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Review

Early stage uterine serous carcinoma: Management updates and genomic advances

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HIGHLIGHTS

- Patients with uterine serous carcinoma should be surgically staged. Adjuvant therapy with platinum/taxane-regimens improves survival.
- Uterine serous carcinoma highly expresses HER2/neu, a potentially promising and rational target for biologic therapy.
- Recent genome-wide analyses have contributed to the identification of key mutations that may further guide drug design against USC tumors.

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ABSTRACT

Objective. Even in cases of early stage disease, uterine serous carcinoma (USC) is associated with high recurrence rates and a disproportionate number of cancer-related deaths. Prospective data to guide therapy for women with this disease are limited. This article reviews the currently available literature regarding optimal management of women with early stage USC.

Methods. MEDLINE was searched for all research articles published in the English language from January 1, 1996 through October 30, 2012 in which the studied population included women diagnosed with early stage USC. Although preference was given to prospective studies, studies were not limited by design or numbers of patients in light of the relative paucity of the available literature.

Results. Early stage USC (Stages I–II) is associated with a risk of recurrence that ranges from 0 to 80%, and is related to the amount of residual uterine disease, cervical involvement and adjuvant therapy. Treatment with platinum and taxane-based chemotherapy may decrease the risk of recurrence and may improve survival outcomes; volume directed radiotherapy may also be of benefit. USC highly expresses HER2/neu, a promising and rational target for biologic therapy. Alterations in the PIK3CA/AKT/ mTOR pathway are also of relevance and offer other potential therapeutic targets.

Conclusions. USC is a unique and biologically aggressive subtype of endometrial cancer, and as such, should be studied as a distinct entity. Prospective trials incorporating traditional chemotherapeutics and radiation as well as targeted therapies are warranted to define the optimal management approach for women with this disease.

Contents

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Introduction

Endometrial cancer is the most common gynecologic malignancy in U.S. women, with estimated 47,130 new cases per year and approximately 8010 deaths annually [1]. Fortunately, 80% of women with endometrial cancer are diagnosed with low grade, early stage tumors, with an associated 85% 5-year survival [2]. However, for those diagnosed with uterine serous carcinoma (USC), a rare and considerably more aggressive variant of endometrial cancer, prognosis is poor at any disease stage. This uncommon histologic subtype represents only 10% of endometrial cancer cases but is responsible for a disproportionate 40% of deaths from this disease [3–5]. The higher rate of observed cancer-related mortality is attributed to the inherent biological aggressiveness of USC compared with the more common endometrioid subtype. In contrast to endometrioid tumors, which present with advanced stage disease in fewer than 20% of cases, USC is diagnosed in advanced stages approximately 40% of the time. In the setting of clinically apparent early stage disease, USC is commonly found to have lymphovascular space invasion (LVSI), lymph node involvement, and microscopic spread to intraperitoneal structures—even when there is minimal or no myometrial invasion. However, even those with stage I disease may have a 0–80.0% risk of recurrence based in part on the high-risk clinicopathologic features described above and whether post-operative adjuvant therapy was administered [3,6–15].

Due to the rarity of USC and relative lack of prospective trials, it has been challenging to define the treatment recommendations for women with this disease [16–19]. Most publications included in this review are retrospective analyses, a critical limitation of this appraisal of the literature. Although several published review articles have concentrated on USC, none have focused primarily on the management of those with early stage disease [20–23], which constitute the majority of cases. Further, advances made in the last year in our understanding of USC biology through genome-wide analyses merit review, as these discoveries are likely to contribute to the future development of drug design against these tumors. Accordingly, an update on the status of current and forthcoming USC treatments is presented in this review.

Methods

MEDLINE was searched for all research articles published in the English language from January 1, 1996 to October 30, 2012 in which the studied population included women diagnosed with early stage USC. In order to identify a comprehensive list of the early stage USC literature, all publications with keywords of “endometrial cancer” and “uterine cancer” were combined and then added to the keywords “serous” and “papillary serous”. The bibliographies of selected publications were then cross-referenced to identify additional publications. Although preference was given to prospective studies, studies were not limited by design or numbers of patients in light of the relative paucity of published USC analyses.

Results

Epidemiology

Hendrickson et al. first described USC as a distinct pathologic entity in 1982 [24]. This led to Bokhman proposing two distinct “types” of endometrial cancer that were distinguished based on microscopic appearance, epidemiology, genetics, and clinical behavior [25]. These differences between “Type I” and “Type II” malignancies are shown in Table 1. The most important distinction between Type I and Type II endometrial malignancies is their behavior, with the higher grade, Type II cancers (including USC) exhibiting more aggressive biological and clinical behavior than their lower grade Type I counterparts. Epidemiologically, those diagnosed with Type I or endometrioid cancers are relatively young, more likely to be obese and have had exposure to endogenous or exogenous unopposed estrogen. Conversely, those diagnosed with USC and other Type II cancers, are thinner and older, more likely to be African American, and do not necessarily have exposure to unopposed estrogen. Given the recent obesity epidemic, however, contemporary studies demonstrate that women with Type II cancers may have a similar incidence of obesity as those with Type I cancer [26]. Age, however, remains a variable associated with an increased risk for USC. Lachance et al. demonstrated that 22% of endometrial cancers diagnosed in women over 75 years of age were USC compared with only 3% in women younger than 45 [27]. Studies also confirm the ethnic distribution of USC tumors. In an ancillary GOG study of women with advanced or recurrent endometrial cancer treated on GOG protocols, the incidence of USC was 39% in African American women versus 16% in Caucasian women [28]. Whether this difference may lead to some of the radical disparities in endometrial cancer survival is speculative [28–32]. Data from The Cancer Genome Atlas (TCGA) will likely shed additional light on the genetic differences between Type I and II malignancies, and may even allow for a more refined stratification of endometrial cancer based on molecular and genetic factors.

USC has been linked to breast cancer in a series of retrospective studies [33–36]. One study noted that women with a history of breast cancer who subsequently developed an endometrial cancer were 2.6 times more likely to develop USC as compared to an endometrioid

Table 1
Clinicopathologic and molecular differences of type I versus type II endometrial cancers. Modified and updated from reference [20]: Boruta et al., Management of women with uterine papillary serous cancer: a Society of Gynecologic Oncology (SGO) review. Gynecol Oncol 2009;115:14253.

Characteristics	Type I cancers	Type II/USC cancers
Demographics/risk factors	Younger age Obesity Exposure to unexposed estrogen Insulin resistance	Older age Thin or obese African American History of breast cancer/ tamoxifen exposure[a]
Patterns of recurrence	Locoregional: vaginal/pelvic	Distant: extrapelvic
Precursor lesion	Atypical hyperplasia	Endometrial glandular dysplasia
Histologic grade	Primarily low/moderate grade	High grade
Molecular features	PTEN inactivation Mismatch repair/ microsatellite instability	P53 mutations[b] HER2/neu gene amplification[b] PIK3CA mutations[b] PPP2R1 mutations[b] FBXW7 mutations[b] CHD4 somatic mutations[b]
Early stage at diagnosis	70–80%	50–60%
Stage I/II: 5-year overall survival	70–95%	50–85%

[a] Not definitive, but increasing data suggestive of an association with USC.
[b] References [65–80].