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REVIEW

TCGA Molecular Subgroups in Endometrial Undifferentiated/Dedifferentiated Carcinoma

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Abstract

We aimed to classify undifferentiated/dedifferentiated carcinoma (UDC/DDC) according to the four TCGA molecular subgroups of endometrial cancer: microsatellite-instable/hypermutated (MSI), POLE-mutant/ultramutated (POLE), copy-number-low/p53-wild-type (p53wt), and copy-number-high/p53-abnormal (p53abn), through a systematic review and meta-analysis. Electronic databases were searched from January 2013 to July 2019 for studies assessing the TCGA classification in endometrial UDC/DDC series. Pooled prevalence of each TCGA subgroup on the total UDC/DDCs was calculated. Three studies with 73 patients were included. Pooled prevalence of the TCGA subgroups were: 12.4% for the POLE subgroup, 44% for the MSI subgroup, 18.6% for the p53abn subgroup, 25% for the p53wt group. All TCGA groups are represented in UDC/DDC, with a predominance of the MSI group, indicating a biological heterogeneity. Hypermutated/ultramutated cancers constitute the majority of UDC/DDC, suggesting a crucial difference with other high-risk histologies of endometrial carcinoma.

Keywords Cancer · Treatment · Endometrium · Risk assessment · PROMISE

Introduction

Endometrial cancer is the most common gynecologic malignancy in developed countries [1–5]. In 2013, The Cancer Genome Atlas (TCGA) Research Network identified four prognostic molecular subgroups of endometrial cancer: the ultramutated group characterized by mutations in the exonuclease domain of polymerase-ε ("POLE" group), the hypermutated group characterized by microsatellite instability ("MSI" group), the copy-number-high group characterized by *TP53* mutations, and the copy-number-low group which lacks a molecular signature [6]. The prognostic value of these subgroups has been confirmed in subsequent studies [7–13]; moreover, the use of immunohistochemical surrogates of molecular markers has opened the way for a wider applicability of the TCGA classification. Indeed, the loss of mismatch repair proteins works as a surrogate of MSI, while abnormal p53 staining works as a surrogate of *TP53* mutations, allowing to identify a "p53-abnormal" group ("p53abn" group, surrogate of the copy-number-high group) and a "p53-wild type" group ("p53wt" group, surrogate of the copy-number-low group) [10–12].

However, the analysis carried out by the TCGA included only endometrioid and serous carcinomas, which are the two most common histotypes of endometrial cancer [8, 13]. On the other hand, the relationship of other less common histotypes with the TCGA classification remains less understood.

In this systematic review and meta-analysis, we focused on undifferentiated/dedifferentiated carcinoma (UDC/DDC). We aimed to define the prevalence of the TCGA molecular groups in endometrial UDC/DDC.

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Materials and Methods

Study Protocol

Review methods were defined a priori according to our previous studies [14–18]. Every review stage was performed by three authors (AT, AR, MG) independently; solution of disagreements, if any, was obtained through consensus among all authors. This study followed the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement [19].

Search Strategy and Study Selection

Seven electronic databases (Web of Sciences, Google Scholar, Scopus, MEDLINE, EMBASE, ClinicalTrial.gov and the Cochrane Library) were searched from January 2013 (year of publication of the TCGA study on endometrial cancer) to July 2019. The following combination of text words was used: (endometrial OR endometrium) AND (undifferentiated OR dedifferentiated) AND (cancer OR carcinoma). Relevant references from each eligible study were also assessed.

All peer-reviewed studies that classified endometrial UDC/DDC series according to the TCGA molecular classification were included. Exclusion criteria, defined a priori, were: sample size <10; incomplete TCGA classification (i.e. not all TCGA groups were assessed); reviews.

Data Extraction

Primary data extracted were the number of endometrial UDC/DDC in each TCGA group and the total number of endometrial UDC/DDC. Each UDC/DDC was assigned to a specific TCGA group based on the hierarchical model proposed by the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE), which is based on 3 steps: 1) mismatch repair proteins immunohistochemistry, 2) *POLE* sequencing and 3) p53 immunohistochemistry. In this way, the MSI surrogate signature (i.e. deficient mismatch repair proteins expression) prevails over the other ones, followed by the POLE signature (i.e. *POLE* mutation) and the p53abn signature (i.e. p53 aberrant expression); the p53wt subgroup is identified by exclusion [10–12].

Risk of Bias Assessment

The QUADAS-2 [20] were used as basis to define four domains to be assessed with regard to the risk of bias, as previously described [20–22]: 1) Patient selection, i.e. if patients were consecutively selected; 2) Index test, i.e. if methods for immunohistochemical/molecular analyses for TCGA classification assessment were clearly described; 3) Reference standard, i.e. if histological slides were reviewed to confirm the pathologic diagnosis of endometrial UDC/DDC; 4) Flow, i.e. if at least 95% of the included patients were available for the assessment of the TCGA classification.

In each study and for each domain, the risk of bias was considered "low", "high" or "unclear", as previously described [23–25].

Data Analysis

Data were analyzed through a meta-analysis of prevalence, by calculating the prevalence of each TCGA subgroup in the study population (i.e. patients with endometrial UDC/DDC). The prevalence of each TCGA subgroup in endometrial UDC/DDC was calculated as the number of UDC/DDC belonging to that subgroup divided by the total number of UDC/DDC, in each included study and as pooled estimates, with 95% confidence interval (CI); the random effect model of DerSimonian-Laird was used to pool data. Results were graphically reported on forest plots. As the p53wt group does not have molecular or immunohistochemical signatures, the pooled prevalence of this group was calculated by using the following formula:

$$\%\text{p53wt} = 100\% - (\%\text{POLE} + \%\text{MSI} + \%\text{p53abn})$$

Statistical heterogeneity among studies was categorized based on the inconsistency index I^2 as null ($I^2 = 0\%$), minimal ($0 < I^2 < 25\%$), low ($25 \leq I^2 < 50\%$), moderate ($50 \leq I^2 < 75\%$) or high ($I^2 \geq 75\%$), as previously reported [26–29].

Data analysis was performed by 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 and Characteristics

After exclusion of non-relevant articles through titles and abstracts screening, seven studies were assessed for eligibility [30–36]; one of these studies was excluded for assessing less than 10 UDC/DDC specimens [30], and another 3 studies were excluded due to incomplete TCGA classification [31–33]. Finally, 3 multicenter studies with a total of 73 patients with endometrial UDC/DDC were included [34–36]. The process of study selection is reported in Supplementary Fig. 1.

Two studies included both UDC and DDC [34, 35], while the remaining study included only UDC [36]. For the assessment of the POLE group and of the MSI group, all studies performed *POLE* sequencing and mismatch repair proteins

Table 1 Characteristics of the included studies

Study	Country	Period of enrollment	Sample size	Methods for TCGA subgroups assessment			
				POLE	MSI	p53abn	P53wt
Rosa-Rosa 2016	Spain, USA	unclear	18 (7 undifferentiated, 11 dedifferentiated)	*POLE* sequencing	mismatch repair proteins immunohistochemistry	p53 mmunohistochemistry, *TP53* sequencing	exclusion
Espinosa 2017	Spain, Canada	unclear	21 (8 undifferentiated, 13 dedifferentiated)	*POLE* sequencing	mismatch repair proteins immunohistochemistry	p53 immunohisochemistry	exclusion
Koebel 2017	Canada, Usa, Australia	unclear	34 (all undifferentiated)	*POLE* sequencing	mismatch repair proteins immunohistochemistry	p53 immunohisochemistry	exclusion

immunohistochemistry, respectively. For the assessment of the p53abn group, all studies performed p53 immunohistochemistry, one of which also performed *TP53* sequencing.

Characteristics of the included studies are reported in Table 1.

Risk of Bias within Studies

For the "patient selection" domain, all studies were considered at unclear risk of bias, since it was not stated whether the patients were consecutively selected, and the period of enrollment was not reported.

For the "TCGA assessment" domain, all studies were considered at low risk of bias, since methods for the TCGA groups were clearly described and based on the ProMisE classifier [10–12].

For the "pathologic assessment" domain, all studies were considered at low risk of bias as histological slides were centrally reviewed by expert pathologists.

For the "flow" domain, all studies were considered at low risk, since no patient was inappropriately excluded from the analysis.

Results of the risk of bias assessment are summarized in Supplementary Fig. 2.

Data Analysis

Among all UDC/DDC patients, 12.4% (95% CI, 3.3%-36.8%) were classified in the POLE group (Fig. 1), with moderate statistical heterogeneity among studies ($I^2 = 66.1\%$); 44% (95% CI, 33%-55.7%) were classified in MSI group (Fig. 2), with null heterogeneity ($I^2 = 0\%$); 18.6% (95% CI, 11.1%-29.5%) were classified in the p53abn group (Fig. 3), with null heterogeneity ($I^2 = 0\%$). The estimated pooled prevalence of the p53wt group was 25%. Molecular features and subgroup assigned for each patient are reported in detail in Supplementary Table 1.

Discussion

Our study showed that 12.4% of endometrial UDC/DDC fall into the POLE group, 44% fall into the MSI group, 18.6% fall into the p53abn group and 25% fall into the p53wt group. To the best of our knowledge, this is the first systematic review and meta-analysis assessing the TCGA classification in endometrial UDC/DDC.

UDC is an aggressive variant of endometrial carcinoma, whose diagnostic criteria have been clarified only with the

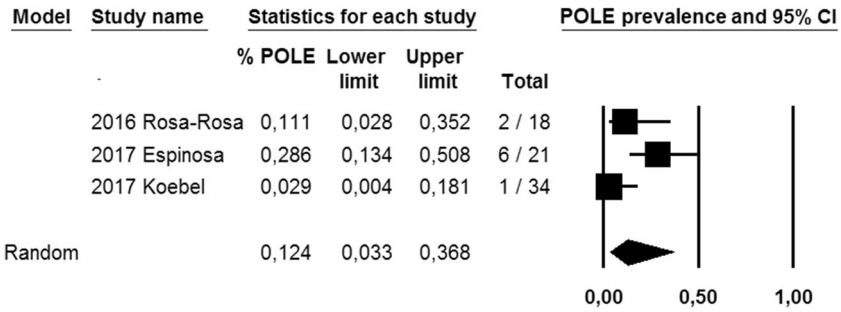

Fig. 1 Forest plot reporting the prevalence of the POLE subgroup in undifferentiated/dedifferentiated endometrial carcinoma

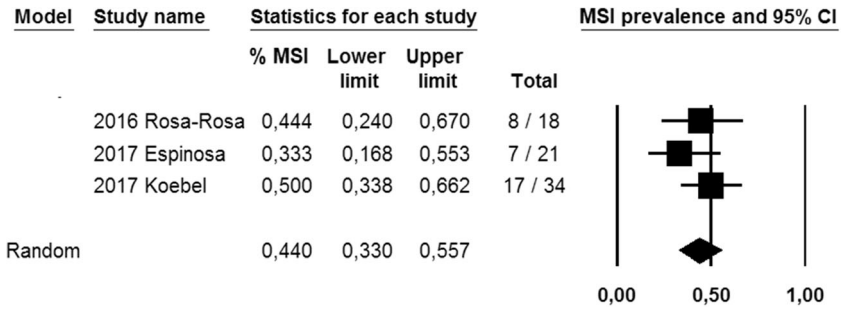

Fig. 2 Forest plot reporting the prevalence of the MSI subgroup in undifferentiated/dedifferentiated endometrial carcinoma

2014 WHO classification [37–39]. DDC identifies a tumor with an UDC component admixed with a low-grade endometrioid component; in DDC, the UDC component is thought to derive from the dedifferentiation of the well-differentiated component [31, 32, 39, 40]. Therefore, UDC and DDC are regarded as a single entity by the WHO [39]. The NCCN guidelines list UDC/DDC among the "high-risk histologies" of endometrial carcinoma (together with serous carcinoma, clear cell carcinoma and carcinosarcoma), which need a more aggressive treatment. Furthermore, together with carcinosarcoma, UDC/DCC is the only endometrial carcinoma histotype that always requires chemotherapy and/or radiotherapy, even in the case of FIGO stage Ia and no residual tumor on hysterectomy specimen [41].

Our study highlighted that all the four TCGA groups are represented in UDC/DDC, indicating a great biological heterogeneity in this histotype.

The MSI group appears as the most common TCGA group in UDC/DDC, representing 44% of cases. Despite being lower than previously reported rates of mismatch repair deficiency in UDC/DDC (about 60%) [31, 32], such percentage appears consistently higher than that found overall in endometrial carcinomas (28% in the TCGA cohort) [6].

Similarly, the prevalence of the POLE group in UDC/DDC (12.4%) appears higher than that overall found in endometrial carcinomas (7.3% in the TCGA cohort). On this account, the MSI and the POLE subgroups lumped together constitute the majority of UDC/DDCs. Thus, most UDC/DDCs are tumors with high mutational load. This indicates a crucial difference between UDC/DDC and the other high-risk histologies of endometrial cancer, where hypermutated/ultramutated tumors are very uncommon. As a comparison, in the TCGA cohorts the prevalence of POLE or MSI genotype was 0% in serous carcinoma and 5% in carcinosarcoma [6, 43]. Probably, the high mutational rate makes POLE and MSI tumors more likely to develop an undifferentiated phenotype. Since the high mutational load is a predictor of response to immunotherapy, most UDC/DDC may benefit from such treatment, with potential improvement in patients' survival [44, 45]. These hyper- and ultramutated UDC/DDCs might also have a better prognosis, as seen in other high-risk histotypes of endometrial carcinoma [42]. Indeed, one of the included studies showed a favorable prognostic value of POLE mutations in UDC/DDC [35].

The prevalence of the p53abn group was 18.6%. Interestingly, this percentage was definitely lower than that found in any other high-risk histology of endometrial carcinoma; indeed, the p53abn group accounts for the vast majority of serous carcinomas and carcinosarcomas [23, 43]. This marks an important difference with the other high-risk histologies, as already discussed for mutational load. Given the poor prognosis associated with the p53abn group [6–12], this subset of UDC/DDC might have a prognosis worse than its hypermutated/ultramutated counterpart.

Finally, the prevalence of the p53wt group in UDC/DDC was 25%. It is useful to remark that the p53wt group lacks molecular signatures and is defined by the exclusion of the signatures of the other TCGA groups [6–12]. Therefore, the prognostic significance of the p53wt group may vary according to histological grade and histotype considered. In well-differentiated endometrioid carcinomas, the p53wt group showed a good-to-intermediate prognosis [6]. Instead, in high-grade carcinomas both the p53wt group was associated with a poor prognosis, comparable to that of the p53abn group

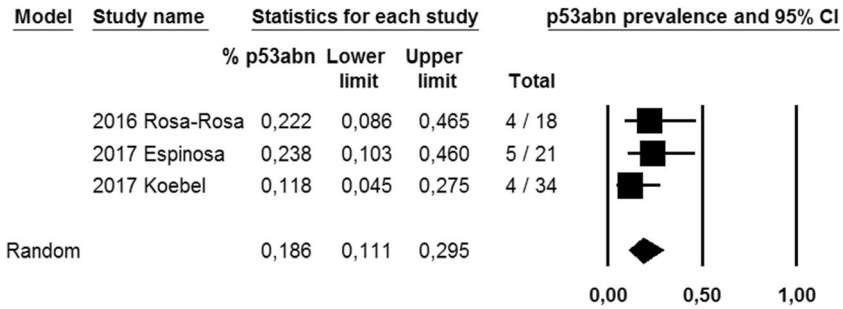

Fig. 3 Forest plot reporting the prevalence of the p53abn subgroup in undifferentiated/dedifferentiated endometrial carcinoma

[42]. Therefore, the possible impact of this group on the prognosis of UDC/DDC is unclear.

Further studies are needed to confirm the prognostic significance of the TCGA classification in endometrial UDC/DDC. Hopefully, these data may help to refine the prognostic stratification in UDC/DDC, allowing a more tailored patient management.

Limitation of our review may lie in the small number of the included studies ($N = 3$), in the patient overlap (14 patients overlapped between the studies, but it was impossible to identify them) and in the lack of data about prognosis.

Conclusion

In endometrial UDC/DDC, all the four TCGA molecular groups are represented, indicating a biological heterogeneity within this histotype, with a clear predominance of the MSI group. The predominance of hypermutated/ultramutated tumors and the low prevalence of the p53abn group indicate a crucial biological difference between UDC/DDC and other high-risk histologies, supporting the possible use of immunotherapy in most UDC/DDCs. Further studies are needed to investigate the prognostic significance and the clinical impact of the TCGA classification in endometrial UDC/DDC.

Author's Contribution AT, AR and MG independently assessed electronic search, eligibility of the studies, inclusion criteria, risk of bias, data extraction and data analysis. Disagreements were resolved by discussion with MM, LI, GFZ and FZ. MG, MM and LI contributed to the elaboration of methods for risk of bias assessment, data extraction and analysis. AT, AR and FZ conceived the study; MM, MG, LI and FZ worked on the design of the study; AT, AR, MG, MM, LI, GFZ and FZ worked on the manuscript preparation; GFZ and FZ supervised the whole study.

Compliance with Ethical Standards

Conflict of Interest Authors report no conflict of interest.

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