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Molecular characteristics and clinical behaviour of epithelial ovarian cancers

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ABSTRACT

Ovarian carcinoma (OC) is an umbrella term for multiple distinct diseases (histotypes), each with their own developmental origins, clinical behaviour and molecular profile. Accordingly, OC management is progressing away from a one-size-fits all approach, toward more molecularly-driven, histotype-specific management strategies. Our knowledge of driver events in high grade serous OC, the most common histotype, has led to major advances in treatments, including PARP inhibitor use. However, these agents are not suitable for all patients, most notably for many of those with rare OC histotypes. Identification of additional targeted therapeutic strategies will require a detailed understanding of the molecular landscape in each OC histotype. Until recently, tumour profiling studies in rare histotypes were sparse; however, significant advances have been made over the last decade. In particular, reports of genomic characterisation in endometrioid, clear cell, mucinous and low grade serous OC have significantly expanded our understanding of mutational events in these tumour types. Nonetheless, substantial knowledge gaps remain. This review summarises our current understanding of each histotype, highlighting recent advances in these unique diseases and outlining immediate research priorities for accelerating progress toward improving patient outcomes.

1. Introduction

Ovarian cancers are a heterogeneous collection of malignancies, together accounting for over 200,000 deaths per year worldwide [1]. The vast majority of cases are tubo-ovarian carcinomas (OC), which are frequently diagnosed at advanced stage and have a high rate of recurrence and mortality [2]. However, this depiction of OC is principally driven by the most common OC type, high grade serous OC (HGSOC), which represent approximately 75% of cases [3,4]. In reality, a wealth of data now demonstrate that OC is a collection of separate disease entities (histotypes), each with distinct molecular landscapes, developmental origins and clinical behaviour [2–5]. While some principles appear to hold true across all histotypes – such as the importance of maximal surgical debulking [4] - viewing OC as a single disease is a major over-simplification. Histotype-specific consideration of OC is crucial to understanding key biological drivers, clinical behaviour, and optimizing treatment strategies to maximise patient survival.

As the most common OC histotype, HGSOC has been the focus of the vast majority of research effort to date [6]. Historical clinical and molecular studies were typically of mixed histotypes, dominated by HGSOC due to their high frequency; even contemporary investigations are often either HGSOC-specific or are dominated by HGSOC. While these studies have led to major advancements in the understanding and treatment of OC, this approach has hindered progress within less common histotypes. Indeed, the molecular characteristics of rarer histotypes has remained poorly understood until recently. Major advances have been made within the last decade, identifying high- and low-risk patient groups in some histotypes, as well as highlighting recurrent molecular abnormalities suggestive of specific targeted treatment opportunities.

This review will summarise our current understanding of each OC histotype: HGSOC, endometrioid OC (EnOC), clear cell OC (CCOC), low grade serous OC (LGSOC), mucinous OC (MOC) and ovarian carcinosarcoma (OCS). The primary focus will be on the uncommon histotypes, which have received far less research attention to date, with a brief overview of the extensive HGSOC literature for comparison.

2. Endometrioid ovarian carcinoma

EnOC accounts for approximately 10% of OC cases [3,5], with a median age at diagnosis of 54–58 years (Table 1) [3,5,7]. The majority are diagnosed at early stage (around 50% FIGO stage I, 20–40% stage II, 10–25% stage III/IV) and are of low pathological grade (50–60% grade

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1, ~30% grade 2, ~20% grade 3) [7–9]. EnOC are associated with an overall favourable prognosis and are relatively chemosensitive; however, a proportion present with higher grade, advanced stage disease and have poorer prognosis [10]. The response rate of EnOC to platinum-based chemotherapy is around 60% [10], though comprehensive data on well curated EnOC cohorts are still lacking.

Historically, high grade EnOC were poorly distinguished from HGSOC, leading to an under-appreciation of this higher-risk population. Indeed, some investigators previously believed that all high grade EnOC essentially represent variants of HGSOC. However, more contemporary studies, utilizing immunohistochemistry (IHC) to help distinguish HGSOC and EnOC, reveal a significant number of these higher-risk EnOC cases [8,11]. WT1 is a helpful discriminatory tool in this context; EnOC are typically WT1 negative, while HGSOC are overwhelmingly WT1 positive (Table 2) [12,13]. EnOC are generally positive for ER (≥75% cases) and PR (>60% cases) [14], and most demonstrate a wild-type p53 staining pattern (~80% cases).

A significant proportion of EnOC are associated with endometriosis (up to 40%) [13], which is the recognised precursor lesion of this tumour type. A number of EnOC are associated with germline MMR gene inactivation (Lynch Syndrome). Overall, 5–10% harbour germline or somatic MMR mutation, around 7% show IHC staining consistent with MMR deficiency, and around 10% demonstrate microsatellite instability [11].

Genomically, EnOC are characterised by frequent mutation of *CTNNB1* (30–50% cases), *PIK3CA* (30–50%), *KRAS* (25–40%), *ARID1A* (20–40%) and *PTEN* (30–45%) (Table 2) [11,15–17]. Consistent with previous misdiagnosis of EnOC in cases that in fact represent variants of HGSOC, historic studies suggested a high *TP53* mutation rate (>50% in some studies) [18]. In contemporary cohorts of well-curated cases, *TP53* mutations are present in around 20% of EnOC [11,15–17] and are most common in those of higher pathological grade. Recently, *SOX8* mutations have been reported in a significant number of cases (20%), and often occur in the context of *TP53* mutation [11]. The *BRCA1/2* mutation rate is around 10% in contemporary cohorts, and around 5% have *POLE* mutations [7,9,11,19].

Several molecular features have recently been associated with clinical phenotypes in EnOC patients. *TP53* mutation has been identified as a poor prognosis marker by both transferring the PROMISE algorithm (derived in endometrial carcinoma: p53 aberrant, MMR deficient, POLE mutant, no specific molecular defect) to EnOC [7,9,19], and via recently identified novel EnOC molecular subtypes (*TP53*-mutant, *CTNNB1*-mutant, *TP53/CTNNB1* wild-type) [11,20]. *TP53* mutation is associated with higher pathological grade, later stage at diagnosis, and greater genomic complexity, with fewer oncogenic activating mutations.

Conversely, *CTNNB1* mutation – which occurs mutually exclusively with *TP53* mutation [11] (Fig. 1A) – and high PR expression, which is correlated with *CTNNB1* mutation [20], have been associated with excellent prognosis [14,20–23], independent of grade and stage. *CTNNB1*-mutant and/or PR-high EnOC show low genomic complexity, and typically present as low grade early stage tumours (Fig. 1A) [11,20]. Within the PROMISE taxonomy, *POLE*-mutant EnOC have been reported to demonstrate exceptional survival [7,9,19]. However, the low *POLE* mutation frequency in this tumour type limits the utility of *POLE* testing and the statistical power of these comparisons; moreover, *POLE*-mutant cases may also commonly harbour *CTNNB1* mutation [11]. PROMISE is further limited in EnOC by the high number of cases in the MMR-deficient and no specific molecular defect groups (>85% of cases allocated to these subgroups in a recent large study [7]), which appear to demonstrate equivalent clinical behaviour [7]. The recently proposed classification by *TP53* and *CTNNB1* status appears to identify three relatively evenly distributed groups (~25% *TP53*-mutant, ~40% *CTNNB1*-mutant, ~30% *TP53/CTNNB1* wild-type), each with distinct clinical outcome.

Endocrine therapy has been highlighted as a potential therapeutic strategy in EnOC [21], and it has been suggested that endocrine agents may represent an opportunity for de-escalation of therapy from cytotoxic agents for low risk cases [21]. Results from clinical studies such as the ongoing MATAO trial of maintenance endocrine therapy in OC should include histotype-specific efficacy data to help inform feasibility assessment of such approaches [24]. Some recurrent mutations in EnOC are suggestive of specific opportunities for targeted therapeutics (e.g. MEK inhibitors for *KRAS* mutant cases); however, many of these events are less common in higher-risk cases such as the *TP53*-mutant population [11]. The WNT pathway has been suggested as a therapeutic target in this population due to frequent concurrent *TP53* and *SOX8* mutation [11]; however, functional studies of *SOX8* mutation are currently lacking. A minority of *TP53*-mutant EnOC harbour *BRCA1/2* mutations and

Table 1
Clinical characteristics of ovarian carcinoma histotypes.

Proportion of OC diagnoses	EnOC ~10%	CCOC ~10%	LGSOC ≤5%	MOC ≤5%	OCS <5%	HGSOC ~75%
Developmental origin and precursor lesion	Endometriosis	Endometriosis	Serous borderline tumour precursor. Likely fallopian tube epithelium origin.	Brenner tumours, teratomas. Mucinous borderline tumour precursor.	Originate from carcinomas, mostly from HGSOC or EnOC. Suspected associated precursors according to carcinomatous component type.	Distal fallopian tube epithelium, serous tubal intraepithelial carcinoma (STIC) precursor lesion.
FIGO stage at diagnosis	40% stage I 40% stage II 20% stage III-IV	70% stage I 20% stage II 10% stage III-IV	5–10% stage I-II 80% stage III 10–15% stage IV	80% stage I 10% stage II ~10% stage III-IV	10–15% stage I 10% stage II 60–70% stage III 10–20% stage IV	10–15% stage I-II 70% stage III 15–20% stage IV
Median age at diagnosis	54–58	53–55	46–48	50–54	66–70	60–61
Overall prognosis	Excellent for early stage low grade cases. Poor prognosis for high grade advanced stage	Favourable for early stage. Extremely poor prognosis for advanced stage/ relapse	Intermediate; high risk of relapse with prolonged post-relapse survival	Excellent for early stage. Extremely poor prognosis for advanced stage/ relapse	Extremely poor	Poor; high risk of relapse which acquires treatment resistance
Survival	60–70% 10-year survival	10-year survival: 80–90% for early stage, 10% for advanced stage	Median 10–11 years	10-year survival: ≥90% for early stage, <20% for advanced stage	Median 13–24 months	~40% 5-year survival for advanced stage
First-line chemosensitivity (platinum-based regimens)	Intermediate sensitivity. Objective response rate (ORR) ~60%	Highly resistant. ORR ~30%	Highly resistant. ORR <25%	Highly resistant. ORR ~25–40%	Resistant. ORR ~25–65%	Highly sensitive. ORR ~80%

Table 2
Molecular characteristics of ovarian carcinoma histotypes.

Research attention to date	EnOC Low	CCOC Low	LGSOC Low	MOC Very low	OCS Very low	HGSOC High
Useful diagnostic markers						
WT1	Negative	Negative	Positive	Negative	Staining patterns consistent with epithelial compartment histotype.	Positive
p53	~80% wild-type	Usually wild-type	Wild-type	60% aberrant		Aberrant
ER	≥75% positive	≥80% negative	≥80% positive	~80% negative		≥75% positive
PR	≥60% positive	>90% negative	55–70% positive	>80% negative		~30% positive
Napsin A	Negative	Positive	Negative	Negative		Negative
Other		HNF1β positive		To distinguish from extra-ovarian metastases	Cytokeratin/vimentin to confirm two compartments. S100 and myogenin/desmin to confirm chondrosarcoma and rhabdomyosarcoma heterologous elements.	
Germline mutations	MMR genes (Lynch syndrome)	MMR genes (Lynch syndrome)	No common germline events recognised	No common germline events recognised	Poorly characterised; suspected according to epithelial component type	*BRCA1*, *BRCA2*, non-BRCA HRR genes
Most common mutations	*CTNNB1*, *PIK3CA*, *ARID1A*, *PTEN*, *KRAS*, *TP53*, *SOX8*, MMR genes.	*PIK3CA*, *ARID1A*, *KRAS*, *PPP2R1A*, *SYNE1*, *TERT* promoter, MMR genes.	*KRAS*, *BRAF*, *NRAS*, *USP9X*, *EIF1AX*, MAPK-associated genes. *CDKN2A* loss.	*KRAS*, *TP53*, *RNF43*, *ARID1A*, *BRAF*, *PIK3CA*, *CDKN2A*. *ERBB2* amplification, *CDKN2A* deletion.	*TP53*	*TP53*, *BRCA1*, *BRCA2*, non-BRCA HRR genes. *NF1*, *RB1* and *PTEN* disruption. *CCNE1* gain/amplification.
Global genomic profile	Low genomic complexity in low grade/*CTNNB1* mutant High genomic complexity in high grade/*TP53* mutant	Relatively low genomic complexity	Low genomic complexity	Typically low genomic complexity; higher grade and advanced stage patients more complex	Available data suggests high genomic complexity with extensive copy number changes	High genomic instability and extensive copy number changes Frequently homologous recombination deficient
Clinically relevant molecular events	*TP53* mutation: shorter survival.*CTNNB1* mutation: improved survival.High PR expression: improved survival.POLE mutation may be associated with improved survival.	*TP53* mutation: candidate marker of poorer survival.	MAPK mutations: prolonged survival, improved response rate to MEK inhibition.	Greater genomic complexity: associated with shorter survival.	None identified to date.	Homologous recombination defects (nb. *BRCA1/2* mutation): improved survival and sensitivity to platinum and PARPi.*CCNE1* gain: poor survival

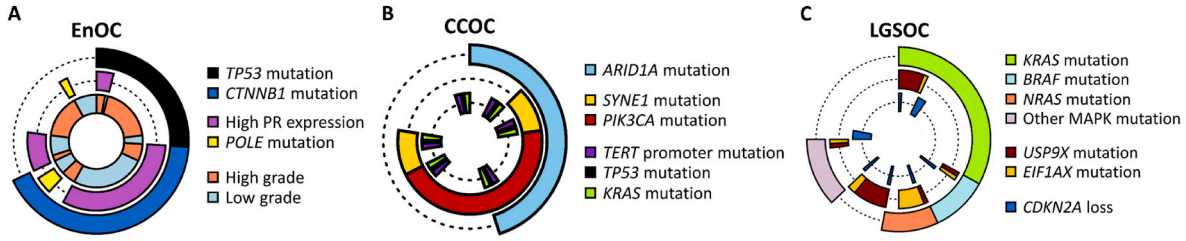

Fig. 1. Layered onion plots of molecular features in endometrioid (EnOC), clear cell (CCOC) and low grade serous ovarian carcinoma (LGSOC). (A) Clinically relevant molecular features of endometrioid ovarian carcinoma [7,9,11,15–17,19,20]. (B) Common genomic features of clear cell ovarian carcinoma [25,30,32–34]. (C) Common genomic features of low grade serous ovarian carcinoma [40–42,44,47,48]. PR, progesterone receptor.

may therefore be expected to benefit from PARP inhibitors [20]. Immunotherapy represents a potential treatment option of interest for EnOC, particularly for MMR deficient cases. It is worth noting that many clinical studies of HGSOC are also open to high grade EnOC, representing an avenue by which additional treatment options for high-risk cases may be identified. To date, there remains a paucity of EnOC-specific trials of molecularly-directed therapeutics.

Immediate research priorities for EnOC include: (i) validating the utility of molecular classifiers (based on *TP53/CTNNB1*, PROMISE or PR expression) in prospective cohorts; (ii) investigating novel therapeutic approaches for patient groups underserved by current treatment modalities (*TP53* mutant, PR-low, *CTNNB1* wild-type or PROMISE no specific molecular defect subgroup); (iii) further investigating the utility of endocrine therapy in EnOC.

3. Clear cell ovarian carcinoma

CCOC accounts for approximately 10% of OC diagnoses [25], with a median age of diagnosis of 53–55 years [26,27]. The vast majority present at early stage (55–70% stage I, 10–15% stage II, 20% stage III, 5–15% at stage IV) [25–27] and are at low risk of relapse following primary debulking surgery (80–90% 10-year survival) (Table 1). However, CCOC demonstrates high levels of intrinsic chemoresistance (response rate to platinum-based chemotherapy around 30%) [27,28], and advanced stage CCOC is associated with exceptionally poor survival (10% 10-year survival) [4,26]. CCOC are considered high pathological grade by definition [13].

Historical studies misclassified a significant proportion of HGSOC demonstrating clear cell change as CCOC [25]. WT1, Napsin A, HNF-1β, ER and PR are useful IHC markers for discriminating CCOC from HGSOC

and EnOC, which can bear morphological resemblance to CCOC (CCOC: WT1 negative, Napsin A/HNF-1β positive, ER/PR negative) (Table 1) [12,13,25]. Contamination with misclassified HGSOC has likely contributed to reports of common aberrant p53 expression in CCOC studies without robust contemporary pathology review (up to 50% in some studies) [29,30]. By contrast, the rate in cohorts that have undergone contemporary review is low (≤15% mutation or aberrant expression) [15,31,32] and this may still represent an over-estimate due to lack of IHC use during review.

As with EnOC, some CCOC are associated with germline MMR gene mutations (Lynch syndrome), though MMR mutations are relatively uncommon in CCOC overall (<10%) [32]. Also similarly to EnOC, the recognised precursor lesion of CCOC is endometrioisis, with around 50% of CCOC cases being identified alongside endometrioitic lesions [25].

The most common mutational events in CCOC occur in *ARID1A* (40–50% of cases), *PIK3CA* (40–50%), *PPP2R1A* (10–20%), *KRAS* (5–20%) and the *TERT* promoter (5–15%) (Table 2) [25,30,32,33]. *ARID1A* mutation appears to be more frequent in patients with a history of endometrioisis [32]. *SYNE1* mutations may also be a common feature (up to 20%), and may occur mutually exclusively with *PIK3CA* mutation (Fig. 1B) [34]. CCOC harbours significantly fewer copy number aberrations compared to HGSOC and EnOC [25].

While some efforts to apply the PROMISE algorithm to CCOC have failed to identify clinically relevant patient groups [31], another study has suggested the p53 aberrant group may experience poor prognosis and that *POLE* or MMR gene defects may be associated with excellent prognosis [35]. However, high frequency of aberrant p53 expression (20%) and advanced stage (37% stage III-IV) suggests possible contamination with HGSOC cases. Moreover, the number of *POLE*/MMR cases was extremely low (n = 1 *POLE*-mutant, n = 4 MMR deficient; <5% of 115 cases) [35]. A subsequent sequencing study has also suggested that *TP53* mutation may be associated with poorer survival [32]; however, this was of only marginal significance in a relatively large cohort and the study acknowledged likely contamination with non-CCOC cases [32].

Gene expression analysis of CCOC has identified a number of transcriptomic subtypes. Initial analysis of 25 cases identified three sample clusters [36], with the CCC-2 subtype showing favourable prognosis; however, statistical power in this study was limited (N = 10 CCC-2 cases) and transcriptomically profiled specimens contained up to 50% non-malignant cells, potentially impacting expression analysis. Later, two expression subtypes were described in CCOC that demonstrated large differences in progression-free survival [37]. This study combined multiple previous CCOC cohorts transcriptomically characterised on different platforms to form discovery and validation datasets. The poor prognosis group was associated with a high transcriptomic score for epithelial to mesenchymal transition (EMT), higher expression of extracellular matrix organisation genes and more frequent advanced stage disease. The favourable prognosis group had a low EMT score and higher expression of cell-cell adhesion genes [37]. A recent analysis also described two transcriptomic clusters of CCOC [32]. Cluster 1 was associated with high expression of transcripts previously identified in CCOC or cancer-associated endometrioisis (*ANXA4*, *GPX3*, *EEF1A2*), frequent *ARID1A* mutation and low *TP53* mutation rate (10%), while Cluster 2 demonstrated features redolent of HGSOC, including higher *WT1* mRNA expression, lower *HNF1B* mRNA expression, low *ARID1A* mutation frequency and common *TP53* mutation (55%) [32]. Cluster 2 also demonstrated poorer survival, but this association was not maintained after adjustment for age, race, stage and residual disease status. However, the authors estimated around 25% of the *TP53* mutant tumours in their cohort were misclassified non-CCOC cases, raising the possibility that observed Cluster 2 phenotypes may be driven by contamination with non-CCOC histotypes. The rates of *ARID1A* and *TP53* mutation in cluster 2 are supportive of this notion. Lack of routine IHC marker use to identify robust cohorts of CCOC remains a major weakness of transcriptomic studies to date.

There remains a paucity of targeted treatment options for CCOC. Results from phase II trials investigating cabozantinib (targeting MET, RET, VEGFR2 and AXL) and sunitinib (targeting PDGF and VEGF receptors) for recurrent disease have been disappointing [25]. A phase II trial investigating first-line temsirolimus (targeting mTOR) in combination with chemotherapy demonstrated objective responses in some patients, but did not improve survival compared to historical controls [38]. Targeting CCOC with immunotherapy has become an area of great interest, with multiple ongoing trials testing the efficacy of immune checkpoint inhibitors either alone or in combination with other agents [25]. Other targeted approaches under investigation include nintedanib, targeting the PDGF, VEGF and FGF receptors.

Though progress has been made in characterising the genomic and transcriptomic landscape of CCOC, major challenges remain. Robust curation of bona fide CCOC cohorts remains a significant obstacle. Immediate research priorities for CCOC include: (i) determining the efficacy of immunotherapies in CCOC; (ii) identification of further targeted treatment options for patients with advanced stage and recurrent disease; (iii) identifying markers of high and low recurrence risk in early stage patients to better inform recommendations for systemic therapy in this context.

4. Low grade serous ovarian carcinoma

LGSOC comprises only around 5% of OC diagnoses. Typical LGSOC is characterised by late stage at diagnosis (≤10% stage I-II, 80% stage III, 10–20% stage IV) (Table 1) and prolonged post-relapse survival [39–41]. While LGSOC is often described as demonstrating more indolent behaviour, it frequently occurs in younger women (median 46–48 years) [40,42] and therefore affects a disproportionate number of life years compared to other histotypes. LGSOC is low grade by definition [39–41], and demonstrates high levels of intrinsic chemoresistance (objective response rate to first-line platinum-based chemotherapy ≤25%) [43]. Treatment of recurrent or persistent LGSOC remains a major clinical challenge.

LGSOC is often conceptualised as ubiquitously *TP53* wild-type [3]; rare cases with p53 defects have been reported in the literature, though these cases may represent occult HGSOC. p53 IHC is therefore a helpful discriminator between LGSOC and HGSOC [12]. LGSOC are WT1 positive [3,12], are almost always ER positive, and express PR in a large proportion of cases [14,44]. LGSOC is frequently associated with serous borderline tumours, which are considered a common precursor lesion [45], with the LGSOC cell of origin thought to initially derive from the fallopian tube [39]. Limited available expression data support the notion of a fallopian tube origin for LGSOC [46], though our current understanding of LGSOC pathogenesis is incomplete. Around 60% of cases have a borderline component, and the risk of progression from serous borderline tumour to LGSOC is 5–10% [45].

LGSOCs are relatively genomically quiet, with an overall low tumour mutational burden and low genomic complexity [47]. The MAPK pathway is the principal target of mutational events in this tumour type: around 33%, 10% and 10% demonstrate mutations in *KRAS*, *BRAF* and *NRAS*, respectively (Fig. 1C) [40–42,44,47]. A number of mutational events in other MAPK-associated genes have been reported, including *NF1* mutations [40–42,44]; however, these are rare events across a large number of genes, and their functional relevance remains to be determined. 13–27% demonstrate inactivating mutations in the deubiquitylase-encoding gene *USP9X* [41,48], and 6–15% harbour *EIF1AX* mutations [40,41,47,48] which frequently co-occurs with *NRAS* mutation [48]. LGSOC also demonstrate frequent *CDKN2A* deletion [41,47].

Accumulating evidence suggests *KRAS* mutation is associated with improved survival in LGSOC, and that this phenotype may extend to a wider group of MAPK active patients with *NRAS* and *BRAF* mutations [40,42,49]; it is currently unclear if this phenotype extends to those with other MAPK-associated mutations. *BRAF* mutations appear to be

associated with serous borderline tumours over invasive LGSOC [39], while MAPK wild-type patients appear to represent cases diagnosed at younger age (median 38 years) [40,42]. In the MILO study, a negative phase III trial of binimetinib for recurrent or persistent LGSOC, post-hoc *KRAS* mutation analysis suggested an association between *KRAS* mutation and greater response rate to MEK inhibition [50]. Consistent with these data, in the positive GOG281 phase II/III study of trametinib for recurrent or persistent LGSOC, combined *KRAS/NRAS/BRAF* status was associated with improved response rate [51]. While MEK inhibitors are now recommended for treatment of recurrent LGSOC, it is clear that not all patients benefit, that resistance can develop, and that specific patient groups may respond less frequently [50,51].

Beyond MAPK, hormone receptor expression patterns may define clinically meaningful subtypes of LGSOC. High PR expression was associated with prolonged survival in the OTTA consortium LGSOC cohort [14], and recent analysis has suggested that high PR and high ER expression are each associated without favourable outcome [52]. Many LGSOC patients benefit from treatment with endocrine therapy [39], which is now recommended as first-line maintenance therapy. There is significant interest in the use of these agents given the low platinum response rate [39,43,53].

Immediate research priorities for LGSOC include: (i) identifying biomarkers for patients most and least likely to benefit from approved regimens, including MEK inhibitors, endocrine therapy and chemotherapy; (ii) determining whether mutations in non-canonical MAPK-associated genes (i.e. those beyond *KRAS*, *NRAS* and *BRAF*) confer a similar phenotype to *KRAS*-mutant cases; (iii) identifying novel treatment strategies and therapeutic targets beyond MEK inhibition to provide additional treatment options for recurrent disease.

5. Mucinous ovarian carcinoma

MOC is an uncommon histotype, accounting for ≤5% of OC cases, with a median age at diagnosis of 50–54 years [54]. Typical MOC presents at early stage (~80% stage I, ~10% stage II, ~10% stage III, ~10% stage IV) [54,55] and is low grade (65%, 30% and 5–10% grade I, II and III in the conventional three-tier grading system) [55], with low risk of recurrence following surgical resection (Table 1) [4,5,55]. However, MOC are highly treatment-resistant; the response rate of MOC to platinum-based chemotherapy is around 25–40% from limited available data [56–58]. Advanced stage and recurrent MOC are therefore a major clinical challenge.

It was previously believed that MOC occurred more frequently; however, many historic cases are now known to represent metastases from other sites, most commonly from the gastrointestinal tract [13]. Indeed, some have hypothesised that all MOC represent metastases from extra-adnexal sites [59]. However, recent analysis has demonstrated that some arise from mature ovarian teratomas [60], and a proportion of MOC are believed to derived from transitional cell (Brenner) neoplasms [54]. MOC are WT1 and Napsin A negative, and demonstrate mutant p53 expression patterns in around 60% of cases (Table 2) [61]. Clinically, large, unilateral mucinous tumours are considered more likely to represent true MOC, while bilateral tumours of smaller size are suspicious of metastases from other sites [13]. A large number of IHC markers can be used to aid discrimination against metastases from extra-ovarian malignancies [62]. Historically, Mullerian type mucinous tumours of the ovary were considered alongside true MOC. These Mullerian type cases were reclassified as a distinct entity termed 'seromucinous' over the last decade, displaying a distinct PAX8-positive and ER-positive immunoprofile (true MOC are PAX8 negative and almost always ER negative), and have since been further reclassified to reflect their recent recognition as variants of EnOC [63]. Recently, subclassification of MOC into expansile (~80% of cases) versus infiltrative invasive types (~20% of cases) has revealed poorer survival within the infiltrative invasive type [64,65].

Genomically, MOC harbours frequent mutation of *TP53*, *KRAS, BRAF* and *PIK3CA* (60–70%, 60–70%, 10% and 10%) (Table 2) [59]. Deletion or mutation of *CDKN2A* occurs in approximately 50% of cases, and *ERBB2* amplification occurs in around 25% of cases (Fig. 2A). While the majority of MOC appear to demonstrate low genomic complexity, higher grade and advanced stage MOC appear to be more genomically complex [59]. Higher genomic complexity may be associated with poorer survival, independent of other clinicopathological features. The transcriptomic landscape of MOC has only recently begun to be unravelled, though contemporary data have identified potential transcriptomic markers of poor prognosis (high *THBS2* expression, high *TAGLN2* expression) [64]. Recent data also suggest MOC are immunogenically cold, with low numbers of tumour-infiltrating immune cells [66].

There is a paucity of novel treatment options available for MOC. Efforts to improve outcomes by implementing gastrointestinal chemotherapy regimens, or by adding the anti-angiogenic agent bevacizumab, failed to improve patient outcomes in GOG241, a randomised international phase III trial of MOC, though this trial suffered from poor recruitment and contamination with metastases from extra-ovarian sites [58]. Some retrospective analyses have suggested improvement in outcomes with gastrointestinal regimens [67], though these are no substitute for prospective randomised studies. While ERBB2 has been identified as a potential target for therapeutic interventions, recent analysis suggests this event most frequently occurs in early stage MOC, with an amplification rate of only ~15% in stage III/IV MOC [64]. This study also identified higher ERBB2 expression in expansile versus infiltrative MOC. Together, these data suggest the utility of ERBB2-targeting strategies in high-risk MOC populations may be limited.

Advanced stage and/or suboptimally debulked MOC remains an area of critical unmet clinical need. Immediate research priorities include the curation of large tissue resources with careful exclusion of metastases from non-ovarian sites. Such cohorts will represent an invaluable opportunity to comprehensively characterise MOC at the genomic, transcriptomic and proteomic level, and will enable identification of potentially actionable biology specifically within MOC that are poorly served by current treatment regimens (advanced stage cases and those of the infiltrative invasive type). Representative laboratory models are also lacking; expansion of available *in vitro* resources will be key for investigating potential new treatment strategies and better characterising the underlying biology of MOC. Clinical trials with strict inclusion criteria to prevent contamination with extra-ovarian metastases represent an opportunity to robustly assess the potential benefit for different combinations of chemotherapeutic regimens, and for investigating the efficacy of targeted treatment options. Owing to the rarity of MOC, BASKET trials of novel therapeutics represent a promising avenue for advancing molecularly-directed treatment of these patients.

6. Ovarian carcinosarcoma

OCS is a rare diagnosis, accounting for <5% of cases, and represents the most aggressive form of OC (median survival approximately 13–24 months) [68,69]. Most are diagnosed at advanced stage (10–15% stage I, 10% stage II, 60–70% stage III, 10–20% stage IV), though recurrence and mortality risk is high across all stages [68,70,71]. Median age at OCS diagnosis is 66–70 years.

OCS is biphasic, demonstrating both high grade carcinomatous and high grade sarcomatous cell populations [69,72], initially leading to their consideration alongside sarcomas. However, OCS are now recognised to have an epithelial origin, with the carcinomatous population having undergone complete EMT to form the sarcomatous component [69]. OCS is highly histopathologically heterogeneous, but is easily distinguished from other histotypes due to its sarcomatous component. The epithelial component is typically of high grade serous type (80% cases), but is endometrioid in a significant proportion of cases (around 20%) (Fig. 2B) [68,72]. Heterologous sarcomatous elements are present in around half of cases, most commonly chondrosarcoma (30% cases) or rhabdomyosarcoma (20% cases) [68,72]; it has been suggested that

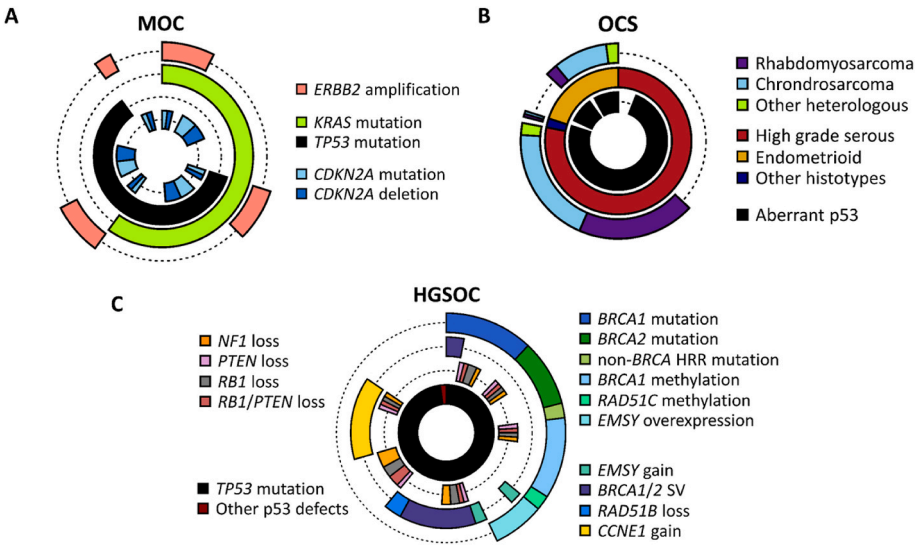

Fig. 2. Layered onion plots of features in mucinous ovarian carcinoma (MOC), ovarian carcinosarcoma (OCS) and high grade serous ovarian carcinoma (HGSOC). (A) Common genomic features of MOC [59]. (B) Histopathological features of OCS; outer layer represents types of heterologous elements present, middle layer represents the histotype of the carcinomatous components [68,72,74,75]. (C) Molecular landscape of HGSOC [84–92].

chondrosarcoma is more common in OCS with endometrioid type carcinomatous components (Fig. 2B) [68]. IHC for cytokeratins and vimentin can be useful for confirming sarcomatous and carcinomatous populations, and markers used for other histotypes can be used to determine the epithelial component type (Table 1). Additional markers may be useful to confirm the presence of specific heterologous elements [68]. A number of OCS cases have been associated with serous tubal intraepithelial carcinoma (STIC) or endometriosis [68], suggesting that OCS may develop via precursors lesions consistent with their epithelial components.

Molecular characterisation of OCS is extremely sparse; very few samples have undergone genomic characterisation to date [73–75]. Beyond high *TP53* mutation frequency (≥90% cases) [68,74], few recurrent mutations have been identified (Table 2) [74,75]. Recent targeted sequencing of 18 OCS has identified *KRAS* and *PTEN* mutations in a low proportion of cases [75], though the true frequency of these is difficult to assess due to limited numbers. From the available data, tumour mutational burden appears relatively low in OCS, with these tumours instead demonstrating high genomic complexity with extensive copy number aberrations [75]. A minority of cases harbour *BRCA1/2* mutations [73–75], and 30–50% show a dominant homologous recombination deficiency mutational signature [73]. These data point toward PARP inhibition as a potentially effective treatment strategy for some patients, and some case reports suggest successful use of these agents in specific cases.

Within IHC studies of combined gynaecological carcinosarcoma cohorts (uterine carcinosarcoma and OCS), HER2, PDGFR, EGFR and immune checkpoint molecules have been suggested as potential therapeutic targets [69]. However, the studies highlighting these molecules have been dominated by tumours of uterine origin, and the limited amount of comparative investigations suggest fundamental molecular differences between OCS and uterine carcinosarcoma [73,74]. Very recently, pre-clinical evidence has suggested the microtubule-targeting drug eribulin may be of therapeutic interest in OCS [75].

It remains unclear whether specific events define clinically distinct OCS subtypes due to the limited amount of available data. Some authors have suggested that presence of heterologous sarcomatous elements may be an indicator of poorer prognosis [76,77]; however, more contemporary studies have reported equivalent clinical behaviour of OCS subgroups defined by the histology of carcinomatous and sarcomatous components [68,78].

Some investigators have conceptualised OCS as variants of HGSOC [13]; however, OCS patients are significantly older at diagnosis [68,71,79], are more frequently diagnosed at earlier stage [68,79], are intrinsically more chemoresistant (objective response rate 25–65%) [68,70,71] and have poorer survival [68,71,79]. Moreover, a recent transcriptomic analysis of a small number of OCS cases has demonstrated significant gene expression differences compared to HGSOC [75]. Together, these data suggest that OCS should be considered separately to other histotypes, rather than regarded as variants of other high grade OC.

Despite its incredibly poor prognosis, OCS has received little research attention to date. Immediate priorities include genomic, transcriptomic and proteomic analysis of OCS cohorts with sufficient statistical power to identify recurrent events and/or molecularly defined subpopulations with distinct behaviour. These analyses hope to uncover potential biological vulnerabilities to targeted agents. Identification of new treatment strategies is urgently needed to improve OCS patient survival; this will require significant investment in developing representative laboratory disease models, which are currently lacking.

7. High grade serous ovarian carcinoma

HGSOC is the most common histotype (75% of cases) and has received the majority of research attention to date [2,6]. Median age at diagnosis is 60–61 years and cases are high grade by definition [5,80]. HGSOC typically present at advanced stage (10–15%, 70% and 15–20% of HGSOC at stage I-II, III and IV) and are initially chemosensitive (response rate to platinum-based chemotherapy around 80%) (Table 1) [6,43,81]. However, recurrence is common and accrues treatment resistance. Five-year survival for advanced stage cases is currently approximately 40%. HGSOC are WT1 positive [3,12], demonstrate mutant p53 expression patterns [3,12], and usually express ER (≥75% cases) (Table 2) [14]. Management of HGSOC has advanced substantially over the last decade with the introduction of PARP inhibitors, previously for recurrent disease, and now for first-line maintenance [82,83].

The developmental origin of HGSOC has historically represented an issue of great contention; however, a consensus has been reached that the majority arise from the distal fallopian tube epithelium, with STIC lesions evident in some cases [3,13]. Germline *BRCA1* and *BRCA2*

mutations – alongside rarer inherited mutations in other homologous recombination DNA repair (HRR) pathway components – represent the principal inherited predisposition syndrome associated with HGSOC [6,84,85].

A large number of studies have characterised HGSOC at the genomic level; these analyses have painted a highly complex genomic landscape dominated by extensive copy number aberrations and structural genomic variants, rather than classical activating oncogenic mutations [86,87]. Historically, mutations in *BRCA1* (8% germline, 4% somatic) and *BRCA2* (6% germline, 3% somatic) were the main recurrently identified driver events, alongside ubiquitous *TP53* mutation (≥95% cases) (Fig. 2C) [87]. *CCNE1* copy number gain occurs in 14% of cases and is mutually exclusive with *BRCA1/2* mutation [87,88]. Less common mutational events in non-BRCA HRR components (e.g. *PALB2* and *RAD51* family members) [84,85] and hypermethylation of *BRCA1* [87,89] have also been identified, and recent analyses suggest that amplification/overexpression of *EMSY* and structural genomic variants (primarily large deletions) affecting *BRCA1/2* may also be important HRR events [90,91]. Beyond HRR, whole genome sequencing has identified frequent large structural genomic variants in *RB1*, *PTEN* and *NF1* [86]. While many of these genomic events, with the exception of *TP53* mutation, were previously conceptualised to occur mutually exclusively with one another, it has become clear this is not the case [88,92]. In particular, loss of RB appears to significantly co-occur in cases with *BRCA1/2* or other HRR gene perturbations [86,88,92] and disruption of *NF1* and *PTEN* do not appear to be mutually exclusive with other events (Fig. 2C) [86,88]. Conversely, *CCNE1* gain appears largely mutual exclusive with many other recurrent genomic features [88].

A huge research effort has also been made to characterise HGSOC at the gene expression level. Numerous studies have performed transcriptomic analysis of HGSOC specimens, initially producing a variety of transcriptomic risk signatures and subtypes which suffered from poor consistency and reproducibility [87,93–95]. More recently, researchers have progressed toward a consensus on transcriptomic molecular subtypes, settling on groups reminiscent of those originally identified by the TCGA investigators, with large studies now demonstrating distinct survival outcomes between these subtypes [80,96]. However, transcriptomic classification, whether by risk signatures or subtyping, is still not utilised in routine clinical practice. Recent analyses have revealed relationships between these subtypes identified at the transcriptomic level, and events identified through genomic analysis. Specifically, the immunoreactive subtype appear enriched for HGSOC harbouring *BRCA1/2* mutations, while those of the proliferative type appear enriched for tumours with *CCNE1* gain [88].

A number of molecular aberrations have been associated with clinical phenotypes in HGSOC. *BRCA1/2* mutations are associated with improved survival, greater response to platinum-based chemotherapy and other DNA damaging agents, alongside marked sensitivity to PARP inhibitors [6,82,83,88,97]. Other identified aberrations in HRR genes have been associated with similar phenotypes (*BRCA1* methylation, *RAD51C* methylation, *EMSY* overexpression, *BRCA1/2* structural variants, non-BRCA HRR gene mutations) [88,90,91,98–100], though these analyses have generally been limited to comparison of survival and platinum response rather than PARP inhibitor sensitivity. Notably, many analyses of rarer HRR events have been exploratory and limited in power, and some studies have reported conflicting results that do not necessarily align with the expected *BRCA1/2*-like phenotype (particularly for *BRCA1* methylation) [100,101].

At the transcriptomic level, the immunoreactive subtype demonstrates favourable survival, while patients in the mesenchymal subtype experience shorter survival [80,96]. Some investigators have suggested differential impact of bevacizumab treatment across transcriptomic subtypes [102], but these data have not yet been independently reproduced. Greater extent of T cell infiltration is associated prolonged survival [6], which itself has been correlated with genomic and transcriptomic features; the immunoreactive transcriptomic subtype and tumours with *BRCA1/2* loss appear to demonstrate the highest levels of infiltration [88,103], while the proliferative subtype and *CCNE1* gained tumours represent cases with extremely low levels of infiltration [88]. Recent data have suggested subtypes of HGSOC based on patterns of associated immune cells which are associated with large differences in patient survival [92], and that specific patterns of genomic perturbation are associated with distinct mechanisms of immune evasion [104].

Major advancements in our understanding and treatment of HGSOC have been made, though several research priorities remain. Identification of additional treatment strategies that are effective in the platinum-resistant disease setting represents a key priority. Moreover, the phenotypes associated with a number of recurrent molecular events remains to be determined; the efficacy of PARP inhibitors in patients whose tumours harbour specific, uncommon HRR-related events remains to be robustly established, and the clinical behaviour of cases with recently identified structural genomic variants have not been characterised in detail. In particular, little is known about the impact of *NF1* and *PTEN* disruption with regard to chemotherapy sensitivity, survival time and response to targeted agents.

8. Concluding remarks

Substantial progress has been made in our understanding of uncommon OC histotypes over the last decade, particularly in our understanding of the genomic landscape in EnOC, CCOC, MOC and LGSOC. These analyses have led to the identification of potential risk stratification opportunities and candidate targeted therapeutic interventions, some of which have progressed toward evaluation in clinical studies. MEK inhibitors for LGSOC are a key example of successful translation of molecular findings into clinical benefits for patients with uncommon OC histotypes. However, significant obstacles and knowledge gaps remain, including logistical challenges of performing disease-specific trials in rare histotypes. International collaboration and recognition of each histotype as distinct clinical and molecular entities are key for furthering our understanding and accelerating scientific findings toward improved outcomes for patients.

Author contributions

RLH – conceptualisation, visualisation, manuscript writing.

Declaration of competing interest

RLH: consultancy fees from GlaxoSmithKline.

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