The survival benefit associated with complete macroscopic resection in epithelial ovarian cancer is histotype-specific

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Short title: Histotype-specific impact of complete cytoreduction in ovarian cancer

ABSTRACT

Background: Complete macroscopic resection (CMR) is a key factor associated with prolonged survival in ovarian cancer. However, most evidence derives from high grade serous ovarian carcinoma (HGSOC), and the benefit of CMR in other histotypes is poorly characterised. We sought to determine which histotypes derive the greatest benefit from CMR to better inform future decisions on radical cytoreductive efforts.

Methods: We performed multivariable analysis of disease-specific survival (DSS) across two independent patient cohorts to determine the magnitude of benefit associated with CMR within each histotype.

Results: Across both cohorts (Scottish, n=1622; SEER, n=18947), CMR was associated with prolonged DSS; this was more marked in the Scottish cohort (multivariable HR 0.44, 95%CI 0.37-0.52 vs 0.59, 95%CI 0.57-0.62 in SEER). In both cohorts, clear cell ovarian carcinoma (CCOC) was among the histotypes to benefit most from CMR (multivariable HR 0.23 and 0.50 in Scottish and SEER cohorts); HGSOC cases demonstrated highly significant and clinically meaningful survival benefit, but this was of lower magnitude than in CCOC and endometrioid ovarian carcinoma (EnOC) across both cohorts. The benefit derived in low grade serous ovarian carcinoma is also high (multivariable HR 0.27 in Scottish cohort). CMR was associated with prolonged survival in mucinous ovarian carcinoma (MOC) patients in the SEER cohort (multivariable HR 0.65), but the associated failed to reach statistical significance in the Scottish cohort.

Conclusions: The overall ovarian cancer patient population demonstrates significant survival benefit associated with CMR; however, the magnitude of benefit differs between histotypes.

Keywords: Ovarian cancer, cytoreduction, surgery, survival

INTRODUCTION

Ovarian cancer remains a major cause of morbidity and mortality in women; around 200,000 ovarian cancer deaths are reported each year worldwide.[1] Epithelial ovarian cancer (ovarian carcinoma) is the most common form disease and comprises multiple histological types (histotypes): high grade serous (HGSOC, 70% of cases), endometrioid (EnOC, 10%), clear cell (CCOC, 10%), low grade serous (LGSOC, ≤5%), and mucinous (MOC, ≤5%).[2-4] Ovarian carcinosarcomas (OCS) – previously considered a separate disease entity – are now recognised to represent metaplastic carcinomas,[4,5] and account for ≤5% of diagnoses. A wealth of evidence now demonstrates that each histotype represents a unique disease entity, each with distinct developmental origins, molecular landscapes, intrinsic chemosensitivity, survival profile and susceptibility to targeted molecular therapeutics.[6-14]

The critical role of maximal cytoreductive surgery in improving ovarian carcinoma patient survival is well documented.[3,15] Historically, achieving a maximal residual disease diameter (RD) of <2cm was considered successful cytoreductive surgery.[16] However, achievement of lower volume RD (<1cm, <0.5cm) is associated with a greater survival advantage,[17-19] and we now recognise that achieving complete macroscopic resection (CMR, also known as zero residual disease or 'R0') confers the most marked survival benefit.[15,17,19,20]

While the importance of optimal cytoreduction is well established, the majority of data derive from HGSOC and have been extrapolated to the other histotypes. However, generalizing these data to other histotypes is problematic given that we now understand each ovarian carcinoma histotype represents a distinct disease entity.[3,9,12,16,21-25] Therefore, it is not known if other histotypes benefit from CMR to the same extent as HGSOC. The magnitude of survival benefit derived from CMR may be modulated by factors such as the baseline chemosensitivity profile of each histotype, and the intrinsic aggressiveness of each of these diseases. This is important as in many instances radical surgery is required in order to achieve CMR, which is associated with significant morbidity and a recognised degree of mortality.[26] Therefore, if women with non-HGSOC histotypes do not gain a meaningful survival benefit from surgery leading to CMR, the potential harms of such radical surgery may not be justified.

Here, we seek to determine the relative impact of CMR on survival across the ovarian carcinoma histotypes to improve our understanding of factors that influence patient survival, and to highlight patients for which the most aggressive surgical approaches are warranted.

METHODS

Scottish ovarian cancer patient cohort

A cohort of tubo-ovarian cancer patients (ovarian, primary peritoneal or fallopian tube cancer) from Scotland was identified using the Edinburgh Ovarian Cancer Database, wherein the diagnosis, treatment and outcome data for all women treated with histopathologically-confirmed ovarian cancer at the Edinburgh Cancer Centre (tertiary oncology centre for South-East Scotland, UK) are prospectively recorded as part of routine care.[16] 4444 ovarian cancer patients were recorded with a diagnosis up to the end of December 2021. Of these, 2856 were HGSOC, LGSOC, EnOC, CCOC, MOC or OCS and diagnosed January 1994 - December 2019, forming the basis of the study cohort (supplementary methods 1) (Figure 1A). Cases of unknown FIGO stage at diagnosis, unknown grade (where applicable) or unknown survival were excluded (n=301). Of the remaining 2555 cases, 2205 received first-line cytoreductive surgery (primary cytoreduction or interval debulking following neoadjuvant chemotherapy) with known residual disease status; remaining cases were screened to exclude duplicated cases and patients with multiple primary diagnoses (n=145), leaving a cohort of 2060 patients with FIGO stage I-IV disease at diagnosis (Figure 1A). Finally, stage I cases (n=438) were removed, with 1622 cases remaining in the final study cohort.

HGSOC cases were divided into those that received primary debulking surgery (HGSOC-PDS) versus those who received neoadjuvant chemotherapy followed by interval debulking surgery (HGSOC-IDS). For other histotypes, too few patients received interval debulking surgery to permit corresponding neoadjuvant-specific analysis. Of the 1622 cases in the Scottish study cohort, 69% had either undergone contemporary pathology review as part of recent molecular profiling studies[11,12,27-34] or represented recent diagnoses (2010 onwards).

Ethical approval

The study received institutional review board approval from the South East Scotland Cancer Information Research Governance Committee (Caldicott guardian approval CG/DF/E164, study reference CIR21087). For all subjects, informed consent was obtained or was waived by the ethics committee due to the retrospective nature of this study. The study complied with all relevant ethical regulations, and was performed in accordance with the declaration of Helsinki.

Survival, Epidemiology, and End Results Database Cohort

A validation cohort of patients from the Surveillance, Epidemiology, and End Results (SEER) database was used to construct a corresponding validation dataset of 18947 cases (supplementary methods 2) (Figure 1B, Supplementary table 1).

Statistical Analysis

Survival time was calculated from date of pathologically-confirmed diagnosis to death from ovarian cancer (disease-specific survival); patients with other causes of death were censored. Cox proportional hazard regression models were used to determine differences in outcome, visualised using the Kaplan-Meier method. Multivariable analysis accounted for patient age, FIGO stage at diagnosis and diagnosis period (5-year intervals). Differences in survival were presented as hazard ratios (HR) and corresponding 95% confidence intervals (CI). Median follow-up time was calculated using the reverse Kaplan-Meier method. Comparisons of frequency were made using the Chi-squared test. Survival analysis with a calculated P value of less than 0.05 was considered statistically significant, while a calculated hazard ratio of ≤0.85 or ≥1.15 was considered a potentially clinically meaningful effect size. Statistical tests were two-sided.

Analyses were performed using R version 4.2.2 within R Studio version 2022.12.0+353, utilizing the following packages: finalfit, ggfortify, ggplot2, ggpubr, ggsurvfit, lifecycle, survival, survivalAnalysis, survminer, survMisc, tab, and table1.

RESULTS

Cohort characteristics

The Scottish study cohort comprised 1622 ovarian cancer patients with a diagnosis of FIGO stage II-IV HGSOC, LGSOC, EnOC, CCOC, MOC or OCS between 1994-2019 (Figure 1A). All cases underwent cytoreductive surgery as part of first-line management (primary or interval debulking) and had known residual disease status (macroscopic RD vs CMR). Characteristics of the study cohort are summarised in Table 1. The median follow up time for the study cohort was 108 months (Table 1).

246 (15.2%), 1044 (64.4%) and 332 (20.5%) cases were of FIGO stage II, III and IV at diagnosis, respectively. 574 patients had CMR after first-line cytoreductive surgery (35.4%). Of those with macroscopic residual disease, 624 (59.5%) had gross residual disease (≥2cm), 362 (34.5%) had RD <2cm and 62 (5.9%) had known macroscopic RD of unknown size. The rate of achieving CMR increased significantly over time (23.5% in pre-2005 to 57.4% in 2015-2019, $P<2.2e-^{16}$) (Figure 2A).

1207 (74.4%), 139 (8.6%), 104 (6.4%), 65 (4.0%), 38 (2.3%) and 69 (4.3%) cases were HGSOC, EnOC, CCOC, LGSOC, MOC and OCS, respectively. For analysis, HGSOC cases were divided into those who received primary debulking surgery (HGSOC-PDS, n=941) versus neoadjuvant chemotherapy and interval debulking surgery (HGSOC-IDS, n=266). Across the histotypes, OCS demonstrated the poorest outcome, while LGSOC demonstrated the most favourable survival (Figure 3A).

Univariable analysis of residual disease status

Univariable survival analysis of all patients according to residual disease status showed a substantial survival benefit associated with CMR compared to those with macroscopic residual disease (HR0.32, 95%CI 0.28-0.37, P<$2e^{-16}$) (Figure 2B).

Univariable analysis suggested achieving CMR was associated with varying degrees of statistically significant survival benefit across histotypes (HR for CMR versus macroscopic RD in MOC 0.29, 95%CI 0.12-0.71; CCOC 0.19, 95%CI 0.11-0.31; EnOC 0.19, 95%CI 0.11-0.33; LGSOC 0.26, 95%CI 0.10-0.69; OCS 0.33, 95%CI 0.17-0.62; HGSOC-PDS 0.32, 95%CI 0.26-0.39; HGSOC-IDS 0.52, 95%CI 0.38-0.72) (Figure 2C-I). However, each histotype was associated with different distributions of stage at diagnosis (Figure 3B), with corresponding differences in frequency of achieving CMR (Figure 3C), highlighting the need for multivariable analysis.

Multivariable analysis

Multivariable analysis confirmed significant associations of stage at diagnosis, histotype, RD status and period of diagnosis with survival time across the cohort (Supplementary figure 1A). Advanced stage at diagnosis (FIGO IV vs II: HR3.47, 95%CI 2.65-4.55, P<$2e^{-16}$), CCOC (HR2.48 vs HGSOC-PDS, 95%CI 1.89-3.26, P=$6.91e^{-11}$) and OCS (HR2.02 vs HGSOC-PDS, 95%CI 1.51-2.70, P=2.18e-^{6}) were associated with significantly poorer survival, while LGSOC (HR 0.42 vs HGSOC-PDS, 95%CI 0.29-0.62, P=$1.26e^{-5}$) and achieving CMR were associated with significantly prolonged survival (HR0.44 vs macroscopic RD, 95%CI 0.37-0.52, P<$2e^{-16}$).

Histotype-specific analysis revealed a spectrum of survival benefit associated with CMR (Supplementary figure 1B-H). CCOC derived the greatest survival benefit associated with CMR (HR 0.23, 95%CI 0.13-0.42, P=$1.20e^{-6}$) (Supplementary figure 1F). The benefit in MOC failed to reach statistically significance (HR 0.33, 95%CI 0.09-1.18, P=0.088) (Supplementary figure 1G). The other histotypes demonstrated a gradient of statistically significant survival benefit associated with CMR (LGSOC HR=0.27, 95%CI 0.09-0.77; EnOC HR=0.39, 95%CI 0.22-0.70; OCS HR=0.45, 95%CI 0.21-0.96; HGSOC-PDS HR=0.47, 95%CI 0.38-0.60; HGSOC-IDS HR=0.57, 95%CI 0.41-0.80).

Similar associations were identified upon analysis is overall (all-cause) survival (supplementary table 2).

Advanced stage disease

Within advanced stage disease specifically (FIGO III-IV at diagnosis), LGSOC and CCOC derived the greatest benefit from achieving CMR (LGSOC multivariable HR 0.17, 95%CI 0.05-0.64; CCOC

multivariable HR=0.19, 95%CI 0.08-0.47) (Figure 4). Conversely, survival benefit associated with CMR within advanced stage MOC cases was not statistically significant (multivariable HR 0.32, 95%CI 0.08-1.25, P=0.102), though power was limited (Figure 4E). The other histotypes demonstrated a gradient of statistically significant survival benefit associated with CMR upon multivariable analysis (HR in OCS 0.34, 95%CI 0.14-0.78; EnOC 0.44, 95%CI 0.23-0.85; HGSOC-PDS 0.49, 95%CI 0.39-0.63; HGSOC-IDS 0.57, 95%CI 0.41-0.80).

Validation within the SEER Database

A second cohort of 18947 ovarian carcinoma patients (diagnosed 2010-2019) were extracted from the SEER database (Figure 1B, Table 2). The median follow-up time for the SEER cohort was 63 months; LGSOC cases were excluded due to low numbers and limited follow-up (Figure 1B). Within the SEER cohort, CMR was associated with significantly longer survival time (multivariable HR 0.59, 95%CI 0.57-0.62) (Figure 5A).

In histotype-specific multivariable analysis, EnOC and CCOC patients derived the greatest survival benefit from achieving CMR (HR0.41, 95%CI 0.31-0.53 and HR0.50, 95%CI 0.39-0.63, respectively). HGSOC (HR 0.61, 95%CI 0.58-0.64), MOC (HR 0.65, 95%CI 0.46-0.91), and OCS (HR 0.66, 95%CI 0.56-0.79) all demonstrated significantly prolonged survival associated with achieving CMR (Figure 5).

Multivariable histotype-specific analysis of SEER cases with 'distant' stage disease demonstrated that EnOC and CCOC cases derived the greatest survival benefit with achievement of CMR (HR 0.42, 95%CI 0.31-0.56 and HR 0.55, 95%CI 0.42-0.72, respectively). MOC, HGSOC, and OCS also derived statistically significant benefit, but of lower magnitude (HR 0.63, 95%CI 0.44-0.91; HR 0.63, 95%CI 0.60-0.66; HR 0.68, 95%CI 0.57-0.82, respectively).

DISCUSSION

Over the last two decades, our understanding of ovarian carcinoma has advanced substantially. We now recognise the existence of multiple clinically and molecularly distinct ovarian cancer histotypes, each with distinct survival and treatment sensitivity profiles.[2] Our knowledge of factors associated with patient outcome has also increased greatly, with achievement of CMR at first-line cytoreduction emerging as a key factor associated with improved survival.[35] However, understanding of such factors has primarily been driven by the most common histotype, HGSOC, which has dominated studies to date.[35] Accordingly, while the importance of optimal cytoreduction has become widely recognised, little is known regarding the relative survival benefit associated with CMR across different histotypes. We sought to improve our understanding of the survival advantage derived when CMR is achieved at

first-line cytoreduction within each histotype. We utilized multivariable analysis to quantify the magnitude of survival benefit independent of other clinicopathological factors, as the distribution of these factors is known to vary across histotypes.[2]

Using an ovarian carcinoma patient cohort from Scotland with rich clinical annotation, we show that CCOC and LGSOC demonstrate the most marked survival benefit associated with CMR compared to other histotypes (multivariable HR 0.23 and 0.27 compared to 0.47 in HGSOC-PDS). It is feasible that differences in intrinsic chemosensitivity may contribute to this difference; LGSOC and CCOC demonstrate marked intrinsic chemoresistance,[36,37] and macroscopic residual disease in these histotypes may lead to rapid progression even in the context of adjuvant chemotherapy. Conversely, in HGSOC, which is highly chemosensitive,[38] residual lesions are more likely to respond to subsequent platinum-based adjuvant therapy, and the benefit from achieving CMR at surgery may therefore be less extreme. In keeping with this notion, OCS – which demonstrates intermediate levels of intrinsic chemosensitivity[11] – derives a significant benefit that is lesser in magnitude versus LGSOC and CCOC. However, EnOC, which demonstrates intermediate chemosensitivity,[2] was among the histotypes to benefit most from CMR, suggesting factors beyond intrinsic chemosensitivity that modulate the benefit from CMR. Alongside chemoresistance, LGSOC is characterised by a more gradual disease progression course, with prolonged post-relapse survival compared to HGSOC.[25] This distinct clinical behaviour of LGSOC may also contribute toward the large impact on survival when achieving CMR; it is feasible that the dramatic reduction in LGSOC cell numbers due to maximal cytoreduction may produce an extended sub-clinical disease course due to the lagging proliferation rate of LGSOC cells. It is also feasible that specific biological events modulate the survival benefit from CMR; within HGSOC, it has been suggested that the burden of tumour-infiltrating immune cells may impact the degree to which CMR improves survival.[39] These data suggest that molecular subtypes within specific histotypes may also demonstrate differences in the survival benefit associated with CMR.

We identified a larger survival benefit associated with CMR in HGSOC cases that underwent PDS compared to those that received neoadjuvant chemotherapy followed by IDS (multivariable HR 0.47 vs 0.57). It is possible that the timing of chemotherapy itself modulates the survival benefit derived from successful cytoreduction; induction of platinum-resistance during neoadjuvant chemotherapy has been raised as a concern in the current era of increased neoadjuvant chemotherapy utilisation.[40] However, inherent differences in the IDS population, rather than neoadjuvant chemotherapy itself, may well underlie this observation. Patients undergoing neoadjuvant chemotherapy typically have widely disseminated, unresectable disease or harbour comorbidities rendering them unsuitable for PDS. Caution is therefore warranted in the interpretation of these findings.

A corresponding patient cohort from the SEER database confirmed CCOC as one of the histotypes that benefits most from CMR. Limited follow-up time and smaller-than-expected numbers of LGSOC cases prevented validation of our findings on this histotype from the Scottish cohort within SEER. We were also unable to account for primary versus interval debulking surgery in the SEER cohort due to the less detailed treatment information available. In contrast to the Scottish cohort, the EnOC patient group within SEER demonstrated the largest degree of survival benefit associated with CMR, though the effect size in both studies was similar (multivariable HR 0.41 in SEER vs 0.39 in Scottish cohort) and EnOC was among the histotypes that benefitted most from CMR across both cohorts. MOC failed to demonstrate a statistically significant survival benefit associated with CMR in the Scottish cohort; in the SEER cohort, the benefit was statistically significant, though the effect size was still lower for MOC in this cohort than CCOC (MOC HR 0.63 in SEER, CCOC HR 0.50 in SEER). Also in contrast to the Scottish cohort, the OCS group appeared to derive the least benefit from CMR. In both cohorts, HGSOC cases represented a patient group who demonstrated a lower magnitude of survival benefit compared to most other histotypes, though it remains clear that the degree of benefit is highly clinically and statistically meaningful. Some of these discrepancies may be due to intrinsic differences between our two study cohorts. In particular, the magnitude of survival benefit associated with CMR across the overall population in SEER was less marked than in the Scottish ovarian cancer cohort (multivariable HR 0.59 in SEER vs 0.44 in the Scottish cohort). Both cohorts identify CCOC and EnOC as histotypes that are among those that derive the largest degree of survival benefit from CMR. These histotypes have a number of shared molecular features, and both are related to endometriosis;[2] strong associations between CMR and improved survival represents an additional commonality between these tumour types.[2]

A major strength of our study is the use of multiple geographically distinct cohorts of ovarian carcinoma patients from contrasting sources. The Scottish cohort represent a smaller group of richly annotated cases from a single tertiary oncology centre in the UK with a single data source specific to ovarian cancer, while the SEER database harbours a large number of cases, aggregated from centres across the US into a pan-cancer database. Long follow-up time, recognition of histotypes as distinct disease entities and multivariable analysis represent further strengths of this work. Lack of central pathology review is a weakness of our study, though 69% of the Scottish cohort had either undergone pathology review as part of previous studies or were contemporary diagnoses. We were unable to review any cases from the SEER database, but we included only relatively recent diagnoses from this source (2010-2019). However, we cannot preclude the possibility of low-level histotype misclassification within both cohorts; in particular, a proportion of LGSOC cases in the Scottish cohort were historic diagnoses of serous grade 1 carcinomas. Moreover, the treatment paradigm in ovarian

cancer has shifted significantly in recent years, particularly with the uptake of maintenance PARP inhibition;[13,41] the bulk of our study populations were treated prior to the era of PARP inhibitor maintenance therapy. In addition, other histotype-specific management strategies are now being adopted or investigated in ovarian cancer, including MEK inhibition for LGSOC and immunotherapy for CCOC.[2] Changes in ovarian cancer management strategies may impact the benefit from CMR across histotypes. Lastly, though our study cohorts represent relatively large populations, particularly of the less common histotypes, statistical power was still limited in some analyses, principally within the Scottish cohort.

Together, these data further underscore the pivotal role of maximal cytoreduction in ovarian cancer management, and highlight patient groups most likely to derive the greatest benefit from radical and ultra-radical surgical approaches. CCOC and LGSOC cases represent some of the patient groups who benefit most from achieving CMR; given that these cases are unlikely to respond well to neoadjuvant chemotherapy, complete primary cytoreduction is a major priority for these patients. EnOC also represents a histotype in which CMR is associated with marked patient survival benefit. Engagement with multiple surgical teams to improve the likelihood of resecting disease at hepatobiliary, gastrointestinal, and other anatomical sites beyond the pelvis will be key for delivering optimal outcomes for such cases that present with extensive advanced-stage disease. More work is also required to understand the impact of resecting disease outside of the pelvis and abdomen.

CONCLUSION

Achievement of CMR across the overall ovarian cancer patient population is associated with markedly prolonged survival time, though differences in the degree of survival benefit are apparent across different histotypes. Patients with CCOC derive one of the greatest survival benefits associated with CMR. HGSOC patients demonstrate highly clinically and statistically meaningful survival benefit, but the magnitude of benefit is lower than in some of the other histotypes. The extent of benefit from CMR does not appear to relate solely to levels of intrinsic chemosensitivity of each histotype.

Conflicts of interest

The authors have the following disclosures; RLH: consultancy fees from GlaxoSmithKline and DeciBio. NAJR: consultancy fees from GlaxoSmithKline. All other authors report no disclosures.

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Data availability

Data from the SEER database is publicly available; users should register for access through the SEER program website (https://seer.cancer.gov/data-software/). Line-by-line data for the Scottish cohort cannot be made publicly available in order to comply with our local ethics framework. We are happy to support access to these data on a project-by-project basis via contact with the corresponding authors; this may require additional ethical approval and is subject to compliance with our ethical regulations.

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Authorship contributions

The authors detail the following contributions to authorship; Conceptualisation: JMP, RLH; data curation: JMP, IM, CB, RLH; formal analysis: JMP; methodology: JMP, RLH; investigation: JMP, RLH, CSH; resources: KC, JM, NR; supervision: RLH; visualisation: JMP, RLH; writing – original draft: JMP, RLH; writing – review and editing: IM, CB, MC, CSH, KC, JM, NR.

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Table 1. Characteristics of ovarian carcinoma patient cohort from the Edinburgh Ovarian Cancer Database

		Overall N=1622		HGSOC N=1207		EnOC N=139		CCOC N=104		LGSOC N=65		MOC N=38		OCS N=69	
		N	% / range	N	% / range	N	% / range	N	% / range	N	% / range	N	% / range	N	% / range
Year of diagnosis	pre-2005	722	44.5	529	43.8	78	56.1	36	34.6	25	38.5	16	42.1	38	55.1
	2005-2009	299	18.4	219	18.1	30	21.6	24	23.1	9	13.8	10	26.3	7	10.1
	2010-2014	317	19.5	222	18.4	23	16.5	33	31.7	14	21.5	11	28.9	14	20.3
	2015 onwards	284	17.5	237	19.6	8	5.8	11	10.6	17	26.2	1	2.6	10	14.5
Age at diagnosis	Median	64	56-71	64	57-72	61	53-69	62	53-69	60	43-68	55.5	48-65	67	61-73
FIGO stage at diagnosis	II	246	15.2	92	7.6	65	46.8	53	51.0	11	16.9	17	44.7	8	11.6
	III	1044	64.4	836	69.3	57	41.0	38	36.5	45	69.2	19	50.0	49	71.0
	IV	332	20.5	279	23.1	17	12.2	13	10.6	9	13.8	2	5.3	12	17.4
Grade	Low grade / well differentiated / grade 1	-		-		37	26.6	-		-		17	44.7	-	
	Moderately differentiated / grade 2	-		-		26	18.7	-		-		15	39.5	-	
	High grade / poorly differentiated / grade 3	-		-		76	54.7	-		-		6	15.8	-	
Neoadjuvant chemo-therapy	Yes	290	17.9	266	22.0	7	5.0	6	5.8	7	10.8	0	0	4	5.8
	No	1332	82.1	941	78.0	132	95.0	98	94.2	58	89.2	38	100	65	94.2
RD status	CMR	574	35.4	358	29.7	74	53.2	64	61.5	29	44.6	23	60.5	26	37.7
	Macroscopic RD, <2cm	362	22.3	299	24.8	17	12.2	13	12.5	16	24.6	1	2.6	16	23.2
	Macroscopic RD, ≥2cm	624	38.5	506	41.9	39	28.1	24	23.1	19	29.2	13	34.2	23	33.3
	Macroscopic RD, unknown size	62	3.8	44	3.6	9	6.5	3	2.9	1	1.5	1	2.6	4	5.8
Vital status	Alive at last follow-up	334	20.6	221	18.3	53	38.1	23	22.1	24	36.9	11	28.9	2	2.9
	Deceased, ovarian cancer	1118	68.9	880	72.9	73	52.5	67	64.4	27	41.5	21	55.3	50	72.5
	Deceased, other causes	170	10.5	106	8.8	13	9.4	14	13.5	14	21.5	6	15.8	17	24.6
Follow-up	Median days	3298		3129		4788		2810		3439		2991		Not reached	

HGSOC, high grade serous ovarian carcinoma; EnOC, endometrioid ovarian carcinoma; CCOC, clear cell ovarian carcinoma; LGSOC, low grade serous ovarian carcinoma; MOC, mucinous ovarian carcinoma; OCS, ovarian carcinosarcoma; CMR, complete macroscopic cytoreduction.

Table 2. Characteristics of the SEER patient cohort. HGSOC, high grade serous ovarian carcinoma; EnOC, endometrioid ovarian carcinoma; CCOC, clear cell ovarian carcinoma; MOC, mucinous ovarian carcinoma; OCS, ovarian carcinosarcoma; CMR, complete macroscopic resection; RD, residual disease.

SEER cohort		**Overall N=18947**		**HGSOC N=14481**		**EnOC N=1759**		**CCOC N=1138**		**MOC N=582**		**OCS N=987**	
		N	%	N	%	N	%	N	%	N	%	N	%
Year of diagnosis	2010-2014	10387	54.8	7810	53.9	1086	61.7	631	55.4	343	58.9	517	52.4
	2015-2019	8560	45.2	6671	46.1	673	38.3	507	44.6	239	41.1	470	47.6
Age at diagnosis	Median age bracket	60-64		60-64		55-59		55-59		55-59		65-69	
Stage at diagnosis	Regional	5245	27.7	2691	18.6	1260	71.6	700	61.5	338	58.1	256	25.9
	Distant	13702	72.3	11790	81.4	499	28.4	438	38.5	244	41.9	731	74.1
RD status	CMR	12179	64.3	8598	59.4	1547	87.9	923	81.1	466	80.1	645	65.3
	Macroscopic RD	6768	35.7	5883	40.6	212	12.1	215	18.9	116	19.9	342	34.7
Vital status	Alive at last follow-up	10009	52.8	7318	50.5	1337	76.0	673	59.1	340	58.4	341	34.5
	Deceased, ovarian cancer	7932	41.9	6412	44.3	339	19.3	408	35.9	195	33.5	578	58.6
	Deceased, other causes	1006	5.3	751	5.2	83	4.7	57	5.0	47	8.1	68	6.9
Follow-up	Median months	63		62		69		63		65		60	

HGSOC, high grade serous ovarian carcinoma; EnOC, endometrioid ovarian carcinoma; CCOC, clear cell ovarian carcinoma; LGSOC, low grade serous ovarian carcinoma; MOC, mucinous ovarian carcinoma; OCS, ovarian carcinosarcoma; CMR, complete macroscopic cytoreduction.

Figures

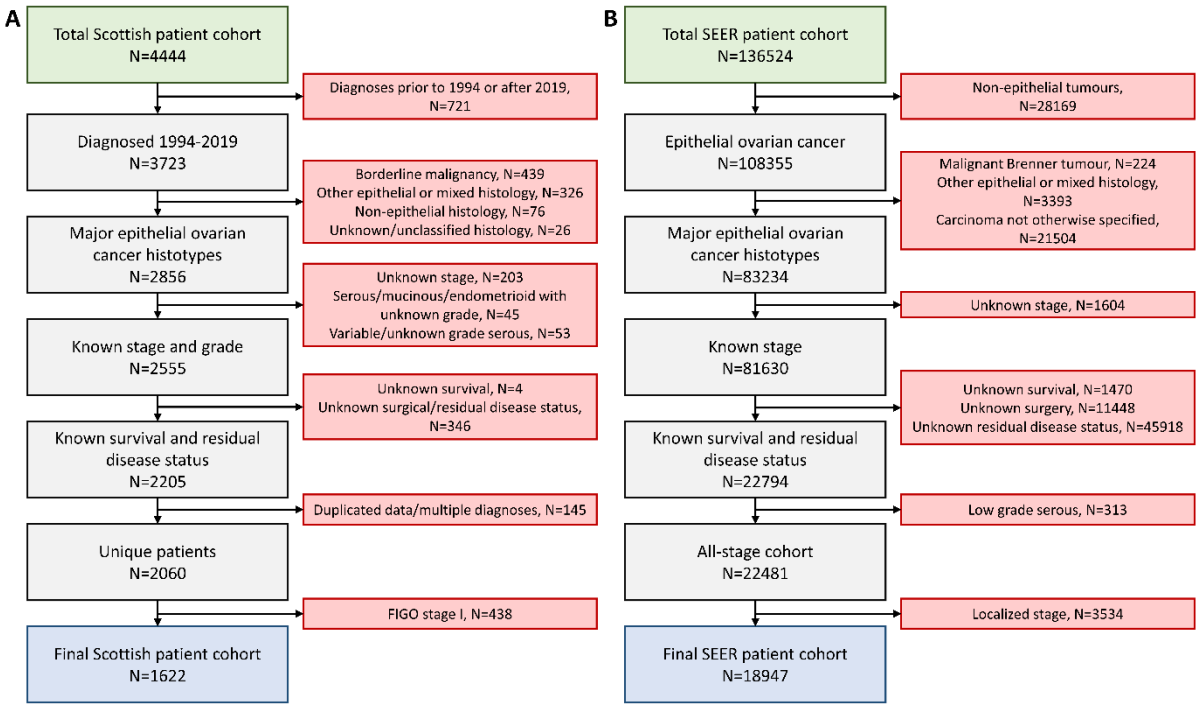

Figure 1. Case flow diagrams for case inclusion. (A) Case flow diagram for identifying the ovarian cancer patient cohort from the Edinburgh Ovarian Cancer Database. (B) Case flow diagram for identifying the ovarian cancer patient cohort from the SEER database.

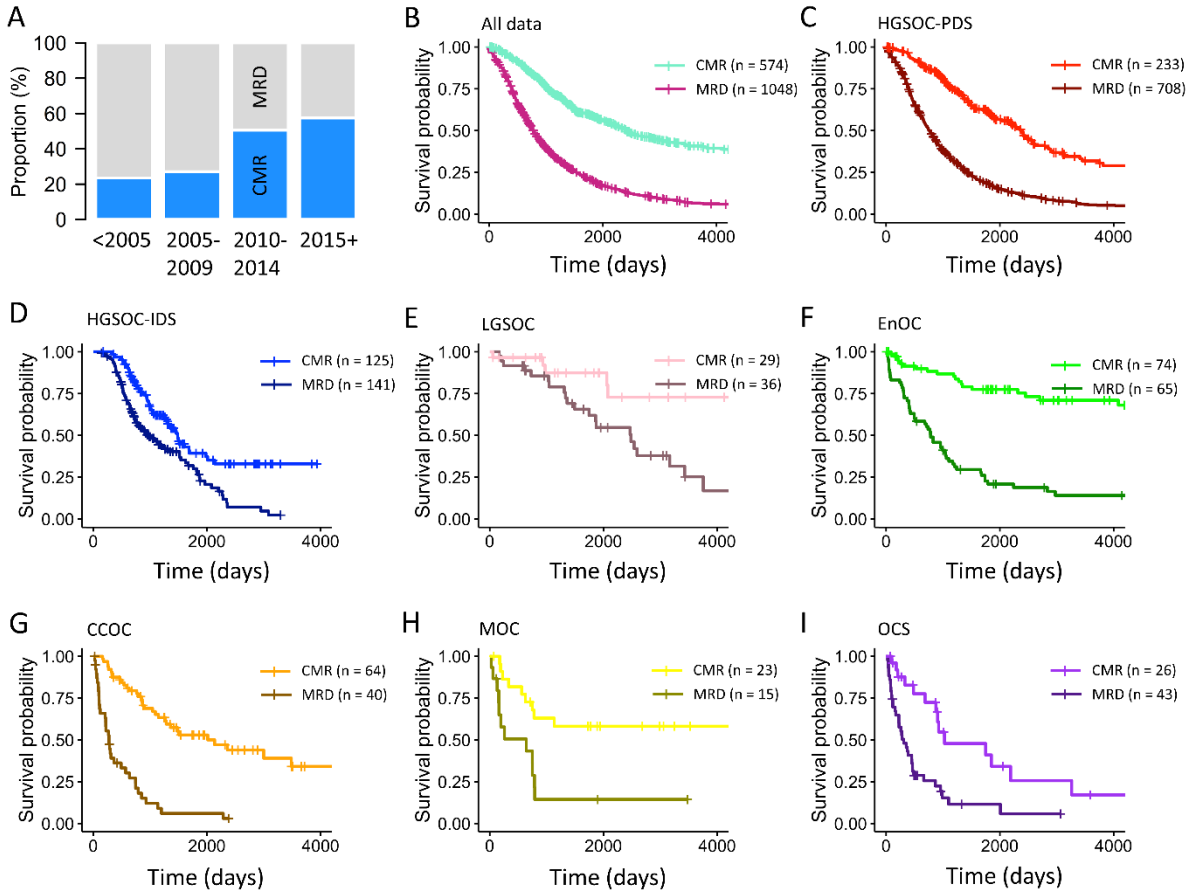

Figure 2. Impact of achieving complete macroscopic resection (CMR) versus macroscopic residual disease (MRD) in ovarian carcinoma (OC). (A) Increase in frequency of achieving CMR over time. (B) Overall impact of achieving CMR on disease-specific survival across the combined Scottish study cohort. (C) Impact of CMR in high grade serous OC (HGSOC) patients treated with primary debulking surgery. (D) Impact of CMR in HGSOC patients treated with neoadjuvant chemotherapy and intervals debulking surgery (IDS). (E) Impact of CMR in low grade serous OC (LGSOC) patients. (F) Impact of CMR in endometrioid OC (EnOC) patients. (G) Impact of CMR in clear cell OC (CCOC) patients. (H) Impact of CMR in mucinous OC (MOC) patients. (I) Impact of CMR in ovarian carcinosarcoma (OCS) patients.

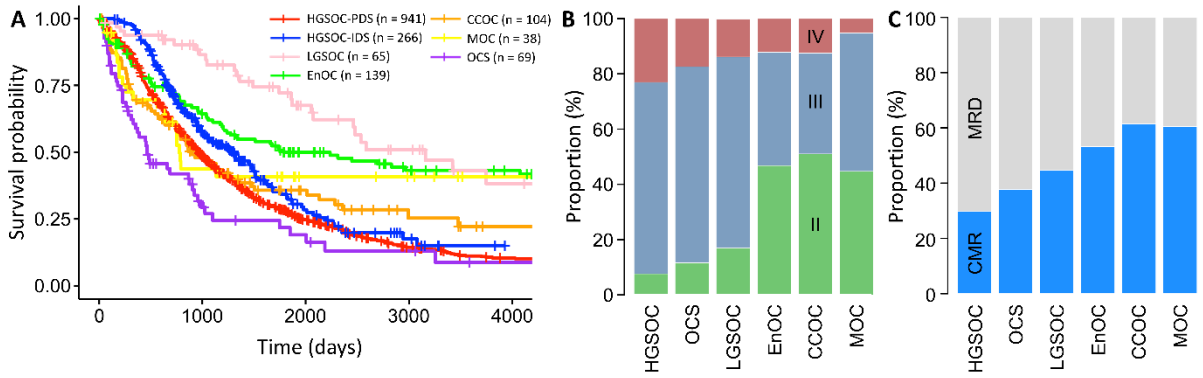

Figure 3. Features of ovarian cancer histotypes in the Scottish cohort. (A) Disease-specific survival profile of each histotype. (B) FIGO stage at diagnosis across histotypes. (C) Proportion of cases achieving complete macroscopic resection (CMR) across each histotype. PDS, primary debulking surgery; IDS, interval bulking surgery. HGSOC, high grade serous ovarian cancer; LGSOC, low grade serous ovarian cancer; EnOC, endometrioid ovarian cancer; CCOC, clear cell ovarian cancer; MOC, mucinous ovarian cancer; OCS, ovarian carcinosarcoma; MRD, macroscopic residual disease.

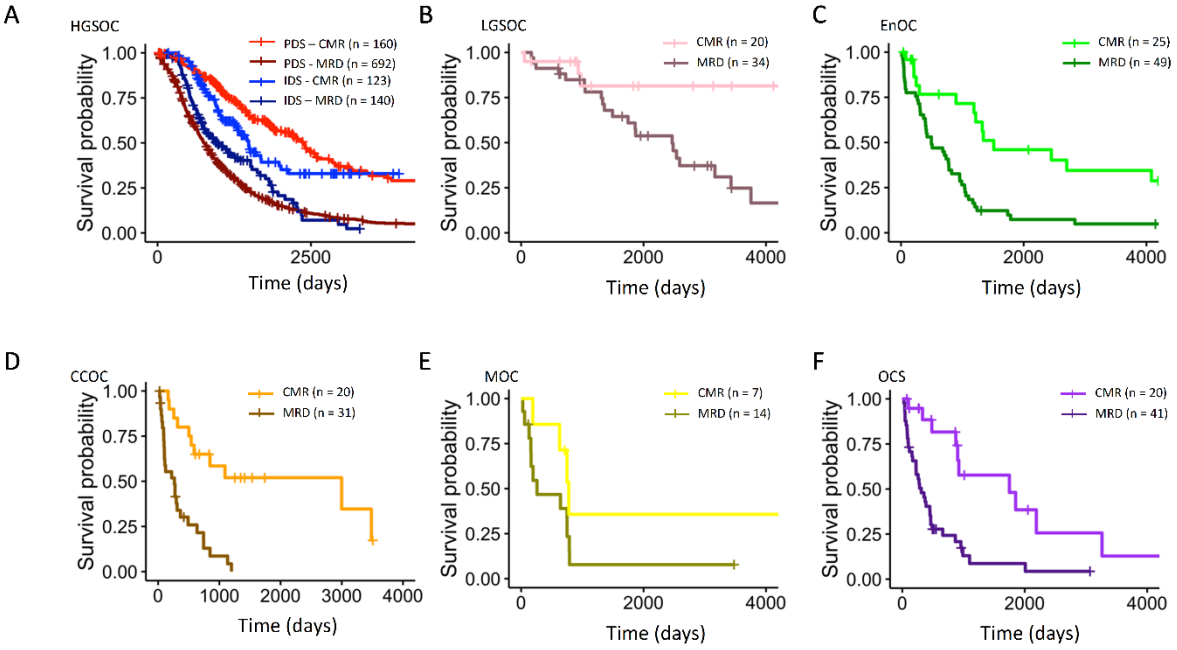

Figure 4. Impact of achieving complete macroscopic resection (CMR) on disease-specific survival specifically in patients presenting with advanced stage disease at diagnoses (FIGO III-IV) in the Scottish cohort. A) Impact of CMR in advanced stage high grade serous OC (HGSOC), stratified into those who received primary debulking surgery (PDS) versus interval debulking surgery (IDS). (B) Impact of CMR in advanced stage low grade serous OC (LGSOC) patients. C) Impact of CMR in advanced stage endometrioid OC (EnOC) patients. (D) Impact of CMR in advanced stage clear cell OC (CCOC) patients. (E) Impact of CMR in advanced stage mucinous OC (MOC) patients. (F) Impact of CMR in advanced stage ovarian carcinosarcoma (OCS) patients. MRD, macroscopic residual disease.

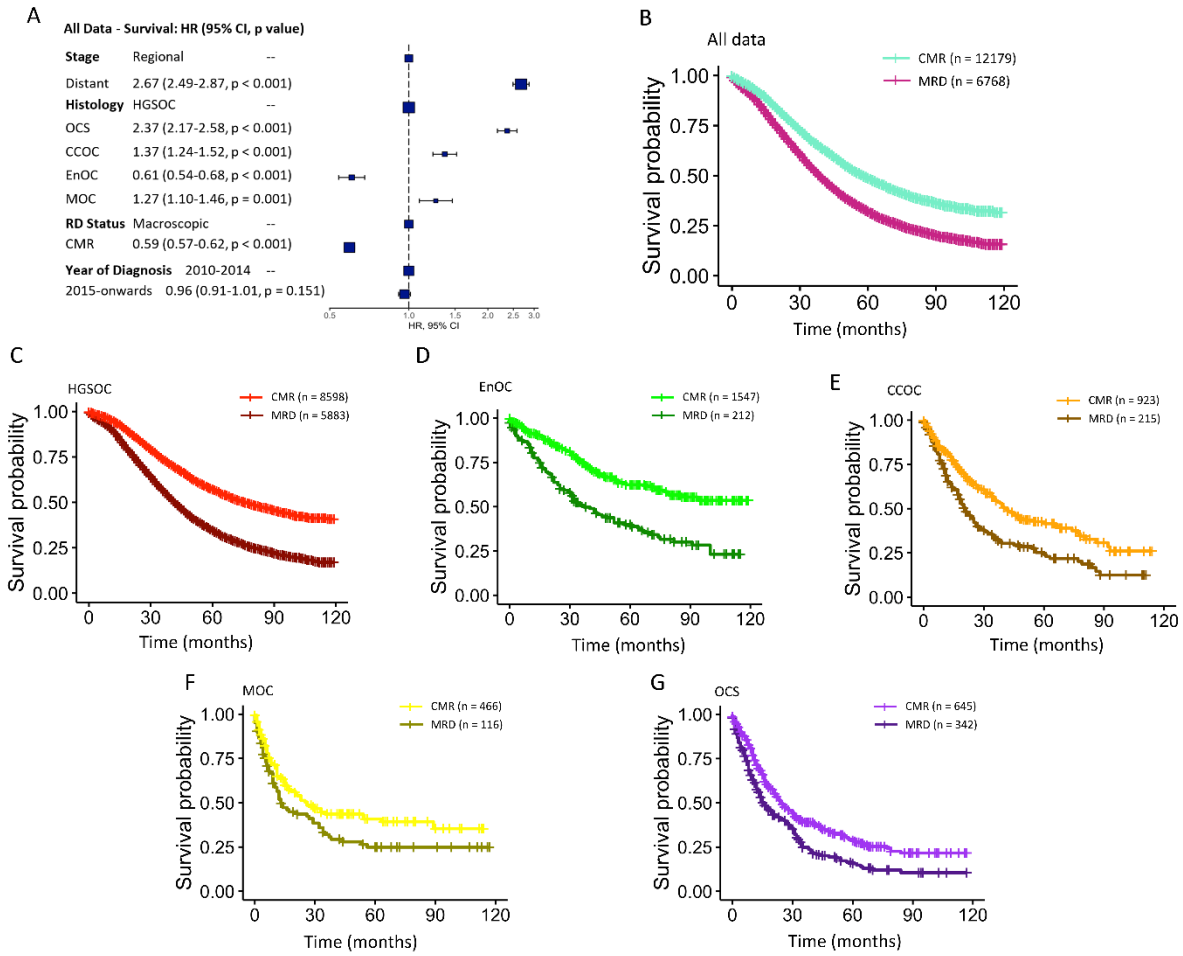

Figure 5. Analysis of the impact of achieving complete macroscopic resection (CMR) in the SEER cohort. (A) Overall multivariable forest plot of disease-specific survival. (B) Impact of achieving CMR across the overall SEER dataset; (C) Impact of CMR in high grade serous OC. (D) Impact of CMR in endometrioid OC (EnOC) patients. (E) Impact of CMR in clear cell OC (CCOC) patients. (F) Impact of CMR in mucinous OC (MOC) patients. G) Impact of CMR in ovarian carcinosarcoma (OCS) patients. MRD, macroscopic residual disease.