Uterine carcinosarcoma vs endometrial serous and clear cell carcinoma: A systematic review and meta-analysis of survival

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Abstract
Background: It is unclear whether uterine carcinosarcoma (UCS) is more aggressive than endometrial serous carcinoma (SC) and clear cell carcinoma (CCC).

Objectives: To compare the prognosis of UCS to that of endometrial SC and CCC, through a systematic review and meta-analysis.

Methods: Four electronic databases were searched from January 2000 to October 2020. All studies assessing hazard ratio (HR) for death in UCS vs SC and/or CCC. HRs for death with 95% confidence interval were extracted and pooled by using a random-effect model. A significant P-value <0.05 was adopted.

Results: Six studies with 11,029 patients (4995 with UCS, 4634 with SC, 1346 with CCC and 54 with either SC or CCC) were included. UCS showed a significantly worse prognosis than SC/CCC both overall (HR = 1.51; P = 0.008) and at early stage (HR = 1.58; P < 0.001). Similar results were found for UCS vs SC (HR = 1.53; P < 0.001) and UCS vs CCC (HR = 1.60; P < 0.001).

Conclusions: Compared to SC and CCC, UCS has a significantly worse prognosis, with a 1.5–1.6-fold increased risk of death. This might justify a more aggressive treatment for UCS compared to SC and CCC. Further studies are necessary to define the prognostic impact of different molecular subgroups.

Keywords
carcinosarcoma, endometrial neoplasms, neoplasm grading, neoplasm staging, prognosis
INTRODUCTION

Endometrial carcinoma is the most common gynecological malignancy in developed countries.\textsuperscript{1-3} The Bokhman classification recognized two types of endometrial carcinoma: type I, which is estrogen-dependent and generally has a favorable prognosis, and type II, estrogen-independent and with a poorer prognosis. Type I carcinomas are mainly constituted by endometrioid histotype, while type II carcinomas mainly include serous carcinoma (SC) and clear cell carcinoma (CCC).\textsuperscript{4} Although such classification is now considered simplistic, the distinction into endometrioid and non-endometrioid is still crucial in terms of patient management.\textsuperscript{4-6} In fact, SC and CCC are considered “high grade” by definition, and both the ESGO and the NCCN guidelines recommend a more aggressive treatment for these histotypes compared to G3 endometrioid carcinomas.\textsuperscript{2,5,6}

In addition to SC and CCC, two further histotypes have more recently been included in the classification of endometrial carcinoma: uterine carcinosarcoma (UCS) and undifferentiated/dedifferentiated carcinoma (UDC-DDC).\textsuperscript{2,7,8}

UCS, also called malignant mixed Müllerian tumor, is a biphasic epithelial-stromal neoplasm characterized by a carcinomatous component and a sarcomatous component.\textsuperscript{7} The classification of UCS has long since been debated. Grouped among the “mixed Müllerian tumors” in the former (2014) WHO classification,\textsuperscript{9} UCS has previously been lumped together with uterine sarcomas in terms of patient management.\textsuperscript{10} To date, UCS is biologically considered as an endometrial carcinoma which secondarily exhibits a mesenchymal differentiation.\textsuperscript{2,7} Based on its aggressive behavior, UCS is now lumped together with SC and CCC for management purpose in both the ESGO and the NCCN guidelines.\textsuperscript{5,6}

UDC-DDC is an uncommon entity which has only been recognized in the last 10 years; it shows some similarities with UCS, such as the presence of high-grade dyscohesive cells which lacks epithelial differentiation, making the differential diagnosis difficult in some cases.\textsuperscript{2,8} As UCS, UDC-DDC is placed among the “high-risk histologies” of endometrial carcinoma in the guidelines.\textsuperscript{5,6}

However, there is evidence that UCS and UDC-DDC may be even more aggressive than SC and CCC.\textsuperscript{11-13} On this account, the NCCN guidelines recommend adjuvant treatment for UCS and UDC-DDC even when limited to the endometrium with no residual tumor on the final hysterectomy specimen.\textsuperscript{6} By contrast, there are some studies that suggested a similar prognosis between these two histotypes and SC/CCC.\textsuperscript{14-16}

Based on these considerations, the objective of this study was to assess whether UCS is consistently more aggressive than SC or CCC, through a systematic review and meta-analysis. UDC-DDC was not considered because there are too few studies assessing its prognosis in comparison to other histotypes. Our aim was to determine if a more aggressive management is justified in UCS.
2.5 Data analysis

HRs with 95% CI were pooled by using a random effect model, based on the assumption that results may vary based on factors such as geographical setting. Results were reported graphically on forest plots with 95% confidence interval (CI). Statistical heterogeneity among studies was quantified by using Higgins’ inconsistency index ($I^2$), as previously described. The risk of bias across studies was assessed through a funnel plot of standard error by logHR; this allowed us to assess whether smaller and less accurate studies might have an excessive impact on the results. Data analysis was performed by using Comprehensive Meta-Analysis (Biostat).

3 RESULTS

3.1 Study characteristics

Six studies with 11029 patients (4995 with UCS, 4634 with SC, 1346 with CCC and 54 with either SC or CCC) were included. The process of study selection is reported in Figure 1. Three studies selected all eligible patients independently of FIGO stage, while the other three studies only selected early-stage cases (stage I–II). One study included UCS and SC, while all the remaining studies included UCS, SC and CCC. Two studies used UCS as reference of survival analysis, allowing to extract HR for both UCS vs SC and UCS vs CCC, among the other studies, two used SC as reference, and one used CCC and one used SC and CCC lumped together (Table 1).

3.2 Risk of bias assessment

For the "patient selection" and the "reference standard" domains all studies were considered at low risk of bias since they exhaustively reported inclusion criteria and period of recruitment and performed multivariate Cox regression survival analysis.

For the "index test" domain, two studies reported that histological slides were reviewed and were considered at low risk, while the remaining studies were considered at unclear risk.

For the "flow and timing" domain two studies were considered at unclear risk since they did not report the follow-up duration, while the remaining studies were considered at low risk.

TABLE 1 Characteristics of the included studies

| Study     | Country | Database                                      | Criterion                  | Period of enrollment | Sample size | Reference | Mean follow-up (range) |
|-----------|---------|-----------------------------------------------|---------------------------|----------------------|-------------|-----------|------------------------|
| Amant 2005 | Belgium | Katholieke Universiteit Leuven St. Maarten Hospital, Duffel Ziekenhuis Oost Limburg, Genk | All stages                | 1990–2004            | 33 54 54    | CC + SC  | 28 (16–13) m            |
| Felix 2011 | USA     | Magee-Women's Hospital                        | All stages                | 1996–2008            | 81 147 73   | UCS      | Not reported            |
| Desai 2014 | USA     | Memorial Sloan Kettering Cancer Center        | Stage I-II                | 2000–2011            | 112 60 0  | SC  | 48 (3–139) m            |
| Lakhman 2015 | USA   | Memorial Sloan Kettering Cancer Center        | All stages                | 1998–2011            | 116 50 27  | UCS      | 38 (1–168) m            |
| Shinde 2018 | USA     | NCDB                                          | Stage I                   | 2004–2015            | 2701 1764 1246 | CC  | 40 m                   |
| Venigalla 2018 | USA   | NCDB                                          | Stage I                   | 2010–2013            | 1952 4386 912 | SC  | Not reported            |
The results of the risk of bias assessment are reported in Figure 2.

3.3 | Meta-analysis

Based on the available data from the primary studies, we consulted to define the following analyses: UCS vs SC/CCC (any stage); UCS vs SC/CCC (early-stage only); UCS vs SC; UCS vs CCC.

UCS showed a significantly increased hazard of death compared to SC/CCC independently of FIGO stage (HR = 1.51, 95% CI 1.11–2.05; P = 0.008); statistical heterogeneity among studies was low (I² = 29.09%) (Figure 3).

Considering only patients at early stage, UCS still showed a significantly increased hazard of death compared to SC/CCC (HR = 1.58, 95% CI 1.46–1.72; P < 0.001), with null statistical heterogeneity among studies (I² = 0%) (Figure 3).

The funnel plot showed no significant risk of publication bias (Figure 5).

4 | DISCUSSION

This study showed that UCS has a significantly increased hazard of death (1.5–1.6 fold) compared to both SC and CCC, independently of FIGO stage.

Histopathological features, such as histotype, grade and lymphovascular space invasion (LVI), are of paramount importance in the prognostic stratification of endometrial carcinoma. In fact, the current ESGO/ESTRO/ESP system identifies five risk categories to drive the patient management: low risk, intermediate risk, high-intermediate risk, high risk, advanced/metastatic. In such system, UCS is lumped together non-endometrioid carcinomas; this means that UCS is considered at intermediate risk when limited to the endometrium, at high-risk in the case of FIGO stage I-II and III-IVA with no residual disease, and advanced/metastatic in the case of FIGO stage III-IVA with residual disease or IVB.

In recent years, The Cancer Genome Atlas (TCGA) and subsequent studies showed that endometrial carcinoma can be subdivided into four molecular prognostic subgroups, i.e. POLE-mutated (POLEmut, good prognosis), microsatellite-instability/mismatch-repair deficient (MSI/MMRd; intermediate prognosis), copy-number-low/no specific molecular profile (CNL/NSMP; good-to-intermediate prognosis) and copy-number-high/p53-abnormal (CNH/p53abn; poor prognosis). Such classification has been integrated in the ESGO/ESTRO/ESP system; in such scenario, the subset of UCSs (and of other histotypes) that show a POLEmut signature is considered at low-risk up to FIGO stage II.

Despite showing an outstanding prognostic value, the TCGA might be affected by further relevant histopathological factors such as tumor budding or microcystic, elongated and fragmented (MELF) invasion pattern; this is particularly evident for endometrioid carcinoma, which is highly heterogeneous in terms of clinicopathological features. Moreover, the prognostic significance of each molecular subgroup might be heavily affected by tumor histotype. For instance, in a large series of high-risk endometrial carcinoma (which included endometrioid carcinomas with unfavorable prognostic factors, SC and CCC), the prognosis of the CNL/NSMP group appeared as poor as that of the CNH/p53abn group, while the POLEmut and MSI/MMRd groups showed a similar good prognosis. Instead, the MSI/MMRd group seems not to have prognostic value in UDC-DDC. Therefore, data regarding the TCGA groups need to be integrated with histopathological prognostic factors rather than replace them. In this scenario, defining the prognostic value of highly aggressive histotypes such as UCS and UDC-DDC is warranted.
**FIGURE 3** Meta-analysis of hazard ratio for uterine carcinosarcoma (UCS) vs serous carcinoma (SC) and/or clear cell carcinoma (CCC) in patients at any FIGO stage (I-IV) and early FIGO stage (I-II). The study by Venigalla et al. included two different cohorts (1 and 2).

| Model | Subgroup | Study name | Hazard ratio | Lower limit | Upper limit | P-value |
|-------|----------|------------|--------------|-------------|-------------|---------|
| any stage | Amanat | 3.10 | 1.46 | 6.60 | 0.003 |
| | Felix (SC) | 1.49 | 0.92 | 2.42 | 0.105 |
| | Felix (CCC) | 1.56 | 0.90 | 2.72 | 0.114 |
| | Lakhman (SC) | 1.06 | 0.67 | 1.70 | 0.794 |
| | Lakhman (CCC) | 1.449 | 0.70 | 3.02 | 0.322 |
| Random | | 1.51 | 1.11 | 2.05 | 0.008 |

**FIGURE 4** Meta-analysis of hazard ratio for uterine carcinosarcoma (UCS) vs serous carcinoma (SC) and UCS vs clear cell carcinoma (CCC). The study by Venigalla et al. included two different cohorts (1 and 2).

| Model | Subgroup | Study name | Hazard ratio | Lower limit | Upper limit | P-value |
|-------|----------|------------|--------------|-------------|-------------|---------|
| CCC | Felix | 1.56 | 0.90 | 2.72 | 0.114 |
| | Lakhman | 1.45 | 0.67 | 3.02 | 0.322 |
| | Shinde | 1.61 | 1.38 | 1.88 | 0.000 |
| Random | | 1.60 | 1.38 | 1.85 | 0.000 |

| Model | Subgroup | Study name | Hazard ratio | Lower limit | Upper limit | P-value |
|-------|----------|------------|--------------|-------------|-------------|---------|
| SC | Felix | 1.49 | 0.92 | 2.42 | 0.105 |
| | Lakhman | 1.06 | 0.67 | 1.70 | 0.794 |
| | Desai | 2.40 | 1.20 | 4.80 | 0.013 |
| | Venigalla (1) | 1.47 | 1.25 | 1.72 | 0.000 |
| | Venigalla (2) | 1.62 | 1.44 | 1.83 | 0.000 |
| Random | | 1.53 | 1.36 | 1.73 | 0.000 |

**FIGURE 5** Funnel plot of standard error by log hazard ratio.
We found that UCS showed a significantly worse prognosis than SC and CCC. Considering all patients independently of FIGO stage, UCS showed a 1.51-fold increased hazard of death compared to SC/CCC. We also performed a subgroup analysis to compare the hazard of death in UCS to that of SC and CCC separately; we found very similar results (HR = 1.534 for SC and 1.600 for CCC). On the one hand, these results support that SC and CCC have a similar prognosis and thus should be included in the same risk category; consistently, our previous study showed that CCCs of the CNL/NSMP and CNH/p53abn groups (which represent the vast majority of CCCs) had a prognosis similar to that of SC. On the other hand, UCS appears at significantly higher risk compared to the classical type II endometrial carcinomas, in agreement with our previous study. Such a result was also confirmed on the subset of patients with early-stage disease (HR = 1.58). The latter finding is probably the most important one in terms of treatment. In fact, the management of patients with early-stage disease may vary from follow-up alone to several types of adjuvant treatment, including vaginal brachytherapy, external beam radiotherapy (EBRT) or systemic therapy. Our results might support a more aggressive treatment for UCS compared to SC and CCC; this might be applied in different clinical scenarios. For tumors limited to the endometrium and completely removed at diagnostic biopsy/curettage, adjuvant treatment might be recommended for UCS but not for SC/CCC (as suggested by the NCCN guidelines). For tumors limited to the endometrium and still present on the hysterectomy specimen, EBRT rather than brachytherapy might be preferable for UCS. For myoinvasive tumors limited to the uterus, the combination of EBRT and chemotherapy currently appears as the most effective approach for CNH/p53abn carcinomas (which include all SCs, about half CCCs and most USCs); therefore, it is difficult to hypothesize a differential treatment for these tumors. A difference could be made between UCS and CCC of the CNL/NSMP group, since published data suggest that they have different aggressiveness, however, data regarding the effectiveness of chemotherapy, EBRT or both in this molecular group are scarce. Regarding the MSI/MMRd cases, a reduced sensitivity to chemotherapy has been reported, probably due to the progressive accumulation of mutations; in CCC, the MSI/MMRd signature appears associated with improved prognosis, while this is still not confirmed in UCS.

All of these hypotheses need to be tested in prospective studies. It is unlikely that the aggressiveness of treatment may be modulated in advanced stages, where the prognosis is expected to be poor regardless of the histotype. In advanced carcinomas, the difference in the systemic therapy might rather be based on molecular features on the tumor. For instance, the subset of UCS which show microsatellite instability might benefit from immunotherapy.

Remarkably, the NCCN guidelines propose the same approach for both UCS and UDC-DDC, as discussed above. Since UDC-DDC has only recently been recognized, there is much less evidence regarding its prognosis. If large series demonstrate a similar prognosis between UCS and UDC-DDC, these two entities might be included in a separate risk category. In renal cell carcinoma, the presence of giant cells, sarcomatoid and/or rhabdoid differentiation warrants a G4 grading. We can hypothesize that such a grading might also be fit for endometrial carcinoma, with UCS and UDC-DDC being classified as G4 carcinomas. In fact, a sarcomatoid differentiation is by definition present in UCS and may also be observed in UDC-DDC; both histotypes show evidence of epithelial-to-mesenchymal transition, with high-grade dyscohesive cells that distinguish them from the other histotypes of endometrial carcinoma, and both may exhibit rhabdoid and/or giant cells. Further studies are necessary in this field.

4.1 | Strengths and limitations

To the best of our knowledge, this is the first systematic review and meta-analysis comparing the prognosis of UCS with those of SC and CCC. We included a very large cohorts of patients, including data from national databases. Our results were mainly based on multivariable analyses from the primary studies, which allowed us to limit the effect of confounding factors. The results were consistent when only early-stage patients were assessed and when SC and CCC were considered separately. The low-to-null statistical heterogeneity found in all analyses further strengthens our findings.

A limitation of our results may lie in the fact that all but one study were from the USA; therefore, we cannot be sure that such results would be the same in other geographical areas. Another limitation may lie in the fact that most studies did not include an expert review of histological slides, as discussed in the risk of bias assessment section. In particular, the differential diagnosis between CCC and SC may sometimes be difficult due to morphologic overlap. Furthermore, UDC-DDC has only recently been described, and older cases might have been misdiagnosed as UCS, as reported in the literature; although UDC-DDC is uncommon, we cannot exclude that it might have had an impact on the results. However, it should be noted that histological review appears not feasible in studies that assessed data from a national database. Finally, our meta-analysis does not take into account the molecular background of the endometrial carcinoma cases assessed. Nonetheless, SC appears a robust reference for survival analysis, since virtually all SC are TP53-mutated and fall into the CNH/p53abn prognostic subgroup. UCS is also quite homogeneous, since it shows a CNH/p53abn signature in about 80% of cases. On the other hand, CCC appears molecularly heterogeneous, although less than endometrioid carcinoma. Further studies in this field should involve different geographic areas, review histological slides to confirm all diagnoses and consider the molecular signature of each case.

5 | CONCLUSION

UCS consistently showed a prognosis worse than SC and CCC, with a 1.5–1.6 times higher hazard of death. The same results were found in the subset of patients at early stage and also when SC and CCC...
were considered separately. This supports that, while it is appropri-
ate to consider SC and CCC together for management purpose, UCS
might need a more aggressive adjuvant treatment. The possibility of
introducing a G4 grade for UCS (and possibly for UDC-DDC) might
be considered. Further studies in this field are warranted to assess
the prognosis and the optimal management of these histotypes stratified according to the molecular signature.

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CONFLICT OF INTEREST
The authors report no conflict of interest.

AUTHOR CONTRIBUTIONS
AT and AR: conception, protocol, data extraction, risk of bias as-
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sion. FZ and LI: conception, protocol, manuscript revision, results
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DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no new data were cre-
ated or analyzed in this study.

REFERENCES
1. Siegel RL, Miller KD, Jemal A, Jemal A. Cancer statistics. CA Cancer
    J Clin. 2015;65(1):5-29.
2. WHO Classification of Tumours Editorial Board. Female genital tu-
mours. Vol. 4. 5th ed. WHO classification of tumours series. IARC
    Publications; 2020.
3. Raffone A, Travaglino A, Mascolo M, et al. TCGA molecular groups of
    endometrial cancer: pooled data about prognosis. Gynecol Oncol.
    2019;155(2):374-383.
4. Suarez AA, Felix AS, Cohn DE. Bokhman Redux: endometrial cancer
    “types” in the 21st century. Gynecol Oncol. 2017;144(2):243-249.
5. Concini N, Matias-Guiu X, Vergeote I, et al. ESGO/ESTRO/ESP guide-
    lines for the management of patients with endometrial carcinoma.
    Int J Gynecol Cancer. 2021;31(1):12-39.
6. Abu-Rustum NR, Yashar CM, Bradley K, et al. NCCN Clinical Practice
    Guidelines in Oncology (NCCN Guidelines®) – Uterine neoplasms.
    Version 1.2021 - October 20, 2020.
7. Travaglino A, Raffone A, Gencarelli A, et al. TCGA classification of
    endometrial cancer: the place of carcinosarcoma. Pathol Oncol Res.
    2020;26(4):2067-2073.
8. Travaglino A, Raffone A, Mascolo M, et al. TCGA molecular sub-
groups in endometrial undifferentiated/dedifferentiated carci-
нома. Pathol Oncol Res. 2020;26(3):1411-1416.
9. Kurman R, Carcangi M, Herrington C, Young R, eds. World Health
    Organization classification of tumors of female reproductive organs,
4th edn. IARC Press; 2014.
10. Nam JH, Park JY. Update on treatment of uterine sarcoma. Curr
    Obstet Gynecol. 2010;22(1):36-42.
11. Taskin OC, Onder S, Topuz S, et al. A selected immunohistochemi-
cal panel aids in differential diagnosis and prognostic stratification
    of subtypes of high-grade endometrial carcinoma: a clinicopatho-
    logic and immunohistochemical study at a single institution. Appl
    Immunohistochem Mol Morphol. 2017;25(10):696-702.
12. Zhang C, Hu W, Jia N, et al. Uterine carcinosarcoma and high-risk
    endometrial carcinomas: a clinicopathological comparison. Int J
    Gynecol Cancer. 2015;25(4):629-636.
13. Pruksaritanond N, Chantape W. Comparative survival outcomes of
    uterine papillary serous carcinoma, clear cell carcinoma, grade 3
    endometrioid adenocarcinoma, and carcinosarcoma of endome-
   trial cancer in Rajavithi Hospital. J Med Assoc Thail. 2016;99(Suppl
    2):S75-S83.
14. Felix AS, Stone RA, Bowser R, et al. Comparison of survival out-
comes between patients with malignant mixed Mullerian tumors and
    high-grade endometrioid, clear cell, and papillary serous endom-
    etrial cancers. Int J Gynecol Cancer. 2011;21(5):877-884.
15. Ganju RG, Tawfik O, Brown L, et al. Undifferentiated endometrial carci-
nomas: clinicopathologic characteristics and treatment outcomes.
    Int J Gynecol Cancer. 2018;28(7):1271-1277.
16. Lakhman Y, Yakar D, Goldman DA, et al. Preoperative CT-based
    nomogram for predicting overall survival in women with non-
    endometrioid carcinomas of the uterine corpus. Abdom Imaging.
    2015;40(6):1761-1768.
17. Travaglino A, Raffone A, Stradella C, et al. Impact of endometrial carci-
noma histotype on the prognostic value of the TCGA molecular
    subgroups. Arch Gynecol Obstet. 2020;301(6):1355-1363.
18. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for
    systematic review and meta-analysis protocols (PRISMA-P) 2015
    statement. Syst Rev. 2015;4:1.
19. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised
    tool for the quality assessment of diagnostic accuracy studies. Ann
    Intern Med. 2011;155(8):529-536.
20. Amant F, Cadron I, Fusio L, et al. Endometrial carcinosarcomas have a
different prognosis and pattern of spread compared to high-risk
    epithelial endometrial cancer. Gynecol Oncol. 2005;98(2):274-280.
21. Desai NB, Kollmeier MA, Makker V, Levine DA, Abu-Rustum
    NR, Alektiar KM. Comparison of outcomes in early stage uter-
ine carcinosarcoma and uterine serous carcinoma. Gynecol Oncol.
    2014;135(1):49-53.
22. Shinde A, Li R, Amini A, et al. Improved survival with adjuvant
    brachytherapy in stage IA endometrial cancer of unfavorable his-
    tology. Gynecol Oncol. 2018;151(1):82-90.
23. Venigalla S, Chowdry AK, Shalowitz DI. Survival implications of
    staging lymphadenectomy for non-endometrioid endometrial car-
    cinomas. Gynecol Oncol. 2018;149(3):531-538.
24. Stelloo E, Nout RA, Osse EM, et al. Improved risk assessment by
    integrating molecular and clinicopathological factors in early-stage
    endometrial cancer-combined analysis of the PORTEC cohorts. Clin
    Cancer Res. 2016;22(16):4215-4224.
25. Rau TT, Bettscchen E, Büchi C, et al. Prognostic impact of tumor
    budding in endometrial carcinoma within distinct molecular sub-
groups. Mod Pathol. 2021;34(1):222-232.
26. He D, Wang H, Dong Y, et al. POLE mutation combined with micro-
cystic, elongated and fragmented (MEFL) pattern invasion in endometrial carcinomas might be associated with poor survival in
    Chinese women. Gynecol Oncol. 2020;159(1):36-42.
27. Zannoni GF, Monterossi G, De Stefano I, et al. The expression ratios of
    estrogen receptor α (ERα) to estrogen receptor β (ERβ) to ERα to
    ERβ1 identify poor clinical outcome in endometrioid endometrial
cancer. Hum Pathol. 2013;44(6):1047-1054.
28. Espinosa I, José Carnicer M, Catasus L, et al. Myometrial inva-
sion and lymph node metastasis in endometrioid carcinomas:
tumor-associated macrophages, microvessel density, and HIF1A have a crucial role. *Am J Surg Pathol.* 2010;34(11):1708-1714.

29. Zannoni GF, Vellone VG, Arena V, et al. Does high-grade endometrioid carcinoma (grade 3 FIGO) belong to type I or type II endometrial cancer? A clinical-pathological and immunohistochemical study. *Virchows Arch.* 2010;457(1):27-34.

30. Stelloo E, Bosse T, Nout RA, et al. Refining prognosis and identifying targetable pathways for high-risk endometrial cancer; a TransPORTEC initiative. *Mod Pathol.* 2015;28(6):836-844.

31. Travaglino A, Raffone A, Gencarelli A, et al. Clinico-pathological features associated with mismatch repair deficiency in endometrial undifferentiated/dedifferentiated carcinoma: a systematic review and meta-analysis. *Gynecol Oncol.* 2021;160(2):579-585.

32. Segura SE, Pedra Nobre S, Hussein YR, et al. DNA mismatch repair-deficient endometrial carcinomas portend distinct clinical, morphologic, and molecular features compared with traditional carcinosarcomas. *Am J Surg Pathol.* 2020;44(11):1573-1579.

33. Travaglino A, Raffone A, Mascolo M, et al. Clear cell endometrial carcinoma and the TCGA classification. *Histopathology.* 2020;76(2):336-338.

34. Travaglino A, Raffone A, Santoro A, et al. Clear cell endometrial carcinomas with mismatch repair deficiency have a favorable prognosis: a systematic review and meta-analysis. *Gynecol Oncol.* 2021;162(3):804-808.

35. Travaglino A, Raffone A, Raimondo D, et al. Prognostic value of the TCGA molecular classification in uterine carcinosarcoma. *Int J Gynaecol Obstet.* Published online September 18, 2021. doi: 10.1002/ijgo.13937

36. Catasus L, Matias-Guiu X, Machin P, et al. Frameshift mutations at coding mononucleotide repeat microsatellites in endometrial carcinoma with microsatellite instability. *Cancer.* 2000;88(10):2290-2297.

37. Delahunt B, Eble JN, Egevad L, Samarutunga H. Grading of renal cell carcinoma. *Histopathology.* 2019;74(1):4-17.

38. Vroobel KM, Attygalle AD. Sarcomatous transformation in undifferentiated/dedifferentiated endometrial carcinoma: an underrecognized phenomenon and diagnostic pitfall. *Int J Gynecol Pathol.* 2020;39(5):485-492.

39. Franceschi T, Durieux E, Morel AP, et al. Role of epithelial-mesenchymal transition factors in the histogenesis of uterine carcinomas. *Virchows Arch.* 2019;475(1):85-94.

40. Kihara A, Amano Y, Matsubara D, et al. BRG1, INI1, and ARID1B deficiency in endometrial carcinoma: a clinicopathologic and immunohistochemical analysis of a large series from a single institution. *Am J Surg Pathol.* 2020;44(12):1712-1724.

41. Mulligan AM, Plotkin A, Rouzbahman M, Soslow RA, Gilks CB, Clarke BA. Endometrial giant cell carcinoma: a case series and review of the spectrum of endometrial neoplasms containing giant cells. *Am J Surg Pathol.* 2010;34(8):1132-1138.

42. Murali R, Davidson B, Fadare O, et al. High-grade endometrial carcinomas: morphologic and immunohistochemical features, diagnostic challenges and recommendations. *Int J Gynecol Pathol.* 2019;38:S40-S63.

43. Kölbel M, Ronnett BM, Singh N, Soslow RA, Gilks CB, McCluggage WG. Interpretation of P53 immunohistochemistry in endometrial carcinomas: toward increased reproducibility. *Int J Gynecol Pathol.* 2019;38:S123-S131.

44. Raffone A, Travaglino A, Mascolo M, et al. Histopathological characterization of ProMisE molecular groups of endometrial cancer. *Gynecol Oncol.* 2020;157(1):252-259.

45. Travaglino A, Raffone A, Mollo A, et al. TCGA molecular subgroups and FIGO grade in endometrial endometrioid carcinoma. *Arch Gynecol Obstet.* 2020;301(5):1117-1125.

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