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Quality of life outcomes following surgery for advanced ovarian cancer: a systematic review and meta-analysis.

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Highlights:

1. Studies on patient reported outcomes after ovarian cancer surgery are limited and potentially confounded.
2. Quality of life after primary surgery or surgery after chemotherapy is not different.
3. There is insufficient evidence for quality of life after extensive surgery for advanced ovarian cancer.

Abstract:

Background: Quality of life after ovarian cancer treatment is an important goal for patients. Complex debulking surgeries and platinum based chemotherapy are often required but quality of life after surgery is rarely reported.

Objectives: To describe quality of life outcomes after surgery for advanced ovarian cancer in a systematic review and meta-analysis.

Search strategy: MEDLINE, EMBASE and CENTRAL through March 2019 with no language restrictions

Selection criteria: Included studies reported quality of life in women diagnosed with primary advanced ovarian cancer, fallopian tube carcinoma or primary peritoneal cancer undergoing cytoreduction surgery.

Data collection and analysis: Data on extent and timing of surgery, quality of life outcomes and surgical complications were extracted and study quality assessed.

Main Results: Three randomised controlled trials comparing primary surgery to neoadjuvant chemotherapy had heterogeneous quality of life outcomes with no difference between arms although there was a clinical improvement in global quality of life scores in both arms at 6 months compared to baseline. Data from two observational studies showed no meaningful difference in quality of life scores between patients undergoing standard or extensive surgery at 6 months.

Conclusions: There was no clinically important difference in the quality of life of patients undergoing either primary debulking surgery or neoadjuvant chemotherapy. There is insufficient evidence on quality of life outcomes of patients undergoing extensive or ultra-radical surgery compared with those undergoing less extensive surgery. Quality of life

outcomes matter to patients but there is little evidence to inform patient choice regarding the extent of surgery.

Keywords Ovarian cancer, quality of life, extensive surgery, ultra-radical surgery, debulking surgery

Introduction:

Whilst overall survival and progression free survival are critical outcomes for cancer patients, quality of life is of fundamental importance to patients [1]. Health related quality of life refers to the effect of an illness and its therapy upon a patient's physical and occupational function, psychological state and social wellbeing which itself can influence treatment decisions [2-4]. Standard treatment in advanced ovarian cancer comprises a combination of cytoreduction surgery and chemotherapy using carboplatin and paclitaxel [5]. Although considerable variations exist in international surgical opinion and practice [6-10], complex surgery is increasingly performed with the goal of complete cytoreduction which may include resections of the bowel and of disease on the liver, diaphragm and spleen.

Multiple studies have shown improved progression free survival and overall survival with complete cytoreduction [11-15] however, initial disease burden remains a prognostic indicator [16]. In a Cochrane review, low quality evidence shows a survival benefit with more extensive surgery, and differences in morbidity and quality of life outcomes of extensive surgery compared to standard surgery are still unclear [17].

Greater morbidity is associated with extensive surgery [18, 19] but knowledge of quality of life is lacking. Whether a patient has primary debulking surgery or neoadjuvant chemotherapy may also impact on quality of life. Understanding quality of life outcomes is critical given randomised controlled trial data on surgical extent is lacking. Robust estimation of survival benefit for any individual patient undergoing extensive surgery is therefore challenging. The putative survival gain from extensive surgery might be offset by deterioration in quality of life as a result of increased morbidity. While much is known about quality of life outcomes during or after chemotherapy [20-24], the impact on quality of life from surgery, particularly extensive surgery remains unknown.

The purpose of this systematic review and meta-analysis is to report patient reported quality of life after surgery in advanced ovarian cancer.

Methods:

We searched Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to Present and EMBASE 1974 to 11th of March, 2019 and current edition of CENTRAL for eligible studies (SK,JL) with no language restrictions (Appendix-S1). Science Citation Index (Web of Science), www.clinicaltrials.gov and metaregister of controlled trials were searched. Reference lists of included studies were screened. Abstracts of meetings from International Gynaecological Cancer Society, British Gynaecological Cancer Society, European Society of Gynaecological Oncology, American Society of Clinical Oncology and Society of Gynaecological Oncology were searched. We included randomised controlled trials, non-randomised trials and prospective observational studies describing any quality of life measures as primary or secondary outcomes. Studies with women aged 18 and over diagnosed with International Federation of Gynaecology and Obstetrics (FIGO) stages 3 or 4 epithelial ovarian cancer, fallopian tube carcinoma or primary peritoneal carcinomatosis undergoing cytoreduction surgery were included [25]. Studies evaluating quality of life only in chemotherapy interventions, intraperitoneal chemotherapy or in recurrent ovarian cancer were excluded.

All identified references were transferred to EndNote bibliographic software and duplicated studies were removed. Two authors (SK,JL) independently reviewed all titles and abstracts and retrieved full text of selected studies. Two authors (CC,SS) reviewed articles where there was any uncertainty. Risk of bias was assessed using the Newcastle–Ottawa quality assessment scale for observational studies [26] and the Cochrane tool [27] for randomised controlled trials.

Data extracted included: author's details and citation index, publication year, country, study-design, participants number, mean age, performance status, FIGO stage, histology, quality of life tools, quality of life scores at different time points, overall survival and progression free survival. Where appropriate, meta-analysis was carried out using random effects and study heterogeneity was assessed. Quality of life was described in the following sub-groups: primary debulking surgery vs neoadjuvant chemotherapy and standard vs extensive surgery. Quality of life scores were recorded as mean with standard deviation and a 10 point difference in quality of life score was considered meaningful as per European Organisation for Research and Treatment of Cancer (EORTC) guidelines. Standard deviation values were calculated using the Cochrane tool if only standard errors were provided [27].

The systematic review protocol was registered on PROSPERO (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016048139).
A PRISMA statement and checklist for systematic reviews is provided in Appendix-S7 [28].

Results:

We identified a total of 10,220 records from the database search and other sources such as science citation index and abstract of meetings. After removing duplicates, we screened title and abstracts of 6464 records and excluded 6452, based on study characteristics, design and reported outcomes. Seven records were excluded after full text review. Five studies were included in the systematic review [29-33]. The authors of all included studies were contacted for additional information [30, 31]. The electronic search criteria, selection process flow diagram and list of excluded studies are given in appendices (S1,S2 and S3).

Three included studies were randomised controlled trials comparing primary debulking surgery with neoadjuvant chemotherapy, evaluating quality of life as secondary outcomes [30, 31, 33]. Two prospective observational studies compared standard surgery and extensive surgery with quality of life as a primary end point (Table-1) [29, 32]. All studies

used the validated EORTC QLQ-C30 tool, and three of these additionally used QLQ-OV28 [29, 32, 33]. The randomised controlled trials had low risk of selection and detection bias, but high or unclear risks regarding attrition and reporting of quality of life (Appendix-S4). There was unclear or high risk of bias in the observational studies (Appendix-S5).

Primary debulking surgery vs neoadjuvant chemotherapy (timing of surgery): Greimel 2013 (EORTC55971 study) [30], Kehoe 2015 (CHORUS MRC trial) [31] and Fagotti 2016 (SCORPION trial) [33] examined quality of life outcomes in patients undergoing primary debulking surgery followed by adjuvant chemotherapy and neoadjuvant chemotherapy followed by surgery. EORTC55971 and CHORUS design and participant characteristics were similar regarding the process of selection, randomisation, follow-up and methods used in reporting the quality of life outcomes. EORTC55971 [30], however, only reported outcomes from 27 out of 59 centres. Centres were included only if they were able to contribute 50% patient data at baseline and at least 35% at follow up. As a result, 337 out of 632 patients (53%), provided baseline data with subsequent loss of follow-up (Table-2) and the reported data is based on 212 patients (34%) at 6 months and 142 patients (22%) at 12 months [30]. Quality of life data in the CHORUS MRC trial [31] is based on 52% and 53% of expected patients at 6 months and 12 months respectively. Patients in these trials had mean baseline EORTC QLQ-C30 global health scores of around 50. The SCORPION trial [33] selectively enrolled patients with high tumour load and had lower mean EORTC QLQ-C30 global health scores of around 33. All expected patients returned their quality of life data at baseline (n=110), as did 99 patients (90%) at 6th cycle of chemotherapy and 95 patients (86%) at 6 month follow-up.

Across all included studies, 1064 patients were recruited, baseline quality of life data were available for 904 patients, with attrition of up to 60% by 6 months (524 of eligible 871) and 49% (275 of eligible 563) by 12 months (Table-2). Despite similar design, methods and attrition, meta-analysis showed considerable statistical heterogeneity in global quality of life

score in patients at all follow-up points. There were no statistically significant differences in baseline quality of life between arms although SCORPION patients had mean scores of around 33 compared to around 50 in the other trials. At the 6th cycle of chemotherapy, the SCORPION trial reported a significantly better quality of life in patients having neoadjuvant chemotherapy but there was no difference between arms in the EORTC55971 study (Figure-1a). At 6 months follow-up, patients in SCORPION and EORTC55971 reported no difference in global quality of life scores but CHORUS favoured NACT (Figure-1b). The meta-analysis of data from all three trials at 6 months follow-up showed no statistical difference (p=0.59) in the presence of important heterogeneity and similar results were noticed at 12 month follow-up in CHORUS and EORTC55971 (p=0.78, Figure-1c). Improvement in the quality of life score at 6 months compared to baseline was maintained at 12 months regardless of treatment received. As these studies were not designed to record the extent of surgery, it was not possible to analyse quality of life data by extent of surgery.

Standard vs Extensive surgery: Two observational studies with unclear or high risk of bias, Angioli 2013 [29] (n=80), and Soo Hoo 2015 [32] (n=56), reported quality of life outcomes after standard (pelvic) surgery or extensive surgery. In both, patients undergoing pelvic surgery alone had lesser disease load than those undergoing extensive surgery. In Soo Hoo 2015 study, 9/32 standard surgery patients were FIGO stage 1 or 2 and 4/32 were not epithelial types, resulting in heterogeneity between standard and extensive groups. Angioli 2013 reported quality of life outcomes at 6 months, without any baseline data and patients in standard surgery group were younger. Soo Hoo 2015 included quality of life at baseline, 6 weeks, 3 months, 6 months and 9 months after surgery.

In Angioli 2013, there were no clinically meaningful differences in global quality of life at 6 months between groups; 75.8 in the extensive and 69.6 in the standard surgery group

(p=0.002). In Soo Hoo 2015, baseline mean EORTC QLQ-C30 global health score was at 58 points for standard and at 63 points for extensive surgery. In the extensive surgery group, there was a clinically meaningful but not statistically significant 10 points fall (63 to 53) in global quality of life score at 3 months followed by gradual improvement at 6 months, returning to baseline values by 9 months. At 6 weeks, there was no difference in global quality of life or symptom burden compared to baseline, but a significant impairment was reported in functional quality of life for patients undergoing extensive surgery. In the standard surgery group, these variations were minimal.

Patient reported symptoms

Three studies explored symptoms impacting on quality of life [30, 32, 33]. Baseline symptom scores were highest for fatigue, insomnia and loss of appetite (n=503). Patients in EORTC55971 reported a clinically meaningful (statistical significance not reported) improvement in overall symptoms after intervention by 6 months, and maintained at 12 months. An improvement of >10 points was reported for fatigue, pain and insomnia in both arms. There were clinically unimportant differences post-baseline between groups for fatigue (p=0.055), pain (p=0.046) and dyspnoea (p=0.049).

Fagotti 2016 found most symptoms improved in both arms except for nausea and vomiting, which deteriorated by >10 points (p=0.047). In the primary debulking surgery group, clinically meaningful improvement was present for appetite loss at 6th cycle of chemotherapy. In the neoadjuvant chemotherapy group, fatigue, pain, dyspnoea, and insomnia improved >10 points by 6th cycle of chemotherapy, maintained at 6 months follow-up (Appendix-S6). On the QLQ-OV28 scale, peripheral neuropathy, hormonal symptoms and body image were worse by >10 points at 6th cycle of chemotherapy. While most symptoms subsided by 6 months, peripheral neuropathy and hormonal / menopausal symptoms persisted.

Soo Hoo et al [32, 34] found only scores for peripheral neuropathy, body image, hormonal symptoms and diarrhoea had >10 points difference at 6 months. Hormonal symptoms worsened in both surgical groups (>10 points) with a 14 point difference at 9 months post-surgery. Statistical significance was not reported.

Discussion:

Main findings: We found sparse evidence on the quality of life of women following ovarian cancer surgery. There were no important differences in the quality of life of patients in 3 randomised controlled trials comparing primary debulking surgery with neoadjuvant chemotherapy with improvements over baseline at 6 and 12 months but with evidence of selection bias, much missing data and substantial loss to follow-up. Only one observational study report results in the immediate postoperative period where differences in quality of life and symptom burden might be expected. Patient populations and baseline quality of life varied, with heterogeneous results, particularly up to 6 months: one single centre randomised controlled trial [33] selected patients with high tumour load using laparoscopy screening before randomisation, with lower median age and higher complete and optimal cytoreduction rate, with all patients in the primary debulking surgery arm undergoing maximal resection with higher reported morbidity. Even in this study there was no difference in quality of life at 6 months.

Regarding quality of life after extensive surgery, two observational studies of unclear or poor quality showed clear evidence of confounding. A prospective study reported worse quality of life scores immediately after extensive surgery with an improvement by 9 months after, comparable to that in those who had standard surgery [32]. Due to sample size, differences in the clinical characteristics and loss to follow-up, the data needs to be interpreted with caution. A further observational study also has substantial limitations, lacking a baseline

assessment and, as patient selection was based on laparoscopic findings, applicability to patients selected by other means is unclear [29].

Based on the limited available data, results show that patients undergoing extensive surgery appeared to tolerate the procedure and chemotherapy well as reflected by comparable quality of life scores in all domains and majority of their symptoms start to return to baseline or show improvement after 6 months post-surgery. Patients having neoadjuvant chemotherapy showed early improvement which may be due to need for less extensive surgery and less morbidity, however, the exact explanation for this remains unknown.

Strengths and limitations: Although the review used robust methods, limitations lie in the quality and quantity of included studies. There was no randomised controlled trial specifically addressing quality of life in women undergoing extensive surgery: the observational studies do not provide evidence of sufficient quality or quantity. This is important given the evolution of surgical practice in advanced ovarian cancer. An inevitable concern with poor response rates in this patient population is that those most ill may not have returned quality of life questionnaires.

Extensive surgery frequently requires upper abdominal surgery that may involve liver mobilisation, liver resection, diaphragmatic stripping / resection, splenectomy, cholecystectomy, single or multiple bowel resections with adverse impact on quality of life. Even so, surgical outcomes at 6 and 12 months may be confounded by chemotherapy. Despite many patients having received bowel resection, two trials only used a generalised instrument, EORTC QLQ-C30 to measure quality of life without any specific instrument for ovarian cancer, stoma care, urological function and psychological stress due to fear of recurrence. More subtle ovarian specific differences between primary debulking surgery and neoadjuvant chemotherapy may not have been identified in the current research. The impact

on sexual function is also not known despite its inclusion on OV28 questionnaire, as measurement tool for this domain is not validated for use.

Interpretation: This is the first systematic review on quality of life in relation to surgery in advanced ovarian cancer. This review summarises current understanding of quality of life in patients having either primary debulking surgery or neoadjuvant chemotherapy, but comparative quality of life remains unknown for patients undergoing more extensive compared to standard surgery. There is little evidence on which symptoms are most prominent in women undergoing extensive surgery and what supportive measures might help. High and potentially biased loss to follow-up means that the available data on quality of life following primary debulking surgery and neoadjuvant chemotherapy should be applied in clinical practice only with significant reservations.

Conclusions: Achieving no residual disease at surgery has been associated with improved survival; however this is confounded by the extent of baseline disease and the patient's perspective is important. A clear knowledge of survival gain weighed against expected quality of life after intervention would help the patient to make an informed choice as some patients may value survival gains that adversely impact on their quality of life less than other patients. There is however little evidence to inform patients.

More research is needed to inform patients of the impact of extensive surgery on their expected quality of life in the light of potential gain in survival. This research should assess quality of life at appropriate time points, using meaningful instruments capable of capturing the impact on patients appropriate for interventions applied without overburdening the patient. The research should also focus on methods of minimising missing data. "Surgery in advanced Ovarian Cancer: Quality of life Evaluation Research-2 (SOCQER-2)" is a prospective multicentre study from the UK, Australia and India, aiming to report on patient reported outcomes [35].

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Figures and tables:

1. Table 1: Characteristics of included studies
2. Table 2: Loss to follow-up rate in the studies comparing primary debulking surgery vs neoadjuvant chemotherapy
3. Figure 1: Meta-analysis - Global QoL at 6th cycle of chemotherapy, 6 month & 12 month follow-up

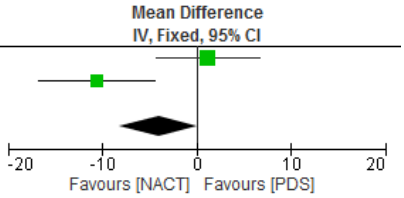
Appendices:

1. Appendix S1: Electronic search strategy
2. Appendix S2: Flow diagram of selection of studies
3. Appendix S3: List and reasons for excluded studies
4. Appendix S4: A. Risk of bias summary: review authors' judgements about each risk of bias item for included randomised controlled trials; B. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included randomised controlled trials.
5. Appendix S5: Risk of bias in observational studies: Newcastle - Ottawa quality assessment scale
6. Appendix S6: EORTC QLQ-C30 – Symptom scale
7. Appendix S7: PRISMA statement and checklist

1a. Global QoL score at 6th cycle (PDS vs NACT)

Study or Subgroup	PDS Mean	PDS SD	PDS Total	NACT Mean	NACT SD	NACT Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Greimel 2013	69.1	23.1	137	67.9	21.6	119	55.6%	1.20 [-4.28, 6.68]	2013
Fagotti 2016	51.4	16	47	62	15	52	44.4%	-10.60 [-16.73, -4.47]	2016
Total (95% CI)			**184**			**171**	**100.0%**	**-4.04 [-8.13, 0.04]**	

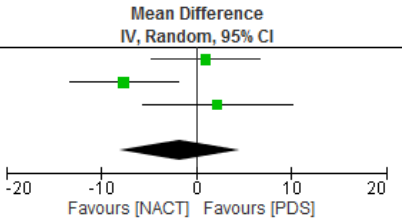
Heterogeneity: Chi² = 7.92, df = 1 (P = 0.005); I² = 87%
Test for overall effect: Z = 1.94 (P = 0.05)



1b. Global QoL score at 6 months follow-up (PDS vs NACT)

Study or Subgroup	PDS Mean	PDS SD	PDS Total	NACT Mean	NACT SD	NACT Total	Weight	Mean Difference IV, Random, 95% CI	Year
Greimel 2013	73.1	21.8	113	72.1	20.3	99	36.0%	1.00 [-4.67, 6.67]	2013
Kehoe 2015	61.5	23.6	103	69.1	18.7	114	35.9%	-7.60 [-13.31, -1.89]	2015
Fagotti 2016	61.3	19.4	46	59.1	19.9	49	28.2%	2.20 [-5.70, 10.10]	2016
Total (95% CI)			**262**			**262**	**100.0%**	**-1.75 [-8.02, 4.52]**	

Heterogeneity: Tau² = 20.07; Chi² = 5.85, df = 2 (P = 0.05); I² = 66%
Test for overall effect: Z = 0.55 (P = 0.59)



1c. Global QoL score at 12 months follow-up (PDS vs NACT)

Study or Subgroup	PDS Mean	PDS SD	PDS Total	NACT Mean	NACT SD	NACT Total	Weight	Mean Difference IV, Random, 95% CI	Year
Greimel 2013	70.4	19.6	78	67.8	18.4	64	54.5%	2.60 [-3.66, 8.86]	2013
Kehoe 2015	61.8	24.2	64	67.5	22.4	69	45.5%	-5.70 [-13.64, 2.24]	2015
Total (95% CI)			**142**			**133**	**100.0%**	**-1.18 [-9.28, 6.92]**	

Heterogeneity: Tau² = 21.13; Chi² = 2.59, df = 1 (P = 0.11); I² = 61%
Test for overall effect: Z = 0.28 (P = 0.78)

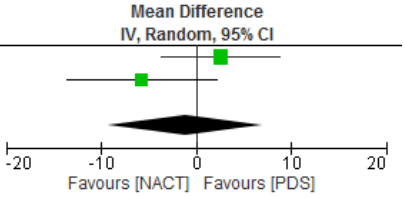


Figure 1: Meta-analysis - Global QoL at 6th cycle of chemotherapy, 6 month & 12 month follow-up

QoL = Quality of life; PDS = Primary debulking surgery; NACT = Neoadjuvant chemotherapy; SD= Standard deviation; CI = Confidence interval [Time points calculated approximately from methods to nearest to 6 months and 12 months]

Table 1: Characteristics of included studies

PDS compared with NACT								
Study	**Country**	**Setting/Design**	**Study groups**	**Study population mean age**	**Number of participants**	**WHO Performance status at baseline**	**FIGO Stage**	**Outcomes**
Greimel 2013	Europe/ Canada	Randomised controlled trial	PDS vs NACT	PDS = 62 NACT = 63	N=404 (for QoL) PDS = 203 NACT = 201	0 – 2	III – IV III – 74% IV – 26%	OS, PFS, QoL
Kehoe 2016	UK / New Zealand	Randomised control trial	PDS vs NACT	PDS = 66 NACT = 65	N=457 (for QoL) PDS = 230 NACT = 227	0 – 3	III – IV III = 75% IV = 25%	OS, PFS, QoL
Fagotti 2016	Italy	Randomised control trial	PDS vs NACT	PDS = 54 NACT = 55	PDS = 55 NACT = 55	0 – 2	IIIC – IV IIIC – 89% IV – 11%	PFS, OS, QoL, Postoperative complications
Standard surgery compared to extensive surgery								
Study	**Country**	**Setting/Design**	**Study groups**	**Study population mean age**	**Number of participants**	**WHO Performance status**	**FIGO Stage**	**Outcomes**
Angioli 2013	Italy	Prospective observational study	Standard surgery (Group 1) vs Ultra-radical surgery (Group 2)	Group 1 = 53.6 Group 2 = 63.9	80 (40 in each group)	0 – 1	III – IV III – 82.5% IV – 17.5%	QoL
Soo Hoo 2015	UK	Prospective observational study	Standard surgery (Group 1) vs Ultra-radical surgery (Group 2)	Group 1 = 61 Group 2 = 63	N=56 Group 1 = 32 Group 2 = 24	ASA I – III	I – IV Group 1: I = 6 (18.8%) II = 3 (9%). IIIB = 1 (3 %) IIIC – IV = 22 (68.8%) Group 2: IIIC – IV = 24 (100%)	QoL

PDS = Primary debulking surgery, NACT = Neoadjuvant chemotherapy, WHO = World Health Organisation, FIGO = International Federation of Gynaecology and Obstetrics, QoL = Quality of life, OS = Overall survival, PFS = Progression free survival, ASA = American Society of Anaesthesiologists.

Table 2: Loss to follow-up rate in the studies comparing primary debulking surgery and neoadjuvant chemotherapy followed by surgery

	Greimel 2013	% of participants expected to return QoL questionnaire	Kehoe 2015	% of participants expected to return QoL questionnaire	Fagotti 2016	% of participants expected to return QoL questionnaire	Overall	% of participants expected to return QoL questionnaire
Number recruited in original study	632	-	550	-	110	-	1292	-
Number of patients participating in QoL study	404	64%	550	100%	110	100%	1064	82%
Baseline: questions returned / Expected to return	337/404	83%	457/550	83%	110/110	100%	904/1064	85%
6 months: questions returned / Expected to return	212/357	59%	217/419	52%	95/95	100%	524/871	60%
12 months: questions returned / Expected to return	142/311	46%	133/252	53%	NA	NA	275/563	49%

QoL=Quality of life, NA=Not available

Appendix S1: Electronic search strategy

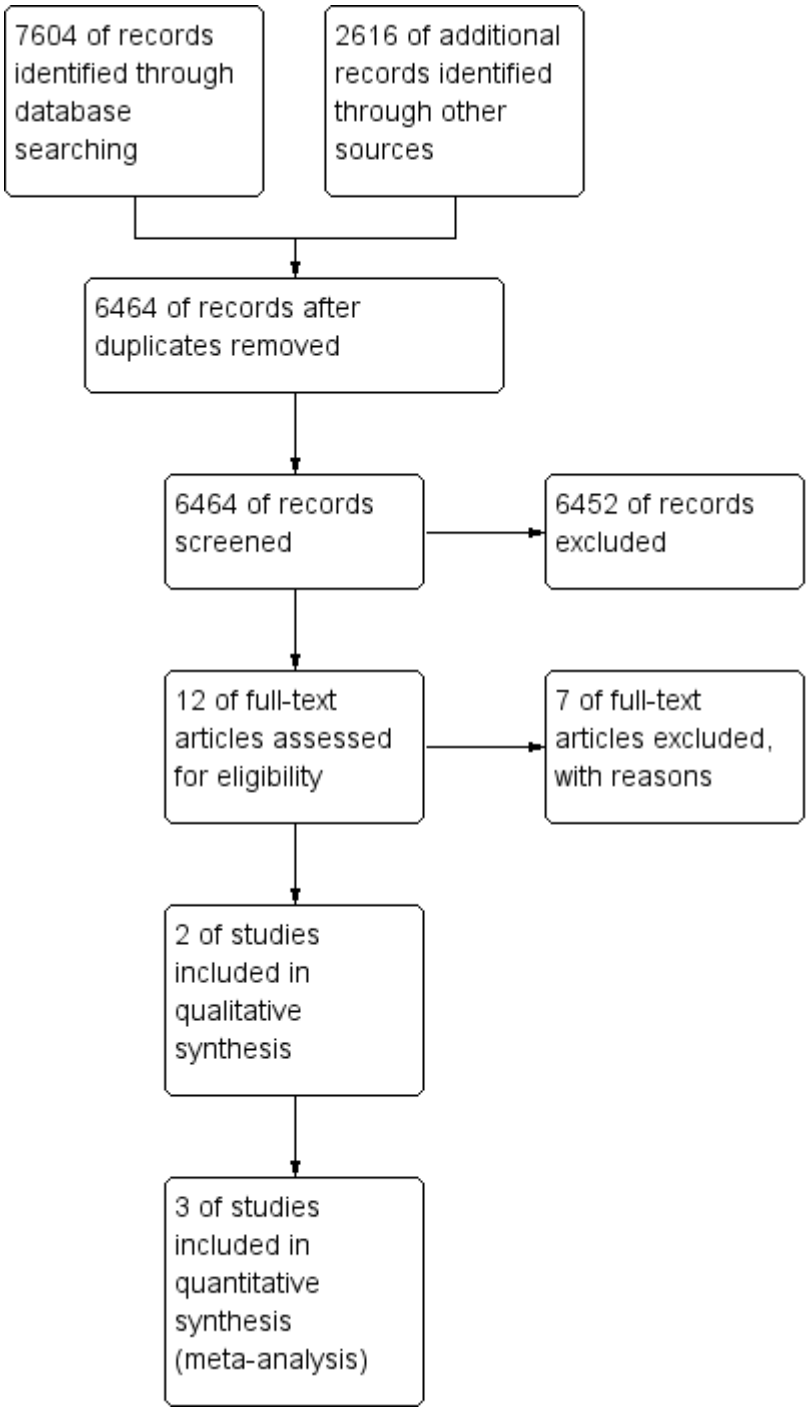
Sample search strategies for MEDLINE and EMBASE are given below.
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present and EMBASE 1974 to 2018 March.

1 exp Ovarian neoplasms/
2 (ovar* adj5 (cancer* or carcinom* or malignan* or neoplas*)).ti,ab.
3 1 or 2
4 Surg*.ti,ab.
5 (cytoreduc* or debulk*).ti,ab.
6 exp general surgery/
7 4 or 5 or 6
8 3 and 7
9 exp quality of life/
10 Quality of life.ti,ab.
11 QoL.ti,ab.
12 Self report/ or outcome assessment/ or patient satisfaction/ or "surveys and questionnaires"/ or treatment outcome/
13 exp "Outcome Assessment (Health Care)"/
14 (outcome* adj3 assess*).ti,ab.
15 Patient reported outcome.mp. or patient reported outcome.ti,tw,ab. or patient reported utcomes.ti,tw,ab
16 9 or 10 or 11 or 12 or 13 or 14 or 15
17 8 and 16

CENTRAL:

#1. Ovarian neoplasms
#2. (ovar* adj5 (cancer* or carcinom* or malignan* or neoplas*)) .ti,ab.
#3. #1 or #2
#4. Surg*.ti,ab.
#5. (cytoreduc* or debulk*) .ti,ab.
#6. General surgery
#7. #4 or #5 or #6
#8. #3 and #7
#9. Quality of life
#10.Patient reported outcome*
#11.Quality of life.ti,ab.
#12.Patient reported outcome.mp. or patient reported outcome.ti,tw,ab. or patient reported outcomes.ti,tw,ab.
#13. #9 or #10 or #11 or #12
#14. #8 and #13

Appendix S2: Flow diagram of selection of studies



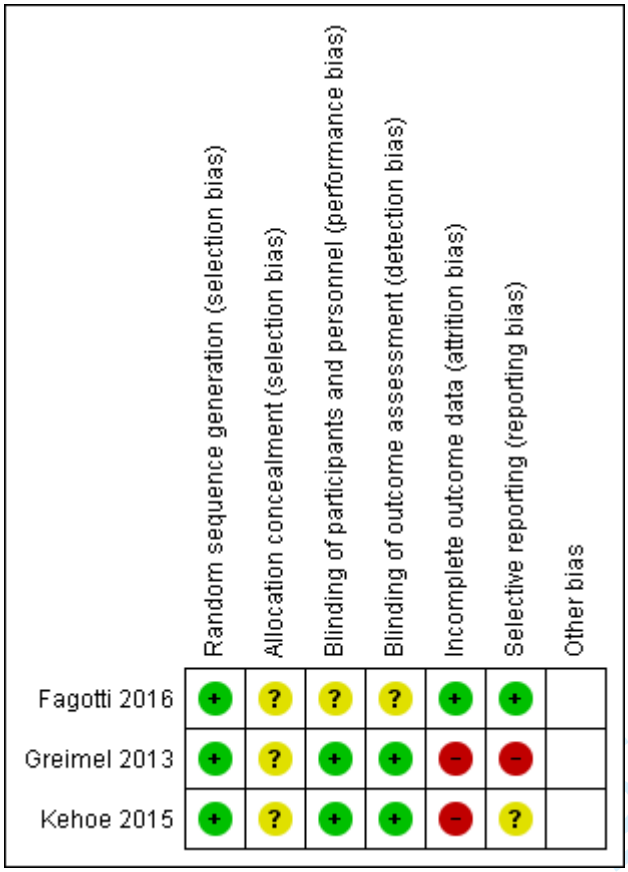
Appendix S3: List and reasons for excluded studies

Study	Reasons for exclusions
Von Hugo 1989	Abstract was not available, therefore full text reviewed. The study was retrospective and based on telephonic interview of patients, relatives or doctors, if patients were not alive. (von Hugo et al., 1989).
Pfleiderer 1995	Abstract was not available, therefore full text reviewed. Paper described different gynaecological and breast surgery (Pfleiderer, 1995).
Chan 2001	Study included all gynaecological cancers & different treatments and included all stages. No subgroup analysis was performed according to cancer types or FIGO stages (Chan et al., 2001).
Greimel 2002	Study included breast and gynaecological cancer sites and all stages. Number of ovarian cancer patients with stage III & IV provided but analysis of QoL outcomes did not report them separately (Greimel et al., 2002).
Chan 2003	The study enrolled 17 patients for NACT followed by surgery, and 13 of them underwent debulking surgery. Optimal debulking was defined as residual disease of <2 cm. The data shows pattern of improvement in QoL score (QLQ-C30), but actual data scores are not provided. The study also compared the QoL scores to the conventional treatment (Chemotherapy only) from historic control (Chan et al., 2003).
Le 2004	The study included patients with recurrent or progressive ovarian cancer and 52% of the patients previously had optimal surgical resection. FACT-O tool was used for QoL assessments, and mainly the effects of different types of chemotherapy were assessed (Le et al., 2004).
Brotto 2016	No Pre-surgical baseline. Randomisation to different arms of chemotherapy after 4-6 weeks after primary surgery. Some patients had interval surgery after randomisation to the study. A large number of patients did not have surgery. FIGO stage IIB - IV included in the study. Data according to stratification by surgery not available (Brotto et al., 2016).

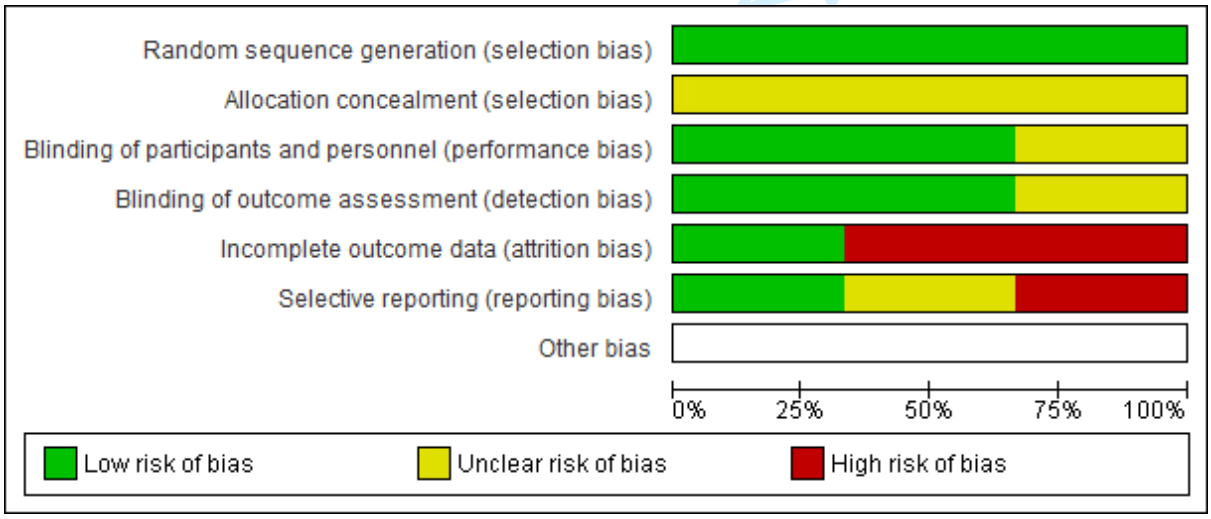
FIGO = International Federation of Gynaecology and Obstetrics, QoL = Quality of life, NACT = Neoadjuvant chemotherapy, QLQ-C30 = EORTC Quality of Life questionnaires for cancer patients, FACT-O = Functional Assessment of Cancer Therapy–Ovarian

Appendix S4:

A. Risk of bias summary: review authors' judgements about each risk of bias item for included RCTs



B. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included RCTs.



Appendix S5: Risk of bias in observational studies: Newcastle - Ottawa quality assessment scale

Domains	Angioli 2012	Author's judgement	Soo Hoo 2015	Author's judgement
Selection				
Representativeness of the exposed cohort	Highly selected group of users, not truly representative of the average advanced ovarian cancer patients in the community	High risk	Truly representative of the average advanced ovarian cancer patients in the community	Low risk
Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	Low risk	Drawn from the same community as the exposed cohort	Low risk
Ascertainment of exposure	Secure record	Low risk	Secure record	Low risk
Demonstration that outcome of interest was not present at start of study	Yes, but no baseline data available	High risk	Yes	Low risk
Comparability				
Comparability of cohorts on the basis of the design or analysis	Study controls for the type of surgery patients received with predefined criteria as standard surgery and extensive upper abdominal surgery, However standard surgery group had high proportion of early stage disease	High risk	Study controls for the type of surgery patients received with predefined criteria as standard surgery and extensive upper abdominal surgery, However standard surgery group had high proportion of early stage disease	High risk
Outcome				
Assessment of outcome	Self-report	Low risk	Self-report	Low risk
Was follow-up long enough for outcomes to occur	No	High risk	Baseline to 9 months post-surgery	Low risk
Adequacy of follow up of cohorts	Complete follow up - all subjects accounted for, but only at single point after completion of treatment.	High risk	Follow up rate at end of study period was approximately 50%, but no description of those lost were documented	High risk

Appendix S6: QLQ-C30 – Symptom scale

		Primary surgery					NACT					p-value
QLQ-C30		**0**	**6 months**	**12 months**	**Points change at 6 months**	**Points change at 12 months**	**0**	**6 months**	**12 months**	**Points change at 6 months**	**Points change at 12 months**	
Fatigue	A	46.2	29.0	29.1	-17.2	-17.1	40	25.7	29.1	-14.3	-10.9	**0.055**
	B	42.9	**50.0**	32.0	7.1	-10.9	52.2	39.9	34.3	- 12.3	-17.9	0.471
Nausea/vomiting	A	12.3	3.2	3.4	-9.1	-8.9	12.7	4.2	5.6	-8.5	-7.1	0.753
	B	20.1	**47.8**	**30.8**	**27.7**	**10.7**	19.1	**31.1**	**34.3**	**12**	**15.2**	**0.047**
Pain	A	36.7	19	19.1	-17.7	-17.6	29.9	15.4	15.1	-14.5	-14.8	**0.046**
	B	30.5	21.4	10.5	-9.1	-20	26.5	14.5	14.9	-12	-11.6	0.155
Dyspnoea	A	22.9	16.8	15.6	-6.1	-7.3	27.9	16.3	18.9	-11.6	-9	**0.049**
	B	37.8	35.7	15.2	-2.1	-22.6	33.7	16.2	20.7	-17.5	-13	**0.013**
Insomnia	A	43.1	26.4	24.8	-16.7	-18.3	37.6	27.2	22.1	-10.4	-15.5	0.112
	B	47.7	46.5	17.9	-1.2	-29.8	38.9	25.8	17.5	-13.1	-21.4	**0.024**
Appetite loss	A	42.9	9.3	9.6	-33.6	-33.3	39.1	9.5	10.6	-29.6	-28.5	0.208
	B	45.8	35.1	23.8	-10.7	-22	42.2	28.5	24.6	-13.7	-17.6	0.126
Constipation	A	26.1	17.9	12.5	-8.2	-13.6	24.8	13.2	14.2	-11.6	-10.6	0.455
	B	31.8	**38.5**	**41.0**	6.7	9.2	33.2	26.6	**41.4**	-6.6	8.2	0.109
Diarrhoea	A	20	4.1	4.7	-15.9	-15.3	17.9	9.4	8.1	-8.5	-9.8	0.053
	B	13.2	13.9	14.0	0.7	0.8	13.0	6.5	7.1	-6.5	-5.9	0.202
Financial difficulties	A	8.3	11.7	12.4	3.4	4.1	10.4	10.2	10	-0.2	-0.4	0.341
	B	39.8	43.9	33.0	4.1	-6.8	28.6	37.7	39.5	9.1	10.9	0.466

A = Greimel 2013, B = Fagotti 2016, QLQ-C30 = EORTC Quality of Life questionnaires for cancer patients

Appendix S8: PRISMA statement and checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1 - 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3 - 4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	AppendixS1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4, Appendix S2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4, Appendix S4, S5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	3, Protocol
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4, Protocol
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Appendix S4, S5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4, Appendix S2, S3
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Appendix S4, S5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	5, Protocol
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Appendix S4, S5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9 - 10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9 - 10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10 – 11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Title page, Protocol

Abstract:

Background: Quality of life after ovarian cancer treatment is an important goal for patients. Complex debulking surgeries and platinum based chemotherapy are often required but quality of life after surgery is rarely reported.

Objectives: To describe quality of life outcomes after surgery for advanced ovarian cancer in a systematic review and meta-analysis.

Search strategy: MEDLINE, EMBASE and CENTRAL through March 2019 with no language restrictions

Selection criteria: Included studies reported quality of life in women diagnosed with primary advanced ovarian cancer, fallopian tube carcinoma or primary peritoneal cancer undergoing cytoreduction surgery.

Data collection and analysis: Data on extent and timing of surgery, quality of life outcomes and surgical complications were extracted and study quality assessed.

Main Results: Three randomised controlled trials comparing primary surgery to neoadjuvant chemotherapy had heterogeneous quality of life outcomes with no difference between arms although there was a clinical improvement in global quality of life scores in both arms at 6 months compared to baseline. Data from two observational studies showed no meaningful difference in quality of life scores between patients undergoing standard or extensive surgery at 6 months.

Conclusions: There was no clinically important difference in the quality of life of patients undergoing either primary debulking surgery or neoadjuvant chemotherapy. There is insufficient evidence on quality of life outcomes of patients undergoing extensive or ultra-radical surgery compared with those undergoing less extensive surgery. Quality of life

outcomes matter to patients but there is little evidence to inform patient choice regarding the extent of surgery.

Keywords Ovarian cancer, quality of life, extensive surgery, ultra-radical surgery, debulking surgery

Introduction:

Whilst overall survival and progression free survival are critical outcomes for cancer patients, quality of life is of fundamental importance to patients [1]. Health related quality of life refers to the effect of an illness and its therapy upon a patient's physical and occupational function, psychological state and social wellbeing which itself can influence treatment decisions [2-4]. Standard treatment in advanced ovarian cancer comprises a combination of cytoreduction surgery and chemotherapy using carboplatin and paclitaxel [5]. Although considerable variations exist in international surgical opinion and practice [6-10], complex surgery is increasingly performed with the goal of complete cytoreduction which may include resections of the bowel and of disease on the liver, diaphragm and spleen.

Multiple studies have shown improved progression free survival and overall survival with complete cytoreduction [11-15] however, initial disease burden remains a prognostic indicator [16]. In a Cochrane review, low quality evidence shows a survival benefit with more extensive surgery, and differences in morbidity and quality of life outcomes of extensive surgery compared to standard surgery are still unclear [17].

Greater morbidity is associated with extensive surgery [18, 19] but knowledge of quality of life is lacking. Whether a patient has primary debulking surgery or neoadjuvant chemotherapy may also impact on quality of life. Understanding quality of life outcomes is critical given randomised controlled trial data on surgical extent is lacking. Robust estimation of survival benefit for any individual patient undergoing extensive surgery is therefore challenging. The putative survival gain from extensive surgery might be offset by deterioration in quality of life as a result of increased morbidity. While much is known about quality of life outcomes during or after chemotherapy [20-24], the impact on quality of life from surgery, particularly extensive surgery remains unknown.

The purpose of this systematic review and meta-analysis is to report patient reported quality of life after surgery in advanced ovarian cancer.

Methods:

We searched Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to Present and EMBASE 1974 to 11th of March, 2019 and current edition of CENTRAL for eligible studies (SK,JL) with no language restrictions (Appendix-S1). Science Citation Index (Web of Science), www.clinicaltrials.gov and metaregister of controlled trials were searched. Reference lists of included studies were screened. Abstracts of meetings from International Gynaecological Cancer Society, British Gynaecological Cancer Society, European Society of Gynaecological Oncology, American Society of Clinical Oncology and Society of Gynaecological Oncology were searched. We included randomised controlled trials, non-randomised trials and prospective observational studies describing any quality of life measures as primary or secondary outcomes. Studies with women aged 18 and over diagnosed with International Federation of Gynaecology and Obstetrics (FIGO) stages 3 or 4 epithelial ovarian cancer, fallopian tube carcinoma or primary peritoneal carcinomatosis undergoing cytoreduction surgery were included [25]. Studies evaluating quality of life only in chemotherapy interventions, intraperitoneal chemotherapy or in recurrent ovarian cancer were excluded.

All identified references were transferred to EndNote bibliographic software and duplicated studies were removed. Two authors (SK,JL) independently reviewed all titles and abstracts and retrieved full text of selected studies. Two authors (CC,SS) reviewed articles where there was any uncertainty. Risk of bias was assessed using the Newcastle–Ottawa quality assessment scale for observational studies [26] and the Cochrane tool [27] for randomised controlled trials.

Data extracted included: author's details and citation index, publication year, country, study-design, participants number, mean age, performance status, FIGO stage, histology, quality of life tools, quality of life scores at different time points, overall survival and progression free survival. Where appropriate, meta-analysis was carried out using random effects and study heterogeneity was assessed. Quality of life was described in the following sub-groups: primary debulking surgery vs neoadjuvant chemotherapy and standard vs extensive surgery. Quality of life scores were recorded as mean with standard deviation and a 10 point difference in quality of life score was considered meaningful as per European Organisation for Research and Treatment of Cancer (EORTC) guidelines. Standard deviation values were calculated using the Cochrane tool if only standard errors were provided [27].

The systematic review protocol was registered on PROSPERO (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016048139).
A PRISMA statement and checklist for systematic reviews is provided in Appendix-S7 [28].

Results:

We identified a total of 10,220 records from the database search and other sources such as science citation index and abstract of meetings. After removing duplicates, we screened title and abstracts of 6464 records and excluded 6452, based on study characteristics, design and reported outcomes. Seven records were excluded after full text review. Five studies were included in the systematic review [29-33]. The authors of all included studies were contacted for additional information [30, 31]. The electronic search criteria, selection process flow diagram and list of excluded studies are given in appendices (S1,S2 and S3).

Three included studies were randomised controlled trials comparing primary debulking surgery with neoadjuvant chemotherapy, evaluating quality of life as secondary outcomes [30, 31, 33]. Two prospective observational studies compared standard surgery and extensive surgery with quality of life as a primary end point (Table-1) [29, 32]. All studies

used the validated EORTC QLQ-C30 tool, and three of these additionally used QLQ-OV28 [29, 32, 33]. The randomised controlled trials had low risk of selection and detection bias, but high or unclear risks regarding attrition and reporting of quality of life (Appendix-S4). There was unclear or high risk of bias in the observational studies (Appendix-S5).

Primary debulking surgery vs neoadjuvant chemotherapy (timing of surgery): Greimel 2013 (EORTC55971 study) [30], Kehoe 2015 (CHORUS MRC trial) [31] and Fagotti 2016 (SCORPION trial) [33] examined quality of life outcomes in patients undergoing primary debulking surgery followed by adjuvant chemotherapy and neoadjuvant chemotherapy followed by surgery. EORTC55971 and CHORUS design and participant characteristics were similar regarding the process of selection, randomisation, follow-up and methods used in reporting the quality of life outcomes. EORTC55971 [30], however, only reported outcomes from 27 out of 59 centres. Centres were included only if they were able to contribute 50% patient data at baseline and at least 35% at follow up. As a result, 337 out of 632 patients (53%), provided baseline data with subsequent loss of follow-up (Table-2) and the reported data is based on 212 patients (34%) at 6 months and 142 patients (22%) at 12 months [30]. Quality of life data in the CHORUS MRC trial [31] is based on 52% and 53% of expected patients at 6 months and 12 months respectively. Patients in these trials had mean baseline EORTC QLQ-C30 global health scores of around 50. The SCORPION trial [33] selectively enrolled patients with high tumour load and had lower mean EORTC QLQ-C30 global health scores of around 33. All expected patients returned their quality of life data at baseline (n=110), as did 99 patients (90%) at 6th cycle of chemotherapy and 95 patients (86%) at 6 month follow-up.

Across all included studies, 1064 patients were recruited, baseline quality of life data were available for 904 patients, with attrition of up to 60% by 6 months (524 of eligible 871) and 49% (275 of eligible 563) by 12 months (Table-2). Despite similar design, methods and attrition, meta-analysis showed considerable statistical heterogeneity in global quality of life

score in patients at all follow-up points. There were no statistically significant differences in baseline quality of life between arms although SCORPION patients had mean scores of around 33 compared to around 50 in the other trials. At the 6th cycle of chemotherapy, the SCORPION trial reported a significantly better quality of life in patients having neoadjuvant chemotherapy but there was no difference between arms in the EORTC55971 study (Figure-1a). At 6 months follow-up, patients in SCORPION and EORTC55971 reported no difference in global quality of life scores but CHORUS favoured NACT (Figure-1b). The meta-analysis of data from all three trials at 6 months follow-up showed no statistical difference (p=0.59) in the presence of important heterogeneity and similar results were noticed at 12 month follow-up in CHORUS and EORTC55971 (p=0.78, Figure-1c). Improvement in the quality of life score at 6 months compared to baseline was maintained at 12 months regardless of treatment received. As these studies were not designed to record the extent of surgery, it was not possible to analyse quality of life data by extent of surgery.

Standard vs Extensive surgery: Two observational studies with unclear or high risk of bias, Angioli 2013 [29] (n=80), and Soo Hoo 2015 [32] (n=56), reported quality of life outcomes after standard (pelvic) surgery or extensive surgery. In both, patients undergoing pelvic surgery alone had lesser disease load than those undergoing extensive surgery. In Soo Hoo 2015 study, 9/32 standard surgery patients were FIGO stage 1 or 2 and 4/32 were not epithelial types, resulting in heterogeneity between standard and extensive groups. Angioli 2013 reported quality of life outcomes at 6 months, without any baseline data and patients in standard surgery group were younger. Soo Hoo 2015 included quality of life at baseline, 6 weeks, 3 months, 6 months and 9 months after surgery.

In Angioli 2013, there were no clinically meaningful differences in global quality of life at 6 months between groups; 75.8 in the extensive and 69.6 in the standard surgery group

(p=0.002). In Soo Hoo 2015, baseline mean EORTC QLQ-C30 global health score was at 58 points for standard and at 63 points for extensive surgery. In the extensive surgery group, there was a clinically meaningful but not statistically significant 10 points fall (63 to 53) in global quality of life score at 3 months followed by gradual improvement at 6 months, returning to baseline values by 9 months. At 6 weeks, there was no difference in global quality of life or symptom burden compared to baseline, but a significant impairment was reported in functional quality of life for patients undergoing extensive surgery. In the standard surgery group, these variations were minimal.

Patient reported symptoms

Three studies explored symptoms impacting on quality of life [30, 32, 33]. Baseline symptom scores were highest for fatigue, insomnia and loss of appetite (n=503). Patients in EORTC55971 reported a clinically meaningful (statistical significance not reported) improvement in overall symptoms after intervention by 6 months, and maintained at 12 months. An improvement of >10 points was reported for fatigue, pain and insomnia in both arms. There were clinically unimportant differences post-baseline between groups for fatigue (p=0.055), pain (p=0.046) and dyspnoea (p=0.049).

Fagotti 2016 found most symptoms improved in both arms except for nausea and vomiting, which deteriorated by >10 points (p=0.047). In the primary debulking surgery group, clinically meaningful improvement was present for appetite loss at 6th cycle of chemotherapy. In the neoadjuvant chemotherapy group, fatigue, pain, dyspnoea, and insomnia improved >10 points by 6th cycle of chemotherapy, maintained at 6 months follow-up (Appendix-S6). On the QLQ-OV28 scale, peripheral neuropathy, hormonal symptoms and body image were worse by >10 points at 6th cycle of chemotherapy. While most symptoms subsided by 6 months, peripheral neuropathy and hormonal / menopausal symptoms persisted.

Soo Hoo et al [32, 34] found only scores for peripheral neuropathy, body image, hormonal symptoms and diarrhoea had >10 points difference at 6 months. Hormonal symptoms worsened in both surgical groups (>10 points) with a 14 point difference at 9 months post-surgery. Statistical significance was not reported.

Discussion:

Main findings: We found sparse evidence on the quality of life of women following ovarian cancer surgery. There were no important differences in the quality of life of patients in 3 randomised controlled trials comparing primary debulking surgery with neoadjuvant chemotherapy with improvements over baseline at 6 and 12 months but with evidence of selection bias, much missing data and substantial loss to follow-up. Only one observational study report results in the immediate postoperative period where differences in quality of life and symptom burden might be expected. Patient populations and baseline quality of life varied, with heterogeneous results, particularly up to 6 months: one single centre randomised controlled trial [33] selected patients with high tumour load using laparoscopy screening before randomisation, with lower median age and higher complete and optimal cytoreduction rate, with all patients in the primary debulking surgery arm undergoing maximal resection with higher reported morbidity. Even in this study there was no difference in quality of life at 6 months.

Regarding quality of life after extensive surgery, two observational studies of unclear or poor quality showed clear evidence of confounding. A prospective study reported worse quality of life scores immediately after extensive surgery with an improvement by 9 months after, comparable to that in those who had standard surgery [32]. Due to sample size, differences in the clinical characteristics and loss to follow-up, the data needs to be interpreted with caution. A further observational study also has substantial limitations, lacking a baseline

assessment and, as patient selection was based on laparoscopic findings, applicability to patients selected by other means is unclear [29].

Based on the limited available data, results show that patients undergoing extensive surgery appeared to tolerate the procedure and chemotherapy well as reflected by comparable quality of life scores in all domains and majority of their symptoms start to return to baseline or show improvement after 6 months post-surgery. Patients having neoadjuvant chemotherapy showed early improvement which may be due to need for less extensive surgery and less morbidity, however, the exact explanation for this remains unknown.

Strengths and limitations: Although the review used robust methods, limitations lie in the quality and quantity of included studies. There was no randomised controlled trial specifically addressing quality of life in women undergoing extensive surgery: the observational studies do not provide evidence of sufficient quality or quantity. This is important given the evolution of surgical practice in advanced ovarian cancer. An inevitable concern with poor response rates in this patient population is that those most ill may not have returned quality of life questionnaires.

Extensive surgery frequently requires upper abdominal surgery that may involve liver mobilisation, liver resection, diaphragmatic stripping / resection, splenectomy, cholecystectomy, single or multiple bowel resections with adverse impact on quality of life. Even so, surgical outcomes at 6 and 12 months may be confounded by chemotherapy. Despite many patients having received bowel resection, two trials only used a generalised instrument, EORTC QLQ-C30 to measure quality of life without any specific instrument for ovarian cancer, stoma care, urological function and psychological stress due to fear of recurrence. More subtle ovarian specific differences between primary debulking surgery and neoadjuvant chemotherapy may not have been identified in the current research. The impact

on sexual function is also not known despite its inclusion on OV28 questionnaire, as measurement tool for this domain is not validated for use.

Interpretation: This is the first systematic review on quality of life in relation to surgery in advanced ovarian cancer. This review summarises current understanding of quality of life in patients having either primary debulking surgery or neoadjuvant chemotherapy, but comparative quality of life remains unknown for patients undergoing more extensive compared to standard surgery. There is little evidence on which symptoms are most prominent in women undergoing extensive surgery and what supportive measures might help. High and potentially biased loss to follow-up means that the available data on quality of life following primary debulking surgery and neoadjuvant chemotherapy should be applied in clinical practice only with significant reservations.

Conclusions: Achieving no residual disease at surgery has been associated with improved survival; however this is confounded by the extent of baseline disease and the patient's perspective is important. A clear knowledge of survival gain weighed against expected quality of life after intervention would help the patient to make an informed choice as some patients may value survival gains that adversely impact on their quality of life less than other patients. There is however little evidence to inform patients.

More research is needed to inform patients of the impact of extensive surgery on their expected quality of life in the light of potential gain in survival. This research should assess quality of life at appropriate time points, using meaningful instruments capable of capturing the impact on patients appropriate for interventions applied without overburdening the patient. The research should also focus on methods of minimising missing data. "Surgery in advanced Ovarian Cancer: Quality of life Evaluation Research-2 (SOCQER-2)" is a prospective multicentre study from the UK, Australia and India, aiming to report on patient reported outcomes [35].

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Figures and tables:

1. Table 1: Characteristics of included studies
2. Table 2: Loss to follow-up rate in the studies comparing primary debulking surgery vs neoadjuvant chemotherapy
3. Figure 1: Meta-analysis - Global QoL at 6th cycle of chemotherapy, 6 month & 12 month follow-up

Appendices:

1. Appendix S1: Electronic search strategy
2. Appendix S2: Flow diagram of selection of studies
3. Appendix S3: List and reasons for excluded studies
4. Appendix S4: A. Risk of bias summary: review authors' judgements about each risk of bias item for included randomised controlled trials; B. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included randomised controlled trials.
5. Appendix S5: Risk of bias in observational studies: Newcastle - Ottawa quality assessment scale
6. Appendix S6: EORTC QLQ-C30 – Symptom scale
7. Appendix S7: PRISMA statement and checklist