REVIEW

Management of Patients with Positive Margins after Cervical Conization: A Review

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Cervical conization in the evaluation and treatment of microinvasive (MIC) or cervical intraepithelial neoplasia (CIN) has been well-established procedure. There is still some problems in the management of cases with positive resection margin of the conization specimen. This review will be on this issue dividing according to the histology of conization specimens, i.e. MIC, CIN, and adenocarcinoma in situ (AIS) respectively. With invasive disease, the management is well defined and will not be discussed here.

Microinvasive squamous cell carcinoma (MIC)

The definition of MIC of the cervix according to FIGO (International Federation of Gynecology and Obstetrics) 1995, stage IA1 is a lesion invading into the stroma no greater than 3 mm. and width no greater than 7 mm. This definition is consistent with MIC established by the Society of Gynecologic Oncologists (SGO) in 1974. There are many published data revealed that lesions no more than 3 mm. of stromal invasion have a negligible risk of both lymphatic spread and recurrence if no lymph vascular space is present.[1]

Diagnosis of MIC is based on cervical specimen obtained from conization, not punch biopsy. Treatment guideline for women in whom cervical conization reveal MIC with positive margin should be based upon the risk of invasive disease in the residual cervix.

Roman et al[2] studied the risk of residual invasion when conization revealed MIC (stromal invasion no more than 3 mm. and no lymph vascular space invasion) by retrospectively reviewed the charts and histopathology slides of 87 women who underwent conization that contained MIC, followed by either a repeat conization or hysterectomy. Depth of invasion, number of invasive foci, status of the internal margin and post-conization endocervical curettage (ECC) were assessed. The internal conization margin was interpretable in 81 of 87 specimens. The margins of the remaining six specimens could not be evaluated due to inappropriate marking. Among 51 cases of positive margins, 50 had high grade dysplasia and one had MIC at the margins. A post-conization ECC was performed in 78 women and was positive in 28 cases. Among 21 patients with positive both internal margin and ECC, 5 (24%) had MIC and 2 (10%) had frank invasion in the residual cervix. Of 23 patients with either positive margin or positive postconization ECC, 1 (4.3%) and 2 (8.7%) patients still had MIC and frank invasion in the remaining cervix respectively. In comparison, only 1 of 27 (3.7%) patients with negative both margin and ECC had MIC in the residual cervix. No invasion cancer was found in case of negative both surgical margin and postconization ECC.

Another papers such as Burghardt and Holzer,[3] especially Greer et al[4] also revealed that the risk of residual invasion was high at 14% and 63% respectively conization margin was positive. According to these data, the risk of residual invasive cancer is high when the conization margins are positive with MIC either with or without positive ECC, accordingly these patients should undergo a repeated conization or modified radical hysterectomy if anatomy of the cervix is not suitable for a repeated conization. On the other hand, if both the margin and ECC are negative, the patients can be followed or undergo simple hysterectomy if fertility is no longer desired.

Cervical intraepithelial neoplasia (CIN)

There is still controversy regarding the management of CIN extending to the resection margin of a conization specimen. The patients may be managed by either one of the following options: 1) follow-up with Papanicolaou smears (Pap smears) and ECC, with colposcopic evaluation if cytology indicates[5,6,7] ; 2) repeated cervical conization[5] ; or 3) hysterectomy.[5,7] Each option has some pitfall. Conservative management is potentially complicated by later occult progression of CIN or loss to follow-up. The repeated conization also has inherent risks and complication. The last one, hysterectomy may miss invasive cervical cancer.

There are several methods to perform cervical conization including laser conization,[8,9] loop electrosurgical excision procedure (LEEP)[10-12] and the conventional method, cold knife conization.[5-7] These methods will be discussed orderly, concerning the management of positive cone margin.

Laser

Andersen et al[8] reviewed 469 patients underwent combined laser conization and laser vaporization for the treatment of CIN. CIN was located in the margins of the cone specimens in 58 cases (12.4%),. Fifty-one patients with positive margins were further evaluated by cytologic examination using Ayre spatula, cytobrush, and ECC. Among 6 patients who had

persistent disease in specimens obtained from repeat conization, 3 (50%) had positive cytology. Hysterectomy was performed in 5 cases, but in only one case was a significant lesion demonstrated in the uterus. The author concluded that conservative management of patient treated with laser combination is justified. These findings agree with the studies of Grundsell et al[9] who found no further evidence of residual disease in 86% of patients with incomplete laser conization. The reason for no residual tumor after laser conization despite positive margin is that the vaporization may eliminate lesion at the excisional margins.[12]

LEEP

The use of loop electrosurgical excision procedure (LEEP) is reputed to be a safe and efficacious method for treating and investigating CIN. Compared with cold-knife conization, LEEP is significantly quicker and is associated with less intraoperative blood loss and fewer post operative complications. One weak point of LEEP is the problem of thermal injury, however there are many studies showed that this problem was minimal and did not interfere with the interpretation of margin adequacy.[14-15]

Felix et al (11) reported that 12 of 19 patients (63%) had residual dysplasia in cervical tissue after LEEP procedure when endocervical margin or ECC was positive and concluded that the status of the internal cone margin could predict residual disease on subsequent histologic evaluation. Bennett et al[12] reported two of four and two of five patients had residual CIN in the uterus when positive margins were found at ectocervix and endocervix respectively and two of 22 patients had residual CIS inspite of free endocervical and ectocervical margins. Gardeil et al [10] studied the factors associated with subsequent intraepithelial neoplasia among patients who had CIN grade III diagnosed on a specimen from previous LEEP and noted that the positive margin increased the risk of treatment failure when followed up these patients with cytology. Murdoch JB et al[16] found that when the endocervix was involved with CIN, the incidence of

incomplete excision would occur more often and more severe with extensive lesions.

Felix et al[11] recommended that patients whose margins from LEEP were involved with CIN should be undergo cold-knife conization 4-6 weeks later. All subsequent specimens should be thoroughly examined histologically for the presence of residual disease. After repeat therapeutic procedure, patients with negative proximal core margins should be follow-up with pelvic examination, cervical cytology and colposcopy at 3 months, 6 months, and 1 year. Gardeil et al[10] and Murdoch et al[16] also gave the same recommendation. From the study of Shafi and coworkers,[17] invasive cervical cancer could be occasionally observed following LEEP. Consequently, in community with high percentage of loss to follow - up, the repeat cold-knife conization may be an appropriate treatment in patients with positive dysplasia at surgical margins. If the pathology report shows only CIN with clear margin, hysterectomy should be offered in patients whose fertility is no longer desired. However, if fertility must be retained, close follow- up with cytology and colposcopy may be another option.

Cold-knife conization (CKC)

The frequency of dysplasia at surgical margins of conization specimens range from 5.7-53%.[5] Management of this problem has changed dramatically over the past 20 years when the data from many studies demonstrated that positive margins often had no residual disease on repeat surgical specimens. Accordingly, more conservative strategies is recommended.[5]

Monk et al[5] retrospectively reviewed the patients who received conservative management with cervical cytology, colposcopy, colposcopically directed biopsies (CDB), and ECC after being found to have squamous cell dysplasia involving the endocervical margins in conization specimens. Only one of 31 patients subsequently had evidence of dysplasia during a follow-up period of 12 to 72 months. The repeat cone biopsy specimens showed only mild dysplasia. The remaining 30 patients did not have any evidence of

dysplasia after follow-up period of 1 to 18 years. They concluded that patients with squamous cell dysplasia at endocervical border of the cervical cone biopsy specimens do not automatically require additional surgery. They can be comprehensively reevaluated and followed up with intensive Pap smear surveillance every 4 months for the first year, every 6 months the second year; and at least annually thereafter to identify those with residual disease who require further treatment from those who do not need such additional therapy. In patients who desire to preserve fertility, pregnant should be deferred for at least 3, if not 6 months after the Pap smears are negative.

Vedel et al[6] reported that there was significantly higher recurrence rate in the group with neoplasia in the resection margins (16.2%), in contrast to 3.9% of patients with normal resection margins. However, 83.8% (75.4-92.2%) of patients with neoplasia in the resection margins can be expected to be free of recurrence after a 5 – year post-operative follow up period. Whether the not- free resection margins were endocervical, ectocervical or both, did not influence the recurrence rate. Due to the increased risk of recurrence when the resection margins had neoplasia, they recommended using Pap smears and cytobrush for follow-up of these patients.

The incidence of residual dysplasia ranged from 30-82% when the cone margin was positive.[7,18-27] Such incidence appeared higher in patients who had higher grades of CIN at cone margin and in patients with positive post cone ECC. The margin status seemed to be a better predictor of residual disease at subsequent surgery than the result of cytologic follow-up. The increasing age and severity of disease in cone specimens were additional predictors of residual dysplasia.[26] Women aged 50 years or older with positive both endocervical margin and postconization ECC should undergo repeat conization if fertility is not desired. Otherwise, close follow-up is recommended to detect possible invasive lesion developed later in the residual cervix.[27] Subsequent hysterectomy either simple or radical may be reserved for patients with invasive cone pathology according to the stage of disease, patients

with concomitant morbid uterine condition, and patients with unreliable long term follow-up.[25]

Although many investigators recommended expectant management for patients with positive cone margins,[7,18,25-27] however this policy may not be suitable in Thailand due to high rate of loss to follow-up. In author's opinion, hysterectomy would be appropriate in these patients unless a repeated conization is done. If fertility is desired, close follow-up with Pap smears, endocervical sampling with cytobrush or ECC and colposcopy should be perform at 3-month interval in the first year, every 6 months in the second year, and annually thereafter.

Adenocarcinoma in situ (AIS)

Adenocarcinoma in situ (AIS), the preinvasive state of adenocarcinoma go through the same spectrum of cellular changes as preinvasive squamous disease, but is much more difficult to detect.[28] Histologically documented AIS has been reported in cytologic cervical screenings to range from 14 cases per 740,000 to 13 cases per 1,500,000 cytologic examinations.[28] AIS is very difficult to identify colposcopically, and is usually a histological diagnosis made at the margin of CIN or invasive squamous cell carcinoma or adenocarcinoma. Although it may occur in any area of the columnar epithelium, it usually develop adjacent to the squamocolumnar junction. The lesions are occasionally localized high in the endocervical canal, involve deeper portions of the endocervical clefts, and are multifocal with "skip lesions" away from the squamocolumnar junction.[29,30]

Fifty percent or more of AIS is found in association with CIN and often the CIN predominates, or is detected earlier by both cytologist and by colposcopist. Progression of AIS to adenocarcinoma has been recorded, and such progression probably takes many years, just as for CIS to invasive cancer. AIS is diagnosed for less frequently than adenocarcinoma, perhap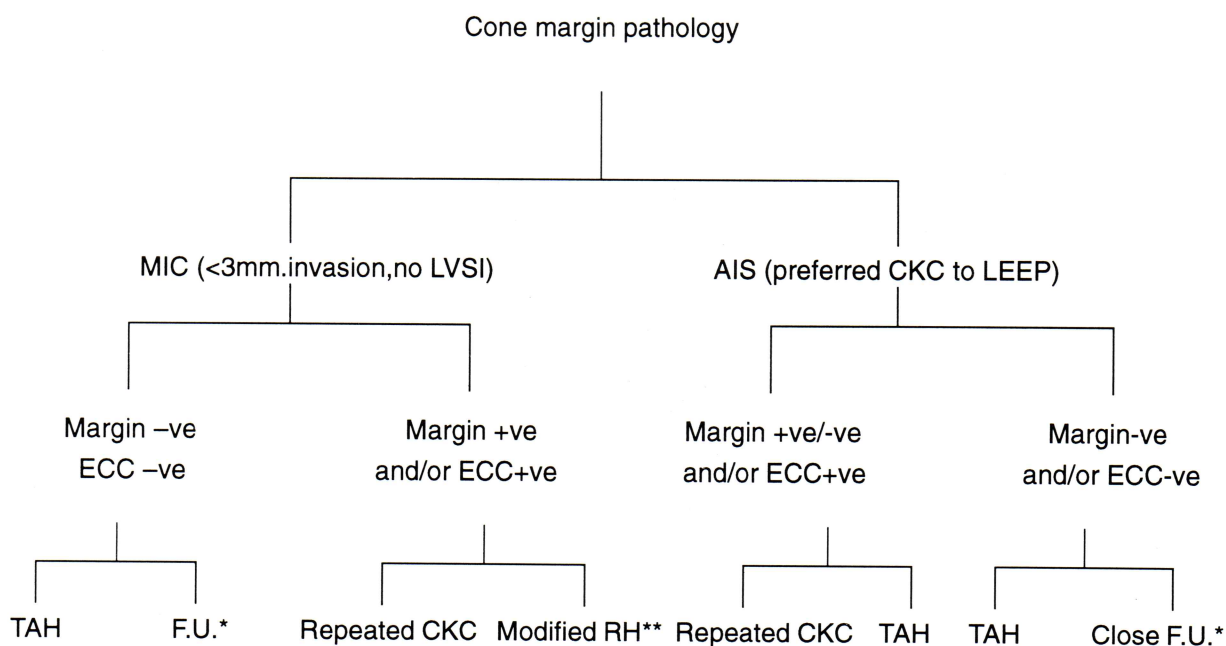s reflecting the difficulty both cytologically and colposcopically of identifying these lesions. The accurate diagnosis of AIS can only be made by cervical conization.[28] Several investigators have suggested that conization is essential if AIS is suspected on cervical cytology or punch biopsy.[31,32] Im et al[28] reported a case of AIS diagnosed by punch biopsy and was subsequently treated by hysterectomy showed invasive adenocarcinoma, this data emphasized the importance of conization.

When the margins of conization specimens was involved by AIS, it is generally accepted that hysterectomy is indicated.[28,33] Denehy et al[33] reported that the rate of positive resection margins in conization specimens was 43% and found that 80% of patients with involved margins or positive ECC had residual disease in the subsequent specimens. This high rate of involved cone margins highlights the difficulty in the conservative management of AIS.

The type of cone performed seems to relate to the incidence of involved margins. Denehy et al[33] found that eight of 24 cold knife cones had positive margins in comparison to nine of 13 LEEP specimens, which is similar to the report by Widrich et al[34] that noted eight of 25 (33%) CKC with positive margins in comparison to nine of 18 (50%) LEEP. In Widrich's study,[34] they demonstrated that the recurrence rate after LEEP was 29% in contrast to 6% after CKC despite a 63.4 month shorter mean follow-up interval for patients undergone LEEP. According to these data and the fact that CKC specimens were of significantly larger volume and of better histologic evaluation than loop procedure, CKC is a preferred method for diagnosis of AIS. Since there have been case reports of recurrence or progression of AIS at vaginal vault after hysterectomy,[32,35,36] so the patients should receive long term follow-up after treatment.

From literature review, the algorithms may be used in management of patients with positive conization margins which are classified according to the pathology at cone margins.

Algorithm for management of positive MIC or AIS at cone margins.

Cone margin pathology

MIC (<3mm.invasion,no LVSI)   AIS (preferred CKC to LEEP)

Margin –ve   Margin +ve   Margin +ve/-ve   Margin-ve
ECC –ve   and/or ECC+ve   and/or ECC+ve   and/or ECC-ve

TAH   F.U.*   Repeated CKC Modified RH** Repeated CKC TAH   TAH   Close F.U.*

MIC = Microinvasive
LVSI = Lymph-vascular space invasion
ECC = Endocervical curettage
TAH = Total abdominal hysterectomy
F.U. = Follow - up
CKC = Cold knife conization
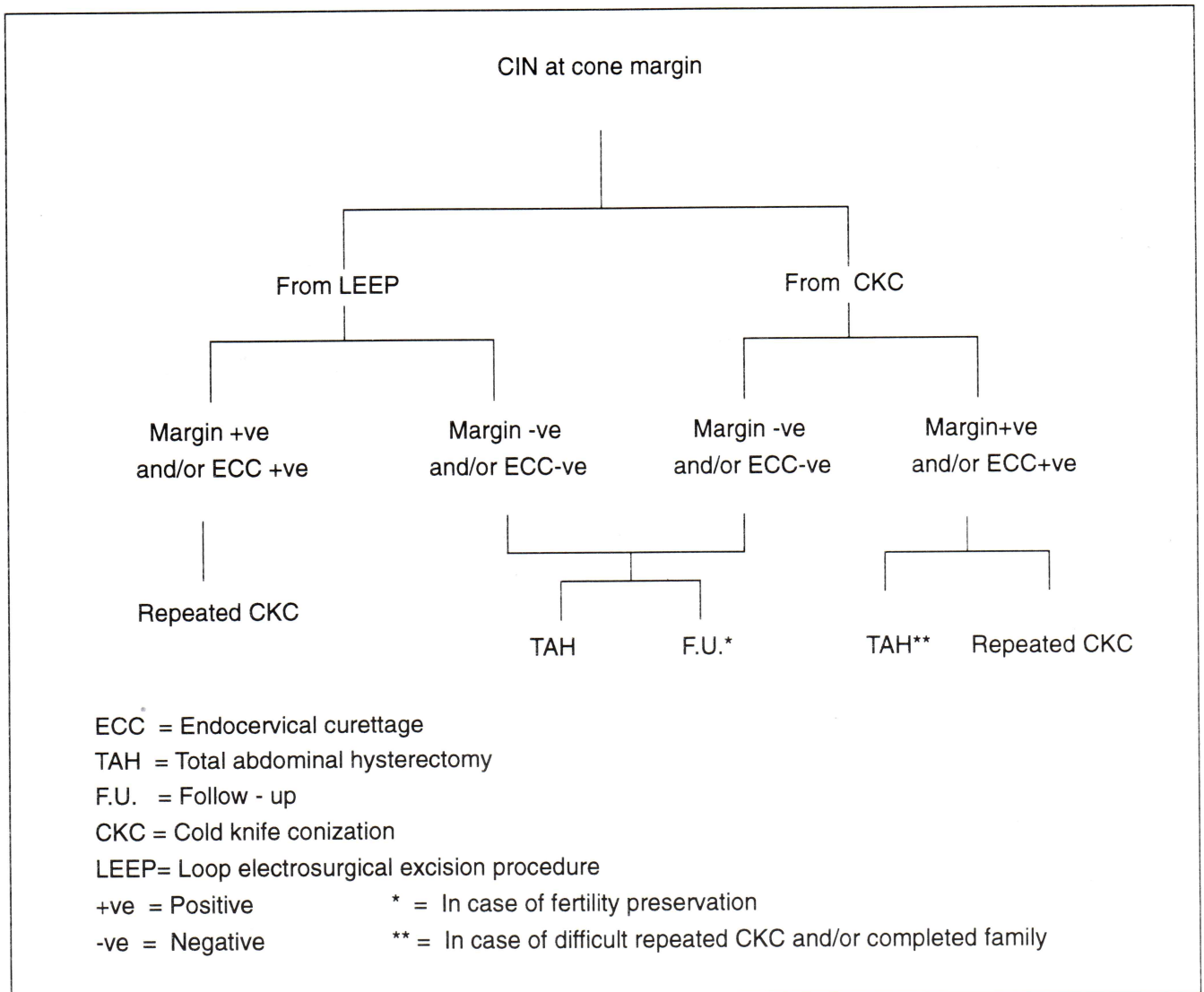RH = Radical hysterectomy
AIS = Adenocarcinoma in situ
LEEP = Loop electrosurgical excision procedure
+ve = Positive   * = In case of fertility preservation
-ve = Negative   ** = In case of difficult repeated CKC and/or completed family

Algorithm for management of positive CIN at cone margins and procedure performed.

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                              CIN at cone margin

                From LEEP                          From CKC

        Margin +ve      Margin -ve        Margin -ve        Margin+ve
        and/or ECC +ve  and/or ECC-ve     and/or ECC-ve     and/or ECC+ve

        Repeated CKC              TAH    F.U.*       TAH**    Repeated CKC
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ECC = Endocervical curettage
TAH = Total abdominal hysterectomy
F.U. = Follow - up
CKC = Cold knife conization
LEEP= Loop electrosurgical excision procedure
+ve = Positive   * = In case of fertility preservation
-ve = Negative   ** = In case of difficult repeated CKC and/or completed family

Conclusion

Management of patients with positive cone margins is based on the pathology of cone margins, the results of ECC and surgical methods of cervical removal. In case of MIC, the risk of residual invasive cancer is unacceptably high if either cone margins or ECC is positive. A repeated conization or modified radical hysterectomy is recommended depending on the patient's desire of future fertility. For CIN, the risk of residual tumor appears to depend on the method of cervical tissue removal. If positive margins are noted after LEEP, further excisional conization is advised to exclude residual disease. Nevertheless, in case of positive margins following CKC, close follow-up with cervical cytology and colposcopy may be appropriate in patients whose fertility should be retained. For AIS, CKC providing larger cervical specimens is preferred for accurate histological diagnosis. Although the risk of residual disease and recurrence after LEEP is significantly greater than that after CKC, hysterectomy with long term follow-up is recommended in case of positive AIS at surgical margins.

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