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Endometrial stromal tumors. Can classification of low-grade tumors still be improved?

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In this issue of Virchows Archiv, there is a comprehensive review article on the most recent advances in our understanding of the pathologic and molecular features of endometrial stromal tumors (1). The review is written by a team, and a senior author, with considerable experience in the field. The manuscript describes the changes made since the first classification based on the number of mitotic figures to the current approach based on the resemblance to normal endometrial stroma of the proliferative phase.

Understanding the molecular basis of these tumors has been important to the improvement of their classification. Until now a high number of gene fusions have been identified. Some of them are characteristic of low grade tumors including low-

grade endometrial sarcomas and endometrial stromal nodules, thus confirming the neoplastic nature of circumscribed stromal tumors. Some other gene fusions have been important in establishing the category of high-grade endometrial sarcoma, and even relevant for reclassifying tumors that are very similar to the myxoid variant of uterine smooth muscle tumors. The most aggressive category, undifferentiated sarcoma, is also much better defined. In this scenario, next generation sequencing (NGS) for the identification of gene fusions appears to be an excellent diagnostic tool, particularly, in tumors showing unusual morphological features. In contrast to fluorescence in situ hybridization (FISH), NGS allows analyzing multiple genes in one step and has been increasingly used in the diagnosis and management of non-small cell lung cancer. Thus, molecular diagnosis seems to be a prerequisite for the diagnosis of high grade uterine sarcomas.

Although the low-grade spectrum of endometrial stromal neoplasms seems to be well established and has been characterized at the molecular level more than a decade ago, there is in our opinion still room for improvement. The diagnosis of endometrial stromal nodule is easy when the lesion is small, and found in a hysterectomy specimen, where tumor margins can be appropriately assessed. However, the diagnosis can be challenging when the nodule is of large dimension, or when there is necrosis. Diagnosis can be even impossible if the lesion is removed during hysteroscopy or laparoscopy with morcellation of the specimen. In particular, focal invasion is allowed for the diagnosis of endometrial stromal nodule, less than three foci not more than 3 mm in size, but the cut-off is arbitrary, and there is no strong scientific evidence in support of such criteria, with few cases, and short follow-up (2). As a matter of fact, endometrial stromal nodules harbor molecular alterations identical to those present in low grade endometrial stromal sarcomas, suggesting that both lesions are related and neoplastic. The controversy is increased by the fact that some tumors are grossly circumscribed but show extensive microscopic myometrial invasion (3) and others with limited myometrial invasion have extrauterine disease (4). In addition, there are reports of circumscribed tumors with myometrial invasion exceeding 3mm (5). Finally, some authors prefer terms such as finger-like projections or protrusions, rather than limited infiltration, emphasizing that such invasive foci

should lack overt permeative growth, which also emphasizes the subjectivity of pathologic interpretation of these areas. Overall, general pathologists and even expert gynecological pathologists feel sometimes uncomfortable diagnosing endometrial stromal nodules when examining cases that show unusual features.

In this scenario, the differential diagnosis between endometrial stromal nodule and low-grade endometrial sarcoma is at some point subjective, and descriptive terms such as 'Low-grade endometrial stromal tumor' are used in difficult cases, in which there is no absolute certainty that the tumor will behave in a benign way. In the setting of endometrial biopsy or curettage the term 'low-grade endometrial stromal neoplasm' is often suggested, since the interface with the myometrium, which is necessary for differential diagnosis, cannot be assessed.

The fact, that the difference between two lesions with identical or similar cytolological and molecular features is the presence or absence of invasion into the surrounding tissue such as currently between endometrial stromal nodule and low-grade endometrial stromal sarcoma is not unique in pathology. In particular, follicular carcinomas of the thyroid can be minimally invasive (associated with very good prognosis, particularly without vascular invasion), or widely invasive (with increased risk of metastasis), but each of them is considered a neoplastic lesion, acknowledging that prognosis depends on the extension of invasion. Maybe we can translate this point of view also to endometrial stromal tumors.

We would like to suggest using the term **Non-invasive low-grade endometrial stromal neoplasia**, for tumors that do not showing clear evidence of invasion; and the term **low-grade endometrial stromal neoplasia with minimal (myometrial) invasion**, for those that show less than 3 foci of less than 3 mm in size, as far as we have updated scientific evidence to use other criteria. On the other hand, the term **low-grade endometrial stromal sarcoma with extensive (myometrial) invasion** is proposed for conventional endometrial stromal sarcoma with traditional pattern of myometrial invasion, and risk of metastasis, particularly at the long term.

Which would be the benefits of the proposed terminology?

1. Updating the current terminology to the molecular knowledge and acknowledging that low-grade stromal tumors, either non-invasive or invasive, have identical molecular alterations. Emphasizing the neoplastic nature of endometrial stromal nodules would clarify the taxonomy of this interesting group of tumors.
2. Recognizing that low grade stromal tumors, non-invasive or invasive, are most likely different steps in the development of the same type of tumor, and that the extent of myometrial invasion is the most important prognostic feature. Tumors with limited invasion could be considered intermediate steps in this tumorigenic procedure.
3. Designating endometrial stromal nodules as neoplastic would be particularly helpful to manage tumors with unusual features, or tumors that are in intermediate phases of this continuum of tumors.

Tumor classification is a continuous process of adapting terminology to novel scientific knowledge, particularly with respect to molecular pathology, and in addition to improved scientific evidence for the prediction of behavior. Future work is needed for this group of tumors, which will require international multicenter collaboration due to its rarity. Prognosis needs to be assessed at long term, since even for low-grade endometrial stromal sarcomas, recurrences occur very late during follow-up, and this is only possible if we are able to gather well-documented cases with paraffin-embedded material available. The current histological criteria need to be evaluated and correlated with molecular changes and probably refined. Moreover, interobserver studies on the reproducibility of the diagnostic criteria, in particular, with respect to tumors with unusual features, are required.

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