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Comparison of cold knife cone biopsy and loop electrosurgical excision procedure in the management of cervical adenocarcinoma *in situ*: What is the gold standard?

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HIGHLIGHTS

- Women treated for ACIS by cold knife cone biopsy or LEEP were monitored for disease persistence.
- There was no difference in ACIS disease persistence between CKC and LEEP after 3.6 years of follow-up.

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ABSTRACT

Objective. To compare the outcomes of patients with cervical adenocarcinoma *in situ* (ACIS) treated with cold knife cone (CKC) biopsy or loop electrosurgical excision procedure (LEEP) for the treatment of cervical adenocarcinoma *in situ* (ACIS).

Study design. This is a retrospective, population-based cohort study of Western Australian patients with ACIS diagnosed between 2001 and 2012. Outcomes included pathological margin status and the incidence of persistent or recurrent endocervical neoplasia (ACIS and adenocarcinoma) during follow-up (<12 months) and surveillance (≥12 months) periods.

Results. The study group comprised 338 patients including 107 (32%) treated initially by LEEP and 231 (68%) treated by CKC biopsy. The mean age was 33.2 years (range 18 to 76 years) and median follow-up interval was 3.6 years (range <1 year to 11.8 years). Overall, 27 (8.0%) patients had ACIS persistence/recurrence while 9 (2.7%) were diagnosed with adenocarcinoma during the follow-up and surveillance periods. No patient died of cervical cancer within the study period. There were no significant differences in the incidence of persistent and/or recurrent endocervical neoplasia according to the type of excisional procedure. Patients with positive biopsy margins were 3.4 times more likely to have disease persistence or recurrence.

Conclusion(s). LEEP and CKC biopsy appear equally effective in the treatment of ACIS for women wishing to preserve fertility. Patients undergoing conservative management for ACIS should be closely monitored, particularly if biopsy margins are positive in initial excision specimens. Patients and their clinicians should be aware of the potential risks of residual and recurrent disease.

Introduction

The incidence of cervical cancer in developed countries has decreased significantly in the past few decades largely due to the adoption of public health screening programmes, but this mainly reflects a decrease in squamous cell carcinoma [1–3]. By contrast, the incidence of cervical adenocarcinoma has increased in both relative and absolute terms, and now represents 20–25% of all cervical cancer cases [1–3]. The recognised precursor to cervical adenocarcinoma is adenocarcinoma *in situ* (ACIS), and this frequently coexists with high-grade squamous intraepithelial neoplasia (CIN) and/or squamous cell carcinoma [4–6]. Cervical cytology is generally less sensitive in the detection of cervical glandular abnormalities compared to CIN,

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and it is reported that ACIS may also evade detection at colposcopy [7–10].

Conservative management of women with ACIS is controversial since these lesions can persist/recur and may co-exist with, or progress to, cervical adenocarcinoma [5,6,11]. Consequently hysterectomy is regarded as the definitive treatment [12,13]. However, ACIS commonly affects young women who may wish to preserve fertility and therefore local excisional procedures such as cold knife cone (CKC) biopsy or loop electrosurgical excision procedure (LEEP) have been utilized as alternatives to hysterectomy [6,7,11–14].

In Australia, CKC is regarded as the 'gold standard' treatment for ACIS [12]. There is a perception that there is a greater likelihood of incomplete excision with LEEP because the depth of excised tissue and the overall dimensions of the specimen tend to be smaller in comparison to CKC. It is also argued that the tissue margins in a LEEP biopsy may show significant thermal artefact, which can interfere with the pathological assessment of biopsy margins [15,16]. Some studies have shown a greater risk of a positive endocervical margin with LEEP but these have included cases in which ACIS was not suspected prior to the excisional procedure [17–19]. Conventional management has also been challenged by recent data which suggest that the risk of positive margins and disease recurrence are equivalent following LEEP or CKC biopsy [6,11]. Such findings could potentially alter treatment guidelines since accepted advantages of LEEP include the avoidance of general anaesthesia, provision of treatment in an outpatient setting, lower morbidity, and reduced rates of obstetric complications, all of which have significant cost benefits [6,11,19–23].

Nevertheless, the efficacy of conservative treatment of ACIS remains uncertain since most studies to date have been limited by small sample size and short follow-up [6,7,17–19]. In the present study we have determined the rates of residual and recurrent endocervical neoplasia in a large, population-based cohort of women in Western Australia (WA) who had conservative management of ACIS. Outcomes were correlated with patient age and socioeconomic background, type of excisional procedure, margin status, and the presence of concurrent high grade CIN.

Methods

Data sources and linkage procedure

The Cervical Screening Register (CSR) of WA is required by legislation to compile all cervical test results (human papillomavirus (HPV) detection, cytology and histology) for women who reside in WA. The CSR is an 'opt out' register and less than 0.05% of women request removal of their demographic information and results. The WA Data Linkage System (WADLS) provided a de-identified extraction of linked cancer registrations and death records for all women with ACIS identified by the CSR of WA from 2001 to 2012. The WADLS is an internationally renowned, population-based, validated and ongoing data linkage system that creates links among a number of state health administrative data sets [24–26].

Follow-up data were available up to May 2013. Death records were used to verify the number of cervical cancer related deaths and to censor women who died during follow-up. Study data were obtained following approval from the Curtin University Human Research Ethics Committee (ethics research project number: HR 86/2012) and the Western Australian Department of Health Human Research Ethics Committee (ethics research project number: 2012/49).

Participants

The CSR was used to identify women aged 18 years or older who were reported to have ACIS on either routine cervical cytology screening or on cervical punch biopsy. Only women who had histological confirmation of ACIS following CKC or LEEP biopsy were included in the study. Patients were excluded if they had prior histological documentation of CIN or cervical cancer. Cervical cytology was classified according to the Australian Modified Bethesda System 2004 [12]. Patient age at the time of treatment was classified as ≤30 years or >30 years. Postcode of residence was used to assign a socioeconomic level using the Australian Bureau of Statistics 2006 Socio Economic Indexes for Areas (SEIFA) [27]. Patients underwent CKC or LEEP procedures according to the surgeon's standard practice.

Histopathology findings

The following biopsy findings were determined from review of the histopathology reports: the type of biopsy (CKC or LEEP), depth of the specimen (measured macroscopic extent along the cervical canal), presence of concurrent CIN and resection margin status. The latter was considered 'positive' if any margin (ectocervical, endocervical or deep/circumferential) was involved by ACIS, 'negative' if all margins were histologically clear, and 'indeterminate' if margins could not be assessed or were not documented.

Follow-up

Management following the initial CKC biopsy or LEEP was determined. Subsequent management potentially included cytological review, repeat CKC biopsy or LEEP, or hysterectomy. The follow-up period was defined as the date of the initial ACIS treatment to the date of the last follow-up procedure (*e.g.,* cervical cytology, biopsy or hysterectomy).

Principal outcomes

The principal outcomes investigated were i) persistence of ACIS or diagnosis of adenocarcinoma during the follow-up period (defined as disease detection <12 months after the initial diagnosis), and ii) recurrence of ACIS or diagnosis of adenocarcinoma within the surveillance period (defined as disease detection ≥12 months after the initial diagnosis). Cancer mortality was a secondary outcome measure.

Statistics

STATA/IC 13.0 (STATA Corporation, College Station, USA) was used for data manipulation and statistical analysis. Fisher's exact test was used to evaluate similarities between the CKC and LEEP groups. Time-to-event (survival) analysis was performed using Cox models to investigate patient and clinical factors associated with disease persistence and/or recurrence. Variables included in the modelling process were age at diagnosis, SEIFA indices, type of treatment (CKC or LEEP), margin status, and depth of excised tissue. Statistical significance was determined as a p-value < 0.05 and the 95% confidence intervals (CI) for hazard rate ratios were calculated. Plausible interaction terms were tested using likelihood ratio tests. Violation of the Cox model proportional hazard assumption was tested using Schoenfeld residuals. Due to small numbers, time to event analysis was not performed for cervical cancers.

Results

Study cohort

There were 338 patients with ACIS eligible for the study following exclusion of 8 patients who had a hysterectomy as initial treatment and 16 patients for whom follow-up data were not available. An overview of the study cohort is presented in Fig. 1. The mean age was 33.2 years (range 18 to 76 years) and the median follow-up interval was 3.6 years (range < 1 year to 11.8 years). Two hundred and thirty one patients (68.3%) had a CKC while the remainder (n = 107, 31.7%) had a LEEP procedure. The clinicopathological findings are summarised in Table 1.