Editorial

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Impact of Pathologic Features on Clinical Practice for Endometrial Cancer Patients

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In this modern era of medicine, with new knowledge and technologies emerging every day, a multidisciplinary team approach is important. Especially in oncology, input from surgical oncologists, radiologists, and pathologists is crucial to optimizing patient care.

In endometrial cancer (EMC), there are several pathologic features which serve as indicators for staging diagnosis and appropriate treatment. Both anatomical pathologists and gynecologic oncologists should recognize the clinical significance of these features in order to optimize patient care. Clinicians should detail patient history, clinical findings, and primary diagnosis in a request form for pathologic study. Pathologists, on the other hand, should detail all important findings in their pathologic reports. Despite good overall practice by both parties, some problems are still encountered in clinical practice.

In this review, some pathologic features and their prognostic influence on the clinical management of EMC patients are described.

Atypical endometrial hyperplasia/endometrioid intraepithelial neoplasia vs endometrial cancer

Atypical hyperplasia (AH) and endometrioid intraepithelial neoplasia (EIN) belong to a spectrum of diseases that range from premalignant AH at one end to EMC at the other end. In 2014, the World Health Organization[1] included AH and EIN together due to their common clonality and similar cancer risk.[2] Furthermore, a pathologic diagnosis is sometimes difficult because of similar histopathologic features. This new entity results in a high diagnostic reproducibility among pathologists.[3]

Some pathologic features which suggest adenocarcinoma rather than AH/EIN are the following: back-to-back glandular lining without or with minimal intervening stroma, a cribriform structure resulting from adjacent glandular bridging, papillary formation, luminal necrosis with neutrophils infiltration, or desmoplastic, or inflammatory stromal reaction.[4]

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From a clinical point of view, both physician and patient should be aware of the possibility of variation in diagnosis, especially when endometrial evaluation is obtained by tissue sampling. Previous studies showed that up to 50.0% of the two diagnoses could be revised interchangeably when the pathological slides were reviewed. The diagnosis of EIN may be upgraded to EMC or downgraded to normal tissue in nearly half the cases.[5] The possible explanations for the discordance are co-existing EMC with AH/EIN, small sampled tissue, small area of pathology, and inter- or intra-personal variation.[5]

When surgery is a selected treatment option for AH/EIN, both the American College of Obstetricians and Gynecologists[6] and a group of European experts[7] have recommended several surgical techniques for endometrial intraepithelial neoplasia. Hysteroscopic endometrial curettage is recommended for examining pathologic and other non-pathologic areas of the endometrium in order to ascertain whether there is no concurrent carcinoma. Endometrial ablation should be avoided. When hysterectomy is indicated, the same surgical procedures should be performed in the same manner as those for EMC by avoiding supracervical hysterectomy, or morcellation to avoid extrauterine spread and to better assess depth of myometrial invasion, if there is co-existing EMC.

In circumstances when medical treatment is an option, one important step is to reassess the endometrial pathology in order to evaluate the response. Long-term follow-up is indicated if hysterectomy has not been performed, due to a high chance of subsequent EMC development.[5]

Tumor size

Tumor size is directly associated with other prognostic factors e.g. lymph node status, depth of myometrial invasion, etc. Pre-operative or intra-operative information about tumor size, along with grade and depth of myometrial invasion, will be assessed together to determine whether a surgical lymph node evaluation is required, especially in the early stages of the disease. One study reported that only 4.0% of nodal metastasis was found in tumors sized less than 2 cm, but increased to 15.0% in tumors larger than 2 cm, and as high as 35.0% when the tumor involved the whole uterine cavity.[8] Another study reported that patients with a tumor size smaller than 3 cm, grade 1-2, and with less than half myometrial invasion had no evidence of nodal metastasis.[9]

Tumor site

The majority of EMC originates from the fundus or body of the uterus, with only 3.0-6.0% occurring at the lower uterine segment (LUS). From a pathologic point of view, differentiation between EMC originating at LUS and EMC extending to endocervix can be achieved by gross and histopathologic assessment. Generally, there is no sharp histological demarcation between LUS and endocervix. Although the ciliated mucinous lining cells can be seen at both LUS and endocervical epithelium, some suggest the presence of the most upper mucinous gland as the point to demarcate endocervix and LUS.[10]

The clinical significance of a tumor at LUS should be recognized. The EMC at LUS was reported to be associated with Lynch syndrome, a high-grade tumor, deeper myometrial invasion, and a higher frequency of nodal involvement than EMC located in the fundus/body.[11] However, data on clinical outcomes are inconsistent. Some reported 2.27 times higher recurrence and 1.76 times risk of death among patients with EMC originating at LUS.[12] Others could not demonstrate such associations particularly in the early stage without nodal metastasis.[13]

Depth of myometrial invasion

Depth of myometrial invasion along with tumor size and grade are important features indicating surgical lymph node evaluation in EMC patients. The depth of invasion is directly related to the presence of extra-uterine metastasis, higher recurrence, and shorter survival.[14] The 5-year survival of patients with early stage I-II without or less than 1/3 myometrial invasion was higher than 90.0%, decreased to 84.0% and 59.0% with invasion lesser than or deeper than 2/3 of depth of invasion respectively.

Clinical evaluation for the depth of myometrial invasion can be performed by pre-operative imaging studies, such as transvaginal ultrasonography, magnetic resonance imaging (MRI), especially contrasted-enhanced MRI, or intra-operative assessment by gross inspection of a frozen section in the operating room.[15-17] However, all have some limitations. The accuracy in determining depth of myometrial invasion may depend on many factors aside from the experience of the examiner or surgeon e.g. high-grade or infiltrative tumors might be difficult to assess, other associated pathologies, or number of frozen sections taken, etc.

For the pathologic evaluation, depth of myometrial invasion is generally measured from the junction of endo- and myo-metrial junction to the deepest point of invasion in millimeters or in proportion to the whole myometrial thickness. In some cases, especially when an endo- and myo-metrial junction is not clearly seen, the distance from the tumor to the serosa of the uterus (tumor-free distance), which is reported to be better associated with higher recurrence and decreased survival, may be used instead.[18]

Lymphovascular invasion

Lymphovascular invasion (LVSI) is directly associated with high-grade tumors, deep myometrial invasion, and higher chance of pelvic and para-aortic lymph node.[19] Many reports found that LVSI is an independent prognostic factor for survival, even in early stage endometrioid cancer.[20]

Aside from its presence, the quantity of LVSI is also important. One study identified ≥3 of LVSI foci were associated with other high-risk features compared with those without or <3 foci.[21] Others reported that patients moderate/prominent LVSI had an almost 5-fold risk of recurrence (6-fold for pelvic recurrence)[21,22] compared with those with no or minimal LVSI and a decreased 5-year survival from 93.0 to 51.0% respectively.[22]

From a pathologic point of view, an assessment of LVSI among pathologists may have both intra- and inter-observer variations. LVSI has similar features and should be distinguished from a retraction artifact due to the tissue autolysis commonly seen in EMC. The retraction artifact often appears widespread with a smooth round contour and without cell lining, whereas LVSI is most commonly seen at the invasive front of the tumor and appears as a slit-like or angulated space lined by endothelial cells. Features suggesting LVSI are a presence of tumor cells within the vessels and peri-vascular lymphocytic infiltration with occasional lymphoid aggregates. An immunohistochemical study with CD31, which stains all vascular structures, and D2-40, which stains lymphatic spaces, may aid in confirmation of LVSI.[19]

In this modern era of minimally invasive surgery, a frequent finding of LVSI artifacts in an hysterectomy specimen, removed by total laparoscopic surgery using an intrauterine balloon manipulator, should be recognized.[23] Several LVSI may be observed in a patient who had laparoscopic surgery when a positive pressure system created by the inflation of an intrauterine balloon manipulator followed occlusion of the fallopian tubes. Features suggest that artifacts were: numerous LVSI-like spaces in the absence of high-grade or advanced stage

tumor, preferential involvement of large thick-walled blood vessels in the outer myometrium, presence of both stromal and glandular tissue within vessels, and an absence of tumor adherence to the vessel wall.[23]

Cervical involvement

One common clinical question when adenocarcinoma is diagnosed from a tissue biopsy is its origin. This is found when cancer is present in both specimens or when the biopsy was performed in a referring hospital and the biopsy site is unknown.

From a clinical point of view, clarifying the site of origin is important because it will designate correct staging and appropriate treatment. Simple hysterectomy is indicated as a standard surgical treatment for EMC, whereas radical hysterectomy or primary chemoradiation is the treatment of choice for cervical carcinoma. Physical, including pelvic, examinations may be able to differentiate the site of origin in some cases. In other cases, imaging study may assist in determining the primary site.

A definite pathologic diagnosis is crucial, especially when it will lead to a proper adjuvant therapy. This is not a problem when the histopathologic features are obvious in the hysterectomy specimen. However, in cases with subtle morphology, the diagnosis might still be difficult. A panel of immunohistochemical markers of oestrogen receptor (ER), vimentin, carcinoembryonic antigen (CEA) and p16 may help to differentiate between endometrioid EMC and endocervical adenocarcinoma.[24] Endometrioid EMC is usually diffusely positive with ER and vimentin and negative or focally positive with CEA and p16, whereas endocervical adenocarcinoma is usually diffusely positive with p16 and CEA, and negative or focally positive with ER and vimentin. A caveat is on high-grade serous carcinoma and undifferentiated carcinoma, which can have diffuse p16 staining and negative or focal staining with ER. Diffuse p53 staining and human papillomavirus (HPV) study may be useful for supporting a diagnosis of serous and undifferentiated carcinomas in the former and cervical carcinoma in the latter.

Co-existing ovarian cancer

Because most gynecologic tumors have a mullerian origin, there is a chance that primary cancers can independently occur at various sites as metachronous or synchronous cancer. The most common synchronous gynecologic cancers are cancers of the endometrium and ovary.[25]

When there is a coexisting ovarian tumor in EMC patients, one report found that preoperative imaging studies can miss the detection of an ovarian mass in 15.0%, while another 15.0% were misinterpreted between benign and malignant natures.[25] In the scenario of a malignant ovarian tumor, another important question to be answered concerns the primary site(s) of cancer, whether it is primary ovarian cancer metastasis to uterus or vice versa, or were they synchronous cancers. These 3 conditions have different clinical importance regarding staging, prognosis, details of surgical procedure, and adjuvant treatment.

From a pathologic point of view, many criteria which help to distinguish metastasis from synchronous cancer determined from their gross features are the sizes of the 2 tumors and the patterns of invasion or metastasis.[26] Most pathologists will make a diagnosis of synchronous cancer with confidence if both cancers are in an early stage and with low-grade endometrioid or a different histology. The diagnosis may be difficult or impossible if the histology is the same, and the cancer is at an advanced stage. Another feature which might help in the diagnosis is an associated pathology e.g. co-existing endometrial hyperplasia in EMC or endometriosis in ovarian cancer. Immuno-

histochemical study with vimentin is positive in 82.0% of EMC and negative in almost all ovarian cancers (97.0%).[27]

Clinical information is also very important for a diagnosis. An impression of the coexisting or metastatic ovarian cancer in EMC should begin with history, clinical findings from physical, including pelvic, examinations, and imaging study. Additional findings of serum tumor markers may aid in a provisional diagnosis; normal or low CA125 level may suggest synchronous cancer rather than widespread metastatic cancer.[28] These clinical findings can certainly guide a surgeon to a proper plan of surgical management and counseling, especially in young patients who require continued fertility.

One point to remember is that a surgeon should not neglect a careful intra-operative evaluation of the pathologic findings, which is crucial for a diagnosis rather than waiting for only a final diagnosis from a pathologist. A surgeon should assess the site or location, the gross features of the lesions, and relationship with the surrounding structures. An assessment of the resected uterus and ovarian mass should be carried out without destroying their orientation (if possible). Sketching of intra-operative findings in a pathological request form may aid a pathologist to better figure the anatomy. Reorientation of the specimen after a primary evaluation is recommended before fixing the specimens in formalin solution in order to prevent a distorted anatomical orientation.

Lymph node metastasis

Preoperative evaluation of lymph node metastasis can be performed by several imaging studies, such as computerized tomography scan (CT scan), MRI, positron emission tomography scan (PET scan), or CT/PET scan. These imaging studies can help a surgeon make an appropriate surgical plan in the advanced stage when there is uncertainty concerning optimal surgical outcome, or in an early stage low-grade tumor when lymph node resection may be omitted.[7,29] There are inconsistencies among several experts and organizations regarding the indications of lymph node surgical evaluation. Some recommend that surgical lymph node evaluation should be performed on all patients, whereas others support a selective approach for patients with high or intermediate risk of recurrence.[30,31]

Among the patients who opt to have lymph node surgical evaluation, adequacy of procedure is an issue due to the relationship of node numbers and the detection rate of nodal metastasis and survival of the patients. Some found a higher rate of up to 1.45 times of nodal metastasis when the numbers reached 21-25 nodes.[32] Others found that more than 11-12 nodes were associated with better survival in all patients with early stage, intermediate or high-risk and advanced stage diseases.[33]

One problem is how to select lymph nodes for resection because 30.0% of metastatic nodes were smaller than 1 cm and may not be palpable clinically.[34] Other nodal features aside from the size, e.g. capsular invasion or consistency, may help in the selection.[35]

Because lymph node metastasis is an important prognostic factor, one condition of lymph nodes deserves special attention here. Mullerian inclusion cyst is a benign, glandular inclusion of an epithelium mimicking metastatic cancer.[36] By itself it has no clinical significance; however, recognition and differentiation from cancer is crucial for an accurate staging and prognosis, which will influence the clinical management.

Vanishing cancer

This is a condition when the hysterectomy specimen has no EMC tissue after a pathologic diagnosis of cancer from preoperative endometrial tissue.[37,38] The

etiology may be the polypoid feature of cancer, which has been totally removed, an inflammatory reaction, or treatment effect.[37-40] The clinical question involves the adjuvant treatment for the patient with vanishing cancer, especially in high-grade serous or clear cells which have been identified from biopsy or curettage specimen. Because there are only a few reports with inconsistent data on this topic, the clinician may have to make a decision based on other factors, as well as the adherence of patients for a follow-up, particularly in patients who want to have only observation.[38]

Conclusion

A pathology review of gynecological cancer specimens and a discussion between the clinician who had clinical information and the pathologist who evaluated the nature of the lesion are important. Clinicopathologic correlation can minimize clinically significant diagnostic discrepancies and help with a correct pathologic interpretation, accurate cancer prognosis, and appropriate management.

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