OncoTargets and Therapy

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ORIGINAL RESEARCH

Meta-analysis of cold-knife conization versus loop electrosurgical excision procedure for cervical intraepithelial neoplasia

This article was published in the following Dove Press journal:
OncoTargets and Therapy
29 June 2016
Number of times this article has been viewed

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Objective: This meta-analysis aimed to compare the superiority of loop electrosurgical excision procedure (LEEP) or large loop excision of the transformation zone (LLETZ) versus cold-knife conization (CKC) in the surgical treatment of cervical intraepithelial neoplasia (CIN).
Methods: Systematic searches were performed in the MEDLINE, EMBASE, Cochrane databases, and the China National Knowledge Infrastructure Databases to identify all potential articles involving patients with CIN treated with LEEP/LLETZ or CKC published up to February 2016. Risk ratios (RRs) or weighted mean difference (MD) with a 95% confidence interval (95% CI) were calculated.
Results: Seven randomized controlled trials, one prospective cohort study, and twelve retrospective cohort studies were included in this meta-analysis. There were no significant differences following LEEP/LLETZ compared with CKC in recurrence rate (RR =1.75, 95% CI =0.99–3.11, P=0.06), positive margin rate (RR =1.45; 95% CI =0.85–2.49, P=0.17), residual disease rate (RR =1.15, 95% CI =0.73–1.81, P=0.48), secondary hemorrhage (RR =1.16, 95% CI =0.74–1.81; P=0.46), or cervical stenosis. Moreover, subgroup analyses based on randomized trials also revealed that no statistical significance was observed in the above outcomes. However, women treated with CKC had a significantly deeper cervical cone than those treated with LLETZ/LEEP (MD =–5.71, 95% CI =–7.45 to –3.96; $P<0.001$).
Conclusion: LEEP/LLETZ is as effective as CKC with regard to recurrence rate, positive margin rate, residual disease rate, secondary hemorrhage, and cervical stenosis for the surgical treatment of CIN. Further large-scale studies are needed to confirm our findings.
Keywords: cervical intraepithelial neoplasia, cold-knife conization, loop electrosurgical excision procedure, meta-analysis

Introduction

Cervical intraepithelial neoplasia (CIN) is a precursor lesion of cervical cancer and is classified by histology as CIN 1, CIN 2, or CIN 3. Widespread cervical screening using cytology combined with human papilloma virus testing has resulted in a considerable increase in the number of women diagnosed with CIN in recent decades.[1] According to laboratory surveys from the College of American Pathologists,[2] more than 1 million women are found to have CIN 1 each year, and 500,000 are diagnosed with CIN 2 and CIN 3, which are referred to as high-grade CIN. As recommended by the American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines,[3] patients with CIN 1 are usually monitored by continued follow-up because the regression rates are high and progression to CIN 2+ is uncommon. Excisional treatment is mainly used to treat CIN 2/3, which might progress to invasive cervical cancer if left untreated.

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The management of CIN has been a public health burden in many parts of the world.

Currently, the two main excisional strategies for CIN treatment are loop electrosurgical excision procedure (LEEP) or large loop excision of the transformation zone (LLETZ) and cold-knife conization (CKC), which offers deep excision of the cervical transformation zone with minimal damage. CKC has been the traditional procedure for CIN and is typically performed in a hospital setting under general or local anesthesia. First described in 1989 by Prendiville,[4] LEEP has been the most commonly used method for CIN and has several advantages, including shorter operative time, ease of performance, and low cost.[5]

Recent years have seen an increase in studies reporting CIN treatments with success rates exceeding 90%.[6–9] However, these studies are inconsistent regarding the therapeutic efficacy and complications associated with the two procedures, and the 2012 ASCCP guidelines[3] do not make any recommendations indicating CKC or LEEP as the optimal therapy option. Although two reviews[10,11] have been published previously, a more comprehensive meta-analysis focusing on treatment failures or operative morbidity and other previously unanalyzed factors is needed. The objective of this meta-analysis is to evaluate the superiority of LLETZ/LEEP versus CKC in the surgical treatment of CIN.

Materials and methods

Search strategy

Systematic searches were performed using the MEDLINE, EMBASE, Cochrane databases, and the China National Knowledge Infrastructure Databases (CNKI) to identify all articles published up to February 2016 involving patients with CIN treated with CKC or LEEP. The searches were restricted to English or Chinese language and included only human studies. The following terms were used to identify studies: "cervical intraepithelial neoplasia", or "cervical dysplasia", "large loop excision of the transformation zone" or "loop electrosurgical excisional procedure" or "cold knife conization". Because of the lack of details regarding research methods and results, abstracts and unpublished works were not included. Searches of the title and abstract of each article were independently conducted by YMJ and LL to determine potentially relevant studies.

Study selection and data extraction

Studies comparing the efficacy of LEEP and CKC to patients with CIN were included. Studies in which more than one treatment procedure was used but the outcomes for each treatment procedure were not reported separately were excluded. We also excluded case reports and studies undertaken during pregnancy. The primary outcome included the rates of residual disease, recurrent disease, positive margins, secondary hemorrhage, cervical stenosis at follow-up, cone depth, and pregnancy outcomes. To determine the validity of the studies, a modified Jadad scale was used to assess the quality of the included randomized studies.[12] For nonrandomized studies, the Newcastle–Ottawa score was determined.[13] The data were independently extracted from each included study by YMJ and LL, and any disagreements were resolved by consensus with a third review author (CXC) as necessary.

Data synthesis

We extracted data from the experimental and the control group for every observed outcome. Relative risks (RRs) or weighted mean difference (MD) with 95% confidence intervals (CIs) were calculated with Revman 5.3 software (Cochrane Informatics & Knowledge Management Department, Copenhagen, Denmark), and heterogeneity was quantified using the I^2 statistic.[14] If heterogeneity is accepted at $I^2<50\%$, a fixed-effects model was used for the meta-analysis. Otherwise, a random effects model was used. Statistical significance was defined as a P-value less than 0.05. Sensitivity analyses based on randomized or nonrandomized trials were performed.

Results

Study identification and selection

We reviewed 112 potentially relevant eligible studies. Based on the inclusion criteria, seven randomized controlled studies, one prospective cohort study, and twelve retrospective cohort studies were included (Figure 1). The vast majority of the participants had CIN 2–3, although some patients with CIN 1 were included because the ASCCP consensus guidelines were not updated until 2006 with the suggestion that CIN 1 could be managed conservatively in adults.[15] The follow-up period ranged from 3 months to 23 years. The mean age ranged from 27.3 to 43.8 years. Table 1 lists the main characteristics of the 20 included studies involving 5,709 patients.[5–9,16–30] Table 1 shows the Newcastle–Ottawa scores and the modified Jadad scale for the quality assessment of the nonrandomized studies and randomized studies. The quality was not high for any of the studies.

Recurrence rate

Seven studies, including two randomized controlled trials (RCTs)[6,7] and five non-RCTs,[17–21] reported recurrence

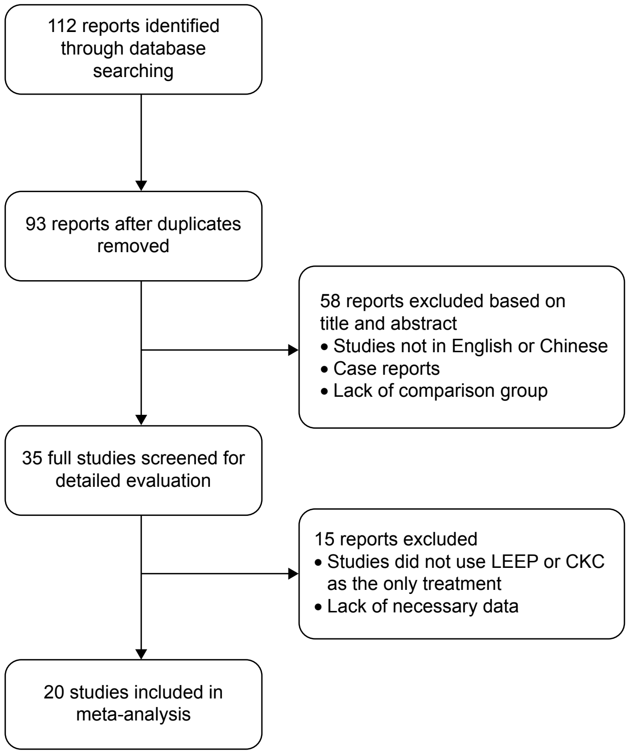

Figure 1 Study selection and exclusion process.
Abbreviations: LEEP, loop electrosurgical excision procedure; CKC, cold-knife conization.

rates, and the results of the individual studies varied. A meta-analysis based on all these seven studies revealed that patients in CKC group had slightly lower recurrence rate than those in LLETZ/LEEP group (RR =1.75, 95% CI =0.99–3.11, *P*=0.06; Figure 2). Moreover, subgroup analyses based on RCTs or non-RCTs also showed similar results (Figure 2).

Positive margin rate

One RCT[7] and eight non-RCTs[9,19,22–26] described positive margin rate. The prevalence of positive margins was 22% (343/1,595) after LLETZ/LEEP and 13% (200/1,596) after CKC. Pooled results exhibited no statistical significance based on all nine studies (RR =1.45; 95% CI =0.85–2.49, *P*=0.17) (Figure 3).

Residual disease rate

Three RCTs[5–7] and one non-RCT[27] described the rate of residual disease. Results from individual studies showed no differences between LLETZ/LEEP and CKC group. Pooled results of all four studies (RR =1.15, 95% CI =0.73–1.81, *P*=0.48) or all three RCTs confirmed that there was no evidence of significant differences in residual disease rate (Figure 4).

Pregnancy outcomes

The differences in pregnancy outcomes between LLETZ/LEEP and CKC were evaluated in two RCTs[6,28] and one non-RCT[29] with small sample size. Michelin et al[29] reported that miscarriages and preterm pregnancies were more frequent in CKC cases versus LEEP: 26% and 5.2%, and 23% and 5.5%, respectively. Liu et al[28] concluded that the rates of preterm premature rupture of membranes (*P*=0.03), preterm delivery (*P*=0.04) and low-birth-weight infants (<2,500 g) (*P*=0.04) were higher in the CKC group than in the LEEP group, but there were no differences in the mean birth weight, cesarean delivery, labor induction, or neonatal intensive care unit admission. Mathevet et al[6] reported that there was no major difference in obstetrical outcomes between CKC and LLETZ/LEEP techniques.

Secondary hemorrhage

The results regarding secondary hemorrhage were reported by five RCTs[5–8,30] and three non-RCTs.[9,18,27] The results of the included individual studies did not differ significantly. After the pooled meta-analysis of the eight studies, the RR for secondary hemorrhage was not different between LLETZ/LEEP and CKC groups based on all eight studies (RR =1.16, 95% CI =0.74–1.81; *P*=0.46) (Figure 5).

Cervical stenosis

Cervical stenosis results were based on three RCTs[6,7,16] and two non-RCTs.[9,19] As shown in Figure 6, the pooled meta-analyses showed that the results were not significantly different across all studies or the RCT subgroup (all *P*>0.05). However, the opposite result was found in the non-RCT subgroup (RR =0.13, 95% CI =0.02–0.67; *P*=0.02).

Cone depth

As shown in Figure 7, the cone depth was reported in two RCTs.[5,6] The two individual studies showed that women treated with CKC had a significantly deeper cervical cone than those treated with LLETZ/LEEP. The pooled results also indicated that cone depth of CKC was statistically deeper (MD =–5.71, 95% CI =–7.45 to –3.96; *P*<0.001).

Discussion

In this review, we found 20 studies in which LLETZ/LEEP was compared with CKC for the treatment of CIN. Differences between the included studies in terms of their setting, research protocol, patient characteristics, and efficacy were observed. No significant heterogeneity

Table 1 Characteristics of the included studies

Source	Intervention		Histology	Study design	Study period	Follow-up period	Outcomes	Quality score[a]
	LEEP	CKC						
Giacalone et al[5]	38	28	CIN 2–3	RCT	1997–1998	3 months	Residual disease, secondary hemorrhage	4
Mathevet et al[6]	36	37	CIN 1–3	RCT	1990–1992	6 months	Residual disease, secondary hemorrhage, cervical stenosis	5
Duggan et al[7]	89	85	CIN 1–3	RCT	1992–1994	12 months	Recurrence, positive margin, residual disease, secondary hemorrhage, cervical stenosis	5
Takač and Gorišek[8]	120	120	CIN 1–3	RCT	1993–1996	3 months	Secondary hemorrhage	3
Bozanovic et al[9]	72	100	CIN 1–3	Retrospective study	NA	Over 2 years	Positive margin, secondary hemorrhage, cervical stenosis	7
Mathevet et al[16]	29	28	CIN 2–3	RCT	NA	38–118 months	Recurrence, cervical stenosis, cesarean section, miscarriage rate, preterm delivery	5
Gonzalez-Bosquet et al[17]	58	25	CIN 1–3	Prospective multicenter project	1991–1994	NA	Recurrence	9
Zeng et al[18]	74	869	NA	Retrospective study	2002–2007	12–78 months	Recurrence, secondary hemorrhage	7
Bornstein et al[19]	52	22	CIN 2–3	Retrospective study	1983–1993	NA	Cone size, recurrence, positive margin, cervical stenosis	8
Serati et al[20]	214	68	CIN 1–3	Retrospective cohort study	1999–2009	6–100 months	Recurrence	6
Murta et al[21]	101	142	CIN 1–3	Retrospective study	1981–2003	≥16 months	Recurrence	8
Chen et al[22]	453	660	NA	Retrospective cohort study	2006–2009	8 months to 8 years	Positive margin	8
Grimm et al[23]	412	392	CIN 1–3	Retrospective multicenter study	2004–2009	NA	Positive margin	7
Shin et al[24]	79	39	CIN 1–3	Retrospective study	2005–2006	NA	Positive margin	7
Miroshnichenko et al[25]	96	61	NA	Retrospective study	2003–2007	NA	Positive margin	7
Panna and Luanratanakorn[26]	269	194	NA	Retrospective study	2002–2007	NA	Positive margin	9
Huang and Hwang[27]	73	43	NA	Retrospective study	1992–1997	NA	Positive margin, residual disease, secondary hemorrhage	9
Liu et al[28]	124	120	CIN 3	RCT	2006–2009	NA	Cesarean delivery, preterm delivery, low birth weight, miscarriage rate	3
Michelin et al[29]	95	102	CIN 1–3	Retrospective study	1981–2004	1–23 years	Preterm delivery, low birth weight, miscarriage rate	9
Girardi et al[30]	38	52	CIN 1–3	RCT	NA	10 months	Cone depth, secondary hemorrhage	3

Notes: [a]Quality assessment: the modified Jadad scale was used for RCTs, and the Newcastle–Ottawa score was used for nonrandomized studies.
Abbreviations: LEEP, loop electrosurgical excision procedure; CKC, cold-knife conization; CIN, Cervical intraepithelial neoplasia; RCT, randomized controlled trial; NA, not available.

Study or subgroup	LLETZ/LEEP Events	LLETZ/LEEP Total	CKC Events	CKC Total	Weight (%)	Risk ratio M–H, random, 95% CI	Year
Randomized controlled trial							
Duggan et al[7]	8	73	3	67	13.2	2.45 (0.68, 8.85)	1999
Mathevet et al[16]	2	29	1	28	5.2	1.93 (0.19, 20.12)	2003
Subtotal (95% CI)		**102**		**95**	**18.4**	**2.32 (0.75, 7.15)**	
Total events	10		4				
Heterogeneity: τ^2=0.00; χ^2=0.03, *df*=1 (*P*=0.86); I^2=0%							
Test for overall effect: *Z*=1.46 (*P*=0.14)							
Nonrandomized controlled trial							
Gonzalez-Bosquet et al[17]	8	52	3	22	14.0	1.13 (0.33, 3.86)	1997
Bornstein et al[19]	8	58	1	25	6.7	3.45 (0.46, 26.13)	1999
Murta et al[21]	11	101	15	142	23.8	1.03 (0.49, 2.15)	2006
Zeng et al[18]	3	74	2	869	8.3	17.61 (2.99, 103.76)	2012
Serati et al[20]	51	214	13	68	28.8	1.25 (0.72, 2.15)	2012
Subtotal (95% CI)		**499**		**1,126**	**81.6**	**1.75 (0.84, 3.63)**	
Total events	81		34				
Heterogeneity: τ^2=0.36; χ^2=9.55, *df*=4 (*P*=0.05); I^2=58%							
Test for overall effect: *Z*=1.51 (*P*=0.13)							
Total (95% CI)		**601**		**1,221**	**100**	**1.75 (0.99, 3.11)**	
Total events	91		38				
Heterogeneity: τ^2=0.22; χ^2=10.30, *df*=6 (*P*=0.11); I^2=42%							
Test for overall effect: *Z*=1.91 (*P*=0.06)							
Test for subgroup differences: χ^2=0.17, *df*=1 (*P*=0.68); I^2=0%							

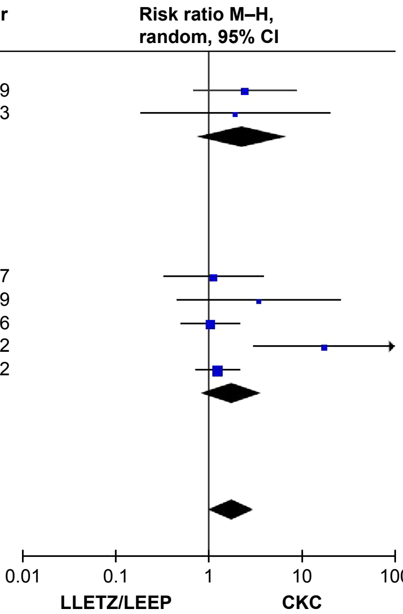

Figure 2 Comparison of LLETZ/LEEP and CKC in recurrence rate.
Abbreviations: LLETZ, large loop excision of the transformation zone; LEEP, loop electrosurgical excision procedure; CKC, cold-knife conization; CI, confidence interval; *df*, degrees of freedom; M–H, Mantel–Haenszel test.

was detected across studies for any of the data evaluated, except for the rates of positive surgical margins and recurrences.

A previous review[31] reported that the prevalence of residual and recurrent disease after incomplete LEEP did not differ significantly (22%; 766/3,476) compared with the results after knife-cone biopsy (27%; 445/1,661). That review did not differentiate between residual and recurrent disease. The availability of the new studies increased the statistical power and sample size and, to the best of our knowledge, enabled us to compare for the first time the differences in recurrence rates and positive margin rates. With respect to efficacy, we concluded that the recurrence rate is not significantly different between the two methods.

Study or subgroup	LLETZ/LEEP Events	LLETZ/LEEP Total	CKC Events	CKC Total	Weight (%)	Risk ratio M–H, random, 95% CI	Year
Randomized controlled trial							
Duggan et al[7]	16	89	20	85	11.6	0.76 (0.43, 1.37)	1999
Subtotal (95% CI)		**89**		**85**	**11.6**	**0.76 (0.43, 1.37)**	
Total events	16		20				
Heterogeneity: not applicable							
Test for overall effect: *Z*=0.90 (*P*=0.37)							
Nonrandomized controlled trial							
Bornstein et al[19]	18	52	5	22	10.1	1.52 (0.65, 3.59)	1999
Huang and Hwang[27]	7	73	4	43	8.2	1.03 (0.32, 3.32)	1999
Bozanovic et al[9]	10	72	8	100	9.9	1.74 (0.72, 4.18)	2008
Chen et al[22]	109	453	32	660	12.7	4.96 (3.41, 7.22)	2009
Miroshnichenko et al[25]	36	96	10	61	11.4	2.29 (1.23, 4.26)	2009
Panna and Luanratanakorn[26]	25	269	33	194	12.2	0.55 (0.34, 0.89)	2009
Shin et al[24]	26	79	7	39	10.8	1.83 (0.87, 3.85)	2009
Grimm et al[23]	96	412	81	392	13.1	1.13 (0.87, 1.46)	2013
Subtotal (95% CI)		**1,506**		**1,511**	**88.4**	**1.58 (0.88, 2.83)**	
Total events	327		180				
Heterogeneity: τ^2=0.59; χ^2=63.23, *df*=7 (*P*<0.00001); I^2=89%							
Test for overall effect: *Z*=1.53 (*P*=0.12)							
Total (95% CI)		**1,595**		**1,596**	**100**	**1.45 (0.85, 2.49)**	
Total events	343		200				
Heterogeneity: τ^2=0.56; χ^2=68.61, *df*=8 (*P*<0.00001); I^2=88%							
Test for overall effect: *Z*=1.36 (*P*=0.17)							
Test for subgroup differences: χ^2=2.96, *df*=1 (*P*=0.09); I^2=66.2%							

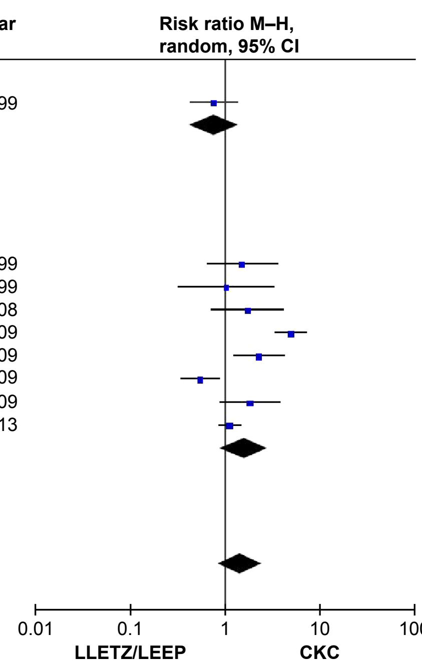

Figure 3 Comparison of LLETZ/LEEP and CKC in positive margin.
Abbreviations: LLETZ, large loop excision of the transformation zone; LEEP, loop electrosurgical excision procedure; CKC, cold-knife conization; CI, confidence interval; *df*, degrees of freedom; M–H, Mantel–Haenszel test.

Study or subgroup	LLETZ/LEEP Events	Total	CKC Events	Total	Weight (%)	Risk ratio M–H, fixed, 95% CI	Year
Randomized controlled trial							
Mathevet et al[6]	2	36	2	37	7.1	1.03 (0.15, 6.91)	1994
Duggan et al[7]	5	89	6	85	22.1	0.80 (0.25, 2.51)	1999
Giacalone et al[5]	6	38	4	28	16.6	1.11 (0.34, 3.55)	1999
Subtotal (95% CI)		**163**		**150**	**45.7**	**0.94 (0.45, 2.00)**	
Total events	13		12				
Heterogeneity: χ^2=0.16, *df*=2 (*P*=0.92); I^2=0%							
Test for overall effect: *Z*=0.15 (*P*=0.88)							
Nonrandomized controlled trial							
Huang and Hwang[27]	27	73	12	43	54.3	1.33 (0.75, 2.33)	1999
Subtotal (95% CI)		**73**		**43**	**54.3**	**1.33 (0.75, 2.33)**	
Total events	27		12				
Heterogeneity: not applicable							
Test for overall effect: *Z*=0.98 (*P*=0.33)							
Total (95% CI)		**236**		**193**	**100**	**1.15 (0.73, 1.81)**	
Total events	40		24				
Heterogeneity: χ^2=0.65, *df*=3 (*P*=0.88); I^2=0%							
Test for overall effect: *Z*=0.61 (*P*=0.54)							
Test for subgroup differences: χ^2=0.50, *df*=1 (*P*=0.48); I^2=0%							

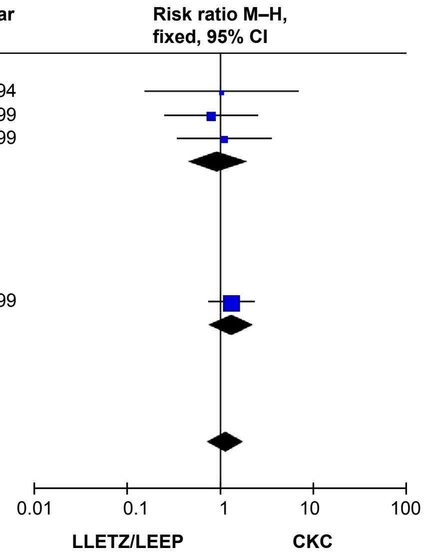

Figure 4 Comparison of LLETZ/LEEP and CKC in residual disease.
Abbreviations: LLETZ, large loop excision of the transformation zone; LEEP, loop electrosurgical excision procedure; CKC, cold-knife conization; CI, confidence interval; *df*, degrees of freedom; M–H, Mantel–Haenszel test.

Incomplete excision of CIN exposes women to a high risk of high-grade cervical disease posttreatment.[31] High-grade posttreatment disease occurred in 18% (597/3,335) of women who had incomplete excision compared with 3% (318/12,493) who had complete excision.[31] This poses a challenge for doctors in choosing appropriate options so as to avoid residual disease resulting from incomplete excision during conization. Disease recurrence is the main problem during the 5-year follow-up period because the risk of recurrence remains elevated for 8 years or more after treatment for CIN.[32] Serati et al[20] found that 22.7% of women developed histologically confirmed recurrence, which does not appear to depend on the surgical technique used. Another study showed that recurrences occurred after 5–31 months in 7.1% and 11.2% of the patients who underwent LEEP and CKC, respectively, and had negative histological findings on surgical specimens.[21] In this meta-analysis, no significant differences in the rates of recurrence or residual disease between the LLETZ/LEEP

Study or subgroup	LLETZ/LEEP Events	Total	CKC Events	Total	Weight (%)	Risk ratio M–H, fixed, 95% CI	Year
Randomized controlled trial							
Girardi et al[30]	2	38	3	52	8.1	0.91 (0.16, 5.20)	1994
Mathevet et al[6]	2	36	0	37	1.6	5.14 (0.26, 103.39)	1994
Duggan et al[7]	9	89	8	85	26.1	1.07 (0.43, 2.66)	1999
Takač and Gorišek[8]	8	120	9	120	28.7	0.89 (0.35, 2.23)	1999
Giacalone et al[5]	2	38	2	28	7.3	0.74 (0.11, 4.92)	1999
Subtotal (95% CI)		**321**		**322**	**71.8**	**1.04 (0.59, 1.81)**	
Total events	23		22				
Heterogeneity: χ^2=1.35, *df*=4 (*P*=0.85); I^2=0%							
Test for overall effect: *Z*=0.13 (*P*=0.90)							
Nonrandomized controlled trial							
Huang and Hwang[27]	2	73	1	43	4.0	1.18 (0.11, 12.61)	1999
Bozanovic et al[9]	2	72	4	100	10.7	0.69 (0.13, 3.69)	2008
Zeng et al[18]	5	74	27	869	13.5	2.17 (0.86, 5.48)	2012
Subtotal (95% CI)		**219**		**1,012**	**28.2**	**1.47 (0.69, 3.13)**	
Total events	9		32				
Heterogeneity: χ^2=1.50, *df*=2 (*P*=0.47); I^2=0%							
Test for overall effect: *Z*=1.01 (*P*=0.31)							
Total (95% CI)		**540**		**1,334**	**100**	**1.16 (0.74, 1.81)**	
Total events	32		54				
Heterogeneity: χ^2=3.73, *df*=7 (*P*=0.81); I^2=0%							
Test for overall effect: *Z*=0.65 (*P*=0.52)							
Test for subgroup differences: χ^2=0.54, *df*=1 (*P*=0.46); I^2=0%							

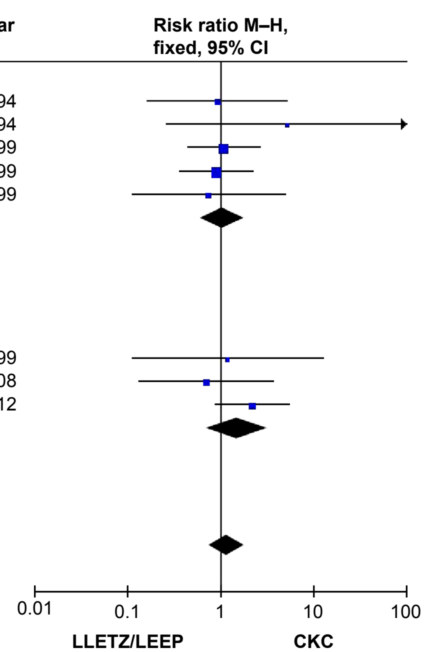

Figure 5 Comparison of LLETZ/LEEP and CKC in secondary hemorrhage.
Abbreviations: LLETZ, large loop excision of the transformation zone; LEEP, loop electrosurgical excision procedure; CKC, cold-knife conization; CI, confidence interval; *df*, degrees of freedom; M–H, Mantel–Haenszel test.

Study or subgroup	LLETZ/LEEP Events	LLETZ/LEEP Total	CKC Events	CKC Total	Weight (%)	Risk ratio M–H, fixed, 95% CI	Year
Randomized controlled trial							
Mathevet et al[6]	21	36	24	37	60.8	0.90 (0.62, 1.29)	1994
Duggan et al[7]	4	89	2	85	5.3	1.91 (0.36, 10.16)	1999
Mathevet et al[16]	1	29	4	28	10.5	0.24 (0.03, 2.03)	2003
Subtotal (95% CI)		**154**		**150**	**76.6**	**0.88 (0.61, 1.27)**	
Total events	26		30				
Heterogeneity: χ^2=2.26, *df*=2 (*P*=0.32); I^2=11%							
Test for overall effect: *Z*=0.68 (*P*=0.49)							
Nonrandomized controlled trial							
Bornstein et al[19]	1	52	5	22	18.1	0.08 (0.01, 0.68)	1999
Bozanovic et al[9]	0	72	2	100	5.4	0.28 (0.01, 5.68)	2008
Subtotal (95% CI)		**124**		**122**	**23.4**	**0.13 (0.02, 0.67)**	
Total events	1		7				
Heterogeneity: χ^2=0.40, *df*=1 (*P*=0.53); I^2=0%							
Test for overall effect: *Z*=2.43 (*P*=0.02)							
Total (95% CI)		**278**		**272**	**100**	**0.70 (0.49, 1.01)**	
Total events	27		37				
Heterogeneity: χ^2=8.42, *df*=4 (*P*=0.08); I^2=52%							
Test for overall effect: *Z*=1.93 (*P*=0.05)							
Test for subgroup differences: χ^2=4.93, *df*=1 (*P*=0.03); I^2=79.7%							

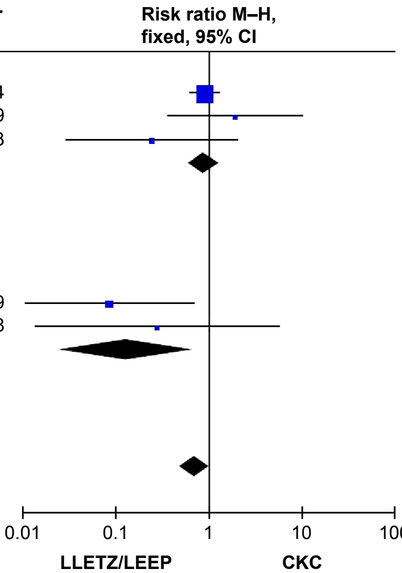

Figure 6 Comparison of LLETZ/LEEP and CKC in cervical stenosis.
Abbreviations: LLETZ, large loop excision of the transformation zone; LEEP, loop electrosurgical excision procedure; CKC, cold-knife conization; CI, confidence interval; *df*, degrees of freedom; M–H, Mantel–Haenszel test.

and CKC groups were observed. The results appear to suggest that LLETZ/LEEP is as effective as CKC in the surgical treatment of CIN and that there is no significant difference in recurrence or residual disease. However, larger sample size and longer follow-up randomized studies are necessary to further confirm these findings.

Increasing concerns have been raised regarding the rate of positive margins after the treatment of CIN, and the effects of different surgical treatments on the positive margin rate remain unclear. In previous years, there was no significant difference in the rates of positive margins reported between the two groups, but in recent years, as the case numbers increased, the results have varied. In our analysis, the rate of positive margins after LLETZ/LEEP was 22% (343/1,595); the rate of positive margins after CKC was 13% (200/1,596). These rates were both lower than previous reports; a possible explanation for these lower rates is that more importance was assigned to the problem of positive margins later. Our pooled analysis indicated that LLETZ/LEEP was associated with a higher incidence of positive margins, which might be because of the significantly deeper conization of CKC and the removal of occult endocervical lesions. The age of the woman is another important factor in determining surgical options. In one study included in this meta-analysis, Shin et al[24] found that in patients aged >45 years, the LLETZ/LEEP group had significantly higher rate of nonnegative surgical margins compared with the CKC group. This result suggests that the use of LLETZ/LEEP might not be recommended if achieving complete negative margin is the only consideration, especially for older women. However, heterogeneity and bias were noted in these data and could be ascribed to the effects of small studies. It was recently reported that for adenocarcinoma in situ of the cervix, positive margins were found in 18% of the women treated with CKC versus 40% of the women treated with LLETZ/LEEP.[33] Based on these results, further research should be performed to evaluate whether LLETZ/LEEP can increase the positive margin rate for cervical precancerous lesions.

Study or subgroup	LLETZ/LEEP Mean	LLETZ/LEEP SD	LLETZ/LEEP Total	CKC Mean	CKC SD	CKC Total	Weight (%)	Mean difference IV, fixed, 95% CI	Year
Mathevet et al[6]	11.7	4.1	36	17	6.5	37	49.3	–5.30 (–7.79, –2.81)	1994
Giacalone et al[5]	12.8	4.3	38	18.9	5.5	28	50.7	–6.10 (–8.55, –3.65)	1999
Total (95% CI)			**74**			**65**	**100**	**–5.71 (–7.45, –3.96)**	
Heterogeneity: χ^2=0.20, *df*=1 (*P*=0.65); I^2=0%									
Test for overall effect: *Z*=6.40 (*P*<0.00001)									

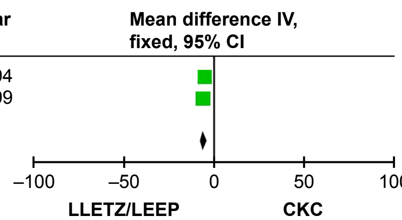

Figure 7 Comparison of LLETZ/LEEP and CKC in cone depth.
Abbreviations: LLETZ, large loop excision of the transformation zone; LEEP, loop electrosurgical excision procedure; CKC, cold-knife conization; SD, standard deviation; CI, confidence interval; *df*, degrees of freedom; IV, independent variable.

In theory, a higher positive margin rate after treatment of CIN should lead to greater recurrence during the follow-up period. A positive surgical margin was a high risk factor for residual disease or relapse after conization of CIN.[34] However, an inconsistent relationship appears to exist between positive surgical margins and recurrence in the two groups in our meta-analysis. Evidence-based research has reported a similar discrepancy; the rate of disease recurrence/persistence in women with positive margins who were followed up was only 9.3%.[22] A possible explanation for this result is that not all of the women with positive surgical margins had residual disease, and longer follow-up periods would be beneficial.

Kyrgiou et al[35] focused on pregnancy outcomes in a previous meta-analysis and found that CKC and LLETZ/LEEP were significantly associated with preterm delivery and low birth weight and that CKC was associated with higher relative risks than LLETZ/LEEP. However, this meta-analysis compared groups with or without a previous conservative intervention on the cervix and did not compare CKC and LLETZ/LEEP groups. We did not identify any meta-analyses comparing pregnancy outcomes between these two procedures. The pooled analysis in our study was not evaluated because of the small sample size. The main findings regarding pregnancy outcomes are consistent with the results of the previous meta-analysis. The available evidence suggested that differences in pregnancy outcomes, such as the rate of miscarriage and low birth weight, between CKC and LLETZ/LEEP were observed in our study. Women with a history of CKC treatment were found to have an increased risk of preterm delivery compared to those with a history of LLETZ/LEEP treatment.[28,29] Few studies on the effects of LLETZ/LEEP and CKC have adequate power to detect a significant difference on subsequent pregnancy. LLETZ/LEEP is more appropriate for patients with CIN for future pregnancies compared with CKC. Moreover, we must take note of the new recommendation by tailoring excision treatment according to the type of the transformation zone to try to avoid unnecessary excision of healthy cervical tissue.[36]

Limitations

Several limitations of this meta-analysis should be considered. First, some of the included studies were retrospective in nature; therefore, there might have been confounders that were not recognized or controlled. However, a subgroup analysis of the data extracted from the studies revealed similar results. Second, the follow-up time, patient age, and disease degree varied among the included studies, and these differences may have affected the results. Finally, it is possible that the exclusion of some missing and unpublished data might have led to a bias in the effect.

Conclusion

The present meta-analysis showed that there was no significant difference regarding residual and recurrence rate in LLETZ/LEEP compared with CKC for treating CIN. A woman should select the surgical procedure after discussing the benefits and risks with her surgeon. Further large-scale and high-quality RCTs are needed to confirm the best procedure.

Disclosure

The authors report no conflicts of interest in this work.

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