoma

Table 2. Characteristics of Cone Specimens of 74 High Grade CIN (CIN2 and 3)

	N	n (%)
Margin status	74	
Free of disease		70 (94.6)
Presence of disease		
Ectocervical margin		3 (4.1)
Both ecto and endocervical margin		1 (1.3)
Glandular involvement	74	
Yes		13 (17.6)
No		61 (82.4)

*CIN, cervical intraepithelial neoplasia

Table 3. Obstetric Outcomes of 16 Patients Undergoing Laser Conization for the Treatment of High Grade CIN at the Faculty of Medicine Siriraj Hospital during 1989-1994

Patient no.	Modes of delivery	Neonatal weight (grams)	Height of Cone (cm)
1	IA	-	1.5
2	ND, ND	4,000; 3,900	1.2
3	M, ND	3,500	1.0
4	IA,IA,ND, ND	3,650; 3,150	1.5
5	CD	2,600	1.5
6	ND	3,600	1.5
7	M,ND,ND	3,300;3,000	1.5
8	ND	2,900	1.2
9	ND	3,790	1.5
10	ND	3,500	1.2
11	ND	2,400	1.5
12	CD	3,050	1.5
13	ND	2,120	1.0
14	ND, ND	3,080; 3,500	1.0
15	ND, CD	3,050; 3,550	1.0
16	ND	2,510	1.5

*CIN, cervical intraepithelial neoplasia; IA, Induced abortion; M, Miscarriage; CD, Caesarean delivery; ND, Normal delivery

Discussion

In 1975, Dorsey introduced carbon dioxide laser beam as a scalpel to obtain a cone biopsy specimen in CIN patients (Dorsey and Diggs, 1979). In addition to excision, the laser beam can destroy the lesions by means of vaporization, therefore laser conization can be used for both diagnostic and therapeutic purposes for CIN, i.e., the former by obtaining cervical tissue for histopathological diagnosis, the latter by excising and vaporizing the lesions. The laser surgery that is performed under colposcopic visualization enables a surgeon to optimize conization. The eventual expectation is to obtain long term outcomes of low recurrence rate and complications.

In the present study, we reported long term outcomes of 71 patients with high grade CIN primarily treated with laser conization and were followed up using cytology and colposcopy for a median duration of 115 (range 12 to 260)

months. Transformation zone could be well visualized in 68.2% of patients undergoing therapeutic conization and still having an intact uterus. A therapeutic failure rate (recurrence and persistence) of 2.8% was found.

There are several follow-up means for the patients with high grade CIN undergoing therapeutic conization depending on the budget, technology and manpower. We followed up our patients using cytology and colposcopy. We found that the transformation zone after laser conization was well visualized in 68.2% of cases. Since colposcopic evaluation was inadequate in 31.8% of cases, the combination with cervical cytology was routinely used in our follow-up protocol. The patients with well visualized transformation zone could be confidently followed up using only colposcopy. Moss reported that previous treatment of cervix did not impair the ability of colposcopy to diagnose cervical lesions if squamo-columnar junction was visible (Moss et al., 2009). However, previous treatment of cervix might compromise the ability of colposcopy to differentiate the negative or low grade lesions from the high grade or invasive lesions (Mitchell et al., 1998).

The failure rate of therapeutic laser conization in our study was not different from that of 1.2%-3.0% in previous reports (Bekassy, 1997; Skjeldestad et al., 1997; Ueda et al., 2006). Various factors affecting recurrent CIN after conization were age older than 40 years, positive endocervical curettage, positive endocervical margins, multi-quadrant disease, and glandular involvement (Paraskevaidis et al., 2000; Lu et al., 2006). Residual lesion was shown to increase recurrence rate (Lu et al., 2006), but laser vaporization at the surgical bases and margins after excision the cone specimen can destroy the residual lesions, consequently reducing recurrence rate (Ueki et al., 1994; Bar-Amet al., 2000). These could explain why our patients who had cone specimens with positive margins did not have recurrent disease. The only factor associated with failure of treatment in our study was age older than 45 years. While Bekassy reported that the cumulative recurrence rate increased with time up to 15 years of follow up (Bekassy, 1997), we did not have any recurrent cases after the first year of 21-year follow-up duration. The low recurrence rate in our study could not be explained by the duration of follow-up.

Regarding long term obstetric outcomes, many studies reported that laser conization or LEEP increased risks of preterm delivery, low birth weight and preterm premature rupture of membranes (Forsmo et al., 1996; Sjoborg et al., 2007; Wuntakal et al., 2013). However Sagot reported no significant difference in rate of preterm delivery in the same patients before and after laser conization (Sagot et al., 1995). There is association between the risk of preterm delivery and the cone specimens height of 1.0 cm or higher (Raio et al., 1997; Sadler et al., 2004). The height of cone specimens of our patients was 1.0-1.5 cm; but the risk of low birth weight infant was 10% which was not higher than the risk of 9.3-11.6% in our general population (data from 1998-2007 Vital Statistic Report of the Faculty of Medicine Siriraj Hospital).

In conclusion, laser conization under colposcopic visualization for the treatment of high grade CIN in Thai women has a failure rate of 2.8%. Post-conization transformation zone cannot be evaluated in approximately 30% of cases; therefore the follow-up protocol should include both cytology and colposcopy. Obstetric outcomes are not adversely affected by this therapeutic procedure.

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