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Residual Disease Threshold After Primary Surgical Treatment for Advanced Epithelial Ovarian Cancer, Part 1: A Systematic Review and Network Meta-Analysis

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Background: We present a systematic review and network meta-analysis (NMA) that is the precursor underpinning the Bayesian analyses that adjust for publication bias, presented in the same edition in AJT. The review assesses optimal cytoreduction for women undergoing primary advanced epithelial ovarian cancer (EOC) surgery.

Areas of Uncertainty: To assess the impact of residual disease (RD) after primary debulking surgery in women with advanced EOC. This review explores the impact of leaving varying levels of primary debulking surgery.

Data Sources: We conducted a systematic review and random-effects NMA for overall survival (OS) to incorporate direct and indirect estimates of RD thresholds, including concurrent comparative, retrospective studies of ≥100 adult women (18+ years) with surgically staged advanced EOC (FIGO stage III/IV) who had confirmed histological diagnoses of ovarian cancer. Pairwise meta-analyses of all directly compared RD thresholds was previously performed before conducting this NMA, and the statistical heterogeneity of studies within each comparison was evaluated using recommended methods.

Therapeutic Advances: Twenty-five studies (n = 20,927) were included. Analyses demonstrated the prognostic importance of complete cytoreduction to no macroscopic residual disease (NMRD), with a hazard ratio for OS of 2.0 (95% confidence interval, 1.8–2.2) for <1 cm RD threshold versus NMRD. NMRD was associated with prolonged survival across all RD thresholds. Leaving NMRD was predicted to provide longest survival (probability of being best = 99%). The results were robust to sensitivity analysis including only those studies that adjusted for extent of disease at primary surgery (hazard ratio 2.3, 95% confidence interval, 1.9–2.6). The overall certainty of evidence was moderate and statistical adjustment of effect estimates in included studies minimized bias.

Conclusions: The results confirm a strong association between complete cytoreduction to NMRD and improved OS. The NMA approach forms part of the methods guidance underpinning policy making in many jurisdictions. Our analyses present an extension to the previous work in this area.

Keywords: network meta-analysis, advanced epithelial ovarian cancer, complete cytoreduction, optimal cytoreduction, primary surgery

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INTRODUCTION

Ovarian cancer is the seventh most common cancer among women up to 75 years of age and is a leading cause of death in women with gynecological malignancies.[1] Age older than 40 years, more than 90% of ovarian cancers originate from the surface (epithelial) cells of the ovary, termed epithelial tumors; the risk increases with age.[2,3] Around 70% of women with ovarian cancer are diagnosed at an advanced stage [International Federation of Gynaecology and Obstetrics (FIGO) stages III and IV].[4] That is, they have widespread tumor dissemination within the abdominal cavity, with the tumor potentially spreading to the liver, lungs, or distant organs.[5] As such, their prognosis is often poor.

Surgery and platinum-based chemotherapy are the mainstay of treatment in advanced epithelial ovarian cancer (EOC). The aim of primary surgery was to achieve "optimal cytoreduction," as the amount of residual disease (RD) (tumor remaining after surgery) is one of the most important prognostic factors for survival,[6–12] along with sensitivity to chemotherapy. The term "optimal cytoreduction" has been variably defined as referring to a maximal diameter of any residual tumor of between 0 and 1 cm, with RD greater than 1 cm being branded suboptimal.[7] "Complete cytoreduction" is achieved when there is no macroscopic residual disease (NMRD) (no visible tumor) left after surgery. A recently published National Ovarian Cancer Audit feasibility pilot report, by a British Gynaecological Cancer Society action group, highlights the need for more attempts at cytoreductive surgery in the United Kingdom.[13] In addition, some centers may not have the expertise to achieve complete cytoreduction, potentially leading to some patients not achieving optimal results for their individual surgery. The results from the Ovarian Cancer Audit feasibility pilot shows that on average only 51% of women with stage 2–4 and unstaged ovarian cancer receive surgery in England.[13] There are large disparities between surgeons and centers in their optimal and complete cytoreduction rates.[14–17] The development of these skills requires a shift in the surgeon's approach to surgery but, given that the additional procedures can be learned over a relatively short period, this could lead to increases in optimal or complete cytoreduction rates with no significant increases in perioperative morbidity.[15] It has previously been shown that optimal cytoreduction rates of up to 88% for primary laparotomy in advanced-stage ovarian cancer by gynecological oncologists working as a team can be achieved without any increase in morbidity.[16] Recent scientific and clinical studies relating to vascular epithelial growth factor receptors and BRCA/HRD status have opened up new avenues of treatment with biological agents, including vascular epithelial growth factor receptor inhibitors[18,19] and PARP inhibitors first line[20–23] and in relapsed setting[24,25] now becoming standard management practice. Thus, redefining the role and impact of complete cytoreduction in the overall survival (OS) outcomes of women with advanced EOC.

However, without reliable guidelines based on adequate empirical evidence, polarized views will continue to exist. Reliable quantification is important in its own right,[26] especially because there is still some resistance to incorporating statistical evidence into practice in many areas.[27] Although few refute the general conclusions of previous evidence suggesting that survival is better where there is complete cytoreduction compared with less-than-complete cytoreduction,[10,28–30] limitations in study design and in the conduct of previous analyses have not taken into account potential biases. Our review necessitated the inclusion of studies that reported adjusted analyses to attempt to minimize confounding bias. For example, if significantly more elderly women were included in a study where they were cytoreduced to NMRD than younger women with suboptimal RD thresholds, then there may be a confounding effect where suboptimal may be seen to have a better survival outcome. This is due to younger aged women being independently associated with prolonged survival, and therefore, NMRD may falsely seem to be associated as having worse survival than suboptimal RD.

Having the most up-to-date and reliable evidence is crucial to the development of clinical guidelines, and thus, it is of paramount importance that optimal analytical methods are used to appraise the available evidence.[31] Network meta-analysis (NMA)[32,33] is an extension to a standard pairwise meta-analysis that can incorporate and synthesize multiple treatments, or in this case RD thresholds, allowing for direct and indirect comparisons between groups that have previously not been compared in published studies. The use of NMA for guideline development is now common practice, with the method being well established within national health technology assessment agencies.[34] Furthermore, the World Health Organization and National Institute for Health and Care Excellence (NICE) have included recommendations on NMA within their clinical guidelines.[35,36] However, current guidelines related to optimal cytoreduction for women undergoing primary EOC surgery are not based on the highest level of evidence. A NMA on the back of the recent comprehensive systematic review (SR) in this area should provide robust evidence to policy makers

in the field.[31,37] The NMA reported in this SR is the precursor underpinning the Bayesian analyses that adjust for publication bias.[38] The Bayesian analyses are presented as the second part of this research and the publication is included in the same edition.

METHODS

Aim

To assess the impact of RD after primary debulking surgery in women with advanced EOC. This review explores the impact of leaving varying levels of RD after primary debulking surgery.

Eligibility criteria

We included retrospective prognostic studies that included adult women (older than 18 years) with surgically staged advanced EOC (FIGO stage III/IV) who had confirmed histological diagnoses of ovarian cancer. The population of interest was women who had received primary cytoreductive surgery followed by adjuvant platinum-based chemotherapy.[7]

The impact on survival of optimal and suboptimal cytoreduction for primary advanced disease was assessed using several RD thresholds reported in the literature. Included studies reported OS for comparisons of RD thresholds after surgery and used statistical adjustment for important baseline characteristics using multivariable analyses (eg, age, stage, and grade), to minimize confounding bias.[32,39] Owing to the nature of these retrospective studies, women were more likely to be allocated surgery by surgeon's preference. Consequently, there may be instances where a higher proportion of younger women, who are in better general health (measured using a performance status score[40]) for level of function and capability of self-care) undergo more aggressive surgery. These women may experience a better outcome than older women but this may be due to their better overall general health rather than the extent of resection. Therefore, adjusting for confounders is important to minimize effect distortion based on baseline imbalances. We included studies with a sample of at least 100 women. Smaller studies would have been restricted for the nature and extent of the adjusted analyses, due to the limited average number of participants per explanatory variable. Exclusion criteria included women with other concurrent malignancies, those who received chemotherapy before surgery (neoadjuvant), or intraperitoneal chemotherapy. This was to avoid the distortion of results to purify the data set and avoid the distorting effects of multitherapeutic interventions. Those with concurrent malignancies are not representative of EOC, and their inclusion would dilute external validity.

Search strategy

Electronic databases were searched from 1950 up to September 2021. Full reporting details are summarized in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart (Figure 1) and in the published review.[7]

Study selection and data management

We followed the methodology as reported in Bryant et al,[7] in accordance with Cochrane guidelines.[32] At least 2 review authors were independently involved in the screening process and subsequently abstracted data.[7]

Risk of bias

At least 2 review authors independently assessed risk of bias. Although the included studies were a combination of RCTs, prospective, and retrospective designs, the comparison of RD was retrospective in nature. We therefore assessed risk of bias (and appraised quality) in the prognostic assessment of residual diease in included studies using the QUality In Prognosis Studies (QUIPS) tool. QUIPS is a tool designed to assess the risk of bias in prognostic factor studies.[41]

Data synthesis

The NMA synthesized studies according to guidance from the Cochrane Handbook for Systematic Reviews of Interventions,[32] NICE technical documents, and technology appraisal guidelines[42] and was reported according to the PRISMA extension for NMAs.[7,43,44] Although NMAs are typically used to synthesize only evidence from RCTs, the highly restrictive eligibility criteria applied to studies included in the SR underpinning the NMA permitted us to include retrospective studies, on the grounds that the women recruited into the studies being reviewed are comparable and could have been given surgery resulting in any of the RD thresholds considered in the network.[37]

The NMA used contrast based data and was conducted using a frequentist framework in Stata IC (version 15).[45–47] The analysis adjusted for multiarm trials and used the augmented approach.[47] Within the network, RD thresholds are depicted as nodes, with lines representing comparisons. All data sets and code in Stata are available on request from the corresponding author.

We did not anticipate design inconsistency to be a concern because our inclusion criteria limited heterogeneity in patient populations, primary disease, and

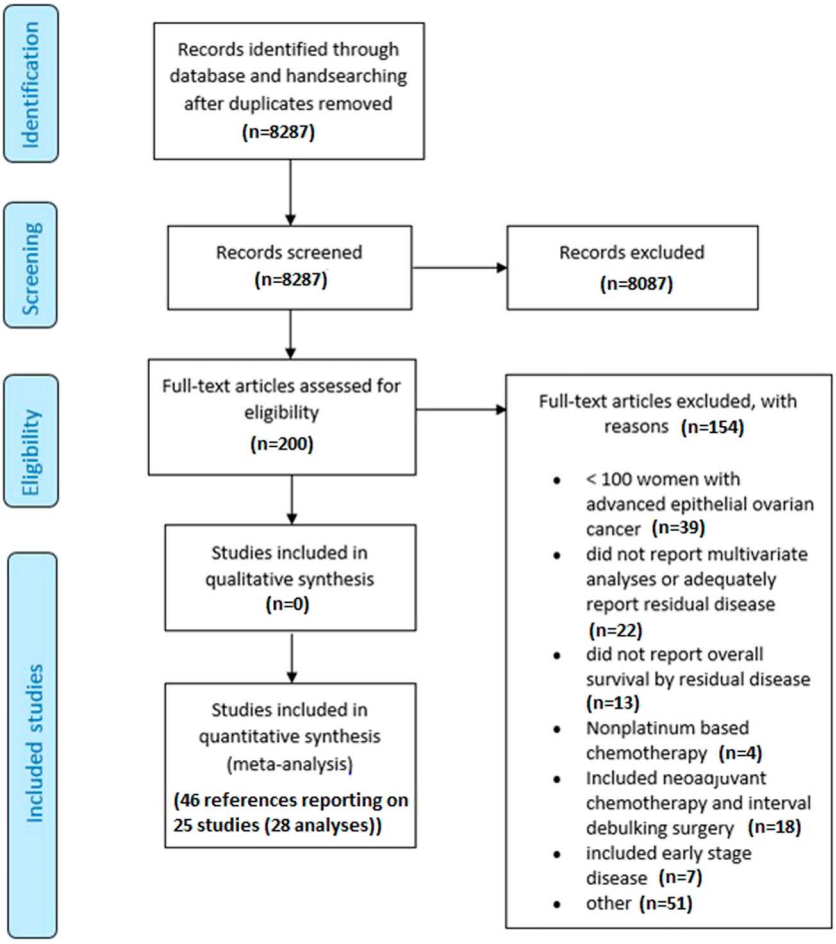

FIGURE 1. PRISMA flow diagram.

outcomes. There was no reason to suspect effect estimates would differ substantially in comparisons of thresholds across studies.

We conducted a network meta-regression for age, stage of disease, and histology to determine the similarity of studies for inclusion in the NMA. We presented the results of the network meta-regression using effect sizes reported as hazard ratios and 95% confidence intervals (CIs) because this is more useful than presenting a single global statistic in this case. All the RD thresholds are relative to the NMRD (0 cm) reference threshold. A meta-regression has been argued to have low power and be at risk of confounding[48,49] so we additionally checked summary and descriptive characteristics of studies to see whether there were any clear systematic differences between studies.

Transitivity in a NMA essentially necessitates that the underlying assumption of any indirect comparisons is that we can learn about the true relative effect of say RD <1 cm versus RD >1 cm through NMRD by combining the true relative effects of NMRD versus RD <1 cm and NMRD versus RD >1 cm. This means that we can compare RD <1 cm and RD >1 cm through NMRD. Therefore, the transitivity assumption underlying the NMA was evaluated by examining characteristics across studies; there were few concerns about potential effect modifiers across treatment comparisons as the distribution of key clinical characteristics, such as age, seemed similar across studies. Consistency, measured in agreement of direct and indirect evidence, was assessed by node-splitting analysis[46,47,50,51] and a formal global test for inconsistency.[46,47,51]

We presented the results of the NMA using effect sizes reported as hazard ratios and 95% CIs alongside results of the pairwise analyses reported in the SR underpinning the NMA. All the thresholds are relative to the NMRD reference threshold. We did not impute missing outcome data.

We also present plots showing the relative rank of all RD thresholds in OS (rankograms), which rank RD

Table 1. Characteristics of included studies in the NMA.

Study	Stage n (%)		RD (cm)		Median	RD reported in all models: covariates used in multivariable cox regression model	Median age in yr (range) or n (%) as reported	Country
	III	IV	Optimal n (%)	Suboptimal n (%)	F-U in mo (range)			
Akahira 2001[55]	0 (0)	225 (100)	<2: 70 (31)	>2: 155 (69)	47.5 (13–112)	Histology and performance status	54 (26–85)	Japan
Aletti 2006[14,56–58]	194 (100)	0 (0)	0: 46 (24) <1: 85 (44)	1–2: 22 (11) >2: 41 (21)	32.4 (0.2–126)	Age, ASA, histology, operative time, and aggressive surgery	64 (24–87)	USA
Ataseven 2016[59]	0 (0)	326 (100)	0: 157 (55) <1: 88 (31)	>1: 41 (14) NS: n = 40 exc	34 (IQR: 12–70)	Age, performance status, stage, and ascites	<65: 205 (63) >65: 121 (37)	Germany Austria
Bristow 2011[60]	405 (100)	0 (0)	0: 209 (52) <1: 196 (48)		33.0	Race, grade, histology, ASA, SCS, albumin, platinum therapy, and operative morbidity	59 Range not reported	USA
Chan 2003[61]	84 (81)	20 (19)	<1: 71 (68)	>1: 33 (32)	33 (6–142)	Age, stage, and performance status	Mean = 50.5 and 61 years for younger and older women, respectively, (range: 22 and 85).	USA
Chang 2012[62]	189 (93)	14 (7)	0: 63 (31) <1: 77 (38)	>1: 63 (31)	43 (1–124)	Age, stage, and type of surgery	54 (30–78)	South Korea
Chang 2012[63]	189 (100)	0 (0)	0: 61 (32) <1: 67 (36)	>1: 61 (32)	Not reported	Age, radical surgery, and lymphadenectomy	54 (30–78)	South Korea
Chi 2001[64]	216 (77)	66 (23)	<1: 71 (25) 1-2: 73 (26)	>2: 137 (49)	32 (1–139)	Age, stage, and ascites	59 (22–87)	USA
Chi 2006[65]	465 (100)	0 (0)	0: 67 (14) <1: 169 (37)	>1: 229 (49)	38 (1–199)	Age and ascites	60 (22–87)	USA
Cuylan 2018[67]	218 (100)	0 (0)	0: 55 (25) <1: 163 (75)		31.5	Age, stage, omental, peritoneal, and bilaterality present	54 (18–78)	Turkey
Eisenkop 2003[69]	408 (100)	0 (0)	0: 351 (86) <1: 41 (10)	>1: 16 (4)	32.8	Sum of rankings	62.8 (24–91)	USA
Feng 2016[70]	n = 567 (91) stage III/IV		0: 209 (33)	>0: 416 (67)	29 (3–100)	Age, stage, and time to chemotherapy	56 (30–84)	China
Hofstetter 2013[71]	158 (83)	33 (17)	0: 121 (63)	>0: 70 (37)	42	TSIC, stage, age, and extent of surgery	<57: 98 >57: 93	Europe

(*Continued on next page*)

Table 1. (*Continued*) Characteristics of included studies in the NMA.

Study	Stage n (%)		RD (cm)		Median	RD reported in all models: covariates used in multivariable cox regression model	Median age in yr (range) or n (%) as reported	Country
	III	IV	Optimal n (%)	Suboptimal n (%)	F-U in mo (range)			
Kahl 2017[72]	428 (54)	365 (46)	0: 482 (61) <1: 226 (39)	>1: 85	47 (IQR: 18–87)	Age adjusted CCI, performance status, stage, RD, histology, ascites, and SCS*	60 (19–88)	Germany
Klar 2016[73–78]	4488/5130 (87.5) stage III/IV; n = 4850 in RD analysis		0: 1779 (37) <1: 1442 (30)	>1: 1629 (33)	0–144	Age, ECOG status, BMI, stage, grade, and histology	Mean 57.4 (SD 10.53)	Germany France Denmark
Langstraat 2011[79]	210 (76)	67 (24)	0: 61 (22) <1: 120 (43)	>1: 95 (35)	3.2 years (0–15.8)	Age, creatinine, SCS, and stage	Mean: 73.5 (65–89)	USA
Luger 2020[80]	91 (51)	87 (49)	0: 133 (75)	>0: 45 (25)	49.6 (IQR: 33–66)	Age, CA-125, histologically positive paraaortic lymph nodes, FIGO, and CPLN.	64.6	Austria
Melamed 2017 [81]	241 (78)	66 (22)	0: 141 (59) <1: 77 (32)	>1: 23 (9) n = 66 missing	34.1	Age, ethnicity, stage, region, insurance status, facility type, hospital annual ovarian cancer volume, and comorbidities	<60: 200 (65) >60: 107 (35)	USA
Melamed 2017[81]	4954 (77)	1506 (23)	0: 2048 (46) <1: 1848 (42)	>1: 546 (12) 1571 missing			<60: 2803 (47) >60: 3210 (53)	
Paik 2018[82]	370 (88)	49 (12)	0: 107 (26) <1: 147 (35)	>1: 165 (39)	43 (3–164)	Age, CA-125, stage, and normal-sized ovary	Mean 54.5 (SD 10.3)	South Korea
Polterauer 2012[83]	II: 15 (7) III: 174 (77)	37 (16)	0: 157 (69)	>0: 69 (31)	25.0 (1–49)	Age, stage, grade, and histology	Mean 57.5 (SD 11.9)	Europe
Tewari 2016[84]	1241 (72)	477 (28)	0: 85 (5) <1: 701 (41)	>1: 932 (54)	Not reported	Age, ethnicity, performance status, grade, stage, histology, ascites, CA-125, and TSIC	58.5–60.2 for 0 to >1 cm RD	USA
Tseng 2018[85]	794 (81)	184 (19)	0: 408 (42) <1: 378 (39)	>1: 192 (19)	77.7 (1–198)	Age, albumin, stage, ASA score, histology, BRCA, OR tumor index, RD, and postop IP chemo	61 (19–95)	USA
Wimberger 2010[12]	573 (100)	0 (0)	0: 70 (12) <1: 168 (29)	>1: 335 (59)	Not reported	Age, performance status, histology, peritoneal carcinomatosis, and multiple sites	59 (19–83)	Germany, France

(*Continued on next page*)

Table 1. (*Continued*) Characteristics of included studies in the NMA.

Study	Stage n (%)		RD (cm)		Median	RD reported in all models: covariates used in multivariable cox regression model	Median age in yr (range) or n (%) as reported	Country
	III	IV	Optimal n (%)	Suboptimal n (%)	F-U in mo (range)			
Winter 2007[86–92]	1895 (100)	0 (0)	0: 437 (23) <1: 791 (42)	>1: 667 (35)	43	Age, race, performance status, histology, and grade	57 (16–86)	USA
Winter 2008[88,89,91,93,94]	360 (100)	0 (0)	0: 29 (8) <1: 78 (22)	1-5: 164 (46) >5: 89 (25)	28	Histology and stage IV disease site	59 (24–86)	USA
Winter 2008			<1: 78 (24)	>1: 253 (76)				
Winter 2008			<2: 50 (20)	>2: 203 (80)				

*SCS was added to multivariate analysis and was obtained through personal correspondence with Mr Beyhan Ataseven and included in the sensitivity analysis depicted in Table 5.

F-U, follow-up; NS, no surgery group excluded; OT, operative time; PS, performance status; ASA, American Society of Anaesthesiology score; SCS, surgical complexity score; omental, omental involvement; peritoneal, peritoneal involvement; CCI, Charlson comorbidity index; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index; CA-125, cancer antigen 125 protein; TSIC, time from surgery to initiation of chemotherapy; BRCA, breast cancer mutation status; OR tumor index, scoring system to reflect extent of disease; IP, intraperitoneal; sum of rankings (numerical ranking system of progressively extensive tumor involvement for 5 anatomic regions); CPLN, cardiophrenic lymph node.

thresholds from having the highest probability (ranked 1) to the lowest probability (ranked 9) of maximizing OS. In addition, we report the "probability of being best" RD threshold, which assigns a probability that each RD threshold results in most prolonged survival relative to all others. Cumulative ranking probabilities using the surface under the cumulative ranking curve (SUCRA) were also calculated.[52] SUCRA presents a single value associated with each RD threshold. A value of 100% indicates the RD threshold is certain to be the most effective in the network (top ranked), while 0% indicates it is certain to be the least effective (in bottom rank). SUCRA was estimated through 10,000 repetitions in Stata using the network rank command.[45]

Sensitivity analysis

Because it was hypothesized that women with more extensive disease may have a poorer prognosis despite the outcome of their surgery, a sensitivity analysis including only studies that adequately adjusted for extent of disease at primary surgery was performed.

Certainty of the evidence

Guidance on the use of GRADE for prognostic factor studies has not yet been published,[53,54] but we appraised the quality and certainty of the evidence following existing guidelines for interventional SRs.[54] We based our judgment on the strength of the body of evidence based on the domains used by the GRADE Working Group (GRADE Working Group[54]). We interpreted our results in light of this graded evidence.

RESULTS

Study selection and characteristics

The flow of literature are shown in in the PRISMA diagram (Figure 1). The search strategy identified 8606 unique references, of which 200 progressed to full-text screening. At this stage, 154 were excluded, leaving 46 references[12,14,55–94] reporting on 25 primary studies[12,14,55,59–65,67,69–73,79–85,92,94] that met our inclusion criteria. Searches of the gray literature did not identify any additional relevant studies (Figure 1).

The 25 included studies assessed a total of 20,927 women, with the most having stage III disease. Three studies included a small proportion of women with early or unknown stage disease (range 3.6%–12.5%).[70,73,83] The analyses in Klar et al[73] included 1182 women with stage IIB-IIIB and 3684 women with stage IIIC-IV disease. This study contributed heavily to the analyses but results remained robust to its exclusion in a sensitivity analysis. See Table 1 for a full list of patient and study characteristics.

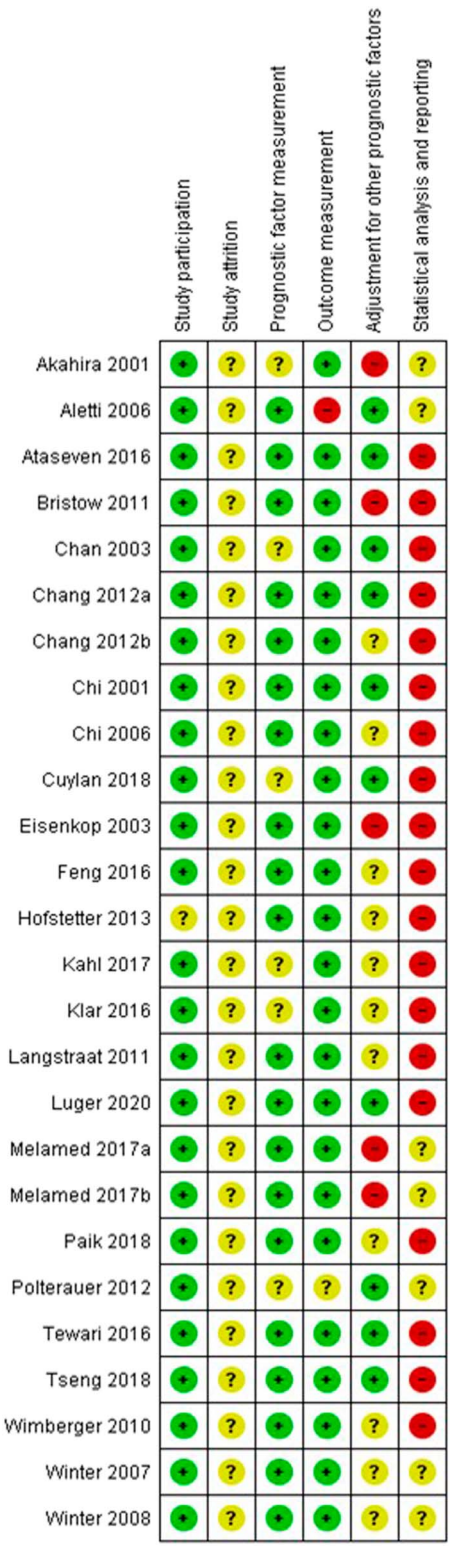

FIGURE 2. Risk of bias in included studies.

Table 2. Network meta-regression exploring age, FIGO stage, and histology.

RD*	Age†			FIGO stage‡			Histology§		
Ref¶ (0 cm)	HR‖	95% CI**	*P*††	HR‖	95% CI**	*P*††	HR‖	95% CI**	*P*††
<1 cm	0.98	0.96 to 1.01	0.24	1.00	1.00 to 1.01	0.13	0.99	0.99 to 1.00	0.02‡‡
>0 cm	1.03	0.93 to 1.13	0.62	1.00	0.97 to 1.03	0.86	0.96	0.93 to 1.00	0.07
1–2 cm	0.97	0.78 to 1.22	0.82	1.00	0.95 to 1.05	0.96	1.01	0.85 to 1.21	0.89
<2 cm	1.25	0.97 to 1.62	0.09	1.03	0.98 to 1.08	0.25	0.97	0.81 to 1.17	0.75
>1 cm	1.00	0.97 to 1.03	0.89	1.00	1.00 to 1.01	0.2	0.99	0.99 to 1.00	0.02‡‡
>2 cm	1.09	0.87 to 1.37	0.46	1.02	0.97 to 1.08	0.37	0.92	0.77 to 1.10	0.38

*RD thresholds of 1–5 cm and >5 cm were dropped due to detection of collinearity.
†Median age reported in this study was used except when not reported and mean was used.
‡Percentage of women in this study with International Federation of Gynecology and Obstetrics (FIGO) stage III EOC.
§Percentage of women in this study with serous histology.
¶Ref, reference: RD = 0 cm was used as the reference group.
‖HR, hazard ratio.
**CI, confidence interval.
††*P*: significance probability. This is the probability of the observed data or data more extreme, given the null hypothesis is true.
‡‡*P* was statistically significant but the HR point estimates and 95% CI's clearly show this is very unlikely to equate to any meaningful clinically significant differences in the percentage of women with serous histology across studies.

Risk of bias

The risk of bias assessments across all studies is shown in Figure 2. In general, most studies were at low to unclear risk of bias across domains but tended to be either at high or unclear risk for the statistical analysis and reporting domain. However, all included studies reported adjusted statistics to potentially minimize confounding bias. Owing to the restrictive inclusion criteria and attempts to minimize biases across the spectrum, studies were not necessarily at overall high risk of bias because they satisfied several of the criteria used to assess risk of bias.

Effects of interventions

The network meta-regression (Table 2) summarizes most covariates (age, stage, and histology) were not statistically significant ($P > 0.05$) in each of the RD comparisons. Although some covariates were statistically significant ($P < 0.05$) in a small number of comparisons, these differences were clearly not clinically meaningful. On examination of summary and descriptive characteristics (Table 1), there were no clear systematic differences between studies. We also checked the consistency assumption after completion of the NMA. There was no evidence of inconsistency in the network (see below).

Before data analysis, it is important to understand the geometry of the network.[95] The network plot shows which RD thresholds have been compared directly in studies and which can only be informed indirectly. The network geometry is depicted using the network diagram in Figure 3 and shows the range of RD thresholds and comparisons after optimal cytoreductive surgery for advanced EOC.[96] The RD thresholds presented in the NMA include complete cytoreduction to 0 cm (NMRD), 0.1–1 cm (0 cm < RD ≤1 cm, labelled as <1 cm for consistency with the published literature), >0 cm, 1–2 cm, >1 cm, 0.1–2 cm (labelled as <2 cm), >2 cm, 1–5 cm, and >5 cm. The nodes of some of the thresholds overlap, for example, >1 cm node overlaps with the 1–2 cm and >2 cm node, but these were all categorized as separate and unique nodes and interpreted accordingly and reflect the nature of data reported. Of note the 1–2 cm and <2 cm nodes included very sparse data so in that respect are less informative. Nodes where there were more comparative data available were for RD thresholds of 0 cm and <1 cm (indicated by the thick edge joining these 2 nodes in Figure 3). The comparisons of <1 cm and >1 cm included the 0 cm group, but this was deemed to have a negligible impact on the results and did not affect risk of bias profiles, certainty of the evidence or distort results because this was only applicable to 3 small studies.[61,64,94]

Table 3 summarizes the results of the NMA with a comparison of direct and indirect effect sizes of optimal and suboptimal RD thresholds. The results seem consistent across all split RD comparisons (sides), and there was no evidence of inconsistency in the network ($P = 0.48$).

The results in Table 4 and Figure 4 demonstrate prolonged survival if primary cytoreductive surgery

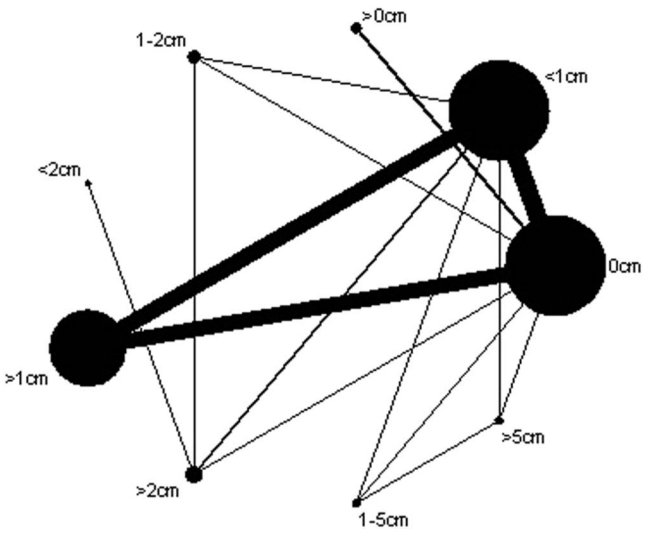

FIGURE 3. Network diagram showing RD comparisons after primary cytoreductive surgery for advanced EOC.

debulked to NMRD compared with any other RD threshold. Complete cytoreduction to NMRD was overwhelmingly the best ranked threshold because it was consistently ranked first (see Table 4 and Figure 5) with a very high probability of being the best RD threshold (SUCRA and *P*-best of 99.9% and 99%, respectively).

Table 4 also summarizes the benefit of incorporating reliable indirect estimates as an additional comparison between 0 cm versus <2 cm, while estimates for comparisons with sparse numbers are now more precise. A full breakdown of results is provided in in the detailed forest plots, which show results of all available comparisons (see Figure 6) and as a league table giving specific effect estimates for each and every comparison (see Table 5). There was no evidence of publication bias (see Figure 7).

Sensitivity analysis

A sensitivity analysis incorporating the results of 8 studies including an adequate adjustment for extent of disease at primary surgery increased the magnitude of effect estimates showed significantly prolonged survival in those with cytoreduction to NMRD (see Table 6). The results of this NMA also seem to be consistent across all sides in the network, and there was no evidence of overall inconsistency ($P = 0.31$). Other key probability and ranking statistics continued to provide strong evidence that NMRD (0 cm) is the best threshold ($P = 99.4\%$) and the SUCRA value remained very high (99.9%). Adjustment for extent of disease included: type (aggressive vs. standard) and extent of surgery; surgical complexity score; and progressively extensive tumor involvement in anatomic regions.

Table 3. Inconsistency test between direct and indirect RD threshold after primary surgery for advanced EOC comparisons in NMA.

Side	Direct		Indirect		Difference		
cm	Coefficient	SE	Coefficient	SE	Coefficient	SE	*P*
0 to <1*	0.688	0.063	0.570	0.353	0.118	0.358	0.741
0 to >0	No indirect estimate						
0 to 1–2	1.383	0.583	1.169	0.276	0.214	0.640	0.739
0 to >1	0.913	0.067	1.320	0.236	−0.406	0.245	0.097
0 to >2	2.119	0.597	1.349	0.265	0.770	0.648	0.235
0 to 1–5*	0.603	0.301	0.655	0.557	−0.052	0.639	0.936
0 to >5*	1.000	0.311	1.052	0.557	−0.052	0.639	0.936
0 to 1–2*	0.474	0.251	1.360	0.937	−0.886	0.957	0.354
0 to >1*	0.279	0.061	−0.356	0.335	0.635	0.340	0.062
<1 to >2*	0.743	0.243	1.629	0.939	−0.886	0.957	0.354
<1 to 1–5*	−0.057	0.308	−0.109	0.547	0.052	0.639	0.936
<1 to >5*	0.340	0.312	0.288	0.555	0.052	0.639	0.936
1–2 to >2*	0.265	0.250	−1.779	490.334	2.044	490.334	0.997
<2 to >2*	0.433	0.168	2.509	469.566	−2.075	469.566	0.996
1–5 to >5	No indirect estimate						

*All the evidence about these contrasts comes from the studies which directly compare them.
cm, centimeter; Coefficient, log hazard ratio; SE, standard error of log hazard ratio; *P*, significance probability (*P*) observed from the Z score.

Table 4. Results of NMA and pairwise analysis of optimal RD threshold after primary cytoreductive surgery for advanced EOC.

RD threshold versus 0 cm (reference)	NMA	Pairwise				
	HR (95% CI)	HR (95% CI)	n studies (participants)	Mean rank	*P* (best) %	SUCRA %
0 cm	Reference			1	99	99.9
<1 cm	1.98 (1.76–2.24)	2.03 (1.80–2.29)	17 (9404)	3.4	0	70.2
>0 cm	1.95 (1.48–2.58)	1.96 (1.44–2.67)	4 (1220)	3.4	0	70.6
1–2 cm	3.34 (2.04–5.47)	3.95 (1.33–11.78)	1 (68)	7.3	0	21.8
<2 cm	2.82 (1.58–5.04)	No direct estimate		6.0	0	36.9
>1 cm	2.57 (2.26–2.93)	2.50 (2.13–2.94)	14 (7988)	5.8	0	40.0
>2 cm	4.36 (2.69–7.04)	8.24 (2.68–25.33)	1 (87)	8.7	0	3.4
1–5 cm	1.85 (1.11–3.08)	1.83 (1.14–2.94)	1 (193)	3.2	1	72.0
>5 cm	2.75 (1.62–4.67)	2.72 (1.65–4.47)	1 (118)	6.2	0	35.3

HR, hazard ratio; *P* (best), probability that RD threshold is the best.

DISCUSSION

We identified 25 studies meeting our inclusion criteria. These studies assessed survival after primary cytoreductive surgery followed by adjuvant platinum-based chemotherapy in women with advanced EOC. The Sundar et al.[13] underpinning the NMA and the results of our updated analysis provides more precise and reliable estimates than seen in previous studies and reviews in this area,[6,8–12,97] which should enable more informed decisions to be made. Although the findings do not enable us to determine whether the survival benefit is a direct effect of the surgical intervention, they may encourage the surgical community to strive toward improving rates of complete cytoreduction and perhaps more centers adopting a more aggressive approach to attempt to improve rates of complete cytoreduction. Factors such as training, high-dependency unit support, patient selection and developing inter-surgical collaborations such as colo-rectal, upper gastrointestinal, hepato-biliary and vascular specialties could be important to help achieve this. RD and complete cytoreduction rates should be part of routinely collected cancer data and should be a quality indicator for advanced ovarian cancer surgery along with other indicators recommended by the British Gynaecological

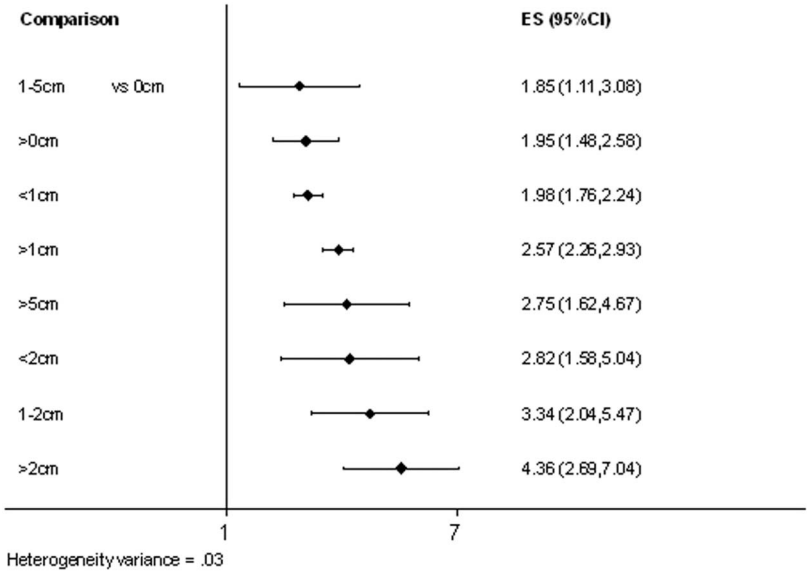

FIGURE 4. Forest plot showing RD thresholds versus complete cytoreduction (0 cm) after primary cytoreductive surgery for advanced EOC.

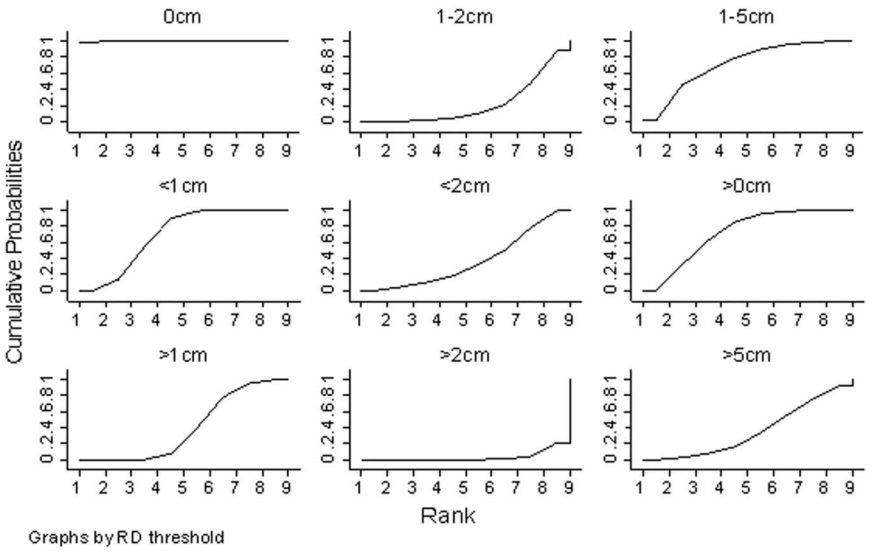

FIGURE 5. Rankograms showing ranks of RD thresholds for probability of being best at prolonging OS.

Cancer Society ovarian cancer action group and ESGO (European Society of Gynaecological Oncologists).

Pairwise analyses and NMAs clearly showed the prognostic importance of complete cytoreduction, with OS significantly prolonged in this RD threshold.[32,33] There should always be concern around "small study" biases, such as publication biases,[32,39] in meta-analyses. Although there was no evidence of publication bias (Figure 7), the results should still be interpreted with some caution. In addition, the nature of model selection procedures in the included studies may have meant study authors with nonstatistically significant *P* values may not have included RD in their final model.[98] However, including only studies that reported adjusted analyses should mean we have examined the best available evidence. Furthermore, a sensitivity analysis of the results of 8 studies that included an adequate adjustment for extent of disease at primary surgery strengthened the main conclusions. We emphasize the importance of this adjustment in this area; the results of the sensitivity analysis are key to proponents of aggressive surgery, as it was hypothesized that women with more extensive disease may have had poor prognosis despite the outcome of their surgery. However, the benefit of achieving complete cytoreduction became more evident after statistical adjustment for extent of disease. Nonetheless, we do suggest that all caveats should be discussed with patients before their primary surgery, especially in cases where there is likely to be a large trade-off between complete cytoreduction to NMRD and morbidity/quality of life.[99–101]

When compared with NMRD, all RD thresholds above this level resulted in shorter patient survival. When we compared different definitions of optimal and suboptimal cytoreduction, we observed the same survival patterns in those with greater removal of disease. However, these were attenuated compared with complete cytoreduction. Consequently, a key question is how much extra effort should be made to minimize RD if complete cytoreduction to NMRD is not possible. Although our findings do not enable us to determine whether the survival benefit is a direct effect of the surgical intervention, they do suggest that every effort should be made to reduce the tumor to microscopic disease. Where this is not considered achievable, attempts should be made to obtain near-optimal cytoreduction, defined as RD $<$ 1 cm. From the magnitude of effect sizes in comparisons of 0 cm versus larger amounts of RD (where there were sufficient evidence available for a give RD threshold), it seems that if RD cannot be limited to an optimal level then the surgeon could potentially prioritize their focus on morbidity and quality of life (QoL). The results of the SOCQER-2[102] study commissioned by NICE, assessed QoL in women undergoing standard or extensive surgery after primary surgery in advanced EOC. This study found no important differences in global QoL scores measured across 6 weeks, 6 months, and 12 months postsurgery in varying complexities of surgery. Patients who underwent low-complexity surgery were associated with higher rates of RD and lower survival compared with those with a similar disease burden undergoing surgery of intermediate complexity. Postoperative RD was associated with poorer OS, particularly in patients undergoing low-complexity surgery.

Table 5. League table giving specific effect estimates for all RD comparisons: HR (and 95% CI HRs) for OS.

	0 cm	<1 cm	>0 cm	1–2 cm	<2 cm	>1 cm	>2 cm	1–5 cm	>5 cm
0 cm	Reference	1.98* (1.76–2.24)	1.95 (1.48–2.58)	3.34 (2.04–5.47)	2.82 (1.58–5.04)	2.57 (2.26–2.93)	4.36 (2.69–7.04)	1.85 (1.11–3.08)	2.75 (1.62–4.67)
<1 cm	0.50* (0.45–0.57)	Reference	0.98 (0.73–1.33)	1.69 (1.04–2.73)	1.42 (0.81–2.52)	1.30 (1.15–1.46)	2.20 (1.38–3.51)	0.93 (0.56–1.56)	1.39 (0.82–2.35)
>0 cm	0.51 (0.39–0.68)	1.02 (0.75–1.38)	Reference	1.71 (0.97–3.02)	1.45 (0.76–2.76)	1.32 (0.97–1.79)	2.23 (1.28–3.89)	0.95 (0.53–1.70)	1.41 (0.78–2.56)
1–2 cm	0.30 (0.18–0.49)	0.59 (0.37–0.96)	0.58 (0.33–1.03)	Reference	0.84 (0.47–1.52)	0.77 (0.47–1.26)	1.30 (0.80–2.13)	0.55 (0.27–1.11)	0.82 (0.40–1.68)
<2 cm	0.35 (0.20–0.63)	0.70 (0.40–1.24)	0.69 (0.36–1.31)	1.18 (0.66–2.13)	Reference	0.91 (0.51–1.63)	1.54 (1.11–2.14)	0.65 (0.30–1.41)	0.97 (0.45–2.12)
>1 cm	0.39 (0.34–0.44)	0.77 (0.68–0.87)	0.76 (0.56–1.03)	1.30 (0.79–2.13)	1.10 (0.61–1.97)	Reference	1.69 (1.05–2.74)	0.72 (0.43–1.21)	1.07 (0.63–1.83)
>2 cm	0.23 (0.14–0.37)	0.46 (0.29–0.73)	0.45 (0.26–0.78)	0.77 (0.47–1.25)	0.65 (0.47–0.90)	0.59 (0.36–0.96)	Reference	0.42 (0.21–0.85)	0.63 (0.31–1.28)
1–5 cm	0.54 (0.32–0.90)	1.07 (0.64–1.79)	1.05 (0.59–1.89)	1.81 (0.90–3.65)	1.53 (0.71–3.28)	1.39 (0.83–2.34)	2.36 (1.18–4.71)	Reference	1.49 (0.82–2.70)
>5 cm	0.36 (0.21–0.62)	0.72 (0.42–1.22)	0.71 (0.39–1.29)	1.22 (0.60–2.48)	1.03 (0.47–2.23)	0.93 (0.55–1.60)	1.58 (0.78–3.20)	0.67 (0.37–1.22)	Reference

*Upper diagonal represents 0 cm versus <1 cm comparisons and inverse (<1 cm vs. 0 cm) in lower diagonal and repeated for other comparisons accordingly.

The overall certainty of the identified available evidence is moderate.[54] The evidence was primarily downgraded by one level from high certainty to moderate because the statistical analysis and reporting domain in the QUIPS tool[41] was assessed as being at high or unclear risk of bias in all included studies. Many study authors reported that statistically significant variables from the univariate analysis were included in the multivariable model, but gave no further details about any conceptual framework. The problem with this method is that there are variables that may not be important in a univariate association but are important in the full model. It is often more appropriate to include all pertinent variables that are plausibly important, potentially using data reduction methods to combine closely related variables.[103] This was the most serious bias from the QUIPS domains that could influence the effect estimates. The results are consistent and seem to be reliable and precise in conclusions drawn. Some comparisons were sparse with wide CIs, but even the lower 95% CI would be clinically significant as a point estimate in many cases, indicating a gain in OS. Consequently, further research is unlikely to change our confidence in the existing estimates of effect.[54] The exact reasons for performing one type of surgery over another were not well documented, and it was likely that women in generally poor health would be subjected to less aggressive surgery and thus would be more likely to have larger RD. This would most likely result in poorer survival. For this reason, we applied strict inclusion criteria and included studies that used statistical adjustment. However, it is generally accepted that the major reason for not achieving complete cytoreduction in most of the cases is not actually related to patient factors but is more associated with a deficiency in surgical skill and/or a lack of willingness in the surgeon to embrace ultraradical surgery.

The evidence suggests the need to redefine the term "optimal cytoreduction" by the Gynecological Cancer InterGroup, from its definition of <1 cm RD to NMRD.[10,104–106] We suggest retaining 3 categories of RD classification but redefining to optimal, "near optimal," and "suboptimal" cytoreduction rather than complete, optimal, and suboptimal for RD of 0 cm, <1 cm, and >1 cm, respectively. Similar suggestions using the terms complete, minimal, and gross have been previously published.[107]

Implications for research

Part 2 of this research is presented in the same edition and focused on adjustments for publication bias using expert elicitation.[38] This research aimed to conduct a series of sensitivity analyses to adjust the results of the

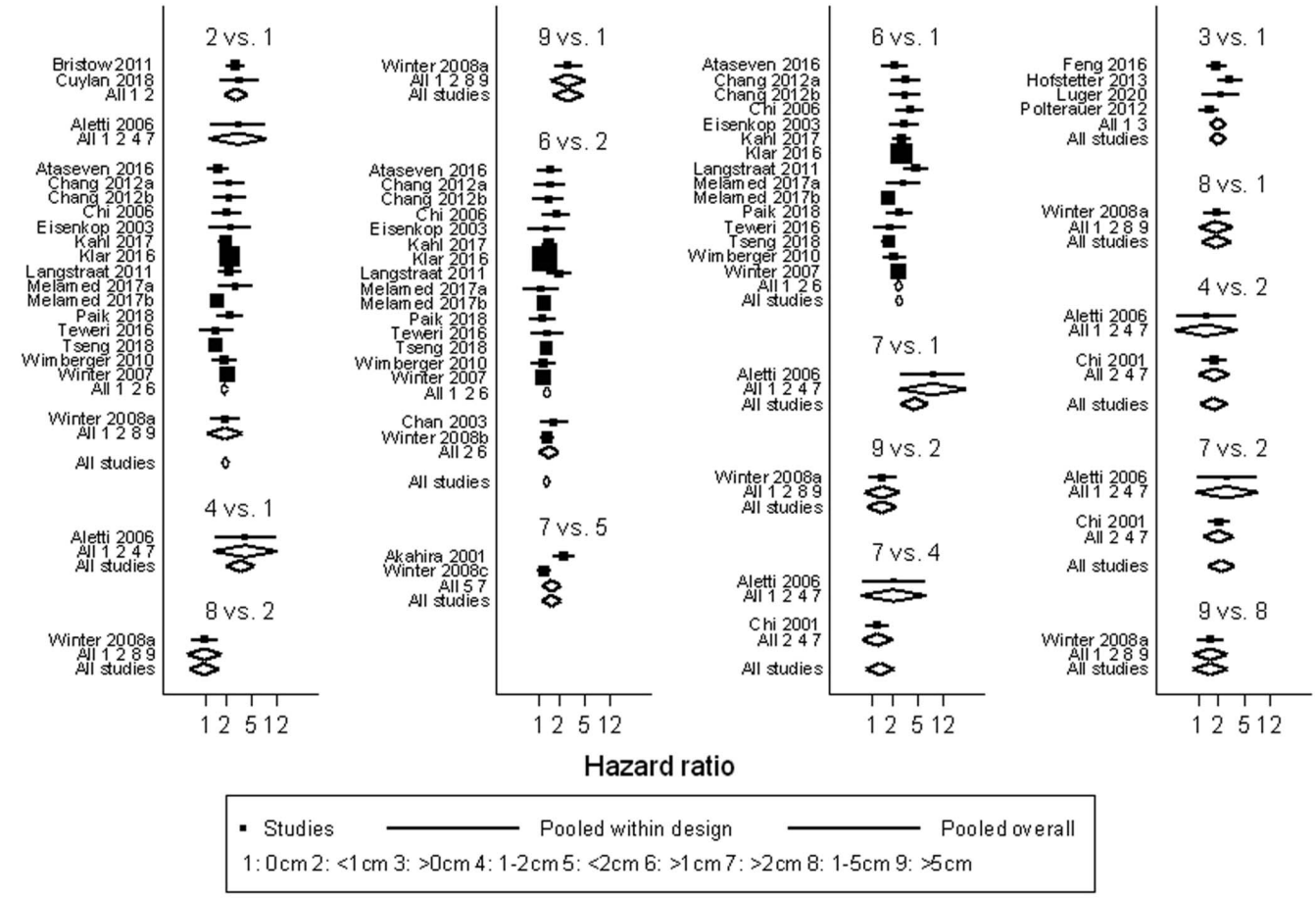

FIGURE 6. Forest plots showing results of all available RD comparisons and global test of consistency.

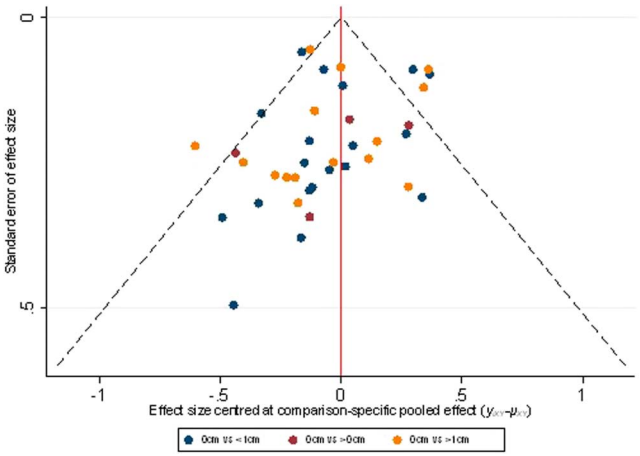

FIGURE 7. Funnel plot showing studies including comparisons of RD <1 cm, >0 cm, and >1 cm with complete cytoreduction (RD 0 cm).

NMA for publication bias, to confirm or refute the existing conclusions. The next piece of research in this area should focus on developing a model for accurately predicting important outcomes such as survival and quality of life based on remaining RD after primary surgery, and the effects of ultraradical surgery, so women can plan for their future and make informed decisions on subsequent treatment. This could be achieved by first conducting a review of prognostic studies to identify all studies reporting prognostic models for OS, as well as disease recurrence in women with advanced EOC following primary surgical debulking and also determine the performance of these models for predicting the risk stratification of women with this disease.[108] Measures should include discrimination, the area under the (curve) receiver operating characteristic curve, calibration, and overall model performance.[109,110] Given the fact that remaining RD after primary surgery is likely to remain the main predictor of survival in this area, a precise prediction

Table 6. Sensitivity analysis showing NMA of optimal RD threshold after primary cytoreductive surgery for advanced EOC including studies using adjustment for extent of disease.

RD threshold versus 0 cm (reference)*	HR (95% CI) NMAs	Mean rank	*P* (best) %	SUCRA %
0 cm	Reference	1	99.4	99.9
<1 cm	2.25 (1.93–2.63)	2.4	0	72.5
>0 cm	2.95 (1.87–4.67)	3.6	0	47.2
1–2 cm	3.32 (1.29–8.58)	3.9	0.7	41.9
>1 cm	3.41 (2.78–4.18)	4.3	0	33.5
>2 cm	6.89 (2.59–18.31)	5.8	0	5.0

*Comparisons involving <2 cm, 1–5 cm, and >5 cm RD thresholds were not reported.
HR, hazard ratio; *P* (best), probability that RD threshold is the best.

model would allow women and their families to plan for the future and aid future decisions on their subsequent further line treatment care pathway.

Because we have presented an updated and finalized analysis of impact of RD after primary surgery for advanced EOC, future research should also be conducted to determine whether increasing attempts at achieving complete cytoreduction have a direct effect on improving survival outcomes. This research should use methodologies and trial designs that reduce or eliminate confounding effects, such as the patient's performance status, disease spread, and tumor biology within the new paradigm of treatment with biological agents and genetic status. Despite the obvious challenges, this should be considered more than feasible because on average only around half of women with stage II–IV and unstaged ovarian cancer receive surgery in England.[13] Existing trials have shown conflicting results when further surgery was performed as an interval procedure after suboptimal cytoreduction at primary surgery.[111] Therefore, it seems best to increase attempts at optimizing to lower levels of RD at first surgery. Because there are large disparities between surgeons and centers in their optimal and complete cytoreduction rates,[14–17] it is worth considering randomizing patients to specialist centers providing more extensive surgery to achieve complete cytoreduction or to nonspecialist centers.[112] This may be best achieved by the conduct of a cluster randomized controlled trial. The increasing practice of offering neoadjuvant chemotherapy followed by interval debulking surgery should not complicate the performance of these trials, by including stratification for this factor within the study design.[113]

Another possible option is to randomize surgeons or hospitals to an intervention to develop their expertise and capability to perform more extensive ultraradical surgery, as additional training may be necessary.[114,115] There is a suggestion that maximal attempts to achieve complete cytoreduction are currently not being performed by most of the practising gynecological oncologists,[91] as previously indicated by low rates of complete cytoreduction to NMRD in many countries.[116,117] The development of these skills requires a shift in the surgeon's approach to surgery. Given that the additional procedures can be learned over a relatively short period, this could potentially lead to increases in optimal/complete cytoreduction rates with no significant increases in perioperative morbidity.[15] Similarly, it has been shown previously that optimal cytoreduction rates of up to 88% at primary laparotomy in advanced-stage ovarian cancer by gynecological oncologists working as a team can be achieved, without any increase in morbidity.[16]

CONCLUSIONS

Our results identified a strong association between achievement of complete cytoreduction and improved OS, highlighting a real need for clinical practice to follow Gynecological Cancer InterGroup recommendations. The NMA forms part of the methods guidance underpinning policy making in many jurisdictions. Part 2 of this research presents an extension to this work.[38]

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