Role of Frozen Section in Gynecological Oncology

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Introduction

The purpose of performing an intraoperative frozen section is to provide the surgeon with information which enables him to perform the most adequate treatment. Proper communication between the pathologist and the surgeon is critical to ensure an accurate intraoperative report. Relevant clinical information should include previous history of malignancy and previous pathology reports, imaging studies, and serum markers, as well as the surgeon’s impression during the operation. Ovarian tumors represent the most common request site for intraoperative diagnosis followed by endometrium, cervix, and vulva (1). Frozen section accuracy in gynecological pathology is estimated to be between 91% and 97% (2).

An intraoperative consultation in gynecological pathology is indicated:
(a) to ensure the tissue sampled is adequate for diagnosis
(b) to distinguish between benign and malignant tumors
(c) to plan for appropriate ancillary studies
(d) to determine tumor spread
(e) to assess margins of resection
(f) to obtain frozen samples for molecular analyses

Frozen section is performed by embedding a fragment of tissue in Tissue-Tek OCT compound (Sakura Finetek, Torrance, CA) and cutting it in 5-10 μm sections. The sections obtained are fixed and stained; therefore, histological preparations are evaluated by a pathologist (3). One of the major problems in frozen section diagnosis is limitation of sampling. Because frozen section diagnosis should be a rapid procedure during surgery and the diagnosis is expected as soon as possible, there is not enough time to make as many sections as in permanent slides.

The main informations obtained in frozen section are:

- A correct diagnosis.
- Inadequate for diagnosis; i.e., more tissue needed.
- Defer the diagnosis to permanent sections e.g. Papillary lesions of the breast.

As expected, the experience of the pathologist performing the frozen section diagnosis will undoubtedly influence the diagnostic accuracy. Not less importantly, the quality of slides will also influence the diagnosis. The tissue used for frozen section usually has process artifact and cytologic atypia is not assessable. Cytologic preparations during intraoperative frozen section are useful since it takes shorter time to prepare them and can provide much better cytoplasmic details than tissue sections; also, cytologic smears are preserved without artifact as permanent sections. On the other hand, stromal infiltration can not be assessed in cytological smears.

Ovary

Ovarian tumors are highly heterogeneous. The diagnostic accuracy rates for frozen-section analysis are high for malignant and benign ovarian tumors, but the accuracy rates in borderline tumors remain relatively low (4). Most misdiagnoses on frozen sections occur in ovarian lesions, most commonly mucinous tumors because of their relative large size and its characteristic heterogeneity (5-6). In fact, ovarian mucinous adenocarcinomas may contain benign and borderline components within the same specimen; also, the surgeon should take into account that the tumor may contain invasive areas which have not been sampled; thus, preventing undertreatment.

The size of an adnexal mass sent for frozen section might also influence diagnostic accuracy (7-9). In ovarian tumors ≥10 cm in greatest diameter, a benign diagnosis at frozen section is less reliable than in patients with tumors <10 cm in diameter (9).

The Most Common Problems in Differential Diagnoses Include

- Distinction of primary versus metastatic carcinomas.
- Distinction of borderline serous or mucinous tumors from serous or mucinous carcinomas.
- Subclassification of a primary malignant tumor.

Distinction of Primary Versus Metastatic Carcinomas

Frozen section may help to distinguish primary versus metastatic tumors; although, in some cases only a tentative diagnosis can be submitted.

Before examining an ovarian tumor histologically, some clinical information may help to establish the correct diagnosis. First, some clinicopathological features such as bilaterality, size less than 10 cm, multinodular growth with solid and cystic areas, and extensive necrosis favor metastasis. On the other hand, unilaterality, presence of benign or borderline areas, and smooth ovarian surface, all suggests a primary ovarian carcinoma; nevertheless, none of the latter findings exclude metastases completely. Presence of mucin on the ovarian surface or elsewhere in the peritoneal cavity (pseudomyxoma peritonei) indicates that most likely the primary tumor is in the appendix.
Secondly, histological patterns consistent with metastases are infiltrative destructive invasion, multinodular growth, single cell invasion, and presence of signet ring cells. The finding of segmental necrosis of glands accompanied by “dirty” necrosis, and coexisting high and low grade nuclear features suggests a metastatic origin particularly in colon cancer and gastric carcinoma of intestinal type (10). However, none of the macroscopic or histological features listed above are unequivocally diagnostic.

**Distinction Between Borderline Serous or Mucinous Tumors and Serous or Mucinous Adenocarcinomas**

Surface epithelial ovarian neoplasms are the most common ovarian tumors. Distinction between adenocarcinoma and borderline tumors may be difficult, especially in serous or mucinous tumors, and these tumors require extensive sampling for proper diagnosis (Figure 1).

In all these cases, a clinical approach may help the pathologist to reach the correct diagnosis, since patients with borderline tumors are 10-15 years younger than patients with carcinoma. On gross examination, most of these tumors are multicystic and may have papillary excrescences; however, borderline tumors usually lack areas of necrosis and hemorrhage which are consistently present in carcinomas. Thus, in cystic tumors, gross examination of all cavities is mandatory. Solid areas or confluent papillary areas should be taken for frozen section.

A recent study of 166 patients reported a sensitivity and positive predictive value for the intraoperative diagnosis of ovarian borderline tumor to be 81.6% and 89.9%, respectively. Whereas the diagnosis was confirmed in 75% of cases, in 8.4% it was upgraded from borderline to carcinoma (11). In frozen section, the only reliable pathological criterion for a diagnosis of adenocarcinoma is the presence of stromal invasion. Cytological atypia is difficult to evaluate since frozen artifact is often observed; thus, diagnosis of tumors with only focal atypia should be deferred.

Peritoneal implants (so called because they are associated with much better prognosis than conventional metastases) are found more frequently in patients with borderline tumors than in those which do not. A major problem encountered rarely by gynecological pathologists is distinguishing invasive versus non-invasive implants of serous borderline tumors on frozen section. Invasive implants contain a higher number of epithelial cells and exhibit a destructively invasive pattern.

Mucinous carcinomas with not obviously invasive (expansile) pattern may be confused with mucinous borderline tumors. Attention should be paid to architectural and nuclear features (cribriform pattern and severe nuclear atypia), both characteristic features of intraepithelial carcinoma. However, finding of these changes in an extension greater than 10 sq mm, favors the diagnosis of confluent or not obviously invasive adenocarcinoma. Nevertheless, the prognosis of borderline mucinous tumor with intraepithelial carcinoma is similar to that of invasive mucinous adenocarcinoma with expansile growth.

Subclassification of other types of ovarian carcinomas may be difficult in some cases:

- Endometrioid carcinomas may mimic sex cord tumors, particularly granulosa or sertoli cell tumors; therefore, the finding of mucinous glands with squamous differentiation is helpful.
- Clear cell carcinoma may be misdiagnosed as serous carcinoma; nevertheless, as long as both are high grade tumors, the distinction may not be important.
- In sex cord-stromal tumors, distinguishing cellular mitotically active fibromas from fibrosarcomas and granulosa cell tumors is important. The finding of a variegated cut surface with necrosis and high grade cytological features favors the diagnosis of fibrosarcoma. Some adult granulosa cell tumors may have a fibromatous background, but the characteristic cellular features (coffee bean-like nuclei) of these tumors are the clue for the correct diagnosis.

- In germ cell tumors, distinction between dysgerminoma and diffuse large B-cell lymphoma, yolk sac tumors, and juvenile granulosa cell tumors are the main issues. Dysgerminoma and large cell lymphoma may share similar cytologic features, but involvement of the fallopian tube suggests the diagnosis of lymphoma. Yolk sac tumors and juvenile granulosa cell tumors occur in the same subset of patients. Both tumors may be hemorrhagic and necrotic. The presence of hyaline globules, a more primitive appearance, and a microcystic pattern suggests the diagnosis of yolk sac tumor.

- The gross appearance of a mature cystic teratoma (dermoid cyst) is diagnostic in most cases. Usually, mature cystic teratomas contain neuroectodermal, endodermal, and mesodermal elements. Sometimes the cyst is lined by respiratory epithelium or glial tissue. Immature or embryonic tissues may be found within areas ranging from 1-21 mm; however, contrary to solid immature teratomas,

Figure 1. Frozen section of serous borderline tumor of the ovary.
such finding does not change the favorable prognosis of dermoid cysts with microscopic foci of immature neural tissue. Variegated or necrotic nodules in a dermoid cyst may reveal a second malignancy, such as squamous cell carcinoma.

**Hemorrhagic Ovarian Tumor**

A hemorrhagic ovarian tumor may represent a difficult issue. The three most common conditions associated with hemorrhagic mass in the ovary are: torsion, granulosa cell tumor, and choriocarcinoma. Differential diagnosis between these entities may be difficult and accurate clinical information and extensive sampling is needed. During an intraoperative consultation, multiple sections of the lesion may help to distinguish them; i.e., an extensive hemorrhagic granulosa cell tumor may contain yellow-tan areas typically associated with this tumor. Nevertheless, in most cases the diagnosis will be deferred to permanent sections.

**Pregnancy Related Lesions**

Lesions in pregnant and puerperal women may be difficult to diagnose; there are lesions such as pregnancy luteoma, hiperreactio luteinalis, solitary luteinized follicle cyst of pregnancy and puerperium, and ectopic decidua.

- **Pregnancy luteomas** are bilateral multiple brown to hemorrhagic nodules in the surface of the ovary. These nodules are composed of masses of luteinized cells which may show mitotic activity. These lesions may be confused with oxyphilic malignancies, typically carcinomas, melanomas and steroid cell tumors.

- **Hiperreactio luteinalis** is characterized macroscopically by bilateral enlargement of both ovaries; the cysts are characterized by a watery fluid and the walls are thin. Microscopic evaluation of the wall reveals luteinized cells.

- **A large solitary luteinized follicle cyst of pregnancy and puerperium** may be confused with a granulosa cell tumor. The history of pregnancy of puerperium and the absence of virilization are the clues for the correct diagnosis.

- **Ectopic decidua** may form nodules in the surface of the ovary or peritoneum simulating a metastatic tumor; however the bland cytologic characteristics of the cells and the history of pregnancy help in the diagnosis.

**Uterus**

**Cervix**

The use of frozen section in cervical specimens should be limited. It may be used to confirm the diagnosis of infiltrating carcinoma, but in most cases diagnosis is established prior to the surgery. Evaluation of cone biopsies have been done for more than 40 years with consistent and accurate results, but this technique is time consuming and the current opinion is that it should be done in permanent sections to avoid freezing artifact and loss of diagnostic material (12).

Vaginal radical trachelectomy is a new alternative surgical procedure to radical hysterectomy for early invasive cervical carcinoma in women who desire to preserve fertility. The specimen includes the cervix, parametria, and the vaginal cuff. The margins of the specimen are evaluated intraoperatively by frozen section. If the tumor margins are positive in frozen section either wider tumor margins or hysterectomy should be performed. There are two different approaches for performing sections of trachelectomy, but there is no defined consensus. Transverse or perpendicular sections may be taken. The most common problem in diagnosis is to distinguish adenocarcinoma in situ from tubal or tuboendometrioid metaplasia, atypical metaplasia, and even normal endometrioid glands.

**Myometrium**

Evaluation of a smooth muscle tumor is a common request for frozen section. Macroscopic evaluation of the specimen will give the diagnosis in most cases. If the gross appearance of the tumor shows abnormal features, namely irregular margins, soft, fleshy consistency, tan to yellow or areas of hemorrhage or necrosis, representative sections of the tumor should be taken. Often only one section is not sufficient to establish a diagnosis and, therefore, a diagnosis of smooth muscle tumor with atypical features should be submitted.

**Endometrium**

The main indication of frozen section in endometrial carcinomas is to identify those patients with risk of extraterine spread of the tumor; i.e., lymph node metastases (Figure 2). The identification of risk factors permits the selection of patients who could potentially benefit from surgical staging with lymphadenectomy. It is generally agreed that low-risk patients are those with disease confined to the uterine corpus, with a histologic grade 1 or 2, endometrioid histologic subtype, and less than 50% myometrial invasion. However, the 4% to 5% rate of positive lymph nodes in this low-risk group is still considered clinically relevant and there is not total agreement (13).

Figure 2. Frozen section of myometrial invasion in endometrial carcinoma.
Lymph Node Evaluation

In breast carcinomas the main indication for pathologic evaluation of lymph nodes is the examination of the sentinel lymph node; however, this procedure might be used in other localizations, such as cervix and vulva. Nevertheless, recent evidence speaks against the evaluation of sentinel lymph node by frozen section in vulva and cervix. The aim of performing frozen section of sentinel lymph node is to confirm intraoperatively the presence of metastasis and, therefore, perform lymphadenectomy in the patients with carcinomas of the breast and vulva. Evaluation of lymph nodes may be done either by making a frozen section or cytologic smears of the cut surface. However subsequent sectioning and immunohistochemical studies make change the diagnosis. False negatives diagnoses are found in approximately in 2 to 5% of cases (14).

References