Frozen Section Diagnosis of Ovarian Epithelial Tumors

Diagnostic Pearls and Pitfalls

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Patients presenting with a newly discovered pelvic/adnexal mass often undergo diagnostic laparoscopy/laparotomy without a definitive preoperative diagnosis because of low sensitivity and specificity of imaging studies and serum markers and lack of accessible sites for a tissue biopsy or cytology sampling. Intraoperative frozen section evaluation plays a critical role in guiding the type and extent of surgery in such cases, yet little has changed in the diagnostic process in the past several decades in this clinical setting. Unlike other areas of diagnostic surgical pathology, where there are a rapidly growing number of ancillary tests available (eg, immunohistochemical stains, molecular studies), frozen section evaluation continues to rely solely on 3 traditional diagnostic elements: the patient’s clinical history (including imaging results), gross examination, and microscopic evaluation of morphologic features. It may be especially challenging for new generations of pathologists to bridge the widening gap between the limited clinical and morphologic assessment of specimens on frozen section and the final precision diagnosis using the help of state-of-the-art ancillary studies.

This review focuses on the frozen section diagnostic challenges and pitfalls of ovarian epithelial tumors, the most commonly encountered group of ovarian tumors in the frozen section laboratory and in routine pathology practice. Ovarian epithelial tumors also represent one of the most problematic areas on frozen section, and significantly contribute to the reported low frozen section diagnostic accuracy and sensitivity rates among ovarian neoplasms. Specifically, mucinous ovarian tumors and borderline tumors in general have been found to have a high false-negative frozen section diagnosis rate, likely, at least in part, because of tumor heterogeneity and nonrepresentative sampling. Ovarian carcinomas can show a wide range of morphologic features, some of which overlap with other ovarian neoplasms of sex cord-stromal or germ cell origin, adding to the complexity of frozen section interpretation.

In addition, the ovaries are commonly involved by metastatic carcinomas, accounting for up to 15% of ovarian malignancies in Western countries. Whenever possible, the frozen section diagnosis should be specific as for the favored primary tumor site, Müllerian or metastatic, especially in patients with a clinical history of or suspicion for another primary. Comprehensive surgical staging, including total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, retroperitoneal lymph node dissection, and peritoneal biopsies, is typically performed for primary
CLINICAL HISTORY, INTRAOPERATIVE GROSS EXAMINATION, AND SAMPLING

The 3 cornerstones of intraoperative consultation are the patient’s clinical history, gross examination, and microscopic morphologic interpretation. Gathering clinical history and reviewing results of diagnostic imaging studies may be time consuming and may be limited by time pressure during frozen section. Ideally, this information could be prepared in advance in anticipation of a frozen section based on the operating room schedule. It would also allow for retrieving relevant prior biopsy slides from the pathology archives, an invaluable resource in patients with history of prior malignancy for comparison of morphologic features during frozen section.

The most important gross parameters of ovarian epithelial tumors are size, laterality (unilateral versus bilateral), and the appearance of cut surface (cystic versus solid). The vast majority of completely cystic ovarian tumors with a smooth lining and without solid nodules are histologically benign, although benign epithelial tumors may also have a partially or entirely solid cut surface, for example, adenofibromas or benign Brenner tumors. Gross presence of intracystic papillary growth should be noted; it is usually scattered and firm in cystadenofibromas, compared with the more abundant, soft, and friable intraluminal projections of serous borderline tumors (Figure 1, A and B). Conversely, malignant ovarian epithelial tumors tend to be solid, at least partially, and often show a soft, fleshy, and heterogeneous cut surface with necrosis and hemorrhage (Figure 1, C and D). Bilaterality is common in serous ovarian tumors, both benign and malignant; however, bilateral mucinous tumors should always raise suspicion for a metastasis. In addition, tumor size may also be a helpful parameter in the differential diagnosis between primary versus metastatic mucinous carcinoma. The gross quality of cyst contents, serous versus mucoid, may provide a clue to the tumor histologic subtype, but not infrequently it may be misleading, and the tumor classification ultimately has to be based on the overall microscopic appearance and cytoplasmic features of the lining epithelial cells.

Sampling for intraoperative frozen section should be directed toward any gross intracystic papillary or solid areas. Mucinous tumors are notoriously heterogeneous; thus, multiple frozen section blocks may be necessary, especially for larger tumors. Frozen section of the contralateral ovary, even if it appears grossly unremarkable, may be helpful in identifying bilateral involvement. If only one of the ovaries is sent for frozen section, information about the gross appearance of the other ovary may be sought from the surgeon.

MUCINOUS TUMORS—PRIMARY OVARIAN VERSUS METASTATIC

One of the most common diagnostic challenges on frozen sections is distinguishing a primary ovarian mucinous tumor from a metastatic mucinous adenocarcinoma. Metastatic low-grade appendiceal mucinous neoplasm, especially when evaluated in isolation, without the appendix, may be deceptively bland on frozen sections, mimicking an ovarian mucinous cystadenoma or mucinous borderline tumor. Low-grade appendiceal mucinous neoplasm typically occurs in patients around 50 years of age, and the presenting clinical symptoms—pelvic mass/pain and increased abdominal girth—are often related to the ovarian metastases and pseudomyxoma peritonei. The average size of the ovarian metastasis is 16 cm, and bilateral ovarian involvement is common.9,10 Grossly, the ovary shows a multiloculated, cystic cut surface filled with abundant mucinous material (Figure 2, A), and frozen sections typically demonstrate disrupted cystic structures lined by flat or slightly undulating mucinous epithelium surrounded by large areas of paucicellular basophilic mucin dissecting through ovarian stroma (pseudomyxoma ovarii) (Figure 2, B through D). Subepithelial clefts are usually present between the lining epithelium and the stroma. The tumor cells are tall and columnar and show relatively uniform, basally located nuclei with no appreciable mitotic activity and abundant pale eosinophilic or basophilic cytoplasm. Numerous goblet cells are also present. If low-grade appendiceal mucinous neoplasm is considered in the differential diagnosis, the surgical team should be contacted intraoperatively to discuss the findings, and surgical evaluation of the appendix and the contralateral ovary should be recommended. The appendix may appear grossly normal or slightly enlarged with a cystic mass on cut surface of the appendiceal tip, showing abundant mucinous contents and a firm, tan-white cyst wall (Figure 3, A). Frozen sections of the appendix show dense fibrosis with calcifications and abundant extracellular mucin pools with rare strips of bland mucinous epithelium, similar to that seen in the ovary (Figure 3, B).

Ovarian mucinous cystadenoma most often has a gastrointestinal-type—gastric foveolar—or intestinal-type epithelial lining, which may be undulating or may form small, filiform papillae, but lacks significant epithelial proliferation, complexity, and nuclear atypia (Figure 4, A and B). Invagination of epithelial lining into the ovarian stroma is common and by itself should not be interpreted as glandular complexity. Mucinous borderline tumors, on the other hand, show epithelial proliferation with stratification, tufting, intraglandular villous or filiform papillary growth, and fusion of papillae, in addition to mild to moderate nuclear atypia and variable mitotic activity (Figure 4, C and D). Acellular mucin spillage into the ovarian stroma (pseudomyxoma ovarii) may be seen in both benign and borderline mucinous ovarian tumors, although it is typically limited to a few small microscopic foci. Despite the morphologic overlap, some distinct clinical and pathologic features should raise the possibility of a metastatic low-
grade appendiceal mucinous neoplasm on frozen section: bilateral ovarian involvement; associated pseudomyxoma peritonei; numerous large, confluent foci of pseudomyxoma ovarii; scalloped glands lined by tall, columnar tumor cells; and presence of subepithelial clefts. However, teratoma-associated primary ovarian mucinous tumors represent a unique exception, as they may have identical morphology and associated pseudomyxoma peritonei. Thorough gross examination and sampling can help identify a background dermoid cyst. Communication with the clinical team is essential in gathering information regarding potential bilaterality, pseudomyxoma peritonei, and gross appearance of the appendix. The intraoperative findings in the appendix may be subtle, and many surgeons opt to perform appendectomy if the frozen section shows a mucinous neoplasm, whether benign, borderline, or overtly malignant, in the ovary, even if the appendix appears grossly unremarkable.

Pancreatobiliary carcinomas metastatic to the ovary are relatively uncommon, presenting at a mean age of 58 to 59 years, and pose a unique diagnostic challenge on frozen section by having deceptively bland cytologic features, referred to as maturation phenomenon. Most cases (>80%) are bilateral, with a mean size of 10 cm. Gross examination of the ovary shows a tan-pink, multiloculated, cystic cut surface, and frozen sections typically demonstrate multiple irregular, variably sized cystic spaces within the ovarian stroma, lined by relatively bland, low columnar epithelium. Most of the tumor may lack significant nuclear atypia or mitotic activity (Figure 5), mimicking an ovarian mucinous cystadenoma or borderline mucinous tumor, especially when the sampling is limited to a few blocks on frozen section. However, careful microscopic examination on medium and high magnification helps reveal scattered foci of infiltrating tumor cells forming small clusters and glandular structures in loose, edematous, myxoid stroma. In addition to obtaining information about the clinical history and the surgeon’s intraoperative findings, adequate sampling is critical to identify small infiltrative tumor cell nests with desmoplastic stromal reaction and increased nuclear atypia.

Similar to appendiceal and pancreatobiliary primaries, mucinous carcinomas from other primary sites—colon, rectum, stomach, breast, and endocervix—may also spread to the ovary, and are more common than primary ovarian mucinous carcinomas. Metastatic mucinous carcinomas...
Figure 2. Metastatic low-grade appendiceal mucinous neoplasm involving the ovary. Gross examination showed an 8 × 6 × 4-cm ovarian mass with multifoculated, cystic cut surface filled with abundant mucinous material (A). Frozen sections revealed abundant paucicellular mucin pools with rare strips of bland mucinous epithelium (B), pseudomyxoma ovarii, and subepithelial clefts (C). The tumor cells are tall and columnar, displaying small, relatively uniform nuclei and abundant mucinous cytoplasm with occasional goblet cells (D) (hematoxylin-eosin, original magnifications ×20 [B], ×100 [C], and ×200 [D]).

Figure 3. Low-grade appendiceal mucinous neoplasm. Gross examination shows a 3-cm cystic, mucin-filled mass at the appendiceal tip (A) and frozen sections reveal paucicellular mucin pools with bland mucinous epithelium, similar to that seen in the ovary, with fibrosis and calcifications (B) (hematoxylin-eosin, original magnification ×40 [B]).
tend to be small (mean diameter of 8 cm) and bilateral, in comparison with primary ovarian mucinous borderline tumors and carcinomas (mean diameter of 18–20 cm). Lee and Young thoroughly evaluated the gross and microscopic features of 50 mucinous carcinomas, 25 primary ovarian and 25 metastatic from pancreas, colon, cervix, and appendix, and found that all primary ovarian carcinomas were unilateral and 88% of them exceeded 10 cm in size. Conversely, 75% of metastatic tumors were bilateral and approximately half of them measured less than 10 cm. Using the 10-cm gross tumor size cutoff and laterality, Seidman et al proposed a simple algorithm designating unilateral mucinous tumors 10 cm or larger as primary ovarian, and all other tumors (bilateral tumors of any size and unilateral tumors <10 cm) as metastatic. After excluding tumors with signet-ring cell features and microinvasion, this approach correctly classified 83% of cases as primary or metastatic. A follow-up study by Yemelyanova et al recommended a modified algorithm to improve the performance by adjusting the tumor size cutoff to 12 or 13 cm. Using a 12-cm cutoff, 100% of primary tumors and 80% of metastases were correctly classified (86% overall), whereas a 13-cm cutoff maintained correct classification for 98% of primary tumors and increased it to 82% of metastases (87% overall). However, it is important to note that metastases from colorectal, endocervical, and appendiceal primaries not uncommonly present an exception to this rule, and may form a large, unilateral ovarian mass.

The microscopic features in favor of metastatic mucinous carcinoma include ovarian surface and/or hilus involvement, lymphovascular invasion, multinodularity, a predominant infiltrative growth pattern, and single-cell infiltration (Table 1). Primary ovarian mucinous carcinomas may also show focal infiltrative growth with stromal desmoplastic reaction; however, a confluent, expansile growth pattern is more common in these tumors (Figure 6, A and B). Signet ring cells may be present in metastases, especially from gastric, colorectal, breast, and appendiceal primaries, but may also be rarely seen in teratoma-associated primary mucinous carcinomas of the ovary.

Although many of the above-described general gross and microscopic characteristics of metastatic mucinous carcinomas also apply for colorectal and endocervical primaries, they have some unique features warranting additional
Figure 5. Metastatic pancreatic adenocarcinoma involving the ovary. Low magnification shows variably sized cystic spaces, mimicking a benign or borderline ovarian mucinous tumor (A). The tumor cells have relatively bland and uniform nuclei (maturation phenomenon) and variable amount of mucinous cytoplasm (B through D). Rare foci of infiltrative invasion with stromal desmoplastic response (arrows) provide helpful diagnostic clues (frozen sections, hematoxylin-eosin, original magnifications ×20 [A], ×100 [B and C], and ×200 [D]).

Figure 6. Primary ovarian mucinous carcinoma most often shows an expansile growth pattern with confluent glandular proliferation (A and B) (frozen sections, hematoxylin-eosin, original magnifications ×40 [A] and ×100 [B]).
Frozen Section Diagnosis of Ovarian Tumors

...discussion. Metastases from colorectal primaries represent the most common type of ovarian metastasis, and hence they are frequently encountered on frozen section. The ovarian metastasis may precede the diagnosis of the primary, and in these cases the patients tend to be younger than those with a known colorectal primary.27 Unlike most other metastatic mucinous carcinomas, nearly half of colorectal metastases are unilateral, and the tumor size exceeds 10 cm in approximately one-quarter of cases.25 In addition to mimicking a primary ovarian mucinous carcinoma, the differential diagnosis also includes endometrioid adenocarcinoma (EAC) of the ovary and Sertoli-Leydig cell tumor (SLCT) with heterologous elements (Table 2). Metastatic colorectal carcinomas form variably sized, irregular glands, which often contain intraluminal “dirty” necrotic debris—eosinophilic necrotic material with karyorrhectic nuclei (Figure 7, A through D). Cribriform glandular and garland patterns are also common. Destructive infiltrative growth with desmoplastic stromal reaction is present at least focally, and single-cell tumor invasion may also be seen. The tumor cell nuclei show moderate to marked atypia and a variable amount of cytoplasm with scattered mucin-filled goblet cells. Squamous differentiation, a distinctive feature of EAC, is notably absent. During frozen section evaluation, if the possibility of a colorectal primary is suspected, the findings should be communicated to the surgeon, and intraoperative survey of the gastrointestinal tract, intestines, and liver surface should be recommended.

Metastatic endocervical adenocarcinoma of the ovary often presents as a large (mean size, 12.7 cm), unilateral, cystic mass with an intraluminal, expansile tumor growth, simulating a mucinous borderline tumor.26 The endocervical primary may be small and may lack unequivocal stromal invasion. The tumor forms confluent glandular, cribriform, or villoglandular architectural patterns, the latter with characteristic sharply angulated tips. Careful attention should be paid to identify the most helpful diagnostic features: columnar cells with nuclear crowding, stratification, basal apoptotic bodies, and apical mitotic figures (Figure 8, A through D). Gross and microscopic examination of the uterine cervix at the time of frozen section may be helpful. The immediate clinical impact of the frozen section diagnosis on the surgical staging may depend on the individual case and should be discussed with the surgeon intraoperatively. The staging procedure for ovarian primaries, including borderline tumors, typically includes omentectomy, whereas omentectomy is not performed for endocervical primaries.

**SEROUS TUMORS—PROPHYLACTIC SALPINGO-OOPHORECTOMY SPECIMENS**

Prophylactic/risk-reducing salpingo-oophorectomy is an increasingly common procedure in women at genetic risk for ovarian/fallopian tube cancer. The risk of ovarian cancer is estimated to be as high as 46% for BRCA1 and 27% for BRCA2 mutation carriers.28,29 The rate of occult malignancy in risk-reducing salpingo-oophorectomy specimens ranges between 5% and 10%, including both in situ and invasive lesions, in most prior studies.30–33 Intraoperative evaluation of risk-reducing salpingo-oophorectomy specimens in high-risk patients offers a unique opportunity to identify clinically undetected malignancies, allowing for immediate surgical staging, and helps avoid a second surgery. However, it presents several challenges and potential diagnostic pitfalls. Preoperative imaging may be misleading, as it may not correctly identify the origin, uterine/myometrial versus adnexal, of a pelvic mass (Figure 9, A). In addition, a large proportion of patients in this setting have a prior clinical history of breast cancer, and the high index of suspicion for metastatic breast carcinoma may result in favoring a metastasis over an ovarian primary when a morphologically challenging or unexpected neoplasm is encountered on frozen section.

A recent study by Wong et al.34 evaluated the frozen section sampling and diagnostic practices in patients

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**Table 1. Gross and Microscopic Features of Primary and Metastatic Mucinous Carcinomas of the Ovary**

| Feature                        | Primary | Metastatic |
|-------------------------------|---------|------------|
| Bilaterality                  | Rare    | Common*    |
| Size <10 cm                   | Rare    | Common*    |
| Surface involvement           | Rare    | Common     |
| Lymphovascular invasion       | Rare    | Common     |
| Hilus involvement             | Rare    | Common     |
| Growth pattern                | Predominantly expansile | Infiltrative |
| Multinodularity               | Rare    | Common     |
| Single-cell infiltration      | Rare    | May be present |
| Signet ring cells             | Rare (in teratoma-associated tumors) | May be present |

* Most common exceptions: colorectal, endocervical, and appendiceal (low-grade appendiceal mucinous neoplasm) primaries.

**Table 2. Differential Diagnosis of Metastatic Colorectal Carcinoma**

| Metastatic Colorectal Adenocarcinoma | Endometrioid Adenocarcinoma | Sertoli-Leydig Cell Tumor |
|--------------------------------------|-----------------------------|---------------------------|
| Age                                  | Older than the fifth decade (median 68 y) | Fifth-sixth decade (mean 58 y) | Commonly in young patients (mean 25–30 y) |
| Bilaterality                         | Common, ~50%–60% of cases | Up to 17% of cases | Very rare |
| Mean tumor size, cm                  | Usually <10–12 | 15 | 12–14 |
| Clinical symptoms                    | Symptoms associated with colonic primary, less commonly pelvic mass/pain | Asymptomatic or pelvic mass/pain | Hormonal manifestations common (androgenic > estrogenic) |
| Squamous differentiation             | Absent | Common | Absent |
| Mucinous differentiation             | Common (with goblet cells) | Uncommon (no goblet cells) | Rare (gastric- or intestinal-type heterologous elements) |
| Necrosis                             | Common (intraluminal “dirty” necrosis) | Common | May be seen (in poorly differentiated tumors) |
undergoing prophylactic surgery for hereditary gynecologic cancer syndromes and reported a 5.4% incidence of occult malignancy (including 8 high-grade serous ovarian carcinomas, 3 serous tubal intraepithelial carcinomas, and 1 adult granulosa cell tumor) among 222 BRCA1/2 patients. None of the patients in this group had ovarian metastases from breast cancer; however, nearly 2% of patients with a strong family and/or personal history of breast/ovarian cancer and no known BRCA1/2 mutations harbored occult metastatic breast cancer involving both ovaries. Rabban et al evaluated 108 risk-reducing salpingo-oophorectomy specimens from BRCA1/2 patients, nearly 70% of whom had a personal history of breast cancer, and found 1 patient (1%) with metastatic breast cancer. Ovarian metastases from breast cancer are typically bilateral and small (<5 cm), and, despite the higher frequency of ovarian involvement among lobular carcinomas, they most often show ductal phenotype because of the significantly higher overall incidence of invasive ductal carcinoma. Metastatic ductal carcinomas may have solid, micropapillary, cribriform, or glandular patterns, whereas lobular carcinomas show single cells, haphazardly or in linear cords, and may also have signet ring cell features. In most cases the breast cancer diagnosis precedes the ovarian metastasis; the median time from the breast cancer diagnosis is 5 years. It is interesting to note that purely from a statistical standpoint, a new adnexal mass in a breast cancer patient has been found to be 3 times more likely to be an ovarian primary.

High-grade serous carcinoma associated with BRCA mutations has been described to show characteristic solid, pseudoendometrioid, and transitional cell carcinoma–like morphologic features, which may overlap with a cribriform pattern of a metastatic ductal breast carcinoma, further complicating the frozen section evaluation (Figure 9, B through D). In addition, BRCA1-associated tumors were also found to have a higher mitotic index, geographic or comedo necrosis, and an increased number of tumor-infiltrating lymphocytes compared with non-BRCA-associated tumors. Other tumor types with a cribriform pattern—EAC, adult granulosa cell tumor, and carcinoid tumor—should also be considered in the differential diagnosis (Table 3). Metastatic tumors from other sites, although less common, may also mimic an ovarian high-grade serous carcinoma, and pose a diagnostic challenge at the time of frozen section (Figure 10, A and B). Thorough review of the patient’s clinical history and morphologic comparison with
the primary tumor are crucial to avoid a potential pitfall. When in doubt, a conservative approach is generally more favorable, and diagnostic uncertainty should be communicated to the surgeon to avoid an unnecessary extensive staging surgery.

**ENDOMETRIOID TUMORS—PITFALLS AND MIMICS**

Endometrioid adenocarcinoma of the ovary may show overlapping morphologic features, especially on frozen sections, with several other tumor types, including metastatic colorectal and breast carcinomas and BRCA-associated high-grade serous carcinomas, which have been discussed in detail above. Additionally, a rare histologic variant, sertoliform EAC, further broadens the differential diagnosis of this entity.

Sertoliform EAC typically presents at a mean age of 60 years and may be bilateral in up to 17% of cases. Intraoperative gross examination shows a multilobulated, solid, tan-yellow, focally hemorrhagic cut surface (Figure 11, A), and frozen sections reveal relatively uniform, small tumor cells forming tubular glandular structures and cords in a prominent fibromatosus stroma (Figure 11, B through D). The tumor cells have mild to moderate nuclear pleomorphism with small nucleoli, abundant eosinophilic cytoplasm, and low mitotic activity. Dense eosinophilic material is often present in the lumen of the tubular structures.

The main differential diagnosis of sertoliform EAC is SLCT, a rare ovarian sex cord–stromal tumor, accounting for less than 0.5% of all ovarian tumors. Unlike sertoliform EAC, SLCT is unilateral in more than 98% of cases, and it typically occurs in patients younger than 30 years, although it may also occur after menopause. More than half of the patients experience androgenic hormonal manifestations: hirsutism, clitoromegaly, and amenorrhea. The histomorphologic features, biological behavior, and clinical implications of SLCT vary greatly depending on the tumor grade. Well-differentiated SLCTs are benign and are typically easily recognizable by the presence of open Sertoli cell tubules and admixed clusters of Leydig cells in the intervening stroma (Figure 12, A). Intermediate-grade tumors are characterized by diffuse sheets or thin cords of Sertoli cells, admixed with fewer clusters of Leydig cells, compared with well-differentiated SLCTs (Figure 12, B). Poorly differentiated SLCT is...
Figure 9. High-grade serous carcinoma of the ovary with solid, pseudoendometrioid, and transitional cell carcinoma–like features in a prophylactic bilateral salpingo-oophorectomy specimen from a BRCA1 mutation carrier. Preoperative imaging showed a pelvic mass, likely representing a leiomyoma. A 6.5-cm nodular mass was identified on intraoperative gross examination, attached to the surface of the right ovary with a solid, tan-yellow, fleshy cut surface (A). A predominantly cribriform architecture with relatively uniform nuclei was seen on frozen sections (B and C). Rare microscopic foci demonstrated irregular, slitlike glandular spaces, more typical of high-grade serous carcinoma (D) (frozen sections, hematoxylin-eosin, original magnifications $\times 100$ [B and D] and $\times 200$ [C]).

Figure 10. Metastatic lung adenocarcinoma in the ovary displaying irregular glandular spaces (A) with marked nuclear pleomorphism, hyperchromasia, prominent nucleoli, and frequent mitoses (B), mimicking primary high-grade serous carcinoma on frozen sections (hematoxylin-eosin, original magnifications $\times 100$ [A] and $\times 200$ [B]).
### Table 3. Differential Diagnosis of Ovarian Tumors With Cribriform Architecture

| High-Grade Serous Carcinoma (BRCA-Associated With SET Features) | Metastatic Breast Adenocarcinoma | Endometrioid Adenocarcinoma | Adult Granulosa Cell Tumor | Carcinoid Tumor (Primary) |
|---|---|---|---|---|
| **Age** | 50–60 y (younger for BRCA-associated tumors) | 50–70 y | Fifth-sixth decade (mean 58 y) | Most often postmenopausal (mean 50–55 y) | 14–79 y (mean 53 y) |
| **Bilaterality** | Common | Common | Up to 17% | Very rare | Very rare (suspect metastasis if bilateral) |
| **Mean tumor size, cm** | Variable, <1–20 | Usually <5 | 15 | 10–12 | Variable |
| **Clinical symptoms** | Asymptomatic/pelvic mass, pain, bloating | Asymptomatic/rarely pelvic mass | Asymptomatic or pelvic mass/pain | Pelvic mass/pain; hormonal (estrogenic > androgenic) manifestations | May be incidental; one-third of patients have carcinoid syndrome |
| **Nuclear features** | Marked atypia with prominent nucleoli; multinucleated, bizarre cells may be seen | Moderate to marked atypia (IDC) or uniform small nuclei (ILC) | Variable nuclear atypia; no grooves | Most often uniform, pale nuclei with membrane folds and grooves | Uniform, small, round nuclei with finely stippled chromatin |
| **Cytoplasmic and other features** | Vacuolization may be present; psammomatous calcifications | Intracytoplasmic lumens with “targetoid” secretions or signet ring-like cells (ILC) | Moderate to abundant cytoplasm; may show squamous and mucinous differentiation | Little cytoplasm, cell membrane not well defined (except luteinized tumors) | Moderate amount of cytoplasm; may show mucinous differentiation (goblet cell carcinoid) |
| **Necrosis** | Common | May be seen (IDC) | Common | May be seen | Absent |

Abbreviations: IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; SET, solid, pseudoendometrioid, and transitional cell carcinoma-like.

### Table 4. Differential Diagnosis of Ovarian Endometrioid Adenocarcinoma With a Sertoliform Pattern

| Endometrioid Adenocarcinoma | Metastatic Signet Ring Cell Carcinoma (Tubular Krukenberg Tumor) | Sertoli-Leydig Cell Tumor | Struma Ovarii (Microfollicular Pattern) |
|---|---|---|---|
| **Age** | Fifth-sixth decade (mean 58 y) | Older than the fifth decade (median 68 y) | Most common in young patients (mean 25–30 y) | Most common during reproductive years |
| **Bilaterality** | Up to 17% of cases | Common, ~60% of cases | Very rare | Rare |
| **Mean tumor size, cm** | 15 | Usually <10–12 | 12–14 | <10 |
| **Clinical symptoms** | Asymptomatic or pelvic mass/pain | Symptoms associated with primary, less commonly pelvic mass/pain | Hormonal manifestations common (androgenic > estrogenic) | Pelvic mass/pain |
| **Squamous differentiation** | Common | Absent | Absent | Absent |
| **Mucinous differentiation** | Uncommon (no goblet cells) | Common (with goblet cells) | Rare (gastric- or intestinal-type heterologous elements) | Absent |
| **Necrosis** | Common | Common | May be seen in poorly differentiated tumors | Absent |
composed of diffuse sheets of immature, sarcomatoid Sertoli cells and rare Leydig cell clusters, primarily around the periphery of the tumor (Figure 12, C). Approximately 20% of SLCTs contain heterologous, most often intestinal or gastric-type mucinous epithelial elements (Figure 12, D), and rare cases show a retiform pattern. Malignant clinical behavior has been reported in 11% of intermediate-grade and up to 59% of poorly differentiated SLCT.\textsuperscript{41,43–45} The presence of heterologous elements and retiform pattern also indicate adverse prognosis. Recognition of Leydig cells on frozen sections can greatly aid the diagnosis, especially in intermediate and poorly differentiated tumors. Leydig cells have round nuclei and abundant eosinophilic cytoplasm, containing lipofuscin pigment and Reinke crystals, which are often better preserved on frozen section slides, compared with the formalin-fixed permanent tissue sections (Figure 12, A).

The differential diagnosis of sertoliform EAC should also include Krukenberg tumor, which is often bilateral, may show a predominant tubular pattern, and may also be associated with stromal hormone production, mimicking sertoliform EAC or even SLCT.\textsuperscript{46,47} The immediate clinical implication of frozen section diagnosis depends on the grade of the SLCT considered in the differential diagnosis and the patient’s age and desire for future fertility. In older patients complete surgical staging is performed for both SLCT (moderately or poorly differentiated) and sertoliform EAC. However, conservative fertility-sparing surgery may be an option for younger patients with stage I SLCT.\textsuperscript{43–45}

**CLEAR CELL TUMORS**

The wide spectrum of morphologic changes and patterns of endometriosis-associated lesions presents yet another challenge on frozen section. Atypical endometriosis, cytologic and/or architectural atypia (similar to that seen in atypical hyperplasia of eutopic endometrium) within an endometriotic cyst, may appear worrisome microscopically; however, by itself, it has been shown to have a benign nature. Potentially difficult to distinguish from EAC of the ovary, especially on frozen section. However, absence of nuclear atypia, intraluminal colloid material, and recognition of calcium oxalate crystals usually resolve the diagnostic uncertainty.
Figure 12. Sertoli-Leydig cell tumor (SLCT) of the ovary. Well-differentiated SLCT shows open Sertoli cell tubules admixed with abundant clusters of Leydig cells with intracytoplasmic Reinke crystals (A, arrowheads). Moderately differentiated SLCT with compressed cords of basophilic Sertoli cells and scattered eosinophilic Leydig cells (B). Poorly differentiated SLCT with diffuse sheets of immature Sertoli cells and rare Leydig cell clusters at the periphery of the tumor (C, arrows). Poorly differentiated SLCT with heterologous elements (D). Gastric-type mucinous epithelium is seen on the top of the image, surrounded by immature Sertoli cells and small clusters of Leydig cells (D, arrowheads) (frozen sections, hematoxylin-eosin, original magnifications ×400 [A], ×200 [B], and ×100 [C and D]).

Figure 13. Krukenberg tumor with a predominant tubular pattern and associated stromal hyperplasia may mimic sertoliform endometrioid adenocarcinoma or Sertoli-Leydig cell tumor on frozen sections (A). Scattered signet ring cells can be recognized on higher magnification (B) (frozen sections, hematoxylin-eosin, original magnifications ×100 [A] and ×400 [B]).
clinical course and does not require extensive surgery. On the other hand, if atypical endometriosis is identified on frozen section slides, the gross appearance of the ovary should be carefully reviewed to assure the absence of intracystic papillary projections or a solid mass. Any suspicious intraluminal growth should be sampled for frozen section evaluation to rule out the possibility of clear cell carcinoma (Figure 14, A through D).

The strong association between clear cell carcinoma and endometriosis has been well documented in the literature. More recently, endometriosis with cytologic atypia has been proposed to be a precursor lesion, based on identical molecular and immunohistochemical alterations, loss of ARID1A and PIK3CA mutations, between clear cell carcinoma and the immediately adjacent foci of atypical endometriosis. Interestingly, another endometriosis-associated ovarian tumor, seromucinous/Müllerian-type mucinous borderline tumor, may also mimic clear cell carcinoma, and rarely the 2 tumors may be admixed within the same cystic lesion, further complicating the frozen section interpretation (Figure 15, A through D). Seromucinous/Müllerian-type mucinous borderline tumor typically shows an admixture of Müllerian-type epithelia in variable proportions: mucinous (endocervical-type), serous, eosinophilic, and endometrioid cell types arranged in hierarchical branching papillae. The papillary architecture, tufting, and pale cytoplasm of mucinous cells may resemble the features of clear cell carcinoma; however, only mild nuclear atypia is seen in seromucinous/Müllerian-type mucinous borderline tumor, whereas marked nuclear atypia is present, at least focally, in clear cell carcinoma (Table 5).

Clear cell carcinoma of the ovary may occur in patients in their third to seventh decade, with a mean age of 50 to 55 years. The clinical presentation most often includes a pelvic mass and pain, and rarely paraneoplastic syndromes, that is, thromboembolic events and hypercalcemia. The tumor is most often unilateral, with a mean size of 15 cm and shows either a solid, heterogeneous cut surface with foci of hemorrhage and necrosis or a predominantly cystic structure with intraluminal solid growth. Microscopically, various architectural patterns may be observed within the same tumor, including tubulo-cystic, solid, and papillary growth with characteristic hyalinized fibrovascular cores. The degree of nuclear atypia may also vary greatly among different areas of the same tumor. Marked nuclear atypia, often with prominent nucleoli, is a hallmark of clear cell carcinoma.
Figure 15. Clear cell carcinoma (CCC) arising in the background of seromucinous borderline tumor (SMBT). Frozen sections of a multiloculated cystic ovarian mass with a predominant SMBT component show epithelial proliferation and tufting (A). Scattered foci with increased nuclear pleomorphism and hyperchromasia are seen (B, lower portion of image). Nuclear atypia is mild and the nuclear to cytoplasmic (n:c) ratio is low in areas of SMBT (C), whereas marked nuclear atypia, high n:c ratio, and hobnailing are seen in foci of CCC within the same tumor (D) (frozen sections, hematoxylin-eosin, original magnifications ×100 [A and B] and ×400 [C and D]).

Table 5. Differential Diagnosis of Ovarian Clear Cell Carcinoma

|                    | Clear Cell Carcinoma | SMBT          | Yolk Sac Tumor | Dysgerminoma       |
|--------------------|----------------------|---------------|----------------|--------------------|
| **Age**            | Third–seventh decade | Mean 42 y     | Second–third decade | Second–third decade |
|                    | (mean 50–55 y)       |               | (mean 16–19 y)  | (mean 22 y)        |
| **Bilaterality**   | Rare                 | Common (up to 40%) | Rare        | 10%–20%            |
| **Clinical symptoms** | Pelvic mass/pain,  | Pelvic mass/pain | Pelvic mass/pain; increased serum AFP | Pelvic mass/pain; increased serum LDH |
|                    | thromboembolic events, |               |                |                    |
|                    | hypercalcemia       |               |                |                    |
| **Background ovary** | Endometriosis       | Endometriosis | No specific changes | Rarely gonadal dysgenesis or gonadoblastoma |
| **Architectural pattern** | Variable: papillary, tubulocystic, solid | Papillary | Variable: reticular, solid, alveolar-glandular | Solid |
| **Nuclear atypia**  | Variable; at least focally high grade | Mild | Moderate to marked with prominent nucleoli | Uniform nuclear enlargement with prominent nucleoli |
| **Necrosis**        | Common               | Absent        | Common         | Common             |

Abbreviations: AFP, α-fetoprotein; LDH, lactate dehydrogenase; SMBT, seromucinous borderline tumor.
carcinoma, although borderline or benign-appearing adenofibromatous areas may also be present and may have deceptively bland nuclear features (Figure 16, A through D). If such an area is encountered on frozen section, additional blocks should be sampled to rule out clear cell carcinoma, keeping in mind that benign and borderline clear cell ovarian tumors are exceedingly rare.2,5 Presence of abundant clear or eosinophilic cytoplasm is a helpful feature on permanent sections; however, cytoplasmic clearing may be difficult to appreciate intraoperatively on frozen sections. Other entities with clear cytoplasm to consider in the differential diagnosis, especially in young patients, include yolk sac tumor and dysgerminoma (Table 5). Although malignant germ cell tumors may be treated with fertility-preserving surgery, the potential role of fertility-sparing surgery in the management of young patients with clear cell carcinoma is more controversial.1,6 Distinction between clear cell carcinoma and other histologic subtypes of ovarian high-grade carcinomas, that is, serous and endometrioid, is typically not crucial on frozen sections, as long as the Müllerian/primary ovarian origin is confirmed and communicated to the surgeon.

Figure 16. Clear cell carcinoma (CCC) with deceptively benign-appearing adenofibromatous and tubulo-cystic areas. Variably sized cystic or tubulo-cystic glands with hobnailing and minimal cytologic atypia (A and B, right side of image) may be admixed with typical CCC (B, left side of image). The degree of nuclear atypia can vary significantly within the tumor (C): note the gland in the center with nuclear enlargement and prominent nucleoli, surrounded by cytologically bland glands. Other areas of the same tumor showed characteristic, easily recognizable marked nuclear atypia (D) (frozen sections, hematoxylin-eosin, original magnifications ×100 [A and B] and ×200 [C and D]).

SUMMARY

Frozen section diagnosis of ovarian epithelial tumors continues to rely on 3 traditional elements: the patient’s clinical history, gross examination, and microscopic interpretation. Awareness of the wide range of morphologic patterns and recognition of clinicopathologic diagnostic clues help distinguish among the large number of mimics for each entity. Understanding the detailed clinical context in each case can facilitate the discussion between the surgeon and pathologist and appropriately guide intraoperative patient management.

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