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REVIEW

Impact of endometrial carcinoma histotype on the prognostic value of the TCGA molecular subgroups

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Abstract

Background The Cancer Genome Atlas (TCGA) identified four prognostic subgroups of endometrial carcinoma: copy-number-low/p53-wild-type (p53wt), POLE-mutated/ultramutated (POLEmt), microsatellite-instability/hypermutated (MSI), and copy-number-high/p53-mutated (p53mt). However, it is still unclear if they may be integrated with the current histopathological prognostic factors, such as histotype.

Objective To assess the impact of histotype on the prognostic value of the TCGA molecular subgroups of endometrial carcinoma.

Methods A systematic review and meta-analysis was performed by searching 7 electronic databases from their inception to April 2019 for studies assessing prognosis in all TCGA subgroups of endometrial carcinoma. Pooled hazard ratio (HR) for overall survival (OS) was calculated in two different groups ("all-histotypes" and "endometrioid"), using p53wt subgroup as reference standard; HR for non-endometrioid histotypes was calculated indirectly. Disease-specific survival and progression-free survival were assessed as additional analyses.

Results Six studies with 2818 patients were included. In the p53mt subgroup, pooled HRs for OS were 4.322 (all-histotypes), 2.505 (endometrioid), and 4.937 (non-endometrioid). In the MSI subgroup, pooled HRs were 1.965 (all-histotypes), 1.287 (endometrioid), and 6.361 (non-endometrioid). In the POLEmt subgroup, pooled HRs were 0.763 (all-histotypes), 0.481 (endometrioid), and 2.634 (non-endometrioid). Results of additional analyses were consistent for all subgroups except for non-endometrioid POLEmt carcinomas.

Conclusion Histotype of endometrial carcinoma shows a crucial prognostic value independently of the TCGA molecular subgroup, with non-endometrioid carcinomas having a worse prognosis in each TCGA subgroup. Histotype should be integrated with molecular characterization for the risk stratification of patients in the future.

Keywords Cancer · Treatment · Endometrium · Risk assessment · ProMisE

Introduction

Endometrial carcinoma is the most common gynecologic cancer in the Western world [1, 2]. In the last decades, both incidence and mortality of endometrial carcinoma have shown an increase [1]. Causes of such an unfavorable trend probably lie in an inaccurate risk stratification, which would cause many patients to be undertreated or overtreated [3, 4].

In 2013, The Cancer Genome Atlas (TCGA) Research Network has identified four novel molecular prognostic subgroups of endometrial carcinoma: copy-number-low/p53-wild-type (p53wt), *POLE*-mutated/ultramutated (POLEmt), microsatellite-instability/hypermutated (MSI), and copy-number-high/p53-mutated (p53mt) [5–11]. This

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reclassification has had great impact on the scientific research, since the TCGA subgroups have the potential of improving the risk stratification in endometrial carcinoma, with consequent improvement in the patient management [6–11]. Given the costs, complex equipment, and expertise required for sequencing techniques, the TCGA classification appears little applicable in the common practice; therefore, great efforts have been made in the search for cheaper surrogates of molecular markers [6–13]. The Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) has proposed the use of immunohistochemistry for mismatch repair proteins and p53 as surrogates of MSI assessment and *TP53* sequencing, respectively [6, 8, 11]. Indeed, immunohistochemistry is cheaper, faster, and more widely available than sequencing techniques [14–22].

While the prognostic value of the TCGA subgroups has been confirmed in several studies [6–11], it is still unclear how they may be integrated with histologic features such as tumor grade and histotype. In fact, while some authors hypothesized that molecular features may completely replace histologic features in the future, other ones consider the value of histology as crucial for the patient management [23, 24].

The objective of this study was to assess if and how histotype affects the prognostic value of the TCGA subgroups of endometrial carcinoma. For this purpose, we calculated pooled hazard ratios (HR) for overall survival (OS), disease-specific survival (DSS), and progression-free survival (PFS) in each TCGA subgroup, assessing how they change based on histotype.

Materials and methods

Study protocol

Study methods were defined a priori. All stages were completed by two reviewers (AT, AR). Disagreements were resolved by discussion among all authors. The study was reported according to the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement [25].

Search strategy

Web of Sciences, Google Scholar, Scopus, MEDLINE, ClinicalTrial.gov, Cochrane Library, and EMBASE were used as electronic databases from their inception to April 2019. Several different combinations of the following text words were used: "survival"; "TP53″; "tumor protein 53"; "p53"; "endometr*"; "copy number"; "POLE"; "MMR"; "mismatch repair"; "MSI"; "EPCAM"; "microsatellite instability"; "MLH1"; "MSH2"; "MSH6"; "PMS2"; "ultramutated"; "hypermutated"; "cancer"; "carcinoma"; "adenocarcinoma"; "neoplas*"; "tumor"; "tumour"; "endometrioid"; "serous"; "clear cell"; "undifferentiated"; "immunohistochemistry"; "immunohistochemical"; "marker"; "prognosis"; "Atlas"; "cancer"; "genome"; "PORTEC"; "TransPORTEC"; "TCGA"; "ProMisE"; "Proactive Molecular Risk Classifier". References from each study were also assessed.

Study selection

All peer-reviewed studies assessing prognosis in each TCGA subgroup of endometrial carcinoma were included. Exclusion criteria, defined a priori, were: sample size < 10 in any TCGA subgroup; minimal follow-up time < 2 years; case reports; reviews; overlapping patient data (in this case, the study with smaller sample size was excluded). Studies not assessing prognosis in any TCGA subgroup were also excluded.

Data extraction

Primary data extracted were HR estimates with 95% confidence interval (CI) for each TCGA subgroup.

To assess the impact of histotype on the prognosis of the TCGA subgroup, pooled HR was calculated separately for two group of studies: the first group was composed of studies that assessed endometrial carcinomas of any histotype ("all-histotypes" group), while the second group was composed of studies that assessed only endometrioid carcinomas ("endometrioid" group). HR from multivariate analyses were not considered, since they were normalized for all clinicopathological factors, not allowing to isolate the impact of histotype.

PICOS were used for data extraction as follows:

"P" (population) of our study was patients with endometrial carcinoma.

"I" (intervention or risk factor) was the TCGA subgroup (p53mt, MSI, POLEmt), assessed by molecular sequencing or immunohistochemical surrogates according to the ProMisE [2, 6, 19].

"C" (comparator) was the p53wt subgroup.

"O" (outcomes) were OS (primary outcome), and DSF and PFS (secondary outcomes). OS (or time to death) was defined as time from surgery until death of any cause. DSF (or time to death from disease) was defined as time from surgery until death due to endometrial cancer. PFS (or time to progression) was defined as time from surgery until there is evidence of recurrent or progressive disease (this is based on either clinical evidence of recurrence or imaging confirmation of recurrence) or if they died of the disease prior to the censoring date.

"S" (study design) was cohort study.

Assessment of risk of bias within studies

The Methodological Index for Non-Randomized Studies (MINORS) was used to assess the risk of bias within studies [26]. Six domains related to risk of bias were assessed in each study: (1) Aim (i.e., clearly stated aim); (2) Patients (i.e., all eligible patients were included in the study during the period of enrollment); (3) Data (i.e., data were collected according to a protocol defined before the beginning of the study); (4) Endpoint (i.e., clear explanation of methods used for outcomes measurement); (5) Bias (i.e., the study endpoints were blindly evaluated, re-evaluated, or evaluated by two or more authors); (6) Follow-up (i.e., follow-up time of at least 2 years).

Authors' judgments were categorized as "low risk", "unclear risk", or "high risk" of bias as previously described [27–31].

Data analysis

Hazard ratio (HR) with 95% CI for each TCGA subgroup was extracted from each study and pooled by using the random effect model of DerSimonian and Laird. HR values with 95% CI were reported for each study and as pooled estimated on forest plots.

HR analysis was performed separately in "all-histotypes" group and "endometrioid" group. Pooled HR of non-endometrioid histotypes was calculated indirectly using the following equation for each TCGA subgroup:

$$\text{HR non endometriod} = \frac{(\text{HR all histotypes} \times n \text{ all histotypes}) - (\text{HR endometrioid} \times n \text{ endometrioid})}{n \text{ non endometrioid}}.$$

Here, n is the number of carcinomas; HR all histotype, n all histotypes, n endometrioid, and n non-endometrioid were extracted from the "all-histotypes" group of studies.

The number of endometrial carcinomas of the "endometrioid" group was excluded from the equation, because it would have altered the proportion among the prevalence of the different histotypes in the four TCGA groups.

Statistical heterogeneity among studies was quantified through the inconsistency index I^2: heterogeneity was categorized as: null for $I^2 = 0\%$, minimal for $I^2 < 25\%$, low for $I^2 < 50\%$, moderate for $I^2 < 75\%$, and high for $I^2 \geq 75\%$, as previously described [32–39].

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

Results

Study selection

Six studies with a total of 2818 patients diagnosed with endometrial carcinomas were included [6–11]. The whole process of study selection is shown in Supplementary Fig. 1.

The patient cohort was retrospective in three studies [6–8], prospective in one study [10], derived from a randomized-controlled trial (RCT) in one study [7], and mixed (RCT + retrospective) in the remaining study [9]. Three studies were included in the "all-histotypes" group [6, 8, 11] and three in the "endometrioid" group [7, 9, 10]. In the "all-histotypes" group, the prevalence of non-endometrioid histotypes was 4% in the p53wt subgroup, 74.7% in the p53mt subgroup, 13.4% in the MSI subgroup, and 13.1% in the POLEmt subgroup.

Characteristics of the included studies are shown in Table 1.

Risk of bias within studies

For the "aim", "data", "endpoint", and "follow-up" domains, all studies were considered at low risk of bias.

For the "patients" domain, two studies were considered at unclear risk of bias, because they did not clearly state if patients were consecutively selected [6, 8]. All the remaining studies were considered at low risk of bias.

For the "bias" domain, one study was considered at unclear risk of bias, since it was unclear if specimens were blindly evaluated, re-evaluated, or evaluated by two or more authors; all the other studies were considered at low risk of bias [9].

Results about risk of bias assessment are shown in Supplementary Fig. 2.

Main analysis

All included studies assessed OS and thus were suitable for the main analysis [6–11].

In the "all-histotypes" group, pooled HR was 4.322 (95% CI 3-6.226; $I^2 = 16{,}89$) for p53mt subgroup, 1.965 (95% CI 1.384–2.789; $I^2 = 0$) for MSI subgroup, and 0.763 (95% CI 0.426–1.367; $I^2 = 0$) for POLEmt subgroup (Fig. 1).

In the "endometrioid" group, pooled HR was 2.505 (95% CI 1.119–5.609; $I^2 = 90{,}69$) for p53mt subgroup, 1.287 (95% CI 0.793–2.089; $I^2 = 81{,}36$) for MSI subgroup, and 0.481

Table 1 Characteristics of the included studies

Year	Study	Country	Patient cohort	Period of enrollment	Sample size	Histotype	
						Endometrioid (%)	Non-endometioid (%)
2015	Talhouk et al.	Canada	Retrospective cohort	2002–2009	143	119 (83)	24 (17)
2016	Stelloo et al.	Netherlands	RCT	1990–1997 2000–2006	546	546 (100)	0 (0)
2017	Talhouk et al.	Canada	Retrospective cohort	1983-2013	319	215 (67)	104 (33)
2018	Bosse et al.	Canada, Spain, USA, Netherlands, UK	RCT + Retrospective cohort	1990–1997 2000–2006	376	376 (100)	0 (0)
2018	Cosgrove et al.	USA	Prospective cohort	2003-2007	982	982 (100)	0 (0)
2018	Kommoss et al.	Germany	Retrospective cohort	2003–2013	452	397 (88)	55 (12)

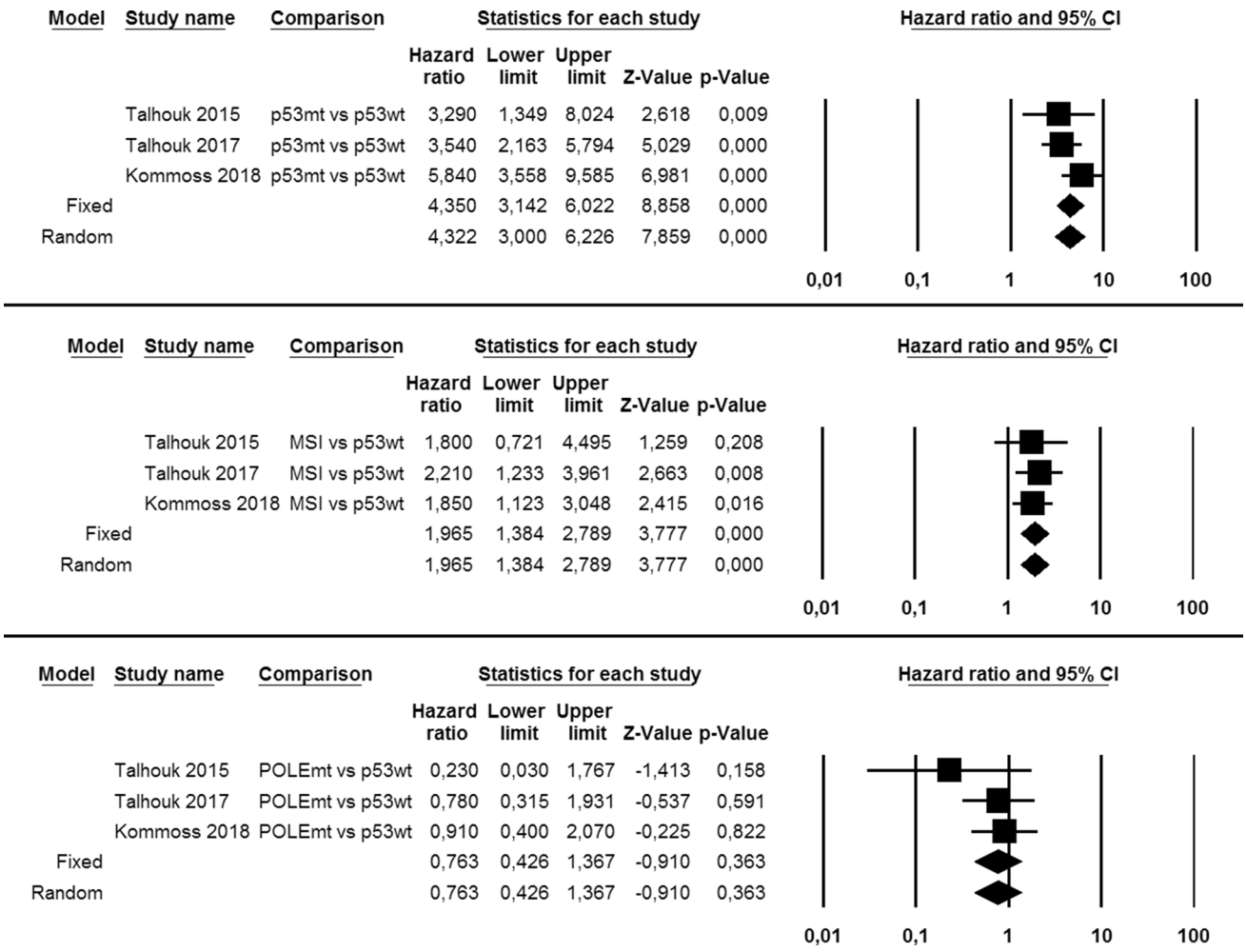

Fig. 1 Forest plots of hazard ratio (HR) for overall survival in the TCGA molecular subgroups of endometrial carcinoma ("all-histotypes" group)

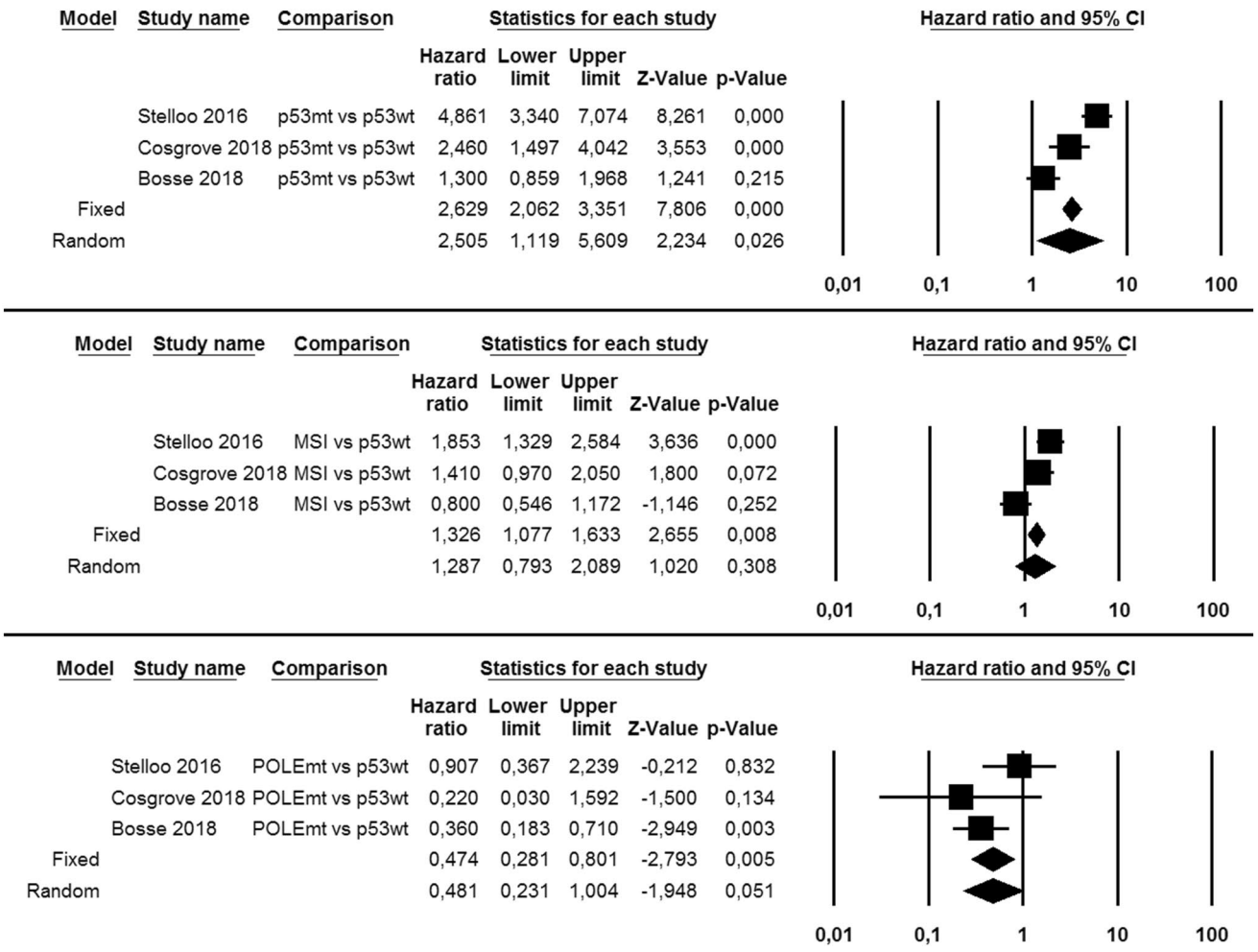

Fig. 2 Forest plots of hazard ratio (HR) for overall survival in the TCGA molecular subgroups of endometrial carcinoma ("endometrioid" group)

(95% CI 0.231–1.004; $I^2 = 37,29$) for POLEmt subgroup (Fig. 2).

The HR estimate for non-endometrioid histotypes was 4.937 for p53mt subgroup, 6.361 for MSI subgroup, and 2.634 for POLEmt subgroup.

Additional analyses

In the "all-histotypes" group, all studies assessed DSS and PFS and, thus, were suitable for additional analyses. With regard to DSS, pooled HR was 5.493 (95% CI 3.045–9.908; $I^2 = 49,1$) for p53mt group, 2.244 (95% CI 1.211–4.157; $I^2 = 25,38$) for MSI group, and 0.565 (95% CI 0.247–1.291; $I^2 = 0$) for POLEmt group (Supplementary Fig. 3). With regard to PFS, pooled HR was 5.509 (95% CI 2.513–12.078; $I^2 = 0$) for p53mt group, 1.85 (95% CI 0.905–3.78; $I^2 = 84,24$) for MSI group, and 0.397 (95% CI 0.162–0.971; $I^2 = 0$) for POLEmt group (Supplementary Fig. 4).

In the "endometrioid" group, only 1 study assessed DSS [10], and only 2 assessed PFS [9, 10]. With regard to DSS, pooled HR was 3.95 (95% CI 2.099–7.435; $I^2 = 0$) for p53mt group, 1.58 (95% CI 0.919–2.717; $I^2 = 0$) for MSI group, and 0.48 (95% CI 0.063–3.671; $I^2 = 0$) for POLEmt group (Supplementary Fig. 5). With regard to PFS, pooled HR was 2.031 (95% CI 1.494–2.762; $I^2 = 0$) for p53mt group, 0.978 (95% CI 0.476–2.012; $I^2 = 84,24$) for MSI group, and 0.207 (95% CI 0.084–0.51; $I^2 = 0$) for POLEmt group (Supplementary Fig. 6).

In non-endometrioid histotypes, the HR estimate for DSS was 6.016 for p53mt subgroup, 6.549 for MSI subgroup, and 1.129 for POLEmt subgroup. The estimated HR for PFS was 6.687 for p53mt subgroup, 7.504 for MSI subgroup, and 1.658 for POLEmt subgroup.

Scales of HR values for OS, DSS, and PFS are summarized in Fig. 3, Supplementary Fig. 7, and Supplementary Fig. 8, respectively.

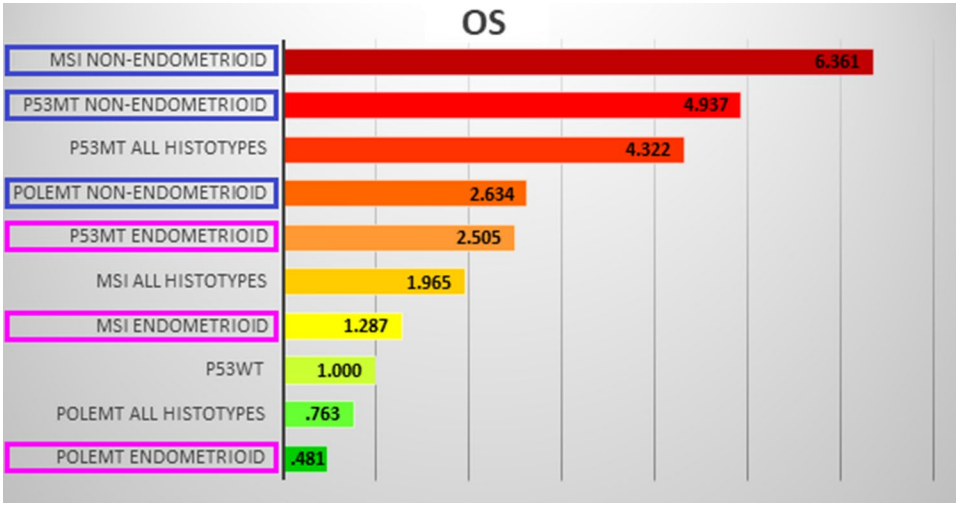

Fig. 3 Scale of hazard ratio for overall survival (OS) in the TCGA subgroups of endometrial carcinoma stratified by histotype: endometrioid (pink squares), non-endometrioid (blue squares), or all histotypes (no squares)

Discussion

Main analysis

Our study showed that, although the prognostic value of TCGA subgroups was confirmed, prognosis was affected by histotype in each TCGA prognostic subgroup.

In accordance with the initial TCGA findings, the overall prognosis of the p53mt subgroup was by far the worst among the four TCGA subgroups [5, 40]. Considering all histotypes, the HR for OS was indeed 4.3, indicating a prognosis more than four times worse than that of the p53wt subgroup. Considering only endometrioid histotypes, the HR showed an important decrease, with a value of 2.5. On the other hand, the HR estimate for non-endometrioid histotypes went up to about 5. This indicates a strong impact of non-endometrioid histotypes on the overall prognosis of the p53mt group. Such impact appeared clearly stronger than that in the other subgroups. In fact, as above mentioned, the p53mt subgroup is mainly composed of serous carcinomas [5–11]. For this reason, the p53mt subgroup was also referred to as "serous" subgroup by the TCGA [5]. These findings suggest that non-endometrioid histotypes account for an important part of the worse prognosis of the p53mt subgroup. However, although decreased, the unfavorable prognostic value of *TP53* mutations remained significant even considering only endometrioid histotypes. In this regard, it may be appropriate to remark that an aberrant p53 expression does not imply a diagnosis of serous carcinoma, given the existence of non-serous p53mt carcinomas and the difference in the prognosis of p53mt carcinomas based on the histotype [41–44].

The MSI subgroup showed the second worst overall prognosis after the p53mt subgroup, although with HR values definitely lower than those in the latter one. This appears consistent with the percentage of non-endometrioid histotypes, which is much higher than that in the p53wt subgroup, but much lower than that in the p53mt subgroup. Considering all histotypes, the HR value was about 2, indicating that the prognosis of the MSI subgroup is about two times worse than that of the p53wt subgroup. Considering only endometrioid histotype, the HR value decreased to 1.3, indicating a prognosis slightly worse than that of the p53wt subgroup, which did not reach a statistically significant difference. For non-endometrioid histotypes, the HR increased to over 6, indicating a prognosis even worse than that of non-endometrioid p53mt carcinomas. This outstanding result might be explained by the high frequency of MSI in highly aggressive histotypes such as undifferentiated and dedifferentiated carcinomas [45–48]. This once again supported the importance of histotype in the risk stratification. Therefore, the suggestion that mismatch repair deficiency and microsatellite instability imply a diagnosis of endometrioid histotype appears inappropriate [24]. However, the similar prognosis between endometrioid MSI carcinomas and p53wt carcinomas does not imply that the MSI subgroup has not its own prognostic value. Indeed, despite being homogeneous about histotype, the p53wt subgroup is genetically heterogeneous and lacks a molecular or immunohistochemical signature [5–11]. There is evidence that the p53wt subgroup can be subdivided in at least two sub-subgroups, based on the presence of *CTNNB1* exon 3 mutations [12, 23]. In this regard, it has been shown that the sub-subgroup with *CTNNB1* may have a prognosis similar to that of the MSI subgroup [7, 12, 23]. This would explain the prognostic overlap observed in our analysis.

In the POLE subgroup, the overall prognosis was the best one, with an HR of about 0.7, indicating a prognosis slightly better than that of the p53wt subgroup. However, such difference was not statistically significant. Considering only endometrioid histotype, the difference with the p53wt group even increased, with a prognosis more than two times better

than that of the p53wt subgroup. On the other hand, in non-endometrioid carcinomas, the prognosis of the POLE subgroup sensibly worsened, with an HR of 2.6; this indicates a prognosis of more than two times and half worse than that of the p53wt subgroup, and even worse than that of endometrioid p53mt carcinomas. Therefore, even in the POLEmt subgroup, histotype seems to have a crucial prognostic value. This appears in contrast with the assumptions that all POLEmt carcinomas should be diagnosed as endometrioid, or that they are not affected by histotype [24].

The scale of HR values reported in Fig. 3 suggests that non-endometrioid carcinomas have a risk of death of any cause worse than that of endometrioid carcinomas, regardless of the TCGA subgroup. However, at the same histotype, the prognosis was very different amongst TCGA subgroup. These findings endorse the efforts for an integration of molecular data with clinicopathological factors in the risk stratification of endometrial cancer [49–55], to achieve an optimal and tailored patient management.

Additional analyses

Analyses of DSS and PFS partially confirmed the findings of the OS analysis, with non-endometrioid MSI carcinomas showing the worst prognosis, followed by non-endometrioid p53mt carcinomas, and with endometrioid POLEmt carcinomas showing the best prognosis.

The main difference lied in the prognosis of non-endometrioid POLEmt carcinomas. Indeed, while the risk of death of any cause was similar to that of endometrioid p53mt carcinomas, the risk of death by cancer was definitely lower, being similar to that of the p53wt subgroup. It might be hypothesized that non-endometrioid POLEmt carcinomas occur preferentially in patients older and/or with more comorbidities if compared to endometrioid POLEmt carcinomas; further studies are necessary to investigate this point. On the other hand, in this subset, the risk of recurrence/progression was intermediate between p53wt subgroup and endometrioid p53mt.

Endometrioid p53mt carcinomas still showed a risk definitely lower than their non-endometrioid counterpart (two times lower for DSS and more than three times lower for PFS).

Regarding endometrioid MSI carcinomas, they still showed a risk higher than p53wt subgroup in DSS analysis, although without statistical significance, while the risk of recurrence/progression was similar.

Strengths and limitations

To the best of our knowledge, this may be the first meta-analysis assessing the prognostic value of histotype regarding the four TCGA molecular subgroups of endometrial cancer. This study provided estimates on the prognosis of each TCGA subgroup separately for endometrioid and non-endometrioid carcinomas. Our results are also strengthened by the reliability of the reference standard about histotype. Indeed, given the low prevalence of non-endometrioid histotypes in the p53wt subgroup, its prognosis was not expected to significantly change between the "all-histotypes" and the "endometrioid" group.

Limitations of our meta-analysis might be the indirect calculation of HR for non-endometrioid histotypes and the impossibility of calculating HR in each non-endometrioid histotype (serous, mucinous, clear cell, and undifferentiated/dedifferentiated, carcinosarcoma).

Conclusion

In endometrial carcinoma, histotype maintains a crucial prognostic value independently from the TCGA molecular subgroups, with non-endometrioid carcinomas having a worse prognosis in each subgroup.

In particular, among all TCGA subgroups, non-endometrioid carcinomas of the MSI subgroup have the highest risk of death of any cause, death by cancer, and recurrence/progression of disease, followed by non-endometrioid carcinomas of the p53mt subgroup; non-endometrioid POLEmt carcinomas showed a variable prognosis instead.

On the other hand, endometrioid carcinomas of the p53mt subgroup showed the worst prognosis among all endometrioid carcinomas, while endometrioid POLEmt carcinomas consistently showed the best prognosis among all endometrial carcinomas; endometrioid MSI carcinomas showed a significant overlap with the p53wt group.

Given these findings, histotype remains as a major prognostic factor in endometrial carcinoma, and it should be integrated with molecular characterization for the risk stratification. Further studies are necessary in this regard.

Author contribution AT and AR independently assessed electronic search, eligibility of the studies, inclusion criteria, risk of bias, data extraction, and data analysis. CS, RE, PM, CG, and GO contributed to the elaboration of methods for risk of bias assessment, data extraction, and analysis. AT, AR, LI, and FZ conceived the study; AT, AR, CS, LI, and FZ worked on the design of the study; AT, AR, RE, PM, and CG worked on the manuscript preparation; LI and FZ supervised the whole study.

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Compliance with ethical standards

Conflict of interest The authors report no conflict of interest.

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