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Survival Outcomes in Patients with Non-Endometrioid Uterine Malignancies at a Tertiary Cancer Centre in North Kerala, India: A Retrospective Analysis

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Abstract

Background and Objectives: Non-endometrioid uterine carcinomas and sarcomas are aggressive, rare malignancies, with the exception of typically indolent low-grade endometrial stromal sarcoma (LG-ESS). This 10.25-year study reports on the relative frequency, clinical presentation and survival outcomes of these tumours from a major tertiary centre in South India.

Methods: Patients diagnosed with non-endometrioid uterine malignancies between 2011 and 2021 were retrospectively analysed. Clinical features, treatment regimens, recurrence patterns and follow-up data were collected to evaluate survival and prognostic variables. Primary objectives were to assess histological distribution, clinical presentation, overall survival (OS) and relapse-free survival (RFS) across non-endometrioid epithelial and non-epithelial subtypes. Secondary objectives were to evaluate subtype-specific recurrence patterns and survival prognostic factors.

Results: Out of the 925 uterine malignancies evaluated, 255 were uncommon histologies (27.6%), comprising epithelial (n=185 (72.5%): serous carcinoma (SC) n=116, carcinosarcoma (CS) n=45, clear cell carcinoma (CCC) n=20, undifferentiated/squamous cell carcinoma n=4) and non-epithelial subtypes (n=70 (27.5%): leiomyosarcoma (LMS) n=35, LG-ESS n=22 and high-grade endometrial stromal sarcoma (HG-ESS) n=10, pleomorphic sarcoma n=3). The median patient age was 59 years, with 158 patients (62%) presenting at stage I and 230 patients (90.2%) undergoing curative-intent treatment. Statistically significant survival variations were observed across both groups ($p<0.05$).

Among epithelial malignancies (median follow-up 56 months; 95% confidence interval (CI): 47.3-64.7), five-year OS and RFS differed significantly ($p=0.003$ and <0.001, respectively), with the highest five-year OS and RFS noted in SC (65.5% OS, 61.2% RFS) and CCC (65.8% OS,52.5% RFS), compared to markedly inferior outcomes in CS (37.1% OS, 23.6% RFS). Stage-stratified outcomes in SCs revealed a significant difference in five-year OS between early (stage I/II) versus advanced stages (stage III/IV) (70.2% vs 59.4%, $p=0.042$), though five-year RFS differences did not reach statistical significance (66.7% vs 53.8%, $p=0.059$).

Similarly, non-epithelial subtypes (median follow-up 79 months; 95% CI: 54.2-103.8), demonstrated marked survival divergence ($p<0.001$ for OS and RFS); LG-ESS exhibited favourable outcomes (89.5% five-year OS, 80% five-year RFS), whereas HG-ESS (35.7% OS, 25% RFS) and LMS (30.8% OS, 16.3% RFS) demonstrated aggressive behaviour. Recurrence rates peaked in LMS (71.4%).

Multivariable analysis identified curative-intent treatment as an independent predictor of improved OS (hazard ratio (HR): 0.33, 95% CI: 0.12-0.94, $p=0.038$). Time-dependent Cox regression revealed that disease recurrence markedly increased mortality hazard overall (HR: 18.9, 95% CI: 11.7-30.7, $p<0.001$), as well as within epithelial (HR: 16.4, $p<0.001$) and non-epithelial subgroups (HR: 33.7, $p<0.001$), with no significant interaction by histological class (epithelial versus non-epithelial; $p=0.199$)

Interpretation and Conclusions: The relative frequency of epithelial subtypes mirrored global literature, whereas low-grade ESS and LMS occurred more frequently. Uterine SCs showed favourable early-stage survival, while local recurrences in LMS warrant multicentre evaluation.

Categories: Obstetrics/Gynecology, Oncology, Epidemiology/Public Health
Keywords: non-endometrioid uterine malignancies, recurrence, serous uterine carcinoma, survival, uterine sarcomas

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Introduction

Globally, uterine malignancies rank as the 16th most common cancer, with 434,620 new cases in 2024 (2.1% of all new cancers) [1]. In India, corpus uterine malignancies had a 1.8% incidence rate in 2024, with a five-year prevalence of 10.5 per 100,000 [2]. Endometrioid adenocarcinomas comprise more than 90% of uterine cancers, whereas less common carcinomas and uterine sarcomas account for nearly 10% [3].

Non-endometrioid epithelial tumours - including uterine serous carcinoma (SC), clear cell carcinoma (CCC), carcinosarcoma (CS) and undifferentiated/dedifferentiated carcinoma (UDCA) - are aggressive malignancies with high rates of extrauterine spread [4]. Uterine sarcomas encompass stromal and mesenchymal tumours, predominantly leiomyosarcoma (LMS), low-grade endometrial stromal sarcomas (LG-ESSs) and high-grade endometrial stromal sarcomas (HG-ESSs), alongside rarer entities like undifferentiated uterine sarcomas, adenosarcomas, rhabdomyosarcomas and PEComas. Except for LG-ESS, these non-epithelial tumours exhibit aggressive behaviour and early systemic dissemination [5].

Limited clinical data exist regarding these tumours in Asia, particularly South India. Retrospective series on uterine sarcomas have been reported from China [6] and Pakistan [7], whereas Indian literature remains largely restricted to isolated subtype series from Northern India and from Tamil Nadu [8-11].

As a tertiary cancer centre receiving referrals from northern Kerala, Karnataka and Tamil Nadu, our institution manages a diverse clinical cohort from across this region of South India, though institutional referral patterns may limit direct population-level generalisability. Accordingly, this study presents our 10.25-year clinical experience with uncommon uterine malignancies. Through a retrospective analysis, we evaluated the clinical presentations, survival outcomes, recurrence patterns and prognostic factors across both epithelial and non-epithelial subtypes, providing a comprehensive overview of the clinicopathological dynamics of these rare malignancies in our region. Given their distinct histogenesis-epithelial malignancies deriving from transformed endometrial lining and sarcomas from mesenchymal tissue-epithelial and non-epithelial uterine tumours follow disparate patterns of dissemination and response to therapy. We, therefore, analysed these entities separately to provide a precise, subtype-specific evaluation of their clinical outcomes. The primary objectives of the study were to evaluate the histological frequency and clinical presentation and to estimate the overall survival (OS) and relapse-free survival (RFS) across specific non-endometrioid epithelial and non-epithelial histological subtypes. Secondary objectives were to analyse subtype-specific patterns of local versus distant recurrence and to analyse the factors associated with survival outcomes in these patients.

Materials And Methods

Malabar Cancer Centre (Post Graduate Institute of Oncology Science and Research) is a tertiary centre in Kerala, India, providing comprehensive cancer care, including screening, diagnosis, surgery, radiotherapy, chemotherapy and bone marrow transplants. Serving patients from northern Kerala and neighbouring Tamil Nadu and Karnataka, the centre registers over 4,500 new cases annually.

Patients with non-endometrioid uterine malignancies undergo evaluation for treatment fitness and metastatic workup. Non-metastatic cases receive primary surgery, followed by adjuvant systemic therapy and radiotherapy based on histopathological staging. Metastatic cases receive palliative chemotherapy and/or hormonal therapy, while palliative radiotherapy is provided for symptom relief or oncological emergencies like spinal cord compression.

This retrospective cohort study included all histologically confirmed non-endometrioid uterine carcinomas (SC, CCC, CS, UDCA) and uterine sarcomas (LMS, LG-ESS, HG-ESS, pleomorphic sarcoma) treated between January 1, 2011, and March 31, 2021. Endometrioid adenocarcinomas (Grades 1-3), primary cervical or ovarian malignancies extending to the uterus, secondary metastatic lesions to the uterus and records with incomplete primary diagnostic confirmation were excluded from the study. Diagnoses were based on institutional pathology reporting without central pathology re-review. Disease staging was assigned retrospectively using the 2009 FIGO staging system for endometrial carcinomas (including CSs) and the 2009 FIGO staging system for uterine sarcomas. In accordance with World Health Organization (WHO) classification criteria, mixed epithelial carcinomas containing ⩾5% of a high-grade non-endometrioid component (serous or clear cell) were classified under that non-endometrioid histological subtype.

Institutional Ethics Committee (IEC) approval was obtained prior to study initiation (IEC Approval No.: 161/IEC-ERC/13/MCC/25-1-2024). Given the retrospective, non-interventional nature of the study, relying on medical records and minimal-risk secondary data collection, all consecutive eligible patients were included and the requirement for written informed consent-including for structured telephonic follow-up inquiries to ascertain vital and recurrence status-was explicitly waived by the IEC.

Data were collected from medical records, including demographics, diagnosis date, treatment details (surgery type, chemotherapy regimens and adjuvant radiotherapy, including external beam radiotherapy (EBRT) and brachytherapy), follow-up dates and survival status. Disease status and recurrence were primarily established through routine clinical follow-up visits, institutional electronic medical records and

surveillance imaging protocols. For patients who were lost to clinical follow-up or referred to regional centres, disease status and vital status were systematically updated via structured telephonic inquiries. To minimise ascertainment bias and ensure data reliability compared to passive vital status collection, telephonic follow-ups were conducted using a standardised institutional questionnaire. Telephonic ascertainment of recurrence relied on documented secondary clinical endpoints: verified reports of disease-related symptoms or confirmed dates of readmission or initiation of secondary systemic/palliative therapies at external facilities. When exact dates of relapse could not be confirmed pathologically or radiologically via telephone, the date of recurrence was conservatively defined as the date of symptom onset documented by the patient/caregiver or the date of first medical consultation at an external facility for progressive disease.

Survival intervals were recorded in months. The final data cut-off date for survival verification and follow-up data collection was December 31, 2023. OS was calculated from the date of diagnosis to the date of death from any cause or the date of last documented contact/follow-up. For patients treated with curative intent, RFS was calculated from the date of treatment completion to the first clinically, radiologically or histopathologically confirmed local, regional or distant recurrence, or death from any cause. For patients who received upfront palliative treatment without achieving a disease-free baseline, RFS was calculated from the date of diagnosis to the date of documented disease progression or death from any cause. Patients lost to clinical follow-up who could not be contacted via telephonic inquiry were right-censored at the date of their last documented clinical interaction.

Analysis and statistics

Double data entry was performed in EpiData (V3.1) and compared for discrepancies. The finalised database was analysed using EpiData Analysis (V2.2.2.183), SPSS (V22) and R software (V4.3.1). Continuous variables like age were summarised as mean ± SD, median (interquartile range (IQR)) or proportions based on distribution, while categorical variables (comorbidities, BMI, stage, histology, diagnosis mode, imaging, treatments, recurrence patterns and follow-up status) were presented as frequencies and percentages.

OS and RFS were analysed using the Kaplan-Meier method, with comparisons across histological subtypes performed via the log-rank test. Clinically relevant clinicopathological variables and covariates demonstrating a univariate association ($p<0.10$) with survival outcomes were entered into multivariable Cox proportional hazards regression models to identify independent prognostic factors. Candidate predictors included age, comorbidities (hypertension, diabetes mellitus, hypothyroidism and hypercholesterolemia), BMI, histological subtype, International Federation of Gynaecology and Obstetrics (FIGO) stage, curative-intent treatment and disease recurrence. Disease recurrence was modeled as a time-varying covariate to prevent immortal-time bias. Survival estimates were reported as three-year and five-year rates with corresponding 95% confidence intervals (CIs) and numbers of patients at risk (n).

Results

Between January 2011 and March 2021, carcinoma of the endometrium accounted for less than 2% of all newly registered malignancies at our institution. Out of the 925 patients with uterine cancers, 255 (27.6%) had uncommon non-endometrioid epithelial and mesenchymal histologies. The uncommon histologies included epithelial (n=185, 72.5%) SC, CCC, CS and UDCA) and non-epithelial (n=70, 27.5%) LMS, LG-ESS and HG-ESS, and pleomorphic sarcomas). The distribution of patients across different histological subtypes is illustrated in Figure *1*.

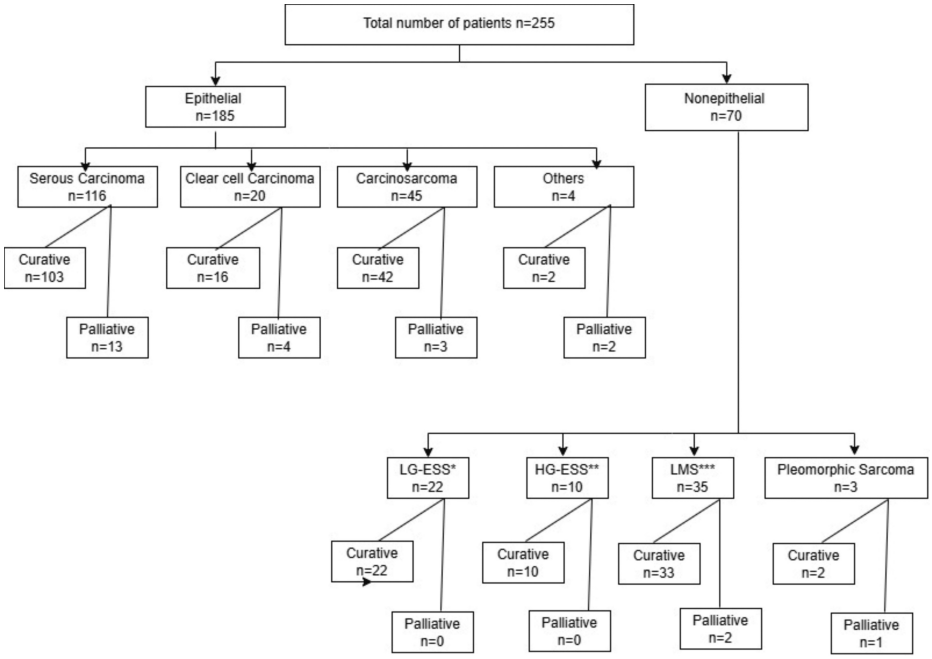


FIGURE 1: Distribution according to histology in patients with non-endometrioid uterine malignancies

LG-ESS: Low-grade endometrial stromal sarcoma; HG-ESS: High-grade endometrial stromal sarcoma; LMS: Leiomyosarcoma

Median age was 59 years (range: 31-87). Common comorbidities included hypertension (n=89, 35%) and diabetes (n=75, 29.4%). 51.6% had a BMI of 18.5-24.9 kg/m^2 (Table *1*).

Demographic Characteristics	Number	%
Age		
25 to 34 years	1	0.4
35 to 44 years	24	9.4
45 to 54 years	69	27.1
55 to 64 years	82	32.2
65 years and older	79	31
Comorbidity		
Hypertension	89	34.9
Diabetes	75	29.4
Hypothyroidism	15	5.9
Hypercholesterolemia	19	7.5
BMI		
Less than 18.5	12	5.3
18.5 -24.9	116	51.6
More than 24.9	97	43.1
Not recorded	30	11.8
Stage at diagnosis		
I	158	62
II	15	5.9
III	54	21.2
IV	27	10.6
Unstaged	1	0.4

TABLE 1: Demographic characteristics of patients with non-endometrioid uterine malignancy registered between 2011 and 2021

Preoperative histological diagnosis was achieved in more than 80% (155/185) of epithelial cases, whereas >78.6% (55/70) of non-epithelial cases were diagnosed post hysterectomy.

Stage I predominated overall (n=158, 62%) (Figures *2A*, *2B*).

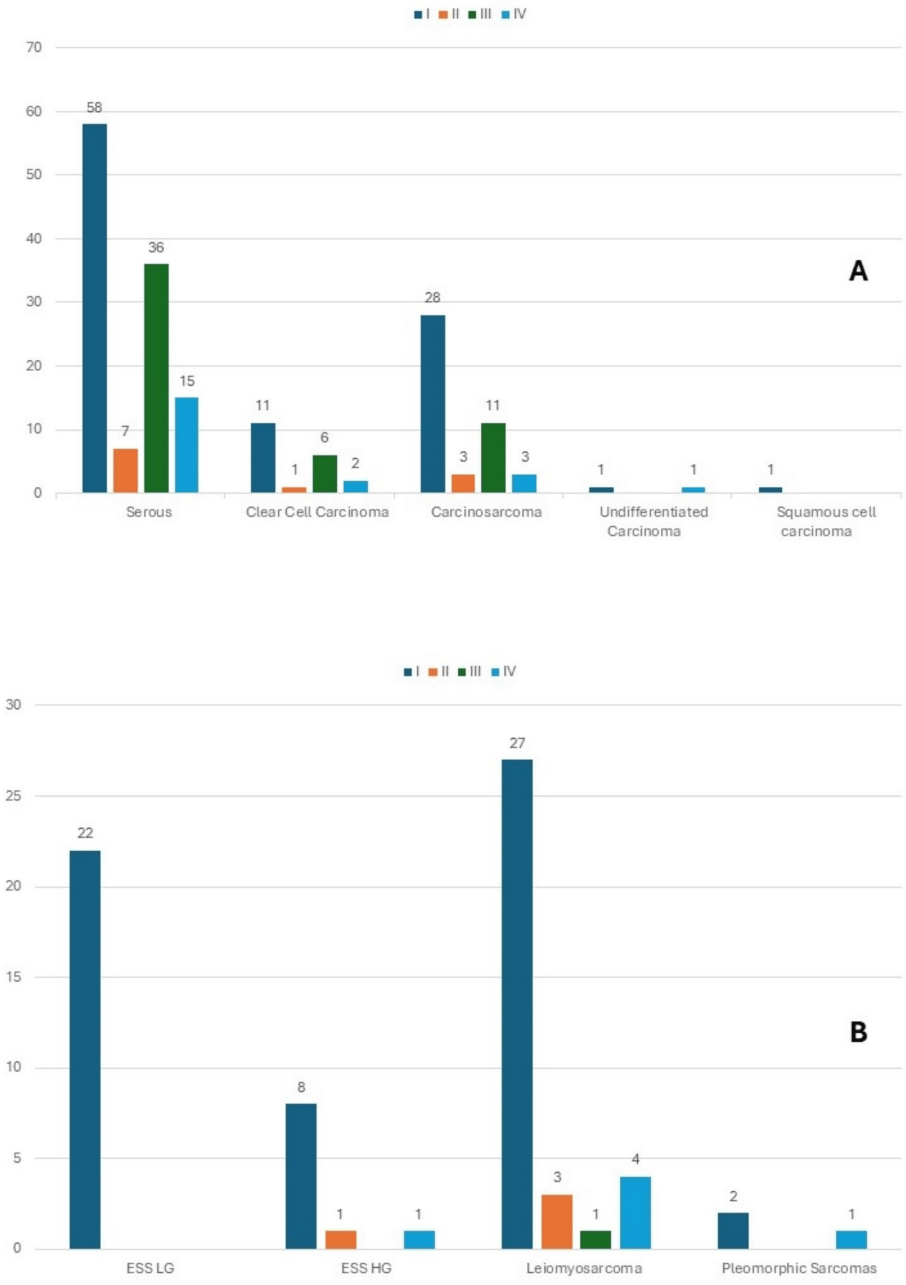


FIGURE 2: Stage-wise distribution of patients with non-endometrioid epithelial (A) and non-epithelial (B) uterine malignancies

Curative-intent treatment was delivered to 229 (89.8%) patients, all undergoing surgery. Adjuvant radiotherapy was administered in 58.9% (109/185) of epithelial and 11.4% (8/70) of non-epithelial malignancies; adjuvant chemotherapy was given in 51% (92/185) of epithelial and 12.8% (9/70) of non-epithelial cases. Subtype-specific characteristics and survival analyses are detailed below. Vital status was successfully verified for 94.5% of the cohort (n=241), while 14 patients (5.5%; eight in the epithelial group and six in the non-epithelial group) were lost to follow-up and censored at the time of their last clinical evaluation. Patients with undifferentiated/squamous cell carcinoma and pleomorphic sarcoma were excluded from further analysis owing to small sample sizes.

Epithelial malignancies (all patients)

SC was the most common subtype (116/185, 62.7%), followed by CS (45/185, 24.3%) and CCC (20/185, 10.8%). Over a median follow-up of 56 months (95% CI: 47.3-64.7), 58 patients (31.4%) relapsed. Overall, the three-year and five-year RFS rates were 57.2% and 51.6% (median RFS 69 months; 95% CI: 38.5-99.5), while

the three-year and five-year OS rates were 65.8% and 58.7% (median OS 94 months; 95% CI: 71.6-116.4). The numbers of patients at risk at three and five years were 84 and 48, respectively.

SC

SC patients presented at a median age of 61.5 years (range: 42-77 years; 93 patients; 80.2%≥55 years); 85% had a normal BMI of 18.5-24.9 kg/m^2. The majority presented with early-stage disease (stages I-II: 65/116,56%; stage III: 36/116, 31%). Pretreatment imaging was available from all patients, with the majority being CT scans (66.4%) or MRI (26.7%). Preoperative endometrial curettage confirmed histology in 99 patients (85.3%). Among 103 (88.8%) patients treated with curative intent (staging laparotomy: total abdominal hysterectomy (TAH) + bilateral salpingo-oophorectomy (BSO) + omentectomy + lymph node dissection), 68 (58.6%)received adjuvant radiotherapy (51 EBRT + brachytherapy; 15 brachytherapy alone) and 53 received adjuvant chemotherapy.

Recurrence occurred in 23.3% (27/116), predominantly at distant sites (liver, lungs and lymph nodes). The three-year and five-year OS rates were 73.1% and 65.5% (median OS 112 months; 95% CI: 65.7-158), while the three-year and five-year RFS rates were 66.2% and 61.2% (median RFS: 112 months; 95% CI: 65-157). The numbers of patients at risk at three and five years were 67 and 36, respectively.

Given that more than half of patients presented with early-stage disease (stages I-II), survival outcomes were compared between early and advanced stages (stages III-IV). For early-stage disease, the three-year and five-year OS rates were 78.8% and 70.2% (median OS 112 months; 95% CI: 61.5-162.5), while the three-year and five-year RFS rates were 71.1% and 66.7%, respectively (median RFS 112 months; 95% CI: 61.5-162.5). Advanced stages demonstrated inferior survival outcomes, the three-year and five-year OS rates were 65.6% and 59.4% (median OS 79 months; 95% CI: 36.8-121.2) and the three-year and five-year RFS rates were 59.6% and 53.8% (median RFS 67 months; 95% CI: 34.1-99.9). The difference in OS between early and advanced stages reached statistical significance (p=0.042), whereas the difference in RFS did not (p=0.0.59).

CCC

CCC patients had a median age of 62 years (range: 48-87years); 55% (11/20) presented with stage I disease. Curative surgery was performed in 16 patients (76.2%); 10 (50%) received adjuvant radiotherapy and nine (45%) received chemotherapy. Six patients (30%) experienced distant relapse (liver and lymph nodes). Both three-year and five-year OS rates were 65.8% (median OS not reached) and three-year and five-year RFS rates were 59.1% and 52.5%, respectively (median RFS not reached). The numbers of patients at risk at three and five years were nine and seven, respectively.

CS

CS patients presented at a median age of 64 years (range: 42-78); 28 patients (62.2%) presented with stage I and 12 patients (26.2%) with stage III disease. Preoperative diagnosis was established in 33 (73.3%) cases and 42 patients (93.3%) underwent curative resection. Adjuvant radiotherapy and chemotherapy were administered to 15 and 10 stage I patients, respectively. Patients with CS exhibited the highest recurrence rate (49%, 22/45; predominantly distant metastases to lymph nodes, lung, liver and bone). The three-year and five-year RFS rates were 32.3% and 23.6% (median RFS 17 months; 95% CI: 9.9-24), while three-year and five-year OS rates were 47.1% and 37.1%, respectively (median OS 31 months; 95% CI: 8.4-53.6). The numbers of patients at risk at three and five years were ten and five, respectively.

Subtype Comparisons

Significant differences in OS (p=0.003) and RFS (p<0.001) were observed across epithelial subtypes: CCC demonstrated superior OS, whereas CS carried the worst RFS (Figure *3*).

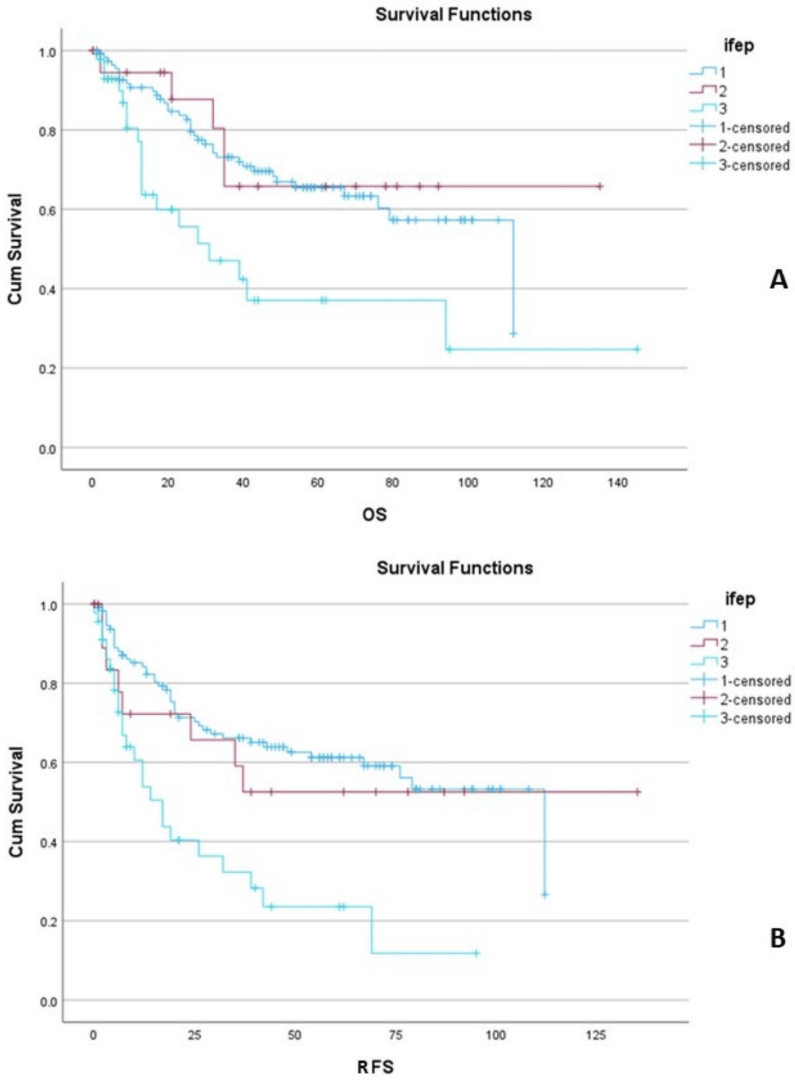


FIGURE 3: Kaplan-Meier survival analysis curve for OS (A) and RFS (B) for subgroups of epithelial malignancies (1: SC, 2: CCC, 3: CS)

OS: Overall survival; RFS: Relapse-free survival; SC: Serous carcinoma; CCC: Clear cell carcinoma; CS: Carcinosarcoma

Non-epithelial malignancies (all cohort)

LMS constituted 50% of non-epithelial cases (35/70), followed by LG-ESS (31.4%, 22/70) and HG-ESS (14.3%,10/70). Over a 79-month median follow-up (95% CI 54.2 to 103.8), 38 patients (54.3%) relapsed. Overall, three-year and five-year OS rates were 55.7% and 51.5% (median OS 119 months), while three-year and five-year RFS rates were 40% and 38% (median RFS 19 months; 95% CI: 5.1-32.9).

LG-ESS

LG-ESS patients had a median age of 45years (range: 36-78); 15 patients (68%) had a normal BMI (18.5-24.9 kg/m^2). Although all patients presented with stage I disease, preoperative diagnosis was achieved in only three (3/22, 13.6%) cases. All 22 patients underwent curative-intent surgery (TAH in all; concurrent BSO in four); two (9%) received adjuvant radiotherapy and none received chemotherapy. Recurrence occurred in five patients (22.7%; two local, five distant, all being pulmonary). RFS rate was 80% at five years and 72.7% at 10 years (median RFS not reached). OS at five years and ten years were 89.5% (median OS not reached). The numbers of patients at risk at five and ten years were fourteen and seven, respectively.

HG-ESS

HG-ESS patients had a median age of 60 years (range: 42-71); eight patients (80%) presented with stage I. Preoperative diagnosis was established in only four (40%) patients. All underwent curative-intent surgery (six TAH + BSO; three concurrent lymph node dissection and omentectomy); two (20%) received chemotherapy and none received radiotherapy. Relapse occurred in six patients (60%; two local, four distant). The three-year and five-year RFS rate were 25% (median RFS 6 months; 95%CI: 0-15). Both the three-year and five-year OS rates were 35.7% (median OS 20 months; 95% CI: 4.8-35.2). The number of patients at risk at three and five years were two.

LMS

LMS patients had a median age of 48 years (range: 31-75). Preoperative biopsy confirmed histology in only 20% (7/35). Curative intent resection was performed in 33 patients (94.3%); stage I disease predominated (27/35, 77.1%). Six patients (17%) received radiotherapy and six (17%) received adjuvant chemotherapy. Relapse occurred in 25 patients (71.4%; nine local, 12 distant and four concurrent), reflecting the highest recurrence rate across all studied subtypes. Recurrences affected 19 out of 27 (70.4%) stage 1 patients, all stage II and III patients. Nodal, pulmonary and hepatic metastasis predominated. The three-year and five-year RFS rate were 20.4% and 16.3%, respectively (median RFS 14 months; 95% CI: 4-24). The three-year and five-year OS rates were 35.2% and 30.8% (median OS 27 months; 95% CI: 21.0-33.0). The numbers of patients at risk at three and five years were nine and five, respectively.

Subtype Comparisons

LG-ESS illustrated significantly superior OS and RFS compared to other subtypes ($p<0.001$), whereas, HG-ESS and LMS demonstrated overlapping, poor survival trajectories (Figure *4*).

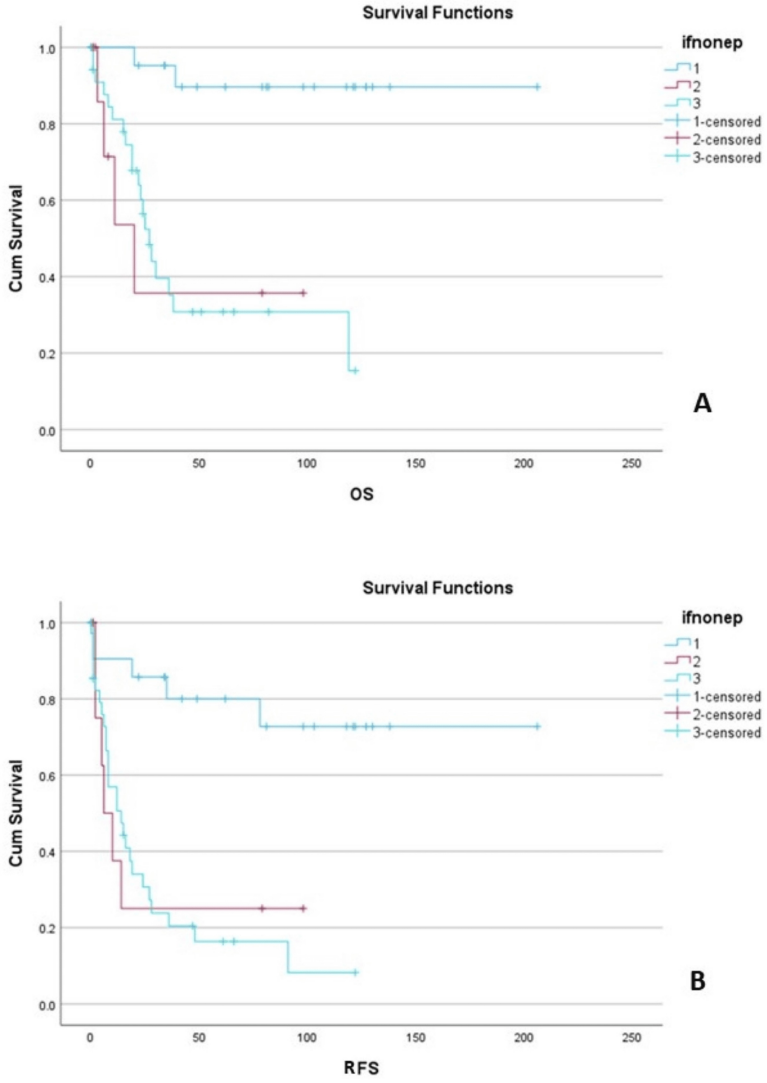


FIGURE 4: Kaplan-Meier survival analysis curve for OS (A) and RFS (B) for subgroups of nonepithelial malignancies (1: LG-ESS; 2: HG-ESS; 3: LMS)

OS: Overall survival; RFS: Relapse-free survival; LG-ESS: Low-grade endometrial stromal sarcoma; HG-ESS: High-grade endometrial stromal sarcoma; LMS: Leiomyosarcoma

Potential prognostic factors - including age, comorbidities, BMI, treatment intent and disease recurrence - were evaluated across the study cohort. On multivariate Cox regression analysis, receiving curative-intent treatment was significantly associated with improved OS (hazard ratio (HR): 0.33, 95% CI: 0.12-0.94, p=0.038). When recurrence was treated as a time-dependent covariate, recurrence was strongly associated with an increased risk of death, with patients experiencing recurrence demonstrating a significantly higher mortality hazard compared with the pre-recurrence period (HR: 18.9, 95% CI: 11.7-30.7, p<0.001). In subgroup analyses, recurrence remained a significant predictor of mortality in both non-epithelial tumours (HR: 33.7, 95% CI: 9.9-114.5, p<0.001) and epithelial tumours (HR: 16.4, 95% CI: 9.5-28.2, p<0.001). The interaction between recurrence and tumour class was not statistically significant (HR: 0.42, 95% CI: 0.11-1.57, p=0.199), suggesting that the effect of recurrence on OS did not differ significantly between epithelial and non-epithelial tumours.

Discussion

Endometrial malignancies are categorised into non-aggressive and aggressive histological types with distinct prognostic profiles. Non-endometrioid uterine malignancies exhibit aggressive clinical behaviour - a distinction reflected in the updated 2023 FIGO endometrial cancer staging system, wherein aggressive

histological subtypes confined to a polyp or the endometrium are classified as Stage IC and those with any myometrial invasion are upstaged to Stage IIC [12]. In early-stage aggressive disease, the estimated five-year OS rate (86.8%) and progression-free survival (PFS) rates (76.4%) are markedly lower than nonaggressive counterparts [13]. In this study, we evaluated the prevalence, clinical presentation, recurrence pattern and survival outcomes of uncommon uterine malignancies, analysing epithelial and non-epithelial subtypes separately due to their distinct biologies.

Among all uterine malignancies treated at our centre, SC accounted for 12.5%, CCC for 2.0% and CS for 4.9% - a distribution aligning with data from the Netherlands Cancer Registry (NCR) and the Surveillance, Epidemiology, and End Results (SEER) database [14,15]. Uterine sarcomas comprised 7.5% of total cases, including LG-ESS 2.3%, HG-ESS 1.0% and LMS 3.8%. Compared to the NCR database and series from China and Pakistan, we observed a higher incidence of LG-ESS and LMS, likely reflecting our centre's role as a regional tertiary referral institute for South India [6,7,14].

SC patients presented at a mean age of 61.5 years (range: 42-77; 93 patients, 80.2%≥55years), consistent with reports by Agarwal et al. (mean age: 61.8 years; >90% aged >50 years) and other South Indian series [8,9]. Classically, SC exhibits high rates of extrauterine disease; the FIGO annual report notes that 46% of patients present with stage II-IV disease [16]. Similar advanced-stage presentations have been documented in other Indian studies [8,9]. Conversely, 65 out of 116 (56%) of our SC cohort presented with early-stage disease (stage I-II). Furthermore, 99 patients (85.3%) achieved preoperative histological confirmation and all patients underwent preoperative staging imaging, highlighting robust regional health awareness and an effective referral network.

In our SC cohort, three-year and five-year OS rates were 73.1% and 65.5% and three-year and five-year RFS rates were 66.2% and 61.2%. Disease recurrence occurred in 23.3% (27/116). These outcomes compare favourably to other Indian series, where reported recurrence rates ranged from 40% to 67% [8,9]. The superior OS and RFS rates in our series likely reflect earlier-stage diagnosis and prompt intervention. Nevertheless, survival deteriorated significantly with advancing stage (five-year OS: 70.2% for stage I-II vs 59.4% for stage III-IV). Notably, Conforti et al. evaluated 10-year outcomes in uterine papillary SC, where >65% presented with stage I-II; despite this early presentation, they observed a lower five-year OS of 41.6%, a disease-free survival of 60.7% and a recurrence rate of 39.0% (46/118) [17].

CCCs are rare, accounting for 2% to 5% of endometrial malignancies, with a median age at presentation of 60-68 years [18]. Although most patients present with early-stage disease, recurrence rates remain high (30%-50%). Findings from our cohort align with the existing literature: the median age at diagnosis was 62 years, the majority presented with early-stage disease and the recurrence rate was 30%. The survival outcomes in our cohort were likewise comparable to published data, with five-year and seven-year OS rates of 65.8% (median OS not reached) and an RFS rate of 52.5%. For comparison, Gupta et al. reported a lower relapse rate of 18.2% alongside a three-year PFS rate of 59.7% and a three-year OS rate of 68.2% [10].

Uterine CS are aggressive tumours characterised by a high propensity for distant metastasis and a poor OS compared to SC and CCC subtypes [19]. Globally, the median age at presentation ranges between 62 and 67 years, with most patients presenting at advanced stages [20]. Patients in our cohort belonged to a similar age demographic; however, a higher proportion presented with early-stage disease. A SEER database population-based analysis reported a five-year survival rate of 39% for uterine CS, while Indian studies reflect an even worse prognosis, with a median survival of under one year [21]. Recurrence rates remain high across published series (30%-70%) - even in early-stage disease [22]. Patients in our study demonstrated a comparable five-year OS rate (37.1%), with a relapse rate of 49% (predominantly distant metastases) and a median RFS of 17 months. The five-year and seven-year RFS rates were 23.6% and 11.8%, respectively. By comparison, an Indian study by Sarkar et al. reported a 3-year PFS rate of 50% regardless of stage [23].

Non-epithelial uterine malignancies, or uterine sarcomas, are rare mesenchymal tumours, accounting for 3% to 6% of all uterine malignancies [24]. LMS represents the most frequent subtype (30%-60%), followed by LG-ESS and HG-ESS [25]. Prognosis varies substantially by tumour histology and grade: HG-ESS exhibits aggressive clinical behaviour, whereas LG-ESS typically demonstrates an indolent course.

In our cohort, uterine sarcomas comprised 7.5% of total corpus malignancies, with LMS representing 50%. In a German single-centre analysis, median age at diagnosis ranged from 48 to 52 years [26]. Khan et al. (Pakistan) reported median ages of 43 years (39.5-52) for LMS, 53.5 years (48-58) for HG-ESS and 42.5 years (37.5-55.5) for LG-ESS, while Wang et al. (China) reported a median age of 48 years (31-81) across subgroups [6,7]. In our study, the median age was 48 years (31-75) for LMS and 45 years (36-78) for LG-ESS. However, HG-ESS patients presented at an older median age of 60 years (42-71), mirroring National Cancer Database findings by Seagle et al. (median age: 59 years; range 51-70) [27]. Uterine sarcomas consistently presented at earlier stages than non-endometrioid epithelial carcinomas globally and in our cohort [19].

LG-ESS tumours carry an excellent long-term prognosis, with five-year OS exceeding 90% [26]. Despite an indolent nature, recurrence rates reach up to 50% after prolonged latency (34-55 months) [28]. Our cohort demonstrated a superior 15-year OS rate of 89.5%, a recurrence rate of 22.7% and a ten-year RFS rate of

72.7%.

In contrast, HG-ESS is characterised by high relapse rates and poor OS. Seagle et al. reported a five-year OS rate of 30%-35% [27], while Huss et al. observed a PFS as short as five months [26]. Asian series report median PFS values between 19 and 52 months and Rai et al. (North India) documented a median OS of 25 months and a median PFS of 8.5 months [6,7,11]. In our series, HG-ESS patients exhibited a similar five-year OS rate of 35.7% with median OS and RFS of 20 months and six months, respectively - reflecting poor outcomes despite 80% of the patients presenting with stage I disease.

Uterine LMS exhibit aggressive behaviour and high recurrence rates even when diagnosed early. Preoperative differentiation between leiomyomas and LMS remains challenging, despite advances in modern imaging modalities [29]. A similar diagnostic challenge was observed in our series, where 80% of patients (28/35) received a definitive diagnosis only after hysterectomy, despite 77.1% (27/35) presenting with stage I disease. In the earlier years of our institutional practice, adjuvant radiotherapy and chemotherapy were administered to a minority of patients; however, these approaches were subsequently phased out in alignment with published meta-analytic evidence demonstrating no OS benefit for adjuvant therapy in stage I-II LMS [30].

Globally, LMS recurrence rates range between 28% and 70%, with a median disease-free interval of 12 to 76 months and a five-year PFS rate between 30% and 50% [6,7]. Our cohort experienced a 71.4% recurrence rate, with a median RFS of 14 months and a five-year RFS rate of 16.3%. Interestingly, 10 of the 13 local recurrences (eight in stage I, one in stage II and one in stage III) occurred in patients who had not received adjuvant local radiotherapy. Although randomised trials have shown that adding local radiotherapy improves local control, this intervention has not translated into an OS benefit [30]. We present this finding as a descriptive institutional pattern that warrants re-evaluation in a prospective, multicentre framework.

Strengths and limitations of the study

Several limitations of this study must be acknowledged. First, the retrospective, single-centre design, which introduces inherent selection and referral biases. Second, the study spans a 10-year period (2011-2021), during which there were evolving changes in WHO histopathological classifications and FIGO staging systems, alongside heterogeneous adjuvant treatment regimens. Third, diagnostic confirmation relied on primary institutional reporting without a central pathology re-review or routine molecular subtyping (e.g., p53, mismatch repair (MMR)/microsatellite instability (MSI) or POLE mutations), which limits contemporary risk stratification. Fourth, modest sample sizes in rare subgroups (e.g., CCC n=20, HG-ESS n=10) constrained statistical power for subgroup-specific multivariable adjustments. Finally, the reliance on structured telephonic ascertainment for out-of-hospital recurrences introduced potential recall and measurement biases compared to objective, in-person clinical surveillance. Additionally, patient attrition, with 5.5% of the cohort (n=14) lost to follow-up despite telephonic tracing, may have introduced censoring bias and led to under-ascertainment of late relapses or mortality events.

Neverthless, this study provides comprehensive long-term data on the relative frequency, clinical presentations and survival outcomes of rare non-endometrioid uterine malignancies. As a tertiary cancer centre receiving referrals from northern Kerala, Karnataka and Tamil Nadu, our institution manages a diverse clinical cohort from across this region of South India. Consequently, our findings offer valuable insights into the epidemiological distribution, clinical characteristics and survival dynamics of these uncommon tumours in our region. Furthermore, because most patients underwent treatment with curative intent, robust data on RFS and OS were successfully captured. Nevertheless, future multi-institutional studies evaluating larger cohorts are necessary to analyse the prognostic significance of specific clinical and histopathological characteristics in detail, which will help refine predictive survival models and tailor individualised treatment strategies.

Conclusions

Non-endometrioid uterine malignancies accounted for 27.0% of all uterine cancers treated at our centre between 2011 and 2021. The incidence of epithelial subtypes was comparable to global literature, whereas LG-ESS and LMS occurred at higher frequencies. The clinical presentations and survival patterns for CCC, CS and non-epithelial subtypes aligned with reported international and regional data. Notably, a substantial proportion of patients with uterine SC in our cohort presented at earlier stages, which was accompanied by relatively favourable RFS and OS outcomes in the context of previously published series. Finally, the high rates of local relapse observed in LMS warrant further prospective evaluation, ideally within a multicentre, collaborative framework.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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