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Review Article

Worthy of further consideration: An updated meta-analysis to address the feasibility, acceptability, safety and efficacy of thermal ablation in the treatment of cervical cancer precursor lesions

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ABSTRACT

Treatment of preinvasive lesions is critical to the success of secondary prevention of cervical cancer. In many settings, however, excision or ablation of preinvasive lesions can prove challenging. Thermal ablation (TA) is a form of treatment for cervical precancer that may present fewer logistical challenges in resource limited settings. In 2013, Dolman and colleagues wrote a meta-analysis of publications reporting cure rates from TA. This included only one article from a low or middle-income country (LMIC). We updated Dolman's meta-analysis to include more recent articles from LMICs.

A formal review of the world literature was performed for the years 2014–2017. Article titles and abstracts were reviewed for relevance; full articles were assessed for quality. The primary endpoint was treatment outcome for cervical intraepithelial neoplasia grade 2 or higher (CIN2+). The I2 statistic was used to assess heterogeneity between studies. Studies were stratified by geographic region, decade that the study was published, World Bank economic classification of the country where the study was performed, and other factors.

We reviewed 34 total reports and included 23 in our meta-analysis, including 10,995 and 6371 patients, respectively. A total of 7 studies were performed in LMICs, including 6 studies included in the meta-analysis. The overall response rate for TA treatment of biopsy proven CIN2+ was 93.8%. Consistent with the wide variety of settings and patient populations, there was significant heterogeneity between studies. TA appears to be an effective treatment for CIN2+ across a variety of settings, including in LMICs.

1. Introduction

Cervical cancer is a preventable disease caused by oncogenic genotypes of the Human Papilloma Virus (HPV), that disproportionately kills women in low- and middle-income countries (LMICs) (Tsu and Jeronimo, 2016). Secondary prevention using cervical cytology (Pap smear) has been highly successful in most developed countries (Vaccarella et al., 2013), but, unfortunately, that success has not been widely replicated by developing countries. Challenges with results reporting, patient follow-up, and safe and reliable delivery of treatment can limit the effectiveness of a secondary prevention program. Primary prevention with the HPV vaccine holds great promise to decrease the burden of the disease, but it does not protect the millions of women already infected with HPV. These women can be protected from cervical cancer through identification of precursors of cervical cancer, also known as cervical intraepithelial neoplasia grade 2–3 or 'CIN2+'. Left untreated, as much as 30% of CIN2+ will progress to cancer (McCredie et al., 2008), but treatment can dramatically decrease that risk (Arbyn et al., 2014). To be clear, secondary prevention of cervical cancer will only decrease the burden of disease when treatment is effectively linked to the identification of precursor lesions. The effectiveness of an overall cervical cancer secondary prevention program, therefore, can be significantly affected by the efficacy of a given treatment technique and practical considerations, such as whether a patient is able to receive treatment and the 'real-world' performance of a given device. It is of significant public health concern to make effective and reliable treatment for CIN2+ available at or proximate to the point where a patient is initially screened.

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CIN2+ lesions can be treated through either excision or ablation. Cervical excision can be performed using a loop electrosurgical excision procedure ('LEEP') or performing a surgical conization with a scalpel or LASER. These procedures are often preferred by practitioners in high resource areas as they yield a tissue specimen for pathologic evaluation. On the other hand, excision procedures are considered technically more difficult, have a somewhat higher risk of surgical complications, and require the use of anesthesia, and therefore many other practitioners prefer ablative techniques. Ablative techniques destroy tissue rather than removing, technically easier to perform and are frequently performed without the use of anesthesia.

The World Health Organization (WHO) endorses the use of cryotherapy (CT), as a safe and effective means of ablating CIN2+ (WHO, 2014). In CT, a refrigerant cooled probe is used to freeze the cervical epithelium to below −80 °C for 3 min, thaw for 5 min and freeze again for another 3 min (at least 11 min), causing tissue necrosis and ablation of CIN2+. An abundant literature supports that this technology is effective in the right circumstances (Sauvaget et al., 2013; Santesso et al., 2015; Santesso et al., 2012) with cure rates ranging between 70 and 90% for CIN2+ (Luciani et al., 2008; Mitchell et al., 1998). The advantages of cryotherapy are its lack of serious side effects or complications, as well as its simplicity making it possible to deliver the treatment even in remote areas, and in theory treatment could be made available proximate to the patient. In addition, while ablative therapies have been shown to be comparably as effective as excisional therapies for the treatment of CIN2 and CIN3, there appears to be less risk to unsuccessful pregnancy (Arbyn et al., 2014). However decades of experience implementing cryotherapy in programs in developing countries have shown that this technology is often fraught with challenges, including availability and affordability of the refrigerant gas, degradation or outright failure of the equipment and the bulky equipment that lends it use less conducive in field settings. Experience in the field suggests that these challenges may at times limit or derail screening programs (Maza et al., 2017).

In 1966, Kurt Semm developed an instrument that uses a probe heated by an electric current to ablate CIN (Semm, 1966). This technology was originally named 'cold-coagulation' to differentiate it from electrocoagulation diathermy. Currently the preferred name is Thermal Ablation (TA). The probe is usually heated to 100 to 120 °C and applied to the lesion for 20 to 45 s. This treatment option is in many ways potentially more suited to low resource settings, although currently used in UK, North Ireland and Scotland. First, it utilizes electricity, including battery power, rather than large tanks of medical grade refrigerant gas. Second, the technology is simple, creating the potential for devices more frugal than conventional cryotherapy. Third, the treatment is shorter, and might therefore be more acceptable to women and care providers. Fourth, electronic sensors within the applicator itself make it possible to have more reliable and stable final probe temperatures.

Members of our team, led by Dolman, published a meta-analysis of TA in 2014 to provide a systematic analysis of the efficacy and acceptability of TA in the treatment of CIN2+. This review identified 22 articles over five decades addressing the use of TA for the treatment of cervical dysplasia and included 13 in its meta-analysis. Overall, 4569 patients were reported in the included studies. Dolman and colleagues concluded that TA has safety and effectiveness comparable to cryotherapy in the treatment of CIN2+, with a lower risk of complications than seen with excisional procedures (Dolman et al., 2014). However, at the time of Dolman's review there were no studies performed in Africa or South America and only two studies performed in Asia. Subsequently, many additional reports have been published on the safety and effectiveness of TA including several from LMICs. We updated Dolman's meta-analysis to more completely summarize the currently available evidence on TA and to confirm that the experience in low resource settings is consistent with that described in the previously reviewed studies.

2. Methods

To update Dolman's meta-analysis, we performed a review of the medical literature on TA as described previously (Dolman et al., 2014). Two medical librarians performed systematic searches for the years 2014 to 2017, using PubMed, EMBASE, Web of Science and regional databases, using the following search:

"('electrocoagulation'/exp OR 'thermocoagulation'/exp OR 'ablation therapy'/exp OR 'gynecologic electrocautery unit'/exp OR 'cauterization'/exp AND 'cold'/exp OR 'cold coagulation':ab,ti OR thermosurgery:ab,ti OR 'thermal coagulation':ab,ti OR thermocoagulation:ab,ti OR 'thermo coagulation':ab,ti OR electrocautery:ab,ti OR 'electro cautery':ab,ti OR semm:ab,ti OR semms:ab,ti OR electrocoagulation:ab,ti OR 'electro coagulation':ab,ti OR ablative:ab,ti OR ablate:ab,ti OR ablation:ab,ti) **AND** ('uterine cervix carcinoma in situ'/exp OR 'cervical intraepithelial neoplasia':ab,ti OR 'cervical intra epithelial neoplasia':ab,ti OR cin:ab,ti)."

Our search was not restricted by language, though we identified only English language publications for review. In addition, we reviewed the references from new studies to identify potential studies missed by our search strategy. One hundred twelve new studies were identified and reviewed for relevance.

The title and abstract of each article was reviewed. Review articles evaluating previously published studies were excluded. To increase inclusion of studies from LMICs, we included studies that considered either CIN (measured by either cytology or histology) or positive visual inspection with acetic acid (VIA) or positive to HPV test as outcomes. We included studies addressing efficacy in the meta-analysis; studies that evaluated TA without reporting these outcomes were reviewed but excluded from the meta-analysis. Of these twelve new studies were included in our review and nine were eligible for inclusion in the meta-analysis assessment of effectiveness of TA. Studies were assessed for the quality of their study design and data reporting using a list of criteria to assess the quality of primary studies in the medical literature to aid in meta-analyses and other systematic reviews. This included assessments of study quality (through ten items), external validity (three items), study bias (seven items), confounding (six items) and study power (one item), as developed by Downs and Black (1998).

Data abstracted from the articles included year of publication, world region, study period, setting, study design, patient age, definition of cases, biopsy confirmation, endocervical involvement, types of providers, treatment details (e.g. probe temperature, duration of application, number of applications), time to follow up, number of patients treated, number of patients following up, number of patients without disease at follow up, definitions of treatment cure and failure, and information on acceptability and safety. Authors of studies published since Dolman's meta-analysis were contacted by email to define or confirm treatment details when those were absent or unclear in the published manuscripts.

2.1. Statistical analysis

Our primary endpoint was cure of CIN 2+ lesions after treatment with TA. The two secondary endpoints assessed were cure of CIN1+ and cure of CIN 3. All meta-analyses were obtained from a random effects model of the metaprop command (Nyaga et al., 2014). This command was used to appropriately deal with proportions close to the limits by using the binomial distribution to model the within-study variability and allow Freeman-Tukey double arcsine transformation to stabilize the variances. To assess heterogeneity among studies, the I^2 statistic was used, where values between 25 and 50% represented moderate heterogeneity and values > 50% large heterogeneity among studies. The combined cure rates of the primary endpoint together with their 95% confidence intervals (CI) were presented in the forest plot and stratified by region of study (North America, South America, Europe, Asia and Africa). Additional stratification to assess the differences in cure rates was done for decade the studies were initiated

Table 1
Summary of 34 studies of thermal ablation treatment of cervical intraepithelial neoplasia.

Author, year	Country	Study year	Setting	Study design	Age of recipient	Case definition	Case confirmed by biopsy	Endocervix involvement	HIV+	Performer	Treatment at 1st visit (screen-and-treat)	Duration of follow-up	Number of women treated	Number (%) of women followed-up	Cure definition
Allam, 2005	UK (Scotland)	1992–2000	IIIry H	TA combined with another procedure	Mean 33	CIN1-2-3	Yes	No	–	Colposcopist	Yes (in some)	12 months	666	541 (81%)	No persistent CIN in cytology & colposcopy
Aref-Adib, 2013[a]	UK	2010–2011	IIIry H	Clinical report	Majority < 25 years	CIN1+	Yes	–	–	Gynaecologist	No	1 year	35	16 (46%)	Normal cytology at follow-up
Bambury, 2013	Jamaica	1994–2004	IIIry H	Clinical report	Mean 33	CIN1+	Yes	–	Yes	Gynaecologist	No	Mean 1.7 years	12	–	Normal cytology at follow-up
Campbell, 2016[a]	Malawi	2013–2015	IIry H	Assessing see-and-treat	16–86	VIA+	No (if no suspicion of cancer)		Yes	Gynaecologist	Yes	3–6 months	381	234 (61%)	Normal VIA at follow-up
Cassidy, 1987[a]	UK (Scotland)	1979–1986	IIIry H	Clinical report	–	CIN1-2-3	–	–	–	Gynaecologist	–	–	924	924 (100%)	Normal cytology or histology
de Cristofaro, 1990[a]	Italy	1985-?	IIIry H	Clinical report	–	CIN1-2-3	Yes	No	–	Gynaecologist	–	6–12 months	212	116 (55%)	Absence of CIN at follow-up cytology
Duncan, 2005	UK (Scotland)	–	IIIry H	Safety and acceptability RCT	Mean 32	CIN1-2-3	Yes	No	–	Colposcopist	Yes	–	93	–	–
Farquharson., 1987	UK (Scotland)	–	IIIry H	Safety and acceptability clinical report	–	CIN2-3	–	–	–	Colposcopist	No	6 months	714 (laser or CC)	–	–
Fergusson, 1974	UK (England)	–	IIIry H	Cryosurgery or TA Clinical report	–	Benign cervical erosion	No	–	–	–	–	2–4 months	24	23 (96%)	No residual erosion
Goodman, 1991[a]	UK (England)	1987–1988	IIIry H	Clinical report	Mean 27	HPV+ or CIN1-2-3	Yes	Yes and no	–	Gynaecologist	–	4 months (83%)	78	62 (79%)	Absence of dyskaryosis at follow-up cytology
Gordon, 1991[a]	UK (Scotland)	1975–1989	IIIry H	Clinical report	15 to > 50	CIN3	Yes	No	–	Colposcopist	Yes	4 months (98%) to 10 years (87%)	1628	1453 (89%)	Normal cytology at follow-up
Grubišić, 2010[a]	Croatia	1999–2000	IIIry H	Clinical report	Mean 30	CIN2	Yes	No	–	Gynaecologist	–	–	30	30 (100%)	Normal cytology at follow-up
Hirae, 2015[a]	UK	2010	IIIry H	Clinical report	–	CIN2	Yes	–	–	Colposcopist	No	6 months	101	(80%)	Normal colposcopy at follow-up
Hughes, 1992	UK (Scotland)	–	IIIry H	TA or laser (combined data given)	–	CIN2-3	Yes	No	–	Colposcopist	–	9 months to 2.5 years	856 (laser or CC)	856 (laser or CC) (100%)	Absence of CIN based on cytology, colposcopy, and biopsy
	UK (Scotland)	1982–1983	IIIry H		–	CIN1-2-3	Yes	No	–	Colposcopist	–		65		

(*continued on next page*)

Table 1 (*continued*)

Author, year	Country	Study year	Setting	Study design	Age of recipient	Case definition	Case confirmed by biopsy	Endocervix involvement	HIV+	Performer	Treatment at 1st visit (screen-and-treat)	Duration of follow-up	Number of women treated	Number (%) of women followed-up	Cure definition
Hussein, 1985[a]				Clinical report								4 months to 2 years		65 (100%)	Normal cytology and colposcopy at follow-up 4 months after treatment
Javaheri, 1981[a]	USA	1974–1979	IIIry H	Clinical report	15 to > 50	CIN1-2	Yes	No	–	Physician	–	1–5 years (> 50% followed-up for 3 years)	43	40 (93%)	Absence of CIN within 1st year follow-up (persistence) and after 1st year follow-up (recurrence)
Joshi, 2013[a]	India	2010–2011	Iry H	Clinical report	21 to 60	CIN1-2-3	Yes	No	Yes	Physician	Yes	6–12 months	83	45 (54%)	No evidence of CIN2 or worse at follow-up
Joshi, 2015	India	2012–2013	IIry H	Assessing screen-and-treat	21–58	VIA+	Yes	No	Yes	Gynaecologist	Yes	Cross-sectional study	27	–	NA
Lee, 2009	Korea	1994–2005	IIIry H	TA combined with another procedure	Median 39 (27 to 67)	CIN1-2-3	Yes	No	–	–	–	Median 81 months (13 to 127 months)	70	70 (100%)	Absence of recurrent disease above CIN1
Loobuyck, 1993[a]	UK (Scotland)	1978–1990	IIIry H	Clinical report	–	CIN1-2	Yes	No	–	Colposcopist	Yes	6 months to 11 years (> 80% followed-up for 3 years)	1165	1104 (95%)	Normal cytology at follow-up
McCarthy, 2016[a]	Ireland	2009–2010	IIIry H	Clinical report	Average age of 29	CIN 1-2-3	Yes	–	–	Colposcopist	No	1 year	93	92 (99%)	Normal cytology at follow-up
Naud, 2016[a]	Brazil	2012–2013	IIIry H	Clinical report	Median 31 (27–40)	CIN 2-3	Yes	–	–	Gynaecologist	No	1 year	52	52 (100%)	Negative screening result or normal colposcopy +/− histology
Nessa, 2014[a]	Bangladesh	2011–2012	IIIry H	Clinical report	Mean 34 (19 to 51)	CIN 1-2-3	Yes	–	–		No	6 months +	30	30 (100%)	Normal colposcopy at follow-up
Oga, 2016[a]	Nigeria	2010–2014	IIIry H	Assessing see-and-treat	Mean 35	VIA/VILI+	No	–	Yes (68%)	Nurse	Yes	6 + months	262	177 (68%)	Normal VIA/VILI at follow-up
Papoutsis, 2017[a]	UK	2010–2011	IIIry H	Clinical report	Median 28	CIN2-3	Yes	–	–	Gynaecologist	No	12 months	178	169 (95%)	Absence of dyskariosis at

(*continued on next page*)

Table 1 (*continued*)

Author, year	Country	Study year	Setting	Study design	Age of recipient	Case definition	Case confirmed by biopsy	Endocervix involvement	HIV+	Performer	Treatment at 1st visit (screen-and-treat)	Duration of follow-up	Number of women treated	Number (%) of women followed-up	Cure definition
															cytology follow-up
Parry-Smith, 2014[a]	UK	2001–2011	IIIry H	Clinical report	Median 27 (18–57)	CIN1-2+	Yes	–	–	Consultant, nurse specialist, trainee	No	1 year	557	557 (100%)	Absence of dyskariosis at follow-up cytology
Rogstad, 1992[a]	UK (England)	1988–1989	IIIry H	Clinical report	–	CIN1-2	Yes	No	–	Physician	–	12–18 months	59	35 (59%)	No persistence or progression of CIN at follow-up
Semple, 1999	UK (England)	1996–1997	IIIry H	Assessing screening and treatment across multiple centers	–	Dyskaryosis or CIN1-2-3	Yes	–	–	Colposcopist or Gynaecologist	Yes (in 41%)	1 year	268	–	Normal cytology and/or colposcopy at follow-up
Singh, 1988[a]	Singapore	1983–1988	IIIry H	RCT	Mean 35 (20 to 53)	CIN1-2-3	Yes	No	–	Colposcopist	–	3 months to 4 years (88% followed-up for > 1 year)	89	89 (100%)	Normal cytology, colposcopy, or biopsy
Smart, 1987	UK (Scotland)	1983-?	IIIry H	Comparing laser with TA	–	CIN2-3	Yes	No	–	Colposcopist	–	2 years	1169 (laser or CC)	–	Normal cytology, colposcopy, or biopsy
Staland, 1978[a]	Sweden	1971-	IIIry H	Clinical report	–	CIN2-3	No	–	–	Gynaecologist	–	3–4 years (80% followed-up for > 2 years)	71	71 (100%)	Normal colposcopic view
Viviano, 2017[a]	Cameroon	2015	IIIry H	Assessing screen-and-treat	30–49	HPV16/18/45+ HrHPV and VIA+	No	No	–	Gynaecologist	Yes	1 month	110	99.1%	Feasibility study, not on efficacy
Williams, 1993[a]	UK (England)	1988–1989	IIIry H	Clinical report	Mean 25 (16 to 46)	CIN2-3	Yes	No	–	Physician	–	18 months (78%)	125	125 (100%)	Absence of abnormality at follow-up cytology and colposcopy
Zawislak, 2003	N. Ireland	1980–1994	IIIry H	Clinical report	Mean 28 (17 to 52)	CIN 1-2-3	Yes	No	–	Colposcopist	Yes	3 months to 12 years	725	619 (85%)	Absence of persistent or recurrent abnormalities

RCT: Randomized Control Trial; HPV: Human Papilloma Virus; HrHPV: High risk Human Papilloma Virus; CIN: Cervical Intra-epithelial Neoplasia; VIA: Visual Inspection with acetic acid; IIIry H: Tertiary Hospital; IIry H: Secondary Hospital; Iry H: Primary Hospital; TA: thermal ablation; NA: Not applicable.

All other studies were excluded due to lack of necessary data; –: missing data (information not reported or not available).

[a] Studies included in the meta-analysis (n = 22).

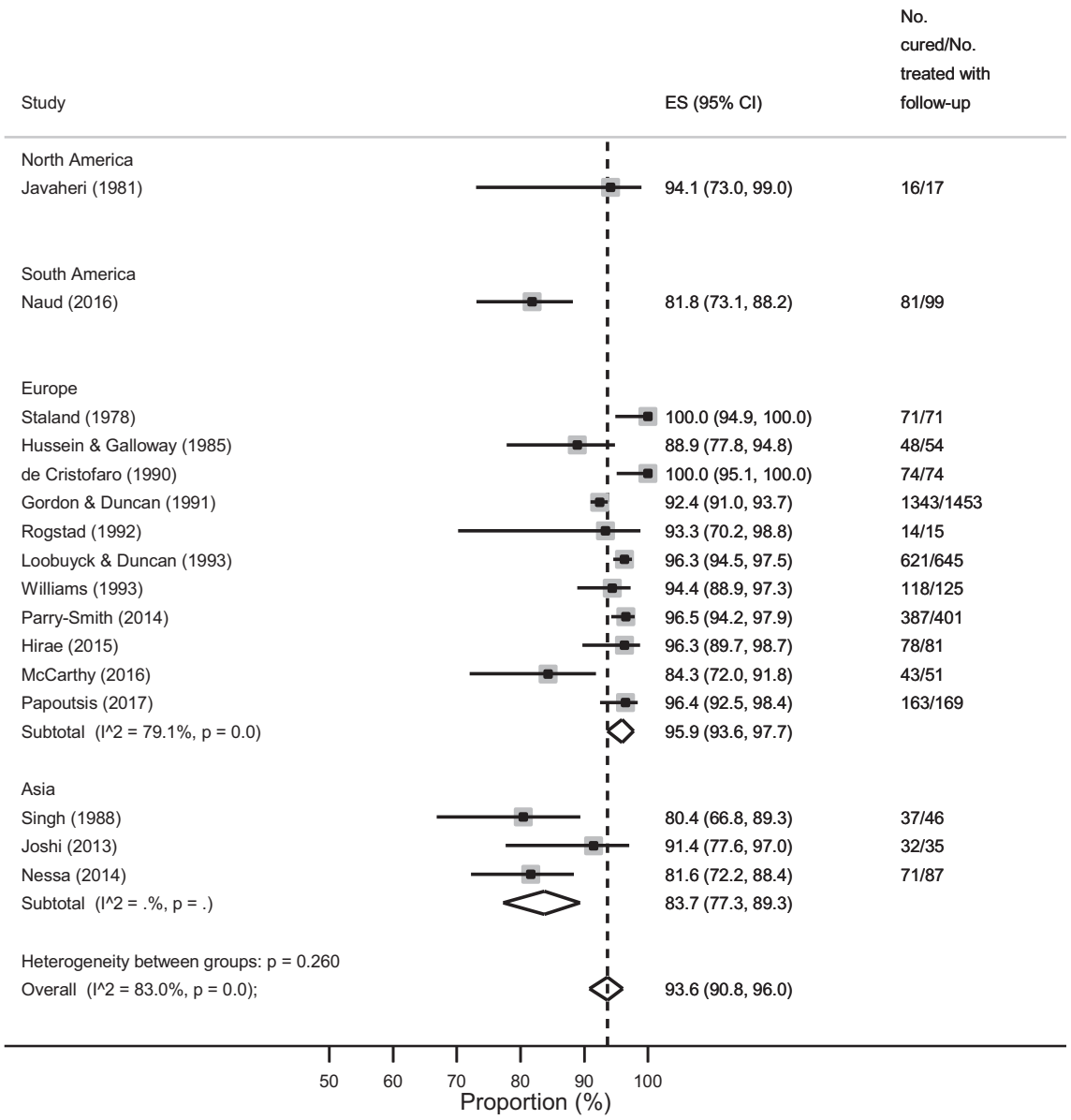

Fig. 1. Biopsy or cytology confirmed cure rates after treatment with thermal ablation among women diagnosed with biopsy confirmed CIN 2+ lesions.

(1970s, 1980s, 1990s, 2000s and 2010s), World Bank economic category (high-income and low- and middle-income countries), duration of application of the heated probe on the cervix (20 s, 30 s and 45 s), mode of disease confirmation during follow-up (cytology solely, cytology +/− colposcopy/biopsy and colposcopy/biopsy), duration of follow-up (≤ 2 years and > 2 years), and inclusion or not of patient treated for recurrent lesions in the study population (primary and combined primary and repeat treatment). STATA version 14.2 (StataCorp, College Station, TX, USA) was used for all the statistical analyses.

3. Results

Combined with the previously identified studies from Dolman's meta-analysis, we reviewed 34 total reports (Table 1) and included 19 in the meta-analysis to estimate effectiveness of the procedure (Allam et al., 2005; Cassidy et al., 1987; Duncan et al., 2005; Farquharson et al., 1987; Ferguson, 1974; Goodman, 1991; Gordon, 1991; Grubisic et al., 2010; Hughes et al., 1992; Hussein, 1985; Javaheri et al., 1981; Joshi et al., 2013; Lee et al., 2009; Lucas et al., 1991; Rogstad et al., 1992; Singh et al., 1988; Semple et al., 1999; Smart et al., 1987; Staland, 1978; Williams et al., 1993; Zawislak et al., 2003; Aref-Adib et al., 2013; Bambury et al., 2013; Nessa et al., 2014; Parry-Smith et al., 2015; Hirae et al., 2015; Joshi et al., 2015; Campbell et al., 2016; McCarthy et al., 2016; Naud et al., 2016; Oga et al., 2016; Viviano et al., 2017; Papoutsis et al., 2017; Loobuyck and Duncan, 1993). The 34 reviewed studies included 10,995 patients. The 23 studies in the meta-analysis involved 6371 patients. Of the studies included in the meta-analysis, only the study reported by Singh and colleagues was a randomized controlled trial clinical trials, while the remainder were clinical reports. The studies cover a broad time period with four studies included in the meta-analysis performed in the 1970s, six performed in the 1980s, three performed in the 1990s and 2000s, and ten performed in the 2010s. Fifteen of the studies were performed in Europe, including eleven performed in the United Kingdom, three were performed in Asia, three in Africa, and one each in North America and South America. In the study in India reported by Joshi, women were screened in a primary care level cervical cancer screening clinic and then treated with TA as indicated at that clinic. In the study from Malawi reported by Campbell and colleagues, TA was administered at a referral hospital and also at two health centers. In the other 32 studies reviewed, including 17 of the

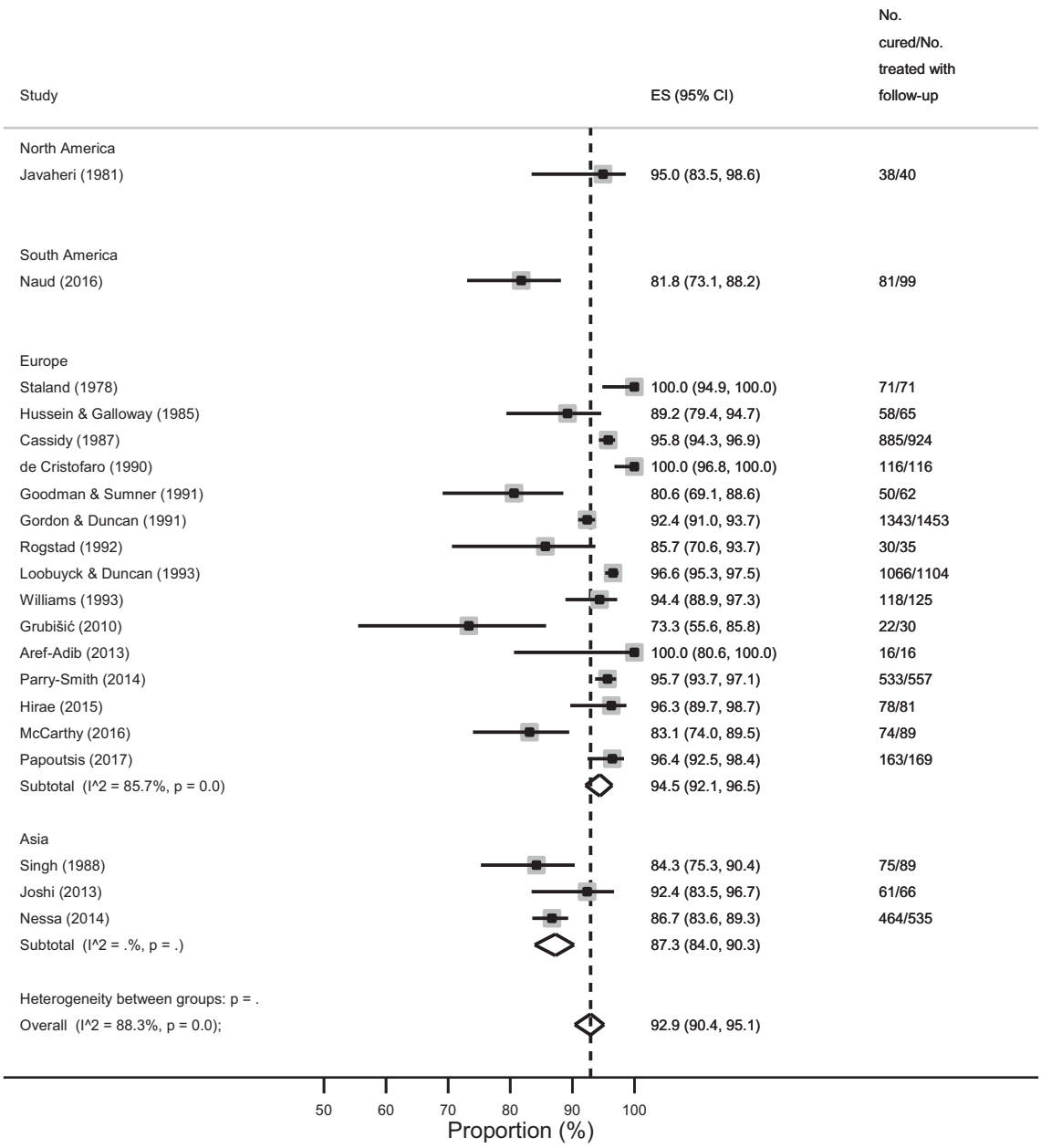

Fig. 2. Cure rates after treatment with cold coagulation among women diagnosed with CIN 1+ lesions.

19 studies we included in the meta-analysis, TA was performed in tertiary medical centers.

As shown in Fig. 1, the overall cure rate in 16 studies in which women were treated for CIN2 or worse lesions was 93.8% (95% CI 90.8% to 96.0%). We observed significant heterogeneity between studies. The I^2 value for these 16 studies was 83%. As shown in Figs. 2 and 3, the overall estimates for CIN 1+ and CIN 3 were 92.9% (95% CI 90.4% to 95.1%) and 87.5% (95% CI 79.0% to 94.2%), respectively (data not shown). The cure rate for those patients treated with TA for CIN2+ in the randomized controlled trial reported by Singh and colleagues was 80.8%.

Table 2 shows the reported cure rates after TA treatment for biopsy proven CIN2+ according to various potential determinants. Cure rates from TA treatment of CIN2+ by World Bank economic category (Bank W, n.d.) of the study country are 84% in the included LMIC studies and 95% in HIC studies.

We reviewed the manuscripts to determine the details of treatment using TA. In studies published over the past 5 years, we contacted the authors when these details were not in the published manuscript. The majority of authors applied the probe tip of the TA multiple times if this was needed to treat the entire lesion. In recent series, the indications for TA have been the same as those widely published for the use of CT. Specifically, lesions were treated with TA if there were no findings suspicious for cancer, no involvement of the endocervical canal, and the lesion did not cover > 75% of the cervix. Investigators report using probe tip temperatures of 100 or 120 °C. As seen in Table 2, the cure rates reported do not significantly vary according to the amount of time that the TA probe is applied to the cervix. A treatment time of 20 s yields a cure rate of 92.9% with 95% confidence intervals from 89.7% to 95.6%, while a treatment time of time of 30 s yields a cure rate of 95.1% (78.7% to 100%), while a 45 s treatment time yielded an overall cure rate of 85% (77.7% to 90.8%). Other treatment factors, such as probe temperature or number of applications of the probe tip to the cervix, were infrequently reported.

Investigators reported a variety of follow up methods to assess cure, including the use of cytology only, cytology with colposcopy and biopsy

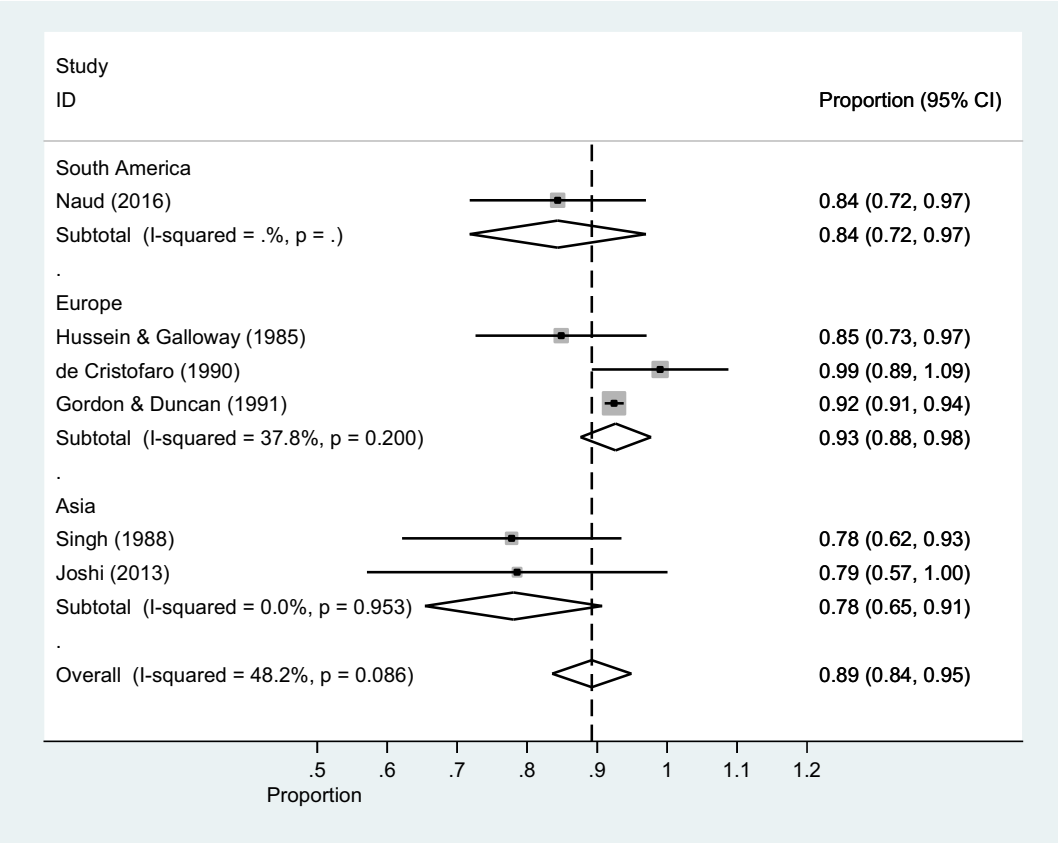

Fig. 3. Cure rates after treatment with thermal ablation among women diagnosed with CIN 3 lesions.

as indicated by findings, or colposcopy and biopsy. As seen in Table 2, pooled results from trials following these varied methods showed comparable clinical results. Two recent studies from Africa identified patients for treatment and made assessments for cure using VIA, with reported cure rates of 83.6% and 94.0% (Campbell et al., 2016; Oga et al., 2016). Comparing cure rates from studies with less than or > 2 years of follow-up revealed variations between studies but no significant difference in the overall cure rates between the two groups.

We identified 8 studies from LMICs of TA, covering a total of 957 patients. Seven of these have been published since the previous review. Five of these studies, covering 808 patients, are included in the meta-analysis (see Table 1.) The studies published to date each cover variously underserved and at-risk populations, such as female sex workers, women with low household incomes and/or limited educational attainment. More patients with HIV infection were included in the LMIC studies.

As seen in Table 1, five of the reviewed studies, among them, three in the meta-analysis included women living with HIV infection. All of these studies were performed in LMICs. Joshi and colleagues reported on 44 women with CIN2 or CIN3 treated with TA in a screening trial in India of HIV+ women (Joshi et al., 2013). Of these women, only 23 followed up at 6–9 months after treatment, of whom 20 (87%) were without evidence of dysplasia. Campbell and colleagues reported a screen and treat trial in Malawi in which 12/12 HIV+ women were VIA negative six months after TA (Campbell et al., 2016). Oga and colleagues reported their experience treating women found to have cervical lesions on VIA with TA as part of their screening program in Nigeria (Oga et al., 2016). Cure rates were comparable for the 120 HIV+ women (81.7%) and for the 57 HIV− women (87.7%, p = 0.31). Overall, 155 HIV+ women are recorded with follow up after TA in our meta-analysis, of whom 120 (84%) were without evidence of dysplasia. The majority of these women were assessed by VIA.

Acceptability of the procedure was mainly reported in terms of adverse effects. Only a minority of the reviewed reports on TA addressed adverse effects of the procedure, though when reported, severe adverse events are rare. Mild to moderate adverse effects appear to be more common. Viviano reported on 109 patients who had undergone TA and followed up one month later. 108 of these women reported a vaginal discharge lasting 1–3 weeks while only 3 required treatment with antibiotics. 105 women reported pain lasting 1–5 days, but for the majority this pain was mild. Naud and colleagues reported 52 patients treated with TA in a hospital setting in Brazil (Naud et al., 2016). They reported mild pain or cramping in 41 of 52 women (79%), a sensation of heat in the vagina in 13 (25%), mild bleeding in 1 and vasovagal reaction in 1. One patient was treated as an outpatient for pelvic inflammatory disease six months after the procedure. In the 13 studies reviewed in the previous meta-analysis, 8 reported on adverse events or side effects: the majority reported no adverse events during the procedure while others reported cramping during the procedure in 25% of patients, moderate pain in 10.5%, and severe pain in 3.5%, while 1% were reported to have mild bleeding or syncope. Campbell and colleagues performed exploratory interviews with providers at the conclusion of their study. Providers interviewed reported high acceptability of the procedure noting that 'almost no pain was reported to the providers when women received treatment' (Campbell et al., 2016). Joshi, in reporting on TA treatment for dysplasia in 26 female sex workers reported that TA 'was well tolerated by all of them, and none had any appreciable side effects from treatment' (Joshi et al., 2015).

We observed no difference in effectiveness of TA between pooled patients treated with analgesia and those who were not. Most reports stated that the procedure was 'well-tolerated' and there are few reports of patients discontinuing the procedure due to pain. On the other hand, Duncan and colleagues reported a randomized trial of TA performed with either local anesthetic or placebo and found that 19% of patients

Table 2
Effect of potential modifying factors on cure rates for thermal ablation treatment of biopsy proven CIN2+.

Determinant	N. of studies included	Cure rate (%)	95% CI	I^2 value (%)
Study decade				
1970s	4	96.7	92.7–99.3	87.0
1980s	5	93.4	84.4–99.1	81.9
2000s	2	96.9	93.7–97.6	–
2010s	5	90.6	82.2–96.6	84.6
Overall	16	93.6	90.8–96.0	83.0
Country level of development				
High income	13	95.3	92.9–97.3	79.2
Low- and middle-income	3	83.6	78.2–88.2	–
Overall	16	93.6	90.8–96.0	83.0
Duration of probe application				
20 s	9	92.9	89.7–95.6	82.0
30 s	3	95.1	77.8–100	–
45 s	2	84.8	77.7–90.8	–
Overall	14	82.6	89.4–95.2	82.6
Method of confirmation of cure				
Cytology solely	4	96.2	91.4–99.3	80.9
Cytology +/− colposcopy	7	91.3	87.1–94.9	83.1
Colposcopy/biopsy	5	94.3	84.5–99.7	84.2
Overall	16	93.6	90.8–96.0	83.0
Duration of follow-up				
≤2 years	8	96.2	93.8–98.2	52.4
> 2 years	8	90.9	85.6–95.1	88.7
Overall	16	93.6	90.8–96.0	83.0
Type of treatment				
Primary solely	9	96.0	92.0–98.8	79.6
Primary and repeated[a]	4	92.0	87.0–95.9	86.6
Overall	13	94.7	91.9–97.0	82.4

[a] Repeated treatment because of recurrence.

not receiving anesthesia reported severe pain (Duncan et al., 2005).

Data on fertility and obstetrical outcomes after TA are limited. In the studies included in our review, no increased risks of infertility or adverse pregnancy outcomes were reported. Gordan and Duncan reported 243 pregnancies among women previously treated with TA (Gordon, 1991). Among these women, 226 pregnancy outcomes were known: 171 had term deliveries, 40 had planned abortions, 9 women had first trimester miscarriages, 3 had preterm live births and three had ectopic pregnancies. Overall, therefore, they observed no evidence of adverse effects on pregnancy outcomes among women previously treated with TA. Similarly, Williams et al. (1993), and Cassidy et al. (1987), reported 19 and 9 patients, respectively, who delivered healthy babies at term after TA treatment for CIN 1–3. There are no reports on reproductive outcomes after use of TA in LMICs.

4. Discussion

TA is a technique that appears feasible, safe, and effective. A growing body of evidence suggests that this can be an effective technology in low resource settings. Our analysis revealed significant heterogeneity among the studies of TA, yet also showed significant efficacy of the technology across a variety of settings and patient populations. The available evidence suggests that TA is highly effective for the treatment of CIN2+. While we identified three clinical trials of TA in the literature, the majority of studies supporting TA are observational. This is also the case with CT, which is endorsed by the WHO for the treatment of CIN. We believe that the evidence for TA is comparable to that for CT, as shown in a recent meta-analysis (Sauvaget et al., 2013), while TA has potential technical advantages that may make it more useful in low resource settings. Cervical cancer predominantly affects women who have limited access to care, and TA, which potentially is more robust and portable in a resource limited setting may help decrease the barriers to care faced by these women. At the time of this writing, the WHO has convened a Guideline Development Group to systematically review the evidence for TA.

One of the great potential advantages is in its relative simplicity and ease of use, particularly with new devices recently made available (Maza et al., 2017). There are currently two manufacturers of thermal ablation devices, each of which make a handheld, battery powered device, and several other manufacturers have thermal ablation devices in development. In addition, a cryotherapy device was recently introduced that uses electric refrigeration rather than refrigerant gas, though this has not yet become widely available. Overall, therefore, one might expect the costs of cervical ablation equipment to decrease. Recent implementation projects from LMICs confirm that TA is feasible in low resource settings and at significant scale.

The majority of studies of TA describe the procedure as acceptable. The available data supports the acceptability of TA in a variety of settings, though we found only limited data on safety and side effects. We recommend that more data be gathered, particularly as TA is implemented for use by generalist physicians and allied providers. In the majority of studies reviewed here, TA has been performed by specialists in a referral hospital setting. Given that TA is a minor surgical procedure, we encourage investigators to consider collecting quality of life and pain data in more detail. Though we found no significant difference in the effectiveness of TA between studies in which anesthesia was used and those in which anesthesia was not used, we consider this only a very basic measure of the need for analgesia, and we encourage more detailed analysis of this question.

Details of treatment, including probe tip temperature, time of applications, and the number of applications varies between studies, though within a limited range. At the time of this writing, studies are underway to further clarify the optimal treatment regimens for ablative therapies, and we encourage the collection of further data to help clarify this aspect of ablative treatments. Interestingly, we found that longer treatment times were associated with lower reported cure rates. We suspect that this may be due to other factors that were infrequently reported. For example, this might be confounded if the clinicians reporting shorter treatment times more often use multiple applications of the thermoablation tip to treat cervical lesions.

We found no evidence that reproductive outcomes were impaired by TA, though data were limited. This is consistent with Arbyn's systematic review showing no association of LASER ablation of cervical lesions with adverse pregnancy outcomes (Arbyn et al., 2014), as well the meta-analysis of Kyrgiou et al. (2017) which showed greater risk with excisional than with ablative treatments for CIN. Given that there is likely to be at most a very low risk of adverse pregnancy outcomes with TA, it may not be an effective use of resources to study this in a clinical trial. Well-designed post-market surveillance might more efficiently study this issue.

Though evidence is limited, recent studies suggest that TA is a safe and effective treatment for CIN in women living with HIV. We strongly encourage continued study of the most effective strategies to protect this group of high risk women from cervical cancer and from other infections.

Screening for cancer is of no utility unless early or pre-malignant lesions can be identified and eliminated. TA appears to be a safe and effective means of treating cervical CIN that may be more easily taken to and used in a low resource setting. We encourage investigators to continue to gather evidence on the best practices and outcomes. Overall, our review does confirm the results of the previous meta-analysis in that TA is comparable in its effectiveness and safety to CT, and we await the conclusions and recommendations of the WHO Guideline Development Group.

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