Validity of Frozen Section in Cervical Conization

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Abstract : Objective: To evaluate the validity of pathological diagnosis of cervical cone specimens prepared by frozen section compared with paraffin section.
Study design : Diagnostic test evaluation
Setting : Pathology division, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University.
Methods : Cervical cone specimens from 78 patients who underwent cold knife conization at Siriraj Hospital from October 1997 to September 1998 were processed by frozen section technique and the pathological diagnoses were made immediately. The remaining cone tissue from each specimen was processed to produce permanent paraffin sections for a final diagnosis. The frozen and permanent pathological diagnoses were compared.
Result : The pathological diagnosis from frozen section was in complete agreement with the permanent section in 60.26% of patients. When the subjects were divided into three groups; normal and CIN I, CIN II – III and MIC and invasive cancer, the Kappa analysis for agreement of the pathological diagnoses between the two methods was 0.46 (fair agreement). For the diagnosis of invasive cancer by frozen section, the sensitivity, specificity, positive and negative predictive value, false negative and false positive were 62.5, 97, 71.4, 95.8, 37.5 and 1.9%, respectively. There were three cases of invasive cancer on permanent paraffin section which were diagnosed by frozen section as MIC in two cases and CIN III in the other.
Conclusion : Frozen section evaluation of a cervical cone specimen carries only a moderate degree of agreement with permanent paraffin section. For the diagnosis of invasive cancer in this study, frozen section has a low sensitivity and a high false negative rate. The diagnosis of microinvasive cancer was subject to significant error. The diagnosis of microinvasive cancer by frozen section needs additional careful review of the permanent section.

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เรื่องย่อ : **ความถูกต้องของการตรวจชิ้นเนื้อปากมดลูกรูปกรวยโดยวิธีแช่แข็ง**

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วัตถุประสงค์ : เพื่อศึกษาความถูกต้องแม่นยำของการตรวจชิ้นเนื้อปากมดลูกรูปกรวย โดยวิธีแช่แข็งเปรียบเทียบกับวิธีสไลด์ถาวร

ชนิดของการวิจัย : การวิจัยเพื่อการวินิจฉัยโรค

สถานที่ทำการวิจัย : สาขาพยาธิวิทยา ภาควิชาสูติศาสตร์นรีเวชวิทยา คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล

วิธีวิจัย : ศึกษาชิ้นเนื้อที่ได้จากการผ่าตัดปากมดลูกเป็นรูปกรวย โดยวิธี cold knife conization ระหว่างเดือนตุลาคม พ.ศ. 2540 ถึงเดือนกันยายน พ.ศ. 2541 จำนวน 78 ราย นำชิ้นเนื้อมาผ่านขบวนการเตรียมชิ้นเนื้อโดยวิธีแช่แข็ง อ่านสไลด์และให้ผลการวินิจฉัยทันที ชิ้นเนื้อที่เหลือทั้งหมดนำมาผ่านการเตรียมชิ้นเนื้อโดยวิธีสไลด์ถาวร นำผลการวินิจฉัยชิ้นเนื้อจากทั้งสองวิธีมาเปรียบเทียบกัน คำนวณหาค่าความถูกต้อง ความไว ความจำเพาะ คุณค่าในการทำนายผลบวก คุณค่าในการทำนายผลลบ ผลบวกลวง ผลลบลวง และค่าความสอดคล้อง

ผลการวิจัย : การตรวจชิ้นเนื้อปากมดลูกรูปกรวยทั้งสองวิธีให้การวินิจฉัยรอยโรคที่ปากมดลูกตรงกันร้อยละ 60.26 เมื่อแบ่งรอยโรคออกเป็น 3 กลุ่ม ได้แก่ normal and CIN I, CIN II – III and MIC และ invasive cancer พบว่ามีค่าความสอดคล้องดีพอใช้ (วิเคราะห์โดยวิธีแคปป้าเท่ากับ 0.46) การวินิจฉัย invasive cancer จากการตรวจชิ้นเนื้อโดยวิธีแช่แข็งมีความไวร้อยละ 62.5 ความจำเพาะร้อยละ 97 คุณค่าในการทำนายผลบวกร้อยละ 71.4 คุณค่าในการทำนายผลลบร้อยละ 95.8 ผลลบลวงร้อยละ 37.5 ผลบวกลวงร้อยละ 1.9 ในผู้ป่วยที่เป็น invasive cancer 8 ราย มีผู้ป่วย 3 รายที่การตรวจชิ้นเนื้อโดยวิธีแช่แข็งให้การวินิจฉัยผิดเป็น MIC 2 ราย และ CIN III 1 ราย

สรุป : การตรวจชิ้นเนื้อโดยวิธีแช่แข็งให้การวินิจฉัยชิ้นเนื้อปากมดลูกมีความถูกต้องแม่นยำดีพอสมควร การวินิจฉัย invasive cancer ยังมีความไวต่ำและมีผลลบลวงสูง การวินิจฉัยผิดพลาดที่สำคัญของการตรวจชิ้นเนื้อโดยวิธีแช่แข็ง ได้แก่ MIC ดังนั้นถ้าตรวจชิ้นเนื้อโดยวิธีแช่แข็งให้การวินิจฉัยเป็น MIC จะต้องตรวจชิ้นเนื้อโดยละเอียดและรอผลจากการตรวจด้วยวิธีสไลด์ถาวร

The frozen section (FS) technique for diagnosis of pathological specimens was developed by De Riemer in 1818. Welch used FS for rapid tissue diagnosis during an operation in 1391. Since then this technique has been widely used as a diagnostic tool in surgery.

Pathological evaluation of cervical cone specimens from cervical conization procedure was

done in order to make a final diagnosis of the cervical lesion as cervical intraepithelial neoplasia (CIN) grade I – III, microinvasive (MIC) or invasive cancer. Surgery for these lesions of the cervix varies from simple hysterectomy for CIN III and MIC[1] to radical hysterectomy with pelvic lymph node dissection for invasive cancer. Patients who have an abnormal pap smear and plan to have a simple hysterectomy for a CIN lesion or associated gynecologic disease would benefit from cervical conization with FS followed by immediate hysterectomy. This procedure has a number of advantages, including reduced costs and inconvenience to the patient, the need for only one anesthetic, and reduced rate of infection and hemorrhage after conization and it also reduces the technical difficulty associated with delayed hysterectomy.[2] However, FS diagnosis of a cervical cone specimen should have a high degree of accuracy because the diagnosis has serious consequences concerning the treatment of the patient. Although many reports[3-5] have shown that FS is a reliable diagnostic procedure for evaluation of a cervical cone specimen, the use of FS on cervical cone specimens at Siriraj Hospital has not been evaluated. This prompted us to study the accuracy of FS in the diagnosis of cervical lesion, especially for invasive cancer.

MATERIALS AND METHODS

This prospective study was done on cervical cone specimens from patients who underwent cervical cold conization in the Department of Obstetrics and Gynecology at Siriraj Hospital from October 1997 to September 1998. The FS technique for processing these cone specimens has been reported previously.[6] The diagnoses by FS were made by one of the authors (PS). A total of less than 30 minutes was spent on the entire process. The remaining tissue was processed for permanent paraffin section in the usual manner which took 48 hours in total. The permanent slides were subjected to routine diagnosis by the staff of the pathology division of the Department of Obstetrics and Gynecology.

To estimate the accuracy of the FS, the cervical pathological diagnoses were classified in details as i) normal, ii) CIN I - III, iii) microinvasive cancer and iv) invasive cancer. Microinvasive cancer (MIC) was defined as stroma invasion to a depth of 3 mm. or less from the basement membrane with no vascular space invasion. We evaluated the sensitivity, specificity, and positive and negative predictive values for the diagnosis of invasive cancer by comparing the FS diagnoses with the paraffin section diagnoses.

RESULTS

We studied 78 cone specimens. The patients' ages ranged from 26 to 45 years and 48.7% of patients were in the 31 to 40 years old group. Fifty two percent of the patients had an abnormal Pap smear as the presenting symptom. Leukorrhea and abnormal vaginal bleeding were presented in 16.7% and 21.8% of the patients. The reasons for having cold conization were an unsatisfactory colposcopy (33.3%) and lack of correlation between cytology, biopsy, and colposcopic findings (26.9%). The final diagnosis of the cervical cone tissue in this group of patients showed invasive cancer in 8 (10.3%), MIC in 7 (9%), CIN III in 42 (53.8%), CIN II in 1 (1.3%), CIN I in 8 (10.3%) and was normal in 12 (15.4%). The FS diagnosis was in complete agreement with the final diagnosis in 47 patients (60.26%). For the diagnosis of invasive cancer on FS, the sensitivity, specificity and positive and negative predictive value were 62.5 , 97.1, 71.8 and 95.8% respectively. The false negative and false positive rate were 37.5% and 1.9%. Frozen section detected invasive cancer in five of eight patients. In three patients that had invasive cancer as a final pathological diagnosis, the FS diagnoses were MIC in two patients and CIN III in one patient. In two patients, the FS diagnoses were invasive cancer but the final pathological diagnosis showed only CIN III.

We divided the subjects into three groups based on the same surgical management (Table 6) . The Kappa analysis was 0.46 which showed fair agreement.

Table 1. Age of the patients

Age (year)	Number (persons)	Percent
21 – 31	3	3.8
31 – 40	38	48.7
41 – 50	26	33.3
51 – 60	7	9.0
≥ 61	4	5.1

Table 2. Presenting symptoms

Presenting Symptoms	Number (persons)	Percent
Abnormal pap smear on regular check up (No symptoms)	41	52.6
Leukorrhea	13	16.7
Abnormal bleeding	17	21.8
Abdominal mass	3	3.8
Pelvic pain	3	3.8
Abortion	1	1.3

Table 3. Indication for conization

Indication for Conization	Number (persons)	Percent
Limits of the lesion cannot be visualized colposcopically	2	2.6
Unsatisfactory colposcopy (squamo – columnar junction not seen)	26	33.3
Positive endocervical curettage	2	2.6
Lack of correlation between cytology, biopsy and colposcopic findings	21	26.9
Microinvasive carcinoma on biopsy or colposcopy	13	16.7
Therapeutic conization	14	17.9

Table 4. Comparison of frozen section and final pathology (paraffin section PS)

FS	PS						Total
	Normal	CIN I	CIN II	CIN III	MIC	Invasive	(persons)
Normal	**7**	3	0	4	0	0	14
CIN I	1	**0**	0	3	0	0	4
CIN II	0	1	**0**	0	0	0	1
CIN III	4	4	1	**34**	5	1	49
MIC	0	0	0	0	**1**	2	3
Invasive	0	0	0	1	1	**5**	7
Total (persons)	12	8	1	42	7	8	78

Normal = No pathology or cervicitis
CIN I– III = Cervical intraepithelial neoplasia grade I - III
MIC = Microinvasive cervical cancer
Invasive = Invasive cervical cancer (squamous cell carcinoma or adenocarcinoma)
Bold numbers indicate complete agreement.

Table 5. Comparison of frozen section and paraffin section for diagnoses of invasive cancer

		PS	
		Invasive	Other
FS	invasive	5	2
	other	3	68

Other = MIC, CIN I – III, and normal
Sensitivity 62.5% (95% CI 25.9 – 89.8)
Specificity 97.1% (95% CI 89.1 – 99.5)
Positive predictive value 71.4% (95% CI 30.3 – 94.9)
Negative predictive value 95.8% (95% CI 87.3 – 98.9)
False negative 37.5%
False positive 1.9%

Table 6. Agreement of frozen section and final pathology (paraffin section)

		PS		
		Normal – CIN I	**CIN II – III, MIC**	**Invasive cancer**
FS	Normal – CIN I	11	7	0
	CIN II – III, MIC	9	41	3
	Invasive cancer	0	2	5

Kappa (K) = 0.46 = Fair agreement

Table 7. Characteristics of invasive cancer patients with diagnostic error on frozen section

7.1 False Negative

No	Age	PAP	Satisfactory Colposcopy	ECC	Biopsy	FS	Procedure
1	37	Squamous Cell CA	No	Dysplastic fragment	Dysplastic fragment	MIC	RH
2	36	CIS	Yes	Not done	Questionable Invasive	MIC	RH
3	57	Not done	Yes	Dysplastic fragment	Not done	CIN III	RH

7.2 False Positive

No	Age	PAP	Satisfactory Colposcopy	ECC	Biopsy	FS	Procedure
1	41	CIN III	No	Not done	CIN III	MIC	SH
2	40	CIN III	Yes	Not done	CIN III	CIN III	SH

RH = radical hysterectomy, SH = simple hysterectomy
ECC = endocervical curettage, CIS = carconoma in situ
FS = fozen section diagnosis of cervical conization
PS = paraffin section diagnosis of cervical conization

DISCUSSION

In gynecological surgery, a FS is occasionally needed when a therapeutic decision must be made promptly such as in surgery for ovarian tumor[7,8], endometrial carcinoma[9], and carcinoma of the cervix.[10] FS evaluation of the cervical cone specimens helps establish the diagnosis of CIN and rules out invasive cancer so that a simple hysterectomy can be planned as the most suitable treatment for CIN, microinvasive cancer or other gynecological disease. Rapid diagnosis avoids a second anesthesia, decreases the incidence of infection from hysterectomy following conization, shortens the hospital stay, and reduces cost and emotional stress. However, FS has a risk of erroneous diagnosis due to the quality of the sections and the limited time in which to make the diagnosis. Previous reports that have studied the accuracy of FS in cervical cone specimens have showed a promising data. Dimusto JC[3] in 1970 reported 490 specimens from gynecological operation. The accuracy of the FS varied from 92% in cervical cone specimens to 96% for other genital organs. Gupta RK[4] in 1971 studied 150 cone specimens. Precise correlation was obtained in 92% when FS diagnoses of severe dysplasia and carcinoma in situ were included in the CIN III lesion category. Hoffman MS[5] studied 159 patients who planned to have hysterectomies immediately after cone biopsies with FS. The FS diagnoses were retrospectively compared with the permanent sections. Complete agreement were found in 87 cases (54.7%). In this study, final pathology identified 8 cases of invasive cancer which FS had misdiagnosed in one case. This patient was diagnosed with microinvasive cancer and had suboptimal surgical treatment. The sensitivity, specificity and positive and negative predictive values for the diagnosis of invasive cancer on FS were 89, 100, 100, and 99%, respectively.

Our study was the first study of FS diagnosis for gynecological surgery at Siriraj Hospital. We performed a prospective study so that FS diagnoses of cone specimens in this study did not have an impact on subsequent surgical treatment in this group of patient. Complete agreement between FS and final pathology diagnoses were found in only 47 patients because CIN lesions of the cervix usually have continuous disease which makes it difficult to give an exact diagnosis and also a likelihood of variation in the diagnosis between pathologists. Therefore, another criterion, based on the therapeutic implications of the diagnosis must be employed. When we divided the diagnoses into 3 groups, based on the same treatment plan (Table 6), the diagnoses of cone specimens made from FS and paraffin sections in this study showed fair agreement.

When immediate surgical intervention is needed after cone biopsy, it is important to be certain that invasive carcinoma exists or not. The misdiagnosis of invasive cancer on FS would result in inappropriate surgical intervention. In our study, the sensitivity for the diagnosis of invasive cancer on FS was only 62.5%. In the three cases that had invasive cancer on paraffin section, the FS diagnoses were MIC in two cases and CIN III in one case. Previous reports on the FS of a cone biopsy have also faced problems when MIC was diagnosed on FS and proceeding with definitive surgery based on the FS report alone is considered controversial.

CONCLUSION

Frozen section evaluation of cervical cone specimens carries a moderate degree of accuracy. The diagnosis of MIC on FS need a careful review of the permanent section before going on to definitive treatment.

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