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Evolving Roles of Histologic Evaluation and Molecular/Genomic Profiling in the Management of Women with Endometrial Cancer

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Abstract

Endometrial cancers are the most common gynecologic malignancies. The staging of endometrial cancer has evolved from a clinical-based system to a comprehensive surgical-pathologic approach that allows for better risk stratification and treatment planning. Over the past few years, the use of the National Comprehensive Cancer Network sentinel lymph node mapping algorithm for the surgical staging of endometrial cancer has gained significant acceptance and is now commonly applied in many practices. However, the pathologic evaluation of prognostic factors is beset by challenges, including the reproducibility of histologic classification and International Federation of Gynecology and Obstetrics grading, as well as the questionable clinical significance of low-volume tumor in sentinel lymph nodes. With the revelation of major genomic classes of endometrial cancer comes the potential for improved, reproducible, and prognostically relevant classification schemes, which integrate traditional pathologic parameters with genomic findings, to aid in treatment decisions. The pathologic identification of new variants of endometrial cancer, such as undifferentiated carcinoma, continue to advance the phenotypic spectrum of these tumors, spurring genomic and functional studies to further characterize their mechanistic underpinnings and potentially reveal new avenues for treatment. In the era of precision medicine, pathologic assessment of biomarkers (such as mismatch repair proteins) and recognition of phenotypes that are amenable to specific targeted therapies (such as *POLE*-mutated tumors) have become integral to the management of women with endometrial carcinoma.

Keywords

Endometrial cancer; Genomics; Pathology; Precision oncology; Prognosis; Prognostic factors; Risk stratification; Sentinel lymph node biopsy, Staging; Targeted therapy

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1. INTRODUCTION

Endometrial cancers comprise more than half of all gynecologic cancer diagnoses in the United States.[1] Pathologic evaluation is an important element of the management of women with this disease. As management approaches continue to evolve, as a result of reported data from clinicopathologic and molecular genetic studies, pathology will continue to play a central role in diagnosis, prognostic assessment, and treatment planning.

2. EVOLUTION OF SURGICAL-PATHOLOGIC STAGING OF ENDOMETRIAL CANCER

Most patients with endometrial cancer present with abnormal bleeding, the investigation of which involves pelvic ultrasonography with endometrial biopsy/curettage. Histopathologic evaluation of the biopsy/curettage specimen confirms the diagnosis.[2,3] Early staging schemes were essentially based on clinical findings, but since 1988, a more accurate surgical-pathologic staging approach has been used (Table 1).[4]

2.1 Comprehensive surgical staging

Preoperatively, staging is performed to estimate recurrence risk, and is based on the imaging evaluation of myometrial invasion, cervical involvement, and lymph node metastasis. Magnetic resonance imaging and transvaginal ultrasonography are effective modalities for the assessment of myometrial and cervical invasion, but imaging is poor at detecting lymph node metastases. Accurate staging, therefore, relies on comprehensive surgical staging to obtain specimens that can be thoroughly examined by pathologists for key prognostic factors, including myometrial invasion; cervical involvement; adnexal, peritoneal, and lymph node metastasis; histologic type and grade; and lymphovascular space involvement. Risk stratification systems incorporating pathologic prognostic factors are crucial in guiding clinical management decisions.[5–7]

Traditional surgical staging of endometrial cancer involves removing the uterus, cervix, adnexa, pelvic and para-aortic lymph nodes, and obtaining pelvic washings, followed by pathologic examination. This allows accurate diagnosis, identification of disease extent, prognostic assessment, and selection of patients for adjuvant therapy. The advantage of surgical-pathologic staging over clinical staging was reported in Gynecologic Oncology Group (GOG) study 33, which showed that 9% of patients with clinically stage I disease had pelvic nodal involvement, 6% had para-aortic lymphadenopathy, 5% had adnexal involvement, and 6% had other extrauterine metastases.[8] Comprehensive surgical staging also identifies patients with advanced-stage disease who require radiation therapy and/or chemotherapy; low-stage patients with high-risk features (high-grade tumors, deep myometrial invasion, lymphovascular space involvement) who should receive adjuvant treatment; and patients without high-risk features who may safely be spared adjuvant chemoradiation and its attendant morbidity.[8,9]

Despite the benefits of a surgical-pathologic staging system, the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system has its limitations, particularly in the setting of corpus-confined carcinoma. Since the current staging scheme

applies uniformly to all cases, irrespective of staging adequacy or tumor type, clinical outcomes are highly variable. For example, using the Memorial Sloan Kettering Cancer Center Endometrial Cancer Nomogram,[10] a 65-year-old woman with FIGO grade 1 endometrioid carcinoma, middle-third myometrial invasion, and a benign lymphadenectomy would have an estimated 5-year overall survival rate of 92%, whereas a 65-year-old woman with serous carcinoma, middle-third myometrial invasion, and no lymph node evaluation would have an estimated 5-year overall survival rate of only 64%. This observation prompted a proposal to amend the current FIGO staging scheme.[11]

Another controversy related to surgical staging in endometrial cancer is the role of para-aortic lymph node dissection. It has been shown that the rate of isolated para-aortic lymph node involvement in the absence of pelvic lymph node involvement is very low (<2%).[12] Patients with high-risk disease have a higher frequency of para-aortic lymph node involvement, suggesting that para-aortic lymphadenectomy should be performed as part of surgical staging in these patients.[13] However, a classification and regression tree analysis found that overall survival was predicted by FIGO stage and grade (a binary system of low- vs. high-grade) but not by para-aortic lymph node status,[14] advocating for an approach with less extensive lymph node dissection.

2.2 Sentinel lymph node mapping for endometrial cancer

Approximately 6–23% of women with endometrial cancer who undergo pelvic lymphadenectomy develop long-term morbidity, such as lymphedema.[15,16] This is likely an underestimation, as patient surveys have indicated leg lymphedema rates as high as 20–40%.[16] To reduce this morbidity and to improve the detection of lymph node metastases, a sentinel lymph node (SLN) mapping approach to the management of endometrial cancer was introduced and has been incorporated as an option in the National Comprehensive Cancer Network (NCCN) guidelines since 2014.[17] The goal of SLN mapping is to initially target and assess the lymph nodes most likely to be involved by metastatic cancer (i.e, the sentinel, or first, nodes in the path of lymphatic flow away from the tumor), thereby limiting the extent of surgery and morbidity associated with extensive lymphadenectomy. This technique identifies SLNs in approximately 85% of patients, of whom 12% have positive SLNs.[18] Detailed pathologic examination of SLNs (ultrastaging), which includes the assessment of multiple sections of the SLNs using routine stains as well immunohistochemistry for epithelial markers,[19] allows for the detection of low-volume metastases that can be missed with standard techniques.[18,19] SLN assessment also can refine surgical-pathologic stage; for example, in one study, SLN biopsy results upstaged 10% of patients with low-risk and 15% of those with intermediate-risk endometrial cancer,[20] with implications for adjuvant treatment planning.

2.3 Challenges in the pathologic evaluation of critical prognostic factors

Assignment of histotype is straightforward in the majority of endometrial cancers, but can be exceedingly difficult in some high-grade tumors exhibiting morphologic ambiguity.[21,22] There are several risk-group stratification systems based on surgical-pathologic staging of endometrial cancer[7,9,13,23–27]; however, the poor reproducibility of histotype and grade classification[21,22,28–30] presents challenges for accurate prognostic assessment,[27] selecting

optimal treatment, determining eligibility for clinical trials, and for comparison of treatment interventions between studies. Integrating pathologic parameters with findings of molecular genetic analyses (described below) may provide a more accurate and prognostically relevant classification of these tumors.[31–34]

Tumor grade and histotype designation in preoperative biopsy and curettage specimens may be incorrect;[35] for example, in one study, 1% of preoperative grade 1 endometrioid adenocarcinomas were upgraded to grade 2–3 cancers, and a further 1% harbored a high-risk histotype (serous or clear cell carcinoma) in the hysterectomy specimens.[36] Similarly, the undifferentiated component of a dedifferentiated carcinoma, which often lies deep to the well-differentiated component, may not be sampled in a biopsy or curettage specimen.[37,38] These sampling errors are more likely to occur with small-volume samples. In these cases, there is a potential for surgical understaging due to the failure to detect high-risk features (high-grade tumor component) in the preoperative specimens.

Although SLN biopsy offers advantages of accurate staging and reduced morbidity from the avoidance of an unnecessary lymphadenectomy, its long-term survival benefits, if any, are unknown.[3] Furthermore, the clinical significance of small volumes of tumor (e.g., isolated tumor cells) in SLNs is unknown, and further studies with long-term follow-up are ongoing.

3. EVOLVING DIAGNOSTIC PARADIGMS IN ENDOMETRIAL CANCER AND THEIR CLINICAL IMPLICATIONS

3.1 Molecular genetic findings and integrated pathologic-genetic classification of endometrial cancer

The Cancer Genome Atlas (TCGA) study of endometrioid and serous carcinomas found mutations in several genes (e.g., *TP53*, *PTEN*, *PIK3CA*, *PPP2R1A*, *FBXW7*, *CTNNB1*, *KRAS* and *POLE*), but more importantly, identified four major genomically defined classes of tumor (*POLE*-ultramutated, microsatellite instability-hypermutated [MSI-H], copy-number-low, and copy-number-high). These groups were also clinically significant, as they correlated with progression-free survival; patients with *POLE*-mutated tumors had an excellent prognosis and those with copy-number-high tumors had poor outcomes, while the MSI-H and copy-number-low groups had intermediate prognoses.[34] DNA ploidy was recently shown to differ between TCGA groups, and was highest in the p53-aberrant group. Abnormal DNA ploidy was associated with higher grade, non-endometrioid histotype, and poorer survival (particularly in mismatch repair-deficient tumors).[39] A recent study of endometrial clear cell carcinomas identified similar genomic classes, which were also associated with prognosis.[40] Uterine carcinosarcomas also frequently harbor mutations in *TP53*, *PTEN*, *PIK3CA*, *PPP2R1A*, *FBXW7*, and *KRAS*, similar to endometrioid and serous carcinomas.[41]

It is also apparent that genomic classes of endometrial carcinoma are associated with phenotypes. Copy-number-high tumors, which are characterized by *TP53* mutations and alterations associated with cell cycle deregulation, comprise some high-grade endometrioid adenocarcinomas and clear cell carcinomas, and all serous cancers.[34,40] Copy-number-low

tumors are predominantly low-grade endometrioid adenocarcinomas.[34] *POLE*-mutated endometrial carcinomas are typically characterized by: high grade; tumor-infiltrating lymphocytes and/or peritumoral lymphocytes; morphologic heterogeneity/ambiguity; and bizarre/giant tumor cell nuclei.[42,43] Endometrioid histotype is most frequent, although *POLE* mutations have also been reported in clear cell carcinomas,[40] undifferentiated carcinomas,[44] and carcinosarcomas.[45] MSI-H endometrial cancers, which may be associated with germline alterations (Lynch syndrome) or sporadic aberrations, are associated with lower uterine segment location, endometrioid histology, mucinous differentiation, tumor-infiltrating lymphocytes, and peritumoral lymphocytes.[46–49]

Molecular classification of endometrial cancer has been shown to be reproducible and associated with clinical outcomes.[31–34] However, these algorithms do have some limitations. P53 immunohistochemistry does not correlate perfectly with *TP53* copy number changes,[39,40] and its use in these algorithms may therefore misclassify some copy-number-high tumors. The algorithms do not address how to categorize tumors harboring more than one classifying genomic aberration (*POLE* mutations, MMR-deficiency or P53-mutations) when the algorithmic components are performed in parallel rather than sequentially. The algorithms do not allow for the exploration of the significant heterogeneity seen within the copy-number-low group.[50,51] Finally, in the ProMisE algorithm, DNA MMR immunohistochemistry is performed before *POLE* sequencing, which may result in failure to detect MMR-deficient tumors with *POLE* mutations, as well as their incorrect classification as MMR-deficient tumors rather than *POLE*-mutated tumors; as a result, our approach differs slightly in performing POLE sequencing before DNA MMR immunohistochemistry (Fig. 1). Despite these limitations, an integrated genomic-pathologic classification scheme incorporating genomic-based classifications with traditional clinicopathologic prognostic parameters (Fig. 1) represents the best available method for stratifying patients into prognostically distinct groups that may benefit from tailored treatment approaches.[52]

3.2 Molecular genetic findings in synchronous endometrial and ovarian carcinomas

The staging of patients with synchronous endometrial and ovarian carcinomas traditionally has been based on pathologic criteria to determine whether the two tumors are independent primaries (each being low-stage disease) or whether one is a metastasis from the other (high-stage disease).[53,54] Two recent studies utilizing massively parallel sequencing analyses showed that the majority of synchronous endometrial and ovarian carcinomas are clonally related, and therefore, the latter scenario applies.[55,56] Nevertheless, many of these patients have excellent clinical outcomes belying their apparently high stage,[57] and further studies are required to determine the mechanisms underlying their indolent behavior.

3.3 Recently recognized types and variants of endometrial carcinoma

There are several recently described phenotypic variants of endometrial carcinoma, which may be associated with specific clinical phenotypes and genotype. A few examples are briefly presented.

3.3.1 Undifferentiated and Dedifferentiated carcinoma—

Undifferentiated and dedifferentiated endometrial carcinomas are uncommon, highly aggressive tumors.[38,58]

Undifferentiated carcinoma is a monomorphic tumor composed of small- to intermediate-sized cells arranged in sheets without any obvious epithelial differentiation, which mimics lymphoma, plasmacytoma, high-grade endometrial stromal sarcoma, or small cell carcinoma.[38,58] Approximately 40% of undifferentiated carcinomas are associated with a component of low-grade endometrioid adenocarcinoma; these cases are termed 'dedifferentiated carcinomas'.[37]

Most undifferentiated carcinomas display immunohistochemical evidence of epithelial differentiation in the form of intense but focal EMA and cytokeratin 18 expression, along with vimentin and CD138 expression.[59,60] Loss of expression of proteins involved in chromatin remodeling through SWI/SNF complexes, such as BRG-1 (the protein product of *SMARCA4*), INI-1 (the protein product of *SMARCB1*), or BAF250a (the protein product of *ARID1A*), may be seen.[61,62] DNA mismatch repair deficiency and loss of expression of MLH1 and PMS2, mostly due to *hMLH1* promoter methylation, is seen in 50–60% of tumors.[63] Genomically, these tumors harbor mutations in *POLE*, *SMARCA4*, *ARID1B*, *CTNNB1*, *PPP2R1A,* or *TP53*.[64]

3.3.2 Corded and hyalinized endometrioid carcinomas—A subset of endometrioid adenocarcinomas (termed 'corded and hyalinized endometrioid carcinomas [CHEC]) shows unusual morphologic features including cords of epithelioid cells, spindle cells, and hyalinized stroma that sometimes forms osteoid.[65] These tumors present mainly at a low stage and have a good prognosis. Their importance lies in their recognition and distinction from endometrial carcinosarcomas, which are usually seen in older patients and are highly aggressive malignancies.[41] Awareness of CHEC allows for the ready morphologic distinction from carcinosarcoma, as the spindle cell component of CHEC lacks conspicuous atypia, in contrast to the high-grade appearance of the sarcomatous component of carcinosarcomas.

3.3.3 Mesonephric-like carcinomas—Mesonephric carcinomas have long been recognized in the uterine cervix. Recent studies have identified tumors involving the uterine corpus that show morphologic and immunohistochemical similarities to the cervical tumors; the uterine tumors are termed 'mesonephric-like carcinomas'.[66,67] The uterine tumors display a uniform appearance, with tubular, solid and papillary architectural patterns, and are composed of cells with atypical, angulated and overlapping, vesicular nuclei. The tubular structures are small and may contain dense luminal eosinophilic material.[66,67] Immunohistochemically, the tumors express TTF-1, as well as CD10, calretinin and GATA3, while estrogen and progesterone receptors are negative.[67] Mutations in *KRAS*, *NRAS,* and chromatin remodeling genes (*ARID1A*, *ARID1B*, *SMARCA4*) have been reported in mesonephric carcinomas.[68]

3.4 Biomarkers for classification and prognostic assessment

3.4.1 Identification of molecular-prognostic subgroups—MSI-H endometrial carcinomas can be effectively identified by assessing morphologic features (described above) and DNA mismatch repair deficiencies in histologic material with immunohistochemistry using antibodies directed against MLH1, PMS2, MSH2, and

MSH6.[69,70] There is a high level of concordance between the results of immunohistochemistry and polymerase chain reaction-based microsatellite instability analysis.[71] Immunohistochemical expression of p53 (classified as aberrant if absent or diffusely overexpressed) is associated with a poor prognosis in endometrial cancer[72,73] and correlates with *TP53* mutation status.[74] The identification of a *POLE* mutation in patients with endometrial cancer (based on morphologic features of the tumor, as described above, and *POLE* sequencing) may help these patients avoid overtreatment given their excellent prognosis.[34] *POLE*-mutated and MSI-H tumors are also amenable to immunotherapy (as discussed below).

Simplified diagnostic algorithms for the molecular classification of endometrial cancers into TCGA classes have been recently proposed.[50,75] The ProMisE (Proactive Molecular Risk Classifier for Endometrial Cancer) algorithm involves immunohistochemistry for DNA mismatch repair proteins, sequencing of mismatch-repair-proficient tumors for *POLE* mutations, and immunohistochemistry for p53 in the *POLE*-wild-type tumors. This algorithm accurately classifies endometrial cancers as mismatch repair-deficient (MSI-H), *POLE*-mutated, p53-wild-type (copy-number-low) or p53-aberrant (copy-number-high),[75] and has potential as a prognostic and risk stratification assay for clinical use.

3.4.2 High-grade endometrial cancers—The copy-number-high group of endometrial carcinomas identified in TCGA study includes high-grade endometrioid adenocarcinomas and serous carcinomas. The histopathologic and immunohistochemical features of these tumors may overlap considerably, leading to poor interobserver reproducibility in the histotyping of high-grade endometrial carcinomas.[22,30] This poor reproducibility doubtless contributes to variability in the reported prognosis of patients with high-grade endometrioid adenocarcinoma compared to those with serous carcinoma.[76–80]

However, a recent study of copy-number-high endometrial carcinomas showed significant differences between high-grade endometrioid adenocarcinomas and serous carcinomas with respect to their stage distributions and sites of recurrence.[81] If these differences also correlate with other differences in clinical behavior, it is important to attempt to distinguish high-grade endometrioid adenocarcinomas from serous carcinomas using available biomarkers to supplement histopathologic interpretation. No single marker is absolutely diagnostic of either histotype, and therefore, a panel of markers, including at least p53 and p16 with either ER or PTEN is recommended. p16-negative/PTEN-negative and/or ARID1A-negative/p16-negative/p53-wild-type tumors are most likely endometrioid, while serous carcinomas are more likely to be p53-aberrant/p16-positive/ER-negative.[82] Tumors with discordant findings may be subjected to an expanded immunohistochemical panel that includes DNA mismatch repair proteins (MLH1, PMS2, MSH2, MSH6), loss of expression of at least one of which would support the diagnosis of endometrioid adenocarcinoma.

3.4.3 CTNNB1-mutated endometrial carcinomas—Patients with low-stage endometrial cancer without high-risk features, as described above, generally have excellent outcomes; however, a small proportion of these patients do poorly. A recent study exploring factors associated with poor outcomes in women with low-grade, early-stage endometrial carcinomas found that in patients with endometrioid adenocarcinomas, *CTNNB1* mutations

were found to be independent predictors of poorer recurrence-free survival.[83] In this study, 84% of tumors with *CTNNB1* mutations showed nuclear expression of beta catenin (the protein product of *CTNNB1*) by immunohistochemistry.[83]

3.5 Pathology and precision medicine in women with endometrial cancer

Pathologists play an important role in the development and implementation of novel therapies targeting molecular/genomic alterations in endometrial cancer. The roles of pathology in the present era of precision oncology include the following: identification of homogenous subsets of tumors, which are critical to obtain meaningful results from exploratory molecular/genomic studies seeking to identify novel targets; evaluation of expression of molecular biomarkers and their localization at the tissue level, which can assist in treatment decisions; phenotype-genotype correlations that assist identification of tumors likely to harbor specific molecular targets or that are likely to be amenable to specific therapy; and selection of suitable patients, based on their phenotypes and biomarker profiles, for entry into clinical trials of novel therapies.

3.5.1 Identification of endometrial cancers that are candidates for immunotherapy—

POLE-mutated and mismatch repair-deficient tumors exhibit tumor-infiltrating lymphocytes, high levels of neoantigens, and expression of immune checkpoint regulators, such as programmed death receptor-1 (PD-1)[84,85] or its ligand, PDL-1,[86] which are thought to promote escape from immune surveillance. Immune checkpoint blockade with the anti-PD1 antibody pembrolizumab has shown responses in patients with *POLE*-mutated[85] and mismatch repair-deficient endometrial cancer,[87] and pembrolizumab has been approved by the FDA for metastatic cancers exhibiting mismatch repair deficiency. PDL-1 expression can be directly examined in tissues using immunohistochemistry, but the optimal methods and antibodies are yet to be standardized.[88]

3.5.2 Identification of endometrial cancers that are candidates for mitogen-activated protein kinase (MAPK) pathway inhibition—

KRAS mutations are common in endometrial cancer,[34] and are associated with mucinous differentiation.[89] *ERBB2* amplifications are also identified in endometrial serous carcinomas.[90] KRAS is not a direct molecular therapeutic target, but the identification of tumors with MAPK pathway activation might be susceptible to therapy directed against other components of the MAPK/ERK pathway, such as members of the EGFR family.

4. CONCLUSIONS

Over the past two decades, there have been numerous *ex vivo*, genomic, translational, pathologic, and clinical studies that have significantly expanded our understanding of endometrial cancer. This improved understanding has led to refinements in our approach to the diagnosis and treatment of women with these tumors. As an integral part of any multidisciplinary team, pathology continues to play an important role in diagnosis and prognostic assessment, risk stratification and therapeutic decision-making, and the development and implementation of novel therapeutic agents and strategies for women with these cancers.

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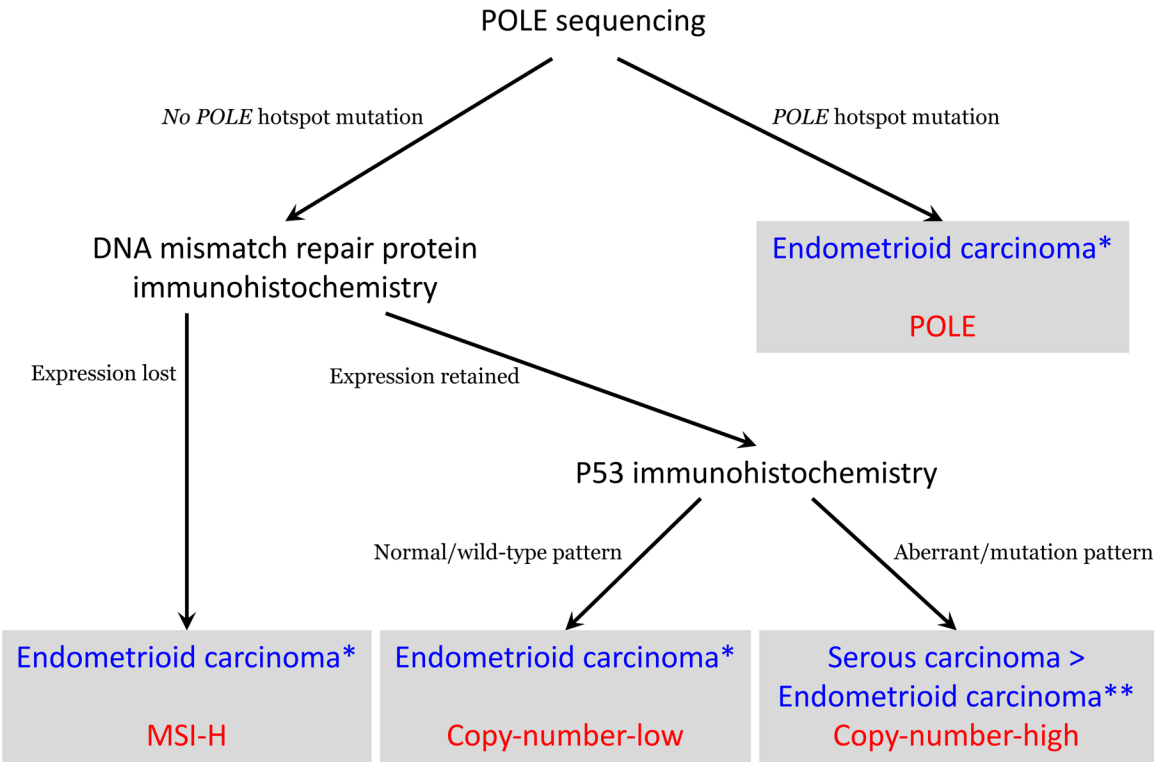

Figure 1.

Diagnostic algorithm for integrated genomic-pathologic classification of endometrial carcinomas (blue=histotyope; red=TCGA genomic class).

MSI-H: microsatellite instability high; *May also apply to clear cell carcinomas; **This algorithm does not distinguish between histotypes of TP53-mutated copy-number-high tumors, i.e., high-grade endometrioid carcinoma, serous carcinoma, or clear cell carcinoma

Table 1.

Evolution of FIGO endometrial cancer staging classification over time[4]

	FIGO staging, 1961–1971	FIGO staging, 1988	FIGO staging, 2009
Basis	**Clinical**	**Surgical-Pathologic**	**Surgical-Pathologic**
Stage 0	Histological findings suspicious for malignancy, but not proven		
Stage I	Carcinoma confined to uterine corpus *IA: Length of uterine cavity is ≤8 cm *IB: Length of uterine cavity is >8 cm	IA: Tumor limited to endometrium IB: Invasion limited to less than half of myometrium IC: invasion of half or greater of myometrium	Tumor confined to corpus uteri IA: No myometrial invasion or invasion to less than half of myometrium; endocervical glandular involvement only IB: Invasion of half or greater of myometrium
Stage II	Carcinoma involves uterine corpus and cervix	IIA: Endocervical glandular involvement only IIB: Cervical stromal invasion	Tumor invades cervical stroma but does not extend beyond uterus
Stage III	Carcinoma extends outside uterus but not outside the pelvis	IIIA: Tumor invades serosa and/or adnexa and/or positive peritoneal cytology IIIB: Vaginal metastases IIIC: Metastases to pelvis and/or para-aortic lymph nodes	Local and/or regional spread of tumor IIIA: Tumor invades serosa of corpus uteri and/or adnexa IIIB: Vaginal and/or parametrial involvement IIIC1: Positive pelvic lymph nodes IIIC2: Positive para-aortic lymph nodes
Stage IV	Carcinoma extends outside the true pelvis or obviously invades mucosa of bladder or rectum	IVA: Tumor invasion of bladder and/or bowel mucosa IVB: Distant metastases including intra-abdominal and/or inguinal lymph nodes	IVA: Tumor invasion of bladder and/or bowel mucosa IVB: Distant metastases including intra-abdominal and/or inguinal lymph nodes
Histologic grade	*Stage I tumors also subgrouped according to histologic type: G1: highly differentiated adenocarcinomas G2: differentiated adenocarcinomas with partly solid areas G3: predominately solid or entirely undifferentiated carcinomas)	Stage is irrespective of grade G1: ≤5% of non-squamous or non-morular solid growth pattern G2: 6–50% of non-squamous or non-morular solid growth pattern G3: >50% of non-squamous or non-morular solid growth pattern Notable nuclear atypia, inappropriate for architectural grade, raises the grade of a grade 1 or 2 tumor by 1	Stage is irrespective of grade G1: ≤5% of non-squamous or non-morular solid growth pattern G2: 6–50% of non-squamous or non-morular solid growth pattern G3: >50% of non-squamous or non-morular solid growth pattern Notable nuclear atypia, inappropriate for architectural grade, raises the grade of a grade 1 or 2 tumor by 1

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*Modifications in 1971