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Endometrial Cancer in the United States: A Review of the Current Literature

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ABSTRACT

Background

Endometrial cancer is cancer of, or from, the endometrium of the uterus. According to the ACS, it is estimated that, in the United States, about 61,880 cases of cancers of the body of the uterus will be diagnosed in 2019 alone, while about 12,160 women will die from the disease. There are several types and classifications of endometrial cancer based on basic histological or clinical features, or a combination of both. Most of the current interventions have been focused on early detection especially in high-risk women. This is a review of the epidemiology and risk factors, public health actions, and latest interventions in the management of endometrial cancer in the United States.

Keywords

Endometrial cancer; the United States; Review.

IINTRODUCTION AND SIGNIFICANCE

In its simplest description, endometrial cancer is cancer of, or from, the endometrium of the uterus-the innermost of the three major layers of the womb. It is worthy of note that there are a few semantic distinctions among recognized expert bodies, for which one should be aware, in consideration of the literature. For example, the Centers for Disease Control and Prevention (CDC) distinguishes between cervical cancer and uterine cancer, of which endometrial cancer is the most common type of uterine cancer.[1] However, by definition, the cervix ('cervix uteri') is part of the uterus,[2] hence the potential confusion in the CDC's classification should be avoided. Further, the International Federation of Gynecology and Obstetrics (FIGO) has described cancer of the body of the uterus ('corpus uteri') as what is typically referred to as endometrial cancer.[3] However, the American Cancer Society (ACS) states that up to 10% of cancers of the body of the uterus are not endometrial cancers; rather, these 10% are sarcomas of the body of the uterus.[4]

According to the ACS, it is estimated that, in the United States, about 61,880 cases of cancers of the body of the uterus will be diagnosed in 2019 alone, while about 12,160 women will die from the disease. This is worth comparing to the estimated 320,000 new cases of endometrial cancers diagnosed globally every year.[3] Further, it was estimated that the total cost of care for cancers of the body of the uterus, in the United States, for the year 2018, will be about $4 billion.[5]

There are several types and classifications of endometrial cancer. Some are based on basic histological features of the cancer tissue, while others are based on a combination of both histological and clinical features of the disease. The ACS recognizesthe following histological types of endometrial cancers: (i) adenocarcinoma; (ii) uterine carcinosarcoma; (iii) squamous cell carcinoma; (iv) small cell carcinoma; (v) transitional carcinoma; and (vi) serous carcinoma. Most endometrial cancers are adenocarcinomas, and these adenocarcinomas comprise a very diverse group. The less common types of endometrial adenocarcinomas are clear-cell carcinoma, mucinous adenocarcinoma, undifferentiated carcinoma, de-differentiated carcinoma, and serous adenocarcinoma. Most endometrial adenocarcinomas, however, are called endometroid cancers. Further, endometroid cancers can be further subdivided into

the following variants: adenocarcinoma (with squamous differentiation), adenoacanthoma, adenosquamous (or mixed cell), secretory carcinoma, ciliated carcinoma, and villoglandularadenocarcinoma.[6]

The ascertainment of the stage of endometrial cancer usually follows a diagnosis, in order to assess the extent of cancer, in terms of amount and spread. FIGO has described a comprehensive staging system for cancers of the body of the uterus, and this has benefitted research and practice, for many years. This staging system is reproduced as Table 1.[7]

The grading of endometrial cancer is a description of the amount of the cancer's cellular architecture that are built into glandular structures, as comparable to a non-cancerous endometrium. Grade 1 cancers are those that have at least 95% of the cancer tissue forming glands. Grade 2 has between 50% and 94%. Grade 3 has less than 50% of the cancer tissue forming glands; these types of endometrial cancers tend to have the worst prognoses, relative to those of Grades 1 and 2.[6]

DESCRIPTIVE EPIDEMIOLOGY AND RISK FACTORS

Endometrial cancer is the sixth most common cancer worldwide,[7] with high-income countries reported to have a higher incidence (5.9%), compared to poorer countries (4.0%). In the United States, by the year 2016, cancers of the uterus ranked fourth highest (among all cancers) in terms of incident cancer cases among women, while also ranking sixth highest (among all cancers) in terms of deaths of women.[8] Other United States data show an increase in age-adjusted uterine cancer incidence rates, since about 2003, to current levels of 27.5 per 100,000 women per year.[9] These current levels of incidence have been accompanied by a death rate of 4.7 per 100,000 women per year, based on measures spanning 2012-2016. The 2016 prevalence of uterine cancer is reported by the National Cancer Institute as 772,245, spread across the United States. The following states reported higher age-adjusted incidence rates compared to others: Minnesota, Iowa, Illinois, Wisconsin, Ohio, West Virginia, Pennsylvania, New York, etc. Further, it has been documented that African-American women suffer worse prognoses of endometrial cancer, compared to non-Hispanic White women.[10]

Elevated estrogen levels, the postmenopausal state and obesity are high-ranking risk factors for endometrial cancer.[11] The ACS also identifies the following risk factors: a history of endometrial hyperplasia, family history of endometrial or colorectal cancer, type II diabetes mellitus, use of an intra-uterine device, and any situation that alters the normal hormone balance in a woman - for example, Tamoxifen (a drug used to treat breast cancer), pregnancy, ovarian tumors, polycystic ovarian syndrome, etc. Overall, the risk of endometrial cancer in a woman increases with age.[12] Lynch syndrome (the most common form of the hereditary colon cancer syndromes) accounts for 2% to 3% of all endometrial cancers in the United States.[13]

PUBLIC HEALTH ACTIONS AND INTERVENTIONS

The most far-reaching public health interventions deployed to mitigate the morbidity and mortality of endometrial cancer in the United States have mainly revolved around early detection of the disease, especially in at-risk women. Building on the Gynecological Cancer Education and Awareness Act of 2005,[14] the United States CDC promotes the Inside Knowledge About Gynecological Cancer Campaign, encouraging women, their families/friends, and their healthcare providers to pay close attention to women's bodies and to identify early warning signs.[15] These messages, from the Inside Knowledge campaign, have made at least 7 billion audience impressions since roll-out in the year 2010.

While the ACS provides (on its website) an important summary of treatment options, it appears that, in the United States, patients are left to seek and attain treatments based on their capacity, or the capacity of their friends and families. Throughout the literature, there did not appear to be a national coverage or subsidized care plan that was specific to endometrial cancers.

NEW INTERVENTIONS

A new approach worth considering in endometrial cancer management is the combination of Lenvatinib (a multi-kinase inhibitor) and Pembrolizumab (an antibody targeting programmed cell death protein 1). In a recent, much-cited study,[16] it was demonstrated that when Lenvatinib and Pembrolizumab are combined, they showed anti-tumor activity in advanced, recurrent endometrial cancer, with comparable safety profiles to the monotherapies of each drug, separately. A limitation of this new combined therapy, however, was an increased risk for hypothyroidism. This study was an open-label, single-arm, phase 2 clinical trial that was building on an earlier phase 1b study. The exposures and outcomes were very clearly elucidated in this trial, even though it was an interim analysis of a longer-duration study. In terms of efficacy and effectiveness of this combination therapy, there was documented anti-tumor activity by 24-weeks of initiation of treatment, even though treatment-related adverse events included hypertension, diarrhea, and hypothyroidism. As for generalizability, it is worthy of note that this analysis occurred based on a study that involved patients from at least 11 centers in the United States. For patients with advanced endometrial cancer with a history of recurrence, the results of this study are moderately generalizable.

POLICY IMPLICATIONS AND RECOMMENDATIONS

These policy recommendations are specific to the United States, given the scope of this review. It is highly recommended that more research studies be supported to uncover more insights about the racial disparities in endometrial cancer incidence and mortality rates. Further, strong potentials for collaboration exists between the United States Government and private biological and pharmaceutical companies, in order to subsidize screening methods, including genetic tests for Lynch syndrome. It will be worthwhile for the United States to maximize these potentials as much as possible, and to roll-out in partnership with states with documented high age-adjusted incidence rates. Other important policy implications include providing incentives to pharmaceutical companies interested in research and development for newer, safer and more effective drugs for the treatment of endometrial cancers in the

United States. Such incentives can go a long way to fast track the innovation pipeline, and advance the reach of life-saving drugs to the much-deserving population of American women.

CONCLUSION

More research is required in exploring the racial disparities in endometrial cancer incidence and mortality rates in the United States, as well as new therapies for treatments that are affordable.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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APPENDIX

Table 1: Cancer of the Corpusuteri

FIGO	Stage
I[a]	Tumor confined to the corpus uteri
IA[a]	No or less than half myometrial invasion
IB[a]	Invasion equal to or more than half of the myometrium
II[a]	Tumor invades cervical stroma, but does not extend beyond the uterusb
III[a]	Localand/orregional spread of the tumor
IIIA[a]	Tumor invades the serosa of the corpus uteri and/oradnexae'
IIIB[a]	Vaginal involvement and/or parametrial involvement'
IIIC'	Metastases to pelvic and/or para-aortic lymph nodes'
IIIC1[a]	Positive pelvic nodes
IIIC2[a]	Positive para-aortic nodes with or without positive pelviclymph nodes
IV[a]	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA[a]	Tumor invasion of bladderand/or bowel mucosa
IVB[a]	Distant metastasis,including intra-abdominalmetastases and/or inguinal nodes)