

## Endometrial Cancer: Contemporary Insights Into Our Most Common Gynecologic Cancer

The last three decades have brought us significant advancements in our understanding of endometrial cancer. In the late 1970s, the collective efforts of investigators in the Gynecologic Oncology Group explored the clinicopathologic aspects in a prospective fashion. The study group enrolled nearly 1,200 patients from 1977 to 1983. The findings generated 17 abstracts and publications and enhanced our knowledge of the spread and metastatic potential of these epithelial cancers. This led to the adoption of surgical staging in 1988 by the International Federation of Gynecology and Obstetrics (FIGO). Surgical staging, in turn, formed the basis of trials of adjuvant therapy that have shaped our current management.

In parallel to investigations focused on surgical and medical management, the explosion of cellular biology, molecular biology, and genetics gave us a deeper understanding of pathogenesis and heritable risk as well as strategies to improve therapy. Our first article by Dr Bansal and associates provides an overview of the various molecular and biochemical processes believed to be important in endometrial cancer. Clinically there has been a convenient dualistic classification model that divides endometrial cancers into two types, based primarily on the phenotypic aggressiveness (which, in turn, is often related to histology). While much of our evolving molecular insights support such a model, not all do. This means the future holds the promise of improved classifications based on fundamental cellular and molecular differences between these cancers. The authors also discuss how knowledge of the dysregulated cellular pathways is shaping current and future trials in the treatment of endometrial cancer by using targeted therapies.

We also now know that approximately 5% of endometrial cancers may be attributed to inherited genetic factors. While this includes rare syndromes such as Cowden's, the most common is the hereditary non-polyposis colorectal cancer syndrome (HNPCC), also called Lynch syndrome. A variety of DNA mismatch repair genes are responsible. These mutated genes confer a risk of endometrial cancer that has been reported to be as significant as the colorectal cancer risk in affected patients. Dr Meyer and associates discuss genetic screening and offer guidelines for clinical screening and prophylaxis for mutation carriers.

In the next part of this issue, we step away from the molecular level to the contemporary clinical management of the disease. A series of three articles discuss the

role of comprehensive surgical staging, the trend toward the use of minimally invasive surgery, and the current treatment of metastatic cancer. Whenever I read articles related to the treatment of endometrial cancer, I am always reminded of the words one of my most respected mentors, Dr John Soper, said, "Endometrial cancer is the one disease that everyone knows how to treat and everyone treats differently." Despite several randomized phase III trials, the role of adjuvant radiation therapy, and more recently chemotherapy, is highly controversial. This is partly due to the nature of the studies and also partly depends on the side of the fence one is looking from. To summarize, with adjuvant radiation we can decrease localized recurrences but do not end up altering survival. Therefore, one's opinion on the role of this treatment is, for the most part, based on the relative importance of one vs the other. Because an adequate, objective discussion of the merits of radiation can, in my opinion, be had only with lengthy articles by authors of differing views, the reader will no doubt notice that articles directly addressing this issue are absent. In fact, an entire issue dedicated to this would be timely and interesting as there is evolving data regarding the role of radiation in intermediate-risk and high-risk disease, as well as newer insights into the mode of therapy (eg, whole pelvic vs brachytherapy, intensity-modulated radiation therapy [IMRT]).

An example of such controversy in management can be seen among surgeons when it comes to the need for comprehensive surgical staging. Drs Frederick and Straughn tackle this important issue in their article. Currently, there are two differing schools of thought: those who believe all cancers should have complete staging and those who believe that the level of staging can be guided by patient and cancer characteristics. The authors do a masterful job in outlining the data regarding risk of metastatic disease, the ability to predict such disease by preoperative and intraoperative findings, the use of radiographic data as a surrogate, and the potential risks of staging. In their conclusion, they appear to favor comprehensive staging for all. While this aligns with my personal treatment bias (which, in addition to the authors' well-known expertise, may partly explain why I invited them to contribute to this issue), there is admittedly a healthy disparity of opinion on this matter.

A discussion of surgical staging for endometrial cancer would not be complete without talking about

the increasing role of minimally invasive surgery. Drs Humphrey and Apte present us with data regarding conventional and robotic laparoscopy that leads them to conclude that it is generally safe and effective compared with laparotomy while sparing negative aspects of surgical recovery attributable to the latter method. Their discussion includes the impact of minimally invasive surgery in the setting of obesity, the completeness of staging, the reports of subcutaneous tissue implants following its use, and the impact of surgical training with the introduction of the robot.

When endometrial cancer is recurrent or metastatic, a selected group of women may be effectively treated with surgery, radiation, or both. For many, however, the cornerstone of treatment becomes systemic involving either cytotoxic chemotherapy or hormones. Drs Temkin and Fleming discuss the various regimens and the data supporting them. Beyond this, there is considerable discussion about the emerging data for targeted therapies that will hopefully lead to significant advancements for our patients.

Our next article separately examines the nonendometrioid endometrial cancers, which include serous, clear cell, mucinous, and squamous histologies that make up about 10% to 15% of all endometrial cancers. These were included with endometrioid cancers in some earlier studies, but they clearly behave differently and need to be considered and treated as unique uterine cancers. The serous and clear cell cancers metastasize much earlier in their course, and the pattern of metastasis differs as well. Dr Mendivil and colleagues expertly review the most recent data and make recommendations for management.

It is difficult to have discussion about a cancer and not consider the role and impact it has on people and society. With the increasing number of overweight and obese women, particularly at such young ages, the number of endometrial cancers we treat is increasing, along with the challenges we face in treating them. Also, we have more recently become acutely aware of a disparity

in the prognosis associated with race. Despite having a lower incidence of disease compared with white women, black women bear a greater proportion of cancer-related deaths, which has continued to rise over the last two decades. Drs Allard and Maxwell explore what appears to be a multifactorial explanation on why this occurs. I like this topic and their paper as it underscores the importance of considering both the patient and the cancer when approaching the management of disease. When we think of personalized medicine, it is tempting to think about genes and proteins. True personalized medicine incorporates all aspects of care. This perspective, in my opinion, will be important to the future of treating endometrial cancer or any other medical malady.

Four other articles are also included in this issue of *Cancer Control*. In the first, Dr Frazier and coworkers discuss how the addition of employment-related items could be a useful adjunct to those included in more standard quality-of-life measures. The second article describes an intriguing case where the administration of bexarotene was associated with complete resolution of sorafenib-induced keratoacanthomas.

In our Cancer, Culture and Literacy feature, Dr Helitzer and colleagues confirm the difficulty of preparing materials for mass education. Among the written materials they reviewed that focus on cervical cancer, most had a readability level that was too high to maximize use and comprehensibility for readers. Finally, Dr Larkey and associates show that the inclusion of storytelling may be an effective approach for changing colorectal cancer risk-related behavioral intentions among Latinos.

I hope you enjoy this issue.

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