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Carcinosarcomas of the Uterine Corpus: Histopronostic Factors and Survival

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Review Article

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Abstract

Background: Uterine carcinosarcomas (UCS) are characterized by the association of carcinomatous and sarcomatous components. The objective of our work was to determine the histopronostic factors, overall survival (OS) and recurrence-free survival (RFS) in UCS.

Methods: Our study was retrospective including 52 cases of UCS collected at the pathology department of the Salah Azaiez Institute in Tunis over a period of 19 years.

Results: The median age was 62 years. Treatment was surgical in all cases. The tumor had a median size of 70 mm. The predominant carcinomatous component was endometrioid (50%). The predominant sarcomatous component was heterologous (56%) often rhabdomyoblastic (42%). These two components were frequently intertwined (94%). The infiltrative mode, myometrial invasion>50% and vascular emboli were found, respectively, in 63%, 56% and 65% of cases. The stages III-IV were the most represented (62%). Adjuvant treatment was performed in 60%. A recurrence was noted in 46% of cases: It was biphasic (50%), carcinomatous (33%) and sarcomatous (17%). The median OS was 29 months and OS at five years was 33%. The median RFS was 24 months and RFS at five years was 37%. The prognostic factors influencing OS and RFS in univariate analysis were: size, myometrial invasion, vascular emboli, rhabdomyoblastic differentiation and type of infiltration.

Conclusions: It is important to type and characterize the two carcinomatous and sarcomatous components of UCS in order to define subgroups of patients.

Keywords: Carcinosarcoma, Uterus, Survival, Recurrence, Prognosis.

Introduction

Uterine carcinosarcomas (UCS) or malignant mixed Müllerian tumors (MMMT) are rare biphasic tumours, representing less than 5% of malignant tumours of the uterus [1]. They are characterized by the association of carcinomatous and sarcomatous component [2], the nature and proportion of which vary from case to case [3]. The origin of these UCS is debated with two main hypotheses: On the one hand, that of a totipotent stem cell which would differentiate in the epithelial and connective direction, the most probable hypothesis and on the other hand the coexistence of two different and independent cellular contingents [4,5].

UCS remain aggressive tumours with an unfavourable prognosis associated with heavy mortality, even at an early stage with an overall survival rate at five years, not exceeding 50% [6-8].

Several prognostic factors have been studied with often contradictory results. In addition to the tumour stage, the histological characteristics of the carcinomatous and sarcomatous components would play a role in tumour progression and patient survival, suggesting their importance also in guiding management decisions. Thus, the identification of the histopronostic factors in this group of tumours would make it possible to define subgroups of patients and to propose an adequate treatment.

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The aim of this study is to determine histological prognostic factors in UCS and to specify overall survival (OS) and recurrence-free survival (RFS) according to these different prognostic factors through a retrospective study of 52 patients.

Materials and Methods

We conducted a retrospective study on a series of patients with UCS whose diagnosis was confirmed on the operative specimen.

All cases were collected in the anatomy and pathological cytology department of the Salah Azaiez Institute in Tunisia (ISA), over a period of 19 years, from January 2000 to December 2018.

We included in our study all patients who presented with a primary UCS on a surgical specimen. These patients were operated in the surgical department of ISA and treated in the oncology department of ISA.

The following patients were not included in this study:

Patients whose file was not found, empty or incomplete and patients who were treated for cervical or ovarian carcinosarcoma extended to the endometrium.

Patients who received neoadjuvant therapy were excluded from the study.

Electronic medical records and pathology reports were reviewed to analyze clinical parameters (age, adjuvant treatment, recurrence and sites of recurrence), pathologic variables (gross appearance, tumour size, depth of myometrial invasion, lymphovascular invasion, metastasis, International Federation of Gynecology and Obstetrics (FIGO) stage and histologic component on primary site, metastasis and recurrence), and survival data (vital status, recurrence-free survival (RFS) and overall survival (OS)). Representative hematoxylin and eosin–stained whole-tissue sections of each tumour were reviewed by two gynecologic pathologists over a multiheaded microscope to confirm the diagnosis as per World Health Organization criteria and to define features to be studied. The average number of hematoxylin and eosin–stained slides reviewed per case was 13 (range, 4–35). Tumours were designated as UCS if they had both malignant epithelial and mesenchymal components. Morphologic features reviewed included the histologic type and grade of carcinomatous and sarcomatous components, percentage of each component, presence of homologous versus heterologous elements, pattern of collision between both components, pattern of myometrial invasion (mode of infiltration) and tumour necrosis. All cases were restaged using the 2015 FIGO staging system [9]. It was used based on pathological data and extension assessment. FIGO clinical stages I to II were considered as early stage whereas FIGO clinical stages III to IV tumours were defined as advanced stage.

For the histological type of the carcinomatous component: we studied the presence or absence of serous carcinoma, endometrioid carcinoma, clear cell carcinoma and undifferentiated carcinoma. The FIGO grading system was used for endometrioid carcinomas [2]; serous, clear cell, and tumours containing any clear cell or serous component were classified as grade 3 tumours. Sarcomatous components were homologous (endometrial stromal sarcoma, leiomyosarcoma, fibrosarcoma, or undifferentiated sarcoma) or heterologous (rhabdomyosarcoma, osteosarcoma, chondrosarcoma, and liposarcoma). The proportion of carcinomatous and sarcomatous components was evaluated and recorded. The presence of a sarcoma component comprising ≥50% of the tumour volume within the primary tumour site was defined as sarcoma-dominant. The pattern of collision between epithelial and mesenchymal elements were classified as juxtaposed when a clear demarcation of both components was present and intertwined when they merged with each other.

The pattern of myometrial invasion or the mode of infiltration was classified as invasion with either destructive or pushing borders. Histologic component (carcinomatous and sarcomatous) at recurrent/metastatic sites as well as within lymphovascular spaces was evaluated when slides were available. Long-term follow-up data were censored at the date of last contact. RFS was calculated from date of diagnosis until date of recurrence, death or last follow-up. OS was calculated from the date of diagnosis until death or date of last follow-up. Statistical analyses were conducted using Kaplan-Meier analysis and the Log-Rank test in univariate analysis for the search for prognostic factors of survival (The test was considered significant if the p-value was less than or equal to 0.05). Statistical analysis was performed by SPSS 23 software.

Results

Clinicopathologic Features

A total of 52 cases with confirmed diagnosis of UCS were included in our study. The demographics and clinicopathologic features of patients and their tumours were detailed in Table 1.

Table 1: Demographics and clinicopathologic characteristics of patients with uterine carcinosarcomas

Parameters	N (%)
Age at diagnosis (years)	
≤60	20 (38%)
>60	32 (62%)
Tumour size (cm)	
<5	10 (19%)
≥5	42 (81%)
Tumour necrosis	
Absent	7 (13%)
Present	45 (87%)
Percentage of sarcomatous component	
<50%	22 (42%)
≥50%	30 (58%)
Histologic subtype of carcinomatous component	
Endometrioid	26 (50%)
Serous	9 (17%)
Mixed	16 (31%)
Undifferentiated	1 (2%)
Grade of carcinomatous component	
Low grade (grade2)	7 (13%)
High grade (grade3)	45 (87 %)
Sarcomatous component	

Homologous	23 (44%)
Heterologous	29 (56%)
Rhabdomyoblastic differentiation	
Present	22 (42%)
Absent	30 (58%)
Pattern of collision	
intertwined	49 (94%)
Juxtaposed	3 (6%)
Mode of infiltration	
Infiltrative	33 (63%)
Pushing	19 (37%)
Myometrium invasion	
< 50%	23 (44%)
≥ 50%	29 (56%)
Lymphovascular invasion	
Present	34 (65%)
Absent	18 (35%)
FIGO stage	
I-II	20 (38%)
III-IV	32 (62%)
Recurrence	
Yes	24 (46%)
No	28 (54%)
Adjuvant external radiotherapy	
Yes	20 (38%)
No	32 (62%)
Adjuvant brachytherapy	
Yes	16 (31%)
No	36 (69%)
Adjuvant chemotherapy	
Yes	16 (31%)
No	36 (69%)

Abbreviation: FIGO indicates International Federation of Gynecology and Obstetric

The median age at diagnosis was 68 years (range, 29–85 years). Older women (>60 years) were more commonly affected (62% vs. 38%). The age group [60; 70] years was the most frequently reached corresponding to 44% of our population. The median tumour size at the time of surgical resection was 7.0 cm (range, 2–19 cm) with 81% (n=42/52) measuring ≥5 cm in greatest dimension. The macroscopic study revealed: a polypoid gross appearance in 29 cases (56%) and ulcerative-budding in 23 cases (44%). The colour was variable whitish, yellowish or greyish. Tumour necrosis was present in 45 patients (87%).

The microscopic study revealed that the carcinomatous and sarcomatous components represented 2% to 98% of the tumour surface. These UCS were classified as predominantly sarcomatous in 58% of cases and predominantly carcinomatous in 42% of cases.

Concerning the carcinomatous component: the endometrioid type was predominant (50%) followed by the mixed type (31%), the serous type (Figure 1) (17%) and undifferentiated carcinoma (2%). Clear cell carcinoma has never been seen on its own. These carcinomas were in most cases of high grade (87%). The remaining cases corresponded to FIGO grade 2 endometrioid carcinoma (13%).

The sarcomatous component was homologous in 44% cases and heterologous in 56% of cases. Rhabdomyoblastic differentiation (Figure 2) was the most represented (42%), followed by chondroblastic (27%), osteoblastic (6%) and lipoblastic (4%) differentiations. These heterologous elements were mixed in 11 cases (21%). All sarcomatous elements were histologically high grade.

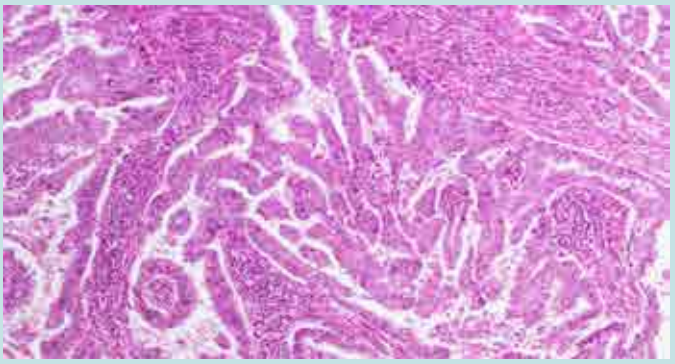

Figure 1: Serous carcinoma

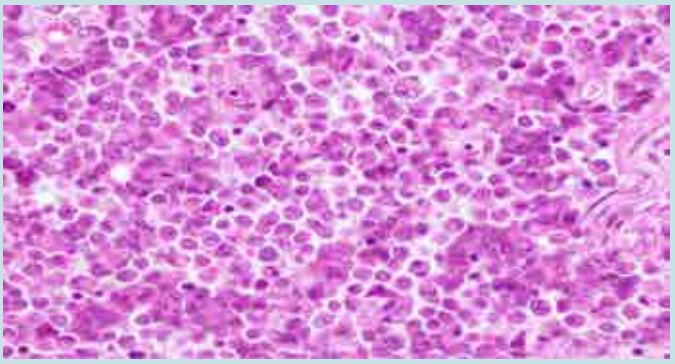

Figure 2: Rhabdomyosarcomatous differentiation.

These two components were intertwined in 94% of cases. The mode of infiltration was infiltrative in 63% of cases. Myometrial invasion exceeded 50% in 56% of cases.

Histologically, we noted an extension of the UCS to : cervical stroma in 34 patients (65%); vagina in three patients (6%); parameters in three patients (6%); uterine serosa in 15 patients (29%); adnexa in 12 patients (23%); lymph nodes in 14 patients (27%) with an inguinal site in one case, appendix in two patients (4%) (association with the rectum in one case) and the small bowel and sigmoid loop in one patient (2%); peritoneum in nine patients (17%); gall bladder in one patient (2%) and spleen and liver in one patient (2%).

For the 41 patients (79%) presenting an extension to another site and for which we have histological proof: the sarcomatous

component was in the minority for 26 cases (63%) and predominant for 15 cases (37%).

Lymphovascular invasion was identified in 34 cases (65%). In the majority of cases: 24 (71%), the vascular emboli were of the carcinomatous type.

Some patients presented with a metastasis on the extension workup (imagery) but without histological proof. This extension assessment was useful for the staging of FIGO.

The tumours were classified into FIGO stage: IA in 10 cases (19%), IB in one case (2%), II in nine cases (17%), IIIA in four cases (8%), IIIB in three cases (6%), IIIC1 in six cases (12%), IIIC2 in five cases (10%), IVA in one case (2%) and IVB in 13 cases (25%).

The follow-up period was between 0 and 147 months. During the follow-up interval, 24 (46%) patients experienced tumour recurrence. This recurrence was locoregional in seven cases (13%), metastatic in three cases (6%) and locoregional and metastatic in 14 cases (27%).

Locoregional recurrence was: pelvic without precise localization in 10 cases (19%) and pelvic and latero-aortic lymph nodes in one case (2%). It was vaginal in six cases (12%), colic in three cases (6%), rectal in two cases (4%) and on bladder in one case (2%). Metastatic recurrence was pulmonary in eight cases (15%), peritoneal in seven cases (13%), hepatic in six cases (12%) and splenic in one case (2%). Of the patients who developed recurrence, data regarding the histologic component at recurrence sites was available on six patients (12%) only. Two patients (4%) had pure carcinomatous components upon recurrence, one (2%) had only sarcomatous elements and three (6%) demonstrated both. There wasn't any pathological difference between initial extension lesions and recurrent lesions.

Treatment Characteristics

All patients underwent total hysterectomy and bilateral salpingo-oopherectomy was performed in 50 patients (96%). We noted the preservation of one uterine adnexa for one patient and two adnexae for the other patient. Lymph node dissection was performed in 39 cases (75%).

Adjuvant treatment was performed in 31 cases (60%). Twenty patients (38%) received adjuvant external radiotherapy. Sixteen patients (31%) received adjuvant brachytherapy. Sixteen patients (31%) received adjuvant chemotherapy. Seven patients (13%) received both chemotherapy and radiotherapy (external radiotherapy and/or brachytherapy).

The molecules used in chemotherapy were: Carboplatin / Taxol in seven cases (13%), Adriamycin / Cisplatin / Ifosfamide in four cases (8%), Adriamycin / Ifosfamide in three cases (6%), Taxol / Ifosfamide in two cases (4%) and Cisplatin alone in one case (2%).

The treatment of locoregional and metastatic tumor recurrence was based on surgery, radiotherapy, chemotherapy or palliative. This treatment was surgical in three cases (6%), radiotherapy-based in two cases (4%), chemotherapy-based for seven cases (13%) and palliative for 12 cases (23%).

Clinical Outcomes and Survival Analysis

In our study, the median RFS was 24 months and the RFS at five years was 37%.

The median OS was 29 months and the OS at five years was 33%.

The univariate analysis allowed to identify as histoprognostic factors directly influencing RFS and OS (Table 2 and 3) were: tumour size, depth of myometrial invasion, lymphovascular invasion, rhabdomyoblastic differentiation and mode of infiltration.

Table 2: Univariate analyses for the correlation of clinicopathologic parameters with recurrence-free survival.

Parameter	12 months	36 months	60 months	P
Age at diagnosis (years)				
≤ 60	71%	63%	63%	0.3115
> 60	57%	37%	25%	
Tumour size (cm)				
< 5	89%	89%	89%	**0.0082**
≥ 5	52%	31%	24%	
Depth of myometrial invasion (%)				
< 50	79%	72%	72%	**0.0038**
≥ 50	44%	21%	10%	
Lymphovascular invasion				
Negative	87%	67%	67%	**0.0095**
Positive	45%	32%	24%	
Figo stage				
I-II	62%	52%	52%	0.4084
III-IV	60%	40%	30%	
Percentage of sarcomatous component in primary site				
< 50%	59%	38%	38%	0.7081
≥ 50%	62%	50%	33%	
Serous carcinoma in primary site				
Presence	45%	37%	19%	0.1935
Absence	69%	49%	49%	
Grade of carcinomatous component				
Low grade	60%	60%	60%	0.4092
High grade	59%	39%	32%	
Sarcomatous component				
Homologous	68%	53%	36%	0.2545
Heterologous	53%	35%	35%	
Rhabdomyoblastic differentiation				
Absence	71%	53%	43%	**0.05**
Presence	45%	30%	30%	
Chondroid differentiation				
Absence	67%	50%	42%	0.4692
Presence	48%	38%	38%	
Tumour necrosis				
Absence	86%	68%	68%	0.127
Presence	54%	38%	32%	
Mode of infiltration				
Pushing	86%	86%	86%	**0.0007**
Infiltrative	48%	25%	17%	
Pattern of collision				
Juxtaposed	50%	50%	50%	0.5964
intertwined	60%	43%	36%	
Percentage of sarcomatous component in secondary site				
< 50%	55%	32%	21%	0.4625
≥ 50%	62%	50%	50%	
Percentage of sarcomatous component in vascular emboli				
< 50%	54%	36%	24%	0.7672
≥ 50%	29%	29%	29%	

Abbreviation: FIGO indicates International Federation of Gynecology and Obstetrics

Discussion

UCS or malignant mixed Müllerian tumors (MMMT) are rare tumours that represent less than 5% of endometrial cancers [1,2].

These cancers are aggressive with a poor prognosis whose OS at five years varies between studies from 31 to 52% [6,10] and the median OS varies from 16 to 29 months [3]. The five-year recurrence rate ranges from 39% to 71% [10] with a médian time to récurrences of 11 to 25 months [3,10].

The median age of patients with UCS ranges from 65 to 68 years [3,10]. Most studies consider age to be a prognostic factor independent of other clinico-pathological factors. In fact, in the multicentre study by Matsuo et al [11] comprising 906 cases, age is significantly correlated with OS and RFS with a negative influence (≥60 years). On the other hand, for Iwasa et al, the prognosis is worse for patients aged less than 65 years [12] with an overall five-year survival of 12.9% versus 59.6% for those whose age > 65 years. Other series [13] do not report a correlation between age, OS and RFS. In our study, we did not find any correlation.

Table 3: Univariate analyses for the correlation of clinicopathologic parameters with recurrence-free survival.

Parameter	12 months	36 months	60 months	P
Age at diagnosis (years)				
≤ 60	64%	52%	52%	0.6203
> 60	70%	41%	20%	
Tumour size (cm)				
< 5	90%	90%	90%	0.0078
≥ 5	60%	31%	21%	
Depth of myometrial invasion (%)				
< 50	86%	66%	66%	0.0061
≥ 50	53%	28%	9%	
Lymphovascular invasion				
Negative	88%	70%	70%	0.0131
Positive	56%	32%	19%	
Figo stage				
I-II	72%	59%	59%	0.1665
III-IV	63%	36%	21%	
Percentage of sarcomatous component in primary site				
< 50%	85%	39%	39%	0.6699
≥ 50%	62%	50%	25%	
Serous carcinoma in primary site				
Presence	61%	30%	15%	0.2645
Absence	70%	53%	44%	
Grade of carcinomatous component				
Low grade	50%	50%	50%	0.5546
High grade	68%	41%	28%	
Sarcomatous component				
Homologous	78%	66%	44%	0.0343
Heterologous	58%	30%	24%	
Rhabdomyoblastic differentiation				
Absence	75%	59%	47%	0.0193
Presence	56%	27%	18%	
Chondroid differentiation				
Absence	72%	50%	42%	0.2096
Presence	57%	39%	29%	
Tumour necrosis				
Absence	100%	75%	75%	0.033
Presence	69%	37%	27%	
Mode of infiltration				
Pushing	76%	68%	68%	0.0495
Infiltrative	73%	32%	16%	
Pattern of collision				
Juxtaposed	100%	100%	100%	0.2037
intertwined	72%	42%	30%	
Percentage of sarcomatous component in secondary site				
< 50%	78%	32%	16%	0.2304
≥ 50%	73%	57%	57%	
Percentage of sarcomatous component in vascular emboli				
< 50%	64%	33%	16%	0.9863
≥ 50%	42%	42%	42%	

The tumour size is often large, exceeding 50 mm [3,6,14]. In the literature [3,11], tumour size is correlated with OS and RFS. This is concordant with our results.

The dominant role of the carcinomatous contingent in the tumour progression is widely accepted. Carcinoma is considered by most authors to be the progenitor or "parent" tumour of UCS and is called "the driving force" [5]. Thus, UCS are considered by many pathologists to be metaplastic carcinomas [15]. The sarcomatous contingent derives from the carcinoma by epithelial-mesenchymal transition phenomena [5].

The proportion of sarcomatous differentiation required to label a tumour as a UCS ranges from 2% [16] to 25% [17]. Some authors even propose a minimum size of 1 mm of the sarcomatous focus to switch the diagnosis of carcinoma to UCS. In our opinion, there is no threshold value because the assessment is often arbitrary. In our series, the proportion of each component varied between 2% and 98%. The sarcomatous component was predominant in 58% of cases. The prognostic significance of the carcinomatous and sarcomatous components of UCS has been debated for decades. While several studies report that the carcinomatous components alone predict outcomes, others demonstrate that, on the contrary, the sarcomatous components have an impact on the prognosis. The more aggressive nature of UCS compared to high-grade endometrial carcinomas (serous, clear cell and grade 3 endometrioid) is established by numerous studies arguing that the sarcomatous component is a histological marker of increased aggressiveness [18].

UCS were considered uterine sarcomas while their prognosis depends mainly on their carcinomatous component [15]. On the other hand, a predominantly sarcomatous differentiation can suggest a more aggressive behaviour and a poor prognosis [16,19-22]. Some studies also suggest that these largely sarcomatous tumours tend to be associated with pure sarcomatous metastases, which spread preferentially hematogenously to distant sites, without peritoneal spread [16,19-21]. The study by Abdulfatah et al [3] as well as that by Matsuo et al [11] show that the predominance of the sarcomatous component influences OS and RFS, in univariate and multivariate analysis.

In our study, the predominant sarcomatous component at the primary site did not influence OS or RFS.

According to Soslow [23], the most common components are serous carcinoma, endometrioid (grade 2 or 3), or ambiguous carcinoma. Endometrioid carcinoma grade 1 and classically defined clear cell carcinoma are present only exceptionally.

In our study, endometrioid carcinomas (grade 2 or 3) were the most frequent (50%).

George et al show that the prognosis is correlated with the type and degree of differentiation of the epithelial component of UCS [18].

Indeed, the prognosis of UCS with serous carcinoma or clear cell carcinoma is worse than those where the epithelial component is endometrioid even grade 3. Moreover, for other authors, the prognosis is similar regardless of the histological type of the associated high-grade carcinomatous component [24-26].

It is clearly recognized that the presence of a serous-like carcinoma component in at least 5-10% of the tumour leads to a serous carcinoma-like prognosis [27,28]. These tumours are more likely to cause poor survival, peritoneal metastasis and recurrence [23]. Likewise, the presence of a clear cell component is associated with a high rate of metastasis [4].

In the study by Abdulfatah et al [3], for the histological type of the carcinomatous component, univariate analysis shows that the presence of a serous component influences OS.

In our study, the histologic type of the carcinoma component did not influence OS or RFS.

World Health Organization 2020 defines the sarcomatous component as a high-grade malignant component [2] and it can be homologous or heterologous.

The homologous sarcomatous component is present in 50% of cases. It is formed, in most cases, of spindle-shaped (fibrosarcoma) or pleomorphic (malignant fibrous histiocytoma) cells. It rarely resembles leiomyosarcoma or endometrial stromal sarcoma [14,19].

Heterologous sarcoma is identified in 50% of cases [2,29]. It is easily recognizable under microscopy and the immunohistochemical study has little room. Rhabdomyosarcoma and chondrosarcoma are the most frequently encountered types [14,19,30]. Lipoblastic, osteosarcomatous and neuroectodermal differentiation may be observed more rarely [3,31]. Rhabdomyosarcoma is identified by the presence of round or elongated cells with an eosinophilic fibrillar cytoplasm and an eccentric nucleus. Striated rhabdomyoblasts may appear.

Mixed heterologous differentiation is noted in 23% of cases [3].

Studies by the institutes of pathology of the armed forces in 1960 [32,33] emphasize the importance of the type of sarcoma and the prognostic significance of distinguishing tumours with homologous elements from those with heterologous elements. Homologous UCS confined to the uterine corpus would have the same evolutionary characteristics as high-grade endometrial carcinomas lacking sarcomatous components [23]. Tumours with heterologous sarcoma behave more aggressively [32,33]. Likewise, in the gynecologic oncology group study of 301 UCS cases [34], the presence of heterologous sarcomatous elements are important independent prognostic factors of tumour recurrence. In the study by Abdulfatah et al [3], the presence of rhabdomyoblastic differentiation is a factor of poor prognosis correlated, in univariate and multivariate analysis, with OS less than 3 years [3]. This differentiation was also correlated with bad RFS in the study by Matsuo [11]. The study by Silverberg et al [19] showed that the presence of chondroblast differentiation is relatively favorable. However, in the study by Barwick and Livolsi [30], the presence of chondroid differentiation is associated with a poor prognosis. In our study the rhabdomyoblastic differentiation was a factor of poor prognosis influencing OS and RFS in univariate analysis.

For other authors, the histological characteristics of the stromal component, including the presence or absence of heterologous elements play no prognostic role [12,21].

Myometrial infiltration is an important prognostic factor for all histologic types of endometrial cancer. UCS are invasive tumours, infiltrating more than 50% of the myometrium in almost 50% of cases [3]. Silverberg et al [19], through a study of 203 cases, show that myometrial invasion is a predictor of extra-uterine extension. When it is greater than 50% of the myometrium, it significantly alters OS and RFS [3]. Our results correlate with the depth of invasion in univariate analysis.

In endometrial cancers, the infiltrative growth pattern is a diffusely infiltrating growth pattern characterized by irregularly distributed glands, masses, cords, tumour cells and randomly infiltrating the myometrium. In contrast, the expansive growth model is one in which the invasive tumour has a lobulated appearance with “pushing” type edges.

In the series by Scholten et al [35], the mode of infiltration correlates with the depth of invasion. However, according to Abdulfatah et al [3], the mode of infiltration influences neither OS nor RFS.

In our study, the mode of infiltration influenced OS and RFS in univariate analysis. The infiltrative mode was the worst prognosis.

The presence of vascular emboli correlates with a poor prognosis, regardless of the histologic subtype. Histopathological examination of tumour emboli in lymphovascular spaces also provides strong evidence for the dominant role of the carcinomatous component. Studies show that these elements always include carcinoma (with or without sarcomatous differentiation), and that pure sarcoma in lymphovascular spaces as in metastatic locations is rare [19,20].

In our study, there was no correlation between type of emboli and prognosis.

Some studies show that for extra-uterine metastases, the epithelial component is predominant, more rarely biphasic or pure sarcomatous. The carcinomatous component is mainly a provider of metastases and the sarcomatous component has only a minor role [20]. The predominance of carcinoma at the secondary site reinforces the hypothesis that UCS are rather particular forms of metaplastic carcinoma [5]. Nevertheless, George et al [21] report, in a series of 47 UCS, that 62% of metastases are biphasic, 20% pure sarcomatous and 18% pure carcinomatous.

In our study, the carcinomatous component was the predominant component in the secondary locations even though these UCS were predominantly sarcomatous in the primary site.

The FIGO stage at time of diagnosis is the most important prognostic factor. In the largest multicenter study by Matsuo et al [11] involving 906 cases, advanced stage is negatively correlated with OS and RFS. Similarly, in the multicenter study by Abdulfatah et al [3], the advanced stages (III-IV) negatively influence OS and RFS.

In our series, we grouped together patients with advanced stage III-IV (62%) and early stage I-II (38%). We did not find any correlation between FIGO stage, OS and RFS. This could be explained by the heterogeneity and the small size of our cohort, responsible for a low statistical power.

In the event of recurrence, the prognosis is poor.

Optimal cytoreductive surgery for the advanced stages (III and IV) remains a fundamental objective in uterine localization, which is shown by the study of Tanner in 2011 [36]. In the event of stage III CSU (ovarian or lymph node involvement), hysterectomy with bilateral adnexectomy remains the standard procedure associated with the removal of any metastatic sites and lymphadenectomy. In the event of stage IV CSU (bladder, rectal, peritoneal involvement, distant metastases), surgery is discussed; nevertheless, hysterectomy with first bilateral adnexectomy seems indicated when technically feasible. When there is rectosigmoid extension without extra pelvic and / or metastatic localization, resection of the rectosigmoid hinge may be indicated [36].

Surgical treatment should be discussed for each case in a multidisciplinary committee.

The main objective of monitoring patients treated for UCS is to facilitate the early detection of recurrence and to improve survival, as local recurrences are mostly curable.

Recurrences are mostly of the carcinomatous type, more rarely biphasic and exceptionally pure sarcomatous (3,20). In our work,

six patients (12%) had a histological analysis of the recurrence: it was biphasic in three cases (6%), pure carcinomatous in two cases (4%) and pure sarcomatous in one case (2%).

Conclusion

It is important to type and characterize the two carcinomatous and sarcomatous components of UCS in order to define subgroups of patients with different prognosis and to offer them a more suitable treatment.

The limitations of our study were the retrospective nature and the limited number of patients. The retrospective nature did not allow optimal control of the data collected. However, most of the series published in the literature were retrospective. Finally, the limited number of patients encourages multicenter studies on this pathology.

Conflicts of Interest Statement

The authors declare no competing interests.

Authors' contributions

Acquisition of data: A. Fitouri and L.Charfi

Analysis and/or interpretation of data: A. Fitouri, L.Charfi, M.Slimane and K.Mrad

Drafting the manuscript: A.Fitouri, G.Sahraoui and K.Mrad.

Revising the manuscript critically for important intellectual content: L.Charfi, G.Sahraoui, R.Doghri, N. Boujelbene and K.Mrad.

All authors read and approved the final version of this manuscript.

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