Intraoperative Consultation in Gynecologic Pathology

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Context.—Gynecologic specimens are commonly submitted for intraoperative consultation, primarily to confirm the presence and histologic type of malignancy, as well as to determine the adequacy of resection by examining the surgical margins.

Objective.—To review and discuss the application, indications, contraindications, and limitations of intraoperative consultation regarding gynecologic specimens, as well as the causes of false-positive or false-negative frozen section results.

Data Sources.—Review of the pertinent literature and the authors’ expertise and experience.

Gynecologic specimens are frequently submitted for intraoperative consultation, primarily to guide the scope of surgery. At The Methodist Hospital, Houston, Tex, approximately 10% of all cases submitted for intraoperative consultation or frozen section analysis are gynecologic specimens. Of these, 4% are from ovarian lesions, 4% are from uterine lesions (including the cervix), and 2% are from vulvar and vaginal samples. The extent or type of surgery often depends on the results of such examinations. Intraoperative consultation is primarily performed to confirm the presence and histologic type of malignancy, as well as to determine the adequacy of resection by examining the surgical margins. Other factors that affect surgery include the status of the pelvic lymph nodes, the presence of peritoneal spread, and the differentiation of primary from metastatic malignant neoplasms.

The accuracy of frozen section analysis in general surgical practice is reported to vary from 91.5% to 97.4%, but it is lower in mesenchymal tumors, in which mitotic counts are critical, and in ovarian mucinous tumors, in which extensive sampling is often needed. In such instances, it is imperative to defer the diagnosis until additional examination is feasible.

This review will consider the application, indications, contraindications, and limitations of intraoperative consultation in gynecologic specimens, as well as the causes of false-positive or false-negative frozen section results. Each organ will be discussed separately, because the consultation plays a different role in each. Information on how to handle gross specimens will be considered as it relates to frozen section analysis and gross consultation carried out in the operating room suite or in the frozen section laboratory.

Conclusions.—In most instances, intraoperative consultation regarding gynecologic specimens accurately determines the type of malignancy, the status of the resection margins or the lymph nodes, and the extent and depth of involvement by a tumor. Although the pathologist and the surgeon must be aware of the limitations, the use of intraoperative consultation represents a highly sensitive and specific technique that can play a critical role in the management of gynecologic disease.

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VULVA

Almost all intraoperative consultations related to vulvar disease are for evaluation of malignant or premalignant lesions. Except for unusual circumstances, biopsy specimens for benign diseases such as vulvar dystrophy or cystic lesions should not be submitted for frozen section analysis. In these conditions, results of frozen section analysis will not change the immediate management of the patient, and freezing artifact often interferes with the ability to reach a diagnosis on subsequent permanent section analysis.

Vulvar Specimens

Specimens from the vulva may range from wide local excision for the treatment of premalignant lesions or minimally invasive cancer (Figure 1) to partial or total vulvectomy for the treatment of invasive squamous cell carcinoma. A portion of the vagina and extensions of the perineum around the anus may also be included. The depth of resection may be variable. “Skinning” vulvectomy includes the epidermis, with a variable amount of dermis and subcutaneous tissue. Radical vulvectomy involves resection to the superficial aponeurosis of the urogenital diaphragm or the pubic peristeum (Figure 2).

Inguinal node dissection can be included in the vulvar resection or submitted separately. Vulvar lymphatics drain primarily into the superficial and deep (femoral) inguinal nodes, and node dissection for carcinoma usually includes both levels of nodes. The superficial inguinal nodes are the most common sites of metastasis. Nodal involvement generally proceeds in a stepwise fashion from the superficial to the deep inguinal nodes and then to the pelvic...
Malignant Neoplasms

Cancer of the vulva is a rare neoplasm, occurring predominantly in postmenopausal women and comprising 3% to 5% of all gynecologic malignant neoplasms. Most malignant neoplasms arise within the squamous epithelium, most commonly on the labia minora, clitoris, fourchette, perineal body, or medial aspect of the labia majora. Rare malignant neoplasms that may be encountered include basal cell carcinoma, malignant melanoma, adenocarcinomas arising from Bartholin glands or sweat glands, and Paget disease. Soft tissue sarcomas, such as leiomyosarcomas, angiosarcomas, liposarcomas, and embryonal rhabdomyosarcoma, are rarely seen in the vulva. In addition, metastatic tumors from other genital organs can appear in the vulvar skin or mucosa.3
Squamous Cell Carcinoma.—Squamous cell carcinoma and its intraepithelial precursors are the most common malignant neoplasms of the vulva. Such invasive lesions account for about 90% of all vulvar cancers and about 5% of all gynecologic cancers.4

Vulvar Intraepithelial Neoplasia.—Approximately 60% of patients with invasive squamous cell carcinoma have adjacent or multifocal vulvar intraepithelial neoplasia (VIN). In patients with superficially invasive carcinomas, the frequency of adjacent VIN approaches 85%.3 Frozen section analysis should not be performed to evaluate grades of dysplasia. However, it is necessary for assessment of the margins for evaluation of the presence of any high-grade VIN, in view of the increased risk of recurrence and progression to invasive disease (Figure 3). A thorough evaluation of all margins in large vulvar resections is only feasible on permanent section analysis. When dealing with these large resections, frozen sections of grossly or clinically suspicious margins can expedite the results and hence the surgical procedure. Multifocal high-grade dysplasias often present a challenge, in view of the difficulty in obtaining a clear resection margin. Foci of unsuspected invasion may occur in up to 20% of patients with VIN.5

In evaluating the presence of invasive carcinoma and its depth of invasion, involvement of adnexal structures by VIN and tangential sectioning are the 2 main causes of misinterpreted invasion (Figure 4). Evidence of a residual VIN and tangential sectioning are the 2 main causes of misinterpreted invasion (Figure 4). Evidence of a residual VIN and tangential sectioning are the 2 main causes of misinterpreted invasion (Figure 4). Evidence of a residual VIN and tangential sectioning are the 2 main causes of misinterpreted invasion (Figure 4). Evidence of a residual VIN and tangential sectioning are the 2 main causes of misinterpreted invasion (Figure 4). Evidence of a residual VIN and tangential sectioning are the 2 main causes of misinterpreted invasion (Figure 4). Evidence of a residual VIN and tangential sectioning are the 2 main causes of misinterpreted invasion (Figure 4). Evidence of a residual VIN and tangential sectioning are the 2 main causes of misinterpreted invasion (Figure 4). Evidence of a residual VIN and tangential sectioning are the 2 main causes of misinterpreted invasion (Figure 4). Evidence of a residual VIN and tangential sectioning are the 2 main causes of misinterpreted invasion (Figure 4). Evidence of a residual VIN and tangential sectioning are the 2 main causes of misinterpreted invasion (Figure 4). Evidence of a residual VIN and tangential sectioning are the 2 main causes of misinterpreted invasion (Figure 4). Evidence of a residual VIN and tangential sectioning are the 2 main causes of misinterpreted invasion (Figure 4). Evidence of a residual VIN and tangential sectioning are the 2 main causes of misinterpreted invasion (Figure 4). Evidence of a residual VIN and tangential sectioning are the 2 main causes of misinterpreted invasion (Figure 4). Evidence of a residual VIN and tangential sectioning are the 2 main causes of misinterpreted invasion (Figure 4). Evidence of a residual VIN and tangential sectioning are the 2 main causes of misinterpreted invasion (Figure 4). Evidence of a residual VIN and tangential sectioning are the 2 main causes of misinterpreted invasion (Figure 4).

The initial evaluation of any vulvar excision must include orientation of the specimen as if viewed in situ. Orientation by the surgeon is critical if the adequacy of resection is to be assessed. Photographs, diagrams, and drawings to demonstrate the margins of resection and the extent of the lesion are helpful. Deep margins should be inked, and different colors should be used for vaginal tissue or any margin toward the anal canal. Margins should be preferably evaluated with sections that are perpendicular rather than parallel to the surgical margin, unless this will result in a large number of sections and an undue delay in surgery. The size of the lesion, maximum depth of invasion, and involvement of margins should be noted.

Lymph Nodes.—Lymph node dissection is usually indicated in patients with more than 1 mm of stromal invasion. Surgical removal of the deep inguinal or femoral lymph nodes is usually performed in conjunction with superficial inguinal lymphadenectomy. In most cases, these samples are submitted independently from the vulvar specimen. Frozen section analysis is not usually requested for node dissections because the results rarely have an effect on the immediate operative management. In the rare instances in which an intraoperative consultation on a node is required, the initial evaluation must include a count of the lymph nodes identified and gross inspection of the cut surface. Touch imprint cytology of the cut surface may aid in the initial evaluation of metastatic disease. Areas of firmness or variation in color should raise suspicion of involvement by metastatic disease, and such areas should be selected for frozen section analysis if necessary. Frozen section diagnosis, however, can be difficult in cases in which only a few atypical cells are noted, and if immediate management is not altered by the status of the lymph nodes, the evaluation should be deferred until permanent sections are examined.

Other Neoplasms.—Some neoplasms other than the classic squamous cancers present special issues for the pathologist. These include verrucous carcinoma, basal cell carcinoma, malignant melanoma, extramammary Paget disease, and primary adenocarcinoma.

Verrucous Carcinoma.—This uncommon, well-differentiated squamous cell carcinoma is locally invasive, but it rarely metastasizes. Consequently, treatment by a wide local excision is usually curative. Local recurrences can occur, especially if the tumor has been incompletely resected. Intraoperative evaluation of these cases includes gross inspection of the lesion and its relationship to the margins of resection. Frozen section analysis of grossly or clinically suspicious margins can be performed. Verrucous carcinomas should be differentiated from condyloma acuminatum and warty invasive squamous cell carcinoma. When lesions are large and exhibit deep penetration and keratinization at the base, the diagnosis of verrucous carcinoma rather than condyloma should be considered. Invasive warty squamous cell carcinomas have a significant degree of atypia and an infiltrative border, unlike the minimal cytologic atypia and mostly pushing borders that characterize verrucous carcinomas (Figure 5).

Basal Cell Carcinoma.—Only 2% to 3% of vulvar carcinomas are of the basal cell type, and they typically occur in older patients. Basal cell carcinomas are cured by wide local excisions. When these tumors lack typical histologic features, such as peripheral palisading, their differentiation from Merckel cell tumors, poorly differentiated squamous cell carcinomas, and metastatic small cell carcinomas may require immunostaining of permanent sections.

Malignant Melanoma.—This is the second most common vulvar malignancy, usually involving the labia majora or the labia minora. The main treatment modality is surgical resection (Figure 1). Sentinel lymph node evaluation is sometimes performed for tumors that are 0.1 cm or greater in thickness or for melanomas with a Clark level of IV or deeper, with the decision regarding lymphadenectomy based on the status of the sentinel lymph node.6 As in other skin sites, frozen section evaluation of margins in pigmented lesions or known melanomas is not recommended because of the difficulty of interpretation associated with freezing artifact and the ensuing cytoplasmic vacuolization. These artifactual changes can be misinterpreted as involvement by atypical melanocytes in the frozen section material and in the permanent sections of previously frozen tissue (Figure 6).

Extramammary Paget Disease.—This uncommon disease has been reported to be associated with an underlying adenocarcinoma of the vulva in 20% of patients, thus necessitating radical vulvectomy.7 Patients with only superficial Paget disease, on the other hand, are treated by local excision with evaluation of margins by frozen section analysis. The differential diagnosis of pagetoid VIN versus superficial spreading malignant melanoma can be difficult.
In pagetoid VIN, the background squamous cells are dysplastic, while they appear less atypical in Paget disease or in superficial spreading melanoma (Figure 7). In difficult cases, application of a modified rapid periodic acid-Schiff stain can be useful in identifying the characteristic Paget cells with their vacuoles that stain positive.8

**Primary Adenocarcinoma.**—Most vulvar adenocarcinomas are deep lesions, arising within Bartholin glands or skin appendages. Approximately 20% to 30% are associated with metastatic disease to the inguinofemoral lymph nodes at the time of the initial diagnosis. Treatment includes a complete surgical resection and inguinal lymphadenectomy. Some benign tumors and ulcers can resemble adenocarcinoma clinically. These include papillary hidradenoma, rare cases of adenosis, hyperplasia of Bartholin glands, ectopic breast tissue, and endometriosis. Frozen section interpretation can be difficult, but features that suggest an adenocarcinoma include irregular infiltrating margins, desmoplastic response of the stroma, cytologic atypia, mitotic activity, and necrosis of neoplastic cells.

**VAGINA**

Most vaginal malignant neoplasms (80%–90%) are metastatic, involving the vagina by direct extension and by lymphatic or hematogenous routes. They occur most commonly on the posterior wall of the upper third of the vagina. Primary vaginal malignant neoplasms are rare, representing 1% to 2% of all gynecologic cancers. Of these primary tumors, around 85% are squamous cell carcinomas, with the remainder being adenocarcinomas and other rare lesions such as clear cell carcinomas and sarcomas.

**Invasive Squamous Cell Carcinoma**

This tumor arises more commonly in the upper third of the vagina and can appear as a polypoid, ulcerating, or flat lesion. Radical surgery can be considered only for a stage I lesion. Ultraradical or exenterative surgery with removal of the bladder or rectum is not usually considered for an early lesion, as these patients do just as well with radiotherapy. The treatment varies with the location of the tumor. For stage I lesions involving the upper third of the vagina, surgical treatment consists of radical hysterecto-
my, upper vaginectomy, and pelvic lymph node dissection. For lesions involving the lower third of the vagina, radical vulvovaginectomy and bilateral inguinal lymph node dissection are performed. Determination of the extent of the tumor to the subvaginal tissue (stage II), to the pelvic wall (stage III), or beyond the true pelvis (stage IV) is essential, because tumor stage is the most important prognostic factor. The lower margins of resection can be submitted for frozen section evaluation. Gross examination of the tumor, its dimensions, its relationship to any attached organs, and the distance to the surgical margins should be noted. The exposed soft tissues that surround the uterus and vagina are inked. In cases in which the bladder or rectum is included in the resection (anterior or posterior exenteration), additional margins to be evaluated include urethral, ureteral, proximal, and distal rectal margins.

**Adenocarcinoma**

Vaginal adenocarcinomas, including the clear cell variant, are uncommon malignant neoplasms. In many cases, adenocarcinomas represent tumor extension from the cervix or endometrium, and careful examination often reveals the primary lesion. Clear cell adenocarcinoma, a neoplasm that may be associated with in utero diethylstilbestrol exposure, is rarely encountered (Figure 8). The vagina can also be involved by several benign lesions that may mimic adenocarcinomas. These include adenosis, fallopian tube prolapse, microglandular hyperplasia, endometriosis, and Arias-Stella reaction. These lesions in general have circumscribed borders and exhibit only minimal cytologic atypia. Inflammatory reactive cytologic atypia, reactive stroma, or architectural distortion can present greater diagnostic difficulty.

**Other Lesions**

Sarcomas, malignant mixed müllerian tumors, and aggressive angiomyxomas may be encountered in the vagina. The diagnosis in most of these cases is established by prior biopsies; the role of frozen section analysis is usually limited to evaluation of resection margins. Biopsy specimens of the vaginal mucosa following radiotherapy for cervical carcinoma, as well as granulation tissue and postoperative spindle cell nodules that develop after vaginal or abdominal hysterectomies, should not be submitted for frozen section evaluation. The marked reactive cytologic atypia and therapy effect may result in a false-positive diagnosis, particularly when freezing artifact hinders accurate evaluation of the nuclear and cytoplasmic features.

**UTERUS**

Uterine samples submitted for intraoperative consultation can be from the cervix, the endometrium, or the entire uterus, with or without the uterine adnexa. Methods of handling these specimens depend on the reason for the surgical procedure and the questions that need to be addressed by the intraoperative consultation. Regarding the cervix, almost all consultations are related to cervical carcinoma, the sixth most common solid malignant neoplasm among women in the United States. When a lesion from the uterine corpus is sent for consultation, it is usually for assessment of an endometrial malignant neoplasm or a smooth muscle neoplasm. Some specimens are submitted for gross consultation only, but most require frozen section examination to assess the presence and extent of malignant invasion in the cervix or the corpus and to evaluate the status of the pelvic lymph nodes.

**CERVICAL SPECIMENS**

In approximately 70% of patients with cervical cancer, the disease is limited to the cervix. Patients with preinvasive disease (International Federation of Gynecology and Obstetrics stage 0) and patients with superficial invasion (stage IA) who desire to preserve fertility may be treated with limited procedures such as a loop electrosurgical excision procedure or cone biopsy of the cervix. Advanced stages require more extensive surgical resections to include the uterine body and, often, the fallopian tubes and ovaries.

**Cervical Punch Biopsy**

This diagnostic office procedure is often performed under colposcopic guidance, and specimens are rarely submitted for intraoperative consultation. If a biopsy specimen is submitted, the pathologist should resist the temptation to freeze the sample to satisfy the curiosity of the surgeon. Freezing artifact may prohibit the establishment of a definitive diagnosis on the permanent paraffin sections; small lesions can be destroyed while attempting to ‘face’ the block, and assessment of margins in such poorly oriented specimens is not feasible.

**Loop Electrosurgical Excision Procedure**

This procedure allows the resection of the transformation zone and nearby abnormal tissue. Many specimens are accompanied by a ‘‘top hat,’’ a separate excision of the endocervical margin at the top of the original loop electrosurgical excision procedure specimen, to ensure a clear endocervical margin. If a consultation is indicated, the transformation zone and top hat specimens are treated in a similar manner to a cervical cone specimen, described in the next paragraph.

**Cervical Cone Biopsy**

This procedure implies a conical excision of the cervical transformation zone and canal, performed with a laser or a surgical blade (‘‘cold knife’’ excision). The height and size of the cone vary with the perceived extent of the lesion. By convention, the ectocervix is described as a clock face, with the most superior midpoint of the anterior lip designated as the 12 o’clock position. This point is usually oriented by the surgeon with a suture. After orientation of the specimen in the laboratory, the lateral and endocervical mucosal margins are inked using different colors, and the specimen is opened along the 12 o’clock line. Radial sections are obtained and designated as to their clockface orientation, so that each section includes the squamo-columnar junction (Figure 9). Irregularly shaped cone biopsy specimens, often occurring in parous women, are sometimes difficult to cut at the 3 o’clock and 9 o’clock positions, and these sections might only include muscle and soft tissues, without any mucosa.

Evaluation of cervical cones by frozen section analysis should be limited to those cases in which the immediate operative management depends on the findings. In patients with carcinoma in situ or extensive high-grade dysplasia who will undergo hysterectomy after biopsy, an examination is performed to determine the extent of disease, to exclude the presence of any invasion and evaluate its depth, and to assess any involvement of the endocervical
or lateral margins of excision. Evaluation of the degree of dysplasia by frozen section analysis is not recommended because freezing artifact may hinder assessment of the nuclear sizes and cause crowding. This results in a higher degree (≈27%) of discrepancy with permanent section findings and may lead to unnecessary hysterectomies.9

Frozen section analysis of conization specimens followed by immediate hysterectomy offers the advantage of a single procedure, compared with a delay of 6 to 8 weeks between conization and hysterectomy. Although frozen section analysis of cone biopsy specimens is fairly accurate in detecting invasive disease, the procedure has limitations. Numerous blocks and slides are prepared for each case, and a considerable amount of time is involved while the patient is on the operating room table. One way of speeding up the process is to put 2 pieces of tissue in each block, thus decreasing the number of slides and the duration of the evaluation roughly by 50% (Figure 10). Such
a technique, however, carries the risk of losing a focal lesion in the first piece while trying to face the block to expose the second piece. Islands of squamous metaplasia may mimic stromal invasion. These islands, however, are well defined, are close to the glands and surface, and are cytologically bland. Despite these limitations, frozen section evaluation of cone biopsy specimens is accurate, enabling the surgeon to make an immediate decision about definitive therapy. When used as treatment for carcinoma in situ and the uterus is to be spared, evaluation of the endocervical margin at the top of the cone becomes critical. Unfortunately, the diathermy artifactual changes in this area can interfere with such essential evaluation.

Simple hysterectomy after cone biopsy is performed in patients with carcinoma in situ who no longer want to conceive, in those with microinvasion (invasion depth ≤5 mm and lateral extent ≤7 mm), and in those in whom the endocervical margin is involved. Handling these hysterectomy specimens will be discussed in the next section.

**Tumors of the Cervix**

The most common tumor of the cervix is squamous cell carcinoma, followed by adenocarcinoma and neuroendocrine tumors. Uncommon carcinomas include glassy cell, transitional cell, mesonephric, adenoid basal, and adenoid cystic carcinomas. Melanomas, sarcomas, lymphomas or leukemias, and metastatic tumors may also be encountered in the cervix.

**Squamous Cell Carcinoma.**—Squamous cell carcinoma accounts for 80% to 90% of invasive cervical cancers. These neoplasms can have an exophytic or endophytic pattern of growth, with endophytic patterns commonly infiltrating the surrounding tissues. Microscopically, the tumors can be of large cell nonkeratinizing, keratinizing, or small cell type. Invasive carcinomas often show variation in their pattern of growth, cell type, and degree of cellular differentiation. Tumor stage, which primarily relates to tumor size and extent, is considered to be the most important prognostic indicator.

**Adenocarcinoma.**—The most common adenocarcinomas are endocervical and intestinal types. In addition, some neoplasms show endometrioid differentiation. The latter type raises the issue of determining the site of origin from the endocervix or the endometrium. Examination of the junction of the endocervical canal and the lower uterine segment becomes critical in this determination. Invasive adenocarcinomas can be exophytic and polyloid or endophytic and deeply infiltrative. Other less frequent types of adenocarcinomas include adenosquamous carcinoma, minimal deviation adenocarcinoma, villoglandular adenocarcinoma, clear cell adenocarcinoma, and serous adenocarcinoma. From a practical standpoint, differentiating these types is not an issue that should be settled at the time of surgery. Curettage or biopsy specimens should be discouraged if the immediate surgical management is not going to be affected. The curiosity of the surgeon or the anxiety of the patient are not valid reasons to freeze these specimens, because there is a risk of misinterpretation due to freezing artifact or of loss of valuable material while facing the block, hindering the ability to render a definitive diagnosis on permanent section analysis.

**Hysterectomy Specimens**

Hysterectomies are performed for a variety of reasons. Common indications include uterine prolapse, leiomyomas, endometrial hyperplasia, and cervical and endometrial cancers. The specimen submitted to the frozen section laboratory and its handling depend on the indication for the operation and the specific questions to be addressed.

**Hysterectomy for Cervical Cancer.**—There are several variations of abdominal hysterectomy for the management of cervical carcinoma. *Total (extrafascial) abdominal hysterectomy* (class I hysterectomy) consists of resection of the uterus and a small cuff of the upper vagina. It is usually performed for patients with preinvasive or microinvasive disease, if childbearing has been completed. In *modified radical or extended hysterectomy* (class II hysterectomy), the uterine body, cervix, and upper vagina are resected, to-
together with the medial paracervical tissues (Figure 13). This procedure is performed in patients with 3 to 5 mm of invasion and for small lesions that do not distort the anatomy. Radical abdominal hysterectomy with bilateral pelvic lymphadenectomy (class III hysterectomy) includes hysterectomy with resection of the parametrial tissues to the pelvic wall, a vaginal cuff of 2 to 3 cm, and bilateral pelvic lymphadenectomy. Extended radical hysterectomies (class IV or class V) are rarely performed because patients with large tumors that encroach on the ureter or parametrium are best treated with radiotherapy. Total pelvic exenterations are performed in cases of recurrent cervical carcinomas. Such specimens include the urinary bladder, uterus with attached adnexa, vagina, and rectum. In cases in which the urinary bladder is included, the resection is classified as an anterior exenteration, while if the rectum is included, the term posterior exenteration is used.3 Gross examination in these cases must include inspection of the urethral, ureteral, vaginal, and rectal margins.

The uterus is oriented using specific landmarks: the round ligaments are most anterior, and the ovaries are most posterior. The peritoneum extends further inferiorly along the posterior aspect of the uterus, to cover the upper part of the vagina. Inspection of the cervix follows, with description of any gross lesions. The paracervical tissue, anterior and posterior soft tissue margins, and vaginal cuff margin are inked. The paracervical tissue is shaved and submitted in its entirety. The uterus is bivalved, and the extent of cervical involvement or any extension to the vagina or lower uterine segment should be noted. If the extent of the lesion is not grossly evident, the entire cervix should be submitted for permanent section analysis in the same manner as a cone biopsy specimen.

**Pelvic Lymph Node Dissection.**—Evaluation of the pelvic lymph nodes, including the right and left internal iliac, obturator, pelvic, and para-aortic nodes, is performed for staging of cervical carcinomas. Metastatic carcinoma is encountered in approximately 9% of women with clinically staged early invasive cervical cancer and most frequently involves the obturator lymph nodes.11 If metastatic disease is detected by frozen section analysis, resection of the uterus is usually not performed, and alternative therapeutic modalities are used.

Cytologic imprints of the cut surface of the lymph nodes may provide a sensitive, specific, and time-efficient method to diagnose nodal metastases (Figure 14). In the case of squamous cell carcinoma, the technique has been reported to have a sensitivity and a specificity of 90% and 100%, respectively.12 Diagnostic difficulties may arise in cases in which only a few atypical or suspicious cells are encountered. Occasionally, frozen section analysis may miss a microscopic subcapsular deposit. To minimize that risk, it is advisable to cut the lymph node at 2 different levels, both of which can be placed on the same glass slide. If more than 1 node is placed in the same block, they should be carefully placed on the same plane and cut to...
expose all nodes adequately. Benign processes, including sinus histiocytosis, squamous or transitional metaplasia of the peritoneum, intranodal ectopic decidua, or hyperplasia of mesothelial cells within the lymph node, can be confused with metastatic squamous cell carcinoma. Similarly, benign glandular inclusions of the müllerian type and endosalpingiosis can be encountered when sampling the pelvic lymph nodes and should be differentiated from metastatic adenocarcinoma (Figure 15). The distinction is usually not difficult because of the malignant cytologic features in adenocarcinomas.

**Hysterectomy for Endometrial Cancer.**—Specimens from hysterectomies performed for endometrial adenocarcinoma are often submitted for intraoperative consultation to determine the depth of myometrial invasion; the diagnosis of adenocarcinoma has been usually established by a previous curettage. The sensitivity of frozen section diagnosis in assessing deep myometrial invasion is 85%, and its specificity is 100%. Other tumor characteristics accurately determined by frozen section analysis include the tumor grade and the presence of cervical invasion. Accurate assessment of these parameters allows the surgeon to correctly determine the need for lymph node sampling, a procedure that adds to the duration and morbidity of the operation. Most endometrial adenocarcinomas are of the endometrioid type. Identification of the type by frozen section analysis is not difficult, except in some less common types such as papillary serous adenocarcinoma.

On gross examination, endometrial adenocarcinomas can appear as sessile or polypoid masses and can be focal or diffuse lesions (Figure 16). Serial transverse section analysis of the uterine corpus and the lower uterine segment is performed. The greatest depth of tumor invasion into the myometrium must be measured. In addition, the total myometrial thickness and the distance from the tumor to the serosal surface must be recorded. The serosa should be inked at the area of deepest myometrial invasion. Determination of the depth of invasion by frozen section analysis is a simple and accurate method that correlates well with permanent section analysis. If frozen section analysis shows that the lesion is confined to the endometrium or that it is a grade I endometrial carcinoma that invades less than one third of the myometrium, lymphadenectomy may be omitted. In all other cases, surgical staging that includes lymph node sampling is performed to avoid undertreatment.

**Resections for Other Uterine Lesions.**—Hysterectomies or more limited resections are frequently used in the management of benign diseases of the uterus. The lesions that are often encountered in the frozen section room include leiomyomas, benign endometrial polyps, adenomyomas, and, less commonly, adenofibroma or other benign tumors. In addition, polypoid lesions may be sarcomas or adenosarcomas.

**Myomectomy.**—Leiomyomas are the most common uterine tumor, occurring in approximately 75% of hysterectomy specimens. Myomectomy specimens are sometimes submitted for frozen section evaluation if the clinical manifestations are alarming, such as a rapid increase in the size, and if hysterectomy is to be avoided for clinical considerations such as desire to maintain fertility. However, frozen section evaluation of cellular smooth muscle neoplasms may be difficult. Accurate mitotic counts are often necessary for a definitive diagnosis and for assessment of the potential for aggressive behavior. Unfortunately, artifacts, including apoptosis, can simulate mitotic figures. In addition, benign smooth muscle tumors may be mitotically active, and unless there is significant atypia and/or areas of coagulative necrosis, the differentiation of leiomyomas from leiomyosarcomas may be difficult (Figure 17).

On gross examination, it is important to note if the tumor is circumscribed as opposed to having poorly demarcated margins. If the serosa is included, the external surface should be inked. The specimen is serially sectioned to evaluate any evidence of necrosis, hemorrhage, myxoid degeneration, or infarction areas. Sections for frozen evaluation should include any of the grossly suspicious areas that have lost the characteristic whorled pattern of a benign leiomyoma. A definitive diagnosis is often deferred until permanent section analysis, in which extensive sampling with accurate mitotic counts and evaluation of other histologic parameters can be performed. If there is any unusual pattern or histologic feature, the temporary diagnosis of smooth muscle tumor of uncertain malignant potential is rendered, and the definitive diagnosis awaits permanent section analysis.

**Hysterectomy for Sarcomas.**—Examination of specimens from hysterectomies for sarcomas is similar to resections for carcinomas. These tumors have a high tendency to spread by hematogenous routes, and examination of ovarian and other resected vascular structures at the time of consultation is important. In smooth muscle neoplasms, the sampling of areas where there is necrosis and loss of
Figure 17. Symplastic leiomyoma with bizarre hyperchromatic smooth muscle cells.

Figure 18. Leiomyosarcoma with a cut surface demonstrating a tan-white, fleshy appearance, with the loss of an interlacing fascicular pattern.

Figure 19. Low-grade endometrial stromal sarcoma with islands of pink soft tissue raised above the surface of the remainder of the myometrium.

an interlacing fascicular pattern is important, because this increases the chance of detecting a focus of malignancy at the time of frozen section analysis (Figure 18). Low-grade endometrial stromal sarcomas produce islands of pink soft tissue that are raised above the surface of the remainder of the myometrium and have a propensity to spread as “wormlike” structures within lymphatics (Figures 19 and 20). High-grade endometrial sarcomas tend to be bulky and show areas of necrosis and hemorrhage, often with a partially intact endometrial surface.

Ovary and Fallopian Tube

Ovarian cancer is the fourth most frequent cause of cancer death in women and accounts for 5% of all cancer deaths, with a death rate that exceeds the combined rates of cervical and endometrial carcinoma. Adnexal masses include a variety of benign and malignant neoplasms of the ovary and, much less frequently, of the fallopian tube. Handling of such specimens should be tailored to the suspected tumor type and size, as well as the clinical presentation. In particular, emphasis should be given to answering the surgeon’s questions that will have an effect on the extent and type of surgical procedure. Intraoperative consultation by frozen section analysis is an important diagnostic tool to determine the nature of an ovarian neoplasm, because many tumors present as adnexal masses or as peritoneal nodules. Diagnosis by frozen section analysis has a sensitivity of 86%, specificity close to 100%, positive predictive value of 100%, and negative predictive value of 95% for malignancy.16

Ovarian and Tubal Specimens

Specimens submitted to the frozen section laboratory from ovarian and other adnexal masses comprise the following forms.

Cystectomy.—These are some of the most common specimens received for consultation. Cysts are resected and submitted for consultation to determine their nature and subsequent planning of the surgery (Figure 21). Cystectomies are usually performed for benign-appearing lesions or in patients who wish to preserve fertility, particularly because many benign tumors, such as teratomas, occur in the third and fourth decades of life.

Ovarian Biopsy.—This is not a common method of sampling the ovary and usually entails a biopsy of a lesion that is encountered on the ovarian surface during surgery, to ensure its benign nature.

Oophorectomy and Salpingo-oophorectomy.—Resection of the ovary is usually associated with resection of the adjoining fallopian tube. This is one of the most common types of ovarian samples submitted for intraoperative consultation. Handling these specimens depends on the size and type of lesion suspected, as discussed later.

Omental and Peritoneal Biopsies.—Nodules discovered at the time of surgery on the omental surface or the serosa of the intestine are often submitted for frozen sec-
Figure 20. Low-grade endometrial stromal sarcoma in which tumor cells resemble normal proliferative endometrial stroma. Rounded nests of tumor cells infiltrate the myometrium and into the lymphatics (hematoxylin-eosin, original magnification ×10).

Figure 21. Multilocular benign mucinous tumor.

Figure 22. Thecoma, representing a solid well-circumscribed tumor with a tan-yellow cut surface.

Figure 23. Mixed germ cell tumor in which a cut surface shows variation among areas. Sampling should include solid areas, foci of necrosis, and any areas of hemorrhage.

Figure 24. Krukenberg tumor with bilateral asymmetrical enlargement of the ovaries.

Figure 25. Krukenberg tumor with signet ring cells associated with plump spindled stromal cells (hematoxylin-eosin, original magnification ×20).
tion analysis. The results of such microscopic examination often determine the course of action and the feasibility of successful resection of a neoplasm. Examination of touch imprint cytology can provide a quick and reliable method to detect malignant cells in such specimens.

**Lymph Node Sampling.**—The pelvic and abdominal nodes may be a part of the surgical procedure when an ovarian cancer is suspected, and such samples may be submitted for frozen section evaluation. Trimming the adipose tissue adjacent to the node may help minimize the technical difficulty in cutting thin and complete sections, in view of the difficulty in freezing fat. The subcapsular sinuses should be carefully examined for microscopic deposits.

**Pelvic, Peritoneal, and Gutter Lavages.**—Although these cytologic specimens are routinely submitted from patients with ovarian malignant neoplasms, they require time for processing and are rarely submitted for immediate evaluation.

**Benign and Nonneoplastic Lesions**

The most common neoplasms that present as adnexal masses are surface epithelial tumors. However, several nonneoplastic tumorlike conditions should be considered in the differential diagnosis of ovarian neoplasms by frozen section analysis. Some benign lesions such as ectopic pregnancy and ovarian torsion may require urgent surgical exploration. Endometriotic cysts, oophoritis, stromal hyperplasia, hyperthecosis, and massive ovarian edema can be clinically worrisome, because they may present as adnexal masses at the time of laparoscopy or gynecologic examination. Frozen section analysis plays an important role in clarifying the nature of these lesions and in differentiating them from malignant neoplasms.

**Primary Ovarian Neoplasms**

**Surface Epithelial Tumors.**—Epithelial neoplasms are the most commonly encountered forms of ovarian tumors. The single most common malignancy of the ovary is serous adenocarcinoma, while its benign counterpart is considered by some as the most common benign ovarian tumor.

Oophorectomies for cystic ovarian neoplasms and ovarian cystectomies are examined in a similar fashion. The external surface of the ovary and fallopian tube is examined for any areas of excrescences, disruption, or adhesions. If the lesion is cystic, the cyst is opened, and the quality and color of the fluid are documented. Cystic neoplasms can be unilocular or multilocular lesions. In general, unilocular cysts with smooth cyst walls are benign. Any areas of thickening of the cyst wall, complex architecture, granularity, intraluminal or surface papillary projections, hemorrhage, or necrosis must be noted. If solid areas are encountered, the size of these areas should be documented, as well as their color and the presence of hemorrhage or necrosis. Sampling for frozen section analysis must include any solid or thickened cyst wall areas that are grossly suspicious. Epithelial tumors of serous, mucinous, endometrioid, clear cell, and transitional cell types often show transition from benign to borderline to malignant areas, thus facilitating the classification of the tumor. This is especially valuable in poorly differentiated carcinomas. Valuable information can also be obtained by using ancillary intraoperative cytologic techniques, including fine-needle aspiration biopsy and touch imprint cytology, because cytologic preparations provide clear nuclear and cytoplasmic details without freezing artifact.

The most problematic cases are borderline and low-grade mucinous tumors. In these cases, the diagnosis can be deferred until a more thorough sampling can be performed on permanent sections. Extensive necrosis, hemorrhage, or inflammation can also obscure the frozen section examination, limiting the diagnostic ability. In cases of borderline malignancy, the cyst is usually lined, at least in part, by lush papillary projections. Extensive sampling of such areas is required to rule out invasion. If invasion is not clearly seen on frozen section analysis, the lesion may be classified as borderline, with a clear statement in the pathology report and an understanding that invasive carcinoma must be ruled out on permanent section analysis when more extensive sampling can be performed.

Surgeons often elect to stage the tumor in cases of borderline malignancy to avoid the need for a second operation if invasion is documented in the final pathology report. If frank malignancy is present and the tumor is apparently confined to the ovary or pelvis, thorough surgical staging is also performed. The staging procedure includes collection of any free fluid or peritoneal washings, omentectomy, multiple biopsies of the peritoneum and diaphragm, and sampling of the pelvic and para-aortic lymph nodes. Adequate staging is crucial because survival of patients with epithelial ovarian cancer is directly correlated with tumor stage. After a rigorous staging laparotomy, many patients initially classified as having localized disease will be upstaged.

**Sex Cord and Stromal Tumors.**—Sex cord and stromal tumors account for approximately 7% to 10% of all ovarian neoplasms. Some of these tumors are hormonally active, accounting for 90% of all functional ovarian neoplasms. Most sex cord and stromal tumors are unilateral lesions, confined to the ovary, and are of low potential for aggressive behavior and metastasis. In younger patients, unilateral oophorectomy is the recommended procedure. In patients in whom childbearing is complete, total abdominal hysterectomy and bilateral salpingo-oophorectomy are recommended. On gross examination, the tumor surface is solid or partially cystic, and in steroid-producing tumors there is a characteristic brown, orange, or yellow color, reflecting their lipid-rich content. Staining of a frozen section with oil red O often demonstrates the presence of small intracytoplasmic lipid droplets. In estrogen-producing tumors, careful examination of the endometrium should be performed to rule out any associated endometrial hyperplasia or carcinoma.

**Granulosa Cell Tumors.**—These tumors are the most commonly encountered sex cord neoplasms. Most patients present with hyperestrogenic manifestations. A variety of admixed histologic patterns are encountered, including solid, trabecular, insular, follicular, watered silk, and gyriform. In the microfollicular pattern, rosette structures reminiscent of Call-Exner bodies can be encountered, facilitating the diagnosis. Intraoperative cytologic preparations are beneficial to demonstrate the characteristic granulosa cells with scant cytoplasm, uniform and angular to oval, often grooved, nuclei. Tumors occurring in children and juveniles are often cystic and hemorrhagic. Although they may demonstrate frequent mitotic figures, almost all of these tumors do not behave aggressively. Any temptation to predict the behavior of granulosa cell tumors on the basis of frozen section analysis should be resisted, be-
cause such behavior cannot be linked to specific histologic parameters, even after additional sampling for permanent section analysis.

Fibromas and Thecomas.—These are the most commonly encountered sex cord and stromal tumors, accounting for approximately 4% of all ovarian tumors, and are generally benign (Figure 22). Large lesions require extensive sampling to rule out malignant transformation, characterized by increased cellularity, nuclear atypia, mitotic activity, hemorrhage, or necrosis. Thecomas typically occur in postmenopausal women and are often associated with estrogenic changes. Twenty percent of postmenopausal patients with thecomas have an associated endometrial adenocarcinoma or, rarely, a malignant mixed müllerian tumor or endometrial stromal sarcoma.4

Sertoli-Leydig Cell Tumors.—Tumors of Sertoli-Leydig cell differentiation are uncommon, accounting for less than 0.2% of all ovarian tumors. Most frequently, they occur in younger women (mean age, 25 years) and may present with virilization. Well-differentiated Sertoli-Leydig cell tumors are characterized by a predominantly tubular pattern. The tubules are lined by Sertoli cells and are separated by fibrous bands and a variable number of Leydig cells. Moderately or poorly differentiated tumors often exhibit a variety of patterns, including cordlike structures or a diffuse spindle sarcoma-like pattern. Similar to granulosa cell tumors, histomorphology does not correlate with the behavior of Sertoli-Leydig neoplasms.

Ovarian Germ Cell Neoplasms.—Mature cystic teratoma, or dermoid cyst, often consists of a cyst containing sebaceous material and hair. The contents of the cyst should be removed and the cyst wall inspected for architectural complexity or solid (Rokitansky) nodules. Mature tissues derived from the 3 germ cell layers are often encountered, particularly ectodermal tissues. Solid areas of thyroid follicles are the major component in cases of strumal ovarii. Malignant transformation is more common when a patient is older than 40 years, and it is often of a squamous cell carcinoma type.18 Therefore, generous sampling, particularly from solid areas, is recommended in patients older than 40 years.

Immature teratomas are characterized by a disorderly mixture of tissues derived from all 3 cell layers. A definitive diagnosis should be deferred until permanent section analysis, because extensive sampling is required to identify foci of immature neural tissue or other immature mesenchymal tissues.

Dysgerminomas typically appear as solid, lobulated tan-pink masses. These tumors usually occur in the second or third decade of life and are bilateral in about 15% of cases. Histologic examination reveals a homogeneous population of large cells with clear cytoplasm, distinct cell boundaries, central round nuclei, and stroma that contains a variable amount of lymphocytes. Differentiation from large cell lymphomas is usually feasible without the need for flow cytometry or immunohistochemistry, but if necessary, a sample should be submitted for flow cytometry and cytogenetic analysis at the time of frozen section analysis.

In view of the sensitivity of dysgerminomas to chemotherapy, unilateral salpingo-oophorectomy with preservation of the contralateral ovary and uterus is sufficient in most patients who desire to preserve fertility, even in the presence of metastatic disease. If fertility need not be preserved, total abdominal hysterectomy and bilateral salpingo-oophorectomy are performed.17 In addition to the involved ovary, the contralateral ovary must be examined in all cases for any obvious gross lesions, capsular rupture, or adhesions.

Other malignant germ cell tumors may involve the ovary, comprising less than 10% of all malignant ovarian germ cell tumors, seen most often in women younger than 30 years. Examples include pure yolk sac tumor, embryonal carcinoma, and choriocarcinoma. More than 1 element may be encountered in some neoplasms, and such tumors are classified as mixed germ cell tumors. These tend to be large and have a variable appearance depending on the components of the lesion. Extensive sampling is necessary and should include any gross areas of hemorrhage or necrosis to identify possible immature neuroepithelium or malignant transformation in immature teratoma, as well as any yolk sac tumor, embryonal carcinoma, or choriocarcinoma components (Figure 23). If dysgerminoma is a component, there is about a 5% to 10% likelihood of contralateral involvement. Inspection and biopsy of the contralateral ovary might be indicated. Poor prognostic indicators include large tumors (>10 cm) and the presence of a major component (>).10% of embryonal carcinoma, choriocarcinoma, or high-grade teratoma.19

Metastatic Tumors

The ovaries are the organs most commonly involved by metastatic disease in the female genital tract. Metastases to the ovary account for 6% to 7% of ovarian cancer found at surgery. The mechanism of spread may include lymphatic spread (from the genitourinary tract, colon, stomach, and breast), hematogenous dissemination, transmural spread from tumors in other areas, or direct extension from tumors arising in the pelvic organs.

Intraoperative consultation may be sought when an adnexal mass is encountered by the surgeon in the absence of a history of malignancy. Occasionally, the primary site, such as in the stomach, may be small and difficult to detect. Gross and microscopic findings that suggest metastatic disease include bilaterality, extensive surface involvement, prominent lymphovascular invasion, and a multinodular growth pattern. Other suggestive features may include small tumors confined to the medulla and tumors that spare the follicular structures, as well as a lack of evidence of transition from a benign component of a cyst wall to a malignant neoplasm. Adequate clinical history and evaluation for an extraovarian primary tumor are important, especially in cases of poorly differentiated malignant neoplasms. In difficult cases, immunohistochemical staining on permanent sections may help determine the source of the neoplasm.

Krukenberg tumor accounts for 3% to 8% of all carcinomas that are metastatic to the ovaries. More than 80% are bilateral. Most Krukenberg tumors originate from the stomach; other sources include the breast, colon, appendix, pancreas, gallbladder, biliary tract, urinary bladder, and cervix. The ovaries usually have a solid, asymmetrically enlarged bosselated appearance, with a firm white or yellow cut surface. The overall gross architecture preserves the ovarian shape (Figure 24). The tumor is predominantly composed of signet ring cells, which may be sparse and easily missed on frozen section analysis. It is associated with plump spindled stromal cells, which can mask the infiltrating neoplastic cells and erroneously lead to the di-
agnosis of mesenchymal tumor (Figure 25). A prominent tubular pattern may resemble lipid-rich Sertoli cell tumors but is uncommon. Although benign signet ring cell tumors can be encountered, these are exceptionally rare and are mucin-negative, unlike true Krukenberg tumors.

**Fallopian Tube Tumors**

Primary neoplasms of the fallopian tube are rare, accounting for only 0.3% of all gynecologic malignant neoplasms. Secondary involvement, primarily by spread from ovarian or endometrial carcinomas, is much more common.

Almost all primary fallopian tube neoplasms are malignant. These carcinomas arise from mullerian epithelium, are similar to ovarian carcinomas, can be of serous, endometrioid type and, rarely, can demonstrate transitional, clear cell, or squamous cell differentiation. In cases of primary fallopian tube carcinoma, the main tumor mass must involve the fallopian tube; the uterus and ovaries must be free of carcinoma or contain significantly less tumor than the fallopian tube. Evidence of transition from benign fallopian tube epithelium to borderline malignancy to malignant neoplasm is helpful in determining the primary site, although the same transition may be seen in some cases of mucosal spread from uterine cancer. Benign conditions that should be considered in the differential diagnosis include salpingitis, endometriosis, tubal pregnancy, tubal torsion, and rare tumors such as adenomatoid tumors, metastatic papillary tumor, and leiomyomas.

**CONCLUSIONS**

Intraoperative consultation should be requested only if the results will affect immediate patient management. It is essential that the surgeon be aware of the use and limitations of intraoperative consultation. An accurate interpretation of frozen section results depends on many critical steps that may be overlooked. The surgeon must provide adequate orientation of the specimen, details of the clinical setting, and specific questions to be addressed.

In most instances, intraoperative consultation involving gynecologic specimens is accurate regarding determination of the type of malignancy, the status of the resection margins or the lymph nodes, and the extent and depth of involvement by a tumor. The role of intraoperative consultation is limited in cases that require an accurate mitotic count, determination of the degree of dysplasia, or extensive sampling to establish the diagnosis. In these cases, a definitive diagnosis must be deferred until evaluation of permanent sections. In addition, the use of frozen section analysis in some situations may in fact alter cytologic or architectural features that are necessary for establishing an accurate diagnosis. With this limitation in mind, the use of intraoperative consultation remains a highly sensitive and specific technique that plays a critical role in the management of gynecologic disease.

**References**