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Tumor Board Report

A tumor board report of an 83-year-old woman with stage IB grade 3 endometrioid endometrial adenocarcinoma

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ABSTRACT

An 83-year-old woman presented with postmenopausal bleeding ultimately leading to surgery and a final diagnosis of stage IB grade 3 endometrioid endometrial adenocarcinoma. The tumor board reviewed current literature regarding the efficacy of sentinel lymph node dissection in appropriately allocating stage in high-grade endometrial cancer. The optimal role of adjuvant treatment in this setting is unclear. Current literature surrounding adjuvant radiation and chemotherapy, as well as current practices in molecular diagnostics for endometrial cancer were reviewed. The tumor board concluded that literature surrounding sentinel lymph node evaluation in high-grade endometrial cancers is robust enough to incorporate into clinical practice. Based on the best available evidence, a decision was made to treat with external beam radiotherapy and withhold chemotherapy.

ARTICLE INFO

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Clinical presentation

An 83-year-old gravida 2 para 2 woman presented to the emergency department with postmenopausal vaginal bleeding. A transvaginal ultrasound was obtained showing a

☆ Declarations of interest: None.

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9.4 × 5.3 × 4.7 cm uterus with a heterogenous echotexture, and a 27 mm endometrial stripe with traces of vascularity. A CT of the abdomen/pelvis obtained in the emergency room showed abnormal hypodense thickening of the endometrium measuring 18 mm, extending into the anterior myometrium, and no lymphadenopathy. Her bleeding stabilized in the emergency department and she subsequently attended a follow-up visit with her primary gynecologist who performed an office endometrial biopsy, which showed fragmented glandular tissue with predominant mucinous features and focal glandular crowding. Given these findings, she was referred to a Gynecologic Oncologist for further management. Her medical/surgical history was significant for atrial fibrillation on apixaban, breast cancer (status post right breast lumpectomy, radiation, and tamoxifen therapy completed several years prior to this presentation), congestive heart failure on furosemide, and hypertension. Her OBGYN history was notable for 2 vaginal deliveries and a lifetime history of normal pap smears. Her family history was notable for colon cancer in her father.

Differential diagnosis

The majority of endometrial cancers are diagnosed at early stage and surgery alone is curative for most women.[1] However, for some women with higher risk disease, adjuvant treatment may be useful. The most recent definitions of low risk, intermediate risk, high-intermediate risk, and high-risk disease are based on several large trials (PORTEC-1, GOG99, ASTEC/EN5) as well as a subsequent meta-analysis.[2-5] High-risk disease is classified as any cancer of nonendometrioid histology regardless of stage, stage I grade 3 endometrioid adenocarcinoma with >50% myometrial invasion, or any stage II or III cancer. See Table 1 for further definitions of intermediate and high-intermediate risk disease.[1] Approximately 15% of patients with endometrial cancer have high-risk disease, putting them at increased risk of distant metastases and endometrial cancer-related death.[6-8]

Pathology

The patient subsequently underwent total laparoscopic hysterectomy, bilateral salpingo-oophorectomy, and bilateral sentinel lymph node (SLN) dissection. Operative findings included

Table 1
Classification of endometrial cancer risk groups to guide in use of adjuvant therapy.

Risk group	Description	Level of evidence
Low	Stage I endometrioid, grade 1-2, <50% myometrial invasion, LVSI negative	I
Intermediate	Stage I endometrioid, grade 1-2, ≥50% myometrial invasion, LVSI negative	I
High-intermediate	Stage I endometrioid, grade 3, <50% myometrial invasion, regardless of LVSI status	I
	Stage I endometrioid, grade 3, LVSI unequivocally positive, regardless of depth of invasion	II
High	Stage I endometrioid, grade 3, ≥50% myometrial invasion, regardless of LVSI	I
	Stage II	I
	Stage III endometrioid, no residual disease	I
	Nonendometrioid (serous, clear cell, undifferentiated carcinoma, or carcinosarcoma)	I
Advanced	Stage III residual disease and stage IVA	I
Metastatic	Stage IVB	I

Adapted from: Colombo et al.[1]

a normal appearing peritoneum, upper and lower abdomen, uterus, ovaries, and fallopian tubes. SLNs were identified and dissected in the right obturator and right external iliac areas, and in the left obturator space. On routine H&E staining a grade 3 endometrial adenocarcinoma of endometrioid type was noted, with squamous differentiation arising in a background of endometrial intraepithelial neoplasia. Final pathology showed a stage IB grade 3 endometrioid endometrial adenocarcinoma, invading 80% of the myometrium, with positive lymphovascular space invasion (LVSI). All 3 right pelvic SLNs and 1 left pelvic SLN were negative for tumor, and pelvic washings were negative. Immunohistochemistry revealed abnormal loss of PMS2 and MLH1, however MLH1 promoter methylation was detected, suggesting that the tumor was likely a sporadic endometrial carcinoma rather than Lynch syndrome related.

Options for management

The type of adjuvant therapy that is indicated for early stage high-risk disease, as in this patient, has yet to be clearly delineated. Should this patient be managed with chemotherapy, radiation therapy, or both? Is external beam radiation (EBRT) more effective than vaginal brachytherapy (VBT) alone, or are they equivalent modalities?

Adjuvant radiation

Current guidelines regarding adjuvant radiation were created following randomized trials such as PORTEC-1 and GOG-99, where greater locoregional control was achieved with adjuvant EBRT in high-intermediate risk women compared to women who did not receive any radiation. However, these trials did not show a survival advantage with radiation.[2,4,8,9] The PORTEC-2 trial established that VBT is not inferior to EBRT in the prevention of vaginal recurrence in high-intermediate risk patients.[10]

However, in a large well-powered retrospective study using the using the National Cancer Database, Wong et al[11] found that adjuvant radiation was associated with improved survival for women with stage IB disease. They found that both EBRT and VBT alone were associated with improved 5-year overall survival (OS) for stage IB grades 1-2 patients. Interestingly, they found that only EBRT was associated with significantly improved 5-year OS for patients with stage IB grade 3 endometrioid endometrial cancer, as in our patient (5-year OS 76.1% for EBRT vs 69.6% with no radiation, $P = 0.002$).11 The authors suggested that VBT alone is sufficient for stage IB grades 1-2 but may not be sufficient for stage IB grade 3. Given contradictory results to PORTEC-1 and GOG-99 with regards to survival benefit, Wong et al posited that perhaps these randomized studies were underpowered to detect survival differences. However, the study by Wong et al included over 60,000 women and was powered to detect survival differences. Furthermore, stage IB grade 3 patients were not included in PORTEC-2 and were likely under-represented in GOG-99, which may account for differences between studies. While it is possible that the randomized trials were underpowered, the Wong et al[11] study was retrospective in nature and susceptible to multiple biases, and therefore should be interpreted with caution.

Chemotherapy alone and combined chemotherapy and radiation

Chemotherapy has also been investigated for its potential to improve outcomes in endometrial cancer patients. There have been 2 randomized trials comparing adjuvant radiation to adjuvant chemotherapy for patients with intermediate to high-risk disease. Neither trial found a difference in progression-free survival or OS.[12,13]

Combined therapy with both adjuvant radiation and chemotherapy has also been investigated for high-risk patients. A combined analysis of separate randomized trials conducted by

the Nordic Society of Gynaecologic Oncology/European Organisation for the Research and Treatment of Cancer and the Mario Negri Institute reported a significant advantage in cancer-specific survival but not OS with the addition of sequential chemotherapy to adjuvant radiation.[14] Wong et al[11] showed no differences in OS after chemotherapy, which remained consistent after stratifying for radiation administration as well.

In PORTEC-3, high risk women were defined as women with stage IA grade 3 endometrial carcinoma with myometrial invasion and positive LVSI; stage IB grade 3; stage II, stage IIIA, or stage IIIC (or IIIB if parametrial invasion only); serous or clear cell histology with stage IA cancer with myometrial invasion, stage IB, stage II, or stage III. Women were randomly assigned to either chemotherapy plus EBRT (CTRT) or EBRT alone. Patients in the CTRT group received 2 cycles of cisplatin 50 mg/m^2 in the first and fourth week of radiotherapy, followed by 4 cycles of carboplatin AUC5 and paclitaxel 175 mg/m^2 at 21-day intervals.[15] The trial found that there was a significant improvement in failure-free survival for women with stage III disease with CTRT; however there was no difference in failure-free survival or OS in high-risk stage I and II disease.[16] There was also a significantly higher incidence of severe adverse events and decreased health-related quality of life with sequential adjuvant chemotherapy compared to radiotherapy alone.[15] The authors concluded that chemoradiotherapy should not be recommended as a new standard for patients with high-risk stage I-II endometrial cancer.

Brachytherapy boost after external beam radiation therapy

Brachytherapy is also used after EBRT in the treatment of high-risk endometrial cancer in some clinical scenarios. The most common use is in the adjuvant treatment of stage II disease, and the second most common use is for stage I disease with >50% myometrial invasion.[17] Per American Society for Radiation Oncology (ASTRO) guidelines, EBRT and VBT "is not generally warranted, unless risk factors for vaginal recurrence are present."[18] Cervical involvement is often cited as a predictor of vaginal recurrence, and therefore EBRT and VBT are frequently considered for patients with stage II or III disease. However, there is no clear group of patients for whom EBRT and VBT has been established as the standard of care. Furthermore, a recent review concluded that for stage I disease, there are no retrospective studies showing a significant benefit in local control with both modalities when compared to either EBRT or VBT alone.[19] Prospective trials have yet to be performed on this topic.

Role of targeted therapy or molecular diagnostics

Studies suggest that the reproducible diagnosis of both histology and grade of endometrial cancer is difficult, and pathology interpretation may be subjective.[20,21] In 1 study, 9.7% of cases of endometrial cancer were noted to have a discrepancy in histology and/or grade between pathologists.[21] However, molecular classification of endometrial cancer is a promising new avenue to predict prognosis and potentially dictate treatment. It has been shown to be reproducible and demonstrates associations with clinical outcomes.[22-25] Four genomic subgroups have been identified by the Cancer Genome Atlas (TCGA): microsatellite instability (MSI), copy-number low (CN low), copy-number high (CN high), and POLE mutations (with an 'ultramutated' phenotype). Specifically, the POLE-ultramutated and the MSI groups exhibit an active immune microenvironment with an abundance of tumor specific neoantigens and high quantity of tumor infiltrating lymphocytes, leading to overexpression of PD-1 and PD-L1. Other immune checkpoints such as CTLA-4 (Cytotoxic T Lymphocyte Antigen-4), LAG-3 (Lymphocyte Activation Gene-3), and IDO (indoleamine 2,3-dioxygenase) may also be upregulated in POLE and MSI endometrial cancer. Thus, patients with POLE-ultramutated and MSI endometrial cancer may benefit from immunotherapy drugs such as anti–PD-1/PD-L1 agents.[26] However, clinical utilization of this molecular classification is currently limited by unknown biologic significance of certain

POLE mutations, conflicting survival benefit data, and most importantly the lack of data regarding treatment efficacy based on molecular class diagnosis.[27] Further study is needed to bring this molecular classification into clinical practice.

Furthermore, universal tumor MSI testing has been increasingly used to identify individuals with Lynch syndrome. As patients with Lynch syndrome are at increased risk for colorectal cancer, testing all endometrial tumors allows for the identification of these individuals so they may receive heightened colorectal cancer screening. The diagnosis of Lynch syndrome also allows for cancer prevention in first-degree relatives of these patients.[28]

Areas of uncertainty

The impact of SLN sampling in the staging and management of endometrial cancer is not yet known. There is a growing body of literature that suggests that detection rates may be as high at 83%-100% with SLN sampling, thus sparing women the side effects of a full pelvic and para-aortic lymphadenectomy. However, some controversy still exists given that the 2 major prospective trials evaluating SLN sampling (the SENTI-ENDO and the FIRES trials) were underpowered to evaluate high-risk histologies and base their conclusions on combined data from all histologies, the majority being low risk.[29,30] More recently, data has emerged from a prospective validation trial among patients with high-risk endometrial cancer (grade 3, serous, clear cell, or carcinosarcoma) from MD Anderson Cancer Center, suggesting the sensitivity of SLN was 95% with a false negative rate of 5% for high risk women compared to complete pelvic and para-aortic lymphadenectomy.[31] Several other studies have since reinforced and validated this work.[32,33] Thus, the most recent data suggest that with negative sentinel nodes, treatment decisions should be based on the clinical risk factors previously discussed.

Conclusion

Based on the PORTEC nomogram, our patient had a recurrence rate of 50% without adjuvant therapy, which was decreased to 19% with VBT and 13% with EBRT.[34] Current national guidelines recommend adjuvant radiation with either EBRT or VBT for early stage high-risk disease. Data from PORTEC-2 showed no difference in survival with VBT or EBRT, suggesting that for individuals with intermediate high-risk disease, these modalities are equivalent and VBT may even be preferred due to improved side effect profiles. However, for high-risk disease there is a paucity of data on which modality is better. Retrospective data by Wong et al[11] suggest this patient would benefit from EBRT and may even have a survival benefit, which was not shown with stage IB grades 1 and 2 in their dataset.

Additionally, routine use of adjuvant chemotherapy for stage I patients is not currently recommended. In the PORTEC-3 trial evaluating sequential treatment with both chemotherapy and RT, there was no difference in OS among stage I-II patients and worse side effects (including hematologic side effects such as leukopenia and anemia, and sensory neuropathy) were seen with sequential therapy. This is echoed by preliminary results from GOG-249, suggesting that the combination of chemotherapy and VBT resulted in increased side effects without a survival advantage.[35]

The risks and benefits of adjuvant treatment were explained to our patient. She was counseled that although she might have more side effects from EBRT, she may also obtain some survival benefit and possibly better locoregional control. The patient underwent 25 fractions of EBRT for a total of 45 Gy, which she tolerated well. After discussion of potential side effects of chemotherapy, as well as data suggesting no overall survival benefit with chemotherapy in stage I disease, she did not receive chemotherapy, concordant with current guidelines.

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