COMMENTARY

Intraoperative Frozen Sections for Assessment of Female Cancers

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Abstract

Frozen sections offer an important and helpful adjunct to intraoperative diagnosis and its use has greatly impacted on the care of gynecological oncology patients. Frozen section diagnosis is a reliable method for surgical management of gynecology oncology patients. Sensitivity of frozen section is acceptable and its specificity is almost perfect. False negative rate is low and false positive rate is negligible. Diagnostic problems can occur due to technical limitations especially in mucinous and borderline tumors. A good communication established between clinicians and pathologists is necessary to obtain more accurate results and to minimize the number of deferred cases.

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Introduction

Frozen sections are used in both gynecological and general surgical practice mainly to aid in the differentiation of benign from malignant disease. Preoperative evaluation of patients with an ovarian mass is usually made by clinical assessment, imaging studies and determination of serum levels of tumor markers .Since these methods have limited value for recognition of ovarian malignancy, this method can assist surgeon to tailor the extent of surgery (Geomini et al., 2005, Ilvan et al., 2005). This diagnostic procedure can reduce regret of doing incomplete surgery for malignant tumors (oophorectomy or cystectomy) or radical surgery for benign condition, in a majority of patients. Frozen section is sometimes referred to as intraoperative consultation, as its practice usually involves liaison between surgeon and gynaecological pathologist, rather than the mere provision of a histological diagnosis (Geomini et al., 2005).

Reviews from 1929 to date, consisting of over 10000 cases, indicate that the accuracy of frozen section ranges from 93 to 99% (Dankwa and Davies ,1985; Scurry and Sumithran, 1989; Rose et al.,1994; Wang et al., 2005).With the advent of sentinel node mapping, laparoscopic lymphadenecetomy and more conservative surgery for young women with ovarian masses desirous of fertility, there is a greater dependence on frozen sections to aid in the surgical management (Fanfani et al., 2004). The purpose of this review is outlining accuracy, role and limitations of frozen section in gynecology oncology.

Accuracy and Limitations of Frozen Sections

Frozen section diagnosis of a specimen may be benign, malignant,borderline or a deferred diagnosis. Accuracy of frozen section depends on a number of factors such as number of specimens processed and number of slices of specimen analyzed and nature of tissue. Of note is that the report of benign histology on frozen section is only a report of that percentage of tissue analyzed.

In a Meta analysis (Geomini et al., 2005), performing a systematic review of all registered articles between January 1966 and June 2003, comparing frozen section diagnosis of ovarian pathology to the final histopathological diagnosis, they found homogeneity among the reported specificity of frozen section diagnosis whereas estimates of the sensitivity of the test varied between 65 and 100%. One explanation for the imperfect sensitivity of frozen section diagnosis is size of tumor. It is not unlikely that malignancy is not detected in case the adnexal mass is large. Another explanation is tissue nature. Histological variation may occur more commonly in mucinous than in serous tumors making the accuracy of frozen section in mucinous tumors less predictable. In conclusion this metaanalysis has demonstrated that the accuracy of frozen section diagnosis for the assessment of the ovarian mass is good, with acceptable sensitivities for almost perfect specificities.

Deferred diagnosis can be due to technical difficulties like sampling errors because of lack of time, decreased pathological processing compared with paraffin diagnosis, inflammatory conditions, hemorrhage or necrosis and non representative tissue (Dankwa and Davies ,1985; Scurry and Sumithran, 1989; Rose et al.,1994; Wang et al., 2005). Another reason for deferring frozen section diagnosis can be lack of communication between pathologist and surgeon (Geomini et al., 2005).

While benefits of frozen section are widely publicized, the limitations prevent a routine frozen section service, especially in overburdened histopathological departments.

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In light of these limitations, protocols need to be developed for individual gynecological cancers taking into account the cost benefit ratio.

Breast Tumors

For many years open biopsy followed by frozen section and mastectomy, if interpreted as malignant, has been the standard approach to the breast nodules. The procedure is highly accurate; false positive is nearly zero and false negative is less than 1%.The main difficulty in frozen section is the evaluation of papillary lesions. Diagnosis of these lesions routinely is deferred to permanent section.

Current management of breast nodules is based on FNA or core biopsy for diagnosis and every effort is carried out to conserve the breast for cosmetic purpose, so lumpectomy is more common. Frozen sections have been used in evaluating margins. The specimen must be labeled by surgeon for proper orientation. Margins are stained with inks of different colors. In case of positive margin, immediate re-excision is recommended (Schnitt and Connolly, 1992). If re-excision will be postponed , the operator will hardly be able to recognize positive margin in the scar tissue of the previous biopsy. In evaluation of lumpectomy specimen, it has been showed that shaved margin is not comparable with standard margin resection (Guidi et al., 1997).

If margins are found to be close to the surgical line in permanent sections (the rim of uninvolved breast tissue< 1mm) and surgical excision line is negative , no further re-excision seems to be necessary. Approximately 5% of margin negative lumpectomies recur (Pittinger et al., 1994). Although this finding may reflect multi-centricity, owing the sampling limitation of frozen section, failure of sampling of residual tumor can not be excluded with certainty (Weber et al., 1997).

Ovarian Tumor

Preoperative evaluation of patients with an ovarian mass is usually made by imaging studies and determination of serum levels of tumor markers (Ilvan et al., 2005). Some authors have developed prediction models that combine patient characteristics, sonographic results and serum markers, however both formal prognostic models as well as clinical judgment of the adnexal mass have demonstrated to lack perfect diagnostic accuracy. (Geomini et al., 2005) Since these methods have limited value for recognition of ovarian malignancy, diagnosis and course of surgery are usually determined by frozen section examination during the operation (Ilvan et al., 2005).

Accuracy of frozen section in this era is important to tailor the extent of surgery. This is especially important for young women who has not completed child bearing. Conservative surgery has been recommended for stage Ia grade I epithelial ovarian tumors (Morice et al., 2002a; Morice et al., 2002b).

Also germ cell tumors can be managed by unilateral salpingoopherectomy even if they are in advanced stage (Moodley and Moudly, 2000; Molina and Hurteau, 2002). (As far as these tumors are extremely sensitive to chemotherapy).

Frozen section has been shown to be accurate in 92.7% of all cases with sensitivity for malignant and borderline tumors of 92% and 44%,respectively (Dankwa and Davies ,1985, Rose et al.,1994, Wang et al., 2005). The sensitivity for borderline tumors especially mucinous types is lower for reasons previously explained. (Slavutin and Rotterdam, 1979, Obiakor et al., 1991; da Cunha Bastos et al., 1983, Twaalfhoven et al., 1991; Ulbright et al., 1984). It has been suggested that one frozen section should be performed for every 10 cm diameter of tumor for very large mucinous ovarian tumors to improve accuracy .

The value of frozen section of ovarian tumors also lies in establishing whether an ovarian tumor is primary or metastastic. Approximately 7% of ovarian tumors represent metastases from primary neoplasms of other organs. While primary ovarian malignancy is treated with surgical staging, metastases from other site to the ovaries are managed by treating the primary tumor (Wang et al., 2005).

In a study by Sennur Ilvan et al (Ilvan et al., 2005) comprising 617 ovarian tumors overall accuracy of frozen section was 97%. Accuracy rates for benign, borderline and malignant tumors were 99%, 97% and 97% respectively. At intraoperative consultation 21 cases were diagnosed incorrectly. All of them were false negatives. There were no false positive cases. 13 cases with intraoperative diagnosis of borderline tumor were later classified as mucinous (11 cases) and serous (2 cases) carcinomas grade I. In 5 cases frozen section diagnosis of benign tumor turned to borderline mucinous (4cases) and serous (1 cases) in paraffin sections. In two cases immature grade I teratoma was misdiagnosed as mature teratoma and in 1 case metastatic tumor from stomach was misdiagnosed as fibroma in frozen examination (due to sparsity of signet ring cells) (Ilvan et al., 2005).

Endometrial Cancer

FIGO staging system for endometrial cancer is a surgically based system, taking into account riskfactors for nodal spread. The degree of differentiation and depth of myometrial invasion are regarded as two most important factors for nodal spread- Patients are spared from the toxic effects of adjuvant radiotherapy in the absence of risk factors and nodal spread, specially considering the evidence that adjuvant radical radiotherapy has not been shown to improve survival (Creutzberg et al., 2000). Sensitivity of determining > 50% myometrial invasion with naked-eye inspection intraoperatively (opening the uterine specimen) is only 72% (Franchi et al., 2000). For this reason intraoperative frozen section of the uterine specimen has been advocated to determine the presence of risk factors and therefore the need for extended staging (Kitchener, 2001; Kir G et al., 2004). Studies of frozen section evaluation of endometrial cancer to detect prognostic factors revealed that there is concordance with the final histology in 72-95% of cases (Fanning et al., 1990; Noumoff et al., 1991).

Lymphadenectomy can select out patients who can be spared from the toxic effects of radiotherapy. It has been shown that frozen section of the uterine specimen to determine endometrial histological type and risk factors, can correctly determine the need for node sampling in 94% of cases (Fanning et al., 1990; Noumoff et al., 1991, Kayikcioglu et al., 2002; Quinlivan et al., 2001).

Cervical Disease

Squamous intraepithelial lesions

Loop excision and cone biopsies are frequently indicated for cervicalsquamous intraepithelial lesions (SIL). However, positive margins occur frequently with a rate of up to 50% (Gardeil et al., 1997). Although there is a tendency to manage such patients conservatively, residual disease frequently persists after cone excision with positive margins (Felix et al., 1994, Weyl et al., 1996, Baldouf et al., 1998, Possover et al., 1998, Huang and Hwang, 1999, Plante and Roy, 2001, Vergote et al., 2002, Bretelle et al., 2003, Buist et al., 2003, Chung et al., 2003). Felix et al (Felix et al., 1994). (1994) documented that positive margins (in up to 90% of patients) is an established factor for treatment failure. Frozen section evaluation of the cone margins would therefore aid in deciding on the need for re-excision.

A retrospective study showed that the use of frozen section in this setting resulted in negative margins (Weyl et al., 1996). However, the impact on residual or recurrent disease was not reported. In a prospective study of frozen section evaluation of endocervical conization margins to predict the prevalence of recurrent or residual disease, it was found that residual or recurrent disease was evident in 1% and 12.6% in the group that did and did not have frozen sections performed, respectively. The re operation rate after conization for positive margins was 31%. The limitations of this study was a sensitivity of frozen section of 57.9% and difficulty of performing frozen section if the specimen was very small or fragmented.(Bretelle et al., 2003). In general, routine frozen section for LLETZ or cone biopsy to determine margin status is limited by: cautery artefact; problems in orientating the tissue; grading areas of SIL and the general large number of patients requiring colposcopic treatment services. In this context, frozen section may not be practical.

Invasive cervical cancer: Lymph node evaluation is crucial for prognosis and therapy of cervical cancer, although it is not an integral part of the FIGO staging. Lymph node removal and frozen section evaluation to determine the need for radical hysterectomy or, radiotherapy instead of radical surgery is well described. Laparoscopic lymph node removal and frozen section evaluation correctly identified all patients with positive nodes (Possover et al., 1998, Plante and Roy, 2001). In 15.4% of patients, the results of frozen section changed the primary therapy. Frozen section analysis of lymph nodes is performed as nodes are removed. Lymphadenectomy is abandoned when one of the nodes are positive on frozen section. Sentinel node mapping and frozen section is well described for cervical cancer (Vergote et al., 2002, Buist et al., 2003). In a study of 25 patients with early stage cervical cancer, it was found that with sentinel node identification, the false negative rate of frozen section was 11%. If radical hysterectomy is aborted in the case of positive sentinel nodes on frozen section, this could prevent potentially harmful and unnecessary surgery.(Chung et al., 2003). 10

Radical trachelectomy is described as conservative surgery for patients with early stage cervical cancer desirous of fertility (Smith et al., 1997, Herod and Shepherd , 2000). Frozen section of pelvic lymph nodes as well as the endocervical margins are performed to determine the need to abandon the procedure in the event of positive nodes or resect a bigger margin of endocervical tissue, respectively (Roy and Plante, 1998). Since micro-metastases in lymph nodes can be missed, a two- stage procedure may be an option consisting of node dissection and histology first, and then followed by radical trachelectomy, if the nodes are negative. In the evaluation of lymph node status for cervical cancer management, it was found that the sensitivity and specificity of frozen section to be 92.3% (Possover et al., 1998). The knowledge of intra-operative positive lymph node status changed the management in 15.4% of patients.

Similary, high rates have been reported in another study of frozen section evaluation of lymph node (Wang et al., 1998). The limitations of frozen section of sentinel node evaluation described for vulval tumors also relevant for cervical cancers. These limitations and the fact that sentinel node evaluation is considered investigational, render frozen section of sentinel nodes problematic for routine managemental.

Tumors of the Vulva

The risk of recurrences of vulvar carcinoma decreases and survival increases with increasing disease free margins. Also vulvar intraepithelial neoplasia as well as other types of neoplasia such as paget's disease usually require surgical excision with a margin of normal surrounding tissue as the best form of therapy. Frozen section may be useful to ensure that clear margins are obtained both laterally and in depth of the
Tumor (Rodolakis et al., 2000). 11

Tumors of vulva may be completely excised and submitted for frozensection to determine depth of invasion, histological type andlymphvascular space invasion for squamous cell cancers. Thisinformation is relevant for stage Ib disease (FIGO) as depth of invasion >1mm necessitates inguinofemoral lymph node dissection from a pathological point of view, the assessment of frozen section of vulvar lesions to determine the depth of invasion can be difficult, as there may be associated vulvar intraepithelial neoplasia with epithelial thickening making such assessment technically difficult. (Wilkinson et al., 1982, Hacker and Vander, 1993, Rodolakis et al., 2000).

Frozen sections for primary vulvar melanomas are also indicated todetermine the need for inguinofemoral lymphadenectomy, on the basis of primary tumor characteristics (Trimble, 1996). Sentinel node identification represents a new method of identifying draining nodes from a particular tumor. This procedure

may result in the omission of inguinofemoral lymphadenectomy in patients identified as not having sentinel node metastases (Moore et al., 2003).

In a study of 21 patients with invasive squamous cell carcinoma of the vulva, sentinel nodes were correctly identified in 100% and 61% of groin dissections using Tc-99 and isosulfan blue dye, respectively. Metastatic disease was present in nine of the groin dissections and in four of these dissections, the sentinel nodes were the only positive nodes. Frozen section assessment of sentinel nodes has been shown to be an accurate predictor of metastatic disease to the inguinal nodes. Although the accuracy of this technique is high, its safety remains to be established and there exists evidence that false- negative sentinel nodes can occur (Raspagliesi et al., 2003). Despite the purported benefits of sentinel node frozen section evaluation, the success of detecting micrometastases depends on multiple small serial sectioning of the nodes.

Conclusions

Frozen section accuracy is good with acceptable sensitivities for almost perfect specificities and is expected to reduce regret in a majority of cases. Although its role in management of gynecological tumors is described, its limitations need to be born in mind. Frozen section should be avoided if the volume of tissue available for biopsy is limited or the lesion is an obviously benign cyst.

All above studies reported difficulties in the diagnosis of borderline ovarian tumors for reasons stated previously. Although data may point to the benefit of frozen section, limitations of frozen section in ovarian neoplasms may be responsible for the lack of 100% accuracy compared with the final diagnosis (Wang et al.,1998; Canis et al., 2004). Most of the incompatible frozen section diagnoses occurred in ovarian lesions, especially mucinous ovarian tumors. This is a major limitation, especially if the ovarian tumor is very large, as it would be difficult to pinpoint the site for sampling leading to errors.

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