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Prognostic outcome of cervical laser ablation using a holmium yttrium-aluminum-garnet (Ho:YAG) laser for the treatment of cervical intraepithelial neoplasia: A single-center retrospective study

Wataru Suzuki, Kana Ietani, Takeshi Makabe, Shinya Oki, Akiko Ohno, Yoshiko Mikami, Hiroshi Yamashita *

Department of Obstetrics and Gynecology, NHO Tokyo Medical Center, Japan

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ABSTRACT

Objective: Although cervical conization is considered a standard treatment for cervical intraepithelial neoplasia (CIN) 2/3, laser ablation can compensate for the disadvantages of the former. CO_2, semiconductor, and holmium yttrium-aluminum-garnet (Ho:YAG) lasers are applied in ablation, but no previous studies have shown the effectiveness of any of these techniques. Here, we retrospectively analyzed the application of the Ho:YAG laser in our hospital to verify its efficacy, and discussed the methods for optimal recurrence detection.

Methods: We evaluated the recurrence rates of the pathological condition in patients who underwent laser ablation with a Ho:YAG laser for CIN2/3 at our institution from June 2012 to November 2021. We defined the recurrence as histologically confirmed CIN2 or more advanced stage. Age, preoperative diagnosis, human papillomavirus (HPV) genotype, and postoperative high-risk HPV status were recorded to establish their association with recurrence rates.

Results: We performed surgery in 607 patients and the 2-year recurrence rate after interventions was 5.6%. Five patients were diagnosed with invasive cancer at the time of recurrence. Older age significantly correlated with higher risk of recurrence, but preoperative CIN grade and preoperative HPV 16/18 status did not significantly affect it. The postoperative high-risk HPV test was 100% sensitive for detecting recurrence.

Conclusions: Laser ablation with the Ho:YAG laser yields promising results. Together with postinterventional management, high-risk HPV test after laser ablation should be conducted after diagnostic conization.

This study received the approval from the Ethics Committee of the NHO Tokyo Medical Center (Ethics Committee approval number: R22-067).

1. Introduction

Cervical intraepithelial neoplasia (CIN) is a premalignancy of the cervix, and CIN2/3 is eligible for treatment if a patient is older than 25 years old and not pregnant. Conization has been regarded as the standard treatment for CIN2/3, but the rate of preterm delivery in pregnancies occurring postsurgically is as high as threefold more (Murakami et al., 2020), and there is also concern that cervical stenosis may exacerbate dysmenorrhea (Martin-Hirsch et al., 2010).

Alternative treatments to conization include laser ablation, cryotherapy, and loop electrosurgical excision procedure (LEEP). The advantages of laser ablation over conventional conization include no evidence for an increase of rate of premature delivery (Kyrgiou et al., 2006), the ability to perform ambulatory surgery, and no exacerbation of dysmenorrhea.

With the exception of diagnostic excisional procedure, laser ablation is a recommended mode of treatment according to the guidelines of the American Society for Colposcopy and Cervical Pathology (ASCCP) 2019 (Perkins et al., 2020).

Currently CO_2 laser, holmium yttrium-aluminum-garnet (Ho:YAG), YAG, KTP, and semiconductor lasers are commonly used for ablation, with CO_2 laser being the predominant type. CO_2 laser was one of the first to be used for medical purposes and is widely used in medicine fields, such as otolaryngology, plastic surgery, urology, and gynecology.

However, few reports have compared the effectiveness of different laser types. Therefore, in this study, we aimed to compare the efficacy of

* Corresponding author at: Department of Obstetrics and Gynecology, NHO Tokyo Medical Center, 2-5-1 Higashigaoka, Meguro-ku, Tokyo 152-0021, Japan.
E-mail address: yama2397@gmail.com (H. Yamashita).

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the Ho:YAG laser used in our hospital with the outcomes of previous reports.

HPV-based testing is recommended in the ASCCP2019 for post-CIN management, with previous reports showing that high-risk HPV test has better sensitivity and specificity for predicting recurrence (Arbyn et al., 2017). In most studies, diagnostic conization was employed as a method of treatment, while there are limited data on the usefulness of the high-risk HPV test after laser ablation.

Therefore, we sought to examine whether high-risk HPV test after laser ablation is predictive of disease recurrence.

2. Materials and methods

2.1. Patients

This retrospective cohort study was conducted to investigate laser ablation at the NHO Tokyo Medical Center from June 2012 to November 2021. For CIN2/3, the eligibility criteria included the absence of intracervical lesions, those not exceeding 75% of the cervical area, and those located within the visible range, with confirmed histological diagnosis, no suspicion of cancer, and no discrepancies in colposcopy, cytology, or histology. We used a Ho:YAG laser with a fiber diameter of 1,000 μm, a frequency of 10 Hz, an output of 1.0 J, and a pulse width of 700 μs. The ablation area was planned with a margin of 5–10 mm outwards from the squamous columnar junction. As for the depth, the ablation was aimed at approximately 5 mm (Fig. S1).

2.2. Recurrent cases

Among the recurrent cases, CIN grade and invasive carcinoma breakdown were tabulated, and the course of invasive carcinoma was evaluated retrospectively.

2.3. Postoperative management

Our postoperative protocol consisted of cytological examination and high-risk HPV test conducted every 3 months for up to 1 year, every 6 months for the 2nd year, and annually for the 3rd–5th years. Colposcopy was performed if the outcomes of cytology showed pathology. If the high-risk HPV test was positive, colposcopy was performed as appropriate at the discretion of the attending physician. Positive cytology was defined as that reflecting atypical squamous cells of undetermined significance (ASC-US) or higher findings, and recurrence was outlined as CIN2 or more advanced stage histologically. The date of recurrence was defined as that when CIN2 or a lesion at a progressed stage was confirmed histologically. The study also examined about the risk of recurrence in terms of age, grade of CIN2/3, and HPV16/18 in the postoperative recurrence and nonrecurrence groups. We recorded the positivity rates of high-risk HPV test and cytology at 6 months, 1 year, and 2 years postsurgically and assessed the utility of each test. High-risk HPVs included types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. HPV genotyping was performed using the PCR-rSSO method, and the high-risk HPV test was conducted using the Hybrid Capture 2 technique.

2.4. Statistical analysis

Data on the patients' age, preoperative diagnosis, HPV genotype, date of surgery, and postoperative follow-up were gathered from medical records and statistically analyzed. The 2-year survival rates were estimated using the Kaplan–Meier method. Differences in recurrence rates by age, grade of CIN2/3, and HPV16/18 were evaluated with univariate analysis using the Cox proportional hazards model.

EZR (Mac OS X version) was used for statistical analysis (Kanda, 2013). Statistical significance was set at $p < 0.05$.

3. Results

3.1. Patient characteristics

The clinical data of 607 patients with CIN 2/3 who underwent laser ablation from June 2012 to November 2021 were extracted from the patients' medical records. The median age at surgery was 36.9 (21–57) years (Table 1).

The preoperative diagnoses were CIN2 in 332 (54.7%) and CIN3 in 275 (45.3%). Preoperative HPV genotyping was implemented in 232 cases, including HPV 16 in 91 cases, HPV 18 in 14 cases, HPV 31 in 24 cases, HPV 52 in 76 cases, HPV 58 in 50 cases, other HPV in 16 cases, and high-risk HPV was negative in six cases.

The overall recurrence rate consisted was 3.5% at 1 year and 5.2% at 2 years (Fig. 1).

Considering the association between recurrence and age, the nonrecurrence group had a mean age at treatment of 37.4 years, and in the opposite, the latter composed 40.2 years with the significant difference (Table 2, P = 0.04).

3.2. Recurrence rate

The 2-year recurrence rate for CIN2 was 5.1% (95% confidence interval [CI]: 3.0%–8.5%) and 5.3% (95% CI: 3.1%–9.0%) for CIN3. Table 2 illustrates the outcomes of univariate analysis of recurrence rates according to age, CIN grade, and HPV 16/18 status. In univariate analysis, age (HR: 1.05; 95% CI: 1.00–1.11; P = 0.04) significantly correlated with recurrence, while CIN grade (HR: 1.36; 95% CI: 0.68–2.73; P = 0.39) and HPV 16/18 status (HR: 2.01; 95% CI: 0.78–5.18; P = 0.15) did not differ significantly between the groups (Fig. 2).

3.3. Invasive cervical cancer

The detected recurrent lesions found after treatment were CIN2 in 15 patients (2.47%), CIN3 in 12 (1.98%), and invasive cancer in five patients (0.82%). Among the patients who relapsed, 81.2% relapsed within 2 years and 18.8% relapsed 3 or 4 years after laser ablation. The pathologic conditions leading to invasive cancer were stage IA1 in one case, stage IB1 in one case, stage IIB2 in two cases, and stage IIIC in one case

Table 1
Patient characteristics.

Patients, n	**607**
Age, years (range)	36.9 (21–57)
Age at nonrecurrence, years (range)	37.4 (28–52)
Age at recurrence, years (range)	40.2 (21–57)
Diagnosis, n (%)	
CIN2	332 (54.7%)
CIN3	275 (45.3%)
HPV genotype, n (%)	
16	91(39.2)
18	14(6.0)
31	24(10.3)
52	76(32.8)
58	50(21.6)
others	16(6.9)
negative	6(2.6)
Recurrence, n (%)	32(5.2)
Recurrence as CIN2, n (%)	15(2.4)
Recurrence as CIN3, n (%)	12(2.0)
Recurrence as invasive cancer, n (%)	5(0.8)
Two-year recurrence rate as CIN2, %	5.1
Two-year recurrence rate as CIN3, %	5.3
Two-year recurrence rate as HPV16/18+, %	10.0
Two-year recurrence rate as HPV16/18−, %	5.0

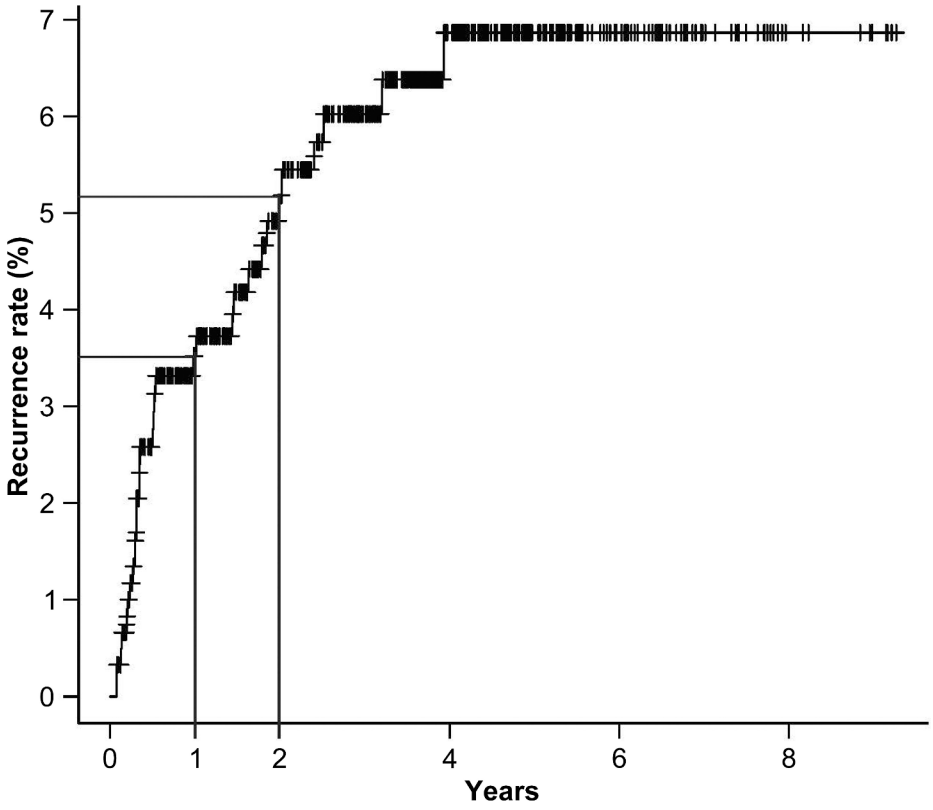

Fig. 1. Recurrence rate: Time until the recurrence of cervical intraepithelial neoplasia requiring retreatment.

Table 2
Recurrence of CIN requiring retreatment (Cox proportional hazards model).

	Univariate analysis	
	HR (95% CI)	**p-value**
Age	1.05 (1.00–1.11)	0.04
CIN2 vs CIN3	1.36 (0.68–2.73)	0.39
HPV16/18+	2.01 (0.78–5.18)	0.15

HR: Hazard ratio, CI: Confidence interval, CIN: Cervical intraepithelial neoplasia.

(FIGO2018 (Bhatla et al., 2019)). At stage IA1, negative for intraepithelial lesion or malignancy (NILM) persisted for 28 months after laser ablation, but high-risk HPV test was positive, so colposcopic diagnostics was performed. Subsequently, the outcomes of the histological examination were characteristic of CIN3, so a total laparoscopic hysterectomy was conducted, and microinvasive cancer was confirmed histologically. In one case of stage IB1, initial postoperative cytology revealed high-grade squamous intraepithelial lesions (HSIL), and histology reflected the features of squamous cell carcinoma (SCC). Similarly, in the one case of stage IB2, initial postoperative cytology indicated diagnosis of atypical squamous cells, cannot exclude HSIL (ASC-H), and histology reflected the features of SCC. In the other case of stage IB2, postsurgical cytology demonstrated abnormalities as HSIL, but with no cancer detected upon histological examination; however, 21 months postsurgery, features consistent with SCC were found. In these three cases, radical hysterectomy was performed and there were no obvious lymph node metastases. A case of stage IIIC was characterized by the absence of cytologic abnormalities for 2 years after the intervention; although the patient completed the hospital visit, they were rereferred for invasive cancer by the family doctor who was providing them with infertility treatment. Pre-operative imaging showed no obvious lymph node metastases, so a radical hysterectomy was conducted, but post-operative pathology was positive for pelvic lymph node metastases, leading to a stage IIIC (Table 3).

Invasive cancer occurred at an incidence rate of 0.0028 per person-year.

3.4. Postoperative high-risk HPV test

The positive rates of high-risk HPV test and cytological evaluation determined at 6 months, 1 year, and 2 years postoperatively are reflected in Table 4.

The sensitivity of the high-risk HPV test was 100% at times. Specificity for high-risk HPV ranged from 65.2%–87.0%, sensitivity for cytology ranged from 47.6%–60%, and specificity for cytology ranged from 92.1%–96.1%.

4. Discussion

Ho:YAG lasers are mainly used in gynecology, urology, gastroenterology, and dentistry. The energy of a Ho:YAG laser is quickly absorbed by tissue containing water and then dissipates heat. A Ho:YAG laser has a wavelength of 2.1 μm, an absorption coefficient of 31.8 cm^{-1} for water, and a slightly lower incisional capacity but safe cauterization characteristics (Kronenberg and Traxer, 2019; Phillips and Landman, 2007). The CO_2 laser has a wavelength of 9.2–10.8 μm and a water absorption coefficient of 1,000 cm^{-1}. The advantages included excellent incisional ability and hemostasis of blood vessels of up to 0.5 mm in diameter (Takac et al., 1998; Natalin et al., 2008). The Ho:YAG laser has a tissue penetration depth of approximately 0.4 mm and can cause thermal damage to the adjacent 0.5–1 mm to the area of preparation (Johnson et al., 1992). In contrast, CO_2 lasers transfuse less than 0.1 mm of tissue (Stein, 1986). Considering that the cervical epithelium has a thickness of 0.2–0.3 mm (Ghosh et al., 2016), CO_2 laser ablation may not fully transpire the lesion unless it is cauterized over time.

Looking at previous studies, the use of CO_2 lasers has been reported most frequently, followed by semiconductors. As yet, there have been no

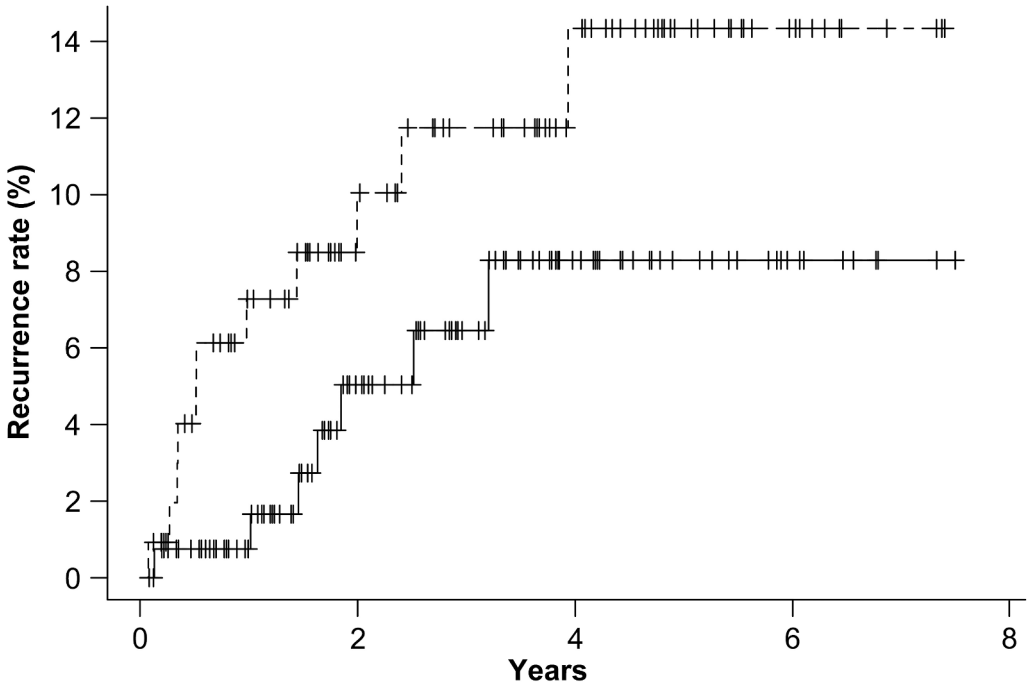

Fig. 2. Recurrence rate**:** Dotted line, Time until the recurrence of cervical intraepithelial neoplasia requiring retreatment of HPV16/18+**.** Solid line, Time until the recurrence of cervical intraepithelial neoplasia requiring retreatment of HPV16/18–.

Table 3
Recurrence of invasive cancer at our hospital.

	Age	Diagnosis	HPV	Time to appearance of cytological abnormalities	Recurrent lesion (FIGO2018 stage)	Time to recurrence	Relapse therapy
1	35	CIN2	NA	4 M	SCC (IB2)	4 M	RH
2	38	CIN2	16	4 M	SCC (IB1)	5 M	RH
3	36	CIN3	16	5 M	SCC (IB2)	24 M	RH
4	52	CIN2	58	NA	SCC (IA1)	31 M	TLH
5	34	CIN3	16	48 M	Undifferentiated cancer (IIIC)	48 M	RH

CIN: Cervical intraepithelial neoplasia, SCC: Squamous cell carcinoma, RH: Radical hysterectomy, TLH: Total laparoscopic hysterectomy, NA: Not available.

Table 4
Postoperative high-risk HPV test, cytology results, sensitivity, and specificity. Each item is 6 months/1 year/2-years after ablation.

	Sensitivity (%)			Specificity (%)		
	6 M	1 Y	2 Y	6 M	1 Y	2 Y
High-risk HPV test	100 (5/5)	100 (3/3)	100 (3/3)	65.2 (30/46)	83.5 (66/79)	87.0 (114/131)
Abnormal cytology	50 (15/30)	47.6 (10/21)	60 (6/10)	92.1 (489/531)	96.1 (464/483)	95.3 (383/402)

Note: The specificity should be regarded as a reference value.

former reports on cervical laser ablation with Ho:YAG lasers. Although recent reports differ in the definition of recurrence, Inaba et al. showed a 22.6% relapse rate 1 year after application of the CO_2 laser (Inaba et al., 2014), Kodama reported a 12.7% relapse rate 2 years after application of the CO_2 laser (Kodama et al., 2021), while Mariya and Shimada reported relapse rates of 6.5% and 6.4% at the same timepoint after the application of semiconductor lasers, respectively (Mariya et al., 2016; Shimada et al., 2019). The data from our hospital revealed a recurrence rate of 6.7% 2 years after using a Ho:YAG laser, which is largely comparable to that from the previous reports on semiconductor lasers and has lower values than that of CO_2 laser (Table S1).

Stentella demonstrated that the cumulative recurrence rate of invasive cancer was 8.9 per 1,000 patients 8 years after laser ablation (Stentella et al., 1995), which is in line with the results of the present study. In our research, invasive cancer was identified in five cases. CIN2 and CIN3 usually require several years to transform into cancer, and it is highly likely that cancer was present at the time of treatment in the two cases that were detected early. Unlike in conization and LEEP, tissue is not removed in laser ablation. In some cases, postoperative squamous metaplasia makes it difficult to diagnose recurrence by colposcopy. Therefore, the indication for surgery should be carefully considered.

The other three cases had to be comprehensively assessed for recurrence during long-term follow-up. As 18.8% of the other recurrence cases also relapsed after 3 or 4 years, long-term follow-up of more than three years was considered desirable, and our institution had a five-year follow-up.

We considered preoperative HPV type and risk of recurrence. Overall, 13 high-risk HPV-positive types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68), especially 16/18-positive, are known to possess higher risks of lesion progression. Additionally, after conization, the risk of recurrence is higher in 16/18-positive patients (Smith et al., 2007; Byun et al., 2018). However, no reports are present on the risk of recurrence after laser ablation. This study suggests a higher, although not significant, recurrence rate in preoperative HPV16/18-positive patients. Therefore, HPV16/18-positive cases should be carefully monitored, keeping in mind that the risk of recurrence is higher in such cases.

Marielle reported that the high-risk HPV test can be used as a more sensitive postoperative evaluator for management after conization or LEEP compared to cytology, although the specificity tends to be higher

for cytology, while having comparable values. We compared the high-risk HPV test and cytology as postoperative tests after laser ablation. The results revealed that the sensitivity was higher for the high-risk HPV test, while the specificity was elevated for cytology at 6 months, 1 year, and 2 years. The outcomes of our study did not differ significantly from those of high-risk HPV test after conization, and we believe that high-risk HPV test after laser ablation is as valid as testing after conization (Kocken et al., 2012).

5. Limitation

HPV genotyping is conducted on a clinical basis at our institution and consequently was not performed in all the cases. Due to factors such as transfer to another hospital postoperatively or interruption in follow-up visits, there may be discrepancies in the number of high-risk HPV tests and cytology. Furthermore, in this validation study, cases were classified as recurrence-free if no recurrence was confirmed at the time each test was conducted. However, there is a possibility that some cases classified as negative may still have hidden recurrences. In such cases, the specificity may actually be slightly lower than estimated. Therefore, the findings should be regarded as indicative rather than definitive. This retrospective study was conducted at a single center. Only a Ho:YAG laser was used at our institution, and the comparisons with other laser types are not entirely accurate.

6. Conclusion

Ho:YAG laser ablation may be associated with a lower recurrence rate than that with a conventional CO_2 laser. Data relating to the results of the former are expected to be accumulated in the future. High-risk HPV testing should be actively implemented after laser ablation and conization.

Presentation

65th Annual Meeting of Japan Society of Gynecologic Oncology, July 14–16, 2023.

Preprint

NA.

Disclaimers

NA.

Synopsis: Original article

The Ho:YAG laser is used in laser ablation, but there are no reports on its effectiveness.

Laser ablation with the Ho:YAG laser is highly effective.

Together with management after diagnostic conization, high-risk HPV test after laser ablation needs to be routinely performed.

CRediT authorship contribution statement

Wataru Suzuki: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Kana Ietani:** Writing – review & editing. **Takeshi Makabe:** Writing – review & editing, Investigation. **Shinya Oki:** Writing – review & editing. **Akiko Ohno:** Writing – review & editing. **Yoshiko Mikami:** Writing – review & editing. **Hiroshi Yamashita:** Writing – review & editing, Supervision, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2024.101405.

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