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TCGA Classification of Endometrial Cancer: the Place of Carcinosarcoma

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Abstract

In 2013, The Cancer Genome Atlas (TCGA) Research Network found four novel prognostic subgroups of endometrial carcinoma: POLE/ultramutated (POLE), microsatellite-unstable/hypermethylated (MSI), copy-number-low/TP53-wild-type (CNL), and copy-number-high/TP53-mutant (CNH). However, poor is known regarding uncommon histotypes of endometrial cancer. We aimed to assess the genetic profile of uterine carcinosarcoma (UCS) on the light of these findings. A systematic review and meta-analysis was performed through electronic databases searching (up to July 2019). All studies assessing UCS series for the TCGA classification were included. For each TCGA subgroup, pooled prevalence on the total UCS number was calculated. Four studies with 231 patients were included. Pooled prevalence of the TCGA subgroups were: 5.3% for the POLE subgroup, 7.3% for the MSI subgroup, 73.9% for the CNH subgroup, 13.5% for the CNL subgroup. The CNH subgroup predominates in UCS, while subgroups with high mutational load (POLE and MSI) are less common. UCS appears as a preferential evolution of CNH carcinomas.

Keywords Cancer · Endometrium · Prognosis · Risk assessment · PROMISE · Treatment · Endometrium

Introduction

Endometrial carcinoma is the most common gynecological malignancy in developed countries [1–5]. The management of patients with endometrial carcinoma is mainly based on pathologic findings, such as histotype, tumor grade and

stage and lymph-vascular space invasion [6]. However, pathologic assessment has shown poor reproducibility, and many authors think that this limitation is at the basis of the increased mortality observed in endometrial cancer in the last decades [7, 8].

Since the publication of The Cancer Genome Atlas (TCGA) data in 2013, it has been shown that specific molecular features have a major prognostic value in endometrial carcinoma. In fact, endometrial carcinomas can be consistently subdivided into four prognostic molecular subgroups: POLE/ultramutated (POLE), microsatellite-unstable/hypermethylated (MSI), copy-number-low/TP53-wild-type (CNL), and copy-number-high/TP53-mutant (CNH) [9–15]. Although molecular analyses used by the TCGA were complex and expensive, it has been shown that such classification can be reproduced by using immunohistochemistry for p53 and mismatch repair proteins and POLE sequencing [10–12].

Given these findings, criteria for the management of endometrial carcinoma will probably be strongly revised in the near future [16]. However, several aspects still have to be clarified, e.g. how tumor histotype should be integrated with molecular data. This point is unclear especially for uncommon histotypes of endometrial cancer, such as undifferentiated/

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dedifferentiated carcinoma (UDC/DDC), clear cell carcinoma and mucinous carcinoma.

In this review, we assessed in particular uterine carcinosarcoma (UCS), which had previously been considered as a type of uterine sarcoma and is now regarded as a “high-risk histology” of endometrial carcinoma [6, 17]. We aimed to assess the immunohistochemical/molecular profile of UCS in the light of the TCGA findings, through a systematic review and meta-analysis.

Materials and Methods

Study Protocol

The study protocol, i.e. the methods for systematic review and meta-analyses, were defined a priori, based on our previous studies [18–20]. Each review stage was performed by tree authors (AT, AR, AM) independently, and all authors were consulted in the case of disagreements. Authors followed The Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement to report this review [21].

Search Strategy and Study Selection

Seven different electronic databases were searched: EMBASE, Scopus, MEDLINE, Web of Sciences, Google Scholar, ClinicalTrials.gov and Cochrane Library. In each database, the search was performed from the database inception to May 2019, by using the following combination of text words: (endometrial OR endometrium OR uterine) AND (carcinosarcoma OR sarcomatoid carcinoma OR malignant mixed müllerian tumor). The research was subsequently updated to October 2019. References from relevant studies were also reviewed.

All peer-reviewed studies assessing UCS series for the TCGA classification were included. The following exclusion criteria, defined a priori, were adopted: sample size <10; incomplete TCGA classification (i.e. not all TCGA subgroup were investigated); sample size <10; reviews.

Data Extraction and Risk of Bias within Studies Assessment

Main data extracted were: the total number of UCS and the number of UCS in each TCGA subgroup; UCS were assigned to a specific TCGA subgroup based on the hierarchical model proposed by the TCGA [9] or the ProMisE [10–12] was used to assign. Four domains related to the risk of bias were assessed following the QUADAS-2 [22–25]: 1) Patient selection (i.e. if patients were consecutively selected); 2) Index test (i.e. if methods for immunohistochemical/molecular analyses are clearly described); 3) Reference standard (i.e. if cases were

reviewed by expert pathologists to confirm the UCS histotype); 4) Flow (i.e. if $\geq 95\%$ of included patients were assessed for the TCGA classification). Concerns about applicability of the domains 1, 2 and 3 were also assessed.

For each domain, the risk of bias was considered “low”, “unclear” or “high”, as previously described [26–29].

Data Analysis

The prevalence of each TCGA subgroup in UCS was calculated as the number of UCSs showing the molecular signature of that subgroup by the total number of UCSs. Data were pooled by using the random effect model of DerSimonian-Laird. Results for each individual study and pooled estimates were graphically reported on forest plots with 95% confidence interval (CI). Since the CNL subgroup is defined by the absence of the markers of the other 3 subgroups, its prevalence was calculated as follows: $\%CNL = 100\% - (\%POLE + \%MSI + \%CNH)$.

Statistical heterogeneity among studies was quantified according to the inconsistency index I^2 : heterogeneity was categorized 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 described [30–34].

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

After the exclusion of non-relevant studies, 13 articles [16, 35–46] were full-text assessed for eligibility: 8 studies were excluded for incomplete TCGA assessment [35–42]; one study was excluded for overlapping patient data with a study already included [43] and another study was excluded for being a review [16]. Finally, 3 studies fulfilled inclusion criteria and thus were included [44–46]. The updated research led to the inclusion of a fourth study [47]. The process of study selection schematically reported in Figure S1.

Study Characteristics

The overall sample was constituted of 231 patients with UCS. The POLE group was assessed by performing *POLE* sequencing in all studies; the MSI group was assessed by molecular analysis in three studies [45–47] and by mismatch repair proteins immunohistochemistry in the remaining study [44]; the CNH subgroup was assessed by using DNA copy number analysis in one study (which also performed *TP53*

Table 1 Characteristics of the included studies

Study	Country	Period of Enrollment	Sample size	Methods to assess TCGA subgroups			
				POLE	MSI	CNH	CNL
McConechy et al. 2015 [44]	Canada	unclear	30	<i>POLE</i> sequencing	mismatch repair proteins immunohistochemistry	p53 immunohistochemistry, <i>TP53</i> sequencing	exclusion
Cherniack et al. 2017 [45]	USA	unclear	57	<i>POLE</i> sequencing	microsatellite instability testing	<i>TP53</i> sequencing	exclusion
Le Gallo et al. 2018 [46]	USA	unclear	53	<i>POLE</i> sequencing	microsatellite instability testing	<i>TP53</i> sequencing	exclusion
Gotoh 2019 [47]	Japan	1998–2015	91	<i>POLE</i> sequencing	microsatellite instability testing	DNA copy number analysis	exclusion

POLE: POLE/ultramutated subgroup; MSI: microsatellite-instable/hypermutated subgroup; CNH: copy-number-high/*TP53*-mutant subgroup; CNL: copy-number-low/*TP53*-wild-type subgroup

sequencing) [47], and *TP53* sequencing in the remaining studies, one of which also performed p53 immunohistochemistry [44]. General characteristics of the included studies are shown in Table 1.

Risk of Bias within Studies Assessment

The risk of bias for the “patient selection” domain was considered low for one study (period of enrollment and inclusion criteria reported [47]) and unclear in the remaining studies. For all the other domains, no risks of bias were highlighted and thus all studies were considered at low risk. No concerns about applicability were raised. Results of the risk of bias assessment are summarized in Figure S2.

Meta-Analysis

Among all UCS patients, 5.3% (95% CI, 2.1%–12.5%) belonged to the POLE subgroup (Fig. 1), with low statistical heterogeneity among studies ($I^2 = 45.9%$); 7.3% (95% CI, 2.2%–21.6%) belonged to the MSI subgroup (Fig. 2), with high heterogeneity ($I^2 = 78.7%$); 73.9% (95% CI, 58.1%–85.2%) belonged to the CNH subgroup (Fig. 3), with high heterogeneity ($I^2 = 80.2%$). The remaining 13.5% was assigned to the CNL subgroup.

Discussion

This study showed that 5.3% of UCS were POLE, 7.3% were MSI, 73.9% were CNH and 13.5% were CNL. To the best of our knowledge, this is the first meta-analysis focused on the molecular background of UCS.

UCS, also called malignant mixed Müllerian tumor, is an aggressive uterine neoplasm constituted by a carcinomatous component and a sarcomatous component. The carcinomatous component often is high-grade and may display features of any endometrial carcinoma histotype (i.e. endometrioid, serous, clear cell), while the sarcomatous component may be homologous or heterologous based on the type of mesenchymal differentiation. Based on molecular studies, the sarcomatous component is now considered as a metaplastic change of the carcinomatous component, through a process of epithelial-to-mesenchymal transition [17]. Therefore, UCS is listed among the “high-risk histologies” of endometrial carcinoma [6] and is considered the most aggressive histotype together with UDC/DDC [48–52]. Indeed, the NCCN guidelines recommend chemo/radiotherapy for these two histotypes even in the earliest stages and in the absence of residual tumor in the hysterectomy specimen [6].

Given the outstanding prognostic value of the TCGA classification [9], it appears crucial to assess the several histotypes

Fig. 1 Forest plot reporting the prevalence of the POLE/ultramutated subgroup in uterine carcinosarcoma

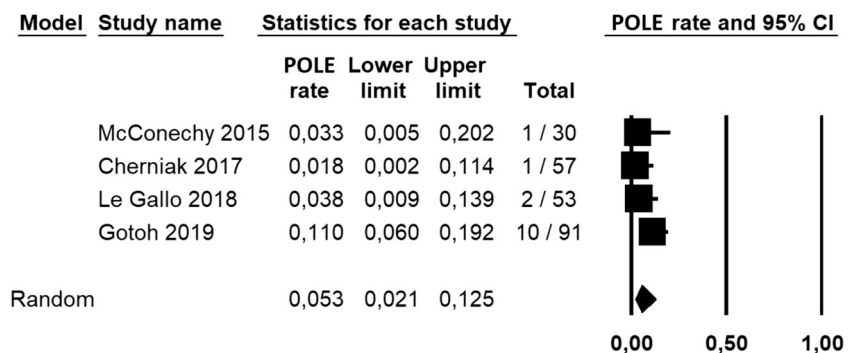
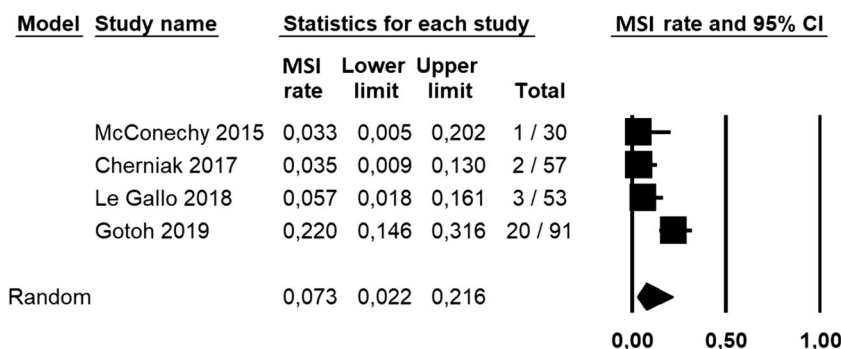


Fig. 2 Forest plot reporting the prevalence of the MSI/hypermethylated subgroup in uterine carcinosarcoma



of endometrial carcinoma in the light of such classification. However, while the TCGA subgroups have repeatedly been assessed in endometrioid and serous carcinoma [10–15], their distribution in less common histotypes is less clear.

Our study showed that the CNH subgroup predominated in UCS, while hypermethylated and ultramethylated tumors were rare.

This evidence marks a crucial difference between the two histotypes with the worst prognosis, i.e. UCS and UDC/DDC. Indeed, while most UDC/DDCs show a high mutational rate, with a large predominance of the MSI subgroup [53–58], the majority of UCSs are tumors with low mutational rates and high copy-number-alteration. This evidence may have several implications.

First, such a molecular difference may be helpful in the differential diagnosis between UDC/DDC and UCS, which is sometimes difficult. In fact, both histotypes can show a biphasic pattern with an epithelial and a non-epithelial component [59]. In difficult cases, immunohistochemistry for mismatch repair proteins (surrogate for MSI testing) and for p53 (surrogate for copy-number assessment) may aid the pathologist.

Second, it may be hypothesized that UDC/DDC and UCS might represent the final evolution of MSI/POLE endometrioid carcinomas and of CNH carcinomas (of any histotype), respectively (Fig. 4). In fact, it has been reported that both the sarcomatous component of UCS and the undifferentiated component of UDC/DDC express the same

markers of epithelial-to-mesenchymal transition; such finding suggests that the same molecular event could turn an endometrial carcinoma into an UCS or an UDC/DDC depending on its baseline features [42]. In this regard, the TCGA groups might account for the different evolution.

Third, the different molecular background might reflect major prognostic difference between these two histotypes. In fact, studies on high-grade endometrial carcinomas have shown that MSI and POLE signatures are associated with a significant improvement in the prognosis [60, 61]. On the other hand, the CNH signature is consistently associated with the worst prognosis among endometrial carcinomas [9–15]. These molecular signatures might maintain their prognostic value in UCS and UDC/DDC [47, 57].

Finally, the molecular difference between UCS and UDC/DDC might be translated into different treatment strategies between these two histotypes, which are currently treated with the same protocol as recommended by the NCCN guidelines [6]. In particular, the high mutational load may support the use of immunotherapy in most UDC/DDC [62].

Further studies are needed to assess the feasibility of a differential approach based on molecular signatures, since our study is limited by the low number of included studies and by the lack of prognostic data. However, the consistency among the results found may strengthen the basis for future investigations in this field.

Fig. 3 Forest plot reporting the prevalence of the copy-number-high subgroup in endometrial clear cell carcinoma

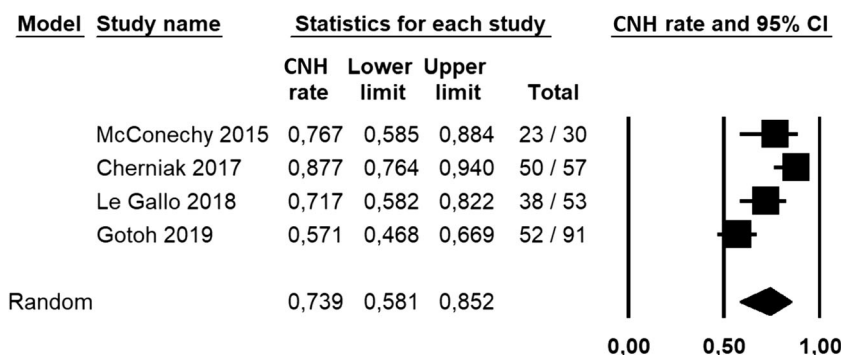
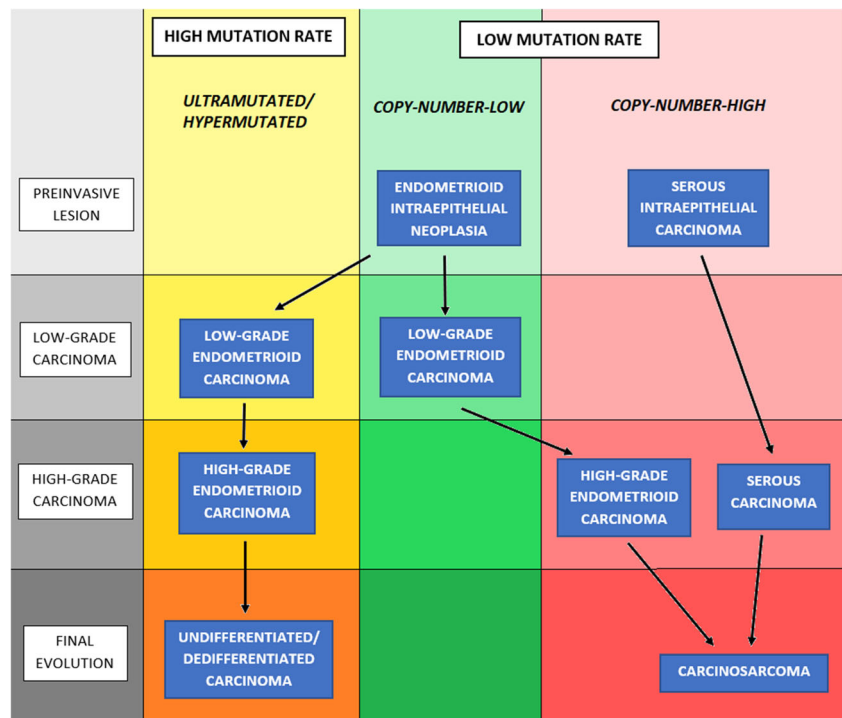


Fig. 4 Flow diagram schematically reporting the hypothetical dual final evolution of endometrial carcinoma, towards undifferentiated carcinoma (in subgroups with high mutational rate, i.e. POLE/ultramutated and MSI/hypermutable) or carcinosarcoma (in subgroups with low-mutational rate, i.e. copy-number-low and copy-number-high)



Conclusion

UCS is mostly constituted of CNH tumors, suggesting that UCS is a preferential evolution of CNH carcinomas. On the other hand, subgroups with high mutational load (i.e. POLE and MSI subgroups) are less common. This evidence could mark a crucial difference with the other highly-aggressive histotype of endometrial carcinoma, i.e. UDC/DDC, which is mainly composed of highly mutated tumors instead. Such a molecular difference may aid in the biologic, diagnostic and prognostic definition of these two histotypes, suggesting the possibility of a differential treatment between these two histotypes, which are currently treated with the same protocol. Further studies are necessary to define the clinical implications of these findings.

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

Compliance with Ethical Standards

Conflict of Interest Authors report no conflict of interest.

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