ORIGINAL ARTICLE

COMPARISON OF CLINICOPATHOLOGICAL AND SURVIVAL ANALYSIS OF ENDOMETRIAL DEDIFFERENTIATED, UNDIFFERENTIATED CARCINOMAS AND CARCINOSARCOMAS

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Background: Endometrial cancer ranks as the sixth frequently detected cancer and the 14th highest contributor, to cancer-related fatalities, among women globally. High-grade endometrial carcinomas encompass a diverse array of clinically aggressive tumours, including FIGO grade 3 endometrioid adenocarcinoma, uterine papillary serous carcinoma (UPSC), clear cell carcinoma, undifferentiated carcinoma, dedifferentiated carcinoma, and carcinosarcoma. The classification and diagnosis of these tumours pose challenges due to the absence of well-established molecular markers or panels. The main purpose of this study is to assess and compare the clinicopathological characteristics of and survival rates of undifferentiated endometrial carcinoma (UEC), dedifferentiated carcinoma (DEC), and carcinosarcoma (CS) in the Pakistani population at SKMCH&RC. **Methods:** All patients diagnosed with DEC, UEC, and CS were analyzed from January 2011 and December 2022. Clinicopathological and survival data was retrospectively reviewed and analyzed using SPSS version 27. Kaplan-Meier analysis was used to calculate overall survival (OS) and disease-free survival (DFS). **Results:** Among 71 selected patients, 47.9% had CS, 29.6% had DEC, and 22.5% had UEC. Mean±SD age at diagnosis was 58.18±11.35 years. A statistically significant association of DEC, UEC, and CS was identified (p-value <0.05) with myometrial invasion (p=0.02), lympho-vascular invasion(p=0.006), positive margins(p=0.003), and involvement of adnexa/ parametria/ vaginal /adnexa/ parametria/ vaginal /another organ (p=0.01). The commonest pathological stage was pT1 38(53.5%). 56.3% of patients received chemotherapy, 29.6% received radiotherapy, and 38.0% received a combination of chemotherapy and radiation treatment. Recurrence occurred in 19.7% and death occurred in 37.7% of patients. The highest 5-year OS rate for pathological stage 1 was 59.1% (95% C.I: 42.9–81.3%) and 5-year-DFS was 62.2% (95% C.I: 42.9–81.3%). **Conclusion:** Patients diagnosed at an early pathological stage demonstrate better survival outcomes compared to an advanced stage, as documented in previous studies. Nevertheless, survival rates remain lower than Western population, indicating a necessity for gathering additional clinical data and alter the management strategies in our population.

Keywords: Endometrial carcinoma; Dedifferentiated; Undifferentiated; Carcinosarcoma; High-grade; Clinicopathological

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INTRODUCTION

Endometrial cancer ranks as the sixth frequently detected cancer and the 14th highest contributor, to cancer-related fatalities, among women globally.[1] High-grade endometrial carcinomas encompass a diverse array of clinically aggressive tumours, including FIGO grade 3 endometrioid adenocarcinoma, uterine papillary serous carcinoma (UPSC), clear cell carcinoma, undifferentiated carcinoma, dedifferentiated carcinoma, and carcinosarcoma. The classification and diagnosis of these tumours pose challenges due to the absence of well-established molecular markers or panels.[2,3] Challenges exist in implementing immunohistochemistry or molecular pathology universally. Traditional pathology remains essential for interpreting and categorizing neoplasms during routine clinical practice, especially in resource-restrained countries.[4,5]

Undifferentiated endometrial carcinoma (UEC) and dedifferentiated endometrial carcinoma (DEC) are two distinct types of malignancies affecting the uterine corpus, each representing around 10% of high-grade endometrial carcinomas. Undifferentiated carcinoma of the endometrium is characterized by a malignant epithelial neoplasm displaying no discernible cell lineage differentiation. Dedifferentiated carcinoma is a composite of an undifferentiated carcinoma and a differentiated

component, typically of FIGO grade 1 or 2 endometrioid carcinoma.[6,7] Carcinosarcoma (CS) of the uterine corpus is defined as a biphasic tumour comprising both high-grade carcinomatous and sarcomatous components. Gynaecologic carcinosarcomas are rare but highly aggressive, accounting for less than 5% of uterine and ovarian cancers. Prognosis remains controversial, with some studies suggesting poorer outcomes for heterologous tumours.[8]

High-grade endometrial cancers, such as dedifferentiated carcinoma, undifferentiated carcinoma, and carcinosarcoma are classified using the International Federation of Gynaecology and Obstetrics FIGO/ The American Joint Committee on Cancer (AJCC) staging system as types of endometrial cancer for treatment, guidance, and prognosis assessment. Detecting early and providing care enhances outcomes for patients, with these aggressive histologic variants.[9,10] In endometrial tumours, besides histological type and grade, factors such as advancing age, depth of myometrial invasion, lymph node involvement, tumour size, lymphovascular invasion, and tumour infiltration of the lower uterine segment are also linked to poorer prognosis.[5]

Our primary goal, in this study is to identify and compare the clinicopathological characteristics of and survival rates of DEC, UEC, and CS diagnosed at our institution. To our knowledge, there have been no studies conducted on these high-grade endometrial cancers in Pakistan. By delving into the details of these challenging types of tumours, we aim to offer a better understanding of these high-grade endometrial cancers leading to more effective medical treatments and ultimately improving patient outcomes in our country.

MATERIALS AND METHODS

This retrospective study was conducted at the Pathology Department of Shaukat Khanum Cancer Hospital and Research Center (SKMCH & RC), Lahore, Pakistan. This center receives biopsies from all the provinces of Pakistan. After ethical clearance from the institutional review board, cases of dedifferentiated endometrial carcinoma (DEC), undifferentiated endometrial carcinoma (UEC), and carcinosarcoma (CS) already diagnosed at our institute were retrospectively analyzed from the archives of SKMCH&RC between January 2011 and December 2022 and selected via convenient sampling technique. Biopsies comprised of both the endometrial curetting and resection specimens. All the consecutive cases of the above-mentioned carcinomas were reviewed by two histopathologists according to the latest W.H.O guidelines (Female Genital Tumours (5th ed.), and 71 cases were finalized to be included in the study. Patients having other types of high-grade endometrial carcinomas, autolyzed tissue with equivocal immunohistochemical results, and tumours from ovarian and cervix biopsies were excluded. Clinicopathological and survival data was collected from the electronic medical records of the hospital information system and patient's telecommunication. Data was collected on age, biopsy type, histopathological diagnosis, size of the tumour, site of tumour in the uterus, myometrial invasion, lymphovascular invasion, the status of serosa and margins, cervix invasion, involvement of adnexa/parametria/vagina and/or other organs, submitted lymph node and omentum involvement, peritoneal washing, metastasis, treatment, overall survival, and disease-free survival.

Clinicopathological and survival data was entered and analyzed using SPSS-27. Frequency was given for each variable and the association between various prognostic variables and tumours under study was analyzed using the Chi-square test. A *p*-value less than 0.05 was considered statistically significant. Patients' survival was studied from their respective date of diagnosis starting from March 2011 till July 2023. Patients' follow-up time ranged between 7–148 months. Overall survival (OS) was calculated from the date of diagnosis to the date of death with patients censored at the date of the last follow-up (July 2023). Disease-free survival (DFS) was calculated from the date of diagnosis to the date of recurrence. Recurrence was recorded based on clinical or radiological data. Survival records could not be assessed for 10 of 71 patients due to loss of contact. Kaplan-Meier analysis was used to calculate overall survival (OS) and disease-free survival (DFS). The log-rank (Mantel-cox) test was applied to assess pairwise and overall comparison of OS and DFS among histopathological diagnosis and pathological stages (pT1, pT2, pT3, and pTx).

RESULTS

A total of 71 patients with dedifferentiated endometrial carcinoma (DEC), Undifferentiated endometrial carcinoma (UEC), and carcinosarcoma (CS) were selected. Of these 71 patients, the most common histopathological diagnosis was CS (34;47.9%), followed by DEC (21;29.6%) and UEC (16;22.5%). The mean age at diagnosis was 58.18±11.35 years. Biopsies comprised of both surgical specimens (63; 88.7%) and endometrial curettings (8;11.3%). Surgical specimens included total abdominal hysterectomy with bilateral salpingoophorectomy, with or without lymphadenectomy and omentectomy. Lymph nodes were not submitted in 61 cases and omentum was not submitted in 58 cases. The mean±SD size of the tumour was 61.01±32.82 mm. Tumours were most

commonly identified in the body of the uterus (54;76.1%). The myometrial invasion was identified in 61 (96.8%) of 63 resection specimens. Among these 61 cases showing myometrial invasion, less than 50% invasion was seen in 20 (28.2%), and more than 50% invasion was identified in 41;57.7% resection specimens. Myometrial invasion was not identified in only two of the resection specimens and was not assessed in endometrial curetting's. Frequencies of clinicopathological parameters are summarized in Table-1.

Lymphovascular invasion was identified in 25;35.2% of cases. Uterine serosa was involved in 5;7.0% and margins were involved in 13;18.3% of cases. Cervix stromal invasion was identified in 16;22.5% of cases and involvement of adnexa/parametria/vagina/other organs was identified in 17;23.9% with only one of these cases showing spread to rectal mucosa histologically. Positive locoregional lymph nodes were identified in 3;4.2% of cases and omentum was involved in 4;5.6% of the total cases. Peritoneal washings were submitted in 15 cases and of these, 4 (5.6%) cases were positive for malignant cells.

Involvement of serosa and margins, invasion of cervix and adnexa/parametria/vagina/and or other organs, lymphovascular invasion, lymph node and omental involvement, and peritoneal washings were assessed and associated with each of the histopathological diagnoses (DEC, UEC, and CS). A statistically significant association was seen (p-value <0.05) with myometrial invasion (p=0.02), lymphovascular invasion (p=0.006), margin involvement (p=0.003), and involvement of adnexa/ parametria/ vaginal /adnexa/ parametria/ vaginal /another organ (p=0.01). No significant association was identified with the invasion of serosa, cervix, lymph node involvement, and peritoneal washing (p-value>0.05). The relationship of prognostically significant histopathological variables with histopathological diagnosis is summarized in Table-2.

Pathological stage was also assessed in all the cases except for endometrial curetting (pT_x). The commonest pathological stage was pT1 38(53.5%) and only one patient (1.4%) was identified with pT4. No significant relationship was identified between the pathological stage and the histopathological diagnosis (p-value 0.1). Frequencies of pathological stage and association with histopathological diagnosis are summarized in Table 3.

Data on survival parameters was unavailable in 10 (14.1%) patients within each survival-related category. Of the 61 followed patients, 23 patients died. Of these 23, 11 patients died of CS and 6 died of each DEC and UEC respectively. The mean±S.D value of months between diagnosis and death was 14.65±17.44 (range 2–90 months). Based on clinical records and patient contact, locoregional metastasis was identified in 30 (42.3%) cases, and distant metastasis was identified in 14 (19.7%) patients. Chemotherapy was given to 40;56.3%, and radiotherapy was given to 42;59.2% of patients. A significant portion of these patients (27;38.0%) received both chemotherapy and radiation treatment. Recurrence occurred in 14 (19.7%) patients. The Mean±SD of overall survival months was 29.31±28.01 (Range 2–143 months). The Mean±SD of disease-free months was 18.10±26.95 (range 0–130 months). Frequencies and Mean±SD of survival-related parameters are summarized in Table 4.

The overall survival (OS) and disease-free survival (DFS) were calculated for each of the three tumours under study. The highest OS in our study was of CS with an estimated mean of 86.50 (S.E 13.34) months, followed by DEC 40.42 (S.E 6.36), and UEC 33.55 (S.E 5.538). Tumour-wise comparison of overall survival via Log Rank, Mantel-Cox revealed no significant difference in OS of these three tumours (p-value>0.05). The comparison of tumour-wise overall survival results is shown in Figure 1 and summarized in Table S1 respectively.

The estimated mean disease-free survival (DFS) for carcinosarcoma was 88.4 (S.E 12.68) months, followed by 34.7 (S.E 6.45) months for DEC and 20.8 (S.E 4.19) months for UEC. Tumour-wise comparison of DFS via Log Rank (Mantel-Cox) test revealed no significant difference among these three tumours (p-value>0.05). Comparison of tumour-wise disease-free survival with their means has been shown in Figure 2 and summarized in Table S2 respectively.

Overall survival (OS) was also calculated concerning pathological stages and it was highest for pathological stage 1 with an estimated mean of 82.538 (S.E:12.882, 95% C.I: 57.2–107.78). These results are summarized in Figure S1 I and Table S3. Overall Disease-free survival (DFS) was also highest for pathological stage 1 as shown in Figure S2.

The 5 years overall survival (OS) rate and disease-free survival (DFS) rate couldn't be statistically calculated for all tumours under study. Therefore, 4-year and 2-year rates were calculated where applicable. The 5-year OS rate was 60.1% (95% C.I: 46.7–73.4%) and the 5-Year DFS rate was 65.7% (95% C.I: 49.8–81.6%) for all patients regardless of diagnosis. The 5-year overall survival (OS) rate of carcinosarcoma and dedifferentiated carcinoma were 63.2% (95% C.I: 46.8–85.2%) and 61.4% (95% C.I: 41.1–91.8%) respectively. The 4-year survival rate of undifferentiated carcinoma was 51.1% (95% C.I: 29%-90%).

The 5-year DFS of carcinosarcoma was 65.7% (C.I: 47.6–90.9%). The 4-year and 2-year DFS for DEC and UEC were 68.2% (C.I: 15.8–43.3%) and 60% (C.I:33.1–100%). These results are summarized in Table 8. The highest 5-year OS rate for pathological stage 1 was 59.1% (95% C.I: 42.9–81.3%) and 5-year-DFS was 62.2% (95% C.I: 42.9–81.3%). The pathological stage of patients with endometrial curetting (pTx) couldn't be assessed. However, statistically, excluding them from the OS rate wasn't possible. The results are summarized in Table S4. Histopathological images are provided in Figures S3, S4, and S5.

Table-1: Frequencies of clinicopathological parameters

Variables		Total n=71 Frequency	Percentage
Age (years) Mean±S.D: 58.18±11.352	≤ 50 51-60 > 60	20 20 31	28.2 28.2 43.7
Biopsy type	Hysterectomy (H) Endometrial curetting (C)	63 8	88.7 11.3
Histopathological diagnosis	Dedifferentiated endometrial carcinoma (DEC) Carcinosarcoma (CS) Undifferentiated endometrial carcinoma (UEC)	21 34 16	29.6 47.9 22.5
Size (mm)	≤40 mm 41-70 mm > 70 mm	27 23 21	38.0 32.4 29.6
Site in uterus	Body Fundus	54 17	76.1 23.9
Myometrial invasion	NS⁂\NI* <50% >50%	10 20 41	14.1 28.2 57.7

⁂NS: Not submitted, *NI: Not identified

Table-2: Patient distribution according to histopathological diagnosis and different clinicopathological factors

		Histopathological diagnosis								Chi-square (*p*-value)
		Dedifferentiated carcinoma (DEC)		Carcinosarcoma (CS)		Undifferentiated carcinoma (UEC)		Total		
		N=21	%	N=34	%	N=16%		N=71	%	
Myometrial Invasion	NS⁂/N.I*	1	1.4	4	5.6	5	7	10	14.1	10.84
	<50%	3	4.2	11	15.5	6	8.5	20	28.2	(***p*=0.028**)
	>50%	17	23.9	19	26.8	5	7.0	41	57.7	
Serosa	NS	1	1.4	2	2.8	5	7.0	8	11.3	
	N⁋	17	23.9	30	42.3	10	14.1	57	80.3	10.82
	P‡	3	4.2	2	2.8	1	1.4	6	8.5	(*p*=0.05)
Margins	NS	1	1.4	2	2.8	5	7.0	8	11.3	
	N	12	16.9	29	40.8	9	12.7	50	70.4	15.84
	P	8	11.3	3	4.2	2	2.8	13	18.3	(***p*=0.003**)
Cervix invasion	NS	1	1.4	2	2.8	5	7.0	8	11.3	
	N	14	19.7	25	35.2	8	11.3	47	66.2	8.74
	P	6	8.5	7	9.9	3	4.2	16	22.5	(*p*=0.068)
Adnexa/ Parametria/ Vaginal involvement /Other organs	NS	1	1.4	2	2.8	5	7.0	8	11.3	
	N	11	15.5	26	36.6	9	12.7	46	64.8	13.31
	P	9	12.7	6	8.5	2	2.8	17	23.9	(***p*=0.010**)
Lymphovascular invasion (LVI)	NS	0	0.0	0	0.0	0	0.0	0	0.0	
	N	9	12.7	22	31.0	15	21.1	46	64.8	10.31
	P	12	16.9	12	16.9	1	1.4	25	35.2	(***p*=0.006**)
Lymph node	NS	17	23.9	28	39.4	16	22.5	61	85.9	
	N	2	2.8	5	7.0	0	0.0	7	9.9	5.07
	P	2	2.8	1	1.4	0	0.0	3	4.2	(*p*=0.280)
Omentum	NS	13	18.3	32	45.1	13	18.3	58	81.7	
	N	5	7.0	1	1.4	3	4.2	9	12.7	10.84
	P	3	4.2	1	1.4	0	0.0	4	5.6	(***p*=0.028**)
Peritoneal washing	NS	18	25.4	23	32.4	15	21.1	56	78.9	
	N	2	2.8	8	11.3	1	1.4	11	15.5	5.44
	P	1	1.4	3	4.2	0	0.0	4	5.6	(*p*=0.245)
	Total	21	29.6	34	47.9	16	22.5	71	100.0	

⁂NS: Not submitted, *NI: Not identified, ⁋N: Negative, ‡P: Positive, Bold *p*- value: Significant value (<0.05)

Table-3: Patient distribution according to histopathological diagnosis and pathological stage

		Histopathological diagnosis			Total
		Dedifferentiated carcinoma (DEC)	Carcinosarcoma (CS)	Undifferentiated carcinoma (UEC)	
Pathological (pT) stage	pT1	10 (14.1%)	20 (28.2%)	8 (11.3%)	38 (53.5%)
	pT2	1 (1.4%)	4 (5.6%)	1 (1.4%)	6 (8.5%)
	pT3	8 (11.3%)	8 (11.3%)	2 (2.8%)	18 (25.4%)
	pT4	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
	pTx	1 (1.4%)	2 (2.8%)	5 (7.0%)	8 (11.3%)
Total		21 (29.6%)	34 (47.9%)	16 (22.5%)	71 (100.0%)

Pearson chi-square value: 13.37 *p*-value: 0.1

Table-4: Clinical and survival characteristics

Locoregional metastasis	Yes No Not available	30 31 10	42.3% 43.7% 14.1%
Distant metastasis	Yes No Not available	14 47 10	19.7% 66.2% 14.1%
Chemotherapy	Yes No Not available	40 21 10	56.3% 29.6% 14.1%
Radiotherapy	Yes No Not available	42 19 10	59.2% 26.8% 14.1%
Alive/Dead	Alive Dead Not available	38 23 10	62.3% 37.7% 14.1%
Recurrence	Yes No Not Available	14 47 10	19.7% 66.2% 14.1%
Overall survival months: Mean±S.D	29.3115±28.01.		
Disease free months: Mean±S.D	18.10±26.955		
Months between diagnosis and death (n=23): Mean±SD	14.65±17.442		

Table S1:-Estimated Mean of overall survival (OS) concerning histopathological diagnosis

Histopathological diagnosis	Mean			
	Estimate (months)	**Standard Error**	**95% Confidence Interval**	
			Lower Bound	Upper Bound
Dedifferentiated endometrial carcinoma (DEC)	40.427	6.362	27.957	52.898
Carcinosarcoma (CS)	86.501	13.342	60.351	112.651
Undifferentiated endometrial carcinoma (UEC)	33.555	5.538	22.702	44.409
Overall	82.739	10.540	62.080	103.399

Overall Comparison Log Rank (Mantel-Cox) Chi-Square 0.036 *p*-value: 0.849

Table S2: Estimated Mean of disease-free survival (DFS) concerning histopathological diagnosis

Histopathological diagnosis	**Mean**			
	Estimate (months)	**Standard Error**	**95% Confidence Interval**	
			Lower Bound	Upper Bound
Dedifferentiated carcinoma (DEC)	34.773	6.450	22.130	47.416
Carcinosarcoma (CS)	88.488	12.688	63.619	113.356
Undifferentiated carcinoma (UEC)	20.800	4.194	12.579	29.021
Overall	88.270	9.630	69.395	107.144

Overall Comparisons DFS Log Rank (Mantel-Cox) Chi-Square 0.043 *p*-value 0.979

Table S3:-Estimated mean of overall survival (OS) concerning pathological stages

pT stage	**Mean**			
	Estimate (Months)	**Std. Error**	**95% Confidence Interval**	
			Lower Bound	**Upper Bound**
pT1	82.538	12.882	57.289	107.788
pT2	41.167	12.462	16.741	65.592
pT3	21.250	3.811	13.780	28.720
pTx	37.714	6.147	25.666	49.762
	82.739	10.540	62.080	103.399

Overall Comparisons OS Log Rank (Mantel-Cox), Chi-Square 0.039 *p*-value 0.843

Table S4:-Years-wise Survival rates according to histopathological diagnosis

Survival	Years	Histopathological diagnosis	Survival rate (%)	95% confidence interval	
				LC	UC
OS	5-Year	DEC	61.4	41.1	91.8
	5-year	CS	63.2	46.8	85.2
	4-year	UEC	51.1	29	90
DFS	4-year	DEC	68.2	15.8	43.3
	5-year	CS	65.7	47.6	90.9
	2-year	UEC	60	33.1	100

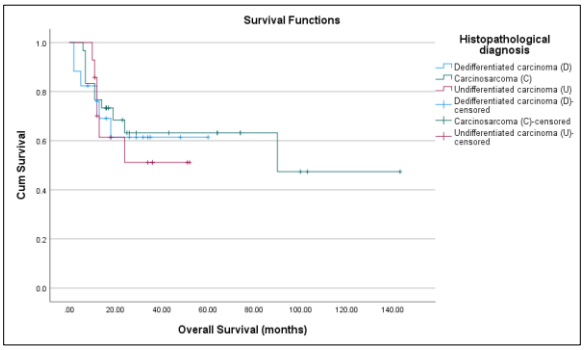

Figure-1: Kaplan-Meier graph showing the overall survival (OS)of patients according to histopathological diagnosis

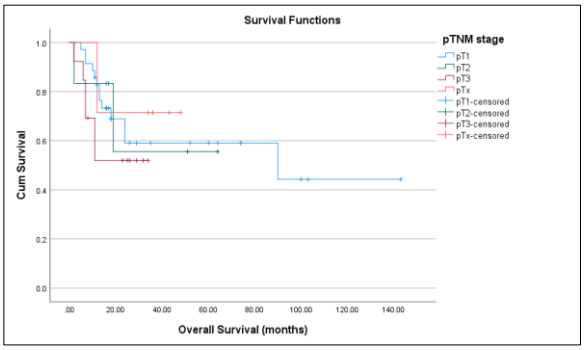

Figure-S1: Overall survival (OS) concerning pathological stages

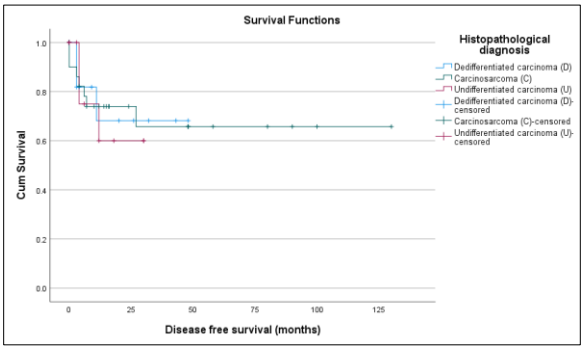

Table-2: Patient distribution according to histopathological diagnosis and different clinicopathological factors.

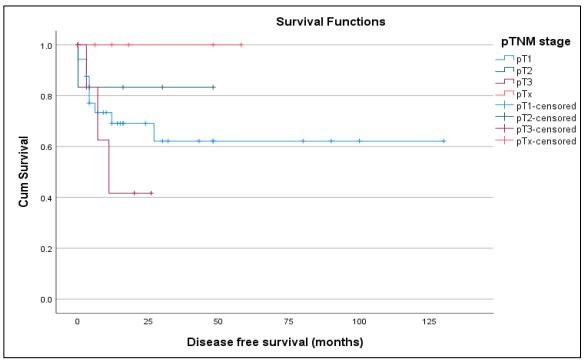

Figure-S2: Disease-free survival (DFS) concerning pathological stages

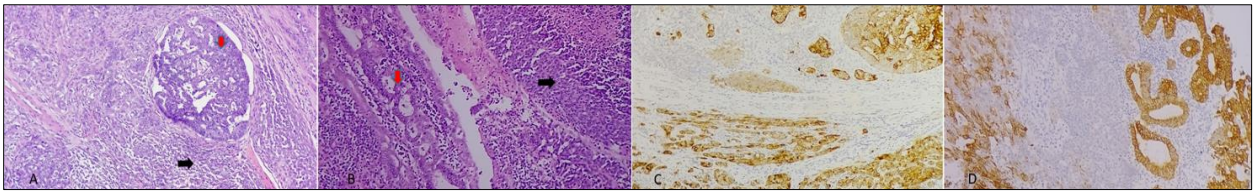

Figure S3:-A&B; Dedifferentiated carcinoma showing differentiated glandular component (red arrow) and an undifferentiated sheet-like component (black arrow), (10X), C&D; Positive expression of CK8/18 in differentiated glandular component and focal positive expression in the undifferentiated sheet-like component (10X)

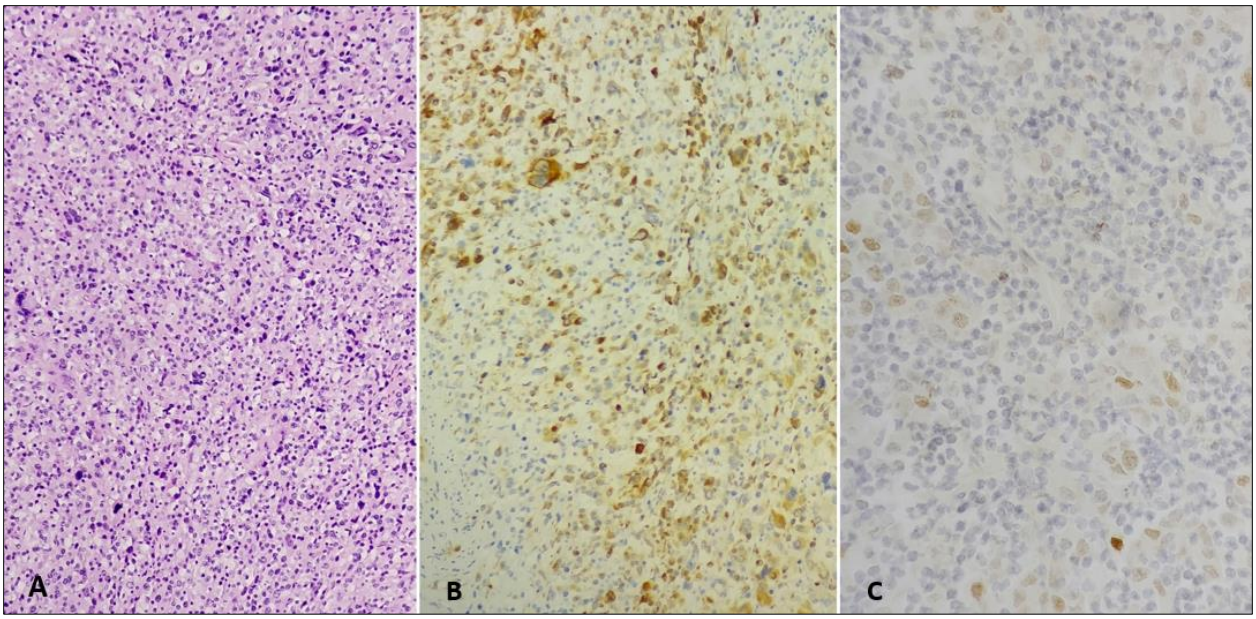

Figure S4: A; Undifferentiated carcinoma showing diffuse sheet of tumour cells with lack of glandular or papillary architecture (10X), B; Focal positive expression of CK8/18 in tumour cells(10X), C; Wild-type expression of p53 in tumour cells (10X)

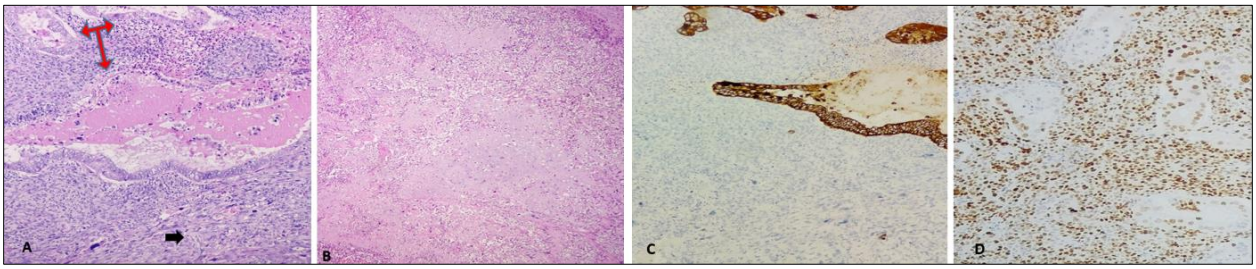

Figure S5: A; Carcinosarcoma showing a biphasic tumour comprising of glandular carcinoma component (red arrows) and stromal sarcoma component (black arrow) (10X), B; Carcinosarcoma showing heterologous element (chondrosarcoma), 4X C; Positive expression of CK8/18 in carcinoma glands and negative in stromal sarcoma (10X), D; Aberrant overexpression of p53 predominantly in stromal sarcoma component (10X)

DISCUSSION

Elucidating the prognostic significance of highly aggressive histological types of endometrial carcinoma is crucial due to their histological overlap. Thus far, no histopathological research is available on high-grade endometrial carcinomas such as DEC, UEC, and CS in Pakistan. Therefore, the main aim of this study was to evaluate and compare the basic clinicopathological and survival parameters of these three high-grade endometrial cancers in our population.

In our study, 71 cases were selected retrospectively. In this study, CS was found to be the commonest tumour (47.9%) followed by DEC (29.6%) and UEC (22.5%) respectively. Multivariate analysis done by Taskin *et al*. reported that older age groups, UEC, DEC, or CS histological diagnosis are associated with a poorer prognosis.[11] In our study, the mean age at diagnosis was 58.9 years and 28.2% were younger than 50. In this study, 61 of 63 (96.8%) cases revealed myometrial invasion with the highest number identified in carcinosarcoma (42.3%). A significant statistical association was identified (p-value <0.05) between myometrial invasion, involvement of margins, adnexa/parametria/vagina/other organs, lymphovascular invasion (LVI), and omentum with histopathological diagnosis. Lymphovascular invasion (LVI) was identified in 35.2% of cases and both CS and DEC revealed 16.9% LVI each, followed by 1.4% UEC. Invasion of the cervix was identified in 16 (22.5%) with 7/16 occurring in carcinosarcoma followed by 6/16 and 3/16 in dedifferentiated and undifferentiated carcinoma respectively. It was revealed that 52.9% of cases with extra corporal spread

were of dedifferentiated carcinoma. Though crucial for prognostic purposes in patient risk stratification according to FIGO staging[5], we didn't receive a significant number of lymphadenectomy, omentectomy, and peritoneal washing/peritoneal samples. Cases, where lymph nodes were received in resection, were not labelled further as pelvic/para-aortic/other. This may be attributed to the limited expertise of surgeons practicing in small towns and rural regions in Pakistan. Omental metastasis upstages the patients to FIGO stage IVB.[5] In our study, omental metastasis was identified in 4 (5.6%) cases with 3/4 occurring in DEC, and lymph node metastasis was identified in 3(4.2%) cases with 2/3 associated with DEC. Hamilton *et al*. reported 12% of patients in the less than 50 age group, myometrial invasion in 77%, LVI in 66%, cervix invasion in 19%, and involvement of fallopian tube and ovary in 14% each.[6] Lakhwani *et al*., reported 22.5% of carcinosarcoma, myometrial invasion in 72.5%, LVI in 40% of cases, cervix invasion in 25%, and involvement beyond the uterus in 15% of high-grade endometrial tumours other than UEC. Paulino *et al*., reported 13.5% of carcinosarcoma among other high-grade endometrial cancers excluding undifferentiated carcinomas in their study, and identified myometrial invasion in 94.8% cases.[12]

In our study, pathological staging was carried out according to CAP guidelines. The commonest pathological stage was pT1 (53.5%), followed by pT3 (25.4%), pT2(8.5%) and PT4 (1.4%). Though the stage is an important prognostic factor, our study didn't reveal a significant *p*-value when the stage was statistically associated with histopathological diagnosis (Table-3). In contrast to our results, the literature indicates that tumours under study tend to present at a higher stage due to an early extra-uterine spread.[9,13,14] Paulino *et al*. reported that 44.8%, 12.4%. 29.8% and 12.9% of the patients diagnosed with high-grade endometrial cancers were in FIGO stages 1, 2, 3, and 4 respectively.[12] Zhang *et al*. reported that 13/21 patients had stage I DEC/UECs and 7/21 patients showed stage III DEC/UEC.[15] Another study done by Scharl *et al*. reported that 58.7% of patients displayed cancer of FIGO stage I, 9.9% patients showed FIGO stage II, 29.7% were diagnosed with FIGO stage III, and 1.7% with FIGO stage IVA.[16] These studies suggested that similar to our results, most patients presented in FIGO stage 1 followed by stage 3. Regarding, survival parameters, death occurred in 23 (37.7%) of the 61 contacted patients and 47.82% died of carcinosarcoma followed by 26.09% DEC and UEC each. The shortest time between diagnosis and death was 2 months in a patient diagnosed with dedifferentiated carcinoma.

In our study, locoregional metastasis was most commonly seen in carcinosarcoma 11/71 (15.5% of the total). Distant metastasis was seen equally in 5/71 (7%) in carcinosarcoma and UEC followed by DEC 4/71 (5.6%). Hamilton *et al.* and Lakhwani *et al*. identified distant metastasis in 32.5% and 15% of high-grade endometrial tumours respectively.[6,9] High-grade endometrial carcinomas are associated with high recurrence rates ranging from 50–95%, especially in cases of UEC/DEC. The recurrence is linked to the stage as it can range between 2–15% at an early stage (stages I and II) and up to 50% in advanced stages (stages III and IV).[9,17] Recurrence was identified in 8/71 (11.3%) of carcinosarcoma and 3/71 (4.2%) each of UEC and DEC respectively. Among patients showing recurrence, death occurred in 9/14 cases. The majority of our patients were in pathological stage 1 (53.5%) so the recurrence rate was not as high as expected. However, recurrence occurred despite receiving regular chemotherapy (15.5%) and radiotherapy (15.5%). Hamilton *et al.* identified locoregional and distant relapse in a higher percentage (58%) with death occurring in 39% of cases.[6]

In this study, the 5-year OS and DFS were 60.1% and 65.7% for all patients respectively. The 5-year OS and DFS for carcinosarcoma were 63.2% (95% C.I: 46.8–85.2%) and 65.7% (C.I: 47.6–90.9%) respectively. In contrast, the 5-year OS of dedifferentiated carcinoma was 61.4% (95% C.I: 41.1–91.8%) and a 4-year OS for undifferentiated carcinoma was 51.1% (95% C.I: 29–90%). The highest 5-year OS and DFS were identified in pathological stage 1 at 59.1% (95% C.I: 42.9–81.3%) and 62.2% (95% C.I: 45–85.8%) respectively. The largest previously published series of dedifferentiated and undifferentiated endometrial carcinomas by Tafe *et al*. presented findings with improved survival, with 72% of patients diagnosed with stage I and II.[18] Hamilton *et al*. reported a 5-year OS rate of 84% for FIGO stage 1/2, 38% for stage 3, and 12% for stage 4. They also performed multivariate analysis suggesting that survival rates increased with adjuvant chemotherapy and lower stage. They also calculated 5-year DFS which was 80% for stages I and II, 29% for stage 3, and 10% for stage 4.[6]

However, Silva *et al*. identified a crude survival rate of 46% (n=6/13) in dedifferentiated carcinomas.[14] A significant portion of these cases (69%) presented with stage III and IV disease at diagnosis, potentially contributing to the comparatively inferior outcomes observed in their study compared to ours. These authors also presented survival outcomes from 16 cases of pure undifferentiated carcinoma, with a reported crude survival rate of 25%.[19] Another study by Al-Hussaini *et al*. focusing on 17 patients with undifferentiated and

dedifferentiated carcinoma highlighted six patients with stage I/II disease with a 50% mortality rate.[20] Ureyen *et al*. conducted a retrospective study involving 18 patients with undifferentiated carcinoma, revealing that after a median follow-up of 66 months, 33% experienced progressive disease, and 16% succumbed to the disease.[21] A comprehensive study based on the National Cancer Database (NCDB) analyzed outcomes from 3,313 patients with UEC, revealing a 5-year OS of 75%, 59%, 44%, and 22% for stage I–IV, respectively.[22] This study showed better outcomes for stage I and similar results to stage II diseases compared to our findings, but worse outcomes for stage III disease. Notably, DEC and CS patients were not included in this study. Gracia *et al*.[23] conducted a study on carcinosarcoma and reported a 5-year OS of 56.5% and 5-year DFS of 50.2%, worse than our patients (63.2% and 65.7%). Another study conducted by Chiang *et al*.,[24] on carcinosarcoma revealed 45.1% 5-year OS of the whole series. Bosquet *et al*. also reported a 5-year DFS in carcinosarcoma of 59% at stages 1 and 2, 22% at stage 3, and 9% at stage 4[25]. The current study faces numerous limitations, predominantly due to its retrospective nature, a small number of cases, the inability to classify patients according to the new molecular classification due to resource limitation, lack of data on comorbidities, and concerns regarding the accuracy of data collection in patients diagnosed at our center but subsequently treated elsewhere. We could only compare pathological stages 1–3 with FIGO clinical stages across different studies, and pathological stage data was unavailable for 11.3% of cases (curetting). However, given the rarity of tumours, a notable strength of the study lies in its inclusion of a substantial number of patients diagnosed at our center between the years 2011 and 2022.

Due to the scarcity of studies concerning high-grade endometrial cancers, coupled with the absence of literature on this topic within our country previously, we aimed to present the clinicopathological characteristics and survival outcomes of DEC, UEC, and CS within our patient cohort. We corroborated international findings indicating the unfavourable prognosis associated with these tumours. Recurrence remains a possibility and can be dismal even in pathological stage 1 disease despite undergoing treatment.

Conflict of interest: The authors declare that there are no conflicts of interest to declare.

AUTHORS' CONTRIBUTION

All authors played an important role in the development of this manuscript. UH: Conceptualization and supervision. IA: Data search. UH, HM: Histological review. HM, MH: Methodology. UH, IA: Write-up. MH, MH: Analysis. AL: Review. HM, IA: Final editing. All authors have read and approved the final manuscript.

REFERENCES

1. Lortet-Tieulent J, Ferlay J, Bray F, Jemal A. International patterns and trends in endometrial cancer incidence, 1978–2013. J Natl Cancer Inst 2018;110(4):354–61.
2. Kobayashi Y, Kitazono I, Akahane T, Yanazume S, Kamio M, Togami S, *et al*. Molecular evaluation of endometrial dedifferentiated carcinoma, endometrioid carcinoma, carcinosarcoma, and serous carcinoma using a custom-made small cancer panel. Pathol Oncol Res 2021;27:1610013.
3. Huvila J, Pors J, Thompson EF, Gilks CB. Endometrial carcinoma: molecular subtypes, precursors and the role of pathology in early diagnosis. J Pathol 2021;253(4):355–65.
4. Santoro A, Angelico G, Travaglino A, Inzani F, Arciuolo D, Valente M, *et al*. New pathological and clinical insights in endometrial cancer in view of the updated ESGO/ESTRO/ESP guidelines. Cancers (Basel) 2021;13(11):2623.
5. Kasius JC, Pijnenborg JM, Lindemann K, Forsse D, van Zwol J, Kristensen GB, *et al*. Risk stratification of endometrial cancer patients: FIGO stage, biomarkers and molecular classification. Cancers (Basel) 2021;13(22):5848.
6. Hamilton SN, Tinker AV, Kwon J, Lim P, Kong I, Sihra S, *et al*. Treatment and outcomes in undifferentiated and dedifferentiated endometrial carcinoma. J Gynecol Oncol 2022;33(3):e25.
7. Li Z, Zhao C. Clinicopathologic and immunohistochemical characterization of dedifferentiated endometrioid adenocarcinoma. Appl Immunohistochem Mol Morphol 2016;24(8):562–8.
8. Bansal N, Herzog TJ, Seshan VE, Schiff PB, Burke WM, Cohen CJ, *et al*. Uterine carcinosarcomas and grade 3 endometrioid cancers: evidence for distinct tumour behavior. Obstet Gynecol 2008;112(1):64–70.
9. Lakhwani P, Agarwal P, Goel A, Nayar N, Pande P, Kumar K. High-Grade Endometrial Cancer—Behaviour and Outcomes at a Tertiary Cancer Centre. Indian J Surg Oncol 2019;10(4):662–7.
10. Murali R, Davidson B, Fadare O, Carlson JA, Crum CP, Gilks CB, *et al*. High-grade endometrial carcinomas: morphologic and immunohistochemical features, diagnostic challenges and recommendations. Int J Gynecol Pathol 2019;38(Suppl 1):S40–63.
11. Taskin OÇ, Onder S, Topuz S, Sozen H, Sen F, Ilhan R, *et al*. A selected immunohistochemical panel aids in differential diagnosis and prognostic stratification of subtypes of high-grade endometrial carcinoma: a clinicopathologic and immunohistochemical study at a single institution. Appl Immunohistochem Mol Morphol 2017;25(10):696–702.
12. Paulino E, de Melo AC. Clinical Characteristics and Outcomes of a High-grade Endometrial Cancer Cohort Treated at Instituto Nacional de Câncer, Brazil. Rev Bras Ginecol Obstet 2023;45(7):e401–8.
13. Ercelep O, Gumus M. Comparison of clinicopathologic and survival characteristics of high-grade endometrial cancers; single center experience. Curr Probl Cancer 2019;43(2):160–6.
14. Silva EG, Deavers MT, Bodurka DC, Malpica A. Association of low-grade endometrioid carcinoma of the uterus and ovary with undifferentiated carcinoma: a new type of dedifferentiated carcinoma? Int J Gynecol Pathol 2006;25(1):52–8.
15. Zhang K, Liu Y, Liu X, Du J, Wang Y, Yang J, *et al*. Clinicopathological significance of multiple molecular

features in undifferentiated and dedifferentiated endometrial carcinomas. Pathology 2021;53(2):179–86.
16. Scharl S, Sprötge T, Gerken M, Scharl A, Ortmann O, Kölbl O, *et al*. Guideline concordant therapy improves survival in high-grade endometrial cancer patients. J Cancer Res Clin Oncol 2023;149(8):4761–9.
17. Sohaib SA, Houghton SL, Meroni R, Rockall AG, Blake P, Reznek RH. Recurrent endometrial cancer: patterns of recurrent disease and assessment of prognosis. Clin Radiol 2007;62(1):28–34.
18. Tafe LJ, Garg K, Chew I, Tornos C, Soslow RA. Endometrial and ovarian carcinomas with undifferentiated components: clinically aggressive and frequently underrecognized neoplasms. Mod Pathol 2010;23(6):781–9.
19. Altrabulsi B, Malpica A, Deavers MT, Bodurka DC, Broaddus R, Silva EG. Undifferentiated carcinoma of the endometrium. Am J Surg Pathol 2005;29(10):1316–21.
20. Al-Hussaini M, Lataifeh I, Jaradat I, Abdeen G, Otay L, Badran O, *et al*. Undifferentiated endometrial carcinoma, an immunohistochemical study including PD-L1 testing of a series of cases from a single cancer center. Int J Gynecol Pathol 2018;37(6):564–74.
21. Üreyen I, Ilgin H, Turan T, Taşçi T, Karalök A, Boran N, *et al*. Undifferentiated uterine carcinoma: analysis of eighteen cases. J Obstet Gynaecol 2015;35(4):372–6.s5
22. AlHilli M, Elson P, Rybicki L, Amarnath S, Yang B, Michener CM, *et al*. Undifferentiated endometrial carcinoma: a National Cancer Database analysis of prognostic factors and treatment outcomes. Int J Gynecol Cancer 2019;29(7):1126–33.
23. Gracia M, Yildirim Y, Macuks R, Mancari R, Achimas-Cadariu P, Polterauer S, *et al*. Influence of clinical and surgical factors on uterine carcinosarcoma survival. Cancers (Basel) 2023;15(5):1463.
24. Chiang CY, Huang HJ, Chang WY, Yang LY, Wu RC, Wang CC, *et al*. Adjuvant therapy and prognosis in uterine carcinosarcoma. J Formos Med Assoc 2021;120(11):1977–87.
25. Bosquet JG, Terstriep SA, Cliby WA, Brown-Jones M, Kaur JS, Podratz KC, *et al*. The impact of multi-modal therapy on survival for uterine carcinosarcomas. Gynecol Oncol 2010;116(3):419–23.

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