Original Article

Prognostic characteristics, recurrence patterns and survival outcomes of uterine papillary serous carcinoma: a single-centre retrospective cohort study

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Background: Uterine papillary serous carcinoma (UPSC) is a rare subtype of endometrial cancer with aggressive characteristics. The aim of our cohort analysis was to examine and present risk factors for recurrence and mortality.

Methods: The study is a retrospective analysis led from April 2010 and November 2019. Women older than 18 years, with a histopathological diagnosis of serous carcinoma (SC) and suitable for surgery were included in this study. Univariate and multivariate Cox proportional hazards analysis was conducted to assess individual risk factors for both recurrence and mortality. Survival rates were calculated using Kaplan-Meier curves and compared using log-rank tests.

Results: One hundred and eighteen cases of SC were surgically managed. For the entire cohort, 5-year overall survival (OS) was 41.6%, while 5-year disease-free survival (DFS) was 60.7%. Advanced stages had the worst survival and recurrence rate (P=0.001 and 0.01, respectively). Univariate analysis revealed an association with a high risk of mortality for myometrial invasion, cervical, parametrial and lymphovascular space invasion (LVSI) and adnexa involvement, whereas only cervical, lymphovascular and parametrium invasion were associated. However, the multivariate analysis confirmed the cervical invasion as a poor predictor for survival with a hazard ratio of 2.230 (95% confidence interval: 1.252–3.971; P=0.006).

Conclusions: UPSC is an aggressive subtype of endometrial cancer where even early stages tend to recur and deteriorate the prognosis. Cervical involvement was the only risk factor associated with increased mortality, while myometrial invasion and LVSI were not confirmed in the multivariate analysis.

Keywords: Uterine cancer; serous carcinoma (SC); serous uterine carcinoma; endometrial cancer

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Introduction

Molecular classification is the new field that is gaining more interest since the new International Federation of Obstetrics and Gynecology (FIGO) 2023 and the Cancer Genome Atlas research results (1,2). Nowadays, the effect of POLE, p53 and deficiency of mismatch repair system (dMMR) is well known, while the non-specific molecular profile (NSMP) category requires further investigations (3). However, endometrial cancers are still classified by morphological type in low-risk (endometrioid G1 and G2) and high-risk tumours, which include endometrioid G3, clear cell, carcinosarcoma, mixed and uterine papillary serous carcinoma (UPSC) (1).

UPSC is an aggressive subtype of endometrial cancer characterised by high-grade histology and represents roughly 10% of all endometrial cancer (4). Despite being often diagnosed in an early stage, serous carcinoma (SC) carries a high recurrence rate and relatively poor prognosis (5). Furthermore, UPSC is more common among black patients (6).

FIGO 2023 not only embedded molecular classification but also re-wrote the staging according to the histopathological risk profile. Therefore, based on this last change, we believe that histopathological features still have a role in the therapeutic decision-making along with the molecular profile and with this research we investigated histopathological features that lead to worst survival and increased recurrences. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-2025-1689/rc).

Highlight box

Key findings

- Cervical involvement emerged as the sole independent factor associated with increased mortality in our cohort of uterine papillary serous tumours, whereas no clinicopathological variables were significantly associated with an increased risk of recurrence.

What is known and what is new?

- Uterine papillary serous carcinoma exhibits an intrinsically aggressive biological behaviour and is characterised by an unfavourable prognosis, even when diagnosed at an early stage, which represents the stage at presentation for the majority of patients.
- Myometrial invasion, parametrial involvement, and lymphovascular space invasion were not identified as predictors of poor survival or recurrence. This finding reflects the ongoing uncertainty regarding the prognostic value of these pathological features, as the existing literature remains inconsistent. Notably, although more than half of our cohort was diagnosed at an early stage, a comparable proportion experienced disease recurrence, further underscoring the aggressive nature of this histological subtype.

What is the implication, and what should change now?

- The integration of molecular profiling is likely to allow a more accurate stratification and classification of this disease, ultimately with the aim of improving patient prognosis. Given that most available studies are retrospective in nature, this may partly explain the marked heterogeneity of published results. Prospective trials incorporating molecular classification are therefore urgently needed to optimise therapeutic strategies for this malignancy.

Methods

Design

This is a retrospective analysis included all patients across the Thames Valley Cancer Alliance (an involving area of 2.3 million people) treated in Oxford University Hospitals NHS Foundation Trust between April 2010 and November 2019 with post-operative histopathology confirming a diagnosis of UPSC. This research is part of a biggest project that aims to evaluate the histopathological features of each endometrial cancer (7-11).

Population and data collection

The women were initially diagnosed through hysteroscopic biopsy, endometrial curettage or Pipelle endometrial biopsy, then staged with computerised tomography (CT) and/or magnetic resonance imaging (MRI). Subsequently, all participants were discussed in a multi-disciplinary meeting (MDT) and referred from peripheral cancer units (Buckinghamshire Healthcare NHS Trust and Royal Berkshire NHS Foundation Trust) to our tertiary cancer centre (Churchill Hospital Oxford University Hospitals NHS Foundation Trust) for surgical management. Each operation was planned on a case-by-case basis, according to national guidelines at the time and tailored to the patient's health [evaluated according to the American Society of Anaesthesiologist (ASA) score and Eastern

Cooperative Oncology Group (ECOG)] and patients' wishes. Surgical approach was determined by patient co-morbidities, planned operating time, anaesthetic assessment and clinical examination findings such as uterus size and suspected cervical, vaginal and parametrial involvement. Standard surgical treatment included hysterectomy and bilateral salpingo-oophorectomy, while omentectomy, lymphadenectomy or lymph glands sampling was performed according to MDT discussion. At the time of in this data collection, sentinel lymph node was not introduced in the clinical practice.

Women older than 18 years, with a histopathological diagnosis of SC and suitable for surgery were included in this study. Patients with histology other than SC, with inadequate follow-up data and unfit for surgery were excluded.

We recorded patients' demographic data, operation parameters and histopathological outcomes, that were reported according to the FIGO 2009 staging system (12). Complete surgical staging was performed in all participants according to national guidelines at the time. Follow-up was recorded from the date of the surgery until the time data collection was completed for this study in November 2022. Patients who did not require adjuvant therapies were checked according to national guidelines (every 3 months for 2 years, then every 6 months up to the fifth year and afterwards yearly) with imaging (transvaginal ultrasound, CT or MRI according to the clinician) and clinical examination. Postoperatively, we recorded type of adjuvant treatment, date and site of recurrence and death. Adjuvant therapies were established after MDT discussion and involved the administration of chemotherapy (6 cycles of chemotherapy with carboplatin and paclitaxel), external beam radiotherapy (EBRT), brachytherapy or a combination of them mainly after the results of the PORTEC trial (13) that highlighted the benefits of adjuvant chemoradiotherapy versus radiotherapy alone. Disease-free survival (DFS) and overall survival (OS) were measured from the date of surgery until November 2022.

The study was registered as a cancer service evaluation project in accordance with Oxford University Hospitals NHS Foundation Trust requirements (registration number 5832). At the time of the operation, all patients consented to data collection for potential future research purposes. All data was extracted from electronic patient records and retrospectively analysed. Patient-identifiable details were redacted to ensure data anonymity. The design, analysis, interpretation of data, drafting and revisions conform to the Helsinki Declaration and its subsequent amendments, the Committee on Publication Ethics' guidelines and the Reporting of Studies Conducted using Observational Routinely collected Health Data (RECORD) Statement validated by the Enhancing the Quality and Transparency of Health Research Network.

Statistical analysis

We performed statistical analysis using IBM© SPSS Statistics 22.0. Categorical variables were reported as frequency counts (n) and proportions (%). Patients with incomplete or unavailable data were excluded from the survival analysis. We used the mean (standard deviation) and median [interquartile range (IQR)] as a measure of central tendency for parametric and non-parametric variables, respectively.

Given the limited number of events, and in accordance with established recommendations regarding the minimum events-per-variable required to avoid overfitting, we first performed univariate analyses to identify clinically and statistically relevant predictors. Histopathological variables were firstly analyzed in univariate, then those statistically significant were subsequently included in the multivariate analysis, respecting the rule of the 10 events per variable. Multivariate Cox proportional hazards analysis was conducted to assess individual risk factors for both recurrence and mortality. Survival rates were calculated using Kaplan-Meier curves and compared using log-rank tests. Statistical significance was considered for $P<0.05$ based on two-sided testing.

Results

Descriptive analysis

Between April 2010 and November 2019, 863 patients underwent surgery for endometrial cancer at our centre. Out of 863 patients, 118 were diagnosed with SC, which represented 13.67% of the endometrial cancer cohort.

The median age of our cohort was 72 years (IQR, 66–76 years) and the median body mass index (BMI) was 27.3 kg/m^2 (IQR, 22.9–31.6 kg/m^2). Surgical approach was laparoscopic for 82 patients (69.5%) and open laparotomy for 36 patients (30.5%). More than half of our study cohort presented at 2009 FIGO stage I (n=59, 50.0%) and II (n=18, 15.2%) disease, whereas advanced stages involved only 33 (28.0%) and 8 (6.8%) women for stage III and IV,

Table 1 Descriptive data for our SC cohort including stage, demographics and operative details

Variables	FIGO 2009			
	I	II	III	IV
Total number	59 (50.0)	18 (15.2)	33 (28.0)	8 (6.8)
Age (years)	71.9 [6.7]	75.6 [7.8]	69.6 [7.1]	67.5 [6.8]
BMI (kg/m^2)	28.0 [6.2]	24.9 [7.6]	26.7 [4.9]	31.4 [12.3]
Laparotomy	12 (20.3)	6 (33.3)	14 (42.4)	4 (50.0)
Laparoscopy	47 (79.7)	12 (66.7)	19 (57.6)	4 (50.0)
Recurrence	19 (32.2)	10 (55.6)	11 (33.3)	6 (75.0)
Death	18 (30.5)	14 (77.8)	22 (66.7)	2 (25.0)

Data are presented as n (%) or mean [standard deviation]. BMI, body mass index; FIGO, International Federation of Obstetrics and Gynecology; SC, serous carcinoma.

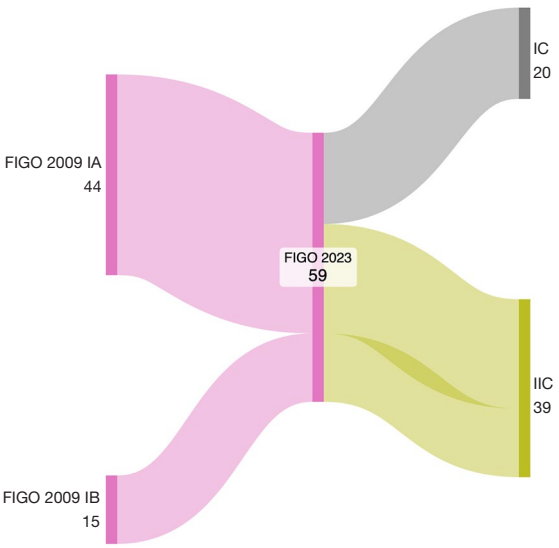

Figure 1 Sankey diagram that illustrates the reallocation of staging from FIGO 2009 to FIGO 2023. FIGO, International Federation of Obstetrics and Gynecology.

respectively. *Table 1* illustrates demographic data of our population broken down for FIGO stages.

Lymph node dissection was performed in 71 patients (60.2%), lymph node sampling was performed in 22 patients (18.6%) and omentectomy was also performed in 93 patients (78.8%). The most common sites of first recurrence included pelvic lymph nodes (12 cases, 26.1%), lungs (12 cases, 26.1%) and para-aortic lymph nodes (10 cases, 21.7%).

Adjuvant therapy was given to 84 out of 110 patients (76.4%) as such data was not available for 8 patients in the study. Single treatment, either chemotherapy, EBRT or brachytherapy alone was given to 59 women (70.2%), while combined therapy to 25 patients (29.8%). In details, 3 patients out of 59 (5.1%) received only EBRT, 27 (45.8%) only brachytherapy and 29 (49.1%) intravenous chemotherapy alone.

Based on our histopathological data, we updated the staging to FIGO 2023 classification. Out of 44 FIGO 2009 stage IA, 20 were upstaged to FIGO 2023 stage IC and 24 to stage IIC. As regards for 15 patients FIGO 2009 stage IB, all of them evolved to stage IIC (*Figure 1*). The situation is different from stage II to IV, because they did not increase their classification.

Survival analysis

For our cohort, 5-year OS was 41.6%, while 5-year DFS was 60.7% (*Figures 2,3*).

Breaking down the survival analysis for FIGO stages, stage II has a median OS of 34.5 months [95% confidence interval (CI): 19–not reached], stage III of 25 (95% CI: 16–not reached) and stage IV of 11.5 (95% CI: 10–not reached), while the median OS for stage I was not reached during the follow-up period (P=0.001). Looking into DFS, the trend is similar, with a median DFS of 43 months for stage II (95% CI: 11–not reached) and of 19.5 for stage IV (95% CI: 7–not reached), whereas stage I and III did not reach the median DFS (P=0.01) (*Figures 4,5*).

Analysis comparing survival and recurrences outcome divided into patients who did not have received adjuvant treatment, single adjuvant treatment or combined adjuvant

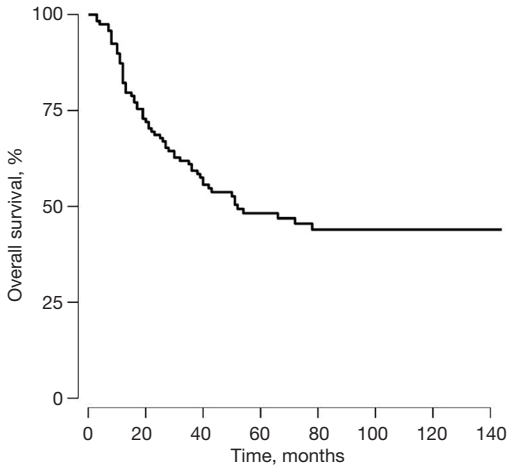

Figure 2 The overall survival of the whole cohort.

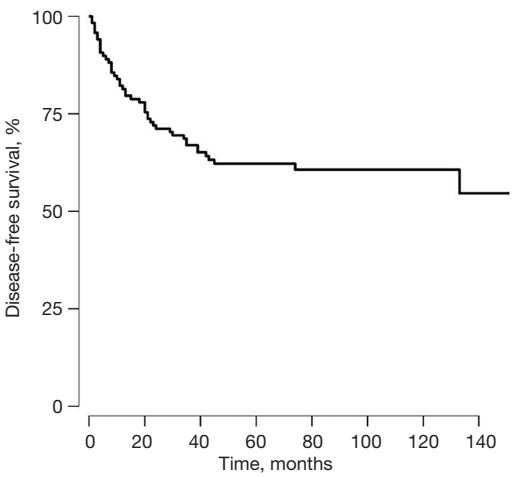

Figure 3 The disease-free survival of the whole cohort.

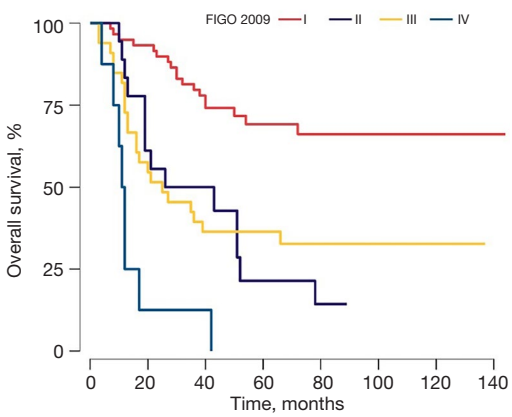

Figure 4 The overall survival split for FIGO 2009. FIGO, International Federation of Obstetrics and Gynecology.

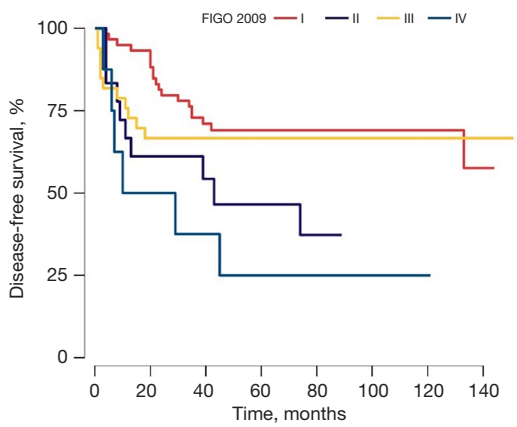

Figure 5 The disease-free survival split for FIGO 2009. FIGO, International Federation of Obstetrics and Gynecology.

treatment did not show a statistical significance for both outcome (P=0.50 and 0.68, respectively; Figures S1,S2).

The univariate analysis included myometrial invasion more than a half, cervical, parametrial and lymphovascular space invasion (LVSI) and adnexa and lymph node involvement. Except for nodes positivity, all other parameters were statistically significant for OS analysis, as shown in *Table 2*, whereas cervical, parametrium invasion and LVSI were the only parameters that had an impact on recurrences, instead.

Our cohort reported a total of 56 deaths (47.5%) and 46 recurrences (38.9%); therefore, we included only the significant variables from univariate analysis in the multivariate, so that rule of the ten events for variable was esteemed. The Cox regression for multivariate analysis (*Table 3*) confirmed only cervical involvement as a risk factor mortality, with a HR of 2.230 (95% CI: 1.252–3.971; P=0.006), refuting myometrial, LVSI, adnexa and parametrium invasion. A divergent result was observed in evaluating the influence of these variables on the likelihood of recurrence, as cervical involvement, LVSI, and parametrial invasion failed to demonstrate an independent effect in the multivariate model. However, parametrium involvement was the only factor close to statistical significance for the risk of recurrence (P=0.06) with a HR of 2.136 (95% CI: 0.957–4.769).

Discussion

UPSC rate in our cohort confirmed that reported in literature, being around 10% of all endometrial cancers (14).

Table 2 Cox regression univariate analysis for mortality and recurrence

Variable	OS		DFS	
	HR (95% CI)	P value	HR (95% CI)	P value
Myometrial invasion >50%	2.039 (1.232–3.375)	0.006	1.471 (0.825–2.625)	0.19
Cervical invasion	2.838 (1.713–4.703)	0.001	1.926 (1.074–3.454)	0.02
Lymphovascular space invasion	2.444 (1.447–4.132)	0.001	1.937 (1.070–3.496)	0.02
Adnexa involvement	2.465 (1.412–4.339)	0.002	1.379 (0.683–2.783)	0.37
Parametrium invasion	2.536 (1.285–5.007)	0.007	2.798 (1.300–6.021)	0.008
Lymph node involvement	1.682 (0.853–3.314)	0.13	1.176 (0.498–2.775)	0.71

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

Table 3 Cox regression multivariate analysis for OS and DFS

Variables	OS		DFS	
	HR (95% CI)	P value	HR (95% CI)	P value
Myometrial invasion >50%	1.420 (0.793–2.542)	0.23	Not significant in univariate	
Cervical invasion	2.230 (1.252–3.971)	0.006	1.488 (0.784–2.825)	0.22
Lymphovascular space invasion	0.754 (0.386–1.472)	0.40	1.474 (0.759–2.865)	0.25
Adnexa involvement	1.577 (0.826–3.012)	0.16	Not significant in univariate	
Parametrium invasion	0.224 (0.571–2.626)	0.60	2.136 (0.957–4.769)	0.06

CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

Furthermore, most of the cases had the disease bordered into the uterus (stage I–II), attesting that UPSC is diagnosed at an early stage (5).

The OS of our population decreased while the stage increased, a fact that find further confirmations from literature, like from the study of McGunigal *et al.* (15), where they reported 5-year OS rates of 74.6% for stage I, 56.7% stage II, and 35.7% for stage III. Their data were from 1998 to 2012, and this reveals that in two decades [1998–2019] therapeutic strategies were not able to improve the survival outcome for these women.

In our cohort, recurrence rate was 38.9% which is in accordance with the literature (16). We found that 41.3% of recurrences occurred in stage I women, while 58.7% in stage II–IV, confirming that higher stage have more risk of relapse (17). Recurrence rates in advanced stage disease are reported between 50–90%, the majority of which is extra-uterine. It is of paramount importance to underline the high rate of recurrence, despite more than half of our population was diagnosed at an early stage and this fact was already reported in literature (18).

Moving to histopathological features for survival and recurrence, surprisingly we found myometrial invasion link to worse prognosis only in univariate analysis, but not in the multivariate. The impact of infiltration of more than half of the myometrium is heterogeneous, ranging from studies that detect muscular involvement as a prognostic factor (19-21), while others which are aligned with our results (16,22,23). LVSI was not associated to a reduction of survival in our research, as opposed to Slomovitz (19) and Solmaz *et al.* (24), but concordant with Wang (16) and Black *et al.* (20). Historically, myometrial invasion, LVSI and positive node were always considered risk factors for type I endometrial cancer, which grouped mainly endometrioid endometrial carcinoma; therefore, all these controversial results might be explained that high risk histologies do not behave like oestrogen-dependent tumour.

Conversely, cervical invasion was the only factor that kept its negative effect on survival even in multivariate analysis, controverting previous works (16,21). This interesting result is confirmed also in other researches focusing only on high grade histologies (9,11) and it was not found for low-

grade tumours (7).

Our upstaging requires cautious interpretation, as it was derived solely from histopathological features and did not incorporate molecular profiling. However Ferrari *et al*. (25) showed overlapping results to ours even considering the molecular classification, hence, given the pronounced rarity of POLE mutations in uterine serous carcinoma (26), we believe that the overall upstaging from FIGO 2009 stage I to FIGO 2023 would likely not have differed substantially, also taking in to account the molecular profile.

Despite better clinical outcome for patients who received adjuvant treatment, our survival analysis did not show a statistical significance. However, we believe that this is due to the retrospective design of our study and the bias related to it, since these results are completely opposite to what literature shows (13,27,28).

UPSC exhibits an aggressive behaviour regardless of myometrial invasion and LVSI (19,29). This is exemplified by the finding that, despite over half of the cohort presenting with early-stage disease, nearly half of all patients subsequently manifested disease recurrence. It is also notorious for occult extra-uterine involvement, even when stage IA disease is expected (12,19,30,31). To add to the complexity, there are already variabilities in the histopathological definitions of LVSI and the new guidelines have been critiqued for an ongoing lack of reproducibility in defining LVSI (32). This highlights the challenges of applying rigid staging criteria (such as LVSI and myometrial invasion) to an inherently aggressive, occult disease. These histopathological markers may not reflect a true risk of recurrence or survival, which would be in favour of the FIGO 2023 updates.

The retrospective design and the lack of the molecular profile and distinguishing patients for ethnicity are the main stumbling block of our study, since the research around endometrial cancer is moving towards molecular classification. However, all the women were treated in a tertiary centre by expert gynaecologist oncologist surgeons, therefore this provides consistency to the surgical treatment. Moreover, every adjuvant treatment, although administrated in different hospitals belonging to the same Trust, were decided within the same MDT giving consistency to every decision.

Conclusions

UPSC is an aggressive subtype of endometrial cancer where even early stages tend to recur and deteriorate the prognosis. From our cohort only cervical involvement resulted risk factor for mortality and advanced stages had worst outcomes. We did not find myometrial invasion and LVSI to be an independent risk factor like happen on older studies. Our findings increase the heterogeneity among the literature, nevertheless, this is a confirmation that prospective multicentric trials are necessary to better define this disease, also in the light of the new molecular classification.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-2025-1689/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037tcr-2025-1689/dss

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. This study was approved by the clinical governance of the Oxford University Hospitals NHS Foundation Trust (registration number 5832) and informed consent was obtained from all individual participants.

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