Endometrial Carcinoma in Women Aged 40 Years and Younger

Karuna Garg, MD; Robert A. Soslow, MD

Context.—Endometrial carcinoma is a disease of older postmenopausal women, and is relatively uncommon in patients younger than 40 years. Endometrial carcinomas in this age group may be familial, associated with Lynch syndrome, or sporadic.

Objectives.—To present our current knowledge of endometrial carcinomas in women younger than 40 years.

Data Sources.—The review is based on previously published articles on this topic.

Conclusions.—Most endometrial carcinomas that occur in this age group are associated with estrogen excess. They are usually low-grade endometrioid carcinomas that present at low stages and are associated with favorable clinical outcomes. Tumors associated with mismatch repair abnormalities and Lynch syndrome appear to be distinct, with worse prognostic factors and, possibly, clinical behavior. Conservative hormonal therapy and ovarian conservation are reasonable considerations in the management of these young patients, but carry the risk of tumor progression, recurrence, and an occult synchronous or metachronous ovarian carcinoma.

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The sporadic tumors and those associated with mismatch repair abnormalities appear to be distinct groups with different pathogenesis and clinicopathologic features (Table 1). In this review we will discuss the clinical and pathologic characteristics of these tumors, with special focus on problematic managerial issues specific to this age group. We will also discuss testing endometrial carcinomas for mismatch repair defects, with particular emphasis on IHC stains. Clinicopathologic findings from prior studies are summarized in Table 2.

CLINICAL FEATURES

Most young patients with endometrial carcinoma typically show a characteristic clinical profile (Table 2). They are often white with high body mass index (BMI) and are overweight (BMI, 25–30) or obese (BMI > 30).1–5,8,11,12 Reported rates of obesity in these patients have varied from 37% to 60%.2,3,8 Diabetes, hypertension, nulliparity, infertility, and irregular menstrual cycles are common in this patient population, and some of these patients likely have polycystic ovarian disease. In contrast, a smaller subset of young patients with endometrial carcinoma consists of thin women with normal BMI.

High BMI correlates with good prognostic features including low tumor grade, endometrioid histology, and presentation at early stage. Patients with low BMI are more likely to have higher-grade tumors, nonendometrioid histology, and may present at advanced stages with worse clinical outcomes.3,13

The group of patients with normal or low BMI is more likely to have DNA mismatch repair abnormalities or Lynch syndrome.8,13,14 In fact, low BMI in young patients with endometrial cancer has been proposed as a screening criterion for detection of Lynch syndrome, although...
occasional overweight or obese patients with Lynch syndrome have been reported.6,8

PATHOLOGIC FEATURES

The most common tumor type in this age group is endometrioid adenocarcinoma, and most tumors (83%–100%) are low grade, FIGO (Fédération Internationale de Gynécologie et d’Obstétrique [International Federation of Gynecologists and Obstetricians]) grade 1.2,3,5,8,9 Higher-grade tumors, including FIGO grade 3 endometrioid and undifferentiated or dedifferentiated carcinomas of the type described by Silva, can also occur in young patients.8,15,16 In our previous study on endometrial carcinoma in patients aged 40 years or younger, there were 5 undifferentiated/dedifferentiated carcinomas (7%).8 In another study on patients aged 40 years or younger, there were 5 undifferentiated/carcinomas consisting of sheets of dyscohesive, high-grade but uniform cells with necrosis within 60 months of diagnosis. Undifferentiated carcinomas consist of sheets of dyscohesive, high-grade but uniform cells with necrosis (Figure 1, A). When associated with a well-differentiated endometrioid carcinoma component, it may be referred to as dedifferentiated carcinoma (Figure 1, B). Undifferentiated carcinomas are frequently misdiagnosed as other entities, most frequently as FIGO grade 3 endometrioid carcinoma. When associated with a well-differentiated carcinoma component, the biphasic appearance may result in a misdiagnosis of carcinosarcoma (malignant mixed Mullerian tumor). Undifferentiated carcinomas often show only focal staining with epithelial markers including cytokeratin and epithelial membrane antigen, which can further contribute to their misdiagnosis as undifferentiated endometrial sarcoma or even lymphoma. In a study from MD Anderson Cancer Center, only 18% of their cases were diagnosed correctly.16

Undifferentiated carcinomas and dedifferentiated carcinomas are associated with mismatch repair abnormalities and Lynch syndrome.8,17,18 A study by Tafe et al19 showed abnormal staining for DNA mismatch repair proteins in 7 of 12 endometrial undifferentiated carcinomas (58%). While many of these tumors may be associated with MLH1 promoter methylation, we have seen cases of undifferentiated carcinoma in association with Lynch syndrome. From these observations, we would recommend staining all cases of undifferentiated carcinoma for DNA mismatch repair proteins, irrespective of patient age. Tumors with nonendometrioid histology are uncommon in this age group, but may be seen in patients with Lynch syndrome. Carcangiu et al19 reported that young patients with Lynch syndrome frequently had uterine tumors with nonendometrioid histology, including clear cell carcinoma, serous carcinoma, and carcinosarcoma. Similarly, Broaddus et al20 reported the occurrence of nonendometrioid tumors in patients with Lynch syndrome.

We have also noted that endometrial tumors associated with mismatch repair abnormalities and Lynch syndrome may show ambiguous morphologic features. These tumors can show overlapping architectural and cytologic features of endometrioid, serous, and/or clear cell carcinoma, and may be difficult to classify.21 Tumors that originate in the lower uterine segment are also associated with mismatch repair abnormalities, and these can display overlapping histologic and immunohistochemical characteristics of endometrial and endocervical adenocarcinomas.22

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Table 1. Features of Sporadic and Lynch Syndrome–Associated Endometrial Carcinoma

<table>
<thead>
<tr>
<th></th>
<th>Sporadic</th>
<th>Lynch Syndrome Associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Estrogen excess</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Pathology</td>
<td>Low-grade endometrioid carcinomas</td>
<td>Higher-grade tumors (including undifferentiated and nonendometrioid types)</td>
</tr>
<tr>
<td>Prognostic factors</td>
<td>Good</td>
<td>Deep myometrial invasion</td>
</tr>
<tr>
<td>Clinical outcome</td>
<td>Good</td>
<td>Not uniformly good</td>
</tr>
</tbody>
</table>

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Table 2. Clinicopathologic Features From Prior Studies on Endometrial Cancer in Patients Aged 40 Years and Younger

<table>
<thead>
<tr>
<th>Source, y</th>
<th>No. of Patients</th>
<th>Age Range, y</th>
<th>Obesity, Nulliparity, Infertility, %</th>
<th>Grade</th>
<th>Stage</th>
<th>Outcome</th>
<th>Synchronous Ovarian Tumor, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crissman, et al,2 1981</td>
<td>32</td>
<td>26–40</td>
<td>37.5</td>
<td>1: 100%</td>
<td>N/A</td>
<td>NED: 93%</td>
<td>DOC: 7%</td>
</tr>
<tr>
<td>Gallup and Stock,4 1984</td>
<td>16</td>
<td>29–40</td>
<td>44</td>
<td>1–2: 100%</td>
<td>1: 94%</td>
<td>2–3: 6%</td>
<td>NED: 100%</td>
</tr>
<tr>
<td>Duska et al,3 2001</td>
<td>95</td>
<td>25–40</td>
<td>≤48</td>
<td>1–2: 87%</td>
<td>3: 13%</td>
<td>DOD: 5%</td>
<td>DOC: 2.5%</td>
</tr>
<tr>
<td>Ota et al,3 2005</td>
<td>31</td>
<td>22–40</td>
<td>48</td>
<td>1–2: 92%</td>
<td>3: 8%</td>
<td>NED: 92.5%</td>
<td>DOD: 3%</td>
</tr>
<tr>
<td>Garg, et al,6 2009</td>
<td>70</td>
<td>24–40</td>
<td>76</td>
<td>1–2: 83%</td>
<td>3: 10%</td>
<td>NED: 94%</td>
<td>DOD: 6%</td>
</tr>
</tbody>
</table>

Abbreviations: DOC, dead of other causes; DOD, dead of disease; DOvC, dead of ovarian carcinoma; N/A, not available; NED, no evidence of disease; Undiff, undifferentiated.

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Endometrioid carcinomas in this setting may display histologic findings that have been noted in association with mismatch repair abnormalities, including tumor heterogeneity, peritumoral lymphocytes, and tumor-infiltrating lymphocytes.8,23 Some endometrial carcinomas in young patients may arise in a background of atypical polypoid adenomyoma.24,25 These tumors are usually low grade and some may show myometrial invasion.24 In a previous study8 we showed that none of the tumors arising in atypical polypoid adenomyomas displayed abnormal staining for the DNA mismatch repair proteins.

CLINICAL OUTCOMES AND PROGNOSIS

Most young patients with endometrial carcinoma have well-differentiated tumors. Patients often present with low-stage disease (80%–100% at stage 1) and have excellent clinical outcomes (90%–100% with no evidence of disease).1,2,4,5,8 A minority of patients have worse clinical outcomes, with reported rates of death from disease varying from 0% to 6% in previous studies (Table 2). Four of 70 patients (6%) died of disease in our previous study on endometrial carcinoma in young patients.8 The tumors from 2 of these 4 patients showed abnormal immunohistochemical staining for DNA mismatch repair proteins.8 Several studies have also noted an association between mismatch repair defects and presence of poor prognostic features in endometrial carcinomas. These include higher tumor grade, presence of deep myometrial invasion, and lymphovascular invasion.7,18,19,26–28 There is currently no consensus regarding impact of mismatch repair abnormalities on patient outcome in endometrial carcinoma. Some studies have reported that presence of mismatch repair defects confers improved survival, others have reported worse outcomes, while some have found no impact on prognosis.29–31 In our study,7 the 5-year survival was found to be inferior for patients with endometrial carcinoma with abnormal immu-
nohistochemical staining for mismatch repair proteins, compared to those with retained staining.

TESTING ENDOMETRIAL CARCINOMA FOR MISMATCH REPAIR ABNORMALITIES AND LYNCH SYNDROME

The gold standard diagnostic test for Lynch syndrome is mutational analysis of the DNA mismatch repair genes. However, this is an expensive and cumbersome test that is best used as a confirmatory test rather than a screening tool. Other tests that aid in the diagnosis of mismatch repair abnormalities include IHC for the DNA mismatch repair proteins, microsatellite instability analysis by polymerase chain reaction, and MLH1 promoter methylation.

Usually the first test that is performed is immunohistochemistry for the 4 DNA mismatch repair proteins (MLH1, PMS2, MSH2, and MSH6) and/or MSI analysis. Some centers routinely perform both tests on every sample in an effort to maximize detection.

The sensitivity and specificity of IHC (compared to MSI analysis), when using all 4 stains, is 91% and 83%, respectively.32 The specificity is likely higher than the reported numbers since MSI analysis may not detect tumors with MSH6 mutations, which may be MS-low or stable. Some endometrial carcinomas with germline mutations, particularly missense mutations, may not be detected by IHC alone.35

Loss of nuclear staining in all tumor cells is interpreted as an abnormal result (Figure 2, A). Immunohistochemical interpretation can sometimes be problematic in endometrial carcinomas. Care must be taken to ensure that there is a positive internal control when assessing these stains: this may include adjacent uninvolved endometrium, inflammatory cells, or stromal cells. Cases where both the tumor and internal control are negative should be interpreted as equivocal. While in most cases with retained staining all or most of the tumor cells are positive, in some cases only portions of the tumor show weak nuclear staining. In general, presence of any staining in tumor cells should be interpreted as normal or retained staining (Figure 2, B). MLH1 and MSH6 staining results, in particular, may be difficult to interpret. In cases with problematic MLH1 staining, evaluation of the PMS2 staining can be helpful (as PMS2 should also be lost in cases of MLH1 abnormalities as explained below). In practice, when one encounters such a situation, it may be helpful to review the staining results with another pathologist or to repeat the staining in an effort to maximize detection.

The DNA mismatch repair proteins may be lost in isolation or in pairs. Owing to dimer formation, abnormalities in MLH1 (both germline mutations and MLH1 promoter methylation) will result in loss of staining for MLH1 and PMS2, and MSH2 mutations will lead to loss in staining for MSH2 and MSH6. Mutations in PMS2 and MSH6 will result in isolated loss of PMS2 and MSH6, respectively. Loss of all 4 proteins is rare and has been described in a patient with a germline MSH2 mutation and MLH1 promoter methylation.34

In most cases, loss of MLH1 and PMS2 by IHC is indicative of sporadic MLH1 promoter methylation, while in some cases this may result from an MLH1 germline mutation. Further testing is required to distinguish between the two. MLH1 promoter methylation is an appropriate follow-up test. If MLH1 promoter methylation is present, a germline mutation is unlikely and vice versa.35,36

Immunohistochemistry can also help with directed gene sequencing, rather than routine sequencing of all 4 genes.37 If there is loss of MSH2 and MSH6 for instance, sequencing can be restricted to these 2 genes. In the event of isolated MSH6 loss, mutational analysis of MSH6 gene should follow. MLH1 gene mutation analysis can be performed with MLH1 and PMS2 loss, in the absence of MLH1 promoter methylation. PMS2 sequencing can be the next step since PMS2 mutations are not common.

If there is an interest in testing endometrial carcinomas for mismatch repair defects by IHC, it is imperative that this decision be made in consultation with the clinicians. In the event of an abnormal result, such patients should be referred for genetic counseling and further testing, as appropriate.

MANAGERIAL ISSUES

The standard-of-care treatment for women with endometrial carcinoma is hysterectomy and bilateral salpingo-oophorectomy with or without lymph node dissection. However, concerns for fertility sparing and avoiding surgical menopause by ovarian preservation make management of these young patients complicated.

Conservative Therapy

Many studies have shown that conservative therapy with hormones may be an effective (and fertility-sparing) therapeutic option for young patients with endometrial carcinoma.38 More recently, progesterone-releasing intrauterine device has been shown to be effective and a good alternative to systemic progesterone.39 Hormonal therapy is typically reserved for patients with complex atypical hyperplasia and selected patients with well-differentiated endometrioid carcinoma without radiologic evidence of myometrial invasion, although occasional patients with higher-grade tumors have been treated successfully.40 Patients who are managed conservatively with hormones are closely followed up with serial endometrial sampling to assess and monitor response to therapy. Results from prior studies are summarized in Table 3.

The reported clinical outcomes have varied, but many patients receiving hormonal therapy have achieved complete regression and successful pregnancies (Table 3).3,41 Reported response rates vary, but are typically in the 40% to 60% range.5,42-44 In the study by Wheeler et al,45 11 of the 26 patients (42%) with well-differentiated endometrioid adenocarcinoma showed complete regression with progesterone, while 15 patients (58%) showed persistent disease at a median follow-up of 12 months. Hysterectomy specimens were available for 14 patients, and of these, 3 showed myometrial invasion.

The duration of progesterone therapy required for adequate response is variable. From the series reported in the literature, it appears that some patients respond within 2 to 3 months, while it may take up to 6 months in other cases. Wheeler et al45 reported a median time of 9 months for regression of hyperplasia/carcinoma. Lack of response within less than 6 months of therapy should not be considered evidence of therapy failure. However, presence of persistent architectural or cytologic abnormalities after 6 months of therapy was usually indicative of treatment failure.45
Conservative hormonal therapy is usually offered only to patients with well-differentiated endometrioid adenocarcinoma. This diagnosis is based on endometrial sampling in the form of biopsy or curettage. Although the hysterectomy diagnosis is often similar to that of the preceding endometrial sampling, discrepancies between the two do occur owing to sampling or interpretational errors. In a prior study from Memorial Sloan-Kettering Cancer Center (New York, New York), the hysterectomy specimen revealed a tumor of higher grade than the preoperative sampling in 7 of 70 cases (10%). This included 2 cases where components of FIGO grade 3 endometrioid adenocarcinoma and undifferentiated carcinoma were present at hysterectomy, but not seen in the preceding endometrial curettage. Therefore, if conservative therapy is a consideration, thorough endometrial sampling in the form of curettage (and not biopsy) is advocated.

There are currently no data specific to conservative therapy in patients with Lynch syndrome who have endometrial carcinoma. There is 1 reported case of metastatic endometrial carcinoma while receiving progesterone therapy for atypical hyperplasia in a patient whose tumor showed loss of MLH1 by IHC due to MLH1 promoter methylation. There is indirect evidence that suggests that patients with Lynch syndrome may not be appropriate candidates for hormonal therapy. Tumors in these patients may be of higher grade and are more likely to invade the myometrium and show lymphovascular invasion. Furthermore, there is some suggestion that Lynch syndrome–mediated endometrial carcinoma may be unrelated to hormones, and the pathogenesis may be different from that of sporadic endometrial carcinoma. Studies have shown that low estrogen levels correlated with decrease in MLH1/MSH2 expression in endometrial cancer cells. Another study showed that estrogens reduce the risk of microsatellite instability–mediated colon cancer, while withdrawal of estrogens increased this risk. Some studies have suggested that progesterone receptor (PR) status by immunohistochemistry may be helpful in predicting a tumor’s response to hormones, that is, a tumor with positive staining for PR is more likely to regress with hormonal therapy than one

### Table 3. Results From Studies Regarding Progesterone Therapy for Endometrioid Adenocarcinoma

<table>
<thead>
<tr>
<th>Source, y</th>
<th>No. of Patients</th>
<th>Response Rate, %</th>
<th>Recurrence Rate, %</th>
<th>No. of Patients With Pregnancies Resulting in Live Births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al,42 1997</td>
<td>21</td>
<td>62</td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td>Randall et al,44 1997</td>
<td>12</td>
<td>75</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Kaku et al,43 2001</td>
<td>12</td>
<td>75</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>Ota et al,3 2005</td>
<td>12</td>
<td>42</td>
<td>40</td>
<td>2</td>
</tr>
<tr>
<td>Wheeler et al,45 2007</td>
<td>26</td>
<td>42</td>
<td>9</td>
<td>N/A</td>
</tr>
<tr>
<td>Laurelli et al,38 2011</td>
<td>14</td>
<td>85</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Koskas et al,52 2012</td>
<td>8</td>
<td>62</td>
<td>40</td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviation: N/A, not available.

Pathologic evaluation of endometrial samplings before and during conservative therapy is important in determining response to therapy. Pathologists should be aware of histologic changes that can be seen in the endometrium with the use of systemic or intrauterine progesterone. These changes are well described in the study by Wheeler et al. Posttreatment biopsy specimens should be compared with pretreatment and other preceding posttherapy biopsy specimens. The presence of carcinoma or atypical hyperplasia should be noted and the amount of residual disease should be compared to the prior biopsy findings. Architectural and cytologic changes seen in the endometrium after progesterone treatment include decrease in glandular complexity and cellularity and metaplastic changes including eosinophilic, mucinous, and squamous metaplasia (Figure 3). In the study by Wheeler et al, the change that correlated most with disease recurrence or persistence was continued presence of cytologic atypia at or after 6 months of treatment. Architectural abnormalities alone (including cribriform and papillary architecture) were not as significant in the absence of cytologic atypia.
which shows no staining for PR. A previous study has shown that tumors with abnormal staining for the DNA mismatch repair proteins also show lower expression for estrogen receptor and PR than those with retained staining, and this difference was statistically significant for PR.

These factors suggest that these tumors may not respond to hormonal treatment. It is also worth noting that endometrioid carcinomas associated with mismatch repair defects typically occur in thin women with low BMI, which also provides indirect evidence that these tumors may be unrelated to estrogen. Further studies need to be done to elucidate the relationship between hormones and Lynch-associated endometrial carcinoma. There are currently not enough data to advocate hysterectomy for all patients with Lynch syndrome, but if conservative therapy is selected, these patients should be monitored carefully.

**Ovarian Conservation**

Ovarian conservation is a reasonable consideration in young patients to avoid surgical menopause and its associated morbidities. This decision is complicated since synchronous endometrial and ovarian carcinomas are not uncommon in young patients. Moreover, in many instances the ovaries involved by carcinoma appear unremarkable on radiology and intraoperative gross evaluation.

Synchronous ovarian carcinomas have been reported in up to 25% of young women with endometrial carcinoma. Patients with synchronous uterine and ovarian tumors are usually young with high BMI. They typically have low-grade endometrioid tumors and show favorable clinical outcomes.

When simultaneous endometrial and ovarian tumors are detected, it is important to differentiate synchronous primary tumors from metastasis. Gross and histologic characteristics of the uterine and ovarian tumors are helpful in making this distinction. Features in the ovarian tumor that favor an independent primary tumor include large size, unilateral involvement, lack of surface involvement, absence of multinodular growth pattern, and presence of background endometriosis or borderline tumor. Features in the uterine tumor that favor synchronous primary tumors include low histologic grade, presence of background hyperplasia, absence of deep myometrial invasion, and absence of lymphovascular invasion. Alterations in the CTNNB1 (β-catenin) pathway are frequently seen in independent primary tumors, but not in metastasis.

While most cases can be classified on the basis of these features, occasional cases show overlapping features. In such cases, it is best to describe all the features and indicate the likelihood of synchronous primary tumors or metastasis in a note in the pathology report.

Since women with Lynch syndrome are at increased risk for both endometrial and ovarian carcinoma, it is reasonable to consider whether Lynch syndrome may predispose to synchronous tumors of the ovary and endometrium. Ovarian carcinomas that are Lynch syndrome-associated are usually of endometrioid or clear cell type. Some authors have suggested that the presence of synchronous endometrioid carcinomas of the ovary and endometrium may be associated with microsatellite instability, but other studies have not drawn this conclusion. Nine of 70 patients with endometrial carcinoma (13%) who were younger than 40 years had a synchronous ovarian tumor, most frequently of endometrioid type. None of the patients with synchronous endometrioid uterine and ovarian tumors had abnormal DNA mismatch repair staining, while 4 of the 45 patients with retained staining had synchronous endometrioid carcinomas of the endometrium and ovary. The 1 patient with loss of MSH2 had a synchronous ovarian clear cell carcinoma. Clear cell carcinomas of the ovary in young patients appear to be particularly associated with Lynch syndrome.

**SUMMARY**

Endometrial carcinomas in patients 40 years of age and younger are uncommon. Most of these tumors are associated with estrogen excess; they are usually low-grade endometrioid carcinomas that present at low stages with excellent prognosis.

Some of these tumors occur in association with DNA mismatch repair abnormalities and Lynch syndrome. A previous study has shown that women with Lynch syndrome have a lower risk of synchronous ovarian tumors. Affected patients are often thin, and the tumors may be of higher grade and can present at advanced stages.

Given the fertility-sparing concerns, conservative therapy with hormones is a reasonable option for selected patients until childbearing is completed. This carries a risk of progression/recurrence and these patients should be carefully monitored and followed up with serial endometrial sampling. Hysterectomy should be considered after childbearing is complete.

Ovarian preservation can be considered to avoid surgical menopause. However, synchronous ovarian carcinomas are not uncommon and may not be apparent on imaging or intraoperative gross evaluation.

**References**

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Endometrial Carcinoma in Young Patients—Garg & Soslows

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Abstract and case study submissions are now being accepted for the College of American Pathologists (CAP) 2014 meeting, which will be held September 7th through the 10th in Chicago, Ill. Submissions for the CAP ’14 Abstract Program will be accepted from:

**Monday, January 13, 2014 through Friday, March 14, 2014**

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