

RESEARCH COMMUNICATION

Role of Frozen Sections in the Evaluation of Moderate to Severe Dysplasia during Uterine Cervix Conization

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Abstract

Background: The utility of frozen section examination (FSE) of cone specimens in evaluation of the resection margin status and in ruling out invasion in patients with high grade cervical intraepithelial neoplasia requires evaluation. **Methods:** Twenty patients with high grade cervical intraepithelial neoplasia who underwent conization biopsy and frozen section examination were studied in a prospective trial from March 2008 through September 2009. The results with permanent paraffin sections were compared with those of FSE. **Results:** Among the twenty cases, 15 (75%) had the same results in frozen and permanent sections of cone biopsy specimens. Among the other 5 patients, 2 had high grade cervical intraepithelial neoplasia in frozen sections and 2 showed a lower grade while only one case was found in which the FSE result was CIN3 while the permanent section showed invasive carcinoma which was of clinical importance and considered as significant. Paired sample t-testing showed no significant difference in the results of the two groups of frozen and permanent sections (P=0.716, CI=95%). **Conclusion:** Frozen section evaluation of cervical cone biopsy specimens in patients with a diagnosis of CIN 3 is accurate, efficient and cost-effective. Because of the great importance of missing even one case, further research is highly recommended on this controversial subject.

Keywords: Cervical cone biopsy - frozen section - high grade intraepithelial neoplasia

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Introduction

Cervical cancer ranks as the third most common gynecologic neoplasm in the United States, but in third world countries where limited health care resources exist, cervical carcinoma remains as a significant cause of mortality. To note, invasive cancer of the cervix is considered a preventable disease because it has a long preinvasive phase. (Berek, 2007) Patients with a biopsy diagnosis of CIN 2 or 3 have a less than 50% chance of regression and a significant chance of progression to in situ carcinoma, so treatment is usually recommended. All CIN 2 and 3 lesions require treatment. This recommendation is based on a Meta-analysis showing that CIN 2 progresses into CIS in 20% of cases and into invasive carcinoma in 5%. Progression of CIS into invasive carcinoma is also 5% (Berek, 2007). High-grade lesions bordering on invasive cancer are best managed by excision, which provides a tissue specimen for examination by the pathologist. A cold-knife cone biopsy under anesthesia in the operating room is indicated when cytology, colposcopy or directed punch biopsy suggests superficially invasive cancer.

A cervical cone biopsy is generally planned to be both diagnostic and therapeutic, and the technique is widely understood and practiced (Rock and Thompson, 2008).

Several studies have reported frozen section examination to be a reliable method in ruling out invasive cancer before hysterectomy. (Rouzier et al,2003) The aim of the present study was to determine the role of frozen section examination (FSE) of the cone specimen in the evaluation of the resection margin status and to rule out invasion in patients with high-grade cervical intraepithelial neoplasia.

Materials and Methods

This prospective study was performed from March 2008 through September 2009 at the gynecology-oncology ward of Qhaem educational hospital. 20 patients with biopsy-proven high-grade cervical intraepithelial neoplasia underwent a cervical cone biopsy procedure during which a frozen section was evaluated.

Inclusion criteria for this study were: 1) High-grade cervical intraepithelial neoplasia (CIN2 or CIN3) based on cervical biopsy; 2) Suspected microinvasion based on biopsy, colposcopy results; 3) The colposcopist being unable to rule out invasive carcinoma. Exclusion criteria were: 1) Stromal invasion over 5 mm; 2) Low grade cervical intraepithelial neoplasia (CIN1) based on cervical biopsy; 3) AGUS based on a Pap test; 4) Endocervical adenocarcinoma.

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The cone specimens were excised under general anesthesia in one piece and promptly sent for FSE, it was then opened longitudinally at the 12 o'clock position. The tissue was then divided into 12 segments and the fragments corresponding to the grossly suspicious area were selected for FSE by the pathologist. In the patient with a positive margin in FSE, secondary excision was performed. The results of the frozen sections were compared with those of the permanent sections by using the SPSS software for statistical analyses. For all statistical tests, a P-value less than 0.05 were considered significant.

Results

A total of 20 consecutive women with High-grade cervical intraepithelial neoplasia were available for analysis. Their mean (±SD) age was 39.3 years (range: 22-48yrs). Their mean (±SD) parity & gravidity was 3 (range: 0-8). All cases had previous cervical biopsies showing CIN2-3. Table 1 lists the frozen and final pathological

Table 1. Comparing Frozen and Final Pathology and Margin Status of Conization Specimen

| Final margin status | Margin involvement | Final pathology | Frozen section | Case (no) |
|---------------------|--------------------|--------------------|----------------|-----------|
| - | - | CIN III | CIN III | 1 |
| - | - | CIN III | CIN III | 2 |
| + | + | CIN III | CIN II | *3 |
| - | - | CIN II | CIN II | 4 |
| + | + | CIN III | CIN III | 5 |
| - | - | CIN II | CIN II | 6 |
| + | + | CIN II | CIN II | 7 |
| - | - | CIN III | CIN III | 8 |
| - | - | CIN I | CIN I | 9 |
| + | - | CIN I | normal | *10 |
| - | - | CIN II | CIN II | 11 |
| - | - | CIN I | CIN I | 12 |
| - | - | CIN II | CIN II | 13 |
| + | + | Invasive carcinoma | CIN III | *14 |
| + | + | CIN III | CIN III | 15 |
| - | - | CIN I | CIN I | 16 |
| - | - | CIN II | CIN II | 17 |
| - | + | normal | CIN III | *18 |
| - | - | CIN I | CIN I | 19 |
| - | - | CIN I | CIN II | *20 |

*Results between FSE& final examination were different.

diagnoses for the 20 patients (Table 1).

In the evaluation of cone margins by FSE and permanent section, 6 patients (30%) had a positive cone margin while 14(70%) had a negative one. The permanent section of margin status was not concordant in 2 cases (Table 2).

Among these twenty cases, 15(75%) had the same results in frozen and permanent sections of cone biopsy specimen, whereas in between the other 5, 2 had a higher grade of CIN in frozen section, 2 showed a lower grade and one was considered the same. Among these differences only one case was found in which the FSE result was CIN3 while permanent sections showed invasive carcinoma which was of clinical importance and considered as significant. The Paired Sample T-test showed no significant difference between the two groups of frozen and permanent section (P=0.716, CI=95%).

Due to small sample size we can not provide the negative and positive predictive values of frozen section evaluation.

Discussion

This study showed no significant difference between frozen and permanent section results in patients with high grade cervical intraepithelial neoplasia (CIN). It seems that frozen section evaluation of cervical cone biopsy is a reliable procedure in selected cases.

In order to evaluate the extent of an early cervical lesion and rule out invasion, cervical conization is required. Its disadvantage is that one must wait at least 24 hours for the diagnosis, during which the cervix becomes edematous, making subsequent surgery technically difficult. In addition, patients have an increased level of anxiety while waiting for the results (Gu and Lin, 2004).

In high-grade cervical intraepithelial neoplasia, frozen section examination can provide immediate and precise evaluation of the cone margin status. Incomplete excision of CIN ranges from 15% to 50% which presents a significant problem if follow-up is insufficient and unfortunately, the disease progresses into invasive carcinoma in many patients after an incomplete treatment for CIN. So far little attention has been paid to the role of FSE in cervical intraepithelial neoplasia. Some authors have demonstrated high concordance with the definitive paraffin exam in grading the lesion, but there are few studies regarding the evaluation by FSE of the resection margin status (Carvalho et al., 2001; Michy et al., 2008).

However, comparing the frozen section results with permanent sections showed no significant difference between their results and margin status of the specimen. This issue has caused controversy in similar studies. The

Table 2. Pathologic Diagnosis by Frozen Section Examination and Permanent Section

| Number | | Frozen section examination | Number | | Permanent section |
|--------|---|----------------------------|--------|---|--------------------|
| % | n | | % | n | |
| 20% | 4 | CIN I | 25% | 5 | CIN I |
| 40% | 8 | CIN II | 35% | 7 | CIN II |
| 35% | 7 | CIN III | 30% | 6 | CIN III |
| 5% | 1 | Normal | 5% | 1 | Normal |
| - | - | - | 5% | 1 | Invasive carcinoma |

only case which was identified as CIN III on frozen section and as invasive carcinoma on permanent section is of great importance as in such cases the frozen section result has a huge impact on the treatment plan, type of surgery and adjuvant modalities; after total surgery there is no need for radio or chemotherapy whereas after incomplete surgery such therapies are necessary. Taking into consideration that this fact is related to cervical cancer, malignancy prognosis, and the extent and complications of surgery, therefore it is a remarkable and promising issue. In this case, margin of cone specimen on FSE was involved. We suggest that the case with involvement margin on FSE, data is not enough for proper surgical management and we must consider permanent result for final surgery.

This issue has been mentioned in various articles, in which Rutledge and Ibanez (1962) found 3 cases with a more extensive disease in the uterine specimen in comparison to specimens taken through cone biopsy. In Dutra and Clement (1962) study in 28 out of 66 patients frozen sections performed on cone biopsy specimens did not give the required data for emergent surgery.

Kaufman et al (1965) conducted a study which included 210 patients. Discrepancies between frozen and permanent section diagnoses were described in only 14 cases, and none were major in that they could influence the proper surgical treatment of the patients. Although many studies have undervalued such discrepancies, there are also other researches which have shown that such differences between the results of frozen and permanent sections taken through conization have lead to over or under treatment.

In Hoffman et al (1993) study sensitivity, specificity, positive and negative predictive values for the diagnosis of invasive cancer on frozen sections were high. In the same study they reported only 1 patient whose frozen section diagnosis was microinvasion but permanent sections showed deeply invasive disease which was treated by suboptimal surgery. They also suggested that for certain groups of patients, such as those with mildly dysplastic cells identified on endocervical curettage and also those with an unsatisfactory colposcopy result, cone biopsy with frozen section might be unnecessary.

The discrepancy between the results of frozen sections and permanent specimens taken through conization tissue has always had various reasons which have been discussed in different studies. Dutra et al., (1962) have shown that the accumulation of malignancy in serial permanent sections have not been revealed in frozen samples. Also Kaufmann et al (1965) proved that in order to achieve a more precise diagnosis additional time is needed which is often due to the multiple sections taken from different surfaces. Fletcher et al (1985) also focused on careful orientation, technical improvements in the clarity of sections, and increasing experience of examiners as major factors in increasing the accuracy of frozen sections.

From what is known it seems that various factors can increase the accuracy level of frozen section results. Factors which attention should be paid to in any related study and which some have not been included in this article. These factors include: technical improvement in preparing tissue specimens and also increasing the number of specimens taken for frozen section through

conization, using more developed and upgraded machines for frozen sections, all specimen being observed by an experienced pathologist in gynecological pathologies and most importantly by a single pathologist. Relying on previous smears and biopsies taken by the gynecologist through colposcopy in order to find the best location for conization and expanding the amount of tissue as much as possible besides using the whole specimen in preparing the required samples for frozen section can play a major role.

What mainly matters is that coordination between the pathology and surgery units and also among gynecologists and pathologists themselves in preparing frozen sections can be greatly effective and helpful.

Dutra et al (1962) showed that the routine review of cervical smears before surgery has a high value for guiding surgeons in identifying the location of atypical cells in order to increase the accuracy of frozen sections. Woodford et al (1970) also suggested that frozen section results taken via cone biopsy can only be accepted as an indication for hysterectomy where the patient has a colposcopy-guided biopsy and a biopsy indicating CIN3. Hoffman et al (1993) in addition to emphasizing on the high accuracy of cone biopsy and its frozen section in making a precise decision about the disease, suggested that in a certain group of patients such as those with mild dysplastic cells in endocervical curettage also cases with non satisfying colposcopy results performing cone biopsy with frozen section seems unnecessary. Kaufman et al (1965) proved that if the specimen in frozen section did not demonstrate the extent of disease or was in contrast with the previous biopsy smears, surgery should be delayed in order to prepare and evaluate permanent sections.

Two other issues which have not been discussed in the current study include the positive effects of frozen section in making an exact decision for the patient's treatment and the complications caused by this method. As it was initially mentioned frozen section has been enlightened because it has many advantages in treating the patients and has been discussed in different studies.

FSE should be included in the treatment plan of women with a high risk of tumor involvement in resection margins and those who cannot participate in a thorough follow up (Behtash et al., 2007). Frozen section of conization specimen is effective and significantly reduces residual or recurrent high grade dysplasia. The finding improves the management of cervical pathology achieving immediate clear margins in most conizations. This is of great interest because high rates of patients are lost to follow up (Bretelle et al., 2003).

Giuntoli et al reported frozen section is reliable and simplified surgical approach in the evaluation of cold knife cone specimens with microinvasive SCC and utilizing frozen section diagnosis as the basis for definitive surgical approach did not negatively impact disease-free survival (Giuntoli et al 2003).

As it can be seen, different studies beside ours have proved the diagnostic accuracy and value of frozen section through conization in identifying intraepithelial cervical lesions; and despite many positive and negative cases in most studies, sub optimal and over treatments have always emphasized on using this method and expanding it in

gynecological operation; however, considering the major significance of cervical cancer and its pre-cervical lesions, legal issues and complications resulting from possible errors even in one case, this method has never been conclusively used for treatment and surgery follow-up of patients. To date, a meta-analysis or multi-center study seems essential in order to assess the cost-effectiveness of this technique in the management of cervical cancer and pre-cancerous lesions.

In conclusion, in high-grade cervical intraepithelial neoplasia, frozen section examination can provide immediate and precise evaluation of the cone margin status. Its clinical relevance has to be demonstrated in a multicenter study.

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