Tumor characteristics and outcome of uterine carcinosarcoma in women aged ≥80 years

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ABSTRACT

Objective: To examine clinico-pathological characteristics and outcomes of uterine carcinosarcoma (UCS) in women aged ≥80 years.

Methods: This is a secondary analysis of a previous multicenter retrospective study examining 906 women with stage I–IV UCS who underwent primary hysterectomy. Patient demographics, treatment types, tumor characteristics, and survival were examined across aged ≥80 (n = 82 [9.1%]), aged 60–79, (n = 526 [58.1%]), and aged < 60 (n = 298 [32.9%]).

Results: Women in the aged ≥80 group were more likely to be Caucasian, undergo simple hysterectomy without lymphadenectomy, and receive no postoperative therapy (all, $P < 0.05$). Tumors in the aged ≥80 group were

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more likely to have high-grade carcinoma, heterologous sarcoma, and sarcoma dominance but less likely to have lympho-vascular space invasion (all, $P < 0.05$). Lymphadenectomy did not improve survival in the aged ≥ 80 group ($P > 0.05$), whereas lymphadenectomy was protective for survival in the younger groups (both, $P < 0.05$). Postoperative chemotherapy was associated with improved progression-free survival (PFS) in the aged ≥ 80 group (hazard ratio [HR] 0.44, 95% confidence interval [CI] 0.22–0.89, $P = 0.021$). With chemotherapy treatment, women in the aged ≥ 80 group had PFS similar to those in the aged 60–79 group (HR 0.97, 95%CI 0.51–1.83, $P = 0.92$). In contrast, without chemotherapy treatment, women in the aged ≥ 80 group had significantly decreased PFS compared to the aged 60–79 group (HR 1.62, 95%CI 1.09–2.40, $P = 0.016$). Similar associations were observed for postoperative radiotherapy.

Conclusion: Nearly 10% of women with UCS are aged ≥ 80 that are characterized by aggressive tumor factors. Postoperative therapy but not extensive surgery may improve survival in this age group.

1. Introduction

Uterine carcinosarcoma (UCS) is a high-grade endometrial cancer exhibiting a characteristic biphasic morphology with a carcinoma and sarcoma component within the uterine tumor [1]. A current consensus regarding the pathophysiology of UCS is that the sarcoma element arises within the carcinoma through dedifferentiation *via* an epithelial-mesenchymal transition [2,3]. UCS is considered a rare tumor but its proportion among endometrial cancer has steadily increased in the past decades in the United States, exceeding 5% in the recent years [4]. UCS is known to be an aggressive disease with poor survival even in early-stage disease [5,6].

UCS is a disease of the elderly. The vast majority of women with UCS are 60 years or over, which is significantly older than women diagnosed with other histologic types of endometrial cancer [4]. Per the current guidelines, the standard treatment for high-grade endometrial cancer, including UCS, is surgery and postoperative therapy [7]. In general, older women are more likely to have medical comorbidities and a decreased physical condition compared to their younger counterparts [8,9]. These are factors that make it difficult to pursue extensive surgical and adjuvant interventions for cancer treatment.

Elderly refers to a diverse range of ages. Specifically, an individual aged 60 years or over is considered "older", which can be further sub-classified into "oldest-old" defined as individual aged 80 years or over [10,11]. Given that a significant proportion of women with UCS may fall into the aged ≥ 80 category, a cohort with decreased physical condition and more comorbidity, extent of surgery and compliance to postoperative therapy may be lower possibly impacting survival. The objective of the study was to examine clinico-pathological characteristics and outcomes of women with UCS who were aged ≥ 80 years.

2. Patients and methods

2.1. Study eligibility

A secondary analysis was performed by utilizing a previously organized database for UCS [5,12,13]. In this multi-center retrospective study, consecutive cases of UCS were examined anywhere it was available between 1993 and 2013 from 26 institutions in the United States and Japan. This surgical database consisted of 906 women with stage I–IV UCS who underwent primary hysterectomy-based surgical treatment. Institutional Review Board approval was obtained at each participating institution. The STROBE guidelines were consulted to outline the results of the cohort study [14].

2.2. Clinical information

For patient demographics age, race/ethnicity, country, pregnancy history, body mass index, history of tamoxifen use, prior pelvic irradiation, personal history of malignancy, and tumor marker with CA-125 levels were abstracted. For tumor characteristics carcinoma type, sarcoma type, presence of sarcoma dominance, tumor size, depth of myometrial tumor invasion, presence of lympho-vascular space invasion (LVSI), number of sampled and tumor-involved lymph nodes (pelvic and para-aortic), and cancer stage were examined.

For treatment types, surgery and postoperative therapy were examined. For surgical performance hysterectomy types (simple, modified radical, and radical), use of pelvic and/or para-aortic lymphadenectomy, and residual tumor at surgery were collected. For postoperative therapy chemotherapy (regimen and cycle) and radiotherapy type (external whole pelvis and/or vaginal brachytherapy) were collected. For survival outcome progression-free survival (PFS), cause-specific survival (CSS), and overall survival (OS) were examined.

2.3. Histology evaluation

Archived histopathology slides for hematoxylin-eosin stains and available immunohistochemistry were pulled and reviewed at each institution for all the cases. Pathologists were blinded to clinical information. In a comprehensive slide review, carcinoma type, sarcoma type, sarcoma dominance, and LVSI cell types were assessed as described previously [5].

2.4. Study definition

Age was grouped as < 60 years, 60–79 years, and ≥ 80 years as described earlier [10,11]. Cutoffs of body mass index, CA-125, tumor size, and depth of myometrial tumor invasion were based on prior studies [5,15]. The 2009 International Federation of Gynecology and Obstetrics system was used to re-classify cancer stage [16]. Carcinoma types and sarcoma elements were grouped based on our prior definition: low-grade carcinoma (grade 1–2 endometrioid) and high-grade carcinoma (grade 3 endometrioid, serous, clear cell, undifferentiated, and mixed); and homologous (endometrial stromal sarcoma, leiomyosarcoma, fibrosarcoma, and undifferentiated sarcoma) or heterologous (rhabdomyosarcoma, osteosarcoma, chondrosarcoma, and liposarcoma) [5]. LVSI cell types were grouped as carcinoma alone *versus* sarcoma ± carcinoma.

Chemotherapy types were grouped as platinum, taxane, ifosfamide, and anthracycline as before [5]. Adequate lymphadenectomy was defined per the GOG Surgical Procedure Manual: ≥ 8 nodes for pelvic lymphadenectomy, and ≥ 2 nodes for para-aortic lymphadenectomy [17]. PFS was defined as the time interval between the hysterectomy-based surgery and the first recurrence/progression of disease or death due to UCS. CSS was defined as the time interval between the hysterectomy-based surgery and the death due to UCS, and OS was defined as the time interval between the surgery and all-cause death. Women without these survival events at the last follow-up visit were censored.

2.5. Statistical analysis

The primary outcome of analysis was to examine the clinico-pathological characteristics of women aged ≥ 80 years. The secondary outcome of analysis was to examine association of treatment

intervention and survival of women aged ≥80 years.

Continuous variables were expressed with mean (± standard deviation) or median (interquartile range) as appropriate base on the normality examined by the Kolmogorov–Smirnov test. The Kruskal-Wallis H test or one-way ANOVA test was used to assess the statistical significance of continuous variables. Categorical variables were evaluated with chi-square test.

Survival curves were plotted with the Kaplan-Meier method, and the log-rank test was used to assess the statistical significance between the curves. A Cox proportional hazard regression model was used to determine the magnitude of statistical significance, expressed with hazard ratio (HR) and 95% confidence interval (CI). A $P < 0.05$ was considered statistically significant (all, two-sided hypothesis), and Statistical Package for Social Science software (IBM SPSS, version 24.0, Armonk, NY, USA) was used for all the analyses.

3. Results

There were 82 (9.1%, 95%CI 7.2–10.9) women aged ≥80 years in the study population ($n = 906$). The most common age range in this study population was aged 60–79 years ($n = 526$, 58.1%) followed by aged < 60 years ($n = 298$, 32.9%). Patient demographics based on age distribution are shown in Table 1.

Women in the aged ≥80 group were more likely to be White (50.0%) and less likely to be Asian (31.6%) compared to other two groups ($P < 0.001$). Women in the aged ≥80 group are less likely to be nulligravida compared to non-older women (11.4% *versus* 25.5%, $P < 0.001$). Body habitus, history of tamoxifen use/pelvic irradiation, prior malignancy, and tumor marker levels were similar across the three age groups (all, $P > 0.05$).

Treatment types were examined based on age groups (Table 2). Women in the aged ≥80 group were more likely to undergo conservative surgery with simple hysterectomy (95.1%) compared to other groups (71.5–84.0%, $P < 0.001$). Pelvic lymphadenectomy (46.3%) was less likely to be performed in the aged ≥80 group compared to other groups (73.6–79.5%, $P < 0.001$). Even among women who underwent pelvic lymphadenectomy, the extent of lymphadenectomy in the aged ≥80 group (median sampled nodes 8.5) was significantly less than other groups (16–22 nodes; $P < 0.001$). Para-aortic lymphadenectomy was rarely performed in the aged ≥80 group (18.3%) compared to nearly half in other groups (45.1–49.7%, $P < 0.001$). Similar to pelvic lymphadenectomy, the extent of para-aortic lymphadenectomy in the aged ≥80 group (median sampled nodes 3.5) was significantly less than other groups (7–12 nodes, $P < 0.001$).

Postoperative treatment types were examined by age groups (Table 2). Women in the aged ≥80 group (29.1%) were less likely to receive postoperative chemotherapy compared to other groups (68.3–75.3%, $P < 0.001$). However, among those who received postoperative chemotherapy, the median cycle of administered chemotherapy in the aged ≥80 group was six, similar to other groups ($P = 0.60$). Women aged ≥80 years (15.2%) were less likely to receive postoperative radiotherapy compared to younger women (26.4–26.8%, $P = 0.05$). For the combination of chemotherapy with radiotherapy, women aged ≥80 years (64.6%) were more likely to receive no postoperative therapy compared to younger women (17.3–25.5%, $P < 0.001$). Among women who received postoperative chemotherapy, women in the aged ≥80 group were less likely to receive anthracycline (8.7%) compared to other groups (13.7–22.1%, $P = 0.019$). Women aged ≥80 years were also less likely to receive ifosfamide (8.7%) compared to younger women (25.7–30.0%), but this did not reach statistical significance ($P = 0.06$).

When tumor characteristics were examined by age group (Table 3), tumors in the aged ≥80 group were more likely to have high-grade carcinoma (82.9% *versus* 64.8–74.0%, $P = 0.001$) and heterologous sarcoma (54.9% *versus* 33.2–43.5%, $P < 0.001$) but less likely to have LVSI (52.4% *versus* 59.2–66.1%, $P = 0.038$) compared to other groups.

Tumors in the aged ≥80 group had a higher proportion of sarcoma dominance compared to the aged < 60 group (46.3% *versus* 32.9%, $P = 0.003$). Tumor size and stage distribution were similar across the three groups (both, $P > 0.05$).

The median follow-up months were 19.3 for the aged ≥80 group, 31.9 for the aged 60–79 group, and 53.2 for the aged < 60 group, respectively (Table 1). During follow-up, survival events occurred in 46, 267, and 116 cases, respectively.

The effects of treatment intervention were examined in each age group (Table 4). In the aged ≥80 group, pelvic lymphadenectomy was not associated with survival (PFS, HR 0.82, $P = 0.50$, Fig. 1A; and CSS, HR 0.91, $P = 0.77$). Contrary, pelvic lymphadenectomy was significantly associated with improved survival in the aged 60–79 group (PFS, HR 0.58, $P < 0.001$, Fig. 1B; and CSS, HR 0.61, $P = 0.002$) and in the aged < 60 group (PFS, HR 0.43, $P < 0.001$, Fig. 1C; and CSS, HR 0.37, $P < 0.001$). Similarly, in the aged ≥80 group, para-aortic lymphadenectomy was not associated with survival (PFS, HR 1.22, $P = 0.61$; and CSS, HR 1.30, $P = 0.53$) whereas this procedure was associated with improved survival in other two groups (HR ranges: PFS 0.71 and CSS 0.56–0.65).

Postoperative chemotherapy was associated with improved PFS in the aged ≥80 group (HR 0.44, $P = 0.021$) and also improved CSS in the aged ≥80 group but did not demonstrate statistical significance (HR

Table 1
Patient demographics per age group.

Characteristic	Aged < 60	Aged 60–79	Aged ≥80	P-value
Subject	$n = 298$	$n = 526$	$n = 82$	
Race/ethnicity				< 0.001
White	85 (28.8%)	161 (31.0%)	38 (50.0%)	
Asian	184 (62.4%)	273 (52.6%)	24 (31.6%)	
Others	26 (8.8%)	85 (16.4%)	14 (18.4%)	
Country				< 0.001
USA	119 (39.9%)	255 (48.5%)	59 (72.0%)	
Japan	179 (60.1%)	271 (51.5%)	23 (28.0%)	
Pregnancy				< 0.001
Nullgravid	75 (25.5%)	55 (10.9%)	9 (11.4%)	
Multigravid	219 (74.5%)	449 (89.1%)	70 (88.6%)	
BMI (kg/m^2)	24.1 (IQR 8.9)	25.2 (IQR 8.3)	25.4 (IQR 7.3)	0.48
< 30	215 (74.9%)	374 (74.8%)	61 (80.3%)	
≥30	72 (25.1%)	126 (25.2%)	15 (19.7%)	
Tamoxifen use				0.06
No	286 (96.6%)	491 (94.1%)	74 (90.2%)	
Yes	10 (3.4%)	31 (5.9%)	8 (9.8%)	
Prior pelvic radiotherapy				0.49
No	293 (98.3%)	517 (98.3%)	82 (100%)	
Yes	5 (1.7%)	9 (1.7%)	0	
Prior malignancy				0.11
No	253 (84.9%)	424 (80.6%)	62 (75.6%)	
Yes	45 (15.1%)	102 (19.4%)	20 (24.4%)	
CA-125 (IU/L)	25 (IQR 47)	22 (IQR 48)	22 (IQR 52)	0.54
< 30	122 (55.7%)	210 (59.3%)	24 (57.1%)	
30–124	59 (26.9%)	97 (27.4%)	11 (26.2%)	
≥125	38 (17.4%)	47 (13.3%)	7 (16.7%)	
Follow-up (months)	53.2 (IQR 61.9)	31.9 (IQR 51.0)	19.3 (IQR 28.0)	< 0.001
< 24	117 (39.3%)	269 (51.1%)	59 (72.0%)	
≥24	181 (60.7%)	257 (48.9%)	23 (28.0%)	

Number (%) per column or median (IQR) is shown. Kruskal-Wallis H test or chi-square test for P-values. Significant P-values are emboldened. Abbreviations: IQR, interquartile range; BMI, body mass index; and CA-125, cancer antigen 125.

Table 2
Treatment types per age group.

Characteristic	Aged < 60	Aged 60-79	Aged ≥80	P-value
Subject	n = 298	n = 526	n = 82	
Hysterectomy type				< 0.001
Simple	213 (71.5%)	442 (84.0%)	78 (95.1%)	
Modified radical	60 (20.1%)	58 (11.0%)	2 (2.4%)	
Radical	25 (8.4%)	26 (4.9%)	2 (2.4%)	
Pelvic LND				< 0.001
No	61 (20.5%)	139 (26.4%)	44 (53.7%)	
Yes	237 (79.5%)	387 (73.6%)	38 (46.3%)	
Sampled pelvic LND	22 (IQR 23)	16 (IQR 19)	8.5 (IQR 11)	< 0.001
Adequate pelvic LND				0.006
No	51 (21.5%)	87 (22.6%)	17 (44.7%)	
Yes	186 (78.5%)	298 (77.4%)	21 (55.3%)	
Para-aortic LND				< 0.001
No	150 (50.3%)	289 (54.9%)	67 (81.7%)	
Yes	148 (49.7%)	237 (45.1%)	15 (18.3%)	
Sampled para-aortic LND	12 (IQR 21)	7 (IQR 17)	3.5 (IQR 5)	< 0.001
Adequate para-aortic LND				0.026
No	10 (6.8%)	27 (11.4%)	4 (28.6%)	
Yes	137 (93.2%)	209 (88.6%)	10 (71.4%)	
Residual disease				0.84
No	253 (87.8%)	454 (89.2%)	67 (88.2%)	
Yes	35 (12.2%)	55 (10.8%)	9 (11.8%)	
Postop chemotherapy				< 0.001
No	73 (24.7%)	166 (31.7%)	56 (70.9%)	
Yes	222 (75.3%)	357 (68.3%)	23 (29.1%)	
Chemotherapy cycle*	6 (IQR 2)	6 (IQR 3)	6 (IQR 1–7)	0.60
1–3	45 (20.6%)	89 (25.6%)	5 (22.7%)	
4–6	162 (74.3%)	247 (71.0%)	16 (72.7%)	
> 6	11 (5.0%)	12 (3.4%)	1 (4.5%)	
Postop radiotherapy				0.05
None	216 (73.6%)	382 (73.2%)	67 (84.8%)	
VBT alone	13 (4.4%)	12 (2.3%)	0	
WPRT ± VBT	65 (22.0%)	128 (24.5%)	12 (15.2%)	
Combined				< 0.001
None	51 (17.3%)	133 (25.5%)	51 (64.6%)	
RT alone	22 (7.5%)	33 (6.3%)	5 (6.3%)	
Chemo alone	165 (55.9%)	250 (47.9%)	16 (20.3%)	
Both	57 (19.3%)	106 (20.3%)	7 (8.9%)	
Platinum				0.014
No	14 (6.3%)	50 (14.1%)	2 (9.1%)	
Yes	208 (93.7%)	305 (85.9%)	20 (90.9%)	
Taxane				0.97
No	64 (28.8%)	106 (29.7%)	7 (30.4%)	
Yes	158 (71.2%)	251 (70.3%)	16 (69.6%)	
Ifosfamide				0.06
No	165 (74.3%)	250 (70.0%)	21 (91.3%)	
Yes	57 (25.7%)	107 (30.0%)	2 (8.7%)	
Anthracycline				0.019
No	173 (77.9%)	308 (86.3%)	21 (91.3%)	
Yes	49 (22.1%)	49 (13.7%)	2 (8.7%)	

Number (%) per column or median (IQR) is shown. Kruskal-Wallis *H* test or chi-square test for *P*-values. Significant *P*-values are emboldened. *among those received chemotherapy with known administered cycle. Abbreviations: IQR, interquartile range; LND, lymphadenectomy; VBT, vaginal brachytherapy; and WPRT, whole pelvic radiotherapy.

Table 3
Tumor characteristics per age group.

Characteristic	Aged < 60	Aged 60-79	Aged ≥80	P-value
Subject	n = 298	n = 526	n = 82	
Carcinoma				0.001
Low-grade	105 (35.2%)	137 (26.0%)	14 (17.1%)	
High-grade	193 (64.8%)	389 (74.0%)	68 (82.9%)	
Carcinoma type				< 0.001
Grade 1 endometrioid	53 (17.8%)	56 (10.6%)	7 (8.5%)	
Grade 2 endometrioid	52 (17.4%)	81 (15.4%)	7 (8.5%)	
Grade 3 endometrioid	100 (33.6%)	114 (21.7%)	17 (20.7%)	
Serous	16 (5.4%)	134 (25.5%)	27 (32.9%)	
Clear cell	5 (1.7%)	10 (1.9%)	2 (2.4%)	
Undifferentiated	8 (2.7%)	22 (4.2%)	2 (2.4%)	
Mixed	60 (20.1%)	105 (20.0%)	19 (23.2%)	
Others	4 (1.3%)	4 (0.8%)	1 (1.2%)	
Sarcoma				< 0.001
Homologous	199 (66.8%)	297 (56.5%)	37 (45.1%)	
Heterologous	99 (33.2%)	229 (43.5%)	45 (54.9%)	
Tumor size (cm)				0.53
< 5	110 (38.3%)	179 (35.0%)	29 (35.4%)	
5–9.9	146 (50.9%)	257 (50.2%)	40 (48.8%)	
≥10	31 (10.8%)	76 (14.8%)	13 (15.9%)	
Sarcoma dominance				0.003
No	196 (67.1%)	286 (55.3%)	43 (53.8%)	
Yes	96 (32.9%)	231 (44.7%)	37 (46.3%)	
Deep myometrial invasion				0.77
No	151 (51.0%)	277 (53.2%)	41 (50.0%)	
Yes	145 (49.0%)	244 (46.8%)	41 (50.0%)	
LVSI				0.038
No	101 (33.9%)	214 (40.8%)	39 (47.6%)	
Yes	197 (66.1%)	310 (59.2%)	43 (52.4%)	
LVSI type				0.21
Carcinoma alone	137 (78.3%)	205 (74.5%)	33 (86.8%)	
Sarcoma	38 (21.7%)	70 (25.5%)	5 (13.2%)	
Pelvic nodal metastasis				0.84
No	178 (75.1%)	285 (73.6%)	27 (71.1%)	
Yes	59 (24.9%)	102 (26.4%)	11 (28.9%)	
Para-aortic nodal metastasis				0.79
No	119 (80.4%)	191 (80.6%)	11 (73.3%)	
Yes	29 (19.6%)	46 (19.4%)	4 (26.7%)	
Stage				0.81
I	146 (49.0%)	257 (48.9%)	42 (51.2%)	
II	23 (7.7%)	37 (7.0%)	5 (6.1%)	
III	84 (28.2%)	169 (32.1%)	23 (28.0%)	
IV	45 (15.1%)	63 (12.0%)	12 (14.6%)	

Number (%) per column or median (IQR) is shown. Kruskal-Wallis *H* test or chi-square test for *P*-values. Significant *P*-values are emboldened. Abbreviations: IQR, interquartile range; and LVSI, lympho-vascular space invasion.

0.55, *P* = 0.13). There was a trend towards an improvement in PFS with postoperative radiotherapy in the aged ≥80 group (HR 0.41, *P* = 0.06) and a significant benefit for CSS (HR 0.29, *P* = 0.044). Postoperative therapy (chemotherapy/radiotherapy) was significantly associated with improved PFS and CSS in the aged 60–79 group (all, *P* < 0.05). Similar results were seen for OS (Supplemental Table S1).

Survival outcome was compared across the three groups (Table 5). In the absence of chemotherapy treatment, women in the aged ≥80 group had significantly decreased PFS compared to the aged 60–79 group (HR 1.62, *P* = 0.016). Contrary, with chemotherapy treatment, women in the aged ≥80 group had PFS similar to those in the aged 60–79 group (HR 0.97, *P* = 0.92). Similarly, with absence of radiotherapy, PFS was worse in the aged ≥80 group compared to the aged

Table 4
Association of survival and treatment intervention based on age group.

Characteristic		Progression-free survival		Cause-specific survival	
		HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Aged < 60	Pelvic LND				
	No	1		1	
	Yes	0.43 (0.29–0.64)	< **0.001**	0.37 (0.23–0.58)	< **0.001**
	Para-aortic LND				
	No	1		1	
	Yes	0.71 (0.49–1.02)	0.06	0.56 (0.35–0.88)	**0.012**
	Chemotherapy				
	No	1		1	
	Yes	0.79 (0.52–1.21)	0.28	0.72 (0.44–1.18)	0.20
	Radiotherapy				
	No	1		1	
	Yes	0.90 (0.58–1.37)	0.61	0.88 (0.53–1.48)	0.64
Aged 60–79	Pelvic LND				
	No	1		1	
	Yes	0.58 (0.45–0.75)	< **0.001**	0.61 (0.45–0.83)	**0.002**
	Para-aortic LND				
	No	1		1	
	Yes	0.71 (0.55–0.90)	**0.005**	0.65 (0.48–0.87)	**0.004**
	Chemotherapy				
	No	1		1	
	Yes	0.72 (0.56–0.93)	**0.012**	0.64 (0.48–0.86)	**0.004**
	Radiotherapy				
	No	1		1	
	Yes	0.72 (0.54–0.95)	**0.02**	0.64 (0.45–0.91)	**0.013**
Aged ≥ 80	Pelvic LND				
	No	1		1	
	Yes	0.82 (0.46–1.47)	0.50	0.91 (0.47–1.75)	0.77
	Para-aortic LND				
	No	1		1	
	Yes	1.22 (0.57–2.64)	0.61	1.30 (0.57–2.99)	0.53
	Chemotherapy				
	No	1		1	
	Yes	0.44 (0.22–0.89)	**0.021**	0.55 (0.26–1.18)	0.13
	Radiotherapy				
	No	1		1	
	Yes	0.41 (0.16–1.04)	0.06	0.29 (0.09–0.97)	**0.044**

Unadjusted HR is shown. Significant *P*-values are emboldened. Abbreviations: HR, hazard ratio; CI, confidence interval; and LND, lymphadenectomy.

60–79 group (HR 1.72, *P* = 0.002) while PFS were similar between the two groups with radiotherapy (HR 0.92, *P* = 0.85). Similar results were seen for OS (Supplemental Table S2).

4. Discussion

Tumors in the aged ≥ 80 group exhibit more aggressive characteristics compared to those in younger groups, with more high-grade carcinoma, heterologous sarcoma, and sarcoma dominance. These tumor factors are known to be poor prognostic factors in UCS irrespective of patient age [5]. Thus, while older age is known to be an independent predictor for decreased survival in UCS [18], it is possible that decreased survival in women aged ≥ 80 years with UCS is largely attributed to these aggressive tumor factors.

Additionally, the specific treatment of UCS in the aged ≥ 80 group likely contributes to the decreased survival. Women in this age group were less likely to have radical surgery including comprehensive lymphadenectomy. Multiple studies have shown that lymphadenectomy improves survival in UCS [19–23]. This association was validated in non-oldest-old groups in our study. In contrast, lymphadenectomy was not beneficial for survival in aged ≥ 80 women. We speculate that this is because tumors in the aged ≥ 80 group were more likely to be sarcoma dominant, which typically metastasizes hematogenously and not lymphatically [24]. Moreover, tumors in the aged ≥ 80 group have a low LVSI rate, which is the major tumor predictor for nodal metastasis in endometrial cancer [25].

Given that lymphadenectomy did not impact survival coupled with the potential to minimize surgical mortality in women aged ≥ 80 years with UCS, sentinel lymph node biopsy may be a consideration to assess nodal status. A recent study demonstrated that survival of women with UCS was similar between sentinel lymph node mapping and comprehensive lymphadenectomy [26]. Further prospective study is warranted to address the role of sentinel lymph node biopsy in elderly with UCS. Finally, if medically appropriate, the use of minimally-invasive surgery would be ideal to reduce surgical and postoperative morbidity.

Postoperative therapy is another salient survival factor in UCS [5,6,18,19]. In our study, chemotherapy use was protective for survival in women aged ≥ 80 years. The benefit of chemotherapy also applies to early-stage disease given the high risk of distant recurrence [6]. There was a clear trend of chemotherapy choice in women aged ≥ 80 years, with ifosfamide and anthracycline rarely used in this population. This is likely due to the toxicity profiles and infusion schedules that may not be suitable for older women in general [1]. Based on our results, the most common chemotherapy choice in women aged ≥ 80 years was a platinum agent followed by taxane, which has shown to be active in UCS and is widely used in this population [27,28]. The vast majority of women aged ≥ 80 years (> 70%) who received postoperative chemotherapy completed 4–6 cycles (median, 6 cycles), suggesting that the schedule and toxicity are possibly tolerable. Scheduling chemotherapy for at least four cycles but aiming for six cycles is reasonable. Additionally, we respectfully suggest that radiotherapy should be tailored to the presence of sarcoma factors as suggested in a prior study [6].

Worldwide societies are steadily aging [29,30]. The proportion of adult aged ≥ 80 years in the United States has significantly grown from 1.1% in 1950 to 3.8% in 2015 [29]. UCS is typically diagnosed in elderly women; our study has shown that nearly one in ten women with UCS were aged ≥ 80 years. This implies that UCS has significantly high proportion of women aged ≥ 80 years compared to general population. Moreover, the incidence of UCS per population will be likely increasing as society aging. Therefore, age-related factors such as comorbidities and functional status are the key to manage women with UCS.

A strength of this investigation is that it is likely the first to examine the characteristics and outcomes of women aged ≥ 80 years with UCS. The multi-center nature of this study allowed us to examine a large sample size of oldest-old population. Comprehensive dataset enriched the analytic quality of the study. There are some limitations to this study. First, this is a retrospective study, and there may be missing confounding factors in the analysis. For example, treatment decision and allocation for surgery, chemotherapy, and radiotherapy were not able to be abstracted in this study. This is particularly applicable if lymphadenectomy was performed for grossly abnormal findings. Second, the median follow-up for women aged ≥ 80 years was less than 24 months. Given that this is a rare age group in whom life expectancy is reduced compared to the younger groups, it is not an unexpected finding; regardless, understanding the outcomes of this advanced-age cohort is clinically valuable. Lastly, dose reduction or postponement of postoperative therapy was not examined.

This investigation includes only women who underwent hysterectomy-based surgical treatment, a potential for selection bias when interpreting the results of this study. We recognize that a considerable fraction of women aged ≥ 80 years with UCS may not be medically fit to undergo surgical exploration. Thus, it is paramount to apply these findings for women aged ≥ 80 years with UCS only to those who are
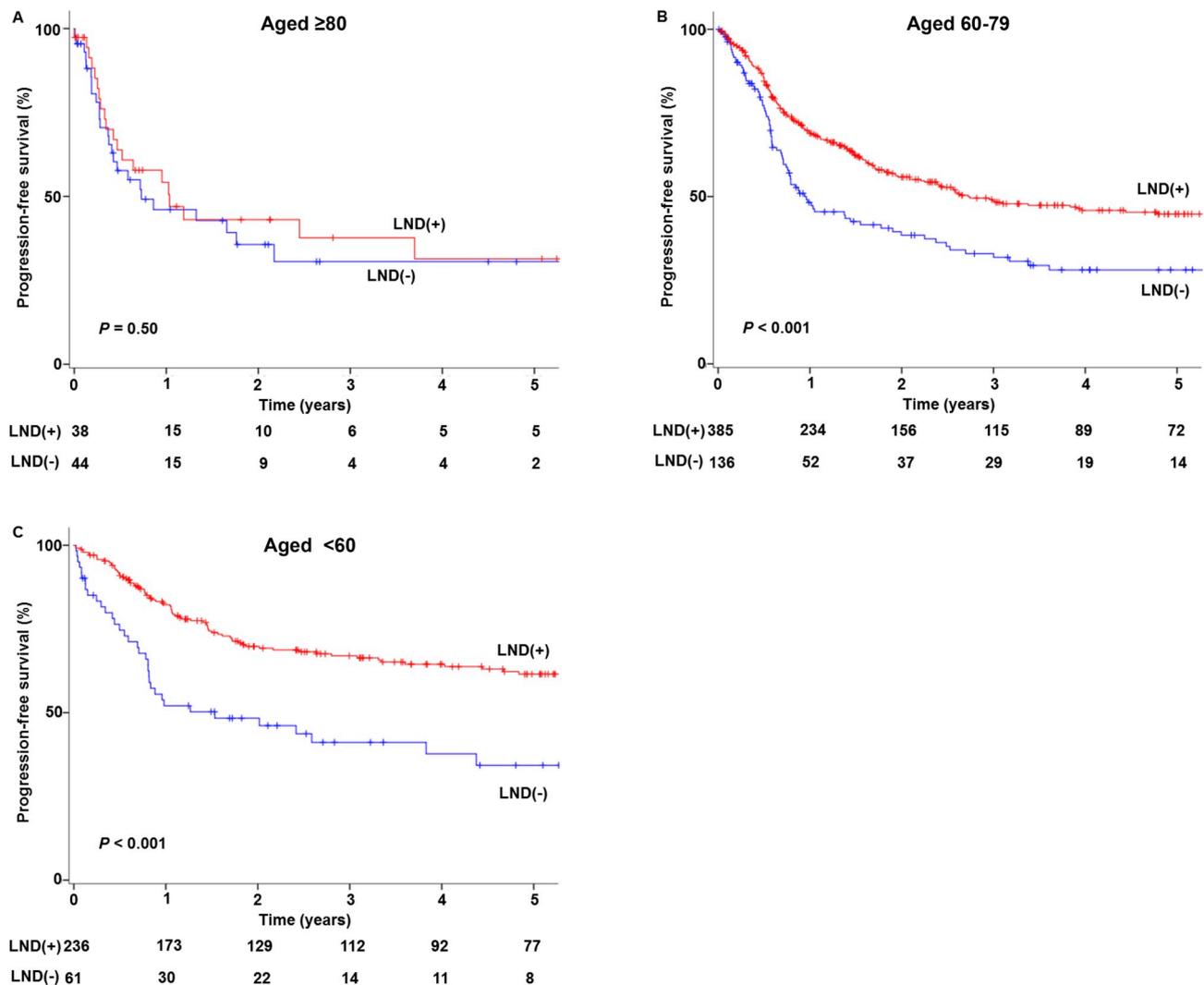
Fig. 1. Survival curves based on lymphadenectomy use.
Log-rank test for *P*-values. Progression-free survival is shown based on age groups: A) aged ≥ 80, B) aged 60–79, and C) aged < 60 for pelvic lymphadenectomy. Abbreviation: LND, pelvic lymphadenectomy.

able to undergo primary hysterectomy. Central pathology review of the archived slides was not performed in this study. Lastly, surgical outcomes and complications are not available in this database, limiting the results regarding surgical performance.

Performance status, medical comorbidities such as Charlson Index, and nutritional factors including albumin levels, and frailty have a well-recognized impact on surgical outcomes and postoperative therapy. This information was absent in this study. Mounting evidence suggests

Table 5
Association of age and survival outcome based on postoperative therapy type.

Characteristic	Progression-free survival				Cause-specific survival			
	Chemotherapy (−)		Chemotherapy (+)		Chemotherapy (−)		Chemotherapy (+)	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Aged < 60	1		1		1		1	
Aged 60-79	1.62 (1.09–2.40)	**0.016**	0.97 (0.51–1.83)	0.92	1.71 (1.08–2.70)	**0.021**	1.45 (0.73–2.85)	0.29
Aged ≥ 80	0.62 (0.41–0.95)	**0.028**	0.64 (0.49–0.83)	**0.001**	0.61 (0.38–0.99)	**0.048**	0.67 (0.49–0.92)	**0.013**

Characteristic	Radiotherapy (−)		Radiotherapy (+)		Radiotherapy (−)		Radiotherapy (+)	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Aged < 60	1		1		1		1	
Aged 60-79	1.72 (1.22–2.42)	**0.002**	0.92 (0.37–2.28)	0.85	2.13 (1.45–3.13)	**< 0.001**	0.82 (0.26–2.66)	0.74
Aged ≥ 80	0.60 (0.46–0.77)	**< 0.001**	0.72 (0.46–1.13)	0.15	0.59 (0.44–0.81)	**0.001**	0.79 (0.46–1.36)	0.39

Unadjusted HR is shown. Significant *P*-values are emboldened. Abbreviations: HR, hazard ratio; and CI, confidence interval.

that frailty and not biological age better reflects physical performance and correlates with surgical outcome and prognosis [9,31,32]. It is likely that physically-fit women aged ≥80 years have better outcomes compared to those who are frail in a younger age range. Without an objective assessment for frailty in our study, this association was not assessable.

The triad of age-related patient factors, aggressive tumor characteristics, and treatment interventions represents the hallmarks of management of women aged ≥80 years with UCS. While aggressive tumor characteristics may warrant more extensive surgery and postoperative therapy, medical and physical conditions may not allow patients in the geriatric population to undergo such radical treatment approaches. Given that women aged ≥80 years who are able to tolerate adjuvant treatment may have survival similar to younger women, careful assessment of patient condition and proper adjustment of treatment regimens is necessary.

Given increasing trends of UCS among endometrial cancer, likely reflecting aging society, the incidence of UCS may increase in the future [4]. It is almost certain that women aged ≥80 years will continue to comprise a significant portion of patients diagnosed with UCS. This makes it imperative that we further study and accurately characterize the tumor factors, appropriate treatment approaches, and outcomes of UCS in the aged ≥80 group.

Author contributions

Conceptualization: K.M.; Data curation: all authors; Formal analysis: K.M.; Funding acquisition: K.M., L.D.R.; Investigation: all authors; Methodology: K.M.; Project administration: K.M.; Resources: all; Software: K.M.; Supervision: K.M.; Validation: K.M.; Visualization: K.M., H.M.; Writing - original draft: K.M.; Writing - review & editing: all authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2019.02.002.

References

[1] L.A. Cantrell, S.V. Blank, L.R. Duska, Uterine carcinosarcoma: a review of the literature, Gynecol. Oncol. 137 (2015) 581–588.
[2] A.D. Cherniack, H. Shen, V. Walter, C. Stewart, B.A. Murray, R. Bowlby, X. Hu, S. Ling, R.A. Soslow, R.R. Broaddus, R.E. Zuna, G. Robertson, P.W. Laird, R. Kucherlapati, G.B. Mills, J.N. Weinstein, J. Zhang, R. Akbani, D.A. Levine, Integrated molecular characterization of uterine carcinosarcoma, Cancer Cell 31 (2017) 411–423.
[3] S. Zhao, S. Bellone, S. Lopez, D. Thakral, C. Schwab, D.P. English, J. Black, E. Cocco, J. Choi, L. Zammataro, F. Predolini, E. Bonazzoli, M. Bi, N. Buza, P. Hui, S. Wong, M. Abu-Khalaf, A. Ravaggi, E. Bignotti, E. Bandiera, C. Romani, P. Todeschini, R. Tassi, L. Zanotti, F. Odicino, S. Pecorelli, C. Donzelli, L. Ardighieri, F. Facchetti, M. Falchetti, D.A. Silasi, E. Ratner, M. Azodi, P.E. Schwartz, S. Mane, R. Angioli, C. Terranova, C.M. Quick, B. Edraki, K. Bilguvar, M. Lee, M. Choi, A.L. Stiegler, T.J. Boggon, J. Schlessinger, R.P. Lifton, A.D. Santin, Mutational landscape of uterine and ovarian carcinosarcomas implicates histone genes in epithelial-mesenchymal transition, Proc. Natl. Acad. Sci. U. S. A. 113 (2016) 12238–12243.
[4] K. Matsuo, M.S. Ross, H. Machida, E.A. Blake, L.D. Roman, Trends of uterine carcinosarcoma in the United States, J Gynecol Oncol 29 (2018) e22.
[5] K. Matsuo, Y. Takazawa, M.S. Ross, E. Elishaev, I. Podzielinski, M. Yunokawa, T.B. Sheridan, S.H. Bush, M.M. Klobocista, E.A. Blake, T. Takano, S. Matsuzaki,

T. Baba, S. Satoh, M. Shida, T. Nishikawa, Y. Ikeda, S. Adachi, T. Yokoyama, M. Takekuma, K. Fujiwara, Y. Hazama, D. Kadogami, M.N. Moffitt, S. Takeuchi, M. Nishimura, K. Iwasaki, N. Ushioda, M.S. Johnson, M. Yoshida, A. Hakam, S.W. Li, A.M. Richmond, H.D. Machida, P. Mhawech-Fauceglia, Y. Ueda, K. Yoshino, K. Yamaguchi, T. Oishi, H. Kajiwara, K. Hasegawa, M. Yasuda, K. Kawana, K. Suda, T.M. Miyake, T. Moriya, Y. Yuba, T. Morgan, T. Fukagawa, A. Wakatsuki, T. Sugiyama, T. Pejovic, T. Nagano, K. Shimoya, M. Andoh, Y. Shiki, T. Enomoto, T. Sasaki, M. Mikami, M. Shimada, I. Konishi, T. Kimura, M.D. Post, M.M. Shahzad, D.D. Im, H. Yoshida, K. Omatsu, F.R. Ueland, J.L. Kelley, R.G. Karabakhtsian, L.D. Roman, Significance of histologic pattern of carcinoma and sarcoma components on survival outcomes of uterine carcinosarcoma, Ann. Oncol. 27 (2016) 1257–1266.
[6] K. Matsuo, K. Omatsu, M.S. Ross, M.S. Johnson, M. Yunokawa, M.M. Klobocista, D.D. Im, S.H. Bush, Y. Ueda, T. Takano, E.A. Blake, K. Hasegawa, T. Baba, M. Shida, S. Satoh, T. Yokoyama, H. Machida, S. Adachi, Y. Ikeda, K. Iwasaki, T.M. Miyake, S. Yanai, M. Nishimura, T. Nagano, M. Takekuma, S. Takeuchi, T. Pejovic, M.M. Shahzad, F.R. Ueland, J.L. Kelley, L.D. Roman, Impact of adjuvant therapy on recurrence patterns in stage I uterine carcinosarcoma, Gynecol. Oncol. 145 (2017) 78–87.
[7] Uterine neoplasms. NCCN Clinical Practice Guideline in Oncology http://www.nccn.org (accessed 9/15/2018).
[8] R. Rozzini, G.B. Frisoni, L. Ferrucci, P. Barbisoni, T. Sabatini, P. Ranieri, J.M. Guralnik, M. Trabucchi, Geriatric Index of Comorbidity: validation and comparison with other measures of comorbidity, Age Ageing 31 (2002) 277–285.
[9] M.A. Gosney, Clinical assessment of elderly people with cancer, Lancet Oncol. 6 (2005) 790–797.
[10] World Population Aging. http://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2015_Report.pdf (accessed 9/16/2018).
[11] Elderly population. < http://www.searo.who.int/entity/health_situation_trends/data/chi/elderly-population/en/ > (accessed 9/16/2018).
[12] K. Matsuo, Y. Takazawa, M.S. Ross, E. Elishaev, M. Yunokawa, T.B. Sheridan, S.H. Bush, M.M. Klobocista, E.A. Blake, T. Takano, T. Baba, S. Satoh, M. Shida, Y. Ikeda, S. Adachi, T. Yokoyama, M. Takekuma, S. Yanai, S. Takeuchi, M. Nishimura, K. Iwasaki, M.S. Johnson, M. Yoshida, A. Hakam, H. Machida, P. Mhawech-Fauceglia, Y. Ueda, K. Yoshino, H. Kajiwara, K. Hasegawa, M. Yasuda, T.M. Miyake, T. Moriya, Y. Yuba, T. Morgan, T. Fukagawa, T. Pejovic, T. Nagano, T. Sasaki, A.M. Richmond, M.D. Post, M.M.K. Shahzad, D.D. Im, H. Yoshida, K. Omatsu, F.R. Ueland, J.L. Kelley, R.G. Karabakhtsian, L.D. Roman, Characterizing sarcoma dominance pattern in uterine carcinosarcoma: homologous versus heterologous element, Surg Oncol 27 (2018) 433–440.
[13] K. Matsuo, Y. Takazawa, M.S. Ross, E. Elishaev, M. Yunokawa, T.B. Sheridan, S.H. Bush, M.M. Klobocista, E.A. Blake, T. Takano, T. Baba, S. Satoh, M. Shida, Y. Ikeda, S. Adachi, T. Yokoyama, M. Takekuma, S. Yanai, S. Takeuchi, M. Nishimura, K. Iwasaki, M.S. Johnson, M. Yoshida, A. Hakam, H. Machida, P. Mhawech-Fauceglia, Y. Ueda, K. Yoshino, H. Kajiwara, K. Hasegawa, M. Yasuda, T.M. Miyake, T. Moriya, Y. Yuba, T. Morgan, T. Pejovic, T. Nagano, T. Sasaki, A.M. Richmond, M.D. Post, M.M.K. Shahzad, D.D. Im, H. Yoshida, T. Enomoto, K. Omatsu, F.R. Ueland, J.L. Kelley, R.G. Karabakhtsian, L.D. Roman, Proposal for a risk-based categorization of uterine carcinosarcoma, Ann. Surg. Oncol. 25 (2018) 3676–3684.
[14] E. von Elm, D.G. Altman, M. Egger, S.J. Pocock, P.C. Gotzsche, J.P. Vandenbroucke, Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies, BMJ 335 (2007) 806–808.
[15] K. Matsuo, M.S. Ross, M. Yunokawa, M.S. Johnson, H. Machida, K. Omatsu, M.M. Klobocista, D.D. Im, S. Satoh, T. Baba, Y. Ikeda, S.H. Bush, K. Hasegawa, E.A. Blake, M. Takekuma, M. Shida, M. Nishimura, S. Adachi, T. Pejovic, S. Takeuchi, T. Yokoyama, Y. Ueda, K. Iwasaki, T.M. Miyake, S. Yanai, T. Nagano, T. Takano, M.M. Shahzad, F.R. Ueland, J.L. Kelley, L.D. Roman, Clinical utility of CA-125 in the management of uterine carcinosarcoma, J Gynecol Oncol 29 (2018) e88.
[16] S. Pecorelli, Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium, Int. J. Gynaecol. Obstet. 105 (2009) 103–104.
[17] C.W. Whitney, N. Spirtos, Gynecologic Oncology Group Surgical Procedures Manual, Gynecologic Oncology Group, Philadelphia, 2010.
[18] J.A. Rauh-Hain, K.D. Starbuck, L.A. Meyer, J. Clemmer, J.O. Schorge, K.H. Lu, M.G. Del Carmen, Patterns of care, predictors and outcomes of chemotherapy for uterine carcinosarcoma: a National Cancer Database analysis, Gynecol. Oncol. 139 (2015) 84–89.
[19] B.L. Seagle, M. Kanis, M. Kocherginsky, J.B. Strauss, S. Shahabi, Stage I uterine carcinosarcoma: matched cohort analyses for lymphadenectomy, chemotherapy, and brachytherapy, Gynecol. Oncol. 145 (2017) 71–77.
[20] K. Harano, A. Hirakawa, M. Yunokawa, T. Nakamura, T. Satoh, T. Nishikawa, D. Aoki, K. Ito, T. Nakanishi, N. Susumu, K. Takehara, Y. Watanabe, H. Watari, T. Saito, Optimal cytoreductive surgery in patients with advanced uterine carcinosarcoma: a multi-institutional retrospective study from the Japanese gynecologic oncology group, Gynecol. Oncol. 141 (2016) 447–453.
[21] D.M. Guttmann, H. Li, P. Sevak, S. Grover, A. Feldman, S. Rubin, C. Chu, S. Bhatia, M.A. Elshaikh, L.L. Lin, The impact of adjuvant therapy on survival and recurrence patterns in women with early-stage uterine carcinosarcoma: a multi-institutional study, Int. J. Gynecol. Canc. 26 (2016) 141–148.
[22] I. Alagkiozidis, J. Weedon, A. Grossman, P. Wang, B. Mize, K. Wilson, T. Shah, K. Economos, G. Salame, O. Abulafia, Y.C. Lee, 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. 24 (2015) 9–13.
[23] D. Nemani, N. Mitra, M. Guo, L. Lin, Assessing the effects of lymphadenectomy and

radiation therapy in patients with uterine carcinosarcoma: a SEER analysis, Gynecol. Oncol. 111 (2008) 82–88.

[24] S.H. Tirumani, P. Deaver, A.B. Shinagare, H. Tirumani, J.L. Hornick, S. George, N.H. Ramaiya, Metastatic pattern of uterine leiomyosarcoma: retrospective analysis of the predictors and outcome in 113 patients, J Gynecol Oncol 25 (2014) 306–312.

[25] K. Matsuo, J. Garcia-Sayre, F. Medeiros, J.K. Casabar, H. Machida, A. Moeini, L.D. Roman, Impact of depth and extent of lymphovascular space invasion on lymph node metastasis and recurrence patterns in endometrial cancer, J. Surg. Oncol. 112 (2015) 669–676.

[26] M.B. Schiavone, O. Zivanovic, Q. Zhou, M.M. Leitao Jr., D.A. Levine, R.A. Soslow, K.M. Alektiar, V. Makker, A. Iasonos, N.R. Abu-Rustum, Survival of patients with uterine carcinosarcoma undergoing sentinel lymph node mapping, Ann. Surg. Oncol. 23 (2015) 196–202.

[27] M.A. Powell, V.L. Filiaci, P.G. Rose, R.S. Mannel, P. Hanjani, K. Degeest, B.E. Miller, N. Susumu, F.R. Ueland, Phase II evaluation of paclitaxel and carboplatin in the treatment of carcinosarcoma of the uterus: a Gynecologic Oncology Group study, J. Clin. Oncol. 28 (2010) 2727–2731.

[28] D. Berton-Rigaud, M. Devouassoux-Shisheboran, J.A. Ledermann, M.M. Leitao, M.A. Powell, A. Poveda, P. Beale, R.M. Glasspool, C.L. Creutzberg, P. Harter, J.W. Kim, N.S. Reed, I. Ray-Coquard, Gynecologic Cancer InterGroup (GCIG) consensus review for uterine and ovarian carcinosarcoma, Int. J. Gynecol. Canc. 24 (2014) S55–S60.

[29] reportAn Aging World: 2015. International Population Reports. < https://www.census.gov/content/dam/Census/library/publications/2016/demo/p95-16-1.pdf > (accessed 9/16/2018).

[30] Ageing. United Nations. < http://www.un.org/en/sections/issues-depth/ageing/index.html > (accessed 9/16/2018).

[31] M. Courtney-Brooks, A.R. Tellawi, J. Scalici, L.R. Duska, A.A. Jazaeri, S.C. Modesitt, L.A. Cantrell, Frailty: an outcome predictor for elderly gynecologic oncology patients, Gynecol. Oncol. 126 (2012) 20–24.

[32] A. Kumar, C.L. Langstraat, S.R. DeJong, M.E. McGree, J.N. Bakkum-Gamez, A.L. Weaver, N.K. LeBrasseur, W.A. Cliby, Functional not chronologic age: frailty index predicts outcomes in advanced ovarian cancer, Gynecol. Oncol. 147 (2017) 104–109.