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A Society of Gynecologic Oncology Evidence-based Review (and Recommendations)

A meta-analysis of morbidity and mortality in primary cytoreductive surgery compared to neoadjuvant chemotherapy in advanced ovarian malignancy

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HIGHLIGHTS

- Primary cytoreductive surgery (PCS) associated with a 20% morbidity rate compared to 8% in neoadjuvant chemotherapy (NACT)
- NACT associated with increased optimal cytoreduction rates but no difference in overall or progression free survival.
- PCS should remain standard of care where complete gross resection is achievable.

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ABSTRACT

Aim

The aim of this meta-analysis is to review the morbidity and mortality associated with primary cytoreductive surgery (PCS) compared to neoadjuvant chemotherapy and interval cytoreductive surgery (NACT + ICS) for advanced ovarian cancer.

Methods. A literature search was performed for publications reporting morbidity and mortality in patients undergoing PCS compared to NACT + ICS. Databases searched were Cochrane, Medline, Pubmed, Pubmed Central, clinicaltrials.gov and Embase. Two independent reviewers applied inclusion and exclusion criteria to select included papers, with differences agreed by consensus. A total of 1341 citations were reviewed; 17 studies comprising 3759 patients were selected for the analysis. The literature search was performed using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Results were reported as mean differences or pooled odds ratios (OR) with 95% confidence intervals (95% CI).

Results. Patients in the PCS group were significantly more likely to have a Clavien-Dindo grade ≥ 3 morbidity with an overall rate of 21.2% compared to 8.8% (95%CI 1.9–4.0, $p < 0.0001$) and were more likely to die within 30 days of surgery (OR 6.1, 95% CI 2.1–17.6, $p = 0.0008$). Patients who underwent NACT + ICS had significantly shorter procedural times (MD −35 min, $p = 0.01$), lost less blood intraoperatively (MD-382 ml, $p < 0.001$) and had an average admission 5.0 days shorter (MD −5.0 days, 95% CI −8.1 to −1.9 days, $p = 0.002$) than those undergoing PCS. While NACT was associated with significantly increased optimal and complete cytoreduction rates (OR 1.9, 95% CI 1.3–2.9, $p = 0.001$, and OR 2.2, 95% CI 1.5–3.3, $p = 0.0001$ respectively), this did not confer any additional survival benefit (OR 1.0, $p = 0.76$).

Conclusion. NACT is associated with less morbidity and mortality and improved complete cytoreduction compared to PCS, with no survival benefit. Hence NACT is an acceptable alternative in selected patients in particular with medical co-morbidities or a high tumour burden.

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Contents

1. Introduction

Ovarian cancer frequently presents at an advanced stage and is associated with the greatest mortality of the gynaecological malignancies [1]. At the time of diagnosis, 75% of patients with epithelial ovarian cancer have advanced disease i.e. International Federation of Gynaecology and Obstetrics (FIGO) stage IIIC or IV [2]' [3]. The prognosis associated with stage IV disease is poor with a 5-year survival of <20% [4]. The international standard treatment for advanced ovarian cancer is extensive cytoreductive surgery followed by platinum-based chemotherapy. A Cochrane review [5] recommended that surgery should proceed with the goal of complete cytoreduction of all macroscopic disease, as this has been shown to significantly prolong survival [6].

The timing of chemotherapy in relation to surgery remains a subject of much debate. Primary cytoreductive surgery (PCS) followed by adjuvant carboplatinum-paclitaxel chemotherapy is considered the standard of care. However patients with a high tumour burden at presentation or a poor performance status may not be suitable candidates for primary surgery as they are unlikely to achieve complete cytoreduction.

Many ovarian cancers are chemosensitive tumours with a high response rate of 80–90% [7], hence NACT followed by interval cytoreductive surgery (ICS) has emerged as an alternative option for those patients not suitable for PCS. Neoadjuvant chemotherapy (NACT) aims to reduce tumour burden as well as to increase the chance of achieving complete cytoreduction [8] with a number of studies demonstrating non-inferior survival outcomes [9], [10]. Previous meta-analyses have shown improved cytoreduction rates and less morbidity with NACT compared to PCS [10], [11]. This meta-analysis aims to add additional data by including a number of recent publications and randomised controlled trials, and in particular to compare morbidity and mortality in patients treated with NACT compared to PCS.

2. Methods

A systematic literature search was performed for all publications that reported on morbidity and mortality in patients undergoing cytoreductive surgery in primary and recurrent ovarian malignancy. Embase, Medline, Pubmed, Pubmed Central, clinicaltrials.gov and Cochrane databases were searched using a Boolean search algorithm for articles published up to January 2019. Additional screening was performed of the reference lists from the relevant literatures. Original studies documenting quality of life, morbidity and mortality in patients undergoing PCS or NACT + ICS for ovarian malignancy were included for meta-analysis. The overall search strategy was inclusive of alternative terms for ovarian cancer such as ovarian neoplasm, ovarian malignancy ovarian carcinoma, epithelial ovarian cancer, and synonyms for primary cytoreductive surgery (debulking surgery OR cytoreduction surgery OR primary cytoreduction) and neoadjuvant chemotherapy (adjuvant chemotherapy OR neoadjuvant drug therapy). Publications were evaluated dependent on predefined inclusion and exclusion criteria as outlined in Fig. 1. All search results were combined in a reference manager database (Endnote™, Version X7, Thompson Reuters, New York, USA) and duplicates were removed by hand. Reference lists of included studies were screened for additional relevant studies.

2.1. Study selection

The inclusion and exclusion criteria were applied to retrieve citations by two independent reviewers and the abstracts were reviewed to select full papers for data analysis. Full text studies were further evaluated, and exclusion criteria were applied to identify final papers for inclusion. Studies reporting on post-operative outcomes (Clavien-Dindo ≥3 morbidity or mortality, mean blood loss, transfusion requirements, mean length of stay), cytoreduction rates and 30-day mortality were included. Morbidities were recorded both qualitatively and quantitatively. Where additional discrepancies were identified these were agreed by consensus.

The meta-analysis was conducted in accordance with PRISMA guidelines. Study methodological quality was assessed by applying the MINORS criteria for observational studies [12] and the Jadad [13] score for randomised trials. Where data was not available or uninterpretable, authors were contacted for further information.

Analyses were performed using RevMan software (Review Manager, version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Continuous data were presented as mean ± standard deviation and statistical significance was interpreted using the two tailed *t*-test. Where median and range were presented, methods described by Hozo and colleagues were followed to derive mean and standard deviation [14]. Where means were displayed without SD, but had *p* values according to Student's *t*-test, the Cochrane method was used to impute SDs and allow meta-analysis. For survival analysis, many studies presented their data with Kaplan-Meier plots, in which cases data was extracted from the plots by hand. Methods to reconstruct survival data from Kaplan-Meier plots have previously been described by Guyot et al. [15]. The majority of studies reported median survival rates with comparative *p* values, without expressly describing range or means with standard deviation (SD). In order to impute this data and allow meta-analysis, the mean was approximated as the median, and SD obtained using the Cochrane method above. Association of categorical variables (differences for dichotomous pre-existing variables between groups) was assessed using chi-square (χ^2)

Inclusion Criteria

Original publication (reviews, opinions, letters, protocols and conference proceedings excluded)

Patients with ovarian malignancy who underwent either Primary Debulking Surgery or Neoadjuvant Chemotherapy and Interval Debulking Surgery

Reported outcome measures studied

- Morbidity (>Grade 3 Clavien Dindo)
- Mortality
- Quality of Life
- Perioperative outcomes: operative duration, operative blood loss, length of hospital stay

Exclusion criteria

Papers in languages other than English.

Papers where data was unavailable or uninterpretable and authors uncontactable

Non-human studies

No data on morbidity for PCS vs NACT-ICS

Fig. 1. Study inclusion and exclusion criteria.

test or Fisher's test where appropriate. Cochran's Q test was used to calculate the I^2 statistic in order to objectively measure heterogeneity for each of the outcome measures; an I^2 value >50% was taken to denote significant heterogeneity between studies. A fixed-effects model was performed for each variable, or where there was appreciable heterogeneity ($I^2 > 50\%$) a random-effects model was used for meta-analysis. For

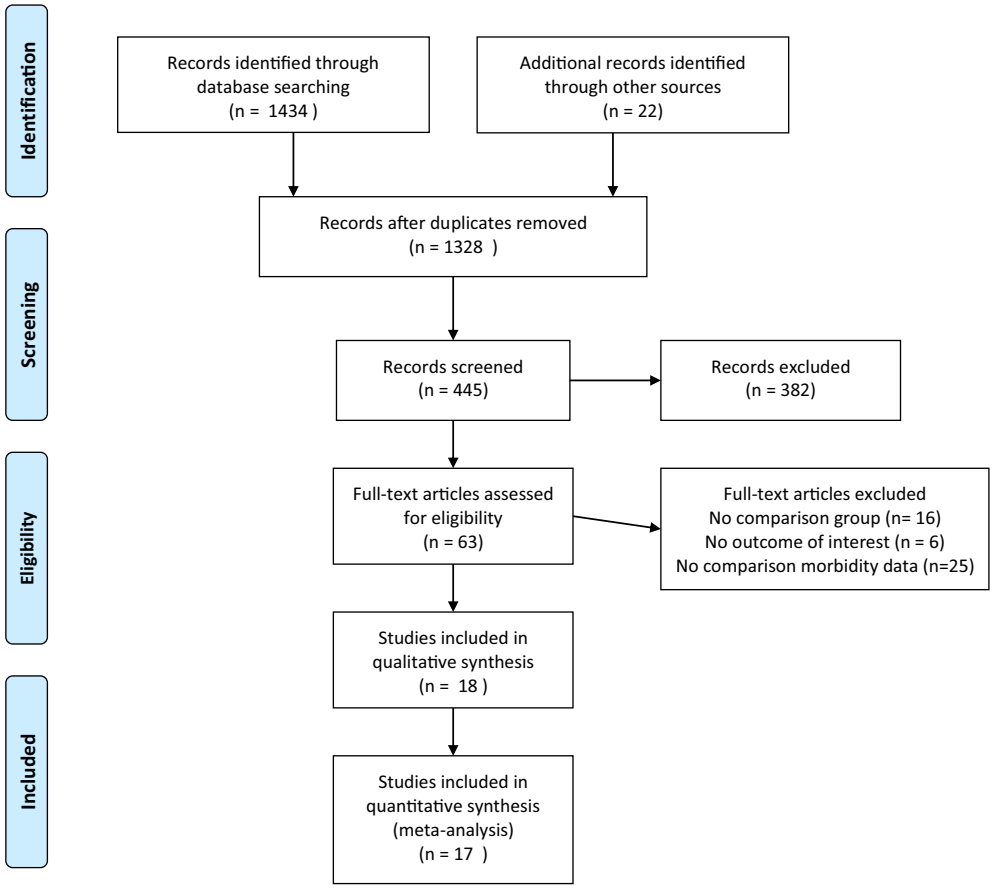


Fig. 2. Flow diagram of systematic review and meta-analysis process.

continuous variables, the weighted mean differences (MD) are presented with 95% confidence intervals (CI). For categorical variables Mantel–Haenszel odds ratios (ORs) were calculated and described with 95% CI. Corresponding funnel plots of log standard error as a function of effect size were used to examine the effect of publication bias visually. *P* values were two tailed, differences of <0.05 were deemed to be significant.

3. Results

A comprehensive search of databases resulted in a total of 1456 papers, of which 1328 remained for review after removal of duplicate papers (Fig. 1). Following review of titles and abstracts, 64 full text papers were reviewed. Seventeen studies were eventually included after meeting the study inclusion criteria (Fig. 2). In total the studies comprised 3759 patients, with study sizes ranging from 60 to 632 patients. Of the 3759 patients, 1619 (43%) received neoadjuvant chemotherapy followed by interval cytoreductive (NACT+ICS), and 2140 (57%) underwent primary cytoreductive surgery (PCS). The studies selected for meta-analysis included 4 randomised trials, 4 prospective and 9 single institution retrospective reviews (Table 1). All papers were published between 2010 and 2018, with patients included from 1995 to 2017.

There was no difference in mean age between the two groups (61 ± 9.9 in NACT vs 60.6 ± 11.4 years for PCS, $p = 0.260$). WHO performance status was reported in 5 studies [16], [17], [18], [19], [20], with a similar number of patients scoring >2 in both groups (17% NACT $n = 170$, 14% PCS $n = 128$, $p = 0.118$).

FIGO stage was reported in all except one study and there was no difference between both groups, with 70% of patients in the NACT having stage IIIC disease compared to 73% in the PCS group ($p = 0.354$). There was also no difference in the proportion of patients with FIGO Stage IV disease, with 29.8% in the NACT group compared to 26.3% in the PCS group ($p = 0.085$). All studies except two reported on tumour histology, with 73.7% of patients having high grade serous carcinoma. Serum cancer antigen 125 (CA 125) was reported in 10 studies with patients in the NACT group having a significantly higher mean level at diagnosis than those in the PCS group (7699.9 ± 3291.8 vs 5593.1 ± 4731.7, $p = 0.0001$).

Chemotherapy treatment protocols used in each study are reflective of standard regimes used during the study period, with the majority giving 3–6 cycles of NACT prior to ICS followed by a further 3 cycles, and PCS being followed by 6–8 cycles of chemotherapy. The median number of NACT cycles was 4.8 (range 1–10). Chemotherapy agents were mostly platinum based with no significant differences between the adjuvant and neoadjuvant regimes. Only one study [17] commented on the interval from commencing NACT to patients undergoing ICS, with patients triaged to surgery within 4 weeks if disease progression was excluded. Hyperthermic intraperitoneal chemotherapy (HIPEC) was not used in any of the included studies.

3.1. Meta-analysis

3.1.1. Perioperative outcomes

The mean length of operative time for all procedures was 208 ± 113 min, with patients who underwent NACT prior having significantly shorter procedural times than those undergoing primary surgery (MD −35 min, $p = 0.01$, Fig. 3A). Patients in the neoadjuvant group lost less blood intraoperatively (MD −382 ml, $p < 0.001$), however there were no differences in the quantities of red cell concentrate units transfused in each group ($p = 0.15$). Overall, 64.7% of patients had optimal cytoreduction (<1 cm residual disease) and 35.2.% had complete macroscopic resection (complete cytoreduction). The optimal cytoreduction rate in the NACT group was 71.3% compared to 59.8% in the PCS group ($p = 0.001$) and the complete cytoreduction rate in the NACT group was 44.4% compared to 28.3% in the PCS group ($p = 0.0001$). Patients in the group undergoing NACT were twice as likely to receive optimal and complete cytoreduction (OR 1.9, 95% CI 1.3–2.9, p = 0.001, and OR 2.2, 95% CI 1.5–3.3, p = 0.0001 respectively, Fig. 3B).

3.1.2. Postoperative morbidity, mortality and length of stay

Patients in the PCS group were 2.8 times more likely to have a Clavien-Dindo grade ≥ 3 morbidity, with a morbidity rate of 21.2% compared to 8.8% in the NACT group (95%CI 1.9–4.0, $p < 0.0001$, Fig. 3C). This remained true for the individually reported morbidities of moderate-to-severe infection (7.1% vs 3%, p = 0.0001, Fig. 3D), venous thromboembolism (3.7% vs 1.9%, $p = 0.02$), and intestinal fistula (1.2% vs 0.1%, $p = 0.06$) (ORs 2.5, 1.9 and 4.0 respectively, supplementary appendix). Significantly more patients required bowel resection in the PCS group compared to the NACT group (23.5% vs 8.8%, OR 3.2, 95% CI 1.6–6.4, $p < 0.001$, supplementary appendix). Chemotherapy morbidity was graded using the Common Terminology Criteria for Adverse Events (CTCAE)

Table 1
Overview of included studies.

Author	Year	Country	Study period	Study type	Total n	NACT + ICS (%)	PCS (%)	Jadad Score
Vergote [15]	2010	Belgium	1998–2006	Randomised prospective	632	322 (51)	310 (49)	3
Kehoe [16]	2015	England/NZ	2004–2010	Randomised non-inferiority trial	550	274 (49)	276 (51)	3
Onda [36]	2016	Japan	2006–2011	Randomised non-inferiority trial	277	130 (43)	147 (57)	3
Fagotti [18]	2016	Italy	2011–2014	Randomised Phase 3 study	110	55 (50)	55 (50)	3

Author	Year	Country	Study period	Study type	Total n	NACT + ICS (%)	PCS (%)	Minors Score
Drews [37]	2016	England	2007–2014	Retrospective	220	149 (67)	71 (33)	19
Hou [38]	2007	USA	1998–2005	Retrospective	172	63 (36)	109 (64)	19
Medina [39]	2017	Mexico	2000–2015	Prospective, Comparative	105	63 (60)	42 (40)	20
Mueller [40]	2015	USA	2008–2013	Retrospective	586	154 (26)	432 (74)	18
Nelson [41]	2010	Canada	2006–2009	Retrospective, single institution	67	38 (56)	29 (44)	19
OShea [42]	2018	USA	2010–2013	Retrospective, single institution	131	66 (50.5)	65 (49.5)	18
Rauh-Hain [43]	2012	USA	1995–2007	Retrospective	242	66 (27)	176 (73)	19
Sayyah-Melli [44]	2013	Iran	2011–2012	Prospective, single institution	60	30 (50)	30 (50)	17
Worley [45]	2013	USA	2000–2010	Retrospective	165	40 (24)	125 (76)	19
Zheng [46]	2012	China	2006–2009	Retrospective	67	30 (44)	37 (56)	19
Chisti [47]	2009	Pakistan	1999–2008	Prospective	118	40 (33)	78 (67)	18
Siesto [48]	2018	Italy	2009–2017	Propensity Matched Analysis Retrospective	100	50 (50)	50 (50)	18
Kobal [49]	2018	Slovenia	2008–2012	Retrospective	157	49 (31.2)	108 (68.8)	18

NACT + ICS = Neoadjuvant Chemotherapy + Interval Cytoreductive Surgery/PCS = Primary Cytoreductive Surgery.

[21] and there was no difference in chemotherapy related morbidities between the two groups (OR 1.0, $p = 0.88$). Patients in the PCS group were more likely to die within 30 days of surgery (OR 6.1, 95% CI 2.1–17.6, $p = 0.0008$, supplementary appendix). The mean LOS in the NACT group was on average 5.0 days shorter than in the PCS group (MD −5.0 days, 95% CI −8.1 to −1.9 days, $p = 0.002$).

3.1.3. Survival

There were no apparent differences in survival rates reported at five years between the two groups (OR 1.0, $p = 0.76$, Supplementary Appendix), and only a one month improved mean survival in the NACT group (MD −1.0 month, 95% CI −1.6 to −0.3, $p = 0.006$). This data was particularly heterogeneous, with an I^2 of 94%, and mean survival ranging from 22.6 to 56.4 months among studies.

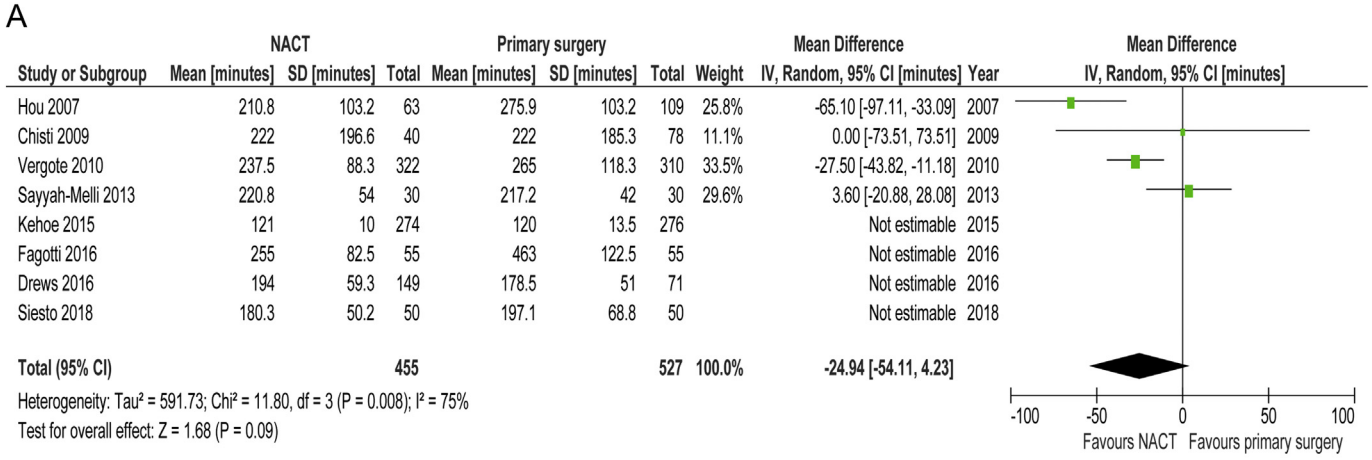
3.1.4. Sensitivity analysis

When studies with mean optimal cytoreduction rates falling outside of one SD of the overall mean optimal cytoreduction rate were excluded, sensitivity analysis revealed three outcomes which lost significance at meta-analysis – operative time, thromboembolism and the incidence of intestinal fistula.

When studies were assessed for quality for sensitivity analysis, only one study attained a MINORs criteria >19 or Jadad score > 3 and so this could not be performed.

3.1.5. Quality of life

Quality of Life (QOL) data was reported in only two studies [15] [18], and was therefore not amenable to meta-analysis. QoL was assessed by the European Organization for Research and Treatment of Cancer (EORTC) QoL questionnaires [22] in all studies that reported on QoL outcomes. The SCOPRION trial [18] found a statistically significant improvement in QoL scores in 6 different scales including emotional and cognitive functioning in the NACT group. The randomised EORTC-NCIC trial [15] found no difference between the groups at any time point. The CHORUS trial [16] reported only on global quality of life scores and found a significantly higher QoL score at 6 months in the NACT patients compared to the PCS group (means difference − 7.6, $p = 0.043$), however at 12 months QoL scores were no different between the groups ($p = 0.97$).



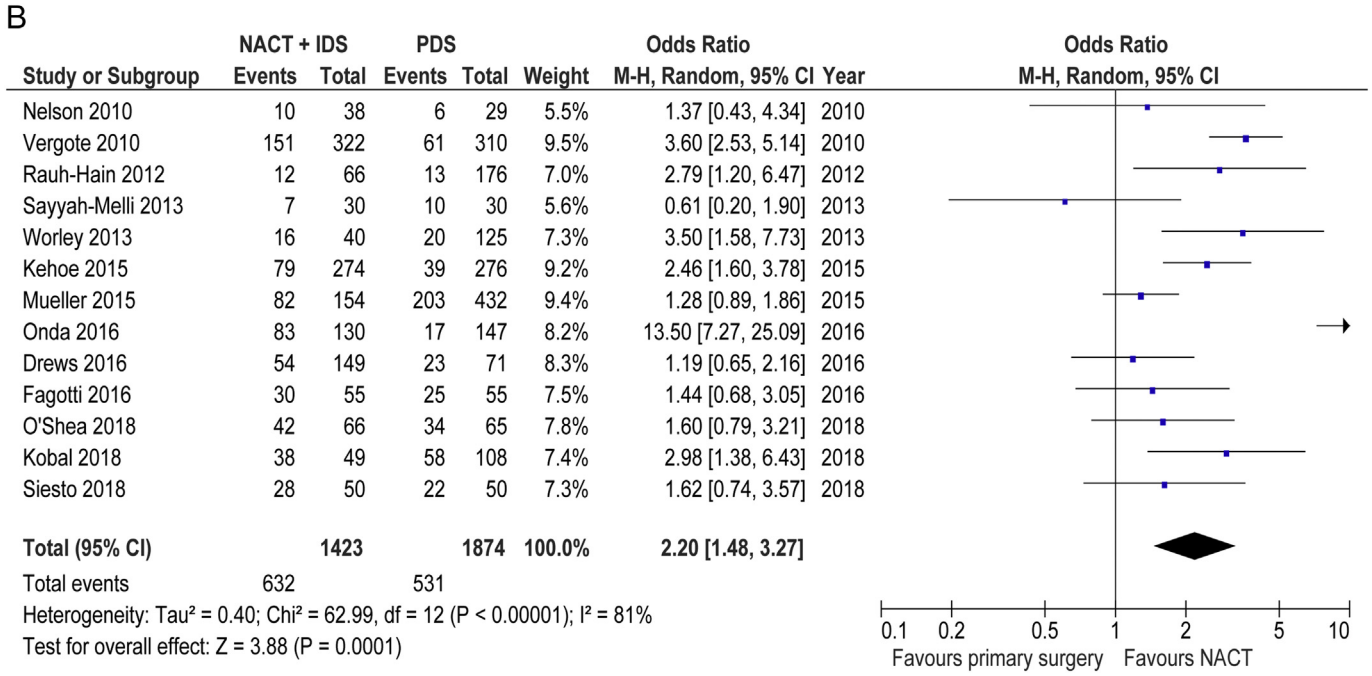
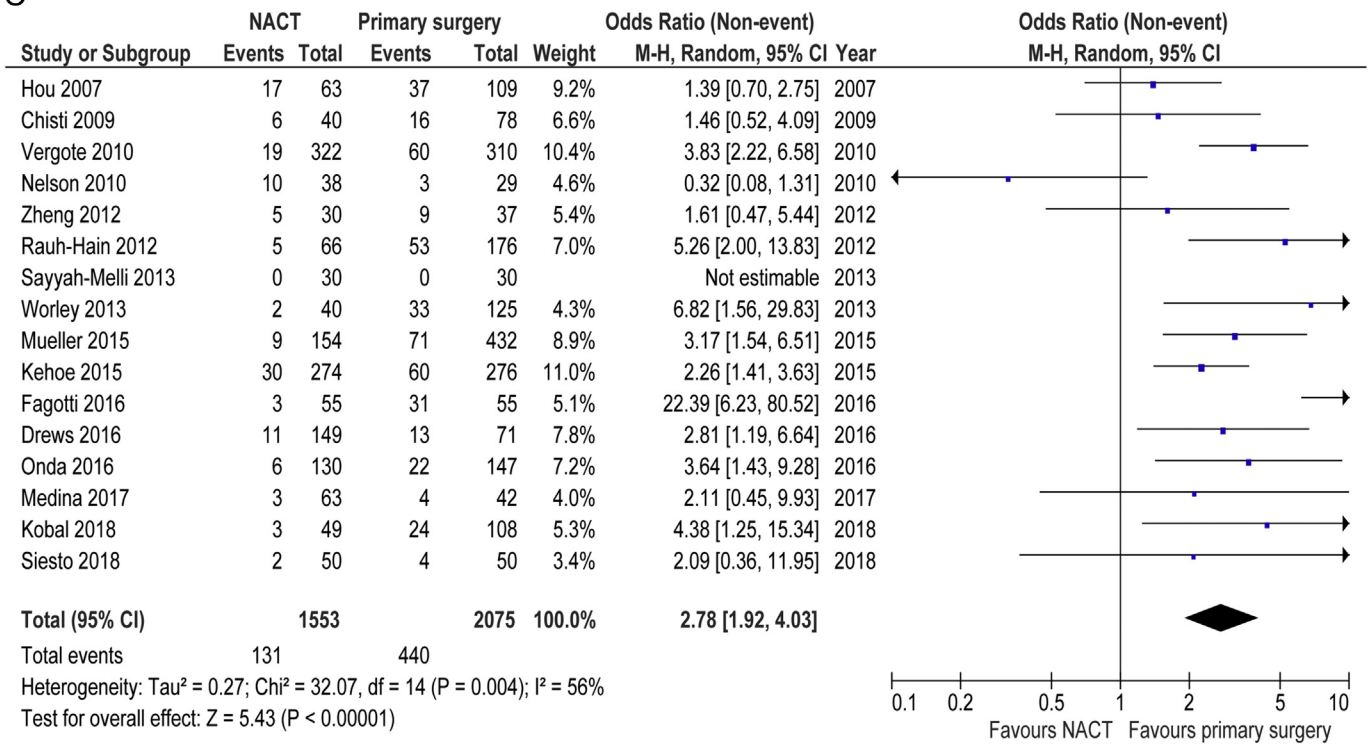


Fig. 3. Forest plots. A: Operative time B: Complete cytoreduction C: Clavien-Dindo morbidity D: Infection.

C



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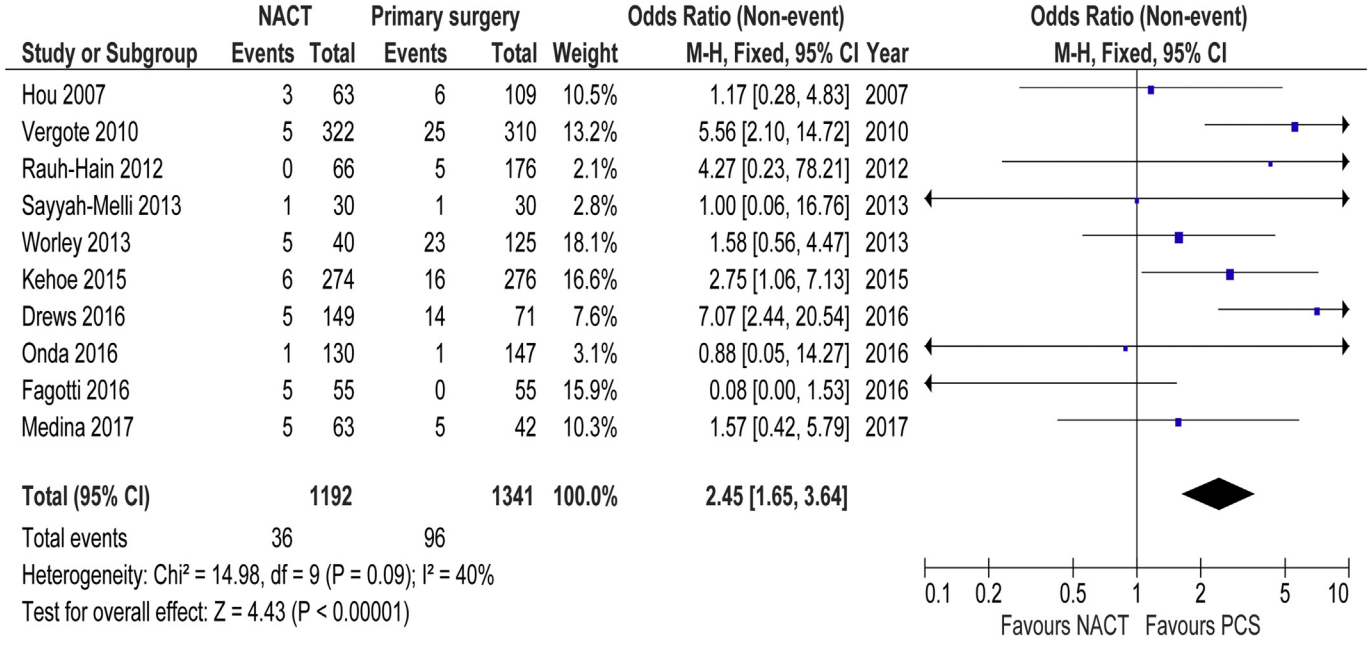

Fig. 3 (*continued*).

4. Discussion

This meta-analysis demonstrates that NACT followed by ICS is associated with significantly less morbidity and mortality compared to PCS. In patients deemed unsuitable for PCS based on performance status or disease distribution NACT followed by ICS was associated with increased complete cytoreduction rates but did not improve on OS or PFS.

Traditionally, NACT was reserved for those patients deemed not suitable for PCS due to medical co-morbidities or extent of tumour burden, based on a number of retrospective studies concluding that NACT was associated with inferior survival outcomes compared to PCS. Retrospective studies by Rosen et al. reported poorer 7-year survival in patients treated with NACT (8.6% versus 41%; $p < 0.0001$) [24], while May et al found similar results with 5 year survival outcomes of 39% vs 27% in PCS and NACT respectively [25]. However, other studies found no difference in survival outcomes [26], including the prospective randomised EORTC-NCIC [15] and the CHORUS [16] trials both of which are included in the current study. In this metaanalysis we found no difference in

survival between the two groups with a range of 22.6–56.4 months, although this data was highly heterogeneous. Of note, the OS and PFS reported in this meta-analysis and in both the EORTC-NCIC and the CHORUS trial ranging from 23 to 30 months in all study arms are still significantly lower than those reported in the GOG 172[26] trial, in which patients with stage 3 ovarian cancer had primary cytoreductive surgery to a residual <1 cm followed by adjuvant intraperitoneal chemotherapy, which reported a median OS of 66 months.

Therefore the standard of care for ovarian cancer remains primary cytoreduction if there is a reasonable prospect of achieving a gross macroscopic resection and the patient's performance status is sufficient to withstand a multivisceral resection. The decision to offer NACT should not be based on the basis that it increases gross macroscopic resection rates. There is a fundamental flaw in the interpretation of NACT studies that report an increase in complete cytoreduction rates, which should correlate with improved survival rates. Interpretation of residual disease after NACT can be extremely difficult and the complexity of ICS can often be reduced, reflected in the significantly lower number of bowel resections in this group compared to at PCS. It is likely that residual disease is higher after ICS than reported.

Importantly, morbidity and mortality were significantly increased in those in the PCS group as was 30-day mortality. This should be interpreted in the context of the performance status of patients included in these studies. Infection and thromboembolism both contributed significantly to the increased morbidity associated with PCS, both of which are potentially preventable complications. Infection and thromboembolism are both associated with modifiable risk factors such as obesity, diabetes and malnutrition, hence pre-operative optimisation and the implementation of intra- and post-operative ERAS protocols may reduce perioperative morbidity. Prevention is the crucial step in reducing patient morbidity and more aggressive strategies to optimize any identifiable risk factors and focusing on the recognised contributors of morbidity, such as infection and thromboembolism, could result in a more favourable outcome in PCS.

The increased morbidity associated with PCS needs to be carefully considered when selecting patients for primary surgery. The ability to achieve complete gross resection will vary between centres, with recent studies demonstrating significantly increased complete resection rates when debulking is performed by an experienced surgeon in a high volume centre [27] [28],.In particular the addition of upper abdominal procedures such as splenectomy, distal pancreatectomy, cholecystectomy and liver wedge resection have shown to increase the optimal cytoreduction rates from 46% to 80% [29]. Both the EORTC-NCIC [15] and the CHORUS [16] included in the current study performed very low rates of radical upper abdominal surgery in the PCS group, likely contributing to the lower complete cytoreduction rates reported. Hence high-volume centres with greater experience can offer patients the best chance of achieving optimal surgical outcomes and improve survival outcomes. A reasonable approach seems to set complete gross resection as the threshold for selecting patients for PCS. Patients with an extensive tumour burden particularly involving the small bowel mesentery and/or stage IV disease are likely to benefit from the reduced morbidity associated with NACT.

Selecting patients for PCS remains challenging however there is increasing evidence to support a staging laparoscopy. A Cochrane review [30] found the use of resectability criteria at laparoscopy has a high specificity which would leave no patient inappropriately explored, however, up to 30% of patients would still be left with residual disease. A systematic review including 9 studies and 778 staging laparoscopy's found that patients who had a staging laparoscopy were less likely to undergo a futile laparotomy (10% vs 39%) [31]. While further randomised trials are needed to fully explore the role of staging laparoscopy to prevent unnecessary laparotomy, its use as a triage tool before initiating treatment is promising.

A significant disadvantage to NACT is the potential increased risk of platinum resistant disease. Rauh-Hain et al reported significantly more patients treated with NACT compared to PCS (88.8% v's 55.3%) developed platinum resistance [32]. The time to developing first platinum resistance may be reduced by up to 50% in those treated with NACT, however this may be reflective of underlying aggressive tumour biology. The number of chemotherapy cycles administered is also related to the development of platinum resistance, with evidence suggesting those patients who received >3 cycles of chemotherapy are at significantly increased risk with no additional survival benefit [33]. Although a number of predictive biomarkers of platinum resistance have been proposed, none have withstood thorough validation. So, while the questionable benefit of NACT in increasing optimal cytoreduction rates has been proposed as a major advance, it has not conferred any survival benefit, probably due to increasing platinum resistance. In conclusion, the development of platinum resistance is a limitation of NACT of which clinicians and patients must be aware when making decision regarding optimal treatment.

This meta-analysis has several strengths and limitations. The main strength is the inclusion of high-quality randomised trials and a number of recent prospective studies. To our knowledge, this is the largest meta-analysis to compare morbidity in NACT and PCS. As with any meta-analysis, the conclusions that can be drawn are limited to the limitations of the original included studies. In particular, the survival data included is highly heterogeneous and was estimated from Kaplan-Meier curves, and as such needs to be interpreted with caution. Furthermore, a number of the included studies were performed in single-institutions and as a consequence are at high risk of bias due to individual clinician decisions regarding patient treatment. This is also reflected in the low MINORS and Jadad scores for the included studies. A previous meta-analysis by Qin et al. [34] of 1220 patients found similar results, however this review adds additional data from 2 further randomised control trials, with survival outcomes now presented and a number of recent publications to add further strength to the results.

Research on QoL is lacking with only two randomised trials reporting on QoL outcomes. A recent single centre study found no difference in symptom burden or functional recovery in patients immediately after undergoing either PCS or ICS [35]. However, the current literature is deficient in evidence to support one treatment option over the other. Additional QoL data would be valuable when counselling patients regarding treatment options allowing more informed choices to be made.

In conclusion, NACT is associated with significantly less perioperative morbidity and 30-day post-operative mortality compared to PCS. Furthermore, complete cytoreduction rates are significantly increased with NACT although this was not found to confer any increase in OS or PFS. Hence, while NACT is an attractive alternative treatment option, particularly in frail patients with medical comorbidities and those with stage IV disease, PCS should remain the standard of care. Ultimately, the timing of surgery should be made on an individual basis taking into account the patient's age, tumour burden, co-morbidities and the likelihood of achieving complete resection. Future research should focus on methods to optimize patient performance status preoperatively and reducing the recognised contributors of morbidity such as thromboembolism and infection.

Author contribution

Study concepts: HC Bartels, DJ Brennan
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Data acquisition: HC Bartels, AC Rogers
Quality control of data and algorithms: HC Bartels, AC Rogers
Data analysis and interpretation: HC Bartels, AC Rogers, V McSharry
Statistical analysis: HC Bartels, AC Rogers
Manuscript preparation: HC Bartels, AC Rogers, R McVey, T Walsh, Donal O'Brien, W D Boyd
Manuscript editing: HC Bartels, DJ Brennan, R McVey, T Walsh, Donal O'Brien, WD Boyd, DJ Brennan, V McSharry

Manuscript review: HC Bartels, DJ Brennan, R McVey, T Walsh, Donal O'Brien, WD Boyd, DJ Brennan, V McSharry

All authors approve the final manuscript.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

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2. All authors who contributed to the manuscript are named authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.07.011.

References

[1] J. Ferlay, I. Soerjomataram, M. Ervik, R. Dikshit, S. Eser, C. Mathers, M. Rebelo, D.M. Parkin, D. Forman, F. Bray, Cancer Incidence and Mortality Worldwide, International Agency for Research on Cancer, IARC Lyon, France, 2014.

[2] du Bois A, Reuss A, Pujade-Lauraine E et al. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO)Cancer, 2009, vol. 115 (pg. 1234–1244).

[3] van der Burg ME, Buyse M et al. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer, N Engl J.

[4] G. Aletti, S.C. Dowdy, K.C. Podratz, W.A. Cliby, Analysis of factors impacting operability in stage IV ovarian cancer: rationale use of a triage system, Gynecol. Oncol. 105 (2007) 84–89.

[5] A. Elattar, A. Bryant, B.A. Winter-Roach, M. Hatem, R. Naik, Optimal primary surgical treatment for advanced epithelial ovarian cancer, Cochrane Database Syst. Rev. 10 (8) (2011) 1–67.

[6] R.E. Bristow, R.S. Tomacruz, D.K. Armstrong, E.L. Trimble, F.J. Montz, Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis, J. Clin. Oncol. 20 (5) (2002) 1248–1259 Mar 1.

[7] W.P. McGuire, W.J. Hoskins, F. Mark, B.S. Brady, R. Kucera, E.E. Partridge, et al., Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer, N. Engl. J. Med. 334 (1996) 1–6.

[8] A. Gallo, L. Frigerio, Neoadjuvant chemotherapy and surgical considerations in ovarian cancer, Curr Opin Obstet Gynecol 20 (2002) 1248–1259.

[9] J.A. Ledermann, F.A. Raja, C. Fotopoulou, A. Gonzalez-Martin, N. Colombo, C. Sessa, on behalf of the ESMO Guidelines Working Group, Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 24 (suppl_6) (October 2013) vi24–vi32.

[10] P.E. Schwartz, J.T. Chambers, R. Makuch, Neoadjuvant chemotherapy for advanced ovarian cancer, Gynaecol. Oncol 53 (1994) 33–37.

[11] L. Yang, B. Zhang, G. Xing, J. Du, B. Yang, Q. Yuan, et al., Neoadjuvant chemotherapy versus primary debulking surgery in advanced epithelial ovarian cancer: a meta-analysis of peri-operative outcome, PLoS One 12 (10) (2017), e0186725. https://doi.org/10.1371/journal.pone.0186725.

[12] K. Slim, E. Nini, D. Forestier, et al., Methodological index for non-randomized studies (MINORS):developmentandvalidation of a new instrument, ANZ J. Surg. 73 (9) (2003) 712–716.

[13] A.R. Jadad, R.A. Moore, D. Carroll, et al., Assessing the quality ofreports of randomized clinical trials: is blinding necessary? Control. Clin. Trials 17 (1996) 1–12.

[14] S.P. Hozo, B. Djulbegovic, I. Hozo, Estimating the mean and variance from the median, range, and the size of a sample, BMC Med. Res. Methodol. 5 (1) (2005) 13.

[15] Patricia Guyot, et al., Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves, BMC Med. Res. Methodol. 12 (9) (2012) 1 , Feb https://doi.org/10.1186/1471-2288-12-9.

[16] I. Vergote, C.G. Trope, F. Amant, et al., Neoadjuvant chemotherapy or primary surgery instage IIIC or IV ovarian cancer, N. Engl. J. Med. 363 (10) (2010) 943–953.

[17] S. Kehoe, J. Hook, M. Nankivell, P.G.C. Jayson, T. Lopez, et al., Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial, Lancet 386 (9990) (2015) 249–257 July 18.

[18] Onda, Takashi, T Satoh, T Saito, T Kasamatsu, T Nakanishi, K Nakamura, M Wakabayashi et al. Comparison of treatment invasiveness between upfront debulking surgery versus interval debulking surgery following neoadjuvant chemotherapy for stage III/IV ovarian, tubal, and peritoneal cancers in a phase III randomised trial: Japan Clinical Oncology Group Study JCOG0602; Eur. J. Cancer, Volume 64, 22 - 31.

[19] A. Fagotti, G. Ferrandina, G. Vizzielli, F. Fanfani, V. Gallotta, V. Chiantera, B. Costantini, G. Scambia, et al., Phase III randomised clinical trial comparing primary surgery versus neoadjuvant chemotherapy in advanced epithelial ovarian cancer with high tumour load (SCORPION trial): final analysis of peri-operative outcome, Eur. J. Cancer 59 (2016) 22–33.

[20] F. Drews, G. Bertelli, K. Lutchman-Singh, Management of advanced ovarian cancer in south West Wales - a comparison between primary debulking surgery and primary chemotherapy treatment strategies in an unselected, consecutive patient cohort. Cancer Epidemiol 49 (2017 Aug) 85–91, https://doi.org/10.1016/j.canep.2017.05.014 (Epub 2017 Jun 7).

[21] Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0, Available at http://evs.nci.nih.gov/ftp1/CTCAE/About.html, Accessed date: 30 January 2019.

[22] E. Greimel, A. Bottomley, A. Cull, A.C. Waldenstrom, J. Arraras, An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-OV28) in assessing the quality of life of patients with ovarian cancer, Eur. J. Cancer 39 (10) (2003) 1402–1408 July.

[24] B. Rosen, S. Laframboise, S. Ferguson, J. Dodge, M. Bernardini, J. Murphy, et al., The impacts of neoadjuvant chemotherapy and of debulking surgery on survival from advanced ovarian cancer, Gynecol. Oncol. 134 (2014) 462–467.

[25] T. May, R. Comeau, P. Sun, J. Kotsopoulos, S.A. Narod, B. Rosen, P. Ghatage, A comparison of survival outcomes in advanced serous ovarian cancer patients treated with primary debulking surgery versus neoadjuvant chemotherapy, Int. J. Gynecol. Cancer 27 (4) (2017) 668–674 May.

[26] C. Bian, K. Yao, L. Li, T. Yi, X. Zhao, Primary debulking surgery vs. neoadjuvant chemotherapy followed by interval debulking surgery for patients with advanced ovarian cancer, Arch. Gynecol. Obstet. 293 (1) (2016) 163–168 Jan.

[27] D.K. Armstrong, B. Bundy, L. Wenzel, et al., Gynecologic Oncology Group. Intraperitoneal cisplatin and paclitaxel in ovarian cancer, N. Engl. J. Med. 354 (2006) 34–43.

[28] F. Vernooij, A.P. Heintz, J.W. Coebergh, et al., Specialized and high-volume care leads to better outcomes of ovarian cancer treatment in the Netherlands, Gynecol. Oncol. 112 (2009) 455–461.

[29] D.S. Chi, E.L. Eisenhauer, O. Zivanovic, et al., Improved progression-free and overall survival in advanced ovarian cancer as a result of a change in surgical paradigm, Gynecol. Oncol. 114 (2009) 26–31.

[30] Rutten MJ, Leeflang MMG, Kenter GG, Mol BWJ, Buist M. Laparoscopy for diagnosing resectability of disease in patients with advanced ovarian cancer. Cochrane Database Syst. Rev. 2014, Issue 2. Art. No.: CD009786. DOI:https://doi.org/10.1002/14651858.CD009786.pub2.

[31] Natalia Zeff, Role of laparoscopy in initial tumour staging in advanced epithelial ovarian cancer: a systematic review, Pleura and peritoneum 3 (1) (2018), 20180106 , 29 Mar https://doi.org/10.1515/pp-2018-0106.

[32] J.A. Rauh-Hain, C.C. Nitschmann, M.J. Worley Jr., L.S. Bradford, R.S. Berkowitz, Platinum resistance after neoadjuvant chemotherapy compared to primary surgery in patients with advanced epithelial ovarian carcinoma, Gynecol. Oncol. 129 (1) (2013 Apr) 63–68, https://doi.org/10.1016/j.ygyno.2013.01.009 (Epub 2013 Jan 18).

[33] H. Akilli, O. Altundag, S. Rahatli, Y.A. Tohma, L.A. Karakas, Effect of increased number of neoadjuvant chemotherapy cycles on tumor resectability and pathologic response in advanced stage epithelial ovarian cancer, J BUON 23 (7) (2018) 111–115 Dec.

[34] M. Qin, Y. Jin, L. Ma, Y.Y. Zhang, L.Y. Pan, The role of neoadjuvant chemotherapy followed by interval debulking surgery in advanced ovarian cancer: a systematic review and meta-analysis of randomized controlled trials and observational studies, Oncotarget 9 (9) (2017) 8614–8628 Dec 27.

[35] L.A. Meyer, Q. Shi, J. Lasala, M.D. Iniesta, H.K. Lin, A.M. Nick, L. Williams, Comparison of patient reported symptom burden on an enhanced recovery after surgery (ERAS) care pathway in patients with ovarian cancer undergoing primary vs. interval tumor reductive surgery, Gynecol. Oncol. 152 (3) (2019) 501–508 Mar.

[36] Onda, Takashi, T Satoh, T Saito, T Kasamatsu, T Nakanishi, K Nakamura, M Wakabayashi et al. Comparison of treatment invasiveness between upfront debulking surgery versus interval debulking surgery following neoadjuvant chemotherapy for stage III/IV ovarian, tubal, and peritoneal cancers in a phase III randomised trial: Japan Clinical Oncology Group Study JCOG0602; Eur. J. Cancer, Volume 64, 22 - 31.

[37] F. Drews, G. Bertelli, K. Lutchman-Singh, Management of advanced ovarian cancer in south West Wales - a comparison between primary debulking surgery and primary chemotherapy treatment strategies in an unselected, consecutive patient cohort, Cancer Epidemiol. 49 (2017 Aug) 85–91, https://doi.org/10.1016/j.canep.2017.05.014 (Epub 2017 Jun 7).

[38] Hou, June, Y.M. Kelly, H Yu, J McAlpine, Masoud Azodi, T Rutherford et al.: Neoadjuvant chemotherapy lessens surgical morbidity in advanced ovarian cancer and leads to improved survival in stage IV disease. Gynecol. Oncol., Volume 105, Issue 1, 211 - 217.

[39] H. Medina-Franco, R. Cortes-Gonzalez, F. Lambreton-Hinojosa, A. Fimbres-Morales, J.C. Vargas-Siordia, Neoadjuvant chemotherapy increases R0 cytoreduction rate but does not improve final outcome in advanced epithelial ovarian cancer, Ann. Surg. Oncol. 24 (2017) 1330–1335.

[40] J.J. Mueller, A. Kelly, Q. Zhou, A. Iasonos, K. Long Roche, Y. Sonoda, R.E. O'Cearbhaill, O. Zivanovic, D.S. Chi, ... G.J. Gardner, Intraperitoneal chemotherapy after interval debulking surgery for advanced-stage ovarian cancer: feasibility and outcomes at a comprehensive cancer center, Gynecol. Oncol. 143 (3) (2016) 496–503.

[41] G. Nelson, C.A. Lucero, P. Chu, J. Nation, P. Ghatage, Intraperitoneal chemotherapy for advanced ovarian and peritoneal cancers in patients following interval debulking surgery or primary cytoreductive surgery: Tom Baker Cancer Centre experience from 2006 to 2009, J. Obstet. Gynaecol. Can. 32 (3) (2010) 263–269 Mar.

[42] A. O'Shea, K. McCool, R. Harrison, E. Sampene, J. Connor, L. Barroilhet, Neoadjuvant chemotherapy is associated with more anemia and perioperative blood transfusions than primary debulking surgery in women with advanced stage ovarian cancer, Gynecol. Oncol. 150 (1) (2018) 19–22.
[43] J.A. Rauh-Hain, N. Rodriguez, W.B. Growdon, A.K. Goodman, D.M. Boruta 2nd, N.S. Horowitz, Primary debulking surgery versus neoadjuvant chemotherapy in stage IV ovarian cancer, Ann. Surg. Oncol. 19 (3) (2012 Mar) 959–965, https://doi.org/10.1245/s10434-011-2100-x (Epub 2011 Oct 13).
[44] M. Sayyah-Melli, G.K. Zonoozi, S. Hashemzadeh, et al., J Obstet Gynecol India 63 (2013) 405https://doi.org/10.1007/s13224-013-0425-z.
[45] M.J. Worley Jr., S.H. Guseh, J.A. Rauh-Hain, K.A. Williams, M.G. Muto, C.M. Feltmate, R.S. Berkowitz, N.S. Horowitz, Does neoadjuvant chemotherapy decrease the risk of hospital readmission following debulking surgery? Gynecol. Oncol. 129 (1) (2013 Apr) 69–73, https://doi.org/10.1016/j.ygyno.2013.01.012 (Epub 2013 Jan 31).
[46] H. Zheng, Y. Gao, Primary debulking surgery or neoadjuvant chemotherapy followed by interval debulking surgery for patients with advanced ovarian cancer, Chin. J. Cancer Res. 24 (4) (2012) 304–309, https://doi.org/10.3978/j.issn.1000-9604.2012.09.02 Dec.
[47] U. Chishti, A.B. Aziz, Primary debulking surgery versus neo-adjuvant chemotherapy in stage III/IV ovarian cancer: comparison of perioperative morbidity and survival data in Pakistani women, J Pak Med Assoc 65 (3) (2015) 306–309 Mar.
[48] G. Siesto, R. Cavina, F. Romano, Fabrizio, D. Vitobello, et al., Primary Debulking surgery versus neoadjuvant chemotherapy in advanced epithelial ovarian Cancer, Am. J. Clin. Oncol. 41 (3) (January 2016).
[49] B. Kobal, M. Noventa, B. Cvjeticanin, M. Barbic, L. Meglic, M. Herzog, G. Bordi, A. Vitagliano, C. Saccardi, E. Skof, Primary debulking surgery versus primary neoadjuvant chemotherapy for high grade advanced stage ovarian cancer: comparison of survivals, Radiol. Oncol. 52 (3) (2018) 307–319, https://doi.org/10.2478/raon-2018-0030.