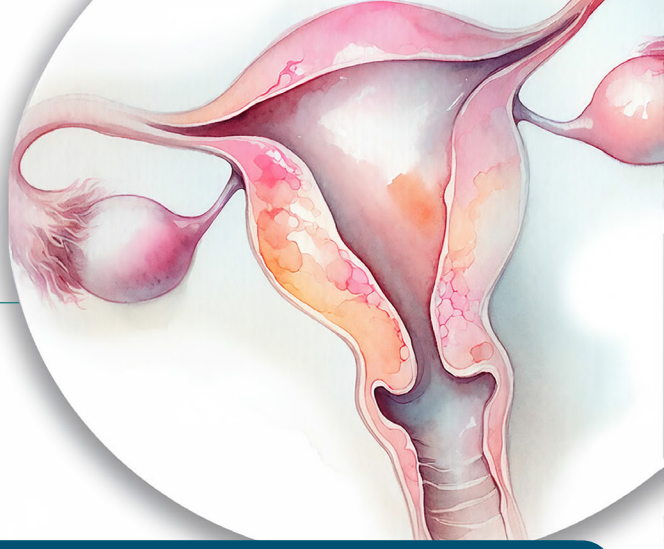
A Guideline-Informed Approach to Advanced/Recurrent **Endometrial Carcinoma:** *Biomarkers, Immunotherapy, and Multidisciplinary Care*



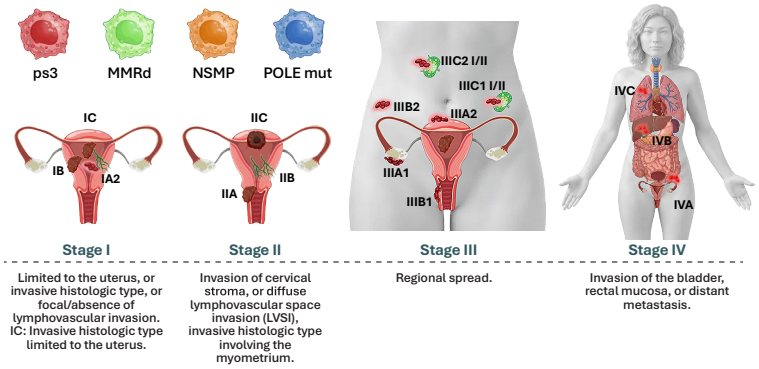
INITIAL EVALUATION[1,2]

- History and physical
- Complete blood count, liver and renal function tests, chemistry profile, and tumor protein testing (CA-125)
- Pathology review, additional endometrial biopsy as clinically indicated
- Imaging
- Molecular evaluation of tumor and assessment of hereditary cancer risk
- Germline and/or multigene testing

STAGING

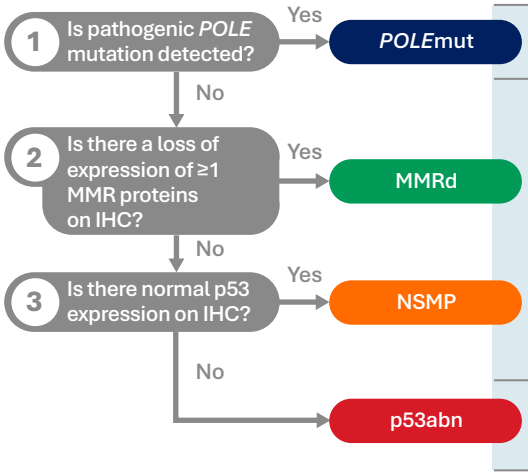
Staging of endometrial carcinoma (EC) should be performed with a multidisciplinary team (MDT) and should be based on a system that incorporates tumor extent, lymphovascular invasion (LVI) status, and molecular classification, such as the 2023 International Federation of Gynaecology and Obstetrics (FIGO) EC classification system **(Figure 1 and 2)**[3,4]

Figure 1. FIGO 2023 EC classification system[3–5]



MMRd = mismatch repair-deficient; mut = mutation; NSMP = no specific molecular profile.

Figure 2. ESGO–ESTRO–ESP prognostic risk groups[4,6,7]



	Low risk	Intermediate risk	High-Intermediate risk	High risk	Advanced/metastatic
POLEmut	Stage I/II, no residual disease				Stage III-VA with residual disease Stage IVB
MMRd	Stage IA, low-grade endometrioid, negative/focal LVSI	Stage IB, low-grade endometrioid, negative/focal LVSI Stage IA, high-grade endometrioid, negative/focal LVSI Stage IA non-endometroid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion	Stage I endometrioid, substantial LVSI, any grade or depth of invasion Stage IB high-grade endometrioid, any LVSI Stage III endometrioid	Stage III-VA endometrioid, no residual disease Stage LIVA serous, mixed, undifferentiated, or carcinosarcoma with myometrial invasion and no residual disease	
NSMP					
p53abn		Stage IA without myometrial invasion		Stage HVA with myometrial invasion and no residual disease	

ESGO = European Society of Gynaecological Oncology; ESP = European Society of Pathology; ESTRO = European Society for Radiotherapy and Oncology; IHC = immunohistochemistry; LVSI = lymphovascular space invasion; MMR = mismatch repair; MMRd = mismatch repair deficient; NSMP = no specific molecular profile; p53abn = abnormal p53; *POLE*mut = *POLE*-mutated.

EC TREATMENT PLANNING

Treatment planning should involve an MDT that includes specialists in the management of gynecologic cancers.[4] Treatment options are based in part on stage of disease and risk status **(Table 1)**[1,6]

Table 1. Risk-based treatment of EC[4,6,7]

Risk level	Surgery	RT	Chemotherapy	ICI	ET
Low	√				
Intermediate	√	√			
High-intermediate	√	√			
High	√	√	√		
Advanced/metastatic	√	√	√	√	√

ET = endocrine therapy; ICI = immune checkpoint inhibitor; RT = radiation therapy.

PRIMARY/ADJUVANT THERAPY FOR STAGE III-IV EC

As a general rule, patients with stage III–IV EC undergo surgery followed by systemic therapy with or without external-beam radiation therapy or vaginal brachytherapy.[1,2] Preferred primary adjuvant therapies for stages I through IV EC include chemoradiation or chemotherapy plus an immune checkpoint inhibitor (ICI), as shown in Table 2.[1]

First- and subsequent-line therapy selection for recurrent/advanced disease should consider patient- and disease-related factors such as biomarkers, patient fitness, and prior therapies **(Tables 3 and 4)**[1]

Table 2. NCCN Guidelines: Primary/adjuvant therapy for stage I–IV EC[1]*

Subgroup	Regimen	Notes
Preferred	**Chemoradiation Therapy** Cisplatin + RT → Carboplatin/Paclitaxel	
	Systemic Therapy Carboplatin/Paclitaxel + Pembrolizumab Carboplatin/Paclitaxel + Dostarlimab Carboplatin/Paclitaxel + Durvalumab Carboplatin/Paclitaxel + Trastuzumab Carboplatin/Paclitaxel + Bevacizumab Carboplatin/Paclitaxel	 Stage III–IV, except carcinosarcoma (Cat. 1) Stage III–IV (Cat. 1) Stage III–IV MMRd only (Cat. 1) Stage III–IV HER2+ uterine serous carcinoma or carcinosarcoma Stage III–IV Standard regimen
Other recommended	Carboplatin/Paclitaxel/Durvalumab + Durvalumab/Olaparib	Stage III–IV MMRp tumors (Cat. 2B)

Table 3. NCCN Guidelines: First-line therapy for recurrent EC[1]*

Subgroup	Regimen	Notes
Preferred	Carboplatin/Paclitaxel + Pembrolizumab Carboplatin/Paclitaxel + Dostarlimab Carboplatin/Paclitaxel + Durvalumab Carboplatin/Paclitaxel + Trastuzumab Carboplatin/Paclitaxel	Except for carcinosarcoma (Cat. 1) Cat. 1 MMRd only (Cat. 1) HER2+ uterine serous carcinoma/carcinosarcoma Cat. 1 for carcinosarcoma
Other recommended	Carboplatin/Docetaxel Carboplatin/Paclitaxel + Bevacizumab	— —
Useful in certain circumstances	Carboplatin/Paclitaxel/Durvalumab → Durvalumab/Olaparib	MMRp (Cat. 2B)
Post-platinum biomarker-directed therapy	Lenvatinib + Pembrolizumab Pembrolizumab Pembrolizumab Dostarlimab	MMRp (Cat. 1) TMB-H MSI-H/MMRd MSI-H/MMRd

Table 4. NCCN Guidelines: Second- or subsequent-line systemic therapy for EC[1]*

Subgroup	Regimen
Other recommended	Chemotherapy or Tyrosine Kinase Inhibition
Useful in certain circumstances (biomarker-directed therapy)	
pMMR	Lenvatinib + Pembrolizumab (Cat. 1) or Axitinib + Avelumab
TMB-H tumors	Pembrolizumab or Ipilimumab + Nivolumab
MSI-H/dMMR tumors	Pembrolizumab, Dostarlimab, Avelumab, Nivolumab, Tislelizumab, or Retifanlimab (Cat. 2B)
HER2+ (IHC 1+/2+/3+)	Trastuzumab Deruxtecan†
***NTRK* gene fusion**	Larotrectinib, Entrectinib, or Repotrectinib†
***RET* gene fusion**	Selpercatinib

*All recommendations are Cat. 2A level of evidence unless otherwise noted. † = limited to carcinosarcoma.
Cat. = category; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; MMR = mismatch repair; MMRd = MMR deficient; MMRp = MMR proficient; MSI-H = microsatellite instability-high; RT = radiation therapy; TMB-H = tumor mutational burden–high.

Patients should be carefully counseled about the suggested diagnostic and treatment plans and potential alternatives, including the risks and benefits of all options.

References

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