Gynecologic Oncology 137 (2015) 581–588

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review

Uterine carcinosarcoma: A review of the literature

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HIGHLIGHTS

- UCS is an aggressive de-differentiated endometrial carcinoma with its own molecular profile.
- Surgical staging and adjuvant chemotherapy are crucial for all stages of disease.
- Future study should focus on UCS specifically and consider targeted therapies.

ARTICLE INFO

Article history:
Received 1 February 2015
Accepted 16 March 2015
Available online 21 March 2015

Keywords:
Endometrial
Carcinosarcoma
Mixed Mullerian
Sarcoma

ABSTRACT

Objective. Uterine carcinosarcomas (UCSs) are aggressive tumors previously considered to be sarcomas, but now recognized as malignancies composed of metaplastic transformation of epithelial elements. Much of the management for UCS has been extrapolated from studies of endometrial carcinomas and sarcomas. This article critically reviews the literature pertinent to the pathology, pathogenesis, diagnosis and management of women with UCS.

Methods. MEDLINE was searched for English language literature on UCS with a focus on the past 20 years. Given the rarity of this tumor, studies were not limited by design or number of reported patients.

Results. UCS is biologically a de-differentiated endometrial carcinoma with its own pathogenesis and molecular profile. It commonly presents with extrauterine disease which can be identified by comprehensive surgical staging. Most UCS patients are candidates for adjuvant chemotherapy. The role of radiation is less clear. Combination therapy, while commonly used, has not been studied in depth. The high recurrence rate and poor overall survival for UCS suggest an ongoing need for clinical trials for UCS specifically.

Conclusions. UCS represents a distinct subtype of uterine malignancy, and should be studied as such via focused clinical trials.

Contents

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http://dx.doi.org/10.1016/j.ygyno.2015.03.041
0090-8258/

1. Introduction

Uterine sarcomas are rare tumors that comprise a diverse group of aggressive malignancies. Of the 52,630 cases of uterine cancer that occurred in the United States in 2014, only 5–6% were classified as uterine sarcomas [1,2]. Uterine carcinosarcoma (USC) has traditionally been included in the sarcoma category, and as such is the most common of the uterine sarcomas; it is also called malignant mixed mesodermal tumor or malignant mixed Mullerian tumor (MMMT). More recently, however, UCS has been categorized as a high grade endometrial cancer (EC). While rare, representing less than 5% of all uterine tumors [3–5], UCS accounts for 15% of all deaths caused by uterine corpus malignancy [6].

UCS is a malignant neoplasm that is composed of both epithelial and mesenchymal elements. Traditionally, UCS was believed to behave as a sarcoma, and therefore was included in clinical trials and treatment protocols that followed sarcoma guidelines. The emergence of more molecular and genetic data has demonstrated that USC is distinct from other sarcomas, and that it is the carcinomatous component that is the primary driver of tumor aggressiveness. Most recent data suggest that the origin of UCS is monoclonal [7–10] and that these tumors are best classified as de-differentiated carcinomas of the endometrium rather than as sarcomas [11]. As a result, UCS is now classified for staging purposes with carcinomas of the endometrium [12].

UCSs are very aggressive tumors. Unlike endometrioid endometrial cancer, where most tumors are of early stage and low grade, UCS presents with extrauterine disease in 60% of cases, and recurrence will occur in more than 50% despite surgery and adjuvant therapy. When compared to high grade endometrial carcinomas, multiple studies have demonstrated that UCS is a far more aggressive tumor [13–16]. The estimated 5-year survival for patients with USC is poor, ranging from 33–39% [17,18] (Table 1). Even in cases where disease is apparently confined to the corpus, the rate of recurrence is high [19,20].

The high recurrence rate and poor overall survival for UCS suggest the need for improved management strategies. Given the rarity of UCS, however, attempts to conduct prospective trials to establish treatment regimens, particularly in the setting of apparently uterine-confined disease, have been challenging. This article is based on a comprehensive review of the published literature with the intent of offering clinicians an overview of the pathology and pathogenesis, epidemiology, presentation, and management of women diagnosed with UCS.

2. Methods

For this article, we reviewed the English language literature for studies on uterine carcinosarcoma. A MEDLINE (PubMed) search of the English literature was performed, with a focus on papers published in the last two decades. Keywords included “uterine sarcoma,” “endometrial sarcoma,” “carcinosarcoma,” “mixed Mullerian” and “mixed mesodermal.” Additional publications were identified via systematic review of all reference lists within publications retrieved from the MEDLINE search. Given the rarity of this tumor, and the resulting dearth of prospective data, all peer-reviewed original report publications with an appropriate number of cases were considered and included. In studies inclusive of all uterine sarcomas, subset analyses specific to UCS were extracted. Similarly, in studies inclusive of both ovarian and uterine carcinosarcomas, data were extracted specific to the uterine tumors. Finally, some studies of endometrial cancers that included UCS were considered.

Table 1
Recurrence and survival rates by stage including new FIGO staging.

	Recurrence rate [93]	5 year survival [93,98]
Stage I	37%	59–65%
Stage II	46%	45–59%
Stage III	63%	22–26%
Stage IV	80%	9–26%

2.1. Epidemiology

UCS accounts for 4.3% of all uterine corpus cancers [21]. The worldwide annual incidence is 0.5–3.3 cases per 100,000 women [2].

UCSs and endometrial adenocarcinomas share some similar risk factors (Table 2). Like endometrial adenocarcinoma, UCS risk is increased in the setting of increased estrogen levels and decreased by a history of oral contraceptive pill use. Other common risk factors include nulliparity and obesity [22]. However, there are also some very important epidemiologic differences. When compared to grade 3 endometrioid endometrial carcinomas, women with UCS are older, with a median age of 70 years [16]. They are more commonly African-American, and more often present with advanced disease [16].

Black race is a significant risk factor both for development of UCS and for poor survival. The relatively higher incidence of both UCS and leiomyosarcoma in black women when compared to white women was first noted by Harlow in 1986 [23] and confirmed by Platz and Benda, who also noted that black women were more likely to be diagnosed with advanced disease than white women [24]. A recent SEER analysis confirmed these reports: the overall age-adjusted incidence for black women was twice that of white women and more than twice that of other races [2]. With respect to survival, analysis of the results of GOG 150 (a Phase 3 randomized study of whole abdominal radiotherapy (WAR) versus combination ifosfamide-mesna with cisplatin in optimally debulked stage I–IV UCS) demonstrated no difference in survival between black and white women with advanced stage disease [25]. However, when only early stage disease was considered, both progression free and overall survival were significantly worse in black women. Moreover, on multivariate analysis, black race remained independently associated with risk of death (HR 2.0, 95% CI 1.25–3.23) [25].

Tamoxifen use and prior pelvic radiation have both been associated with the development of UCS. Multiple small series have reported patients who developed UCS following prolonged use of tamoxifen [26]. In one study, the median length of exposure to tamoxifen was 9 years (5–20), and the median time from the initiation of tamoxifen to the diagnosis of the uterine malignancy was 9 years (7–20) [27]. Prior pelvic radiation has also been identified as a risk factor for the development of UCS. A series of 23 patients who developed uterine

Table 2
Comparison of epidemiological risk factors between endometrial cancer (EC) and UCS [2,16,26].

Low risk EC	High risk EC	UCS
Estrogen/obesity	Estrogen	Estrogen
Caucasian	African-American	African-American
Nulliparity	Nulliparity	Nulliparity
Tamoxifen	Tamoxifen	Tamoxifen
		Pelvic radiation

EC = endometrial cancer, UCS = uterine carcinosarcoma.