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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Uterine Neoplasms
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Uterine Neoplasms

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships:

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To view all of the conflicts of interest for the NCCN Guidelines panel, go to [NCCN.org/disclosures/guidelinepanellisting.aspx](https://www.nccn.org/disclosures/guidelinepanellisting.aspx).

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Uterine Neoplasms, Version 3.2021

Featured Updates to the NCCN Guidelines

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ABSTRACT

The NCCN Guidelines for Uterine Neoplasms provide recommendations for diagnostic workup, clinical staging, and treatment options for patients with endometrial cancer or uterine sarcoma. These NCCN Guidelines Insights focus on the recent addition of molecular profiling information to aid in accurate diagnosis, classification, and treatment of uterine sarcomas.

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PRINCIPLES OF PATHOLOGY AND MOLECULAR ANALYSIS^{a,1,2}**Procedure:**

- TH/BSO: Total hysterectomy + bilateral salpingo-oophorectomy
- RH: Radical hysterectomy

Pathologic assessment for sarcoma (including leiomyosarcoma, adenosarcoma, endometrial stromal sarcoma, and undifferentiated sarcoma):

- Expert gynecologic pathology review is highly recommended
- Uterus
 - Hysterectomy type
 - Specimen integrity (intact, opened, morcellated, other)
 - Tumor size
 - Myometrial invasion (for adenosarcoma only)
 - Histologic type
 - Histologic grade (for adenosarcoma only)
 - LVSI
- Other tissue/organ involvement (fallopian tubes, ovaries, vagina, parametrium, peritoneum, omentum, other)
- Peritoneal/ascitic fluid cytology^b
- Lymph nodes (when resected)
 - Level of nodal involvement (ie, pelvic, common iliac, para-aortic)
 - Number of lymph nodes with metastasis

Molecular analysis for sarcoma

- Molecular profiling is informative in many mesenchymal malignancies for accurate classification³
(See Uterine Sarcoma: Mesenchymal Tumors & Mixed Epithelial and Mesenchymal Tumors [UTSARC-A 2 of 5])
- Comprehensive genomic profiling with a validated and/or FDA-approved assay is informative for predicting rare pan-tumor targeted therapy opportunities and should include at least *NTRK*, *MSI*, and *TMB*.

Footnotes

^aAlso see Principles of Evaluation and Surgical Staging (ENDO-C).

^bAlthough cytology by itself does not affect FIGO staging, cytology results should still be obtained because positive cytology is an adverse risk factor.

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Overview

An estimated 66,570 new cases of uterine cancer will be diagnosed in the United States in 2021, and 12,940 people will die of the disease.¹ Most uterine cancers are epithelial-derived and arise in the endometrium (endometrial carcinoma). Stromal or mesenchymal sarcomas are uncommon malignant tumors, accounting for approximately 3% of all uterine cancers.² Uterine sarcomas include low-grade and high-grade endometrial stromal sarcoma (LGESS and HGESS, respectively), undifferentiated uterine sarcoma (UUS), uterine leiomyosarcoma (ULMS) including epithelioid and myxoid variants, uterine tumor resembling ovarian sex cord tumor (UTROSCT), rhabdomyosarcoma (RMS), and perivascular epithelioid cell tumors (PEComas). According to the WHO, Müllerian adenosarcoma is a “biphasic neoplasm composed of a benign epithelial component and a malignant stromal component”³; the malignant component is typically low-grade. According to a 2012 systematic review of data from 1970 to 2011, ULMS was the most common subtype (63%) of uterine sarcoma, followed by ESS (21%) and less common subtypes such as UUS.⁴ RMS and PEComas are the rarest subtypes of uterine sarcomas.⁵

Recent advances have expanded the NCCN Uterine Neoplasms Guidelines panel’s understanding of the

molecular features of these tumors, leading to the identification of genetic signatures that characterize some of the uterine sarcoma subtypes. Historically, mesenchymal tumors were primarily diagnosed using histopathologic criteria, and the results of molecular studies were not used in routine pathologic evaluation. However, given the overlap in histopathologic features of these tumors, molecular analysis (eg, identification of characteristic translocations and/or mutations) may help clinicians classify difficult cases and also provide insight into future therapeutic targets.⁶ In recent years, validated and FDA-approved comprehensive genomic profiling tests have become increasingly available, and have helped to facilitate cancer diagnoses and/or selection of targeted therapies. Additional gene- and/or tumor-specific confirmatory molecular tests may also be useful for these purposes. Therefore, the panel recently expanded the Principles of Pathology and Molecular Analysis section of the Uterine Sarcoma Guidelines in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Uterine Neoplasms. In addition to the introductory page (UTSARC-A 1 of 5, above), this section now includes a table containing information on histologic and molecular findings, relevant confirmatory molecular tests, prognostic features, and other clinically useful information to help

PRINCIPLES OF PATHOLOGY AND MOLECULAR ANALYSIS

Table 1

Uterine Sarcoma: Mesenchymal Tumors & Mixed Epithelial and Mesenchymal Tumors					
Tumor	Hallmarks for Histologic Diagnosis	Relevant Molecular Finding	Additional Confirmatory Tests	Relevant Prognostic Features	Other
Epithelioid Leiomyosarcoma ¹	Epithelioid morphology comprising >50% of the tumor with moderate to severe atypia and either tumor necrosis or mitotic index (MI) >4/10 high-power fields (HPF).	<i>PGR</i> fusions by FISH and/or targeted RNA sequencing in a small subset with uniform nuclear atypia and rhabdoid features.	Immunoeexpression of desmin and SMA without HMB45 and melan A is confirmatory.	Unknown	Tumors morphologically and immunohistochemically overlap with malignant perivascular epithelioid cell neoplasms (PEComa) for which there is no gold standard. Detection of <i>TSC</i> mutations by DNA sequencing may favor PEComa.
Myxoid Leiomyosarcoma ^{2,3}	Infiltrative spindle cell proliferation with variable myxoid matrix and tumor necrosis or any degree of atypia or MI ≥1/10 HPF.	<i>PLAG1</i> fusion FISH and/or targeted RNA sequencing in a subset (~25%).	IHC panel of CD10, ER, progesterone receptor (PR), desmin, SMA, BCOR, cyclin D1, pan-Trk, ALK, and <i>PLAG1</i> is recommended to exclude morphologic mimics. Desmin and/or <i>PLAG1</i> expression and/or <i>PLAG1</i> fusion by FISH and/or targeted RNA sequencing is confirmatory.	Unknown	

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clinicians differentiate between and classify uterine sarcoma subtypes (see UTSARC-A 2 of 5 through UTSARC-A 5 of 5, pages 891–894).

Molecular Profiling for Uterine Sarcomas

This Insights article focuses on biomarkers specific to each sarcoma subtype that may help clinicians to differentiate between them and help provide a definitive diagnosis when used alongside histopathological evaluation. Of note, this article does not include certain tumors in Table 1 (ie, Müllerian adenosarcoma, carcinosarcoma) for which the panel does not currently recommend ancillary molecular testing.

LGESS and HGESS

Following smooth muscle neoplasms, endometrial stromal tumors are second most common mesenchymal tumors of the uterus. The most recent WHO classification schema for endometrial stromal tumors is as follows: endometrial stromal nodule (a benign entity), LGESS, HGESS, and UUS (see next subsection).³ LGESSs are composed of small fusiform cells resembling endometrial stromal cells in the proliferative phase.^{5,7} LGESS have distinct fingerlike patterns of myometrial invasion, and lymphovascular space invasion

is usually present. LGESS displays a heterogeneous mix of morphologic and genetic features, with many harboring *JAZF1*, *PHF1*, or *EPC1* gene fusions and presenting as earlier-stage tumors.^{6,8–11} The panel notes that diagnosis of LGESS can be confirmed by identifying any LGESS-associated gene fusion by using fluorescence in situ hybridization (FISH) and/or targeted RNA sequencing, though the lack of rearrangement or fusion does not exclude the diagnosis. It is worth noting that in rare instances, LGESS can transform into HGESS (either at the time of primary diagnosis or recurrence), which will require histopathological and molecular (eg, *JAZF1* or *PHF1* translocation) confirmation.¹²

Recently, a more aggressively behaving ESS with distinctive morphology (eg, uniform epithelioid cells with eosinophilic cytoplasm, angulated high grade nuclei, and vesicular chromatin) and a unique genetic rearrangement, *YWHAЕ-FAM22A/B* (also known as *YWHAЕ-NUTM2A/B*), was identified. This subtype is now known as HGESS.¹³ More recently, another distinct subtype of HGESS harboring *BCOR* alterations was described, either in the form of a *ZC3H7B-BCOR* fusion^{14,15} or an internal tandem duplication (ITD).¹⁶ Both *ZC3H7B-BCOR* fusion-positive and *BCOR* ITD HGESS have spindle and/or round cells embedded in myxoid matrix, and demonstrate strong and diffuse

PRINCIPLES OF PATHOLOGY AND MOLECULAR ANALYSIS

Table 1 (continued)

Uterine Sarcoma: Mesenchymal Tumors & Mixed Epithelial and Mesenchymal Tumors					
Tumor	Hallmarks for Histologic Diagnosis	Relevant Molecular Finding	Additional Confirmatory Tests	Relevant Prognostic Features	Other
Low-Grade Endometrial Stromal Sarcoma (LGESS) ⁴⁻⁶	Cytologically bland spindle cell proliferation resembling proliferative endometrial stroma with myoinvasion and/or LVSI.	JAZF1-SUZ12 fusion most common (>50%) followed by JAZF1-PHF1, EPC1-PHF1, and MEAF6-PHF1 fusions; MBTD1-CXorf67, BRD8-PHF1, EPC2-PHF1, and EPC1-SUZ12 in rare reports.	Ancillary testing is usually not required. CD10, ER positivity, PR positivity, and/or demonstration of an LGESS-associated fusion by FISH and/or targeted RNA sequencing is confirmatory.	Stage is the most important prognostic factor.	
High-Grade Endometrial Stromal Sarcoma ⁴⁻¹²	YWHAE-NUTM2 fusion-positive tumors have a high-grade round cell component with MI ≥10/10 HPF and necrosis that may be associated with a low-grade fibrous or fibromyxoid spindle cell component with low MI. ZC3H7B-BCOR fusion-positive tumors have high-grade spindle cells embedded in myxoid matrix. BCOR internal tandem duplication (ITD)-positive tumors share features of both YWHAE-NUTM2 and ZC3H7B-BCOR fusion-positive tumors. Tongue-like infiltration and LVSI are present in all subtypes.	YWHAE-NUTM2 fusion, ZC3H7B-BCOR fusion, BCOR ITD most common.	IHC panel of CD10, ER, PR, cyclin D1, and BCOR are recommended. Diffuse strong expression of cyclin D1 and/or BCOR is present in all subtypes. CD10 is negative in the high-grade round cell component of YWHAE-NUTM2 fusion subtype, but positive in BCOR mutant subtypes. ER and PR are negative in the high-grade round cell component of YWHAE-NUTM2 fusion subtype, and variably positive in BCOR mutant tumors.	Slightly higher rate of lymph node involvement and trend towards worse outcomes when compared to LGESS.	
Undifferentiated Uterine Sarcoma ¹²⁻¹⁵	Infiltrative sheets of pleomorphic epithelioid and/or spindle cells. SMARCA4-deficient subset consists of epithelioid/rhabdoid cells associated with myxoid matrix. LVSI, high MI, and necrosis are common.	SMARCA4 mutation in a small subset.	IHC panel of CD10, BCOR, cyclin D1, desmin, SMA, pan-CK, EMA, BRG1, INI1, pan-Trk, ALK, HMB45, melan A, SOX10, and STAT6 is recommended to exclude other tumor types. Absence of ESS-associated fusions by FISH and/or targeted RNA sequencing is recommended. Absent CK expression and BRG1 loss (SMARCA4) and/or SMARCA4 mutation detectable by DNA sequencing is confirmatory of SMARCA4-deficient tumors.	ER and/or PR expression may correlate with improved survival. MI ≥11/mm ² is associated with decreased survival.	

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positivity for cyclin D1 and variable positivity for CD10, estrogen receptor (ER), and progesterone receptor (PR).^{15,16} Immunohistochemistry (IHC) testing for CD10, cyclin D1, and BCOR and, in some cases, molecular analysis of *BCOR* alterations, may help differentiate between *BCOR*-altered HGESS and myxoid uterine leiomyosarcoma (myxoid ULMS) due to overlapping morphologic features. It is currently unclear whether specific types of HGESS (ie, *YWHAE*-altered or *BCOR*-altered) differ in prognosis and/or response to chemotherapy.

These findings provided additional support for subdividing ESS into distinct low-grade and high-grade categories based on distinct histopathology, clinical behavior, and patient outcomes. In light of this new information, WHO released an updated (4th) edition of the *WHO Classification of Tumors of Female Reproductive Organs* in 2014.¹⁷ WHO subsequently published a 5th edition on *Female Genital Tumors* in 2020,³ which also recognizes *BCOR*-altered sarcomas as a distinct subtype of HGESS.

Undifferentiated Uterine Sarcoma

UUSs are a group of high-grade/aggressive sarcomas characterized by infiltrative sheets of epithelioid and/or spindle cells that may be uniform or pleomorphic. As a class, it is a

heterogenous group of high-grade mesenchymal neoplasms of the uterus that fail to meet the diagnostic threshold for other characterized uterine mesenchymal neoplasms. As such, UUS is usually reserved as a diagnosis of exclusion, after other defined uterine mesenchymal neoplasms have been excluded using a multiprong approach that often requires a combination of extensive IHC panel and next-generation sequencing molecular analysis. For example, HGESS is often misdiagnosed as UUS due to a shared lack of smooth muscle differentiation.^{18,19} The panel notes that molecular testing for *BCOR* alterations, which can occur in HGESS as noted above, is useful to exclude an HGESS diagnosis before rendering a diagnosis of UUS.

A subset of UUSs called SMARCA4-deficient uterine sarcomas (SDUSs) have distinctive morphology (eg, phyllodiform architecture) along with biallelic inactivation of *SMARCA4* that results in loss of SMARCA4/BRG1 expression. These tumors occur in younger women and may be associated with very aggressive clinical behavior.^{20,21} The panel recommends analysis of SMARCA4/BRG1 by IHC and/or *SMARCA4* by DNA sequencing to confirm a diagnosis of SDUS with otherwise appropriate morphologic and immunophenotypic features. However, loss of SMARCA4/BRG1 alone does not constitute a diagnosis of

PRINCIPLES OF PATHOLOGY AND MOLECULAR ANALYSIS

Table 1 (continued)

Uterine Sarcoma: Mesenchymal Tumors & Mixed Epithelial and Mesenchymal Tumors					
Tumor	Hallmarks for Histologic Diagnosis	Relevant Molecular Finding	Additional Confirmatory Tests	Relevant Prognostic Features	Other
Uterine Tumor Resembling Ovarian Sex Cord Tumor ¹⁶⁻¹⁸	Bland spindle cell proliferation with extensive sex cord-like differentiation and no endometrial stromal component.	<i>ESR1</i> or <i>GREB1</i> fusions in a subset.	Immunohistochemical expression of sex cord markers (inhibin, calretinin, SF1, FOXL2) and/or detection of <i>GREB1</i> or <i>ESR1</i> fusions by FISH and/or targeted RNA sequencing is confirmatory.	Tumors have uncertain malignant potential with ~25% being malignant. Necrosis and MI ≥2/10 HPF and/or presence of <i>GREB1</i> fusion may portend malignant behavior.	
Rhabdomyosarcoma ¹⁹⁻²¹	Embryonal subtype consists of small primitive cells which may form a cambium layer in botryoid tumors; strap cells and fetal cartilage can be seen. Marked atypia defines the pleomorphic subtype. Alveolar subtype consists of small primitive cells growing in nests or alveoli.	<i>FGFR4/RAS/AKT</i> pathway mutations in embryonal tumors. <i>PIK3CA</i> and <i>TP53</i> mutations in pleomorphic tumors. <i>FOXO1</i> fusion in alveolar tumors. <i>DICER1</i> mutations are present in up to 95% of embryonal rhabdomyosarcoma.	IHC expression of myogenin and/or myoD1 is confirmatory. Extensive sampling must be performed to exclude carcinosarcoma or adenosarcoma with sarcomatous overgrowth. FISH and/or targeted RNA sequencing for <i>FOXO1</i> fusion is recommended to confirm alveolar subtype.	Embryonal subtype has better prognosis than pleomorphic and alveolar subtypes. Age and stage are prognostic factors. Anaplasia in embryonal subtype is a poor prognostic factor.	
Müllerian Adenosarcoma ²²⁻²⁵	Biphasic tumor with benign often metaplastic epithelium associated with an atypical usually low-grade spindle cell proliferation exhibiting phyllodes growth and periglandular stromal condensation; Sarcomatous overgrowth is defined by sarcoma comprising ≥25% of the tumor volume.	8q13 amplification and copy number gains of <i>MYBL1</i> in a subset; <i>NCOA2/3</i> fusions in a subset; rare <i>FGFR2</i> , <i>KMT2C</i> , <i>DICER1</i> , <i>ATRX</i> , and <i>TP53</i> mutations; <i>MDM2/CDK4</i> and <i>TERT</i> amplifications.	Ancillary testing is usually not required.	Myoinvasion, high-grade features and sarcomatous overgrowth are poor prognostic factors.	
Carcinosarcoma ²⁶	Biphasic tumor with carcinomatous and sarcomatous components.	<i>TP53</i> , <i>PTEN</i> , <i>PIK3CA</i> , <i>PPP2R1A</i> , <i>FBXW7</i> , and <i>KRAS</i> mutations; EMT gene signature.	Ancillary testing is usually not required.	Heterologous differentiation portends worse prognosis.	

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SDUS, and other aggressive malignancies such as undifferentiated endometrial carcinoma may show loss of expression of this protein.^{22,23}

Uterine Leiomyosarcoma

ULMSs are usually of the spindle cell (conventional) type, but less common variants with myxoid^{24,25} or epithelioid²⁶ morphology also exist. Although morphology differs between subtypes, all express varying degrees of the smooth muscle markers, including desmin, smooth muscle actin (SMA), and caldesmon. The panel recommends an IHC panel including desmin and SMA to support a ULMS diagnosis, particularly if myxoid or epithelioid ULMS is suspected.

Myxoid ULMSs may appear histologically similar to *BCOR*-altered HGEs or inflammatory myofibroblastic tumor. The panel recommends cyclin D1 and/or *BCOR* IHC to help exclude an HGE diagnosis, as the latter is often overexpressed in HGE. A subset (25%) of myxoid ULMSs also harbor *PLAG1* fusions. Therefore, a myxoid ULMS diagnosis may be supported by positive desmin and SMA IHC along with *PLAG1* rearrangement by FISH assay or RNA sequencing.^{24,25}

One differential diagnosis that must be considered for epithelioid ULMS is PEComa, given the observed

similarities in morphology and IHC for smooth muscle markers. IHC testing for HMB45 and melan A may be performed if a diagnosis of PEComa is being considered, with HMB45 being fairly sensitive and melan A being specific for PEComa compared with ULMS. However, it is recognized that uterine mesenchymal tumors with myomelanocytic differentiation can still be challenging to classify solely by IHC. Recently, a study examining this specific group of diagnostically challenging tumors supported the use of genomic profiling to aid in their classification.²⁷

Uterine Tumor Resembling Ovarian Sex Cord Tumor

UTROSCTs are very rare tumors with sex cord-like differentiation, but without a stromal component as observed in ESSs. Most of these tumors harbor either *ESR1* or *GREB1* fusions.²⁸⁻³⁰ The panel recommends an IHC panel that includes sex cord markers (eg, inhibin, calretinin, SF1, FOXL2); UTROSCTs are often positive for a broad range of biomarkers. In some cases, FISH or RNA sequencing for *ESR1* or *GREB1* fusions may be helpful to confirm the diagnosis. Approximately 25% of these tumors are malignant³¹; the panel notes that the presence of necrosis, high mitotic index, and *GREB1* fusions may be associated with malignant behavior.

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UTSARC-A
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Rhabdomyosarcoma

Uterine RMSs are an aggressive, heterogeneous group of tumors that are extremely rare in adult women. Subtypes include alveolar, embryonal, and pleomorphic³²; all express myogenic biomarkers (eg, myogenin and MyoD1).³³ Therefore, the panel notes that diffuse expression of ≥ 1 myogenic biomarkers by IHC can help confirm a uterine RMS diagnosis. Prognosis differs between subtypes, with embryonal RMS having the best prognosis of the 3 subtypes.³⁴ Molecular alterations also differ between subtypes. *FOXO1* fusions are found in alveolar RMS, whereas *PIK3CA* and *TP53* mutations are found in pleomorphic RMS. *DICER1* mutations are present in up to 95% of embryonal RMS.^{35,36} The embryonal subtype also is known to harbor *FGFR4*/RAS/*AKT* pathway mutations.³³ The panel notes that extensive sampling should be performed to exclude epithelial components and diagnoses of carcinosarcoma and adenocarcinoma with heterologous rhabdomyosarcomatous differentiation.⁶ The panel recommends FISH and/or RNA sequencing

for *FOXO1* to help confirm cases of suspected uterine alveolar RMS.

Conclusions

Emerging evidence informs panel recommendations in the NCCN Guidelines for Uterine Neoplasms as well as all other NCCN Guidelines. Recent updates to the NCCN Uterine Neoplasms Guidelines include molecular profiling information for uterine sarcomas. This information is intended to complement histopathologic testing to improve differential diagnosis of relatively rare uterine sarcoma subtypes and provide safer, more effective care for patients with the disease. The panel notes that this information is not exhaustive, and intends to update these recommendations as more data become available.

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