Endometrial Cancer: Recent Developments in Evaluation and Treatment

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Although endometrial cancer is the most common gynecologic malignancy diagnosed in US women, it has not received the same attention from health care professionals and the lay public as its more lethal counterpart in the female gonad—epithelial ovarian cancer. This relative invisibility is probably a product of multiple realities: (1) In many cases, endometrial cancer is effectively cured by a relatively simple surgical procedure that can be performed by most of the country’s 33,000 gynecologists. (2) The vast majority of women affected by endometrial cancer will survive their disease and suffer limited long-term sequelae. (3) This entity is more common in socioeconomic groups that are less likely to have access to the lay press and to action groups that often help inflate the importance of a given disease in an attempt to fulfill a specific agenda.

Points Requiring Further Clarification

Chen and associates have summarized much of what is now known about the evaluation and treatment of this disease. However, certain points made by the authors require clarification, as well as additional, critical information.

Should Tamoxifen-Treated Women Be Screened?—A significant segment of the article by Chen et al focuses on the issue of tamoxifen (Nolvadex) and its role as a risk factor for endometrial cancer. However, the authors skirt the issues and controversy regarding what, if any, focused screening for endometrial pathology should be recommended for these “at-risk” women. As Barakat has stated[1] in a recent editorial review of a peer-reviewed article that reported on the limited value of endometrial screening in these women,[2] “breast cancer patients receiving tamoxifen are anxious about developing a second cancer.” It is our obligation as health care professionals to help these women to understand what their real risks are, and to perform only appropriate, not emotionally demanded, interventions.

Type I vs Type II Endometrial Cancer—Chen et al distinguish between types I and II endometrial cancers. Unfortunately, the clinical reality is that these two pathologic types are not as separate and distinct as the authors imply. There is a significant degree of overlap between the unequivocally estrogen-dependent lesions, which have more in common with an endocrinopathy than with a true oncogenic process, and the highly aggressive, often fatal histologic cell types.[3] Historical data support the belief that these latter types are more common in familial cancer syndromes and in patients who have previously received pelvic radiation therapy.

Merits of Transvaginal Ultrasound—There remains a significant degree of controversy surrounding the proposed merits of transvaginal ultrasonographic evaluation of the endometrium. Using 5 mm as the threshold of endometrial thickness above which one would recommend that endometrial sampling be performed does ensure that ultrasound has an adequate sensitivity. Unfortunately, using this “cut-off” leads to a very high rate of false-positive scans and negative biopsies.[4]

Extent of Surgical Staging—By International Federation of Gynecology and Obstetrics (FIGO) definition, surgical staging cannot be limited to total abdominal hysterectomy and bilateral salpingo-oophorectomy. Patients who do not undergo the recommended pelvic and para-aortic lymph node sampling with collection of intraperitoneal fluid/lavage have not been adequately staged.[5] However, there is a subset of patients in whom the risk of extracorporeal spread is so low that the risks of surgical staging are difficult to justify. At The Johns Hopkins Hospital, we believe that such is the case for patients with grade 1 disease and no or only superficial myometrial invasion. We agree with Chen and colleagues that the uterine specimen should always be opened in the
operating room and inspected. If the merits of performing a complete surgical staging remains in question, a frozen section should be obtained. However, the clinician must fully appreciate the limitations of frozen-section biopsy in accurately predicting the depth of myometrial invasion, as well as any limitations unique to the pathologist performing the frozen-section analysis at their particular institution.

**Laparoscopic Surgery**
The feasibility of laparoscopic surgery in managing patients with early-stage endometrial cancer (presumed stage I and IIa) has been proven by Gynecologic Oncology Group (GOG) study 9206. This limited-access trial confirmed reports from multiple centers of laparoscopic excellence that the [minimally invasive] approach could be used both safely and effectively in a variety of clinical settings—not simply for [low-risk] disease, as implied by Chen and coauthors.

The unanswered question is whether or not these relatively new, complex laparoscopic techniques can be used outside of the centers that first described and performed them. It was this answer that was hoped for when GOG LAP-1, a prospective trial comparing traditional and laparoscopic surgical management of early endometrial cancer, was conceived and opened for enrollment. The results of this trial are still pending.

**Progestins**
There is an expanding experience using progestins to treat women with presumed stage Ia, grade 1 endometrial cancer who wish to preserve their fertility.[6] The optimal progestin dose is unknown, and this therapy may take up to 9 months to achieve an optimal effect. Regardless of the dose used, systemically administered progestins are associated with unpleasant side effects that frequently lead to suboptimal compliance.

At The Johns Hopkins Hospital, we are investigating, under the auspices of an institutionally approved study protocol, the merits of administrating the progestin directly to where it is needed (the endometrium) by using a device (the progestosterone-containing intrauterine device) that has proven to be devoid of associated progestin-related systemic side effects. Our study is still ongoing; therefore, it would be premature to report on the experience to date.

**Management of Intermediate- and High-Risk Patients**
Some of the most significant information deficits in gynecologic oncology relate to our knowledge of how best to manage patients with early-stage endometrial cancer who are at intermediate or high risk of suffering a recurrence. Chen et al allude to some of the limitations of the available data and describe the results of cooperative group trials.

Aggressive recruitment of this relatively rare group of heterogeneous patients into well-constructed, adequately stratified, prospective, randomized trials is necessary if we are ever to obtain the data needed to define standard therapeutic regimens. Because these diseases have a complex pattern of recrudescence, regimens that can effectively deal with the risk of both locoregional and systemic recurrence are needed.

**Prevention**
Finally, perhaps the single most important issue relates to the prevention of endometrial cancer. For many women who develop endometrial cancer, their disease is the end result of exposure to excess endogenous estrogens that are produced by peripheral conversion of androstenedione to estrone by adipose tissue. The more adipose tissue a woman has, the more conversion occurs, and the higher is her risk of developing endometrial cancer.[7] Chen and associates emphasize this reality.

In most instances, obesity is preventable by an appropriate lifestyle. This phenomenon offers the possibility for an organized campaign for disease prevention. Intense educational efforts directed toward the lay public, as well as mobilization of the medical profession to speak out against high-risk lifestyle behaviors, should be considered in an attempt to decrease both the public health and economic impact of endometrial cancer in this country.[8]

Any changes in the rate of obesity in women, even those resulting from aggressive public health campaigns, will come slowly, if at all. Thus, consideration should be given to the possible use of chemoprevention in very high-risk women (ie, those who are 15% or more above ideal body weight). The best agent to use for such chemoprevention is unknown, although low-dose continuous oral progestins may be a rational approach.

**References:**


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