Micropapillary Pattern in Newly Diagnosed Borderline Tumors of the Ovary: What's in a Name?

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The ovary is an organ prone to developing “tumors.” Fortunately, the majority of these tumors are normal or benign, with no long-term consequences other than the possible effects of surgical procedures needed to “treat” them. Then there are the frankly invasive tumors that have an aggressive course, recur frequently, and ultimately lead to the death of the patient in a relatively short period of time. Finally, there is a set of ovarian tumors that appear to behave themselves most of the time, but not always, and can present with extraovarian spread, recur, and sometimes lead to death. The International Federation of Gynecology and Obstetrics (Fédération Internationale de Gynécologie et d’Obstétrique [FIGO]) recognized their existence and named them borderline tumors in 1971 [1]. Or was it “low malignant potential tumors”? These not-so-aggressive but not-quite-benign tumors of the ovary have been struggling for a name ever since FIGO recognized them as a distinct entity in the 1970s. The various names used to identify the same tumor can often confuse clinicians, leading to inappropriate and unnecessary treatment approaches to patients with these tumors. The unfortunate patient will have the words “malignant” or “carcinoma” tagged to her tumor, resulting in associated lifelong anxiety, extra exposure to radiation to make sure the tumor hasn’t returned, and, in the

very unfortunate, toxic therapies to make sure their tumor won’t return. The most unfortunate of all patients are those who are young and have not yet started or completed their family. And so, I prefer the term “borderline.”

Borderline tumors of the ovary are confined to the ovaries (FIGO stage I) in >80% of the patients initially diagnosed with these tumors in the general population [2]. Survival is essentially (but not quite) 100% at 10 years for stage I ovarian borderline tumors as a whole, regardless of the name one chooses to call them [2]. These patients should be told to enjoy the rest of their lives and should not be put through any additional surgeries, treatments, or imaging after initial evaluation reveals no obvious extraovarian disease. The risk for death is slightly higher for patients who present with FIGO stage II–IV (extraovarian) disease, but the 10-year survival rate is still 98% for stage II and 96% for stage III patients [2]. The 10-year survival rate is still nearly 80% for the <5% of patients who present with stage IV borderline tumors [2]. Although death from these tumors is rare, it does happen, mostly many years after diagnosis. Many investigators have tried to better identify which borderline tumors result in higher risk for a bad outcome. Identifying such tumors is critical to understanding the biology of the more aggressive variants of these “indo-

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lent” tumors. In the process, however, certain “names” and “risks” have been created that have not altered the outcome of patients with borderline tumors since FIGO recognized them in 1971, but they have increased the chances that these patients will undergo more aggressive treatments and surveillance, with no benefit at all.

Burks and colleagues proposed a new name for a certain subgroup of borderline tumors (“micropapillary serous carcinoma”) that they described as being a distinct and much more aggressive borderline tumor [3]. Those authors proposed that a micropapillary pattern in borderline tumors was clearly associated with an unfavorable outcome. Many years earlier, Katzenstein and colleagues had not found such an association with a micropapillary pattern and outcome in borderline tumors [4]. The majority of investigators since Burks et al. [3], including Uzan and colleagues in this issue [5], have reported that a micropapillary pattern is not associated with an adverse outcome, especially when accounting for the presence or absence of invasive extraovarian implants [6–15].

A micropapillary pattern in the ovary in the absence of extraovarian disease (stage I) does not confer a worse prognosis. Combining all series that specifically provide their outcome data on patients with a stage I micropapillary borderline tumor, only one (1.4%) in 70 cases recurred and died. All others were alive without evidence of disease recurrence at the time the various series were published [3, 7, 8, 11, 13–15]. It is absolutely not in the best interest of these patients, or their treating physicians, to associate the word “carcinoma” with their tumor.

The presence of invasive extraovarian implants is really the only prognostic factor that has been consistently reported to be associated with an adverse outcome. In a companion article to Burks et al. [3], Seidman and Kurman [6] concluded that “from this study, it is clear that the most important prognostic factor for borderline tumors is invasive implants.” Since then, many others have evaluated the presence of a micropapillary pattern and invasive implants and have agreed [8, 9, 11–15]. A micropapillary pattern in the primary ovarian tumor is of no clinical significance in the absence of extraovarian invasive implants. The only consistent adverse prognostic factor has been the presence of invasive extraovarian implants whether there is a micropapillary pattern in the primary ovarian tumor or not [8, 9, 11–15]. In fact, patients with typical borderline tumors with invasive implants do just as poorly as those with micropapillary tumors with invasive implants. Some authors have suggested that a micropapillary pattern in the ovary is asso-

ciated with the presence of extraovarian implants [3, 6, 15, 16]. This association was not found in series that were not mostly consultative series [9, 13]. Great care must be taken not to overinterpret results from mostly referral and consultation-based centers. These series can be strongly influenced and skewed, because cases with an already unfavorable outcome are the ones being seen at such centers. Patients with straightforward pathologic interpretations who do well often will have no need to seek treatment or consultation at a specialized referral center.

Uzan and colleagues [5] report on the largest series, to my knowledge, of advanced ovarian borderline tumors comparing those with a micropapillary pattern with typical borderline tumors. Smith Sehdev et al. [7] had the largest series of patients with micropapillary tumors but they did not compare them with patients with typical borderline tumors [7]. The authors used strict modern pathologic criteria. There were so few deaths that overall survival could not be compared. This series provides additional important data that confirms the lack of independent prognostic value for the presence of a micropapillary pattern. The main criticisms of this series are the limitations inherent to any retrospective series and the relatively short follow-up in a cohort of cases that generally do well and experience events only many years after diagnosis.

Clinically, the fact remains that, other than surgically, we cannot alter the predetermined outcome of these patients, irrespective of the name given to their tumor, using currently available chemotherapy [17, 18]. However, there has been a tremendous benefit from all the work and effort of the many investigators referenced. It is now apparent that the molecular basis of borderline tumors and their more aggressive variants is quite different from that of high-grade serous ovarian carcinomas [19–21]. It is beyond the scope of an editorial to review these molecular findings. However, the identification of more aggressive variants of borderline tumors led to molecular studies that led to promising investigations of targeted therapies for these tumors.

What’s in a name? In terms of borderline tumors? A lot! From a clinical standpoint, we must be extremely careful of the names we give these tumors. All that can result from “names” is iatrogenic bad outcomes in this cohort of patients. Continued understanding of these tumors, however, is of utmost importance to identify treatments that will have an impact on the outcome of the small minority of patients who will unfortunately be affected by the aggressive variants of ovarian borderline tumors.

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