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REVIEW

Prognostic factors in Krukenberg tumor

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Abstract

Background Krukenberg tumor (KT) is a rare secondary ovarian tumor. Little is known about clinicopathologic factors affecting prognosis in KT.

Objective To assess the prognostic value of clinicopathologic factors in KT through a systematic review and meta-analysis.

Methods Electronic databases were searched from their inception to February 2019 for studies assessing the association of clinicopathologic factors with overall survival in KT. Pooled hazard ratio (HR) was calculated for each factor; a p value <0.05 was considered significant.

Results Twenty-three studies with 1743 patients were included. A decreased overall survival was significantly associated with peritoneal involvement (HR 1.944; $p=0.003$), ascites (HR 2.055; $p=0.034$), synchronous presentation (HR 1.679; $p=0.034$) and increased serum CEA levels (HR 1.380; $p=0.010$), but not with age > 50 (HR 0.946; $p=0.743$), menopausal status (HR 1.565; $p=0.204$), gastric origin (HR 1.600; $p=0.201$), size > 5 cm (HR 1.292; $p=0.119$), size > 10 cm (HR 0.925; $p=0.714$), bilateral ovarian involvement (HR 1.113; $p=0.347$), non-peritoneal extaovarian metastases (HR 1.648; $p=0.237$), liver metastases (HR 1.118, $p=0.555$), predominant signet ring cell morphology (HR 1.322; $p=0.208$) and levels of CA125 (HR 0.933; $p=0.828$) and CA19.9 (HR 0.996; $p=0.992$).

Conclusion Peritoneal involvement, synchronous presentation, ascites and increased serum CEA levels appear as unfavorable prognostic factors in KT and might affect the patient management.

Keywords Cancer · Metastasis · Prognosis · Management · Oncology · Hazard ratio · Therapy

Introduction

Krukenberg tumor (KT) is a rare secondary ovarian neoplasm that accounts for about 1–2% of all ovarian tumors. In most cases, it derives from a primary tumor of the gastroenteric tract, in particular the stomach and the colorectum [1–3]. In a small percentage of cases KT may originate from breast, appendix, small bowel, gallbladder, pancreas, bladder; sometimes the site of origin is unknown [4, 5]. The diagnostic criteria of KT diagnose were identified by Novak and Gray and consist of: ovarian neoplasm, signet ring cells producing mucin, sarcomatoid proliferation of the ovarian stroma [6]. Signs and symptoms in patients with KT are nonspecific, early diagnosis is difficult and the prognosis is often poor. In our previous study, we showed that many different treatment protocols are used for KT, such as cytoreductive surgery, adjuvant systemic chemotherapy, neoadjuvant systemic chemotherapy and intraperitoneal chemotherapy. Overall, cytoreductive surgery with negative surgical margins appeared as the most effective treatment, and intraperitoneal chemotherapy appeared preferable as adjuvant treatment [7]. However, we pointed out that the feasibility and efficacy of each therapeutic approach may be affected by clinicopathologic features of KT. Therefore, identifying relevant prognostic factors in KT might be crucial in

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determining the optimal management. Nonetheless, to date there is no clarity about which clinicopathologic factors are actually related to a significant difference in the overall survival in KT (OS). The purpose of this review is to systematically analyze the Literature and to define which clinicopathologic factors bear a significant prognostic value in KT.

Materials and methods

Study methods followed those of our previous studies [8–11]. Methods for electronic search, study selection, risk of bias assessment and data extraction were defined before the beginning of the study. All stages of the review were conducted independently by three reviewers (RL, MDL, ADC). Disagreements were resolved by consensus among all authors. The study was reported according to the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement [12].

Search strategy

MEDLINE, Web of Sciences, EMBASE, OVID and Google Scholar were used as electronic databases. Relevant articles from the inception of each database and February 2019. Several searches were performed using combinations of the following text words: "krukenberg"; "ovarian"; "ovary"; "ovaries"; "metastasis"; "metastases"; "metastatic"; "tumor"; "cancer"; "neoplasm"; "survival". References from relevant studies were also assessed.

Study selection

All retrospective or prospective studies assessing the association of clinicopathologic factors with the overall survival in Krukenberg tumors were included.

Exclusion criteria, defined a priori, were: sample size < 10; case reports; reviews. No language restrictions were adopted.

Risk of bias assessment

According to our previous studies [13–15], we used the Methodological Index for Non-Randomized Studies (MINORS) [16] to evaluate the risk of bias for each study, in relation to 7 domains: (1) aim (i.e. clearly stated aim); (2) patients (i.e. all patients meeting the criteria for inclusion were included in the study during the study period); (3) data (i.e. data were collected according to a protocol established before the beginning of the study); (4) endpoint (i.e. unambiguous explanation of the criteria used to measure outcomes); (5) bias (i.e. the study endpoint was assessed without bias); (6) follow-up (i.e. the follow-up was sufficiently long to allow the assessment of the main endpoint), (7) loss (i.e. no more than 5% of patients were lost to follow-up).

The risk of bias was categorized as "low" (criterion met), "high" (criterion not met) or "unclear", as previously described [17–21]

Data extraction

Data from original studies were not modified during extraction. Clinicopathologic factors extracted were age, menopausal status, primary tumor site, tumor size, laterality (i.e. unilateral or bilateral), metastatic extent, ascites, chronology (i.e. synchronous or metachronous), serum tumor markers. Data were extracted according to the PICOS: P (population) = patients with KT; I (intervention or risk factor) = presence of the clinicopathologic factor; C (comparator) = absence of the clinicopathologic factor; O (outcome) = overall survival; S (study design) = comparative cohort study.

Data analysis

The association between each clinicopathologic factor and OS was assessed using hazard ratio (HR) with 95% confidence interval (CI); a p value < 0.05 was considered significant. For each clinicopathologic factor, HR was calculated for each study and as pooled estimate and reported graphically on forest plots. The random effect model of DerSimonian and Laird was used to pool data. Statistical heterogeneity among studies was assessed using Higgins' I^2 statistics. Heterogeneity was categorized as null ($I^2 = 0\%$), minimal ($0 < I^2 \leq 25\%$), low ($25\% < I^2 \leq 50\%$), moderate ($50\% < I^2 \leq 75\%$) or high ($75\% < I^2 \leq 100\%$), as previously described [22–26]. Wherever possible, data related to multivariate analysis were used, to reduce the effect of confounding factors.

The data analysis was performed independently by two reviewers (AT, AR) using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014) and Comprehensive Meta-Analysis (Biostat, 14 North Dean Street, Englewood, NJ 07631, USA).

Results

Selection and characteristics of the studies

Twenty-three studies, with a total sample size of 1743, were included [27–49]. The whole process of study selection is reported in detail in Supplementary Fig. 1.

Characteristics of the included studies, patients and KTs were shown in Table 1.

Risk of bias within studies assessment

About the "Aim", "Data" and "Endpoints" domains, all studies were classified at low risk of bias.

About "patients" domain, four articles [31, 33, 36, 45] were considered at unclear risk of bias because they lumped together KT and other metastatic ovarian cancers. The remaining 19 studies were categorized at low risk of bias since they reported at least inclusion criteria and period of enrolment.

About the "bias" domain, seven studies were considered at unclear risk as they did not carry out multivariate analysis to confirm results [27, 30, 34, 41, 45, 48]. All the remaining studies were considered at low risk.

About the "follow-up" domain, 7 studies were considered at unclear risk because they did not clearly specify how long the follow-up was [29, 31, 33, 35, 39, 48, 49]. The remaining studies were considered at low risk.

About the "loss" domain, 3 studies were categorized at low risk of bias [32, 42, 47], while other 3 studies at high risk of bias because they lost more than 5% of the patients during follow-up [29, 30, 48]. The remaining 17 studies were considered at unclear risk because they did not specify how many patients completed follow-up.

Results about the risk of bias for each included study were graphically reported in Supplementary Fig. 2.

Age

The association between age and OS was assessed in 19 studies [27–29, 31–38, 40, 42–48]. Meta-analysis of 7 suitable studies [33, 35, 36, 40, 42, 47, 48] showed that an age > 50 years did not significantly affect OS (HR 0.946, 95% CI 0.678–1.319; $p = 0.734$) (Fig. 1). Statistical heterogeneity among studies was moderate ($I^2 = 52.596\%$).

Studies not suitable for meta-analysis considered an age > 40 years [45], > 45 years [43], > 50 years [27–29, 31, 34, 38, 44], > 60 years [46], > 65 [32], or a 1-year-increment [37], and none of them found significant association with OS.

Menopausal status

The association of menopausal status with OS was assessed in 7 studies [31, 34, 39, 41, 42, 46, 49]. Meta-analysis performed on 3 suitable studies [39, 42, 49] showed that menopausal status was not significantly associated with OS (HR

Table 1 Characteristics of the included studies

Study	Country	Design	Study period	Sample size
Tai et al. [49]	China	Observational	2000–2015	65
Seow-en et al. [48]	Singapore	Observational	Jan 2004–Dec 2015	38
Yu et al. [47]	China	Observational	Jan 2005–Dec 2014	152
Xu et al. [46]	China	Observational	1994–2013	57
Kammar et al. [45]	India	Observational	Jan 2012–Dec 2015	25
Ganesh et al. [44]	USA	Observational	Jan 1999–Jan 2015	195
Rosa et al. [43]	Italia	Observational	Jan 1990–Dec 2012	63
Wu et al. [42]	China	Observational	Jan 1990–Dec 2010	128
Jeung et al. [41]	Korea	Observational	Jan 2001–Dec 2010	156
Cho et al. [40]	Korea	Observational	Mar 2004–Feb 2012	216
Wu et al. [39]	China	Observational	Jan 2000–Dec 2010	62
Peng et al. [38]	China	Observational	Mar 1998–Mar 2011	133
Lu et al. [37]	Taiwan	Observational	Mar 2000–Jul 2010	85
Guzel et al. [36]	Turkey	Observational	Jan 2001–Jan 2009	48
Ojo et al. [35]	USA	Observational	Nov 1994–Feb 2010	26
Jun et al. [34]	Korea	Observational	1981–2008	22
Kim et al. [33]	Korea	Observational	1994–2006	34
Jiang et al. [32]	China	Observational	Mar 1997–Dec 2003	54
Yook et al. [31]	S. Korea	Observational	Jan 1992–Dec 2000	37
McCormick et al. [30]	USA	Observational	1980–2005	40
Cheong et al. [29]	S. Korea	Observational	1987–2000	34
Kim et al. [28]	Korea	Observational	1987–1996	34
Rayson et al. [27]	Canada	Observational	1984–1998	39
Total				1743

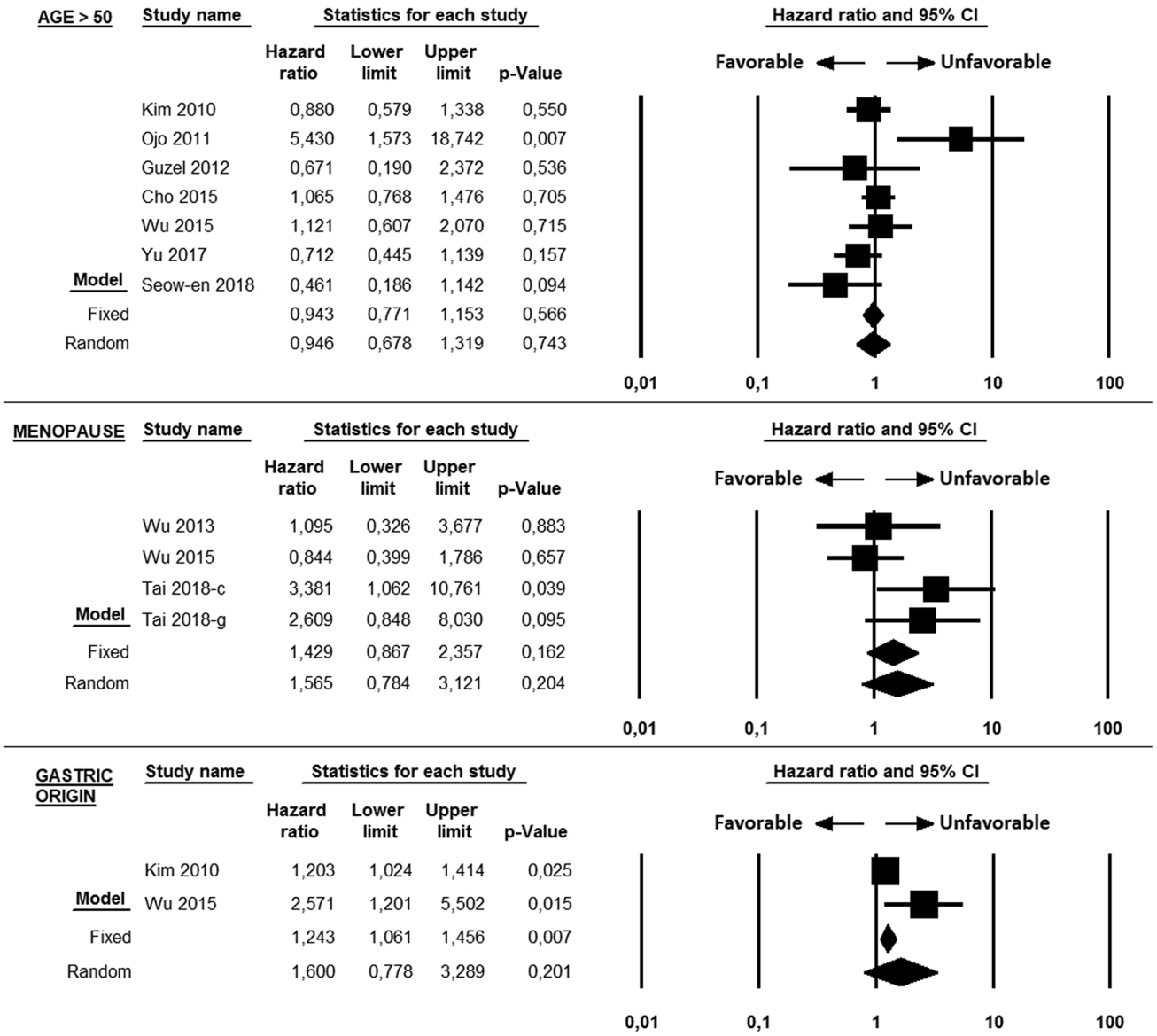

Fig. 1 Forest plots reporting pooled hazard ratios (HR) for the impact of age > 50, menopausal status and gastric origin on the overall survival in patients with Krukenberg tumor

1.565, 95% CI 0.784–3.121; $p = 0.204$) (Fig. 1). Statistical heterogeneity among studies was low ($I^2 = 43.479\%$).

Among the studies not suitable for meta-analysis, only one showed a significant association between pre-menopausal status and decreased OS, although a multivariate analysis was not performed [41].

Primary tumor site

The association of the primary tumor site with OS was assessed in five studies [32, 33, 41, 42, 48]. Meta-analysis performed on two suitable studies [33, 42] showed a non-significant association between gastric origin and decreased OS (HR 1.600, 95% CI 0.778–3.289; $p = 0.201$) (Fig. 1). Statistical heterogeneity among studies was high ($I^2 = 72.705$).

In the studies not suitable for meta-analysis, gastric origin was significantly associated with decreased OS [32, 41].

Size

The association between KT size and OS was assessed in 14 studies [28, 29, 31, 33, 34, 37, 39, 40, 42, 43, 46–49]. Two meta-analyses of 4 [39, 40, 47, 49] and 3 studies [33, 37, 42] showed that neither a KT size > 5 cm (HR 1.292, 95% CI 0.936–1.783; $p = 0.119$), nor a KT size > 10 cm (HR 0.925, 95% CI 0.612–1.400; $p = 0.714$) were

associated with significant decrease of OS (Fig. 2). Statistical heterogeneity among studies was low ($I^2 = 36.639\%$) and moderate ($I^2 = 56.607\%$), respectively.

Among the studies not suitable for meta-analysis, a KT size > 5 cm, > 10 cm or > 12 cm did not result to be associated with OS; only one study reported a significant association between a size > 10 cm and decreased OS, which was not confirmed on multivariate analysis [43].

Laterality

The association of laterality (i.e. monolateral or bilateral ovarian involvement) with OS was assessed in 14 studies [29, 31, 33, 36–38, 40–42, 44, 46–49]. Meta-analysis of 8 suitable studies [33, 37, 40, 42, 44, 47–49] showed that bilaterality was not associated with a significant decrease in the OS (HR 1.113, 95% CI 0.890–1.392; $p = 0.347$) (Fig. 2). Statistical heterogeneity among studies was low ($I^2 = 39.317\%$).

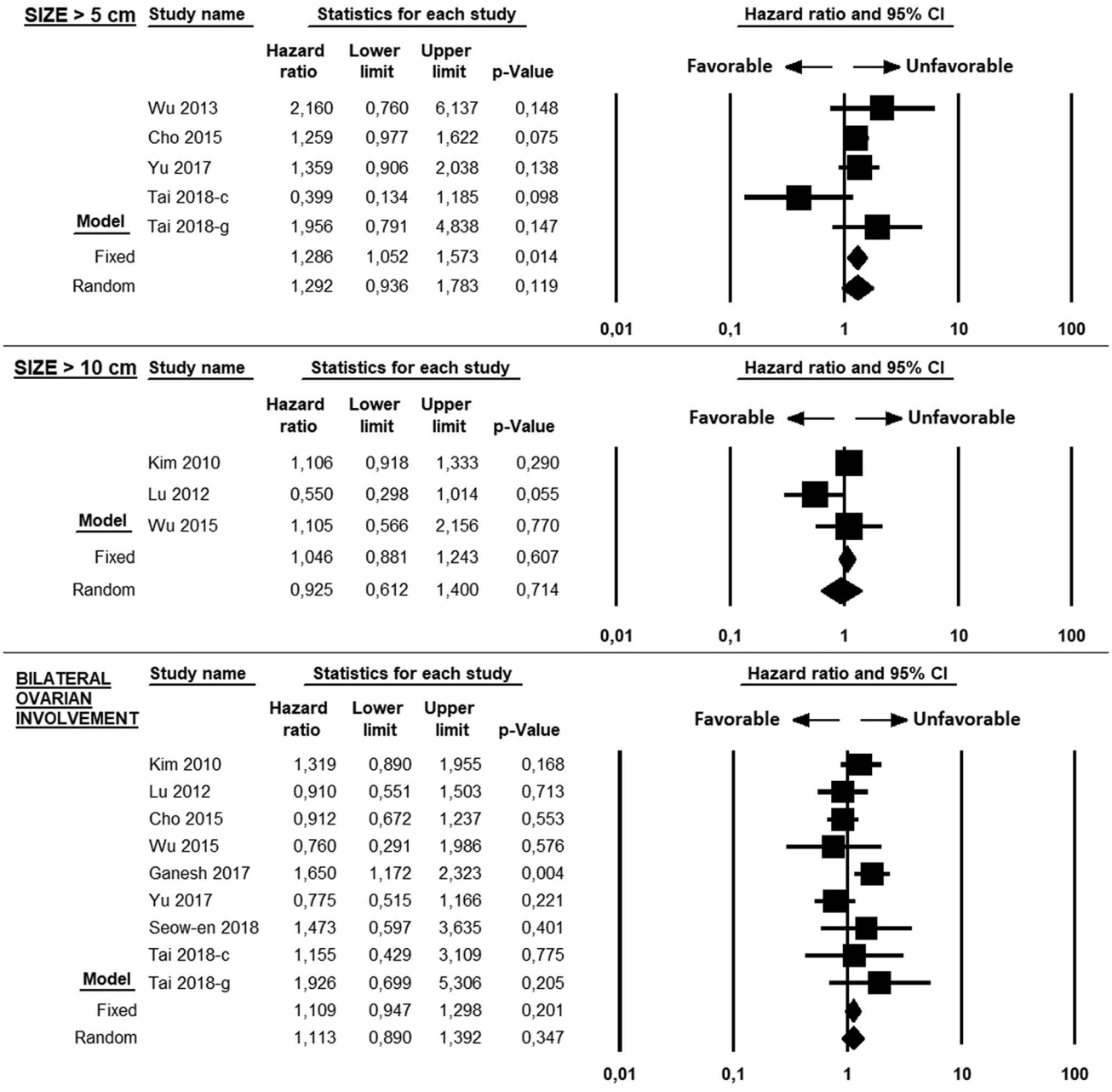

Fig. 2 Forest plots reporting pooled hazard ratios (HR) for the impact of size > 5 cm, size > 10 cm and bilateral ovarian involvement on the overall survival in patients with Krukenberg tumor

Among the studies not suitable for meta-analysis, only one found a significant association of bilaterality with decreased OS, despite not performing a multivariate analysis [41].

Extraovarian involvement

The association between peritoneal involvement and OS was assessed in 9 studies [31, 35–37, 40, 43, 44, 47, 48]. Meta-analysis of 6 suitable studies [35–37, 40, 47, 48] showed that peritoneal involvement was significantly associated with decreased OS (HR 1.944, 85% CI 1.263–2.992; $p = 0.003$) (Fig. 3). Statistical heterogeneity among studies was moderate ($I^2 = 51.466\%$). Among the studies not suitable for meta-analysis, the association was significant in 2 studies [31, 43], one of which also performed a multivariate analysis, not confirming the significance [43].

The presence of extraovarian metastases (any site) was assessed in 7 studies. A meta-analysis of 2 suitable studies showed that the presence of any extraovarian metastasis (excluding peritoneum) was not significantly associated with decreased OS (HR 1.648, 95% CI 0.720–3.773, $p = 0.237$) (Fig. 3). Statistical heterogeneity among studies was null ($I^2 = 0$). Among the studies not suitable for meta-analysis, in 2 studies [30, 32] the presence of any extraovarian metastasis (with or without peritoneal involvement) was significantly associated a decreased OS; one of them [32] also performed a multivariate analysis, not confirming the association.

The presence of extrapelvic metastases was assessed in 5 studies, and all of them showed a significant association

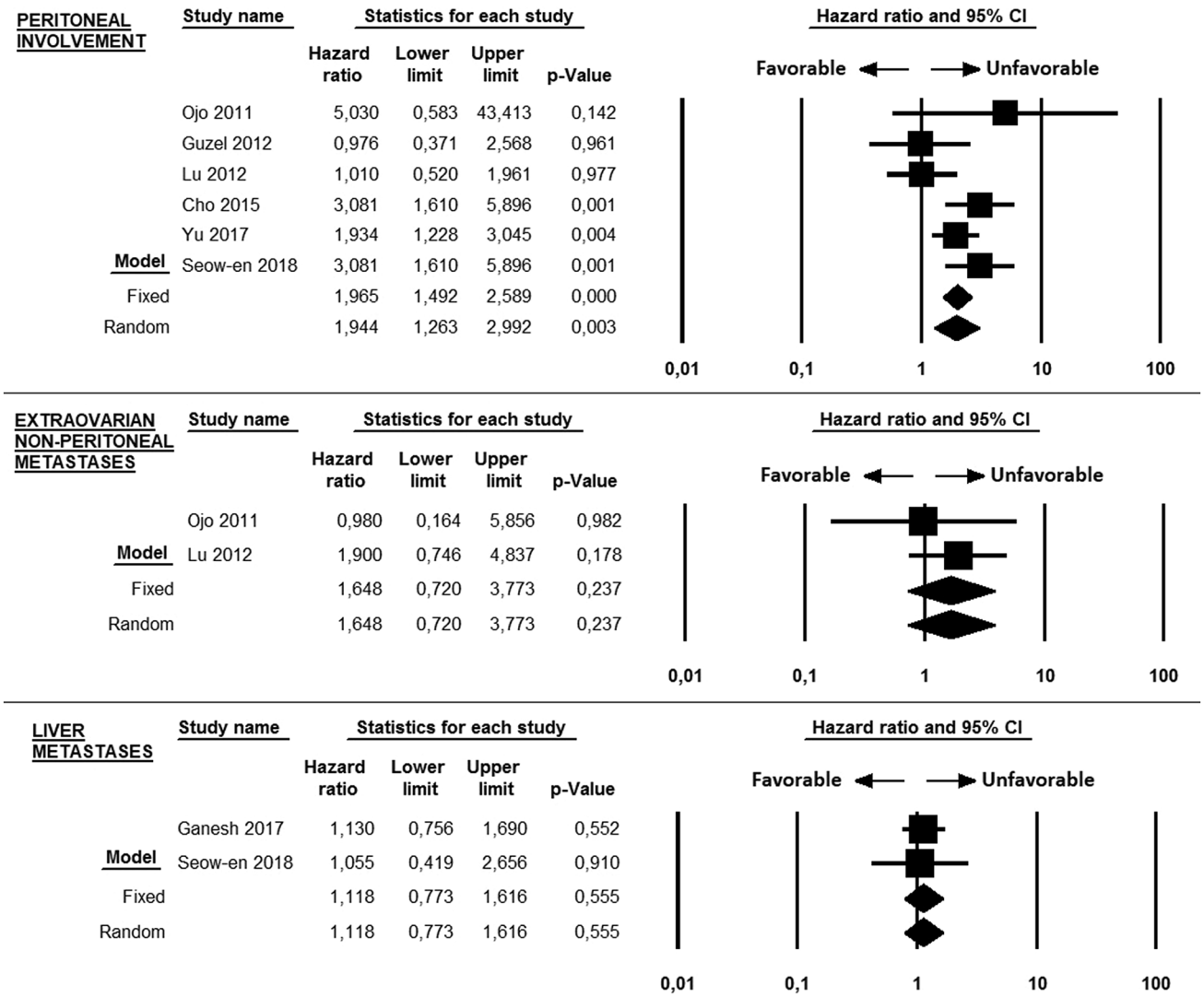

Fig. 3 Forest plots reporting pooled hazard ratios (HR) for the impact of peritoneal involvement, extraovarian non-peritoneal metastases and liver metastases on the overall survival in patients with Krukenberg tumor

with a decreased overall survival [27–29, 42, 46]; unfortunately, a meta-analysis was not feasible.

The presence of liver metastases was assessed in two studies [44, 48]; the meta-analysis showed that liver metastases were not significantly associated with decreased OS (HR 1.118, 95% CI 0.773–1.616, $p = 0.555$) (Fig. 3). Statistical heterogeneity among studies was null ($I^2 = 0\%$).

Ascites

The association between ascites and OS was assessed in five studies [33, 38, 41, 42, 47]. Meta-analysis performed on three suitable studies [33, 42, 47] showed that the presence of ascites was significantly associated with decreased OS (HR 2.055, 95% CI 1.054–4.005; $p = 0.034$) (Fig. 4). Statistical heterogeneity among studies was high ($I^2 = 82{,}397\%$).

Out of the two studies not suitable for meta-analysis, one showed a significant association between ascites and decrease OS on multivariate analysis [38].

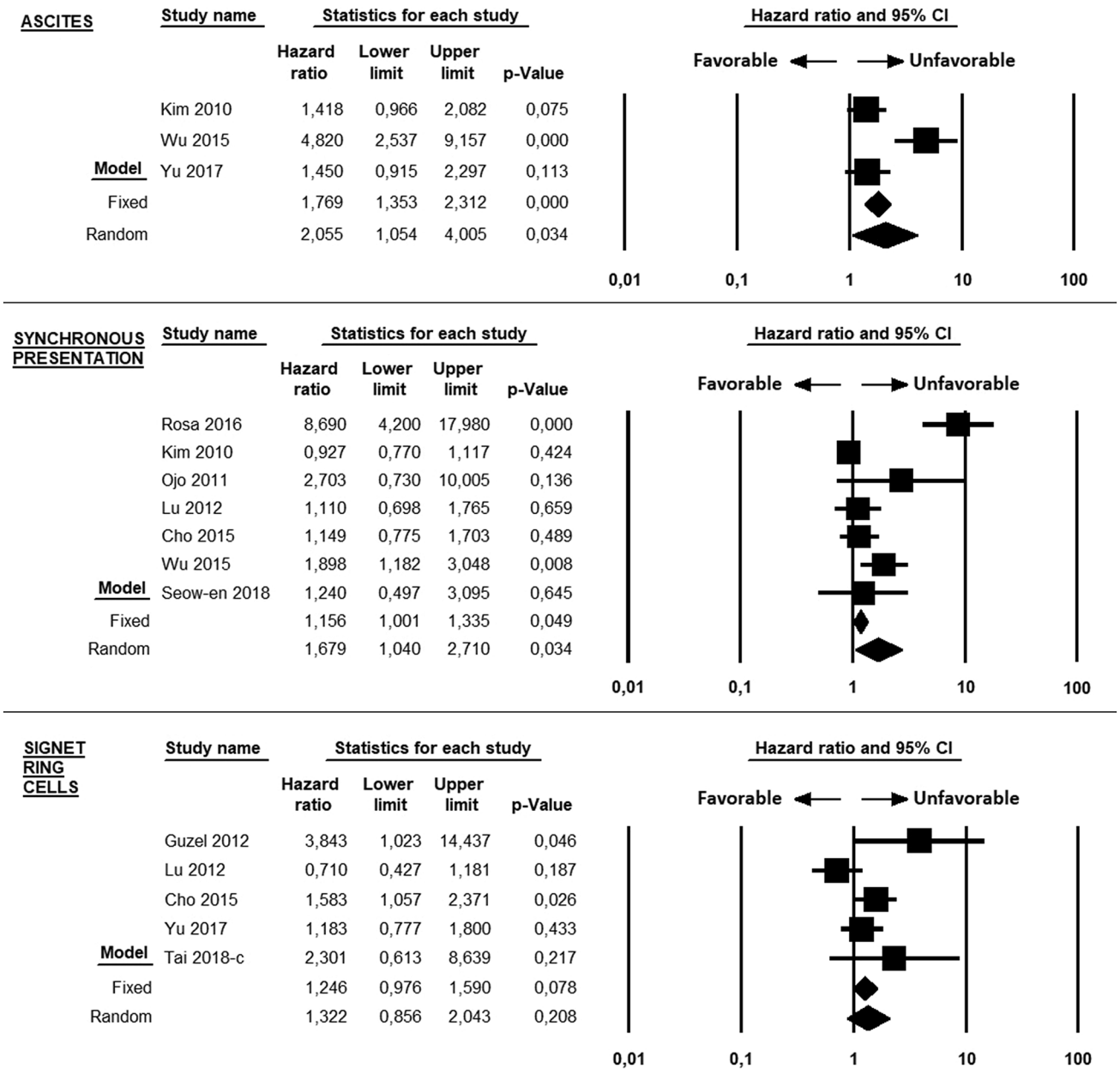

Fig. 4 Forest plots reporting pooled hazard ratios (HR) for the impact of ascites, synchronous presentation and predominant signet ring cell morphology on the overall survival in patients with Krukenberg tumor

Chronology

The association between chronology (e.g. synchronous or metachronous presentation) and OS was assessed in 15 studies [27, 30, 31, 33, 35, 37, 38, 40–46, 48]. Mata-analysis performed on 7 suitable studies [33, 35, 38, 40, 42, 43, 48] showed that a synchronous presentation was significantly associated with decreased OS (HR 1.679, 95% CI 1.040–2.710; $p=0.034$) (Fig. 4). Statistical heterogeneity among studies was high ($I^2=85.315\%$).

Among the studies not suitable for meta-analysis, two studies showed a significant association between synchronous presentation and decreased OS [41, 46]; one of these also performed a multivariate analysis, confirming the significant association [46].

Signet ring cells

The association between a predominant signet ring cell morphology and OS was assessed in seven studies [33, 36, 37, 40, 45, 47, 49]. Meta-analysis of five suitable studies [36, 37, 40, 47, 49] showed that a predominant signet ring cell morphology was not significantly associated with decreased OS (HR 1.322, 95% CI 0.856–2.043; $p=0.208$) (Fig. 4). Statistical heterogeneity among studies was moderate ($I^2=58.79\%$).

Among the study not suitable for meta-analysis, one showed a significant association instead, despite not performing a multivariate analysis [45].

Serum markers

Two studies assessed the association of serum tumor markers CA125, CEA and CA19.9 with OS [40, 47], while another one assessed only CEA and CA125 [48]; all studies were suitable for meta-analysis. Increased CEA levels were significantly associated with decreased OS (HR 1.380, 95% CI 1.080–1.736; $p=0.10$), with no heterogeneity ($I^2=0\%$), while levels of CA125 (HR 0.933, 95% CI 0.500–1.743; $p=0.828$) and CA19.9 (HR 0.996, 95% CI 0.477–2.079; $p=0.992$) were not associated with OS, with moderate ($I^2=69.274\%$) and high ($I^2=84.03\%$) heterogeneity, respectively (Fig. 5).

Discussion

Main findings and interpretation

This study showed that peritoneal involvement, ascites, synchronous presentation, and increased serum CEA levels were significant unfavorable prognostic factors in KT; on the other hand, age, menopausal status, KT size, bilateral ovarian involvement, non-peritoneal extraovarian metastases, liver metastases, signet ring cell morphology and levels of CA125 and CA19.9 did not show significant association with the OS. Results about gastric origin were inconclusive.

Age was the most studied factor in the literature. In the included studies, the mean age ranged from 40 to 65 years, and the most assessed threshold was 50 years. The irrelevance of age as a prognostic factor was consistent among studies, even considering other thresholds [27–29, 31–38, 40, 42–48]. Therefore, it may be reasonably concluded that age is not a prognostic factor in KT. Menopausal status was assessed instead of age in a smaller amount of studies. Menopause showed a non-significant trend towards the association with a worse prognosis; further evidence may be useful on this point.

Regarding the primary tumor site, in our review the stomach was the most common site of origin, followed by colon-rectum and breast. In the individual studies, gastric origin appeared as an unfavorable prognostic factor compared to both colorectal and breast origin, while meta-analysis showed a non-significant result. Remarkably, only two studies were available for meta-analysis, and the statistical heterogeneity observed was high. Furthermore, the pooled result obtained with the fixed-effect model showed a significant unfavorable prognostic value for a gastric origin. Therefore, evidence in this regard appears inconclusive. Appendix, gallbladder, small intestine, pancreas, peritoneum, lung, endometrium, urinary bladder and bile ducts were occasional site of origins and thus were not suitable for comparison [32, 33, 41, 42, 48].

With regard to KT size, an association with a decreased OS might be hypothesized. Nonetheless, our study did not show significant impact of KT size on OS with any threshold considered (5 cm, 10 cm, 12 cm), in the pooled estimates as well as in the individual studies [28, 29, 31, 33, 34, 37, 39, 40, 42, 43, 46–49]. For the 5 cm thresholds, a non-significant trend between a KT size > 5 cm and worse prognosis was observed, despite appearing too weak to be relevant in the clinical practice. As with KT size, also a bilateral ovarian involvement might be expected to be an unfavorable prognostic factor. Instead, laterality was not found to be associated with significant variations in the OS.

Peritoneal involvement appeared as one of the stronger unfavorable prognostic factors, with twofold increased mortality. Furthermore, extrapelvic involvement was consistently observed to be significant unfavorable prognostic factors, although a meta-analysis was not feasible [27–29, 42, 46]. On the other hand, extraovarian non-peritoneal involvement was not found to be associated with OS, as well as liver metastases. These finding suggest that extensive involvement of the abdomino-pelvic cavity is more important than distant metastases in determining the prognosis of HR. Consistently, the presence of ascites showed

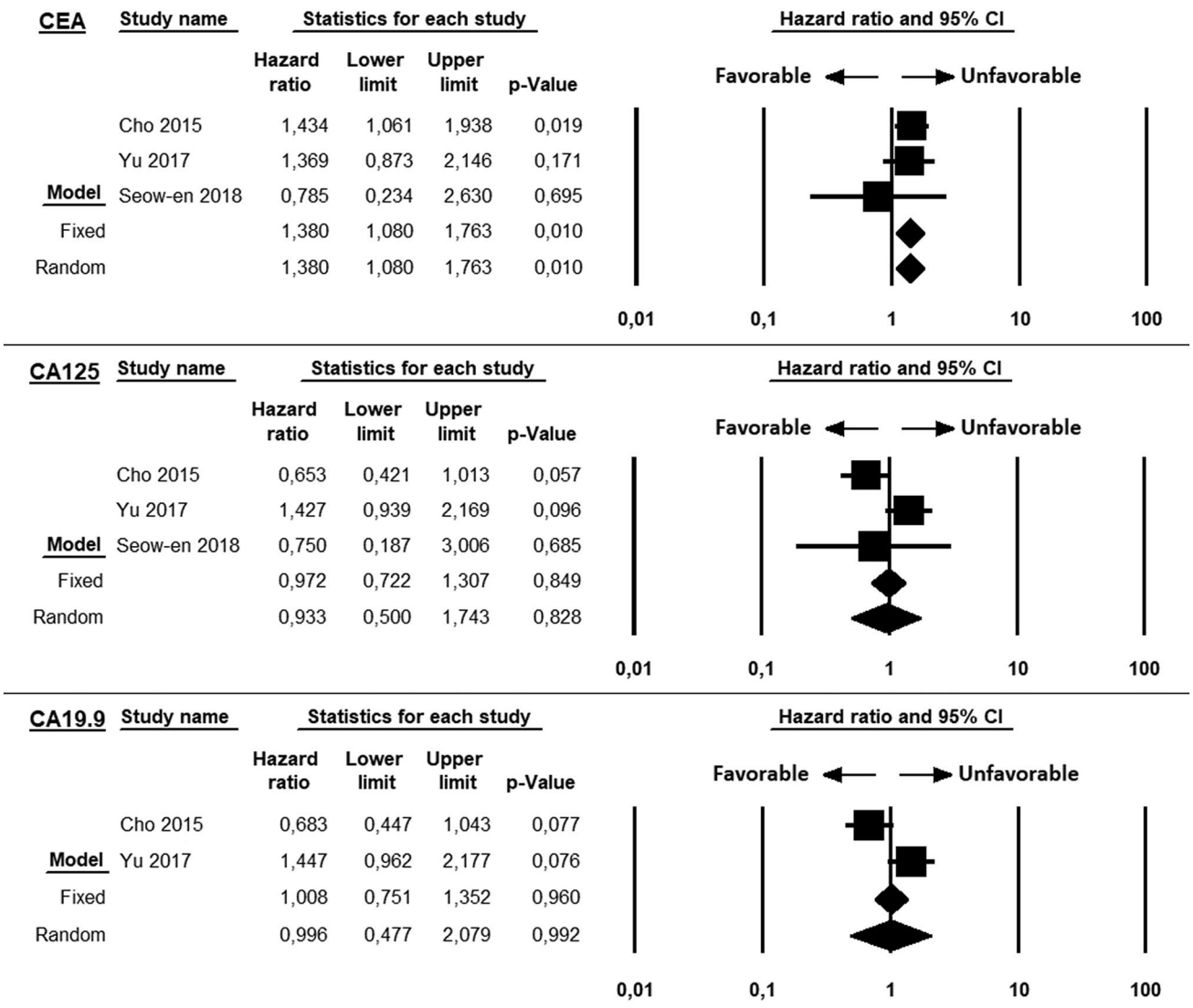

Fig. 5 Forest plots reporting pooled hazard ratios (HR) for the impact of serum levels of CEA, CA125 and CA19.9 on the overall survival in patients with Krukenberg tumor

an about twofold increase in the risk of death, similarly to that found for peritoneal involvement.

Regarding chronology, a synchronous presentation resulted to be a significant unfavorable prognostic factor. This finding might be due to the fact that more aggressive tumors are more likely to cause early metastases, or alternatively to a delayed diagnosis of the primary tumor.

The presence of signet ring cell is regarded as a hallmark of KT. However, the percentage of signet ring cells may be highly variable among tumors. Since signet ring cells are considered as a sign of aggressiveness, a predominance of this morphology was a candidate unfavorable prognostic factor [33, 36, 37, 40, 45, 47, 49]. Unexpectedly, a predominant signet ring cell morphology did not appear to affect the OS. Maybe, the prognostic value of signet ring cell might be lost in advanced cases with ovarian metastases; such hypothesis needs to be clarified by further studies.

Serum tumor markers studies were CEA, CA19.9 and CA 125. Increase serum levels of CEA appeared as a significant unfavorable prognostic factor in the pooled estimate, despite being non-significant in the individual studies. On the other hand, CA19.9 and CA 125 were not found to have a prognostic value. However, given the small amount of studies assessing tumor markers, further research is needed to define whether the assessment of these markers may be of value in the prognostic stratification of KT.

Strengths and limitations

To the best of our knowledge, this is the first meta-analysis on prognostic factors in KT. In spite of the rarity of KT, this study included quite a large sample, with a total of 1743 patients. All available clinicopathologic factors studied in the literature were assessed in this study, performing both a qualitative and a quantitative synthesis.

Limitations of our study are the lack of randomized controlled trials, which are difficult to perform in a rare disease such as KT. In this regard, the heterogeneity in the baseline characteristics of the study population, in the study methods and in the patient management might have affected the results of this study.

Conclusion

In KT peritoneal involvement, ascites, synchronous presentation and increased serum CEA levels appear as significant unfavorable prognostic factors. The assessment of such factors may be considered in a prognostic algorithm for the risk stratification in KT, to achieve a more tailored management of patients.

On the other hand, age, menopausal status, KT size, bilateral ovarian involvement, non-peritoneal extaovarian metastases, signet ring cell morphology and levels of CA125 and CA19.9 does not seem to affect the OS. Evidence on the prognostic value of a gastric origin appears inconclusive. Further studies are necessary in this field.

Author contributions RL, MDL: study conception, electronic search, eligibility of the studies, inclusion criteria, risk of bias, data extraction and data analysis. AR, AT: study conception, disagreement resolution, manuscript preparation, data extraction and data analysis. GS, ADC: electronic search, eligibility of the studies, inclusion criteria, risk of bias, data extraction and data analysis. MM: methods supervision, manuscript preparation. MDA, LI: study design, methods supervision, manuscript preparation. FZ: study design, manuscript preparation, whole study supervision. FC: study design, methods supervision, whole study supervision.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical approval Given the study design (systematic review and meta-analysis), Institutional Review Board approval was not requested, since no new patients' data were handled.

References

1. Al-Agha OM, Nicastri AD (2006) An in-depth look at Krukenberg tumor: an overview. Arch Pathol Lab Med 130(11):1725–1730
2. Yang C, Sun L, Zhang L et al (2018) Diagnostic utility of SATB2 in metastatic Krukenberg tumors of the ovary: an immunohistochemical study of 70 cases with comparison to CDX2, CK7, CK20, chromogranin, and synaptophysin. Am J Surg Pathol 42(2):160–171
3. Kubeček O, Laco J, Špaček J et al (2017) The pathogenesis, diagnosis, and management metastatic tumors to the ovary: a comprehensive review. Clin Exp Metastasis 34(5):295–307
4. Turan T, Aykan B, Koc S et al (2006) Analysis of metastatic ovarian tumors from extragenital primary sites. Tumori 92(6):491–495
5. Kiyokawa T, Young RH, Scully RE (2006) Krukenberg tumors of the ovary: a clinicopathologic analysis of 120 cases with emphasis on their variable pathologic manifestations. Am J Surg Pathol 30(3):277–299
6. Novak E, Gray LA (1938) Krukenberg tumors of the ovary: clinical and pathological study of 21 cases. Surg Gynecol Obstet 66:157–167
7. Lionetti R, De Luca M, Travaglino A et al (2019) Treatments and overall survival in patients with Krukenberg tumor. Arch Gynecol Obstet 300(1):15–23
8. Travaglino A, Raffone A, Saccone G et al (2018) Loss of B-cell lymphoma 2 immunohistochemical expression in endometrial hyperplasia: a specific marker of precancer and novel indication for treatment: A systematic review and meta-analysis. Acta Obstet Gynecol Scand 97(12):1415–1426
9. Travaglino A, Raffone A, Saccone G et al (2019) Endometrial hyperplasia and the risk of coexistent cancer: WHO versus EIN criteria. Histopathology 74(5):676–687
10. Raffone A, Travaglino A, Saccone G et al (2019) PAX2 in endometrial carcinogenesis and in differential diagnosis of endometrial hyperplasia. A systematic review and meta-analysis of diagnostic accuracy. Acta Obstet Gynecol Scand 98(3):287–299
11. Raffone A, Travaglino A, Saccone G et al (2019) Loss of PTEN expression as diagnostic marker of endometrial precancer: a systematic review and meta-analysis. Acta Obstet Gynecol Scand 98(3):275–286
12. Moher D, Shamseer L, Clarke M et al (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 4:1
13. Travaglino A, Raffone A, Saccone G et al (2018) PTEN as a predictive marker of response to conservative treatment in endometrial hyperplasia and early endometrial cancer. A systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 231:104–110
14. Raffone A, Travaglino A, Saccone G et al (2019) Management of women with atypical polypoid adenomyoma of the uterus: a quantitative systematic review. Acta Obstet Gynecol Scand 98(7):842–855
15. Travaglino A, Raffone A, Saccone G et al (2019) Immunohistochemical predictive markers of response to conservative treatment of endometrial hyperplasia and early endometrial cancer: a systematic review. Acta Obstet Gynecol Scand. https://doi.org/10.1111/aogs.13587 **[Epub ahead of print]**
16. Slim K, Nini E, Forestier D et al (2003) Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg 73(9):712–716
17. Travaglino A, Raffone A, Saccone G et al (2019) Immunohistochemical nuclear expression of β-catenin as a surrogate of CTNNB1 exon 3 mutation in endometrial cancer. Am J Clin Pathol 151(5):529–538

18. Raffone A, Travaglino A, Saccone G et al (2019) Should progesterone and estrogens receptors be assessed for predicting the response to conservative treatment of endometrial hyperplasia and cancer? A systematic review and meta-analysis. Acta Obstet Gynecol Scand 98(8):976–987
19. Travaglino A, Raffone A, Saccone G et al (2019) Complexity of glandular architecture should be reconsidered in the classification and management of endometrial hyperplasia. APMIS 127(6):427–434
20. Travaglino A, Raffone A, Saccone G et al (2019) PTEN immunohistochemistry in endometrial hyperplasia: which are the optimal criteria for the diagnosis of precancer? APMIS 127(4):161–169
21. Raffone A, Travaglino A, Saccone G et al (2019) Endometrial hyperplasia and progression to cancer: which classification system stratifies the risk better? A systematic review and meta-analysis. Arch Gynecol Obstet 299(5):1233–1242
22. Raffone A, Travaglino A, Saccone G et al (2019) PTEN expression in endometrial hyperplasia and risk of cancer: a systematic review and meta-analysis. Arch Gynecol Obstet 299(6):1511–1524
23. Travaglino A, Raffone A, Saccone G et al (2019) Nuclear expression of β-catenin in endometrial hyperplasia as marker of premalignancy. APMIS. https://doi.org/10.1111/apm.12988 **[Epub ahead of print]**
24. Raffone A, Travaglino A, Saccone G et al (2019) Diagnostic and prognostic value of ARID1A in endometrial hyperplasia: a novel marker of occult cancer. APMIS 127(9):597–606
25. Raffone A, Travaglino A, Saccone G et al (2019) Diabetes mellitus is associated with occult cancer in endometrial hyperplasia. Pathol Oncol Res. https://doi.org/10.1007/s12253-019-00684-3 **[Epub ahead of print]**
26. Raffone A, Travaglino A, Saccone G et al (2019) Diabetes mellitus and responsiveness of endometrial hyperplasia and early endometrial cancer to conservative treatment. Gynecol Endocrinol. https://doi.org/10.1080/09513590.2019.1624716 **[Epub ahead of print]**
27. Rayson D, Bouttell E, Whiston F, Stitt L (2000) Outcome after ovarian/adnexal metastectomy in metastatic colorectal carcinoma. J Surg Oncol 75(3):186–192
28. Kim HK, Heo DS, Bang YJ, Kim NK (2001) Prognostic factors of Krukenberg's tumor. Gynecol Oncol 82(1):105–109
29. Cheong JH, Hyung WJ, Chen J, Kim J, Choi SH, Noh SH (2004) Surgical management and outcome of metachronous Krukenberg tumors from gastric cancer. J Surg Oncol 87(1):39–45
30. McCormick CC, Giuntoli RL 2nd, Gardner GJ et al (2007) The role of cytoreductive surgery for colon cancer metastatic to the ovary. Gynecol Oncol 105(3):791–795
31. Yook JH, Oh ST, Kim BS (2007) Clinical prognostic factors for ovarian metastasis in women with gastric cancer. Hepatogastroenterology 54(75):955–959
32. Jiang R, Tang J, Cheng X, Zang RY (2009) Surgical treatment for patients with different origins of Krukenberg tumors: outcomes and prognostic factors. Eur J Surg Oncol 35(1):92–97
33. Kim WY, Kim TJ, Kim SE et al (2010) The role of cytoreductive surgery for non-genital tract metastatic tumors to the ovaries. Eur J Obstet Gynecol Reprod Biol 149(1):97–101
34. Jun SY, Park JK (2011) Metachronous ovarian metastases following resection of the primary gastric cancer. J Gastric Cancer 11(1):31–37
35. Ojo J, De Silva S, Han E et al (2011) Krukenberg tumors from colorectal cancer: presentation, treatment and outcomes. Am Surg 77(10):1381–1385
36. Guzel AB, Kucukgoz G, Paydas S et al (2012) Preoperative evaluation, clinical characteristics and prognostic factors of nongenital metastatic ovarian tumors: review of 48 patients. Eur J Gynaec Oncol 33(5):493–497
37. Lu LC, Shao YY, Hsu CH et al (2012) Metastasectomy of Krukenberg tumors may be associated with survival benefits in patients with metastatic gastric cancer. Anticancer Res 32(8):3397–3401
38. Peng W, Hua RX, Jiang R, Ren C, Jia YN, Li J, Guo WJ (2013) Surgical treatment for patients with Krukenberg tumor of stomach origin: clinical outcome and prognostic factors analysis. PLoS ONE 8(7):e68227
39. Wu XJ, Yuan P, Li ZY et al (2013) Cytoreductive surgery and hypertermic intraperitoneal chemotherapy improves the survival of gastric cancer patients with ovarian metastasis and peritoneal dissemination. Tumour Biol 34(1):463–469
40. Cho JH, Lim JY, Choi AR et al (2015) Comparison of surgery plus chemotherapy and palliative chemotherapy alone for advanced gastric cancer with krukenberg tumor. Cancer Res Treat 47(4):697–705
41. Jeung YJ, Ok HJ, Kim WG, Kim SH, Lee TH (2015) Krukenberg tumors of gastric origin versus colorectal origin. Obstet Gynecol Sci 58(1):32–39
42. Wu F, Zhao X, Mi B et al (2015) Clinical characteristics and prognostic analysis of Krukenberg tumor. Mol Clin Oncol 3(6):1323–1328
43. Rosa F, Marrelli D, Morgagni P et al (2016) Krukenberg tumors of gastric origin: the rationale of surgical resection and perioperative treatments in a multicenter western experience. World J Surg 40(4):921–928
44. Ganesh K, Shah RH, Vakiani E et al (2017) Clinical and genetic determinants of ovarian metastases from colorectal cancer. 123(7):1134–1143
45. Kammar PS, Engineer R, Patil PS, Ostwal V, Shylasree TS, Saklani AP (2017) Ovarian metastases of colorectal origin: treatment patterns and factors affecting outcomes. Indian J Surg Oncol 8(4):519–526
46. Xu KY, Gao H, Lian ZJ, Ding L, Li M, Gu J (2017) Clinical analysis of Krukenberg tumours in patients with colorectal cancer—a review of 57 cases. World J Surg Oncol 15(1):25
47. Yu P, Huang L, Cheng G et al (2017) Treatment strategy and prognostic factors for Krukenberg tumors of gastric origin: report of a 10-year single-center experience from China. Oncotarget 8(47):82558–82570
48. Seow-En I, Hwarng G, Tan GHC, Ho LML, Teo MCC (2018) Palliative surgery for Krukenberg tumors—12-year experience and review of the literature. World J Clin Oncol 9(1):13–19
49. Tai H, Yang Q, Wu Z et al (2018) PD-L1 expression predicts a distinct prognosis in Krukenberg tumor with corresponding origins. J Immunol Res 2018:9485285