Gynecologic Oncology 124 (2012) 72–77

Contents lists available at SciVerse ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

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

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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.

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.

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0090-8258/$ – see front matter © 2011 Published by Elsevier Inc.
doi:10.1016/j.ygyno.2011.09.006

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.

	Cold knife cone (N = 58)		Loop cone excision (N = 54)		P-value
Variable					
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.