



Predictive factors for residual disease in hysterectomy specimens after conization in early-stage cervical cancer



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ABSTRACT

Objective: To identify predictive factors for residual disease in hysterectomy specimens after a loop electrical excision procedure (LEEP) or cold knife conization in early-stage cervical cancer.

Study design: A retrospective review was undertaken of the clinical records and pathology reports of 108 consecutive patients who were diagnosed with early invasive cervical cancer stage IA1 to IB1 by cold knife conization or LEEP, and underwent subsequent hysterectomy or radical hysterectomy at the Gynaecology Unit, Queen Elizabeth Hospital between 2000 and 2012. Residual disease was defined as the presence of cervical intra-epithelial neoplasia (CIN) 2–3 or invasive carcinoma in hysterectomy specimens. Clinicopathological factors associated with residual disease were analyzed. Risk factors for the prediction of residual disease were identified by univariate and multivariate analysis.

Results: Residual disease was found in 32 (29.7%) patients. Stage, tumour size, depth of invasion, lymphovascular space invasion, ectocervical margin, endocervical margin, and combined ectocervical and endocervical margin were significantly associated with residual disease in hysterectomy specimens on univariate analysis. On multivariate analysis, depth of invasion (odds ratio 2.1, $p = 0.033$) and combined margin status (odds ratio 10.8, $p \leq 0.001$) were independent risk factors for residual disease. In a subgroup analysis using depth of invasion ≤ 5 mm and a negative combined margin, none (0%) of the 52 patients who met the criteria had residual disease.

Conclusions: Conization (combined ectocervical and endocervical) margin and tumour depth of invasion are independent predictors of residual disease in hysterectomy specimens. A negative conization margin and depth of invasion ≤ 5 mm are associated with low risk of residual disease in patients with early-stage cervical cancer.

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Introduction

Early-stage cervical cancers, which include all International Federation of Gynecology and Obstetrics stage IA1 and IA2 disease and preclinical IB1 disease, are usually diagnosed histologically by cold knife cone biopsy or loop electrical excision procedure (LEEP). Due to the risk of residual disease in the remaining cervical stroma and the potential spread of disease to the parametrium or pelvic lymph nodes [1], standard surgical treatment for cervical cancer diagnosed after cone biopsy or LEEP is simple extrafascial hysterectomy for stage IA1 disease; and radical hysterectomy

plus pelvic lymphadenectomy for stage IA1 disease with lymphovascular invasion (LVSI), stage IA2 disease and stage IB1 disease. Radical trachelectomy is an alternative for selected patients with tumour < 2 cm who wish to preserve their fertility.

Radical hysterectomy is associated with significant morbidities. There are increased risks of blood loss, transfusion, nerve or vascular injury, hospital stay, bladder or bowel dysfunction, sexual dysfunction and fistula formation compared with simple hysterectomy [2–4]. Although radical trachelectomy for tumour < 2 cm allows preservation of fertility and has shown similar oncological outcomes [5,6], the associated morbidities arising from removal of the parametrium remain. The risk of obstetric complications such as second trimester loss and preterm birth are also increased compared with the general population [7].

In recent years, efforts have been made to identify a subgroup of low-risk early-stage cervical cancers so that less radical surgery can

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be contemplated to preserve fertility, reduce surgical morbidity and minimize obstetric complications without compromising oncological outcome. Previous studies have shown that the risk of parametrial involvement is <1% in patients with favourable prognostic factors such as tumour size <2 cm, limited depth of invasion, absence of LVSI and negative pelvic lymph nodes [8–10]. It has been suggested that cold knife cone biopsy with clear margins can be performed instead of simple hysterectomy for stage IA1 disease, and parametrectomy could be omitted in a selected group of stage IA2 and stage IB1 diseases [11,12]. Several small retrospective series have reported favourable oncological outcomes in patients with low-risk early-stage cervical cancer treated by conization, simple trachelectomy, or simple hysterectomy plus pelvic lymph node dissection [13].

Within the last decades, the proportion of early-stage cervical cancers diagnosed in women of reproductive age has increased due to increased cervical smear screening and colposcopy examination [14]. In Hong Kong, 28% of cervical cancers were diagnosed in patients aged <45 years [15]. The option of fertility-sparing treatment is important to these women. The objectives of this study were: (a) to identify pathological factors in conization specimens that predict residual disease in hysterectomy specimens in early-stage cervical carcinoma; and (b) to evaluate the possibility of offering less radical surgery to patients who are at low risk of having residual disease.

Materials and methods

This study was approved by the Clinical Research Ethics Committee of the Kowloon Central Cluster, Hospital Authority, Hong Kong Special Administrative Region. The records of 108 consecutive patients who were diagnosed with early invasive cervical cancer stage IA1 to IB1 by cold knife conization or LEEP, and underwent subsequent hysterectomy or radical hysterectomy at the Gynaecology Unit, Queen Elizabeth Hospital between 2000 and 2012 were retrieved from the electronic patient record system. Diseases were staged retrospectively in accordance with the 2009 International Federation of Gynecology and Obstetrics (FIGO) classification. Cold knife cone biopsy was usually performed for high-grade cervical intra-epithelial neoplasia (CIN) with endocervical involvement, or when there was suspicion of micro-invasive disease. LEEP was usually performed for high-grade CIN with satisfactory colposcopy. None of the patients had a gross cervical tumour clinically. All cone biopsies and LEEPs were performed by gynaecologists. Patients who did not have diagnostic conization, patients who did not have subsequent hysterectomy, and patients who presented with unusual histology (e.g. neuroendocrine tumour) were excluded from the study.

Patients were counselled in the gynaecology clinic for definitive surgery following a diagnosis of cervical cancer by cone biopsy/LEEP. Simple extrafascial hysterectomy with or without oophorectomy was offered to patients with FIGO stage IA1 disease without LVSI. Patients with FIGO stage IA1 disease with LVSI, IA2 and microscopic IB1 disease were offered radical hysterectomy (Piver type III), or radical trachelectomy and bilateral pelvic lymphadenectomy, with or without oophorectomy, depending on their wish to preserve their fertility. All surgical procedures were performed by gynaecologists in the unit. There were no major changes in surgical treatment protocols over the study period. Radical trachelectomy was introduced in the unit in 2010 as fertility-sparing treatment for early-stage cervical cancer. Adjuvant radiotherapy was considered after discussion at tumour board meetings if the patient had positive pelvic nodes, positive surgical margins, parametrial involvement or the presence of two of the following risk factors: (1) greater than one-third stromal invasion; (2) presence of LVSI; and (3) cervical tumour ≥ 3 cm. All patients

were followed up in the gynaecology unit for 5 years by physical examination and vault smears.

Clinical records and pathology reports of conization specimens and hysterectomy specimens were reviewed. All the pathology reports were issued by experienced gynaecological pathologists in a standard format. Histopathological data including tumour size, depth of stromal invasion, presence of LVSI, histological type, multifocal or unifocal disease, margin status of conization specimen, depth of conization, residual disease in hysterectomy specimen, parametrial involvement and lymph node status were recorded and analyzed. Tumour size referred to the maximum tumour diameter (in mm) measured along the surface epithelium perpendicular to stromal infiltration. Tumour depth of invasion (in mm) was measured perpendicularly from the basement membrane of the surface epithelium. In the case of multifocal disease, the dimension of the largest focus was used for analysis. Margins were marked with different inks, and lesions touching the marked margin were considered to be positive. The margin status of conization or LEEP specimens was recorded as follows: negative, no residual disease; low grade, presence of human papilloma virus infection or CIN 1; high grade, presence of CIN 2–3; and invasive carcinoma, tumour involved the margin. Site of margin involvement, namely ectocervical or endocervical involvement, was recorded. Depth of conization referred to the perpendicular distance along the endocervical canal between the ectocervical surface and the endocervical end. Residual disease in hysterectomy specimens was defined as the presence of CIN 2–3 or invasive carcinoma. All tumours were staged in accordance with the FIGO classification after review of both conization and hysterectomy specimens. If residual tumour was observed in the hysterectomy specimen, summation of the depth of invasion from the corresponding site in the conization specimen was performed to give the best estimation. Clinical data including age, stage, nature of surgery, adjuvant treatment, recurrence and follow-up period were retrieved from the electronic patient records.

Patients were divided into two groups according to the presence or absence of residual disease in hysterectomy specimens. Statistical analysis was performed to compare clinicopathological variables between the two groups. Pearson's Chi-squared test or Fisher's exact test was used for categorical data analysis, and Student's *t*-test or Mann–Whitney *U*-test was used for continuous data analysis, as appropriate. $p < 0.05$ was considered to indicate statistical significance. All statistical analyses were performed using Statistical Package for the Social Sciences Version 19.0 (IBM Corp., Armonk, NY, USA).

Results

In total, 108 consecutive patients were included in the study. Patient and tumour characteristics are summarized in Table 1. The median age was 47 years (range 25–80 years). Seventy-seven patients (71.3%) underwent LEEP, and 31 patients (28.7%) underwent cold knife cone biopsy. Simple extrafascial hysterectomy was performed in 70 patients with stage IA1 disease. Radical hysterectomy and pelvic lymphadenectomy was performed in eight patients with stage IA1 disease with LVSI, four patients with stage IA2 disease and 24 patients with stage IB1 disease. Radical hysterectomy was performed in two patients for preservation of fertility: one with stage IA1 disease with LVSI, and one with stage IB1 disease. All definitive surgeries were performed within 3 months of conization or LEEP. Disease was not upstaged in any of the patients following definitive surgery.

Residual disease was found in 32 (29.7%) of 108 patients. Of the 38 patients treated by radical hysterectomy or radical trachelectomy, no cases were found to have parametrial disease in the resected specimen. One patient with stage IB1 disease diagnosed

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