

Fertility-sparing treatment in younger women with adenocarcinoma in situ of the cervix

Nehalennia van Hanegem^{a,b}, Lisa M. Barroilhet^a, Marisa R. Nucci^c, Marilyn Bernstein^a, Sarah Feldman^{a,*}

^a Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

^b Department of Obstetrics and Gynecology, Academic Medical Center, Amsterdam, The Netherlands

^c Division of Women's and Perinatal Pathology, Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

ARTICLE INFO

Article history:

Received 30 June 2011

Accepted 7 September 2011

Available online 24 October 2011

Keywords:

Adenocarcinoma in situ

Cervix

Loop excision

Cold knife conization

ABSTRACT

Objective. For women who have completed childbearing, the treatment of choice for adenocarcinoma in situ (ACIS) of the cervix is hysterectomy. In women who desire future fertility, however, conservative therapy is an acceptable alternative. In this study we compare the outcomes for young women who underwent loop conization or were treated with cold knife conization.

Methods. We performed a retrospective analysis in 112 patients with ACIS, age 30 or younger, treated with cold knife conization or loop conization between 1998 and 2010. Decision to perform office loop conization was based on the size of the cervix and the colposcopic lesion. Main outcomes were negative margins after the procedure and recurrence of ACIS.

Results. Fifty-eight patients (52%) were treated with cold knife conization and 54 (48%) underwent loop conization. The odds ratio for cold knife conization to achieve negative cone margins compared with loop conization was 1.4 (95% CI 0.6–3.5). We observed no difference in residual or recurrent ACIS between patients treated with loop conization versus cold knife conization.

Conclusions. In select young patients who desire future fertility, loop conization and cold knife conization have equivalent rates of negative margins and negative follow-up. For optimal results, patients must have a lesion which can be removed in one pass of a loop, confirmed by expert colposcopy. Loop excision should be considered the treatment of choice in this specific group of patients.

© 2011 Published by Elsevier Inc.

Introduction

In the last few decades the incidence of cervical cancer has decreased. However, the incidence of adenocarcinoma has mainly relative to the incidence of squamous cell carcinoma of the cervix, due to better detection of squamous lesions. In the 1950s and 1960s adenocarcinoma accounted for only 5% of cervical cancers, while this ratio has increased to 20–25% in the 1990s, due to a decrease in squamous carcinomas [1–3]. In younger patients with invasive adenocarcinoma, a small increase is seen in prevalence, mainly in patients 30 years and younger (16%) [2]. The increased prevalence in younger women is also found for adenocarcinoma in situ (ACIS), the precursor of adenocarcinoma of the uterine cervix [4, 5].

Historically, the treatment of choice for women with ACIS has been hysterectomy. However, because the mean age of patients with ACIS is 37 years, [6] many patients have not completed childbearing and desire more conservative treatment. Fertility-sparing

treatment with conization has gained acceptance in the treatment of women with ACIS. Since patients with positive margins have a 50% risk of residual ACIS and a risk of about 6% for coexistent invasive disease, achieving negative margins is critical [7, 8].

Several studies have compared cold knife conization with loop conization, favoring cold knife conization because this procedure is more likely to yield negative margins [7–10]. Historically, doctors think of ACIS as a lesion of the endocervical canal with 'skip'-lesions. However, multifocal disease is found in only 13–17% of cases; the lesion is usually unicentric, contiguous with the SCJ, and extends up the canal for a variable distance [11]. Further data show a relationship between age and proximal linear extent of disease, suggesting that more limited excision of the endocervix, until 1 cm above the SCJ, may be reasonable in young women [12].

No data are available about treatment of women under 30 years, in whom the least invasive treatment is very important in order to prevent adverse pregnancy outcomes [13, 14]. In this study we describe a specific group of patients: young women with ACIS who desire future fertility. The aim of this study is to compare the effectiveness of loop conization in select young women with small colposcopic lesions of ACIS and a small cervix versus cold knife conization in women aged 30 years and younger with a diagnosis of ACIS.

* Corresponding author at: Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Brigham and Women's Hospital, 75 Francis street, Boston, MA, 02115, USA. Fax: +1 617 738 5124.

E-mail address: sfeldman@partners.org (S. Feldman).

Methods

We performed a retrospective cohort study at Brigham and Women's hospital (BWH) and the Dana Farber Cancer Institute (DFCI). After approval by the Institutional Review Board (protocol 2010P002059), we identified women with ACIS aged 30 years or younger at the time of diagnosis by searching the computerized hospital databases, between January 1998 and January 2011. Pathology reports were reviewed, and patients with ACIS on Papanicolaou (Pap) smear, cervical biopsy or loop specimen were ultimately included in the study. Medical records were abstracted for Pap smear history, demographic data, cervical biopsy results, mode of treatment and follow-up. Pathology reports were analyzed for histology, margin status of the specimen, depth of specimen after fixation and human papillomavirus (HPV) results. The follow-up period was defined as the time between initial ACIS diagnosis and the date the patient was last seen in our clinic. Patients were excluded if no detailed pathology data were available or if ACIS was found in coexistence with invasive carcinoma in the initial cervical biopsy. We included patients with ACIS found on initial cervical biopsy and patients with known squamous dysplasia whose cone or loop specimen ultimately showed ACIS.

In all patients, a colposcopy was performed to assess the size of the cervix and transformation zone and the size of colposcopic abnormality. The procedure (loop conization versus cold knife conization) was chosen based on these colposcopic findings. A loop conization was only performed when the cervix, transformation zone and/or the colposcopic abnormality was small enough to perform the loop conization in one pass, with a medium (15×12 mm) or a large (20×12 mm) loop, to allow for better evaluation of the margins. Procedures at BWH or DFCI were performed by 5 different physicians, all of them specialized gynecologic oncologists. Patients referred to our hospital with biopsy proven ACIS underwent pathology review and repeat expert colposcopy prior to a decision on further treatment.

All loop conizations were performed as standard office procedures. When a loop was performed in our hospital for a known diagnosis of ACIS, the specimen was in general removed in one pass with a medium or a large loop and a small loop (10×10 mm) was used for the endocervical sample. The cutting edges were inked black for better orientation. The cone depth was calculated by adding the depth of the cervical button to the original loop specimen. Cold knife conization was performed in the operating room in the standard fashion, labeled at 12 o'clock, and endocervical curettage was obtained.

Adenocarcinoma in situ was histologically defined by standard criteria [15]. All pathology slides from patients referred from an outside hospital were reviewed by a gynecologic pathologist at BWH. When necessary, if histologic diagnosis was unclear, immunohistochemistry was performed with p16 and MiB-1 to support the diagnosis of ACIS. If positive margins or positive endocervical curettage (ECC) for ACIS were found, the patient underwent additional procedures until negative margins were obtained. When ACIS was found within 1 mm of the margin, this was regarded as a negative margin and the patient was followed closely. Residual disease was defined as ACIS found in the pathology specimen of the second procedure.

Follow-up of patients was routinely done with Pap smears every 3–4 months after the procedure with negative margins, until a normal Pap smear was seen at least four times. ECC was added for cases with an insufficient endocervical sample or a stenotic os. As follow-up guidelines evolved over the study period, HPV testing was not initially part of post treatment surveillance. Once available, HPV testing was performed as part of follow-up. After four normal consecutive Pap tests were obtained, patients were followed by annual Pap testing, either in one of our hospitals or by the referring gynecologist. Patients were considered lost to follow-up if data were available for less than 3 months after treatment.

Comparison of the groups was done with the student's *t*-test or Mann Whitney *U* test for means and with the Fisher's exact test for categorical data. *P*-values below 0.05 were used to indicate statistical significance. For categorical data we also calculated odds ratios (OR) and 95% confidence intervals. For calculations to compare the percentage of positive margins, we excluded patients with invasive carcinoma and patients with unevaluable margins. Patients with close margins (ACIS within 1 mm from margin) were regarded as negative margins, as we think that the cautery-effect on the 'patient side' of the margin increases the effective margin beyond what the pathologist measures in the cone or loop specimen. Patients diagnosed with invasive cancer were then treated appropriately and follow-up was dependent on the treatment.

Results

We identified 112 women with ACIS age 30 years or younger at the time of diagnosis between 1998 and 2010. Fifty-eight patients (52%) underwent cold knife conization and 54 patients (48%) were treated with loop conization. Baseline characteristics, shown in Table 1, were comparable between the groups.

Table 1 also shows characteristics of pathology before treatment. In 88 of 112 (79%) of patients, ACIS was detected by cytology or histology before the procedure was performed. In patients treated with cold knife conization the diagnosis ACIS was significantly more often made by cervical biopsy than in patients treated with loop excisional cone ($p<0.001$). In 22 of 54 patients (43%) ACIS was diagnosed in the pathology specimen of a loop conization performed because of high-grade dysplasia.

Table 1
Baseline characteristics.

Variable	Cold knife cone (N = 58)		Loop cone excision (N = 54)		P-value
Age (years)					
Mean	25		26		0.15
Range	15–30		18–30		
Race					
White	44	76%	41	76%	1.0
Black	1	1.7%	1	1.9%	
Hispanic	2	3.4%	1	1.9%	
Asian	3	5.2%	4	7.4%	
Unknown	8	14%	7	13%	
Parity					
0	48	83%	48	89%	0.56
≥ 1	8	14.0%	5	9.3%	
Unknown	2	3.5%	1	1.9%	
Oral contraceptives					
Yes	31	53%	33	61%	1.0
No	17	29%	17	32%	
Unknown	10	17%	4	7.4%	
High-risk HPV					
Positive	18	31%	16	30%	0.7
Unknown	40	66%	38	65%	
Duration abnormal cytology ^a					
Mean (months)	12		16		0.41
Range (months)	0–96		1–122		
Abnormal cytology ^a					
Atypical glandular cells	4	8.9%	10	21%	0.43
Adenocarcinoma in situ	4	8.9%	2	4.3%	0.15
Combination glandular/squamous	5	11%	2	4.3%	0.26
Squamous dysplasia only	32	71%	33	70%	1.00
Unknown	13	22%	7	13%	
ACIS detected by					
Papanicolaou test	8	14%	3	5.6%	0.21
Cervical biopsy	47	81%	23	43%	<0.001
ECC	2	3.4%	5	9.3%	0.26
Procedure only	1	1.7%	23	43%	<0.001

^a Before diagnosis of adenocarcinoma in situ.

Table 2 shows the assessment of cone margins in a total of 103 patients whose margins have been assessed. There were 78 patients with negative margins (76%) and 25 patients having positive cone margins, of which 11 had been treated with cold knife conization (21% within treatment group) and 14 patients with loop conization (27%). No significant difference is seen in the percentage of positive margins when comparing cold knife cone and loop cone specimens (OR 0.7 (95% CI 0.3 to 1.8)). The depth of the cone was significantly different for the two procedures. In cold knife cones the mean cone depth was 1.48 cm, for loop conization it was 0.78 cm ($p < 0.0001$). When ACIS was diagnosed before treatment by cervical biopsy, the chance of having invasive adenocarcinoma in this population was 3.41%.

Fig. 1 shows different primary fertility-sparing treatments and their outcomes. A second procedure was either a hysterectomy in case of invasive carcinoma, a cold knife conization or a second loop conization. Patients with unevaluable margins were followed closely, with the exception of two patients underwent a second cold knife conization and residual ACIS was found in one of them. None of these patients had recurrent ACIS during follow-up. Patients with close margins were followed; 6 patients were followed for 4–51 months with no recurrence and one patient was lost to follow-up. One of these patients underwent a second procedure, no residual ACIS was found in the pathology specimen.

Our follow-up data show no statistically significant difference in residual ACIS in patients with positive cone margins; in cold knife cone specimens we found residual ACIS in 3 patients (27.3%) and in loop cone specimens in 3 patients (21.4%). In patients treated with a loop conization with occult ACIS ($N = 22$), we found neither residual ACIS nor recurrent ACIS during follow up. In this study a total of 18 patients (16.1%) were lost to follow-up. In none of the 94 patients with follow up data available, recurrent ACIS or invasive adenocarcinoma was seen. For 68 patients (61%) we have follow up data of one year or more, with no difference in duration of follow-up between cold knife conization and loop cone conization ($p = 0.18$).

Discussion

In this retrospective cohort study, we found that in select, young women with adenocarcinoma in situ, cold knife conization and loop conization were equally effective to achieve negative cone margins and there was no statistical difference in the rates of residual or recurrent ACIS. To our knowledge this is the first article on treatment of women with ACIS with an age of 30 years or younger and the largest collection of retrospective cases of women with ACIS treated with loop or cold knife conization. Conservative treatment with loop conization for women with ACIS is only described in retrospective cohorts, with six cohort studies comparing cold knife cone with loop conization [7–10, 16, 17]. Patient characteristics in our series were similar to those series with regard to contraceptive use [8, 10, 18] and race [9, 17, 18], but as noted above other studies include a wider range of ages [7–10, 18].

In most studies cold knife conization is found to be the superior technique for achieving negative margins in the cone specimen (Table 3) [7–10, 17, 18]. The difference between our and earlier studies is the fact that we included only patients of 30 years or younger, who were preselected based on the size of the lesion; small lesions were treated with a loop conization, large lesions with cold knife conization. In this study we found similar effectiveness in achieving negative cone margins in loop conization compared to cold knife conization (OR 1.4 (95% CI 0.6 to 3.5)) in select young patients. This similar outcome was found despite the fact that the specimen excised by loop conization had a smaller cone depth ($p < 0.0001$). Achieving negative margins is very important because positive conization margins are associated with a 4-fold increase in the risk of residual disease and with a 2.5-fold increase in risk of recurrence [6]. Our results suggest that loop conization is an effective treatment in young women with ACIS-lesions.

For treatment of squamous intraepithelial neoplasia loop excision is regarded as the treatment of choice, because it is less expensive, technically easier, less painful, associated with less hemorrhage and

Table 2
Treatment results.

	Cold knife conization	(N = 58)	Loop conization	(N = 54)	OR	(95% CI)	P
	N		N				
Pathology cone specimen							
Invasive adenocarcinoma	3	5.1%	0				
Only ACIS	16	28%	9	16.7%	2.1	(0.8–5.2)	0.18
ACIS/CIN 2/3	21	36%	35	64.8%	0.3	(0.2–0.7)	0.007
CIN 2/3	11	19%	3	5.6%	0.06	(1.1–15)	0.04
Negative	7	12%	7	13.0%	1	(0.3–3.1)	1
Adenocarcinoma in situ ^a							
Focal	49	89%	51	94%			
Multifocal	6	11%	3	5.5%	2.2	(0.5–8.8)	0.5
Evaluation of cone margins ^b							
Negative ^c	41	79%	37	73%	1.4	(0.6–3.5)	0.7
Positive	11	21%	14	27%	0.7	(0.3–1.8)	0.7
ACIS <1 mm from margin	4	6.9%	7	13%			
Difficult to assess	3		3				
Immunohistochemistry with p16/MiB1							
Performed	7	12%	12	22%			
Not performed	51	88%	42	78%	0.5	(0.2–1.3)	0.2
Depth of cone specimen (cm)							
Mean (range)	1.48	(0.4–3.5)	0.78	(0.3–1.4)			<0.0001
Procedure performed at							
BWH/DFCI	49	84%	28	52%			
Outside hospital	9	16%	26	48%			
Duration of follow-up (months) ^d							
Mean (range)	37	(3–135)	26	(3–145)			0.18

^a Patients with invasive carcinoma excluded.

^b Calculations of OR: invasive carcinoma and difficult margins excluded.

^c Including close (<1 mm) margins.

^d 18 patients were lost to follow-up (16%).

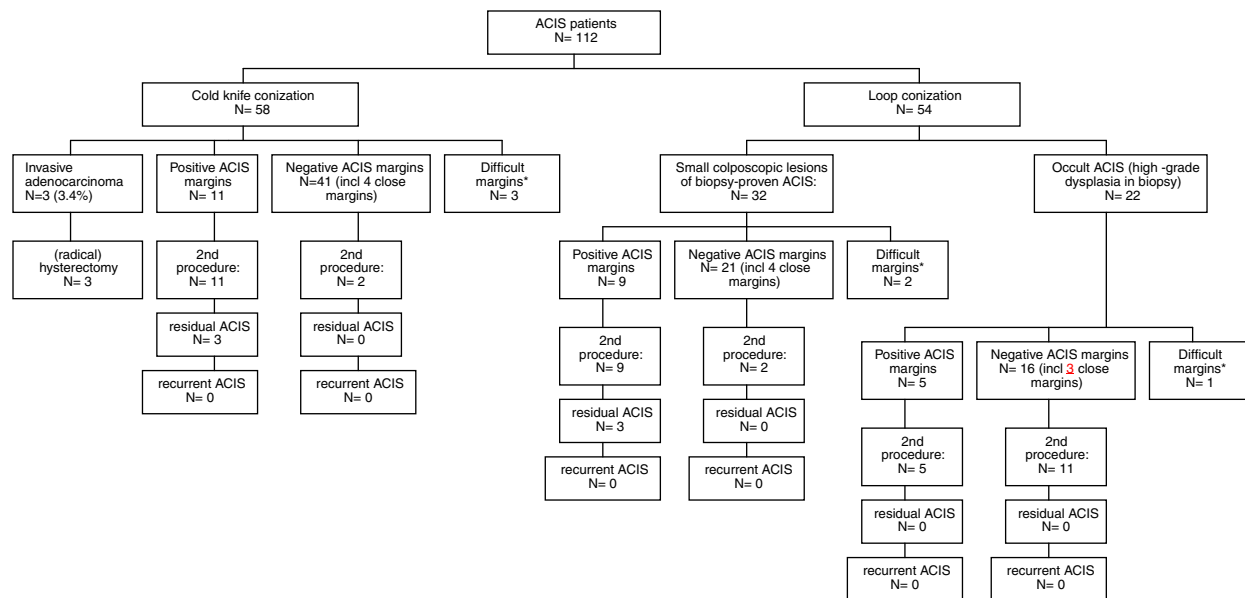


Fig. 1. Treatment and outcomes of patients with ACIS.

less cervical stenosis and can be performed in an office setting, with the same efficacy as cold knife conization [19–23]. Furthermore, loop conization is the preferred treatment when we focus on obstetric outcomes after cervical surgery, which is especially important in our specific group of women with an age of 30 and younger. Two large meta-analyses showed an increased risk of preterm delivery for treatment with cold knife conization (OR 2.8) compared to treatment with loop conization (OR 1.7) [13, 14]. A large cohort-study showed that increased cone depth of a loop conization is directly associated with an increasing risk of preterm delivery, with a 6% increase in risk per each additional millimeter of tissue excised [24, 25].

We did not find a significant difference in the percentage of positive margins when we compared loop conizations (mean cone depth 8 mm) to cold knife conizations (mean cone depth 15 mm). Fourteen of 51 loop patients (27%) had positive cone margins and therefore had an indication for a second procedure. One could argue that if these patients had been treated primarily with a cold knife conization, the percentage of positive margins would have been lower. However, in this group of young patients it is important to find a balance between the risk of a positive margin and the number of patients who need a larger procedure. Because a cold knife conization has important obstetric risks we think a percentage of 27% positive margins in patients treated with a loop conization is acceptable. This allows 73% of these young women to have a smaller procedure with less adverse obstetric outcomes, committing only the 27% with positive margins to the risks of a second procedure. Of note, no cancers were observed in this group. Furthermore, we advocate treating young patients with 'close' margins as if they were negative. Our results show that none of the patients with 'close' margins had neither residual ACIS in a subsequent procedure nor a clinical recurrence.

In this study we did not find residual or recurrent ACIS in the follow-up of patients with negative cone margins. However, it is important to counsel patients that other studies reveal that residual or recurrent ACIS and invasive cancer have been detected during follow-up in about 5% of cases even though the conization had negative margins [8, 10, 16–18, 26–28] and three studies report a recurrence/residual rate of as high as 40% [9, 29, 30]. In patients who have completed childbearing there are still arguments to advise hysterectomy in patients with ACIS [17, 31].

The main limitation of this study is its retrospective design. A prospective or randomized trial is difficult to perform due to the very low incidence of ACIS. We were able to include a relatively large number of patients in this retrospective cohort compared to other studies [7–10, 16, 17]. An important limitation of retrospective studies is selection bias. The selection bias in this study is based on the size of the lesion. The aim was to assess whether a loop conization performed in young patients, with small colposcopic abnormalities is safe and effective. Large lesions were more likely to be treated with cold knife than with loop conization, because it is important to perform the loop conization in one specimen. Increased fragmentation of the specimens makes histological assessment much more difficult [32].

Another important limitation of this study relates to changes in standard of care over time. In the beginning of the study period, patients with ACIS in their loop specimen were treated with a second loop, regardless of positive or negative margins. During the years this local policy changed and patients with ACIS in their loop specimen and negative margins were followed closely. Looking at the amount of patients who really needed a second procedure, we see no difference between cold knife conization (14 patients) and loop conization (16 patients) ($p = 0.53$).

Table 3

Literature on achieving negative margins with cold knife vs. loop conization.

Author, year	Mean age	Study design	Cold knife conization (N)	Positive margins (N)	Loop conization (N)	Positive margins (N)	OR	95% CI
Azodi, 1999 [10]	37	Retrospective cohort	25	8	8	7	14.9	1.6–142.2
Bull-Phelps, 2007 [17]	29 (median)	Retrospective cohort	63	13	26	11	2.8	1.1–7.6
Denehy, 1997 [7]	37	Retrospective cohort	24	16	13	4	4.5	1.1–19.2
Kennedy, 2002 [8]	37	Retrospective cohort	33	9	49	28	3.6	1.4–9.2
Wolf, 1996 [9]	36	Retrospective cohort	42	18	7	5	3.3	0.6–19.2

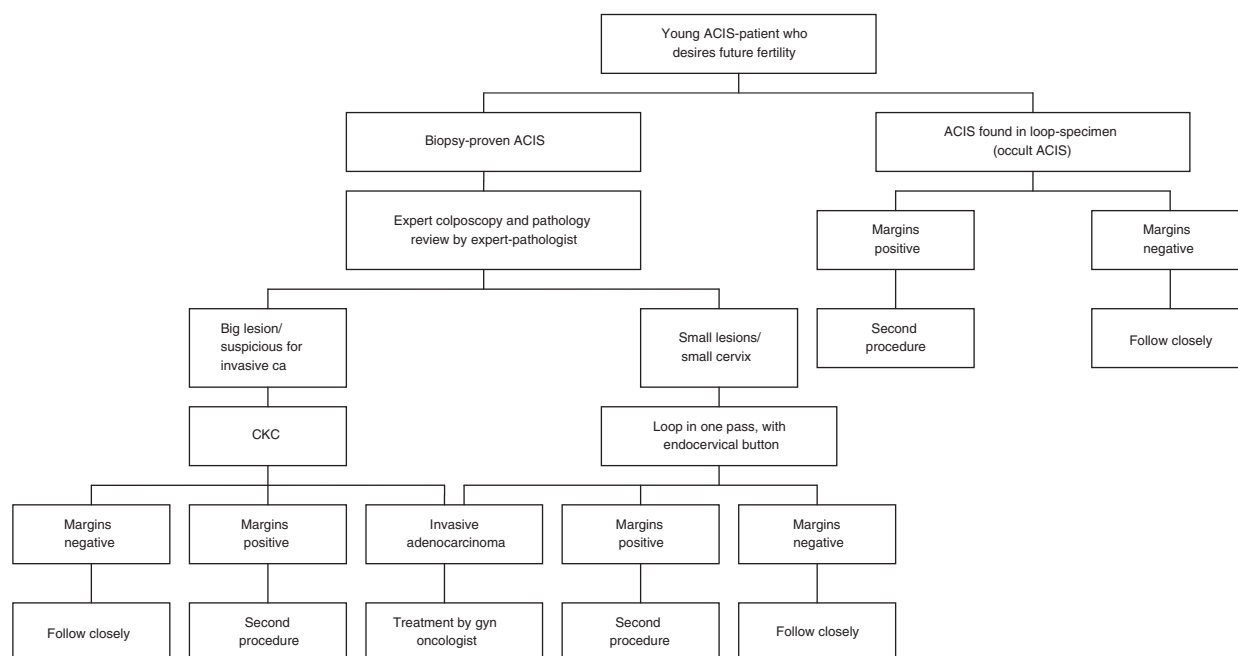


Fig. 2. Suggested pathway for diagnosis and treatment of young women with ACIS.

We decided to include patients for whom occult ACIS was found in the loop specimen. Although our numbers are small, given that we did not see residual ACIS in any of these patients, we think it is safe to follow these patients closely instead of performing a second cervical procedure. Fig. 2 shows an algorithm with our recommendations for diagnosis and treatment of young women with ACIS who desire future fertility.

In this study we demonstrated similar outcomes in achieving negative cone margins and residual or recurrent ACIS in young patients treated with cold knife cone or loop conization. The patients were carefully selected; patients with small colposcopic abnormalities and a small cervix were treated with loop conization, the other patients were treated with a cold knife cone. Given the fact that the cervix is excised to a shallower depth with loop conization, and the known increased obstetric risks with each additional millimeter of tissue excised, we think that loop conization should be considered for women with lesions of ACIS who are 30 years or younger and who desire future fertility.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Acknowledgements

We would like to thank Dr. Michael Muto (Gynecologic Oncologist at Brigham and Women's Hospital, Boston, MA, USA), Prof. Ben Willem Mol (Professor Obstetrics and Gynecology at the Academic Medical Center in Amsterdam, the Netherlands) and Prof. Matthe Burger (Professor Gynecology at the Academic Medical Center in Amsterdam, the Netherlands) for their very helpful comments on earlier drafts.

References

- [1] Smith HO, Tiffany MF, Qualls CR, Key CR. The rising incidence of adenocarcinoma relative to squamous cell carcinoma of the uterine cervix in the United States—a 24-year population-based study. *Gynecol Oncol* Aug 2000;78:97–105.
- [2] Bulk S, Visser O, Rozendaal L, Verheijen RH, Meijer CJ. Cervical cancer in the Netherlands 1989–1998: decrease of squamous cell carcinoma in older women, increase of adenocarcinoma in younger women. *Int J Cancer* Mar 1 2005;113:1005–9.
- [3] Hemminki K, Li X, Vaittinen P. Time trends in the incidence of cervical and other genital squamous cell carcinomas and adenocarcinomas in Sweden, 1958–1996. *Eur J Obstet Gynecol Reprod Biol* Feb 10 2002;101:64–9.

- [4] Shin CH, Schorge JO, Lee KR, Sheets EE. Conservative management of adenocarcinoma in situ of the cervix. *Gynecol Oncol* Oct 2000;79:6–10.
- [5] Wang SS, Sherman ME, Hildesheim A, Lacey Jr JV, Devesa S. Cervical adenocarcinoma and squamous cell carcinoma incidence trends among white women and black women in the United States for 1976–2000. *Cancer* Mar 1 2004;100:1035–44.
- [6] Salani R, Puri I, Bristow RE. Adenocarcinoma in situ of the uterine cervix: a meta-analysis of 1278 patients evaluating the predictive value of conization margin status. *Am J Obstet Gynecol* Feb 2009;200:182.e1–5.
- [7] Deney TR, Gregori CA, Breen JL. Endocervical curettage, cone margins, and residual adenocarcinoma in situ of the cervix. *Obstet Gynecol* Jul 1997;90:1–6.
- [8] Kennedy AW, Biscotti CV. Further study of the management of cervical adenocarcinoma in situ. *Gynecol Oncol* Sep 2002;86:361–4.
- [9] Wolf JK, Levenback C, Malpica A, Morris M, Burke T, Mitchell MF. Adenocarcinoma in situ of the cervix: significance of cone biopsy margins. *Obstet Gynecol* Jul 1996;88:82–6.
- [10] Azodi M, Chambers SK, Rutherford TJ, Kohorn EI, Schwartz PE, Chambers JT. Adenocarcinoma in situ of the cervix: management and outcome. *Gynecol Oncol* Jun 1999;73:348–53.
- [11] Teshima S, Shimosato Y, Kishi K, Kasamatsu T, Ohmi K, Uei Y. Early stage adenocarcinoma of the uterine cervix. Histopathologic analysis with consideration of histogenesis. *Cancer* Jul 1 1985;56(1):167–72.
- [12] Nicklin JL, Wright RG, Bell JR, Samarasinghe H, Cox NC, Ward BG. A clinicopathological study of adenocarcinoma in situ of the cervix. The influence of cervical HPV infection and other factors, and the role of conservative surgery. *Aust N Z J Obstet Gynaecol* May 1991;31(2):179–83.
- [13] Kyrgiou M, Koliopoulos G, Martin-Hirsch P, Arbyn M, Prendiville W, Paraskevaides E. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. *Lancet* Feb 11 2006;367:489–98.
- [14] Arbyn M, Kyrgiou M, Simoons C, Raifu AO, Koliopoulos G, Martin-Hirsch P, et al. Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis. *BMJ* Sep 18 2008;337:a1284.
- [15] Kindelberger DW, Krane JF, Lee KR. Glandular neoplasia of the cervix. In: Crum CP, Nucci MR, Lee KR, editors. *Diagnostic obstetric and gynecologic pathology*. 2nd Edition. Philadelphia, PA: Elsevier; 2011. p. 338.
- [16] Widrich T, Kennedy AW, Myers TM, Hart WR, Wirth S. Adenocarcinoma in situ of the uterine cervix: management and outcome. *Gynecol Oncol* Jun 1996;61:304–8.
- [17] Bull-Phelps SL, Garner EI, Walsh CS, Gehrig PA, Miller DS, Schorge JO. Fertility-sparing surgery in 101 women with adenocarcinoma in situ of the cervix. *Gynecol Oncol* Nov 2007;107:316–9.
- [18] Young JL, Jazaeri AA, Lachance JA, Stoler MH, Irvin WP, Rice LW, et al. Cervical adenocarcinoma in situ: the predictive value of conization margin status. *Am J Obstet Gynecol* Aug 2007;197:195.e1–7 [discussion 195.e7–8].
- [19] Mathevet P, Dargent D, Roy M, Beau G. A randomized prospective study comparing three techniques of conization: cold knife, laser, and LEEP. *Gynecol Oncol* Aug 1994;54:175–9.
- [20] Duggan BD, Felix JC, Muderspach LI, Gebhardt JA, Groshen S, Morrow CP, et al. Cold-knife conization versus conization by the loop electrosurgical excision procedure: a randomized, prospective study. *Am J Obstet Gynecol* 1999 Feb;180:276–82.

- [21] Naumann RW, Bell MC, Alvarez RD, Edwards RP, Partridge EE, Helm CW, et al. LLETZ is an acceptable alternative to diagnostic cold-knife conization. *Gynecol Oncol* 1994 Nov;55:224–8.
- [22] Kyrgiou M, Tsoumpou I, Vrekoussis T, Martin-Hirsch P, Arbyn M, Prendiville W, et al. The up-to-date evidence on colposcopy practice and treatment of cervical intraepithelial neoplasia: the Cochrane colposcopy & cervical cytopathology collaborative group (C5 group) approach. *Cancer Treat Rev* Nov 2006;32:516–23.
- [23] Martin-Hirsch PP, Keep SL, Bryant A. Interventions for preventing blood loss during the treatment of cervical intraepithelial neoplasia. *Cochrane Database Syst Rev* Jun 16 2010;6:CD001421.
- [24] Noehr B, Jensen A, Frederiksen K, Tabor A, Kjaer SK. Loop electrosurgical excision of the cervix and subsequent risk for spontaneous preterm delivery: a population-based study of singleton deliveries during a 9-year period. *Am J Obstet Gynecol* Jul 2009;201(1):33.e1–6.
- [25] Noehr B, Jensen A, Frederiksen K, Tabor A, Kjaer SK. Depth of cervical cone removed by loop electrosurgical excision procedure and subsequent risk of spontaneous preterm delivery. *Obstet Gynecol* Dec 2009;114(6):1232–8.
- [26] Soutter WP, Haidopoulos D, Gornall RJ, McIndoe GA, Fox J, Mason WP, et al. Is conservative treatment for adenocarcinoma in situ of the cervix safe? *BJOG* Nov 2001;108:1184–9.
- [27] Andersen ES, Nielsen K. Adenocarcinoma in situ of the cervix: a prospective study of conization as definitive treatment. *Gynecol Oncol* Sep 2002;86:365–9.
- [28] Costa S, Negri G, Sideri M, Santini D, Martinelli G, Venturoli S, et al. Human papillomavirus (HPV) test and PAP smear as predictors of outcome in conservatively treated adenocarcinoma in situ (AIS) of the uterine cervix. *Gynecol Oncol* Jul 2007;106:170–6.
- [29] Poyner EA, Barakat RR, Hoskins WJ. Management and follow-up of patients with adenocarcinoma in situ of the uterine cervix. *Gynecol Oncol* May 1995;57:158–64.
- [30] Im DD, Duska LR, Rosenshein NB. Adequacy of conization margins in adenocarcinoma in situ of the cervix as a predictor of residual disease. *Gynecol Oncol* Nov 1995;59:179–82.
- [31] Krivak TC, Rose GS, McBroom JW, Carlson JW, Winter III WE, Kost ER. Cervical adenocarcinoma in situ: a systematic review of therapeutic options and predictors of persistent or recurrent disease. *Obstet Gynecol Surv* Sep 2001;56:567–75.
- [32] Dalrymple C, Russell P. Thermal artefact after diathermy loop excision and laser excision cone biopsy. *Int J Gynecol Cancer* May 1999;9:238–42.