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Review

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Comparison of survival outcomes among patients with uterine carcinosarcoma and those with grade 3 uterine carcinoma: A systematic review of the literature

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Abstract

Introduction: Endometrial carcinosarcoma is an aggressive form of cancer that has been classified in type II endometrial carcinomas. However, survival outcomes seem to differ considerably compared to grade 3 endometrioid adenocarcinoma, the predominant form of cancer in this group of patients. The purpose of the present systematic review is to investigate overall and progression free survival in patients with endometrial carcinosarcoma to those of patients with grade 3 endometrioid adenocarcinoma.

Methods: We used Medline, Scopus, EMBASE, Cochrane Central Register of Controlled Trials CENTRAL, Clinicaltrials.gov and Google Scholar databases. Statistical analysis was performed using the Sidik-Jonkman random effect model (REM) in Rstudio.

Findings: Overall, 10.121 patients from 8 studies were investigated. The results of the present meta-analysis indicate that patients with Gr3EC had better overall survival rates HR 2.41 (95% CI 1.29, 4.51). However, this effect might be influenced by selection bias and underpowered studies as following adjustment of the aggregated estimate for small study effects we observed that it was not significant (HR 1.00, 95%CI 0.96, 1.05, *p=.858*). Although it was not possible to accumulate data concerning the progression free survival, individual studies reported worse outcomes in patients with carcinosarcoma.

Conclusions: Carcinosarcoma is a particularly aggressive form of endometrial cancer and deserves fur-

ther attention from researchers as current treatment alternatives do not seem to reach survival outcomes of patients suffering from grade 3 endometrioid adenocarcinoma.

Key words: Carcinosarcoma, endometrial cancer, endometrioid adenocarcinoma, meta-analysis

Introduction

Endometrial Cancer (EC) is the sixth most prevalent malignancy in women worldwide.[1,2] Approximately 320,000 new cases annually are diagnosed annualy and 76,000 women eventually succumb from it. Clinicopathologically endometrial cancer is categorized in type I and type II, which differ in incidence, responsiveness to estrogen, and prognosis.[3,4] Type II EC is responsible for 20% of the cases and Grade 3 Endometrioid Adenocarcinomas (G3EC), represent the major histological subtype in this subgroup. Uterine carcinosarcomas (UCSs), previously called Malignant Mixed Müllerian Tumors (MMMTs) of the uterus, account for 3–5% of all malignant uterine neoplasms and are characterized by their aggressiveness.[5] These tumours combine epithelial and mesenchymal components. Due to its sarcomatous component UCS was traditionally grouped in the sarcoma category. However, histological molecular and genetic research has shown that in contrast with uterine sarcomas, UCS metastasizes via the lymphatic system rather than the blood and has a monoclonal origin.[6,7]

As a result, in 2009 the staging guidelines of the International Federation of Gynecology and Obstetrics (FIGO) suggested that UCS should be staged as a de-differentiated uterine carcinoma and treated in line with the guidelines for high-grade endometrial cancer, known as type II EC.[8,9]

Even in this case, however, UCS seems to differ substantially from other histological subtypes that are included in type II EC. Several studies have observed that survival outcomes of patients with UCS differ substantially from those of patients with other subtypes of type II EC. In the present systematic review, we sought to investigate survival outcomes of UCS patients and compare them to those of patients with G3EC, the prominent group of type II EC patients.

Materials and methods

The present meta-analysis was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[10] and is registered in Open Science Framework (Registration DOI: 10.17605/OSF.IO/A7THX). All data were retrieved in aggregated form from published studies in this field; hence, institutional board approval and patient consent were not retrieved.

Information sources and search methods

We used the Medline (1966–2021), Scopus (2004–2021), Clinicaltrials.gov (2008–2021), EMBASE (1980-2021), Cochrane Central Register of Controlled Trials CENTRAL (1999-2021) and Google Scholar (2004-2021) databases in our primary search along with the reference lists of electronically retrieved full-text papers. The date of our last search was set at February 10, 2021. Our search strategy included the text words "carcinosarcoma; mixed Mullerian tumor; endometrioid adenocarcinoma; grade 3; uterine carcinoma" and is summarized in Figure 1.

Studies were selected in three consecutive stages. Following deduplication, the titles and abstracts of all electronic articles were screened by two authors (V.P. and D.H.) to assess their eligibility. The decision for inclusion of studies in the present meta-analysis was taken after retrieving and reviewing the full text

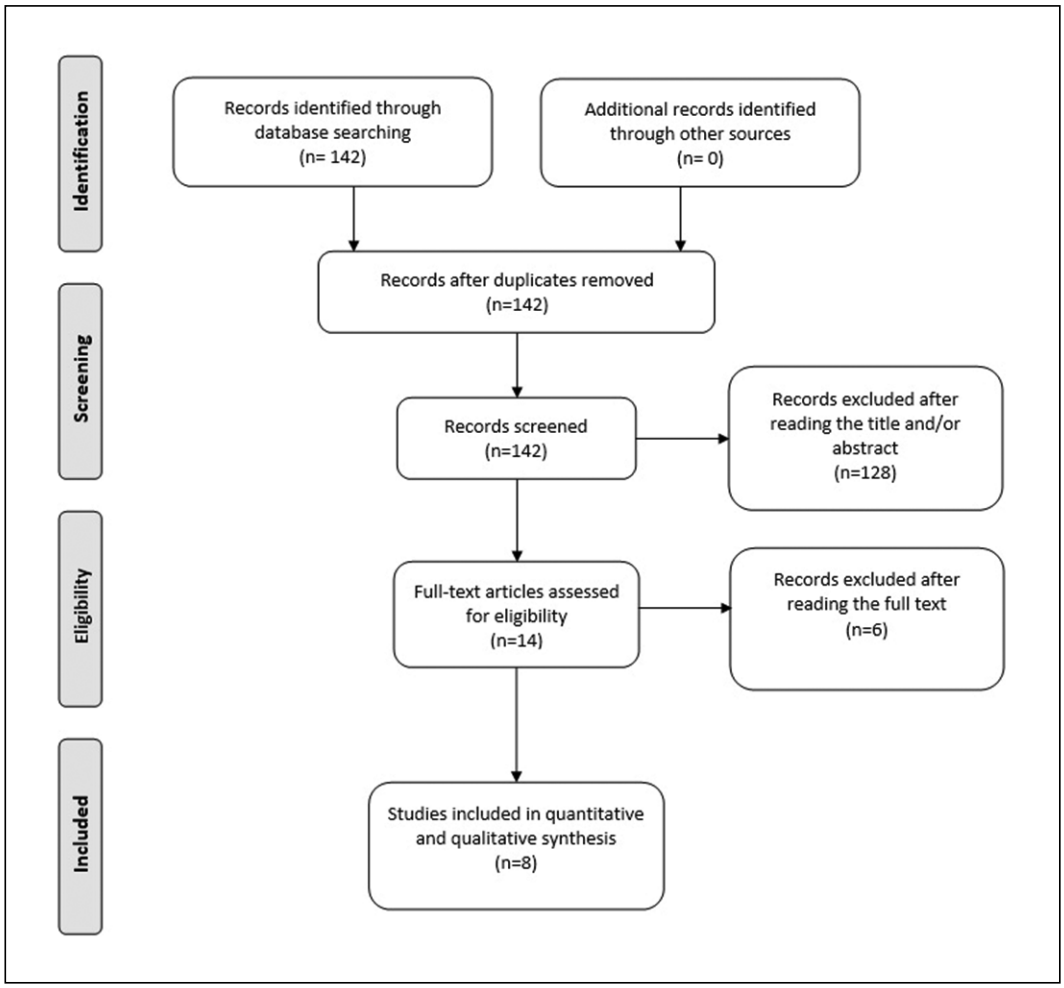

Figure 1. Search plot diagram.

of articles that were held potentially eligible. Possible discrepancies in this latter stage were resolved by consensus from all authors.

Types of studies and patients

The eligibility criteria for the inclusion of studies were predetermined. All observational studies (prospective and retrospective) and randomized controlled trials that compared survival outcomes of patients with uterine carcinosarcoma to those of patients with grade 3 endometrioid adenocarcinoma were selected for inclusion. Published conference proceedings that were included in the databases that were used in our search were also tabulated. Case reports as well as experimental animal studies and reviews were excluded from the present systematic review. Following the completion of the article retrieval process we selected the data that were necessary for inclusion using a modified data form that was based in Cochrane`s extraction form for intervention reviews for RCT`s and non-RCTs.[11]

Outcome measures

Outcome measures were predefined during the design of the present systematic review. Hazard ratios (HR) of survival rates (both DFS and OS) were defined as our primary outcome. Variables that influenced survival outcomes of patients were also retrieved and differences of their significance among patients with endometrioid adenocarcinoma and those with grade 3 adenocarcinoma were documented.

Quality assessment

The methodological quality of the included studies was assessed by two independent reviewers (V.P and D.H.). The Newcastle-Ottawa Scale (NOS) was used in this stage. The scale examines the risk of bias in observational studies by evaluating the selection of the study groups (maximum rating 4 points), the comparability of the groups (maximum rating 2 points – 1 for stage of the disease and another one for tumor size) and the ascertainment of the exposure or outcome of interest (maximum rating 3 points).[12]

Types of analyses

Statistical meta-analysis was performed with RStudio using the *meta and metafor* packages (RStudio Team (2015). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA URL http://www.rstudio.com/). Statistical heterogeneity was not considered during the evaluation of the appropriate model of statistical analysis as the anticipated methodological heterogeneity of included studies did not leave space for assumption of comparable effect sizes among studies included in the meta-analysis.[13] Confidence intervals were set at 95%. We calculated pooled hazard ratios (HR) and 95% confidence intervals (CI) with the Hartung-Knapp-Sidik-Jonkman instead of the traditional Dersimonian-Laird random effects model analysis (REM).[14] The decision to proceed with this type of analysis was taken after taking into consideration recent reports that support its superiority compared to the Dersimonian-Laird model when comparing studies of varying sample sizes and between-study heterogeneity. When log(HR) and SEs were not available among the included studies we used the Cochrane`s tutorial on Meta-analysis time-to-event data to compute them.[15]

Prediction intervals

Prediction intervals (PI) were also calculated, using the *meta* function in RStudio, to evaluate the estimated effect that is expected to be seen by future studies in the field. The estimation of prediction intervals takes into account the inter-study variation of the results and express the existing heterogeneity at the same scale as the examined outcome.

Sensitivity analysis

Evaluation of the effect of outliers on the aggregated effect estimate was performed by: i) identifying studies that had extremely small effects (their upper bound of the 95% confidence interval was lower than the lower bound of the pooled effect confidence interval) and ii) identifying studies that had extremely large effects (their lower bound of the 95% confidence interval was higher than the upper bound of the pooled effect confidence interval).

The potential presence of small-study effects was evaluated with Rücker's Limit Meta-Analysis and the possibility of p-hacking was investigated with inspection of the results of the p-curve analysis.

Results

Overall, eight studies were included in the present meta-analysis that comprised 10.121 patients.[16-23] The majority of the studies were retrospective except for one.[18] Their methodological characteristics are summarized in Table 1. With the exception of one study that had a short follow-up interval, the majority of the studies that were included exceeded a median follow-up of 3 months.[18] One large population-based

Table 1. Methodological characteristics of included studies.

DATE; AUTHOR	TYPE OF STUDY	PATIENT N (GRADE 3 EC VS. CS)	INCLUSION CRITERIA	EXCLUSION CRITERIA	FOLLOW UP, MONTHS
2005; Amant	Retrospective Cohort study	83 (50 vs. 33)	All patients with Grade 3 EC and CS	No follow up data	25 vs 28
2007; Akahira	Retrospective Cohort study	171 (100 vs 71)	All patients with Grade 3 EC and CS		47.5 (median)
2008; Bansal	Retrospective Cohort study	8.986 (5.024 vs 3.962)	All patients with Grade 3 EC and CS		-
2011; de Jong	Prospective Cohort study	99 (56 vs 43)	All patients with Grade 3 EC and CS	Undifferentiated tumor type or unknown tumor type in the epithelial component were excluded	12 (median)
2015; Zhang	Retrospective cohort study	162 (118 vs 44)	All patients with Grade 3 EC and CS	Apparent residual tumors after surgery	61 (median)
2016; Prueksaritanond	Retrospective review	88 (58 vs 30)	Patients with G3EC or CS who underwent treatment for FIGO stage I-IV endometrial cancers	Synchronous cancer or mixed subtype	37.5 (median)
2016; Zhu	Retrospective cohort study	175 (115 vs 60)	All patients with Grade 3 EC (consecutive patients who underwent primary surgery) and CS	Patients who underwent secondary cytoreductive surgery	49.2 (median)
2020; Güngördüka	Multicenter retrospective cohort study	357 (196 vs 161)	All patients with Grade 3 EC and CS	Patients with incomplete data and a follow-up period <12 months	39 (median)

cohort was identified among smaller cohort.[17] The proportion of women that had pelvic lymphadenectomy ranged from 20.9% up to 89.4% of cases, indicating that heterogeneity among studies included was significant (Table 2). Similarly, the proportion of patients that received adjuvant therapy significantly differed among studies included ranging from 20.9% to 89.4% for radiotherapy and from 0% up to 64.8% for chemotherapy. The Newcastle-Ottawa scale assessment revealed that studies were of moderate quality (score 6-7) due to their retrospective nature (outcome of interest was present at the start of the study) and in some cases due to the fact that comparability (in terms of stage of the disease among patients with uterine carcinosarcoma and Gr3EC) was not ascertained.

Overall survival

The results of the present meta-analysis indicate that patients with Gr3EC had significantly better overall survival rates [HR 2.41 (95% CI 1.29, 4.51), outcome based in 7 studies]. Prediction intervals analysis indicated that future studies may identify even wider confidence intervals (Figure 2a). The study of Akahira et al was identified as a potential outlier.[23] However, even after its exclusion the result continued to be significant (HR 3.00, 95% CI 1.68, 5.36, *p=.005*). On the other hand, following adjustment of the aggregated effect estimate for small study effects we observed that the aggregate effect was not significant (HR 1.00, 95%CI 0.96, 1.05, *p=.858*). Taking this into consideration we the p-curve of our analysis to evaluate if there is potential p-hacking

Table 2. Tumor characteristics and therapeutic modalities.

DATE; AUTHOR	STAGE (GRADE 3 EC VS. CS)	LYMPHADENECTOMY (GRADE 3 EC VS. CS)	RADIOTHERAPY (GRADE 3 EC VS. CS)	POSITIVE PERITONEAL WASHING (GRADE 3 EC VS. CS)	CHEMOTHERAPY (GRADE 3 EC VS. CS)
2005; Amant	*I-II : 66.7% vs 78.1% III-IV: 33.3% vs 21.9%	Vs 45%	4.0% vs 3.0%	13% vs 19%	10% vs 12.1%
2007; Akahira	I: 40 % vs 39.4% II: 15% vs 9.9% III: 32% vs 33.8% IV: 13% vs 16.9%	73% vs 60.6%	27% vs 11.3%		58% vs 64.8%
2008; Bansal	*IA: 9.4% vs 7.0% *IB: 27.2% vs 17.5% *IC: 15.0% vs 7.8% *INOS: 4.7% vs 5.5% *II: 10.5% vs 8.8% *III: 19.7% vs 18.0% *IV: 10.8% vs 22.6% *Unknown: 2.8% vs 12.7%	67.0% vs 52.8%*	42.5% vs 29.8%*	-	-
2011; de Jong	I: 32% vs 42% II: 20% vs 8% III: 36% vs 33% IV: 12% vs 17%	-	-	20% vs 19%	-
2015; Zhang	I: 72% vs I: 59.1% II: 9.3% vs II: 6.8% III: 15.3% vs III: 22.7% IV: 2.6% vs IV: 9.1%	96.6% vs 79.5%	5.1% vs 0	-	44.1% vs 75%
2016; Prueksaritanond	I: 53.4% vs I: 40% II: 10.3% vs II: 10% III: 29.3% vs III: 30% IV: 6.9% vs IV: 20%	87.9% vs 86.7%	29.3% vs 13.3% *	3.4% vs 10% *	17.2% vs 36.7% *
2016; Zhu	I: 48.7% vs I: 46.7% II: 14.8% vs II: 15% III: 21.7% vs III:23.3% IV: 14.8% IV: 15%	20.9% vs 41.7%	14% vs 6%	0.9% vs 0	16% vs 20%
2020; Güngördüka	IA: 39.8% vs 42.2% IB:45.9% vs 41.6% II: 14.3% vs 16.1%	87.7% vs 89.4%	89.3% vs 91.9%	16.7% vs 46.6%(peritoneal failure)	0 vs 6.2%

among studies included; however, the presence of evidential value was observed (Figure 2b)

Progression-free survival (PFS) was also examined, however, the significant heterogeneity that was noted in terms of reporting precluded combination of outcomes in the meta-analysis. Specifically, Zhang et al observed that the 5-year disease free survival rates were 52.9% for UCS and 83.2% for Gr3EC.[19] Prueksaritanond et al that recurrences in the UCS group were nearly tripled compared to those of Gr3EC patients (23.3% vs 8.6%)[20]; however, neither the 2-year nor the 5-year disease free survival differed substantially (95.5% vs 92.7% and 92.7% vs 89.2%). Finally, Güngördük et al reported that the hazard ratio of relapse was higher in the UCS group (HR 2.8, 95% CI 1.5-4.6).[22]

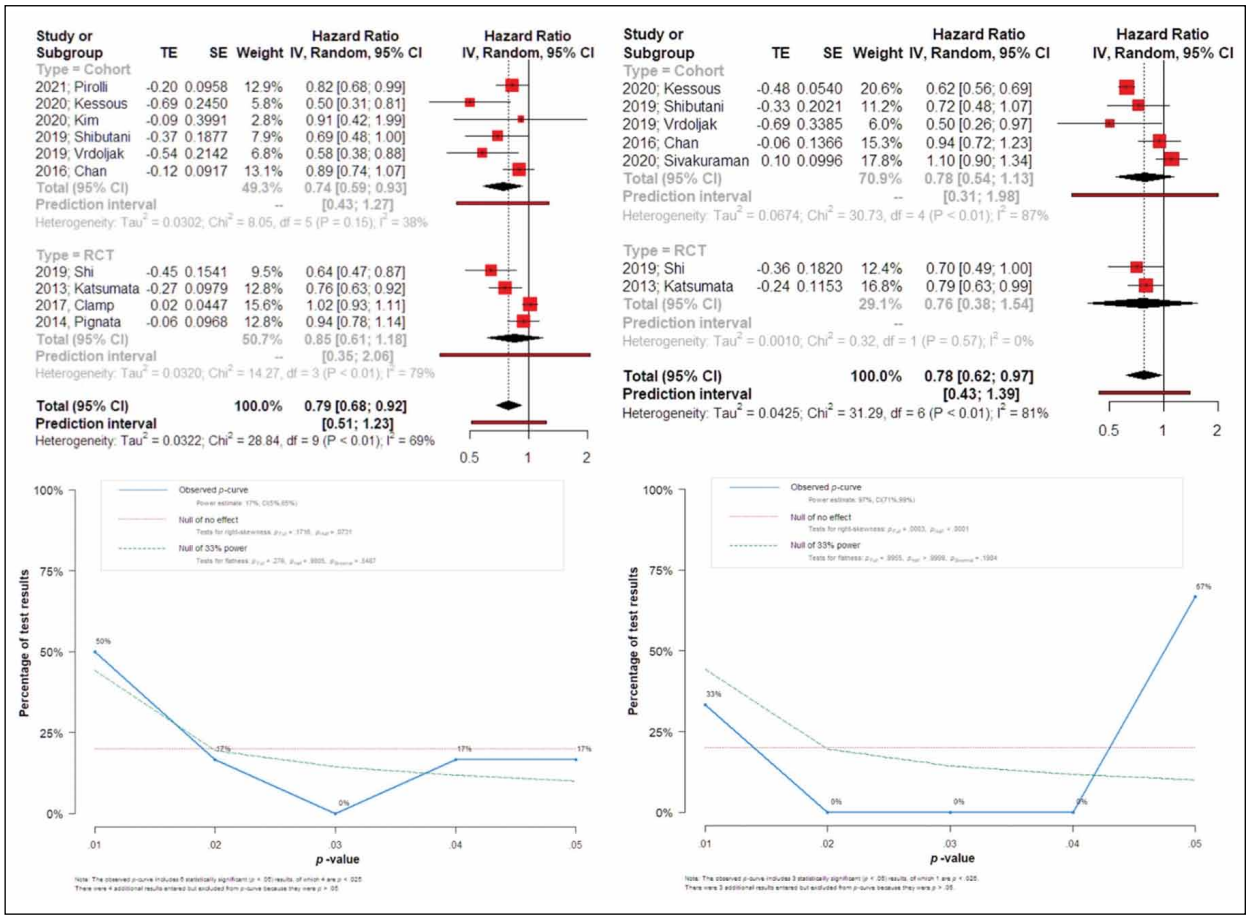

Figure 2. A. Forest plot of overall survival. Vertical line = "no difference" point between the two groups. Red squares = odds (hazard) ratios; Diamond = pooled mean odds (hazard)radio and 95% CI for all studies; Horizontal black lines = 95% CI. B. Results of the p-curve analysis.

Discussion

The findings of our meta-analysis suggest confirm that uterine carcinosarcoma is considerably more aggressive compared to Gr3EC in terms of overall survival and progression free survival. Current evidence suggests that the median survival rates as well as the median progression free survival rates are also considerably shorter among patients that develop UCS (median time to recurrence 7.3 months and death 23 months for UCS and 25 months and 60 months for Gr3EC).[16,19] This directly affects both the 2-year and 5-year progression free and overall survival rates.[20]

As with other forms of endometrial carcinomas, survival in UCS is significantly affected by the depth of myometrial invasion, presence of lymph node metastases and stage of the disease. According to Zhu et al, the largest discrepancy in survival seems to be evident in patients with early stage disease (stages I and II) (HR of survival 2.85, 95% CI 1.06, 7.68).[21] On the other hand, patients with advanced stage (stages III and IV) are not expected to differ significantly (HR 1.58, 95% CI 0.74, 3.36). These findings were confirmed by Güngördük et al who also reported that patients with early stage UCS have

significantly shorter disease-free survival and overall survival compared to Gr3EC patients.[22] Apart from those, however, it seems that the histological subtype of the epithelial component of UCS is another significant indicator as patients with non-endometrioid epithelial cells tend to have significantly shorter survival.[18,19]

The impact of multimodal therapy (surgery combined with chemotherapy and/or radiotherapy) remains in question as current evidence seems to be conflicting.[21,22] Even after the implementation of a multimodal approach UCS patients seem to have lower chances of survival compared to Gr3EC patients.[20] An additive effect in survival rates has been implied by Akahira et al in UCS patients (HR 0.458 for the pelvic part and 0.212 for the paraortic part)[23]; however, this has not been confirmed by other investigators. Recently, McEachron et al reported that combination of chemo- and radio-therapy following surgery significantly increases survival of patients suffering from UCS, irrespective of the stage of the disease.[24] Even in this case; however, the prognosis remains dismal at all stages according to the results of a multi-institutional study.[25]

Analysis of the genetic background of uterine carcinosarcoma with whole-exome sequencing indicates that these tumors show overexpress the Her2/neu gene and have an aberrant activation of the PI3K/AKT/mTOR pathway.[26-30] Targeted therapies may, therefore, be another option for patients with these aggressive tumors although it should be noted that the frequent genetic heterogeneity in the clonal evaluation of these tumors results in an unstable phenotypic diversity that does not allow a very promising benefit. Nevertheless, some studies indicate that these therapies may serve as an additive option to current treatment modalities.[31-33] However, evidence is still scarce to allow definitive conclusions that could be used as guidance for clinical practice.

Study limitations

Our meta-analysis accumulates for the first time, differences in progression free and overall survival rates among patients with UCS and those with Gr3EC. Despite the random effects model that was used, there was considerable heterogeneity in the methodological characteristics as well as patient and tumor characteristics that may imply selection bias. The impact of stage of the disease as well as other tumor related factors on survival outcomes could not be used to perform subgroup analyses or meta-regression analysis as there were no relevant data in the retrieved studies. Treatment schemes, although reported in the majority of studies were not used to evaluate differences in survival outcomes; hence sub-analysis was not possible. Lastly, due to the rarity of tumors the majority of included studies was retrospective; hence, increasing the possibility of recall bias.

Implications for current clinical practice and future research

The results of our meta-analysis suggest that although UCS is currently classified in type II endometrial carcinomas it is considerably more aggressive with an estimated overall survival that decreases more than twice that of Gr3EC, which is the predominant histological subtype of this group. The impact of the UCS histology seems to affect more patients during the first stages of the disease and the interval to recurrence seems to be as small as 7 months post-treatment. Several factors seem to affect disease prognosis, including the implementation of a multimodal approach that combines surgery with adjuvant therapy; however, even in this case the results do not seem to reach survival outcomes reported in cases of Gr3EC.

Future research should focus on the impact of adjuvant treatment alternatives at different stages of the disease to clarify if combined chemo-radiotherapy should be used in patients with early stage UCS, as, to

date, it remains unclear if this aggressive approach actually affects survival outcomes. Given the importance of the type of the non-epithelial component (endometrioid vs non-endometrioid) on survival outcomes it would be useful to also evaluate if these latter cases should be re-classified as sarcomas and treated accordingly or if physicians should regard them as a particular subtype that deserves a more aggressive approach.

Conclusion

Concluding, the findings of our study suggest that uterine carcinosarcoma, despite being classified in type II endometrial carcinomas behaves more aggressively than standard epithelial endometrioid carcinoma and even multimodal approaches do not suffice to reach comparable survival rates. Nevertheless, the evidence remains scarce and more studies are needed to help establish robust treatment guidelines that will help better progression free and overall survival.

Statement of ethics

The present study is based in aggregate data that have been already published in the international literature; hence and IRB approval was not sought as well as consent to participate statement,

Disclosure of conflicts of interest

The authors report that they have no conflicts of interest to disclose.

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Data availability statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Ethical approval

Not applicable, because this article does not contain any studies with human or animal subjects.

Informed consent

Not applicable, because this article does not contain any studies with human or animal subjects.

Author contributions

VP and DH: conceived the idea, VP and NT: designed the project; EG, AKG, IK and MM tabulated data, VP and DH performed the statistical analysis and wrote the manuscript; VP and NT assessed bias among included studies and wrote the manuscript; All authors: contributed to manuscript writing; VP and DH: supervised the project and revised the manuscript.

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