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Editorial

Lumping and splitting: The need for precision medicine and "personomics" in endometrial cancer

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- See the article "Substantial lymph-vascular space invasion (LVSI) as predictor of distant relapse and poor prognosis in low-risk early-stage endometrial cancer" in volume 32, e11.
- See the article "Recurrence risk factors in stage IA grade 1 endometrial cancer" in volume 32, e22.

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Endometrial cancer is the most common gynecologic malignancy in developed countries [1,2]. Following standard surgical treatment, patients with low grade and "low risk" [1] tumor confined to the uterus have a very good prognosis, with a 5-year cancer related survival over 95% [3,4]. While the overall oncologic outcomes of women with endometrial cancer are favorable, still a significant rate of recurrences occurs in patients with apparently uterine-confined disease [5].

The current risk classification in endometrial cancer is mainly based on age, tumor grade, International Federation of Gynecology and Obstetrics stage, histologic subtype, depth of myometrial invasion, and absence or presence of lymphovascular space invasion (LVSI) [4,6-8]. Worse prognosis is known to be associated with the presence of LVSI, >50% myometrial invasion, grade 3, and non-endometrioid histology [3,4,9]. Based on the estimated risk of recurrence, patients may be observed or receive adjuvant treatment after surgery [10].

Invasion of lymphatic-vascular spaces by tumor cells is a well-known risk factor and has been associated with aggressive tumor behavior. Endometrial cancer with LVSI likely demonstrates extra-uterine spread, positive lymph nodes, and propensity to recur, especially at distant sites [3,4,7]. Our group had identified LVSI as a predictor of both vaginal and lymphatic recurrences [3]. In most of the literature, LVSI has been described as a binomial variable (i.e., positive or negative) [4]. Only most recently the PORTEC group implemented a 3-tiered scoring system and demonstrated its relevance [11-15].

For the last few decades, both at the Mayo Clinic and in many other Institutions [16,17], gynecologic oncologists have been studying patients with early-stage endometrial cancer with the aim of identifying risk factors and biomarkers, for directing and modulating postoperative treatment and defining prognosis [4,5,7,18]. Approximately 20 years ago, our group published a study describing patients with "low risk" endometrial cancer (i.e., women with grade 1 or 2 endometrioid tumor, with ≤50% myometrial invasion, no intraoperative evidence of macroscopic disease) [4]. Our goal was to identify those patients who can be treated with hysterectomy alone, with no need for surgical staging or adjuvant therapy. At that time, we observed that tumor diameter ≤2 cm, utilized in this "low risk" cohort, was a powerful tool for selecting patients at negligible risk of lymph node dissemination and at

minimal risk of recurrence. Also, at that time, we identified LVSI as the strongest risk factor for recurrence and death in otherwise "low risk" women. However, while tumor diameter—a simple and readily available tool for selecting patients for surgical staging—had been widely and quickly adopted during subsequent years [19-21], the use of LVSI to direct postoperative therapy in otherwise "low risk" patients has been much slower to enter into clinical practice.

In this issue of the journal, Nwachukwu et al. [22] assessed predictors of recurrences in stage IA grade 1 endometrioid endometrial cancer. The authors observed 3 independent clinical and pathological risk factors for recurrence: time from biopsy to surgery >6 months, tumor size >2 cm, and any myometrial invasion. In particular, it is interesting to note that recurrence was observed in approximately half (54%) of patients who had a time from biopsy to surgery of more than 6 months. The authors suggest that they can identify subgroups of early-stage IA grade 1 endometrial cancer that would benefit from "a closer follow up" [22].

Furthermore, in this issue of the journal, Tortorella et al. [23] evaluated the prognostic impact of a three-tiered scoring system of LVSI in patients with endometrial cancer and "low risk" pathologic features. This innovative approach focused on the effect of LVSI quantification on the prognosis of a selected population of early-stage endometrioid endometrial cancer with no other known histologic risk factors (<50% myometrial invasion, grade 1 or 2). Patients with "substantial LVSI" were more likely to have higher rates of myometrial invasion, grade 2, and greater tumor dimension than those with absent or focal LVSI. Those patients with substantial LVSI were more likely to undergo adjuvant treatment (approximately half of them underwent radiotherapy in this study) and experience distant recurrences. The authors reported that LVSI was present in about 10.9% of "low risk" endometrial cancer. However, only 4.2% of all patients had "substantial LVSI". The investigators emphasized that "substantial LVSI" is an independent risk factor for distant recurrence and the strongest predictor of poor prognosis in terms of overall survival and disease-free survival, when no other histologic risk factors are found in early-stage endometrial cancer. It is impressing to see that this very small subgroup of patients with substantial LVSI had in fact, a very high (22.7%) rate of distant recurrence, and their 5-year relapse-free survival was as low as 56.5% [23].

In both studies we observe that, as expected, only few patients (<10%) in the "low risk" [1] endometrial cancer population actually experience a recurrence. However, both studies demonstrate that, by utilizing clinical (i.e., time interval from the biopsy to surgery) or pathologic (3-tiered LVSI) parameters, we can possibly identify patients at very high risk of recurrence who may potentially benefit of more intensive therapy.

However, which type of treatment should we give to these patients who have been identified at high risk of recurrence? In retrospect, should these patients have received chemotherapy? For example, in the Tortorella et al.'s study [23], approximately 45% of patients with "substantial LVSI" had in fact received external beam radiotherapy and/or vaginal brachytherapy, but still approximately 20% of them had a distant recurrence. This important observation had been reported also in previous studies, in which about 17%–20% of "low risk" patients with LVSI (either categorized as "substantial" or "positive") had in fact distant recurrence [4,11,15]. It is well known that distant recurrences cannot be prevented by radiotherapy and may need some type of systemic treatment. However, it is interesting to note that early-stage endometrial cancer patients with LVSI, in the absence of other risk factors, have not been usually recommended systemic therapy [2,8,14] until very recently [1].

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Should we recommend chemotherapy in all patients with substantial LVSI, including those with otherwise "low risk" characteristics?

Unfortunately, the answer to the above question is not as simple. In fact, considering the whole "low risk" cohort, only 4% of patients have substantial LVSI [23]. This finding is true also in the previous literature. In fact, in the Mayo Clinic experience, we observed that LVSI (described as positive vs. negative) was present in 5% of "low risk" tumors. Similarly, 4.5% substantial LVSI was identified in the PORTEC 1 and 2 population [4,11]. Therefore, there are very few patients, with otherwise "low risk" characteristics, who actually have LVSI. These limited number restricts our ability to draw definitive conclusions about the type of postoperative treatment needed.

Understanding how these patients need to be treated is challenging, because current medical wisdom appropriately suggests that, in order to provide a specific treatment (with its potentially associated costs and morbidity), evidence from prospective randomized trials is needed. In fact, we have recent examples, even in our specialty, which have demonstrated that "taking shortcuts" may be dangerous [24]. At the same time, due to the low incidence of specific subgroups of patients, it is difficult (and sometimes impossible) to achieve adequate study numbers and statistical power to investigate clinically relevant benefits of certain treatments.

For practical reasons, general recommendations for the treatment of early-stage endometrial cancer are based on studies that lumped together different subgroups of endometrial cancer with heterogenous risks and benefits from adjuvant treatment [8]. In medicine, it is possible "to lump and to split" [25]. "Lumping", which is at the basis of evidence-based medicine (EBM), is very important to generate statistics and reproducible data [26]. This allows us to appropriately distinguish those results that may be simply due to chance, from those that are likely to be associated to the real effect of a specific therapy. However, in our everyday practices, we are all aware of the limitations and difficulties of utilizing data from randomized trials for individual patient treatment decisions. In fact, EBM describes results that are applicable to a general population, but does not always consider the heterogeneity of the groups, with individual variabilities of patients and environment. For this reason, medical science is rapidly recognizing the need of "precision medicine and personalized therapy" [26-28].

An important step towards the individualization of treatment in endometrial cancer is the introduction of molecular biomarkers into clinical practice, with the innovative work of the PORTEC team [1,11,12,14,29]. Integrating the molecular classification with clinicopathologic risk factors will allow clinicians to split their recommendations based on an individualized risk assessment that is not solely relying on traditional clinical-pathological variables.

In the current issue of the journal, the investigators identify predictors of poor prognosis in "low risk" endometrial cancer. LVSI is a pathologic characteristic of the tumor [23], while the time from biopsy to surgery [22] is associated to a social, behavioral or medical characteristic of the patient (not of the tumor itself), and to the availability of societal resources. However, both variables underline the fact that every cancer is different and every patient is unique.

It has been appropriately said that "good clinical practice is an amalgamation of personalized medicine with evidence-based medicine in the best interest of the patient" [27]. The prognostic relevance of the "time from biopsy to surgery" pertains to the "interpersonal" aspect of patient care, and reminds us that an important aspect of "precision medicine" is

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also social, cultural and behavioral [30]. This is what some authors have judiciously called "personomics" [31]: a word that needs to enter into our vocabulary to help spread a medical culture that considers the individuality of the person, in his or her social environment [31]. Also, in order to facilitate more individualized treatment of relatively uncommon subcategories of tumors, it is crucial, in our specialty, that we unite our forces and increase our numbers, by encouraging multi-institutional prospective studies and registries.

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