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Histopathological characterization of ProMisE molecular groups of endometrial cancer

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HIGHLIGHTS

- Histopathological characteristics of ProMisE groups of endometrial cancer are still undefined.
- This characterization may help understand how the novel molecular classifier may change the current patients' management.
- This may be the first meta-analysis to provide a histopathological characterization of ProMisE groups.
- Many patients are currently undertreated or overtreated (in particular in the POLE-mt and MMR-d groups).
- An integration of molecular and histological features in a tailored risk assessment may be crucial for endometrial cancer.

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ABSTRACT

Background. After the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) development, endometrial cancer (EC) may be reclassified in four novel prognostic groups: POLE-mutated (POLE-mt), mismatch-repair-deficient (MMR-d), p53-abnormal (p53abn), p53-wild-type (p53wt). However, histopathological characteristics of each ProMisE group are still undefined. Such characterization may be useful to understand how this novel molecular classifier may change the current patient management, reducing over- and undertreatment.

Aim. To provide a histopathological characterization of ProMisE groups of EC, in terms of histological grade (G3 *vs* G1–2), histotype, lymphovascular space invasion (LVSI), deep myometrial invasion (>50%), lymph node involvement, and European Society for Medical Oncology (ESMO) risk category.

Materials and methods. A systematic review and meta-analysis was performed by searching seven electronic databases from their inception to May 2019, for studies that reported histopathological characteristics of each ProMisE group. Pooled prevalence of each histopathological characteristic of EC in each ProMisE group was calculated.

Results. Four studies with 1171 patients were included in the systematic review, out of which three studies with 912 patients were included in the meta-analysis. Pooled prevalence estimates were:

- in the MMR-d group, G3 = 47.4%, G1–2 = 52.6%; endometrioid = 85.8%, non-endometrioid = 14.2%; LVSI-present = 41.3%, −absent = 58.7%; deep myometrial invasion-present = 44.5%, −absent = 55.5%; lymph node involvement-present = 9.9%, −absent = 90.1%; low-risk = 30.1%, intermediate risk = 19.9%, high-risk = 50%;
- in the POLE-mt group, G3 = 39.6%, G1–2 = 60.4%; endometrioid = 86.1%, non-endometrioid = 13.9%; LVSI-present = 32.7%, −absent = 67.3%; deep myometrial invasion-present = 27.3%, −absent = 72.7%; lymph node involvement-present = 0%, −absent = 100%; low-risk = 44.1%, intermediate-risk = 22.5%, high-risk = 33.4%;

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- in the p53-wt group, G3 = 15.6%, G1–2 = 84.4%; endometrioid = 96.7%, non-endometrioid = 3.3%; LVSI-present = 13.8%, −absent = 86.2%; deep myometrial invasion-present = 27.4%, −absent = 72.6%; lymph node involvement-present = 4.3%, −absent = 95.7%; low-risk = 59.5%, intermediate-risk = 17.3%, high-risk = 23.2%;
- in the p53-abn group, G3 = 90%, G1–2 = 10%; endometrioid = 27%, non-endometrioid = 73%; LVSI-present = 48.8%, −absent = 51.2%; deep myometrial invasion-present = 48.9%, −absent = 51.1%; lymph node involvement-present = 23.7%, −absent = 76.3%; low-risk = 7.2%, intermediate-risk = 8.1%, high-risk = 84.7%.

Conclusions. The histopathological characterization of the ProMisE groups suggests that many patients are currently undertreated or overtreated (especially in the POLE-mt and MMR-d groups).

1. Introduction

Endometrial cancer (EC) shows the highest prevalence among gynecologic cancers in the developed world, with even an increase in incidence and mortality in the last years [1–3]. Such increase has been related to the risk stratification, still based on poorly reproducible histopathologic assessment of specimens [4,5]. As a result, both patient management and clinical trials have been affected, leading to over- and undertreatment of patients, and wrong findings within trials [4–6].

After The Cancer Genome Atlas (TCGA) Research Network findings on EC [7], the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) is coming as a novel molecular classifier [2,6,8,9]. Such classifier uses immunohistochemistry as a surrogate of molecular sequencing, given that immunohistochemistry is easier to be performed, more diffused in the routine practice and less expensive [10–23]. Based on results by TCGA, the ProMisE classifier identified four molecular group of EC with different prognosis:

- POLE-mutated (POLEmt), characterized by good prognosis, very high mutational rate and mutations in the exonuclease domain of Polymerase-ε (*POLE*); such group may be identified only by sequencing;
- mismatch repair-deficient (MMR-d), characterized by intermediate prognosis, high mutational rate and microsatellite-instability; such group may be detected by immunohistochemistry for mismatch repair proteins;
- p53-abnormal (p53-abn), characterized by poor prognosis, *TP53* mutations, low mutational rate, and high somatic copy number alterations rate; such group may be diagnosed by abnormal immunohistochemical expression of p53;
- p53-wild-type (p53-wt), characterized by good-to-intermediate prognosis, low mutational and somatic copy number alterations rates; such group is the less defined one, showing no specific molecular signature [2,6,20,24].

However, a precise histopathological profiling of each ProMisE group is still lacking. Such characterization may be useful in order to understand how this novel molecular classifier may affect the current patient management, which is based on a histopathological risk assessment. Moreover, histopathological and molecular characterization might be integrated within a tailored risk assessment in the next future.

We aimed to provide a histopathological characterization of ProMisE groups of EC, in terms of histological grade, histotype, lymphovascular space invasion (LVSI), myometrial invasion, lymph node involvement, and European Society for Medical Oncology (ESMO) risk category.

2. Materials and methods

2.1. Study protocol

The study protocol including methods for search strategy, study selection, risk of bias assessment, data extraction and analysis was *a priori* defined. Two reviewers (AR, AT) independently performed all steps of the review process. Disagreements were solved by discussion with a third author (MG). The study was reported as described by the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement [25].

2.2. Search strategy

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

2.3. Study selection

All peer-reviewed studies that allowed extraction of histopathological characteristics of each ProMisE group of EC were included in our study. Reviews and case reports were *a priori* defined as exclusion criteria. Studies with patient selection based on histopathological characteristics were also excluded from our analyses because they would affect overall prevalence of each histopathological characteristic in each ProMisE group.

2.4. Data extraction

Data extraction from each included study were performed without modification and following the PICO (Population, Intervention, Comparator, Outcomes) items [25].

"Population" of this study was women diagnosed with EC; overlapping patients were excluded.

"Intervention" (or risk factor) was the ProMisE group of EC.

"Comparator" was not applicable given the study design (meta-analysis of prevalence).

"Outcomes" were the prevalence of several histopathological characteristics in each ProMisE group of EC. In particular, the histopathological characteristics assessed were the following: histological grade 3 (G3), endometrioid histotype, present LVSI, deep myometrial invasion (>50% of the myometrial thickness), lymph node involvement, ESMO 2013 low- and high-risk category [26]. Regarding lymph node involvement, patients that did not undergo lymph node dissection were considered as not having lymph node involvement.

2.5. Risk of bias within studies assessment

The Methodological Index for Non-Randomized Studies (MINORS) was followed to perform the risk of bias within studies assessment [27]. Six applicable domains related to risk of bias were evaluated for each included study: 1) Aim (if the study had a clearly stated aim); 2) Inclusion of consecutive patients (if patient selection included all eligible patients during the study period); 3) Prospective collection of data (if data collection was performed following a protocol *a priori* defined); 4) Endpoints appropriate to the aim (if criteria to assess outcomes were clearly stated); 5) Unbiased assessment of the study endpoint (if a blind evaluation, re-evaluation or evaluation by two or more authors of study endpoints was performed); 6) Follow-up period appropriate to the aim (if the follow-up period was at least 2 years, as this time is a reasonable minimal clinical follow-up time for women with endometrial cancer).

Authors judgments were categorized as "high risk", "unclear risk" or "low risk" of bias based on data about each domain were "reported but inadequate", "not reported" or "reported and adequate", respectively.

2.6. Data analysis

Prevalence of each histopathological characteristic of EC in each ProMisE group was calculated as the number of EC with the specific characteristic in the specific ProMisE group by the total number of EC in that ProMisE group. Prevalence was calculated for each included study and as pooled estimate, and graphically reported on forest plots with 95% confidence interval (CI). In each ProMisE group, prevalence of ECs that lacked the specific histopathological characteristic was calculated as 100% minus the prevalence of that characteristic.

Statistical heterogeneity among studies was assessed by the inconsistency index I^2 as previously described [28–35]. 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 $I^2 \geq 75\%$. The random effect model of DerSimonian and Laird was adopted for all analyses.

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) were used as software for data analysis.

3. Results

3.1. Study selection

4958 articles were identified after electronic searches. 815 articles remained after duplicates removal. 44 articles remained after title screening. 14 articles were evaluated for eligibility after abstracts screening. Four articles were finally included in the qualitative analysis [2,6,8,9], and 3 articles in the quantitative analysis [2,6,8].

The whole process of study selection is graphically reported in Supplementary Fig. 1.

3.2. Study and patients' characteristics

A total of 1171 patients with EC was included in the systematic review. We excluded the study by Britton et al. from the meta-analysis [9], since it was impossible to identify the patients that overlapped with the other three included studies. We finally included 912 patients from three studies with no overlapping cases in the meta-analysis. Out of these 912 patients, 232 (25.4%) were MMR-d, 84 (9.2%) were POLE-mt, 430 (47.1%) were p53-wt and 166 (18.2%) were p53-abn. Overall, 729 carcinomas (79.9%) were pure endometrioid and 138 (15.1%) were pure serous. The remaining cases were mixed histotypes (at least 8), clear cell (at least 5), small cell (at least 3), dedifferentiated and carcinosarcoma (at least 1 each). Histotype was not reported for the remaining cases in the study by Kommos et al., although it was stated that they were either clear cell or mixed [8].

Characteristics of the included studies and patients were reported in Supplementary Tables 1 and 2, respectively.

3.3. Risk of bias within studies assessment

All included studies were considered at "low risk" of bias in all domains, with the exception of "Inclusion of consecutive patients" domain. In such a domain, 3 studies were considered at "unclear risk" of bias, as they did not report if patients' selection included all eligible patients during the study period [2,6,9]. Moreover, one study only selected patients aged 49 or younger [9]. The other one was considered at "low risk" of bias.

Risk of bias within studies evaluation was graphically reported in Supplementary Fig. 2.

3.4. Meta-analysis

Pooled prevalence of G3 was 47.4% (95% CI: 14.4–82.8%) in the MMR-d group, 39.6% (95% CI: 11–77.6%) in the POLE-mt group, 15.6% (95% CI: 6.1–34.5%) in the p53-wt group, and 90% (95% CI: 77.5–95.9%) in the p53-abn group (Fig. 1). Statistical heterogeneity among studies was high (I^2: 96.3), high (I^2: 89.9), high (I^2: 92.5), and moderate (I^2: 64.9), respectively. Prevalence of G1–2 was 52.6% in the MMR-d group, 60.4% in the POLE-mt group, 84.4% in the p53-wt group, and 10% in the p53-abn group.

Pooled prevalence of endometrioid histotype was 85.8% (95% CI: 70.5–93.9%) in the MMR-d group, 86.1% (95% CI: 76.5–92.1%) in the POLE-mt group, 96.7% (95% CI: 86.4–99.3%) in the p53-wt group, and 27% (95% CI: 17.9–38.6%) in the p53-abn group (Fig. 2). Statistical heterogeneity among studies was high (I^2: 81.4), null (I^2: 0), high (I^2: 82.3), and moderate (I^2: 52.6), respectively. Prevalence of non-endometrioid histotype was 14.2% in the MMR-d group, 13.9% in the POLE-mt group, 3.3% in the p53-wt group, and 73% in the p53-abn group.

Based on the above-mentioned pooled prevalence of G3 and endometrioid histotype, pooled prevalence of G3 endometrioid ECs was 33.2% in the MMR-d group, 25.7% in the POLE-mt group, 12.3% in the p53-wt group, and 17% in the p53-abn group.

Pooled prevalence of present LVSI was 41.3% (95% CI: 18.7–68.2%) in the MMR-d group, 32.7% (95% CI: 12–63.3%) in the POLE-mt group, 13.8% (95% CI: 0.66–26.4%) in the p53-wt group, and 48.8% (95% CI: 27.5–70.6%) in the p53-abn group (Fig. 3). Statistical heterogeneity among studies was high (I^2: 92.7), high (I^2: 81.8), high (I^2: 86), and high (I^2: 85.6),

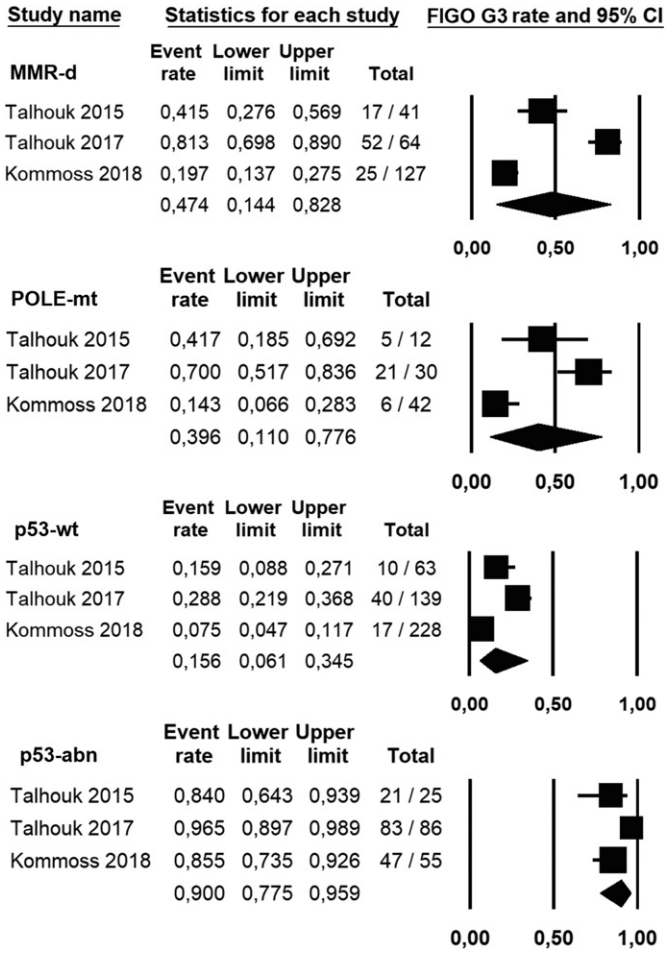

Fig. 1. Forest plot of prevalence of FIGO grade 3 in each ProMisE group of endometrial cancer, for individual study and as pooled estimate.

respectively. Prevalence of absent LVSI was 58.7% in the MMR-d group, 67.3% in the POLE-mt group, 86.2% in the p53-wt group, and 51.2% in the p53-abn group.

Pooled prevalence of present deep myometrial invasion was 44.5% (95% CI: 37.6–51.6%) in the MMR-d group, 27.3% (95% CI: 16.5–41.7%) in the POLE-mt group, 27.4% (95% CI: 23.1–32.2%) in the p53-wt group, and 48.9% (95% CI: 40.5–57.3%) in the p53-abn group (Fig. 4). Statistical heterogeneity among studies was null (I^2: 0), low (I^2: 32), null (I^2: 0), and minimal (I^2: 1.8), respectively. Prevalence of absent deep myometrial invasion was 55.5% in the MMR-d group, 72.7% in the POLE-mt group, 72.6% in the p53-wt group, and 51.1% in the p53-abn group.

Pooled prevalence of present lymph node involvement was 9.9% (95% CI: 3.2–27%) in the MMR-d group, 0% in the POLE-mt group, 4.3% (95% CI: 2.7–6.6%) in the p53-wt group, and 23.7% (95% CI: 12.8–39.7%) in the p53-abn group (Fig. 5). Statistical heterogeneity among studies was minimal (I^2: 81.5), null (I^2: 0), null (I^2: 0), and moderate (I^2: 72.6), respectively. Prevalence of absent lymph node involvement was 90.1% in the MMR-d group, 100% in the POLE-mt group, 95.7% in the p53-wt group, and 76.3% in the p53-abn group.

Considering only the patients that underwent lymph node dissection, pooled prevalence of lymph node involvement was 6.8% (95% CI: 1.7–23.6%) in the MMR-d group, 0% in the POLE-mt group, 8.7% (95% CI: 3–22.7%) in the p53-wt group, 27.7% (95% CI: 11–54.3%) in the p53abn group (Supplementary Fig. 3), with a heterogeneity moderate (I^2: 56) null (I^2: 0), high (I^2: 77), high (I^2: 85.7), respectively.

Pooled prevalence of ESMO 2013 low-risk category was 30.1% (95% CI: 15–51.4%) in the MMR-d group, 44.1% (95% CI: 15–77.9%) in the POLE-mt group, 59.5% (95% CI: 53.4–65.4%) in the p53-wt group, and 7.2% (95% CI: 2.4–19.6%) in the p53-abn group (Supplementary Fig. 4). Statistical heterogeneity among studies was high (I^2: 87.3), high (I^2: 88.2), low (I^2: 34.9), and moderate (I^2: 60), respectively.

Pooled prevalence of ESMO 2013 high-risk category was 50% (95% CI: 30.8–69.2%) in the MMR-d group, 33.4% (95% CI: 16.1–56.6%) in the POLE-mt group, 23.2% (95% CI: 13.6–36.9%) in the p53-wt group, and 84.7% (95% CI: 73.4–91.7%) in the p53-abn group (Supplementary Fig. 5). Statistical heterogeneity among studies was high (I^2: 87.8), moderate (I^2: 72), high (I^2: 86.5), and moderate (I^2: 57.7), respectively.

Prevalence of ESMO 2013 intermediate-risk category was 19.9% in the MMR-d group, 22.5% in the POLE-mt group, 17.3% in the p53-wt group, and 8.1% in the p53-abn group.

Pooled prevalence of histological characteristics in each ProMisE group are summarized in Supplementary Table 3.

4. Discussion

4.1. Main findings and interpretation

This study aimed to provide a histopathological characterization of the ProMisE prognostic groups of EC in order to assess how such novel

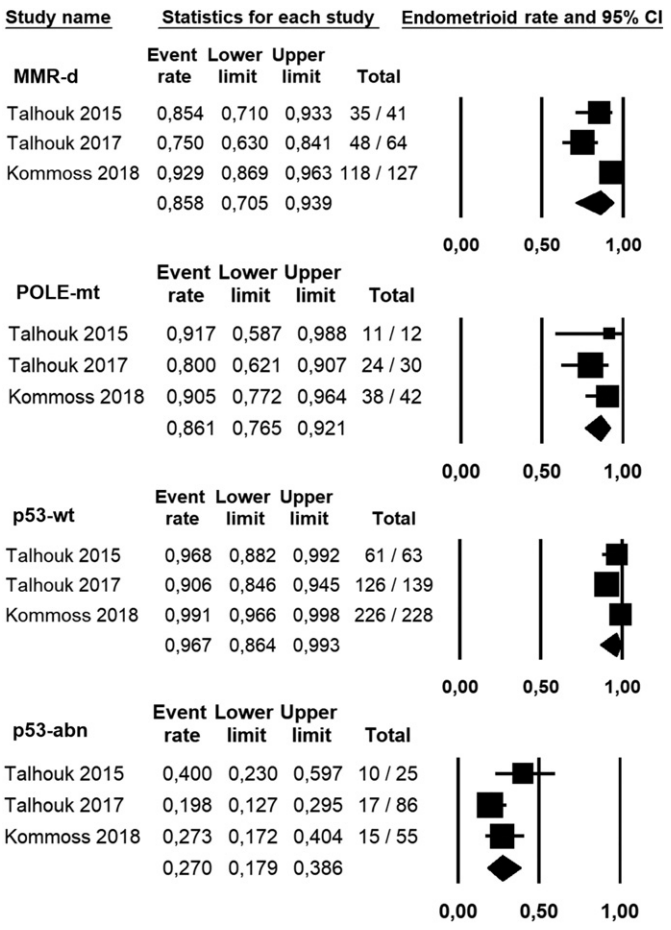

Fig. 2. Forest plot of prevalence of endometrioid histotype in each ProMisE group of endometrial cancer, for individual study and as pooled estimate.

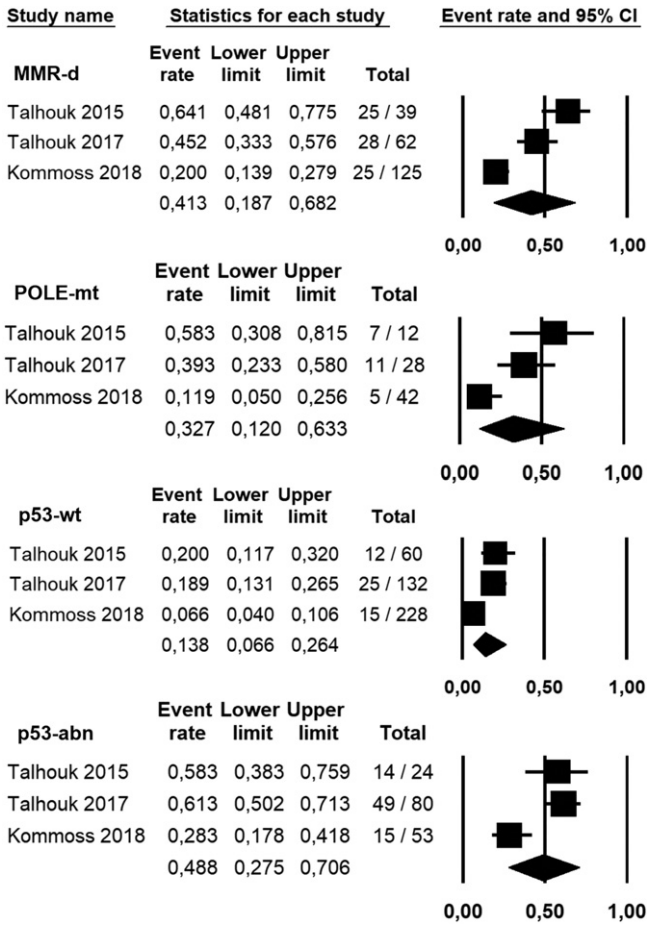

Fig. 3. Forest plot of prevalence of present lymph vascular space invasion in each ProMisE group of endometrial cancer, for individual study and as pooled estimate.

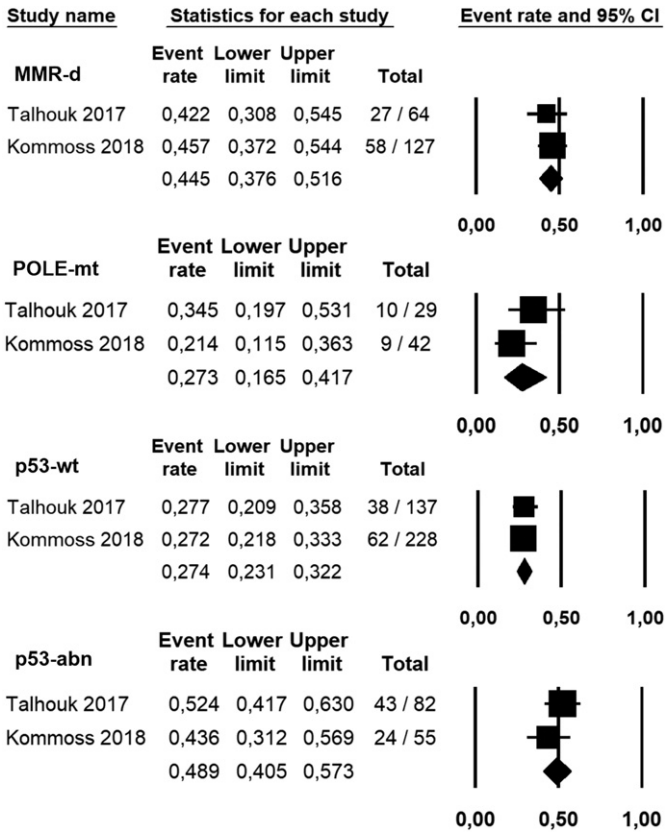

Fig. 4. Forest plot of prevalence of myometrial invasion>50% in each ProMisE group of endometrial cancer, for individual study and as pooled estimate.

molecular risk assessment may affect the current histopathological risk stratification of patients. This study provides pooled prevalence of G3, endometrioid histotype, LVSI, deep myometrial invasion, lymph node involvement, ESMO 2013 low- and high-risk categories in each ProMisE group.

4.2. MMR-d group

In the MMR-d group, prevalence of all unfavorable histopathological factors was intermediate between the p53-wt and the p53-abn groups. MMR-d ECs were endometrioid in most cases (85.8%), and showed G3, LVSI, and deep myometrial invasion in almost half cases. Therefore, there is a high percentage of patients that would be classified at high risk based on the both 2013 and 2016 ESMO risk assessment systems [26,36]. Thus, given the intermediate prognosis of the MMR-d group, these patients might currently be overtreated. On the other hand, 30% of patients in this group were classified at low-risk according to the 2013 ESMO system; these patients might be undertreated instead. In fact, in cohorts of early stage endometrioid ECs (which are considered at good prognosis), the MMR-d signature seems to have an unfavorable prognostic value [37]; on the other hand, in G3 ECs (which are considered at poor prognosis), such signature appears as a favorable prognostic factor [38]. This apparent variation might reflect a high consistency in the intermediate prognosis of this group [2,3,6–9]. It would be interesting to assess whether the intermediate prognosis of this group

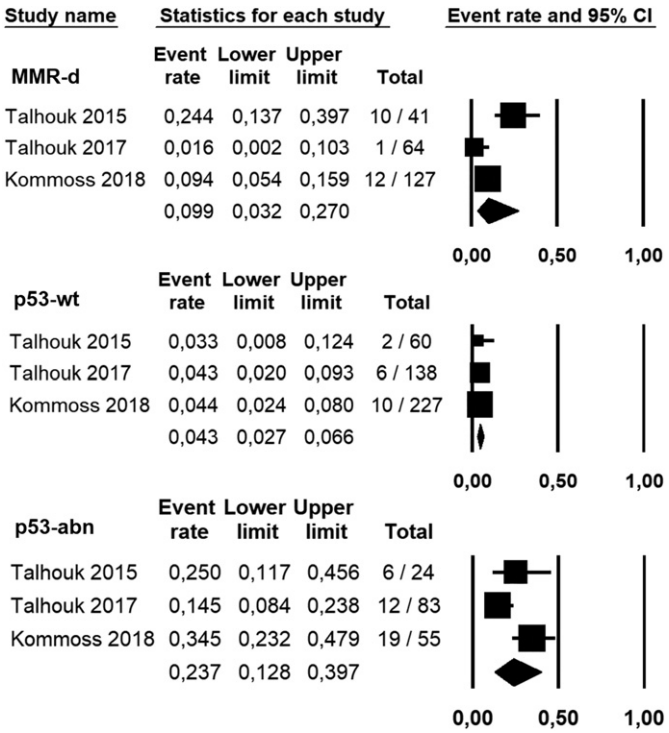

Fig. 5. Forest plot of prevalence of lymph node involvement in each ProMisE group of endometrial cancer, for individual study and as pooled estimate. Patients who did not undergo lymph node dissection were considered as having negative lymph nodes.

might be due to a mixture of subgroups with different prognosis. Indeed, McMeekin et al. showed that, within the MMR-d group, MLH1-methylated ECs showed worse oncologic outcomes compared to unmethylated ones [39]. However, in the absence of a sub-stratification of the MMR-d group, our results suggest that the ProMisE classifier may heavily affect the management of patients in this group.

4.3. POLE-mt group

Compared to MMR-d group, the POLE-mt group showed a similar prevalence of G3 (39.6%) and endometrioid histotype (6.1%); the histological similarity between these two groups is probably based on the high mutational load (hence the terms "hypermutated" and "ultramutated" for the MMR-d and POLE. mt groups, respectively) [7]. On the other hand, the prevalence of parameters of aggressiveness (LVSI-positive = 32.7%, deep myometrial invasion = 27.3%) was lower in the POLE-mt group. In particular, the POLE-mt group was the only group that showed null prevalence of lymph node involvement (0%). Given the crucial prognostic value of lymph node involvement, these findings supports the exceptionally favorable prognosis of the POLE-mt group [40]. Interestingly, in the 2016 ESMO risk assessment system LVSI is used as a surrogate of lymph node involvement when lymph node staging is not performed [36]. In spite of this, the POLE-mt showed a higher prevalence of LVSI than the p53-wt group (32.7% *vs* 13.8%), but a lower prevalence of lymph node involvement (0% *vs* 4.3%). Therefore, the POLE-mt signature seems to be even more important than LVSI as a prognostic factor. This finding also strengthens the proposal of considering POLE-mt stage I ECs at low risk regardless of other factors [3,7,41,42]. Since less than half of POLE-mt patients resulted to be classified at low-risk, such a molecular-based reclassification might avoid many overtreatments.

4.4. P53-wt group

The p53-wt group showed the most favorable clinicopathological profile among the 4 groups. Indeed, most p53-wt ECs were low-grade endometrioid carcinomas (G3 = 15.6%, endometrioid = 96.7%), hence the name "endometrioid group" [7]. Parameters of aggressiveness showed low prevalence (LVSI = 13.8%, deep myometrial invasion = 27.4%, lymph node involvement = 4.3%), and more than half of the tumors in this group were in the 2013 ESMO low-risk category (59.5%), while ECs classified at high-risk were uncommon (23.2%). Therefore, since the prognosis of the p53-wt group varies from good to moderate [3], the management of patients in this group might be little affected by a molecular-based reclassification. However, an accurate assessment of the impact of such a reclassification on this group is difficult, as the p53-wt group is the least molecularly and prognostically characterized ProMisE group [3,7]. In fact, in some subsets of high-risk ECs, the prognosis of the p53-wt group was found to be even poor, suggesting that it is heavily affected by other factors [20,43]. For this reason, several biomarkers are being studied to sub-stratify this group. Mutation in the exon 3 of *CTNNB1* is one of the most interesting markers in this field, since it seems to characterize a subset at intermediate prognosis within the p53-wt group [15,19]. In the absence of a further molecular and prognostic stratification of the p53-wt group, clinicopathological factors remain crucial to assess the risk within this group. A molecular and prognostic sub-stratification of this subgroup is therefore a priority for future researches.

4.5. P53-abn group

The p53-abn group showed the most unfavorable histopathological profile among the four ProMisE groups. Prevalence of all unfavorable histopathological characteristics was the highest in this group (G3 = 90%, deep myometrial invasion = 48.9%, LVSI = 48.8%, lymph node involvement = 23.7%), as well as prevalence of endometrioid histotype was the lowest (27%). Indeed, TCGA referred to this group as the "serous group" [7]. Although such a histopathological profile might explain the worst prognosis of this group, the unfavorable prognostic value of the p53-abn signature has been shown to be independent from other clinicopathological factors. In fact, in our previous study, we found that this group had a prognosis about 2 times worse than that of the p53-wt group (control group) when normalized for clinicopathological factors [3]. In consideration of these histopathological characteristics, the 2013 ESMO system for the risk stratification classified most p53-abn ECs in the high-risk category (84.7%), while only a minority was classified at low-risk (7.2%). Therefore, similarly to the p53-wt group, the p53-abn group may be little affected by a molecular-based revision of the risk assessment system. Such a revision would affect about 15% of EC patients who would be reclassified as high risk regardless of favorable histological characteristics [41,42]. These patients might be women affected by endometrioid stage I EC, with histopathological features not defining a high-risk category. Given the p53-abn signature, these patients might have a higher risk of recurrence and thus the need of a more aggressive treatment.

4.6. Strengths and limitations

To our knowledge, this may be the first systematic review and meta-analysis to provide a histopathological characterization of ProMisE groups of EC, laying the groundwork for a future possible integration between molecular and histopathological features in a tailored risk stratification system. This study also provides estimates of current under- and overtreatment of patients with EC, underlying the great need of molecular-driven clinical trials in this field. Our results are based on a very high overall quality of the evidence. In fact, risk of bias within studies assessment showed "low risk" of bias in all domains for all included studies, with the exception of "Inclusion of consecutive patients" domain (where 3 studies were at "unclear risk" of bias). No study was categorized at high risk of bias.

A limitation of this study might lie in the low number of included studies in the meta-analysis ($n = 3$). However, they were the only studies in the Literature to meet the selection criteria.

5. Conclusion

The histopathological characterization of ProMisE groups of EC shows that a great percentage of patients are currently under- or overtreated across the several ProMisE groups, with major benefits obtainable for POLE-mt and MMR-d groups and a subset of p53-abn EC. On the other hand, further evidence is needed to estimate the possible benefits for the p53-wt group. Pooled prevalence of all histopathological characteristics considered in the current risk stratification system, for each ProMisE group, might lay the groundwork for a future possible integration between molecular and histopathological features in a tailored risk stratification system. Molecular-driven clinical trials are a priority to date.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2020.01.008.

Contribution

AR and AT independently assessed electronic search, eligibility of the studies, inclusion criteria, risk of bias, data extraction and data analysis. MM, CC and AM contributed to the elaboration of methods for risk of bias assessment, data extraction and analysis. MG, AR and AT conceived the study. FZ, MG and LI worked on the design of the study. AR, AT, MM, CC, MG, LI and AM worked on the manuscript preparation. LI, FZ and MG supervised the whole study.

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Declaration of competing interest

Authors report no conflict of interest.

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