IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 17, Issue 9 Ver. 7 (September. 2018), PP 62-67
www.iosrjournals.org

Comparison of Survival And Prognostic Factors In Patients With Carcinosarcoma And Non Endometrioid Carcinoma of The Uterine Corpus

Ines Ben Safta[1], Olfa Jaidane[1], Houyem Mansouri[1], Raoudha Doghri[2], Azza Chabchoub[1], Jamel Ben Hassouna[1], Khaled Rahal[1].
1Departement of surgical oncology, Salah Azaïz Institute of Cancerology, Tunisia.
2 Departement of pathology, Salah Azaïz Institute of Cancerology, Tunisia.
Corresponding Author:Ines Ben Safta

Abstract:*Carcinosarcome (CS) of the uterine corpus (malignant mixed Müllerian tumor) is an uncommon and extremely aggressive histologic subtype of endometrial carcinoma. Treated like the non endometrioid carcinoma (NEC), this study aims to compare survival rates between CS and NEC and to identify histopronostic risk factors influencing their outcomes.This was a retrospective study including 50 women treated over a period of 17 years (1998-2015). We analyzed difference in clinical and survival characteristics between the two types of endometrial cancer CS (n=27) and the control group of NEC (n=23). Disease specific survival (DSS) and disease free survival (DFS) curves were performed.The stage distribution was: stage IA (30%), stage IB (12%), stage II (16%), stage IIIA (2%), stage IIIB (2%), stage IIIC1 (12%), stage IIIC2 (8%) and stage IV (18%). Median DFS was 19 and 22 months for NEC and CS, respectively. 5-years DFS were 48.5% in NEC and 48.7% in CS (p=0.570). Median DSS was 35 months for NEC and 21 months for CS. The 1, 2 and 5-years DSS were 84%, 65% and 40.6% for NEC and 84.4%, 48%, 34.4% for CS (p=0.938). Univariate analysis demonstrated a significant correlation between elder age (p=0.03), presence of LVSI (p=0.016) and the DSS. Multivariate analysis found that the LVSI was the only independent predictive factor of DSS (p=0.022; HR=0.355; CI [0.147; 0.859]. Our study emphasizes the similarity of survival rates of CS and NEC. It also underscore the importance of LVSI as an independent prognostic factor of DSS.*

Keywords:*Carcinosarcoma, Endometrial cancer, Survival, Clinicopathologic prognostic factors*

Date of Submission: 06-09-2018 Date of acceptance: 21-09-2018

I. Introduction

Carcinosarcomas (CS) are an aggressive histologic type of endometrial cancer (EC) with high grade carcinomatous and sarcomatous components (1). Also called malignant mixed mullerian tumor (MMMT) or malignant mixed mesodermal tumor, they are known as a very uncommon ECs tumors representing less than 5% of uterine invasive tumors and responsible for 16% of death (2). Because of the rarity of CS, most of the trials included them among high risk ECs: non endometrioid carcinomas (NEC) and/or high grade endometrioid cancers. Consequently, CS treatment are modeled on the high-risk ECs management which is based on hysterectomy, bilateral annexectomie and systematic pelvic and para-aortic lymphadenectomy and in most of the time is associated to adjuvant chemotherapy and radiotherapy.

The aim of our study was to compare clinical features between CSs and NECs and to identify prognostic factors influencing their survival.

II. Material And Methods

This is a retrospective study including 50 patients treated with curative intention of (CS) and (NEC) of the uterine corpus from January 1998 to December 2015 in Salah Azaiz institute. We excluded metastatic patients. All our patients presented with a clinical disease confined to the uterus. We reviewed all the specimens to detect LVSI which were not described systematically several years ago by an experienced pathologist in gynecologic oncology. We collected clinical data (age, physical examination and imaging features) histological tumor characteristics (tumor size, histologic subtypes and characteristics, TNM stage by FIGO2009, extent of lymphadenectomy and number of lymph node removed) therapeutic modalities (type of surgery, the extent of lymphadenectomy, chemotherapy, external beam radiotherapy and vaginal brachytherapy) and outcomes (median follow up in months).

Statistical analysis

The data was collected and analyzed with SPSS software version 20. We analyzed difference in clinical and survival characteristics between the two types of endometrial cancer CS (n=27) and the control group of NEC (n=23), using Chi square, Fisher's exact tests and Mann-Whitney U test, if applicable. P values 2-sided were considered as statistically significant if <0.05.

Since NEC and CS usually occur in patients elderly with multiple co-morbidities, we chose Disease specific survival (DSS) rather than the overall survival (OS). DSS was defined as the interval between the surgical procedure and the date of specific death or last follow up. Disease free survival (DFS) was defined as the interval between the date of surgery to the date of locoregional or distant relapse. Patients were censored at the date of death or the last contact. Survival were estimated by the Kaplan-Meir methods. Univariate analysis was performed by the Log-Rang Test and multivariate analysis by the Cox Regression method to identify the most predictive factors of survival (p<0.05). Hazard ratio (HR) were estimated with 95% confidential intervals (CI).

III. Result

The median age was 64 years [range: 41-88]. The surgical procedure of tumor resection were hysterectomy with bilateral oophorectomy in 49 cases and Hudson exenteration in one case. Forty-two patients had lymph node dissection (LND) (84%). Within the 8 patients who didn't underwent LND, 4 were at high anesthetic risks. Thirty patients underwent pelvic LND (60%), LND in both pelvic and para-aortic area in 9 cases (18%) and lymph node sampling in the para-aortic area in 3 cases (6%).

Based on the 2014 WHO classification, we found 27 cases of mixed epithelial and mesenchymal tumors: CS (54%) and 23 cases of NEC in the control group (46%): 10 cases of serous carcinoma (20%), 9 cases of clear cell carcinomas (18%), 4 cases of mixed cell adenocarcinoma (6%) and one case of dedifferentiated carcinoma (2%).

The stage distribution according to FIGO 2009 was: stage IA (30%, n=15), stage IB (12%, n=6), stage II (16%, n=8), stage IIIA (2%, n=1), stage IIIB (2%, n=1), stage IIIC1 (12%, n=6), stage IIIC2 (8%, n=4) and stage IV (18%, n=9).

Three patients had residual disease: 2 microscopic involved margins and 1 residual disease (non-removable pelvic lymph node metastases). The mean number of lymph node removed were 15 [range, 1-53] and the mean number of positive lymph node were 2 [range, 1-16].

Clinical, surgical procedure, extent of lymphadenectomy, histological, stage, treatment modalities and outcomes were summarized in table 1. Non-significant results were found when we compared the characteristics of the two different types groups (table 2).

Median DFS was 19 and 22 months for NEC and CS, respectively. 5-years DFS were 48.5% in NEC and 48.7% in CS (p=0.570) (figure1). No association between the prognostic factors and DFS of CS and NEC was found in the univariate analysis (Table 3). Administration of adjuvant chemotherapy trend to improved survival and from 46.3% to 75%, respectively (p=0.746). Number of lymph node resected did also trend to improve survival from 36.5% in case of no lymphadenectomy (median DFS of 22 months) to 61% in case of a number of lymph node resected greater than 16 (median DFS of 100 months) but not significantly (p=0.903).Median DSS was 35 months for NEC and 21 months for CS. The 1, 2 and 5-years DSS were 84%, 65% and 40.6% for NEC and 84.4%, 48%, 34.4% for CS (p=0.938) (figure2).

Table no 1: Characteristics of our cohort.

		N	%
Age (years)	Median	64	
	Range	41-88	
Stage	I/II	29	58
III/IV		21	42
Histologic subtype	Carcinosarcoma	27	54
Serous carcinoma		10	20
Clear cell carcinoma		9	18
Mixed cell adenocarcinoma		3	6
Dedifferentiated carcinoma		1	2
Myometrial invasion	<50%	26	52
>50%		24	48
LVSI	Yes	20	40
No		30	60
Tumor size (mm)	Unknown	13	26
Median		50	
Range		3-150	
Lymphadenectomy	Yes	42	84
No		8	16

Lymph node status LN-	LN+	27 15	64.3 35.7
Cervical stromal invasion No	Yes	19 31	38 62
Extra-uterine invasion No	Yes	19 31	38 62
Chemotherapy		9	18
External bean radiotherapy		24	48
Vaginal brachytherapy		19	38
Locoregional relapse		7	14
Distant relapse		17	34
LN+: Lymph node positive; LN-: Lymph node negative			

Table no2: Comparison of clinical and histological features of CS and NEC.

		CS N (%)	NEC N (%)	P
Age (years) median, range		64 [41-88]	64 [50-76]	0.696
Stage III/IV	I/II	16 (55.2) 11 (52.4)	13 (44.8) 10 (47.6)	1.0
Myometrial invasion >50%	<50%	13 (50) 14 (58.3)	13 (50) 10 (41.7)	0.54
LVSI No	Yes	11 (40.7) 16 (59.3)	9 (39.1) 14 (60.9)	0.526
Tumor size (cm) Median, range	Unknown	4 7 [1-13]	9 4.75 [3-15]	0.087
Lymphadenectomy No	Yes	21 (77.8) 6 (22.2)	21 (91.3) 2 (8.7)	0.261
Lymph node status LN-	LN+	14 (66.7) 7 (33.3)	13 (61.9) 8 (38.1)	1.0
Cervical stromal invasion No	Yes	8 (34.8) 15 (65.2)	11 (40.7) 16 (59.3)	0.773
Extra-uterine invasion No	Yes	12 (44.4) 15 (55.6)	7 (30.4) 16 (69.6)	0.387
Chemotherapy		3 (11.1)	6 (26.1)	0.462
External bean radiotherapy		12 (44.4)	12 (52.1)	0.215
Vaginal brachytherapy		12 (44.4)	7 (30.4)	0.215
Locoregional relapse		2 (7.4)	5 (21.7)	0.407
Distant relapse		5 (18.5)	12 (52.1)	0.407
LN+: Lymph node positive; LN-: Lymph node negative				

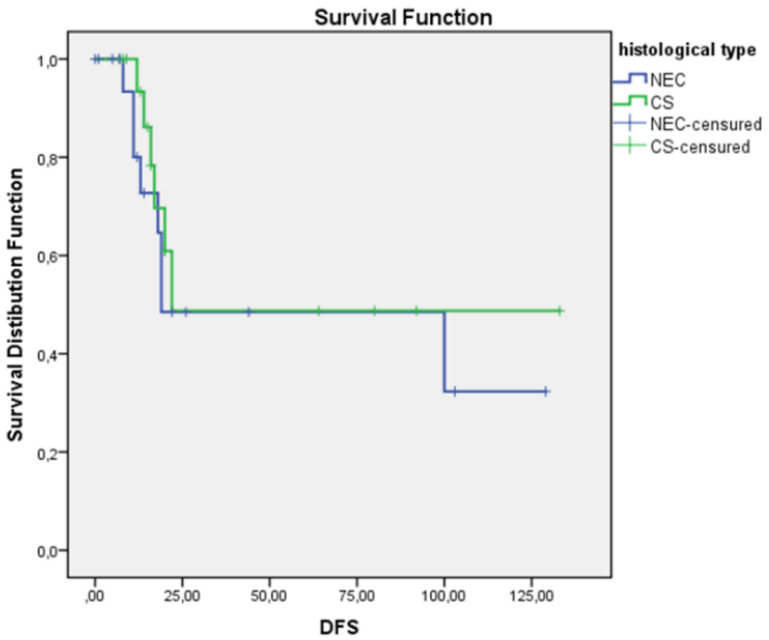

Figure no 1: Kaplan-Meier curves of disease free survival comparing the non endometrioid carcinomas (NEC) and the carcinomas (CS) of uterine corpus (p=0.938).

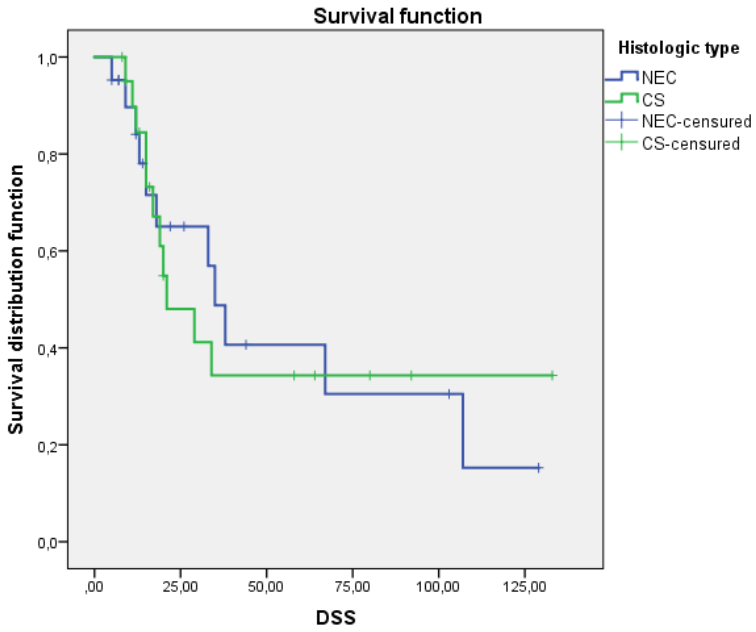

Figure no 2: Kaplan-Meier curves of disease specific survival comparing the non endometrioid carcinomas (NEC) and the carcinomas (CS) of uterine corpus (p=0.570).

Univariate analysis demonstrated a significant correlation between elder age (p=0.03), presence of LVSI (p=0.016) (figure 3) and the DSS of our cohort (Table 3). Multivariate analysis found that the LVSI was the only independent predictive factor of DSS (p=0.022; HR=0.355; CI [0.147; 0.859].

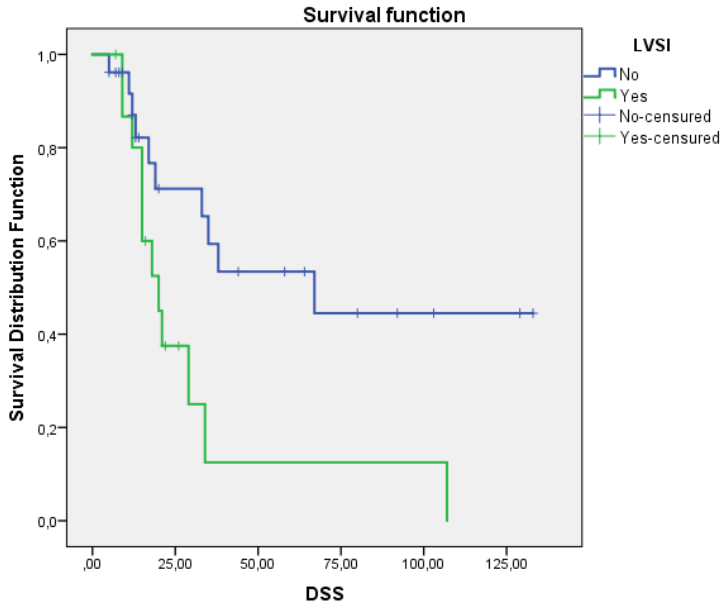

Figure no 3: Kaplan-Meier curves of disease specific survival in patients with and without LVSI (p=0.016).

Table no3: Univariate analysis of prognostic factors influencing the 5-years DSS and DFS**.**

Characteristics		5-years DFS %	p	5-years DSS %	p
Age, years	≤60	67.5	0.267	60.6	**0.03**
	>60	39.1		26.9	
Histologic type	NEC	48.5	0.570	40.6	0.938
	CS	48.7		34.4	
Stage	I/II	52.3	0.717	40.3	0.574
	III/IV	46.7		31.8	

Myometrial invasion	<50%	55.4	0.477	49.7	0.155
≥50%		46.7		20.8	
LVSI	Yes	43.8	0.622	53.4	**0.016**
	No	52.2		12.5	
LN involvement	Yes	42.9	0.424	26.9	0.268
No		52.2		45.1	
Number of resected LN	0	36.5	0.903	33.3	0.977
1-8		40		33.3	
9-16		61.7		31.2	
>16		61		48.6	
≤9		35.7	0.465	33.8	0.902
>9		60.8		41.2	
Cervical stromal invasion	Yes	46.9	0.825	34.5	0.504
No		51.9		40	
Extra-uterine extension	Yes	46.7	0.703	24.2	0.749
No		51.4		37.1	
Chemotherapy	Yes	75	0.746	50	0.398
No		46.3		39.4	
External bean Radiotherapy	Yes	45.4	0.924	40.9	0.477
No		55.4		35.7	
Brachytherapy	Yes	48.3	0.805	50.6	0.09
No		45.7		25.9	
LN: lymph node					

IV. Discussion

In the past, CS has been described as an histological subtype of uterine sarcomas and has been traditionally incorporated in this category in most clinical trials of endometrial cancer. In 1990, Silverberg et al demonstrated several differences in both clinical and pathological features of CS concluding that MMMT might be considered as metaplastic carcinomas (3), in which the mesenchymal part retains epithelial features (4). Other studies emphasized these findings that CS might be treated like aggressive high grade EC (5,6). In the in the most recent WHO Classification of Tumors of the Female Genital Tract of 2014 , MMMT are included among the mixed epithelial and mesenchymal tumors with the possible presence of heterologous elements (rhabdomyosarcoma, chondro¬sarcoma and in rare cases osteosarcoma) (7).

The extremely aggressiveness of endometrial CS may underscore the therapeutic challenge of this kind of tumors. But, the lack of randomized trials including only CS contrasting with many other papers including CS among several histological high grade of Endometrioid and NEC, highlights the rarity of these uncommon endometrial neoplasm. In fact, including CSs in clinical trials with NEC because of the arguments of the endometrial epithelial origin of CS and for their same biologic and aggressive behavior were interesting but with many a disparity in the survival rate results. George et al, published in 1995 one of the first comparative studies of this kind (8). In fact when compared MMMT versus serous/clear cell carcinomas, the survival of patients with CS were lower than NEC. In 2005, Amant et al findings that in the multivariate analysis the CS were independent prognostic factor of recurrence free survival (RFS) and had a significantly poorer outcome when compared to NEC (9). OS in all stages suggested a trend towards to a worse outcome of CS when compared to serous carcinoma. Vaidya et al in 2006, finded that patients with CS had significantly shorter median overall survival comparing to FIGO grade 3 endometrioid adenocarcinoma , serous and clear cell carcinomas (10). Prueksaritanond et al, suggested a significantly a poorer progression free survival of CS than other high risk EC subtypes. These findings were not reported for the 2-years OS (11). Even if these authors suggested poorer survival for CS, some others failed to demonstrate it. In 2011, the publication of Felix et al was the first to suggest that RFS,OS and DSS survival rates were similar among MMMT, high-grade endometrioid carcinomas, NEC subtypes (12). Alagkiozidis et al reported that there was no statistically difference between median OS between CS and serous carcinoma (13). Our results go along with these two recent literature data as we found non-significant results between the survival rates of CS and NEC. In fact, there was not statistically significant difference in 5-years RFS and DSS between CS and NEC (p=0.570 for DFS and p=0.938 for DSS), and this allowed us to group them together to determine the prognostic factor influencing their survival.

After performing surgical staging, most of the patients with CS presented a disease located outside of the uterus. Vaidya et al, reported that the majority of patients with CS (53%) presented with advanced disease (10). Amant et al reported more than 33% of patients with CS presenting with extrauterine disease at diagnosis (14). In fact, CSs are most often found at an advanced stage contrasting with endometrioid adenocarcinomas that are mostly confined to the uterus at the time of diagnosis. Rates of extrauterine extension and spread to pelvic and para-aortic lymph nodes were similar to those reported for serous and clear cell carcinomas (9). These findings were in accordance with our results that there were no statically significant difference in extrauterine extension (p=0.387) and in lymph node involvement (p=1) between CS and NEC.

In 2015, the new ESMO-ESGO-ESTRO consensus conference on endometrial cancer, recommended to perform for CS and NEC a complete lymphadenectomy including systematic removal of pelvic and para-aortic nodes up to the level of the renal veins (15). In our study, lymphadenectomy was performed in 84% of the cases. The more lymph nodes removed during lymphadenectomy, the higher the survival rate enhanced: from 36.5% and 33.3% in case of the absence of lymphadenectomy to 61% and 48.6% in case of a number exceeded 17 LN resected for 5-years DFS and DSS, respectively. This findings were in accordance in the findings of Alagkiozidis and al (11). In fact, the authors find no difference between serous carcinomas and CS in lymph node count and in the improvement of the OS according to the lymph node performance. Moreover, the risk of death is reduced if extensive lymphadenectomy were performed.

In Univariate analysis, we found significant association between elder age (p=0.03), presence of LVSI (p=0.016) and the DSS and we demonstrate in the multivariate analysis that the LVSI was the only independent predictive factor of DSS (p=0.022; HR=0.355; CI [0.147; 0.859]. In the literature, LVSI was described as a poor prognostic factor in endometrial cancer regardless of the several histologic subtypes (16–18). Since CS and NEC were known to be less frequent in most of these studies, the real prognostic impact of LVSI in this particular subtypes remain uncertain.

The limits of our studies are due to the retrospective, uni-centric character and the small number of our cohort. The need of multi-center study to include more patients with the help of experienced pathologists would be useful to validate these findings and perhaps even a more aggressive therapeutic approach in the presence of LVSI.

V. Conclusion

Our study emphasizes the similarity in terms of survival of CSs when compared to NECs. It also underscore the importance of LVSI detection even if they have not been yet taken into consideration for the therapeutic management of these high-risk endometrial cancers.

References

[1]. Cantrell LA, Blank SV, Duska LR. Uterine carcinosarcoma: A review of the literature. GynecolOncol . 2015;137:581–8.
[2]. Artioli G, Wabersich J, Ludwig K, Gardiman MP, Borgato L, Garbin F. Rare uterine cancer: Carcinosarcomas. Review from histology to treatment. Crit Rev OncolHematol. 2015;94:98–104.
[3]. Silverberg S, Major F, Blessing J et al. Carcinosarcoma (malignant mixed mesodermal tumor) of the uterus. A Gynecologic Oncology Group pathologic study of 203 cases. Int J GynecolPathol. 1990;9:1—19.
[4]. Horn LC, Dallacker M, Bilek K. Carcinosarcomas (malignant mixed Mulleriantumors) of the uterus. Morphology, pathogenetic aspects and prognostic factors. Pathol. 2009;30:292–301.
[5]. McCluggage WG. Uterine carcinosarcomas (malignant mixed Mulleriantumors) are metaplastic carcinomas. Int J Gynecol Cancer. 2002;12:687–90.
[6]. Kernochan LE, Garcia RL. Carcinosarcomas (malignant mixed Mülleriantumor) of the uterus: advances in elucidation of biologic and clinical characteristics. J NatlComprCancNetw. 2009;7:550–557.
[7]. Kurman RJ, Carcangiu ML, Herrington CS, Young RH. In: WHO classification of tumours of female reproductive organs. 4th ed. Lyon: International Agency for Research on Cancer; 2014.
[8]. George E, Lillemoe TJ, Twiggs LB, Perrone T. Malignant mixed mülleriantumor versus high-grade endometrial carcinoma and aggressive variants of endometrial carcinoma: a comparative analysis of survival. Int J GynecolPathol. 1995;14:39–44.
[9]. Amant F, Cadron I, Fuso L et al. Endometrial carcinosarcomas have a different prognosis and pattern of spread compared to high-risk epithelial endometrial cancer. GynecolOncol. 2005;98:274–280.
[10]. Vaidya AP, Horowitz NS, Oliva E, Halpern EF, Duska LR. Uterine malignant mixed mulleriantumors should not be included in studies of endometrial carcinoma. GynecolOncol. 2006 Nov;103:684–7.
[11]. Prueksaritanond N, Chantape W. Comparative Survival Outcomes of Uterine Papillary Serous Carcinoma, Clear Cell Carcinoma, Grade 3 Endometrioid Adenocarcinoma, and Carcinosarcoma of Endometrial Cancer in RajavithiHospital.J Med Assoc Thai. 2016;99 :S75-83.
[12]. Felix AS, Stone RA, Bowser R et al. Comparison of survival outcomes between patients with malignant mixed mulleriantumors and high-grade endometrioid, clear cell, and papillary serous endometrial cancers. Int J Gynecol Cancer. 2011;21:877–84.
[13]. Alagkiozidis I, Weedon J, Grossman A et al. Extent of lymph node dissection and overall survival in patients with uterine carcinosarcoma, papillary serous and endometrioid adenocarcinoma: A retrospective cohort study. Int J Surg.. 2015;24:9-13.
[14]. Amant F. The rationale for comprehensive surgical staging in endometrial carcinosarcoma. GynecolOncol. 2005;99:521–522.
[15]. Colombo N, Creutzberg C, Amant F et al. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up. Ann Oncol. 2015;27:16–41.
[16]. Narayan K, Khaw P, Bernshaw D, Mileshkin L, Kondalsamy-Chennakesavan S. Prognostic significance of lymphovascular space invasion and nodal involvement in intermediate-and high-risk endometrial cancer patients treated with curative intent using surgery and adjuvant radiotherapy. Int J Gynecol Cancer. 2012;22:260–266.
[17]. Koskas M, Bassot K, Graesslin O et al. Impact of lymphovascular space invasion on a nomogram for predicting lymph node metastasis in endometrial cancer. GynecolOncol. 2013;129:292–297.
[18]. Briët JM, Hollema H, Reesink N et al. Lymphvascular space involvement: an independent prognostic factor in endometrial cancer. GynecolOncol. 2005;96:799–804.

Ines Ben Safta"Comparison of Survival And Prognostic Factors In Patients With Carcinosarcoma And Non Endometrioid Carcinoma of The Uterine Corpus. "IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 17, no. 9, 2018, pp 62-67.