Ovarian Tumors of Low Malignant Potential

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The article by Trimble and Trimble nicely summarizes the state of knowledge on ovarian tumors of low malignant potential (LMP) and underscores the fact that gaps in that knowledge have led to confusion and controversy regarding several issues related to these interesting neoplasms. Many of these controversies can be characterized as debates between the "lumpers" and the "splitters." The Johns Hopkins group has long been at the forefront of research on ovarian LMP tumors. In this review, I will attempt to place some of the authors' comments into perspective and, at times, present a different point of view.

Classification, Nomenclature, and Molecular Biology

Since the original description of "semimalignant tumors" by Taylor in 1929, no consensus has been reached about the nomenclature for ovarian LMP tumors.[1] Although we have generally used the term "borderline" in numerous publications, it has been used simply because it is less cumbersome than "tumor of low malignant potential." However, I actually prefer the latter. I totally agree with the Trimbles that the term "borderline" sends the wrong message-that the tumor is intermediate between benign and malignant. Most of the molecular biology studies of these tumors strongly suggest that they are quite distinct from frankly malignant ovarian cancers and have a very different pathogenesis. On the other hand, I strongly disagree with the use of the term "atypical proliferating tumors," which has been advanced by the Johns Hopkins group to imply that these tumors almost always behave in a benign fashion. This paradigm fundamentally fits the biology associated with stage I LMP tumors but breaks down when one considers stage II-IV tumors. The Trimbles suggest that peritoneal implants associated with ovarian LMP tumors, particularly invasive peritoneal implants, are, in fact, primary peritoneal cancers and not somehow related to the primary ovarian tumor. However, this statement is speculative and not clearly supported by molecular and genetic data. I do agree, however, that the ultimate answer to these types of theories will emerge from further molecular and clonal investigations. The Trimbles also briefly discuss the introduction of the term "micropapillary," which designates a proliferative histopathologic pattern distinct from the typical serous borderline pattern. The Johns Hopkins group has proposed that so-called micropapillary serous carcinomas be split from tumors with the typical serous borderline pattern,[2] but, as mentioned in their article, this "splitting" has not been universally accepted by either the gynecologic pathology community or the gynecologic oncology community. In fact, most prominent gynecologic pathology groups have advocated maintaining the micropapillary pattern as a subset of serous LMP tumors based on their clinicopathologic findings.[3-5] Surgical Management Issues

Because of the imprecise clinical findings associated with ovarian LMP tumors, general obstetrician/gynecologists (rather than gynecologic oncologists) are more likely to encounter these neoplasms while operating for an adnexal mass. Approximately 50% of serous tumors and 80% to 90% of mucinous LMP tumors are confined to one ovary at diagnosis. Therefore, in a high proportion of these patients who have not completed childbearing, fertility-sparing surgery-ovarian cystectomy, unilateral salpingo-oophorectomy, or some combination thereof- is feasible and highly desirable. After resection of the ovarian tumor(s), a frozen-section examination is recommended, whenever possible. Most expert gynecologic pathologists should be able to diagnose serous ovarian LMP tumors, but mucinous tumors are more problematic. I agree with the Trimbles that many pathologists may be able to state only that the tumor is "at least LMP." The diagnosis of either an ovarian LMP tumor or a frankly malignant tumor on frozen section has implications for comprehensive surgical staging. The issue of surgical staging is also controversial, even among expert gynecologic oncologists. Because these tumors, particularly those that are stage I, are
associated with an excellent prognosis, and because no evidence suggests that postoperative treatment is warranted, some advocate that surgical staging is unnecessary. However, I would submit that comprehensive surgical staging is indicated when an ovarian LMP tumor is diagnosed, for the following reasons: (1) The information gained will further elucidate the biologic behavior of these tumors; (2) precise staging information will allow patients and their families to better understand their prognosis, because the risk of recurrence and death is higher in patients with extraovarian spread; (3) in some cases in which frozen-section examination suggests the diagnosis of an ovarian LMP tumor, the final diagnosis will indicate invasive ovarian cancer. In addition, once effective therapy for advanced-stage ovarian LMP tumors has been developed, there will be even more compelling reasons to justify comprehensive surgical staging. **Postoperative Therapy, Prognosis, and Use of Biomarkers**

The Trimbles are correct-no postoperative therapy has been shown to be effective in reducing the relapse rate or improving survival in women with advanced-stage disease. However, essentially all of these studies are retrospective, and many suffer from small numbers. Approximately 30% of women with serous tumors have disease spread beyond the ovary in the form of peritoneal implants. In reported studies, approximately 18% of patients with noninvasive peritoneal implants relapse, and approximately 6% have died of tumor.[2,6-14] Among patients with invasive peritoneal implants, approximately 36% relapse, and 25% have died of tumor.[2,6-12,14,15] Zanetta and colleagues have suggested that the prognosis of patients with advanced-stage tumors may be better than previously reported.[14] However, longer follow-up may be necessary to demonstrate relapse rates reflected in the prior studies, particularly the M. D. Anderson series.[13,15] The studies from M. D. Anderson indicate that, of all patients who relapse, approximately 75% have low-grade serous carcinomas, and 25% have recurrent LMP tumors.[16] Several clinical or clinicopathologic factors appear to be prognostic. These include FIGO stage, age at diagnosis, and residual disease at completion of primary surgery. Although several biomarkers-DNA ploidy, p53 overexpression, K-ras, and so forth-have been studied in an effort to identify patients at high risk of relapse, none have been validated in prospective trials. The Trimbles' contention that so-called recurrent LMP tumors represent either a primary peritoneal cancer missed at initial diagnosis or a new ovarian or primary peritoneal cancer is, once again, speculative. They may be correct, but the data are thus far inconclusive. The molecular biology of this phenomenon has not yet been resolved. Although studies of ovarian LMP tumors and their peritoneal implants suggest multifocality or polyclonality rather than monoclonality, the numbers of patients in these studies were small and the techniques used were few.[17,18] In addition, mutational analysis of advanced-stage serous LMP tumors that subsequently "recurred" suggested a second primary tumor rather than a true recurrence.[19] Further study is clearly indicated. **Future Directions**

Future research that will allow us to bridge the gaps in our knowledge of ovarian LMP tumors should focus on the following: (1) causative factors in the pathogenesis of these tumors; (2) the value of comprehensive surgical staging; (3) elucidation of clinical, pathologic, and molecular predictive and prognostic factors to select patients who are at high risk of relapse and who may benefit from postoperative therapy; (4) a search for more effective systemic therapies for advanced-stage tumors and for subsequent low-grade serous carcinomas; (5) the role of microinvasion and micropapillary pattern in prognosis and in determining optimal treatment; and (6) the clonality of the primary ovarian tumors, their peritoneal implants, and subsequent low-grade carcinomas. Such information will begin to blur the differences between the "splitters" and the "lumpers."

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