

## **Thermal ablation of premalignant lesions of uterine cervix using a portable battery-driven device**

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### **Summary**

Thermal ablation as an alternative to cryotherapy for the treatment of cervical premalignant lesions has shown great promise in the observational studies. The transformation zone of the cervix along with the lesion is destroyed using dry heat applied with a probe over 20 to 45 seconds. The most commonly used device is relatively bulky and requires electricity to operate. International Agency for Research on Cancer, France collaborated with LIGER Medical, USA to finalize the design of a hand-held, light-weight, portable battery-operated thermal ablator and evaluate the safety and performance of the new device in a randomized controlled trial (RCT) in Zambia. The Liger thermal ablator incorporates a lithium-ion battery and an integrated electronic circuitry which controls the probe tip at the appropriate temperature for ablation (~100-120°C). The reusable probe (sizes 16mm, 19 mm flat, 19 mm nipple) has been designed to provide a non-stick surface and includes a stable hybrid circuit heating element, and microprocessor control for safety as well as timing features.

The pilot RCT conducted in the primary care clinics in Lusaka, Zambia randomly allocated 750 women positive on visual inspection with acetic acid (VIA) eligible for ablative treatment to receive either thermal ablation (N=250) or cryotherapy (N=250) or large loop electrosurgical excision (N=250). The intensity of pain experienced during treatment, post-treatment bleeding and infective complications

were very low in the women receiving thermal ablation and comparable to the other treatment methods. There was no difference in the treatment success rate between the three randomized groups at 6 months of follow up, irrespective of HIV infection status.

**Key words**

Cervical screening, Cervical precancer, thermal ablation, cryotherapy, ablative treatment, randomized controlled trial, safety, efficacy

**Running Head**

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## 1. Introduction

Cervical cancer is responsible for more than 300,000 deaths globally, most of which are in low or middle income countries (LMICs) where it is the second most common cause of female cancer deaths **(1)**. The disease has been successfully prevented in many developed countries through effective implementation of high coverage, well organised screening programmes. Over 85% of incident cases and deaths from cervical cancer occur in the developing world where the implementation of organized screening programmes has faced many challenges. The profound societal and humanitarian impact of the death of a woman in her prime is highlighted by the fact that 14 children die for every 100 mothers losing their lives to cervical or breast cancer in Sub-Saharan Africa **(2)**.

Global elimination of cervical cancer as a public health problem is feasible through effective implementation of HPV vaccination and screening programmes **(3)**. A critical component of any elimination strategy is to ensure access to safe, simple and effective treatment of premalignant lesions detected through screening **(4)**.

While large loop excision of the transformation zone (LLETZ aka LEEP) has become the 'standard of care' in high resourced settings, the ideal technology for limited resource settings remains elusive **(5)**. A technology to be considered suitable for the low resourced countries should be effective, affordable with low running and maintenance cost, technically simple, be easy to learn and be safe **(6)**.

The practice of thermal ablation (also known as thermo-coagulation) to treat cervical precancer dates back more than 50 years. It was first introduced to clinical practice in Germany by Kurt Semm **(7)**. The technology used by Semm to treat cervical epithelium with a metal probe heated to 100° C was initially called 'cold' coagulation to differentiate it from radical electro-diathermy which achieved temperatures of 300° C. The technique did not initially gain widespread popularity and was practiced by only a limited number of gynaecologists in Europe. It has remained the treatment of choice in many centres in Scotland.

The increasing awareness in LMIC of the practical difficulties of cryotherapy (e.g. cost and supply of gas cylinders, equipment failure, and duration of treatment) has led to renewed interest in thermal ablation as an alternative ablative method for the treatment of screen positive women, especially in the context of *screen and treat* programmes. Also, the available evidence has pointed to the equivalent or superior efficacy of thermal ablation when compared to cryotherapy **(8)**.

The original '*bench top*' thermo-coagulator (WISAP Medical Technology, Brunnthal, Germany) is a light weight machine that is not entirely portable and needs to be connected to an electrical circuit to operate. The cost of the machine is approximately \$3,000.

The International Agency for Research on Cancer (IARC), Lyon France in collaboration with LIGER Medical (Utah, USA) has developed, bench tested and evaluated in a pilot randomized study a portable, lightweight battery-driven thermal ablator. The study was implemented within the framework of a project funded by National Institute of Health, USA (Grant number 1UH2CA202721-01). The study is registered with the U.S. Clinical Trial Registry (<https://clinicaltrials.gov/ct2/show/NCT02956239>).

### *1.1 Principles of ablative techniques to treat cervical precancer*

In the latest edition of the histopathologic classification of tumours of female reproductive organs by the World Health Organization (WHO) (2014) cervical pre-cancers are classified using a two-tiered system – low grade squamous intraepithelial lesions (LSIL) and high grade squamous intraepithelial lesions (HSIL) **(9)**. Condyloma and cervical intraepithelial neoplasia (CIN) 1 are the morphological manifestations of productive human papillomavirus (HPV) infections and very few of them will progress to invasive cancer. Such lesions are categorized as LSIL and may be followed up without immediate treatment. CIN 2 and CIN 3 are the true cervical cancer precursors with a more significant risk of progression and are categorized as HSIL. Integration of the high-risk HPV genome within the host genome followed by over-expression of E6/E7 oncoprotein and consequential inactivation of the p63 and pRB tumour suppressor genes leads to high grade lesions. At least 10% of the CIN 2 lesions and 20%

of the CIN 3 lesions will progress to invasive cancer, if left untreated **(10)**. Due to such high risk of progression, immediate treatment is recommended for all high grade lesions unless detected in very young women or during pregnancy.

High grade lesion arises from the squamo-columnar junction (SCJ) and is largely confined to the transformation zone (TZ) of the cervix. The TZ is the area where columnar epithelium undergoes metaplastic changes into immature and mature squamous epithelium and is limited by the SCJ proximally. There is ample evidence that the high grade lesions originate from a discrete population of embryonic cells residing at the SCJ **(11)**. These 'junctional' cells are cuboidal epithelial cells of embryonic origin with morphology and gene expression profile different to the adjacent squamous or columnar cells. They over-express keratin (Krt) 7, anterior gradient (AGR) 2, cluster differentiation (CD) 63, matrix metalloproteinase (MMP) 7 and guanine deaminase (GDA) genes and can be identified by staining with antibodies corresponding to these junction cell specific transcripts **(12)**. All cervical cancers (both squamous and adeno), almost all HSILs and a small fraction of LSILs express the immunological markers specific to the junctional cells, suggesting their common origin from these cell population **(13)**. Similar embryonic junctional cells found at the SCJ between the oesophageal and gastric mucosa are known initiators of Barrett's oesophagus, the precursor of oesophageal carcinoma **(12)**. High risk HPV infection of the junctional cells leads to lesions that progress to invasive cancer, while HPV infection of the more mature squamous epithelium is responsible for transient and regressive LSIL changes.

This new theory of origin of the HSILs explains why ablation or excision of the TZ along with the SCJ is so efficient in preventing subsequent development of cervical cancers. Studies have demonstrated that the junctional cells do not regenerate after successful excision of the TZ **(14)**. On the other hand, the presence of post-excision residual (unexcised) disease expressing the SCJ immuno-phenotypes have very high risk of recurrence of CIN 2/CIN 3 **(15)**.

The junctional cellular origin of the high grade lesions also explains the prevention of cervical cancer observed after pre-emptive ablation of these susceptible embryonic cell population. Prophylactic

ablation of the ectropion (columnar epithelium extending to the ectocervix) with electrodiathermy was a common practice among gynaecologists in the 1950s. The procedure involved cauterization with a ball diathermy which started at the external os, radially extending over the visible columnar epithelium up to and including the SCJ, so that all the SC junctional cells were potentially ablated. In a case series involving a total of 13,897 women attending a private gynaecological practice in USA it was observed that the women treated with diathermy (N=6364) had a very low rate of detection of carcinoma in situ and cancer compared to the untreated women (0.5/1,000 vs. 27/1,000) during subsequent follow up **(16)**. In fact, no cancers were detected in the treated women. The protective value of diathermy ablation of SCJ and the adjacent columnar epithelium was also demonstrated in a Finnish follow up study of 429,832 women **(17)**. The prevalence of carcinoma in situ and invasive cancers were 4.3 and 6.3 times higher in the untreated women compared to the treated women.

All such evidence indicates that the destruction of the junctional cells is crucial to success using any ablative technique, including thermal ablation. Though not yet adequately investigated, it is possible that the junctional cells are present across the TZ at each crypt opening having an SCJ. This probably explains the reason why the treatment of CIN necessitates treatment (either excision or ablation) of the entire TZ and not just the lesion. Since thermal ablation can treat only the ectocervix, the technique should be attempted only on cases with fully visible SCJs and with SCJ positioned on the ectocervix (type 1 TZ). Location of the TZ inside the endocervical canal, partially or fully (TZ types 2 or 3), is an exclusion criterion of thermal ablation. The other eligibility criteria for thermal ablation are as follows:

1. The lesion should not be occupying more than 75% (3 quadrants) of the ectocervix
2. The visible lesion on the cervix should not extend to the vagina or endocervix
3. There should not be any suspicion of invasive cancer
4. There should not be any suspicion of glandular abnormalities (on cytology, colposcopy or histopathology)

## *1.2 Advantages of thermal ablation over cryotherapy as an ablative technique*

Ablation of the TZ with cryotherapy has been highly successful in curing cervical precancers. In a recent Cochrane systematic review the success rate of cryotherapy to treat CIN 3 lesions ranges from 77% to 93% **(18)**. The significant protective effect of prophylactic cryotherapy of the transformation zone in HPV positive women (with or without any visible lesion after application of dilute acetic acid on the cervix) has been demonstrated in a South African randomized controlled trial (RCT) **(19)**.

The relative success rate of cryotherapy, the simplicity of the technique, low rates of complications led the WHO to recommend cryotherapy as the ablative treatment of choice in 2013 **(20)**. However, the technology has several drawbacks and implementation challenges. Refrigerant gas (either CO<sub>2</sub> or N<sub>2</sub>O) is needed to achieve the Joule-Thomson cooling effect. Procurement and ensuring regular supply of refrigerant gas is quite difficult, indeed impossible, in many limited resourced countries. Moreover, the gas is supplied in heavy cylinders. Transporting these cylinders from the factory to the primary care settings incurs additional expenses and adds to logistic complexities. Impurities in the gas may block the gas flow, which may lead to incomplete treatment. The prolonged treatment time (freezing for 3 minutes, thawing for 5 minutes and repeat freezing for 3 minutes) is taxing for the patient as well as the provider. Cryotherapy is not suitable to treat a large transformation zone as multiple application of the probe on the cervix is not possible.

Due to these shortcomings of cryotherapy, thermal ablation is being evaluated as a suitable alternative to treat CIN lesions effectively and at an affordable price for LMICs. A meta-analysis of 13 studies by Dolman et al published in 2014 involving treatment of 4569 women with CIN 1, CIN 2 or CIN 3 with thermal ablation demonstrated a cure rate of 95% for CIN 2/CIN 3 lesions **(8)**. The technology was observed to have minimal complications and no effect on subsequent fertility. However, all the included studies in this review were observational cohort studies except for one trial conducted in Singapore that randomized 154 women with biopsy proved CIN 1-CIN 3 to receive treatment either by thermal ablation or cryotherapy. The RCT observed a cure rate of 95.5% for thermal ablation and 93.8% for cryotherapy

**(21)**. This set the stage not only for further evaluation of thermal ablation in an LMIC setting but also to replace the traditional bench top and electricity driven thermo-coagulator with an inexpensive, robust, fully portable and battery-driven thermal ablation device.

## **2. Materials**

Within the framework of an NIH grant IARC collaborated with LIGER Medical to produce a technically innovative thermal ablation device that is inexpensive, portable, battery-operated, hand-held and practical for use in rural environments. This battery-operated thermal ablator was developed with the specific ambition of improving delivery of screen and treat programs for cervical pre-cancer in LMICs. It is FDA cleared, CE Mark certified, commercially available and is currently being used in over 40 countries world-wide.

### *2.1 The new thermal ablator device*

The Liger thermal ablator incorporates a lithium-ion battery (equivalent ones are readily available in hand-held screwdrivers or drills) and an integrated electronic circuitry which controls the probe tip at the appropriate temperature for ablation (~100-120°C). The reusable probe has been designed to provide a non-stick surface with a sterilizable and biocompatible probe. It includes a stable hybrid circuit heating element, and microprocessor control for safety as well as timing features to make the procedure as easy to perform as possible. The device is packaged in a rugged hard outer case with inner foam for protection in transport. Each device kit is comprised of a handle, 4 probes (sizes 16mm, 19 mm flat, 19 mm nipple), two lithium-ion rechargeable batteries, universal AC recharge adapter, and instructions for use (IFU) as shown in **Figure 1**. Each probe is guaranteed to function optimally for at least 200 treatment cycles.

### *2.2 Safety features of the new thermal ablator*

The device has several novel safety features

- The probe tip is heated by a specially developed thick-film hybrid resistive element screened onto a precision-machined aluminum cap (Figure 2). It has a resistance of 3-5 ohms depending on the tip size thereby using 30-50 watts from the 12-volt lithium-ion battery. The battery has 2 amp-hour capacity and can be recharged in 2-3 hours from standard AC wall power (100-240v, 50-60Hz). A thermistor (NTC) is assembled onto the thick-film circuit for feedback control turning on and off the voltage to the resistor element thereby maintaining the therapeutic temperature, typically 100°C, but accommodating any temperature selected between 80°C and 120°C. Once charged fully, each battery can complete at least 50 treatment cycles.
- An electronic circuit (Figure 3) has hardware and software controls which provide safety and special user-friendly features for ease of use. For example, to ensure that the probe tip does not get into a “run-away” or over-heating mode, due for example to failure of the heating resistor or to thermistor failure, the design contains both hardware and software that monitors the current, power consumption, resistances, and treatment duration and, where necessary, will shut off power and notify the user as to the condition of the problem.
- The biocompatible probe tip is coated with PEEK (polyetheretherketone), that is exceptionally abrasion resistant and does not stick to cervical tissue at any temperature. Because PEEK has superior chemical resistance – as well as resistance to steam and water, it is often used in applications where performance at elevated temperatures is required.
- The device has a microprocessor that can choose different times and temperatures if preferred by the clinician. This is accomplished by using the membrane switch on the handle. The function cannot be inadvertently activated. Temperature or treatment duration may be changed by holding down the ON/OFF button for 13 seconds to enter this mode, then stepping through an

BCD code for a matrix of 16 different combinations of temperatures of 80°C to 120 °C and times from 20-60 seconds. This makes the unit very versatile.

### 3. Methods

#### 3.1 Physics of thermal effects in biological tissue

Cervical tissue becomes coagulated if its temperature reaches about 60°C. When this temperature is exceeded, the structure of the cell changes causing a change in color of the tissue, formation of derivatives of collagen, e.g. and glucose, and contraction of collagen. Thermal desiccation is defined as heat-induced dehydration of tissue. If the temperature of tissue is equal to the boiling temperature of intra or extracellular water (c. 100°C), the desiccation effect can dehydrate the tissue quickly, depending on the density of power applied to the target tissue. Thermal desiccation causes significant contraction of tissue by drying and shrinkage of vessels, resulting in hemostasis of small vessels. Desiccation of glucose as a derivative of collagen results in a glue effect, which in turn causes sticking of desiccated tissue to coagulation probes. Desiccated tissue has a relatively high specific electric and thermal resistance. The thermal destruction of cervical tissue most commonly uses 100°C, for a time of 20-30 seconds to achieve cellular and viral protein denature.

#### 3.2 Operation of Liger Thermal ablator unit (Figure 4)

**Activation (ON/OFF) Button:** Press once to turn unit on. The activation button will illuminate green and one of the blue lights flashes to indicate unit is turned on. White illumination LED's on front of unit will also turn on. Press a second time to begin treatment cycle. The unit will shut itself off after the treatment cycle if needed.

**Timer Lights:** When the activation button is pressed a second time, the lights will all illuminate blue.

After each ¼ of the treatment cycle is completed one light will turn off. An audio sound is also given to indicate cycle count down. When all timer lights are turned off the treatment cycle is complete and the unit shuts itself off.

**Activating the thermal ablator - practical steps :**

Step 1: Insert the desired treatment probe (19mm or 16mm) connector into the mating connector at the front of the unit. Ensure that the probe is tightly inserted. If the probe is not securely connected, inserted improperly, missing, or is broken when the ON/OFF button is pressed, the ablator will power on briefly, flash all lights three times, then shut itself off.

Step 2: Turn ON the ablator by pressing the ON/OFF button located on the handle, one time, and verify that the green LED is on. The white illumination LED's on the front of the unit will also turn on, and one blue light will flash showing unit is ready for placement (tip not heated yet).

Step 3: When the probe has been placed against the tissue needing treatment, press the ON/OFF button a second time to start the procedure. Four blue timer LEDs will flash sequentially from left to right for a few seconds indicating that the probe tip is heating. When the blue timer LEDs turn solid and a single audible beep is heard, the treatment cycle is running. The blue timer LEDs turn off with an audible beep, one at a time, after each 1/4 of the procedure has finished. When all four (4) blue timer LEDs are turned off a longer audible beep is heard, the unit is no longer applying heat. It has commenced its cool down cycle. Once the cool down cycle is complete, the front white LED lights will turn off, and the probe may then be removed from the treatment area. If a second treatment area is needed, repeat the above steps before removing the probe.

*3.3 Field evaluation of the thermal ablator*

The IARC in collaboration with the University of North Carolina (USA) initiated a randomized controlled study in 2017 which is ongoing and compares the new thermal ablator with double freeze cryotherapy and large loop excision of the transformation zone (LLETZ). The study setting is the cervical cancer screening service operated by the Ministry of Health in Lusaka, Zambia. Women between 25 and 49 years of age with intact uterus have screening with VIA (visual inspection after acetic acid application) test. VIA positive women are assessed to check if the case is suitable for cryotherapy (type 1 transformation zone, lesion fully visible on the ectocervix, no extension of lesion to the vagina, no suspicion of cancer, can be covered by the largest cryotherapy probe). Informed and freely consenting women positive at VIA who are eligible for cryotherapy and not pregnant are recruited to the study. Every participant has a cervical sample collected for high risk human papillomavirus (HPV) detection test prior to VIA. The samples are tested using Xpert™ technology (Cepheid, Sunnyvale, CA, USA) to detect 14 high risk HPV types, along with type specific information.

A concealed randomization process is followed to allocate treatment method. While cryotherapy and thermal ablation are performed without anaesthesia, local anaesthesia is used before LLETZ. After completion of treatment, every participant is asked to indicate the intensity of pain experienced by her during the treatment on a visual scale ranging between 1 (no pain at all) and 9 (pain so severe that the procedure has to stop). All the participants are advised to return for follow up after 6 months when the sample collection for HPV test and VIA are repeated. Since no histopathology evaluation is possible either before or after treatment, we use a composite end point to determine the cure rate after treatment. The HPV positive participants at VIA screening who are HPV negative at follow up are considered to have cleared the disease. Resolution of the lesion on VIA is considered as the test of cure for women who are HPV negative at baseline.

Though the RCT aims to randomize more than 3,000 women, an interim planned analysis was performed after recruiting 250 participants in each treatment group. The very high prevalence of HIV infection in the target population was highlighted by the fact that 52.3% of the recruited participants

were HIV positive. High risk HPV was detected in 57.5% of the participants, with nearly one third being positive for HPV 16. There was no significant difference in the HIV and HPV positivity and different socio-demographic characteristics among the three randomized groups.

At six months follow up, 64.1% of the participants treated by thermal ablation had no evidence of disease as per the definition of cure mentioned earlier. Similar treatment success rates were observed in the cryotherapy arm (60.0%) and the LLETZ arm (63.8%). HIV positive women had significantly lower success rates (thermal ablation – 44.2%, cryotherapy – 45.9% and LLETZ – 54.5%) again without any statistically significant difference between the groups. The vast majority of the participants receiving either thermal ablation (97.6%) or cryotherapy (97.2%) complained of no or minimal pain (ratings of 1-3 on the visual scale). Overall, the acceptance of both the techniques was very high. However, a questionnaire survey among the nurse providers revealed that they were much more in favour of using the thermal ablation in routine practice due to its simplicity, lower treatment time and robustness of the technique.

#### **4. Notes**

It is perhaps reasonable to expect thermal ablation to perform as effectively as cryotherapy given the fundamental acceptance that destroying or removing transformation zone epithelium is the ambition of every method of treatment for cervical precancer or screen positive women used today. It is also entirely laudable that bioengineering efforts continue to develop technology that is superior in design, function, portability and affordability. An updated meta-analysis of thermal ablation has recently been published and concludes that TA appears to be an effective treatment for CIN 2/CIN 3 across a variety of settings, including in LMICs (22). Also a clinical guidelines group convened by the WHO has recently recommended that thermal ablation be used wherever an ablative method is appropriate, including women with HIV infection (23). Finally, thermal ablation has continued to be used in a rigorously

controlled screening programme in Scotland where long term assessment of its' efficacy is currently under evaluation. If the results of our ongoing RCT in Zambia and other studies confirm the pilot data from this study and confirm the conclusion of the recently updated meta-analysis, it is likely that thermal ablation using portable cordless and battery operated devices will become the treatment method of choice for screen positive women in the context of screen and treat programmes in LMIC. Selection of cases suitable for ablation, as opposed to excision, remains a challenge in see and treat programmes. It may be that the growing interest in artificial intelligence image recognition systems will provide more accurate and quality controlled assessment of which women should have ablation and which should be referred for excision by properly trained personnel in suitably equipped facilities.

### **Disclaimer**

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### Figure Captions

**Figure 1. Liger thermal ablator** device kit comprising of a handle, 4 probes (sizes 16mm, 19 mm flat, 19 mm nipple), two lithium-ion rechargeable batteries and universal AC recharge adapter

**Figure 2.** Liger thermal ablator probe tip heater

**Figure 3.** Circuit of the liger thermal ablator

**Figure 4.** Operation of the Liger thermal ablator unit